SPIROCYCLIC COMPOUNDS AS MODULATORS OF KRAS AND USES THEREOF

CROSS REFERENCE TO PRIOR APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/565,476, filed March 14, 2024, and U.S. Provisional Patent Application No. 63/645,612, filed May 10, 2024, each of which is incorporated by reference in its entirety.

FIELD

[0002] The present disclosure provides compounds having activity as inhibitors of mutant KRAS proteins. This disclosure also provides pharmaceutical compositions comprising the compounds, uses and methods of treating certain disorders, such as cancer, including but not limited to non-small cell lung cancer, colorectal cancer, pancreatic cancer, appendiceal cancer, endometrial cancer, esophageal cancer, cancer of unknown primary, ampullary cancer, gastric cancer, small bowel cancer, sinonasal cancer, bile duct cancer, or melanoma.

BACKGROUND

[0003] From its identification as one of the first human oncogenes in 1982 (Der et al., 1982), KRAS (the Kirsten rat sarcoma viral oncogene homologue) has been the focus of extensive academic and industrial research, as a key node in the MAPK signal transduction pathway, as a transforming factor in a network of parallel effector pathways (e.g., PI3K/AKT) (Vojtek et al., 1998) and as a potential target for anti-cancer agents (Malumbres et al., 2003). Despite progress in the development of inhibitors of upstream and downstream nodes in the MAPK pathway (e.g., EGFR (Sridhar et al., 2003), BRAF (Holderfield et al., 2014) and MEK (Caunt et al., 2015), the KRAS protein has historically proven resistant to direct inhibition.

[0004] KRAS is a G-protein that couples extracellular mitogenic signaling to intracellular, pro-proliferative responses. KRAS serves as an intracellular "on/off" switch. Mitogen stimulation induces the binding of GTP to KRAS, bringing about a conformational change which enables the interaction of KRAS with downstream effector proteins, leading to cellular proliferation. Normally, pro-proliferative signaling is regulated by the action of GTPase-activating proteins (GAPs), which return KRAS to its GDP-bound, non-proliferative state. Mutations in KRAS impair the regulated cycling of KRAS between these GDP- and GTP-bound states, leading to the accumulation of the GTP-bound active state and dysregulated cellular proliferation (Simanshu et al., 2017).

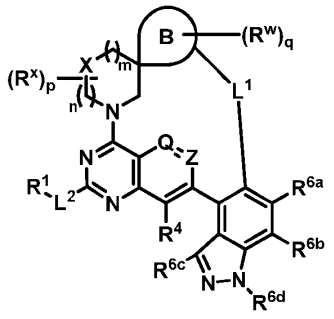
[0005] Attempts to develop inhibitors of mutated KRAS proteins have historically been thwarted by the absence of druggable pockets on the surface of the protein (Cox et al., 2014). In 2013, Shokat

and colleagues identified covalent inhibitors of a common (O'Bryan, 2019) oncogenic mutant of KRAS, KRAS G12C, which bound to a previously unrecognized allosteric pocket on GDP-KRAS G12C and prevented its subsequent activation (Ostream et al., 2013). This discovery brought about significant new efforts in the KRAS inhibitor research, which have recently culminated in the entry of KRAS inhibitors in human clinical trials.

[0006] While some progress has been made on KRAS G12C inhibitors, there is a continued interest and effort to develop inhibitors of KRAS, particularly inhibitors of other KRAS such as KRAS G12D, G12V, G12A, G12S, G12R, G13D, Q61H, Q61L, Q61R or G12C. Thus, there is a need to develop new inhibitors for KRAS G12D, G12V, G12A, G12S, G12R, G13D, Q61H, Q61L, Q61R or G12C for the treatment of disorders, such as cancer.

SUMMARY

[0007] One aspect of the disclosure provides a compound of Formula (**I**):



(**I**)

or a pharmaceutically acceptable salt thereof, wherein:

X is $-CH_2-$ or -O-

Z is C-H, C-halogen, C-CN, C-C_{1-4} alkyl, C-C_{1-4} haloalkyl, C-C_{1-4} alkoxy, C-C_{1-4} haloalkoxy, C-C_{3-7} cycloalkyl or N;

Q is CH, C-halogen, C-C_{1-4} alkyl, C-C_{1-4} haloalkyl or N;

B is a C_{3-7} cycloalkyl or 3-7 membered heterocycloalkyl;

n is 0, 1 or 2;

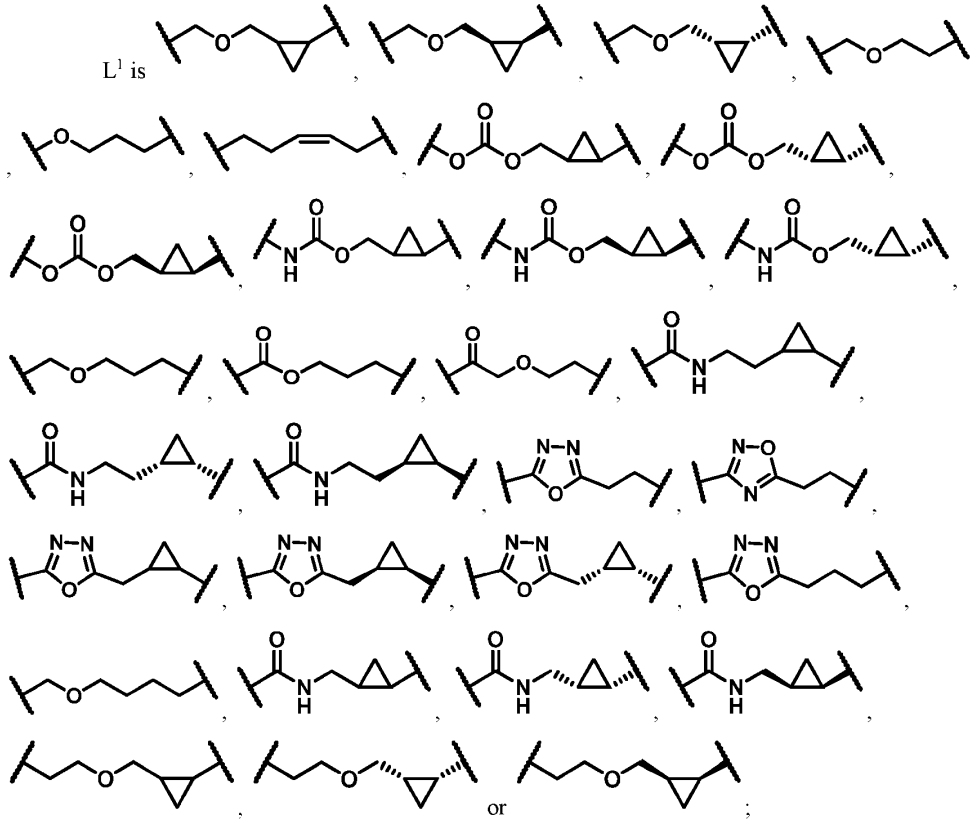
m is 0, 1 or 2;

p is 0, 1 or 2;

q is 0, 1 or 2;

each R^x independently is hydroxyl, halogen, oxo, cyano, $-N(R^z)_2$, C_{1-4} alkyl, C_{1-4} deuteroalkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{1-4} hydroxyalkylene, 5-7 membered

heteroaryl, -S(O)$_2$-C$_{1-4}$alkyl, -S(O)$_2$N(R^z)$_2$, -C(O)R^z, -C(O)OR^z, -C(O)N(R^z)$_2$, -C$_{1-4}$ alkylene-C(O)-C$_{1-4}$alkyl, -C$_{1-4}$ alkylene-C(O)N(R^z)$_2$, C$_{1-4}$ alkylene-S(O)$_2$-C$_{1-4}$alkyl, or -S-C$_{1-4}$alkyl;

L^1 is 

L^2 is a bond, C$_{1-6}$ alkylene, -O-C$_{1-6}$ alkylene, -S-C$_{1-6}$ alkylene, NR^z, O or S, wherein each C$_{1-6}$ alkylene, -O-C$_{1-6}$ alkylene and -S-C$_{1-6}$ alkylene chain is substituted with 0-2 occurrences of R^2;

R^1 is hydrogen, hydroxyl, C$_{6-10}$ aryl, 5-10 membered heteroaryl, C$_{3-8}$ cycloalkyl or 4-15 membered heterocycloalkyl, wherein each aryl, heteroaryl, cycloalkyl or heterocycloalkyl is substituted with 0-3 occurrences of R^5;

each R^2 independently is halogen, deuterium, hydroxyl or C$_{1-4}$ alkyl;

wherein two geminal R^2 groups, together with the atom to which they are attached form a spiro-C$_{3-7}$ cycloalkyl group substituted with 0-2 occurrences of R^w; or wherein two adjacent R^2 groups, together with the atoms to which they are attached form a fused-C$_{3-7}$ cycloalkyl group substituted with 0-2 occurrences of R^w;

R^4 is hydrogen, hydroxyl, halogen, C$_{1-4}$ alkyl, C$_{1-4}$ alkoxy, C$_{1-4}$ haloalkyl, C$_{2-4}$ alkenyl, C$_{2-4}$ alkynyl, C$_{3-7}$ cycloalkyl or cyano;

each R^5 independently is halogen, cyano, oxo, -T-R^y, hydroxyl, -N(R^z)$_2$, C$_{1-4}$ alkyl, C$_{1-4}$ haloalkyl, C$_{1-4}$ alkoxy or -O-C$_{2-4}$ alkynyl;

each R^{6a}, R^{6b} and R^{6c} independently is hydrogen, halogen, hydroxyl, cyano, $-N(R^z)_2$, $-C(O)R^z$, $-C(O)OR^z$, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{2-4} alkynyl or C_{3-6} cycloalkyl or R^{6a} and R^{6b}, together with the atom to which they are attached form a fused C_{3-7} cycloalkyl;

R^{6d} is hydrogen, $-C(O)-C_{1-8}$ alkyl or $-C(O)-OC_{1-8}$ alkyl;

T is C_{1-4} alkylene, $-S(O)_2-$, $-C(O)-$, $-C_{1-4}$ alkylene-$C(O)-$, C_{1-4} alkylene-$S(O)_2-$ or $-S-$;

each R^w independently is C_{1-4} alkyl, C_{1-4} alkoxy, $-C(O)-C_{1-4}$ alkyl, $-C(O)-O-C_{1-4}$ alkyl, halogen, hydroxyl or C_{1-4} haloalkyl;

R^y is halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyl, cyano or $-N(R^z)_2$; and

each R^z independently is hydrogen or C_{1-4} alkyl.

[0008] Another aspect of the disclosure provides a pharmaceutical composition comprising a compound or salt of Formula (**I**) and a pharmaceutically acceptable excipient.

[0009] Yet another aspect of the disclosure provides method of treating cancer in a subject in need of treatment, the method comprising administering to the subject a therapeutically effective amount of the compound or salt of Formula (**I**) or a pharmaceutical composition comprising the compound or salt of Formula (**I**).

[0010] Still another aspect of the disclosure provides a compound or salt of Formula (**I**) for use as a medicament. Another aspect of the disclosure provides a compound or salt disclosed herein, or the pharmaceutical composition disclosed herein for use in the treatment of cancer.

[0011] Yet another aspect of the disclosure provides a compound or salt of Formula (**I**), or the pharmaceutical composition comprising a compound or salt of Formula (**I**), for the manufacture of a medicament for the treatment of cancer. Another aspect of the disclosure provides the use of a compound or salt disclosed herein, or the pharmaceutical composition of the disclosure, wherein the cancer is non-small cell lung cancer, colorectal cancer, pancreatic cancer, appendiceal cancer, endometrial cancer, esophageal cancer, cancer of unknown primary, ampullary cancer, gastric cancer, small bowel cancer, sinonasal cancer, bile duct cancer, or melanoma, or any combination of the foregoing. In some cases, the cancer is non-small cell lung cancer, colorectal cancer, pancreatic cancer, appendiceal cancer, endometrial cancer, esophageal cancer, cancer of unknown primary, ampullary cancer, gastric cancer, small bowel cancer, sinonasal cancer, bile duct cancer, or melanoma.

[0012] Further aspects and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description. The description hereafter includes specific cases, embodiments, and examples with the understanding that the disclosure is illustrative and is not intended to limit the embodiments of the present disclosure to the specific cases, embodiments, and examples described herein.

DETAILED DESCRIPTION

[0013] Disclosed herein are compounds having activity as inhibitors of KRAS such as KRAS G12D, G12V, G12A, G12S, G12R, G13D, Q61H, Q61L, Q61R or G12C, pharmaceutical compositions comprising the compounds, and uses and methods of treating disorders, such as cancer (e.g., non-small cell lung cancer, colorectal cancer, pancreatic cancer, appendiceal cancer, endometrial cancer, esophageal cancer, cancer of unknown primary, ampullary cancer, gastric cancer, small bowel cancer, sinonasal cancer, bile duct cancer, or melanoma), with the compounds and pharmaceutical composition described herein.

DEFINITIONS

[0014] The following definitions are provided to assist in understanding the scope of this disclosure. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0015] The term "alkyl" refers to a saturated straight chain hydrocarbon or saturated branched chain hydrocarbon containing the indicated number of carbon atoms. For example, C_3alkyl means an alkyl group that has 3 carbon atoms (e.g., n-propyl or isopropyl). For example, a C_{1-6}alkyl refers to an alkyl group having 1 to 6 carbon atoms. Where a range is indicated, all members of that range and all subgroups within that range are envisioned. For example, a C_{1-6}alkyl includes alkyl groups having 1, 2, 3, 4, 5, or 6 carbon atoms (or any combination of the foregoing), as well as all subgroups in the indicated range (e.g., 1-2, 1-3, 1-4, 1-5, 1-6, 2-3, 2-4, 2-5, 2-6, 3-4, 3-5, 3-6, 4-5, 4-6, or 5-6 carbon atoms, or any combination of the foregoing ranges)). A "C_{1-4} alkyl" includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, or t-butyl. Nonlimiting examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, and n-hexyl.

[0016] The term "alkenyl" refers to a straight or branched chain hydrocarbon containing the indicated number of carbon atoms and having one or more carbon-carbon double bonds. For example, C_3alkenyl means the alkenyl group has 3 carbon atoms (e.g., 1-propenyl or 2-propenyl). For example, a C_{2-6}alkenyl refers to an alkenyl group having 2 to 6 carbon atoms. Where a range is indicated, all members of that range and all subgroups within that range are envisioned. For example, a C_{2-6}alkenyl includes alkenyl groups having 2, 3, 4, 5, or 6 carbon atoms (or any combination of the foregoing), as well as all subgroups in the indicated range (e.g., 2-3, 2-4, 2-5, 2-6, 3-4, 3-5, 3-6, 4-5, 4-6, or 5-6 carbon atoms, or any combination of the foregoing ranges). A C_{2-4}alkenyl includes, for example, ethenyl, 1-propenyl, 2-propenyl, isopropenyl, 1-butenyl, 2-butenyl, or 3-butenyl. Non-limiting examples of alkenyl groups include ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), isopropenyl, 2-

methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, and 5-hexenyl.

[0017] The term "alkynyl" refers to a straight or branched chain hydrocarbon containing the indicated number of carbon atoms and having one or more carbon-carbon triple bonds. For example, C_3alkynyl means the alkynyl group has 3 carbon atoms. For example, a C_{2-6}alkynyl refers to an alkynyl group having 2 to 6 carbon atoms. Where a range is indicated, all members of that range and all subgroups within that range are envisioned. For example, a C_{2-6}alkynyl includes any alkynyl groups having 2, 3, 4, 5, or 6 carbon atoms (or any combination of the foregoing), as well as all subgroups in the indicated range (e.g., 2-3, 2-4, 2-5, 2-6, 3-4, 3-5, 3-6, 4-5, 4-6, or 5-6 carbon atoms, or any combination of the foregoing ranges). For illustration, C_{2-4}alkynyl includes, for example, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, or 3-butynyl. Nonlimiting examples of alkynyl groups include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, and 5-hexynyl.

[0018] The term "cycloalkyl" refers to a saturated, hydrocarbon monocyclic ring, or a saturated, hydrocarbon polycyclic ring system containing the indicated number of carbon atoms as ring members in the ring or ring system. No ring in a cycloalkyl ring or ring system has s double bond, a heteroatom, or is aromatic. When a cycloalkyl is a ring system, two or more rings may be joined together in a fused-, bridged-, or spiro-connected fashion. For example, C_5cycloalkyl refers to a cycloalkyl group that has 5 carbon atoms in the ring or ring system. Where a range is indicated, all members of that range and all subgroups within that range are envisioned. For example, a C_{3-7}cycloalkyl includes cycloalkyl groups having 3, 4, 5, 6, or 7 carbon atoms in the ring (or any combination of the foregoing), as well as all subgroups in the indicated range (e.g., 3-4, 3-5, 3-6, 3-7, 4-5, 4-6, 4-7, 5-6, 5-7, or 6-7 carbon atom ring members, or any combination of the foregoing ranges). Nonlimiting examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, norbornyl, decalinyl, and 7,7-dimethylbicyclo[2.2.1]heptanyl.

[0019] The term "aryl" refers to a monocyclic aromatic, hydrocarbon ring (i.e., phenyl, ) or a polycyclic (e.g., bicyclic, tricyclic, or tetracyclic) aromatic hydrocarbon ring system containing the indicated number of carbon atoms. For example, C_{10}aryl refers to an aryl group that has 10 carbon atoms in the ring system (e.g., naphthyl). When an aryl group is a polycyclic ring system, each ring in the ring system is aromatic, and no ring in the ring system contains a heteroatom. Where a range is indicated, all members of that range and all subgroups within that range are envisioned. For example, a C_{6-14}aryl includes aryl groups having 6-14 (e.g., 6, 10, or 14) carbon atoms in the ring or ring system (or combinations of the foregoing), as well as all subgroups in the indicated range (e.g., 6-10 or 10-14

carbon atom ring members in the ring or ring system, or combinations of the foregoing). Nonlimiting examples of aryl groups include phenyl, naphthyl, and anthracenyl.

[0020] The term "heteroatom," unless otherwise stated herein, refers to oxygen, sulfur, nitrogen, and phosphorus.

[0021] The term "heterocycloalkyl" refers to a saturated, monocyclic ring or saturated, polycyclic ring system comprising carbon atoms and one or more heteroatoms (e.g., one or more of N, O, and S), and having the indicated number of total ring atoms (the sum of carbon atoms and heteroatoms in the ring). When a heterocycloalkyl is a ring system, two or more rings may be joined together in a fused-, bridged-, or spiro-connected fashion. No ring in a heterocycloalkyl ring or ring system contains a double bond or is aromatic. For example, a heterocycloalkyl group having 5 total atoms and 2 heteroatoms independently selected from N, O, and S, refers to a ring having 3 carbon atoms and 2 heteroatoms, wherein each heteroatom of the ring independently is N, O, or S. Where a range is indicated, all members of that range and all subgroups within that range are envisioned. For example, a heterocycloalkyl group having 5-7 total ring atoms and 1-3 heteroatoms independently selected from N, O, and S includes rings having 5, 6, or 7 total atoms, or any combination of the foregoing, as well as all subgroups in the indicated range (e.g., 5-6 or 6-7 total ring atoms, or any combination of the foregoing), wherein 1, 2, or 3 of the atoms in the ring are heteroatoms and each heteroatom independently is selected from N, O, and S. Thus, a heterocycloalkyl having 5-7 total ring atoms and 1-3 heteroatoms independently selected from N, O, and S encompasses rings containing, for example, 4 carbon atoms and 1 heteroatom, 3 carbon atoms and 2 heteroatoms, 2 carbon atoms and 3 heteroatoms, 5 carbon atoms and 1 heteroatom, 4 carbon atoms and 2 heteroatoms, 3 carbon atoms and 3 heteroatoms, 6 carbon atoms and 1 heteroatom, 5 carbon atoms and 2 heteroatoms, and 4 carbon atoms and 3 heteroatoms, wherein each heteroatom of the foregoing is independently selected from N, O, and S. Nonlimiting examples of heterocycloalkyl groups include but are not limited to aziridinyl, oxiranyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophene-yl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl, oxazolidinyl, isothiazolidinyl, thiazolidinyl, oxathiolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, dioxanyl, dithianyl, morpholinyl, thiomorpholinyl, azepanyl, hexahydro-1H-pyrrolizinyl, and 1,4-diazepanyl.

[0022] The term "heteroaryl" refers to a monocyclic aromatic ring comprising carbon and one or more heteroatoms, and having the indicated number of total ring atoms (the sum of carbon atoms and heteroatoms in the ring), or a polycyclic (e.g., bicyclic, tricyclic, or tetracyclic) aromatic ring system having one or more heteroatoms and the indicated number of total ring atoms (the sum of carbon atoms and heteroatoms in the ring system). When a heteroaryl group is a polycyclic ring system, each ring in the ring system is aromatic. For example, a heteroaryl group having 5 total atoms and 2 heteroatoms independently selected from N, O, and S, refers to an aromatic ring having 3 carbon

atoms and 2 heteroatoms, wherein each heteroatom of the ring independently is N, O, or S. Where a range is indicated, all members of that range and all subgroups within that range are envisioned. For example, a heteroaryl having 5-7 total ring atoms and 1-3 heteroatoms independently selected from N, O, and S refers to an aromatic ring having a total number of ring atoms in the indicated range (e.g., 5, 6, or 7 total atoms, or any combination of the foregoing), as well as encompassing all subgroups (e.g., 5-6 or 6-7 total ring atoms, or any combination of the foregoing), wherein 1, 2, or 3 of the atoms in the ring are heteroatoms and each heteroatom is independently selected from N, O, and S. A heteroaryl having 5-7 total ring atoms and 1-3 heteroatoms independently selected from N, O, and S encompasses rings containing, for example, 4 carbon atoms and 1 heteroatom, 3 carbon atoms and 2 heteroatoms, 2 carbon atoms and 3 heteroatoms, 5 carbon atoms and 1 heteroatom, 4 carbon atoms and 2 heteroatoms, 3 carbon atoms and 3 heteroatoms, 6 carbon atoms and 1 heteroatom, 5 carbon atoms and 2 heteroatoms, and 4 carbon atoms and 3 heteroatoms, wherein each heteroatom of the foregoing independently is selected from N, O, and S. Nonlimiting examples of monocyclic heteroaryl groups include: pyrrolyl, furanyl, thiophene-yl (or thienyl), pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, triazolyl, oxadiazolyl, 1,3,4-oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl (or pyridyl), pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl. Nonlimiting examples of bicyclic heteroaryl groups include benzofuranyl, benzothienyl, benzimidazolyl, benzoisoxazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, benzotriazolyl, furopyridinyl (e.g., furo[2,3-b]pyridinyl), imidazopyridinyl (imidazo[4,5-b]pyridinyl), imidazothiazolyl (e.g., imidazo[4,5-d]thiazolyl), indolizinyl, indolyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolinyl, naphthyridinyl, oxazolopyridinyl (e.g., oxazolo[5,4-b]pyridinyl), phthalazinyl, pteridinyl, purinyl, pyrrolopyridyl (e.g., pyrrolo[2,3-b]pyridyl), quinolinyl, quinoxalinyl, quinazolinyl, benzoxazolyl, cinnolinyl, isoquinolyl, pyrazolopyridinyl (e.g., pyrazolo[3,4-b]pyridinyl), and thiazolopyrindinyl (e.g., thiazolo[5,4-b]pyridinyl). Nonlimiting examples of tricyclic heteroaryl groups include carbazolyl, 4,5-benzindolyl, dibenzofuranyl, dibenzothiophene-yl, phenazinyl, and acridinyl.

[0023] The term "alkylene" refers to a divalent saturated, straight or branched hydrocarbon chain diradical containing the indicated number of carbon atoms. For example, C_3 alkylene means the alkylene group has 3 carbon atoms. Where a range is indicated, all members of that range and all subgroups within that range are envisioned. For example, $C_{1\text{-}6}$alkylene means an alkylene group having a 1, 2, 3, 4, 5, or 6 carbon atoms, or any combination of the foregoing), as well as all subgroups in the indicated range (e.g., 1-2, 1-3, 1-4, 1-5, 1-6, 2-3, 2-4, 2-5, 2-6, 3-4, 3-5, 3-6, 4-5, 4-6, and 5-6 carbon atoms, or any combination of the foregoing). When the number of carbon atoms in an alkylene group is indicated as "C_0," then the alkylene group is not present and the recited substituent is directly attached to the rest of the compound. For example, the term $C_{0\text{-}6}$alkylene-OH indicates that the OH group can be directly attached to the compound or through a $C_{1\text{-}6}$alkylene linker. Examples of alkylene groups include methylene (—CH_2—), ethylene (—CH_2CH_2—), n-propylene (—

$CH_2CH_2CH_2$—), isopropylene (—$CH(CH_3)CH_2$—), 1-butylene (—$CH_2CH_2CH_2CH_2$—), 1-methylbutylene (—$CH(CH_3)CH_2CH_2$—), 2-methylbutylene (—$CH_2CH(CH_3)CH_2$—), and 3-methylbutylene (—$CH_2CH_2CH(CH_3)$—).

[0024] The term "halogen" or "halo" refers to fluoro (F), chloro (Cl), bromo (Br), or iodo (I).

[0025] The term "haloalkyl" refers to an alkyl group in which one or more of the hydrogen atoms is replaced by a halogen. The halogen is independently selected at each occurrence. The term includes, for example, monohaloalkyl (e.g., CH_2F, $CH(CH_2F)CH_3$) dihaloalkyl (e.g., CHF_2, $CH(CHF_2)CH_3$), trihaloalkyl (e.g., CF_3, $CH(CF_3)CH_3$), and polyhaloalkyl (e.g., $CF(CF_3)CH_3$). A haloalkyl group may or may not be perhalogenated (e.g., perfluorinated, such as $CF(CF_3)CF_3$). For example, the term "C_{1-4}haloalkyl" refers to a C_{1-4}alkyl, wherein one or more hydrogen atoms is substituted with a halogen. For illustration, C_{1-4}haloalkyl includes, for example, CH_2F, CHF_2, CF_3, CHFCl, CH_2CF_3, $CFHCF_3$, CF_2CF_3, $CH(CF_3)_2$, $CF(CHF_2)_2$, $CH(CH_2F)(CF_3)$, CH_2Cl, $CHCl_2$, CCl_3, CHFCl, CH_2CCl_3, $CClHCCl_3$, CCl_2CCl_3, $CH(CCl_3)_2$, $CCl(CHCl_2)_2$, $CH(CH_2Cl)CCl_3$, and $CH_2CF(CH_3)_2$.

[0026] The term "hydroxyalkylene" or "hydroxylalkylene" refers to a saturated straight chain alkylene or saturated branched chain alkylene containing the indicated number of carbon atoms substituted with one or two hydroxy groups in place of a hydrogen, provided that if two hydroxy groups are present they are not both on the same carbon atom. Nonlimiting examples hydroxyalkylene include but are not limited to, hydroxymethylene, 2-hydroxyethylene, 2-hydroxypropylene, 3-hydroxypropylene, 1-(hydroxymethyl)-2- methylpropylene, 2-hydroxybutylene, 3-hydroxybutylene, 4-hydroxybutylene, 2,3-dihydroxypropylene, 1-(hydroxymethyl)-2-hydroxyethylene, 2,3-dihydroxybutylene, 3,4-dihydroxybutylene and the like.

[0027] The term "oxo" refers to a substituent oxygen atom connected to another atom by a double bond (e.g., =O). For example, an oxo substituent on a cyclopentyl ring can be depicted as: .

[0028] The term "carbonyl" refers to a divalent C=O radical, such as .

[0029] The terms "hydroxy" and "hydroxyl" are interchangeable and refer to a —OH group.

[0030] The terms "alkoxy" and "alkoxyl" are interchangeable and refer to an —O-alkyl group, where the alkyl group is as defined elsewhere herein. For example, a C_3alkoxy group means the alkoxy group has 3 carbon atoms (e.g., $OCH_2CH_2CH_3$). Where a range is indicated, all members of that range and all subgroups within that range are envisioned. For example, a C_{1-6}alkoxy includes alkoxy groups having 2, 3, 4, 5, or 6 carbon atoms, or any combination of the foregoing, as well as all

subgroups in the indicated range (e.g., 2-3, 2-4, 2-5, 2-6, 3-4, 3-5, 3-6, 4-5, 4-6, and 5-6 carbon atoms, or any combination of the foregoing). Nonlimiting examples of alkoxy groups include methoxy, ethoxy, n-propoxy, 1-methylethyloxy (iso-propoxy), n-butoxy, isobutoxy, sec-butoxy, and tert-butoxy.

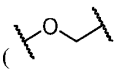
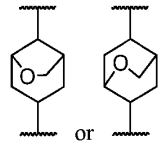
[0031] The terms "haloalkoxy" and "haloalkoxyl" are interchangeable and refer to an alkoxy group in which one or more of the hydrogen atoms is replaced by a halogen. The halogen is independently selected at each occurrence. The term includes monohaloalkoxy (e.g., OCH_2F, $OCH(CH_2F)CH_3$) dihaloalkoxy (e.g., $OCHF_2$, $OCH(CHF_2)CH_3$), trihaloalkoxy (e.g., OCF_3, $OCH(CF_3)CH_3$), and polyhaloalkoxy (e.g., $OCF(CF_3)CH_3$). A haloalkoxy group may or may not be perhalogenated (e.g., perfluorinated, such as $OCF(CF_3)CF_3$). For example, the term "C_{1-4}haloalkoxy" refers to a C_{1-4}alkoxy as defined herein, wherein one or more hydrogen atoms is substituted with a halogen. Representative examples of C_{1-4}haloalkoxy include OCH_2F, $OCHF_2$, OCF_3, OCHFCl, OCH_2CF_3, $OCFHCF_3$, OCF_2CF_3, $OCH(CF_3)_2$, $OCF(CHF_2)_2$, $OCH(CH_2F)(CF_3)$, OCH_2Cl, $OCHCl_2$, OCF_3, OCHFCl, OCH_2CCl_3, $OCClHCCl_3$, $OCCl_2CCl_3$, $OCH(CCl_3)_2$, $OCCl(CHCl_2)_2$, $OCH(CH_2Cl)CCl_3$, and $OCH_2CF(CH_3)_2$.

[0032] The term "cyano" refers to a —CN group.

[0033] The term "deutero" as used herein as a prefix to another term for a chemical group refers to a modification of the chemical group, wherein one or more hydrogen atoms are substituted with deuterium ("D" or "^{2}H"). For example, the term "C_{1-4}deuteroalkyl" refers to a C_{1-4}alkyl as defined herein, wherein one or more hydrogen atoms are substituted with D. Representative examples of C_{1-4}deuteroalkyl include, but are not limited to, $-CH_2D$, $-CHD_2$, $-CD_3$, $-CH_2CD_3$, $-CDHCD_3$, $-CD_2CD_3$, $-CH(CD_3)_2$, $-CD(CHD_2)_2$, and $-CH(CH_2D)(CD_3)$.

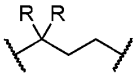
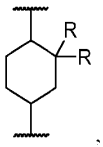
[0034] The term "amino" refers to —NH_2.

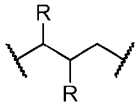
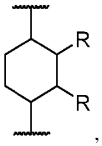
[0035] The term "alkylamino" refers to a — NRH group in which R is alkyl.

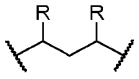
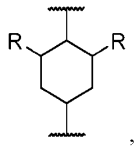
[0036] The term "ether" refers to an oxygen atom bonded to two alkyl or aryl groups (R-O-R). The term "ether bridge" refers to an ether group that forms a bridge on a ring, wherein the bridge has the indicated number of carbon atoms. For example, a C_1 ether bridge () on a cyclohexylene ring cyclohexylene ring can be depicted as, for example,  or .

[0037] The term "solvate" refers to a molecular aggregate comprising a compound or a pharmaceutically acceptable salt thereof as described herein and a stoichiometric or non-stoichiometric amount of one or more pharmaceutically acceptable solvent molecules.

[0038] The term "hydrate" refers to a solvate in which the solvent is water.

[0039] The term "geminal" refers to substituents that are attached to the same atom. Geminal R groups on a chain and ring can be depicted as:  and , respectively.

[0040] The term "vicinal" refers to substituents that are attached to adjacent atoms along a chain or within a ring. Vicinal R groups along a chain and within a ring can be depicted as  and , respectively.

[0041] The term "non-neighboring" refers to substituents that are attached to atoms along a chain or within a ring that are not attached to adjacent atoms and that are not geminal. Non-neighboring R groups along a chain and within a ring can be depicted as  and , respectively.

[0042] The term "protecting group" refers to a removable moiety that modifies a desired functional group to block the desired functional group from reacting in a subsequent chemical reaction. For example, the term "nitrogen protecting group" refers to a removable moiety that modifies a functional group having a nitrogen atom to block the functional group having a nitrogen atom from reacting in a subsequent chemical reaction (e.g., tert-butyloxycarbonyl). Examples of protecting groups are detailed in Greene, T. W., Wuts, P. G, "Protective Groups in Organic Synthesis", Third Edition, John Wiley & Sons, New York: 1999 (and other editions of the book, such as Wuts, P.G.M. and Greene, T.W. "Greene's Protective Groups in Organic Synthesis," Fourth Edition, John Wiley & Sons, Hoboken: 2007).

[0043] As used herein, if 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.

[0044] The term "substituted" refers to the replacement of one or more hydrogen radicals in a given structure or functional group with the radical of a specified substituent. A substituted structure or functional group may have a substituent at any substitutable position of the structure or functional

group. When more than one position in a given structure can be substituted with more than one substituent, the substituent may be either the same or different at each position.

[0045] The term "pharmaceutically acceptable" refers to a species or component that is generally safe, non-toxic, and neither biologically nor otherwise undesirable for use in a subject.

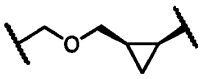
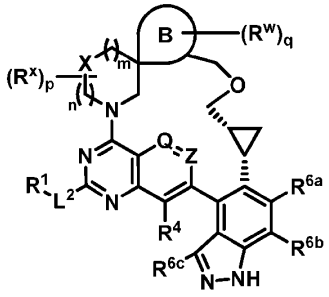
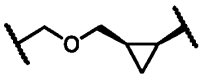
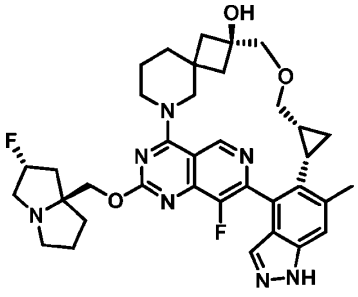
[0046] The term "pharmaceutically acceptable salt" refers to a salt of a compound that possesses the desired pharmacological activity of the parent compound and that is not biologically or otherwise undesirable for its end use. Pharmaceutically acceptable salts include, for example, acid addition salts formed with inorganic acids (e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid) or formed with organic acids (e.g., acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid). Pharmaceutically acceptable salts also include, for example, salts formed when an acidic proton present in the parent compound either is replaced by a metal ion (e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion) or associates with an organic base (e.g., ethanolamine, diethanolamine, triethanolamine, N-methylglucamine, dicyclohexylamine). Additionally, the salts of the compounds described herein, can exist in either hydrated or anhydrous form or as solvates with other solvent molecules.

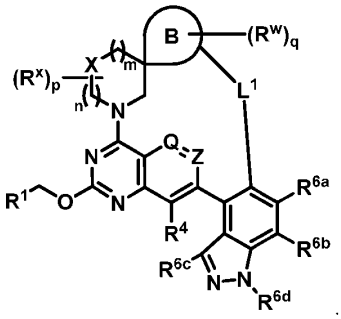
[0047] The term "pharmaceutically acceptable excipient" refers to a broad range of ingredients that may be combined with a compound, solvate, or salt disclosed herein to prepare a pharmaceutically acceptable composition or formulation. Excipients include, for example, vehicles (e.g., solvents, dispersion media), coatings, isotonic and absorption delaying agents, diluents, colorants, glidants, disintegrants, flavoring agents, coatings, binders, sweeteners, lubricants, sorbents, and preservatives (e.g., antibacterial and antifungal agents).

[0048] The term "therapeutically effective amount" as used herein refers to that amount of a compound disclosed herein that elicits a desired biological or medical response in a cell, a tissue, a system, or a subject.

[0049] The term "patient" or "subject" refers to humans and other mammals. The term "mammal" as used herein includes, for example, humans, non-human primates, cattle, sheep, goats, pigs, horses, cats, dog, rabbits, rodents (e.g., rats or mice), and monkeys. Human subjects include neonates, infants, juveniles, adults, and geriatric subjects.

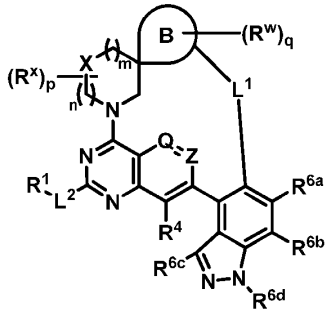
[0050] For clarity and avoidance of doubt, the divalent structural elements of L^1 as provided herein are to be inserted into Formula (I) such that the left hand side is attached to the nitrogen-containing hetercycloalkyl group and the right hand side is attached to the aryl ring. For example, if L^1 is


, then the compound of Formula (**I**) is . A specific example is if L^1 is , then the Example **1.040** is  (Example **1.040**).

[0051] For clarity and avoidance of doubt, the divalent structural elements of L^2 as provided herein are to be inserted into Formula (**I**) such that the left hand side in the markush definition (e.g., -O-C_{1-4} alkylene) is attached to the nitrogen-containing heterocycloalkyl and the right hand side is attached to the R^1 moiety. For example, if L^2 is -O-methylene or -O-CH_2-, then the compound of Formula (**I**) is .

COMPOUNDS OF FORMULA (I)

[0052] Provided herein as Embodiment 1 are compounds of Formula (**I**):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

X is $-CH_2-$ or -O-

Z is C-H, C-halogen, C-CN, C-C_{1-4} alkyl, C-C_{1-4} haloalkyl, C-C_{1-4} alkoxy, C-C_{1-4} haloalkoxy, C-C_{3-7} cycloalkyl or N;

Q is CH, C-halogen, C-C_{1-4} alkyl, C-C_{1-4} haloalkyl or N;

B is a C_{3-7} cycloalkyl or 3-7 membered heterocycloalkyl;

n is 0, 1 or 2;

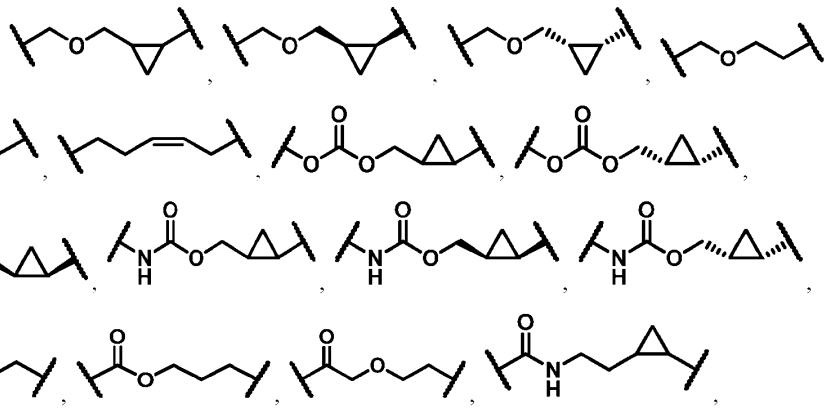
m is 0, 1 or 2;

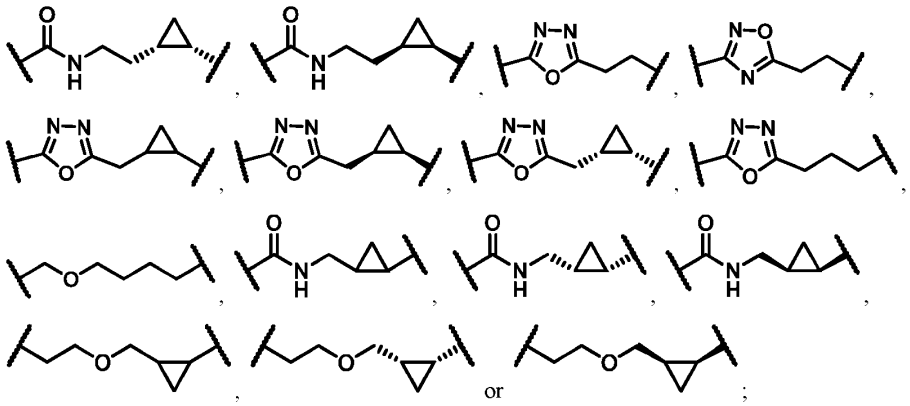
p is 0, 1 or 2;

q is 0, 1 or 2;

each R^x independently is hydroxyl, halogen, oxo, cyano, $-N(R^z)_2$, C_{1-4} alkyl, C_{1-4} deuteroalkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{1-4} hydroxyalkylene, 5-7 membered heteroaryl, $-S(O)_2-C_{1-4}$alkyl, $-S(O)_2N(R^z)_2$, $-C(O)R^z$, $-C(O)OR^z$, $-C(O)N(R^z)_2$, $-C_{1-4}$ alkylene-C(O)-C_{1-4}alkyl, $-C_{1-4}$ alkylene-$C(O)N(R^z)_2$, C_{1-4} alkylene-$S(O)_2-C_{1-4}$alkyl, or -S-C_{1-4}alkyl;

L^2 is a bond, C_{1-6} alkylene, -O-C_{1-6} alkylene, -S-C_{1-6} alkylene, NR^z, O or S, wherein each C_{1-6} alkylene, -O-C_{1-6} alkylene and -S-C_{1-6} alkylene chain is substituted with 0-2 occurrences of R^2;

L^1 is 



or ;

R^1 is hydrogen, hydroxyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-8} cycloalkyl or 4-15 membered heterocycloalkyl, wherein each aryl, heteroaryl, cycloalkyl or heterocycloalkyl is substituted with 0-3 occurrences of R^5;

each R^2 independently is halogen, deuterium, hydroxyl or C_{1-4} alkyl;

wherein two geminal R^2 groups, together with the atom to which they are attached form a spiro-C_{3-7} cycloalkyl group substituted with 0-2 occurrences of R^w; or wherein two adjacent R^2 groups, together with the atoms to which they are attached form a fused-C_{3-7} cycloalkyl group substituted with 0-2 occurrences of R^w;

R^4 is hydrogen, hydroxyl, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl or cyano;

each R^5 independently is halogen, cyano, oxo, -T-R^y, hydroxyl, -N(R^z)$_2$, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy or -O-C_{2-4} alkynyl;

each R^{6a}, R^{6b} and R^{6c} independently is hydrogen, halogen, hydroxyl, cyano, -N(R^z)$_2$, -C(O)R^z, -C(O)OR^z, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{2-4} alkynyl or C_{3-6} cycloalkyl or R^{6a} and R^{6b}, together with the atom to which they are attached form a fused C_{3-7} cycloalkyl;

R^{6d} is hydrogen, -C(O)-C_{1-8} alkyl or -C(O)-OC_{1-8} alkyl;

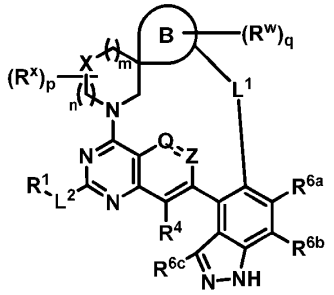
T is C_{1-4} alkylene, -S(O)$_2$-, -C(O)-, -C_{1-4} alkylene-C(O)-, C_{1-4} alkylene-S(O)$_2$- or -S-;

each R^w independently is C_{1-4} alkyl, C_{1-4} alkoxy, -C(O)-C_{1-4} alkyl, -C(O)-O-C_{1-4} alkyl, halogen, hydroxyl or C_{1-4} haloalkyl;

R^y is halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyl, cyano or -N(R^z)$_2$; and

each R^z independently is hydrogen or C_{1-4} alkyl.

[0053] Provided herein as Embodiment 2 is the compound or salt of Embodiment 1, wherein the compound is a compound of Formula (**I-B**):



(**I-B**)

or a pharmaceutically acceptable salt thereof, wherein;

X is $-CH_2-$ or -O-

Z is C-H, C-halogen, C-CN, C-C_{1-4} alkyl, C-C_{1-4} haloalkyl, C-C_{1-4} alkoxy, C-C_{1-4} haloalkoxy, C-C_{3-7} cycloalkyl or N;

Q is CH, C-halogen, C-C_{1-4} alkyl, C-C_{1-4} haloalkyl or N;

B is a C_{3-7} cycloalkyl or 3-7 membered heterocycloalkyl;

n is 0, 1 or 2;

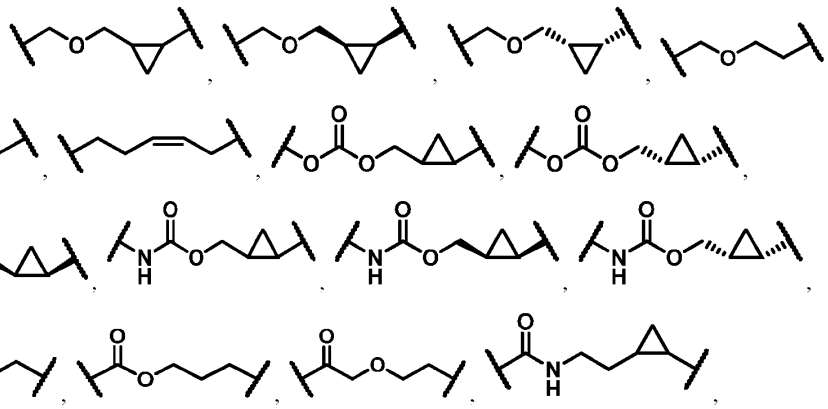
m is 0, 1 or 2;

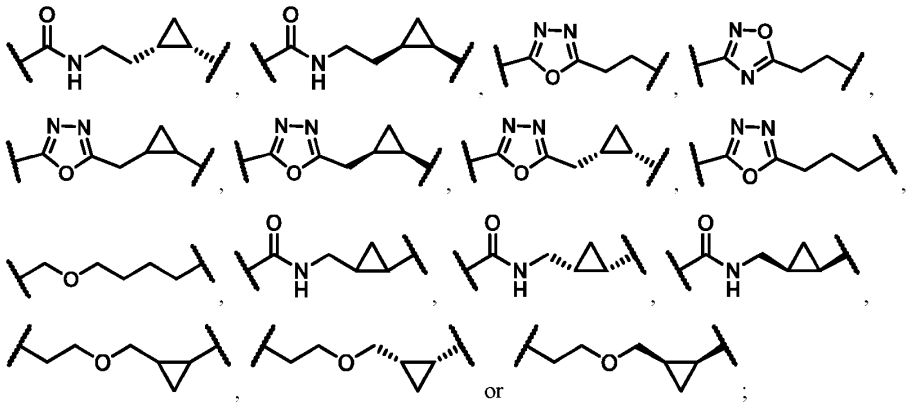
p is 0, 1 or 2;

q is 0, 1 or 2;

each R^x independently is hydroxyl, halogen, oxo, cyano, $-N(R^z)_2$, C_{1-4} alkyl, C_{1-4} deuteroalkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{1-4} hydroxyalkylene, 5-7 membered heteroaryl, $-S(O)_2-C_{1-4}$alkyl, $-S(O)_2N(R^z)_2$, $-C(O)R^z$, $-C(O)OR^z$, $-C(O)N(R^z)_2$, $-C_{1-4}$ alkylene-C(O)-C_{1-4}alkyl, $-C_{1-4}$ alkylene-$C(O)N(R^z)_2$, C_{1-4} alkylene-$S(O)_2-C_{1-4}$alkyl, or $-S-C_{1-4}$alkyl;

L^2 is a bond, C_{1-6} alkylene, $-O-C_{1-6}$ alkylene, $-S-C_{1-6}$ alkylene, NR^z, O or S, wherein each C_{1-6} alkylene, $-O-C_{1-6}$ alkylene and $-S-C_{1-6}$ alkylene chain is substituted with 0-2 occurrences of R^2;

L^1 is 


or ;

R^1 is hydrogen, hydroxyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-8} cycloalkyl or 4-15 membered heterocycloalkyl, wherein each aryl, heteroaryl, cycloalkyl or heterocycloalkyl is substituted with 0-3 occurrences of R^5;

each R^2 independently is halogen, deuterium, hydroxyl or C_{1-4} alkyl;

wherein two geminal R^2 groups, together with the atom to which they are attached form a spiro-C_{3-7} cycloalkyl group substituted with 0-2 occurrences of R^w; or wherein two adjacent R^2 groups, together with the atoms to which they are attached form a fused-C_{3-7} cycloalkyl group substituted with 0-2 occurrences of R^w; R^4 is hydrogen, hydroxyl, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl or cyano;

each R^5 independently is halogen, cyano, oxo, -T-R^y, hydroxyl, -$N(R^z)_2$, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy or -O-C_{2-4} alkynyl;

each R^{6a}, R^{6b} and R^{6c} independently is hydrogen, halogen, hydroxyl, cyano, -$N(R^z)_2$, -$C(O)R^z$, -$C(O)OR^z$, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{2-4} alkynyl or C_{3-6} cycloalkyl or R^{6a} and R^{6b}, together with the atom to which they are attached form a fused C_{3-7} cycloalkyl;

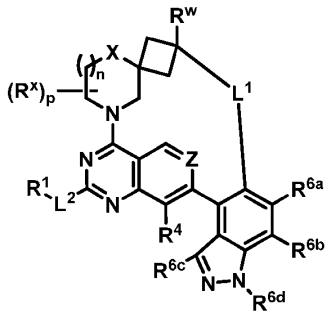
T is C_{1-4} alkylene, -$S(O)_2$-, -C(O)-, -C_{1-4} alkylene-C(O)-, C_{1-4} alkylene-$S(O)_2$- or -S-;

each R^w independently is C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxyl or C_{1-4} haloalkyl;

R^y is halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyl, cyano or -$N(R^z)_2$; and

each R^z independently is hydrogen or C_{1-4} alkyl.

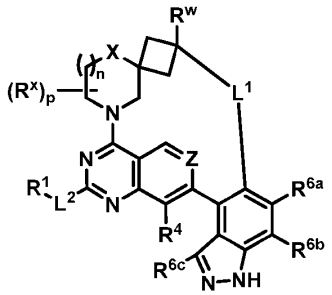
[0054] Provided herein as Embodiment 3 is the compound or salt of Embodiment 1, wherein the compound is a compound of Formula (**II**):



(**II**)

or a pharmaceutically acceptable salt of said compound, wherein X, Z, p, n, R^x, L^2, L^1, R^1, R^2, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^w, T, R^y and R^z are as defined above for Formula (**I**).

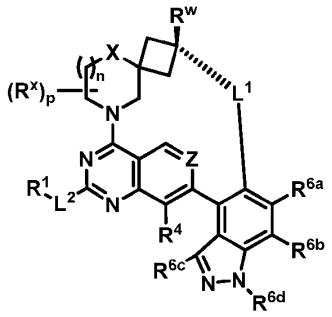
[0055] Provided herein as Embodiment 4 is the compound or salt of Embodiment 2, wherein the compound is a compound of Formula (**II-B**):



(**II-B**)

or a pharmaceutically acceptable salt of said compound, wherein X, Z, p, n, R^x, L^2, L^1, R^1, R^2, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^w, T, R^y and R^z are as defined above for Formula (**I-B**).

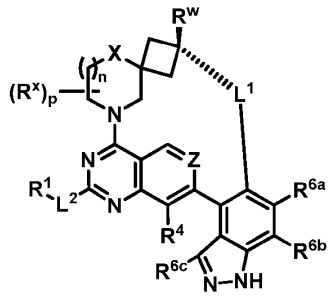
[0056] Provided herein as Embodiment 5 is the compound or salt of Embodiment 1, wherein the compound is a compound of Formula (**III**):



(III)

or a pharmaceutically acceptable salt of said compound, wherein X, Z, p, n, R^x, L^2, L^1, R^1, R^2, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^w, T, R^y and R^z are as defined above for Formula (**I**).

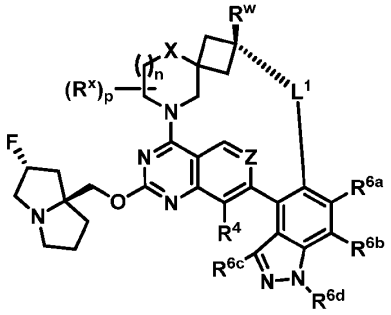
[0057] Provided herein as Embodiment 6 is the compound or salt of Embodiment 2, wherein the compound is a compound of Formula (**III-B**):



(**III-B**)

or a pharmaceutically acceptable salt of said compound, wherein X, Z, p, n, R^x, L^2, L^1, R^1, R^2, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^w, T, R^y and R^z are as defined above for Formula (**I-B**).

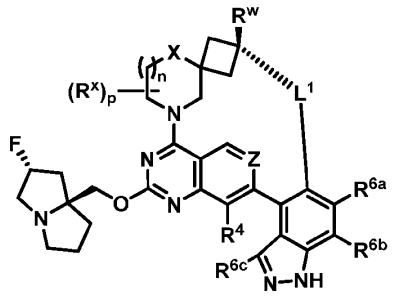
[0058] Provided herein as Embodiment 7 is the compound or salt of Embodiment 1, wherein the compound is a compound of Formula (**IV**):



(**IV**)

or a pharmaceutically acceptable salt of said compound, wherein X, Z, p, n, R^x, L^1, R^4, R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^w, T, R^y and R^z are as defined above for Formula (**I**).

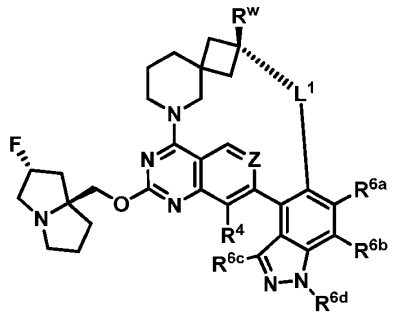
[0059] Provided herein as Embodiment 8 is the compound or salt of Embodiment 2, wherein the compound is a compound of Formula (**IV-B**):



(**IV-B**)

or a pharmaceutically acceptable salt of said compound, wherein X, Z, p. n, R^x, L^1, R^4, R^{6a}, R^{6b}, R^{6c}, R^w, T, R^y and R^z are as defined above for Formula (**I-B**).

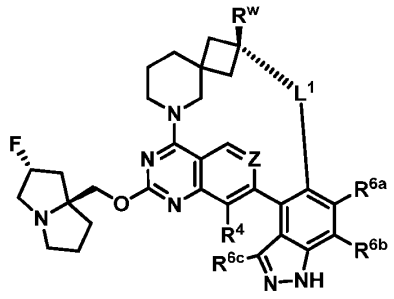
[0060] Provided herein as Embodiment 9 is the compound or salt of Embodiment 1, wherein the compound is a compound of Formula (**V**):



(**V**)

or a pharmaceutically acceptable salt of said compound, wherein Z, L^1, R^4, R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^w, T, R^y and R^z are as defined above for Formula (**I**).

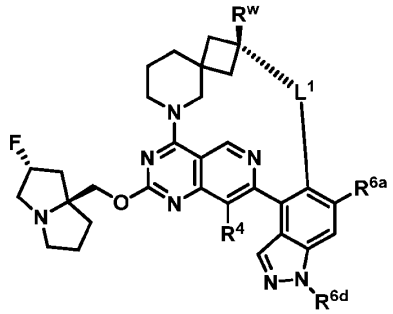
[0061] Provided herein as Embodiment 10 is the compound or salt of Embodiment 2, wherein the compound is a compound of Formula (**V-B**):



(**V-B**)

or a pharmaceutically acceptable salt of said compound, wherein Z, L^1, R^d, R^{6a}, R^{6b}, R^{6c}, R^w, T, R^y and R^z are as defined above for Formula (**I-B**).

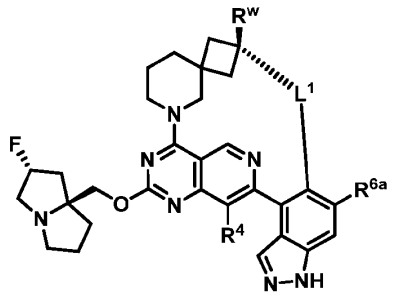
[0062] Provided herein as Embodiment 11 is the compound or salt of Embodiment 1, wherein the compound is a compound of Formula (**VI**):



(**VI**)

or a pharmaceutically acceptable salt of said compound, wherein L^1, R^{6a}, R^{6d}, R^w, T, R^y and R^z are as defined above for Formula (**I**).

[0063] Provided herein as Embodiment 12 is the compound or salt of Embodiment 2, wherein the compound is a compound of Formula (**VI-B**):



(**VI-B**)

or a pharmaceutically acceptable salt of said compound, wherein L^1, R^{6a}, R^w, T, R^y and R^z are as defined above for Formula (**I-B**).

[0064] Provided herein as embodiment 13 is the compound or salt of any of Embodiments 1-2, wherein Z is C-H, C-F, C-CN, C-CH_3, C-CF_3, C-OMe, C-Cl or N. Provided herein as embodiment 14 is the compound or salt of embodiment 13, wherein Z is N. Provided herein as embodiment 15 is the compound or salt of embodiment 13, wherein Z is CH. Provided herein as embodiment 16 is the compound or salt of embodiment 13, wherein Z is CF.

[0065] Provided herein as Embodiment 17 is the compound of salt of any of Embodiments 1-16, wherein Q is CH, C-C_{1-4} alkyl or N. Provided herein as Embodiment 18 is the compound or salt of Embodiment 17, wherein Q is CH. Provided herein as Embodiment 19 is the compound or salt of Embodiment 17, wherein Q is C-CH_3. Provided herein as Embodiment 20 is the compound or salt of Embodiment 17, wherein Q is N.

[0066] Provided herein as Embodiment 21 is the compound or salt of Embodiment 1, wherein Z is N and Q is CH. Provided herein as Embodiment 22 is the compound or salt of Embodiment 1, wherein Z is N and Q is C-CH_3. Provided herein as Embodiment 23 is the compound or salt of Embodiment 1, wherein Z is N and Q is N.

[0067] Provided herein as Embodiment 24 is the compound or salt of any of Embodiments 1-23, wherein L^2 is -O-methylene, -O-ethylene or -O-*n*-propylene substituted with 0-2 occurrences of R^2.

[0068] Provided herein as Embodiment 25 is the compound or salt of Embodiment 24, wherein L^2 is -O-methylene substituted with 0 occurrences of R^2. Provided herein as Embodiment 26 is the compound or salt of Embodiment 25, wherein R^1 is heterocycloalkyl substituted with 0-3 occurrences of R^5.

[0069] Provided herein as Embodiment 27 is the compound or salt of Embodiment 26, wherein R^1 is 7a-(hexahydro-1H-pyrrolizinyl), 2-azetidinyl or 2-pyrrolidinyl substituted with 0-3 occurrences of R^5. Provided herein as Embodiment 28 is the compound or salt of Embodiment 27, wherein R^1 is unsubstituted 7a-(hexahydro-1H-pyrrolizinyl), unsubstituted 5-(1-azabicyclo[3.2.0]heptanyl), unsubstituted 2-azetidinyl or unsubstituted 2-pyrrolidinyl. Provided herein as Embodiment 29 is the compound or salt of Embodiment 28, wherein R^1 is unsubstituted 7a-(hexahydro-1H-pyrrolizinyl). Provided herein as Embodiment 30 is the compound or salt of Embodiment 28, wherein R^1 is unsubstituted 2-pyrrolidinyl. Provided herein as Embodiment 31 is the compound or salt of Embodiment 28, wherein R^1 is unsubstituted 5-(1-azabicyclo[3.2.0]heptanyl).

[0070] Provided herein as Embodiment 32 is the compound or salt of Embodiment 27 wherein R^1 is 7a-(hexahydro-1H-pyrrolizinyl), 2-azetidinyl or 2-pyrrolidinyl substituted with one occurrence of R^5. Provided herein as Embodiment 33 is the compound or salt of Embodiment 32, wherein R^5 is halogen or C_{1-4} alkyl. Provided herein as Embodiment 34 is the compound or salt of Embodiment 33, wherein R^5 is fluorine or methyl.

[0071] Provided herein as Embodiment 35 is the compound or salt of Embodiment 32, wherein R^1 is 7a-(hexahydro-1H-pyrrolizinyl) substituted with one occurrence of R^5. Provided herein as Embodiment 36 is the compound or salt of Embodiment 35, wherein R^5 is halogen (e.g., fluorine).

[0072] Provided herein as Embodiment 37 is the compound or salt of Embodiment 32, wherein R^1 is 2-pyrrolidinyl substituted with one occurrence of R^5. Provided herein as Embodiment 38 is the compound or salt of Embodiment 37, wherein R^5 is C_{1-4} alkyl (e.g., methyl or ethyl).

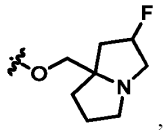
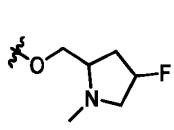
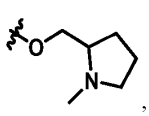
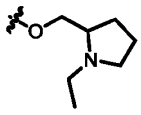
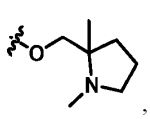
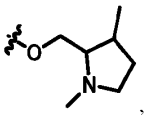
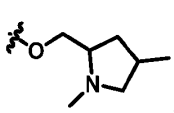
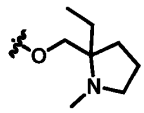
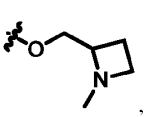
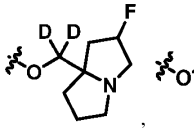
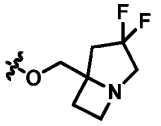
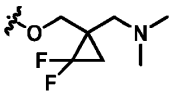
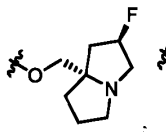
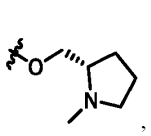
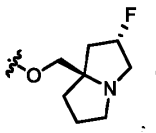
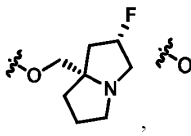
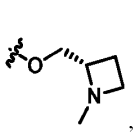
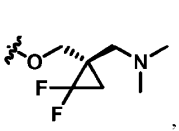
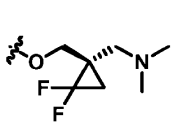
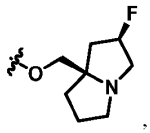
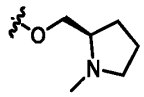
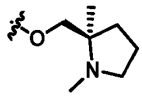
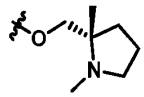
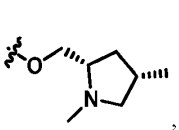
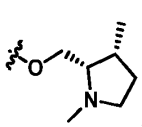
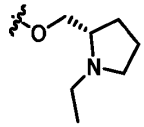
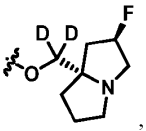
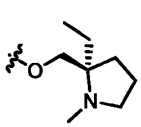
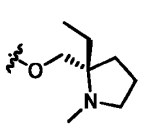
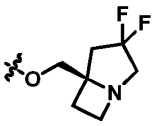
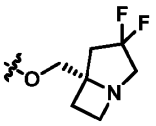
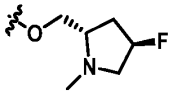
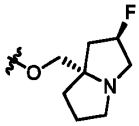
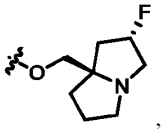
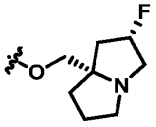
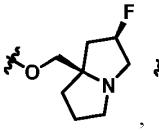
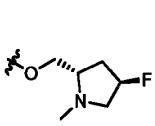
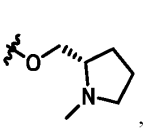
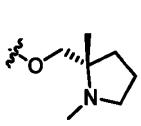
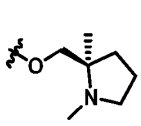
[0073] Provided herein as Embodiment 39 is the compound or salt of Embodiment 32, wherein R^1 is 2-azetidinyl substituted with one occurrence of R^5. Provided herein as Embodiment 40 is the compound or salt of Embodiment 39, wherein R^5 is C_{1-4} alkyl (e.g., methyl).

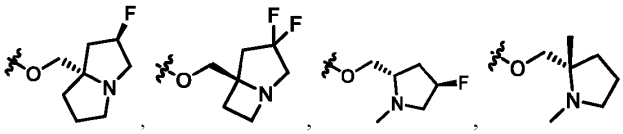
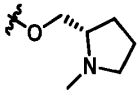
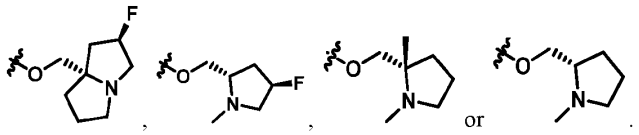
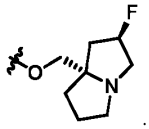
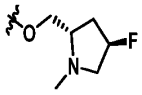
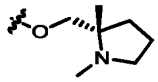
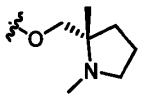
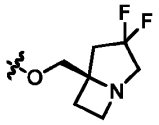
[0074] Provided herein as Embodiment 41 is the compound or salt of Embodiment 27, wherein R^1 is 2-pyrrolidinyl or 5-(1-azabicyclo[3.2.0]heptanyl) substituted with two occurrences of R^5. Provided herein as Embodiment 42 is the compound or salt of Embodiment 41, wherein R^1 is 2-pyrrolidinyl substituted with two occurrences of R^5. Provided herein as Embodiment 43 is the compound or salt of Embodiment 42, wherein one R^5 is methyl and the other R^5 is halogen (e.g., fluorine). Provided herein as Embodiment 44 is the compound or salt of Embodiment 42, wherein both R^5 are C_{1-4} alkyl (e.g., methyl or ethyl). Provided herein as Embodiment 45 is the compound or salt of Embodiment 44, wherein both R^5 are methyl. Provided herein as Embodiment 46 is the compound or salt of Embodiment 44, wherein one R^5 is methyl and the other R^5 is ethyl.

[0075] Provided herein as Embodiment 47 is the compound or salt of Embodiment 41, wherein R^1 is 5-(1-azabicyclo[3.2.0]heptanyl) substituted with two occurrences of R^5. Provided herein as Embodiment 48 is the compound or salt of Embodiment 47, wherein both R^5 are halogen (e.g., fluorine).

[0076] Provided herein as Embodiment 49 is the compound or salt of Embodiment 24, wherein L^2 is -O-methylene substituted with 2 occurrences of R^2. Provided herein as Embodiment 50 is the compound or salt of Embodiment 49, wherein both R^2 are deuterium. Provided herein as Embodiment 51 is the compound or salt of Embodiment 50, wherein R^1 is 7a-(hexahydro-1H-pyrrolizinyl) substituted with one occurrence of R^5. Provided herein as Embodiment 52 is the compound or salt of Embodiment 51, wherein R^5 is halogen (e.g., fluorine).

[0077] Provided herein as Embodiment 53 is the compound or salt of Embodiment 24, wherein L^2 is -O-*n*-propylene substituted with two occurrences of R^2. Provided herein as Embodiment 54 is the compound or salt of Embodiment 53, wherein two geminal R^2 groups, together with the atom to which they are attached form a spiro-C_{3-7} cycloalkyl (e.g., cyclopropyl) substituted with 0-2 occurrences of R^w. Provided herein as Embodiment 55 is the compound or salt of Embodiment 54, wherein two geminal R^2 groups, together with the atom to which they are attached form a spiro-cyclopropyl substituted with two occurrences of R^w. Provided herein as Embodiment 56 is the compound or salt of Embodiment 55, wherein both R^w are halogen (e.g., fluorine). Provided herein as Embodiment 57 is the compound or salt of Embodiment 56, wherein R^1 is $-N(R^z)_2$ and R^z are methyl.

[0078] Provided herein as Embodiment 58 is the compound or salt of any of Embodiments 24-57, wherein -L^2-R^1 is , , , , , , , , , , , or . Provided herein as Embodiment 59 is the compound or salt of Embodiment 58, wherein -L^2-R^1 is , , , , , , , , , , , , , , , , , , , or . Provided herein as Embodiment 60 is the compound or salt of Embodiment 58, wherein -L^2-R^1 is , , , , , , , , , or . Provided herein as Embodiment 61 is the compound or salt of

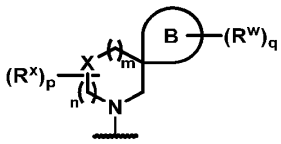
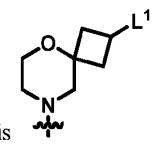
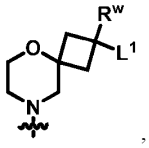
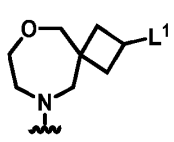
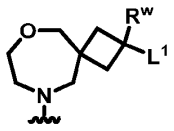
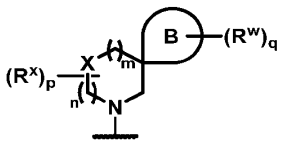
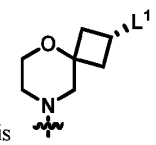
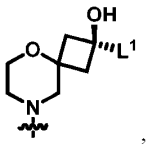
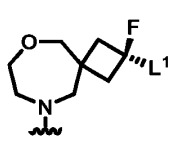
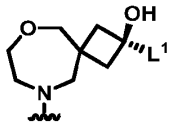
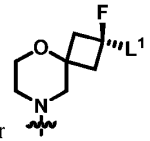
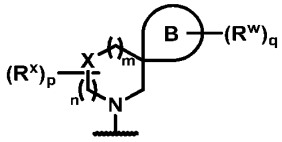
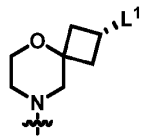
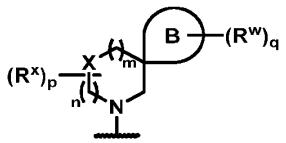
Embodiment 60, wherein -L^2-R^1 is , or . Provided herein as Embodiment 62 is the compound or salt of Embodiment 61, wherein -L^2-R^1 is . Provided herein as Embodiment 63 is the compound or salt of Embodiment 62, wherein -L^2-R^1 is . Provided herein as Embodiment 64 is the compound or salt of Embodiment 62, wherein -L^2-R^1 is . Provided herein as Embodiment 65 is the compound or salt of Embodiment 62, wherein -L^2-R^1 is . Provided herein as Embodiment 66 is the compound or salt of Embodiment 62, wherein -L^2-R^1 is . Provided herein as Embodiment 67 is the compound or salt of Embodiment 61, wherein -L^2-R^1 is .

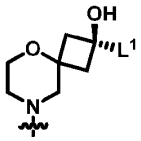
[0079] Provided herein as Embodiment 68 is the compound or salt of any of Embodiments 1-67, wherein X is O.

[0080] Provided herein as Embodiment 69 is the compound or salt of Embodiment 68, wherein n is 2 and m is 0. Provided herein as Embodiment 70 is the compound or salt of Embodiment 69, wherein p is 0. Provided herein as Embodiment 71 is the compound or salt of Embodiment 70, wherein B is C_{3-7} cycloalkyl. Provided herein as Embodiment 72 is the compound or salt of Embodiment 71, wherein B is cyclobutyl and q is 0. Provided herein as Embodiment 73 is the compound or salt of Embodiment 71, wherein B is cyclobutyl and q is 1. Provided herein as Embodiment 74 is the compound or salt of Embodiment 73, wherein R^w is halogen or hydroxyl. Provided herein as

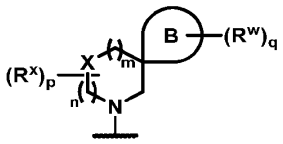
Embodiment 75 is the compound or salt of Embodiment 74, wherein R^w is hydroxyl. Provided herein as Embodiment 76 is the compound or salt of Embodiment 74, wherein R^w is fluorine.

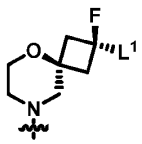
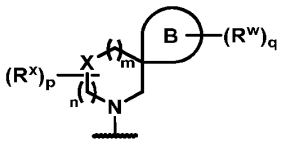
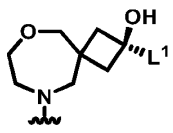
[0081] Provided herein as Embodiment 77 is the compound or salt of Embodiment 68, wherein n is 2 and m is 1. Provided herein as Embodiment 78 is the compound or salt of Embodiment 77, wherein p is 0. Provided herein as Embodiment 79 is the compound or salt of Embodiment 78, wherein B is C_{3-7} cycloalkyl. Provided herein as Embodiment 80 is the compound or salt of Embodiment 79, wherein B is cyclobutyl and q is 0. Provided herein as Embodiment 81 is the compound or salt of Embodiment 79, wherein B is cyclobutyl and q is 1. Provided herein as Embodiment 82 is the compound or salt of Embodiment 81, wherein R^w is halogen or hydroxyl. Provided herein as Embodiment 83 is the compound or salt of Embodiment 82, wherein R^w is hydroxyl. Provided herein as Embodiment 84 is the compound or salt of Embodiment 82, wherein R^w is fluorine.

[0082] Provided herein as Embodiment 85 is the compound or salt of any of Embodiments 68-84, wherein  is , ,  or . Provided herein as Embodiment 86 is the compound or salt of Embodiment 85, wherein  is , , ,  or . Provided herein as Embodiment 87 is the compound or salt of Embodiment 86, wherein  is . Provided herein as Embodiment 88 is the compound or salt of Embodiment 86, wherein  is

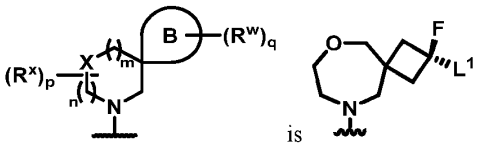


. Provided herein as Embodiment 89 is the compound or salt of Embodiment 86,



wherein is  . Provided herein as Embodiment 90 is the compound or salt of Embodiment 86, wherein  is  .

Provided herein as Embodiment 91 is the compound or salt of Embodiment 86, wherein



is .

[0083] Provided herein as Embodiment 92 is the compound or salt of any of Embodiments 1-67, wherein X is $-CH_2-$.

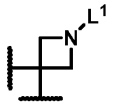
[0084] Provided herein as Embodiment 93 is the compound or salt of Embodiment 92, wherein n is 1 and m is 0 or n is 0 and m is 1. Provided herein as Embodiment 94 is the compound or salt of Embodiment 93, wherein p is 0. Provided herein as Embodiment 95 is the compound or salt of Embodiment 94, wherein B is C_{3-7} cycloalkyl. Provided herein as Embodiment 96 is the compound or salt of Embodiment 95, wherein B is cyclobutyl and is q is 0.

[0085] Provided herein as Embodiment 97 is the compound or salt of Embodiment 92, wherein n is 2 and m is 0. Provided herein as Embodiment 98 is the compound or salt of Embodiment 97, wherein p is 0.

[0086] Provided herein as Embodiment 99 is the compound or salt of Embodiment 98, wherein B is C_{3-7} cycloalkyl. Provided herein as Embodiment 100 is the compound or salt of Embodiment 99, wherein B is cyclobutyl and q is 0. Provided herein as Embodiment 101 is the compound or salt of Embodiment 99, wherein B is cyclobutyl and q is 1. Provided herein as Embodiment 102 is the compound or salt of Embodiment 101, wherein R^w is hydroxyl, $-C(O)-C_{1-4}$ alkyl or halogen. Provided herein as Embodiment 103 is the compound or salt of Embodiment 102, wherein R^w is hydroxyl or halogen. Provided herein as Embodiment 104 is the compound or salt of Embodiment 103, wherein R^w is hydroxyl. Provided herein as Embodiment 105 is the compound or salt of Embodiment 103,

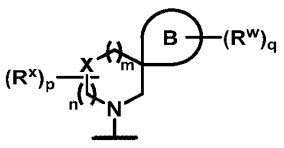
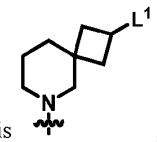
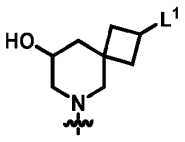
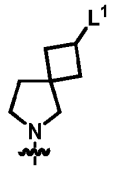
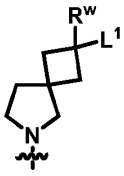
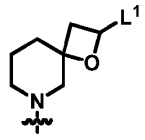
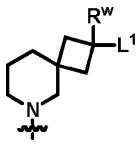
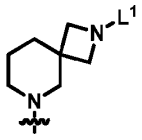
wherein R^w is fluorine. Provided herein as Embodiment 106 is the compound or salt of Embodiment 102, wherein R^w is -C(O)-CH_3.

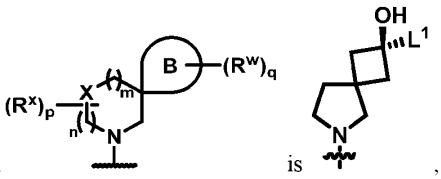
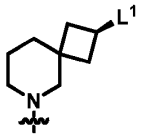
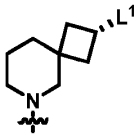
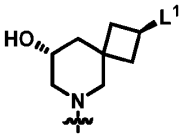
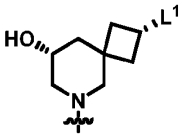
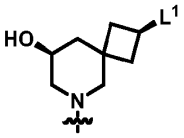
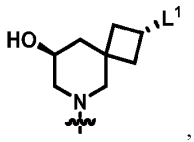
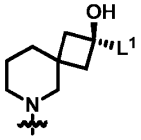
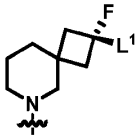
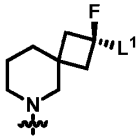
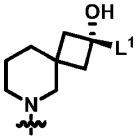
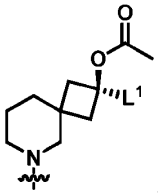
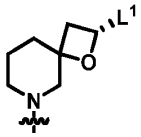
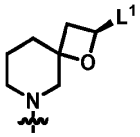
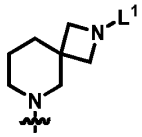
[0087] Provided herein as Embodiment 107 is the compound or salt of Embodiment 98, wherein B is 3-7 membered heterocycloalkyl. Provided herein as Embodiment 108 is the compound or salt of Embodiment 107, wherein B is 2-oxetanyl and q is 0.

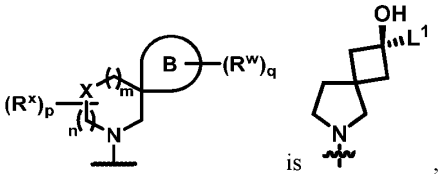
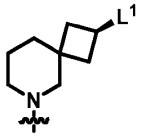
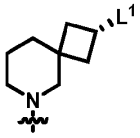
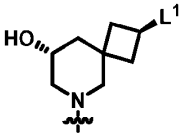
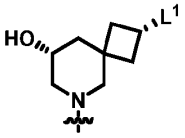
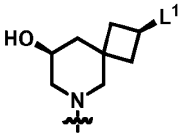
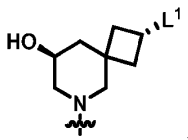
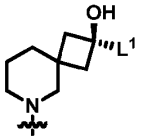
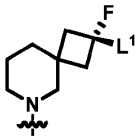
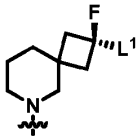
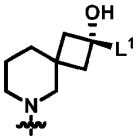
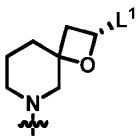
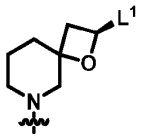
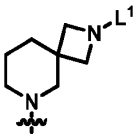
[0088] Provided herein as Embodiment 109 is the compound or salt of Embodiment 107, wherein B is  and q is 0.

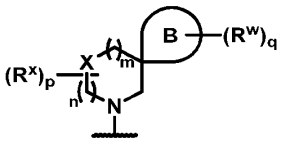
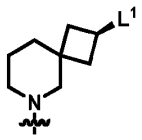
[0089] Provided herein as Embodiment 110 is the compound or salt of Embodiment 97, wherein p is 1. Provided herein as Embodiment 111 is the compound or salt of Embodiment 110, wherein R^x is hydroxyl, halogen, C_{1-4} alkyl or C_{1-4} haloalkyl. Provided herein as Embodiment 112 is the compound or salt of Embodiment 111, wherein R^x is hydroxyl.

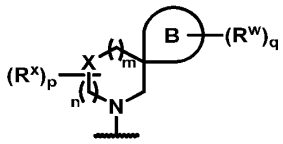
[0090] Provided herein as Embodiment 113 is the compound or salt of Embodiment 112, wherein B is C_{3-7} cycloalkyl. Provided herein as Embodiment 114 is the compound or salt of Embodiment 113, wherein B is cyclobutyl and q is 0. Provided herein as Embodiment 115 is the compound or salt of Embodiment 113, wherein B is cyclobutyl and q is 1. Provided herein as Embodiment 116 is the compound or salt of Embodiment 115, wherein R^w is hydroxyl, -C(O)-C_{1-4} alkyl or halogen. Provided herein as Embodiment 117 is the compound or salt of Embodiment 116, wherein R^w is hydroxyl or halogen. Provided herein as Embodiment 118 is the compound or salt of Embodiment 117, wherein R^w is hydroxyl. Provided herein as Embodiment 119 is the compound or salt of Embodiment 117, wherein R^w is fluorine. Provided herein as Embodiment 120 is the compound or salt of Embodiment 116, wherein R^w is -C(O)-C_{1-4} alkyl (e.g., -C(O)-CH_3).

[0091] Provided herein as Embodiment 121 is the compound or salt of any of Embodiments 92-120, wherein  is , , , , ,  or . Provided herein as Embodiment 122

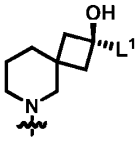
is the compound or salt of Embodiment 121, wherein  is ,     ,      ,    or . Provided herein as Embodiment 123 is the

compound or salt of Embodiment 122, wherein  is ,     ,      ,   or . Provided herein as Embodiment 124 is the compound or salt of

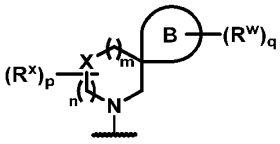
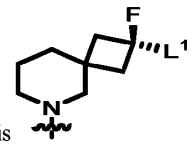
Embodiment 123, wherein  is . Provided herein as

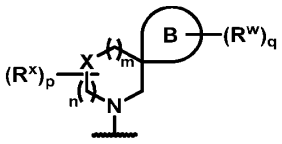
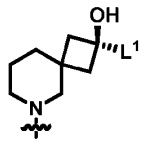


Embodiment 125 is the compound or salt of Embodiment 123, wherein

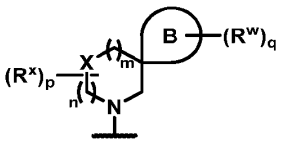


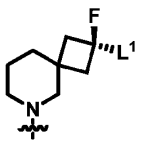
is . Provided herein as Embodiment 126 is the compound or salt of Embodiment 123,

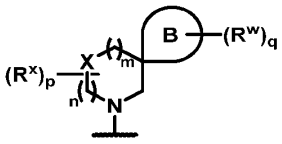
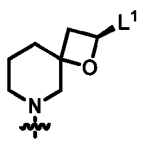
wherein  is . Provided herein as Embodiment 127 is

the compound or salt of Embodiment 123, wherein  is .

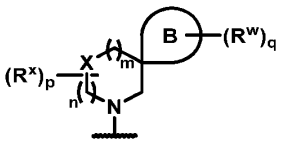
Provided herein as Embodiment 128 is the compound or salt of Embodiment 123, wherein

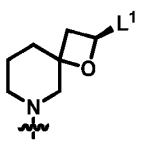


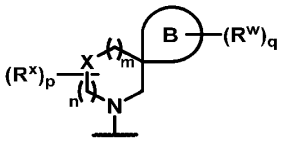
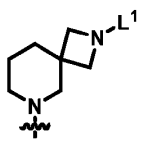
is . Provided herein as Embodiment 129 is the

compound or salt of Embodiment 123, wherein  is .

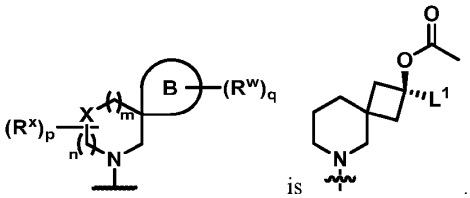
Provided herein as Embodiment 130 is the compound or salt of Embodiment 123, wherein



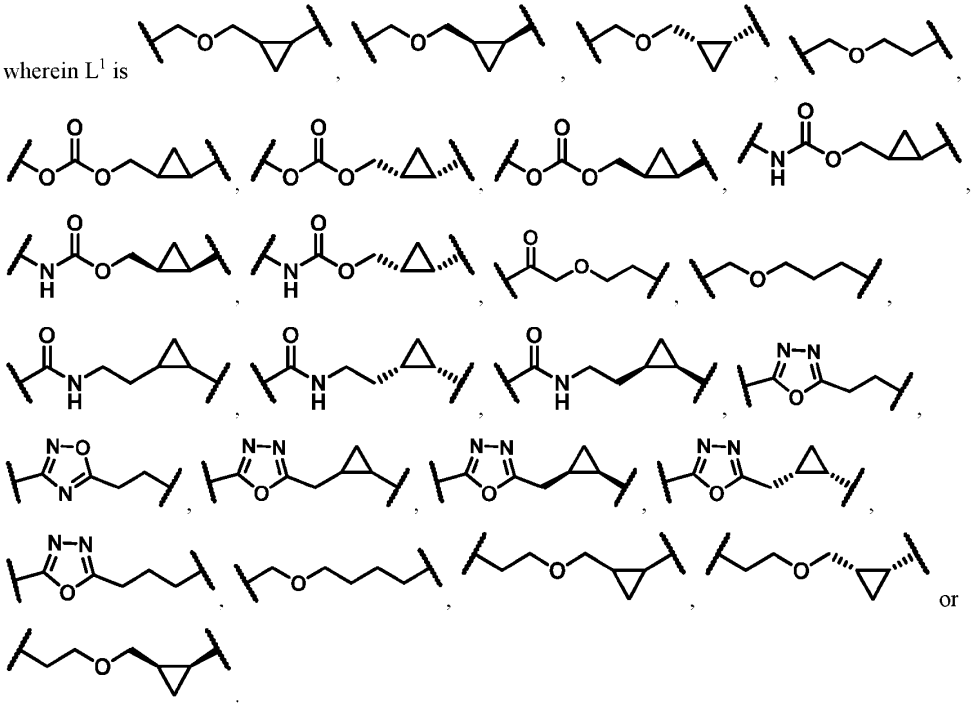
is . Provided herein as Embodiment 131 is the

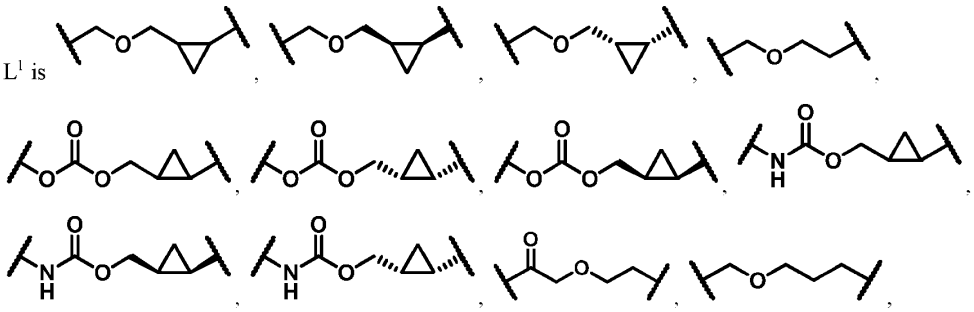
compound or salt of Embodiment 123, wherein  is .

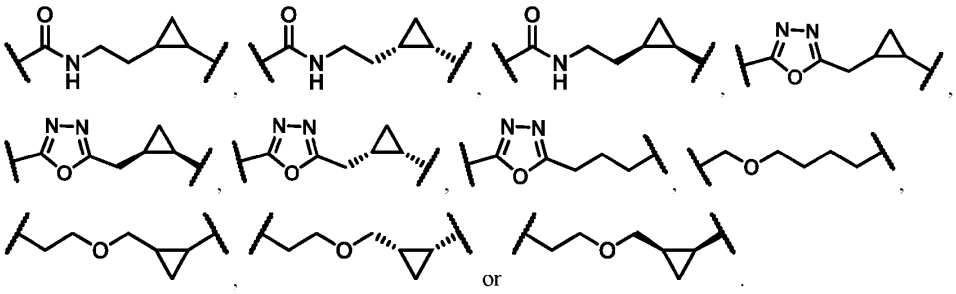
Provided herein as Embodiment 132 is the compound or salt of Embodiment 122, wherein



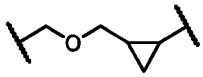
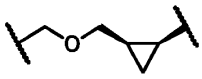
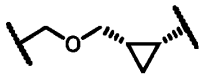
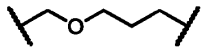
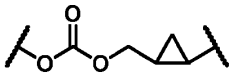
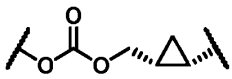
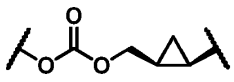
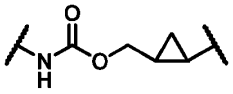
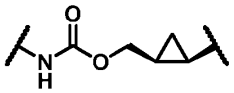
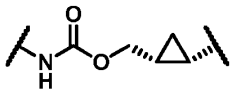
is .

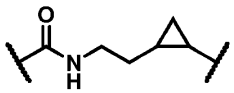
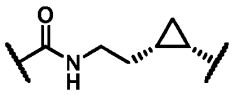
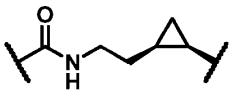
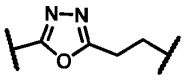
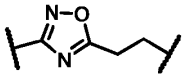
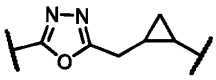
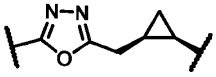
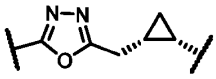
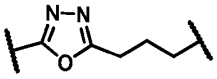
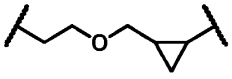
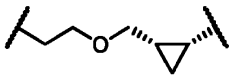
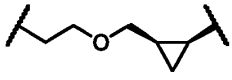
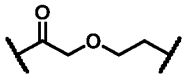
[0092] Provided herein as Embodiment 133 is the compound or salt of any of Embodiments 1-132, wherein L^1 is , or .

[0093] Provided herein as Embodiment 134 is the compound or salt of Embodiment 133, wherein L^1 is .



or

[0094] Provided herein as Embodiment 135 is the compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 136 is the compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 137 is the compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 138 is the compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 139 is the compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 140 is the compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 141 is the compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 142 is the compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 143 is the compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 144 is the compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 145 is the

compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 146 is the compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 147 is the compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 148 is the compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 149 is the compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 150 is the compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 151 is the compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 152 is the compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 153 is the compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 154 is the compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 155 is the compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 156 is the compound or salt of Embodiment 133, wherein L^1 is . Provided herein as Embodiment 157 is the compound or salt of Embodiment 133, wherein L^1 is .

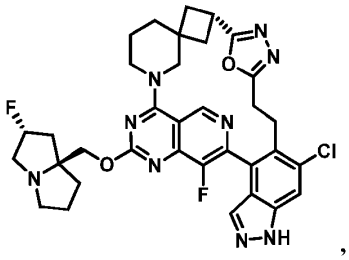
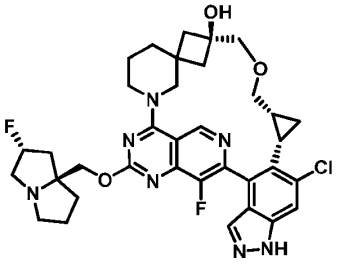
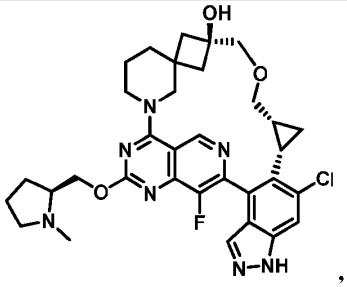
[0095] Provided herein as Embodiment 158 is the compound or salt of any of Embodiments 1-157, wherein R^4 is hydrogen, hydroxyl, halogen, C_{1-4} alkyl or C_{1-4} alkoxy. Provided herein of Embodiment 159 is the compound or salt of Embodiment 158, wherein R^4 is halogen or C_{1-4} alkyl. Provided herein of Embodiment 160 is the compound or salt of Embodiment 159, wherein R^4 is fluorine.

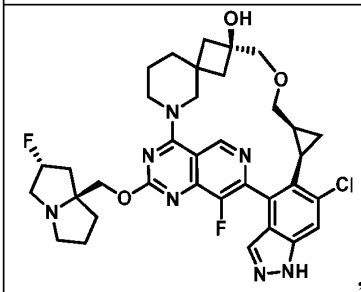
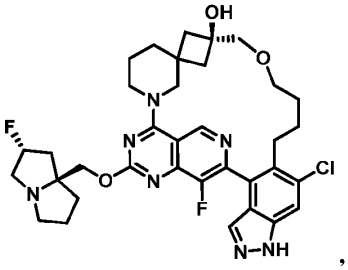
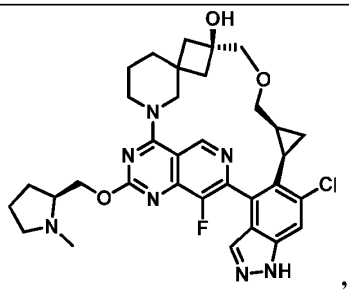
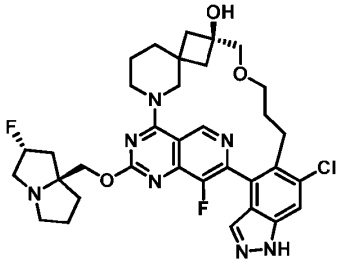
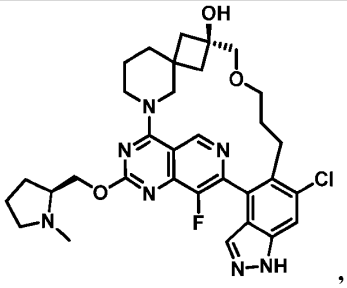
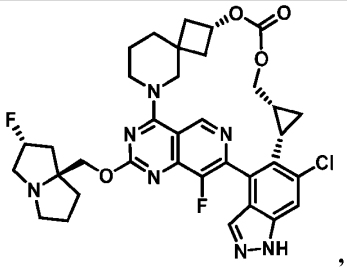
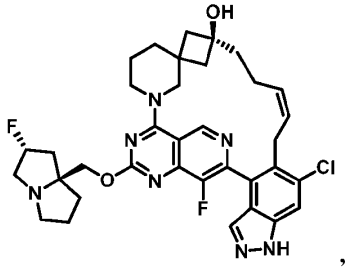
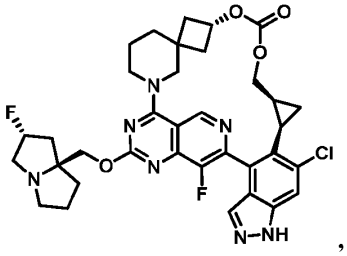
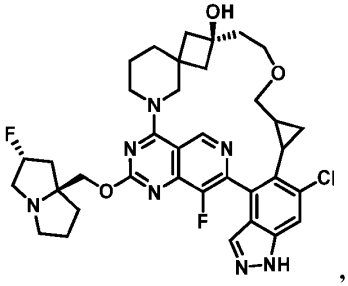
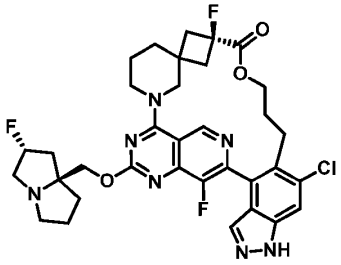
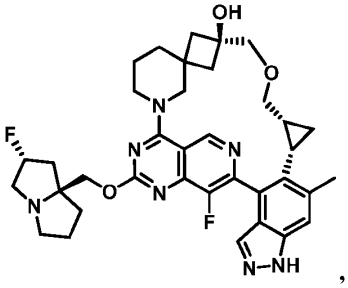
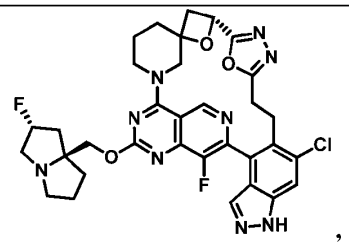
[0096] Provided herein as Embodiment 161 is the compound or salt of any of Embodiments 1-160, wherein each R^{6a}, R^{6b} and R^{6c} independently is hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy or C_{1-4} haloalkyl. Provided herein as Embodiment 162 is the compound or salt of Embodiment 161, wherein R^{6a}, R^{6b} and R^{6c} are each hydrogen. Provided herein as Embodiment 163 is the compound or salt of Embodiment 161, wherein R^{6b} and R^{6c} are each hydrogen and R^{6a} is halogen (e.g., fluorine or chlorine). Provided herein as Embodiment 164 is the compound or salt of Embodiment 163, wherein R^{6b} and R^{6c} are each hydrogen and R^{6a} is chlorine. Provided herein as Embodiment 165 is the compound or salt of Embodiment 163, wherein R^{6b} and R^{6c} are each hydrogen and R^{6a} is fluorine. Provided herein as Embodiment 166 is the compound or salt of Embodiment 161, wherein R^{6b} and R^{6c} are each hydrogen and R^{6a} is C_{1-4} alkyl (e.g., methyl or ethyl). Provided herein as Embodiment 167 is the compound or salt of Embodiment 166, wherein R^{6b} and R^{6c} are each hydrogen and R^{6a} is methyl.

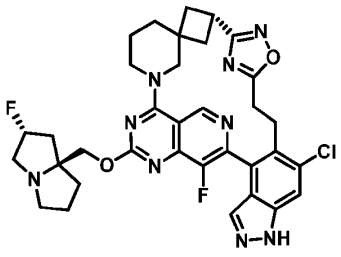
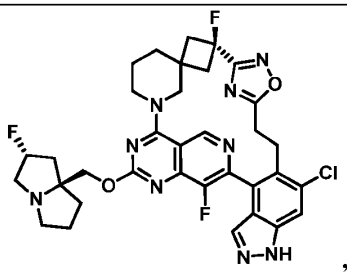
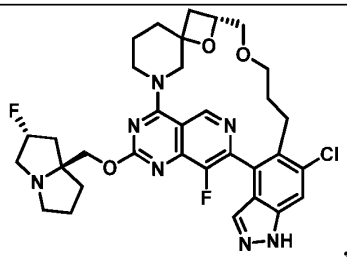
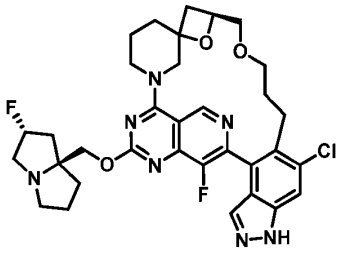
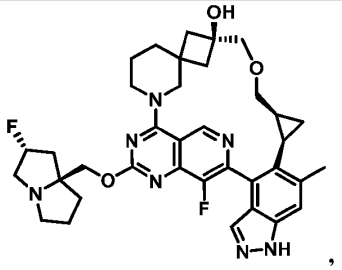
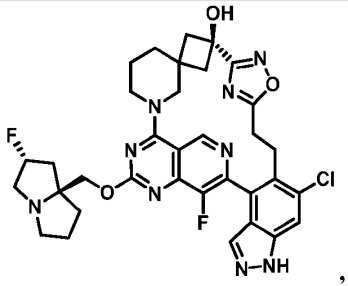
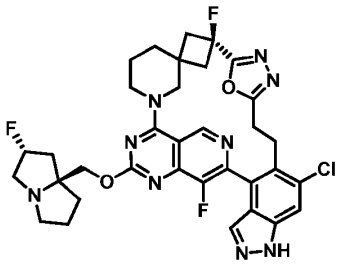
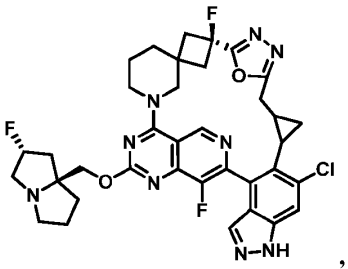
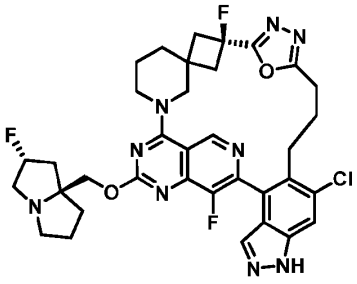
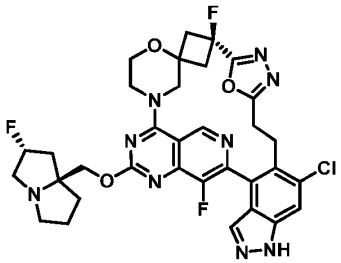
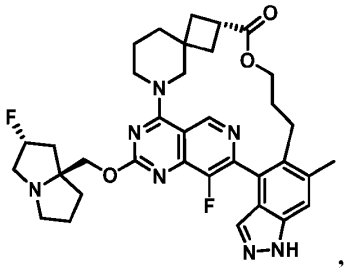
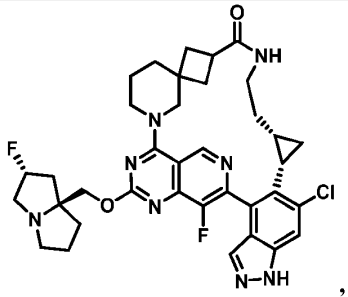
[0097] Provided herein as Embodiment 168 is the compound or salt of any of Embodiments 1-167, wherein R^{6d} is hydrogen. Provided herein as Embodiment 169 is the compound or salt of any of Embodiments 1-167, wherein R^{6d} is -C(O)-C_{1-8} alkyl. Provided herein as Embodiment 170 is the compound or salt of Embodiment 169, wherein R^{6d} is -C(O)Me

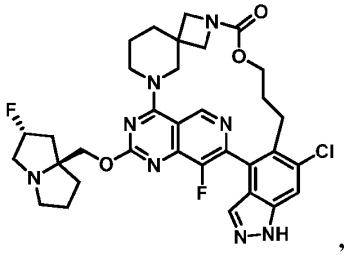
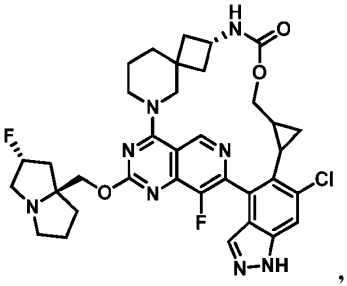
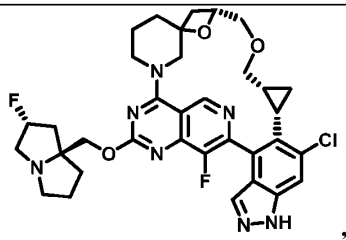
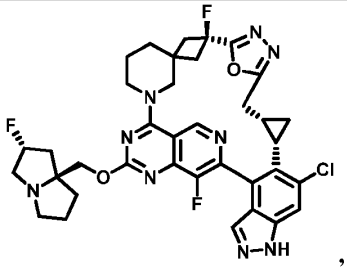
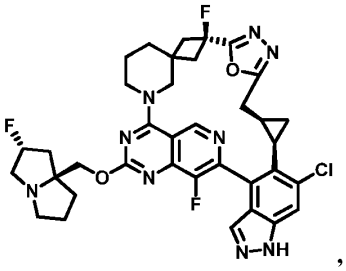
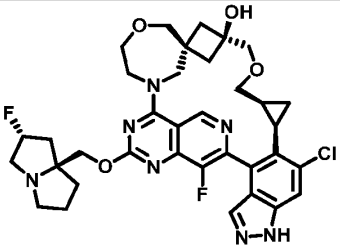
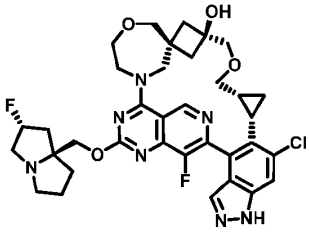
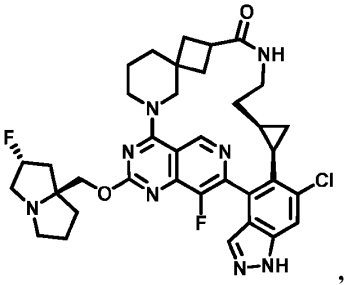
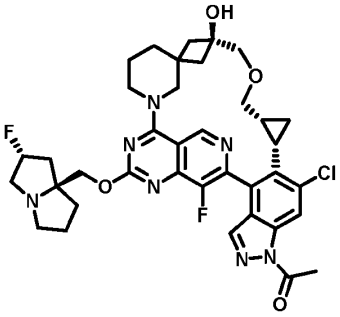
[0098] Provided herein as Embodiment 171 is the compound or salt of Embodiment 1, wherein the compound is:

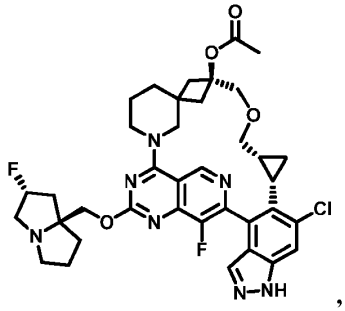
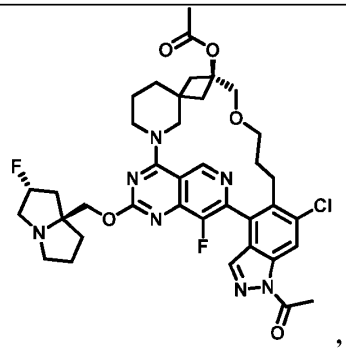
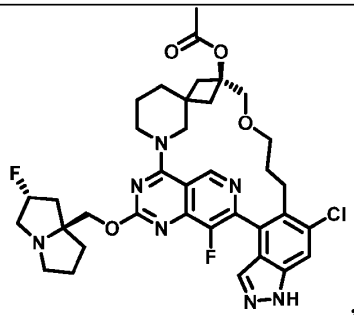
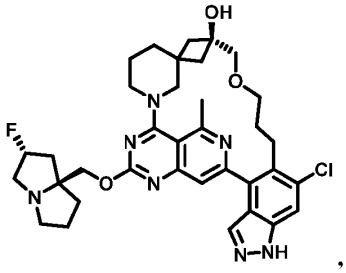
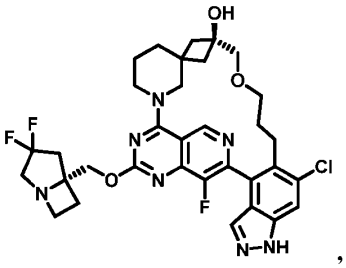
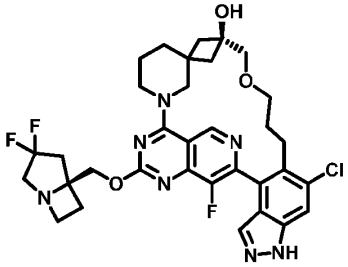
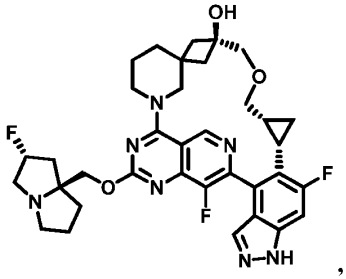
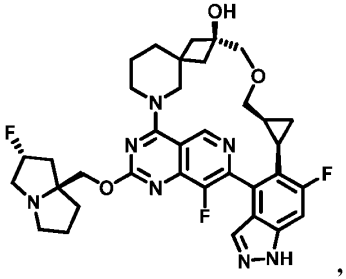
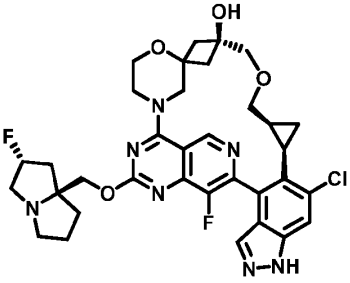
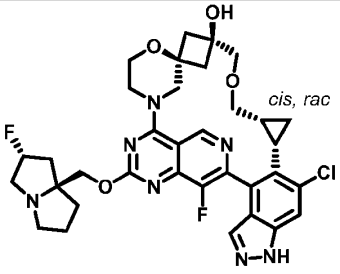
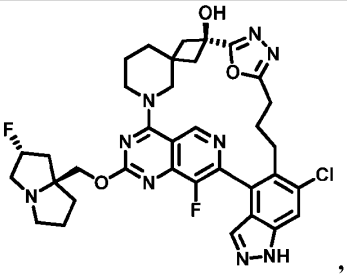
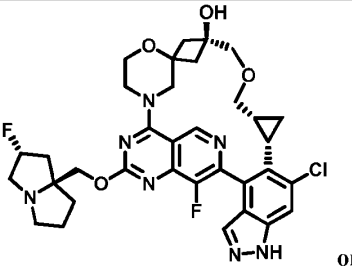
Table 1

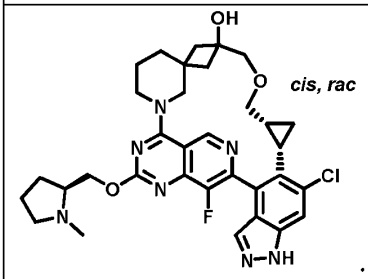
Compound	Compound	Compound
 , **1.001**	 , **1.002**	 , **1.003**

Compound	Compound	Compound
 , 1.004	 , 1.005	 , 1.006
 , 1.010	 , 1.012	 , 1.033
 , 1.035	 , 1.036	 , 1.037
 , 1.039	 , 1.040	 , 1.041

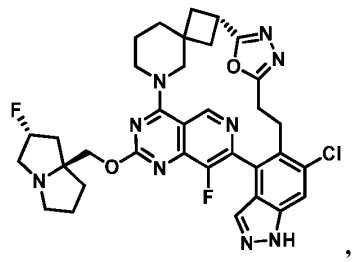
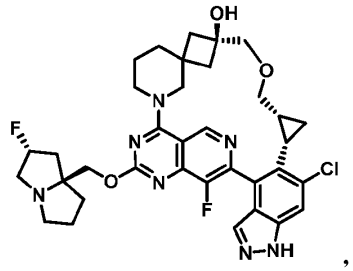
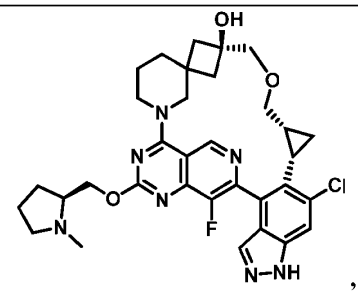
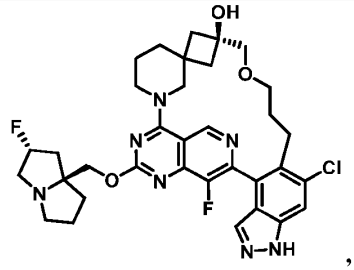
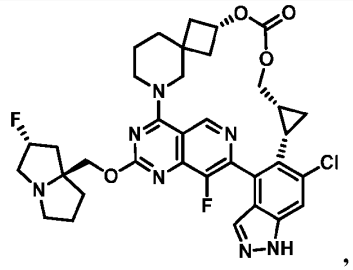
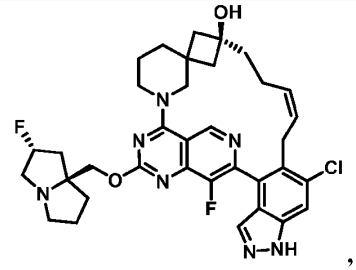
Compound	Compound	Compound
 , 1.042	 , 1.043	 , 1.044
 , 1.046	 , 1.049	 , 1.050
 , 1.052	 , 1.054	 , 1.055
 , 1.059	 , 1.061	 , 1.062

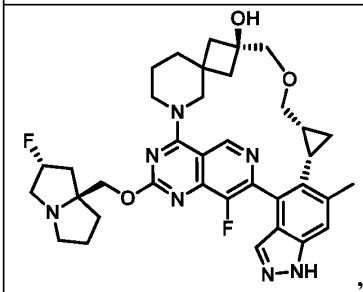
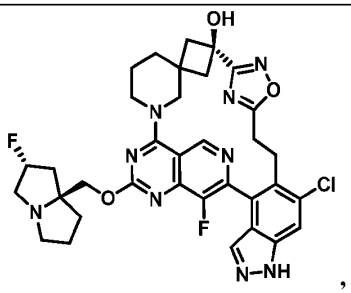
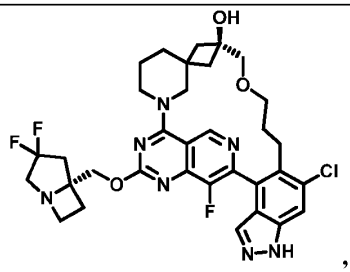
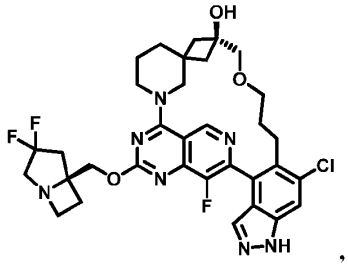
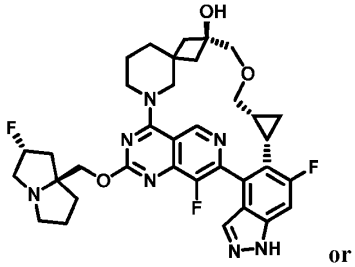
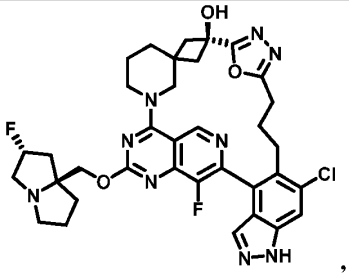
Compound	Compound	Compound
 , 1.065	 , 1.066	 , 1.067
 , 1.068	 , 1.069	 , 1.070
 , 1.071	 , 1.073	 , 1.074

Compound	Compound	Compound
 , 1.075	 , 1.076	 , 1.077
 , 1.081	 , 1.082	 , 1.083
 , 1.084	 , 1.086	 , 1.087
 , 1.088	 , 1.089	 or 1.090

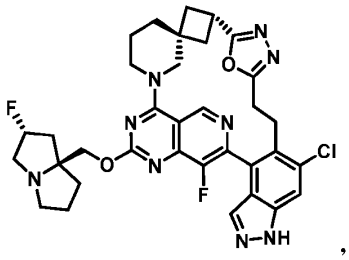
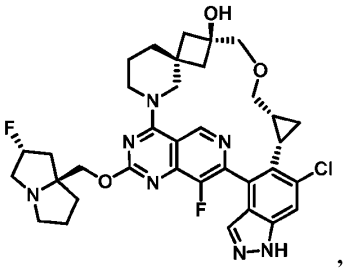
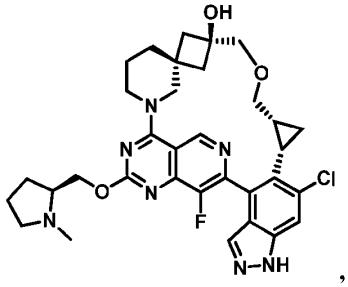
Compound	Compound	Compound
 1.091		

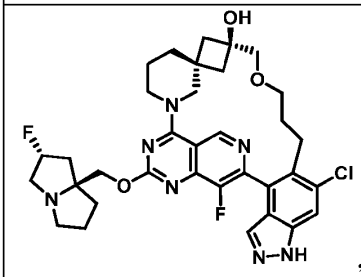
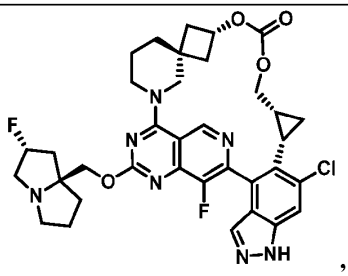
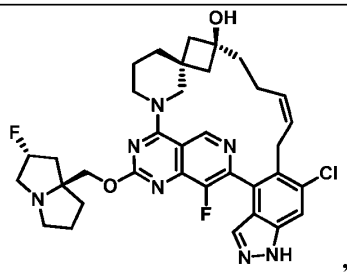
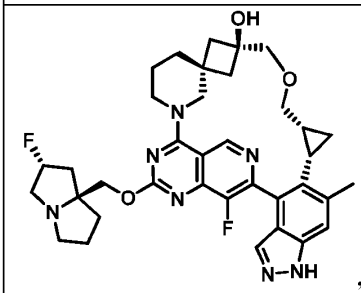
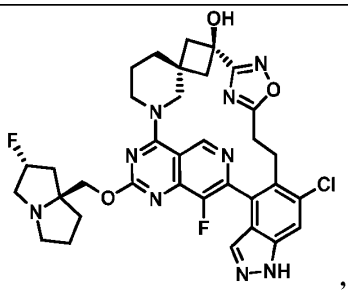
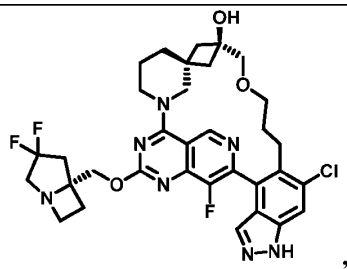
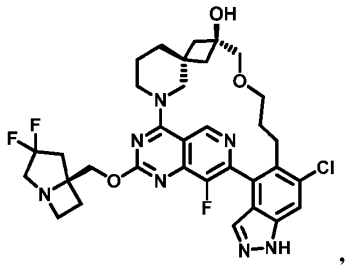
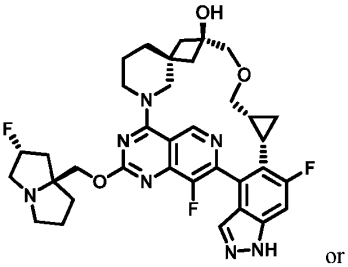
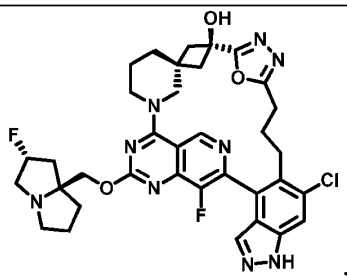
[0099] Provided herein as Embodiment 172 is the compound or salt of Embodiment 1, wherein the compound is:

Compound	Compound	Compound
 1.001	 1.002	 1.003
 1.010	 1.033	 1.035

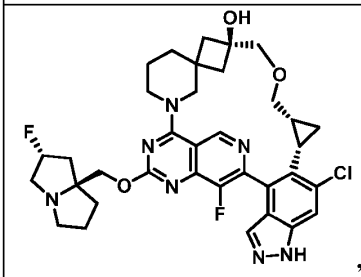
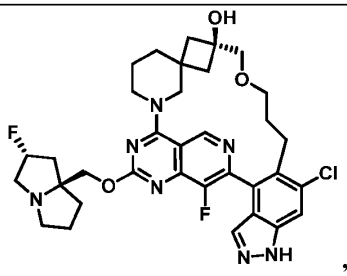
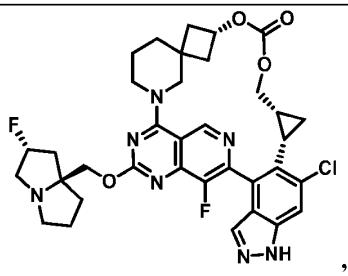
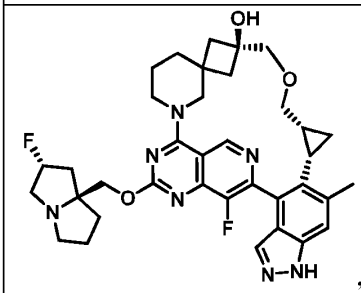
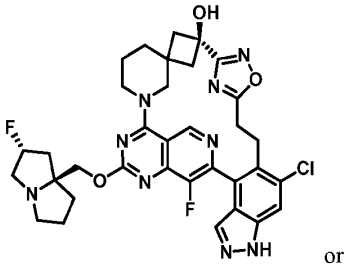
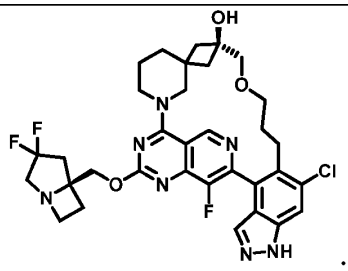
Compound	Compound	Compound
 , 1.040	 , 1.050	 , 1.082
 , 1.083	 or 1.084	 , 1.089

[00100] Provided herein as Embodiment 173 is the compound or salt of Embodiment 1, wherein the compound is:

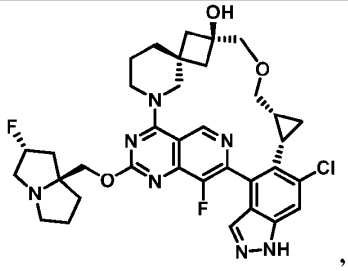
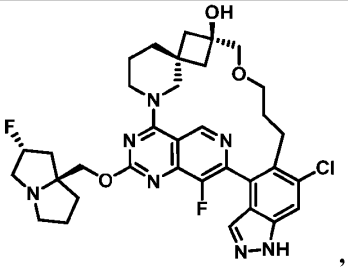
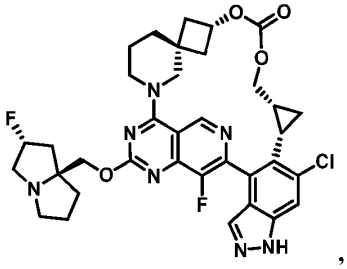
Compound	Compound	Compound
 , 1.001a	 , 1.002a	 , 1.003a

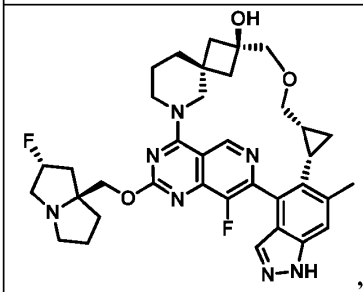
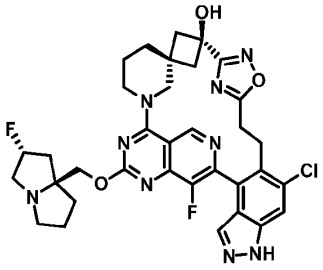
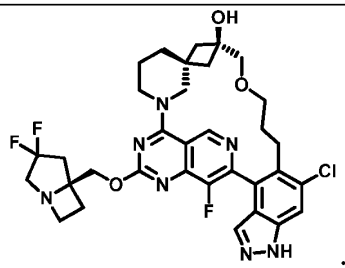
Compound	Compound	Compound
 , 1.010a	 , 1.033a	 , 1.035a
 , 1.040a	 , 1.050a	 , 1.082a
 , 1.083a	 or 1.084a	 . 1.089a

[00101] Provided herein as Embodiment 174 is the compound or salt of Embodiment 1, wherein the compound is:

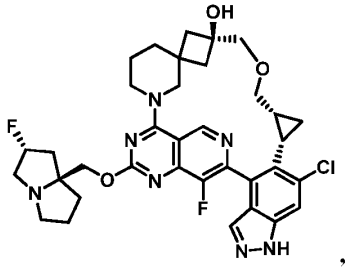
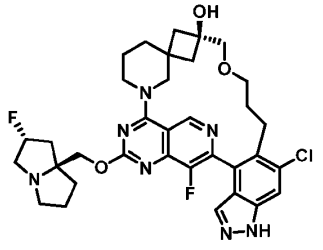
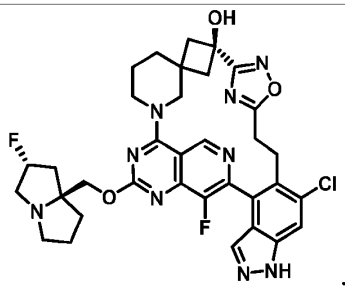
Compound	Compound	Compound
 , 1.002	 , 1.010	 , 1.033
 , 1.040	 or 1.050	 . 1.083

[00102] Provided herein as Embodiment 175 is the compound or salt of Embodiment 1, wherein the compound is:

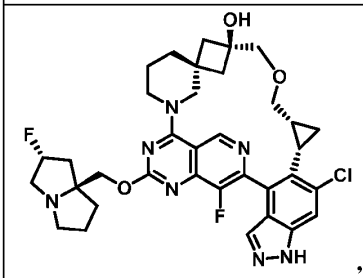
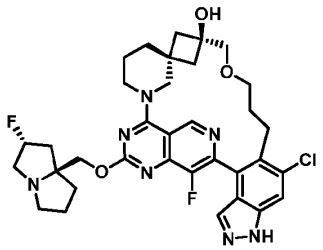
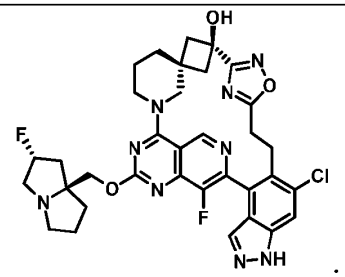
Compound	Compound	Compound
 , 1.002a	 , 1.010a	 , 1.033a

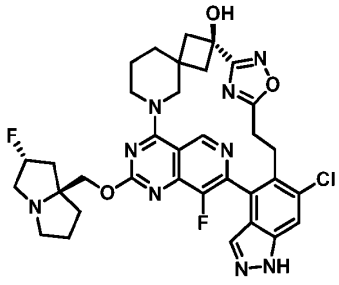
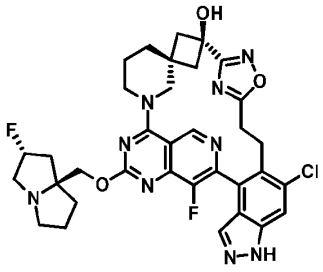
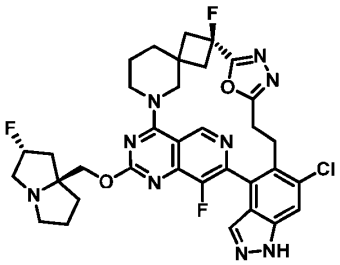
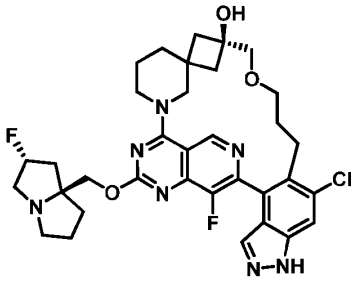
Compound	Compound	Compound
 , 1.040a	 or 1.050a	 . 1.083a

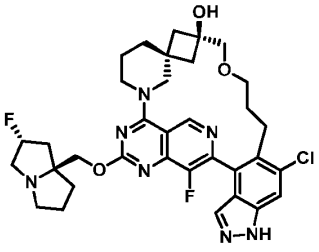
[00103] Provided herein as Embodiment 176 is the compound or salt of Embodiment 1, wherein the compound is:

Compound	Compound	Compound
 , 1.002	 or 1.010	 . 1.050

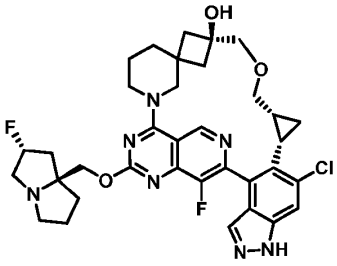
[00104] Provided herein as Embodiment 177 is the compound or salt of Embodiment 1, wherein the compound is:

Compound	Compound	Compound
 , 1.002a	 or 1.010a	 . 1.050a

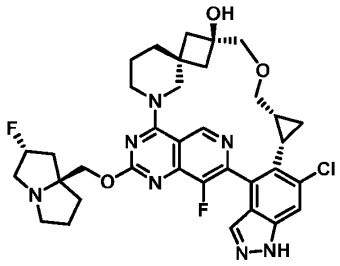
[00105] Provided herein as Embodiment 178 is the compound or salt of Embodiment 171, wherein the compound is  (**Compound 1.050**). Provided herein as Embodiment 179 is the compound or salt of Embodiment 173, wherein the compound is  (**Compound 1.050a**). Provided herein as Embodiment 180 is the compound of salt of Embodiment 171, wherein the compound is  (**Compound 1.052**). Provided herein as Embodiment 181 is the compound of salt of Embodiment 171, wherein the compound is  (**Compound 1.010**). Provided herein as Embodiment 182 is the compound of salt of Embodiment 173, wherein the compound is



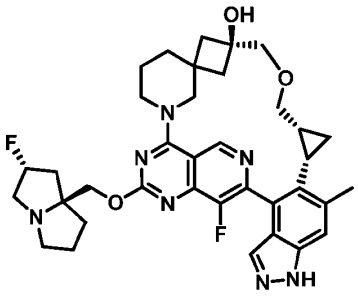
(**Compound 1.010a**). Provided herein as Embodiment 183 is the compound of salt of Embodiment 171, wherein the compound is



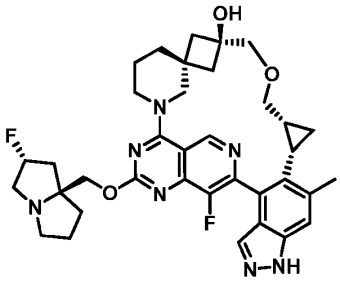
(**Compound 1.002**). Provided herein as Embodiment 184 is the compound of salt of Embodiment 173, wherein the compound is



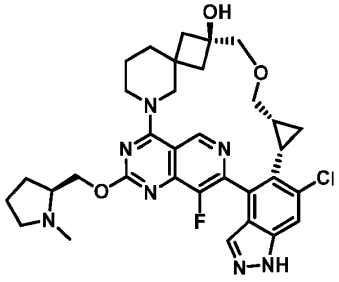
(**Compound 1.002a**). Provided herein as Embodiment 185 is the compound of salt of Embodiment 171, wherein the compound is



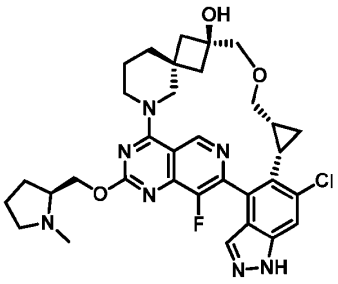
(**Compound 1.040**). Provided herein as Embodiment 186 is the



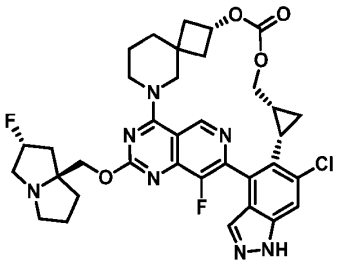
compound of salt of Embodiment 173, wherein the compound is (**Compound 1.040a**). Provided herein as Embodiment 187 is the compound of salt of Embodiment



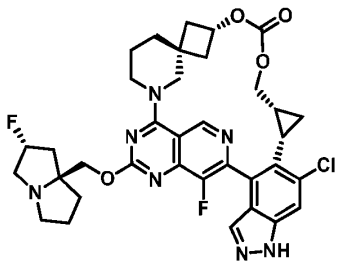
171, wherein the compound is (**Compound 1.003**). Provided herein as Embodiment 188 is the compound of salt of Embodiment 173, wherein the compound is



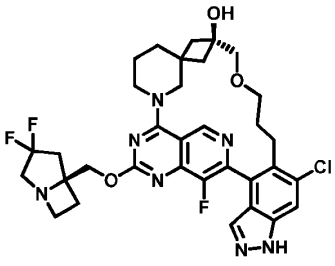
(**Compound 1.003a**). Provided herein as Embodiment 189 is the



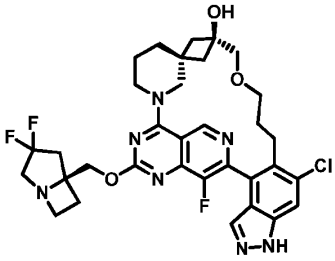
compound of salt of Embodiment 171, wherein the compound is (**Compound 1.033**). Provided herein as Embodiment 190 is the compound of salt of Embodiment



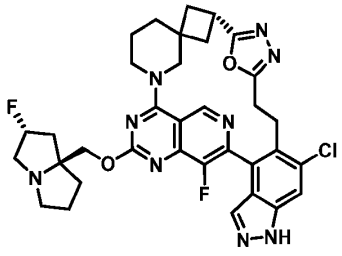
173, wherein the compound is (**Compound 1.033a**). Provided herein as Embodiment 191 is the compound of salt of Embodiment 171, wherein the compound is



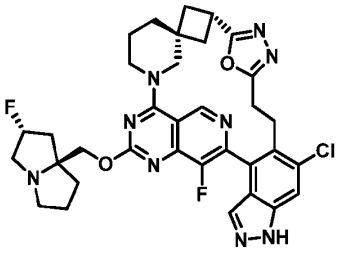
(**Compound 1.083**). Provided herein as Embodiment 192 is the compound of salt of Embodiment 173, wherein the compound is



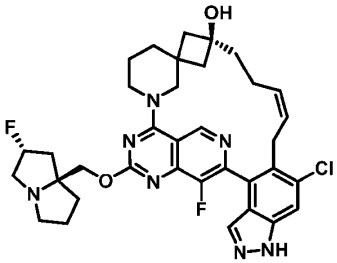
(**Compound 1.083a**). Provided herein as Embodiment 193 is the compound of salt of Embodiment 171, wherein the compound is



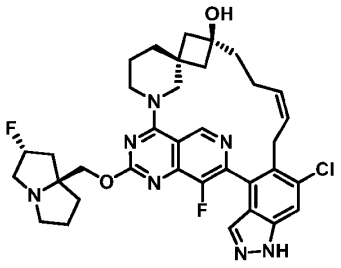
(**Compound 1.001**). Provided herein as Embodiment 194 is the compound of salt of Embodiment 173, wherein the compound is



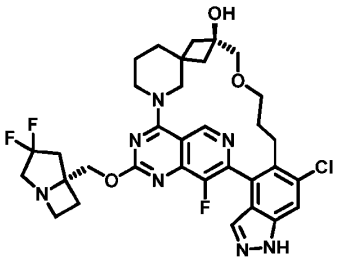
(**Compound 1.001a**). Provided herein as Embodiment 195 is the



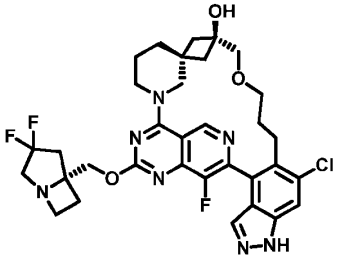
compound of salt of Embodiment 171, wherein the compound is (**Compound 1.035**). Provided herein as Embodiment 196 is the compound of salt of Embodiment 173, wherein the compound is



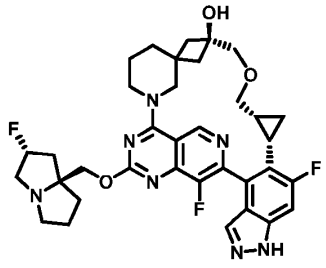
(**Compound 1.035a**). Provided herein as Embodiment 197 is the compound of salt of Embodiment 171, wherein the compound is



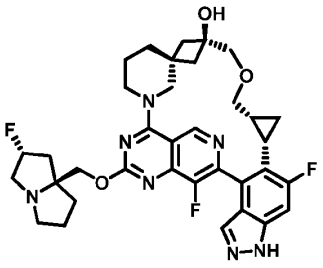
(**Compound 1.082**). Provided herein as Embodiment 198 is the compound of salt of Embodiment 173, wherein the compound is



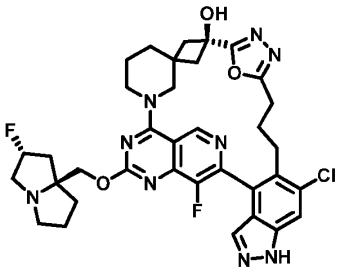
(**Compound 1.082a**). Provided herein as Embodiment 199 is the compound of salt of Embodiment



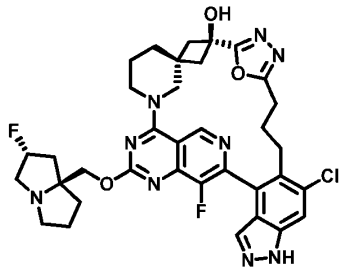
171, wherein the compound is (**Compound 1.084**). Provided herein as Embodiment 200 is the compound of salt of Embodiment 173, wherein the compound is



(**Compound 1.084a**). Provided herein as Embodiment 201 is the compound of salt of Embodiment 171, wherein the compound is



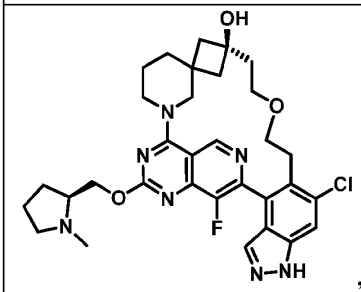
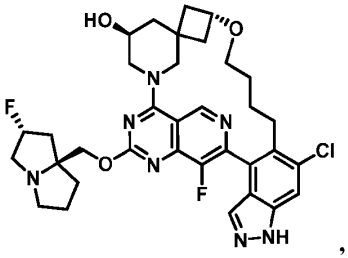
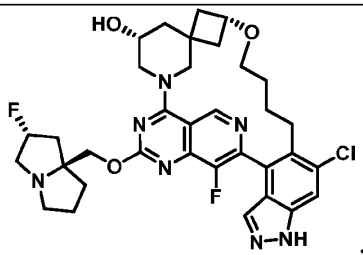
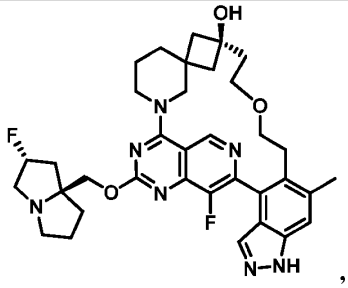
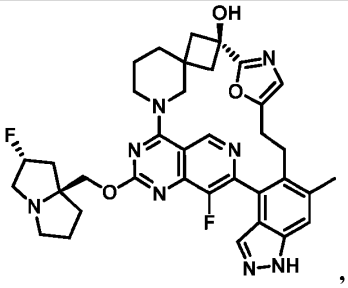
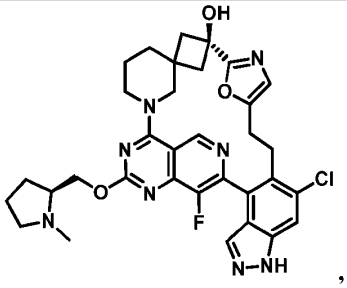
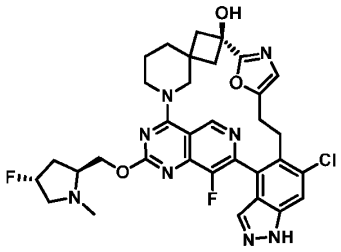
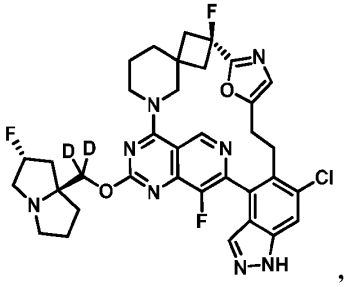
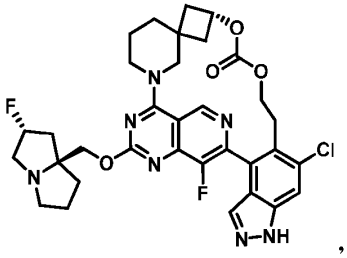
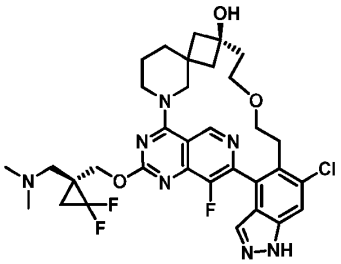
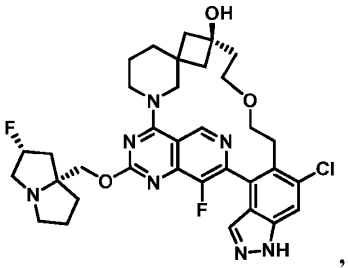
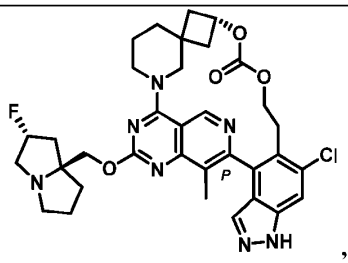
(**Compound 1.089**). Provided herein as Embodiment 202 is the compound of salt of Embodiment 173, wherein the compound is

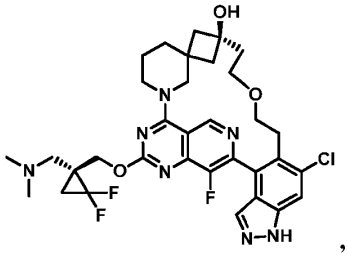
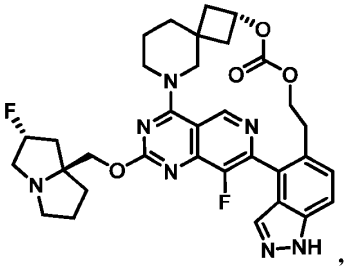
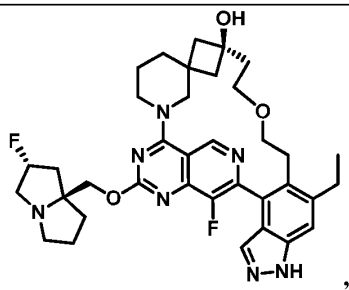
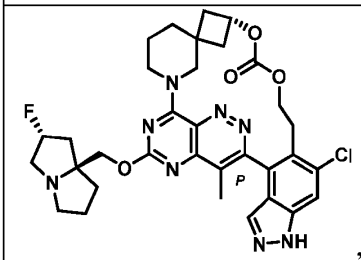
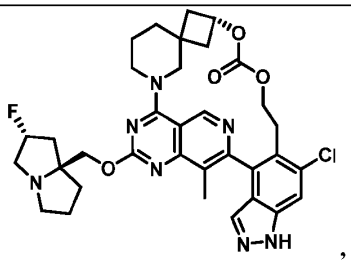
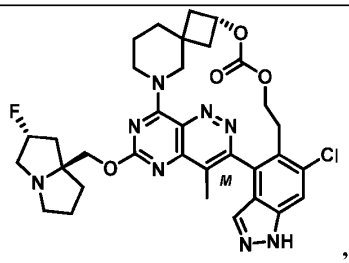
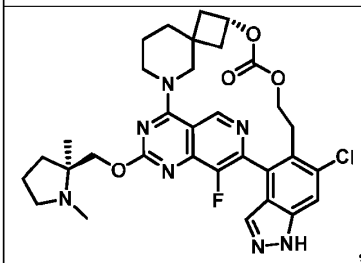
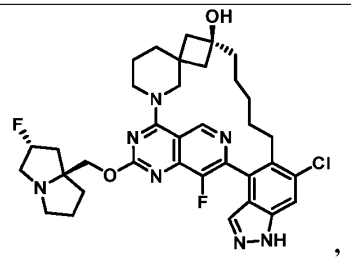
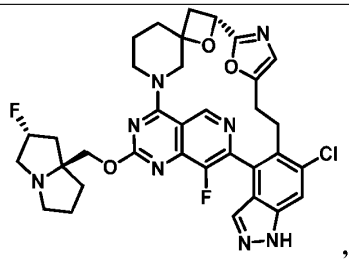
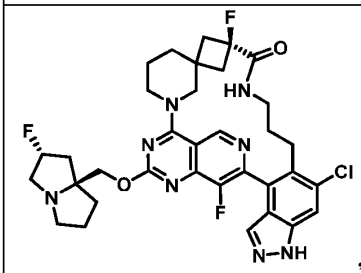
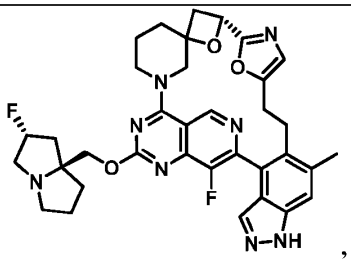
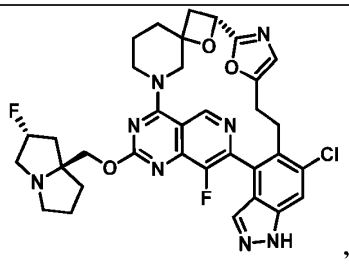


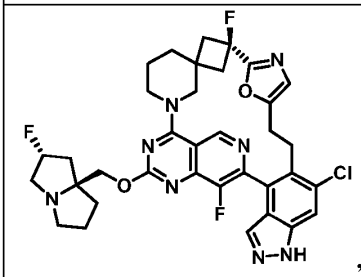
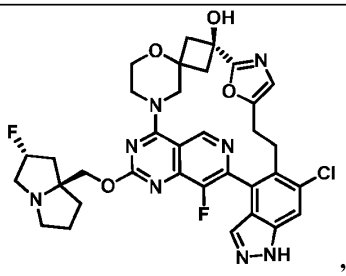
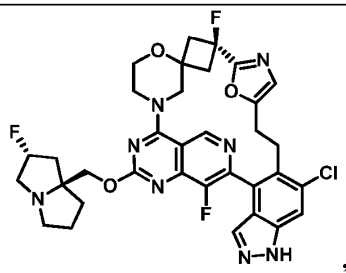
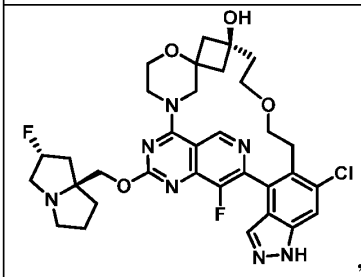
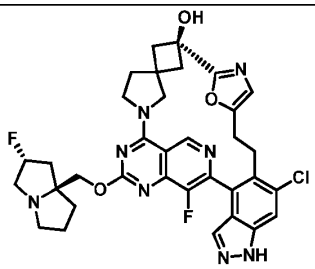
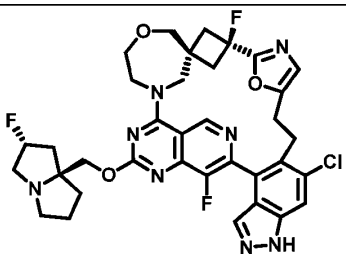
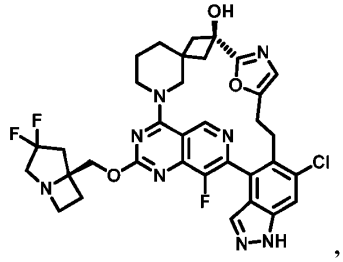
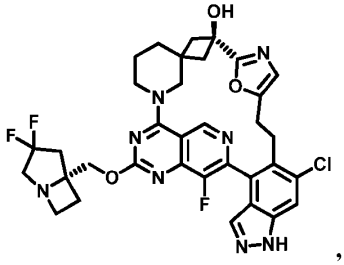
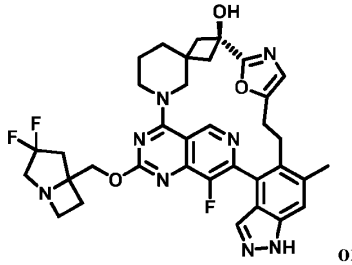
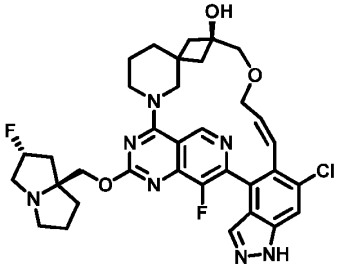
(**Compound 1.089a**).

[00106] In another aspect of the disclosure, Embodiment 203 provides a compound from the table below:

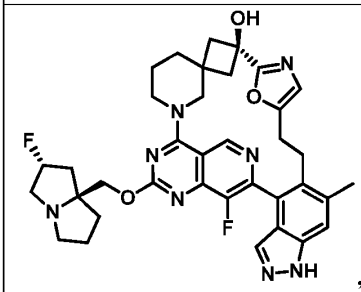
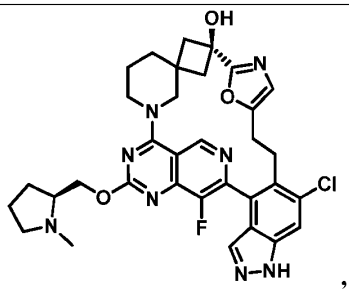
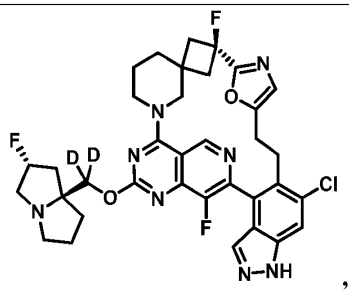
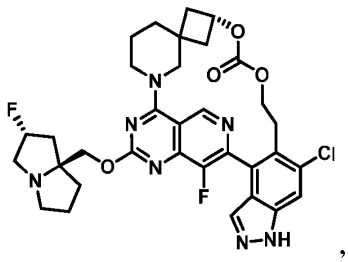
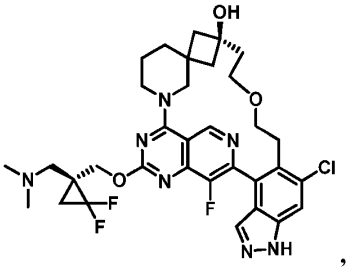
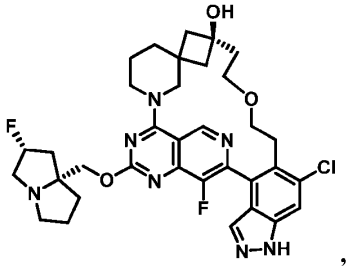
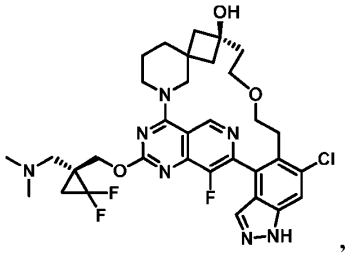
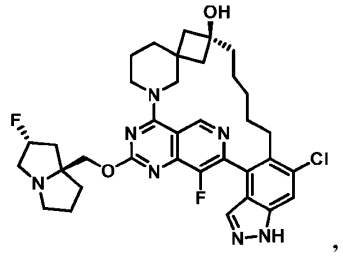
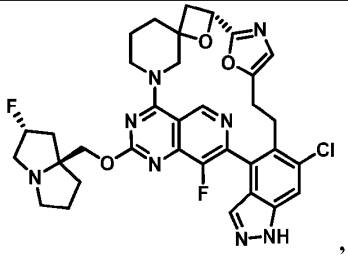
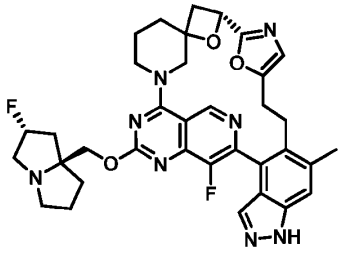
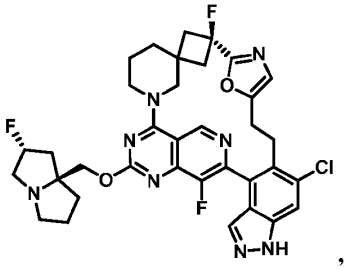
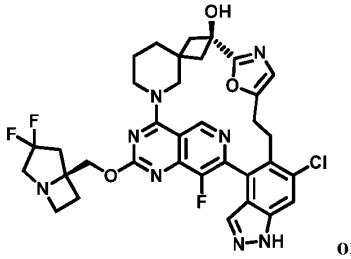
Table 2

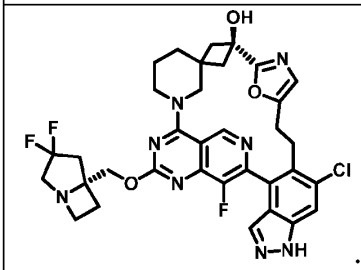
Compound	Compound	Compound
 , 1.007	 , 1.008	 , 1.009
 , 1.011	 , 1.013	 , 1.014
 , 1.015	 , 1.018	 , 1.019
 , 1.020	 , 1.021	 , 1.022

Compound	Compound	Compound
 , 1.024	 , 1.025	 , 1.027
 , 1.028	 , 1.029	 , 1.030
 , 1.032	 , 1.034	 , 1.038
 , 1.045	 , 1.047	 , 1.048

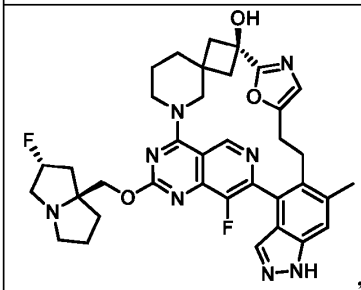
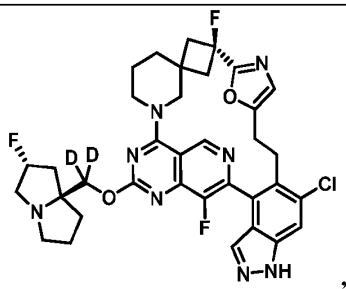
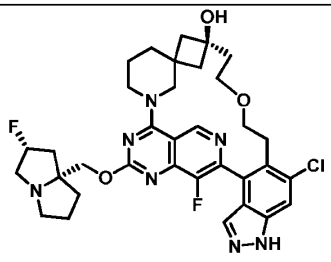
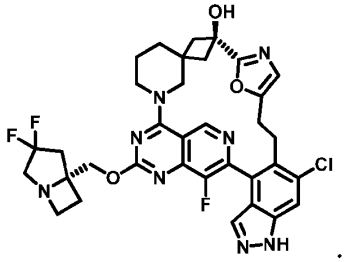
Compound	Compound	Compound
 , 1.051	 , 1.053	 , 1.056
 , 1.057	 1.058	 . 1.072
 , 1.078	 , 1.079	 or 1.080
 . 1.085		

[00107] Provided herein as Embodiment 204 is the compound or salt of Embodiment 203, wherein the compound is:

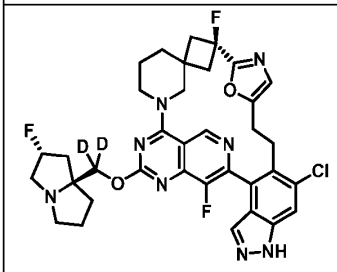
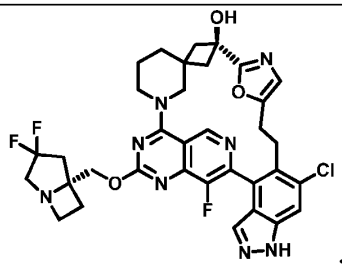
Compound	Compound	Compound
 , 1.013	 , 1.014	 , 1.018
 , 1.019	 , 1.020	 , 1.021
 , 1.024	 , 1.034	 , 1.038
 , 1.047	 , 1.051	 or 1.078

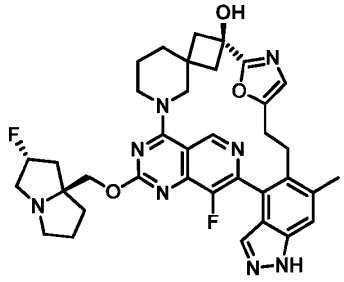
Compound	Compound	Compound
 1.079		

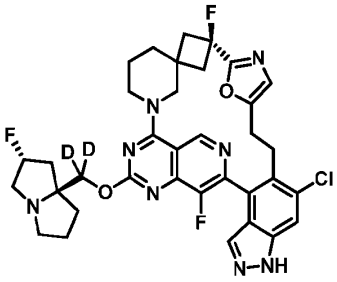
[00108] Provided herein as Embodiment 205 is the compound or salt of Embodiment 203, wherein the compound is:

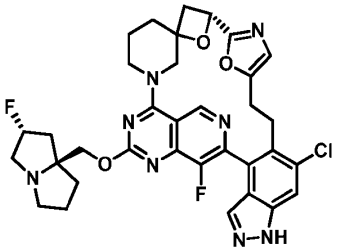
Compound	Compound	Compound
 1.013	 1.018	 or 1.021
 1.079		

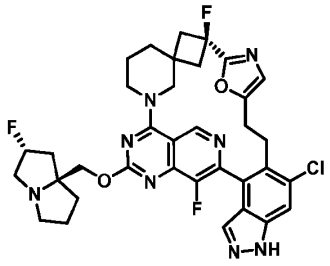
[00109] Provided herein as Embodiment 206 is the compound or salt of Embodiment 203, wherein the compound is:

Compound	Compound	Compound
 or 1.018	 1.079	

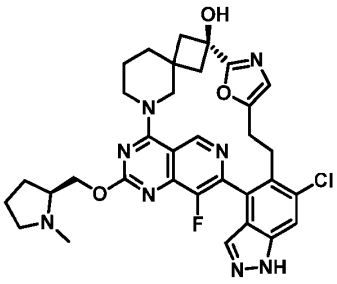
[00110] Provided herein as Embodiment 207 is the compound or salt of Embodiment 203, wherein the compound is:  (**Compound 1.013**). Provided herein as Embodiment 208 is the compound or salt of Embodiment 203, wherein the compound is:

 (**Compound 1.018**). Provided herein as Embodiment 209 is the compound or salt of Embodiment 203, wherein the compound is:

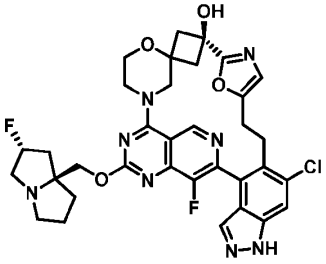
 (**Compound 1.038**). Provided herein as Embodiment 210 is the compound or salt of Embodiment



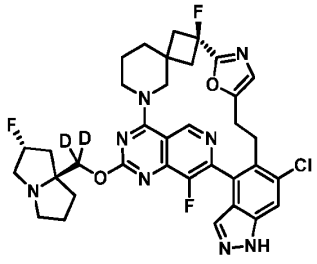
203, wherein the compound is: (**Compound 1.051**). Provided herein as Embodiment 211 is the compound or salt of Embodiment 203, wherein the compound is:



(**Compound 1.014**). Provided herein as Embodiment 212 is the compound or salt of Embodiment 203, wherein the compound is:

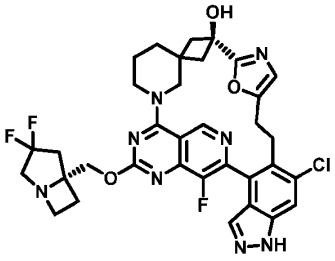


(**Compound 1.053**). Provided herein as Embodiment 213 is the compound or salt of Embodiment 203, wherein the compound is:



(**Compound 1.018**). Provided

herein as Embodiment 214 is the compound or salt of Embodiment 203, wherein the compound is:

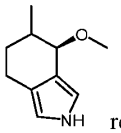
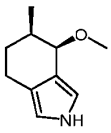
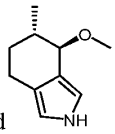


(**Compound 1.079**).

[00111] It is understood that selections of values of each variable are those that result in the formation of stable or chemically feasible compounds.

Stereoisomers

[00112] The compounds of the present disclosure may contain, for example, double bonds, one or more asymmetric carbon atoms, and bonds with a hindered rotation, and therefore, may exist as stereoisomers, such as double-bond isomers (*i.e.*, geometric isomers (E/Z)), enantiomers, diastereomers, and atropoisomers. Accordingly, the scope of the present disclosure is to be understood to encompass all possible stereoisomers of the illustrated compounds, including the stereoisomerically pure form (for example, geometrically pure, enantiomerically pure, diastereomerically pure, and atropoisomerically pure) and stereoisomeric mixtures (for example, mixtures of geometric isomers, enantiomers, diastereomers, and atropoisomers, or mixture of any of the foregoing) of any chemical structures disclosed herein (in whole or in part), unless the stereochemistry is specifically identified.

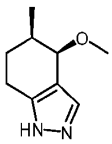
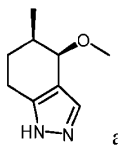
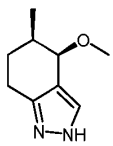
[00113] If the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of the structure. If the stereochemistry of a structure or a portion of a structure is indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing only the stereoisomer indicated, unless otherwise noted. For example,  represents  and . Similarly, for example, the chemical name (4R)-4-methoxy-5-methyl-4,5,6,7-tetrahydro-2H-isoindole represents (4R,5R)-4-methoxy-5-methyl-4,5,6,7-tetrahydro-2H-isoindole and (4R,5S)-4-methoxy-5-methyl-4,5,6,7-tetrahydro-2H-isoindole. A bond drawn with a wavy line may be used to indicate that both stereoisomers are encompassed. This is not to be confused with a wavy line drawn perpendicular to a bond which indicates the point of attachment of a group to the rest of the molecule.

[00114] The term "stereoisomer" or "stereoisomerically pure" compound refers to one stereoisomer (for example, geometric isomer, enantiomer, diastereomer and atropoisomer) of a compound that is

substantially free of other stereoisomers of that compound. For example, a stereoisomerically pure compound having one chiral center will be substantially free of the mirror image enantiomer of the compound and a stereoisomerically pure compound having two chiral centers will be substantially free of the other enantiomer and diastereomers of the compound. A typical stereoisomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and equal or less than about 20% by weight of other stereoisomers of the compound, greater than about 90% by weight of one stereoisomer of the compound and equal or less than about 10% by weight of the other stereoisomers of the compound, greater than about 95% by weight of one stereoisomer of the compound and equal or less than about 5% by weight of the other stereoisomers of the compound, or greater than about 97% by weight of one stereoisomer of the compound and equal or less than about 3% by weight of the other stereoisomers of the compound.

[00115] This disclosure also encompasses the pharmaceutical compositions comprising stereoisomerically pure forms and the use of stereoisomerically pure forms of any compounds disclosed herein. Further, this disclosure also encompasses pharmaceutical compositions comprising mixtures of stereoisomers of any compounds disclosed herein and the use of said pharmaceutical compositions or mixtures of stereoisomers. These stereoisomers or mixtures thereof may be synthesized in accordance with methods well known in the art and methods disclosed herein. Mixtures of stereoisomers may be resolved using standard techniques, such as chiral columns or chiral resolving agents. *See*, for example, Jacques *et al.*, Enantiomers, Racemates and Resolutions (WileyInterscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725; Eliel, Stereochemistry of Carbon Compounds (McGrawHill, NY, 1962); and Wilen, Tables of Resolving Agents and Optical Resolutions, page 268 (Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

Tautomers

[00116] As known by those skilled in the art, certain compounds disclosed herein may exist in one or more tautomeric forms. Because one chemical structure may only be used to represent one tautomeric form, it will be understood that for convenience, referral to a compound of a given structural formula includes other tautomers of said structural formula. For example,  represents  and . Similarly, for example, the chemical name (4R,5R)-4-methoxy-5-methyl-4,5,6,7-tetrahydro-1H-indazole represents (4R,5R)-4-methoxy-5-methyl-4,5,6,7-tetrahydro-1H-indazole and (4R,5R)-4-methoxy-5-methyl-4,5,6,7-tetrahydro-2H-indazole.

Accordingly, the scope of the present disclosure is to be understood to encompass all tautomeric forms of the compounds disclosed herein.

Isotopically-Labeled Compounds

[00117] In some cases, the scope of the present disclosure includes pharmaceutically acceptable isotopically-labeled compounds of the compounds disclosed herein, wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds disclosed herein include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulfur, such as ^{35}S. Certain isotopically-labelled compounds of the compounds disclosed herein, such as those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium (^{3}H) and carbon-14 (^{14}C) are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with isotopes such as deuterium (^{2}H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be advantageous in some circumstances. As such, the term "deuterated" refers to the substitution of one or more hydrogen atoms with one or more deuterium atoms on a particular structure or functional group. Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies, for example, for examining target occupancy. Isotopically-labelled compounds of the compounds disclosed herein can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying GENERAL SYNTHETIC PROCEDURES and EXAMPLES sections using an appropriate isotopically-labelled reagent in place of the non-labelled reagent previously employed.

BIOLOGICAL ACTIVITY

[00118] In some cases, the compounds or salts disclosed herein (such as compounds of Formula (**I**), Formula (**I-B**), Formula (**II**), Formula (**II-B**), Formula (**III**), Formula (**III-B**), Formula (**IV**), Formula (**IV-B**), Formula (**V**), Formula (**V-B**), Formula (**VI**) or Formula (**VI-B**), or compounds listed in Table 1, Table 2 or compounds of Embodiments 1-214, or a pharmaceutically acceptable salt of any of the foregoing), have an IC_{50} value of less than 5 μM, or less than 4 μM, or less than 3 μM, or less than 2 μM, or less than 1 μM, or less than 0.9 μM, or less than 0.7 μM, or less than 0.6 μM, or less than 0.5 μM, or less than 0.4 μM, or less than 0.3 μM, or less than 0.2 μM, or less than 0.1 μM, or less than 0.09 μM, or less than 0.08 μM, or less than 0.07 μM, or less than 0.06 μM, or less than 0.05 μM, or less than 0.04 μM, or less than 0.03 μM, or less than 0.02 μM, or less than 0.01 μM in the G12D Couple Exchange assay, AsPC-1 p-ERK assay, AsPC-1 CTG assay or the SW620 CTG assay,

described in "SECTION 3: Biochemical and Cellular Assays." In some cases, the compounds disclosed herein, and pharmaceutically acceptable salts of the foregoing, have an IC_{50} value of between 0.001 to 0.200 μM.

FORMULATION AND ROUTE OF ADMINISTRATION

[00119] While it may be possible to administer a compound disclosed herein alone in the uses described, the compound administered normally will be present as an active ingredient in a pharmaceutical composition. Thus, further provided herein is a pharmaceutical composition comprising a compound or salt disclosed herein (such as compounds of Formula (**I**), Formula (**I-B**), Formula (**II**), Formula (**II-B**), Formula (**III**), Formula (**III-B**), Formula (**IV**), Formula (**IV-B**), Formula (**V**), Formula (**V-B**), Formula (**VI**) or Formula (**VI-B**), or compounds listed in Table 1, Table 2 or compounds of Embodiments 1-214, or a pharmaceutically acceptable salt of any of the foregoing), in combination with one or more pharmaceutically acceptable excipients and, if desired, other active ingredients. *See, e.g.*, Remington: The Science and Practice of Pharmacy, Volume I and Volume II, twenty-second edition, edited by Loyd V. Allen Jr., Philadelphia, PA, Pharmaceutical Press, 2012; Pharmaceutical Dosage Forms (Vol. 1-3), Liberman et al., Eds., Marcel Dekker, New York, NY, 1992; Handbook of Pharmaceutical Excipients (3rd Ed.), edited by Arthur H. Kibbe, American Pharmaceutical Association, Washington, 2000; Pharmaceutical Formulation: The Science and Technology of Dosage Forms (Drug Discovery), first edition, edited by GD Tovey, Royal Society of Chemistry, 2018. In some cases, the pharmaceutical composition described herein comprises a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof.

[00120] The compound(s) disclosed herein may be administered by any suitable route in the form of a pharmaceutical composition adapted to such a route and in a dose effective for the treatment intended. The compounds and compositions presented herein may, for example, be administered orally, mucosally, topically, transdermally, rectally, pulmonarily, parentally, intranasally, intravascularly, intravenously, intraarterial, intraperitoneally, intrathecally, subcutaneously, sublingually, intramuscularly, intrasternally, vaginally or by infusion techniques, in dosage unit formulations containing conventional pharmaceutically acceptable excipients.

[00121] The pharmaceutical composition may be in the form of, for example, a tablet, chewable tablet, minitablet, caplet, pill, bead, hard capsule, soft capsule, gelatin capsule, granule, powder, lozenge, patch, cream, gel, sachet, microneedle array, syrup, flavored syrup, juice, drop, injectable solution, emulsion, microemulsion, ointment, aerosol, aqueous suspension, or oily suspension. In some cases, the pharmaceutical composition is made in the form of a dosage unit containing a particular amount of the active ingredient.

[00122] Thus, a further aspect of the disclosure is a pharmaceutical composition comprising one or more of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. Further provided herein is a compound of the disclosure, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described herein, for use as a medicament.

[00123] Provided herein as Embodiment 215 is pharmaceutical composition comprising the compound or salt of any one of Embodiments 1 to 214, and a pharmaceutically acceptable excipient.

METHODS OF USE

[00124] The compounds described herein (such as compounds of Formula (**I**), Formula (**I-B**), Formula (**II**), Formula (**II-B**), Formula (**III**), Formula (**III-B**), Formula (**IV**), Formula (**IV-B**), Formula (**V**), Formula (**V-B**), Formula (**VI**) or Formula (**VI-B**), or compounds listed in Table 1, Table 2 or compounds of Embodiments 1-214, or a pharmaceutically acceptable salt of any of the foregoing) can competitively bind to KRAS G12D, G12V, G12A, G12S, G12R, G13D, Q61H, Q61L, Q61R or G12C or a mutated KRAS comprising one or more mutations selected from G12D, G12V, G12A, G12S, G12R, G13D, Q61H, Q61L, Q61R and G12C. In some cases, the compounds described herein can act as inhibitors of KRAS G12D. In some cases, the compounds described herein can act as inhibitors of KRAS G12V. In some cases, the compounds described herein can act as inhibitors of KRAS G12A. In some cases, the compounds described herein can act as inhibitors of KRAS G12S. In some cases, the compounds described herein can act as inhibitors of KRAS G13D. In some cases, the compounds described herein can act as inhibitors of KRAS Q61H. In some cases, the compounds described herein can act as inhibitors of KRAS Q61R. In some cases, the compounds described herein can act as inhibitors of KRAS Q61L. In some cases, the compounds described herein can act as inhibitors of KRAS G12R. In some cases, the compounds described herein can act as inhibitors of KRAS G12C. Without intending to be bound by any particular theory, the compounds of the disclosure can, in some cases, inhibit KRAS G12D, G12V, G12A, G12S, G12R, G13D, Q61H, Q61L, Q61R or G12C, leading to an improvement in conditions or symptoms mediated by a KRAS G12D, G12V, G12A, G12S, G12R, G13D, Q61H, Q61L, Q61R or G12C mutation (e.g., reduction in tumor size).

[00125] Besides being useful for human treatment, the compounds provided herein may be useful for veterinary treatment of companion animals, exotic animals, and farm animals, including mammals, rodents, and the like. For example, animals including horses, dogs, and cats may be treated with compounds provided herein.

[00126] In several embodiments, as disclosed elsewhere herein, a method of treating a patient is provided. In several embodiments, the method comprises administering a therapeutic amount of a compound or salt disclosed herein (such as compounds of Formula (**I**), Formula (**I-B**), Formula (**II**),

Formula (**II-B**), Formula (**III**), Formula (**III-B**), Formula (**IV**), Formula (**IV-B**), Formula (**V**), Formula (**V-B**), Formula (**VI**) or Formula (**VI-B**), or compounds listed in Table 1, Table 2 or compounds of Embodiments 1-214, or a pharmaceutically acceptable salt of any of the foregoing) to a patient.

[00127] Another aspect of the disclosure provides methods of using the compounds disclosed herein, or pharmaceutically acceptable salts thereof, or the pharmaceutical compositions of the present disclosure to treat disease conditions, including but not limited to conditions mediated by a KRAS G12D, G12V, G12A, G12S, G12R, G13D, Q61H, Q61L, Q61R or G12C mutation.

[00128] Another aspect of the disclosure provides a compound or salt disclosed herein (such as compounds of Formula (**I**), Formula (**I-B**), Formula (**II**), Formula (**II-B**), Formula (**III**), Formula (**III-B**), Formula (**IV**), Formula (**IV-B**), Formula (**V**), Formula (**V-B**), Formula (**VI**) or Formula (**VI-B**), or compounds listed in Table 1, Table 2 or compounds of Embodiments 1-214, or a pharmaceutically acceptable salt of any of the foregoing), or a pharmaceutical composition disclosed herein, for use in treating cancer.

[00129] Yet another aspect of the disclosure provides a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the preparation of a medicament for treating cancer.

[00130] A further aspect provided by the disclosure is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein.

[00131] In some cases, the cancer disclosed herein is non-small cell lung cancer, small bowel cancer, appendiceal cancer, colorectal cancer, cancer of unknown primary, endometrial cancer, mixed cancer types, pancreatic cancer, hepatobiliary cancer, small cell lung cancer, cervical cancer, germ cell cancer, ovarian cancer, gastrointestinal neuroendocrine cancer, bladder cancer, myelodysplastic/myeloproliferative neoplasms, head and neck cancer, esophagogastric cancer, soft tissue sarcoma, mesothelioma, thyroid cancer, leukemia, or melanoma. In some cases, the cancer is non-small cell lung cancer, colorectal cancer, pancreatic cancer, appendiceal cancer, endometrial cancer, esophageal cancer, cancer of unknown primary, ampullary cancer, gastric cancer, small bowel cancer, sinonasal cancer, bile duct cancer, or melanoma. In some cases, the cancer is non-small cell lung cancer. In some cases, the cancer is colorectal cancer. In some cases, the cancer is pancreatic cancer.

[00132] Provided herein as Embodiment 216 is a method of treating cancer in a subject in need of treatment, the method comprising administering to the subject a therapeutically effective amount of the compound or salt of any one of Embodiments 1 to 214, or the composition of Embodiment 215.

[00133] Provided herein as Embodiment 217 is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound according of any one of Embodiments 1 to 214, or the composition of Embodiment 215, wherein one or more cells express KRAS G12D mutant protein.

[00134] Provided herein as Embodiment 218 is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound according of any one of Embodiments 1 to 214, or the composition of Embodiment 215, wherein one or more cells express KRAS G12V mutant protein.

[00135] Provided herein as Embodiment 219 is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound according of any one of Embodiments 1 to 214, or the composition of Embodiment 215, wherein one or more cells express KRAS G12A mutant protein.

[00136] Provided herein as Embodiment 220 is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound according of any one of Embodiments 1 to 214, or the composition of Embodiment 215, wherein one or more cells express KRAS G12S mutant protein.

[00137] Provided herein as Embodiment 221 is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound according of any one of Embodiments 1 to 214, or the composition of Embodiment 215, wherein one or more cells express KRAS G13D mutant protein.

[00138] Provided herein as Embodiment 222 is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound according of any one of Embodiments 1 to 214, or the composition of Embodiment 215, wherein one or more cells express KRAS Q61H mutant protein.

[00139] Provided herein as Embodiment 223 is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound according of any one of Embodiments 1 to 214, or the composition of Embodiment 215, wherein one or more cells express KRAS Q61L mutant protein.

[00140] Provided herein as Embodiment 224 is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound according of any one of Embodiments 1 to 214, or the composition of Embodiment 215, wherein one or more cells express KRAS Q61R mutant protein.

[00141] Provided herein as Embodiment 225 is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the

compound according of any one of Embodiments 1 to 214, or the composition of Embodiment 215, wherein one or more cells express KRAS G12R mutant protein.

[00142] Provided herein as Embodiment 226 is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound according of any one of Embodiments 1 to 214, or the composition of Embodiment 215, wherein one or more cells express KRAS G12C mutant protein.

[00143] Provided herein as Embodiment 227 is the method according to any one of embodiments 216-226, wherein the cancer is non-small cell lung cancer, small bowel cancer, appendiceal cancer, colorectal cancer, cancer of unknown primary, endometrial cancer, mixed cancer types, pancreatic cancer, hepatobiliary cancer, small cell lung cancer, cervical cancer, germ cell cancer, ovarian cancer, gastrointestinal neuroendocrine cancer, bladder cancer, myelodysplastic/myeloproliferative neoplasms, head and neck cancer, esophagogastric cancer, soft tissue sarcoma, mesothelioma, thyroid cancer, leukemia, or melanoma.

[00144] Provided herein as Embodiment 228 is the method according to Embodiment 227, wherein the cancer is non-small cell lung cancer, colorectal cancer, pancreatic cancer, appendiceal cancer, endometrial cancer, esophageal cancer, cancer of unknown primary, ampullary cancer, gastric cancer, small bowel cancer, sinonasal cancer, bile duct cancer, or melanoma. Provided herein as Embodiment 229 is the method according to Embodiment 228, wherein the cancer is non-small cell lung cancer. Provided herein as Embodiment 230 is the method according to Embodiment 228 wherein the cancer is colorectal cancer. Provided herein as Embodiment 231 is the method according to Embodiment 228, wherein the cancer is pancreatic cancer.

[00145] Provided herein as Embodiment 232 is the compound or salt of any one of Embodiments 1 to 214, or the pharmaceutical composition of Embodiment 215 for use as a medicament.

[00146] Provided herein as Embodiment 233 is the compound or salt of any one of Embodiments 1 to 214, or the pharmaceutical composition of Embodiment 215 for use in the treatment of cancer.

[00147] Provided herein as Embodiment 234 is the use of the compound or salt of any one of Embodiments 1 to 214, or the pharmaceutical composition of Embodiment 215, for the manufacture of a medicament for the treatment of cancer.

[00148] Provided herein as Embodiment 235 is the use of the compound or salt of any one of Embodiments 232 to 234, wherein the cancer is cancer is non-small cell lung cancer, small bowel cancer, appendiceal cancer, colorectal cancer, cancer of unknown primary, endometrial cancer, mixed cancer types, pancreatic cancer, hepatobiliary cancer, small cell lung cancer, cervical cancer, germ cell cancer, ovarian cancer, gastrointestinal neuroendocrine cancer, bladder cancer, myelodysplastic/myeloproliferative neoplasms, head and neck cancer, esophagogastric cancer, soft

tissue sarcoma, mesothelioma, thyroid cancer, leukemia, or melanoma, or any combination of the foregoing.

[00149] Provided herein as Embodiment 236 is the method according to Embodiment 235, wherein the cancer is non-small cell lung cancer, colorectal cancer, pancreatic cancer, appendiceal cancer, endometrial cancer, esophageal cancer, cancer of unknown primary, ampullary cancer, gastric cancer, small bowel cancer, sinonasal cancer, bile duct cancer, or melanoma. Provided herein as Embodiment 237 is the method according to Embodiment 236, wherein the cancer is non-small cell lung cancer. Provided herein as Embodiment 238 is the method according to Embodiment 236, wherein the cancer is colorectal cancer. Provided herein as Embodiment 239 is the method according to Embodiment 236, wherein the cancer is pancreatic cancer.

Combination therapy

[00150] The present disclosure also provides methods for combination therapies in which an agent known to modulate other pathways, or other components of the same pathway, or even overlapping sets of target enzymes are used in combination with a compound or salt disclosed herein (such as compounds of Formula (**I**), Formula (**I-B**), Formula (**II**), Formula (**II-B**), Formula (**III**), Formula (**III-B**), Formula (**IV**), Formula (**IV-B**), Formula (**V**), Formula (**V-B**), Formula (**VI**) or Formula (**VI-B**), or compounds listed in Table 1, Table 2 or compounds of Embodiments 1-214, or a pharmaceutically acceptable salt of any of the foregoing). In one aspect, such therapy includes but is not limited to the combination of one or more compounds of the disclosure with chemotherapeutic agents, therapeutic antibodies, and radiation treatment, to provide a synergistic or additive therapeutic effect. *See, e.g.*, *See, e.g.*, U.S. Patent No. 10,519,146 B2, issued December 31, 2019; specifically, the sections from column 201 (line 37) to column 212 (line 46) and column 219 (line 64) to column 220 (line 39), which are herewith incorporated by reference.

[00151] The compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound in any of the methods described herein. In some cases, the second compound is wherein the second compound is an Aurora kinase A inhibitor, AKT inhibitor, arginase inhibitor, CDK4/6 inhibitor, ErbB family inhibitor, ERK inhibitor, FAK inhibitor, FGFR inhibitor, glutaminase inhibitor, IGF-1R inhibitor, KIF18A inhibitor, MCL-1 inhibitor, MEK inhibitor, mTOR inhibitor, PD-1 inhibitor, PD-L1 inhibitor, PI3K inhibitor, Raf kinase inhibitor, SHP2 inhibitor, SOS1 inhibitor, Src kinase inhibitor, or one or more chemotherapeutic agent. In some cases, the second compound is administered as a pharmaceutically acceptable salt. In some cases, the second compound is administered as a pharmaceutical composition comprising the second compound or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

[00152] Aurora Kinase A Inhibitors. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein the second compound is an Aurora kinase A inhibitor.

[00153] Exemplary Aurora kinase A inhibitors for use in the methods provided herein include, but are not limited to, alisertib, cenisertib, danusertib, tozasertib, LY3295668 ((2R,4R)-1-[(3-chloro-2-fluorophenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]pyridin-2-yl]methyl]-2-methylpiperidine-4-carboxylic acid), ENMD-2076 (6-(4-methylpiperazin-1-yl)-N-(5-methyl-1H-pyrazol-3-yl)-2-[(E)-2-phenylethenyl]pyrimidin-4-amine), TAK-901 (5-(3-ethylsulfonylphenyl)-3,8-dimethyl-N-(1-methylpiperidin-4-yl)-9H-pyrido[2,3-b]indole-7-carboxamide), TT-00420 (4-[9-(2-chlorophenyl)-6-methyl-2,4,5,8,12-pentazatricyclo[8.4.0.03,7]tetradeca-1(14),3,6,8,10,12-hexaen-13-yl]morpholine), AMG 900 (N-[4-[3-(2-aminopyrimidin-4-yl)pyridin-2-yl]oxyphenyl]-4-(4-methylthiophen-2-yl)phthalazin-1-amine), MLN8054 (4-[[9-chloro-7-(2,6-difluorophenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-yl]amino]benzoic acid), PF-03814735 (N-[2-[(1R,8S)-4-[[4-(cyclobutylamino)-5-(trifluoromethyl)pyrimidin-2-yl]amino]-11-azatricyclo[6.2.1.02,7]undeca-2(7),3,5-trien-11-yl]-2-oxoethyl]acetamide), SNS-314 (1-(3-chlorophenyl)-3-[5-[2-(thieno[3,2-d]pyrimidin-4-ylamino)ethyl]-1,3-thiazol-2-yl]urea), CYC116 (4-methyl-5-[2-(4-morpholin-4-ylanilino)pyrimidin-4-yl]-1,3-thiazol-2-amine), TAS-119, BI 811283, and TTP607.

[00154] AKT Inhibitors. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein the second compound is an AKT inhibitor.

[00155] Exemplary AKT inhibitors for use in the methods provided herein include, but are not limited to, afuresertib, capivasertib, ipatasertib, uprosertib, BAY1125976 (2-[4-(1-aminocyclobutyl)phenyl]-3-phenylimidazo[1,2-b]pyridazine-6-carboxamide), ARQ 092 (3-[3-[4-(1-aminocyclobutyl)phenyl]-5-phenylimidazo[4,5-b]pyridin-2-yl]pyridin-2-amine), MK2206 (8-[4-(1-aminocyclobutyl)phenyl]-9-phenyl-2H-[1,2,4]triazolo[3,4-f][1,6]naphthyridin-3-one), SR13668 (indolo[2,3-b]carbazole-2,10-dicarboxylic acid, 5,7-dihydro-6-methoxy-, 2,10-diethyl ester), ONC201 (11-benzyl-7-[(2-methylphenyl)methyl]-2,5,7,11-tetrazatricyclo[7.4.0.02,6]trideca-1(9),5-dien-8-one), ARQ 751 (N-(3-aminopropyl)-N-[(1R)-1-(3-anilino-7-chloro-4-oxoquinazolin-2-yl)but-3-ynyl]-3-chloro-2-fluorobenzamide), RX-0201, and LY2780301.

[00156] Arginase Inhibitors. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein the second compound is an Arginase inhibitor. Exemplary arginase inhibitors for use in the methods provided herein include, but are not limited to, numidargistat and CB 280.

[00157] CDK4/6 Inhibitors. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein

the second compound is an CDK4/6 inhibitor. The term "CDK 4/6" as used herein refers to cyclin dependent kinases ("CDK") 4 and 6, which are members of the mammalian serine/threonine protein kinases. The term "CDK 4/6 inhibitor" as used herein refers to a compound that is capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of CDK 4 and/or 6.

[00158] Exemplary CDK 4/6 inhibitors for use in the methods provided herein include, but are not limited to, abemaciclib, palbociclib, ribociclib, trilaciclib, and PF-06873600 ((pyrido[2,3-d]pyrimidin-7(8H)-one, 6-(difluoromethyl)-8-[(1R,2R)-2-hydroxy-2-methylcyclopentyl]-2-[[1-(methylsulfonyl)-4-piperidinyl]amino]).

[00159] ErbB Family Inhibitors. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein the second compound is an ErbB Family inhibitor. The term "ErbB family" as used herein refers to a member of a mammalian transmembrane protein tyrosine kinase family including: ErbB1 (EGFR HER1), ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4). The term "ErbB family inhibitor" as used herein refers to an agent, *e.g.*, a compound or antibody, that is capable of negatively modulating or inhibiting all or a portion of the activity of at least one member of the ErbB family. The modulation or inhibition of one or more ErbB tyrosine kinase may occur through modulating or inhibiting kinase enzymatic activity of one or more ErbB family member or by blocking homodimerization or heterodimerization of ErbB family members.

[00160] In one embodiment, the ErbB family inhibitor is an EGFR inhibitor, *e.g.*, an anti-EGFR antibody. Exemplary anti-EGFR antibodies for use in the methods provided herein include, but are not limited to, zalutumumab, nimotuzumab, matuzumab, necitumumab, panitumumab, and cetuximab.

[00161] In another embodiment the ErbB family inhibitor is a HER2 inhibitor, *e.g.*, an anti-HER2 antibody. Exemplary anti-HER-2 antibodies for use in the methods provided herein include, but are not limited to, pertuzumab, trastuzumab, and trastuzumab emtansine.

[00162] In yet another embodiment the ErbB family inhibitor is a HER3 inhibitor, *e.g.*, an anti-HER3 antibody, such as HMBD-001 (Hummingbird Bioscience).

[00163] In one embodiment, the ErbB family inhibitor is a combination of an anti-EGFR antibody and anti-HER2 antibody.

[00164] In one embodiment, the ErbB family inhibitor is an irreversible inhibitor. Exemplary irreversible ErbB family inhibitors for use in the methods provided herein include, but are not limited to, afatinib, dacomitinib, canertinib, poziotinib, AV 412 ((N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butyn-1-yl]-6-quinazolinyl]-2-propenamide)), PF 6274484 ((N-[4-[(3-chloro-4-fluorophenyl)amino]-7-methoxy-6-quinazolinyl]-2-propenamide), and HKI 357

((E)-N-[4-[3-chloro-4-[(3-fluorophenyl)methoxy]anilino]-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)but-2-enamide).

[00165] In one embodiment, the ErbB family inhibitor is a reversible inhibitor. Exemplary reversible ErbB family inhibitors for use in the methods provided herein include, but are not limited to erlotinib, gefitinib, sapitinib, varlitinib, tarloxotinib, TAK-285 (N-(2-(4-((3-chloro-4-(3-(trifluoromethyl)phenoxy)phenyl)amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl)-3-hydroxy-3-methylbutanamide), AEE788 ((S)-6-(4-((4-ethylpiperazin-1-yl)methyl)phenyl)-N-(1-phenylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine), BMS 599626 ((3S)-3-morpholinylmethyl-[4-[[1-[(3-fluorophenyl)methyl]-1H-indazol-5-yl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamate), and GW 583340 (N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[2-[(2-methylsulfonylethylamino)methyl]-1,3-thiazol-4-yl]quinazolin-4-amine).

[00166] ERK Inhibitors. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein the second compound is an ERK inhibitor.

[00167] Exemplary ERK inhibitors for use in the methods provided herein include, but are not limited to, ulixertinib, ravoxertinib, CC-90003 (N-[2-[[2-[(2-methoxy-5-methylpyridin-4-yl)amino]-5-(trifluoromethyl)pyrimidin-4-yl]amino]-5-methylphenyl]prop-2-enamide), LY3214996 (6,6-dimethyl-2-[2-[(2-methylpyrazol-3-yl)amino]pyrimidin-4-yl]-5-(2-morpholin-4-ylethyl)thieno[2,3-c]pyrrol-4-one), KO-947 (1,5,6,8-tetrahydro-6-(phenylmethyl)-3-(4-pyridinyl)-7H-pyrazolo[4,3-g]quinazolin-7-one), ASTX029, LTT462, and JSI-1187.

[00168] FAK Inhibitors. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein the second compound is an FAK inhibitor.

[00169] Exemplary FAK inhibitors for use in the methods provided herein include, but are not limited to, GSK2256098 (2-[[5-chloro-2-[(5-methyl-2-propan-2-ylpyrazol-3-yl)amino]pyridin-4-yl]amino]-N-methoxybenzamide), PF-00562271 (N-methyl-N-[3-[[[2-[(2-oxo-1,3-dihydroindol-5-yl)amino]-5-(trifluoromethyl)pyrimidin-4-yl]amino]methyl]pyridin-2-yl]methanesulfonamide), VS-4718 (2-[[2-(2-methoxy-4-morpholin-4-ylanilino)-5-(trifluoromethyl)pyridin-4-yl]amino]-N-methylbenzamide), and APG-2449.

[00170] FGFR Inhibitors. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein the second compound is an FGFR inhibitor.

[00171] Exemplary FGFR inhibitors for use in the methods provided herein include, but are not limited to, futibatinib, pemigatinib, ASP5878 (2-[4-[[5-[(2,6-difluoro-3,5-

dimethoxyphenyl)methoxy]pyrimidin-2-yl]amino]pyrazol-1-yl]ethanol), AZD4547 (N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-[(3S,5R)-3,5-dimethylpiperazin-1-yl]benzamide), debio 1347 ([5-amino-1-(2-methyl-3H-benzimidazol-5-yl)pyrazol-4-yl]-(1H-indol-2-yl)methanone), INCB062079, H3B-6527 (N-[2-[[6-[(2,6-dichloro-3,5-dimethoxyphenyl)carbamoyl-methylamino]pyrimidin-4-yl]amino]-5-(4-ethylpiperazin-1-yl)phenyl]prop-2-enamide), ICP-105, CPL304110, HMPL-453, and HGS1036.

[00172] Glutaminase Inhibitors. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein the second compound is a glutaminase inhibitor.

[00173] Exemplary glutaminase inhibitors for use in the methods provided herein include, but are not limited to, telaglenastat, IPN60090, and OP 330.

[00174] IGF-1R Inhibitors. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein the second compound is an IGF-1R inhibitor.

[00175] Exemplary IGF-1R inhibitors for use in the methods provided herein include, but are not limited to, cixutumumab, dalotuzumab, linsitinib, ganitumab, robatumumab, BMS-754807 ((2S)-1-[4-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]pyrrolo[2,1-f][1,2,4]triazin-2-yl]-N-(6-fluoropyridin-3-yl)-2-methylpyrrolidine-2-carboxamide), KW-2450 (N-[5-[[4-(2-hydroxyacetyl)piperazin-1-yl]methyl]-2-[(E)-2-(1H-indazol-3-yl)ethenyl]phenyl]-3-methylthiophene-2-carboxamide), PL225B, AVE1642, and BIIB022.

[00176] KIF18A Inhibitors. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein the second compound is a KIF18A inhibitor.

[00177] Exemplary KIF18A inhibitors for use in the methods provided herein include, but are not limited to, the inhibitors disclosed in US 2020/0239441, WO 2020/132649, WO 2020/132651, and WO 2020/132653, each of which is herewith incorporated by reference in its entirety.

[00178] MCL-1 Inhibitors. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein the second compound is an MCL-1 inhibitor.

[00179] Exemplary MEK inhibitors for use in the methods provided herein include, but are not limited to, murizatoclax, tapotoclax, AZD 5991 ((3aR)-5-chloro-2,11,12,24,27,29-hexahydro-2,3,24,33-tetramethyl-22H-9,4,8-(metheniminomethyno)-14,20:26,23-dimetheno-10H,20H-pyrazolo[4,3-l][2,15,22,18,19]benzoxadithiadiazacyclohexacosine-32-carboxylic acid), MIK 665 ((αR)-α-[[(5S)-5-[3-Chloro-2-methyl-4-[2-(4-methyl-1-piperazinyl)ethoxy]phenyl]-6-(4-

fluorophenyl)thieno[2,3-d]pyrimidin-4-yl]oxy]-2-[[2-(2-methoxyphenyl)-4-pyrimidinyl]methoxy]benzenepropanoic acid), and ABBV-467.

[00180] MEK Inhibitors. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein the second compound is an MEK inhibitor.

[00181] Exemplary MEK inhibitors for use in the methods provided herein include, but are not limited to, trametinib, cobimetinib, selumetinib, pimasertib, refametinib, PD-325901 (N-[(2R)-2,3-dihydroxypropoxy]-3,4-difluoro-2-(2-fluoro-4-iodoanilino)benzamide), AZD8330 (2-(2-fluoro-4-iodoanilino)-N-(2-hydroxyethoxy)-1,5-dimethyl-6-oxopyridine-3-carboxamide), GDC-0623 (5-(2-fluoro-4-iodoanilino)-N-(2-hydroxyethoxy)imidazo[1,5-a]pyridine-6-carboxamide), RO4987655 (3,4-difluoro-2-(2-fluoro-4-iodoanilino)-N-(2-hydroxyethoxy)-5-[(3-oxooxazinan-2-yl)methyl]benzamide), TAK-733 (3-[(2R)-2,3-dihydroxypropyl]-6-fluoro-5-(2-fluoro-4-iodoanilino)-8-methylpyrido[2,3-d]pyrimidine-4,7-dione), PD0325901 (N-[(2R)-2,3-dihydroxypropoxy]-3,4-difluoro-2-(2-fluoro-4-iodoanilino)benzamide), CI-1040 (2-(2-chloro-4-iodophenylamino)-N-(cyclopropylmethoxy)-3,4-difluorobenzamide), PD318088 (5-bromo-N-(2,3-dihydroxypropoxy)-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzamide), PD98059 (2-(2-amino-3-methoxyphenyl)-4H-chromen-4-one), PD334581 (N-[5-[3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl]-1,3,4-oxadiazol-2-yl]-4-morpholinecthanaminc), FCN-159, CS3006, HL-085, SHR 7390, and WX-554.

[00182] mTOR Inhibitors. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein the second compound is an mTOR inhibitor.

[00183] Exemplary mTOR inhibitors for use in the methods provided herein include, but are not limited to, everolimus, rapamycin, zotarolimus (ABT-578), ridaforolimus (deforolimus, MK-8669), sapanisertib, buparlisib, pictilisib, vistusertib, dactolisib, Torin-1 (1-(4-(4-propionylpiperazin-1-yl)-3-(trifluoromethyl)cyclohexyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one), GDC-0349 ((S)-1-ethyl-3-(4-(4-(3-methylmorpholino)-7-(oxetan-3-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)phenyl)urea), and VS-5584 (SB2343, (5-(8-methyl-2-rnorpholin-4-yl-9-propan-2-ylpurin-6-yl)pyrimidin-2-amine).

[00184] PD-1 Inhibitors. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein the second compound is a PD-1 inhibitor.

[00185] Exemplary PD-1 inhibitors for use in the methods provided herein include, but are not limited to, pembrolizumab, nivolumab, cemiplimab, spartalizumab (PDR001), camrelizumab (SHR1210), sintilimab (IBI308), tislelizumab (BGB-A317), toripalimab (JS 001), dostarlimab (TSR-042, WBP-285), INCMGA00012 (MGA012), AMP-224, AMP-514, and the anti-PD-1 antibody as

described in US 10,640,504 B2 (the "Anti-PD-1 Antibody A," column 66, line 56 to column 67, line 24 and column 67, lines 54-57), which is incorporated herein by reference.

[00186] PD-L1 Inhibitors. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein the second compound is a PD-L1 inhibitor.

[00187] Exemplary PD-L1 inhibitors for use in the methods provided herein include, but are not limited to, atezolizumab, avelumab, durvalumab, ZKAB001, TG-1501, SHR-1316, MSB2311, MDX-1105, KN035, IMC-001, HLX20, FAZ053, CS1001, CK-301, CBT-502, BGB-A333, BCD-135, and A167.

[00188] PI3K Inhibitors. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein the second compound is a PI3K inhibitor.

[00189] Exemplary PI3K inhibitors for use in the methods provided herein include, but are not limited to, idelalisib, copanlisib, duvelisib, alpelisib, taselisib, perifosine, buparlisib, umbralisib, pictilisib, dactolisib, voxtalisib, sonolisib, tenalisib, serabelisib, acalisib, CUDC-907 (N-hydroxy-2-[[2-(6-methoxypyridin-3-yl)-4-morpholin-4-ylthieno[3,2-d]pyrimidin-6-yl]methyl-methylamino]pyrimidine-5-carboxamide), ME-401 (N-[2-methyl-1-[2-(1-methylpiperidin-4-yl)phenyl]propan-2-yl]-4-(2-methylsulfonylbenzimidazol-1-yl)-6-morpholin-4-yl-1,3,5-triazin-2-amine), IPI-549 (2-amino-N-[(1S)-1-[8-[2-(1-methylpyrazol-4-yl)ethynyl]-1-oxo-2-phenylisoquinolin-3-yl]ethyl]pyrazolo[1,5-a]pyrimidine-3-carboxamide), SF1126 ((2S)-2-[[(2S)-3-carboxy-2-[[2-[[(2S)-5-(diaminomethylideneamino)-2-[[4-oxo-4-[[4-(4-oxo-8-phenylchromen-2-yl)morpholin-4-ium-4-yl]methoxy]butanoyl]amino]pentanoyl]amino]acetyl]amino]propanoyl]amino]-3-hydroxypropanoate), XL147 (N-[3-(2,1,3-benzothiadiazol-5-ylamino)quinoxalin-2-yl]-4-methylbenzenesulfonamide), GSK1059615 ((5Z)-5-[(4-pyridin-4-ylquinolin-6-yl)methylidene]-1,3-thiazolidine-2,4-dione), and AMG 319 (N-[(1S)-1-(7-fluoro-2-pyridin-2-ylquinolin-3-yl)ethyl]-7H-purin-6-amine).

[00190] Raf Kinase Inhibitors. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein the second compound is a Raf Kinase inhibitor. The term "RAF kinase" as used herein refers to a member of a mammalian serine/threonine kinases composed of three isoforms (C-Raf, B-Raf and A-Raf) and includes homodimers of each isoform as well as heterodimers between isoforms, *e.g.*, C-Raf/B-Raf heterodimers. The term "Raf kinase inhibitor" as used herein refers to a compound that is capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of one or more member of the Raf family kinases or is capable of disrupting Raf homodimer or heterodimer formation to inhibit activity.

[00191] Exemplary Raf kinase inhibitors include, but is not limited to, encorafenib, sorafenib, lifirafenib, vemurafenib, dabrafenib, PLX-8394 (N-(3-(5-(2-cyclopropylpyrimidin-5-yl)-3a,7a-dihydro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl)-3-fluoropyrrolidine-1-sulfonamide), Raf-709 (N-(2-methyl-5,-morpholino-6`-((tetrahydro-2H-pyran-4-yl)oxy)-[3,3'-bipyridin]-5-yl)-3-(trifluoromethyl)benzamide), LXH254 (N-(3-(2-(2-hydroxyethoxy)-6-morpholinopyridin-4-yl)-4-methylphenyl)-2-(trifluoromethyl)isonicotinamide), LY3009120 (1-(3,3-dimethylbutyl)-3-(2-fluoro-4-methyl-5-(7-methyl-2-(methylamino)pyrido[2,3-d]pyrimidin-6-yl)phenyl)urea), Tak-632 (N-(7-cyano-6-(4-fluoro-3-(2-(3-(trifluoromethyl)phenyl)acetamido)phenoxy)benzo[d]thiazol-2-yl)cyclopropanecarboxamide), CEP-32496 (1-(3-((6,7-dimethoxyquinazolin-4-yl)oxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea), CCT196969 (1-(3-(tert-butyl)-1-phenyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-((3-oxo-3,4-dihydropyrido[2,3-b]pyrazin-8-yl)oxy)phenyl)urea), and RO5126766 (N-[3-fluoro-4-[[4-methyl-2-oxo-7-(2-pyrimidinyloxy)-2H-1-benzopyran-3-yl]methyl]-2-pyridinyl]-N'-methyl-sulfamide).

[00192] SHP2 Inhibitors. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein the second compound is a SHP2 inhibitor.

[00193] Exemplary SHP2 inhibitors for use in the methods provided herein include, but are not limited to, SHP-099 (6-(4-amino-4-methylpiperidin-1-yl)-3-(2,3-dichlorophenyl)pyrazin-2-amine dihydrochloride), RMC-4550 ([3-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-6-(2,3-dichlorophenyl)-5-methylpyrazin-2-yl]methanol), TNO155, (3S,4S)-8-[6-amino-5-(2-amino-3-chloropyridin-4-yl)sulfanylpyrazin-2-yl]-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine), and vociprotafib (RMC-4630 - Revolution Medicine).

[00194] In another embodiment, exemplary SHP2 inhibitors for use in the methods provided herein include, but are not limited to, 3-[(1R,3R)-1-amino-3-methoxy-8-azaspiro[4.5]dec-8-yl]-6-(2,3-dichlorophenyl)-5-methyl-2-pyrazinemethanol (CAS 2172651-08-8), 3-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-6-[(2,3-dichlorophenyl)thio]-5-methyl-2-pyrazinemethanol (CAS 2172652-13-8), 3-[(3*S*,4*S*)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-6-[[3-chloro-2-(3-hydroxy-1-azetidinyl)-4-pyridinyl]thio]-5-methyl-2-pyrazinemethanol (CAS 2172652-38-7), and 6-[(2-amino-3-chloro-4-pyridinyl)thio]-3-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-5-methyl-2-pyrazinemethanol (CAS 2172652-48-9).

[00195] In another embodiment, exemplary SHP2 inhibitors for use in the methods provided herein include, but are not limited to, 1-[5-(2,3-dichlorophenyl)-6-methylimidazo[1,5-a]pyrazin-8-yl]-4-methyl-4-piperidinamine (CAS 2240981-75-1), (1R)-8-[5-(2,3-dichlorophenyl)-6-methylimidazo[1,5-a]pyrazin-8-yl]-8-azaspiro[4.5]decan-1-amine (CAS 2240981-78-4), (3S,4S)-8-[7-(2,3-

dichlorophenyl)-6-methylpyrazolo[1,5-a]pyrazin-4-yl]-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine (CAS 2240982-45-8), (3S,4S)-8-[7-[(2-amino-3-chloro-4-pyridinyl)thio]pyrazolo[1,5-a]pyrazin-4-yl]-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine (CAS 2240982-57-2), 4-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-7-(2,3-dichlorophenyl)-6-methyl-pyrazolo[1,5-a]pyrazine-2-methanol (CAS 2240982-69-6), 7-[(2-amino-3-chloro-4-pyridinyl)thio]-4-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-6-methyl-pyrazolo[1,5-a]pyrazine-2-methanol (CAS 2240982-73-2), and (3S,4S)-8-[7-[(2-amino-3-chloro-4-pyridinyl)thio]-6-methylpyrazolo[1,5-a]pyrazin-4-yl]-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine (CAS 2240982-77-6).

[00196] In another embodiment, exemplary SHP2 inhibitors for use in the methods provided herein include, but are not limited to 3-[(1R)-1-amino-8-azaspiro[4.5]dec-8-yl]-6-(2,3-dichlorophenyl)-5-hydroxy-2-pyridinemethanol (CAS 2238840-54-3), 3-[(1R)-1-amino-8-azaspiro[4.5]dec-8-yl]-6-[(2,3-dichlorophenyl)thio]-5-hydroxy-2-pyridinemethanol (CAS 2238840-56-5), 5-[(1R)-1-amino-8-azaspiro[4.5]dec-8-yl]-2-(2,3-dichlorophenyl)-3-pyridinol (CAS 2238840-58-7), 3-[(1R)-1-amino-8-azaspiro[4.5]dec-8-yl]-6-(2,3-dichlorophenyl)-5-methyl-2-pyridinemethanol (CAS 2238840-60-1), (1R)-8-[6-(2,3-dichlorophenyl)-5-methyl-3-pyridinyl]-8-azaspiro[4.5]decan-1-amine (CAS 2238840-62-3), 3-[(1R)-1-amino-8-azaspiro[4.5]dec-8-yl]-6-[(2,3-dichlorophenyl)thio]-5-methyl-2-pyridinemethanol (CAS 2238840-63-4), (1R)-8-[6-[(2,3-dichlorophenyl)thio]-5-methyl-3-pyridinyl]-8-azaspiro[4.5]decan-1-amine (CAS 2238840-64-5), 5-(4-amino-4-methyl-1-piperidinyl)-2-[(2,3-dichlorophenyl)thio]-3-pyridinol (CAS 2238840-65-6), 5-[(1R)-1-amino-8-azaspiro[4.5]dec-8-yl]-2-[(2,3-dichlorophenyl)thio]-3-pyridinol (CAS 2238840-66-7), 6-[(2-amino-3-chloro-4-pyridinyl)thio]-3-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-5-hydroxy-2-pyridinemethanol (CAS 2238840-67-8), 3-(4-amino-4-methyl-1-piperidinyl)-6-(2,3-dichlorophenyl)-5-hydroxy-2-pyridinemethanol (CAS 2238840-68-9), 3-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-6-(2,3-dichlorophenyl)-5-methyl-2-pyridinemethanol (CAS 2238840-69-0), 6-[(2-amino-3-chloro-4-pyridinyl)thio]-3-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-5-methyl-2-pyridinemethanol (CAS 2238840-70-3), 3-(4-amino-4-methyl-1-piperidinyl)-6-(2,3-dichlorophenyl)-5-methyl-2-pyridinemethanol (CAS 2238840-71-4), 6-[(2-amino-3-chloro-4-pyridinyl)thio]-3-(4-amino-4-methyl-1-piperidinyl)-2-pyridinemethanol (CAS 2238840-72-5), 5-[(2-amino-3-chloro-4-pyridinyl)thio]-2-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-6-methyl-3-pyridinemethanol (CAS 2238840-73-6), 2-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-5-(2,3-dichlorophenyl)-6-methyl-3-pyridinemethanol (CAS 2238840-74-7), 3-[(3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]dec-8-yl]-6-(2,3-dichlorophenyl)-5-hydroxy-2-pyridinemethanol (CAS 2238840-75-8), and 2-[(2-amino-3-chloro-4-pyridyl)sulfanyl]-5-[(3S,4S)-4-amino-3- methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-6-(hydroxymethyl)pyridin-3-ol.

[00197] In one embodiment, the SHP inhibitor for use in the methods provided herein is 3-[(1R)-1-amino-8-azaspiro[4.5]dec-8-yl]-6-[(2,3-dichlorophenyl)thio]-5-hydroxy-2-pyridinemethanol (CAS

2238840-56-5). In one embodiment, the SHP2 inhibitor for use in the methods provided herein is an inhibitor disclosed in US 10,590,090 B2, US 2020/017517 A1, US 2020/017511 A1, or WO 2019/075265 A1.

[00198] SOS1 Inhibitors. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein the second compound is a SOS1 inhibitor.

[00199] Exemplary SOS1 inhibitors for use in the methods provided herein include, but are not limited to, BI 3406 (N-[(1R)-1-[3-amino-5-(trifluoromethyl)phenyl]ethyl]-7-methoxy-2-methyl-6-[(3S)-oxolan-3-yl]oxyquinazolin-4-amine), and BI 1701963.

[00200] Src Kinase Inhibitors. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein the second compound is a Src Kinase inhibitor. The term "Src kinase" as used herein refers to a member of a mammalian nonreceptor tyrosine kinase family including: Src, Yes, Fyn, and Fgr (SrcA subfamily); Lck, Hck, Blk, and Lyn (SrcB subfamily), and Frk subfamily. The term "Src kinase inhibitor" as used herein refers to a compound that is capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of one or more member of the Src kinases.

[00201] Exemplary Src kinase inhibitors for use in the methods provided herein include, but are not limited to, dasatinib, ponatinib, vandetanib, bosutinib, saracatinib, KX2-391 (N-benzyl-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide), SU6656 ((Z)-N,N-dimethyl-2-oxo-3-((4,5,6,7-tetrahydro-1H-indol-2-yl)methylene)indoline-5-sulfonamide), PP 1 (1-(tert-butyl)-3-(p-tolyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine), WH-4-023 (2,6-dimethylphenyl(2,4-dimethoxyphenyl)(2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)carbamate), and KX-01 (N-benzyl-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide).

[00202] Chemotherapeutic Agents. In some cases, the compounds of the disclosure can be administered simultaneously, separately, or sequentially with an effective amount of a second compound, wherein the second compound is one or more chemotherapeutic agents.

[00203] Exemplary chemotherapeutic agents for use in the methods provided herein include, but are not limited to, leucovorin calcium (calcium folinate), 5-fluorouracil, irinotecan, oxaliplatin, cisplatin, carboplatin, pemetrexed, docetaxel, paclitaxel, gemcitabine, vinorelbine, chlorambucil, cyclophosphamide, and methotrexate.

GENERAL SYNTHETIC PROCEDURES

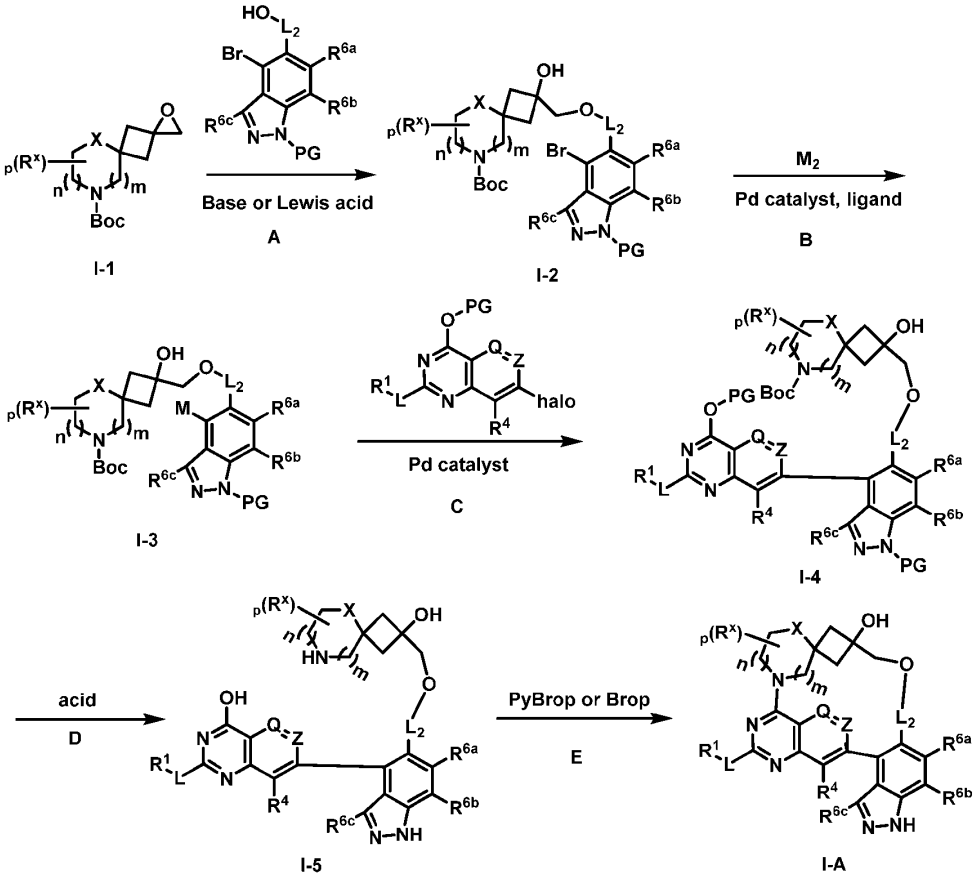
[00204] The compounds provided herein can be synthesized according to the procedures described in this and the following sections. The synthetic methods described herein are merely exemplary, and

the compounds disclosed herein may also be synthesized by alternate routes utilizing alternative synthetic strategies, as appreciated by persons of ordinary skill in the art. It should be appreciated that the general synthetic procedures and specific examples provided herein are illustrative only and should not be construed as limiting the scope of the present disclosure in any manner.

[00205] Generally, the compounds of Formula (**I**) can be synthesized according to the following schemes. Variables used in the following schemes are the variables as defined for Formula (**I**), unless otherwise noted. All starting materials are either commercially available, for example, from Sigma-Aldrich, Combi-Blocks, Strem, Oakwood, TCI America, Fisher, Arcos, Alfa Aesar or known in the art and may be synthesized by employing known procedures using ordinary skill. Starting materials may also be synthesized via the procedures disclosed herein. Suitable reaction conditions, such as solvent, reaction temperature, and reagents, for the Schemes discussed in this section, may be found in the examples provided herein.

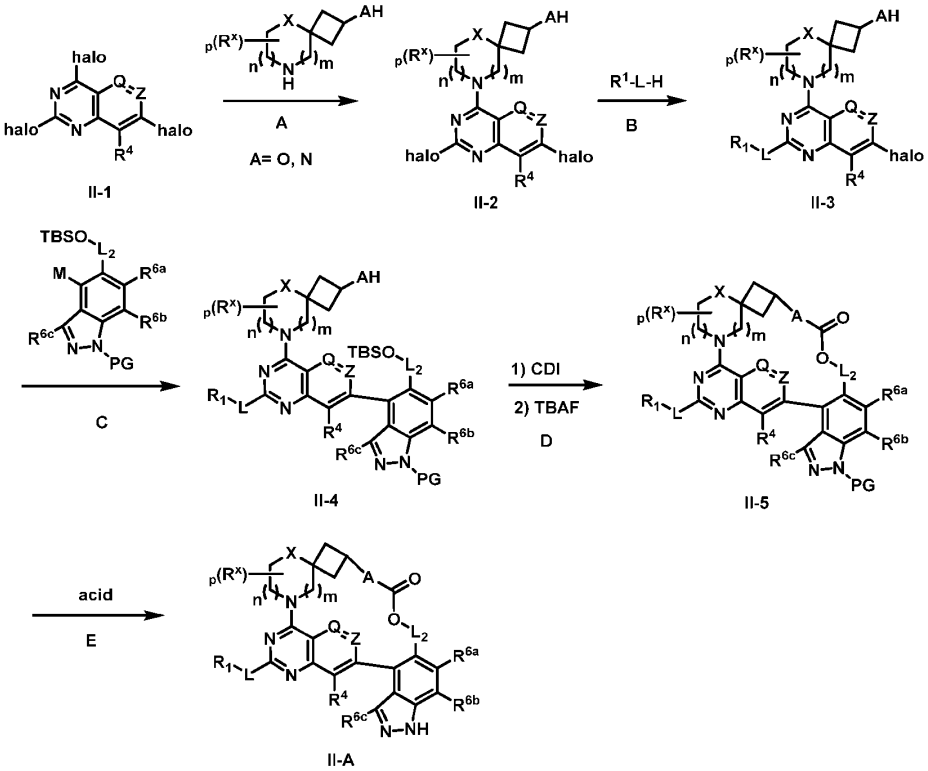
[00206] In general, the compounds of Formula (**I**) can be synthesized according to **Schemes I-IV** as shown below:

Scheme I



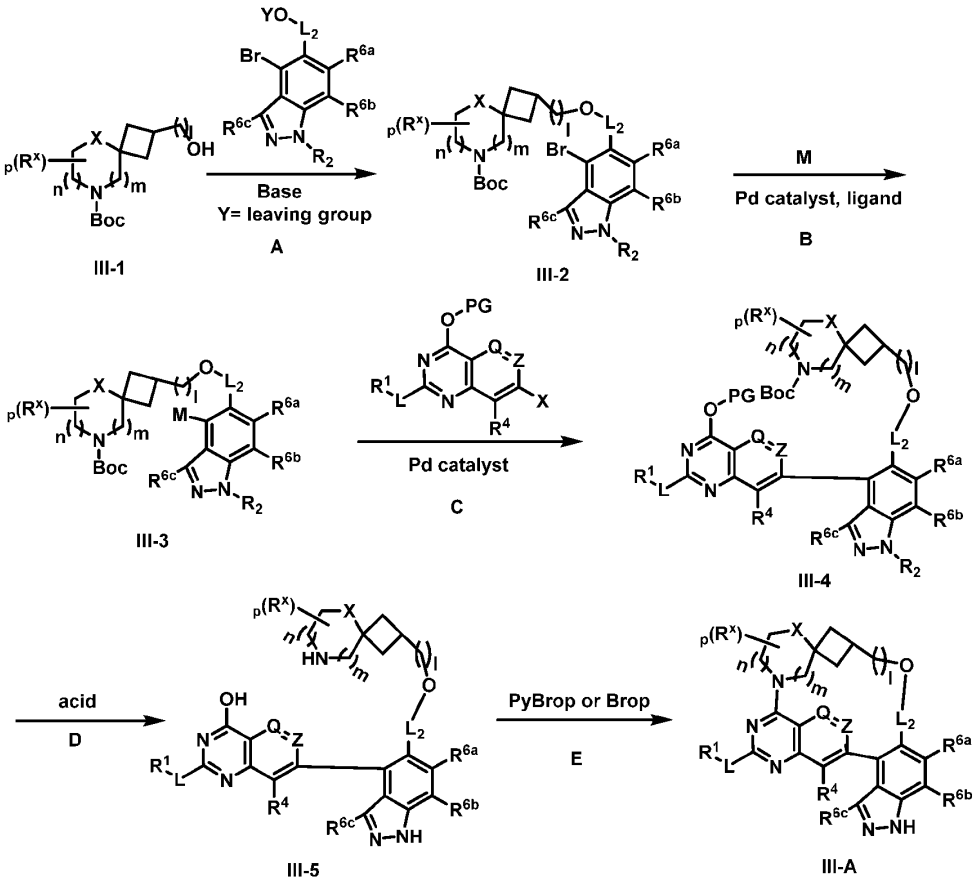
[00207] Compounds of Formula (**I-A**) can be prepared according to Scheme **I**. In step **A**, compound (**I-1**) reacts with an alcohol under strong base such as NaH or Lewis acid in a solvent such as THF/DMF or toluene to give compound (**I-2**). In step **B**, compound (**I-2**) undergoes borylation with a reagent, such as $\mathbf{M_2}$ (e.g., bis(pinacolate)diboron) under Pd catalyzed conditions to give compound (**I-3**). In step **C**, compound (**I-3**) is coupled with a bromide on a pyridopyrimidine to give compound (**I-4**). This coupling reaction proceeds in a solvent or mixture of solvents such as 2-Me THF and water, and a catalyst such as cataCXium A Pd G3 (CAS No. 1651823-59-4), with or without a base such as potassium phosphate. In step **D**, compound (**I-4**) is hydrolyzed to give compound (**I-5**) using a reagent such as HCl in dioxane or TFA. In step **E**, compound (**I-5**) is cyclized under conditions such as PyBrop or Brop and DIPEA in a solvent such as CH_3CN and DMSO to give compounds of Formula (**I-A**).

Scheme II



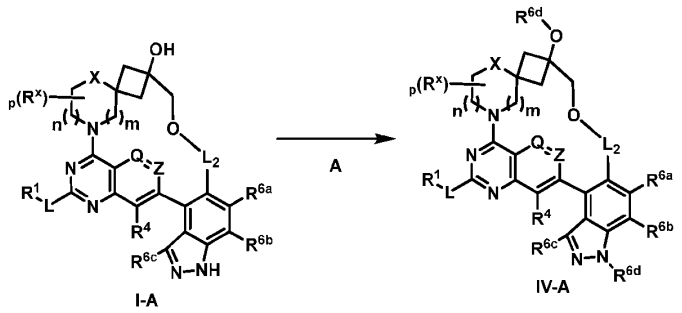
[00208] Compounds of Formula (**II-A**) can also be prepared according to Scheme **II**. In step **A**, compound (**II-1**) undergoes S_NAr reaction with an optionally substituted cyclic amine or aliphatic amine bearing an alcohol or protected amine in a solvent such as acetonitrile and in the presence of a base such as Hunig's base to give compound (**II-2**). In step **B**, compound (**II-2**) undergoes S_NAr reaction with a nucleophile having the formula R^1-L-H in a solvent such as acetonitrile, in the presence of a base such as Hunig's base to give compound (**II-3**). In step **C**, compound (**II-3**) is coupled with an organometallic reagent or a boronic acid (ester) attached to a aryl or hetereoaryl bearing a terminal TBS protected alcohol to give compound (**II-4**). This coupling reaction proceeds in a solvent or mixture of solvents such as 2-Me THF and water, and a catalyst such as cataCXium A Pd G3 (CAS No. 1651823-59-4), with or without a base such as potassium phosphate. In step **D**, compound (**II-4**) is reacted with CDI, followed by treated with a desilyated regent such as TBAF in solvent such as THF to give compounds of Formula (**II-5**). In step **E**, compound (**II-5**) is hydrolyzed to give compound (**II-A**) using a reagent such as HCl in dioxane or TFA.

Scheme III



[00209] Compounds of Formula (**III-A**) can be prepared according to Scheme **III**. In step **A**, compound (**III**-1) reacts with a mesylate or tosylate under strong base such as NaH or KO^{t}Bu in a solvent such as THF/DMF to give compound (**III-2**). In step **B**, compound (**III-2**) undergoes borylation with a reagent such as bis(pinacolate)diboron under Pd catalyzed conditions to give compound (**III-3**). In step **C**, compound (**III-3**) is coupled with a bromide on a pyridopyrimidine to give compound (**III-4**). This coupling reaction proceeds in a solvent or mixture of solvents such as 2-Me THF and water, and a catalyst such as cataCXium A Pd G3 (CAS No. 1651823-59-4), with or without a base such as potassium phosphate. In step **D**, compound (**III-4**) is hydrolyzed to give compound (**III-5**) using a reagent such as HCl in dioxane or TFA. In step **E**, compound (**III-5**) is cyclized under conditions such as PyBrop or Brop and DIPEA in a solvent such as CH_3CN and DMSO to give compounds of Formula (**III-A**).

Scheme IV



[00210] Compounds of Formula (**IV-A**) can also be prepared according to Scheme **IV**. In step **A**, compound (**I-A**) undergoes an acylation reaction with an acyl chloride in a solvent such as DCM, THF or acetonitrile and in the presence of a base such as Hünig's base or triethylamine to produce **IV-A**. Alternatively, compound (**I-A**) can undergo an acylation reaction upon treatment with an acid anhydride or a chloroformate in a solvent such DCM, THF or acetonitrile in the presence of a catalyst such as DMAP and a base such as Hünig's base or triethylamine to produce **IV-A**.

[00211] As can be appreciated by the skilled artisan, the above synthetic scheme and representative examples are not intended to comprise a comprehensive list of all means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps described above may be performed in an alternate sequence or order to give the desired compounds.

[00212] Purification methods for the compounds described herein are known in the art and include, for example, crystallization, chromatography (for example, liquid, gas phase, and supercritical fluid), filtration, sublimation, lyophilization, extraction, distillation, trituration, and reverse phase HPLC.

[00213] The following examples are given for the purpose of illustrating various embodiments of the disclosure and are not meant to limit the present disclosure in any fashion. One skilled in the art will appreciate readily that the present disclosure is well-adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those objects, ends, and advantages inherent herein. Changes therein and other uses which are encompassed within the spirit of the disclosure as defined by the scope of the claims will occur to those skilled in the art.

EXAMPLES

[00214] This section provides specific examples of compounds of Formula (**I**) and methods of making the same.

List of Abbreviations

Ac	acetyl

AcCl	acetyl chloride
AcOH	acetic acid
aq or aq.	aqueous
Bn	benzyl
B_2Pin_2	bis(pinacolato)diboron
BOC or Boc	*tert*-butyloxycarbonyl
BroP	bromotris(dimethylamino)phosphonium hexafluorophosphate
Burgess reagent	methyl *N*-(triethylammoniumsulfonyl)carbamate
BuOH	*n*-butanol
cataCXium A Pd G3 (CAS No. 1651823-59-4)	[(di(1-adamantyl)-butylphosphine)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate
Cbz	benzyloxycarbonyl
CbzCl	benzyl chloroformate
CDI	carbonyldiimidazole
COD or cod	1,5-cyclooctadiene
DABCO	1,4-diazabicyclo[2.2. 2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DHP	3,4-dihydro-2*H*-pyran
DIPEA	diisopropylethylamine
DMA	*N,N*-dimethylacetamide
DMAP	*N,N*-dimethylpyridin-4-amine
DMC	dimethyl carbonate
DMF	*N,N*-dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMSO	dimethyl sulfoxide
Dppf, DPPF or dppf	1,1'-bis(diphenylphosphino)ferrocene
Dtbbpy	4,4'-di-*tert*-butyl-2,2'-dipyridyl
eq or eq. or equiv.	equivalent
ESI or ES	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate

EtOH	ethanol
g or gr	gram(s)
h	hour(s)
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HBpin	4,4,5,5-tetramethyl-1,3,2-dioxaborolane
HMPA	hexamethylphosphoramide
HOAc	acetic acid
HPLC	high pressure liquid chromatography
IBX	2-iodoxybenzoic acid
iPr	*iso*-propyl
iPr_2NET or DIPEA	*N*-ethyl diisopropylamine (Hünig's base)
KOAc	potassium acetate
KOtBu	potassium *tert*-butoxide
LAH	lithium aluminum hydride
LC MS, LCMS, LC-MS or LC/MS	liquid chromatography mass spectroscopy
LHMDS or LiHMDS	lithium hexamethyldisilazide
m/z	mass divided by charge
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligrams
min	minutes
mL	milliliters
MS	mass spectra
MTBE	methyl *tert*-butyl ether
NaHMDS	sodium hexamethylsilazide
NFSI	*N*-fluorobenzenesulfonimide
NIS	*N*-iodosuccinimide
NMO	4-methylmorpholine 4-oxide
NMP	N-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance

PCy_3 Pd G2	Chloro[(tricyclohexylphospine)-2-(2'-aminobiphenyl)]palladium (II)
Pd-diAc	palladium diacetate
$Pd(dppf)Cl_2 \cdot DCM$, $Pd(dppf)Cl_2$	[1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane
$Pd(dtbpf)Cl_2$	[1,1′-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II)
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
PEPPSI-IPr	[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
Ph	phenyl
PhMe	toluene
Pin	pinacolato
Piv	pivaloyl
PivCl	pivaloyl chloride
PMB	4-methoxybenzyl
PPNCI	bis(triphenylphosphoranylidene)ammonium chloride
PTSA or *p*TsOH	*p*-toluenesulfonic acid
Rbf or rbf	round-bottomed flask
RP-HPLC	reverse phase high pressure liquid chromatography
RT or rt or r.t.	room temperature
sat. or satd.	saturated
SFC	supercritical fluid chromatography
TBACl	*tetra-n*-butylammonium chloride
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBDPSCl	*tert*-butyldiphenylsilyl chloride
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
tBu	*tert*-butyl
TC	thiophene-2-carboxylate
TEA or Et_3N	triethylamine
temp	temperature
Tf	trifluoromethylsulfonyl

TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TIPSCl	triisopropylsilyl chloride
TLC	thin layer chromatography
UV	ultraviolet
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl
$Y(OTf)_3$	yttrium (III) triflate

[00215] Provided in this section are descriptions of the general analytical and purification methods used to prepare the specific examples provided herein.

[00216] Chromatography: Unless otherwise indicated, product-containing residues were purified by passing the material or concentrate through (a) Biotage High Capacity D column or (b) ISCO RediSep Gold High Performance column or (c) ISCO RediSep Rf HP C18 Gold column or (d) Biotage Isolute SCX-2 column; and eluting the product from the column with a solvent gradient as indicated.

[00217] Preparative HPLC Method: Where indicated, the compounds described herein were purified via reversed phase HPLC using Waters FractionLynx or Gilson semi-preparative HPLC-MS system using one of the following two HPLC columns: (a) Phenomenex Gemini column (5 micron, C18, 150 x 30 mm) or (b) Waters X-select CSH column (5 micron, C18, 100 x 30 mm). A typical run through the instrument included: eluting at 45 mL/min with a linear gradient of 10% (v/v) to 100% MeCN (0.1% v/v formic acid) in water (0.1% formic acid) over 10 minutes. Conditions can be varied to achieve improved separations.

[00218] Proton NMR Spectra: Unless otherwise indicated, all ^{1}H NMR spectra were collected on a Bruker NMR instrument at 300, 400 or 500 MHz. All observed protons are reported as parts-per-million (ppm) downfield from tetramethylsilane (TMS) using the internal solvent peak as reference. Some ^{1}H signals may be missing due to exchange with D from MeOD, or due to signal suppression.

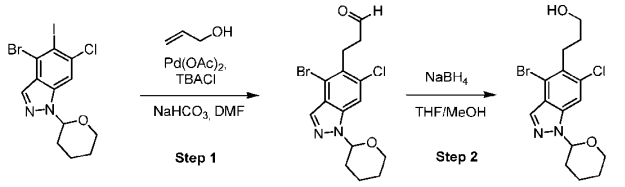
[00219] Mass Spectra (MS): Unless otherwise indicated, all mass spectral data for starting materials, intermediates and/or exemplary compounds are reported as mass/charge (m/z), having an $[M+H]^+$ molecular ion. The molecular ion reported was obtained by electrospray detection method (commonly referred to as an ESI MS) utilizing a Waters Acquity UPLC/MS system. Compounds having an isotopic atom, such as bromine and the like, are generally reported according to the detected isotopic pattern, as appreciated by those skilled in the art.

[00220] Fluorine NMR Spectra: Unless otherwise indicated, all ^{19}F NMR spectra were collected on a Bruker NMR instrument at 300, 400 or 500 MHz under ^{1}H-decoupled conditions. All observed fluorines are reported as parts-per-million (ppm).

[00221] Provided in this section is the synthesis of various intermediates used to prepare compounds of Formula (I). All starting materials are either commercially available from Sigma-Aldrich, Combi-Blocks, Enamine, PharmaCore, PharmaBlock, Synnovator, Chemscene, AA blocks, Oakwood or Ambeed, or similar vendors, unless otherwise noted, or known in the art and may be synthesized by employing known procedures using ordinary skill.

SECTION 1: Synthesis of Intermediates

Intermediate A: 3-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propan-1-ol.

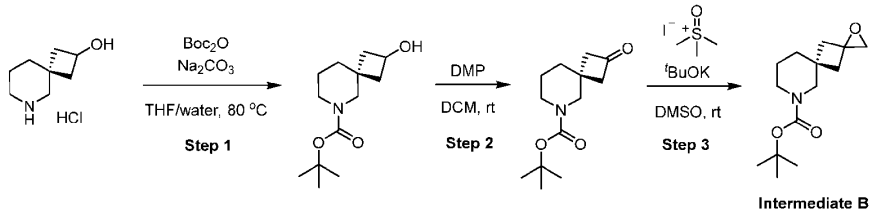


Intermediate A

[00222] Step 1: 3-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propanal. To a 40 mL vial was charged with 4-bromo-6-chloro-5-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (3.00 g, 6.80 mmol, Lab Network), sodium bicarbonate (1.43 g, 17.0 mmol), TBACl (1.95 g, 6.82 mmol), and *N*,*N*-dimethylformamide (14 mL). The solution was degassed by nitrogen bubbling for 10 min. Then palladium(II) acetate (77 mg, 0.34 mmol) and allyl alcohol (0.7 mL, 10 mmol) were added at 50 °C. The reaction mixture was stirred at 50 °C for 18 h. After cooling to room temperature, the reaction was diluted with saturated aqueous ammonium chloride and extracted with EtOAc. The organic layer was washed with saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0–50% 3:1 EtOAc/EtOH in heptane, to provide 3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propanal (2.12 g, 5.70 mmol, 84% yield). *m/z* (ESI): 371.0 $(M+H)^+$.

[00223] Step 2: 3-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propan-1-ol. To a 100-mL round-bottom flask was added 3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propanal (1.06 g, 2.86 mmol) in tetrahydrofuran (5 mL)/methanol (5 mL). The reaction mixture was cooled to 0 °C. Then, sodium borohydride (0.11 g, 2.86 mmol) was slowly added in portion. The reaction mixture was stirred at 0 °C for 30 minutes, then was slowly quenched with saturated NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide 3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propan-1-ol (1.03 g, 2.76 mmol, 97% yield). *m/z* (ESI): 289.0 $(M\text{-}THP+H)^+$.

Intermediate B: *tert*-Butyl 1-oxa-7-azadispiro[2.1.5^5.1^3]undecane-7-carboxylate.



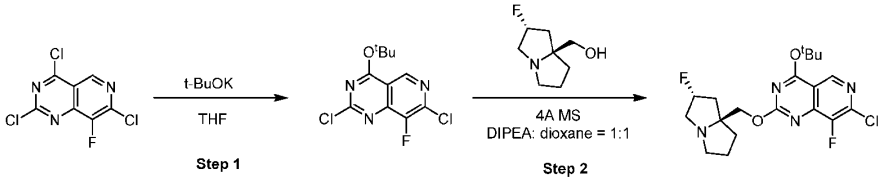
[00224] Step 1: *tert*-Butyl 2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate. A 250-mL round-bottom flask was charged with 6-azaspiro[3.5] nonan-2-olhydrochloride (15 g, 84 mmol, Ambeed, Inc.), di-*tert*-butyl dicarbonate (22.11 g, 101 mmol) and sodium carbonate (17.90 g, 169 mmol) in tetrahydrofuran (61 mL)/water (23 mL). The reaction mixture was stirred at 80 °C for 2 h. After cooling to room temperature, saturated aqueous sodium chloride was added and the reaction was extracted with EtOAc, dried over sodium sulfate, filtered, and concentrated to give *tert*-butyl 2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (20.4 g, 84 mmol, 100% yield) as crude product which was used in the subsequent step without further purification. *m/z* (ESI): 186.1 $(M+H-^tBu)^+$.

[00225] Step 2: *tert*-Butyl 2-oxo-6-azaspiro[3.5]nonane-6-carboxylate. A 250-mL round-bottom flask was charged with *tert*-butyl 2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (20.4 g, 84 mmol) and dichloromethane (150 mL). The reaction mixture was cooled to 0 °C and Dess-Martin periodinane (38.7 g, 91 mmol) was added slowly. The reaction mixture was allowed to stir at room temperature for 18 h, poured into an aqueous sodium thiosulfate solution (10%) and filtered. The aqueous phase was extracted with DCM and the combined organic phases were dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 0–80% EtOAc in heptane, to give *tert*-butyl 2-oxo-6-azaspiro[3.5]nonane-6-carboxylate (14.2 g, 59.3 mmol, 71% yield). *m/z* (ESI): 184.2 $(M+H-^tBu)^+$. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 3.46 (s, 2H), 3.4 – 3.4 (m, 2H), 2.8 – 2.9 (m, 2H), 2.6 – 2.8 (m, 2H), 1.7 – 1.8 (m, 2H), 1.6 – 1.6 (m, 2H), 1.46 (s, 9H).

[00226] Step 3: *tert*-Butyl 1-oxa-7-azadispiro[2.1.5^5.1^3]undecane-7-carboxylate. To a 150-mL round-bottom flask was charged with trimethylsulfoxonium iodide (3.73 g, 17.0 mmol) in dimethyl sulfoxide (22 mL). Potassium *tert*-butoxide (2.00 g, 17.8 mmol) was added and the reaction was stirred at 0 °C to room temperature over 1 h. Then, *tert*-butyl 2-oxo-6-azaspiro[3.5]nonane-6-carboxylate (2.03 g, 8.48 mmol) in *N,N*-dimethylformamide (2 mL) was added dropwise. The reaction mixture was stirred at room temperature for 1 h, then diluted with sat. $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on

silica gel, eluting with a gradient of 0–40% EtOAc in hexanes, to provide *tert*-butyl 1-oxa-7-azadispiro[2.1.5^5.1^3]undecane-7-carboxylate (0.39 g, 1.5 mmol, 18% yield). *m/z* (ESI): 276.1 $(M+Na)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.41 (s, 2H), 3.3 – 3.4 (m, 2H), 2.7 – 2.8 (m, 2H), 2.0 – 2.3, (m, 4H), 1.6 – 1.8 (m, 2H), 1.5 – 1.6 (m, 2H), 1.4 – 1.5 (m, 9H). Mixture of two diastereomers.

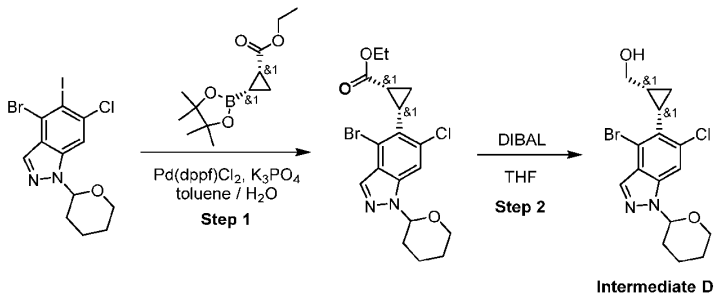
Intermediate C: 4-(*tert*-Butoxy)-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)yl)methoxy)pyrido[4,3-*d*]pyrimidine.



[00227] Step 1: 4-(*tert*-Butoxy)-2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidine. To a solution of 2,4,7-trichloro-8-fluoropyrido[4,3-*d*]pyrimidine (50.0 g, 198 mmol) in tetrahydrofuran (1.5 L) was added *t*-BuOK (1 M in THF, 190 mL, 190 mmol) dropwise at -60 °C and the reaction mixture was stirred at -60 °C for 2 h. The mixture was diluted with EtOAc and water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was triturated with petroleum ether at room temperature for 1 h. The suspension was filtered, and the cake was concentrated under reduced pressure to give 4-(*tert*-butoxy)-2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidine (30 g, 103 mmol, 54% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.08 (s, 1 H), 1.74 (s, 9 H).

[00228] Step 2: 4-(*tert*-Butoxy)-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)yl)methoxy)pyrido[4,3-*d*]pyrimidine. To a solution of 4-(*tert*-butoxy)-2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidine (50.0 g, 172 mmol) and 4Å MS (10 g) in 1,4-dioxane (1 L) was added ((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol (30.2 g, 190 mmol) and DIPEA (60.0 g, 431 mmol) in sequence. Then the mixture was stirred at 80 °C for 5 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc and water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was triturated with MTBE at room temperature for 1 h. The suspension was filtered, and the cake was concentrated under reduced pressure to give 4-(*tert*-butoxy)-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)yl)methoxy)pyrido[4,3-*d*]pyrimidine (40 g, 97 mmol, 56% yield). *m/z* (ESI): 413.2/415.2 $(M+H)^+$.

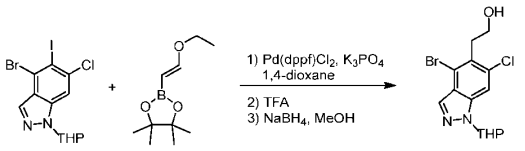
Intermediate D: ***rac*-((1*R*,2*S*)-2-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methanol**.



[00229] Step 1. *rac*-Ethyl (1*R*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropane-1-carboxylate. A vial was charged with 4-bromo-6-chloro-5-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (0.75 g, 1.70 mmol, Lab Network), *rac*-ethyl (1*R*,2*S*)-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropane-1-carboxylate (0.49 mL, 2.04 mmol, Enamine), 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride (0.12 g, 0.17 mmol), potassium phosphate tribasic (1.26 g, 5.95 mmol) in toluene (5 mL) and water (1 mL). The reaction mixture was flushed with nitrogen and heated at 100 °C for 16 h. After cooling to room temperature, the reaction mixture was concentrated and the residue purified by column chromatography on silica gel, eluting with a gradient of 0–60% EtOAc/heptane to provide *rac*-ethyl (1*R*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropane-1-carboxylate (0.24 g, 0.56 mmol, 33% yield). *m/z* (ESI): 448.8 $(M+Na)^+$.

[00230] Step 2. *rac*-((1*R*,2*S*)-2-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methanol. To a stirred solution of *rac*-ethyl (1*R*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropane-1-carboxylate (0.95 g, 2.23 mmol) in tetrahydrofuran (6 mL) at -78 °C was added diisobutylaluminum hydride solution (1.0 M in DCM, 5.6 mL, 5.6 mmol) slowly. The resulting mixture was allowed to warm to room temperature and stirred for another 30 minutes. The reaction mixture was poured slowly into Rochelle's salt aqueous solution in an ice bath and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 0–60% EtOAc/heptane to afford *rac*-((1*R*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methanol (0.69 g, 1.78 mmol, 80% yield). *m/z* (ESI): 384.8 $(M+H)^+$.

Intermediate E: **2-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethan-1-ol.**

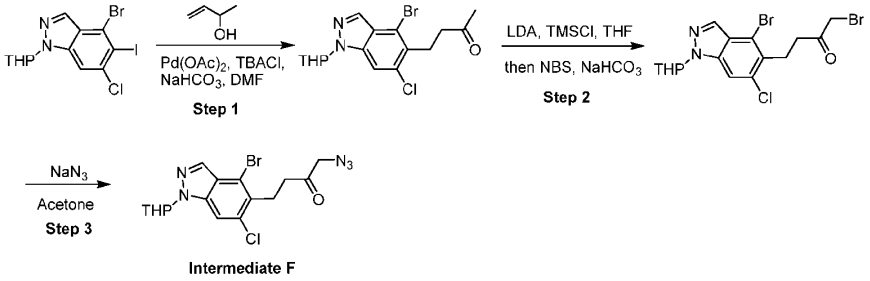


Intermediate E

[00231] A vial was charged with (*E*)-1-ethoxyethene-2-boronic acid pinacol ester (2.02 g, 10.2 mmol, Aurum Pharmatech), 4-bromo-6-chloro-5-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (3.00 g, 6.80 mmol, LabNetwork), tripotassium phosphate (5.05 g, 23.8 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride (0.50 g, 0.68 mmol), water (4 mL) and 1,4-dioxane (19 mL). The reaction mixture was heated to 100 °C for 1.5 h. After cooling to room temperature, the crude material was diluted with EtOAc and saturated aqueous sodium bicarbonate. The aqueous layer was extracted with EtOAc, and the combined organics were dried (Na_2SO_4) and concentrated. This crude product was then diluted with 1,4-dioxane (18 mL) and water (1 mL) and to it was added trifluoroacetic acid (7.8 mL, 102 mmol) dropwise. The reaction mixture was stirred at 40 °C for 6 h. After cooling to room temperature, the reaction mixture was concentrated and the residue was purified by column chromatography on silica gel, eluting with 0–100% (3:1 EtOAc:EtOH + 2% triethylamine) in heptane, to provide 2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)acetaldehyde (2.40 g, 6.71 mmol, 99% yield), which was treated with triethylamine and filtered to neutralize the remaining TFA. *m/z* (ESI): 357.0 $(M+H)^+$.

[00232] To a 250 mL round-bottom flask was charged with the above aldehyde (2.40 g, 6.71 mmol) and ethanol (70 mL). The reaction mixture was cooled to 0 °C and sodium borohydride (0.53 g, 14 mmol) was added portionwise. The solution was allowed to warm to room temperature with stirring for 30 minutes. The reaction was then carefully quenched by the addition of methanol, water, and saturated aqueous ammonium chloride. The resulting solution was extracted with EtOAc. The combined organics were dried (Na_2SO_4) and concentrated. The residue was purified by reverse phase chromatography using a C18 column, eluting with 0–100% acetonitrile + 0.1% TFA in water + 0.1% TFA, to provide 2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethan-1-ol (0.20 g, 0.56 mmol, 8% yield). *m/z* (ESI): 359.0 $(M+H)^-$.

Intermediate F: 1-Azido-4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one.



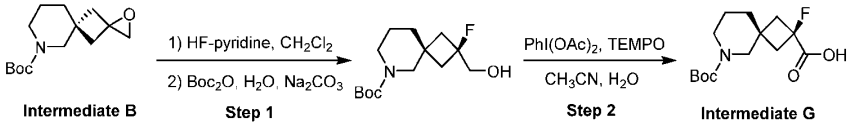
[00233] Step 1. 4-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one. To a 40 mL vial was charged with 4-bromo-6-chloro-5-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (2.04 g, 4.62 mmol, Pharmablock, Inc.), sodium bicarbonate (0.97 g, 11.6 mmol), TBACl (1.28 g, 4.62 mmol), palladium(II) acetate (52 mg, 0.23 mmol), 3-buten-2-ol (0.6 mL, 6.9 mmol) and *N*,*N*-dimethylformamide (10 mL). The reaction mixture was heated at 65 °C for 68 h. After cooling to room temperature, the reaction was diluted with saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate, filtered, and concentrated. The crude material was purified by column chromatography on silica gel, eluting with 0–50% EtOAc in heptane to provide 4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one (1.42 g, 3.68 mmol, 80% yield). *m/z* (ESI): 406.9/408.9 $(M+Na)^+$.

[00234] Step 2. 1-Bromo-4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one. To a 250-mL round-bottom flask was charged with lithium diisopropylamide (1 M solution in THF/hexanes, 4.1 mL, 4.1 mmol) in anhydrous tetrahydrofuran (35 mL). The mixture was cooled to 78 °C and 4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one (1.33 g, 3.45 mmol) in 8 mL anhydrous THF was added dropwise under nitrogen. The reaction mixture was stirred at -78 °C for 30 minutes. Chlorotrimethylsilane (0.70 mL, 5.5 mmol) was then added dropwise at -78 °C. The reaction mixture was stirred at -78 °C for an additional 30 minutes. Saturated $NaHCO_3$ solution was added, and the mixture was allowed warm to room temperature. Ethyl acetate was added, the layers were separated, and the organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was diluted in anhydrous THF (10 mL) and cooled to 0 °C. Sodium bicarbonate (0.44 g, 5.17 mmol) and *N*-bromosuccinimide (0.61 g, 3.45 mmol) was then added and the mixture was stirred at room temperature for 15 h. The reaction mixture was filtered and concentrated. The crude material was purified by column chromatography on silica gel, eluting with 0–100% EtOAc in heptane, to provide 1-bromo-4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one (1.16 g, 2.50 mmol, 72% yield). m/z (ESI): 462.8/464.8/466.8 $(M+H)^+$.

[00235] Step 3. 1-Azido-4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one. To a 40-mL vial was added 1-bromo-4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one (1.16 g, 2.50 mmol) in acetone (10 mL). Sodium azide (0.21 g, 3.3

mmol) was added, and the reaction mixture was stirred at room temperature for 2 h. The mixture was filtered over celite, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel, eluting with 0–50% EtOAc in heptane, to provide 1-azido-4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one (0.70 g, 1.64 mmol, 66% yield). *m/z* (ESI): 448.0/450.0 $(M+Na)^+$.

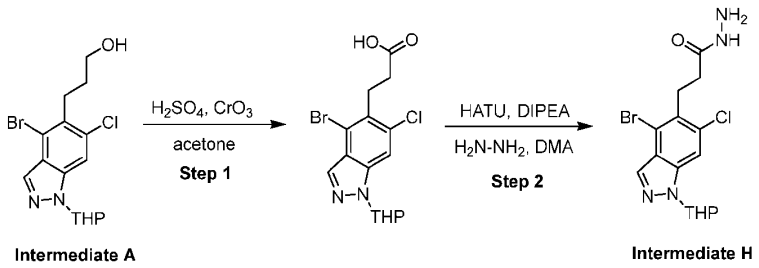
Intermediate G: (2*S*,4*R*)-6-(*tert*-Butoxycarbonyl)-2-fluoro-6-azaspiro[3.5]nonane-2-carboxylic acid.



[00236] Step 1. *tert*-Butyl (2*S*,4*R*)-2-fluoro-2-(hydroxymethyl)-6-azaspiro[3.5]nonane-6-carboxylate. In a 250-mL round-bottom flask was added hydrogen fluoride (70% in 30% pyridine, 4.76 g, 48.0 mmol) and the flask was cooled to -78 °C. *tert*-Butyl 1-oxa-7-azadispiro[2.1.5^5.1^3]undecane-7-carboxylate (**Intermediate B**, 4.30 g, 17.0 mmol) in dichloromethane (15 mL) was added dropwise, and the reaction mixture was stirred at -78 °C for 2 h. The mixture was quenched by addition of 1 M Na_2CO_3 solution and dichloromethane and then allowed to warm to 0 °C. Di-*tert*-butyl dicarbonate (3.70 g, 17 mmol) was added at 0 °C and the mixture was gradually warmed to room temperature with stirring for 16 h. The resulting mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude was purified by column chromatography on silica gel, eluting with 0–50% EtOAc in heptane (detected by an ELS detector), to provide *tert*-butyl (2*S*,4*R*)-2-fluoro-2-(hydroxymethyl)-6-azaspiro[3.5]nonane-6-carboxylate (0.96 g, 3.5 mmol, 21% yield). *m/z* (ESI): 218.2 $(M-^tBu+H)^+$.

[00237] Step 2. (2*S*,4*R*)-6-(*tert*-Butoxycarbonyl)-2-fluoro-6-azaspiro[3.5]nonane-2-carboxylic acid. To a 40-mL vial was charged with *tert*-butyl (2*S*,4*R*)-2-fluoro-2-(hydroxymethyl)-6-azaspiro[3.5]nonane-6-carboxylate (0.96 g, 3.5 mmol) in water (8 mL) and acetonitrile (12 mL). TEMPO (0.11 g, 0.70 mmol) and (diacetoxyiodo)benzene (2.83 g, 8.78 mmol) was added, and the reaction mixture was heated at 60 °C for 2 h. Acetonitrile was removed under vacuum, and the resulting aqueous mixture was basified with saturated $NaHCO_3$ solution, washed with EtOAc. The aqueous phase was acidified by 1 M $KHSO_4$ solution and extracted by EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to provide (2*S*,4*R*)-6-(*tert*-butoxycarbonyl)-2-fluoro-6-azaspiro[3.5]nonane-2-carboxylic acid (0.62 g, 2.2 mmol, 61% yield). *m/z* (ESI): 310.1 $(M+Na)^+$.

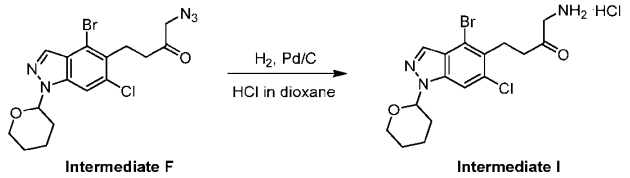
Intermediate H: 3-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propanehydrazide.



[00238] Step 1. 3-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propanoic acid. To a solution of 3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propan-1-ol (**Intermediate A**, 4.30 g, 11.5 mmol) at 0 °C in acetone (115 mL) was added chromium trioxide solution in sulfuric acid (7.0 mL, 15 mmol) dropwise. The reaction mixture was stirred at room temperature for 16 h. Sodium thiosulfate was added, and the solution was stirred for 10 minutes, filtered and the filtrate was concentrated *in vacuo* to provide 3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propanoic acid (4.40 g, 11.0 mmol, 99% yield). *m/z* (ESI): 387.0/389.0 $(M+H)^+$. ^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 12.1-12.5 (m, 1H), 8.0-8.1 (m, 1H), 8.02 (s, 1H), 5.88 (dd, 1H, *J*=2.4, 9.4 Hz), 3.8-3.9 (m, 1H), 3.7-3.8 (m, 1H), 3.2-3.3 (m, 2H), 2.4-2.5 (m, 2H), 2.3-2.4 (m, 1H), 1.9-2.1 (m, 2H), 1.6-1.8 (m, 1H), 1.5-1.6 (m, 2H).

[00239] Step 2. 3-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propanehydrazide. To solution of 3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propanoic acid (1.02 g, 2.63 mmol) in acetonitrile (8 mL) and *N*,*N*-dimethylacetamide (2 mL) was added DIPEA (0.5 mL) and HATU (1.26 g, 3.32 mmol). The mixture was stirred at room temperature for 20 minutes. Then the solution was added dropwise to the solution of hydrazine (0.19 mL, 6.1 mmol) and DIPEA (0.5 mL) in MeCN (10 mL) cooled in an ice bath. The reaction mixture was diluted with EtOAc and saturated NH_4Cl. The organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0-100% 3:1 EtOAc/EtOH in heptane, to provide 3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propanehydrazide (0.62 g, 1.50 mmol, 58%). *m/z* (ESI): 423/425 $(M+Na)^+$. ^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 9.06 (br s, 1H), 8.06 (s, 1H), 8.01 (s, 1H), 5.9-5.9 (m, 1H), 4.19 (br s, 2H), 3.8-3.9 (m, 1H), 3.7-3.8 (m, 1H), 3.1-3.3 (m, 2H), 2.2-2.4 (m, 3H), 2.0-2.1 (m, 2H), 1.7-1.8 (m, 1H), 1.5-1.6 (m, 2H).

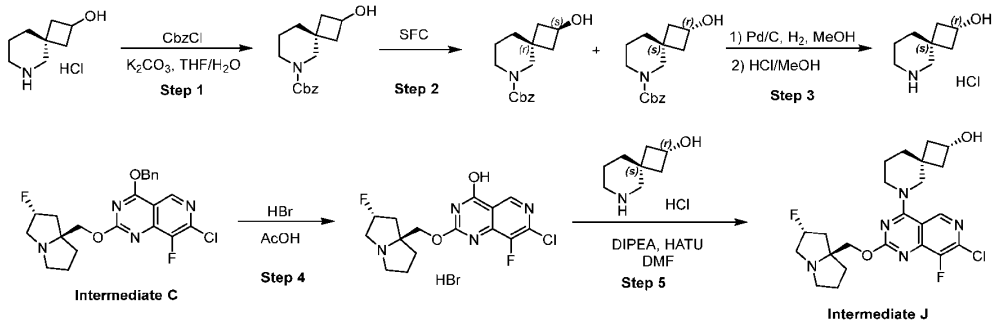
Intermediate I: 1-Amino-4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one.



Intermediate F Intermediate I

[00240] To a solution of 5% Pd on activated carbon (5.00 g, 46.9 mmol) in ethanol (1 L) was added 1-azido-4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one (20.0 g, 46.9 mmol) and HCl (4 M in 1,4-dioxane, 8.0 mL, 32 mmol). The suspension was degassed and purged with H_2 three times. The reaction mixture was stirred under 15 psi of hydrogen at room temperature for 15 minutes. Upon completion the reaction was filtered through celite and concentrated. The crude material was triturated with ethyl acetate to give 1-amino-4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one (8.50 g, 19.4 mmol, 42% yield).

Intermediate J: (2*S*,4*S*)-6-(7-Chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol.



Intermediate C Intermediate J

[00241] **Step 1. Benzyl 2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate.** To a solution of 6-azaspiro[3.5]nonan-2-ol hydrochloride (50.0 g, 281 mmol, LabNetwork) and K_2CO_3 (78.0 g, 563 mmol) in tetrahydrofuran (500 mL) and water (500 mL) was added CBz-Cl (44 mL, 310 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The reaction was combined with another 8 batches (50 g scale), diluted with H_2O, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 5-30% EtOAc in petroleum ether, to provide benzyl 2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (550 g, 2.00 mol, 79% yield).

[00242] **Step 2. Benzyl (2*R*,4*S*)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate.** Benzyl 2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (550 g) was separated by SFC (Column: DAICEL

CHIRALCEL OZ, 25 cm x 5 cm, 10 mm; Mobile phase: 25% EtOH (0.1% NH_3 in H_2O); Flow rate: 200 mL/min) to give peak 1 benzyl (2*S*,4*R*)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (270 g, 981 mmol, 49% yield) and peak 2 benzyl (2*R*,4*S*)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (92 g, 334 mmol, 17% yield).

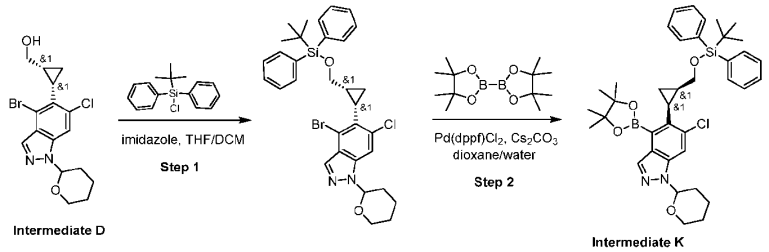
[00243] Step 3. (2*R*,4*S*)-6-Azaspiro[3.5]nonan-2-ol hydrochloride. To a solution benzyl (2*R*,4*S*)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (45.0 g, 163 mmol) in MeOH under argon atmosphere was added Pd/C (10%, 5 g, 4.7 mmol). The mixture was stirred under H_2 (45 psi) at 40 °C for 12 h. HCl (4 M in MeOH, 100 mL, 400 mmol) was added to the reaction mixture and stirring was continued for 0.5 h. The reaction was combined another two batches (45 g scale, 2 g scale), filtered through a pad of celite. The filtrate was concentrated under reduced pressure to give (2*R*,4*S*)-6-azaspiro[3.5]nonan-2-ol hydrochloride (60.0 g, 338 mmol, 100% yield). ^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 9.00 (s, 2H), 4.00-4.15 (m, 1H), 2.81-2.93 (m, 4H), 2.00-2.11 (m, 2H), 1.49-1.76 (m, 6H).

[00244] Step 4. 7-Chloro-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)quinazolin-4-ol hydrobromide. 4-(*tert*-Butoxy)-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)yl)methoxy)pyrido[4,3-*d*]pyrimidine (**Intermediate C**, 29.4 g, 71.4 mmol) in HBr (33% in AcOH, 250 mL, 71.4 mmol) was stirred at room temperature for 4 h. This procedure was repeated on similar scale 2 additional times. The reaction mixtures were diluted with EtOAc, and the suspension was filtered. The filter cake was triturated with EtOAc (100 mL) at room temperature for 20 minutes. The suspension was filtered, and the filter cake was washed with EtOAc, dried under vacuum to give 7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol hydrobromide (96.0 g, 219 mmol, HBr salt). *m/z* (ESI): 357.2 $(M+H)^+$.

[00245] Step 5. (2*S*,4*S*)-6-(7-Chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol. To a 100 mL round-bottom flask was charged with 7-chloro-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol hydrobromide (2.59 g, 5.90 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (3.1 mL, 18 mmol) in DMF (29 mL). HATU (3.36 g, 8.8 mmol) was added in one portion and the reaction mixture was stirred at room temperature for 30 minutes. (2*R*,4*S*)-6-Azaspiro[3.5]nonan-2-ol hydrochloride (1.15 g, 6.5 mmol) was then added. The reaction mixture was stirred at room temperature for 2 h. The mixture was partitioned between ethyl acetate and saturated aqueous sodium chloride solution. The aqueous layer was extracted with EtOAc, and the combined organics were washed with brine, dried, and concentrated. The crude material was purified by column chromatography on silica gel, eluting with 0–100% 3:1 (EtOAc:EtOH with 2% triethylamine) in heptane, to provide (2*S*,4*S*)-6-(7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol (2.60 g, 5.80 mmol, 98% yield). *m/z* (ESI): 479.2 $(M+H)^+$. ^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 8.90 (s, 1 H), 5.34 (d, J=54.0

Hz, 1H), 4.94 (s, 1H), 4.15-4.32 (m, 2H), 4.02-4.11 (m, 1H), 3.88 (s, 2H), 3.80 (s, 2H), 3.58-3.64 (m, 1H), 3.09-3.19 (m, 2H), 2.89 (s, 1H), 2.73 (s, 1H), 2.12-2.27 (m, 2 H), 2.00-2.10(m, 3H), 1.79-1.88 (m, 2H), 1.67 (s, 4H), 1.52-1.60 (m, 2H).

Intermediate K: *rac*-5-((1*S*,2*R*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)cyclopropyl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole.

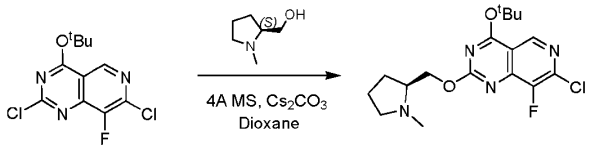


[00246] Step 1. *rac*-4-Bromo-5-((1*S*,2*R*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopropyl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole. To a solution of ((1*R*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methanol (**Intermediate D**, 35.0 g, 91.0 mmol) in dichloromethane (125 mL) and tetrahydrofuran (125 mL) was added imidazole (9.27 g, 136 mmol) and TBDPS-Cl (25.6 mL, 100 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h, was then diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 2–5% EtOAc in petroleum ether, to give 4-bromo-5-((1*S*,2*R*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopropyl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (42.5 g, 68.4 mmol, 75% yield).

[00247] Step 2. *rac*-5-((1*S*,2*R*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)cyclopropyl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole. To the mixture of 4-bromo-5-((1*S*,2*R*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopropyl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (50.0 g, 80.0 mmol) in 1,4-dioxane (800 mL) and water (100 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (92.0 g, 361 mmol), cesium carbonate (78.0 g, 240 mmol) and $Pd(dppf)Cl_2$ (5.86 g, 8.0 mmol) under nitrogen. The reaction mixture was heated at 120 °C for 2 h. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by reversed phase MPLC (70-90% 25 min; 90% 20 min using CH_3CN as eluent) to give *rac*-5-((1*S*,2*R*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopropyl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole (24.8 g, 37 mmol, 46% yield). *m/z* (ESI):

671.3/673.2 $(M+H)^+$. ^1H NMR (400 MHz, *DMSO-d_6*) δ ppm 8.08 (m, 1 H), 7.88 (d, J=7.2 Hz, 1 H), 5.85-5.80 (m,1 H), 3.85-3.83 (m, 1 H), 3.77-3.72 (m, 1 H), 3.58-3.56 (m, 1H), 2.91-2.81 (m, 1 H), 2.37-2.25(m, 2 H), 2.02 - 1.99 (m, 1 H), 1.91-1.88 (m, 1 H), 1.72-1.70 (m, 1 H), 1.56 (br s, 3 H), 1.40-1.34 (m, 12 H), 1.23-1.15 (m, 2 H), 0.84 (br s, 9 H).

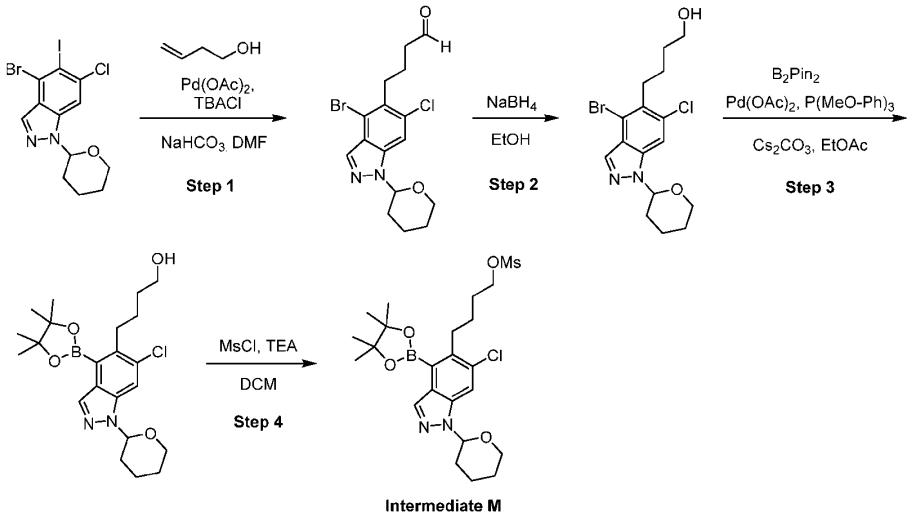
Intermediate L: (*S*)-4-(*tert*-Butoxy)-7-chloro-8-fluoro-2-((1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-*d*]pyrimidine.



Intermediate L

[00248] To a mixture of 4-(*tert*-butoxy)-2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidine (**Step 1 in Intermediate A**, 14.0 g, 48.3 mmol) and 4Å MS (2.5 g) in 1,4-dioxane (280 mL) was added (*S*)-(1-methylpyrrolidin-2-yl)methanol (8.34 g, 72.4 mmol) and Cs_2CO_3 (39.3 g, 121 mmol) in sequence. The reaction mixture was stirred at room temperature for 10 h, then was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was triturated with MTBE for 2 h. The suspension was filtered, and the filter cake was washed with MTBE and concentrated under reduced pressure to give (*S*)-4-(*tert*-butoxy)-7-chloro-8-fluoro-2-((1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-*d*]pyrimidine (7.89 g, 21.4 mmol, 44% yield). *m/z* (ESI): 369.1/371.1. ^1H NMR (400 MHz, *$CDCl_3$*) δ ppm 8.86 (s, 1 H), 4.58 (br d, *J* = 3.2 Hz, 1 H), 4.41 - 4.47 (m, 1 H), 3.07 - 3.28 (m, 1 H), 2.73 - 2.89 (m, 1 H), 2.55 (br s, 3 H), 2.28 - 2.45 (m, 1 H), 2.04 - 2.19 (m, 1 H), 1.78 - 1.93 (m, 3 H), 1.76 (s, 9 H). ^{19}F NMR (376 MHz, *$CDCl_3$*) δ ppm -135.34 (s).

Intermediate M: 4-(6-Chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)butyl methanesulfonate.



[00249] Step 1: 4-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butanal. To a solution of 4-bromo-6-chloro-5-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (25.0 g, 56.6 mmol, Lab Network) in *N,N*-dimethylformamide (300 mL) was added $NaHCO_3$ (11.9 g, 142 mmol) and TBACl (14.8 g, 56.6 mmol) under N_2. The reaction mixture was stirred at room temperature for 15 minutes, then but-3-en-1-ol (8.17 g, 113 mmol) and $Pd(OAc)_2$ (1.27 g, 5.66 mmol) was added under N_2. The mixture was stirred at 80 °C for 12 h under N_2. After cooling to room temperature, the residue was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a gradient of 5–10% ethyl acetate in petroleum ether, to give 4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butanal (15 g, 39 mmol, 70% yield). *m/z* (ESI): 385.1/ 387.1 $(M+H)^+$.

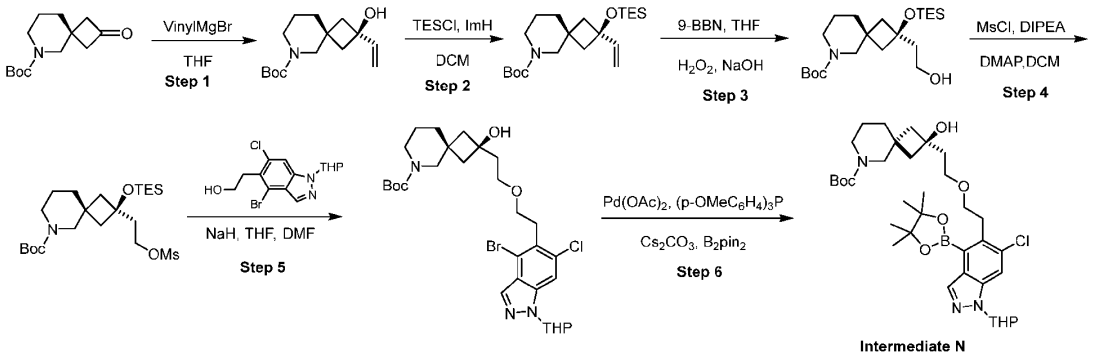
[00250] Step 2. 4-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-1-ol. To a solution of 4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butanal (15 g, 39 mmol) in EtOH (300 mL) was added $NaBH_4$ (4.41 g, 117 mmol) in portions at 0 °C. The mixture was stirred at room temperature for 2 h, then was quenched by addition of saturated NH_4Cl and water. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 5–10% ethyl acetate in petroleum ether, to give 4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-1-ol (11 g, 28 mmol, 73% yield). *m/z* (ESI): 387.0/ 389.0 $(M+H)^+$.

[00251] Step 3. 4-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)butan-1-ol. A vial was charged with tris(4-methoxyphenyl)phosphine (1.45 g, 4.13 mmol, Ambeed, Inc.), palladium acetate (0.46 g, 2.06 mmol,

Combi-Blocks Inc.), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (3.93 g, 15.5 mmol, Ambeed, Inc.), cesium carbonate (6.72 g, 20.6 mmol), 4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-1-ol (4.00 g, 10.3 mmol) and ethyl acetate (10 mL), then sparged with nitrogen and heated to 80 °C for 12 h. The reaction mixture was cooled to room temperature then the crude material was filtered through a plug of celite and concentrated. The crude material was purified by chromatography on silica gel, eluting with a gradient of 0–20% 3:1 EtOAc/EtOH (with 2% TEA) in heptane, to provide 4-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)butan-1-ol (3.05 g, 7.03 mmol, 68% yield). *m/z* (ESI): 435.1 $(M+H)^+$.

[00252] Step 4. 4-(6-Chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)butyl methanesulfonate. A vial was charged with 4-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)butan-1-ol (3.20 g, 7.36 mmol), triethylamine (1.24 mL, 8.83 mmol) and dichloromethane (36 mL), then cooled to 0 °C. Methanesulfonyl chloride (0.63 mL, 8.10 mmol) was added dropwise and upon completion, the mixture was allowed to warm to room temperature with stirring. The crude mixture was and purified by column chromatography on silica gel, eluting with a gradient of 0–50% (3:1 EtOAc/EtOH with 2% TEA)/heptane, to provide 4-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)butyl methanesulfonate (3.25 g, 6.34 mmol, 86% yield). *m/z* (ESI): 513.0 $(M+H)^+$.

Intermediate N: *tert*-Butyl 2-(2-(2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate.



[00253] Step 1. *tert*-Butyl (2*S*,4*R*)-2-hydroxy-2-vinyl-6-azaspiro[3.5]nonane-6-carboxylate. A 250 mL round-bottom flask was charged with *tert*-butyl 2-oxo-6-azaspiro[3.5]nonane-6-carboxylate (18.0 g, 75.0 mmol, Pharmablock Inc.) in tetrahydrofuran (350 mL) and cooled to 0 °C.

Vinylmagnesium bromide (0.7 M solution in THF, 114 mL, 80 mmol) was added and the reaction was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The crude was purified by column chromatography on silica gel, eluting with a gradient of 0–80% ethyl acetate in heptane, to yield *tert*-butyl (2*S*,4*R*)-2-hydroxy-2-vinyl-6-azaspiro[3.5]nonane-6-carboxylate (4.82 g, 18.0 mmol, 24% yield). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 5.99 - 6.20 (m, 1 H), 4.94 - 5.34 (m, 2 H), 3.47 - 3.58 (m, 2 H), 3.29 - 3.40 (m, 2 H), 2.01 (s, 4 H), 1.55 - 1.57 (m, 1 H), 1.45 - 1.52 (m, 13 H) and *tert*-butyl (2*s*,4*r*)-2-hydroxy-2-vinyl-6-azaspiro[3.5]nonane-6-carboxylate (5.25 g, 19.7 mmol, 26% yield). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 6.14 (dd, *J*=17.2, 10.6 Hz, 1 H), 5.07 - 5.39 (m, 2 H), 3.20 - 3.39 (m, 4 H), 2.14 - 2.32 (m, 2 H), 1.84 - 1.94 (m, 2 H), 1.65 1.80 (m, 3 H), 1.45 - 1.52 (m, 11 H). Diastereoisomers have been determined by NOESY NMR spectrocopy.

[00254] Step 2. *tert*-Butyl (2*S*,4*R*)-2-((triethylsilyl)oxy)-2-vinyl-6-azaspiro[3.5]nonane-6-carboxylate. In a 100 mL round-bottom flask was charged with *tert*-butyl (2*s*,4*r*)-2-hydroxy-2-vinyl-6-azaspiro[3.5]nonane-6-carboxylate (5.25 g, 19.7 mmol), imidazole (3.48 g, 51.1 mmol) in dichloromethane (100 mL). The mixture was cooled to 0 °C and chlorotriethylsilane (4.3 mL, 25.5 mmol) was added. The mixture was allowed to warm to room temperature with stirring for 30 minutes. Water was added and the aqueous phase was extracted with EtOAc. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The crude was purified by column chromatography on silica gel, eluting with a gradient of 0–50% ethyl acetate (0.1% Et_3N as an additive) in heptane, to yield *tert*-butyl (2*S*,4*R*)-2-((triethylsilyl)oxy)-2-vinyl-6-azaspiro[3.5]nonane-6-carboxylate (7.40 g, 19.4 mmol, 99% yield). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 5.97 - 6.27 (m, 1 H), 5.21 - 5.46 (m, 1 H), 5.04 - 5.21 (m, 1 H), 3.20 - 3.36 (m, 4 H), 2.15 - 2.42 (m, 2 H), 1.83 - 2.04 (m, 2 H), 1.60 - 1.75 (m, 2 H), 1.46 - 1.57 (m, 11 H), 0.94 - 1.05 (m, 8 H), 0.57 - 0.65 (m, 6 H).

[00255] Step 3. *tert*-Butyl (2*S*,4*R*)-2-(2-hydroxyethyl)-2-((triethylsilyl)oxy)-6-azaspiro[3.5]nonane-6-carboxylate. In a 150 mL flask under nitrogen was charged with *tert*-butyl (2*s*,4*r*)-2-((triethylsilyl)oxy)-2-vinyl-6-azaspiro[3.5]nonane-6-carboxylate (7.40 g, 19.4 mmol) in tetrahydrofuran (100 mL). The contents were cooled to 0 °C and 9-borabicyclo[3.3.1]nonane (80 mL, 40 mmol) was added slowly. The reaction mixture was allowed to warm to room temperature with stirring for 5 h. The mixture was cooled again to 0 °C and 3 N NaOH (42 mL, 14 mmol) and hydrogen peroxide (12.9 mL, 126 mmol) was added. The mixture was allowed to warm to room temperature with stirring for 3 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The crude was purified by column chromatography on silica gel, eluting with a gradient of 0–100% ethyl acetate in heptane, to give *tert*-butyl (2*S*,4*R*)-2-(2-hydroxyethyl)-2-((triethylsilyl)oxy)-6-azaspiro[3.5]nonane-6-carboxylate (6.23 g, 15.6 mmol, 80% yield). ^{1}H NMR

(400 MHz, *CDCl3*) δ ppm 3.77 - 3.97 (m, 2 H), 3.20 - 3.40 (m, 4 H), 2.53 - 2.70 (m, 1 H), 2.10 - 2.22 (m, 2 H), 1.85 - 2.00 (m, 4 H), 1.61 - 1.68 (m, 2 H), 1.43 - 1.53 (m, 11 H), 0.92 - 1.02 (m, 9 H), 0.59 - 0.71 (m, 6 H).

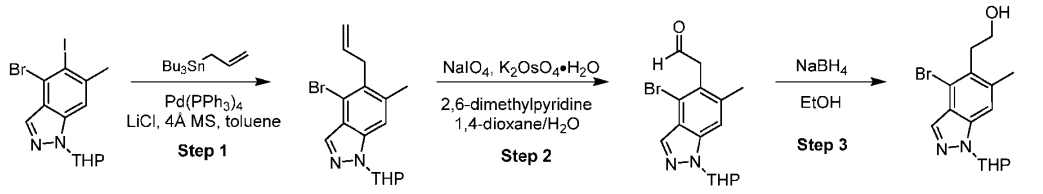
[00256] Step 4. *tert*-Butyl (2*S*,4*R*)-2-(2-((methylsulfonyl)oxy)ethyl)-2-((triethylsilyl)oxy)-5-azaspiro[3.5]nonane-5-carboxylate. To a 100-mL round bottom flask was charged with *tert*-butyl (2*S*,4*R*)-2-(2-hydroxyethyl)-2-((triethylsilyl)oxy)-6-azaspiro[3.5]nonane-6-carboxylate (6.23 g, 15.6 mmol) and triethylamine (6.5 mL, 47 mmol) in dichloromethane (80 mL). Methanesulfonyl chloride (2.4 mL, 31 mmol) and *N*,*N*-dimethylpyridin-4-amine (0.38 g, 3.11 mmol) was added sequentially. After 2 h of stirring at room temperature, the mixture was quenched with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0–100% ethyl acetate in heptane, to provide *tert*-butyl (2*S*,4*R*)-2-(2-((methylsulfonyl)oxy)ethyl)-2-((triethylsilyl)oxy)-5-azaspiro[3.5]nonane-5-carboxylate (6.66 g, 13.9 mmol, 90% yield). ^{1}H NMR (400 MHz, *CDCl3*) δ ppm 4.47 – 4.24 (m, 2H), 3.40 – 3.26 (m, 4H), 3.06 – 2.96 (m, 3H), 2.20 – 2.07 (m, 4H), 1.94 – 1.86 (m, 2H), 1.67 – 1.60 (m, 2H), 1.53 – 1.44 (m, 11H), 1.02 – 0.94 (m, 9H), 0.72 – 0.52 (m, 6H).

[00257] Step 5. *tert*-Butyl (2*S*,4*R*)-2-(2-(2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate. A 100 mL round-bottom flask was charged with 2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethan-1-ol (Step 1 of **Intermediate E**, 5.08 g, 14.1 mmol), tetrahydrofuran (20 mL), and *N*,*N*-dimethylformamide (7 mL). Sodium hydride (60 wt% in mineral oil, 0.28 g, 7.08 mmol) was added, and the reaction mixture was stirred at room temperature for 30 minutes. *tert*-Butyl (2*S*,4*R*)-2-(2-((methylsulfonyl)oxy)ethyl)-2-((triethylsilyl)oxy)-5-azaspiro[3.5]nonane-5-carboxylate (1.69 g, 3.54 mmol) in THF (5 mL) was added and the reaction mixture was warmed to 50 °C for 72 h. The mixture was quenched carefully with water and extracted with EtOAc. The combined organic layer was dried over sodium sulfate, filtered, and concentrated. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0–100% ethyl acetate in heptane, to give *tert*-butyl (2*S*,4*R*)-2-(2-(2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (0.68 g, 1.08 mmol, 31% yield). *m/z* (ESI): 648.0 $(M+Na)^+$. ^{1}H NMR (400 MHz, *CDCl3*) δ ppm 7.92 - 8.09 (m, 1 H), 7.65 - 7.76 (m, 1 H), 5.58 - 5.74 (m, 1 H), 3.98 - 4.07 (m, 1 H), 3.64 - 3.80 (m, 5 H), 3.27 - 3.44 (m, 4 H), 3.21 - 3.26 (m, 2 H), 2.42 - 2.55 (m, 1 H), 2.08 - 2.23 (m, 2 H), 1.90 - 2.04 (m, 4 H), 1.65 - 1.85 (m, 7 H), 1.42 - 1.53 (m, 11 H).

[00258] Step 6. *tert*-Butyl (2*S*,4*R*)-2-(2-(2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate. A vial was charged with tris(4-methoxyphenyl)phosphine (46

mg, 0.13 mmol), palladium acetate (24 mg, 0.11 mmol), bis(pinacolato)diboron (0.41 g, 1.62 mmol), cesium carbonate (0.71 g, 2.16 mmol), *tert*-butyl (2*S*,4*R*)-2-(2-(2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (0.68 g, 1.08 mmol) and ethyl acetate (4 mL). The reaction mixture was then sparged with N_2 for 3 min and heated to 80 °C for 1 h. After cooling to room temperature, the mixture was filtered through a pad of celite and and the filtrate was purified by column chromatography on silica gel, eluting with a gradient of 0–100% ethyl acetate in heptane, to provide *tert*-butyl (2*S*,4*R*)-2-(2-(2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (0.49 g, 0.72 mmol, 67% yield, purity: 63%). *m/z* (ESI): 674.4 $(M+H)^+$.

Intermediate O: 5-(2-((*tert*-Butyldimethylsilyl) oxy)ethyl)-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole.



Intermediate O

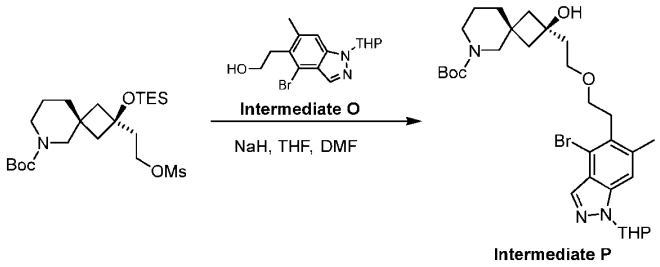
[00259] Step 1. 5-Allyl-4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole. To a solution of 4-bromo-5-iodo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (120 g, 285 mmol, Advanced ChemBlocks) in toluene (1.2 L) was added 4Å MS (40 g, 285 mmol), LiCl (59.8 g, 1.43 mol) and $Pd(PPh_3)_4$ (32.9 g, 28.5 mmol) under N_2. Then allyltributylstannane (132 g, 399 mmol) was added in one portion under N_2. The mixture was stirred at 110 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organics were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a gradient of 1–100% ethyl acetate in petroleum ether, to give 5-allyl-4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (80 g, 250 mmol, 87% yield).

[00260] Step 2. 2-(4-Bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)acetaldehyde. To a solution of 5-allyl-4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (40.0 g, 119 mmol) in 1,4-dioxane (800 mL) and water (400 mL) was added $K_2OsO_4•H_2O$ (1.98 g, 5.97 mmol) and 2,6-dimethylpyridine (38.4 g, 358 mmol), then sodium periodate (77.0 g, 358 mmol) was added and the reaction was stirred at room temperature for 2 h. The reaction mixture was quenched by addition of sat. Na_2SO_3 at 0 °C for 1 h. The reaction mixture was diluted with water and

extracted with ethyl acetate. The combined organics were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a gradient of 1–100% ethyl acetate in petroleum ether, to give 2-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)acetaldehyde (27.5 g, 82 mmol, 69% yield).

[00261] Step 3. 2-(4-Bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethan-1-ol. To a solution of 2-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)acetaldehyde (40.0 g, 119 mmol) in ethanol (800 mL) was added sodium tetrahydroborate (13.5 g, 356 mmol) in portions at 0 °C. Then the reaction was stirred at room temperature for 2 h under N_2. The reaction mixture was quenched by addition of sat. NH_4Cl (1 L) at 0 °C. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organics were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a gradient of 1–100% ethyl acetate in petroleum ether, to give 2-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethan-1-ol (36.2 g, 107 mmol, 90% yield). *m/z* (ESI): 339.0/341.0 $(M+H)^+$.

Intermediate P: *tert*-Butyl (2*S*,4*R*)-2-(2-(2-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate.

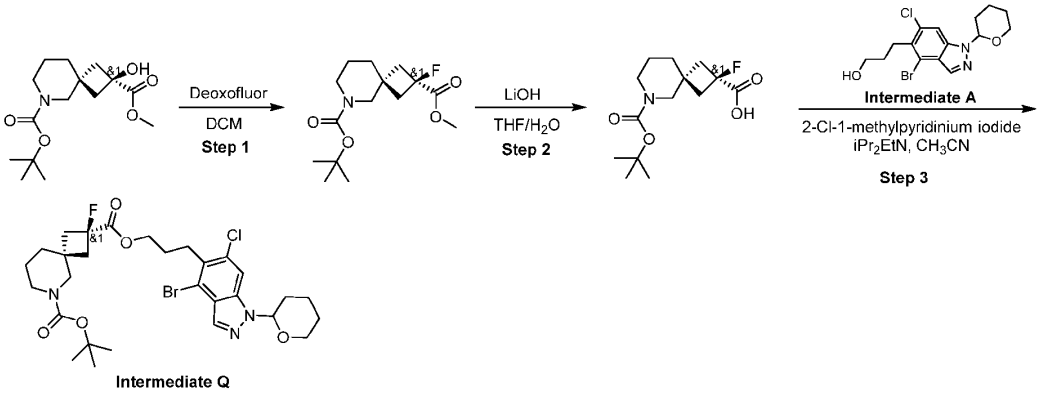


Intermediate P

[00262] *tert*-Butyl (2*S*,4*R*)-2-(2-(2-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate. A 150-mL round-bottom flask was charged with 2-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethan-1-ol (**Step 3** in **Intermediate O**, 3.79 g, 11.2 mmol) and tetrahydrofuran (18 mL) at room temperature under N_2. Then sodium hydride (60 wt% in mineral oil, 0.39 g, 9.70 mmol) was added and the reaction mixture was stirred at room temperature for 30 minutes. *tert*-Butyl (2*S*,4*R*)-2-(2-((methylsulfonyl)oxy)ethyl)-2-((triethylsilyl)oxy)-6-azaspiro[3.5]nonane-6-carboxylate (**Step 4** in **Intermediate N**, 2.32 g, 4.86 mmol) in *N*,*N*-dimethylformamide (6 mL) was added. The reaction mixture was stirred at 50 °C for 1.5 h, cooled to room temperature and was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography on silica gel,

eluting with a graduent of 0–100% EtOAc in heptane, followed by reversed phase column chromatography using a C18 column, eluting with a gradient of 0–100% (0.1% formic acid in CH_3CN/H_2O), then basified with saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give *tert*-butyl (2*S*,4*R*)-2-(2-(2-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (0.46 g, 0.76 mmol, 16% yield). *m/z* (ESI): 606.2 $(M+H)^+$. ^1H NMR (400 MHz, *CDCl3*) δ ppm 7.94 (s, 1H), 7.35 (s, 1H), 5.65 (br d, J = 9.0 Hz, 1H), 4.01 (br d, J = 11.1 Hz, 1H), 3.71 (br t, J = 4.8 Hz, 3H), 3.61 (br t, J = 7.2 Hz, 2H), 3.30 (br s, 2H), 3.22 (s, 2H), 3.21 – 3.16 (m, 2H), 2.54 (s, 3H), 2.16 (br s, 1H), 2.06 (br d, J = 12.1 Hz, 1H), 1.99 (br d, J = 12.5 Hz, 2H), 1.95 – 1.90 (m, 2H), 1.78 (br d, J = 12.8 Hz, 3H), 1.68 – 1.65 (m, 2H), 1.56 (s, 4H), 1.48 (br s, 2H), 1.46 (s, 9H).

Intermediate Q: 2-(3-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl) 6-(*tert*-butyl) 2-fluoro-6-azaspiro[3.5]nonane-2,6-dicarboxylate.



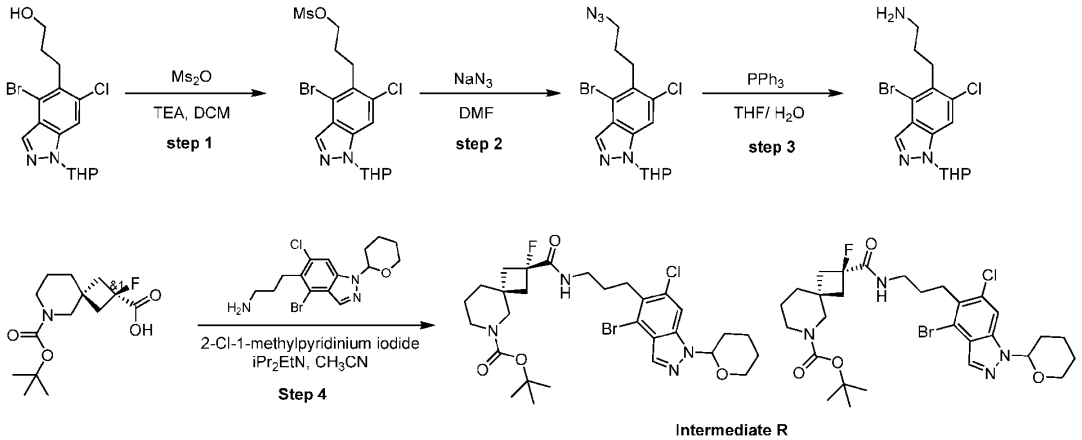
Intermediate Q

[00263] Step 1. 6-(*tert*-Butyl) 2-methyl 2-fluoro-6-azaspiro[3.5]nonane-2,6-dicarboxylate. To a vial containing dichloromethane (25 mL) purged with nitrogen was added bis(2-methoxyethyl)aminosulfur trifluoride (1.4 mL, 7.5 mmol) at -78 °C. To this was added 6-(*tert*-butyl) 2-methyl 2-hydroxy-6-azaspiro[3.5]nonane-2,6-dicarboxylate (2.05 g, 6.85 mmol) as a solution in dichloromethane (25 mL) dropwise. The reaction mixture was stirred at -78 °C for 2 h and then was allowed to warm to room temperature with stirring for 16 h. The reaction mixture was carefully quenched with saturated aqueous sodium bicarbonate and the dichloromethane layer was decanted, dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 0–45% ethyl acetate in heptane, to give 6-(*tert*-butyl) 2-methyl 2-fluoro-6-azaspiro[3.5]nonane-2,6-dicarboxylate (0.21 g, 0.69 mmol, 10% yield) as a mixture of diastereomers. *m/z* (ESI): 246.2 $(M-^tBu+H)^+$.

[00264] Step 2. 6-(*tert*-Butoxycarbonyl)-2-fluoro-6-azaspiro[3.5]nonane-2-carboxylic acid. To a 20-mL vial was charged with 6-(*tert*-butyl) 2-methyl 2-fluoro-6-azaspiro[3.5]nonane-2,6-dicarboxylate (0.21 g, 0.69 mmol), tetrahydrofuran (3.5 mL), water (3.5 mL), and lithium hydroxide, monohydrate (58 mg, 1.40 mmol). The reaction was warmed to 45 °C with stirring for 1 h. After cooling to room temperature, the mixture was frozen in a dry-ice acetone bath and lyophilized to give 6-(*tert*-butoxycarbonyl)-2-fluoro-6-azaspiro[3.5]nonane-2-carboxylic acid (0.20 g, 0.69 mmol, 100% yield). *m/z* (ESI): 232.1 $(M-^{t}Bu+H)^{+}$.

[00265] Step 3. 2-(3-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl) 6-(*tert*-butyl) 2-fluoro-6-azaspiro[3.5]nonane-2,6-dicarboxylate. To a 40-mL vial was charged with 6-(*tert*-butoxycarbonyl)-2-fluoro-6-azaspiro[3.5]nonane-2-carboxylic acid (0.11 g, 0.37 mmol), acetonitrile (1.8 mL), 1,1'-dimethyltriethylamine (0.3 mL, 1.8 mmol), and 2-chloro-1-methylpyridinium iodide (0.33 g, 1.30 mmol). The reaction mixture was stirred at room temperature and then 3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propan-1-ol (**Intermediate A**, 0.21 g, 0.54 mmol) was added. The solution was heated to 60 °C for 20 h. After cooling to room temperature, the reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 0–60% ethyl acetate in heptane, to yield 2-(3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl) 6-(*tert*-butyl) 2-fluoro-6-azaspiro[3.5]nonane-2,6-dicarboxylate (0.17 g, 0.26 mmol, 72% yield). *m/z* (ESI): 664.0 $(M+Na)^{+}$.

Intermediate R: *tert*-Butyl (2*R*,4*S*)-2-((3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl)carbamoyl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate and ***tert*-butyl (2*S*,4*R*)-2-((3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl)carbamoyl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate.**



[00266] Step 1. 3-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl methanesulfonate. To a solution of 3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propan-1-ol (**Intermediate I**, 8.00 g, 21.41 mmol) in dichloromethane (80 mL) was added TEA (9.0 mL, 64 mmol) and Ms_2O (5.59 g, 32.1 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h, was then diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a gradient of 0–15% EtOAc in petroleum ether, to provide 3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl methanesulfonate (9.0 g, 20 mmol, 93% yield). *m/z* (ESI): 475.0 $(M+Na)^+$.

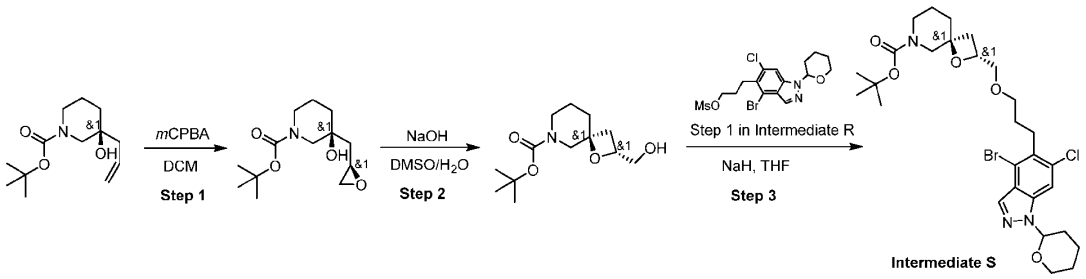
[00267] Step 2. 5-(3-Azidopropyl)-4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole. To a solution of 3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl methanesulfonate (9.0 g, 20 mmol) in *N*,*N*-dimethylformamide (90 mL) was added NaN_3 (1.51 g, 23.2 mmol) in portions. Then the mixture was stirred at 80 °C for 2 h. After cooling to room temperature, the reaction mixture was diluted with water and adjusted to pH 9 with 1 N NaOH solution, and then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product containing 5-(3-azidopropyl)-4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (8.0 g, 20 mmol) was used in the next step without further purification.

[00268] Step 3: 3-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propan-1-amine. To a solution containing 5-(3-azidopropyl)-4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (8.0 g, 20 mmol) in tetrahydrofuran (80 mL) was added H_2O (2.2 mL, 120 mmol) and PPh_3 (10.5 g, 40.1 mmol). The reaction mixture was stirred at 60 °C for 2 h, was then diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a gradient of 0–100% EtOAc in petroleum ether, to provide 3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propan-1-amine (6.8 g, 18.2 mmol, 91% yield). *m/z* (ESI): 374.0 $(M+H)^+$. ^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 7.96 (s, 1 H), 7.64 (s, 1 H), 5.60 - 5.67 (m, 1 H), 3.94 - 4.06 (m, 1 H), 3.67 - 3.82 (m, 1 H), 3.09 (t, *J*=8.0 Hz, 2 H), 2.85 (t, *J*=7.2 Hz, 2 H), 2.38 - 2.57 (m, 1 H), 2.11 - 2.19 (m, 1 H), 2.05 - 2.11 (m, 1 H), 1.74 - 1.82 (m, 7 H).

[00269] Step 4: *tert*-Butyl (2*R*,4*S*)-2-((3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl)carbamoyl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate and ***tert*-butyl (2*S*,4*R*)-2-((3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl)carbamoyl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate.** To a 40-mL vial was charged with 6-(*tert*-butoxycarbonyl)-2-fluoro-6-azaspiro[3.5]nonane-2-carboxylic acid (0.20 g, 0.69 mmol), *N*,*N*-dimethylformamide (2.5 mL), and Hunig's base (0.42 mL, 2.4 mmol). The mixture was

treated with HATU (0.52 g, 1.38 mmol) and stirred for 15 minutes. Then 3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propan-1-amine (0.31 g, 0.83 mmol) was added in *N*,*N*-dimethylformamide (2 mL). The reaction mixture was stirred for 2.5 h and upon completion directly injected onto a C18 column, and eluted with 5–100% acetonitrile (0.1% formic acid) in water (0.1% formic acid) to give *tert*-butyl (2*R*,4*S*)-2-((3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl)carbamoyl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (0.12 g, 0.19 mmol, 28% yield). *m/z* (ESI): 641.0 $(M+H)^+$ and *tert*-butyl (2*S*,4*R*)-2-((3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl)carbamoyl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (0.27 g, 0.43 mmol, 62% yield). *m/z* (ESI): 641.0 $(M+H)^+$ (stereochemistry arbitrarily assigned).

Intermediate S: *tert*-Butyl 2-((4-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)butoxy)methyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate.



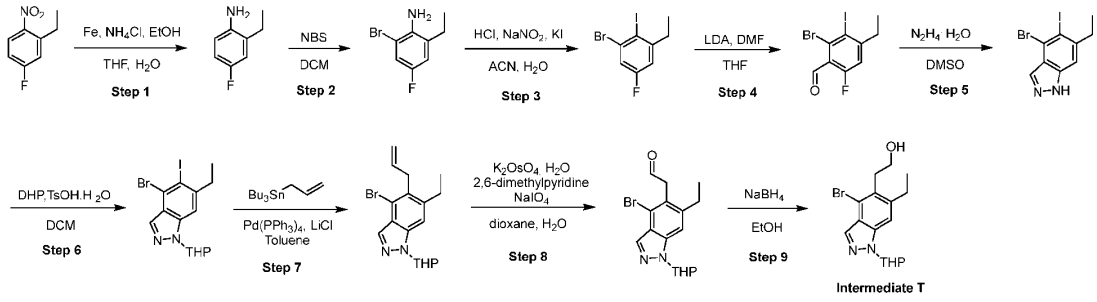
[00270] Step 1. *tert*-Butyl 3-hydroxy-3-(oxiran-2-ylmethyl)piperidine-1-carboxylate. To a 250 mL round-bottom flask was charged with 3-chloroperoxybenzoic acid (7.43 g, 33.1 mmol) and dichloromethane (90 mL). The solution was cooled to 0 °C and 1-Boc-3-allyl-3-hydroxypiperidine (4.0 mL, 16.6 mmol) was added as a solution in dichloromethane (30 mL). The solution was allowed to warm to room temperature with stirring for 24 h. The reaction mixture was diluted with aqueous sodium thiosulfate solution until no peroxide was detected by peroxide test strips. The aqueous was extracted with dichloromethane, and the dichloromethane layer was washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, and concentrated. The crude oil was purified by flash column chromatograpghy on silica gel, eluting with 0–80% ethyl acetate in heptane, to give *tert*-butyl 3-hydroxy-3-(oxiran-2-ylmethyl)piperidine-1-carboxylate (2.68 g, 10.41 mmol, 62% yield). *m/z* (ESI): 202.1 $(M-^tBu+H)^+$.

[00271] Step 2. *tert*-Butyl 2-(hydroxymethyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate. To a 250 mL round-bottom flask was charged with *tert*-butyl 3-hydroxy-3-(oxiran-2-ylmethyl)piperidine-1-carboxylate (2.50 g, 9.72 mmol), dimethyl sulfoxide (29 mL), and water (10 mL) under nitrogen. To this was added 10 M aqueous sodium hydroxide (1.0 mL, 10 mmol) and the reaction was heated to

140 °C for 1 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and saturated aqueous sodium chloride. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated. The crude oil was purified by column chromatography on silica gel, eluting with 0–80% 3:1 EtOAc/EtOH (with 2% tritethylamine) in heptane, to yield *tert*-butyl 2-(hydroxymethyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate (0.93 g, 3.60 mmol, 37% yield) as a mixture of diastereomers. *m/z* (ESI): 202.1 $(M-^{t}Bu+H)^{+}$.

[00272] Step 3. *tert*-Butyl 2-((4-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)butoxy)methyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate. To a 40 mL vial was charged with *tert*-butyl 2-(hydroxymethyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate (0.86 g, 3.30 mmol), tetrahydrofuran (19 mL), and sodium hydride (60 wt% in mineral oil, 0.21 g, 5.30 mmol). The reaction was stirred at room temperature under nitrogen for 15 minutes. Upon completion 3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl methanesulfonate (**Step 1** in **Intermediate R**, 2.25 g, 4.99 mmol) was added and the solution was heated to 55 °C for 20 h. After cooling to room temperature, the reaction was carefully quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The organics were dried over sodium sulfate, concentrated, and the residue was purified by column chromatography on silica gel, eluting with 0–40% ethyl acetate in heptane, following by reversed phase column chromatography to yield *tert*-butyl 2-((3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propoxy)methyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate (1.18 g, 1.92 mmol, 58% yield) as a mixture of diastereomers.

Intermediate T: 2-(4-Bromo-6-ethyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethan-1-ol.



[00273] Step 1. 2-Ethyl-4-fluoroaniline. To a solution of 2-ethyl-4-fluoro-1-nitrobenzene (15 g, 89 mmol) in tetrahydrofuran (90 mL) and ethanol (90 mL) and water (18 mL) was added NH_4Cl (7.11 g, 133 mmol) and iron (24.76 g, 443 mmol) under N_2 then the mixture was stirred at 90 °C for 2 h. The reaction mixture was combined with three other batches (15 g x 2, 5 g) and concentrated under

reduced pressure. The residue was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give 2-ethyl-4-fluoroaniline (40 g in total). *m/z* (ESI): 140.3 $(M+H)^+$.

[00274] Step 2. 2-Bromo-6-ethyl-4-fluoroaniline. To a solution of 2-ethyl-4-fluoroaniline (17.5 g, 126 mmol) in dichloromethane (180 mL) was added NBS (24.62 g, 138 mmol) at -10°C. Then the mixture was stirred at room temperature for 1.5 h. The reaction mixture was combined with two other batches (17.5 g, 5 g) and diluted with water and extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 0–100% EtOAc in petroleum ether, to give 2-bromo-6-ethyl-4-fluoroaniline (33.5 g in total). *m/z* (ESI): 220.1 $(M+H)^+$.

[00275] Step 3. 1-Bromo-3-ethyl-5-fluoro-2-iodobenzene. To a solution of 2-bromo-6-ethyl-4-fluoroaniline (9.50 g, 43.6 mmol) in acetonitrile (100 mL) was added HCl (37%, 11.6 mL, 139 mmol) and $NaNO_2$ (3.91 g, 56.6 mmol) in water (20 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 0.5 h, and then KI (9.40 g, 56.6 mmol) in water (20 mL) was added dropwise at 0 °C. The resulting mixture was stirred at room temperature for 2 h. The mixture was combined with three batches (9.5 g x 2, 5 g) and adjusted to pH 8 - 9 with 1 M aq. NaOH and diluted with water. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a gradient of 0–10% EtOAc in petroleum ether, to give 1-bromo-3-ethyl-5-fluoro-2-iodobenzene (45 g in total). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 7.27 - 7.31 (m, 1 H), 6.87 – 6.96 (m, 1 H), 2.85 (q, *J*=7.6 Hz, 2 H), 1.22 (t, *J*=7.2 Hz, 3 H).

[00276] Step 4. 2-Bromo-4-ethyl-6-fluoro-3-iodobenzaldehyde. To a solution of 1-bromo-3-ethyl-5-fluoro-2-iodobenzene (17.5 g, 53.2 mmol) in tetrahydrofuran (180 mL) was added LDA (2 M in THF, 29.3 mL, 58.5 mmol) dropwise at -78 °C. The mixture was stirred at -78 °C for 0.5 h and then DMF (5.4 mL, 69 mmol) was added dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 1.5 h. The reaction mixture was combined with two batches (17.5 g, 5 g) and quenched by sat. NH_4Cl at 0 °C, and then diluted water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 0–10% EtOAc in petroleum ether, to give 2-bromo-4-ethyl-6-fluoro-3-iodobenzaldehyde (27 g in total). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 10.20 (s, 1 H), 7.11 (d, *J*=11.2 Hz, 1 H), 2.92 (q, *J*=7.6 Hz, 2 H), 1.26 (t, *J*=7.2 Hz, 3 H).

[00277] Step 5. 4-Bromo-6-ethyl-5-iodo-1*H*-indazole. To a solution of 2-bromo-4-ethyl-6-fluoro-3-iodobenzaldehyde (27 g, 76 mmol) in dimethyl sulfoxide (300 mL) was added hydrazine monohydrate (19.52 g, 382 mmol). Then the mixture was stirred at 110 °C for 12 h. After cooling to room temperature, the reaction mixture was poured into water. The solid was collected by filtration

and the filter cake was concentrated under reduced pressure to give 4-bromo-6-ethyl-5-iodo-1*H*-indazole (23 g, 65.5 mmol, 87% yield). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.01 (s, 1 H), 7.33 (s, 1 H), 2.98 (q, *J*=7.6 Hz, 2 H), 1.29 (t, *J*=7.6 Hz, 3 H).

[00278] Step 6. 4-Bromo-6-ethyl-5-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole. To a solution of 4-bromo-6-ethyl-5-iodo-1H-indazole (23.0 g, 65.5 mmol) in dichloromethane (300 mL) was added TsOH·H$_2$O (0.62 g, 3.30 mmol) and DHP (18 mL, 197 mmol) under N_2. Then the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water and extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give 4-bromo-6-ethyl-5-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (30 g in total).

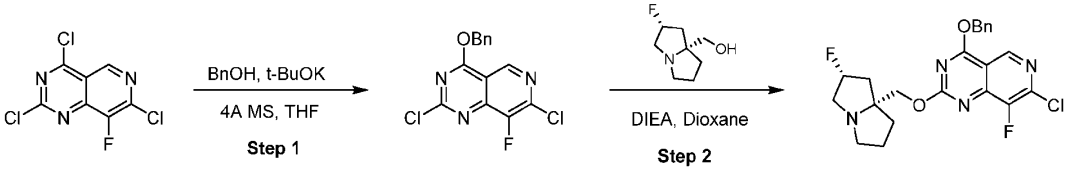
[00279] Step 7. 5-Allyl-4-bromo-6-ethyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole. To a solution of 4-bromo-6-ethyl-5-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (14.0 g, 32.2 mmol) in toluene (200 mL) was added LiCl (6.82 g, 161 mmol) and allyltributylstannane (22.95 g, 69.3 mmol) and $Pd(PPh_3)_4$ (3.72 g, 3.22 mmol) under N_2. Then the mixture was stirred at 110 °C for 12 h. The reaction mixture was combined with another batch (14 g scale) and diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a gradient of 0–10% EtOAc in petroleum ether, to give 5-allyl-4-bromo-6-ethyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (6.4 g in total). *m/z* (ESI): 349.2 $(M+H)^+$.

[00280] Step 8. 2-(4-Bromo-6-ethyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)acetaldehyde. To a solution of 5-allyl-4-bromo-6-ethyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (5.9 g, 16.9 mmol) in 1,4-dioxane (100 mL) and water (20 mL) was added $K_2OsO_4·2H_2O$ (1.25 g, 3.38 mmol), 2,6-dimethylpyridine (3.62 g, 33.8 mmol) and $NaIO_4$ (14.45 g, 67.6 mmol). Then the reaction mixture was stirred at 50 °C for 2 h. The reaction mixture was combined with two other batches (5.9 g, 1 g), diluted with water, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 0–10% EtOAc in petroleum ether, to give 2-(4-bromo-6-ethyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)acetaldehyde (3.9 g in total). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 9.75 (s, 1 H), 7.99 (s, 1 H), 7.41 (s, 1 H), 5.67 - 5.73 (m, 1 H), 4.08 (s, 2 H), 3.98 - 4.06 (m, 1 H), 3.71 - 3.80 (m, 1 H), 2.76 (q, *J*=7.6 Hz, 2 H), 2.50 - 2.62 (m, 1 H), 2.06 - 2.22 (m, 2 H), 1.65 - 1.83 (m, 3 H), 1.25 - 1.30 (m, 3 H).

[00281] Step 9. 2-(4-Bromo-6-ethyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethan-1-ol. To a solution of 2-(4-bromo-6-ethyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)acetaldehyde (3.9 g, 11 mmol) in ethanol (40 mL) was added $NaBH_4$ (1.14 g, 30.1 mmol) in portion at 0 °C. Then the mixture was stirred at room temperature for 1 h. The reaction mixture was quenched by water at 0 °C,

and then diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 0–20% EtOAc in petroleum ether, to give 2-(4-bromo-6-ethyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethan-1-ol (3.4 g, 9.6 mmol, 87% yield). *m/z* (ESI): 353.1 $(M+H)^+$.

Intermediate U: 4-(Benzyloxy)-7-chloro-8-fluoro-2-(((2*R*,7a*R*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine.

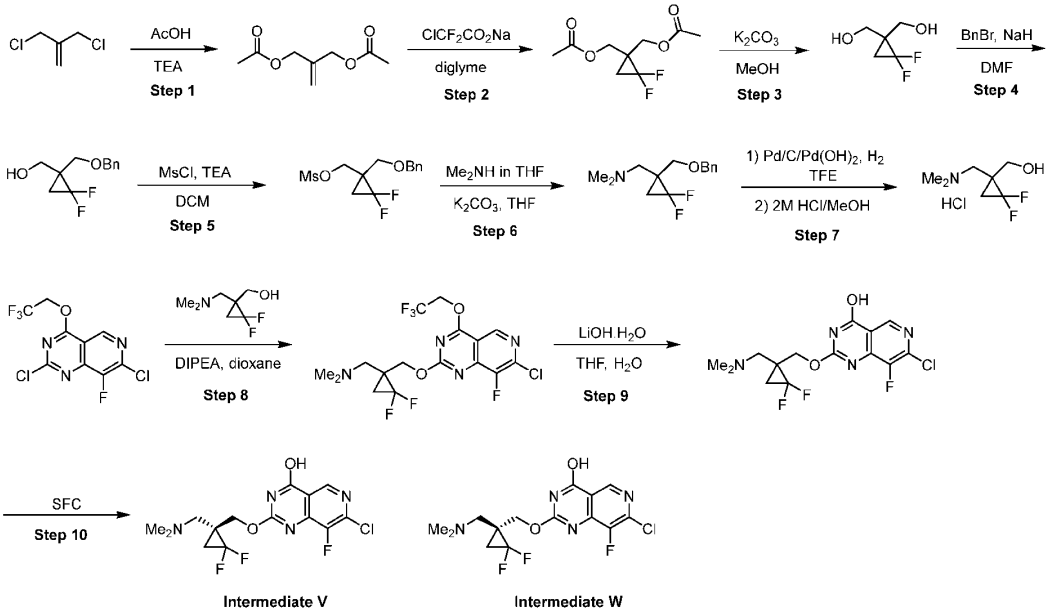


Intermediate U

[00282] Step 1. 4-(Benzyloxy)-2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidine. To a solution of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (50.0 g, 198 mmol) and 4Å molecular sieves (20 g, 198 mmol) in tetrahydrofuran (1.5 L) was added phenylmethanol (20.4 g, 188 mmol) in t-BuOK (1M in THF , 188 mL, 188 mmol) dropwise at -60 °C. The reaction mixture was stirred at -60 °C for 2 h, was then diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was triturated with petroleum ether at room temperature for 30 minutes, filtered and concentrated under reduced pressure to give 4-(benzyloxy)-2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidine (51.2 g, 158 mmol, 80% yield). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.20 (s, 1 H), 7.55 - 7.65 (m, 2 H), 7.39 - 7.48 (m, 3 H), 5.72 (s, 2 H).

[00283] Step 2. 4-(Benzyloxy)-7-chloro-8-fluoro-2-(((2*R*,7a*R*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine. A solution of 4-(benzyloxy)-2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidine (1.0 g, 3.1 mmol) and ((2*R*,7a*R*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol (0.69 g, 4.3 mmol) in DIPEA (5 mL, 29 mmol) and 1,4-dioxane (5 mL) was stirred at 100 °C for 1 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 250 x 70 mm x 10 μm; mobile phase: [A: H_2O (10 mM NH_4HCO_3); B: ACN]; B%: 50–80 %, 20 min) to give 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2*R*,7a*R*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (0.25 g, 36 mmol, 18% yield). *m/z* (ESI): 447.2 $(M+H)^+$.

Intermediate V & W: (*R*)-7-Chloro-2-((1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoropyrido[4,3-*d*]pyrimidin-4-ol & (*S*)-7-chloro-2-((1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoropyrido[4,3-*d*]pyrimidin-4-ol.



[00284] Step 1. 2-Methylenepropane-1,3-diyl diacetate. To a solution of 3-chloro-2-(chloromethyl)prop-1-ene (60.0 g, 480 mmol) in triethylamine (146 g, 1.44 mol) was added acetic acid (72.1 g, 1.20 mol) dropwise. The resulting mixture was heated and stirred at 70 °C for 12 h under N_2. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 5–100% EtOAc in petroleum ether, to provide 2-methylenepropane-1,3-diyl diacetate (56.4 g, 328 mmol, 67% yield). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 5.21 (s, 2 H), 4.54 (s, 4 H), 2.02 (s, 6 H).

[00285] Step 2. (2,2-Difluorocyclopropane-1,1-diyl)bis(methylene) diacetate. To a solution of 2-methylenepropane-1,3-diyl diacetate (80.0 g, 465 mmol) in diglyme (640 mL) was added the solution of $ClCF_2CO_2Na$ (353 g, 2.32 mol) in diglyme (640 mL) dropwise at 180 °C under nitrogen over 5 h. The resulting mixture was stirred at 180 °C for 1 h. After cooling to room temperature, the reaction mixture was diluted with water and extracted with petroleum ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the crude containing (2,2-

difluorocyclopropane-1,1-diyl)bis(methylene) diacetate (80 g) which was used directly without further purification.

[00286] Step 3. (2,2-Difluorocyclopropane-1,1-diyl)dimethanol. To a solution of (2,2-difluorocyclopropane-1,1-diyl)bis(methylene) diacetate (100 g, 450 mmol) in methanol (1.25 L) was added potassium carbonate (124 g, 900 mmol). The resulting mixture was stirred at room temperature for 12 h under N_2, was then diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 5–100% EtOAc in petroleum ether, to provide (2,2-difluorocyclopropane-1,1-diyl)dimethanol (43.0 g, 312 mmol, 69% yield).

[00287] Step 4. (1-((Benzyloxy)methyl)-2,2-difluorocyclopropyl)methanol. To a solution of (2,2-difluorocyclopropane-1,1-diyl)dimethanol (64.0 g, 463 mmol) in *N,N*-dimethylformamide (1.18 L) was added sodium hydride (60 wt% in mineral oil, 22.2 g, 927 mmol) in portions under N_2 at 0 °C. The mixture was stirred at 0 °C for 1 h. Then the solution of (bromomethyl)benzene (95.0 g, 556 mmol) in *N,N*-dimethylformamide (100 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 1 h under N_2, was then diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 5–100% EtOAc in petroleum ether, to provide (1-((benzyloxy)methyl)-2,2-difluorocyclopropyl)methanol (47.75 g, 209 mmol, 45% yield).

[00288] Step 5. (1-((Benzyloxy)methyl)-2,2-difluorocyclopropyl)methyl methanesulfonate. To a 3-L three-neck bottle was added the solution of (1-((benzyloxy)methyl)-2,2-difluorocyclopropyl)methanol (58.0 g, 254 mmol) in dichloromethane (1.2 L), TEA (142 mL, 1016 mmol) was added slowly at 0 °C, then methanesulfonyl chloride (57.7 g, 504 mmol) was added dropwise at 0 °C under N_2. The resulting mixture was stirred at room temperature for 3 h, was then diluted with ice water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 5–100% EtOAc in petroleum ether, to provide (1-((benzyloxy)methyl)-2,2-difluorocyclopropyl)methyl methanesulfonate (70.0 g, 228 mmol, 90% yield).

[00289] Step 6. 1-(1-((Benzyloxy)methyl)-2,2-difluorocyclopropyl)-*N,N*-dimethylmethanamine. To a solution of (1-((benzyloxy)methyl)-2,2-difluorocyclopropyl)methyl methanesulfonate (40.0 g, 131 mmol) in tetrahydrofuran (400 mL) was added Me_2NH in THF (326 mL, 653 mmol) and K_2CO_3 (36.1 g, 261 mmol) in sequence. The resulting mixture was stirred at 50 °C for 24 h under N_2, was then diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column

chromatography on silica gel, eluting with a gradient of 5–100% EtOAc in petroleum ether, to provide 1-(1-((benzyloxy)methyl)-2,2-difluorocyclopropyl)-*N*,*N*-dimethylmethanamine (24 g, 94 mmol, 72% yield).

[00290] Step 7. (1-((Dimethylamino)methyl)-2,2-difluorocyclopropyl)methanol. To a solution of 10% Pd/C (8 g) and 20% $Pd(OH)_2$ (8 g) in 2,2,2-trifluoroethan-1-ol (1 L) was added 1-(1-((benzyloxy)methyl)-2,2-difluorocyclopropyl)-*N*,*N*-dimethylmethanamine (50 g, 196 mmol) under an Argon atmosphere. The suspension was degassed and purged with H_2 for 3 times. The reaction mixture was stirred under H_2 (15 psi) at room temperature for 12 h, was then filtered through a pad of celite and washed with methanol. To the combined filtrate was treated with HCl (3 M in MeOH, 100 mL, 300 mmol), then was concentrated under reduced pressure to give (1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methanol (20.49 g, 102 mmol, 52% yield, as its HCl salt).

[00291] Step 8. 1-(1-(((7-Chloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-2-yl)oxy)methyl)-2,2-difluorocyclopropyl)-*N*,*N*-dimethylmethanamine. To a solution of 2,7-dichloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidine (**Step 1** in **Intermediate C**, 20.0 g, 63.3 mmol) in 1,4-dioxane (400 mL) was added (1-((dimethylamino)methyl)-2,2-difluorocyclopropyl) methanol hydrochloride (15.31 g, 76 mmol) and DIPEA (27.6 mL, 158 mmol) in sequence under N_2 at 0 °C. The reaction mixture was stirred at room temperature for 3 h, was then diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give 1-(1-(((7-chloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-2-yl)oxy)methyl)-2,2-difluorocyclopropyl)-*N*,*N*-dimethylmethanamine (12.3 g, 27 mmol, 44% yield).

[00292] Step 9. 7-Chloro-2-((1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoropyrido[4,3-*d*]pyrimidin-4-ol. To a solution of 1-(1-(((7-chloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-2-yl)oxy)methyl)-2,2-difluorocyclopropyl)-*N*,*N*-dimethylmethanamine (32.3 g, 72.6 mmol) in tetrahydrofuran (640 mL) and water (128 mL) was added LiOH·H_2O (12.2 g, 290 mmol). The reaction mixture was stirred at 60 °C for 2 h. After cooling to room temperature, the mixture was combined with another batch (10 g) and diluted with H_2O and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 5–100% EtOAc in petroleum ether, to provide 7-chloro-2-((1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoropyrido[4,3-*d*]pyrimidin-4-ol (25.5 g, 70 mmol, 74% yield).

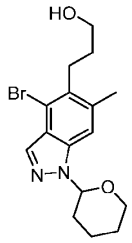
[00293] Step 10. (*R*)-7-Chloro-2-((1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoropyrido[4,3-*d*]pyrimidin-4-ol & (*S*)-7-chloro-2-((1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoropyrido[4,3-*d*]pyrimidin-4-ol. 7-Chloro-2-((1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoropyrido[4,3-

d]pyrimidin-4-ol (33 g, 91 mmol) was separated by SFC (Column: Chiralpak IG 250 x 50 mm, 10 µm, Mobile phase: A for CO_2 and B for EtOH (0.1%$NH_3 H_2O$), Gradient: B%=60% isocratic, Flow rate: 200 mL/min) to give two compounds (the structures were temporary assigned) as follows:

Peak 1: (*R*)-7-chloro-2-((1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoropyrido[4,3-*d*]pyrimidin-4-ol (13.8 g, 38.1 mmol, 42% yield). *m/z* (ESI): 363.1/365.0 $(M+H)^+$. ^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 8.72 (s, 1 H), 4.48 - 4.59 (m, 2 H), 2.98 (d, *J* = 13.6 Hz, 1 H), 2.77 (d, *J* = 12.8 Hz, 1 H), 2.52 (s, 6 H), 1.76 – 1.79 (m, 1 H), 1.51 – 1.54 (m, 1 H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -136.99 – -137.42 (m, 1 F), -138.84 -139.55 (m, 2 F). SFC: ee % = 99.9%

Peak 2: (*S*)-7-chloro-2-((1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoropyrido[4,3-*d*]pyrimidin-4-ol (16.7 g, 47.7 mmol, 52% yield). *m/z* (ESI): 363.1/365.0 $(M+H)^+$. ^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 8.74 (s, 1 H), 4.50 (s, 2 H), 2.86 (d, *J* = 16.4 Hz, 1 H), 2.40 (d, *J* = 14.4 Hz, 1 H), 2.26(s, 6 H), 1.64 – 1.65 (m, 1 H), 1.32 – 1.33 (m, 1 H). ^{19}F NMR (400 MHz, *METHANOL-d4*) δ ppm-137.31 – -137.73 (m, 1 F), -138.94 -139.70 (m, 2 F). SFC: ee% = 99.7%.

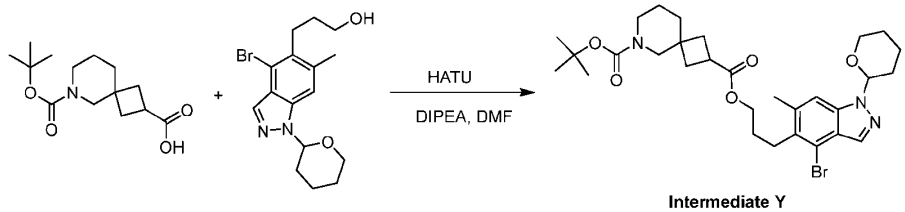
Intermediate X: 3-(4-Bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propan-1-ol.



Intermediate X

[00294] The title compound was synthesized analogous to **Intermediate A** using 4-bromo-5-iodo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (Advanced ChemBlocks) in **Step 1**. *m/z* (ESI): 353.0 $(M+H)^+$. ^{1}H NMR (400 MHz, *CDCl3*) δ ppm 7.95 (s, 1 H), 7.35 (s, 1 H), 5.58 - 5.76 (m, 1 H), 3.97 - 4.08 (m, 1 H), 3.68 - 3.884 (m, 3 H), 2.91 - 3.07 (m, 2 H), 2.47 - 2.64 (m, 4 H), 2.12 - 2.25 (m, 1 H), 2.06 - 2.12 (m, 1 H), 1.63 - 1.91 (m, 5 H).

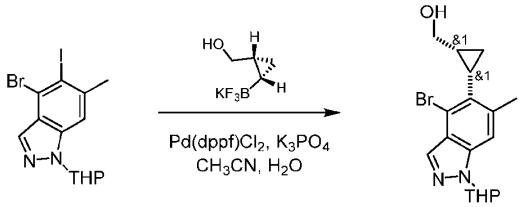
Intermediate Y: 2-(3-(4-Bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl) 6-(*tert*-butyl) 6-azaspiro[3.5]nonane-2,6-dicarboxylate.



Intermediate Y

[00295] A 40-mL vial was charged with HATU (1.86 mg, 4.90 mmol, AA BLOCKS LLC), 1,1'-dimethyltriethylamine (2.1 mL, 12 mmol), 6-(*tert*-butoxycarbonyl)-6-azaspiro[3.5]nonane-2-carboxylic acid (1.10 g, 4.08 mmol, Aurum Pharmatech LLC), 3-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propan-1-ol (**Intermediate X**, 2.16 g, 6.13 mmol) and *N*,*N*-dimethylformamide (20 mL). The reaction mixture was stirred at room temperature for 16 h, the crude mixture was purified by column chromatography on silica gel, eluting with a gradient of 0–85% EtOAc in heptane, to yield 2-(3-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl) 6-(*tert*-butyl) 6-azaspiro[3.5]nonane-2,6-dicarboxylate (**Intermediate Y**, 2.16 g, 3.57 mmol, 87% yield). *m/z* (ESI): 606.2 $(M+H)^+$.

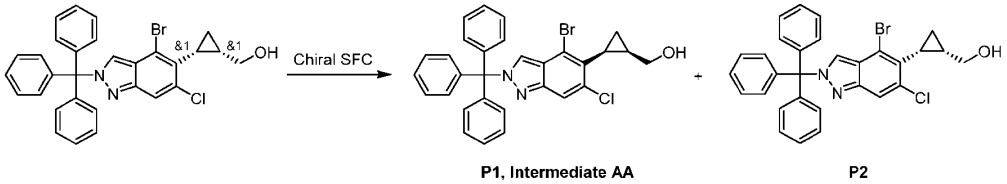
Intermediate Z: *rac*-((1*R*,2*S*)-2-(4-Bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl) methanol.



Intermediate Z

[00296] To a solution of 4-bromo-5-iodo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (45 g, 107 mmol, Advanced ChemBlocks) in acetonitrile (1 L) and water (250 mL) was added potassium trifluoro ((1*S*,2*R*)-2-(hydroxymethyl)cyclopropyl) borate (38.0 g, 214 mmol, Lab Network), K_3PO_4 (113 g, 534 mmol) and $Pd(dppf)Cl_2$ (15.64 g, 21.37 mmol) in sequence under nitrogen. The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with 10–35% EtOAc in petroleum ether, to give *rac*-((1*R*,2*S*)-2-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl) methanol (**Intermediate Z**, 12.9 g, 35.6 mmol, 33% yield). *m/z* (ESI): 365.0/367.0 $(M+H)^+$.

Intermediate AA. ((1*R*,2*S*)-2-(4-Bromo-6-chloro-2-trityl-2*H*-indazol-5-yl)cyclopropyl)methanol.

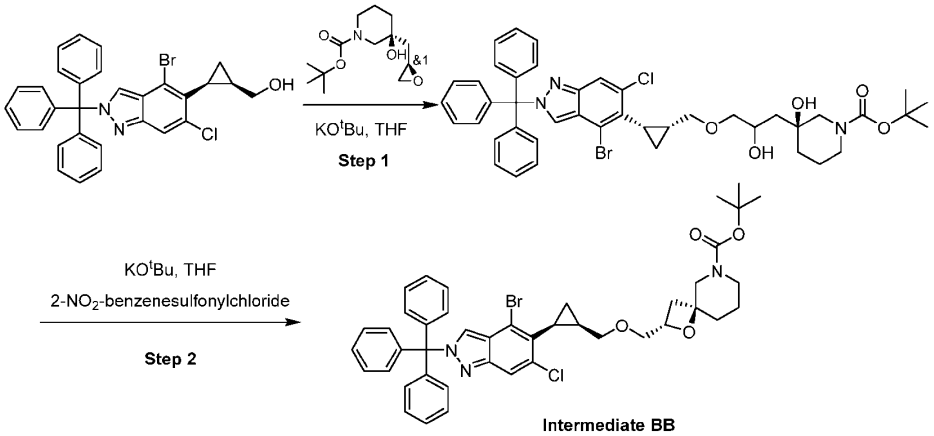


[00297] Total 115 g of *rac*-(2-(4-bromo-6-chloro-2-trityl-2*H*-indazol-5-yl)cyclopropyl)methanol was separated by SFC [Instrument: Waters SFC350; Column: DAICEL CHIRALPAK IE (250 mm x 50 mm, 10 μm); Mobile phase: A for CO_2 and B for EtOH; Gradient: B%=55% isocratic elution mode; Flow rate: 200 mL/min; Wavelength: 220 nm; Column temperature: 40 °C; System back pressure: 100 bar]. The eluent was concentrated to remove organic solvents.

[00298] Compound ((1*R*,2*S*)-2-(4-bromo-6-chloro-2-trityl-2*H*-indazol-5-yl)cyclopropyl)methanol (44 g as **P1**, 100% ee, the structure was temporary assigned) was obtained. *m/z* (ESI): 243.3 $(M+H)^+$.

[00299] Compound ((1*S*,2*R*)-2-(4-bromo-6-chloro-2-trityl-2*H*-indazol-5-yl)cyclopropyl)methanol (45 g as **P2**, 98% ee, the structure was temporary assigned) was obtained. *m/z* (ESI): 243.3 $(M+H)^+$.

Intermediate BB: *tert*-Butyl (2*S*,4*S*)-2-((((1*R*,2*S*)-2-(4-bromo-6-chloro-2-trityl-2*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate.

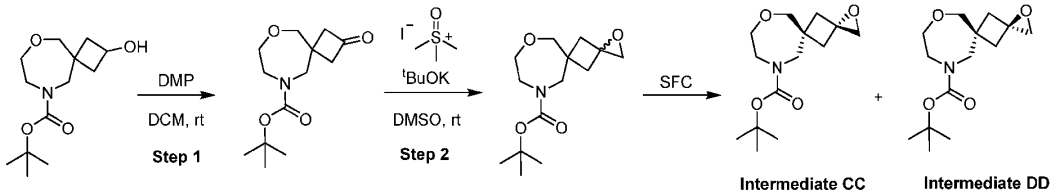


[00300] Step 1. *tert*-Butyl (3*S*)-3-(3-(((1*R*,2*S*)-2-(4-bromo-6-chloro-2-trityl-2*H*-indazol-5-yl)cyclopropyl)methoxy)-2-hydroxypropyl)-3-hydroxypiperidine-1-carboxylate. To a stirred mixture of ((1*R*,2*S*)-2-(4-bromo-6-chloro-2-trityl-2*H*-indazol-5-yl)cyclopropyl)methanol

(**Intermediate AA**, 1.78 g, 3.26 mmol) in tetrahydrofuran (12 mL) at 0 °C under nitrogen, was added potassium *tert*-butoxide (0.40 g, 3.54 mmol, Sigma Aldrich). This was stirred at 0 °C for 10 minutes, then *tert*-butyl (3*S*)-3-hydroxy-3-(oxiran-2-ylmethyl)piperidine-1-carboxylate (**Step 1 in Example 1.038,** 0.70 g, 2.72 mmol,) was added a solution in tetrahydrofuran (6 mL). The resulting mixture was stirred at 50 °C for 2 h. The reaction was concentrated and the crude material purified by column chromatography on silica gel, eluting with a gradient of 0–100% EtOAc in heptane to provide *tert*-butyl (3*S*)-3-(3-(((1*R*,2*S*)-2-(4-bromo-6-chloro-2-trityl-2*H*-indazol-5-yl)cyclopropyl)methoxy)-2-hydroxypropyl)-3-hydroxypiperidine-1-carboxylate (0.82 g, 1.03 mmol, 37% yield). *m/z* (ESI): 821.6 $(M+Na)^+$.

[00301] Step 2. *tert*-Butyl (2*S*,4*S*)-2-((((1*R*,2*S*)-2-(4-bromo-6-chloro-2-trityl-2*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate. To a stirred mixture of *tert*-butyl (3*S*)-3-(3-(((1*R*,2*S*)-2-(4-bromo-6-chloro-2-trityl-2*H*-indazol-5-yl)cyclopropyl)methoxy)-2-hydroxypropyl)-3-hydroxypiperidine-1-carboxylate (1.38 g, 1.72 mmol) in tetrahydrofuran (17 mL) at 0 °C under nitrogen, was added potassium *tert*-butoxide (0.43 g, 3.79 mmol). The resulting mixture was stirred at 0 °C for 30 minutes. To this was added 2-nitrobenzenesulfonyl chloride (0.53 g, 2.41 mmol) and the reaction was warmed to room temperature over 16 h. Upon completion the reaction was diluted with water and extracted with ethyl acetate. The ethyl acetate was dried over sodium sulfate and concentrated. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0–70% EtOAc in heptane to provide *tert*-butyl (2*R*,4*S*)-2-((((1*R*,2*S*)-2-(4-bromo-6-chloro-2-trityl-2*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate (0.35 g, 0.44 mmol, 25% yield). *m/z* (ESI): 804.0 $(M+Na)^+$ and *tert*-butyl (2*S*,4*S*)-2-((((1*R*,2*S*)-2-(4-bromo-6-chloro-2-trityl-2*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate (0.26 g, 0.33 mmol, 19% yield). *m/z* (ESI): 804.0 $(M+Na)^+$.

Intermediate CC: *tert*-Butyl (3*R*,5*R*)-1,7-dioxa-10-azadispiro[2.1.6^5.1^3]dodecane-10-carboxylate and **Intermediate DD: *tert*-butyl (3*S*,5*S*)-1,7-dioxa-10-azadispiro[2.1.6^5.1^3]dodecane-10-carboxylate.**



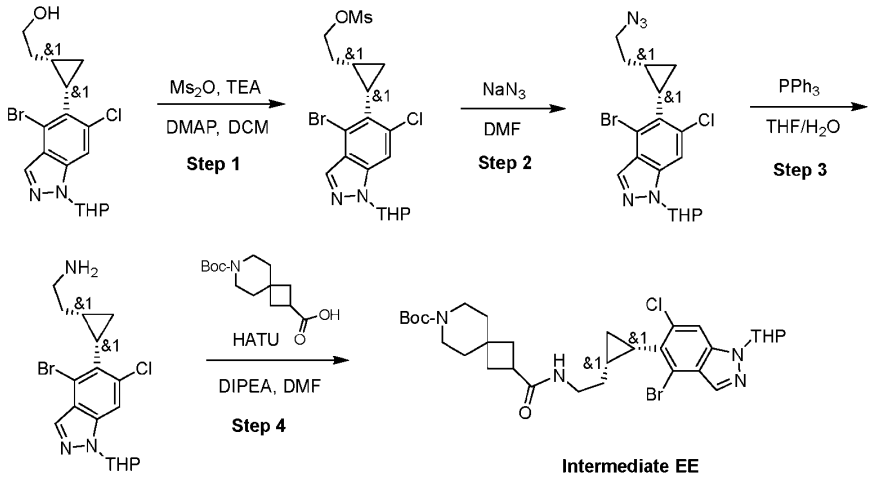
[00302] Step 1. *tert*-Butyl 2-oxo-6-oxa-9-azaspiro[3.6]decane-9-carboxylate. To a 250-mL round-bottom flask was added *tert*-butyl 2-hydroxy-6-oxa-9-azaspiro[3.6]decane-9-carboxylate (2.50 g, 9.72 mmol, Enamine) in dichloromethane (50 mL). The mixture was cooled to 0 °C and Dess-

Martin periodinane (4.94 g, 11.7 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 1 h. The reaction mixture was quenched with a mixture of 0.1 N sodium thiosulfate solution and saturated sodium bicarbonate solution (1:1). The aqueous layer was extracted with dichloromethane and the combined organic layers were dried over sodium sulfate, filtered, and concentrated. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 5–80% EtOAc in heptane, to give *tert*-butyl 2-oxo-6-oxa-9-azaspiro[3.6]decane-9-carboxylate (2.6 g, 10 mmol, crude). *m/z* (ESI): 200.0 (M-^{t}Bu+H)$^+$. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 3.89 – 3.69 (m, 6H), 3.65 – 3.50 (m, 2H), 3.11 – 2.78 (m, 4H), 1.49 (s, 9H).

[00303] Step 2. *tert*-Butyl 1,7-dioxa-10-azadispiro[2.1.6^5.1^3]dodecane-10-carboxylate. To a solution of potassium *tert*-butoxide (2.69 g, 23.9 mmol) in dimethyl sulfoxide (50 mL) was added trimethylsulfoxonium iodide (5.87 g, 26.7 mmol) under nitrogen. The reaction mixture was stirred at room temperature for 1.5 h, 1,2-dimethoxyethane (10 mL) was added at 0 °C. Then *tert*-butyl 2-oxo-6-oxa-9-azaspiro[3.6]decane-9-carboxylate (4.7 g, 18 mmol) in 1,2-dimethoxyethane (10 mL) and dimethyl sulfoxide (2.5 mL) was added at 0 °C. The mixture was stirred at 0 °C for 2 h and at room temperature for 1 h. The mixture was quenched by addition of water at 0 °C, and then extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 5–80% EtOAc in heptane, to give *tert*-butyl 1,7-dioxa-10-azadispiro[2.1.6^5.1^3]dodecane-10-carboxylate (3.15 g, 11.7 mmol, 64% yield). *m/z* (ESI): 214.0 (M-^{t}Bu+H)$^+$. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 3.78 – 3.50 (m, 8H), 2.80 – 2.68 (m, 2H), 2.48 – 2.21 (m, 4H), 1.51 – 1.48 (m, 9H).

[00304] Step 3. *tert*-Butyl (3*R*,5*R*)-1,7-dioxa-10-azadispiro[2.1.6^5.1^3]dodecane-10-carboxylate and *tert*-butyl (3*S*,5*S*)-1,7-dioxa-10-azadispiro[2.1.6^5.1^3]dodecane-10-carboxylate. *tert*-Butyl 1,7-dioxa-10-azadispiro[2.1.6^5.1^3]dodecane-10-carboxylate (3.12 g, 11.6 mmol) was purified via SFC using a ChiralPak IG, 3 x 25 cm, 5 µm column with a mobile phase of 10% EtOH using a flowrate of 200 mL/min to generate 0.98 g of *tert*-butyl (3*R*,5*R*)-1,7-dioxa-10-azadispiro[2.1.6^5.1^3]dodecane-10-carboxylate with an ee of 99%. *m/z* (ESI): 214.0 (M-^{t}Bu+H)$^+$. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 3.81 – 3.63 (m, 5H), 3.61 (s, 1H), 3.58 – 3.45 (m, 2H), 2.76 – 2.70 (m, 2H), 2.48 – 2.36 (m, 2H), 2.29 – 2.22 (m, 2H), 1.52 – 1.47 (m, 9H) and 1.7 g of *tert*-butyl (3*S*,5*S*)-1,7-dioxa-10-azadispiro[2.1.6^5.1^3]dodecane-10-carboxylate with an ee of 99%. *m/z* (ESI): 214.0 (M-^{t}Bu+H)$^+$. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 3.81 – 3.67 (m, 6H), 3.60 – 3.50 (m, 2H), 2.76 (d, *J* = 9.0 Hz, 2H), 2.39 – 2.14 (m, 4H), 1.48 (d, *J* = 6.5 Hz, 9H).

Intermediate EE: *rac-tert*-Butyl 2-((2-((1*S*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)ethyl)carbamoyl)-6-azaspiro[3.5]nonane-6-carboxylate.



[00305] Step 1. *rac*-2-((1*S*,2*S*)-2-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)ethyl methanesulfonate. To a solution of *rac*-2-((1*S*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)ethan-1-ol (**Step 4** in **Intermediate LL**, 2.0 g, 5.0 mmol) in dichloromethane (20 mL) was added TEA (2.0 mL, 14.3 mmol) and DMAP (61 mg, 0.50 mmol). The contents were cooled to 0 °C, then Ms_2O (1.31 g, 7.51 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, then was combined with three other batches (3 g), diluted with water, and extracted with DCM. The combined organic layers were dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a gradient of 5–25% EtOAc in petroleum ether, to yield *rac*-2-((1*S*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)ethyl methanesulfonate (total 8 g). *m/z* (ESI): 501.1 $(M+Na)^+$.

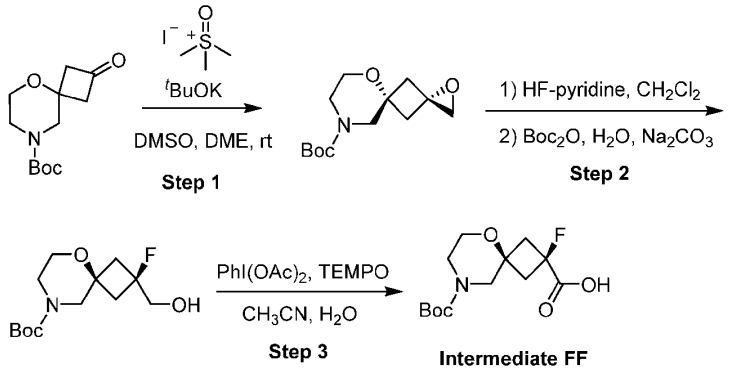
[00306] Step 2. *rac*-5-((1*S*,2*S*)-2-(2-Azidoethyl)cyclopropyl)-4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole. To a solution of *rac*-2-((1*S*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)ethyl methanesulfonate (2.0 g, 4.2 mmol) in *N*,*N*-dimethylformamide (20 mL) was added NaN_3 (0.23 g, 3.50 mmol). The reaction mixture was stirred at 80 °C for 1 h. After cooling to room temperature, the mixture was diluted with water and adjusted to pH 9 with sat. NaOH. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give crude product of *rac*-5-((1*S*,2*S*)-2-(2-azidoethyl)cyclopropyl)-4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (1.8 g). *m/z* (ESI): 424.1 $(M+H)^+$.

[00307] Step 3. *rac*-2-((1*S*,2*S*)-2-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)ethan-1-amine. To a solution of *rac*-5-((1*S*,2*S*)-2-(2-azidoethyl)cyclopropyl)-4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (1.8 g, 4.2 mmol) in tetrahydrofuran (20

mL) was added water (0.5 mL) and PPh_3 (2.22 g, 8.48 mmol). The mixture was stirred at 60 °C for 1 h. The reaction mixture was purified by column chromatography on silica gel, eluting with a gradient of 0–10% MeOH in DCM, to give *rac*-2-((1*S*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)ethan-1-amine (1.2 g). *m/z* (ESI): 400.2 $(M+H)^+$.

[00308] Step 4. *rac-tert*-Butyl 2-((2-((1*S*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)ethyl)carbamoyl)-6-azaspiro[3.5]nonane-6-carboxylate. To a solution of 6-(*tert*-butoxycarbonyl)-6-azaspiro[3.5]nonane-2-carboxylic acid (0.74 g, 2.8 mmol) in *N*,*N*-dimethylformamide (10 mL) was added HATU (1.43 g, 3.76 mmol), DIPEA (1.5 mL, 8.6 mmol) and *rac*-2-((1*S*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)ethan-1-amine (1.0 g, 2.5 mmol) in *N*,*N*-dimethylformamide (2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, was then combined with another 0.2 g batch, diluted with water, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a gradient of 10–100% EtOAc in petroleum ether, to yield *rac-tert*-butyl 2-((2-((1*S*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)ethyl)carbamoyl)-6-azaspiro[3.5]nonane-6-carboxylate (1.6 g). *m/z* (ESI): 673.3 $(M+Na)^+$.

Intermediate FF: (2*S*,4*S*)-8-(*tert*-Butoxycarbonyl)-2-fluoro-5-oxa-8-azaspiro[3.5]nonane-2-carboxylic acid.



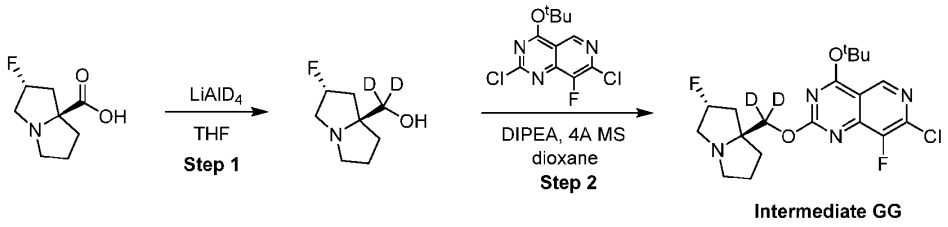
[00309] Step 1. *tert*-Butyl (3*R*,5*R*)-1,6-dioxa-9-azadispiro[2.1.5^5.1^3]undecane-9-carboxylate. To a solution of potassium *tert*-butoxide (2.84 g, 25.3 mmol) in dimethyl sulfoxide (50 mL) was added trimethylsulfoxonium iodide (6.22 g, 28.2 mmol) under nitrogen atmosphere. The mixture was stirred at room temperature for 1.5 h, then 1,2-dimethoxyethane (10 mL) was added at 0 °C, followed by *tert*-butyl 2-oxo-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate (4.70 g, 19.5 mmol, Pharmablock Inc.) in

1,2-dimethoxyethane (10 mL) and dimethyl sulfoxide (2.5 mL). The mixture was stirred at 0 °C for 1 h and room temperature for 1 h. The mixture was quenched by the addition of water at 0 °C, and then extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with 0–100% EtOAc in heptane, to provide *tert*-butyl (3*R*,5*R*)-1,6-dioxa-9-azadispiro[2.1.5^5.1^3]undecane-9-carboxylate (0.82 g, 3.20 mmol, 16% yield). *m/z* (ESI): 200.0 (M-^{t}Bu+H)$^+$.

[00310] Step 2. *tert*-Butyl (2*S*,4*S*)-2-fluoro-2-(hydroxymethyl)-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate. In a 250-mL round-bottom flask was added hydrogen fluoride (70% in 30% pyridine, (0.90 g, 9.1 mmol) and the flask was cooled to -78 °C. *tert*-Butyl (3*R*,5*R*)-1,6-dioxa-9-azadispiro[2.1.5^5.1^3]undecane-9-carboxylate (0.82 g, 3.20 mmol) in dichloromethane (3 mL) was added dropwise, and the reaction mixture was stirred at -78 °C for 6 h. To the mixture was added 1 M Na_2CO_3 solution (70 mL) and dichloromethane (50 mL), and the mixture was allowed to warm to 0 °C. di-*tert*-Butyl dicarbonate (0.70 g, 3.20 mmol) was added and the mixture was gradually warmed to room temperature with stirring for 16 h. The resulting mixture was extracted by CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude was purified by column chromatography on silica gel, eluting with 0–100% EtOAc in heptane, to provide *tert*-butyl (2*S*,4*S*)-2-fluoro-2-(hydroxymethyl)-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate (0.28 g, 1.00 mmol, 32% yield). *m/z* (ESI): 298.1 (M+Na)$^+$. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 3.70 – 3.60 (m, 2H), 3.59 – 3.54 (m, 2H), 3.34 (br s, 2H), 3.28 (s, 2H), 3.00 (br s, 1H), 2.44 – 2.33 (m, 2H), 2.33 – 2.20 (m, 2H), 1.42 (s, 9H).

[00311] Step 3. (2*S*,4*S*)-8-(*tert*-Butoxycarbonyl)-2-fluoro-5-oxa-8-azaspiro[3.5]nonane-2-carboxylic acid. To a 40-mL vial was dissolved *tert*-butyl (2*S*,4*S*)-2-fluoro-2-(hydroxymethyl)-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate (0.73 g, 2.70 mmol) in water (8 mL) and acetonitrile (12 mL). TEMPO (83 mg, 0.53 mmol) and (diacetoxyiodo)benzene (2.15 g, 6.66 mmol) was added, and the mixture was heated at 60 °C for 3 h. Acetonitrile was removed, and the resulting aqueous mixture was basified with saturated $NaHCO_3$ solution and extracted with EtOAc. The aqueous phase was acidified by 1 M $KHSO_4$ solution and extracted by EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to provide (2*S*,4*S*)-8-(*tert*-butoxycarbonyl)-2-fluoro-5-oxa-8-azaspiro[3.5]nonane-2-carboxylic acid (0.69 g, 2.40 mmol, 89% yield). *m/z* (ESI): 312.1 (M+Na)$^+$. ^{1}H NMR (500 MHz, *DMSO-d$_6$*) δ ppm 13.87 – 13.13 (m, 1H), 3.56 – 3.52 (m, 2H), 3.34 – 3.30 (m, 2H), 3.30 – 3.26 (m, 2H), 2.69 (br d, J = 2.6 Hz, 2H), 2.42 – 2.31 (m, 2H), 1.42 – 1.38 (m, 9H). ^{19}F NMR (471 MHz, *DMSO-d$_6$*) δ ppm -142.59 – -144.38 (m, 1F).

Intermediate GG: 4-(*tert*-Butoxy)-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy-d_2)pyrido[4,3-*d*]pyrimidine.

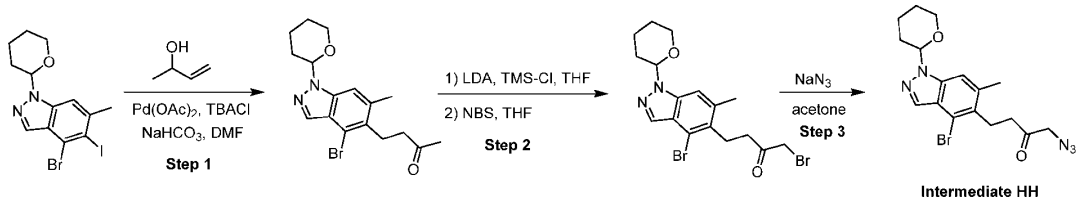


Intermediate GG

[00312] Step 1. ((2*R*,7a*S*)-2-Fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methan-d_2-ol. To a solution of methyl (2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (9.00 g, 48.1 mmol) in tetrahydrofuran (200 mL) was added $LiAlD_4$ (2.0 M in THF, 3.74 g, 89 mmol) slowly. The mixture was stirred at 0 °C for 1 h under a N_2 atmosphere. Then sodium sulfate decahydrate (45 g) was added to quench the reaction followed by ethyl acetate. The reaction mixture was stirred at room temperature for 1 h, then filtered and the filtrate was concentrated under reduced pressure. The residue was combined with two other 9 g batches and purified by column chromatography on silica gel, eluting with a gradient of 50–100% EtOAc in petroleum ether, to provide ((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methan-d_2-ol (22.0 g, 136 mmol, 88% yield). ^{1}H NMR (400 MHz, *CDCl3*) δ ppm 5.13 (d, *J*=3.2 Hz, 1 H), 2.99 - 3.26 (m, 4 H), 2.87 - 2.96 (m, 1 H), 2.00 - 2.16 (m, 2 H), 1.74 - 1.98 (m, 4 H).

[00313] Step 2. 4-(*tert*-Butoxy)-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy-d_2)pyrido[4,3-*d*]pyrimidine. To a solution of ((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methan-d_2-ol (2.89 g, 17.9 mmol) in 1,4-dioxane (40 mL) was added 4-(*tert*-butoxy)-2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidine (**Step 1** in **Intermediate A**, 4.00 g, 13.8 mmol), DIPEA (7.2 mL, 41 mmol) and 4Å MS (4 g). The reaction mixture was stirred at 80 °C for 2 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the residue was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was triturated with MTBE for 30 minutes to give 4-(*tert*-butoxy)-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy-d_2)pyrido[4,3-*d*]pyrimidine (3.0 g, 7.2 mmol, 52% yield). *m/z* (ESI): 415.1 $(M+H)^+$. ^{1}H NMR (400 MHz, *CDCl3*) δ ppm 8.86 (s, 1 H), 5.23 - 5.40 (m, 1 H), 3.28 - 3.38 (m, 1 H), 3.14 - 3.28 m, 2 H), 2.98 - 3.06 (m, 1 H), 2.29 (s, 1 H), 2.11 - 2.24 (m, 2 H), 1.90 - 2.02 (m, 3 H), 1.75 (s, 9 H).

Intermediate HH: 1-Azido-4-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one.



[00314] Step 1. 4-(4-Bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one. To a 40-mL vial was charged with 4-bromo-5-iodo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (2.0 g, 4.8 mmol, Advanced ChemBlocks), sodium bicarbonate (1.0 g, 12 mmol), TBACl (1.37 g, 4.94 mmol), palladium(II) acetate (54 mg, 0.24 mmol), 3-buten-2-ol (0.62 mL, 7.2 mmol) and *N,N*-dimethylformamide (10 mL). The reaction mixture was heated at 65 °C for 16 h. After cooling to room temperature, the reaction was diluted with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined organics were washed with water and brine, dried over sodium sulfate, filtered, and concentrated. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0–50% EtOAc in heptane, to yield 4-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one. *m/z* (ESI): 365.0 $(M+H)^+$.

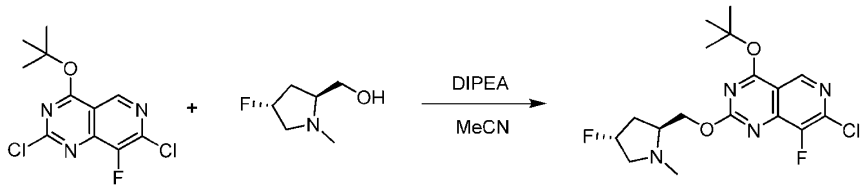
[00315] Step 2. 1-Bromo-4-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one. To a 250-mL round-bottom flask was charged with lithium diisopropylamide (1 M solution in THF/hexanes, 4.9 mL, 4.9 mmol) in anhydrous tetrahydrofuran (35 mL). The mixture was cooled to -78 °C and 4-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one (1.50 g, 4.11 mmol) in THF (8 mL) was added dropwise under a nitrogen atmosphere. The reaction mixture was stirred at -78 °C for 30 minutes. Chlorotrimethylsilane (0.78 mL, 6.2 mmol) was then added dropwise at -78 °C and the reaction mixture was stirred at -78 °C for 30 minutes. The reaction was quenched with saturated $NaHCO_3$ solution, and the mixture was allowed to warm to room temperature and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated.

[00316] The crude oil was diluted in anhydrous THF (10 mL) and cooled to 0 °C. Sodium bicarbonate (0.52 g, 6.20 mmol) and *N*-bromosuccinimide (0.73 g, 4.10 mmol) was added and the mixture was stirred at room temperature for 15 h. The reaction mixture was filtered and concentrated. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0–50% EtOAc in heptane, to give 1-bromo-4-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one (0.74 g, 1.60 mmol, 40% yield). *m/z* (ESI): 444.2 $(M+H)^+$.

[00317] Step 3. 1-Azido-4-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one. To a 250-mL flask was added 1-bromo-4-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one (5.00 g, 11.3 mmol) in acetone (50 mL). Sodium azide (0.95 g, 14.6 mmol) was then added, and the mixture was stirred at room temperature for 16 h. The mixture

was filtered over a pad of celite, and the filtrate was concentrated *in vacuo* to provide 1-azido-4-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one (4.51 g, 11.1 mmol, 99% yield). *m/z* (ESI): 406.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.96 (d, *J*=0.8 Hz, 1 H), 7.38 (s, 1 H), 5.68 (dd, *J*=9.1, 2.8 Hz, 1 H), 4.01 - 4.05 (m, 1 H), 4.00 (s, 2 H), 3.76 (ddd, *J*=11.5, 10.4, 2.9 Hz, 1 H), 3.20 - 3.25 (m, 2 H), 2.68 - 2.74 (m, 2 H), 2.53 - 2.59 (m, 1 H), 2.53 (d, *J*=0.8 Hz, 3 H), 2.15 - 2.21 (m, 1 H), 2.05 - 2.13 (m, 1 H), 1.73 - 1.82 (m, 2 H), 1.65 - 1.72 (m, 1 H).

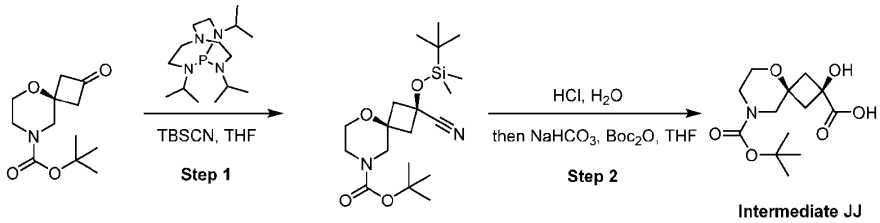
Intermediate II: 4-(*tert*-Butoxy)-7-chloro-8-fluoro-2-(((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-*d*]pyrimidine.



Intermediate II

[00318] The title compound was synthesized analogous to **Intermediate C** using ((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)methanol (CAS#: 2206737-78-0, PharmaBlock) in step 2. *m/z* (ESI): 387.0 $(M+H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.87 (s, 1H), 5.1-5.3 (m, 1H), 4.5-4.6 (m, 2H), 3.5-3.6 (m, 1H), 3.12 (br d, 1H, *J*=4.8 Hz), 2.6-2.7 (m, 1H), 2.5-2.6 (m, 3H), 2.3-2.4 (m, 1H), 1.9-2.1 (m, 1H), 1.7-1.8 (m, 9H).

Intermediate JJ: (2*S*,4*S*)-8-(*tert*-Butoxycarbonyl)-2-hydroxy-5-oxa-8-azaspiro[3.5]nonane-2-carboxylic acid.



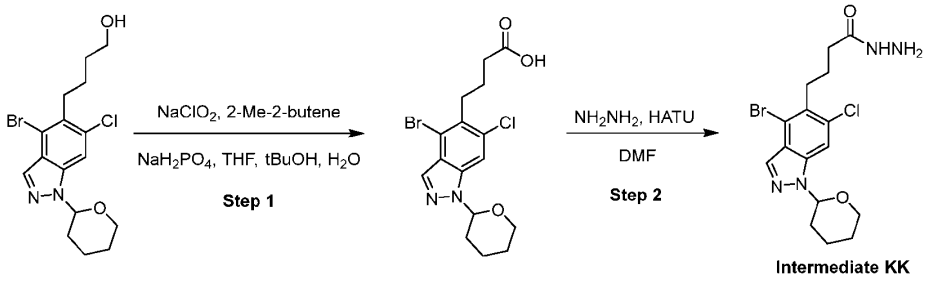
Intermediate JJ

[00319] Step 1. *tert*-Butyl (2*S*,4*S*)-2-((*tert*-butyldimethylsilyl)oxy)-2-cyano-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate. To a 40-mL vial was added *tert*-butyldimethylsilyl cyanide (1.23 g, 8.70 mmol, AbovChem) and *tert*-butyl 2-oxo-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate (2.0 g, 8.3 mmol, AA BLOCKS LLC) in tetrahydrofuran (15 mL). 2,8,9-Triisopropyl-2,5,8,9-tetraaza-1-phosphabicyclo[3,3,3]undercane (0.10 g, 0.33 mmol) was added and the reaction mixture was stirred

at room temperature for 3 h. The resulting mixture was concentrated and directly purified by column chromatography on silica gel, eluting with a gradient of 0–100% EtOAc in heptane, to give *tert*-butyl (2*S*,4*S*)-2-((*tert*-butyldimethylsilyl)oxy)-2-cyano-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate (2.63 g, 6.87 mmol, 83% yield). *m/z* (ESI): 327.1 $(M-^tBu+H)^+$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 3.62 - 3.57 (m, 4 H), 3.46 - 3.41 (m, 2 H), 2.89 - 2.81 (m, 2 H), 2.38 - 2.33 (m, 2 H), 1.52 (s, 9 H), 0.94 - 0.92 (m, 9 H), 0.24 (s, 6 H).

[00320] Step 2. (2*S*,4*S*)-8-(*tert*-Butoxycarbonyl)-2-hydroxy-5-oxa-8-azaspiro[3.5]nonane-2-carboxylic acid. To a 250-mL round-bottom flask was added *tert*-butyl (2*S*,4*S*)-2-((*tert*-butyldimethylsilyl)oxy)-2-cyano-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate (2.63 g, 6.87 mmol) in hydrochloric acid (37%, 10 mL, 122 mmol). The mixture was heated to reflux for 1 h, then concentrated. The residue was redissolved in water (30 mL) and basified to pH 11 by solid Na_2CO_3. THF (30 mL), sodium bicarbonate (1.16 g, 13.8 mmol) and di-*tert*-butyl dicarbonate (1.65 g, 7.56 mmol) was then sequentially added. The mixture was stirred at room temperature for 1 h, then diluted with water and washed with EtOAc. The aqueous phase was then acidified to pH 1.5 with 1 M $KHSO_4$ solution and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to provide (2*S*,4*S*)-8-(*tert*-butoxycarbonyl)-2-hydroxy-5-oxa-8-azaspiro[3.5]nonane-2-carboxylic acid (1.35 g, 4.70 mmol, 68% yield). *m/z* (ESI): 310.0 $(M+Na)^+$.

Intermediate KK: 4-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butanehydrazide.



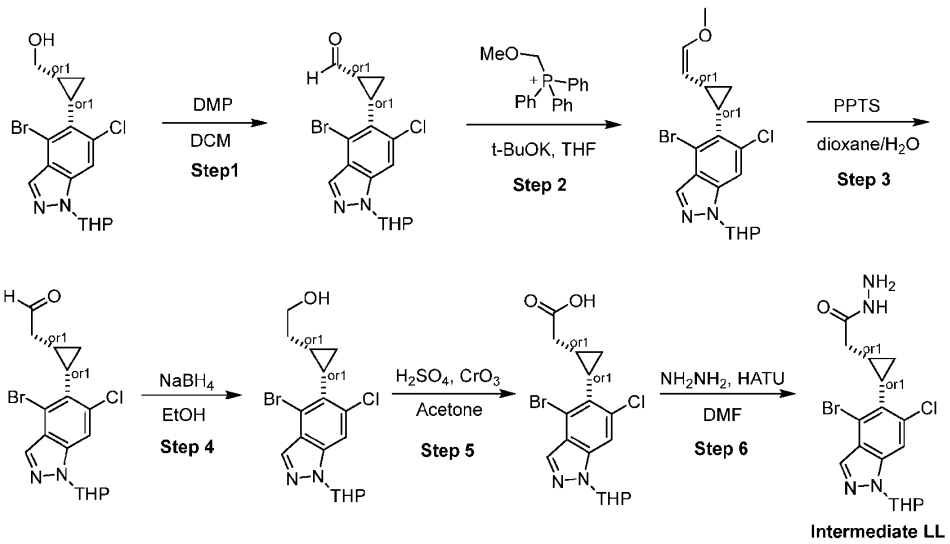
Intermediate KK

[00321] Step 1. 4-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butanoic acid. To a 40 mL vial was charged with 4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-1-ol (**Step 2** in **Intermediate M**, 0.61 g, 1.58 mmol) and *tert*-butanol (9 mL). To this was added 2-methyl-2-butene (0.18 mL, 1.58 mmol), and then sodium chlorite (0.60 g, 6.6 mmol) and sodium phosphate monobasic (0.19 g, 1.58 mmol) in water (18 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature with stirring for 1 h, was then concentrated and dissolved in MeOH. The crude was injected onto a C18 column and eluted with 5–100% acetonitrile (with 0.1%

formic acid) in water (with 0.1% formic acid) to give 4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butanoic acid (0.38 g, 0.95 mmol, 60% yield). *m/z* (ESI): 401.8 $(M+H)^+$.

[00322] Step 2. 4-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butanehydrazide. In a 250-mL round-bottom flask, to a solution of 4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butanoic acid (2.04 g, 5.08 mmol) in *N,N*-dimethylformamide (10 mL) was added diisopropylethylamine (2.0 mL, 11 mmol) and HATU (2.12 g, 5.59 mmol). The mixture was stirred at room temperature for 20 minutes, then the solution was added dropwise to the solution of anhydrous hydrazine (0.65 mL, 20.3 mmol) and diisopropylethylamine (2.0 mL, 11 mmol) in DMF (10 mL) at 0 °C over 20 minutes. The reaction mixture was stirred at room temperature for 2 h, was then quenched by the addition of water and filtered. The filter cake was washed with water and triturated in EtOAc. The solid was collected by filtration to provide 4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butanehydrazide (1.51 g, 3.63 mmol, 72% yield). *m/z* (ESI): 415.0/417.1 $(M+H)^+$. ^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 8.96 (s, 1H), 8.06 (s, 1H), 8.00 (s, 1H), 5.88 (dd, *J* = 9.5, 2.4 Hz, 1H), 4.15 (br s, 2H). 3.91 – 3.84 (m, 1H), 3.80 – 3.73 (m, 1H), 3.01 – 2.96 (m, 2H), 2.40 – 2.30 (m, 1H), 2.15 (t, *J* = 7.6 Hz, 2H), 2.06 – 1.94 (m, 2H), 1.82 – 1.71 (m, 3H), 1.63 – 1.56 (m, 2H).

Intermediate LL: *rac*-2-((1*R*,2*R*)-2-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)acetohydrazide.



[00323] Step 1. *rac*-(1*R*,2*S*)-2-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropane-1-carbaldehyde. To a solution of *rac*-((1*R*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-

2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methanol (**Intermediate D**, 5.00 g, 13 mmol) in dichloromethane (75 mL) was added Dess-Martin periodinane (11.0 g, 25.9 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a gradient of 5–10% EtOAc in petroleum ether, to give *rac*-(1*R*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropane-1-carbaldehyde (4.16 g, 10.9 mmol, 85% yield).

[00324] Step 2. *rac*-4-Bromo-6-chloro-5-((1*S*,2*R*)-2-((*Z*)-2-methoxyvinyl)cyclopropyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole. To the mixture of (methoxymethyl)triphenylphosphonium (24.0 g, 78.0 mmol) in tetrahydrofuran (200 mL) was added *t*-BuOK (1 M in THF, 78 mL, 78 mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes, then the solution of *rac*-(1*R*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropane-1-carbaldehyde (10.0 g, 26.1 mmol) in tetrahydrofuran (200 mL) was added dropwise at 0 °C to the mixture. The reaction mixture was stirred at room temperature for 30 minutes, then was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 5–10% EtOAc in petroleum ether, to give *rac*-4-bromo-6-chloro-5-((1*S*,2*R*)-2-((*Z*)-2-methoxyvinyl)cyclopropyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (9.62 g, 23.0 mmol, 90% yield).

[00325] Step 3. *rac*-2-((1*S*,2*S*)-2-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)acetaldehyde. To the mixture of *rac*-4-bromo-6-chloro-5-((1*S*,2*R*)-2-((*Z*)-2-methoxyvinyl)cyclopropyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (33 g, 80 mmol) in 1,4-dioxane (790 mL) and water (130 mL) was added pyridine 4-methylbenzenesulfonate (32.4 g, 128 mmol). The reaction mixture was stirred at 70 °C for 12 h. After cooling to room temperature, the reaction mixture was quenched by addition of water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 5–10% EtOAc in petroleum ether, to give *rac*-2-((1*S*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)acetaldehyde (20.0 g, 50.3 mmol, 63% yield).

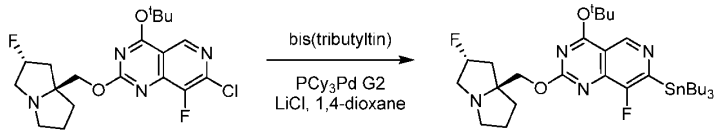
[00326] Step 4. *rac*-2-((1*S*,2*S*)-2-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)ethan-1-ol. To the mixture of *rac*-2-((1*S*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)acetaldehyde (20.0 g, 50.3 mmol) in ethanol (200 mL) was added $NaBH_4$ (3.23 g, 85 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, was then quenched by addition of saturated NH_4Cl solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 20–35%

EtOAc in petroleum ether, to give *rac*-2-((1*S*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)ethan-1-ol (19.1 g, 48.0 mmol, 95% yield). *m/z* (ESI): 401.0/399.0 $(M+H)^+$. ^1H NMR (400 MHz, *DMSO-d6*) δ ppm 8.06 (s, 1 H), 7.99 (s, 1 H), 5.87 (dd, *J* = 9.6, 2.4 Hz, 1 H), 4.29 - 4.33 (m, 1 H), 3.85 - 3.88 (m, 1 H), 3.76 - 3.77 (m, 1 H), 3.36 - 3.41(m, 2 H), 2.29 - 2.38 (m, 1 H), 1.97 – 2.03 (m, 3 H), 1.84 - 1.86 (m, 1 H), 1.69 - 1.73 (m, 1 H), 1.54 - 1.60 (m, 2 H), 1.38 - 1.48 (m, 1 H), 1.31 - 1.37 (m, 1 H), 0.80 - 0.92 (m, 1 H), 0.20 - 0.26 (m, 1 H).

[00327] Step 5. *rac*-2-((1*S*,2*S*)-2-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)acetic acid. To a 250-mL round-bottom flask was charged *rac*-2-((1*S*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)ethan-1-ol (4.0 g, 10 mmol) in acetone (100 mL). At 0 °C, chromium trioxide solution in sulfuric acid (7.5 mL, 15.0 mmol) was added dropwise. The mixture was allowed to warm to room temperature with stirring for 1.5 h. Upon completion of the reaction, 0.1 M sodium thiosulfate solution (100 mL) was added to quench the reaction. The mixture was extracted by EtOAc, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to provide *rac*-2-((1*S*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)acetic acid (4.35 g, 10.5 mmol, crude). *m/z* (ESI): 412.9/415.0 $(M+H)^+$. ^1H NMR (400 MHz, *CDCl3*) δ ppm 10.05 (br s, 1H), 8.00 (d, *J* = 0.8 Hz, 1H), 7.68 (s, 1H), 5.66 (dd, *J* = 8.9, 2.4 Hz, 1H), 4.03 (br dd, *J* = 9.8, 2.1 Hz, 1H), 3.81 – 3.72 (m, 1H), 2.90 – 2.79 (m, 1H), 2.55 – 2.44 (m, 1H), 2.21 – 2.09 (m, 3H), 1.85 – 1.70 (m, 4H), 1.63 – 1.52 (m, 1H), 1.38 (dd, *J* = 16.5, 10.5 Hz, 1H), 1.11 (q, *J* = 6.3 Hz, 1H).

[00328] Step 6. *rac*-2-((1*S*,2*S*)-2-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)acetohydrazide. In a 250-mL round-bottom flask, *rac*-2-((1*S*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)acetic acid (4.35 g, 10.5 mmol) was dissolved in *N*,*N*-dimethylformamide (20 mL) and the solution was cooled to 0 °C. HATU (4.80 g, 12.6 mmol) and *N*,*N*'-diisopropylethylamine (4.0 mL, 23 mmol) was sequentially added and the mixture was stirred at room temperature for 30 minutes. The resulting solution was added dropwise to a separate flask containing a solution of anhydrous hydrazine (1.3 mL, 42 mmol) and *N*,*N*'-diisopropylethylamine (4.0 mL, 23 mmol) in *N*,*N*-dimethylformamide (20 mL) at 0 °C. The resulting mixture was stirred at room temperature for 1.5 h, was then quenched by the addition of water, and extracted by EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to provide *rac*-2-((1*S*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)acetohydrazide (4.50 g, 10.5 mmol, 100% yield). *m/z* (ESI): 427.0/429.0 $(M+H)^+$. ^1H NMR (400 MHz, *CDCl3*) δ ppm 7.99 (s, 1H), 7.67 (s, 1H), 6.92 (br s, 1H), 5.69 – 5.62 (m, 1H), 4.06 – 3.98 (m, 1H), 3.78 – 3.73 (m, 1H), 2.70 (dt, *J* = 15.6, 4.0 Hz, 1H), 2.55 – 2.43 (m, 1H), 2.21 – 2.08 (m, 3H), 1.82 – 1.74 (m, 3H), 1.60 – 1.54 (m, 1H), 1.49 – 1.44 (m, 3H), 1.24 – 1.07 (m, 2H).

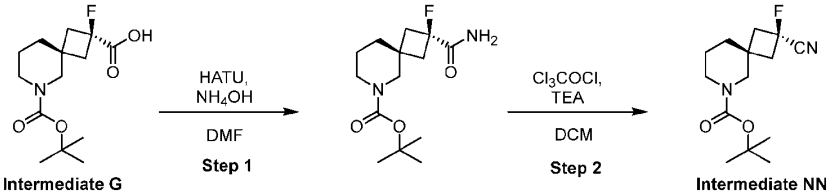
Intermediate MM: 4-(*tert*-Butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-7-(tributylstannyl)pyrido[4,3-*d*]pyrimidine.



Intermediate MM

[00329] To a solution of 4-(*tert*-butoxy)-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (**Intermediate C**, 34 g, 82 mmol,) in 1,4-dioxane (680 mL) was added PCy_3 Pd G_2 (19.5 g, 32.9 mmol) and LiCl (17.5 g, 412 mmol), then bis(tributyltin) (177 g, 305 mmol) was added in one portion under N_2. The mixture was stirred at 80 °C for 36 h under N_2. After cooling to room temperature, the reaction was filtered and the filtrate was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with 0–7% ethyl acetate in petroleum ether, to provide 4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-7-(tributylstannyl)pyrido[4,3-*d*]pyrimidine (29.8 g, 44.7 mmol, 54% yield). *m/z* (ESI): 667.4/669.4 $(M+H)^+$. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 9.21 (s, 1H), 5.21–5.36 (m, 1H), 4.20–4.29 (m, 2H), 3.24–3.28 (m, 2H), 2.05–2.30 (m, 3H), 1.80–2.05 (m, 4H), 1.34–1.60 (m, 9H), 1.20–1.32 (m, 18H), 0.86–0.93 (m, 9H).

Intermediate NN: *tert*-Butyl (2*S*,4*R*)-2-cyano-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate.



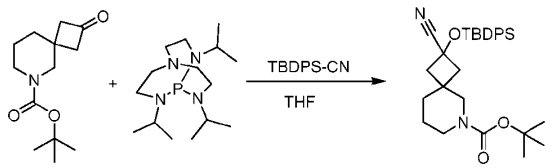
Intermediate G **Intermediate NN**

[00330] **Step 1. *tert*-Butyl (2*S*,4*R*)-2-carbamoyl-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate.** To a 40-mL vial was charged with (2*S*,4*R*)-6-(*tert*-butoxycarbonyl)-2-fluoro-6-azaspiro[3.5]nonane-2-carboxylic acid (**Intermediate G**, 1.04 g, 3.62 mmol), *N*,*N*-dimethylformamide (15 mL), *N*,*N*-diisopropylethylamine (1.9 mL, 10.9 mmol), and HATU (1.51 g, 3.98 mmol) at 0 °C. The contents were stirred for 35 minutes and then ammonium hydroxide (2.3 mL, 18 mmol) was added. The reaction mixture was stirred at 0 °C for 30 minutes, was then diluted with ethyl acetate and saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate and the combined organics were washed with water and brine, dried over sodium sulfate, filtered, and concentrated to

yield *tert*-butyl (2*S*,4*R*)-2-carbamoyl-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (1.0 g, 3.5 mmol, 96% yield). *m/z* (ESI): 309.2 $(M+Na)^+$.

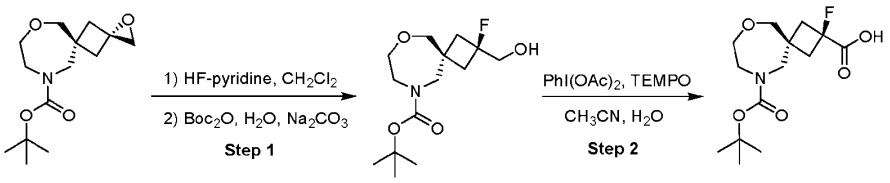
[00331] Step 2. *tert*-Butyl (2*S*,4*R*)-2-cyano-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate. To a 40-mLvial was charged with *tert*-butyl (2*S*,4*R*)-2-carbamoyl-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (1.0 g, 3.5 mmol), dichloromethane (30 mL), and triethylamine (0.98 mL, 6.98 mmol) under a nitrogen atmosphere. The contents were cooled to 0 °C and 2,2,2-trichloroacetyl chloride (0.8 mL, 7 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature with stirring for 1 h, was then diluted with water, and extracted with dichloromethane. The combined organics were dried with sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel, eluting with 0–60% ethyl acetate in heptane, to provide *tert*-butyl (2*S*,4*R*)-2-cyano-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (0.86 g, 3.20 mmol, 91% yield). *m/z* (ESI): 213.2 $(M-Boc+H)^+$.

Intermediate OO: *tert*-Butyl 2-((*tert*-butyldiphenylsilyl)oxy)-2-cyano-6-azaspiro[3.5]nonane-6-carboxylate.



[00332] To a 40-mL vial was added *tert*-butyl 2-oxo-6-azaspiro[3.5]nonane-6-carboxylate (2.5 g, 10.5 mmol,) and *tert*-butyldiphenylsilanecarbonitrile (2.91 g, 11 mmol) in tetrahydrofuran (15 mL). 2,8,9-Triisopropyl-2,5,8,9-tetraaza-1-phosphabicyclo[3,3,3]undecane (0.13 g, 0.42 mmol) was added and the reaction mixture was stirred at room temperature for 2.5 h. The resulting mixture was concentrated, and the residue was purified by column chromatography on silica gel, eluting with a gradient of 0–60% EtOAc in heptane, to provide *tert*-butyl 2-((*tert*-butyldiphenylsilyl)oxy)-2-cyano-6-azaspiro[3.5]nonane-6-carboxylate (5.10 g, 10.1 mmol, 97% yield) as a mixture of diastereomers. *m/z* (ESI): 449.2 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.73 – 7.77 (m, 5 H), 7.44 – 7.51 (m, 5 H), 3.35 – 3.42 (m, 2 H), 3.18 – 3.30 (m, 3 H), 2.17 – 2.40 (m, 3 H), 1.94 – 2.08 (m, 2 H), 1.57 – 1.69 (m, 1 H), 1.42 – 1.44 (m, 9 H), 1.32 – 1.36 (m, 1 H), 1.09 (s, 9 H).

Intermediate PP: (2*S*,4*S*)-9-(*tert*-Butoxycarbonyl)-2-fluoro-6-oxa-9-azaspiro[3.6]decane-2-carboxylic acid.

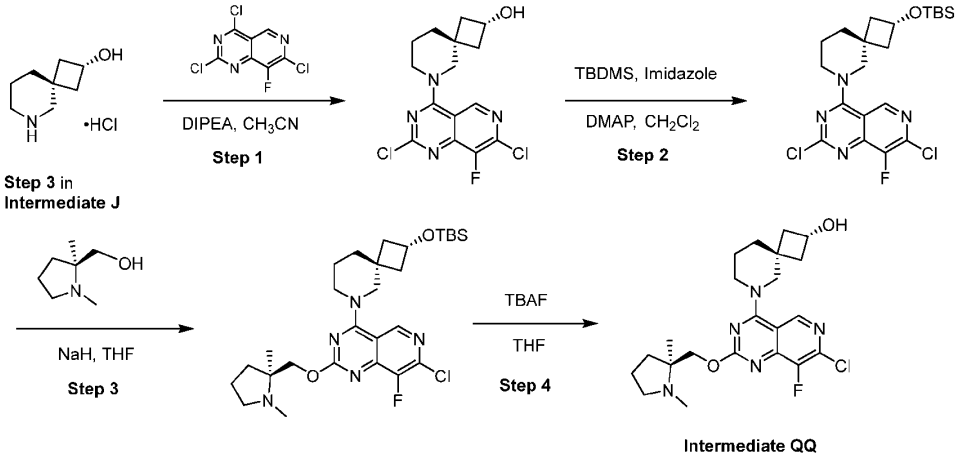


Intermediate CC Intermediate PP

[00333] Step 1. *tert*-Butyl (2*S*,4*S*)-2-fluoro-2-(hydroxymethyl)-6-oxa-9-azaspiro[3.6]decane-9-carboxylate. In a 100-mL plastic round-bottom flask was added hydrogen fluoride (70% in 30% pyridine, 1.02 g, 10.3 mmol) and the contents were cooled to -78 °C. *tert*-Butyl (3*R*,5*R*)-1,7-dioxa-10-azadispiro[2.1.6^5.1^3]dodecane-10-carboxylate (**Intermediate CC**, 0.98 g, 3.60 mmol) in dichloromethane (5 mL) was added dropwise, and the mixture was stirred at -78 °C for 3 h. The resulting mixture was poured into a mixture of 1 M Na_2CO_3 solution and DCM at 0 °C. The resulting mixture was extracted with DCM and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude was purified by column chromatography on silica gel, eluting with a gradient of 0–100% EtOAc in heptane, to give *tert*-butyl (2*S*,4*S*)-2-fluoro-2-(hydroxymethyl)-6-oxa-9-azaspiro[3.6]decane-9-carboxylate (0.52 g, 1.80 mmol, 50% yield). *m/z* (ESI): 312.1 $(M+Na)^+$. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 3.83 – 3.65 (m, 6H), 3.64 – 3.45 (m, 4H), 2.63 (t, *J* = 7.1 Hz, 1H), 2.31 – 2.02 (m, 4H), 1.54 – 1.46 (m, 9H). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ ppm -143.08 – -147.71 (m, 1F).

[00334] Step 2. (2*S*,4*S*)-9-(*tert*-Butoxycarbonyl)-2-fluoro-6-oxa-9-azaspiro[3.6]decane-2-carboxylic acid. To a stirred mixture of *tert*-butyl (2*S*,4*S*)-2-fluoro-2-(hydroxymethyl)-6-oxa-9-azaspiro[3.6]decane-9-carboxylate (0.52 g, 1.80 mmol) and (diacetoxyiodo)benzene (1.46 g, 4.52 mmol) in water (4 mL) and acetonitrile (6 mL) was added TEMPO (57 mg, 0.36 mmol) under nitrogen. The resulting mixture was stirred at 60 °C for 2 h. The acetonitrile was removed, and the resulting aqueous mixture was basified with saturated $NaHCO_3$ solution and washed with EtOAc. The aqueous phase was acidified by 1 M $KHSO_4$ solution, and extracted by EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give (2*S*,4*S*)-9-(*tert*-butoxycarbonyl)-2-fluoro-6-oxa-9-azaspiro[3.6]decane-2-carboxylic acid (0.42 g, 1.30 mmol, 77% yield). *m/z* (ESI): 326.1 $(M+Na)^+$. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 3.87 – 3.64 (m, 6H), 3.57 – 3.45 (m, 2H), 2.84 – 2.65 (m, 2H), 2.41 – 2.28 (m, 2H), 1.49 (d, *J* = 4.4 Hz, 9H). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ ppm -151.90 (s, 1F).

Intermediate QQ: (2*S*,4*S*)-6-(7-Chloro-2-(((*S*)-1,2-dimethylpyrrolidin-2-yl)methoxy)-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol.



[00335] Step 1. (2*R*,4*S*)-6-(2,7-Dichloro-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol. A 100-mL round bottom flask was charged with 2,4,7-trichloro-8-fluoropyrido[4,3-*d*]pyrimidine *tert*-butyl 6-hydroxy-1,4-thiazepane-4-carboxylate (3.00 g, 11.8 mmol, LabNetwork Inc.) and acetonitrile (40 mL). The reaction mixture was cooled to 0 °C and (2*R*,4*S*)-6-azaspiro[3.5]nonan-2-ol hydrochloride (**Step 3** in **Intermediate J**, 1.66 g, 10.8 mmol) and DIPEA (6.2 mL, 36 mmol) were added. The reaction mixture was stirred at 0 °C for 30 minutes, was then concentrated. The residue was purified by column chromatography on silica gel, eluting with 0–50% 3:1 EtOAc/EtOH (with 2% triethylamine) in heptane, to yield (2*R*,4*S*)-6-(2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol (2.50 g, 7.00 mmol, 59% yield). *m/z* (ESI): 356.9 $(M+H)^+$.

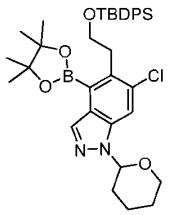
[00336] Step 2. 4-((2*R*,4*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-6-azaspiro[3.5]nonan-6-yl)-2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidine. A 100 mL round bottom flask was charged with (2*R*,4*S*)-6-(2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol (1.50 g, 4.20 mmol), dichloromethane (28 mL), DMAP (50 mg, 0.42 mmol), imidazole (0.71 g, 10.5 mmol), and *tert*-butyldimethylsilyl chloride (0.76 g, 5.04 mmol). The reaction mixture was stirred at room temperature for 6 h, was then quenched with saturated aqueous sodium bicarbonate and extracted with DCM. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude material was purified by column chromatography on silica gel, eluting with 0–80% 3:1 EtOAc/EtOH (with 2% triethylamine) in heptane, to yield 4-((2*R*,4*S*)-2-((*tert*-butyldimethylsilyl)oxy)-6-azaspiro[3.5]nonan-6-yl)-2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidine (1.40 g, 2.97 mmol, 71% yield). *m/z* (ESI): 470.9 $(M+H)^+$.

[00337] Step 3. 4-((2*S*,4*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-6-azaspiro[3.5]nonan-6-yl)-7-chloro-2-(((*S*)-1,2-dimethylpyrrolidin-2-yl)methoxy)-8-fluoropyrido[4,3-*d*]pyrimidine. A 40 mL vial was charged with [(2*S*)-1,2-dimethylpyrrolidin-2-yl]methanol (0.41 g, 3.20 mmol, Pharmablock Inc.)

and tetrahydrofuran (17 mL). The reaction mixture was cooled to 0 °C and sodium hydride (60 wt% in mineral oil, 0.19 g, 4.70 mmol) was added, and the suspension was stirred for 10 minutes at 0 °C. 4-((2*R*,4*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-6-azaspiro[3.5]nonan-6-yl)-2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidine (1.00 g, 2.21 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was slowly quenched via the addition of saturated aqueous ammonium chloride solution, and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine solution, dried over sodium sulfate, filtered, and concentrated. The crude material was purified by column chromatography on silica gel, eluting with 0–60% 3:1 EtOAc/EtOH (with 2% triethylamine) in heptane, to yield 4-((2*S*,4*S*)-2-((*tert*-butyldimethylsilyl)oxy)-6-azaspiro[3.5]nonan-6-yl)-7-chloro-2-(((*S*)-1,2-dimethylpyrrolidin-2-yl)methoxy)-8-fluoropyrido[4,3-*d*]pyrimidine (0.87 g, 1.50 mmol, 72% yield). *m/z* (ESI): 563.9 $(M+H)^+$.

[00338] Step 4. (2*S*,4*S*)-6-(7-Chloro-2-(((*S*)-1,2-dimethylpyrrolidin-2-yl)methoxy)-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol. A 40-mL vial was charged 4-((2*S*,4*S*)-2-((*tert*-butyldimethylsilyl)oxy)-6-azaspiro[3.5]nonan-6-yl)-7-chloro-2-(((*S*)-1,2-dimethylpyrrolidin-2-yl)methoxy)-8-fluoropyrido[4,3-*d*]pyrimidine (1.07 g, 1.90 mmol) and tetrahydrofuran (23 mL). Tetramethylammonium fluoride (1 M in THF, 2.8 mL, 2.8 mmol) was added, and the reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was partitioned between ethyl acetate and half-saturated aqueous sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure, and the crude material was used in the next step without any purification. *m/z* (ESI): 449.9 $(M+H)^+$.

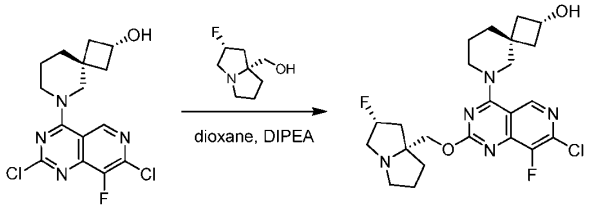
Intermediate RR: 5-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole.



[00339] The title compound was prepared in an analogous fashion to **Intermediate K** using 2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethan-1-ol (**Intermediate E**) and *tert*-butyl(chloro)diphenylsilane (CAS#: 58479-61-1, Aldrich) and imidazole in DCM and THF in **Step 1.** *m/z* (ESI): 645.3/647.3 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.33 (s, 1 H), 7.68 (s, 1 H), 7.58-7.66 (m, 4 H), 7.30-7.40 (m, 6 H), 5.62-5.66 (m, 1 H), 3.86-3.99 (m, 1 H), 3.82-3.84 (m, 2 H), 3.72-

3.74 (m, 1 H), 3.54-3.58 (m, 2 H), 2.46-2.55 (m, 1 H), 2.08-2.16 (m, 1 H), 1.98-2.06 (m, 1 H), 1.62-1.80 (m, 3 H), 1.37 (s, 12 H), 1.03 (s, 9 H).

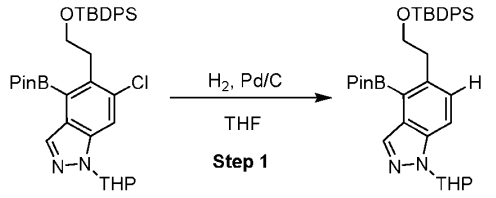
Intermediate SS: (2*R*,4*S*)-6-(7-Chloro-8-fluoro-2-(((2*R*,7a*R*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol.



Intermediate SS

[00340] To a solution of (2*R*,4*S*)-6-(2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol (**Step 1** in **Intermediate QQ,** 0.39 g, 1.10 mmol) in 1,4-dioxane (3.5 mL) was added ((2*R*,7a*R*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol (0.35 g, 2.20 mmol) and DIPEA (3.5 mL, 20 mmol). Then the mixture was stirred at 120 °C for 12 h under a N_2 atmosphere. The crude reaction mixture was combined with 9 other baches (0.4 g) and concentrated under reduced pressure. The residue was purified by prep-HPLC using a C18 column, eluting with a gradient of 20–45% of CH_3CN in H_2O (10 mM NH_4HCO_3), to provide (2*R*,4*S*)-6-(7-chloro-8-fluoro-2-(((2*R*,7a*R*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4.3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol (2.50 g, 5.20 mmol, 46% yield). *m/z* (ESI): 502.2 $(M+Na)^+$. ^1H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 8.88 (s, 1 H), 5.26 - 5.44 (m, 1 H), 4.93 (d, *J*=6.4 Hz, 1 H), 4.10 - 4.18 (m, 2 H), 4.03 - 4.09 (m, 1 H), 3.86 (d, *J*=3.2 Hz, 2 H), 3.74-3.79 (m, 2 H), 3.23 - 3.30 (m, 1 H), 2.91 - 2.99 (m, 1 H), 2.74 - 2.90 (m, 1 H), 2.52-2.59 (m, 1 H), 2.24 - 2.35 (m, 1 H), 1.99 - 2.05 (m, 2 H), 1.78 - 1.93 (m, 4 H), 1.63 - 1.71 (m, 5 H), 1.54 - 1.60 (m, 2 H).

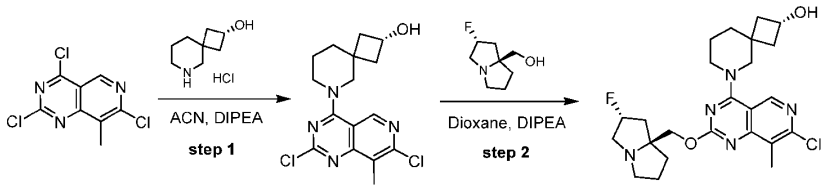
Intermediate TT: 5-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole.



Intermediate TT

[00341] To a mixture of Pd/C (6.0 g, 10% on charcoal, 6.2 mmol) in tetrahydrofuran (100 mL) was added 5-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole (**Intermediate RR,** 4.0 g, 6.2 mmol) under an argon atmosphere. The suspension was degassed and purged with H_2 and then stirred under H_2 (50 psi) at 50 °C for 12 h. After cooling to room temperature, the crude reaction mixture was combined with another batch (same scale), filtered through a pad of Celite, and rinsed with tetrahydrofuran. The filtrate was concentrated under reduced pressure and the residue was purified by prep-HPLC on a C18 column, eluting with a gradient of 80–100% CH_3CN in H_2O (10 mM NH_4HCO_3), to provide 5-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole (2.0 g, 26% yield). *m/z* (ESI): 611.4 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.42 (s, 1H),7.50-7.60 (m, 5H), 7.27-7.35 (m, 7H), 5.70-5.75 (m, 1H), 3.95-4.05 (m, 1H), 3.80-3.90 (m, 2H), 3.65-3.80 (m, 1H), 3.25-3.35 (m, 2H), 2.50-2.60 (m, 1H), 2.10-2.20 (m, 1H), 2.00-2.10 (m, 1H), 1.60-1.80 (m, 3H), 1.32 (s, 12H), 1.02 (s, 9H).

Intermediate UU: (2*R*,4*S*)-6-(7-Chloro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-8-methylpyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol.



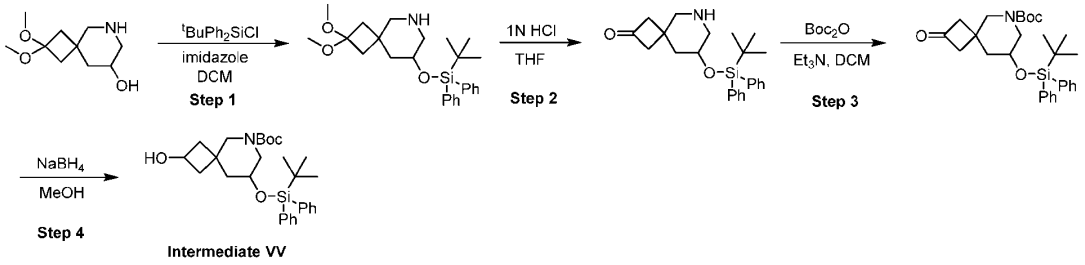
Intermediate UU

[00342] Step 1: (2*R*,4*S*)-6-(2,7-Dichloro-8-methylpyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol. To a solution of 2,4,7-trichloro-8-methylpyrido[4,3-*d*]pyrimidine (3.0 g, 12 mmol) in tetrahydrofuran (20 mL) at 0 °C was added DIPEA (6.3 mL, 36 mmol) followed by a solution of (2*R*,4*S*)-6-azaspiro[3.5]nonan-2-ol hydrochloride (2.15 g, 12.1 mmol) in tetrahydrofuran (50 mL). The resulting mixture was stirred at 0 °C for 2 h, was then partitioned between water and EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a gradient of 5–100% ethyl acetate in petroleum ether, to give (2*R*,4*S*)-6-(2,7-dichloro-8-methylpyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol (3.5 g, 9.9 mmol, 82% yield). *m/z* (ESI): 353.4 $(M+H)^+$.

[00343] Step 2: (2*R*,4*S*)-6-(7-Chloro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-8-methylpyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol. A mixture of ((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol (1.19 g, 7.47 mmol), (2*R*,4*S*)-6-(2,7-dichloro-8-methylpyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol (2.2 g, 6.2 mmol), DIPEA

(11 mL, 63 mmol) and 4Å MS (5 g) in 1,4-dioxane (11 mL) was stirred at 120 °C for 12 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC on a C18 column, eluting with a gradient of 30–65% CH_3CN in H_2O (10 mM NH_4HCO_3), to provide (2*R*,4*S*)-6-(7-chloro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-8-methylpyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol (2.0 g, 4.2 mmol, 67% yield). *m/z* (ESI): 498.3 $(M+Na)^+$. ^1H NMR (400 MHz, *CDCl3*) δ ppm 8.81 (s, 1H), 5.19-5.39 (m, 1H), 4.26-4.37 (m, 2H), 4.19 (d, *J*=10.49 Hz, 1H), 3.86 (s, 2H), 3.76 (d, *J*=5.36 Hz, 2H), 3.22-3.33 (m, 2H), 3.18 (s, 1H), 2.92-3.03 (m, 1H), 2.58 (s, 3H), 2.27-2.33 (m, 1H), 2.12-2.26 (m, 5H), 1.88-2.01 (m, 4H), 1.75-1.84 (m, 4H), 1.26 (t, *J*=7.15 Hz, 1H).

Intermediate VV: *tert*-Butyl 8-((*tert*-butyldiphenylsilyl)oxy)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate.



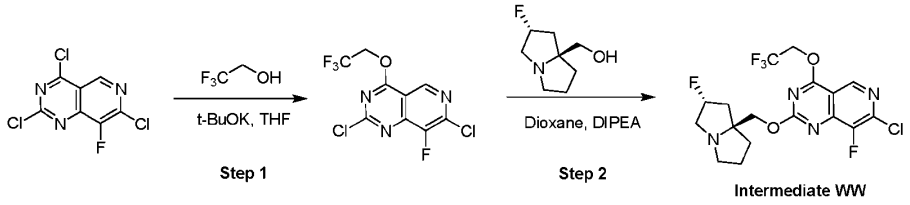
[00344] Step 1. 8-((*tert*-Butyldiphenylsilyl)oxy)-2,2-dimethoxy-6-azaspiro[3.5]nonane. A mixture of dimethoxy-6-azaspiro[3.5]nonan-8-ol (3.40 g, 16.9 mmol, Enamine), imidazole (4.60 g, 67.6 mmol), and *tert*-butylchlorodiphenylsilane (8.8 mL, 34 mmol) were stirred in dichloromethane (84 mL) at room temperature for 16 h. The crude mixture was purified by column chromatography on silica gel, eluting with a gradient of 0–50% EtOAc in heptane, to yield 8-((*tert*-butyldiphenylsilyl)oxy)-2,2-dimethoxy-6-azaspiro[3.5]nonane (7.0 g, 15.9 mmol, 94% yield). *m/z* (ESI): 440.0 $(M+1)^+$.

[00345] Step 2. 8-((*tert*-Butyldiphenylsilyl)oxy)-6-azaspiro[3.5]nonan-2-one hydrochloride. In a 150-mL RBF was charged with 8-((*tert*-butyldiphenylsilyl)oxy)-2,2-dimethoxy-6-azaspiro[3.5]nonane (4.31 g, 9.80 mmol) and tetrahydrofuran (65 mL). Hydrochloric acid (1 M in THF, 10.6 mL, 10.6 mmol) was added dropwise and the mixture was stirred at 50 °C for 20 h. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic phase was dried over sodium sulfate, filtered, and concentrated to give 8-((*tert*-butyldiphenylsilyl)oxy)-6-azaspiro[3.5]nonan-2-one hydrochloride (3.74 g, 8.70 mmol, 89% yield). *m/z* (ESI): 394.2 $(M+1)^+$.

[00346] Step 3. *tert*-Butyl 8-((*tert*-butyldiphenylsilyl)oxy)-2-oxo-6-azaspiro[3.5]nonane-6-carboxylate. In a 250 mL round-bottom flask was charged with 8-((*tert*-butyldiphenylsilyl)oxy)-6-azaspiro[3.5]nonan-2-one hydrochloride (3.67 g, 8.53 mmol) and di-*tert*-butyl dicarbonate (2.79 g, 12.8 mmol) in dichloromethane (43 mL). Triethylamine (3.6 mL, 25.6 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 1 h. Water was added to quench the reaction and the layers were separated. The aqueous layer was extracted with DCM and the combined organics were dried (Na_2SO_4) and concentrated. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0–40% EtOAc in hexane, to provide *tert*-butyl 8-((*tert*-butyldiphenylsilyl)oxy)-2-oxo-6-azaspiro[3.5]nonane-6-carboxylate (4.05 g, 8.20 mmol, 96% yield). *m/z* (ESI): 515.9 $(M+Na)^+$.

[00347] Step 4. *tert*-Butyl 8-((*tert*-butyldiphenylsilyl)oxy)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate. To the solution of *tert*-butyl 8-((*tert*-butyldiphenylsilyl)oxy)-2-oxo-6-azaspiro[3.5]nonane-6-carboxylate (3.87 g, 7.83 mmol) in methanol (39 mL) cooled in a 0 °C ice bath was added sodium borohydride (0.44 g, 11.8 mmol) in portions. The reaction mixture was stirred at 0 °C for 1 h, then diluted with water and extracted with ethyl acetate. The combined organics were dried, filtered, and concentrated. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0–50% ethyl acetate in heptane, to give *tert*-butyl 8-((*tert*-butyldiphenylsilyl)oxy)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (3.63 g, 7.32 mmol, 93% yield). *m/z* (ESI): 518.9 $(M+Na)^+$.

Intermediate WW: 7-Chloro-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidine.

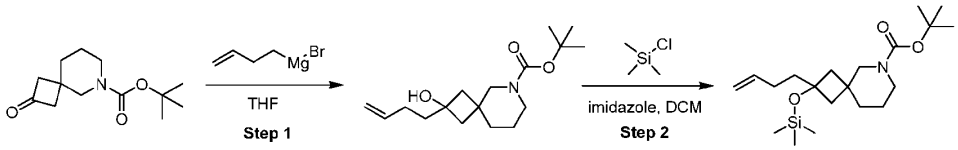


[00348] Step 1. 2,7-Dichloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidine. To a solution of 2,4,7-trichloro-8-fluoropyrido[4,3-*d*]pyrimidine (50.0 g, 198 mmol, LabNetwork) in tetrahydrofuran (750 mL) cooled to -60 °C was added 2,2,2-trifluoroethan-1-ol (18.82 g, 188 mmol), followed by *t*-BuOK (1 M in THF, 188 mL, 188 mmol) dropwise. The mixture was stirred at -60 °C for 2 h. The reaction mixture was quenched by addition of H_2O (1-L) at room temperature and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was washed with petroleum ether (50 mL), then filtered. The filter cake was concentrated under reduced pressure to give 2,7-dichloro-8-fluoro-4-(2,2,2-

trifluoroethoxy)pyrido[4,3-*d*]pyrimidine (50.0 g, 158 mmol, 84% yield). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 9.18 (s, 1 H), 5.06 – 5.12 (m, 2 H).

[00349] Step 2. 7-Chloro-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidine. To a solution of 2,7-dichloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidine (28 g, 89 mmol) in 1,4-dioxane (280 mL) was added ((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol (16.9 g, 106 mmol) and DIPEA (46.4 mL, 266 mmol) in sequence then the mixture was stirred at 80 °C for 10 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 5–100% EtOAc in petroleum ether, to provide 7-chloro-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidine (28.0 g, 63.8 mmol, 72% yield). *m/z* (ESI): 439.1/441.1 $(M+H)^+$.

Intermediate XX: *tert*-Butyl 2-(but-3-en-1-yl)-2-((trimethylsilyl)oxy)-6-azaspiro[3.5]nonane-6-carboxylate.



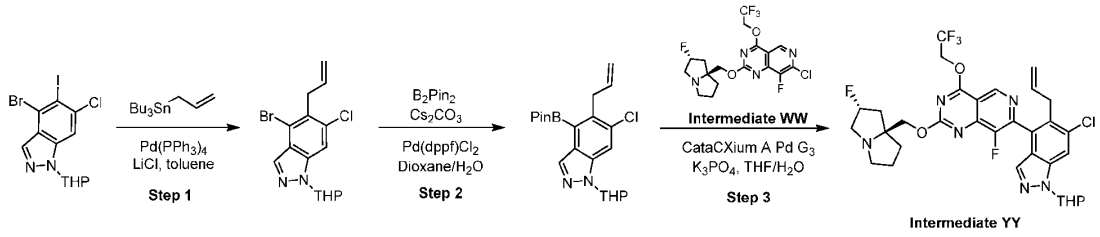
Intermediate XX

[00350] Step 1. *tert*-Butyl 2-(but-3-en-1-yl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate. To a solution of *tert*-butyl 2-oxo-6-azaspiro[3.5]nonane-6-carboxylate (10.0 g, 41.8 mmol) in tetrahydrofuran (100 mL) was added but-3-en-1-ylmagnesium bromide (1 M in THF, 84 mL, 84 mmol) at 0 °C under nitrogen. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was combined with another 10 g batch and quenched by addition of sat. NH_4Cl, then extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give *tert*-butyl 2-(but-3-en-1-yl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (total 12 g, 49% yield).

[00351] Step 2. *tert*-Butyl 2-(but-3-en-1-yl)-2-((trimethylsilyl)oxy)-6-azaspiro[3.5]nonane-6-carboxylate. To a solution of *tert*-butyl 2-(but-3-en-1-yl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (6.0 g, 20.3 mmol) in dichloromethane (120 mL) was added imidazole (6.91 g, 102 mmol) and TMSCl (13 mL, 102 mmol) in sequence. The reaction mixture was stirred at room temperature for 2 h, then was diluted with water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was

purified by column chromatography on silica gel, eluting with a gradient of 2–100% ethyl acetate in petroleum ether, to give *tert*-butyl 2-(but-3-en-1-yl)-2-((trimethylsilyl)oxy)-6-azaspiro[3.5]nonane-6-carboxylate (4.26 g, 11.6 mmol, 57 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.79 - 5.97 (m, 1 H), 4.91 - 5.08 (m, 2 H), 3.25 - 3.39 (m, 4 H), 2.16 - 2.26 (m, 2 H), 1.97 - 2.07 (m, 2 H), 1.78 - 1.86 (m, 2 H), 1.59 - 1.75 (m, 4 H), 1.47 (d, *J*=5.6 Hz, 11 H), 0.12 - 0.18 (m, 9 H).

Intermediate YY: 7-(5-Allyl-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine.



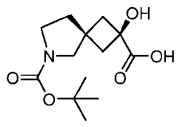
[00352] Step 1. 5-Allyl-4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole. To a solution of 4-bromo-6-chloro-5-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (50.0 g, 113 mmol) in toluene (500 mL) was added allyltributylstannane (41.3 g, 125 mmol) and LiCl (24.0 g, 566 mmol) in sequence. The reaction mixture was degassed and purged with nitrogen. $Pd(PPh_3)_4$ (13.1 g, 11.3 mmol) was added and the reaction mixture was stirred at 110 °C for 12 h. After cooling to room temperature, the reaction was combined with another 50 g batch and filtered. The filtrate was quenched by addition of water, and then extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a gradient of 2–100% ethyl acetate in petroleum ether, to give 5-allyl-4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (60.0 g, 169 mmol, 75% yield). *m/z* (ESI): 356.9/354.9 $(M+H)^+$.

[00353] Step 2. 5-Allyl-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole. To a solution of 5-allyl-4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (30 g, 84 mmol) in 1,4-dioxane (600 mL) and water (75 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (107 g, 422 mmol), Cs_2CO_3 (82.4 g, 253 mmol) and $Pd(dppf)Cl_2$ (6.17 g, 8.44 mmol) under N_2. The mixture was heated at 120 °C for 1 h under N_2. After cooling to room temperature, the reaction mixture was combined with another 30 g batch and diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reversed phase MPLC to give 5-allyl-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-

tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole (29 g, 72 mmol, 43% yield). *m/z* (ESI): 403.2/405.2 $(M+H)^+$.

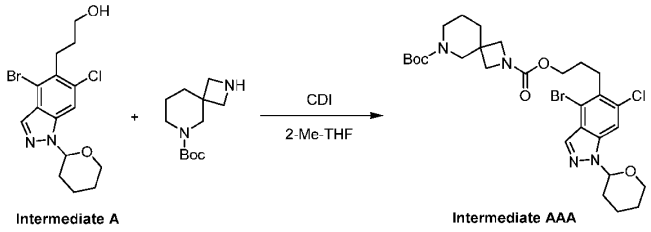
[00354] Step 3. 7-(5-Allyl-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidine. To a solution of 7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidine (**Intermediate WW**, 15.0 g, 34.2 mmol) in THF (150 mL) and water (15 mL) was added 5-allyl-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole (16.5 g, 41.0 mmol), K_3PO_4 (21.7 g, 103 mmol) and CataCXium A Pd G3 (CAS No. 1651823-59-4) (3.73 g, 5.13 mmol) under nitrogen. The reaction mixture was stirred at 80 °C for 10 h, was then diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a gradient of 2–100% ethyl acetate in petroleum ether, to give 7-(5-allyl-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidine (11.5 g, 17.0 mmol, 50% yield). *m/z* (ESI): 679.2/681.2 $(M+H)^+$. ^1H NMR (400 MHz, *CDCl3*) δ ppm 9.25 (d, *J* = 3.6 Hz, 1 H), 7.77 (d, *J* = 15.2 Hz, 1 H), 7.47 (d, *J* = 4.0 Hz, 1 H), 5.64 - 5.71 (m, 2 H), 5.13 - 5.36 (m, 1 H), 5.00 (q, *J* = 8.0 Hz, 2 H), 4.81 (d, *J* = 9.6 Hz, 1 H), 4.65 (d, *J* = 17.2 Hz, 1 H), 4.23 - 4.40 (m, 2 H), 3.88 - 4.03 (m, 1 H), 3.64 - 3.77 (m, 1 H), 3.50 - 3.60 (m, 1 H), 3.38 - 3.47 (m, 1 H), 3.20 - 3.30 (m, 1 H), 3.11 - 3.18 (m, 1 H), 2.88 - 2.98 (m, 1 H), 2.36 - 2.53 (m, 1 H), 2.13 - 2.27 (m, 2 H), 2.00 - 2.10 (m, 3 H), 1.80-1.95 (m, 3 H), 1.59 - 1.71 (m, 4 H). ^{19}F NMR (376 MHz, *CDCl3*) δ ppm -73.292 (s, 5 F).

Intermediate ZZ: (2*S*, 4*R*)-6-(*tert*-Butoxycarbonyl)-2-hydroxy-6-azaspiro[3.4]octane-2-carboxylic acid.



[00355] The title compound was synthesized analogous to **Intermediate JJ** using *tert*-butyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate (Pharmablock, Inc.) in **Step 1**. *m/z* (ESI): 294.1 $(M+Na)^+$.

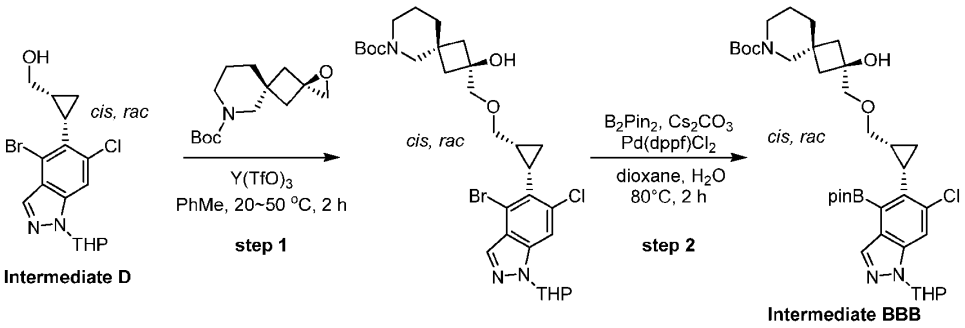
Intermediate AAA: 2-(3-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl) 6-(*tert*-butyl) 2,6-diazaspiro[3.5]nonane-2,6-dicarboxylate.



Intermediate A Intermediate AAA

[00356] To a stirred solution of 3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propan-1-ol (**Intermediate A**, 1.5 g, 4.0 mmol) in 2-methyltetrahydrofuran (7 mL) was added 1,1'-carbonyldiimidazole (0.72 g, 4.4 mmol). The reaction mixture was stirred at room temperature for 30 minutes. Then, *tert*-butyl 2,6-diazaspiro[3.5]nonane-6-carboxylate (1.6 g, 7.2 mmol) was added and the reaction mixture was heated at 80 °C for 18 h. The mixture was cooled to room temperature and diluted with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0–100% EtOAc in hexane, to provide 2-(3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl) 6-(*tert*-butyl) 2,6-diazaspiro[3.5]nonane-2,6-dicarboxylate (2.2 g, 3.5 mmol, 86% yield). *m/z* (ESI): 625.2 $(M+H)^+$.

Intermediate BBB: ***tert*-Butyl (2*s*,4*R*)-2-((((1*R*,2*S*)-2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate**



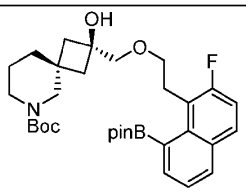
[00357] **Step 1: *tert*-Butyl (2*s*,4*R*)-2-((((1*R*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate, Intermediate BBB.1.** To a mixture of **Intermediate D** (5.0 g, 13 mmol) and **Intermediate B** (3.3 g, 13 mmol) in PhMe (115 mL) was added $Y(TfO)_3$ (1.8 g, 3.2 mmol) under N_2 at room temperature, and the reaction mixture was stirred at 50 °C for 2 h. The reaction mixture was quenched by addition of sat. aq. NH_4Cl (100 mL) and extracted with EtOAc (3 x 80 mL). The

combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by reversed phase chromatography, eluting with a gradient of 35-65% ACN in H_2O (0.1% NH_3H_2O), to obtain **Intermediate BBB.1** (4.5 g, 7.0 mmol, 54% yield). *m/z* (ESI): 638.4 $(M+H)^+$.

[00358] Step 2: *tert*-Butyl (2*s*,4*R*)-2-((((1*R*,2*S*)-2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate, Intermediate BBB. To a mixture of **Intermediate BBB.1** (2.0 g, 3.1 mmol), B_2Pin_2 (4.0 g, 15.6 mmol), Cs_2CO_3 (3.1 g, 9.4 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was added $Pd(dppf)Cl_2$ (0.2 g, 0.3 mmol). The reaction mixture was sparged with nitrogen and stirred at 80 °C for 2 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chromatography, eluting with a gradient of 20:1 to 0:1 of pet. ether in EtOAc, to obtain **Intermediate BBB** (1.5 g, 2.2 mmol, 67% yield). *m/z* (ESI): 686.5 $(M+H)^+$.

[00359] Compounds in Table 23 were prepared following a procedure analogous to the one described above for Intermediate BBB, using appropriate starting materials. All starting materials are commercially available or are described in the Intermediates section above.

Table 23. Additional Intermediates Prepared in Analogous Manner to Intermediate BBB.

Intermediate	Structure	Name	Reagents	Method Changes
CCC		*tert*-butyl (2*s*,4*r*)-2-((2-(2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate	2-(2-fluoro-8-iodonaphthalen-1-yl)ethan-1-ol	

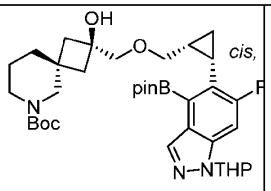
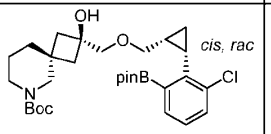
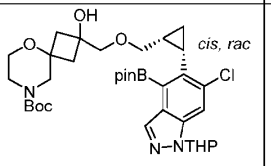
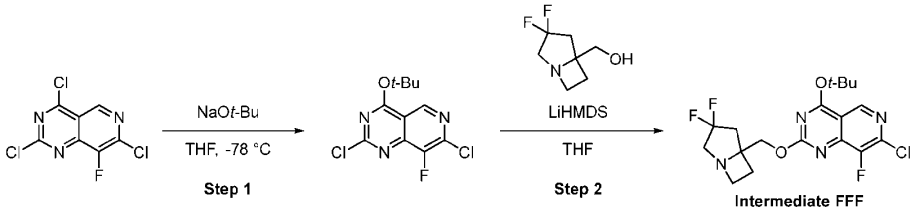
DDD		*tert*-butyl (2*s*,4*R*)-2-((((1*RS*,2*SR*)-2-(6-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate	*rac*-((1*R*,2*S*)-2-(4-bromo-6-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methanol	
EEE		*tert*-butyl (2*s*,4*R*)-2-((((1*RS*,2*SR*)-2-(2-chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropyl)methoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate	*rac*-((1*R*,2*S*)-2-(2-bromo-6-chlorophenyl)cyclopropyl)methanol	
III		*tert*-butyl 2-((((1*S*,2*R*)-2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-2-hydroxy-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate	((1*S*,2*R*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methanol	**Step 2:** $Pd(OAc)_2$ was used in lieu of $Pd(dppf)Cl_2$, EtOAc was used in lieu of dioxane and H_2O

Table 24. Analytical data for Examples

Cmpd.#	**MS** *m/z* (ESI): $(M+H)^+$	**^{1}H NMR**
CCC	592.4 $(M+Na)^+$	N/A
DDD	670.5	N/A

Cmpd.#	MS *m/z* (ESI): $(M+H)^+$	^{1}H NMR
EEE	584.3 $(M+Na)^+$	^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 7.38 (d, *J*=7.2 Hz, 1 H), 7.29 (m, 1 H), 7.04 - 7.09 (m, 1 H), 3.16 - 3.25 (m, 3 H), 3.00 - 3.15 (m, 5 H), 2.75 - 2.94 (m, 1 H), 2.28 - 2.45 (m, 1 H), 1.70 - 1.88 (m, 3 H), 1.48 - 1.64 (m, 7 H), 1.34 - 1.37 (m, 9 H), 1.17 - 1.20 (m, 12 H), 0.76 - 0.85 (m, 1 H).
III	688.2	^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 8.20 – 8.12 (m, 1H), 7.72 – 7.66 m, 1H), 5.71 – 5.63 (m, 1H), 4.07 – 3.97 (m, 1H), 3.83 – 3.70 (m, 1H), 3.58 – 3.42 (m, 5H), 3.39 – 3.31 (m, 3H), 3.28 – 3.13 (m, 3H), 2.62 – 2.41 (m, 3H), 2.20 – 2.08 (m, 3H), 1.98 – 1.93 (m, 3H), 1.78 – 1.69 (m, 2H), 1.46 (br d, *J* = 17.6 Hz, 25H), 1.31 – 1.27 (m, 3H).

Intermediate FFF: **4-(*tert*-Butoxy)-7-chloro-2-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-8-fluoropyrido[4,3-*d*]pyrimidine**.

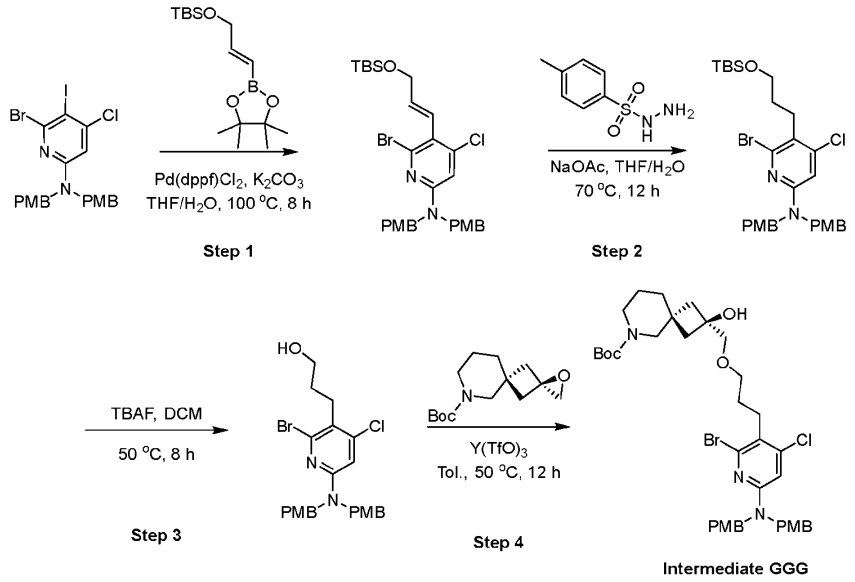


[00360] Step 1: 4-(*tert*-Butoxy)-2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidine, Intermediate FFF.1. To a stirred mixture of 2,4,7-trichloro-8-fluoropyrido[4,3-*d*]pyrimidine (1.5 g, 6.0 mmol, LabNetwork Inc.) in TFA (12 mL) at -78 °C under N_2 was added sodium *tert*-butoxide (2 M in THF, 3.55 g, 3.9 mL, 7.8 mmol, Oakwood Products, Inc.), and the resulting mixture was stirred at -78 °C for 10 minutes. The reaction mixture was diluted with sat. aq. NH_4Cl (15 mL) at -78 °C and allowed to warm to room temperature. The biphasic mixture was extracted with EtOAc (3 x 20 mL), and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated to provide **Intermediate FFF.1** (1.5 g, 5.2 mmol, 87%, yield). *m/z* (ESI): 234.0 $(M-tBu+H)^+$. ^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 9.07 – 8.99 (m, 1H), 1.84 – 1.79 (m, 9H). ^{19}F NMR (376 MHz, *CDCl*$_3$) δ ppm -132.21 – -132.60 (m, 1F).

[00361] Step 2: 4-(*tert*-Butoxy)-7-chloro-2-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-8-fluoropyrido[4,3-*d*]pyrimidine, Intermediate FFF. To a stirred mixture of (3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methanol (0.37 g, 2.24 mmol, Pharmablock) in THF (5.5 mL) at 0 °C under N_2 was added lithium bis(trimethylsilyl)amide solution in THF (1 M in THF, 2.1 mL, , 2.1 mmol, Sigma-Aldrich) and the resulting mixture stirred at 0 °C for 10 minutes. To this solution was added **Intermediate FFF.1** (0.50 g, 1.7 mmol) in THF (2.75 mL), and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with sat. aq. NH_4Cl (10 mL) and

extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give a residue which was purified by chromatography, eluting with a gradient of 0-50% EtOH/EtOAc (1:3, 2% TEA) in heptane, to provide **Intermediate FFF** (0.57 g, 1.4 mmol, 80% yield). *m/z* (ESI): 417.0 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.97 – 8.83 (m, 1H), 4.62 – 4.48 (m, 2H), 3.84 – 3.67 (m, 1H), 3.49 – 3.05 (m, 3H), 2.65 – 2.52 (m, 3H), 2.51 – 2.39 (m, 1H), 1.83 – 1.77 (m, 9H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -90.36 (d, J = 234.9 Hz, 1F), -99.81 (d, J = 234.9 Hz, 1F), -135.29 (s, 1F).

Intermediate GGG: ***tert*-Butyl (2*s*,4*r*)-2-((3-(6-(bis(4-methoxybenzyl)amino)-2-bromo-4-chloropyridin-3-yl)propoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate**



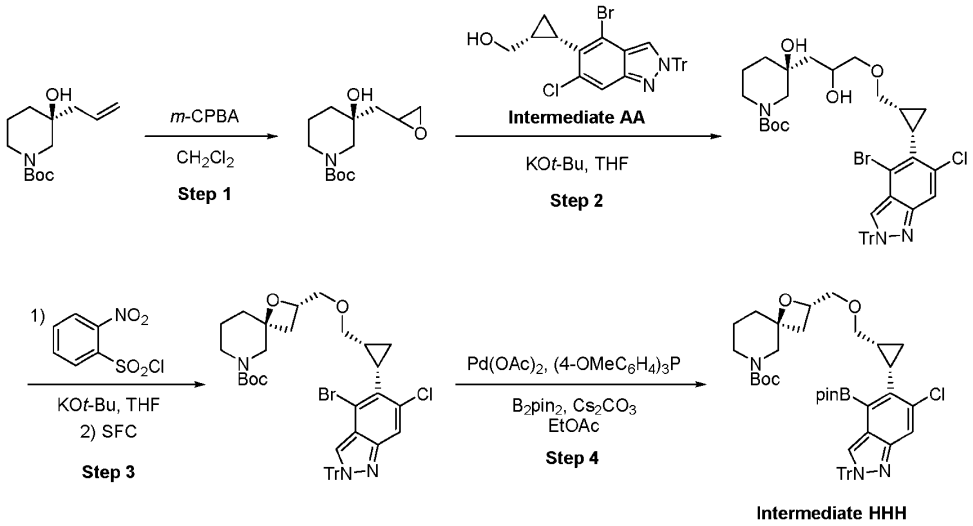
[00362] Step 1: (*E*)-6-Bromo-5-(3-((*tert*-butyldimethylsilyl)oxy)prop-1-en-1-yl)-4-chloro-*N*,*N*-bis(4-methoxybenzyl)pyridin-2-amine, Intermediate GGG.1. To a solution of 6-bromo-4-chloro-5-iodo-*N*,*N*-bis(4-methoxybenzyl)pyridin-2-amine (3.0 g, 5.2 mmol, CAS: 3064753-60-9) and (*E*)-*tert*-butyldimethyl((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)oxy)silane (2 g, 6.8 mmol, CAS: 114653-19-9) in THF (30 mL) and water (3 mL) was added K_2CO_3 (3.1 g, 26.1 mmol) and $Pd(dppf)Cl_2$ (0.4 g, 0.5 mmol), and the mixture was stirred at 100 °C for 8 h. The reaction mixture was diluted with H_2O (200 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chromatography on silica gel, eluting with a gradient of 50:1 to 20:1 pet. ether in EtOAc, to obtain **Intermediate GGG.1** (4.0 g, 6.5 mmol, 41% yield). *m/z* (ESI): 617.2 $(M+H)^+$.

[00363] Step 2: **6-Bromo-5-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-4-chloro-*N*,*N*-bis(4-methoxybenzyl)pyridin-2-amine, Intermediate GGG.2.** To a solution of **Intermediate GGG.1** (4.0 g, 6.5 mmol) in THF (40 mL) and water (4 mL) was added NaOAc (3.2 g, 38.8 mmol) and 4-methylbenzenesulfonohydrazide (7.23 g, 38.8 mmol), and the mixture was stirred at 70 °C for 12 h. The reaction mixture was diluted with H_2O (80 mL) and extracted with EtOAc (2 x 40 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chromatography on silica gel, eluting with a gradient of 50:1 to 20:1 pet. ether in EtOAc, to obtain **Intermediate GGG.2** (3.0 g, 4.8 mmol, 75% yield). *m/z* (ESI): 621.2 $(M+H)^+$.

[00364] Step 3: 3-(6-(bis(4-Methoxybenzyl)amino)-2-bromo-4-chloropyridin-3-yl)propan-1-ol, Intermediate GGG.3. To a solution of **Intermediate GGG.2** (2.8 g, 4.5 mmol) in DCM (28 mL) was added TBAF (1 M in THF, 13.5 mL, 13.5 mmol) and the mixture was stirred at 50 °C for 8 h. The reaction mixture was diluted with H_2O (50 mL) and extracted with DCM (2 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chromatography on silica gel, eluting with a gradient of 10:1 to 1:1 pet. ether in EtOAc, to obtain **Intermediate GGG.3** (1.7 g, 3.3 mmol, 70% yield). *m/z* (ESI): 507.2 $(M+H)^+$. ^1H NMR (400 MHz, *CDCl3*) δ ppm 7.15 (d, *J*=8.4 Hz, 4 H), 6.86 (d, *J*=8.4 Hz, 4 H), 6.39 (s, 1 H), 5.31 (s, 1 H), 4.61 (s, 4 H), 3.81 (s, 6 H), 3.71 - 3.76 (m, 2 H), 2.82 - 2.92 (m, 2 H), 1.80 - 1.91 (m, 2 H).

[00365] Step 4: *tert*-Butyl (2*s*,4*r*)-2-((3-(6-(bis(4-methoxybenzyl)amino)-2-bromo-4-chloropyridin-3-yl)propoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate, Intermediate GGG. To a solution of **Intermediate GGG.3** (1.3 g, 5.0 mmol) in PhMe (34 mL) was added $Y(TfO)_3$ (0.4 g, 0.8 mmol), and the mixture was stirred at 50 °C for 12 h. The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (2 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by reversed phase medium pressure LC, eluting with a gradient of 60-90% ACN in H_2O (0.1% $NH_3{\cdot}H_2O$), to obtain **Intermediate GGG** (0.90 g, 1.19 mmol, 35% yield). *m/z* (ESI): 760.2 $(M+H)^+$.

Intermediate HHH: ***tert*-Butyl (2*S*,4*S*)-2-((((1*R*,2*S*)-2-(6-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-trityl-2*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate**.



[00366] Step 1: *tert*-Butyl (3*S*)-3-hydroxy-3-(oxiran-2-ylmethyl)piperidine-1-carboxylate, Intermediate HHH.1. To a stirred mixture of *tert*-butyl (*S*)-3-allyl-3-hydroxypiperidine-1-carboxylate (1.75 g, 7.3 mmol, Pharmablock, Inc.) in DCM (48.3 mL) at 0 °C, was added 3-chlorobenzene-1-carboperoxoic acid (5.0 g, 22 mmol, Sigma-Aldrich), and the mixture was stirred at room temperature for 16 h. The reaction was cooled to 0 °C and quenched with a solution of $Na_2S_2O_3$, then diluted with aq. $NaHCO_3$. The aqueous layer was extracted with DCM, washed with aq. $NaHCO_3$ (3x), dried over Na_2SO_4 and concentrated to provide **Intermediate HHH.1** (1.7 g, 6.5 mmol, 89% yield), which was used in subsequent steps without further purification. *m/z* (ESI): 280.0 $(M+Na)^+$.

[00367] Step 2: *tert*-Butyl (3*S*)-3-(3-(((1*R*,2*S*)-2-(4-bromo-6-chloro-2-trityl-2*H*-indazol-5-yl)cyclopropyl)methoxy)-2-hydroxypropyl)-3-hydroxypiperidine-1-carboxylate, Intermediate HHH.2. To a stirred mixture of **Intermediate AA** (1.78 g, 3.3 mmol) in TFA (12 mL) at 0 °C under nitrogen, was added KOtBu (0.40 g, 3.5 mmol, Sigma Aldrich), and the mixture stirred at 0 °C for 10 minutes. Then, a solution of **Intermediate HHH.1** (0.70 g, 2.7 mmol) in TFA (6.00 mL) was added, and the resulting mixture was stirred at 50 °C for 2 h. The reaction was concentrated and purified by column chromatography on silica gel, eluting with a gradient of 0-100% EtOAc in heptane, to provide **Intermediate HHH.2** (0.98 g, 1.2 mmol, 45% yield). *m/z* (ESI): 822.0 $(M+Na)^+$.

[00368] Step 3: *tert*-Butyl (2*S*,4*S*)-2-((((1*R*,2*S*)-2-(4-bromo-6-chloro-2-trityl-2*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate, Intermediate HHH.3. To a stirred mixture of **Intermediate HHH.2** (1.4 g, 1.7 mmol) in THF (17 mL) at 0 °C under N_2 was added KOtBu (0.4 g, 3.8 mmol, Sigma Aldrich), and the resulting mixture was stirred at 0 °C for 30 minutes. Then, 2-nitrobenzenesulfonyl chloride (0.5 g, 2.4 mmol, Combi-Blocks Inc.) was added, and the reaction warmed to room temperature over 16 h. The reaction mixture was diluted with

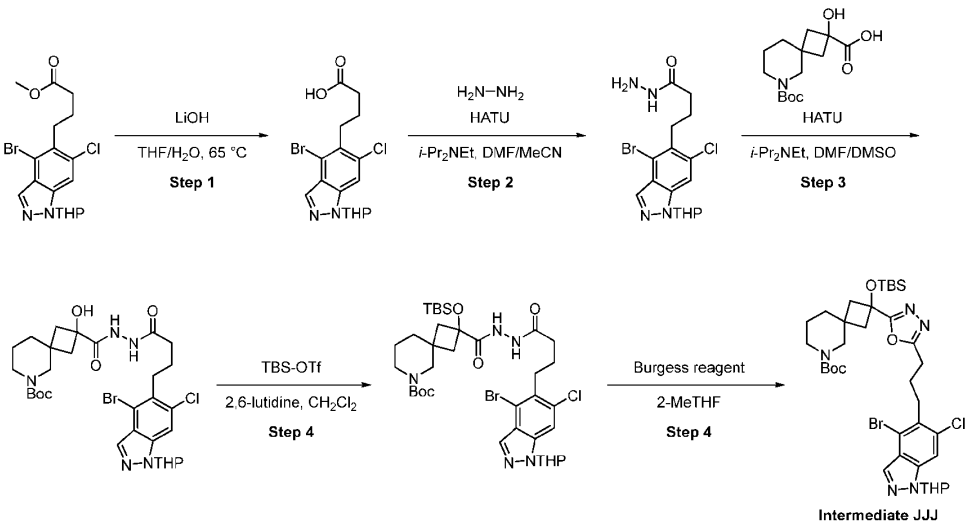
H_2O, extracted with EtOAc, dried over Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography on silica gel, eluting with a gradient of 0-70% EtOAc in heptane.

Peak 1: *tert*-Butyl (2*R*,4*S*)-2-((((1*R*,2*S*)-2-(4-bromo-6-chloro-2-trityl-2*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate (0.35 g, 0.40 mmol, 26% yield). *m/z* (ESI): 804.0 $(M+Na)^+$.

Peak 2: *tert*-Butyl (2*S*,4*S*)-2-((((1*R*,2*S*)-2-(4-bromo-6-chloro-2-trityl-2*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate (**Intermediate HHH.3**, 0.3 g, 0.3 mmol, 19% yield). *m/z* (ESI): 804.0 $(M+Na)^+$.

[00369] Step 4: *tert*-Butyl (2*S*,4*S*)-2-((((1*R*,2*S*)-2-(6-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-trityl-2*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate. To a stirred and degassed mixture of $Pd(OAc)_2$ (20 mg, 0.07 mmol, Sigma-Aldrich), tris(4-methoxyphenyl)phosphine (50 mg, 0.13 mmol, Combi-Blocks), Cs_2CO_3 (0.2 g, 0.5 mmol, Ambeed, Inc.), **Intermediate HHH.3** (0.26 g, 0.33 mmol) in EtOAc (1.7 mL) under N_2 was added B_2Pin_2 (0.1 g, 0.4 mmol, Combi-Blocks Inc.), and the resulting mixture was stirred at 80 °C for 10 h. The reaction mixture was filtered and concentrated. The resulting residue was purified by column chromatography on silica gel, eluting with a gradient of 0-80% EtOAc in heptane, to provide **Intermediate HHH** (0.1 g, 0.1 mmol, 43% yield). *m/z* (ESI) 852.2 $(M+Na)^+$.

Intermediate JJJ: ***tert*-Butyl 2-(5-(3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl)-1,3,4-oxadiazol-2-yl)-2-((*tert*-butyldimethylsilyl)oxy)-6-azaspiro[3.5]nonane-6-carboxylate**



[00370] Step 1: 4-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butanoic acid, Intermediate JJJ.1. To a stirred mixture of methyl 4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butanoate (2.1 g, 5.0 mmol) in THF (13 mL) in H_2O (13 mL) at 55 °C under ambient atmosphere was added lithium hydroxide, monohydrate (0.4 g, 10 mmol, Sigma-Aldrich), and the resulting mixture was stirred at 55 °C for 2 h. The reaction was concentrated, diluted with EtOAc, and acidified (pH ~ 2-3) by addition of HCl solution (0.5 M). The aqueous phase was extracted with EtOAc, dried over Na_2SO_4 and concentrated to provide **Intermediate JJJ.1** (2 g, 5 mmol, 99% yield). *m/z* (ESI): 401.0 $(M+H)^+$.

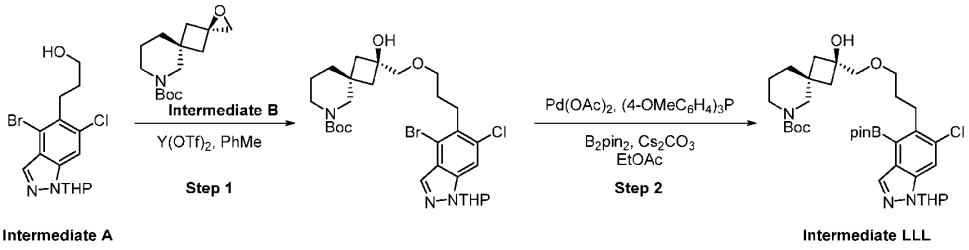
[00371] Step 2: 4-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butanehydrazide., Intermediate JJJ.2 To a stirred mixture of **Intermediate JJJ.1** (2 g, 5 mmol) and DIPEA (2 mL, 11 mmol, Sigma-Aldrich) in DMF (3.3 mL)/ACN(13.3 mL) at room temperature under N_2 was added HATU (2.3 g, 6.0 mmol, Combi-Blocks Inc.), and the resulting mixture was stirred at room temperature for 30 minutes. To this mixture, a solution of hydrazine, anhydrous (0.6 mL, 20 mmol, Sigma-Aldrich) and DIPEA (1.9 mL, 11 mmol, Sigma-Aldrich) in DMF (3.3 mL)/ACN (13.3 mL) was added, and the reaction was stirred at room temperature for 1 h. The reaction mixture was diluted with H_2O (150 mL), filtered, washed with H_2O and dried to provide **Intermediate JJJ.2** (1.5 g, 3.7 mmol, 74% yield). *m/z* (ESI): 415.0 $(M+H)^-$.

[00372] Step 3: *tert*-Butyl 2-(2-(4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butanoyl)hydrazine-1-carbonyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate. Intermediate JJJ.3. To a stirred mixture of DIPEA (2.6 mL, 14.8 mmol, Sigma-Aldrich Corporation),4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butanehydrazide (1.54 g, 3.70 mmol) and 6-(*tert*-butoxycarbonyl)-2-hydroxy-6-azaspiro[3.5]nonane-2-carboxylic acid (1.27 g, 4.45 mmol) in *N,N*-dimethylformamide (20.5 mL)/dimethyl sulfoxide (4.1 mL) at room temperature under ambient atmosphere, was added HATU (1.62 g, 4.26 mmol, Combi-Blocks Inc.). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with brine (30 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude material was purified by reversed phase chromatography, eluting with a gradient of 5-100% acetonitrile (0.1% formic acid) in water (0.1% formic acid) to afford *tert*-butyl 2-(2-(4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butanoyl)hydrazine-1-carbonyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (2.35 g, 3.44 mmol, 93% yield). *m/z* (ESI): 682.0 $(M+H)^+$. ^1H NMR (400 MHz, *CDCl*$_3$) δ ppm 8.88 - 9.11 (m, 1 H), 7.96 (s, 2 H), 7.61 - 7.69 (m, 1 H), 5.58 - 5.70 (m, 1 H), 3.95 - 4.07 (m, 1 H), 3.74 - 3.85 (m, 1 H), 3.43 - 3.52 (m, 3 H), 3.34 (br d, *J*=5.0 Hz, 3 H), 3.10 - 3.21 (m, 2 H), 2.48 - 2.77 (m, 3 H), 2.37 - 2.46 (m, 3 H), 2.08 - 2.30 (m, 3 H), 1.87 - 2.03 (m, 2 H), 1.69 - 1.83 (m, 6 H), 1.47 (d, *J*=2.9 Hz, 9 H)

[00373] Step 4: *tert*-Butyl 2-(2-(4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butanoyl)hydrazine-1-carbonyl)-2-((*tert*-butyldimethylsilyl)oxy)-6-azaspiro[3.5]nonane-6-carboxylate, Intermediate JJJ.4. To a stirred mixture of **Intermediate JJJ.3** (2.4 g, 3.4 mmol) and 2.6-lutidine (1.1 g, 1.2 mL, 10.3 mmol, Sigma-Aldrich) in DCM (22.94 mL) at 0 °C under N_2 was added TBS triflate (1.2 mL, 5.2 mmol, Sigma-Aldrich Corporation), and the resulting mixture warmed to room temperature and stirred for 3 h. The reaction mixture was diluted with sat. aq. Na_2CO_3 (10 mL) and extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography on silica gel, eluting with a gradient of 0-40% EtOH/EtOAc (1:3) in heptane, to provide **Intermediate JJJ.4** (2.6 g, 3.3 mmol, 95% yield). *m/z* (ESI): 818.0 $(M+Na)^+$.

[00374] Step 5: *tert*-Butyl 2-(5-(3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl)-1,3,4-oxadiazol-2-yl)-2-((*tert*-butyldimethylsilyl)oxy)-6-azaspiro[3.5]nonane-6-carboxylate, Intermediate JJJ. To a stirred mixture of **Intermediate JJJ.4** (2.6 g, 3.3 mmol) in Me-THF (22 mL) at room temperature under N_2 was added Burgess reagent (4.7 g, 19.6 mmol, Combi-Blocks Inc.), and the resulting mixture was stirred at 80 °C for 4 h. The reaction mixture was concentrated and purified by column chromatography on silica gel, eluting with a gradient of 0-80% EtOAc in heptane, to provide **Intermediate JJJ** (0.9 g, 1.1 mmol, 35% yield). *m/z* (ESI): 778.2 $(M+H)^+$.

Intermediate LLL: ***tert*-Butyl (2*s*,4*r*)-2-((3-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)propoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate**.

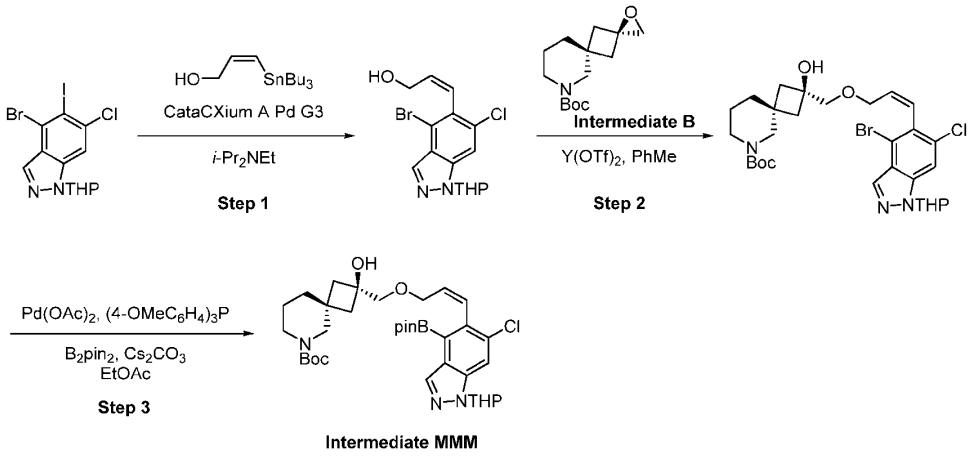


[00375] Step 1: *tert*-Butyl (2*s*,4*r*)-2-((3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate, Intermediate LLL.1. To a stirred mixture of **Intermediate A** (0.40 g, 1.1 mmol) and $Y(TfO)_3$ (0.14 g, 0.27 mmol, Combi-Blocks Inc.) in PhMe (5 mL) at room temperature under N_2 was added **Intermediate B** (0.41 g, 1.6 mmol) and the resulting mixture stirred at 40 °C for 16 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give a residue which was purified by

column chromatography on silica gel, eluting with a gradient of 0-80% EtOAc in heptane, to provide **Intermediate LLL.1** (0.37 g, 0.6 mmol, 55% yield). *m/z* (ESI): 648.0 $(M+Na)^+$. ^1H NMR (400 MHz, *CDCl3*) δ ppm 8.05 – 7.87 (m, 1H), 7.72 – 7.57 (m, 1H), 5.73 – 5.54 (m, 1H), 4.07 – 3.94 (m, 1H), 3.83 – 3.68 (m, 1H), 3.68 – 3.56 (m, 2H), 3.56 – 3.42 (m, 2H), 3.38 – 3.21 (m, 4H), 3.20 – 3.06 (m, 2H), 2.94 – 2.79 (m, 1H), 2.60 – 2.41 (m, 1H), 2.22 – 1.84 (m, 7H), 1.80 – 1.73 (m, 3H), 1.70 – 1.64 (m, 3H), 1.54 – 1.42 (m, 11H).

[00376] Step 2: *tert*-Butyl (2*s*,4*r*)-2-((3-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)propoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate, Intermediate LLL. To a stirred mixture of **Intermediate LLL.1** (0.37 g, 0.6 mmol), B_2Pin_2 (0.30 g, 1.2 mmol, Combi-Blocks Inc.) and Cs_2CO_3 (0.58 g, 1.8 mmol, Ambeed, Inc.) in EtOAc (3 mL) at room temperature under N_2 was added $Pd(OAc)_2$ (18 mg, 0.1 mmol, Sigma-Aldrich Corporation) and tris(4-methoxyphenyl)phosphine (27 mg, 0.1 mmol, Combi-Blocks Inc.). The resulting mixture was sparged with N_2 for 15 minutes and stirred at 80 °C for 1 h 15 minutes. The reaction mixture was filtered and concentrated. The resulting residue was purified by column chromatography on silica gel, eluting with a gradient of 0-80% EtOAc in heptane, to provide **Intermediate LLL** (0.29 g, 0.4 mmol, 74% yield). *m/z* (ESI): 696.2 $(M+Na)^+$. ^1H NMR (400 MHz, *CDCl3*) δ ppm 8.40 – 8.30 (m, 1H), 7.80 – 7.71 (m, 1H), 5.74 – 5.59 (m, 1H), 4.07 – 3.95 (m, 1H), 3.80 – 3.69 (m, 1H), 3.66 – 3.54 (m, 2H), 3.52 – 3.41 (m, 2H), 3.36 – 3.28 (m, 2H), 3.27 – 3.24 (m, 2H), 3.24 – 3.15 (m, 2H), 3.03 – 2.82 (m, 1H), 2.64 – 2.42 (m, 1H), 2.22 – 2.12 (m, 2H), 2.08 – 1.99 (m, 3H), 1.95 – 1.82 (m, 3H), 1.82 – 1.73 (m, 4H), 1.71 – 1.65 (m, 3H), 1.55 – 1.44 (m, 12H), 1.42 – 1.41 (m, 9H).

Intermediate MMM: ***tert*-Butyl (2*s*,4*r*)-2-((((*Z*)-3-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)allyl)oxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate.**



Intermediate MMM

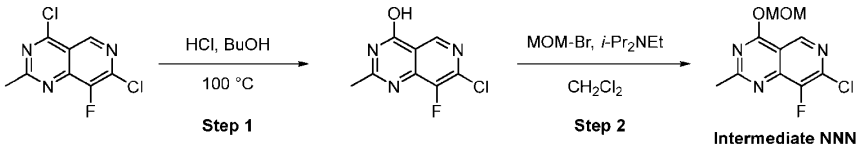
[00377] Step 1: (Z)-3-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)prop-2-en-1-ol, Intermediate MMM.1. To a mixture of *(Z)*-2-propen-3-(tributylstannyl)-1-ol (2.3 g, 6.6 mmol, AA BLOCKS LLC), 4-bromo-6-chloro-5-iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (2.34 g, 5.30 mmol,CAS: 74141-13-2), and CataCXium A Pd G3 (CAS No. 1651823-59-4)(0.2 g, 0.3 mmol, Ambeed, Inc.) was added DIPEA (11 mL). The mixture was sparged with N_2, and stirred at 100 °C for 1 h. The reaction mixture was diluted with 10% aq. LiCl (10 mL) and EtOAc (15 mL). The organic layer was washed with 10% aq. LiCl (10 mL), dried with Na_2SO_4, filtered, and concentrated. The resulting residue was purified via chromatography, eluting with a gradient of 0-40% EtOAc in heptane, to provide **Intermediate MMM.1** (0.97 g, 2.6 mmol, 49% yield). *m/z* (ESI): 370.8 $(M+H)^+$.

[00378] Step 2: *tert*-Butyl (2*s*,4*r*)-2-((((*Z*)-3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)allyl)oxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate, Intermediate MMM.2. To a solution of **Intermediate MMM.1** (0.52 g, 1.4 mmol) in PhMe (9.3 mL), was added $Y(TfO)_3$ (0.19 g, 0.30 mmol, Combi-Blocks Inc.) and **Intermediate B** (0.53 g, 2.1 mmol). The reaction was stirred at 40 °C for 22 h. The reaction mixture was then concentrated and purified via RP-HPLC, using a gradient of 10-100% MeCN (0.1% formic acid) in water (0.1% formic acid), to provide **Intermediate MMM.2** (0.38 g, 0.6 mmol, 43% yield). *m/z* (ESI): 646 $(M+Na)^+$.

[00379] Step 3: *tert*-Butyl (2*s*,4*r*)-2-((((*Z*)-3-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)allyl)oxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate, Intermediate MMM. To **Intermediate MMM.2** (0.38 g, 0.6 mmol) was added Cs_2CO_3 (0.30 g, 0.9 mmol, Combi-Blocks Inc.), B_2Pin_2 (0.18 g, 0.7 mmol, Combi-Blocks Inc.), $Pd(OAc)_2$ (6.8 mg, 0.03 mmol, AK Scientific, Inc.) and tris(4-methoxyphenyl)phosphine (21 mg, 0.1 mmol, Combi-Blocks Inc) in EtOAc (1.2 mL). The mixture was sparged with N_2 for 5 minutes and stirred at 80 °C for 2.5 h. The reaction was cooled to room temperature, filtered, and concentrated. The resulting residue was purified by column chromatography on silica gel, eluting with

a gradient of 0-40% EtOAc in heptane, to provide **Intermediate MMM** (0.16 g, 0.20 mmol, 40% yield). *m/z* (ESI): 671.2 $(M+H)^+$.

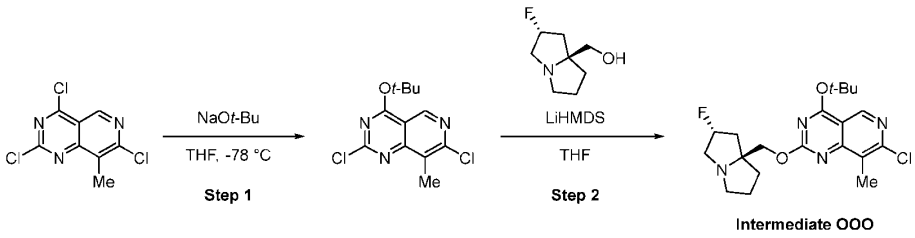
Intermediate NNN: **7-Chloro-8-fluoro 4-(methoxymethoxy)-2-methylpyrido[4,3-*d*]pyrimidine**.



[00380] Step 1: 7-Chloro-8-fluoro-2-methylpyrido[4,3-*d*]pyrimidin-4-ol, Intermediate NNN.1. To a stirred mixture of 4,7-dichloro-8-fluoro-2-methylpyrido[4,3-*d*]pyrimidine (0.5 g, 2.2 mmol, PharmaBlock) in BuOH (6 mL) at room temperature under ambient atmosphere was added HCl (2 N, 7.1 g, 6 mL, 12 mmol, Thermo Fisher Scientific) and the resulting mixture was stirred at 100 °C for 1 h. The reaction was cooled to room temperature then diluted with EtOAc and sat. aq. Na_2HCO_3. The aqueous phase was extracted with EtOAc, dried over Na_2SO_4, and concentrated to give **Intermediate NNN.1** (0.50 g, 2.2 mmol, 100% yield). *m/z* (ESI): 214.2 $(M+H)^+$.

[00381] Step 2: 7-Chloro-8-fluoro 4-(methoxymethoxy)-2-methylpyrido[4,3-*d*]pyrimidine, Intermediate NNN. To a stirred mixture of **Intermediate NNN.1** (0.4 g, 2 mmol) and DIPEA (1.8 mL, 10.1 mmol, Sigma-Aldrich) in DCM (13.4 mL) at 0 °C under N_2 was added bromomethyl methyl ether (0.3 mL, 3 mmol, Sigma-Aldrich), the reaction allowed to warm to room temperature and stirred for 3 h. The reaction mixture was diluted with sat. aq. Na_2HCO_3 (20 mL) and extracted with DCM (3 x 15 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography on silica gel, eluting with a gradient of 0-100% EtOH/EtOAc (1:3, 2% TEA) in heptane, to provide **Intermediate NNN** (0.4 g, 1.7 mmol, 83% yield). *m/z* (ESI): 258.0 $(M+H)^+$.

Intermediate OOO: 4-(*tert*-Butoxy)-7-chloro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methylpyrido[4,3-*d*]pyrimidine.



[00382] Step 1: 4-(*tert*-Butoxy)-2,7-dichloro-5-methylpyrido[4,3-*d*]pyrimidine, Intermediate OOO.1. To a stirred mixture of 2,4,7-trichloro-5-methylpyrido[4,3-*d*]pyrimidine (3.0 g, 12.1 mmol, CAS: 2454396-72-4) in THF (15 mL) at -78 °C under N_2, was added sodium *tert*-butoxide (2 M in THF, 6.6 mL, 13.3 mmol, Oakwood Products. Inc.), and the resulting mixture was stirred at -78 °C for 3 h. The reaction mixture was diluted with sat. aq. NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give a residue which was purified by column chromatography on silica gel, eluting with a gradient of 0-80% EtOH/EtOAc (1:3, 2% TEA) in heptane, to provide **Intermediate OOO.1** (0.3 g, 1.1 mmol, 10% yield). *m/z* (ESI): 286.2 $(M+H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.54 (s, 1H), 3.01 (s, 3H), 1.80 (s, 9H).

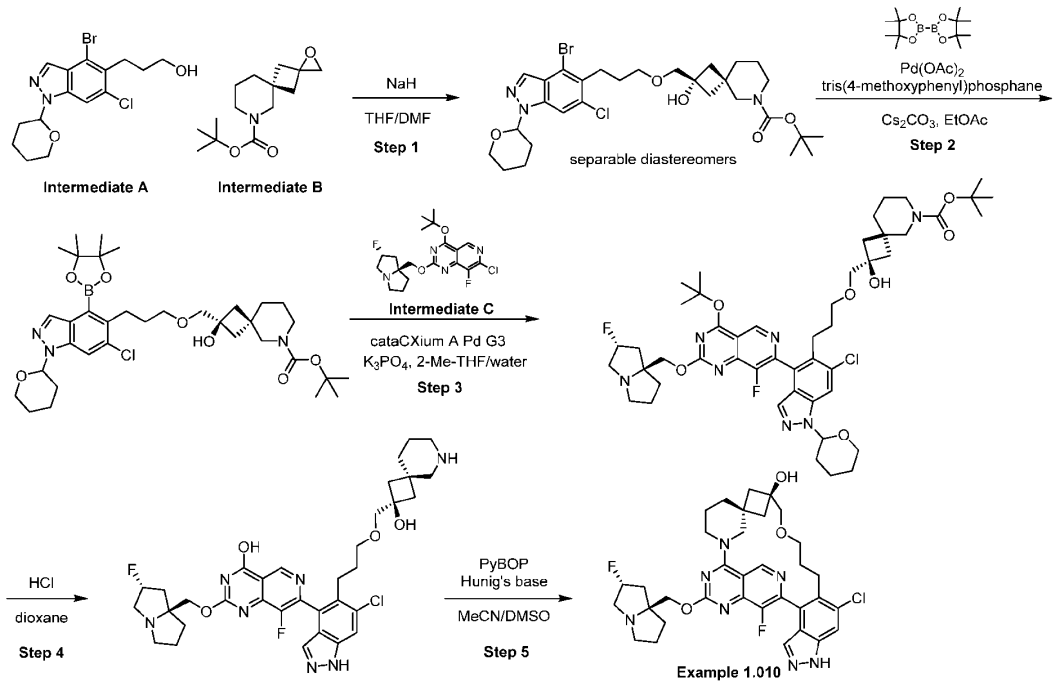
[00383] Step 2: 4-(*tert*-Butoxy)-7-chloro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methylpyrido[4,3-*d*]pyrimidine, Intermediate OOO. To a stirred mixture of ((2*r*,7*as*)-2-fluorohexahydro-1*h*-pyrrolizin-7a-yl)methanol (0.4 g, 2.5 mmol, Pharmablock, Inc.) in THF (5 mL) at room temperature under N_2 was added lithium bis(trimethylsilyl)amide solution in THF (1 M in THF, 3.3 mL, 3.3 mmol, Sigma-Aldrich Corporation), and the resulting mixture was stirred at room temperature for 10 minutes. Then a solution of **Intermediate OOO.1** (0.3 g, 1.1 mmol) in THF (4 mL) was added, and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel, eluting with a gradient of 0-70% EtOH/EtOAc (1:3, 2% TEA) in heptane, to provide **Intermediate OOO** (0.4 g, 0.9 mmol, 81% yield). *m/z* (ESI): 409.3 $(M+H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.37 (s, 1H), 5.42 – 5.15 (m, 1H), 4.26 – 4.15 (m, 2H), 3.31 – 3.22 (m, 2H), 3.21 – 3.14 (m, 1H), 3.00 (td, J = 9.2, 5.7 Hz, 1H), 2.94 (s, 3H), 2.30 – 2.06 (m, 3H), 2.01 – 1.83 (m, 3H), 1.77 (s, 9H).

SECTION 2: Synthesis of Example Compounds

[00384] Provided in this section is the synthesis of examples described herein. It would be understood that compounds described herein (such as compounds of Formula (**I**), Formula (**I-B**), Formula (**II**), Formula (**II-B**), Formula (**III**), Formula (**III-B**), Formula (**IV**), Formula (**IV-B**), Formula (**V**), Formula (**V-B**), Formula (**VI**) or Formula (**VI-B**), or compounds listed in Table 1, Table 2 or compounds of Embodiments 1-214, or a pharmaceutically acceptable salt of any of the foregoing) whose preparation is not specifically described in this section could be prepared in an analogous manner.

Example 1.010: (1*R*,3*R*)-10-Chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-5-oxa-13,14,19,23,25,27-

hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-3-ol.



[00385] Step 1. *tert*-Butyl (2*R*,4*S*)-2-((3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate. A vial was charged with 3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propan-1-ol (**Intermediate A**, 1.09 g, 2.93 mmol) and tetrahydrofuran (3 mL) at room temperature under nitrogen. Sodium hydride (60 wt% in mineral oil, 0.12 g, 2.90 mmol) was added and the reaction mixture was stirred at room temperature for 15 minutes. *tert*-Butyl 1-oxa-7-azadispiro[2.1.5^{5}.1^{3}]undecane-7-carboxylate (**Intermediate B**, 0.37 g, 1.46 mmol) in 1 mL DMF was added. The reaction mixture was stirred at 50 °C under nitrogen for 18 h. After cooling to room temperature, the reaction was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0-100% of EtOAc in hexane, followed by reversed phase C18 column chromatography using 0–100% of 0.1% formic acid in CH_3CN/H_2O. The product containing fractions were collected and diluted with saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The two diastereomers could be separated under reverse phase conditions. *tert*-Butyl (2*R*,4*S*)-2-((3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (0.29 g, 0.46 mmol, 32% yield)

was obtained. *m/z* (ESI): 647.8 $(M+Na)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.95 (s, 1 H), 7.64 (s, 1 H), 5.64 (dd, J=9.0, 2.7 Hz, 1 H), 3.95 – 4.04 (m, 1 H), 3.70 – 3.79 (m, 1 H), 3.61 (t, J=6.3 Hz, 2 H), 3.47 (s, 2 H), 3.28 – 3.33 (m, 2 H), 3.25 (s, 2 H), 3.07 – 3.16 (m, 2 H), 2.41 – 2.53 (m, 1 H), 2.06 – 2.22 (m, 2 H), 1.98 – 2.03 (m, 2 H), 1.85 – 1.94 (m, 2 H), 1.61 – 1.83 (m, 8 H), 1.47 – 1.52 (m, 2 H), 1.44 – 1.47 (m, 9 H).

[00386] Step 2. *tert*-Butyl (2*R*,4*S*)-2-((3-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)propoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate. To a vial was added cesium carbonate (0.23 g, 0.70 mmol), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.15 g, 0.60 mmol) and *tert*-butyl (2*S*,4*R*)-2-((3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (0.29 g, 0.46 mmol) in ethyl acetate (1.5 mL). The reaction was flushed with nitrogen for 5 minutes. To this was added $Pd(OAc)_2$ (10 mg, 0.046 mmol) and tris(4-methoxyphenyl)phosphine (20 mg, 0.056 mmol). The vial was sealed under nitrogen and the reaction mixture was heated to 80 °C for 1.5 h. After cooling to room temperature, the reaction mixture was filtered through a pad of celite and rinsed with EtOAc. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0–80% of EtOAc in hexane, to provide *tert*-butyl (2*R*,4*S*)-2-((3-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)propoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (0.18 g, 0.26 mmol, 57% yield). *m/z* (ESI): 674.1 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.34 (d, J = 0.6 Hz, 1H), 7.75-7.72 (m, 1H), 5.66 (dd, J = 9.0, 2.9 Hz, 1H), 4.02 – 3.96 (m, 1H), 3.73 (br s, 1H), 3.61 (t, J = 6.6 Hz, 2H), 3.47 (s, 2H), 3.31 (br s, 3H), 3.27 – 3.23 (m, 2H), 3.23 – 3.16 (m, 2H), 2.84 (br s, 1H), 2.57 – 2.45 (m, 1H), 2.20 – 2.10 (m, 1H), 2.10 – 2.03 (m, 1H), 2.02 – 1.97 (m, 2H), 1.91 – 1.84 (m, 2H), 1.81 – 1.64 (m, 8H), 1.46 (s, 9H), 1.41 (s, 12H).

[00387] Step 3. *tert*-Butyl (2*R*,4*S*)-2-((3-(4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate. A vial was charged with *tert*-butyl (2*R*,4*S*)-2-((3-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)propoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (0.18 g, 0.26 mmol), 4-(*tert*-butoxy)-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)yl)methoxy)pyrido[4,3-*d*]pyrimidine (**Intermediate C**, 0.11 g, 0.26 mmol), potassium phosphate (0.14 g, 0.66 mmol), methanesulfonato(diadamantyl-*n*-butylphosphino)-2'-amino-1,1'-biphenyl-2-yl)palladium(II) dichloromethane adduct (19 mg, 0.026 mmol) and degassed 2-methyltetrahydrofuran (1.1 mL)/water (0.15 mL). The reaction mixture was heated to 80 °C for 45 min, cooled to room temperature, and was purified by column chromatography on silica gel, eluting with a gradient of 0–100% 3:1 EtOAc/EtOH in heptanes with 1% TEA, to provide *tert*-butyl (2*R*,4*S*)-

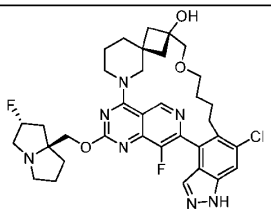
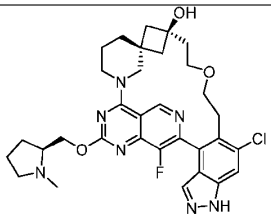
2-((3-(4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (0.16 g, 0.18 mmol, 67% yield). *m/z* (ESI): 924.3 $(M+H)^+$. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 9.19 (d, J = 3.1 Hz, 1H), 7.80 (d, J = 13.2 Hz, 1H), 7.52 (d, J = 3.6 Hz, 1H), 5.70 (ddd, J = 11.5, 9.0, 2.6 Hz, 1H), 5.38 – 5.18 (m, 1H), 4.36 – 4.24 (m, 2H), 4.09 – 3.98 (m, 1H), 3.84 – 3.70 (m, 1H), 3.36 (br t, J = 5.7 Hz, 3H), 3.31 – 3.19 (m, 6H), 3.19 – 3.15 (m, 3H), 3.03 – 2.95 (m, 1H), 2.95 – 2.87 (m, 1H), 2.74 (br s, 1H), 2.68 – 2.62 (m, 1H), 2.56 – 2.44 (m, 1H), 2.28 (d, J = 2.7 Hz, 1H), 2.22 – 2.07 (m, 4H), 2.00 – 1.83 (m, 5H), 1.79 – 1.60 (m, 6H), 1.58 (s, 9H), 1.56 – 1.50 (m, 2H), 1.48 – 1.44 (m, 2H), 1.43 (s, 9H). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ ppm -137.99 (br d, J = 71.1 Hz, 1F), -173.01 (d, J = 4.3 Hz, 1F).

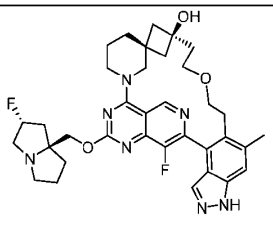
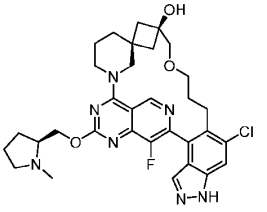
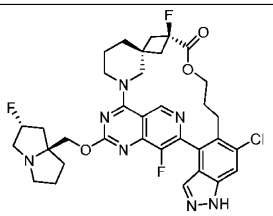
[00388] Step 4. 7-(6-Chloro-5-(3-(((2*R*,4*S*)-2-hydroxy-6-azaspiro[3.5]nonan-2-yl)methoxy)propyl)-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol. To a 6-mL vial was added *tert*-butyl (2*R*,4*S*)-2-((3-(4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (0.16 g, 0.18 mmol) in isopropanol (0.4 mL). Then HCl (4 M in 1,4-dioxane, 1.1 mL, 4.4 mmol) was added and the reaction was stirred at room temperature for 1 h. The reaction mixture was concentrated, azeotroped with heptanes and the crude material was used in the next step without further purification. *m/z* (ESI): 683.8 $(M+H)^+$.

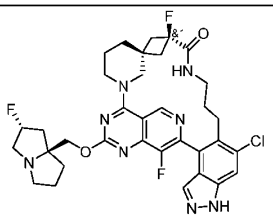
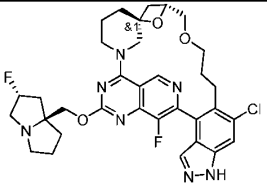
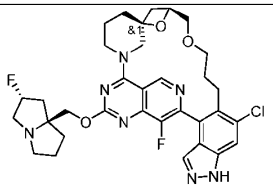
[00389] Step 5. (1*R*,3*R*)-10-Chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-5-oxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-3-ol. A 150-mL round-bottom flask was charged with 7-(6-chloro-5-(3-(((2*R*,4*S*)-2-hydroxy-6-azaspiro[3.5]nonan-2-yl)methoxy)propyl)-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol (0.18 g, 0.26 mmol) and 1,1'-dimethyltriethylamine (0.45 mL, 2.6 mmol) in acetonitrile (46 mL)/dimethyl sulfoxide (5.5 mL). PyBOP (benzotriazol-1-yl-oxytrispyrrolidinophosphonium hexafluorophosphate) (0.15 g, 0.3 mmol) was added in one portion, and the reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated, and the crude material was diluted with EtOAc and washed with saturated $NaHCO_3$ solution. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified by reversed phase column chromatography, eluting with a gradient of 5–40% 0.1% formic acid in CH_3CN/H_2O, to provide (1*R*,3*R*)-10-chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-5-oxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-

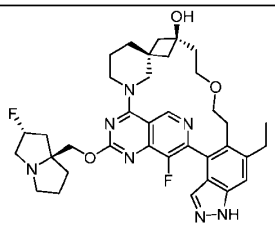
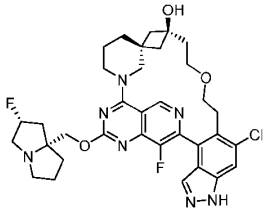
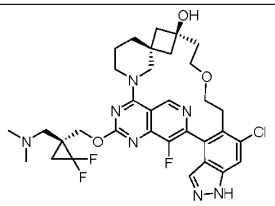
9,11,14,16,18(32),19,21,23,25-nonaen-3-ol (32 mg, 0.048 mmol, 19% yield). *m/z* (ESI): 665.9 $(M+H)^+$. ^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.19 (s, 1H), 7.79 (s, 2H), 5.43 – 5.26 (m, 1H), 4.91 (br d, J = 12.3 Hz, 1H), 4.64 (br d, J = 13.4 Hz, 1H), 4.45 – 4.27 (m, 2H), 3.62 (br d, J = 13.4 Hz, 1H), 3.51 – 3.42 (m, 1H), 3.35 (br s, 1H), 3.28 – 3.21 (m, 1H), 3.18 – 3.07 (m, 2H), 3.04 – 2.94 (m, 2H), 2.82 – 2.71 (m, 1H), 2.42 (br d, J = 14.0 Hz, 2H), 2.36 – 2.22 (m, 2H), 2.21 – 2.12 (m, 1H), 2.10 – 2.00 (m, 3H), 1.96 – 1.69 (m, 9H), 1.64 (br d, J = 13.2 Hz, 1H), 1.49 – 1.45 (m, 1H), 1.38 (q, J = 12.8 Hz, 1H) OH proton not observed. ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -142.68 (d, J = 8.7 Hz, 1F), -173.76 (d, J = 12.1 Hz, 1F).

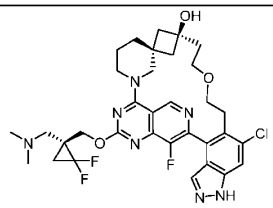
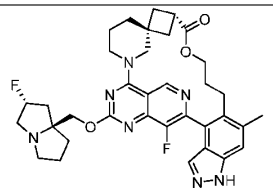
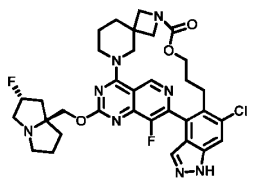
Table 4: Additional Examples Prepared in an Analogous Manner to Example 1.010.

Cmpnd	Structure	Name	Reagents	Method Changes
1.005		(1*S*,3*R*)-11-chloro-33-fluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-5-oxa-14,15,20,24,26,28-hexaazaheptacyclo[26.3.1.1~1,3~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]tetratriaconta-10,12,15,17,19(33),20,22,24,26-nonaen-3-ol	**Step 3**. 4-(4-Bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-1-ol **(Step 2** in **Intermediate M)**	
1.007		(1*S*,3*R*)-10-chloro-32-fluoro-24-(((2*S*)-1-methyl-2-pyrrolidinyl)methoxy)-6-oxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-3-ol	**Step 3.** *tert*-butyl (2*s*,4*r*)-2-(2-(2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (**Intermediate N**) and (*S*)-4-(*tert*-butoxy)-7-chloro-8-fluoro-2-((1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-*d*]pyrimidine (**Intermediate L**)	

Cmpnd	Structure	Name	Reagents	Method Changes
1.011		(1*R*,3*S*)-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-10-methyl-6-oxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-3-ol	**Step 2.** *tert*-butyl (2*s*,4*r*)-2-(2-(2-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (**Intermediate P**)	
1.012		(1*R*,3*S*)-10-chloro-32-fluoro-24-(((2*S*)-1-methyl-2-pyrrolidinyl)methoxy)-5-oxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-3-ol	**Step 3:** (*S*)-4-(*tert*-butoxy)-7-chloro-8-fluoro-2-((1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-*d*]pyrimidine **(Intermediate L)**	
1.039		(1*S*,3*R*)-10-chloro-3,32-difluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-5-oxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-4-one	**Step 2:** 2-(3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl) 6-(*tert*-butyl) 2-fluoro-6-azaspiro[3.5]nonane-2,6-dicarboxylate (**Intermediate Q**)	

Cmpnd	Structure	Name	Reagents	Method Changes
1.045		(1*RS*,3*SR*)-10-chloro-3,32-difluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-5,13,14,19,23,25,27-heptaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-4-one	**Step 2:** *tert*-butyl (2*rs*,4*sr*)-2-((3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl)carbamoyl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (**Intermediate R**)	
1.044		(1*RS*,3*R*)-10-chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-2,5-dioxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaene	**Step 2:** *tert*-butyl 2-((3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propoxy)methyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate (**Intermediate S**)	
1.046		(1*RS*,3*S*)-10-chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-2,5-dioxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaene	**Step 2:** *tert*-butyl 2-((3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propoxy)methyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate (**Intermediate S**)	

Cmpnd	Structure	Name	Reagents	Method Changes
1.027		(1*S*,3*R*)-10-ethyl-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-6-oxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-3-ol	**Step 1:** *tert*-butyl (2*s*,4*r*)-2-(2-((methylsulfonyl)oxy)ethyl)-2-((triethylsilyl)oxy)-5-azaspiro[3.5]nonane-5-carboxylate (**Step 4** in **Intermediate N**) and 2-(4-bromo-6-ethyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethan-1-ol (**Intermediate T**)	
1.021		(1*R*,3*S*)-10-chloro-32-fluoro-24-(((2*R*,7a*R*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-6-oxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-3-ol	**Step 3:** *tert*-butyl (2*s*,4*r*)-2-(2-(2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (**Intermediate N**) and 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2*R*,7a*R*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-*d*]pyrimidine **(Intermediate U)**	
1.020		(1*S*,3*R*)-10-chloro-24-(((1*S*)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-32-fluoro-6-oxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-3-ol	**Step 3:** *tert*-butyl (2*s*,4*r*)-2-(2-(2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (**Intermediate N**) and (*S*)-7-Chloro-2-((1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoropyrido[4,3-*d*]pyrimidin-4-ol **(Intermediate W)**	

Cmpnd	Structure	Name	Reagents	Method Changes
1.024		(1*R*,3*S*)-10-chloro-24-(((1*S*)-1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-32-fluoro-6-oxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-3-ol	**Step 3:** *tert*-butyl (2*s*,4*r*)-2-(2-(2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (**Intermediate N**) (*R*)-7-Chloro-2-((1-((dimethylamino)methyl)-2,2-difluorocyclopropyl)methoxy)-8-fluoropyrido[4,3-*d*]pyrimidin-4-ol **(Intermediate V)**	
1.061		(1*R*,3*S*)-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-10-methyl-5-oxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-4-one	**Step 2:** 2-(3-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl) 6-(*tert*-butyl) 6-azaspiro[3.5]nonane-2,6-dicarboxylate (**Intermediate Y**)	
1.065		10-chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-5-oxa-3,13,14,19,23,25,27-heptaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-4-one	**Step 2.** 2-(3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propyl) 6-(*tert*-butyl) 2,6-diazaspiro[3.5]nonane-2,6-dicarboxylate (**Intermediate AAA**)	**Step 1 was not performed.**

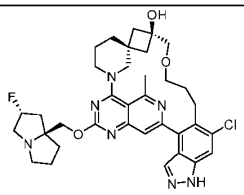
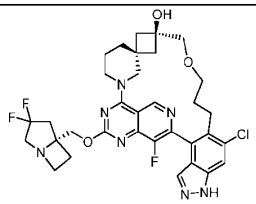
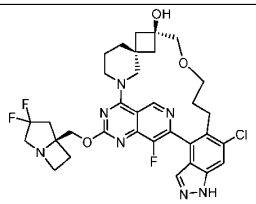
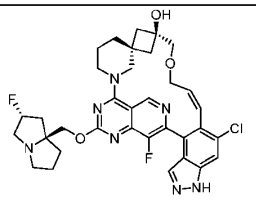
Cmpnd	Structure	Name	Reagents	Method Changes
1.081		(13*r*,93*R*)-36-chloro-22-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-25-methyl-31*H*-7-oxa-2(4,7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-9(1,3)-cyclobutananonaphan-93-ol	**Step 3:** Intermediate LLL, Intermediate OOO	**Step 5**: BrOP was used in lieu of PyBOP. THF was used, ACN, DMSO were omitted.
1.082		(13*r*,93*R*)-36-chloro-22-(((*S*)-3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-28-fluoro-31*H*-7-oxa-2(4,7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-9(1,3)-cyclobutananonaphan-93-ol	**Step 3:** Intermediate LLL, Intermediate FFF	**Step 5**: BrOP was used in lieu of PyBOP. **Chiral separation** after Step 5, details below.
1.083		(13*r*,93*S*)-36-chloro-22-(((*R*)-3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-28-fluoro-31*H*-7-oxa-2(4,7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-9(1,3)-cyclobutananonaphan-93-ol	**Step 3:** Intermediate LLL, Intermediate FFF	**Step 5**: BrOP was used in lieu of PyBOP. **Chiral separation** after Step 5, details below.
1.085		(13*r*,93*R*,*Z*)-36-chloro-28-fluoro-22-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-31*H*-7-oxa-2(4.7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-9(1,3)-cyclobutananonaphan-4-en-93-ol, hexafluorophosphate(V) salt	**Step 3:** Intermediate MMM, Intermediate C	**Step 5**: BrOP was used in lieu of PyBOP.

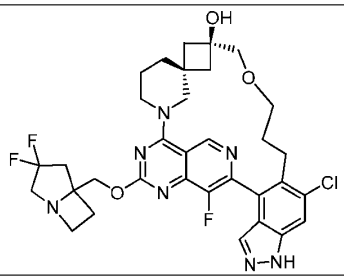
Table 5. Analytical Data for Examples of Table 4.

Cmpd.#	MS *m/z* (ESI): $(M+H)^+$	^{1}H NMR
1.005	680.1	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.42 – 9.15 (m, 1H), 7.87 – 7.62 (m, 2H), 5.74 – 5.46 (m, 1H), 4.79 – 4.63 (m, 3H), 4.59 – 4.46 (m, 1H), 4.13 – 3.61 (m, 4H), 3.58 – 3.38 (m, 2H), 3.30 – 1.58 (m, 20H), 1.56 – 1.11 (m, 5H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -76.54 – -78.18 (m, 1F), -140.11 – -141.31 (m, 1F), -174.06 (br d, *J* = 39.0 Hz, 1F).
1.007	622.2	^{1}H NMR (500 MHz, *METHANOL-d4*) δ ppm 9.29 (s, 1H), 7.84 (d, *J* = 2.5 Hz, 2H), 5.02 – 4.90 (m, 1H), 4.78 – 4.73 (m, 1H), 4.61 – 4.48 (m, 2H), 3.73 – 3.62 (m, 2H), 3.57 – 3.46 (m, 1H), 3.20 – 3.06 (m, 4H), 2.96 – 2.85 (m, 3H), 2.59 (d, *J* = 1.8 Hz, 3H), 2.50 – 2.41 (m, 1H), 2.20 – 2.12 (m, 1H), 1.95 – 1.78 (m, 7H), 1.73 – 1.62 (m, 2H), 1.57 – 1.45 (m, 2H), 1.34 – 1.24 (m, 3H). ^{19}F NMR (471 MHz, *METHANOL-d4*) δ ppm -141.45 (br d, *J* = 7.1 Hz, 1F).
1.011	646.0	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.25 (s, 1H), 7.71 (d, J = 4.4 Hz, 1H), 7.54 (s, 1H), 5.47 – 5.30 (m, 1H), 4.92 (br d, J = 12.1 Hz, 1H), 4.70 (br d, J = 13.8 Hz, 1H), 4.48 – 4.34 (m, 2H), 3.68 (br d, J = 13.4 Hz, 1H), 3.48 – 3.38 (m, 5H), 3.18 – 3.08 (m, 3H), 2.97 – 2.89 (m, 2H), 2.86 – 2.77 (m, 1H), 2.54 (s, 3H), 2.47 – 2.31 (m, 2H), 2.26 – 2.19 (m, 1H), 2.14 – 2.06 (m, 2H), 2.01 – 1.84 (m, 4H), 1.81 – 1.66 (m, 5H), 1.58 (dt, J = 10.9, 5.2 Hz, 2H), 1.46 (br d, J = 13.0 Hz, 1H), 1.28 (br d, J = 12.5 Hz, 1H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -141.71 (d, J = 7.8 Hz, 1F), -173.78 (d, J = 11.3 Hz, 1F).
1.012	622.2	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.18 (s, 1H), 7.81 (s, 1H), 7.80 – 7.77 (m, 1H), 4.89 (br d, J = 12.8 Hz, 1H), 4.63 (br d, J = 13.6 Hz, 1H), 4.58 – 4.41 (m, 2H), 3.61 (br d, J = 13.4 Hz, 1H), 3.45 (br s, 1H), 3.29 – 3.23 (m, 1H), 3.17 – 3.07 (m, 2H), 3.05 – 2.94 (m, 2H), 2.85 – 2.74 (m, 2H), 2.52 (s, 3H), 2.48 – 2.41 (m, 1H), 2.37 (q, J = 8.8 Hz, 1H), 2.17 – 2.06 (m, 1H), 2.04 – 1.97 (m, 1H), 1.91 – 1.69 (m, 9H), 1.67 – 1.61 (m, 1H), 1.45 – 1.34 (m, 2H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -142.54 (d, J = 6.9 Hz, 1F).
1.039	682.2	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.29 – 9.31(m, 1H), 8.51 – 8.52 (m, 1H), 7.82 – 7.84 (m, 2H), 5.32 – 5.45 (m, 1H), 4.95 – 4.99 (m, 1H), 4.42 – 4.49 (m, 2H), 4.25 – 4.31 (m, 1H), 3.79 – 3.82 (m, 1H), 3.37 – 3.44 (m, 3H), 3.15 – 3.18 (m, 2H), 2.77 – 2.89 (m, 1H), 2.41 – 2.50 (m, 1H), 2.19 – 2.43 (m, 4H), 2.07 – 2.18 (m, 4H), 1.87 – 2.17 (m, 9H), 1.31 – 1.41 (m, 2H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm –142.21 (s, 1F), –149.98 (m, 1F), –173.82 (m, 1F).
1.045	652.2	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.16 (s, 1H), 8.55 (s, 1H), 7.9 – 7.82 (m, 2H), 5.70 – 5.73 (m, 1H), 5.29 – 5.43 (m, 1H), 4.92 – 4.79 (m, 1H), 4.71 – 4.69 (m, 1H), 4.34 – 4.60 (m, 3H), 3.78 – 4.00 (m, 1H), 3.43 – 3.50 (m, 3H), 2.61 – 3.29 (m, 7H), 2.20 – 2.48 (m, 7H), 2.00 – 2.21 (m, 2H), 1.83 – 2.05 (m, 2H), 1.72 –1.85 (m, 2H), 1.18-1.23 (m, 2H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm –143.6 – –142.5 (m, 1F), –173.9 – –173.6 (m, 1F).

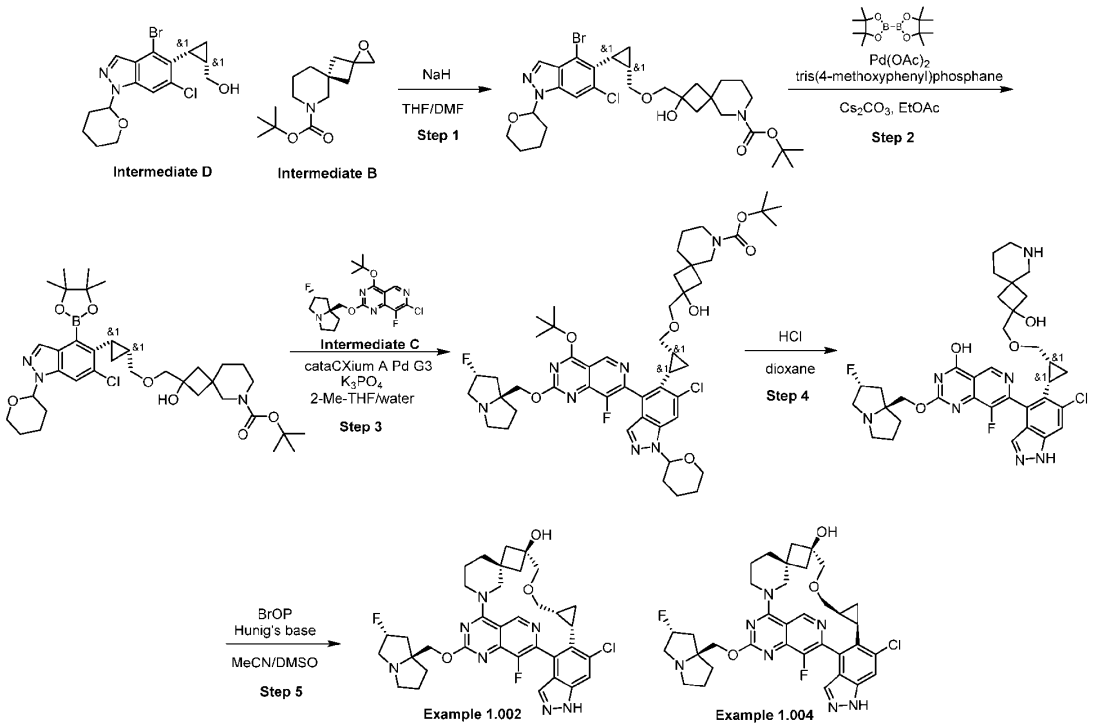
Cmpd.#	MS *m/z* (ESI): $(M+H)^+$	^{1}H NMR
1.044	652.2	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.14 (s, 1H), 7.8-8.0 (m, 2H), 6.1-6.3 (m, 1H), 5.2-5.4 (m, 1H), 4.3-4.4 (m, 2H), 3.9-4.0 (m, 1H), 3.5-3.6 (m, 2H), 3.0-3.2 (m, 6H), 2.5-2.8 (m, 3H), 2.2-2.4 (m, 2H), 2.0-2.2 (m, 6H), 1.8-2.0 (m, 8H), 1.5-1.6 (m, 1H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -144.5--143.9 (m, 1F), -173.9--173.5 (m, 1F).
1.046	660.3	^{1}H NMR (400 MHz, *DMSO-d6*) δ ppm 13.03 (s, 1 H), 9.30 (s, 1 H), 7.27 - 7.76 (m, 2 H), 5.17 - 5.39 (m, 1 H), 4.84 (s, 1 H), 4.49 - 4.77 (m, 2 H), 3.98 - 4.23 (m, 2 H), 3.56 - 3.68 (m, 1 H), 3.20 - 3.31 (m, 2 H), 2.96 - 3.14 (m, 5 H), 2.71 - 2.88 (m, 5 H), 2.60 - 2.70 (m, 1 H), 1.96 - 2.21 (m, 3 H), 1.73 - 1.89 (m, 5 H), 1.55 - 1.71 (m, 4 H), 1.37 - 1.46 (m, 2 H), 1.25 - 1.37 (m, 4 H), 1.04 - 1.16 (m, 1 H). ^{19}F NMR (376 MHz, *DMSO-d6*) δ ppm -141.55 (s, 1 F), -172.10 (s, 1 F).
1.027	666.3	^{1}H NMR (400 MHz, *DMSO-d6*) δ ppm 13.31 (s, 1 H), 9.33 (s, 1 H), 7.73 - 7.90 (m, 2 H), 5.24 - 5.49 (m, 1 H), 4.83 (s, 1 H), 4.55 - 4.78 (m, 2 H), 4.08 - 4.22 (m, 2 H), 3.58 - 3.66 (m, 1 H), 3.44 - 3.54 (m, 1 H), 3.34 - 3.40 (m, 1 H), 3.21 - 3.29 (m, 1 H), 3.01 - 3.10 (m, 1 H), 2.91 - 3.00 (m, 3 H), 2.65 - 2.90 (m, 3 H), 2.54 - 2.59 (m, 1 H), 2.24 - 2.38 (m, 1H), 1.90 - 1.97 (m, 1 H), 1.73 - 1.89 (m, 5 H), 1.56 - 1.72 (m, 5H), 1.30 - 1.49 (m, 3H), 1.08 - 1.16 (m, 1 H). ^{19}F NMR (377 MHz, *DMSO-d6*) δ ppm -141.51 (s, 1 F), -172.39 (s, 1 F).
1.021	672.1	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.28 (s, 1 H), 7.82 (s, 2 H), 4.91 - 4.97 (m, 1 H), 4.64 - 4.78 (m, 2 H), 4.51 - 4.60 (m, 1 H), 3.59 - 3.74 (m, 2 H), 3.46 - 3.54 (m, 1 H), 3.02 - 3.17 (m, 3 H), 2.77 - 2.97 (m, 3 H), 2.39 - 2.55 (m, 1 H), 2.28 (s, 6 H), 1.73 - 1.97 (m, 5 H), 1.61 - 1.73 (m, 3 H), 1.39 - 1.56 (m, 3 H), 1.26 - 1.32 (m, 1 H).
1.020	672.1	^{1}H NMR (400 MHz, *CDCl3*) δ ppm 10.18 (s, 1 H), 9.18 (s, 1 H), 7.88 (d, *J*=3.20 Hz, 1 H), 7.70 (s, 1 H), 4.55 - 5.09 (m, 4 H), 3.62 - 3.71 (m, 1 H), 3.55 (d, *J*=24.00 Hz, 1 H), 3.43 - 3.51 (m, 1 H), 3.06 - 3.25 (m, 2 H), 2.96 - 3.06 (m, 3 H), 2.72 - 2.95 (m, 4 H), 2.14 - 2.43 (m, 4 H), 1.77 - 1.95 (m, 5 H), 1.65 - 1.76 (m, 4 H), 1.41 - 1.51 (m, 3 H), 1.34 (d, *J*=20.00 Hz, 1 H).
1.024	644.2	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.17 - 9.33 (m, 1 H), 7.68 - 7.74 (m, 1 H), 7.51 - 7.57 (m, 1 H), 5.19 - 5.47 (m, 1 H), 4.84 - 4.96 (m, 2 H), 4.21 - 4.46 (m, 2 H), 4.05 - 4.18 (m, 1 H), 3.84 - 3.97 (m, 1 H), 3.59 - 3.72 (m, 1 H), 3.19 - 3.29 (m, 2 H), 3.02 - 3.18 (m, 2 H), 2.89 - 3.00 (m, 1 H), 2.72 (br s, 1 H), 2.51 - 2.63 (m, 3 H), 2.34 - 2.48 (m, 2 H), 2.23 - 2.33 (m, 1 H), 2.12 - 2.22 (m, 1 H), 2.09 (br s, 9 H), 1.64 - 1.80 (m, 4 H), 1.21 - 1.36 (m, 1 H).

Cmpd.#	MS *m/z* (ESI): $(M+H)^+$	^{1}H NMR
1.061	665.2	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.34 (s, 1H), 7.86 – 7.75 (m, 2H), 5.43 – 5.20 (m, 1H), 5.04 – 4.88 (m, 2H), 4.63 (br t, J = 9.3 Hz, 1H), 4.44 – 4.28 (m, 2H), 3.88 (br d, J = 13.6 Hz, 1H), 3.67 – 3.61 (m, 1H), 3.60 – 3.52 (m, 2H), 3.51 – 3.33 (m, 3H), 3.28 – 3.12 (m, 2H), 3.12 – 3.05 (m, 1H), 2.77 (br d, J = 9.0 Hz, 1H), 2.67 – 2.62 (m, 2H), 2.46 – 2.23 (m, 2H), 2.23 – 2.14 (m, 1H), 2.04 (br d, J = 12.1 Hz, 3H), 1.99 – 1.91 (m, 1H), 1.89 – 1.72 (m, 3H), 1.71 – 1.57 (m, 3H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -141.49 (d, J = 6.9 Hz, 1F), -173.75 (s, 1F).
1.081	662	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 7.82 (s, 1H), 7.75 (s, 1H), 7.20 (s, 1H), 5.47 – 5.21 (m, 1H), 4.92 – 4.89 (m, 1H), 4.44 – 4.13 (m, 2H), 3.72 (br d, *J* = 13.2 Hz, 1H), 3.60 – 3.48 (m, 2H), 3.30 – 3.19 (m, 4H), 3.18 – 3.08 (m, 1H), 3.07 – 2.99 (m, 1H), 2.94 (d, *J* = 9.0 Hz, 1H), 2.85 (d, *J* = 9.2 Hz, 1H), 2.74 (s, 3H), 2.73 – 2.65 (m, 2H), 2.41 – 2.20 (m, 2H), 2.19 – 1.95 (m, 5H), 1.94 – 1.68 (m,7H), 1.65 – 1.56 (m, 2H), 1.34 – 1.20 (m, 2H). ^{19}F (376 MHz, *METHANOL-d4*) δ ppm -173.72 (d, *J* = 23.7 Hz, 1F).
1.082	670	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.27 – 9.13 (m, 1H), 7.92 – 7.70(m, 2H), 4.99 – 4.90 (m, 1H), 4.71 – 4.62 (m, 1H), 4.62 – 4.46 (m, 2H), 3.88 – 3.68 (m, 1H), 3.68 – 3.58 (m, 1H), 3.51 – 3.38 (m, 2H), 3.31 – 3.23 (m, 2H), 3.23 – 3.09 (m, 2H), 3.08 – 2.94 (m, H), 2.87 – 2.73 (m, 1H), 2.72 – 2.51 (m, 3H), 2.51 – 2.39 (m, 2H), 2.10 – 1.98 (m, 1H),1.96 – 1.61 (m,7H), 1.49 – 1.34(m, 2H).^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -92.24 (dd, *J* = 236.3, 21.2 Hz, 1F), -101.93 (dd, *J* = 236.7, 118.8 Hz, 1F), -142.50 (d, *J* = 12.1 Hz, 1F).
1.083	670	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.33 – 9.09 (m, 1H), 7.93 – 7.69 (m, 2H), 5.00 – 4.90 (m, 1H), 4.73 – 4.62 (m, 1H), 4.62 – 4.44 (m, 2H), 3.82 – 3.70 (m, 1H), 3.69 – 3.58 (m, 1H), 3.54 – 3.38 (m, 2H), 3.31 – 3.23 (m, 2H), 3.23 – 3.09 (m, 2H), 3.08 – 2.94 (m, 2H), 2.89 – 2.72 (m, 1H), 2.72 – 2.52 (m, 3H), 2.52 – 2.35 (m, 2H), 2.12 – 1.99 (m, 1H), 1.95 – 1.62 (m, 7H), 1.47 – 1.32 (m, 2H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -92.24 (br dd, *J* =236.3, 22.1 Hz, 1F), -101.93 (br dd, *J* =236.7, 121.4 Hz, 1F), -142.50 (brd, *J* = 13.9 Hz, 1F).
1.085	664	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.26 (s, 1 H), 8.06 (s, 1 H), 7.84 (s, 1 H), 6.58 (br d, *J* = 11.9 Hz, 1 H), 5.63 (br s, 1 H), 5.39 - 5.58 (m, 1 H), 4.91 - 4.94 (m, 1 H), 4.71 - 4.81 (m, 1 H), 4.39 - 4.65 (m, 2 H), 3.47 - 3.86 (m, 7 H), 3.14 (s, 2 H), 3.03 (d, *J* = 0.0 Hz, 1 H), 2.40 - 2.63 (m, 2 H), 2.29 - 2.38 (m, 1 H), 2.18 - 2.29 (m, 2 H), 2.01 - 2.15 (m, 1 H), 1.78 - 1.93 (m, 4 H), 1.72 (br d, *J* = 13.0 Hz, 2 H), 1.47 - 1.56 (m, 1 H), 1.39 (s, 1 H).^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -76.27 - -73.80 (m, 1 F), -140.14 (br d, J=16.5 Hz, 1 F), -173.97 (d, *J* = 28.6 Hz, 1 F).

Chiral Separation Information

	Column: CHIRALPAK AD, 2 x 25 cm, 5 µm. Mobile phase: 40% iPrOH with 0.2% DEA. Flowrate of 80 mL/min	Peak 1: **Example 1.082** Peak 2: **Example 1.083**

Examples 1.002 and 1.004: (1*R*,3*R*,7*R*,9*S*)-11-Chloro-33-fluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-5-oxa-14,15,20,24,26,28-hexaazaoctacyclo[26.3.1.1~1,3~.1~19,23~.0~7,9~.0~10,18~.0~13,17~.0~22,27~]tetratriaconta-10,12,15,17,19(33),20,22,24,26-nonaen-3-ol and (1*S*,3*R*,7*S*,9*R*)-11-chloro-33-fluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-5-oxa-14,15,20,24,26,28 hexaazaoctacyclo[26.3.1.1~1,3~.1~19,23~.0~7,9~.0~10,18~.0~13,17~.0~22,27~]tetratriaconta-10,12,15,17,19(33),20,22,24,26-nonaen-3-ol.



[00390] Step 1. *rac-tert*-Butyl 2-((((1*R*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate. To a 250 mL flask was charged with *rac*-((1*R*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-

1*H*-indazol-5-yl)cyclopropyl)methanol (**Intermediate D**, 15.2 g, 39.5 mmol), tetrahydrofuran (65 mL) and sodium hydride (60 wt% in mineral oil, 1.58 g, 39.5 mmol). The mixture was stirred for 30 minutes. To this was added *tert*-butyl 1-oxa-7-azadispiro[2.1.5^5.1^3]undecane-7-carboxylate (**Intermediate B**, 5.00 g, 19.7 mmol) in DMF (5 mL). The solution was warmed to 50 °C and stirred for 24 h. The reaction was carefully quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The combined organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting crude was purified by reversed phase chromatography, eluting with a gradient of 0-100% of MeCN in H_2O (0.1% TFA as additive). The combined fractions were dried over sodium sulfate, filtered and the volatiles were removed under reduced pressure. The residue was purified again by column chromatography on silica gel, eluting with a gradient of 0–70% EtOAc in hexane to give *rac-tert*-butyl 2-((((1*R*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (5.40 g, 8.45 mmol, 43% yield). *m/z* (ESI): 659.8 $(M+Na)^+$. ^1H NMR (400 MHz, *CDCl₃*) δ ppm 8.12 – 7.93 (m, 1H), 7.70 – 7.51 (m, 1H), 5.74 – 5.56 (m, 1H), 4.07 – 3.97 (m, 1H), 3.88 – 3.68 (m, 2H), 3.52 – 3.13 (m, 6H), 2.88 – 2.61 (m, 2H), 2.59 – 2.39 (m, 1H), 2.19 – 2.11 (m, 2H), 1.92 – 1.57 (m, 10H), 1.55 – 1.38 (m, 14H).

[00391] Step 2. *rac-tert*-Butyl 2-((((1*R*,2*S*)-2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate. A vial was charged with tris(4-methoxyphenyl)phosphine (0.18 g, 0.52 mmol), palladium (II) acetate (97 mg, 0.43 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.64 g, 6.46 mmol), cesium carbonate (2.80 g, 8.61 mmol), *rac-tert*-butyl 2-((((1*R*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (2.75 g, 4.30 mmol) and ethyl acetate (20 mL). The contents were sparged with nitrogen and heated to 80 °C for 2 h. After cooling to room temperature, the mixture was filtered through a pad of celite and the filtrate was purified by column chromatography on silica gel, eluting with a gradient of 0–100% of EtOAc in hexane, to provide of *rac-tert*-butyl 2-((((1*R*,2*S*)-2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (1.74 g, 2.54 mmol, 59% yield). *m/z* (ESI): 686.1 $(M+H)^+$. ^1H NMR (400 MHz, *CDCl₃*) δ ppm 8.26 – 7.46 (m, 2H), 5.76 – 5.54 (m, 1H), 4.17 – 3.70 (m, 2H), 3.49 – 3.05 (m, 7H), 2.94 – 2.43 (m, 3H), 2.28 – 2.02 (m, 3H), 1.88 – 1.78 (m, 3H), 1.52 – 1.40 (m, 23H), 1.34 – 1.24 (m, 9H).

[00392] Step 3. *rac-tert*-Butyl 2-((((1*R*,2*S*)-2-((4*R*)-4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate. To a suspension of *rac-tert*-butyl 2-((((1*R*,2*S*)-2-(6-chloro-1-

(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (5.20 g, 7.58 mmol) and 4-(*tert*-butoxy)-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (**Intermediate C**, 3.44 g, 8.34 mmol) in 2-methyltetrahydrofuran (18 mL) and water (1.8 mL) were added potassium phosphate (4.02 g, 18.9 mmol) and cataCXium A Pd G3 (CAS No. 1651823-59-4) (1.10 g, 1.52 mmol). The reaction mixture was sparged with nitrogen and stirred at 80 °C for 2 h. After cooling to room temperature, the mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with eluting with 0–100% (3:1 EtOAc/EtOH with 0.2% Et_3N) in heptane, to give *rac-tert*-butyl 2-((((1*R*,2*S*)-2-((4*R*)-4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (3.30 g, 3.52 mmol, 47% yield). *m/z* (ESI): 936.0 $(M+H)^+$. ^1H NMR (400 MHz, *METHANOL-d*$_4$) δ ppm 9.28 – 9.12 (m, 1H), 8.06 – 7.93 (m, 1H), 7.91 – 7.64 (m, 1H), 5.95 – 5.67 (m, 1H), 5.62 – 5.12 (m, 1H), 4.42 – 4.32 (m, 2H), 4.16 – 3.53 (m, 4H), 3.43 – 3.34 (m, 2H), 3.30 – 2.97 (m, 9H), 2.91 – 1.87 (m, 15H), 1.82 – 0.62 (m, 25H), 0.11 – -0.18 (m, 1H).

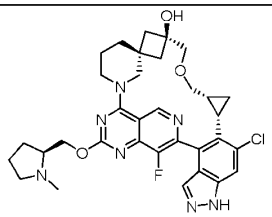
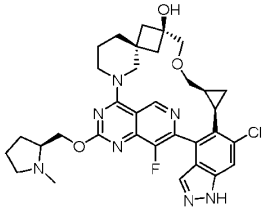
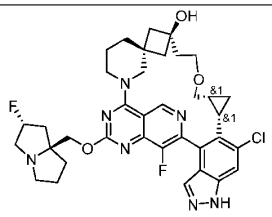
[00393] Step 4. *rac*-7-((*R*)-6-Chloro-5-((1*S*,2*R*)-2-(((2-hydroxy-6-azaspiro[3.5]nonan-2-yl)methoxy)methyl)cyclopropyl)-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol. To a solution of *rac-tert*-butyl 2-((((1*R*,2*S*)-2-((4*R*)-4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (3.39 g, 3.62 mmol) in dichloromethane (27 mL) was added hydrogen chloride (4 M in 1,4-dioxane, 18 mL, 72 mmol). The reaction mixture was stirred at room temperature for 1 h, then concentrated to provide *rac*-7-((*R*)-6-chloro-5-((1*S*,2*R*)-2-(((2-hydroxy-6-azaspiro[3.5]nonan-2-yl)methoxy)methyl)cyclopropyl)-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol (2.52 g, 3.62 mmol, 100% yield). *m/z* (ESI): 696.0 $(M+H)^+$. ^1H NMR (400 MHz, *METHANOL-d*$_4$) δ ppm 9.21 – 8.78 (m, 1H), 7.94 – 7.36 (m, 2H), 5.53 – 5.09 (m, 1H), 4.45 – 4.16 (m, 2H), 3.82 – -0.16 (m, 32H).

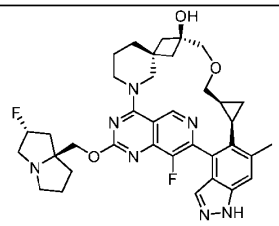
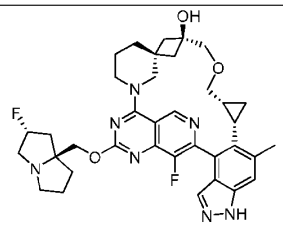
[00394] Step 5. (1*R*,3*R*,7*R*,9*S*)-11-Chloro-33-fluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-5-oxa-14,15,20,24,26,28-hexaazaoctacyclo[26.3.1.1~1,3~.1~19,23~.0~7,9~.0~10,18~.0~13,17~.0~22,27~]tetratriaconta-10,12,15,17,19(33),20,22,24,26-nonaen-3-ol and (1*S*,3*R*,7*S*,9*R*)-11-chloro-33-fluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-5-oxa-14,15,20,24,26,28 hexaazaoctacyclo[26.3.1.1~1,3~.1~19,23~.0~7,9~.0~10,18~.0~13,17~.0~22,27~]tetratriaconta-10,12,15,17,19(33),20,22,24,26-nonaen-3-ol. To a 2-L round-bottom flask was added 1,1'-

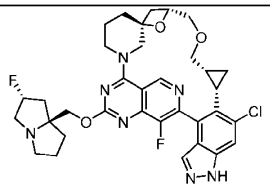
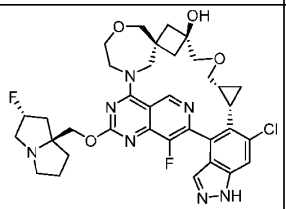
dimethyltriethylamine (6.3 mL, 36 mmol) and bromotris(dimethylamino)phosphonium hexafluorophosphate (1.83 g, 4.71 mmol) in acetonitrile (1.1-L). A solution of *rac*-7-((*R*)-6-chloro-5-((1*S*,2*R*)-2-(((2-hydroxy-6-azaspiro[3.5]nonan-2-yl)methoxy)methyl)cyclopropyl)-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol (2.52 g, 3.62 mmol) in dimethyl sulfoxide (110 mL) was then added dropwise and the mixture was stirred at room temperature under nitrogen for an additional 16 h. More BroP (1.00 g) was added, and the reaction mixture was stirred at room temperature for additional 48 h. The volatiles were removed under reduced pressure and the residue was diluted with water and basified with $NaHCO_3$. The aqueous phase was extracted with EtOAc, and the combined organics were dried over sodium sulfate, filtered, and concentrated. The residue was purified by reversed phase chromatography, eluting with a gradient of 0–50% of MeCN in H_2O (0.1% TFA as an additive) to give the product as a mixture of two diastereoisomers (0.38 g). The mixture was purified via SFC using a Chiralcel OD, 2 x 25 cm, 5 µm column with a mobile phase of 40% MeOH with 0.2% DEA using a flowrate of 80 mL/min to generate (1*R*,3*R*,7*R*,9*S*)-11-chloro-33-fluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-5-oxa-14,15,20,24,26,28-hexaazaoctacyclo[26.3.1.1~1,3~.1~19,23~.0~7,9~.0~10,18~.0~13,17~.0~22,27~]tetratriaconta-10,12,15,17,19(33),20,22,24,26-nonaen-3-ol (**Example 1.002,** 99 mg, 0.15 mmol, 4% yield). *m/z* (ESI): 678.0 $(M+H)^+$. ^1H NMR (500 MHz, *METHANOL-d4*) δ ppm 9.37 – 9.05 (m, 1H), 8.48 – 8.03 (m, 1H), 8.03 – 7.76 (m, 1H), 5.45 – 5.17 (m, 1H), 5.01 – 4.89 (m, 1H), 4.78 – 4.57 (m, 1H), 4.47 – 4.18 (m, 2H), 3.77 – 3.56 (m, 1H), 3.29 – 3.12 (m, 4H), 3.09 – 2.97 (m, 2H), 2.93 – 2.81 (m, 1H), 2.67 – 2.51 (m, 1H), 2.43 – 2.11 (m, 5H), 2.07 – 1.75 (m, 7H), 1.74 – 1.60 (m, 2H), 1.56 – 1.40 (m, 3H), 1.36 – 1.25 (m, 2H), 1.10 – 0.92 (m, 1H), 0.52 – 0.39 (m, 1H). ^{19}F NMR (471 MHz, *METHANOL-d4*) δ ppm -136.28 – -140.24 (m, 1F), -171.17 – -177.51 (m, 1F). Stereochemistry was confirmed by x-ray crystallographic analysis.

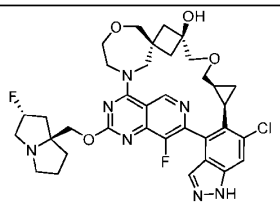
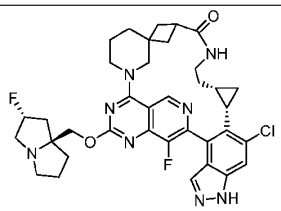
(1*S*,3*R*,7*S*,9*R*)-11-chloro-33-fluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-5-oxa-14,15,20,24,26,28-hexaazaoctacyclo[26.3.1.1~1,3~.1~19,23~.0~7,9~.0~10,18~.0~13,17~.0~22,27~]tetratriaconta-10,12,15,17,19(33),20,22,24,26-nonaen-3-ol (**Example 1.004,** 0.10 g, 0.15 mmol, 4% yield,). *m/z* (ESI): 678.0 $(M+H)^+$. ^1H NMR (500 MHz, *METHANOL-d4*) δ ppm 9.34 – 9.12 (m, 1H), 8.24 – 8.02 (m, 1H), 7.94 – 7.64 (m, 1H), 5.49 – 5.20 (m, 1H), 5.01 – 4.89 (m, 1H), 4.78 – 4.65 (m, 1H), 4.40 – 4.12 (m, 2H), 3.73 – 3.59 (m, 1H), 3.37 – 3.34 (m, 1H), 3.31 – 3.11 (m, 4H), 3.10 – 2.96 (m, 1H), 2.91 – 2.79 (m, 1H), 2.68 – 2.51 (m, 1H), 2.41 – 2.10 (m, 5H), 2.06 – 1.62 (m, 9H), 1.57 – 1.27 (m, 3H), 1.09 – 0.91 (m, 1H), 0.51 – 0.40 (m, 1H) (NH/OH not observed). ^{19}F NMR (471 MHz, *METHANOL-d4*) δ ppm -136.60 – -139.03 (m, 1F), -173.31 – -174.15 (m, 1F).

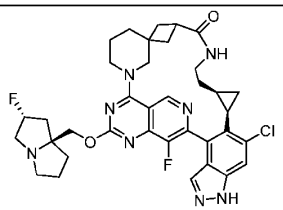
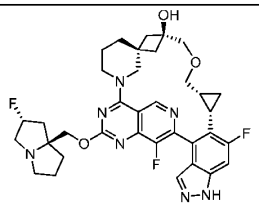
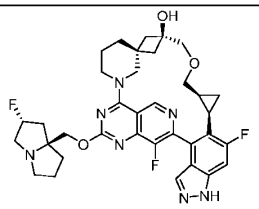
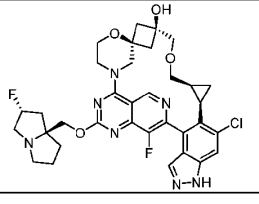
Table 6: Additional Examples Prepared in an Analogous Manner to Example 1.002 and 1.004.

Cmpd.#	Structure	Name	Reagents	Method Changes
1.003		(1*R*,3*R*,7*R*,9*S*)-11-chloro-33-fluoro-25-(((2*S*)-1-methyl-2-pyrrolidinyl)methoxy)-5-oxa-14,15,20,24,26,28-hexaazaoctacyclo[26.3.1.1~1,3~.1~19,23~.0~7,9~.0~10,18~.0~13,17~.0~22,27~]tetratriaconta-10,12,15,17,19(33),20,22,24,26-nonaen-3-ol	**Step 3:** (*S*)-4-(*tert*-butoxy)-7-chloro-8-fluoro-2-((1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-*d*]pyrimidine **(Intermediate L)**	
1.006		(1*S*,3*R*,7*S*,9*R*)-11-chloro-33-fluoro-25-(((2*S*)-1-methyl-2-pyrrolidinyl)methoxy)-5-oxa-14,15,20,24,26,28-hexaazaoctacyclo[26.3.1.1~1,3~.1~19,23~.0~7,9~.0~10,18~.0~13,17~.0~22,27~]tetratriaconta-10,12,15,17,19(33),20,22,24,26-nonaen-3-ol	**Step 3:** (*S*)-4-(*tert*-butoxy)-7-chloro-8-fluoro-2-((1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-*d*]pyrimidine **(Intermediate L)**	
1.037		(1*RS*,3*R*,8*RS*,10*SR*)-12-chloro-34-fluoro-26-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-6-oxa-15,16,21,25,27,29-hexaazaoctacyclo[27.3.1.1~1,3~.1~20,24~.0~8,10~.0~11,19~.0~14,18~.0~23,28~]pentatriaconta-11,13,16,18,20(34),21,23,25,27-nonaen-3-ol	**Step 1.** *tert*-butyl (2*s*,4*r*)-2-(2-((methylsulfonyl)oxy)ethyl)-2-((triethylsilyl)oxy)-5-azaspiro[3.5]nonane-5-carboxylate (**Step 4** in **Intermediate N)**	**No chiral separation after Step 5.**

Cmpd.#	Structure	Name	Reagents	Method Changes
1.049		(1*S*,3*R*,7*S*,9*R*)-33-fluoro-25-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7*a*(5*H*)-yl)methoxy)-11-methyl-5-oxa-14,15,20,24,26,28-hexaazaoctacyclo[26.3.1.1~1,3~.1~19,23~.0~7,9~.0~10,18~.0~13,17~.0~22,27~]tetratriaconta-10,12,15,17,19(33),20,22,24,26-nonaen-3-ol	**Step 1:** *rac*-((1*R*,2*S*)-2-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methanol (**Intermediate Z)**	
1.040		(1*S*,3*R*,7*S*,9*R*)-33-fluoro-25-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7*a*(5*H*)-yl)methoxy)-11-methyl-5-oxa-14,15,20,24,26,28-hexaazaoctacyclo[26.3.1.1~1,3~.1~19,23~.0~7,9~.0~10,18~.0~13,17~.0~22,27~]tetratriaconta-10,12,15,17,19(33),20,22,24,26-nonaen-3-ol	**Step 1:** *rac*-((1*R*,2*S*)-2-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)methanol (**Intermediate Z)**	

Cmpd.#	Structure	Name	Reagents	Method Changes
1.067		(1*S*,3*R*,7*R*,9*S*)-11-chloro-33-fluoro-25-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7*a*(5*H*)-yl)methoxy)-2,5-dioxa-14,15,20,24,26,28-hexaazaoctacyclo[26.3.1.1~1,3~.1~19,23~.0~7,9~.0~10,18~.0~13,17~.0~22,27~]tetratriaconta-10,12,15,17,19(33),20,22,24,26-nonaene	**Step 2.** *tert*-butyl (2*S*,4*S*)-2-((((1*R*,2*S*)-2-(4-bromo-6-chloro-2-trityl-2*H*-indazol-5-yl)cyclopropyl)methoxy)methyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate (**Intermediate BB**)	
1.071		(1*R*,3*R*,7*R*,9*S*)-11-chloro-34-fluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-5,31-dioxa-14,15,20,24,26,28-hexaazaoctacyclo[26.4.1.1~1,3~.1~19,23~.0~7,9~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-10,12,15,17,19(34),20,22,24,26-nonaen-3-ol	**Step 1:** *tert*-butyl (3*s*,5*s*)-1,7-dioxa-10-azadispiro[2.1.6^{5}.1^{3}]dodecane-10-carboxylate (**Intermediate DD**)	$Y(OTf)_3$ and toluene were used instead of NaH and THF in **Step 1.** Chiral separation after **Step 5**. Details included below.

Cmpd.#	Structure	Name	Reagents	Method Changes
1.070		(1*R*,3*R*,7*S*,9*R*)-11-chloro-34-fluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-5,31-dioxa-14,15,20,24,26,28-hexaazaoctacyclo[26.4.1.1~1,3~.1~19,23~.0~7,9~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-10,12,15,17,19(34),20,22,24,26-nonaen-3-ol	**Step 1:** *tert*-butyl (3*s*,5*s*)-1,7-dioxa-10-azadispiro[2.1.6^5.1^3]dodecane-10-carboxylate (**Intermediate DD**)	Y(OTf)$_3$ and toluene were used instead of NaH and THF in **Step 1**. Chiral separation after **Step 5**. Details included below.
1.062		(8*S*,10*S*)-12-chloro-34-fluoro-26-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-5,15,16,21,25,27,29-heptaazaoctacyclo[27.3.1.1~1,3~.1~20,24~.0~8,10~.0~11,19~.0~14,18~.0~23,28~]pentatriaconta-11,13,16,18,20(34),21,23,25,27-nonaen-4-one	**Step 2:** *rac-tert*-butyl 2-((2-((1*S*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)ethyl)carbamoyl)-6-azaspiro[3.5]nonane-6-carboxylate (**Intermediate EE**)	**Step 2:** Pd(dppf)Cl$_2$, Cs$_2$CO$_3$, dioxane were used. Chiral separation after **Step 5**. Details included below.

Cmpd.#	Structure	Name	Reagents	Method Changes
1.073		(8*R*.10*R*)-12-chloro-34-fluoro-26-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-5,15,16,21,25,27,29-heptaazaoctacyclo[27.3.1.1~1,3~.1~20,24~.0~8,10~.0~11,19~.0~14,18~.0~23,28~]pentatriaconta-11,13,16,18,20(34),21,23,25,27-nonaen-4-one	**Step 2:** *rac-tert*-butyl 2-((2-((1*S*,2*S*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)ethyl)carbamoyl)-6-azaspiro[3.5]nonane-6-carboxylate (**Intermediate EE**)	**Step 2:** $Pd(dppf)Cl_2$, Cs_2CO_3, dioxane were used. Chiral separation after **Step 5**. Details included below.
1.084		(13*R*,41*S*,42*R*,83*R*)-28,36-difluoro-22-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-31*H*-6-oxa-2(4,7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-8(1,3)-cyclobutana-4(1,2)-cyclopropanaoctaphan-83-ol		Chiral separation of diastereomeric mixture
1.086		(13*S*,41*R*,42*S*,83*R*)-28,36-difluoro-22-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-31*H*-6-oxa-2(4,7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-8(1,3)-cyclobutana-4(1,2)-cyclopropanaoctaphan-83-ol		Chiral separation of diastereomeric mixture
1.087		(41*R*,42*S*)-36-chloro-28-fluoro-22-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-31*H*-6-oxa-1(4,2)-morpholina-		Chiral separation of diastereomeric mixture

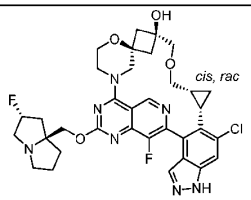
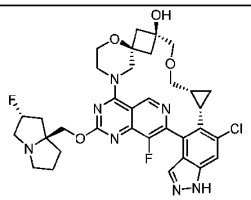
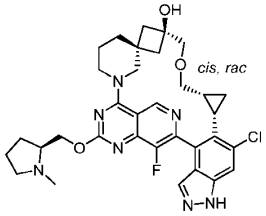
Cmpd.#	Structure	Name	Reagents	Method Changes
		2(4,7)-pyrido[4.3-*d*]pyrimidina-3(4,5)-indazola-8(1,3)-cyclobutana-4(1,2)-cyclopropanaoctaphan-83-ol		
1.088		(41*S*,42*R*)-36-chloro-28-fluoro-22-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*pyrrolizin-7a(5*H*)-yl)methoxy)-31*H*-6-oxa-1(4,2)-morpholina-2(4,7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-8(1,3)-cyclobutana-4(1,2)-cyclopropanaoctaphan-83-ol	**Step 3:** Intermediate III, Intermediate C	Step 5: DCM and MeOH were added. No chiral separation
1.090		(41*S*,42*R*)-36-chloro-28-fluoro-22-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-31*H*-6-oxa-1(4,2)-morpholina-2(4,7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-8(1,3)-cyclobutana-4(1,2)-cyclopropanaoctaphan-83-ol		Chiral separation of diastereomeric mixture
1.091		(13*R*,41*S*,42*R*,83*R*)-36-chloro-28-fluoro-22-(((*S*)-1-methylpyrrolidin-2-yl)methoxy)-31*H*-6-oxa-2(4,7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-8(1,3)-cyclobutana-4(1,2)-cyclopropanaoctaphan-83-ol.	**Step 3:** Intermediate BB and Intermediate L	**Step 5**: TFA used in lieu of HCl in dioxane.

Table 7. Analytical Data for Table 6.

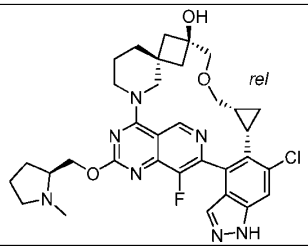
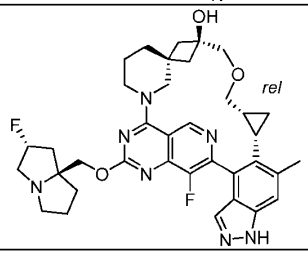
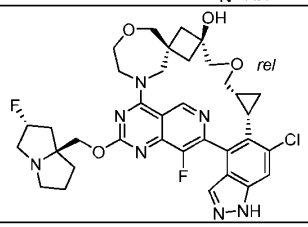
Cmpd.#	MS *m/z* (ESI): $(M+H)^+$	^{1}H NMR
1.003	633.8	^{1}H NMR (400 MHz, *DMSO-d$_6$*) δ ppm 13.65 – 12.63 (m, 1H), 9.62 – 9.10 (m, 1H), 8.32 – 7.98 (m, 1H), 7.98 – 7.56 (m, 1H), 4.97 – 4.80 (m, 1H), 4.79 – 4.54 (m, 2H), 4.53 – 4.13 (m, 2H), 3.71 – 3.53 (m, 1H), 3.27 – 3.18 (m, 2H), 3.16 – 2.90 (m, 2H), 2.80 – 2.62 (m, 2H), 2.47 – 2.36 (m, 4H), 2.19 – 2.10 (m, 1H), 2.03 – 1.89 (m, 2H), 1.83 – 1.38 (m, 10H), 1.36 – 1.27 (m, 2H), 0.96 – 0.71 (m, 1H), 0.43 – 0.21 (m, 1H). ^{19}F NMR (376 MHz, *DMSO-d$_6$*) δ ppm -138.06 – -138.26 (m, 1F)
1.006	634.0	^{1}H NMR (400 MHz, *DMSO-d$_6$*) δ ppm 13.47 – 12.92 (m, 1H), 9.33 – 9.07 (m, 1H), 8.13 – 7.98 (m, 1H), 7.89 – 7.55 (m, 1H), 4.94 – 4.80 (m, 1H), 4.79 – 4.51 (m, 2H), 4.46 – 4.15 (m, 2H), 3.68 – 3.54 (m, 1H), 3.27 – 3.13 (m, 2H), 3.13 – 2.87 (m, 2H), 2.73 – 2.59 (m, 2H), 2.46 – 2.35 (m, 4H), 2.30 – 2.09 (m, 2H), 2.05 – 1.88 (m, 2H), 1.77 – 1.39 (m, 10H), 0.94 – 0.73 (m, 1H), 0.42 – 0.29 (m, 1H). ^{19}F NMR (376 MHz, *DMSO-d$_6$*) δ ppm -137.65 – -138.79 (m, 1F).
1.037	691.8	^{1}H NMR (400 MHz, *METHANOL-d$_4$*) δ ppm 9.40 (s, 1H), 8.13 (s, 1H), 7.86 (s, 1H), 5.71 – 5.50 (m, 1H), 5.12 – 5.02 (m, 1H), 4.74 – 4.62 (m, 2H), 4.14 – 3.80 (m, 5H), 3.57 – 3.45 (m, 1H), 3.24 – 3.10 (m, 2H), 2.86 – 2.56 (m, 3H), 2.53 – 2.32 (m, 5H), 2.29 – 2.16 (m, 1H), 2.12 – 1.95 (m, 5H), 1.90 – 1.79 (m, 4H), 1.71 – 1.58 (m, 2H), 1.56 – 1.44 (m, 3H), 1.22 – 1.09 (m, 1H), 0.61 (br d, *J* = 6.3 Hz, 1H). ^{19}F NMR (376 MHz, *METHANOL-d$_4$*) δ ppm -73.69 – -75.83 (m, 1F), -77.71 (s, 1F), -136.67 (d, *J* = 13.9 Hz, 1F), -174.10 (d, *J* = 8.7 Hz, 1F).
1.049	658.2	^{1}H NMR (500 MHz, *DMSO-d$_6$*) δ ppm 12.89 - 13.05 (m, 1 H), 9.18 - 9.28 (m, 1 H), 7.90 - 8.08 (m, 1 H), 7.40 - 7.65 (m, 1 H), 5.12 - 5.48 (m, 1 H), 4.86 (s, 1 H), 4.44 - 4.77 (m, 2 H), 4.03 - 4.23 (m, 2 H), 3.55 - 3.66 (m, 1 H), 3.20 - 3.26 (m, 1 H), 2.99 - 3.18 (m, 4 H), 2.88 - 2.97 (m, 1 H), 2.79 - 2.88 (m, 1 H), 2.62 - 2.67 (m, 1 H), 2.59 (s, 3 H), 2.32 - 2.38 (m, 1 H), 2.01 - 2.18 (m, 4 H), 1.65 - 1.89 (m, 8 H), 1.48 - 1.54 (m, 1 H), 1.28 - 1.37 (m, 3 H), 0.75 - 0.86 (m, 1 H), 0.19 - 0.31 (m, 1 H). ^{19}F NMR (471 MHz, *DMSO-d$_6$*) δ ppm -139.19 - -138.01 (m, 1 F), -172.83 - -171.82 (m, 1 F).
1.040	658.2	^{1}H NMR (400 MHz, *DMSO-d$_6$*) δ ppm 12.89 - 13.01 (m, 1 H), 9.19 - 9.26 (m, 1 H), 7.86 - 8.00 (m, 1 H), 7.47 - 7.54 (m, 1 H), 5.13 - 5.42 (m, 1 H), 4.84 - 4.92 (m, 1 H), 4.54 - 4.80 (m, 2 H), 4.05 - 4.26 (m, 2 H), 3.53 - 3.65 (m, 1 H), 3.20 - 3.25 (m, 1 H), 3.03 - 3.16 (m, 4 H), 2.80 - 2.88 (m, 1 H), 2.62 - 2.68 (m, 1 H), 2.57 - 2.61 (m, 3 H), 2.32 - 2.38 (m, 1 H), 1.98 - 2.22 (m, 5 H), 1.63 - 1.90 (m, 10 H), 1.49 - 1.54 (m, 1 H), 1.33 - 1.34 (m, 1 H), 0.78 - 0.86 (m, 1 H), 0.21 - 0.30 (m, 1 H). ^{19}F NMR (376 MHz, *DMSO-d$_6$*) δ ppm -138.61 - -138.50 (m, 1 F), -172.08 - -172.03 (m, 1 F).

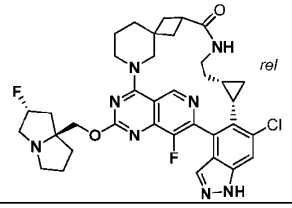
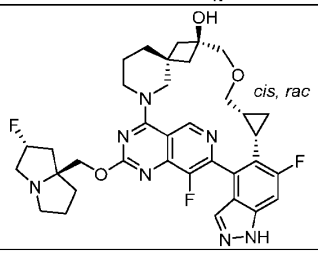
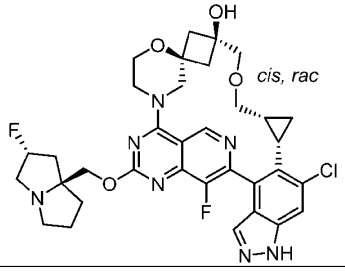
Cmpd.#	MS *m/z* (ESI): $(M+H)^+$	^{1}H NMR
1.067	664.2	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.29 - 9.37 (m, 1 H), 8.09 - 8.18 (m, 1 H), 7.83 - 7.85 (m, 1 H), 6.23 - 6.29 (m, 1 H), 5.23 - 5.44 (m, 2 H), 4.39 - 4.46 (m, 1 H), 4.29 - 4.33 (m, 1 H), 4.00 - 4.08 (m, 1 H), 3.90 - 3.99 (m, 1 H), 3.45 - 3.55 (m, 2 H), 3.14 - 3.22 (m, 2 H), 3.01 - 3.08 (m, 1 H), 2.78 - 2.90 (m, 1 H), 2.51 - 2.65 (m, 1 H), 2.33 - 2.40 (m, 1 H), 2.11 - 2.32 (m, 6 H), 1.98 - 2.08 (m, 6 H), 1.81 - 1.87 (m, 2 H), 1.65 - 1.71 (m, 1 H), 1.45 - 1.50 (m, 1 H), 0.96 - 1.06 (m, 1 H), 0.43 - 0.51 (m, 1 H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -139.90 - -139.65 (m, 1 F), -173.72 - -173.64 (m, 1 F).
1.071	694.2	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.33 (s, 1H), 8.08 (s, 1H), 7.86 – 7.80 (m, 1H), 5.41 – 5.23 (m, 1H), 5.02 (br d, *J* = 14.6 Hz, 1H), 4.49 – 4.36 (m, 2H), 4.36 – 4.30 (m, 1H), 4.29 – 4.22 (m, 1H), 3.98 – 3.83 (m, 1H), 3.83 – 3.72 (m, 4H), 3.41 – 3.35 (m, 1H), 3.31 – 3.17 (m, 4H), 3.03 (td, *J* = 9.5, 5.7 Hz, 1H), 2.95 (d, *J* = 10.9 Hz, 1H), 2.76 (dd, *J* = 10.1, 5.5 Hz, 1H), 2.52 (dd, *J* = 10.2, 4.2 Hz, 1H), 2.40 – 2.29 (m, 1H), 2.28 – 2.11 (m, 3H), 2.05 – 1.79 (m, 4H), 1.69 (br d, *J* = 13.6 Hz, 1H), 1.60 – 1.46 (m, 3H), 1.37 – 1.25 (m, 1H), 1.08 – 0.99 (m, 1H), 0.49 – 0.40 (m, 1H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -140.35 (s, 1F), -175.21 (s, 1F).
1.070	694.1	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.33 (s, 1H), 8.11 – 8.04 (m, 1H), 7.84 – 7.82 (m, 1H), 5.41 – 5.24 (m, 1H), 5.01 (br d, *J* = 14.6 Hz, 1H), 4.48 – 4.37 (m, 2H), 4.34 – 4.26 (m, 2H), 3.96 – 3.87 (m, 1H), 3.81 – 3.70 (m, 4H), 3.36 (br d, *J* = 2.9 Hz, 1H), 3.31 – 3.20 (m, 4H), 3.08 – 3.00 (m, 1H), 2.94 (d, *J* = 10.9 Hz, 1H), 2.75 (dd, *J* = 10.2, 5.4 Hz, 1H), 2.52 (dd, *J* = 10.1, 4.1 Hz, 1H), 2.44 – 2.05 (m, 5H), 2.04 – 1.88 (m, 3H), 1.85 – 1.75 (m, 1H), 1.68 (br d, *J* = 13.6 Hz, 1H), 1.59 – 1.44 (m, 3H), 1.08 – 0.95 (m, 1H), 0.49 – 0.37 (m, 1H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -140.30 (s, 1F), -175.33 (s, 1F).
1.062	689.3	^{1}H NMR (400 MHz, *CDCl3*) δ ppm 9.18 (d, *J*=17.2 Hz, 1 H), 8.04 (d, J = 23.2Hz, 1H), 7.65 (d, *J*=9.6 Hz, 1 H), 5.40 -5.60 (m, 1 H), 5.21 - 5.40 (m, 1 H), 4.83 - 5.19 (m, 2 H), 4.13 - 4.46 (m, 2 H), 3.44 - 3.56 (m, 2 H), 3.19 - 3.37 (m, 2 H), 2.96 -3.10 (m, 1 H), 2.84 - 2.96 (m, 1 H), 2.62 - 2.83 (m, 2 H), 2.18 - 2.38 (m, 4 H), 1.87 - 2.06 (m, 5 H), 1.71 - 1.85 (m, 3 H), 1.57 - 1.70 (m, 3 H), 0.97 - 1.17 (m, 2 H), 0.77 - 0.94 (m, 1 H), 0.55 - 0.70 (m, 1 H), 0.31 - 0.53 (m, 1 H), -1.15 - 0.05 (m, 1 H). ^{19}F NMR (376 MHz, *DMSO-d6*) δ ppm -135.98 (s, 1 F), -138.60 (s, 1 F).
1.073	689.4	^{1}H NMR (400 MHz, *CDCl3*) δ ppm 9.18 (d, *J*=16.0 Hz, 1 H), 8.05 (d, J = 20.8Hz, 1H),, 7.65 (d, *J*=6.4 Hz, 1 H), 5.40 - 5.50 (m, 1 H), 5.20 - 5.39 (m, 1 H), 4.84 - 5.19 (m, 2 H), 4.10 - 4.36 (m, 2 H), 3.44 - 3.58 (m, 2 H), 3.22 - 3.37 (m, 2 H), 3.01 (br s, 1 H), 2.86 - 2.96 (m, 1 H), 2.58 - 2.86 (m, 2 H), 2.17 - 2.41 (m, 4 H), 1.89 - 2.04 (m, 4 H), 1.71 - 1.86 (m, 3 H), 1.56 - 1.70 (m, 3 H), 1.27 - 1.40 (m, 1 H), 1.12 - 1.22 (m, 1 H), 0.78 - 1.10 (m, 2 H), 0.57 - 0.69 (m, 1 H), 0.33 - 0.53 (m, 1 H), -1.10 - 0.05 (m, 1 H). ^{19}F NMR (376 MHz, *DMSO-d6*) δ ppm -135.96 (s, 1 F), -138.61 (s, 1 F).

Cmpd.#	MS *m/z* (ESI): $(M+H)^+$	^{1}H NMR
1.084	662.3	^{1}H NMR (400 MHz, *DMSO-d6*) δ ppm 13.22 (s, 1 H), 9.23 (s, 1 H), 8.04 (s, 1 H), 7.48 (d, *J* = 10.4 Hz, 1 H), 5.15 - 5.39 (m, 1 H), 4.87 (s, 1 H), 4.48 - 4.78 (m, 2 H), 4.01 - 4.19 (m, 2 H), 3.58 (d, *J* = 13.2 Hz, 1 H), 2.97 - 3.22 (m, 5 H), 2.75 - 2.90 (m, 1 H), 2.65 (d, J=10.4 Hz, 1 H), 2.41 - 2.48 (m, 1 H), 1.94 - 2.17 (m, 5 H), 1.57 - 1.91 (m, 8 H), 1.47 - 1.56 (m, 1 H), 1.31 (s, 3 H), 0.78 (s, 1 H), 0.38 (s, 1 H). ^{19}F NMR (377 MHz, *DMSO-d6*) δ ppm -112.52 (s, 1 F), -138.60 (s, 1 F), -172.16 (s, 1 F).
1.086	662.3	^{1}H NMR (400 MHz, *DMSO-d6*) δ ppm 13.22 (s, 1 H), 9.23 (s, 1 H), 8.04 (s, 1 H), 7.48 (d, *J* = 10.4 Hz, 1 H), 5.17 - 5.37 (m, 1 H), 4.86 (s, 1 H), 4.49 - 4.76 (m, 2 H), 4.18 (d, *J* = 10.4 Hz, 1 H), 4.05 (d, *J* = 10.4 Hz, 1 H), 3.57 (d, *J* = 14.0 Hz, 1 H), 2.97 - 3.23 (m, 5 H), 2.76 - 2.92 (m, 1 H), 2.65 (d, *J* = 11.2 Hz, 1 H), 2.44 - 2.49 (m, 1 H), 1.92 - 2.22 (m, 5 H), 1.58 - 1.89 (m, 8 H), 1.43 - 1.55 (m, 1 H), 1.24 - 1.39 (m, 3 H), 0.77 (s, 1 H), 0.37 (s, 1 H). ^{19}F NMR (377 MHz, *DMSO-d6*) δ ppm -112.52 (s, 1 F), -138.61 (s, 1 F), -172.03 (s, 1 F).
1.087	680	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.27 – 9.14 (m, 1H), 8.20 – 8.09 (m, 1H), 7.88 – 7.77 (m, 1H), 5.44 – 5.22 (m, 1H), 4.57 (br d, *J* = 13.8 Hz, 1H), 4.35 – 4.28 (m, 2H), 3.98 – 3.78 (m, 3H), 3.52 – 3.42 (m, 2H), 3.27 – 3.15 (m, 2H), 3.09 – 2.99 (m, 1H), 2.81 – 2.71 (m, 1H), 2.54 – 2.48 (m, 1H), 2.30 – 2.12 (m, 4H), 2.12 – 1.89 (m, 7H), 1.81 – 1.70 (m, 3H), 1.58 –1.48 (m, 1H), 1.33 (br s, 1H), 1.09 – 0.96 (m, 1H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -136.63 – -138.75 (m, 1F), -172.50 – -174.78 (m, 1F).
1.089	680	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.38 – 9.22 (m, 1H), 8.28 – 8.19 (m, 1H), 7.99 – 7.91 (m, 1H), 5.55 – 5.37 (m, 1H), 5.02 – 4.93 (m, 1H), 4.70 – 4.63 (m, 1H), 4.57 – 4.38 (m, 2H), 4.08 – 3.86 (m, 3H), 3.61 – 3.47 (m, 3H), 3.24 – 3.12 (m, 1H), 2.91 – 2.82 (m, 1H), 2.65 – 2.58 (m, 1H), 2.55 – 2.23 (m, 5H), 2.21 – 2.12 (m, 3H), 2.12 – 1.95 (m, 4H), 1.91 – 1.76 (m, 2H), 1.68 – 1.54 (m, 1H), 1.17 – 1.03 (m, 1H), 0.63 – 0.50 (m, 1H).^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -136.66 – -138.94 (m, 1F), -172.78 – -174.57 (m, 1F).

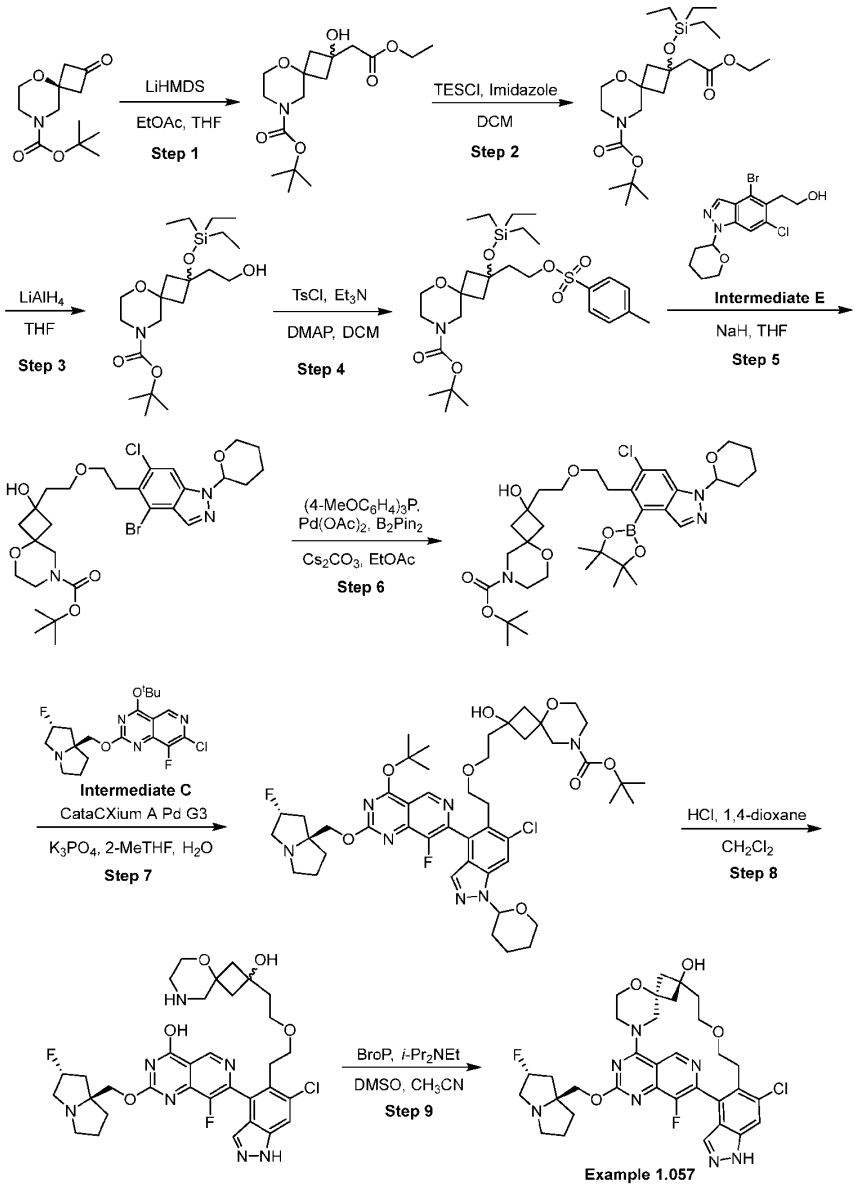
Cmpd.#	MS *m/z* (ESI): $(M+H)^+$	^{1}H NMR
1.090	680	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.30 – 9.12 (m, 1H), 8.21 – 8.10 (m, 1H), 7.88 – 7.74 (m, 1H), 5.47 – 5.20 (m, 1H), 4.60 – 4.53 (m, 1H), 4.40 – 4.34 (m, 1H), 4.30 – 4.23 (m, 1H), 3.96 – 3.79 (m, 3H), 3.51 – 3.46 (m, 1H), 3.45 – 3.39 (m, 1H), 3.27 – 3.18 (m, 2H), 3.07 – 2.99 (m, 1H), 2.80 – 2.73 (m, 1H), 2.54 – 2.47 (m, 1H), 2.37 – 2.33 (m, 1H), 2.29 – 2.22 (m, 2H), 2.19 – 2.12 (m, 1H), 2.07 – 2.00 (m, 3H), 2.00 – 1.97 (m, 1H), 1.97 – 1.87 (m, 2H), 1.77 – 1.73 (m, 1H), 1.54 (br s, 1H), 1.35 – 1.24 (m, 2H), 1.06 – 0.96 (m, 1H), 0.96 – 0.87 (m, 1H), 0.52 – 0.46 (m, 1H).^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -136.63 – -139.40 (m, 1F), -173.52 (s, 1F).
1.091	634.3	^{1}H NMR (400 MHz, *CDCl3*) δ ppm 10.0 - 10.5 (m, 1 H), 9.00 - 9.30 (m, 1 H), 8.12 - 8.43 (m, 1 H), 7.65 - 7.95 (m, 1 H), 4.91 - 5.06 (m, 1 H), 4.51 - 4.72 (m, 2 H), 4.31 - 4.57 (m, 1 H), 3.56 - 3.65 (m, 2 H), 3.43 - 3.54 (m, 1 H), 3.17 - 3.21 (m, 1 H), 3.03 - 3.16 (m, 1 H), 2.74 - 2.92 (m, 2 H), 2.57 - 2.74 (m, 5 H), 2.17 - 2.45 (m, 5 H), 1.98 - 2.03 (m, 1 H), 1.72 - 1.92 (m, 9 H), 1.14 - 1.25 (m, 1 H), 0.56 - 0.67 (m, 1 H).^{19}F NMR (377 MHz, *CDCl3*) δ ppm -135.08 (s, 1 F).

Table 8. Conditions for Chiral SFC Separation.

	Column: Chiralcel OD, 2 x 25 cm, 5 µm Mobile phase: 40% MeOH with 0.2% DEA Flowrate of 80 mL/min. Yield : 109 mg to give 43.8 mg of peak 1 with an ee of 99% and 41.9 mg of peak 2 with an ee of 99%.	Peak 1: **Example 1.006** Peak 2: **Example 1.003**
	Column: Chiralcel OD, 2 x 25 cm, 5 µm Mobile phase: 40% MeOH with 0.2% DEA Flowrate: 80 mL/min. Yield: 493 mg to generate 144 mg of peak 1 with an ee of 99% and 154 mg of peak 2 with an ee of 99%.	Peak 1: **Example 1.049** Peak 2: **Example 1.040**
	Column: Chiralcel OD, 2 x 25 cm, 5 µm Mobile phase: 45% iPrOH with 0.2% DEA Flowrate: 80 mL/min. Yield: 133 mg to generate 67 mg of peak 1 with an ee of >99% and 66 mg of peak 2 with an ee of >99%.	Peak 1: **Example 1.070** Peak 2: **Example 1.071**

	Column: REGIS(*S,S*)WHELK-O1, 2.5 x 25 cm, 10 µm Mobile phase: 45% MeOH with 0.1% $NH_3 \cdot H_2O$ Flowrate: 75 mL/min. Yield: 50 mg to generate 12 mg of peak 1 with an ee of >99% and 11 mg of peak 2 with an ee of >99%.	Peak 1: **Example 1.062** Peak 2: **Example 1.073**
	Column: CHIRACEL OJ, 2 x 25 cm, 5 µm. Mobile phase: 25% iPrOH in 0.2% DEA Flowrate: 80 mL/min.	Peak 1: **Example 1.084** Peak 2: **Example 1.086**
	Column: CHIRALCEL OD, 2 x 25 cm, 5 µm. Mobile phase: 40% MeOH with 0.2% DEA. Flowrate of 80 mL/min	Peak 1: **Example 1.087** Peak 2: **Example 1.090**

Example 1.057: (1*S*,3*R*)-10-Chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-6,30-dioxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-3-ol bis(2,2,2-trifluoroacetate).



[00395] Step 1. *tert*-Butyl 2-(2-ethoxy-2-oxoethyl)-2-hydroxy-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate. In a 40-mL vial was added ethyl acetate (1.2 mL, 12 mmol) in tetrahydrofuran (50 mL). The mixture was cooled to -78 °C and lithium bis(trimethylsilyl)amide (1 M in THF, 12.4 mL, 12.4 mmol) was added dropwise under nitrogen. The reaction was stirred at -78 °C for 1 h, and then a solution of *tert*-butyl 2-oxo-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate (2.00 g, 8.29 mmol, Pharmablocks) in THF (5 mL) was added. The reaction mixture was stirred at -78 °C for 1 h, then quenched with the addition of saturated NH_4Cl solution, and was allowed to gradually warm to room

temperature. The reaction mixture was extracted with EtOAc, and the combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0–100% EtOAc in heptane (product detected with ELS detector), to provide *tert*-butyl 2-(2-ethoxy-2-oxoethyl)-2-hydroxy-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate (2.62 g, 7.94 mmol, 96% yield). *m/z* (ESI): 352.0 $(M+Na)^+$.

[00396] Step 2. *tert*-Butyl 2-(2-ethoxy-2-oxoethyl)-2-((triethylsilyl)oxy)-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate. In a 250-mL round-bottom flask was charged with *tert*-butyl 2-(2-ethoxy-2-oxoethyl)-2-hydroxy-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate (2.52 g, 7.65 mmol) in dichloromethane (40 mL). Imidazole (1.35 g, 19.9 mmol) was added, and the reaction mixture was cooled to 0 °C and chlorotriethylsilane (1.7 mL, 10 mmol) was added. The reaction mixture was allowed to warm to room temperature with stirring for 3 h. Water was added to the mixture and the aqueous phase was extracted with DCM. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0–100% EtOAc in heptane (product detected with ELS detector), to provide *tert*-butyl 2-(2-ethoxy-2-oxoethyl)-2-((triethylsilyl)oxy)-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate (3.01 g, 6.78 mmol, 89% yield). *m/z* (ESI): 466.1 $(M+Na)^+$.

[00397] Step 3. *tert*-Butyl 2-(2-hydroxyethyl)-2-((triethylsilyl)oxy)-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate. To a 250-mL round-bottomed flask was added *tert*-butyl 2-(2-ethoxy-2-oxoethyl)-2-((triethylsilyl)oxy)-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate (2.88 g, 6.49 mmol) in tetrahydrofuran (30 mL). The mixture was cooled to 0 °C and lithium aluminum hydride solution (2.0 M in THF, 6.5 mL, 13 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h, then quenched with Rochelle's salt solution and extracted with EtOAc. The combined organic layers were and dried over Na_2SO_4, filtered and concentrated. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0–100% EtOAc in heptane, to provide *tert*-butyl 2-(2-hydroxyethyl)-2-((triethylsilyl)oxy)-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate (1.14 g, 2.84 mmol, 44% yield). *m/z* (ESI): 424.1 $(M+Na)^+$.

[00398] Step 4. *tert*-Butyl 2-(2-(tosyloxy)ethyl)-2-((triethylsilyl)oxy)-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate. To a 40-mL vial was added *tert*-butyl 2-(2-hydroxyethyl)-2-((triethylsilyl)oxy)-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate (1.14 g, 2.84 mmol), 4-toluenesulfonyl chloride (0.60 g, 3.10 mmol) and 4-(dimethylamino)pyridine (0.03 g, 0.23 mmol) in dichloromethane (5 mL). The mixture was cooled to 0 °C and triethylamine (0.79 mL, 5.7 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature with stirring for 4 h. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0–100% EtOAc in heptane, to provide *tert*-butyl 2-(2-(tosyloxy)ethyl)-2-((triethylsilyl)oxy)-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate (0.52 g, 0.94 mmol, 33% yield). *m/z* (ESI): 578.0 $(M+Na)^+$. ^1H NMR (500 MHz, *$CDCl_3$*) δ ppm 7.80 (d, *J* = 8.3 Hz, 2H), 7.36 (dd, *J* = 8.2, 2.1 Hz, 2H), 4.18 – 4.12

(m, 2H), 3.55 (br dd, J = 9.9, 5.1 Hz, 2H), 3.37 – 3.32 (m, 2H), 3.30 (br s, 1H), 2.46 (s, 3H), 2.28 – 2.22 (m, 1H), 2.20 – 2.14 (m, 2H), 2.11 – 2.02 (m, 2H), 1.97 – 1.89 (m, 1H), 1.48 (d, J = 4.2 Hz, 10H), 0.92 – 0.87 (m, 9H), 0.57 – 0.51 (m, 6H).

[00399] Step 5. *tert*-Butyl 2-(2-(2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate. A 50 mL round-bottom flask was charged with 2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethan-1-ol (**Intermediate E**, 0.85 g, 2.35 mmol) in tetrahydrofuran (8 mL) and *N*,*N*-dimethylformamide (1 mL). Sodium hydride (60 wt% dispersion in mineral oil, 94 mg, 2.40 mmol) was added and the reaction mixture was stirred at room temperature for 30 minutes. To this was added *tert*-butyl 2-(2-(tosyloxy)ethyl)-2-((triethylsilyl)oxy)-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate (0.52 g, 0.94 mmol) in THF (2 mL). The reaction mixture was stirred at 50 °C for 90 h. After cooling to room temperature, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 0–100% EtOAc in heptane, to provide *tert*-butyl 2-(2-(2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate (0.20 g, 0.32 mmol, 34% yield). *m/z* (ESI): 650.2, 652.1 $(M+Na)^-$.

[00400] Step 6. *tert*-Butyl 2-(2-(2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate. A 40-mL vial was charged with tris(4-methoxyphenyl)phosphine (13.6 mg, 0.04 mmol), palladium acetate (7.2 mg, 0.03 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.12 g, 0.48 mmol), cesium carbonate (0.21 g, 0.64 mmol), *tert*-butyl 2-(2-(2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate (0.20 g, 0.32 mmol) and ethyl acetate (1.5 mL). The reaction mixture was sparged with nitrogen and then heated to 80 °C for 1 h. After cooling to room temperature, the mixture was filtered over celite, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 0–100% EtOAc in heptane, to provide *tert*-butyl 2-(2-(2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate (98 mg, 0.15 mmol, 45% yield). *m/z* (ESI): 676.3 $(M+H)^+$.

[00401] Step 7. *tert*-Butyl 2-(2-(2-(4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate. To a suspension of *tert*-butyl 2-(2-(2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-5-oxa-8-

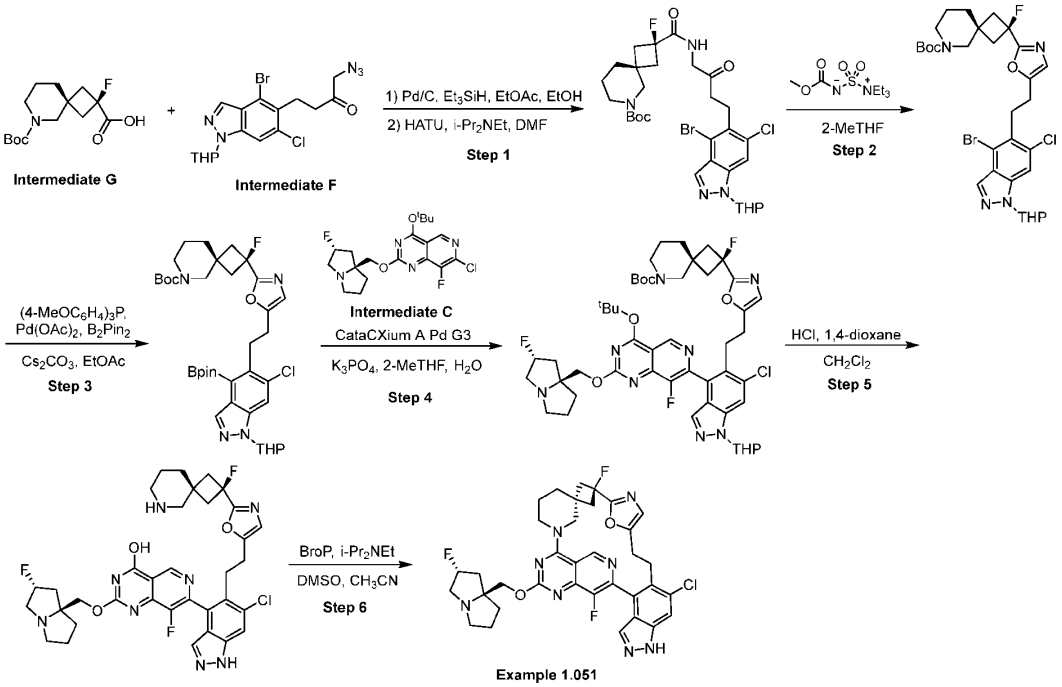
azaspiro[3.5]nonane-8-carboxylate (98 mg, 0.15 mmol) and 4-(*tert*-butoxy)-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (**Intermediate C**, 60 mg, 0.15 mmol) in 2-methyltetrahydrofuran (2 mL) and water (0.2 mL) were added potassium phosphate (77 mg, 0.36 mmol) and cataCXium A Pd G3 (CAS No. 1651823-59-4) (21 mg, 0.03 mmol). The reaction mixture was sparged with nitrogen and then stirred at 80 °C for 1 h. After cooling to room temperature, the organic layer was isolated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude material was purified by reversed phase chromatography using a C18 column, eluting with a gradient of 0–100% (water with 0.1% formic acid)/(acetonitrile with 0.1% formic acid), to provide *tert*-butyl 2-(2-(2-(4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate (42 mg, 0.05 mmol, 31% yield). *m/z* (ESI): 926.0 $(M+H)^+$.

[00402] Step 8. 2-(2-(2-(6-Chloro-4-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-5-oxa-8-azaspiro[3.5]nonan-2-ol. To a solution of *tert*-butyl 2-(2-(2-(4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-2-hydroxy-5-oxa-8-azaspiro[3.5]nonane-8-carboxylate (42 mg, 0.05 mmol) in dichloromethane (1 mL) was added hydrogen chloride (4 M in 1,4-dioxane, 0.45 mL, 1.8 mmol). The reaction mixture was stirred vigorously at room temperature for 1.5 h. Solvent was removed, and the residue was loaded onto a SCX column with MeOH, and eluting with 2 M NH_3 in MeOH to provide 2-(2-(2-(6-chloro-4-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-5-oxa-8-azaspiro[3.5]nonan-2-ol (30 mg, 0.04 mmol, 98% yield). *m/z* (ESI): 686.0 $(M+H)^+$.

[00403] Step 9. (1*S*,3*R*)-10-Chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-6,30-dioxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-3-ol bis(2,2,2-trifluoroacetate). To a 250-mL round-bottom flask was added 1,1'-dimethyltriethylamine (0.02 mL, 0.13 mmol) and bromotris(dimethylamino)phosphonium hexafluorophosphate (26 mg, 0.07 mmol) in acetonitrile (10 mL). A solution of 2-(2-(2-(6-chloro-4-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)-1*H*-indazol-5-yl)ethoxy)ethyl)-5-oxa-8-azaspiro[3.5]nonan-2-ol (30 mg, 0.04 mmol) in dimethyl sulfoxide (2 mL) was then added dropwise over 20 minutes via a syringe pump. The reaction mixture was stirred at room temperature under nitrogen for 30 minutes before it was concentrated, and acetonitrile was removed. The residue was

purified by reversed phase HPLC using a C18 column, eluting with 0–50% CH_3CN with 0.1% TFA/water with 0.1% TFA, to provide (1*S*,3*R*)-10-chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-6,30-dioxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9.11,14.16,18(32),19,21,23,25-nonaen-3-ol bis(2,2,2-trifluoroacetate) (11 mg, 0.012 mmol, 28% yield). *m/z* (ESI): 667.9 $(M+H)^+$. ^1H NMR (500 MHz, *METHANOL-d4*) δ ppm 9.36 (s, 1H), 7.86 (d, *J* = 0.9 Hz, 1H), 7.83 (s, 1H), 5.69 – 5.54 (m, 1H), 4.96 (br d, *J* = 11.8 Hz, 1H), 4.71 (s, 4H), 4.09 – 3.91 (m, 4H), 3.86 – 3.80 (m, 2H), 3.68 – 3.62 (m, 1H), 3.54 – 3.47 (m, 3H), 3.19 – 3.12 (m, 2H), 2.91 – 2.76 (m, 2H), 2.75 – 2.57 (m, 2H), 2.50 – 2.43 (m, 1H), 2.41 – 2.34 (m, 2H), 2.30 – 2.08 (m, 4H), 1.77 (br d, *J* = 12.7 Hz, 1H), 1.74 – 1.66 (m, 1H), 1.56 (ddd, *J* = 12.9, 3.5, 3.3 Hz, 1H), 1.44 (ddd, *J* = 13.9, 10.8, 5.6 Hz, 1H). ^{19}F NMR (471 MHz, *METHANOL-d4*) δ ppm -142.93 (br s, 1F), -175.37 (br d, *J* = 24.3 Hz, 1F).

Example 1.051: (1*S*,3*R*)-11-Chloro-3,33-difluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-34-oxa-5,14,15,20,24,26,28-heptaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaene bis(2,2,2-trifluoroacetate).



[00404] Step 1. *tert*-Butyl (2*S*,4*R*)-2-((4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-oxobutyl)carbamoyl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate. To a 250-mL round-bottom flask was charged with 1-azido-4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one (**Intermediate F**, 1.66 g, 3.90 mmol) in ethyl acetate (15 mL) and ethanol (20 mL). Palladium on activated carbon (0.24 g, 2.30 mmol) was added and under nitrogen, 3-ethyl-3-silapentane (2.4 mL, 15 mmol) was added dropwise through a syringe pump over 30 minutes. The reaction mixture was stirred at room temperature for additional 30 minutes. The mixture was filtered through a pad of celite, and the volatiles were evaporated. The residue was dissolved in *N*,*N*-dimethylformamide (7.5 mL). (2*S*,4*R*)-6-(*tert*-Butoxycarbonyl)-2-fluoro-6-azaspiro[3.5]nonane-2-carboxylic acid (**Intermediate G**, 0.94 g, 3.3 mmol), HATU (1.61 g, 4.23 mmol), and diisopropylethylamine (2.8 mL, 16 mmol) was sequentially added. The reaction mixture was stirred at room temperature for 30 min, then quenched by the addition of saturated NH_4Cl solution and extracted by EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0–100% EtOAc in heptane, to provide *tert*-butyl (2*S*,4*R*)-2-((4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-oxobutyl)carbamoyl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (1.60 g, 2.39 mmol, 73% yield). *m/z* (ESI): 690.8, 692.8 $(M+Na)^+$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.98 (d, *J* = 0.8 Hz, 1H), 7.68 (s, 1H), 5.67 (dd, *J* = 9.0, 2.9 Hz, 1H), 4.25 (d, *J* = 4.7 Hz, 2H), 4.04 – 3.99 (m, 1H), 3.79 – 3.74 (m, 1H), 3.54 – 3.49 (m, 2H), 3.41 – 3.33 (m, 4H), 2.78 – 2.74 (m, 2H), 2.62 – 2.47 (m, 3H), 2.18 – 2.08 (m, 4H), 1.84 – 1.74 (m, 5H), 1.73 – 1.70 (m, 1H), 1.57 – 1.52 (m, 2H), 1.51 – 1.46 (m, 9H). ^{19}F NMR (471 MHz, $CDCl_3$) δ ppm -149.12 (br s, 1F).

[00405] Step 2. *tert*-Butyl (2*S*,4*R*)-2-(5-(2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate. In a 40-mL vial was added *tert*-butyl (2*S*,4*R*)-2-((4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-oxobutyl)carbamoyl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (1.60 g, 2.39 mmol) and Burgess Reagent (3.41 g, 14.3 mmol, Combi-Blocks Inc.) in 2-methyltetrahydrofuran (10 mL). The reaction mixture was purged with N_2, and then heated at 75 °C for 2 h. After cooling to room temperature saturated NaCl solution was added, and the mixture was extracted with EtOAc. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 0–100% EtOAc in heptane, to provide *tert*-butyl (2*S*,4*R*)-2-(5-(2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (0.74 g, 1.10 mmol, 48% yield). *m/z* (ESI): 651.1, 653.2 $(M+H)^+$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.98 (d, *J* = 0.8 Hz, 1H), 7.68 (d, *J* = 0.8 Hz, 1H), 6.76 (s, 1H), 5.68 – 5.65 (m, 1H), 4.05 – 3.99 (m, 1H), 3.81 – 3.73 (m, 1H), 3.46 – 3.38 (m, 2H), 3.35 (br t, *J* = 5.3 Hz, 2H), 3.30 (s, 2H), 3.03 – 2.96 (m, 2H), 2.81 – 2.68 (m, 2H), 2.55 – 2.46 (m, 1H), 2.41 – 2.29 (m, 2H), 2.19 – 2.09 (m, 2H), 1.81 – 1.76 (m, 4H), 1.72 –

1.68 (m, 1H), 1.58 – 1.53 (m, 2H), 1.41 (s, 9H). ^{19}F NMR (471 MHz, *CDCl*$_3$) δ ppm -134.50 (br s, 1F).

[00406] Step 3. *tert*-Butyl (2*S*,4*R*)-2-(5-(2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate. A 250-mL round-bottom flask was charged with tris(4-methoxyphenyl)phosphine (48 mg, 0.14 mmol), palladium acetate (26 mg, 0.11 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.43 g, 1.70 mmol), cesium carbonate (0.74 g, 2.3 mmol), *tert*-butyl (2*S*,4*R*)-2-(5-(2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (0.74 g, 1.10 mmol) and ethyl acetate (10 mL). The reaction mixture was then sparged with nitrogen and heated to 80 °C for 2.5 h. After cooling to room temperature, the mixture was filtered over celite, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 0–100% EtOAc in heptane, to provide *tert*-butyl (2*S*,4*R*)-2-(5-(2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (0.51 g, 0.73 mmol, 64% yield). *m/z* (ESI): 699.1 $(M+H)^+$. ^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 8.39 (s, 1H), 7.78 (d, *J* = 0.8 Hz, 1H), 6.82 (s, 1H), 5.69 (dd, *J* = 9.1, 2.8 Hz, 1H), 4.02 (br d, *J* = 9.8 Hz, 1H), 3.79 – 3.73 (m, 1H), 3.53 – 3.47 (m, 2H), 3.35 (br t, *J* = 5.2 Hz, 2H), 3.30 (s, 2H), 2.98 – 2.93 (m, 2H), 2.81 – 2.72 (m, 2H), 2.58 – 2.49 (m, 1H), 2.41 – 2.29 (m, 2H), 2.21 – 2.13 (m, 1H), 2.12 – 2.07 (m, 1H), 1.85 – 1.70 (m, 5H), 1.54 – 1.49 (m, 2H), 1.43 – 1.42 (m, 12H), 1.41 (br s, 9H). ^{19}F NMR (376 MHz, *CDCl*$_3$) δ ppm -134.14 (br s, 1F).

[00407] Step 4. *tert*-Butyl (2*S*,4*R*)-2-(5-(2-(4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate. To a suspension of *tert*-butyl (2*S*,4*R*)-2-(5-(2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (0.50 g, 0.72 mmol) and 4-(*tert*-butoxy)-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (**Intermediate C**, 0.33 g, 0.79 mmol) in 2-methyltetrahydrofuran (6 mL) and water (0.6 mL) were added potassium phosphate (0.38 g, 1.80 mmol) and cataCXium A Pd G3 (CAS No. 1651823-59-4) (0.10 g, 0.14 mmol). The reaction mixture was sparged with nitrogen and stirred at 80 °C for 1 h. After cooling to room temperature, the organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude material was purified reverse phase HPLC using a C18 column, eluting with 0–100% (water + 0.1% formic acid/acetonitrile + 0.1% formic acid) to provide *tert*-butyl (2*S*,4*R*)-2-(5-(2-(4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-

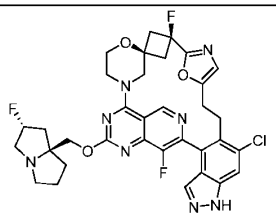
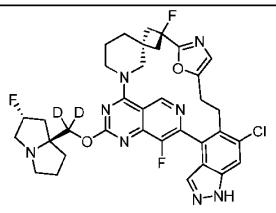
yl)ethyl)oxazol-2-yl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (0.46 g, 0.48 mmol, 68% yield). *m/z* (ESI): 949.0 $(M+H)^+$. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 9.19 (d, *J* = 2.9 Hz, 1H), 7.85 (d, *J* = 10.5 Hz, 1H), 7.57 (s, 1H), 6.64 (s, 1H), 5.73 (br s, 1H), 5.39 – 5.22 (m, 1H), 4.37 – 4.25 (m, 2H), 4.11 – 4.00 (m, 1H), 3.84 – 3.74 (m, 1H), 3.34 – 3.15 (m, 9H), 3.07 – 2.89 (m, 4H), 2.74 – 2.62 (m, 2H), 2.33 – 2.20 (m, 4H), 2.14 (br d, *J* = 10.9 Hz, 3H), 2.01 – 1.91 (m, 3H), 1.82 (s, 9H), 1.79 – 1.72 (m, 4H), 1.59 (s, 9H), 1.56 – 1.49 (m, 3H). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ ppm -134.18 – -134.79 (m, 1F), -137.83 – -138.13 (m, 1F), -173.07 (d, *J* = 3.5 Hz, 1F).

[00408] Step 5. 7-(6-Chloro-5-(2-(2-((2*S*,4*R*)-2-fluoro-6-azaspiro[3.5]nonan-2-yl)oxazol-5-yl)ethyl)-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol. To a solution of *tert*-butyl (2*s*,4*r*)-2-(5-(2-(4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (0.46 g, 0.48 mmol) in dichloromethane (5 mL) was added hydrogen chloride (4 M in 1,4-dioxane, 2.4 mL, 9.6 mmol). The reaction was stirred vigorously at room temperature for 1 h. Solvent was removed, and the mixture was loaded onto a SCX column with MeOH (20 mL), eluting with 2 M NH_3 in MeOH and concentrated to provide 7-(6-chloro-5-(2-(2-((2*S*,4*R*)-2-fluoro-6-azaspiro[3.5]nonan-2-yl)oxazol-5-yl)ethyl)-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol (0.34 g, 0.48 mmol, 99% yield). *m/z* (ESI): 709.0 $(M+H)^+$. ^{1}H NMR (400 MHz, *DMSO-d$_6$*) δ ppm 8.92 (s, 1H), 7.81 (d, *J* = 1.0 Hz, 1H), 7.65 (s, 1H), 6.75 (s, 1H), 5.38 – 5.19 (m, 1H), 4.10 – 3.97 (m, 2H), 3.18 – 3.09 (m, 4H), 3.04 (br d, *J* = 3.3 Hz, 1H), 3.00 – 2.76 (m, 9H), 2.67 – 2.55 (m, 2H), 2.31 – 2.12 (m, 2H), 2.05 – 1.97 (m, 2H), 1.93 – 1.60 (m, 9H). ^{19}F NMR (376 MHz, *DMSO-d$_6$*) δ ppm -132.93 (br s, 1F), -141.63 (br s, 1F), -171.91 – -171.99 (m, 1F).

[00409] Step 6. (1*S*,3*R*)-11-Chloro-3,33-difluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-34-oxa-5,14,15,20,24,26,28-heptaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaene bis(2,2,2-trifluoroacetate). To a 250-mL round-bottom flask was added Hunig's base (0.25 mL, 1.4 mmol) and bromotris(dimethylamino)phosphonium hexafluorophosphate (0.28 g, 0.72 mmol) in acetonitrile (35 mL). A solution of 7-(6-chloro-5-(2-(2-((2*S*,4*R*)-2-fluoro-6-azaspiro[3.5]nonan-2-yl)oxazol-5-yl)ethyl)-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol (0.34 g, 0.48 mmol) in dimethyl sulfoxide (7 mL) was then added dropwise over 20 minutes via a syringe pump and the mixture was stirred at room temperature under nitrogen for 16 h. The mixture was concentrated to remove acetonitrile and the residue was purified by reversed phase HPLC using a C18 column, eluting with 0–50% CH_3CN/0.1% TFA and 0.1% to provide (1*S*,3*R*)-11-chloro-3,33-difluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-

a]pyrrol-7a(5*H*)-yl)methoxy)-34-oxa-5,14,15,20,24,26,28-heptaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaene bis(2,2,2-trifluoroacetate) (0.20 g, 0.22 mmol, 46% yield). *m/z* (ESI): 690.9 $(M+H)^+$. ^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.14 (s, 1H), 7.90 – 7.88 (m, 1H), 7.81 (s, 1H), 6.66 (s, 1H), 5.67 – 5.50 (m, 1H), 5.00 (br d, *J* = 12.8 Hz, 1H), 4.77 – 4.66 (m, 3H), 4.13 – 3.76 (m, 5H), 3.53 – 3.46 (m, 1H), 3.30 – 3.16 (m, 2H), 3.15 – 3.05 (m, 1H), 2.97 – 2.87 (m, 1H), 2.83 – 2.51 (m, 4H), 2.50 – 2.32 (m, 5H), 2.29 – 2.17 (m, 2H), 2.05 – 1.76 (m, 6H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -78.50 (s, 6F, TFA), -138.29 (d, *J* = 20.8 Hz, 1F), -143.60, (s, 1F), -175.20 – -175.31 (m, 1F).

Table 9: Additional Examples Prepared in an Analogous Manner to Example 1.051.

Cmpnd	Structure	Name	Reagents	Method Changes
1.056		(1*R*,3*R*)-11-chloro-3,33-difluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-31, 34-dioxa-5,14,15,20,24,26,28-heptaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaene	**Step 1**: (2*s*,4*s*)-8-(*tert*-butoxycarbonyl)-2-fluoro-5-oxa-8-azaspiro[3.5]nonane-2-carboxylic acid (**Intermediate FF**)	
1.018		(1*S*,3*R*)-11-chloro-3,33-difluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)(~2~H_2_)methyl)oxy)-34-oxa-5,14,15,20,24,26,28-heptaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaene	**Step 4**: 4-(*tert*-butoxy)-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy-d_2)pyrido[4,3-*d*]pyrimidine (**Intermediate GG**)	

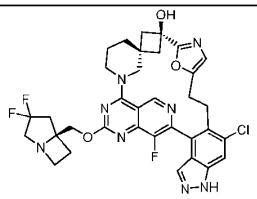
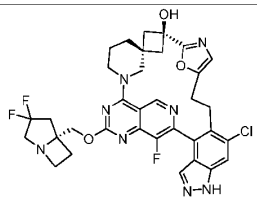
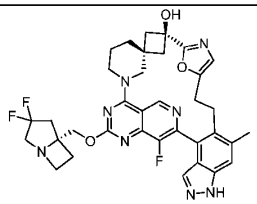
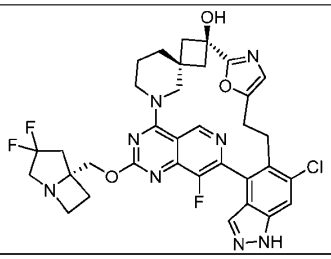
Cmpnd	Structure	Name	Reagents	Method Changes
1.078		(13*r*,73*S*)-36-chloro-22-(((*R*)-3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-28-fluoro-31*H*-6(5,2)-oxazola-2(4,7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-7(1,3)-cyclobutanaheptaphan-73-ol		Chiral purification of diastereomeric mixture. Stereochemistry was confirmed by x-ray crystallographic analysis.
1.079		(13*r*,73*R*)-36-chloro-22-(((*S*)-3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-28-fluoro-31*H*-6(5,2)-oxazola-2(4,7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-7(1,3)-cyclobutanaheptaphan-73-ol		Chiral purification of diastereomeric mixture
1.080		(13*r*,73*s*)-22-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-28-fluoro-36-methyl-31*H*-6(5,2)-oxazola-2(4,7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-7(1,3)-cyclobutanaheptaphan-73-olbis(2,2,2-trifluoroacetate)	**Step 3:** *tert*-butyl (2*s*,4*r*)-2-(5-(2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-2-(methoxymethoxy)-6-azaspiro[3.5]nonane-6-carboxylate, Intermediate FFF	Step 5: TFA used in lieu of HCl and dioxane.

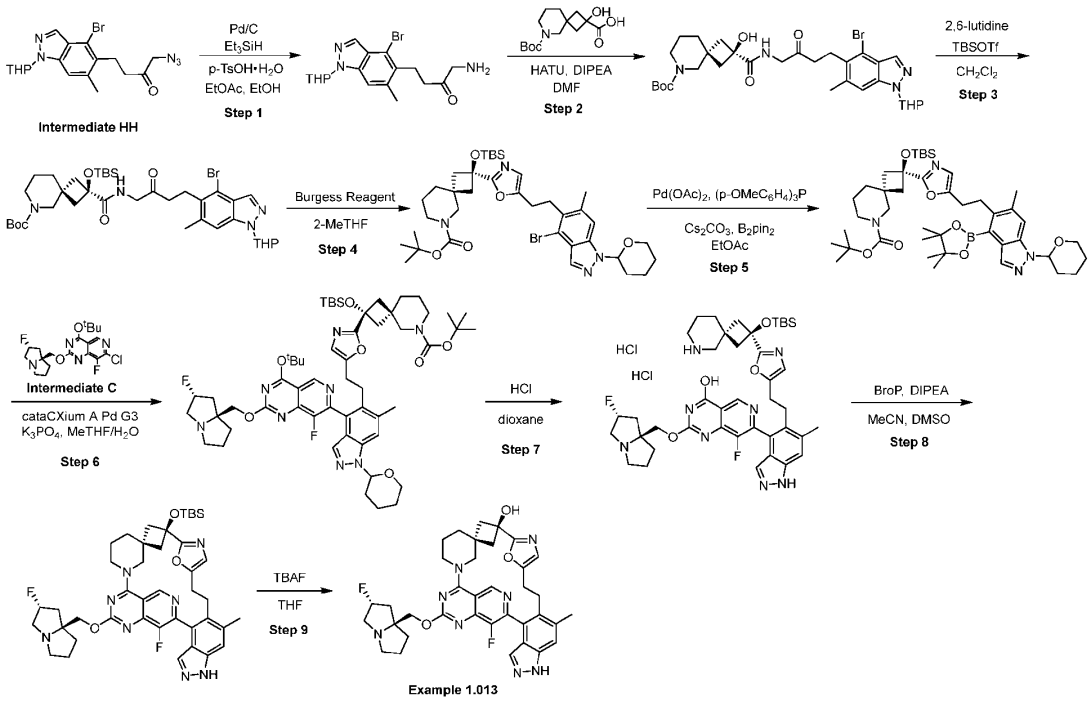
Table 10. Analytical Data for Examples in Table 9.

Cmpd.#	MS *m/z* (ESI): $(M+H)^+$	^{1}H NMR
1.056	693.1	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.14 (s, 1H), 7.89 (s, 1H), 7.81 (s, 1H), 6.71 (s, 1H), 5.69 – 5.49 (m, 1H), 4.99 – 4.93 (m, 1H), 4.74 – 4.68 (m, 2H), 4.67 – 4.60 (m, 1H), 4.07 (br d, *J* = 14.0 Hz, 2H), 3.98 – 3.77 (m, 5H), 3.60 – 3.45 (m, 2H), 3.23 (br dd, *J* = 13.8, 6.5 Hz, 1H), 3.17 – 3.07 (m, 1H), 3.05 – 2.85 (m, 2H), 2.82 – 2.57 (m, 3H), 2.54 – 2.32 (m, 5H), 2.20 (br s, 2H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -78.50 (br s, 6F) (TFA), -138.88 (br d, *J* = 8.7 Hz, 1F), -143.50 (br d, *J* = 6.9 Hz, 1F), -175.22 (br d, *J* = 11.3 Hz, 1F).
1.018	693.2	^{1}H NMR (400 MHz, *CDCl3*) δ ppm 10.10 - 10.92 (m, 1 H), 8.91 (s, 1 H), 7.82 (s, 1 H), 7.73 (s, 1 H), 6.54 (s, 1 H), 5.19 - 5.39 (m, 1 H), 4.93 (d, J=12.0 Hz, 1 H), 4.70 (d, J=13.6 Hz, 1 H), 3.60 (d, J=13.2 Hz, 1 H), 3.17 - 3.30 (m, 3 H), 2.97 - 3.06 (m, 3 H), 2.81-2.89 (m, 1 H), 2.72 - 2.80 (m, 1 H), 2.53 - 2.61 (m, 1 H), 2.28 - 2.42 (m, 2 H), 2.11 - 2.25 (m, 3 H), 1.89 - 2.03 (m, 4 H), 1.71 - 1.89 (m, 5 H). ^{19}F NMR (376 MHz, *CDCl3*) δ ppm -134.46 (d, J=37.6 Hz, 1 F), -139.74 (s, 1 F), -173.06 (d, J=20.3 Hz, 1 F).
1.078	693	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.23 – 9.09 (m, 1H), 7.94 – 7.79 (m, 2H), 6.70 – 6.49 (m, 1H), 5.02 – 4.94 (m, 1H), 4.81 – 4.73 (m, 1H), 4.61 – 4.45 (m, 2H), 3.81 – 3.67 (m, 2H), 3.46 – 3.38 (m, 1H), 3.23 – 3.00 (m, 4H), 2.92 – 2.78 (m, 1H), 2.73 – 2.52 (m, 3H), 2.52 – 2.38 (m, 3H), 2.12 – 1.99 (m, 3H), 1.95 – 1.70 (m, 6H), 1.67 –1.50 (m, 1H).^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -90.94 – -93.42 (m, 1F), -101.89 (brdd, *J* =236.7, 107.5 Hz, 1F), -142.29 (brd, *J* = 15.6Hz, 1F).
1.079	693	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.26 – 9.06 (m, 1H), 7.94 – 7.79 (m, 2H), 6.72 – 6.50 (m, 1H), 5.02 – 4.93 (m, 1H), 4.81 – 4.71 (m, 1H), 4.65 – 4.43 (m, 2H), 3.85 – 3.66 (m, 2H), 3.47 – 3.37 (m, 1H), 3.22 – 3.00 (m, 4H), 2.94 – 2.77 (m, 1H), 2.69 – 2.34 (m, 6H), 2.13 – 1.98 (m, 3H), 1.94 – 1.68 (m, 6H), 1.67 – 1.50 (m, 1H).^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -91.12 – -93.77 (m, 1F), -100.30 – -103.03 (m, 1F), -141.56 – -143.30 (m, 1F).
1.080	673	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.29 – 9.20 (m, 1H), 7.77 – 7.70 (m, 1H), 7.63 – 7.57 (m, 1H), 6.72 – 6.65 (m, 1H), 5.08 – 4.96 (m, 2H), 4.85 – 4.76 (m, 2H), 4.70 – 4.57 (m, 1H), 4.13 – 3.94 (m, 3H), 3.87 – 3.74 (m, 1H), 3.29 – 3.15 (m, 1H), 3.06 – 2.71 (m, 7H), 2.67 – 2.62 m, 3H), 2.55 – 2.33 (m, 2H), 2.18 – 2.04 (m, 2H), 1.96 – 1.79 (m, 5H).^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -77.35 (s, 1F), -92.53 – -93.74 (m, 1F), -102.36.

Chiral Separation

	Column: ENANTIOCEL C9-5, 3 x 25 cm, 5 µm. Mobile phase: 40% iPrOH with 0.2% DEA. Flowrate of 90 mL/min	Peak 1: **Example 1.078** Peak 2: **Example 1.079**

Example 1.013: (1*S*,3*R*)-33-Fluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-11-methyl-34-oxa-5,14,15,20,24,26,28-heptaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaen-3-ol



[00410] Step 1. 1-Amino-4-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one. To a 250-mL round-bottom flask containing 1-azido-4-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one (**Intermediate HH**, 4.00 g, 9.88 mmol) in ethanol (60 mL) and ethyl acetate (60 mL) was added *p*-toluenesulfonic acid monohydrate (0.69 g, 3.6 mmol) and palladium on activated carbon (0.66 g, 0.62 mmol). Under a nitrogen atmosphere, 3-ethyl-3-silapentane (6.1 mL, 38 mmol) was added dropwise over 10 minutes. The reaction mixture was

stirred at room temperature for an additional 30 minutes, was then filtered over celite and the volatiles were evaporated. The crude product was used in the next step without further purification. *m/z* (ESI): 380.1 $(M+H)^+$.

[00411] Step 2. *tert*-Butyl (2*s*,4*r*)-2-((4-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-oxobutyl)carbamoyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate. The residue from the previous step was dissolved in DMF (30 mL). 6-*tert*-Butoxycarbonyl-2-hydroxy-6-azaspiro[3.5]nonane-2-carboxylic acid (2.35 g, 8.24 mmol, Pharmablock, Inc.), HATU (4.7 g, 12 mmol), and diisopropylethylamine (7.2 mL, 41 mmol) were sequentially added. The mixture was stirred at room temperature for 1 h, was then quenched by the addition of saturated NH_4Cl solution. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0–70% of 3:1 EtOAc/EtOH (with 2% Et_3N) in heptane, to afford *tert*-butyl (2*r*,4*s*)-2-((4-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-oxobutyl)carbamoyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (2.20 g, 3.40 mmol, 41% yield). *m/z* (ESI): 647.2 $(M+H)^+$. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 7.94 (s, 1 H), 7.89 (t, *J*=5.6 Hz, 1 H), 7.59 (s, 1 H), 6.04 (s, 1 H), 5.80 (dd, *J*=9.6, 2.6 Hz, 1 H), 3.98 (d, *J*=5.6 Hz, 2 H), 3.83 - 3.92 (m, 1 H), 3.69 - 3.79 (m, 1 H), 3.38 (br s, 1 H), 3.29 (s, 1 H), 3.16 - 3.24 (m, 2 H), 2.98 - 3.06 (m, 2 H), 2.87 (s, 1 H), 2.72 (br s, 1 H), 2.61 - 2.66 (m, 2 H), 2.48 (s, 3 H), 2.33 - 2.43 (m, 1 H), 2.27 (br d, *J*=12.7 Hz, 2 H), 2.00 - 2.07 (m, 1 H), 1.95 (dq, *J*=13.0, 3.3 Hz, 1 H), 1.71 - 1.79 (m, 1 H), 1.64 - 1.70 (m, 4 H), 1.55 - 1.62 (m, 2 H), 1.36 (s, 9 H).

[00412] Step 3. *tert*-Butyl (2*s*,4*r*)-2-((4-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-oxobutyl)carbamoyl)-2-((*tert*-butyldimethylsilyl)oxy)-6-azaspiro[3.5]nonane-6-carboxylate. To a 100-mL round-bottom flask was charged with *tert*-butyl (2*r*,4*s*)-2-((4-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-oxobutyl)carbamoyl)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (2.5 g, 3.9 mmol) in dichloromethane (15 mL) and 2,6-lutidine (0.9 mL, 7.7 mmol). The reaction mixture was cooled to 0 °C and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.97 mL, 4.30 mmol) was added. The reaction mixture was allowed to warm to room temperature with stirring for 3 h. The mixture was quenched with saturated $NaHCO_3$ solution, and the aqueous was extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel, eluting with a gradient of 0–100% of EtOAc in heptane, to afford *tert*-butyl (2*s*,4*r*)-2-((4-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-oxobutyl)carbamoyl)-2-((*tert*-butyldimethylsilyl)oxy)-6-azaspiro[3.5]nonane-6-carboxylate (1.8 g, 2.4 mmol, 61% yield). *m/z* (ESI): 761.3 $(M+H)^+$. ^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 7.96 (d, *J*=0.6 Hz, 1 H), 7.37 (s, 1 H), 7.10 (t, *J*=4.8 Hz, 1 H), 5.67 (dd, *J*=9.2, 2.9 Hz, 1 H), 4.22 (br d, *J*=3.2 Hz, 2 H), 3.97 - 4.07 (m, 1 H), 3.71 - 3.83 (m, 1 H), 3.55 (s, 2 H), 3.32 (br s, 2 H), 3.14 - 3.26 (m, 2 H), 2.67 -

2.73 (m, 2 H), 2.57 (br s, 1 H), 2.52 (d, *J*=0.6 Hz, 3 H), 2.14 - 2.21 (m, 1 H), 2.04 - 2.12 (m, 1 H), 1.94 (s, 1 H), 1.91 (s, 1 H), 1.73 - 1.85 (m, 2 H), 1.66 - 1.71 (m, 3 H), 1.49 - 1.54 (m, 2 H), 1.47 (s, 9 H), 1.30 - 1.35 (m, 1 H), 1.00 (s, 9 H), 0.80 - 0.88 (m, 1 H), 0.19 (s, 6 H).

[00413] Step 4. *tert*-Butyl (2*s*,4*r*)-2-(5-(2-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-2-((*tert*-butyldimethylsilyl)oxy)-6-azaspiro[3.5]nonane-6-carboxylate. To a 40-mL vial was added *tert*-butyl (2*s*,4*r*)-2-((4-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-oxobutyl)carbamoyl)-2-((*tert*-butyldimethylsilyl)oxy)-6-azaspiro[3.5]nonane-6-carboxylate (1.8 g, 2.4 mmol), 2-methyltetrahydrofuran (12 mL), and Burgess Reagent (3.4 g, 14 mmol). The reaction mixture was purged with N_2, then was heated to 75 °C for 2 h. After cooling to room temperature, the reaction mixture was diluted with saturated aqueous NaCl and extracted with EtOAc. The organic extract was washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel, eluting with a gradient of 0–100% of EtOAc in heptane, to afford *tert*-butyl (2*s*,4*r*)-2-(5-(2-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-2-((*tert*-butyldimethylsilyl)oxy)-6-azaspiro[3.5]nonane-6-carboxylate (0.67 g, 0.90 mmol, 38% yield). *m/z* (ESI): 761.3 $(M+H)^+$. ^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 7.98 (d, *J*=0.6 Hz, 1 H), 7.39 (s, 1 H), 6.79 (s, 1 H), 5.68 (dd, *J*=9.2, 2.9 Hz, 1 H), 4.01 - 4.06 (m, 1 H), 3.71 - 3.80 (m, 1 H), 3.32 (br s, 2 H), 3.21 - 3.29 (m, 4 H), 2.87 (br dd, *J*=8.9, 7.6 Hz, 2 H), 2.77 - 2.79 (m, 1 H), 2.76 (s, 1 H), 2.55 (d, *J*=0.6 Hz, 4 H), 2.15 - 2.23 (m, 1 H), 2.06 - 2.13 (m, 3 H), 1.74 - 1.84 (m, 2 H), 1.66 - 1.73 (m, 3 H), 1.49 - 1.56 (m, 2 H), 1.38 (br s, 9 H), 0.90 (s, 9 H), -0.06 (s, 6 H).

[00414] Step 5. *tert*-Butyl (2*s*,4*r*)-2-((*tert*-butyldimethylsilyl)oxy)-2-(5-(2-(6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-6-azaspiro[3.5]nonane-6-carboxylate. A vial was charged with tris(4-methoxyphenyl)phosphine (49 mg, 0.14 mmol), palladium acetate (14 mg, 0.06 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.27 g, 1.10 mmol), cesium carbonate (0.44 g, 1.40 mmol), *tert*-butyl (2*s*,4*r*)-2-(5-(2-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-2-((*tert*-butyldimethylsilyl)oxy)-6-azaspiro[3.5]nonane-6-carboxylate (0.67 g, 0.90 mmol) and ethyl acetate (6 mL), then sparged with N_2. The reaction mixture was heated to 80 °C for 2 h. Upon completion, the reaction mixture was filtered, concentrated, and used directly in the next step without further purification. *m/z* (ESI): 791.5 $(M+H)^+$.

[00415] Step 6. *tert*-Butyl (2*s*,4*r*)-2-(5-(2-(4-(4-(tert-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-2-((*tert*-butyldimethylsilyl)oxy)-6-azaspiro[3.5]nonane-6-carboxylate. A vial was charged with potassium phosphate tribasic (0.57 g, 2.70 mmol), cataCXium A Pd G3 (CAS No. 1651823-59-4) (98 mg, 0.13 mmol), *tert*-butyl (2*s*,4*r*)-2-((*tert*-butyldimethylsilyl)oxy)-2-(5-(2-(6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-

1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-6-azaspiro[3.5]nonane-6-carboxylate (0.71 g, 0.90 mmol), 4-(*tert*-butoxy)-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (**Intermediate C**, 0.48 g, 1.20 mmol), water (0.4 mL) and 2-methyltetrahydrofuran (4 mL). The reaction mixture was sparged with N_2, then heated to 80 °C for 4 h. After cooling to room temperature, the crude material was purified by column chromatography on silica gel, eluting with a gradient of 0–75% of 3:1 EtOAc/EtOH (with 2% Et_3N) in heptane, to afford *tert*-butyl (2*s*,4*r*)-2-(5-(2-(4-(4-(tert-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-2-((*tert*-butyldimethylsilyl)oxy)-6-azaspiro[3.5]nonane-6-carboxylate (0.51 g, 0.49 mmol, 54% yield). ^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 9.19 (d, *J*=4.4 Hz, 1 H), 7.57 (dd, *J*=13.8, 4.8 Hz, 1 H), 7.53 (d, *J*=1.3 Hz, 1 H), 6.57 (dd, *J*=16.3, 2.2 Hz, 1 H), 5.69 - 5.80 (m, 1 H), 5.23 - 5.28 (m, 1 H), 4.22 - 4.39 (m, 2 H), 4.03 - 4.12 (m, 1 H), 3.74 - 3.83 (m, 1 H), 3.37 (d, *J*=3.9 Hz, 1 H), 3.24 - 3.33 (m, 4 H), 3.20 (br s, 2 H), 2.81 - 3.06 (m, 4 H), 2.64 - 2.78 (m, 2 H), 2.52 - 2.62 (m, 5 H), 2.28 (br d, *J*=5.8 Hz, 1 H), 2.13 - 2.25 (m, 4 H), 2.07 - 2.13 (m, 1 H), 2.03 (br d, *J*=12.1 Hz, 1 H), 1.93 - 2.01 (m, 3 H), 1.88 - 1.93 (m, 1 H), 1.82 (s, 9 H), 1.80 (br s, 1 H), 1.76 - 1.78 (m, 2 H), 1.64 - 1.71 (m, 2 H), 1.26 - 1.31 (m, 10 H), 0.83 - 0.86 (m, 9 H), -0.22 - -0.15 (m, 6 H). ^{19}F NMR (471 MHz, *CDCl*$_3$) δ ppm -138.44, -173.05. *m/z* (ESI): 1041.6 $(M+H)^+$.

[00416] Step 7. 7-(5-(2-(2-((2*s*,4*r*)-2-((*tert*-Butyldimethylsilyl)oxy)-6-azaspiro[3.5]nonan-2-yl)oxazol-5-yl)ethyl)-6-methyl-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol dihydrochloride. Hydrogen chloride (4.0 M in dioxane, 3.5 mL, 14 mmol) was added to a solution of *tert*-butyl (2*s*,4*r*)-2-(5-(2-(4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-2-((*tert*-butyldimethylsilyl)oxy)-6-azaspiro[3.5]nonane-6-carboxylate (0.51 g, 0.49 mmol) in dichloromethane (4 mL). The reaction mixture was stirred at room temperature for 1.5 h, was then concentrated to afford 7-(5-(2-(2-((2*s*,4*r*)-2-((*tert*-butyldimethylsilyl)oxy)-6-azaspiro[3.5]nonan-2-yl)oxazol-5-yl)ethyl)-6-methyl-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol dihydrochloride which was taken to the next step without further purification. *m/z* (ESI): 801.4 $(M+H)^+$.

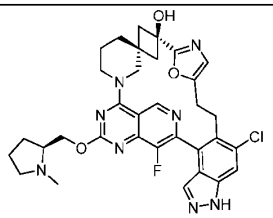
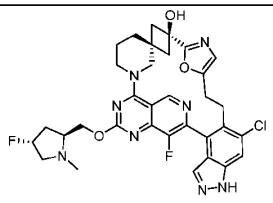
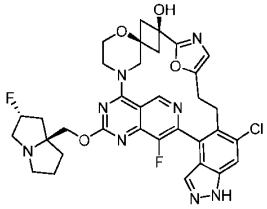
[00417] Step 8. (13*r*,73*R*)-73-((*tert*-Butyldimethylsilyl)oxy)-28-fluoro-22-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-36-methyl-31*H*-6(5,2)-oxazola-2(4,7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-7(1,3)-cyclobutanaheptaphane. A 250-mL round-bottom flask was charged with 7-(5-(2-(2-((2*s*,4*r*)-2-((*tert*-butyldimethylsilyl)oxy)-6-azaspiro[3.5]nonan-2-yl)oxazol-5-yl)ethyl)-6-methyl-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol dihydrochloride

(0.43 g, 0.49 mmol), acetonitrile (89 mL), DMSO (8.9 mL) and DIPEA (8.6 mL, 4.9 mmol). Bromotris(dimethylamino)phosphonium hexafluorophosphate (0.95 g, 2.50 mmol) was added, and the reaction mixutre was stirred at room temperature for 3 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was diluted with water and extracted with EtOAc. The combined organic layeres were dried, filtered, and concentrated. The crude material was purified by reversed phase chromatography on a C18 column, eluting with a gradient of 10–100% CH_3CN (with 0.1% formic acid) in water (with 0.1% formic acid). The desired fractions were combined, diluted with saturated aqueous $NaHCO_3$, and extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated to provide (13*r*,73*R*)-73-((*tert*-butyldimethylsilyl)oxy)-28-fluoro-22-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-36-methyl-31*H*-6(5,2)-oxazola-2(4,7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-7(1,3)-cyclobutanaheptaphane (0.10 g, 0.13 mmol, 26% yield). *m/z* (ESI): 783.4 $(M+H)^+$. ^1H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 13.04 (d, *J*=1.2 Hz, 1 H), 9.01 (s, 1 H), 7.62 - 7.66 (m, 1 H), 7.54 (s, 1 H), 6.53 (d, *J*=1.9 Hz, 1 H), 5.22 - 5.34 (m, 1 H), 4.66 - 4.74 (m, 1 H), 4.57 (br d, *J*=13.5 Hz, 1 H), 3.70 (br d, *J*=13.5 Hz, 1 H), 3.05 - 3.12 (m, 3 H), 2.97 - 3.04 (m, 2 H), 2.78 - 2.92 (m, 2 H), 2.65 - 2.73 (m, 2 H), 2.56 (s, 3 H), 2.10 - 2.13 (m, 1 H), 2.04 - 2.10 (m, 1 H), 1.78 - 1.83 (m, 3 H), 1.62 - 1.71 (m, 3 H), 0.85 (s, 5 H), 0.80 (s, 9 H), -0.03 (s, 3 H), -0.08 (s, 3 H), -0.33 (d, *J*=1.8 Hz, 3 H). ^{19}F NMR (471 MHz, *DMSO-d*$_6$) δ ppm -70.93, -142.33, -172.16.

[00418] Step 9. (1*S*,3*R*)-33-Fluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-11-methyl-34-oxa-5,14,15,20,24,26,28-heptaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaen-3-ol. Tetrabutylammonium fluoride (1 M in THF, 0.2 mL, 0.2 mmol) was added to a solution of (13*r*,73*R*)-73-((*tert*-butyldimethylsilyl)oxy)-28-fluoro-22-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-36-methyl-31*H*-6(5,2)-oxazola-2(4,7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-7(1,3)-cyclobutanaheptaphane (0.10 g, 0.13 mmol) in tetrahydrofuran (1 mL). The mixture was stirred at room temperature for 16 h. The mixture was concentrated and the crude product was purified by reversed phase chromatography to afford (1*S*,3*R*)-33-fluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-11-methyl-34-oxa-5,14,15,20,24,26,28-heptaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaen-3-ol (32 mg, 0.048 mmol, 38% yield). *m/z* (ESI): 669.3 $(M+H)^+$. ^1H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 13.05 (d, *J*=1.0 Hz, 1 H), 9.12 (s, 1 H), 7.67 (d, *J*=1.3 Hz, 1 H), 7.52 (s, 1 H), 6.57 (d, *J*=1.0 Hz, 1 H), 5.88 (s, 1 H), 5.16 - 5.38 (m, 1 H), 4.73 (br d, *J*=11.1 Hz, 1 H), 4.64 (br d, *J*=13.8 Hz, 1 H), 3.99 - 4.22 (m, 2 H), 3.70 (br d, *J*=12.8 Hz, 1 H), 2.99 - 3.14 (m, 4 H), 2.79 - 2.96 (m, 3 H), 2.68 - 2.76 (m, 1 H), 2.56 (s, 3 H), 2.38 (br d, *J*=12.5 Hz, 1 H), 2.20 -

2.30 (m, 1 H), 2.10 - 2.17 (m, 1 H), 2.03 - 2.09 (m, 1 H), 1.97 - 2.03 (m, 1 H), 1.92 - 1.97 (m, 1 H), 1.82 - 1.91 (m, 2 H), 1.60 - 1.80 (m, 7 H). ^{19}F NMR (471 MHz, *CDCl*$_3$) δ ppm -140.27, -173.24.

Table 11: Additional Examples Prepared in an Analogous Manner to Example 1.013.

Cmpd.#	Structure	Name	Reagents	Method Changes
1.014		(1*S*,3*R*)-11-chloro-33-fluoro-25-(((2*S*)-1-methyl-2-pyrrolidinyl)methoxy)-34-oxa-5,14,15,20,24,26,28-heptaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaen-3-ol	**Step 6:** (*S*)-4-(*tert*-butoxy)-7-chloro-8-fluoro-2-((1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-*d*]pyrimidine (**Intermediate L**)	
1.015		(1*S*,3*R*)-11-chloro-33-fluoro-25-(((2*S*,4*R*)-4-fluoro-1-methyl-2-pyrrolidinyl)methoxy)-34-oxa-5,14,15,20,24,26,28-heptaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaen-3-ol	**Step 6.** 4-(*tert*-butoxy)-7-chloro-8-fluoro-2-(((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-*d*]pyrimidine (**Intermediate II**)	
1.053		(1*r*,3*r*)-11-chloro-33-fluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-31,34-dioxa-5,14,15,20,24,26,28-heptaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaen-3-ol	**Step 2.** 1-amino-4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one (**Intermediate I**) and (2*s*,4*s*)-8-(*tert*-butoxycarbonyl)-2-hydroxy-5-oxa-8-azaspiro[3.5]nonane-2-carboxylic acid (**Intermediate JJ**)	**Step 1** was not performed

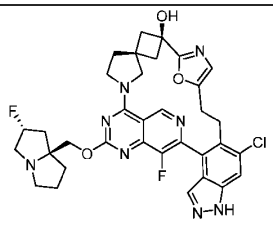
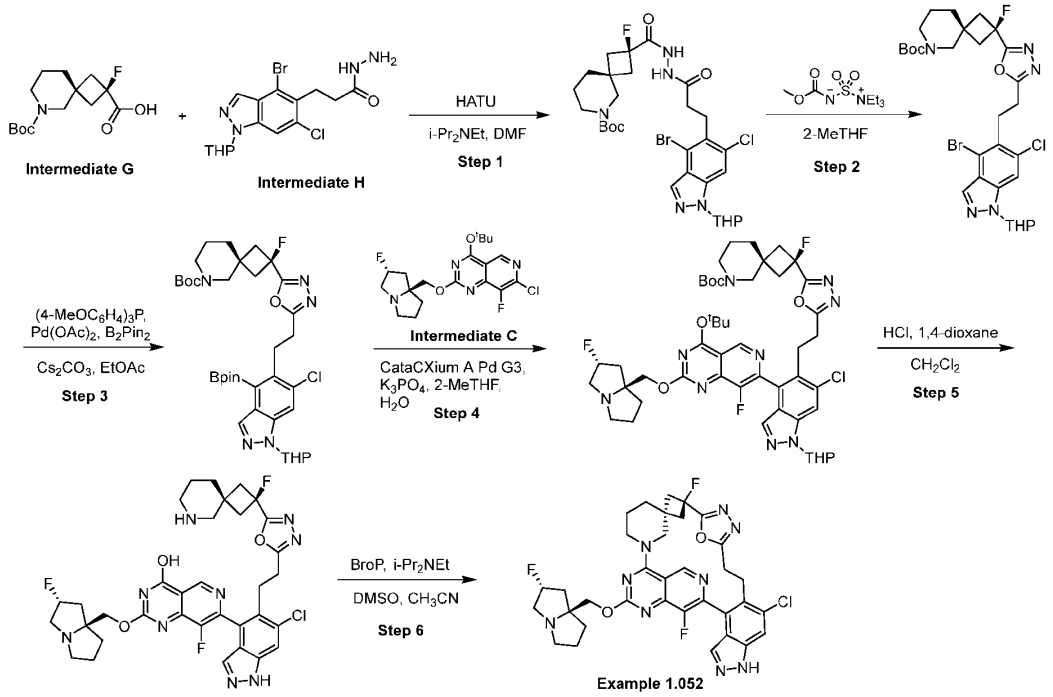
1.058		(17*R*,19*S*)-9-chloro-31-fluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-a]pyrrol-7a(5*H*)-yl)methoxy)-34-oxa-5,6,15,22,24,26,30-heptaazaoctacyclo[25.3.1.1~13,16~.1~17,19~.1~19,22~.0~2,10~.0~3,7~.0~23,28~]tetratriaconta-1(31),2,4,7,9,13,15,23,25,27,29-undecaen-17-ol	**Step 2.** 1-amino-4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one (**Intermediate I**) and (2*S*, 4*R*)-6-(*tert*-Butoxycarbonyl)-2-hydroxy-6-azaspiro[3.4]octane-2-carboxylic acid (**Intermediate ZZ**)	**Step 1** was not performed

Table 12. Analytical Data for Examples in Table 11.

Cmpd.#	MS *m/z* (ESI): $(M+H)^+$	^{1}H NMR
1.014	645.0	^{1}H NMR (400 MHz, *METHANOL-d$_4$*) δ ppm 9.2-9.2 (m, 1H), 7.8-7.9 (m, 2H), 6.6-6.6 (m, 1H), 4.9-5.0 (m, 1H), 4.9-4.9 (m, 1H), 4.7-4.7 (m, 1H), 3.9-4.0 (m, 1H), 3.7-3.8 (m, 2H), 3.1-3.2 (m, 3H), 3.1-3.1 (m, 4H), 3.0-3.1 (m, 2H), 2.8-2.9 (m, 1H), 2.3-2.4 (m, 2H), 2.0-2.1 (m, 5H), 1.8-1.9 (m, 5H). ^{19}F NMR (376 MHz, *METHANOL-d$_4$*) δ ppm -77.2 (s, 9F), -142.7 (s, 1F).
1.015	663.0	^{1}H NMR (400 MHz, *METHANOL-d$_4$*) δ ppm 9.12 (s, 1H), 7.8-7.9 (m, 2H), 6.60 (s, 1H), 5.1-5.3 (m, 1H), 4.9-5.0 (m, 1H), 4.5-4.6 (m, 2H), 3.7-3.8 (m, 1H), 3.4-3.6 (m, 1H), 3.2-3.3 (m, 1H), 3.1-3.2 (m, 3H), 3.0-3.1 (m, 1H), 2.8-2.9 (m, 1H), 2.6-2.7 (m, 1H), 2.4-2.5 (m, 2H), 2.0-2.1 (m, 3H), 1.8-1.9 (m, 3H), 1.7-1.8 (m, 1H), 1.6-1.7 (m, 1H), 1.4-1.5 (m, 1H), 1.2-1.3 (m, 1H), 1.0-1.1 (m, 2H). ^{19}F NMR (376 MHz, *METHANOL-d$_4$*) δ ppm -142.4 (d, 1F), -171.8 (d, 1F).
1.053	691.0	^{1}H NMR (500 MHz, *METHANOL-d$_4$*) δ ppm 9.17 (s, 1H), 7.89 (d, *J* = 0.9 Hz, 1H), 7.82 (s, 1H), 6.63 (s, 1H), 5.69 – 5.52 (m, 1H), 4.95 (br d, *J* = 12.8 Hz, 1H), 4.76 – 4.65 (m, 3H), 4.08 – 3.98 (m, 1H), 3.98 – 3.82 (m, 5H), 3.55 – 3.47 (m, 2H), 3.22 – 3.16 (m, 1H), 3.11 (ddd, *J* = 14.6, 7.2, 7.1 Hz, 1H), 2.96 – 2.90 (m, 1H), 2.86 (dd, *J* = 14.1, 4.3 Hz, 1H), 2.81 – 2.55 (m, 3H), 2.50 – 2.30 (m, 6H), 2.26 – 2.18 (m, 2H), 2.11 – 2.03 (m, 1H). ^{19}F NMR (471 MHz, *METHANOL-d$_4$*) δ ppm -143.87 (s, 1F), -175.26 (d, *J* = 25.8 Hz, 1F).
1.058	674.9	^{1}H NMR (400 MHz, METHANOL-*d$_4$*) δ 9.23 (s, 1H), 8.53 (s, 1H), 8.01 (s, 1H), 7.84 (s, 1H), 6.87 (s, 1H), 5.49 – 5.32 (m, 1H), 4.52 – 4.37 (m, 2H), 4.12 (td, J = 12.1, 7.8 Hz, 1H), 3.97 (br d, J = 11.1 Hz, 1H), 3.84 – 3.75 (m, 1H), 3.57 – 3.40 (m, 4H), 3.20 – 3.15 (m, 2H), 2.94 – 2.83 (m, 1H), 2.75 (d, J = 13.4 Hz, 1H), 2.60 (dd, J = 13.2, 3.8 Hz, 1H), 2.52 – 2.41 (m, 1H), 2.41 – 2.32 (m, 2H), 2.31 – 2.20 (m, 3H), 2.20 – 2.08 (m, 6H), 2.04 – 1.92 (m, 3H). ^{19}F NMR (376 MHz, METHANOL-*d$_4$*) δ -144.26 (d, J = 1.0 Hz, 1F), -173.76 (br d, J = 14.7 Hz, 1F).

Example 1.052: (1*S*,3*R*)-11-Chloro-3,33-difluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-34-oxa-5,6,14,15,20,24,26,28-octaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaene bis(2,2,2-trifluoroacetate).



[00419] Step 1. *tert*-Butyl (2*S*,4*R*)-2-(2-(3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propanoyl)hydrazine-1-carbonyl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate. In a 40-mL vial was charged with (2*S*,4*R*)-6-(*tert*-butoxycarbonyl)-2-fluoro-6-azaspiro[3.5]nonane-2-carboxylic acid (**Intermediate G**, 0.62 g, 2.20 mmol) and 3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propanehydrazide (**Intermediate H**, 0.86 g, 2.20 mmol) in *N*,*N*-dimethylformamide (6 mL). The reaction mixture was stirred at 0 °C, then HATU (0.90 g, 2.40 mmol) was added, followed by diisopropylethylamine (1.1 mL, 6.4 mmol). The reaction mixture was stirred at room temperature for 1 h, then was quenched by the addition of saturated NH_4Cl solution. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0–100% EtOAc in heptane, to provide *tert*-butyl (2*S*,4*R*)-2-(2-(3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propanoyl)hydrazine-1-carbonyl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (0.57 g, 0.85 mmol, 39% yield). *m/z* (ESI): 670.1/672.1 $(M+H)^+$. ^1H NMR (500 MHz, *CDCl*$_3$) δ ppm 8.04 (s, 2H),

8.00 – 7.96 (m, 1H), 7.68 (s, 1H), 5.69 – 5.65 (m, 1H), 4.02 (br d, *J* = 9.7 Hz, 1H), 3.80 – 3.73 (m, 1H), 3.56 – 3.41 (m, 4H), 3.38 – 3.32 (m, 2H), 2.62 – 2.45 (m, 4H), 2.22 – 2.05 (m, 5H), 1.75 (br d, *J* = 8.0 Hz, 5H), 1.53 (br s, 2H), 1.49 – 1.46 (m, 9H). ^{19}F NMR (471 MHz, *CDCl*$_3$) δ ppm -153.01 (br s, 1F).

[00420] Step 2. *tert*-Butyl (2*S*,4*R*)-2-(5-(2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)-1,3,4-oxadiazol-2-yl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate. In a vial was added *tert*-butyl (2*S*,4*R*)-2-(2-(3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propanoyl)hydrazine-1-carbonyl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (0.57 g, 0.85 mmol) and Burgess Reagent (0.81 g, 3.40 mmol) in 2-methyltetrahydrofuran (3 mL). The reaction mixture was purged with nitrogen, then heated at 75 °C for 2 h. After cooling to room temperature, saturated NaCl solution was added and the mixture was extracted by EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 0–100% EtOAc in heptane, to provide *tert*-butyl (2*S*,4*R*)-2-(5-(2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)-1,3,4-oxadiazol-2-yl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (0.16 g, 0.25 mmol, 29% yield). *m/z* (ESI): 651.8/653.8 $(M+H)^+$. ^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 8.00 – 7.98 (m, 1H), 7.70 (d, *J* = 0.8 Hz, 1H), 5.68 (dd, *J* = 9.0, 2.9 Hz, 1H), 4.04 – 3.99 (m, 1H), 3.79 – 3.74 (m, 1H), 3.62 – 3.57 (m, 2H), 3.46 – 3.42 (m, 1H), 3.38 – 3.31 (m, 4H), 3.23 – 3.18 (m, 2H), 2.83 – 2.75 (m, 2H), 2.54 – 2.36 (m, 3H), 2.19 – 2.07 (m, 3H), 1.84 – 1.76 (m, 4H), 1.71 (td, *J* = 8.7, 4.7 Hz, 1H), 1.43 (s, 9H). ^{19}F NMR (471 MHz, *CDCl*$_3$) δ ppm -139.21 (br s, 1F).

[00421] Step 3. *tert*-Butyl (2*S*,4*R*)-2-(5-(2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethyl)-1,3,4-oxadiazol-2-yl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate. A 250-mL round-bottom flask was charged with tris(4-methoxyphenyl)phosphine (10 mg, 0.03 mmol), palladium acetate (5.5 mg, 0.03 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (93 mg, 0.37 mmol), cesium carbonate (0.16 g, 0.49 mmol), *tert*-butyl (2*S*,4*R*)-2-(5-(2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)-1,3,4-oxadiazol-2-yl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (0.16 g, 0.25 mmol) and ethyl acetate (2.5 mL). The reaction mixture was sparged with nitrogen and then heated to 80 °C for 9 h. After cooling to room temperature, the mixture was filtered over celite, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 0–100% EtOAc in heptane, to provide *tert*-butyl (2*S*,4*R*)-2-(5-(2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethyl)-1,3,4-oxadiazol-2-yl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (94 mg, 0.13 mmol, 55% yield). *m/z* (ESI): 700.3 $(M+H)^+$. ^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 8.37 (s, 1H), 7.77 (d, *J* = 0.8 Hz, 1H), 5.67 (dd, *J* = 9.1, 2.9 Hz, 1H), 4.02 – 3.97 (m, 1H), 3.77 – 3.71 (m, 1H), 3.65 – 3.60 (m, 2H), 3.35 – 3.32 (m, 2H), 3.31 (s, 2H), 3.21 – 3.14 (m, 2H), 2.80 – 2.72 (m, 2H), 2.55 – 2.46 (m, 1H), 2.43 – 2.33 (m,

2H), 2.18 – 2.11 (m, 1H), 2.10 – 2.02 (m, 1H), 1.81 – 1.64 (m, 7H), 1.40 (s, 21H). ^{19}F NMR (471 MHz, *CDCl*$_3$) δ ppm -139.22 (br s, 1F).

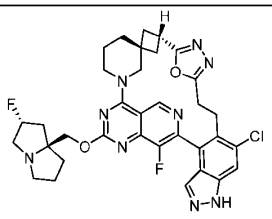
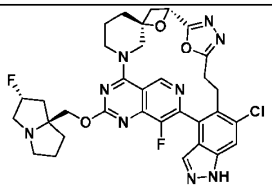
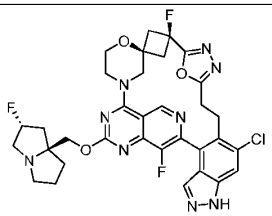
[00422] Step 4. *tert*-Butyl (2*S*,4*R*)-2-(5-(2-(4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)-1,3,4-oxadiazol-2-yl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate. To a suspension of *tert*-butyl (2*S*,4*R*)-2-(5-(2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethyl)-1,3,4-oxadiazol-2-yl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (94 mg, 0.13 mmol) and 4-(*tert*-butoxy)-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (**Intermediate C**, 61 mg, 0.15 mmol) in 2-methyltetrahydrofuran (1.2 mL) and water (0.1 mL) were added potassium phosphate (71 mg, 0.34 mmol) and cataCXium A Pd G3 (CAS No. 1651823-59-4) (20 mg, 0.03 mmol). The reaction mixture was sparged with nitrogen and stirred at 80 °C for 1 h. After cooling to room temperature, the organic layer was separated and concentrated. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0–100% [3:1 EtOAc/EtOH with 2% Et_3N]/heptane, to provide *tert*-butyl (2*S*,4*R*)-2-(5-(2-(4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)-1,3,4-oxadiazol-2-yl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (41 mg, 0.04 mmol, 32% yield). *m/z* (ESI): 950.3 $(M+H)^+$. ^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 9.18 (d, *J* = 1.7 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.58 (s, 1H), 5.73 (br d, *J* = 2.5 Hz, 1H), 5.44 – 5.32 (m, 1H), 4.46 – 4.21 (m, 2H), 4.09 – 4.01 (m, 1H), 3.85 – 3.73 (m, 1H), 3.44 – 3.30 (m, 5H), 3.28 (s, 3H), 3.23 – 3.13 (m, 2H), 3.13 – 2.97 (m, 2H), 2.77 – 2.63 (m, 2H), 2.58 – 2.47 (m, 1H), 2.44 – 2.24 (m, 4H), 2.23 – 2.09 (m, 4H), 2.03 – 1.93 (m, 2H), 1.81 (s, 9H), 1.76 (br t, *J* = 5.7 Hz, 4H), 1.57 – 1.50 (m, 3H), 1.37 (br s, 9H). ^{19}F NMR (376 MHz, *CDCl*$_3$) δ ppm -137.90 – -138.37 (m, 1F), -139.29 – -140.06 (m, 1F), -173.08 (br s, 1F).

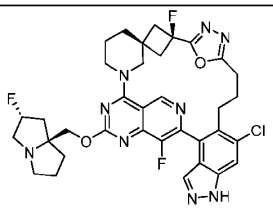
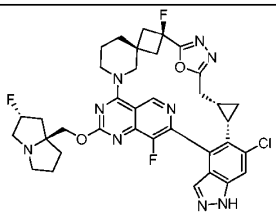
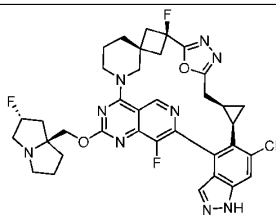
[00423] Step 5. 7-(6-Chloro-5-(2-(5-((2*s*,4*r*)-2-fluoro-6-azaspiro[3.5]nonan-2-yl)-1,3,4-oxadiazol-2-yl)ethyl)-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol. To a solution of *tert*-butyl (2*S*,4*R*)-2-(5-(2-(4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)-1,3,4-oxadiazol-2-yl)-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (44 mg, 0.05 mmol) in dichloromethane (0.5 mL) was added hydrogen chloride (4.0 M in 1,4-dioxane, 0.23 mL, 0.92 mmol). The reaction was stirred vigorously at room temperature for 1 h. Solvent was removed, and the mixture was loaded onto a SCX column with MeOH (9 mL), eluting with 2 M NH_3 in MeOH, to provide 7-(6-chloro-5-(2-(5-((2*S*,4*R*)-2-fluoro-6-azaspiro[3.5]nonan-2-yl)-1,3,4-oxadiazol-2-yl)ethyl)-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol (22

mg, 0.03 mmol, 67% yield). *m/z* (ESI): 710.2 $(M+H)^+$. ^{1}H NMR (500 MHz, *DMSO-d6*) δ ppm 8.83 (s, 1H), 7.82 (s, 1H), 7.63 (s, 1H), 5.38 – 5.17 (m, 1H), 4.01 (br dd, *J* = 10.4, 4.7 Hz, 1H), 3.93 (br dd, *J* = 10.4, 2.4 Hz, 1H), 3.85 – 3.50 (m, 3H), 3.29 – 3.20 (m, 1H), 3.14 – 2.99 (m, 4H), 2.98 – 2.88 (m, 1H), 2.87 – 2.79 (m, 1H), 2.71 – 2.56 (m, 5H), 2.36 – 2.19 (m, 2H), 2.17 – 2.11 (m, 1H), 2.06 – 1.92 (m, 3H), 1.90 – 1.70 (m, 4H), 1.68 – 1.59 (m, 2H), 1.50 – 1.39 (m, 2H). ^{19}F NMR (471 MHz, *DMSO-d6*) δ ppm -137.39 (br s, 1F), -142.11 (br s, 1F), -171.87 (br s, 1F).

[00424] Step 6. (1*S*,3*R*)-11-Chloro-3,33-difluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-34-oxa-5,6,14,15,20,24,26,28-octaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaene bis(2,2,2-trifluoroacetate). To a 40-mL vial was added 1,1'-dimethyltriethylamine (0.02 mL, 0.09 mmol) and bromotris(dimethylamino)phosphonium hexafluorophosphate (18 mg, 0.05 mmol) in acetonitrile (4 mL). A solution of 7-(6-chloro-5-(2-(5-((2*S*,4*R*)-2-fluoro-6-azaspiro[3.5]nonan-2-yl)-1,3,4-oxadiazol-2-yl)ethyl)-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol (22 mg, 0.03 mmol) in dimethyl sulfoxide (0.8 mL) was then added dropwise and the reaction mixture was stirred at room temperature under nitrogen for 30 minutes. The volatiles were concentrated and the resulting mixture was purified by reversed phase HPLC using a C18 column, eluting with 0–50% CH_3CN with 0.1% TFA/water with 0.1% TFA to provide (1*S*,3*R*)-11-chloro-3,33-difluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-34-oxa-5,6,14,15,20,24,26,28-octaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaene bis(2,2,2-trifluoroacetate) (10 mg, 0.01 mmol, 37% yield). *m/z* (ESI): 692.2 $(M+H)^+$. ^{1}H NMR (500 MHz, *METHANOL-d4*) δ ppm 9.27 (s, 1H), 7.90 (d, *J* = 0.9 Hz, 1H), 7.82 (s, 1H), 5.68 – 5.53 (m, 1H), 5.06 (br d, *J* = 12.5 Hz, 1H), 4.76 – 4.66 (m, 2H), 4.10 – 3.98 (m, 1H), 3.98 – 3.85 (m, 4H), 3.54 – 3.46 (m, 1H), 3.41 – 3.35 (m, 1H), 3.30 – 3.15 (m, 3H), 2.81 – 2.67 (m, 2H), 2.67 – 2.61 (m, 1H), 2.60 – 2.54 (m, 1H), 2.54 – 2.31 (m, 6H), 2.27 – 2.14 (m, 1H), 2.11 – 2.02 (m, 2H), 2.01 – 1.94 (m, 1H), 1.88 – 1.80 (m, 2H). ^{19}F NMR (471 MHz, *METHANOL-d4*) δ ppm -77.28 (br s, 6F, TFA), -142.36 (br s, 1F), -143.95 (br s, 1F), -174.14 (br d, *J* = 18.6 Hz, 1F).

Table 13: Additional Examples Prepared in an Analogous Manner to Example 1.052.

Cmpd.#	Structure	Name	Reagents	Method Changes
1.001		(1*R*,3*S*)-11-chloro-33-fluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-34-oxa-5,6,14,15,20,24,26,28-octaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaene diformate	**Step 1**: 6-(*tert*-butoxycarbonyl)-6-azaspiro[3.5]nonane-2-carboxylic acid (CAS# 1374659-03-6, Aurum Pharmatech LLC)	
1.041		(1*S*,3*R*)-11-chloro-33-fluoro-25-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7*a*(5*H*)-yl)methoxy)-2,34-dioxa-5,6,14,15,20,24,26,28-octaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaene	**Step 1.** (4*S*)-6-(*tert*-butoxycarbonyl)-1-oxa-6-azaspiro[3.5]nonane-2-carboxylic acid (**Step 3** in **example 1.038**)	
1.059		(1*R*,3*R*)-11-chloro-3,33-difluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-31,34-dioxa-5,6,14,15,20,24,26,28-octaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaene	**Step 1**: (2*s*,4*s*)-8-(*tert*-butoxycarbonyl)-2-fluoro-5-oxa-8-azaspiro[3.5]nonane-2-carboxylic acid (**Intermediate FF**)	

Cmpd.#	Structure	Name	Reagents	Method Changes
1.055		(1*S*,3*R*)-12-chloro-3,34-difluoro-26-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-35-oxa-5,6,15,16,21,25,27,29-octaazaoctacyclo[27.3.1.1~1,3~.1~4,7~.1~20,24~.0~11,19~.0~14,18~.0~23,28~]hexatriaconta-4,6,11,13,16,18,20(34),21,23,25,27-undecaene	**Step 1**: 4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butanehydrazide (**Intermediate KK**)	
1.068		(1*R*,3*R*,9*S*,11*S*)-13-chloro-3,35-difluoro-27-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-36-oxa-5,6,16,17,22,26,28,30-octaazanonacyclo[28.3.1.1~1,3~.1~4,7~.1~21,25~.0~9,11~.0~12,20~.0~15,19~.0~24,29~]heptatriaconta-4,6,12,14,17,19,21(35),22,24,26,28-undecaene	**Step 1**: *rac*-2-((1*R*,2*R*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)acetohydrazide (**Intermediate LL**)	Chiral separation after **Step 6**. Details included below.
1.069		(1*R*,3*R*,9*R*,11*R*)-13-chloro-3,35-difluoro-27-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-36-oxa-5,6,16,17,22,26,28,30-octaazanonacyclo[28.3.1.1~1,3~.1~4,7~.1~21,25~.0~9,11~.0~12,20~.0~15,19~.0~24,29~]heptatriaconta-4,6,12,14,17,19,21(35),22,24,26,28-undecaene	**Step 1**: *rac*-2-((1*R*,2*R*)-2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)cyclopropyl)acetohydrazide (**Intermediate LL**)	Chiral separation after **Step 6**. Details included below.

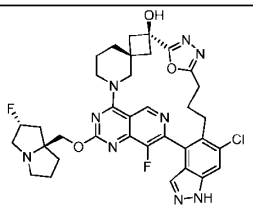
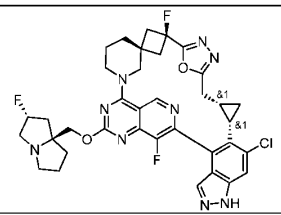
Cmpd.#	Structure	Name	Reagents	Method Changes
1.089		(13*r*,83*R*)-36-chloro-28-fluoro-22-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*pyrrolizin-7a(5*H*)-yl)methoxy)-31*H*-7(2,5)-oxadiazola-2(4,7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-8(1,3)-cyclobutanaoctaphan-83-ol,hexafluorophosphate(V) salt	**Step 4:** Intermediate JJJ, Intermediate MM	**Step 4:** lithium chloride, anhydrous (Sigma-Aldrich) and CuI_2 (Sigma-Aldrich) were used in lieu of K_3PO_4.

Table 14. Analytical Data for Examples in Table 13.

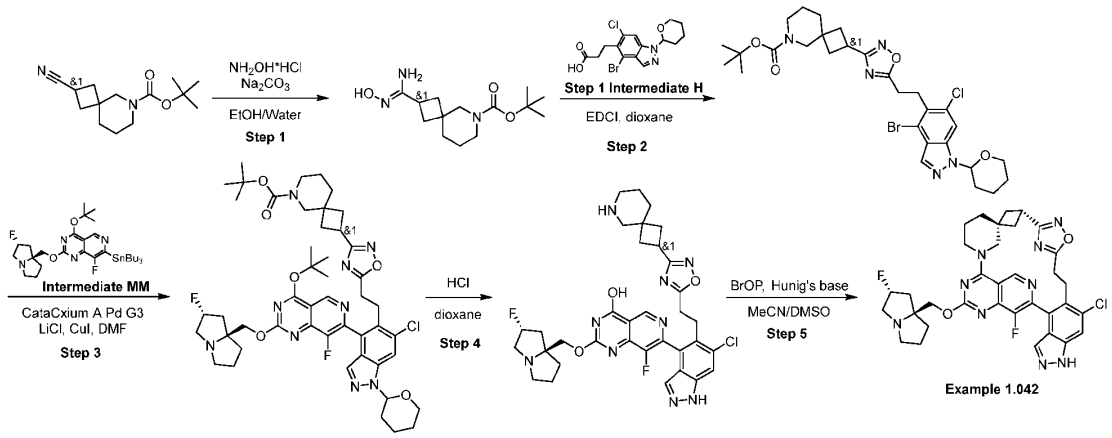
Cmpd.#	MS *m/z* (ESI): $(M+H)^+$	^{1}H NMR
1.001	673.9	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.37 (s, 1H), 7.90 (d, 1H, *J*=7.1 Hz), 7.87 (d, 1H, *J*=0.8 Hz), 5.2-5.5 (m, 1H), 5.0-5.1 (m, 2H), 4.3-4.5 (m, 2H), 3.7-3.8 (m, 2H), 3.3-3.6 (m, 4H), 3.1-3.3 (m, 5H), 2.3-2.4 (m, 4H), 2.2-2.3 (m, 3H), 1.9-2.1 (m, 6H), 1.78 (br s, 3H), 1.57 (br dd, 1H, *J*=5.3, 13.1 Hz).. ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -142.5--142.1 (m, 1F), -173.82 (s, 1F).
1.041	676.2	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.32 - 9.44 (m, 1 H), 8.29 - 8.43 (m, 1 H), 7.87 - 7.92 (m, 2 H), 5.23 - 5.73 (m, 4 H), 4.93 - 5.02 (m, 1 H), 4.50 - 4.64 (m, 4 H), 4.01 -4.11 (m, 1 H), 3.63 - 3.81 (m, 4 H), 3.14 - 3.24 (m, 2 H), 2.83 - 3.08 (m, 2 H), 2.64 - 2.72 (m, 1 H), 2.43 - 2.55 (m, 3 H), 2.23 - 2.37 (m, 3 H), 1.97 - 2.13 (m, 4 H), 1.76 - 1.85 (m, 1 H), 1.28 - 1.39 (m, 2 H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -143.10 - -142.04 (m, 1F), -174.55 - -173.78 (m, 1 F).
1.059	694.2	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.30 (s, 1H), 7.89 (d, *J* = 1.0 Hz, 1H), 7.86 (s, 1H), 5.69 – 5.52 (m, 1H), 5.03 (br d, *J* = 13.8 Hz, 1H), 4.78 – 4.65 (m, 3H), 4.18 – 4.02 (m, 2H), 4.02 – 3.83 (m, 6H), 3.58 – 3.38 (m, 3H), 3.29 – 3.20 (m, 2H), 3.08 – 2.82 (m, 2H), 2.78 – 2.60 (m, 3H), 2.51 – 2.27 (m, 6H), 2.21 (br s, 1H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -78.50 (s, 6F, TFA), -143.54 – -143.62 (m, 1F), -145.49 (br d, *J* = 10.4 Hz, 1F), -175.41 (d, *J* = 3.5 Hz, 1F).
1.055	706.2	^{1}H NMR (500 MHz, *DMSO-d6*) δ ppm 9.09 (s, 1H), 8.97 (s, 1H), 7.88 (s, 1H), 7.70 – 7.70 (m, 2H), 7.61 (s, 1H), 5.68 – 5.50 (m, 1H), 4.71 – 4.57 (m, 2H), 4.41 (br s, 1H), 4.01 – 3.71 (m, 6H), 3.34 – 3.23 (m, 2H), 3.13 – 2.96 (m, 4H), 2.94 – 2.84 (m, 1H), 2.76 – 2.57 (m, 2H), 2.45 – 2.29 (m, 2H), 2.25 – 2.10 (m, 3H), 2.09 – 1.99 (m, 2H), 1.93 (br d, *J* = 5.1 Hz, 2H), 1.84 – 1.64 (m, 3H). ^{19}F NMR (471 MHz, *DMSO-d6*) δ ppm -78.50 (br s, 6F, TFA), -136.60 (br s, 1F), -143.05 (br s, 1F), -177.73 (s, 1F).

Cmpd.#	MS *m/z* (ESI): $(M+H)^+$	^{1}H NMR
1.068	718.0	^{1}H NMR (500 MHz, *METHANOL-d4*) δ ppm 9.09 (d, *J* = 8.2 Hz, 1H), 7.96 (br d, *J* = 11.2 Hz, 1H), 7.94 – 7.84 (m, 1H), 5.40 – 5.24 (m, 1H), 5.15 (br d, *J* = 13.1 Hz, 1H), 4.71 – 4.61 (m, 1H), 4.39 – 4.21 (m, 2H), 3.91 – 3.81 (m, 1H), 3.30 – 3.23 (m, 2H), 3.23 – 3.08 (m, 3H), 3.04 (br d, *J* = 5.7 Hz, 1H), 2.86 – 2.73 (m, 1H), 2.61 – 2.53 (m, 1H), 2.51 – 2.28 (m, 3H), 2.27 – 2.19 (m, 2H), 2.17 – 1.99 (m, 5H), 1.98 – 1.77 (m, 5H), 1.68 – 1.54 (m, 1H), 1.03 – 0.82 (m, 1H), -0.94 – -0.99 (m, 1H). ^{19}F NMR (471 MHz, *METHANOL-d4*) δ ppm -137.42 – -140.51 (m, 1F), -140.65 – -144.69 (m, 1F), -173.57 – -173.93 (m, 1F).
1.069	718.0	^{1}H NMR (500 MHz, *METHANOL-d4*) δ ppm 9.08 (d, *J* = 6.1 Hz, 1H), 7.96 (br d, *J* = 11.9 Hz, 1H), 7.93 – 7.83 (m, 1H), 5.39 – 5.23 (m, 1H), 5.16 – 4.97 (m, 1H), 4.65 (br t, *J* = 12.1 Hz, 1H), 4.37 – 4.21 (m, 2H), 3.84 (br dd, *J* = 17.8, 14.1 Hz, 1H), 3.28 – 3.08 (m, 4H), 3.07 – 2.98 (m, 1H), 2.85 – 2.72 (m, 1H), 2.60 – 2.52 (m, 1H), 2.50 – 2.29 (m, 3H), 2.28 – 2.12 (m, 3H), 2.08 – 1.97 (m, 4H), 1.95 – 1.82 (m, 3H), 1.65 – 1.53 (m, 1H), 1.38 – 1.28 (m, 2H), 1.08 – 0.81 (m, 2H), -0.98 (t, *J* = 6.2 Hz, 1H). ^{19}F NMR (471 MHz, *METHANOL-d4*) δ ppm -137.33 – -140.50 (m, 1F), -140.56 – -144.77 (m, 1F), -173.77 (br s, 1F).
1.089	704	^{1}H NMR (400 MHz, *DMSO-d6*) δ ppm 13.21 - 13.34 (m, 1 H), 8.80 - 8.98 (m, 1 H), 7.77 - 7.94 (m, 1 H), 7.56 - 7.71 (m, 1 H), 6.26 - 6.40 (m, 1 H), 5.27 - 5.58 (m, 1 H), 4.17 - 4.41 (m, 3 H), 3.96 - 4.06 (m, 1 H), 3.84 - 3.91 (m, 1 H), 3.03 - 3.17 (m, 2 H), 2.88 - 3.02 (m, 3 H), 2.77 - 2.86 (m, 1 H), 2.72 (br t, *J* = 6.6 Hz, 1 H), 2.10 - 2.35 (m, 4 H), 1.80 - 2.07 (m, 10 H), 1.52 - 1.78 (m, 3 H), 1.07 - 1.34 (m, 1 H). ^{19}F NMR (376 MHz, *DMSO-d6*) δ ppm -72.67 - -68.22 (m, 6 F), -138.68 - -138.24 (m, 1 F), -172.77 - -172.03 (m, 1 F)

Table 15. Conditions for Chiral SFC Separation.

	Column: Chiralcel OJ, 2 x 25 cm, 5 µm column Mobile phase: 25% iPrOH with 0.2% DEA Flowrate: 80 mL/min. Yield: 525 mg to generate 45.1 mg of peak 1 with an ee of >99% and 25.6 mg of peak 2 with an ee of 96%.	Peak 1: **Example 1.069** Peak 2: **Example 1.068**

Example 1.042: (1*R*,3*S*)-11-Chloro-33-fluoro-25-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7*a*(5*H*)-yl)methoxy)-6-oxa-5,14,15,20,24,26,28,34-octaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,7(34),10,12,15,17,19(33),20,22,24,26-undecaene



[00425] Step 1. *tert*-Butyl (*Z*)-2-(*N*'-hydroxycarbamimidoyl)-6-azaspiro[3.5]nonane-6-carboxylate. To a 40-mL vial was charged with sodium carbonate (0.34 g, 3.20 mmol), *tert*-butyl 2-cyano-6-azaspiro[3.5]nonane-6-carboxylate (0.40 g, 1.60 mmol), hydroxylamine HCl (0.44 g, 6.4 mmol), ethanol (6 mL), and water (4 mL). The reaction mixture was heated to 80 °C for 18 h. After cooling to room temperature, the reaction was concentrated and the residue was diluted with saturated aqueous sodium chloride and extracted with ethyl acetate and dichloromethane. The combined organics were dried over sodium sulfate, filtered, and concentrated to give *tert*-butyl (*Z*)-2-(*N*'-hydroxycarbamimidoyl)-6-azaspiro[3.5]nonane-6-carboxylate (0.45 g, 1.60 mmol, 99% yield). *m/z* (ESI): 284.2 $(M+H)^+$.

[00426] Step 2. *tert*-Butyl 2-(5-(2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)-1,2,4-oxadiazol-3-yl)-6-azaspiro[3.5]nonane-6-carboxylate. To a 40-mL vial was charged with *tert*-butyl (*Z*)-2-(*N*'-hydroxycarbamimidoyl)-6-azaspiro[3.5]nonane-6-carboxylate (0.33 g, 1.20 mmol), 3-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)propanoic acid (**Step 1** in **Intermediate H**, 0.45 g, 1.20 mmol), and 1,4-dioxane (8 mL). To this stirring solution was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.25 g, 1.30 mmol) and the reaction was sealed and heated to 100 °C for 20 h. After cooling to room temperature, the reaction mixture was concentrated and the residue was diluted with ethyl acetate. This solution was washed with aqueous 0.1 M acetic acid, followed by saturated aqueous sodium bicarbonate. The organics were dried (Na_2SO_4), filtered and concentrated and the residue was purified by reversed phase column chromatography, eluting with a gradient of 5–100% 0.1% formic acid in CH_3CN/H_2O, to provide *tert*-butyl 2-(5-(2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)-1,2,4-oxadiazol-3-yl)-6-azaspiro[3.5]nonane-6-carboxylate (0.38 g, 0.59 mmol, 50% yield). *m/z* (ESI): 634.0 $(M+H)^+$.

[00427] Step 3. *tert*-Butyl 2-(5-(2-(4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-chloro-1-(tetrahydro-2*H*-

pyran-2-yl)-1*H*-indazol-5-yl)ethyl)-1,2,4-oxadiazol-3-yl)-6-azaspiro[3.5]nonane-6-carboxylate. To a vial was charged *tert*-butyl 2-(5-(2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)-1,2,4-oxadiazol-3-yl)-6-azaspiro[3.5]nonane-6-carboxylate (0.15 g, 0.23 mmol), 4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-7-(tributylstannyl)pyrido[4,3-*d*]pyrimidine (**Intermediate MM**, 0.28 g, 0.42 mmol), anhydrous lithium chloride (20 mg, 0.46 mmol), and *N,N*-dimethylformamide (1.5 mL). This was sparged with nitrogen for 15 minutes, then cataCXium A Pd G3 (CAS No. 1651823-59-4) (34 mg, 0.046 mmol) and copper(I) iodide (22 mg, 0.12 mmol) were added. The reaction vial was placed on a preheated block (100 °C) and stirred for 3 h. After cooling to room temperature, the reaction mixture was purified by reversed phase column chromatography, eluting with a gradient of 5–100% 0.1% formic acid in CH_3CN/H_2O, to provide *tert*-butyl 2-(5-(2-(4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)-1,2,4-oxadiazol-3-yl)-6-azaspiro[3.5]nonane-6-carboxylate (0.14 g, 0.15 mmol, 65% yield). *m/z* (ESI): 932.4 $(M+H)^+$.

[00428] Step 4. 7-(5-(2-(3-(6-Azaspiro[3.5]nonan-2-yl)-1,2,4-oxadiazol-5-yl)ethyl)-6-chloro-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol. To a 40-mL vial was charged *tert*-butyl 2-(5-(2-(4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)-1,2,4-oxadiazol-3-yl)-6-azaspiro[3.5]nonane-6-carboxylate (0.14 g, 0.15 mmol), dichloromethane (1 mL), and hydrogen chloride (4 M in 1,4-dioxane, 0.95 mL, 3.8 mmol). The reaction mixture was stirred at room temperature for 15 minutes, then was concentrated. The residue was diluted with methanol, absorbed onto a 5g SCX column, and eluted with 2 M ammonia in methanol to give 7-(5-(2-(3-(6-azaspiro[3.5]nonan-2-yl)-1,2,4-oxadiazol-5-yl)ethyl)-6-chloro-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol (69 mg, 0.10 mmol, 65% yield). *m/z* (ESI): 692.2 $(M+H)^+$.

[00429] Step 5. (1*R*,3*S*)-11-Chloro-33-fluoro-25-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7*a*(5*H*)-yl)methoxy)-6-oxa-5,14,15,20,24,26,28,34-octaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,7(34),10,12,15,17,19(33),20,22,24,26-undecaene. To a 250-mL round bottom flask was charged with 7-(5-(2-(3-(6-azaspiro[3.5]nonan-2-yl)-1,2,4-oxadiazol-5-yl)ethyl)-6-chloro-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol (64 mg, 0.092 mmol), dimethylsulfoxide (1.5 mL), acetonitrile (7.5 mL), and *N,N*-diisopropylethylamine (0.05 mL, 0.27 mmol). To this was added with vigorous stirring bromotris(dimethylamino)phosphonium hexafluorophosphate (57 mg, 0.15 mmol). The reaction mixture was stirred at ambient temperature for 1.5 h and then concentrated.The crude material was

purified purified by reversed phase column chromatography, eluting with a gradient of 5–100% 0.1% formic acid in CH_3CN/H_2O, followed by purification by column chromatography on silica gel, eluting with a gradient of 0-100% 3:1 EtOAc/EtOH (with 2% TEA) in heptane, then purification again by reversed phase column chromatography, eluting with a gradient of 5–100% 0.1% formic acid in CH_3CN/H_2O to give (1*R*,3*S*)-11-chloro-33-fluoro-25-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7*a*(5*H*)-yl)methoxy)-6-oxa-5,14,15,20,24,26,28,34-octaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,7(34),10,12,15,17,19(33),20,22,24,26-undecaene formate (5.0 mg, 6.9 μmol, 7% yield). *m/z* (ESI): 674.0 $(M+H)^+$. ^1H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.29-9.36 (m, 1H), 8.48-8.60 (m, 1H), 7.75 – 7.86 (m, 2H), 5.45 – 5.55 (m, 1H), 5.19-5.41 (m, 1H), 5.01-5.12 (m, 1H), 4.09 – 4.38 (m, 2H), 3.49 – 3.78 (m, 2H), 3.12 -3.20 (m, 5H), 2.98 -3.12 (m, 1H), 2.15 – 2.36 (m, 6H), 1.65 – 2.10 (m, 7H), 1.38 – 1.57 (m, 2H), 1.28 – 1.42 (m, 3H), 0.88 – 0.95 (m, 1H) ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -142.9–142.8 (m, 1F), -173.8 - -173.7 (m, 1F).

Table 16: Additional Examples Prepared in an Analogous Manner to Example 1.042.

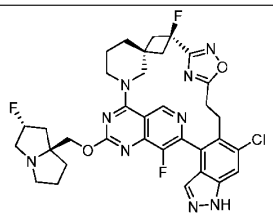
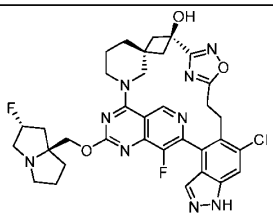
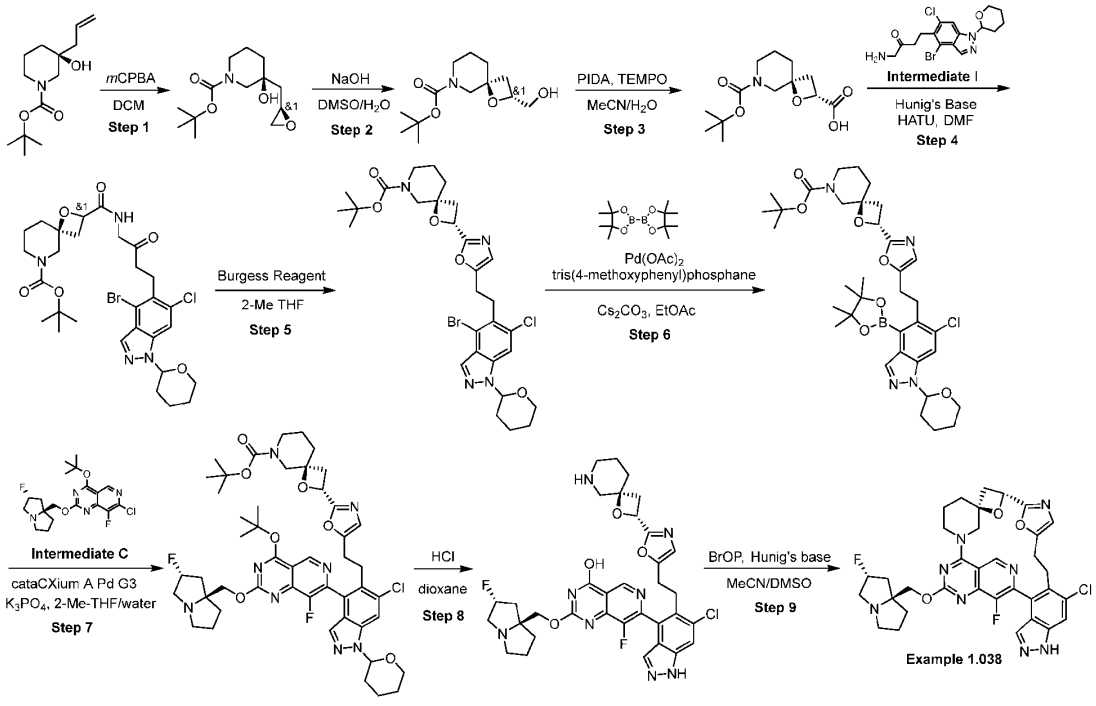
Cmpd.#	Structure	Name	Reagents	Method Changes
1.043		(1*S*,3*R*)-11-chloro-3,33-difluoro-25-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7*a*(5*H*)-yl)methoxy)-6-oxa-5,14,15,20,24,26,28,34-octaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,7(34),10,12,15,17,19(33),20,22,24,26-undecaene	**Step 1.** *tert*-butyl (2*S*,4*R*)-2-cyano-2-fluoro-6-azaspiro[3.5]nonane-6-carboxylate (**Intermediate NN**)	
1.050		(1*S*,3*R*)-11-chloro-33-fluoro-25-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7*a*(5*H*)-yl)methoxy)-6-oxa-5,14,15,20,24,26,28,34-octaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,7(34),10,12,15,17,19(33),20,22,24,26-undecaen-3-ol	**Step 1**. *tert*-butyl 2-((*tert*-butyldiphenylsilyl)oxy)-2-cyano-6-azaspiro[3.5]nonane-6-carboxylate (**Intermediate OO**)	Deprotection of silyl ether after **Step 5** using TMAF in MeCN/THF

Table 17. Analytical Data for Examples in Table 16.

Cmpd.#	MS *m/z* (ESI): $(M+H)^+$	^{1}H NMR
1.043	692.0	^{1}H NMR (400 MHz, *DMSO-d6*) δ ppm 13.16 - 13.65 (m, 1 H), 9.02 - 9.34 (m, 1 H), 7.88 (s, 2 H), 4.74 - 5.46 (m, 3 H), 4.01 - 4.26 (m, 2 H), 3.65 - 3.81 (m, 1 H), 3.25 (br s, 6 H), 2.79 - 2.95 (m, 1 H), 2.40 - 2.50 (m, 2 H), 1.61 - 2.34 (m, 14 H). ^{19}F NMR (376 MHz, *DMSO-d6*) δ ppm -71.86 - -68.91 (m, 6 F), -142.43 - -141.82 (m, 1 F), -143.71 - -143.10 (m, 1 F), -172.18 - -172.08 (m, 1 F).
1.050	690.2	^{1}H NMR (400 MHz, *DMSO-d6*) δ ppm 13.29 – 13.56 (m, 1 H), 9.18 – 9.28 (m, 1 H), 8.10 – 8.19 (m, 1 H), 7.86 – 7.94 (m, 2 H), 5.96 – 6.12 (m, 1 H), 4.77 – 5.54 (m, 3 H), 3.92 – 4.22 (m, 2 H), 3.59 – 3.73 (m, 1 H), 2.99 – 3.31 (m, 10 H), 2.79 – 2.90 (m, 1 H), 2.32 – 2.40 (m, 1 H), 2.01 – 2.25 (m, 4 H), 1.60 – 1.95 (m, 8 H); ^{19}F NMR (376 MHz, *DMSO-d6*) δ ppm -142.44 - -141.97 (m, 1 F), -172.52 - -171.99 (m, 1 F).

Example 1.038: (1*S*,3*R*)-11-Chloro-33-fluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-2,34-dioxa-5,14,15,20,24,26,28-heptaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaene.



[00430] Step 1. *tert*-Butyl (3*S*)-3-hydroxy-3-(oxiran-2-ylmethyl)piperidine-1-carboxylate. To a 250 mL round-bottom flask was charged with *tert*-butyl (*S*)-3-allyl-3-hydroxypiperidine-1-carboxylate (2.50 g, 10.4 mmol, AbovChem) and dichloromethane (70 mL). This was cooled to 0 °C and 3-chloroperoxybenzoic acid (6.96 g, 31.1 mmol) was added. The ice bath was removed and the reaction was allowed to warm to room temperature with stirring for 12 h. Upon completion the reaction was cooled to 0 °C and diluted with an aqueous solution of sodium thiosulfate. The organic layer was washed with saturated aqueous sodium bicarbonate, dried (Na_2SO_4), filtered and concentrated to dryness to yield *tert*-butyl (3*S*)-3-hydroxy-3-(oxiran-2-ylmethyl)piperidine-1-carboxylate (1.88 g, 7.31 mmol, 70% yield) as a mixture of diastereomers. *m/z* (ESI): 280.2 $(M+Na)^+$.

[00431] Step 2. *tert*-Butyl (4*S*)-2-(hydroxymethyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate. To a 250 mL round-bottom flask under nitrogen was charged with *tert*-butyl (3*S*)-3-hydroxy-3-(oxiran-2-ylmethyl)piperidine-1-carboxylate (4.99 g, 19.4 mmol), dimethyl sulfoxide (145 mL), and water (48 mL). To this was added sodium hydroxide (1.55 g, 38.8 mmol) and the reaction mixture was heated to 140 °C for 1 h. After cooling to room temperature, the mixture was diluted with ethyl acetate and saturated aqueous sodium chloride. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and concentrated. The crude oil was purified by column chromatography on silica gel, eluting with a gradient of 0–100% EtOAc in hexane, to yield *tert*-butyl (4*S*)-2-(hydroxymethyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate (1.58 g, 6.14 mmol, 31% yield) as a mixture of diastereomers. *m/z* (ESI): 280.2 $(M+Na)^+$.

[00432] Step 3. (4*S*)-6-(*tert*-Butoxycarbonyl)-1-oxa-6-azaspiro[3.5]nonane-2-carboxylic acid. To a 100 mL round-bottom flask was dissolved *tert*-butyl (4*S*)-2-(hydroxymethyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate (1.28 g, 4.97 mmol) in water (13 mL) and acetonitrile (20 mL). TEMPO (78 mg, 0.50 mmol) and (diacetoxyiodo)benzene (4.01 g, 12.4 mmol) was added, and the reaction mixture was stirred at 60 °C for 2 h. After cooling to room temperature, the mixture was concentrated, and the residue was diluted with EtOAc and saturated aqueous sodium bicarbonate. The EtOAc layer was further washed with saturated aqueous sodium bicarbonate and the combined aqueous layer was cooled to 0 °C and acidified to pH 4-5 using 2 M HCl. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to give (4*S*)-6-(*tert*-butoxycarbonyl)-1-oxa-6-azaspiro[3.5]nonane-2-carboxylic acid (1.52 g, 5.60 mmol, contains iodobenzene impurity). *m/z* (ESI): 294.0 $(M+Na)^+$.

[00433] Step 4. *tert*-Butyl (4*S*)-2-((4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-oxobutyl)carbamoyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate. To a 250 mL round-bottom flask was charged with (4*S*)-6-(*tert*-butoxycarbonyl)-1-oxa-6-azaspiro[3.5]nonane-2-carboxylic acid (2.97 g, 10.9 mmol), 1-amino-4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butan-2-one (**Intermediate I**, 7.90 g, 19.70 mmol), and *N,N*-dimethylformamide (73

mL). The reaction was cooled to 0 °C and HATU (4.99 g, 13.1 mmol) was added. The reaction was stirred for 2 minutes and then diisopropylethylamine (5.7 mL, 33 mmol) was added. The reaction mixture was stirred at room temperature for 1 h and then was diluted with EtOAc and saturated aqueous sodium chloride. The aqueous layer was extracted with ethyl acetate, and the EtOAc layer was washed with saturated aqueous sodium chloride, filtered through sodium sulfate, and concentrated. The crude oil was purified by column chromatography on silica gel, eluting with a gradient of 0–80% 3:1 (EtOAc/EtOH with 1% TEA) in heptanes, to yield *tert*-butyl (4*S*)-2-((4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-oxobutyl)carbamoyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate (4.48 g, 6.85 mmol, 62% yield). *m/z* (ESI): 653.0 $(M+H)^+$.

[00434] Step 5. *tert*-Butyl (2*R*,4*S*)-2-(5-(2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate. In a 40-mL vial was added *tert*-butyl (4*S*)-2-((4-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)-2-oxobutyl)carbamoyl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate (2.24 g, 3.43 mmol) and 2-methyltetrahydrofuran (17 mL). The mixture was purged with nitrogen, Burgess Reagent (4.90 g, 20.6 mmol) was added, and the reaction mixture was heated at 75 °C for 30 minutes. After cooling to room temperature, the mixture was concentrated and the residue was purified by column chromatography on silica gel, eluting with a gradient of 0–100% EtOAc in hexane to provide *tert*-butyl (2*R*,4*S*)-2-(5-(2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate (0.29 g, 0.45 mmol, 13% yield), separated from the other diastereomer, *tert*-butyl (2*S*,4*S*)-2-(5-(2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate. *m/z* (ESI): 635.0 $(M+H)^+$.

[00435] Step 6. *tert*-Butyl (2*R*,4*S*)-2-(5-(2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate. To a 40 mL vial was charged with *tert*-butyl (2*R*,4*S*)-2-(5-(2-(4-bromo-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate (0.57 g, 0.90 mmol), cesium carbonate (0.53 g, 1.60 mmol), palladium(II) acetate (20 mg, 0.09 mmol), bis(pinacalato)diboron (0.34 g, 1.3 mmol), tris(4-methoxyphenyl)phosphine (63 mg, 0.18 mmol), and ethyl acetate (1.8 mL). The reaction mixture was degassed by purging with nitrogen, and then heated to 80 °C for 2.5 h. After cooling to room temperature, the reaction mixture was filtered through celite, washed with EtOAc and the filtrate was concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 0–100% EtOAc in hexane to give *tert*-butyl (2*R*,4*S*)-2-(5-(2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate (0.26 g, 0.37 mmol, 41% yield). *m/z* (ESI): 683.2 $(M+H)^+$.

[00436] Step 7. *tert*-Butyl (2*R*,4*S*)-2-(5-(2-(4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-chloro-1-

(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate. To a 40 mL vial was charged with 4-(*tert*-butoxy)-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)yl)methoxy)pyrido[4,3-*d*]pyrimidine (**Intermediate C**, 0.19 g, 0.45 mmol), *tert*-butyl (2*R*,4*S*)-2-(5-(2-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1.3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate (0.26 g, 0.37 mmol), methanesulfonato(diadamantyl-*n*-butylphosphino)-2'-amino-1,1'-biphenyl-2-yl)palladium(II) dichloromethane adduct (55 mg, 0.075 mmol), potassium phosphate tribasic (0.24 g, 1.10 mmol), 2-methyltetrahydrofuran (2.2 mL), and water (0.2 mL). The reaction mixture was degassed by sparging with nitrogen for 10 minutes and then placed on a preheated 80 °C stir plate with stirring for 1.5 h. After cooling to room temperature, the organic layer was decanted from the aqueous layer and concentrated. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0–65% 3:1 (EtOAc/EtOH with 1% TEA) in heptanes to yield *tert*-butyl (2*R*,4*S*)-2-(5-(2-(4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate (0.30 g, 0.32 mmol, 85% yield). *m/z* (ESI): 933.4 $(M+H)^+$.

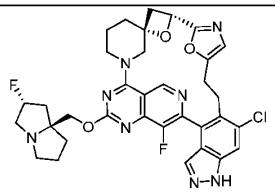
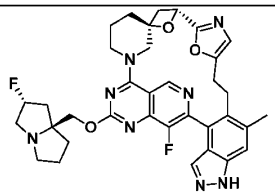
[00437] Step 8. 7-(5-(2-(2-((2*R*,4*S*)-1-Oxa-6-azaspiro[3.5]nonan-2-yl)oxazol-5-yl)ethyl)-6-chloro-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol. To a 40-mL vial was charged with *tert*-butyl (2*R*,4*S*)-2-(5-(2-(4-(4-(*tert*-butoxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)ethyl)oxazol-2-yl)-1-oxa-6-azaspiro[3.5]nonane-6-carboxylate (0.30 g, 0.32 mmol), dichloromethane (2 mL), and hydrochloric acid (4 M in 1,4-dioxane, 2.8 mL, 11.2 mmol). The reaction mixture was stirred at room temperature for 30 minutes, was then concentrated. The residue was loaded onto a SCX column with methanol, and eluted with 2 M ammonia in methanol to give 7-(5-(2-(2-((2*R*,4*S*)-1-oxa-6-azaspiro[3.5]nonan-2-yl)oxazol-5-yl)ethyl)-6-chloro-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol (0.16 g, 0.22 mmol, 71% yield). *m/z* (ESI): 693.0 $(M+H)^+$.

[00438] Step 9. (1*S*,3*R*)-11-Chloro-33-fluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-2,34-dioxa-5,14,15,20,24,26,28-heptaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaene. To a 150 mL round-bottom flask was charged with 7-(5-(2-(2-((2*R*,4*S*)-1-oxa-6-azaspiro[3.5]nonan-2-yl)oxazol-5-yl)ethyl)-6-chloro-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol (0.15 g, 0.22 mmol), dimethylsulfoxide (3.3 mL), acetonitrile (16 mL), and *N*,*N*-diisopropylethylamine (0.11 mL, 0.66 mmol). To this was added with vigorous stirring

bromotris(dimethylamino)phosphonium hexafluorophosphate (0.14 g, 0.35 mmol). The reaction mixture was stirred at room temperature for 1.5 h and then concentrated. The crude material was purified by reversed phase column chromatography on a C18 column, eluting with a gradient of 5–100% 0.1% formic acid in CH_3CN/H_2O, to yield (1*S*,3*R*)-11-chloro-33-fluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-2,34-dioxa-5,14.15,20,24,26,28-heptaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaene (40 mg, 0.059 mmol, 26% yield). *m/z* (ESI): 674.8 $(M+H)^+$. ^1H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.12 – 9.47 (m, 1 H), 7.80 – 7.97 (m, 2 H), 6.59 – 7.10 (m, 1 H), 5.21 – 5.45 (m, 3 H), 4.36 (s, 3 H), 3.14 – 3.29 (m, 5 H), 2.96 – 3.08 (m, 2 H), 2.58 – 2.85 (m, 2 H), 2.34 – 2.48 (m, 2 H), 1.74 – 2.25 (m, 9 H), 1.27 – 1.37 (m, 3 H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -143.01 – -142.03 (m, 1 F), -174.01 – -173.49 (m, 1 F). Stereochemistry was confirmed by x-ray crystallographic analysis.

[00439] Alternate Conditions. To a mixture of intermediate (0.2 mmol) in DCM (3 mL) was added DAST (0.1 mL, 0.5 mmol) in DCM (3 mL) dropwise at 0 °C, and the reaction mixture stirred at 0 °C for 1 hr. The reaction mixture was diluted with H_2O (20 mL) and extracted with DCM (2 x 20 mL), then the combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered and concentrated to give a residue which was purified by prep-HPLC eluting with a gradient of 50-80% ACN in H_2O (10 mM NH_4HCO_3) to provide desired product.

Table 18: Additional Examples Prepared in an Analogous Manner to Example 1.038.

Cmpd.#	Structure	Name	Reagents	Method Changes
1.048		(1*R*,3*R*)-11-chloro-33-fluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-2,34-dioxa-5,14,15,20,24,26,28-heptaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaene	**Step 1:** *tert*-butyl 3-allyl-3-hydroxypiperidine-1-carboxylate (CAS#: 1331825-48-9, PharmaBlock)	Chiral separation after **Step 6**. Details included below.
1.047		(1*S*,3*R*)-33-fluoro-25-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7*a*(5*H*)-yl)methoxy)-11-methyl-2,34-dioxa-5,14,15,20,24,26,28-	**Step 4.** 1-amino-4-(4-bromo-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-	

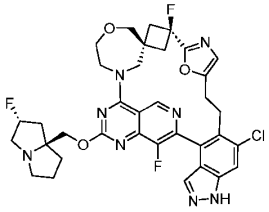
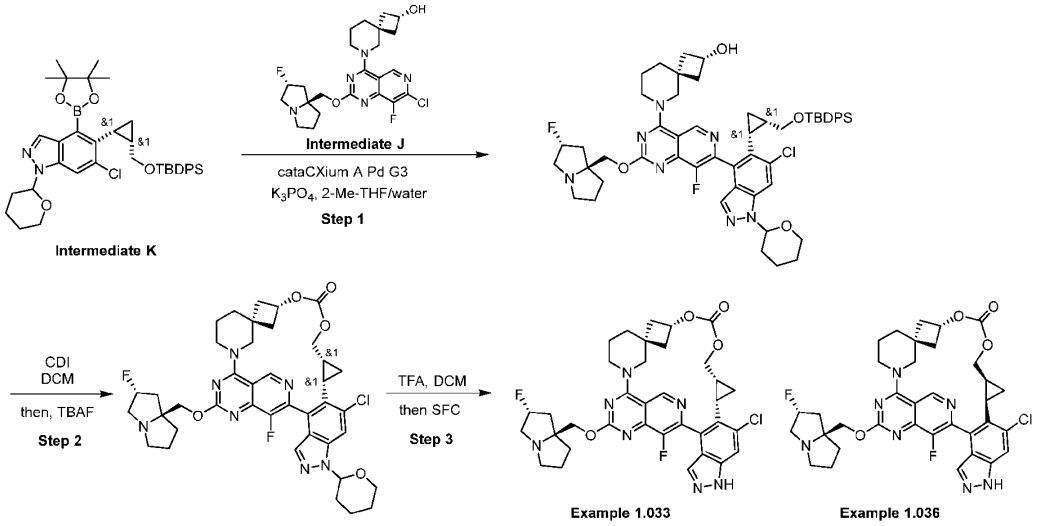
		heptaazaoctacyclo[26.3.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]pentatriaconta-4,6,10,12,15,17,19(33),20,22,24,26-undecaene	yl)butan-2-one (**Step 1** in **Example 1.013**)	
1.072		(1*R*,3*R*)-11-chloro-3,34-difluoro-25-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-31,35-dioxa-5,14,15,20.24,26,28-heptaazaoctacyclo[26.4.1.1~1,3~.1~4,7~.1~19,23~.0~10,18~.0~13,17~.0~22,27~]hexatriaconta-4,6,10,12,15,17,19(34),20,22,24,26-undecaene	**Step 4**: (2*s*,4*s*)-9-(*tert*-butoxycarbonyl)-2-fluoro-6-oxa-9-azaspiro[3.6]decane-2-carboxylic acid (**Intermediate PP**)	

Table 19. Analytical Data for Examples in Table 18.

Cmpd.#	MS *m/z* (ESI): $(M+H)^+$	^{1}H NMR
1.048	674.8	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.12 - 9.37 (m, 1H), 7.81 - 7.93 (m, 2H), 6.65 - 6.82 (m, 1H), 5.29 - 5.42 (m, 3H), 4.81 - 4.95 (m, 2H), 4.30 (br s, 2H), 3.84 - 4.18 (m, 1H), 3.14 - 3.28 (m, 6H), 2.92 - 3.06 (m, 2H), 2.32 - 2.88 (m, 3H), 2.13 - 2.30 (m, 2H), 1.81 - 2.07 (m, 4H), 1.62 - 1.81 (m, 1H), 1.30 - 1.39 (m, 3H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -142.29 (s, 1F), -173.82 (s, 1F).
1.047	655.2	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.21 - 9.44 (m, 1 H), 7.72 - 7.82 (m, 1 H), 7.50 - 7.67 (m, 1 H), 6.68 - 6.93 (m, 1 H), 5.20 - 5.55 (m, 3 H), 4.88 - 4.99 (m, 1 H), 4.43 - 4.61 (m, 2 H), 3.79 - 4.08 (m, 1 H), 3.48 - 3.74 (m, 3 H), 3.08 - 3.31 (m, 3 H), 2.73 - 3.07 (m, 3 H), 2.67 (s, 2 H), 2.63 - 2.66 (m, 3 H), 2.35 - 2.62 (m, 5 H), 2.12 - 2.34 (m, 4 H), 1.87 - 2.11 (m, 3 H), 1.74 - 1.88 (m, 1 H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -142.99 - -142.48 (m, 1 F), -174.26 - -173.75 (m, 1 F).
1.072	707.1	^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.29 (s, 1H), 7.89 (d, *J* = 1.0 Hz, 1H), 7.76 (s, 1H), 6.74 (s, 1H), 5.69 – 5.50 (m, 1H), 5.05 (br d, *J* = 14.6 Hz, 1H), 4.70 (quin, *J* = 12.3 Hz, 2H), 4.49 – 4.40 (m, 2H), 4.12 – 3.83 (m, 9H), 3.53 – 3.46 (m, 1H), 3.31 – 3.25 (m, 1H), 3.14 – 2.96 (m, 2H), 2.84 – 2.56 (m, 4H), 2.50 – 2.33 (m, 5H), 2.27 – 2.14 (m, 1H), 2.06 – 1.94 (m, 1H). ^{19}F NMR (376 MHz, *METHANOL-d44*) δ ppm -78.50 (s, 6F, TFA), -138.69 (br s, 1F), -142.98 (d, *J* = 17.3 Hz, 1F), -175.19 – -175.33 (m, 1F).

Example 1.033 and 1.036: (1*S*,3*S*,8*R*,10*S*)-12-Chloro-34-fluoro-26-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-4,6-dioxa-15,16,21,25,27,29-

hexaazaoctacyclo[27.3.1.1~1,3~.1~20,24~.0~8,10~.0~11,19~.0~14,18~.0~23,28~]pentatriaconta-11,13,16,18,20(34),21,23,25,27-nonaen-5-one and (1*R*,3*S*,8*S*,10*R*)-12-chloro-34-fluoro-26-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-4,6-dioxa-15,16,21,25,27,29-hexaazaoctacyclo[27.3.1.1~1,3~.1~20,24~.0~8,10~.0~11,19~.0~14,18~.0~23,28~]pentatriaconta-11,13,16,18,20(34),21,23,25,27-nonaen-5-one.



[00440] Step 1. *rac*-(2*S*,4*S*)-6-(7-((4*R*)-5-((1*RS*,2*SR*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)cyclopropyl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol. To a suspension of *rac*-5-((1*S*,2*R*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopropyl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole (**Intermediate K**, 3.57 g, 5.31 mmol) and (2*S*,4*S*)-6-(7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol (**Intermediate J**, 1.70 g, 3.54 mmol) in 2-methyltetrahydrofuran (11 mL) and water (1.1 mL) were added potassium phosphate tribasic (2.26 g, 10.6 mmol) and cataCXium A Pd G3 (CAS No. 1651823-59-4) (0.39 g, 0.53 mmol). The reaction mixture was sparged with argon and stirred at 80 °C for 2 h. After cooling to room temperature, the reaction mixture was directly loaded onto a C18 column, eluting with a gradient of 5–100% (0.1% formic acid MeCN)/(0.1% formic acid water). The desired fractions were basified and extracted with EtOAc to provide *rac*-(2*S*,4*S*)-6-(7-((4*R*)-5-((1*RS*,2*SR*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopropyl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol (1.5 g, 1.5 mmol, 43% yield). *m/z* (ESI): 988.0 $(M+H)^+$.

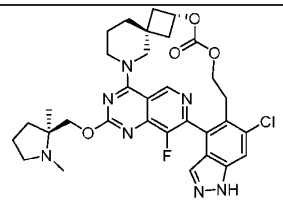
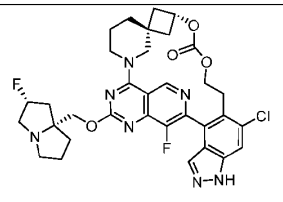
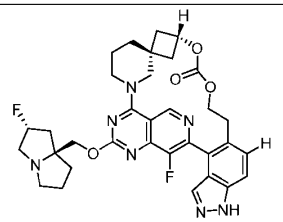
[00441] Step 2. *rac*-(1*S*,3*S*,8*R*,10*S*)-12-Chloro-34-fluoro-26-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-*N*-(tetrahydro-2*H*-pyran-2-yl)-4,6-dioxa-15,16,21,25,27,29-hexaazaoctacyclo[27.3.1.1~1,3~.1~20,24~.0~8,10~.0~11,19~.0~14,18~.0~23,28~]pentatriaconta-11,13,16,18,20(34),21,23,25,27-nonaen-5-one. To a solution of *rac*-(2*S*,4*S*)-6-(7-((4*R*)-5-((1*RS*,2*SR*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopropyl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol (1.7 g, 1.7 mmol) in 2-methyltetrahydrofuran (11 mL) was added CDI (0.84 g, 5.20 mmol). The reaction was stirred at 50 °C for 20 minutes was then transferred to a 250-mL round bottom flask and diluted with 2-MeTHF (100 mL). Tetrabutylammonium fluoride (1 M in THF, 6.9 mL, 6.9 mmol) was added, and the reaction was stirred at 40 °C for 48 h. The reaction mixture was concentrated, and the residue was loaded onto a C18 column, eluting with a gradient of 5–100% (0.1% formic acid MeCN)/(0.1% formic acid water). The desired fractions were basified, extracted with EtOAc, and concentrated. The crude product was purified by column chromatography on silica gel, eluting with a gradient of 40–100% (3:1 EtOH/EtOAc + 2% Et_3N) in heptane, to provide *rac*-(1*S*,3*S*,8*R*,10*S*)-12-chloro-34-fluoro-26-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-*N*-(tetrahydro-2*H*-pyran-2-yl)-4,6-dioxa-15,16,21,25,27,29-hexaazaoctacyclo[27.3.1.1~1,3~.1~20,24~.0~8,10~.0~11,19~.0~14,18~.0~23,28~]pentatriaconta-11,13,16,18,20(34),21,23,25,27-nonaen-5-one (0.28 g, 0.37 mmol, 21% yield). *m/z* (ESI): 776.2 $(M+H)^+$.

[00442] Step 3. (1*S*,3*S*,8*R*,10*S*)-12-Chloro-34-fluoro-26-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-4,6-dioxa-15,16,21,25,27,29-hexaazaoctacyclo[27.3.1.1~1,3~.1~20,24~.0~8,10~.0~11,19~.0~14,18~.0~23,28~]pentatriaconta-11,13,16,18,20(34),21,23,25,27-nonaen-5-one and **(1*R*,3*S*,8*S*,10*R*)-12-chloro-34-fluoro-26-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-4,6-dioxa-15,16,21,25,27,29-hexaazaoctacyclo[27.3.1.1~1,3~.1~20,24~.0~8,10~.0~11,19~.0~14,18~.0~23,28~]pentatriaconta-11,13,16,18,20(34),21,23,25,27-nonaen-5-one.** A vial was charged with *rac*-(1*S*,3*S*,8*R*,10*S*)-12-chloro-34-fluoro-26-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-*N*-(tetrahydro-2*H*-pyran-2-yl)-4,6-dioxa-15,16,21,25,27,29-hexaazaoctacyclo[27.3.1.1~1,3~.1~20,24~.0~8,10~.0~11,19~.0~14,18~.0~23,28~]pentatriaconta-11,13,16,18,20(34),21,23,25,27-nonaen-5-one (0.28 g, 0.37 mmol) and dichloromethane (3.5 mL). 2,2,2-Trifluoroacetic acid (0.7 mL, 9.2 mmol) was added dropwise, and then the reaction mixture was stirred at room temperature for 2 h. The volatiles were removed under reduced pressure and the residue was purified by reversed phase chromatography on a C18 column, eluting with a gradient of

10–40% (0.1% formic acid MeCN)/(0.1% formic acid water), then via SFC using a Chiralcel OD, 2 x 25 cm, 5 µm column with a mobile phase of 40% MeOH with 0.2% DEA using a flowrate of 80 mL/min to generate peak 1 as (1*R*,3*S*,8*S*,10*R*)-12-chloro-34-fluoro-26-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-4,6-dioxa-15,16,21,25,27,29-hexaazaoctacyclo[27.3.1.1~1,3~.1~20,24~.0~8,10~.0~11,19~.0~14,18~.0~23,28~]pentatriaconta-11,13,16,18,20(34),21,23,25,27-nonaen-5-one (21 mg, 0.03 mmol, 8% yield). *m/z* (ESI): 692.3 $(M+H)^+$. ^{1}H NMR (500 MHz, *METHANOL-d4*) δ ppm 9.35 – 9.24 (m, 1H), 7.84 (s, 1H), 5.43 – 5.19 (m, 1H), 5.15 – 5.02 (m, 1H), 4.99 – 4.90 (m, 1H), 4.44 – 4.22 (m, 2H), 3.91 – 3.80 (m, 1H), 3.29 – 3.16 (m, 4H), 3.16 – 2.94 (m, 2H), 2.55 – 2.41 (m, 1H), 2.41 – 2.12 (m, 4H), 2.10 – 1.96 (m, 3H), 1.96 – 1.87 (m, 1H), 1.87 – 1.67 (m, 5H), 1.51 – 1.44 (m, 1H), 1.37 – 1.28 (m, 3H), 1.26 – 1.17 (m, 1H), 1.02 – 0.83 (m, 1H), 0.79 – 0.69 (m, 1H). ^{19}F NMR (471 MHz, *METHANOL-d4*) δ ppm -136.92 (br s, 1F), -173.12 – -175.12 (m, 1F). Also isolated peak 2 as (1*S*,3*S*,8*R*,10*S*)-12-chloro-34-fluoro-26-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-4,6-dioxa-15,16,21,25,27,29-hexaazaoctacyclo[27.3.1.1~1,3~.1~20,24~.0~8,10~.0~11,19~.0~14,18~.0~23,28~]pentatriaconta-11,13,16,18,20(34),21,23,25,27-nonaen-5-one (22 mg, 0.032 mmol, 9% yield). *m/z* (ESI): 692.3 $(M+H)^+$. ^{1}H NMR (500 MHz, *METHANOL-d4*) δ ppm 9.34 – 9.23 (m, 1H), 7.84 (s, 1H), 5.41 – 5.22 (m, 1H), 5.06 (br d, J = 13.8 Hz, 1H), 4.96 – 4.89 (m, 1H), 4.38 (d, J = 10.5 Hz, 1H), 4.25 (d, J = 10.5 Hz, 1H), 3.87 – 3.79 (m, 1H), 3.30 – 3.15 (m, 5H), 3.08 – 2.99 (m, 1H), 2.48 (q, J = 8.1 Hz, 1H), 2.39 – 2.20 (m, 3H), 2.18 – 2.11 (m, 1H), 2.06 – 1.97 (m, 3H), 1.94 – 1.88 (m, 1H), 1.86 – 1.70 (m, 5H), 1.54 – 1.44 (m, 1H), 1.35 – 1.26 (m, 3H), 1.24 – 1.19 (m, 1H), 0.97 – 0.86 (m, 1H), 0.79 – 0.69 (m, 1H). ^{19}F NMR (471 MHz, *METHANOL-d4*) δ ppm -139.59 - -135.34 (m, 1 F), -177.05 - -170.49 (m, 1 F).

Table 20: Additional Examples Prepared in an Analogous Manner to Example 1.033 and 1.036.

Cmpd.#	Structure	Name	Reagents	Method Changes

1.032		**(1*R*,3*S*)-10-chloro-24-(((2*S*)-1,2-dimethyl-2-pyrrolidinyl)methoxy)-32-fluoro-4,6-dioxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-5-one**	**Step 1.** (2*S*,4*s*)-6-(7-chloro-2-(((*S*)-1,2-dimethylpyrrolidin-2-yl)methoxy)-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol (**Intermediate QQ**) and 5-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole (**Intermediate RR**)	
1.019		**(1*S*,3*R*)-10-chloro-32-fluoro-24-(((2*R*,7a*R*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-4,6-dioxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-5-one**	**Step 1.** 5-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole (**Intermediate RR**) and (2*r*,4*s*)-6-(7-chloro-8-fluoro-2-(((2*R*,7a*R*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol (**Intermediate SS**)	
1.025		**(1*R*,3*S*)-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-4,6-dioxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-5-one**	**Step 1.** 5-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole (**Intermediate TT**)	

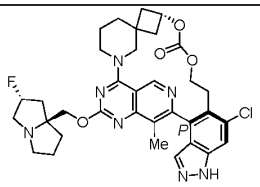
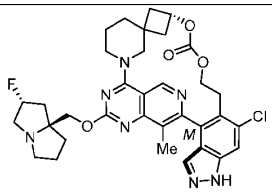
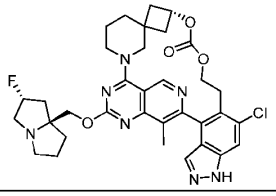
1.022		***p*-(1*R*,3*S*)-10-chloro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-32-methyl-4,6-dioxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-5-one**	**Step 1.** 5-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole **(Intermediate RR)** and (2*r*,4*s*)-6-(7-chloro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5H)-yl)methoxy)-8-methylpyrido[4,3-d]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol **(Intermediate UU)**	
1.029		***m*-(1*R*,3*S*)-10-chloro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-32-methyl-4,6-dioxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-5-one**	**Step 1.** 5-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole **(Intermediate RR)** and (2*r*,4*s*)-6-(7-chloro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5H)-yl)methoxy)-8-methylpyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol **(Intermediate UU)**	

Table 21. Analytical Data for Examples in Table 20.

Cmpd.#	**MS** *m/z* (ESI): $(M+H)^+$	**^{1}H NMR and 19F**
1.048	635.9	^{1}H NMR (400 MHz, *METHANOL-d$_4$*) δ ppm 9.21 – 9.39 (m, 1 H), 7.90 (d, *J*=0.6 Hz, 1 H), 7.81(d, J=0.8 Hz, 1 H), 5.06 (br d, *J*=13.6 Hz, 1 H), 4.88 – 4.98 (m, 2 H), 4.67 – 4.74 (m, 3 H), 3.78 – 3.92 (m, 2 H), 3.72 – 3.78 (m, 1 H), 3.35 – 3.59 (m, 2 H), 3.07 – 3.31 (m, 2 H), 2.93 – 3.04 (m, 3H), 2.72 – 2.92 (m, 1 H), 2.33 (br d, *J*=5.4 Hz, 1 H), 1.98 – 2.27 (m, 6 H), 1.86 (br s, 1 H), 1.67 – 1.86 (m, 6 H), 1.53 (br s, 3 H), 1.06 (br dd, *J*=14.1, 4.5 Hz, 1 H). ^{19}F NMR (376 MHz, *METHANOL-d$_4$*) δ ppm -143.09 – -142.59 (m, 1 F), -77.35 (s, 6 F).

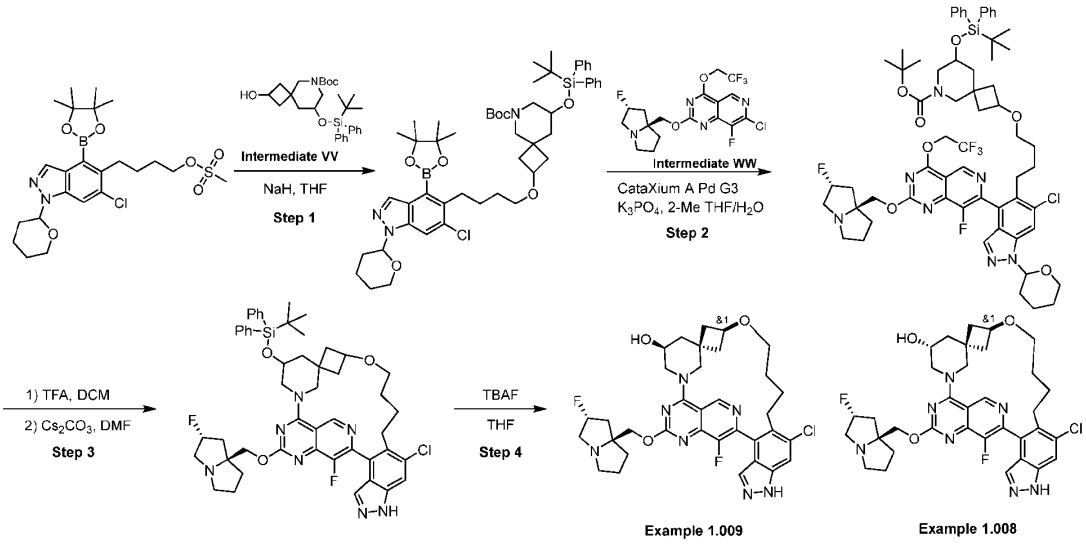
Cmpd.#	MS *m/z* (ESI): $(M+H)^+$	^{1}H NMR and 19F
1.047	666.2	^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 10.19 - 10.57 (m, 1 H), 9.16 (s, 1 H), 7.88 (s, 1 H), 7.73 (s, 1 H), 5.27 - 5.45 (m, 1 H), 5.07 (d, *J*=13.6 Hz, 1 H), 4.97 (d, *J*=10.0 Hz, 1 H), 4.80 - 4.86 (m, 1 H), 4.64 (t, *J*=6.4 Hz, 1 H), 4.23 - 4.60 (m, 2 H), 3.79 (t, *J*=10.4 Hz, 1 H), 3.51 (d, *J*=13.2 Hz, 1 H), 3.38 - 3.46 (m, 1 H), 3.15 - 3.34 (m, 1 H), 2.96 - 3.04 (m, 1 H), 2.79 - 2.90 (m, 2 H), 2.61 - 2.78 (m, 2 H), 2.08-2.15 (m, 1 H), 1.88 - 2.01(m, 4 H), 1.64 - 1.86 (m, 8 H), 1.02 (d, *J*=14.0 Hz, 1 H).
1.072	632.3	^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 9.16 (s, 1H),7.97 (s, 1H),7.59 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 5.33 (d, *J* = 52.0 Hz, 1H), 5.07 (d, *J* = 12.0 Hz, 1H), 4.93 (d, *J* = 20.0 Hz, 1H), 4.81 (d, *J* = 8.0 Hz, 1H), 4.65-4.75 (m, 1H), 4.20-4.40 (m, 2H), 3.70-3.85 (m, 1H), 3.57 (d, *J* = 16.0 Hz, 1H), 3.20-3.50 (m, 4H), 2.95-3.20 (m, 5H), 2.15-2.40 (m, 4H), 1.85-2.20 (m, 8H), 1.00-1.10 (m, 1H). ^{19}F NMR (377 MHz, *CDCl$_3$*) δ ppm -141.20 (s, 1F), -173.08 (s, 1F).
1.048	662.3	^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 10.00-10.51(m, 1H), 9.24 (s, 1H), 7.77 (s, 1H), 7.68 (s, 1H), 5.28-5.48 (m, 1H), 5.19 (d, *J*=13.13 Hz, 1H), 4.97 (d, *J*=11.38 Hz, 1H), 4.74-4.78 (m, 1H), 4.70 (t, *J*=6.44 Hz, 1H), 4.38-4.52 (m, 1H), 3.89-3.99 (m, 1H), 3.58 (d, *J*=13.01 Hz, 1H), 3.20-3.47 (m, 3H), 3.03-3.15 (m, 1H), 2.91-3.02 (m, 1H), 2.50-2.63 (m, 1H), 2.33-2.48 (m, 2H), 2.27 (s, 3H), 1.97-2.14 (m, 4H), 1.87-1.92 (m, 1H), 1.82-1.85 (m, 1H), 1.64-1.76 (m, 6H), 1.24-1.33 (m, 1H), 1.13-1.17 (m, 1H).
1.047	662.3	^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 10.00-10.51(m, 1H), 9.24 (s, 1H), 7.76 (s, 1H), 7.68 (s, 1H), 5.25-5.47 (m, 1H), 5.18 (d, *J*=12.88 Hz, 1H), 4.97 (d, *J*=11.88 Hz, 1H), 4.75-4.90 (m, 1H), 4.70 (t, *J*=6.50 Hz, 1H), 4.35-4.56 (m, 1H), 3.87-3.99 (m, 1H), 3.58 (d, *J*=13.13 Hz, 1H), 3.21-3.45 (m, 3H), 3.08 (d, *J*=9.63 Hz, 1H), 2.90-3.02 (m, 1H), 2.51-2.64 (m, 1H), 2.30-2.50 (m, 3H), 2.26 (s, 3H), 1.97-2.15 (m, 4H), 1.78-1.97 (m, 3H), 1.65-1.77 (m, 4H), 1.23-1.29 (m, 1H), 1.14-1.19 (m, 1H).

Table 22. Conditions for Chiral SFC Separation.

	Column: DAICEL CHIRALPAK AD, 2 x 25 cm, 5 μm column Mobile phase: 35% iPrOH with 0.1% NH_3H_2O Flowrate: 80 mL/in. Yield: 47 mg to generate 11 mg of peak 1 with an ee of 99% and 12 mg of peak 2 with an ee of 99%.	Peak 1: **Example 1.022** Peak 2: **Example 1.029**

Example 1.009 and 1.008: (1*RS*,3*SR*,29*RS*)-10-Chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-4-oxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-29-ol and (1*RS*,3*SR*,29*SR*)-10-chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-4-oxa-

13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-29-ol



[00443] Step 1. *tert*-Butyl 8-((*tert*-butyldiphenylsilyl)oxy)-2-(4-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)butoxy)-6-azaspiro[3.5]nonane-6-carboxylate. To a 100 mL round-bottom flask was charged with *tert*-butyl 8-((*tert*-butyldiphenylsilyl)oxy)-2-hydroxy-6-azaspiro[3.5]nonane-6-carboxylate (**Intermediate VV**, 2.00 g, 4.04 mmol), tetrahydrofuran (25 mL), and sodium hydride (60 wt% in mineral oil, 0.31 g, 7.8 mmol). This was allowed to stir at room temperature for 15 minutes. 4-(6-Chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)butyl methanesulfonate (**Intermediate M**, 1.80 g, 3.51 mmol) as a solution in tetrahydrofuran (10 mL) was added. The reaction mixture was stirred at 50 °C for 18 h. After cooling to room temperature, the reaction mixture was carefuly quenched with saturated aqueous ammonium chloride and extracted with EtOAc. The combined organics were dried (Na_2SO_4) and concentrated. The crude oil was purified by column chromatography on silica gel, eluting using 0–50% ethyl acetate in heptane, to give *tert*-butyl 8-((*tert*-butyldiphenylsilyl)oxy)-2-(4-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)butoxy)-6-azaspiro[3.5]nonane-6-carboxylate. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.34 (dd, *J*=2.30, 0.84 Hz, 1 H), 7.69 - 7.76 (m, 2 H), 7.64 - 7.71 (m, 4 H), 7.34 - 7.47 (m, 5 H), 5.67 (dd, *J*=8.88, 2.61 Hz, 1 H), 4.03 - 4.04 (m, 1 H), 3.95 - 4.08 (m, 1 H), 3.69 - 3.82 (m, 1 H), 3.63 (td, *J*=8.36, 4.18 Hz, 2 H), 3.24 - 3.36 (m, 2 H), 3.10 - 3.20 (m, 2 H), 2.83 (br dd, *J*=7.52, 2.72 Hz, 1 H), 2.69 (br dd, *J*=12.54, 9.41 Hz, 1 H), 2.45 - 2.60 (m, 1 H), 2.11 - 2.22 (m, 1 H),

1.92 - 2.09 (m, 2 H), 1.50 - 1.82 (m, 10 H), 1.40 - 1.43 (m, 12 H), 1.24 - 1.32 (m, 9 H), 1.09 (d, *J*=5.64 Hz, 7 H), 0.87 - 0.96 (m, 5 H).

[00444] Step 2. *tert*-Butyl 8-((*tert*-butyldiphenylsilyl)oxy)-2-(4-(6-chloro-4-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butoxy)-6-azaspiro[3.5]nonane-6-carboxylate. In a vial were charged with 7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidine (**Intermediate WW**, 0.37 g, 0.83 mmol), *tert*-butyl 8-((*tert*-butyldiphenylsilyl)oxy)-2-(4-(6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-5-yl)butoxy)-6-azaspiro[3.5]nonane-6-carboxylate (0.88 g, 0.96 mmol), cataCXium A Pd G3 (CAS No. 1651823-59-4) (0.12 g, 0.17 mmol), and potassium phosphate (0.71 g, 3.3 mmol). The contents was evacuated under vacuum and then flushed with nitrogen. 2-Methyltetrahydrofuran (3.8 mL) and water (0.4 mL) were added, and the reaction mixture was stirred at 80 °C for 1.5 h. After cooling to room temperature, Na_2SO_4 was added to dry the reaction mixture. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 0–40% 3:1 EtOAc/EtOH with 2% Et_3N in heptane, to provide *tert*-butyl 8-((*tert*-butyldiphenylsilyl)oxy)-2-(4-(6-chloro-4-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butoxy)-6-azaspiro[3.5]nonane-6-carboxylate (0.61 g, 0.52 mmol, 62% yield). *m/z* (ESI): 1188.0 $(M+H)^+$.

[00445] Step 3. 15-((*tert*-Butyldiphenylsilyl)oxy)-36-chloro-28-fluoro-22-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-31*H*-8-oxa-2(4,7)-pyrido[4,3-d]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-9(1,3)-cyclobutananonaphane. In a 150 mL round-bottom flask was charged with *tert*-butyl 8-((*tert*-butyldiphenylsilyl)oxy)-2-(4-(6-chloro-4-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)butoxy)-6-azaspiro[3.5]nonane-6-carboxylate (0.61 g, 0.51 mmol) in DCM (2 mL). 1,1,1-Trifluoroacetic acid (1.1 mL, 15.4 mmol) was added dropwise, and the reaction mixture was stirred at room temperature under nitrogen for 1 h. The solvent was removed *in vacuo* and the residue was dissolved in DCM and evacuated. The residue was used directly in the following step.

[00446] To the solution of 7-(5-(4-((8-((*tert*-butyldiphenylsilyl)oxy)-6-azaspiro[3.5]nonan-2-yl)oxy)butyl)-6-chloro-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidine (0.52 g, 0.51 mmol) in *N*,*N*-dimethylformamide (64 mL) was added cesium carbonate (1.82 g, 5.47 mmol). The reaction mixture was heated to 80 °C for 1 h, then at 60 °C for 16 h. After cooling to room temperature, the reaction mixture was passed through two SCX-2 columns (5 g) and washed with DCM. The column was briefly dried and eluted with 2 N NH_3 in MeOH. The collected material was concentrated under

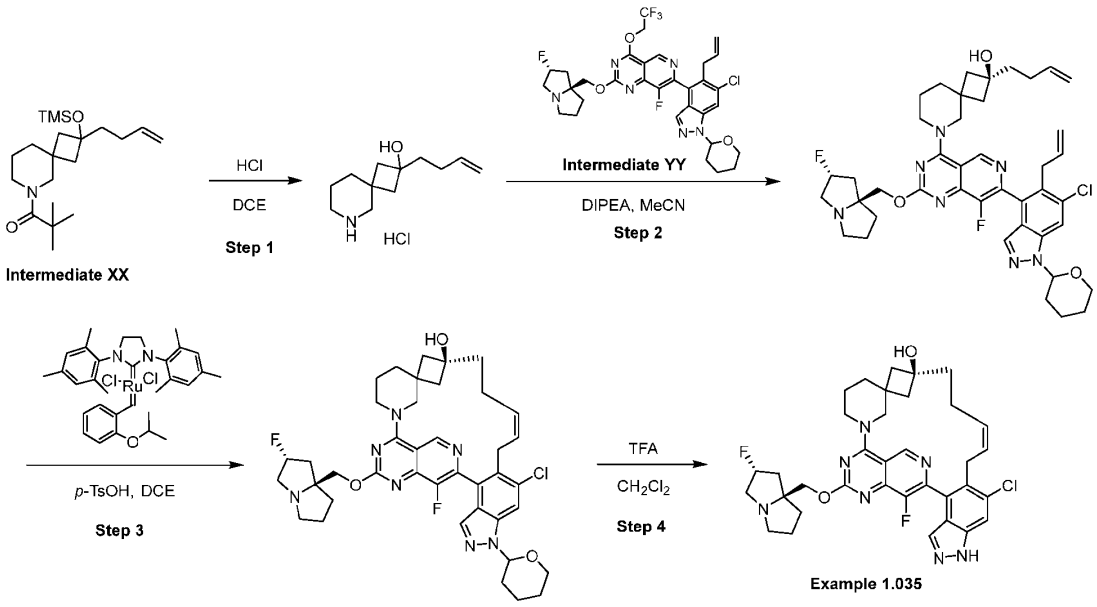
reduced pressure which was purified by column chromatography on silica gel, eluting with a gradient of 0–40% 3:1 EtOAc/EtOH with 2% Et_3N in heptanes, to provide 15-((*tert*-butyldiphenylsilyl)oxy)-36-chloro-28-fluoro-22-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-31*H*-8-oxa-2(4.7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-9(1,3)-cyclobutananonaphane. *m/z* (ESI): 903.8 $(M+H)^+$.

[00447] Step 4. (1*RS*,3*SR*,29*RS*)-10-Chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-4-oxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonacn-29-ol and (1*RS*,3*SR*,29*SR*)-10-chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-4-oxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-29-ol. To a solution of 15-((*tert*-butyldiphenylsilyl)oxy)-36-chloro-28-fluoro-22-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-31*H*-8-oxa-2(4.7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-9(1,3)-cyclobutananonaphane (0.44 g, 0.49 mmol) in THF (2.5 mL) was added tetrabutylammonium fluoride (1 M in THF, 1.5 mL, 1.5 mmol) dropwise. The reaction mixture was stirred at room temperature for 1 h, then concentrated *in vacuo*. The residue was purified by reversed phase preparative HPLC using a Phenomenex Gemini column, 10 mm, C18, 110 Å, 150 x 30 mm, eluting with a gradient of 10–90% 0.1% TFA in CH_3CN/0.1% TFA in H_2O, to provide TFA salt of the racemic product (0.18 g, 0.23 mmol, 48% yield). *m/z* (ESI): 666.0 $(M+H)^+$.

[00448] The sample was purified via SFC using a Chiralcel OD, 2 x 25 cm, 5 µm column with a mobile phase of 35% MeOH with 0.2% DEA using a flowrate of 80 mL/min to generate 12.4 mg of peak 1 as (1*RS*,3*SR*,29*RS*)-10-chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-4-oxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-29-ol **(Example 1.009)** with an ee of 99%. ^{1}H NMR (400 MHz, *METHANOL-d4*) δ ppm 9.26 (s, 1 H), 7.80 (br d, *J*=17.14 Hz, 2 H), 5.28 - 5.50 (m, 1 H), 4.92 - 5.06 (m, 2 H), 4.38 (br s, 1 H), 4.09 - 4.23 (m, 1 H), 3.73 - 3.89 (m, 2 H), 3.65 (br d, *J*=13.38 Hz, 1 H), 3.50 (s, 1 H), 3.07 - 3.17 (m, 2 H), 2.84 - 3.00 (m, 2 H), 2.73 - 2.83 (m, 2 H), 2.40 - 2.49 (m, 1 H), 2.26 - 2.40 (m, 3 H), 2.16 - 2.24 (m, 1 H), 1.73 - 1.80 (m, 1 H), 1.51 - 1.72 (m, 7 H), 1.40 - 1.51 (m, 4 H), 0.96 - 1.05 (m, 1 H), 0.88 - 0.96 (m, 2 H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -142.11 (s, 1 F), -173.73 (s, 1 F), and 19 mg of peak 2 as (1*RS*,3*SR*,29*SR*)-10-chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-4-oxa-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-29-ol **(Example 1.008)** with an ee of 95.9%. ^{1}H NMR (400

MHz, *METHANOL-d4*) δ ppm 9.27 (s, 1 H), 7.73 - 7.84 (m, 2 H), 5.29 - 5.48 (m, 2 H), 4.92 - 5.04 (m, 3 H), 4.43 - 4.49 (m, 1 H), 4.27 - 4.40 (m, 3 H), 4.09 - 4.23 (m, 5 H), 4.03 (br d, *J*=4.81 Hz, 1 H), 3.83 (br t, *J*=5.96 Hz, 2 H), 3.62 - 3.80 (m, 5 H), 3.53 - 3.60 (m, 2 H), 3.10 - 3.17 (m, 1 H), 2.85 - 2.99 (m, 2 H), 2.74 - 2.82 (m, 2 H), 2.42 - 2.49 (m, 2 H), 1.70 - 1.81 (m, 3 H), 0.96 - 1.04 (m, 1 H). ^{19}F NMR (376 MHz, *METHANOL-d4*) δ ppm -142.12 (s, 1 F), -173.78 (s, 1 F).

Example 1.035: (1*S*,3*S*,6Z)-10-Chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-6,9,11,14,16,18(32),19,21,23,25-decaen-3-ol



[00449] Step 1. 2-(But-3-en-1-yl)-6-azaspiro[3.5]nonan-2-ol hydrochloride. A 40-mL vial was charged with 1-(2-(but-3-en-1-yl)-2-((trimethylsilyl)oxy)-6-azaspiro[3.5]nonan-6-yl)-2,2-dimethylpropan-1-one (**Intermediate XX**, 1.00 g, 2.84 mmol) in 1,2-dichloroethane (11 mL). The solution was cooled to 0 °C and hydrogen chloride (4.0 M in 1,4-dioxane, 3.6 mL, 14.4 mmol) was slowly added. The reaction mixture was stirred at 0 °C for 2 h. Then, the mixture was concentrated, and the crude residue was directly used in the next step. *m/z* (ESI): 196.2 $(M+H)^+$.

[00450] Step 2. 6-(7-(5-Allyl-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-(but-3-en-1-yl)-6-azaspiro[3.5]nonan-2-ol. A 40-mL vial was charged with 2-(but-3-en-1-yl)-6-azaspiro[3.5]nonan-2-ol hydrochloride (0.65 g, 2.80 mmol), 7-(5-allyl-6-chloro-1-(tetrahydro-2*H*-

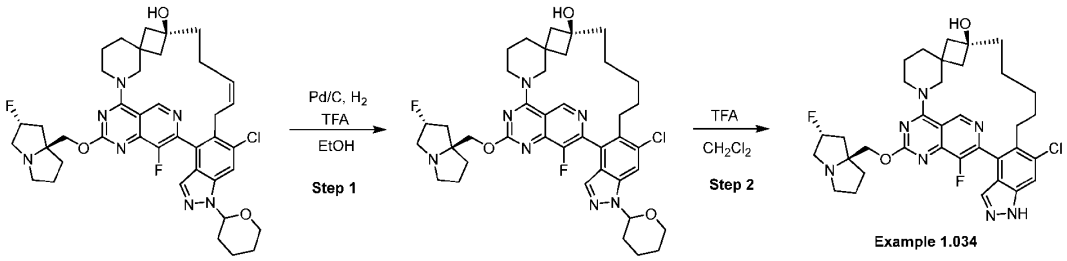
pyran-2-yl)-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidine (**Intermediate YY,** 1.91 g, 2.82 mmol) and DIPEA (2.5 mL, 14 mmol) in acetonitrile (11 mL). The reaction mixture was stirred at 60 °C for 18 h. After cooling to room temperature, the reaction mixture was concentrated, and the crude residue was purified by reversed phase chromatography to yield 6-(7-(5-allyl-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-(but-3-en-1-yl)-6-azaspiro[3.5]nonan-2-ol (0.95 g, 1.20 mmol, 44% yield). *m/z* (ESI): 774.3 $(M+H)^+$.

[00451] Step 3. (1*S*,3*S*,6Z)-10-Chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-*N*-(tetrahydro-2*H*-pyran-2-yl)-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-6,9,11,14,16,18(32),19,21,23,25-decaen-3-ol. A 250 mL round-bottom flask was charged with 6-(7-(5-allyl-6-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-(but-3-en-1-yl)-6-azaspiro[3.5]nonan-2-ol (0.31 g, 0.40 mmol), *p*-toluenesulfonic acid monohydrate (90 mg, 0.47 mmol), and 1,2-dichloroethane (132 mL). The reaction mixture was purged with N_2 for 5 minutes and then Hoveyda-Grubbs catalyst, 2nd generation (99 mg, 0.16 mmol) was quickly added. The reaction mixture was heated to 80 °C for 10 h. After cooling to room temperature, the crude reaction mixture was purified by column chromatography on silica gel, eluting with a gradient of 0–100% (3:1 EtOAc/EtOH with 2% Et_3N) in heptanes, to provide (1*S*,3*S*,6Z)-10-chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-*N*-(tetrahydro-2*H*-pyran-2-yl)-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-6,9,11,14,16,18(32),19,21,23,25-decaen-3-ol (0.12 g, 0.16 mmol, 39% yield). *m/z* (ESI): 746.2 $(M+H)^+$.

[00452] Step 4. (1*S*,3*S*,6Z)-10-Chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-6,9,11,14,16,18(32),19,21,23,25-decaen-3-ol. (1*S*,3*S*,6Z)-10-Chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-*N*-(tetrahydro-2*H*-pyran-2-yl)-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-6,9,11,14,16,18(32),19,21,23,25-decaen-3-ol (80 mg, 0.11 mmol) dissolved in 1,2-dichloromethane (1.1 mL) was treated with trifluoroacetic acid (0.20 mL, 2.7 mmol), and the reaction mixture was stirred at room temperature for 1 h. The volatiles were removed under reduced pressure and the crude product was purified by reversed phase chromatography to yield (1*S*,3*S*,6Z)-10-chloro-32-fluoro-24-

(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-6,9,11,14,16,18(32),19,21,23,25-decaen-3-ol (6.3 mg, 0.10 mmol, 9% yield). *m/z* (ESI): 662.0 $(M+H)^+$. ^{1}H NMR (500 MHz, *METHANOL-d*$_4$) δ ppm 9.30 – 9.20 (m, 1H), 7.87 – 7.81 (m, 1H), 7.77 – 7.68 (m, 1H), 5.50 (br t, *J* = 10.6 Hz, 1H), 5.39 – 5.34 (m, 1H), 5.28 – 5.22 (m, 1H), 5.11 (br t, *J* = 9.9Hz, 1H), 4.72 (br d, *J* = 13.1 Hz, 1H), 4.37 – 4.25 (m, 2H), 3.67 (br d, *J* = 13.6 Hz, 2H), 3.50 – 3.44 (m, 2H), 3.21 – 3.17 (m, 1H), 3.15 – 3.08 (m, 1H), 3.06 – 2.97 (m, 1H), 2.39 – 2.32 (m, 1H), 2.30 – 2.20 (m, 2H), 2.18 – 2.10 (m, 2H), 2.07 – 1.97 (m, 3H), 1.85 (br d, *J* = 9.5 Hz, 3H), 1.80 – 1.76 (m, 1H), 1.73 – 1.68 (m, 1H), 1.66 – 1.60 (m, 1H), 1.50 – 1.42 (m, 3H), 1.35 – 1.26 (m, 2H). ^{19}F NMR (471 MHz, *METHANOL-d*$_4$) δ ppm -140.90 (br d, *J*=15.73 Hz, 1 F), -173.68 (br d, *J*=10.02 Hz, 1 F).

Example 1.034: (1*S*,3*S*)-10-Chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-3-ol

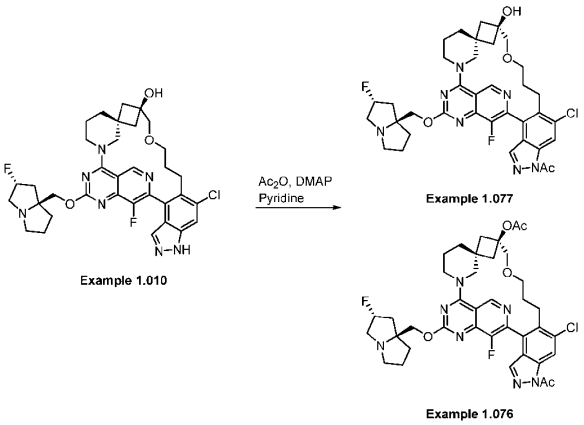


[00453] Step 1. (1*S*,3*S*)-10-Chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-*N*-(tetrahydro-2*H*-pyran-2-yl)-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-3-ol. To a hydrogenation reaction vessel was added (1*S*,3*S*,6*Z*)-10-chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-*N*-(tetrahydro-2*H*-pyran-2-yl)-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-6,9,11,14,16,18(32),19,21,23,25-decaen-3-ol (80 mg, 0.11 mmol) and EtOH (1.8 mL). The reaction vessel was purged with N_2. Palladium on activated carbon (11 mg, 0.01 mol) was added and the reaction mixture was stirred under hydrogen (40 psi) for 18 h. The catalyst was filtered through celite and the filtrate was concentrated to provide (1*S*,3*S*)-10-chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-*N*-(tetrahydro-2*H*-pyran-2-yl)-13,14,19,23,25,27-

hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-3-ol, which was directly used in the next step. *m/z* (ESI): 748.3 $(M+H)^+$.

[00454] Step 2. (1*S*,3*S*)-10-Chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-3-ol. (1*S*,3*S*)-10-Chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-*N*-(tetrahydro-2*H*-pyran-2-yl)-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-3-ol (80 mg, 0.11 mmol) dissolved in 1,2-dichloromethane (1.1 mL) was treated with trifluoroacetic acid (0.20 mL, 2.7 mmol), and the reaction mixture was stirred at room temperature for 1 h. The volatiles were removed under reduced pressure and the crude product was purified by reversed phase chromatography to yield (1*S*,3*S*)-10-chloro-32-fluoro-24-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolo[1,2-*a*]pyrrol-7a(5*H*)-yl)methoxy)-13,14,19,23,25,27-hexaazaheptacyclo[25.3.1.1~1,3~.1~18,22~.0~9,17~.0~12,16~.0~21,26~]tritriaconta-9,11,14,16,18(32),19,21,23,25-nonaen-3-ol (6.5 mg, 0.10 mmol, 9% yield). *m/z* (ESI): 664.0 $(M+H)^+$. ^{1}H NMR (500 MHz, *METHANOL-d4*) δ ppm 9.27 – 9.24 (m, 1H), 7.84 – 7.81 (m, 1H), 7.80 – 7.76 (m, 1H), 5.41 – 5.35 (m, 1H), 5.30 – 5.25 (m, 1H), 4.93 (br d, *J* = 12.2 Hz, 1H), 4.72 – 4.65 (m, 1H), 4.40 – 4.36 (m, 1H), 4.34 – 4.31 (m, 1H), 4.26 (d, *J* = 10.6 Hz, 1H), 3.69 – 3.65 (m, 1H), 3.49 – 3.42 (m, 1H), 3.26 (br d, *J* = 3.0 Hz, 2H), 3.14 (br t, *J* = 11.4 Hz, 1H), 3.07 – 3.01 (m, 2H), 2.97 – 2.88 (m, 1H), 2.55 – 2.46 (m, 1H), 2.40 – 2.34 (m, 1H), 2.28 – 2.22 (m, 2H), 2.18 – 2.11 (m, 2H), 2.06 – 1.99 (m, 3H), 1.80 (s, 1H), 1.72 (br s, 1H), 1.62 (br d, *J* = 6.7 Hz, 2H), 1.45 – 1.42 (m, 1H), 1.34 – 1.32 (m, 1H), 1.29 – 1.26 (m, 2H), 1.18 – 1.13 (m, 2H), 0.92 (td, *J* = 6.5, 2.4 Hz, 1H), 0.65 – 0.55 (m, 1H). ^{19}F NMR (471 MHz, *METHANOL-d4*) δ ppm δ -140.79 (s, 1F), -173.36 (s, 1F).

Examples 1.099 and 1.100: **(13*r*,93*R*)-31-acetyl-36-chloro-28-fluoro-22-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-31*H*-7-oxa-2(4,7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-9(1,3)-cyclobutananonaphane-93-yl acetate and (13*r*,93*R*)-36-chloro-28-fluoro-22-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-31*H*-7-oxa-2(4,7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-9(1,3)-cyclobutananonaphane-93-yl acetate**.

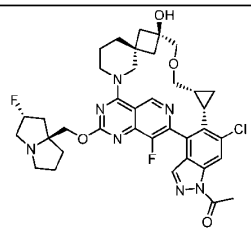
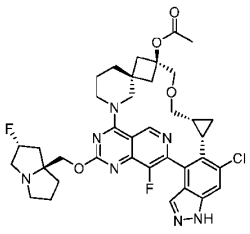


[00455] To a stirred mixture of **Example 1.010** (0.5 g, 0.7 mmol) and pyridine (1.1 mL, 13.5 mmol, Sigma Aldrich) at room temperature under N_2 was added DMAP (83 mg, 0.7 mmol, Sigma Aldrich) and acetic acid anhydride (1.4g, 13.5 mmol). The resulting mixture was stirred at room temperature for 16 h. The sample was purified via SFC using a IC, 2 x 15 cm, 5 µm column with a mobile phase of 50% methanol using a flowrate of 100 mL/min to generate peak 1 and peak 2. Peak 2 was repurified by HPLC using an XBridge C18, 19 x 100 mm, 5 µm, with a gradient from 40-100% acetonitrile (0.1% NH_4OH) in water (0.1% NH_4OH)

Peak 1: **Example 1.076,** (13*r*,93*R*)-31-acetyl-36-chloro-28-fluoro-22-(((2R,7aS)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-31*H*-7-oxa-2(4,7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-9(1,3)-cyclobutananonaphane-93-yl acetate (80 mg, 0.1 mmol, 15% yield). *m/z* (ESI): 750.1 $(M+H)^+$. ^1H NMR (400 MHz, *DMSO-d6*) δ ppm 9.20 - 9.45 (m, 1 H), 8.45 - 8.52 (m, 1 H), 8.28 - 8.35 (m, 1 H), 5.19 - 5.42 (m, 1 H), 4.52 - 4.79 (m, 2 H), 4.02 - 4.25 (m, 2 H), 3.58 - 3.69 (m, 1 H), 2.98 - 3.27 (m, 7 H), 2.80 - 2.90 (m, 1 H), 2.74 (s, 4 H), 2.28 - 2.39 (m, 1 H), 1.98 - 2.17 (m, 4 H), 1.91 (s, 15 H), 1.34 - 1.46 (m, 1 H). ^{19}F NMR (376 MHz, *DMSO-d6*) δ ppm -142.03 (s, 1 F), -172.18 (s, 1 F).

Peak 2: **Example 1.077**, (13*r*,93*R*)-36-chloro-28-fluoro-22-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-31*H*-7-oxa-2(4,7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-9(1,3)-cyclobutananonaphane-93-yl acetate (0.14 g, 0.2 mmol, 29% yield). *m/z* (ESI): 708.3 $(M+H)^+$. ^1H NMR (400 MHz, *DMSO-d6*) δ ppm 13.22 - 13.42 (m, 1 H), 9.28 (s, 1 H), 7.82 (s, 2 H), 5.14 - 5.42 (m, 1 H), 4.48 - 4.77 (m, 2 H), 3.98 - 4.24 (m, 2 H), 3.54 - 3.69 (m, 1 H), 2.94 - 3.22 (m, 6 H), 2.61 - 2.89 (m, 2 H), 2.20 - 2.34 (m, 1 H), 1.96 - 2.20 (m, 5 H), 1.91 (s, 15 H), 1.32 - 1.45 (m, 1 H). ^{19}F NMR (376 MHz, *DMSO-d6*) δ ppm -142.40 (s, 1 F), -172.14 (s, 1 F).

[00456] **Examples 1.074** and **1.075** were made in similar fashion as **Examples 1.076** and **1.077**, each starting from **Example 1.002** and separated by chromatography, eluting with a gradient of 0-100% EtOH in EtOAc (1:3) with 2% triethylamine in heptane

Cmpnd	Structure	Name	MS and NMR
1.074		1-((41*S*,42*R*)-36-chloro-28-fluoro-22-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-83-hydroxy-31*H*-6-oxa-2(4,7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-8(1,3)-cyclobutana-4(1,2)-cyclopropanaoctaphane-31-yl)ethan-1-one	*m/z* (ESI): 720.4 $(M+H)^+$. ^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 9.31 – 9.23 (m, 1H), 8.55 – 8.47 (m, 1H), 8.43 – 8.39 (m, 1H), 5.39 – 5.18 (m, 1H), 4.89 – 4.85 (m, 1H), 4.77 – 4.69 (m, 1H), 4.62 – 4.52 (m, 1H), 4.20 – 4.13 (m, 1H), 4.08 – 4.02 (m, 1H), 3.61 (br d, *J* = 13.8 Hz, 1H), 3.24 – 3.17 (m, 1H), 3.08 (br s, 3H), 3.05 – 2.99 (m, 1H), 2.88 – 2.80 (m, 1H), 2.76 – 2.72 (m, 3H), 2.71 – 2.64 (m, 1H), 2.45 – 2.39 (m, 1H), 2.23 – 2.13 (m, 2H), 2.10 – 2.03 (m, 2H), 2.01 – 1.96 (m, 1H), 1.91 – 1.84 (m, 2H), 1.81 – 1.72 (m, 3H), 1.69 – 1.60 (m, 3H), 1.56 – 1.38 (m, 2H), 1.35 – 1.26 (m, 2H), 0.98 – 0.90 (m, 1H), 0.45 – 0.36 (m, 1H). ^{19}F NMR (376 MHz, *DMSO-d*$_6$) δ ppm -136.68 – -138.97 (m, 1F), - 171.00 – -172.80 (m, 1F).
1.075		(41*S*,42*R*)-36-chloro-28-fluoro-22-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-31*H*-6-oxa-2(4,7)-pyrido[4,3-*d*]pyrimidina-3(4,5)-indazola-1(1,3)-piperidina-8(1,3)-cyclobutana-4(1,2)-cyclopropanaoctaphane-83-yl acetate	*m/z* (ESI): 720.4 $(M+H)^+$. ^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 13.31 – 13.22 (m, 1H), 9.32 – 9.25 (m, 1H), 8.11 – 8.05 (m, 1H), 7.87 – 7.79 (m, 1H), 5.79 – 5.70 (m, 1H), 5.43 – 5.17 (m, 1H), 4.80 – 4.70 (m, 1H), 4.66 – 4.58 (m, 1H), 4.25 – 4.12 (m, 1H), 4.09 – 4.04 (m, 1H), 3.81 – 3.75 (m, 1H), 3.70 – 3.60 (m, 1H), 3.14 – 3.01 (m, 4H), 2.88 – 2.77 (m, 2H), 2.46 – 2.41 (m, 1H), 2.18 – 2.11 (m, 2H), 2.08 – 2.07 (m, 1H), 2.03 – 1.95 (m, 2H), 1.94 – 1.89 (m, 2H), 1.88 (s, 3H), 1.81 – 1.69 (m, 4H), 1.63 (br d, *J* = 12.1 Hz, 3H), 1.48 – 1.35 (m, 2H), 0.90 – 0.82 (m, 1H), 0.41 – 0.31 (m, 1H). ^{19}F NMR (376 MHz, *DMSO-d*$_6$) δ ppm -137.17 – -138.97 (m, 1F), - 171.33 – -172.96 (m, 1F).

SECTION 3: Biochemical and Cellular Assays

[00457] Provided in this section is the biological evaluation of the specific examples provided herein.

KRAS G12D Coupled Nucleotide Exchange Assay

[00458] Purified GDP-bound KRAS protein (aa 1-169), containing both G12D and C118A amino acid substitutions and an *N*-terminal His-tag, was pre-incubated in assay buffer (25 mM HEPES pH 7.4, 10 mM $MgCl_2$, and 0.01% Triton X-100) with a compound dose-response titration for 2 hours. Following compound pre-incubation, purified SOS protein (aa 564-1049) and GTP (Roche 10106399001) were added to the assay wells and incubated for an additional 30 min. To determine the extent of inhibition of SOS-mediated nucleotide exchange, purified GST-tagged cRAF (aa 1-149), nickel chelate AlphaLISA acceptor beads (PerkinElmer AL108R), and AlphaScreen glutathione donor beads (PerkinElmer 6765302) were added to the assay wells and incubated for 10 minutes. The assay plates were then read on a PerkinElmer EnVision Multilabel Reader, using AlphaScreen® technology, and data were analyzed using a 4-parameter logistic model to calculate IC_{50} values.

Phospho-ERK1/2 MSD Assay

[00459] AsPC-1 (ATCC® CRL-1682™) cells were cultured in RPMI 1640 Medium (ThermoFisher Scientific 11875093) containing 10% fetal bovine serum (ThermoFisher Scientific 16000044) and 1x penicillin-streptomycin-glutamine (ThermoFisher Scientific 10378016). Sixteen hours prior to compound treatment, AsPC-1 cells were seeded in 96-well cell culture plates at a density of 25,000 cells/well and incubated at 37 °C, 5% CO_2. A compound dose-response titration was diluted in growth media, added to appropriate wells of a cell culture plate, and then incubated at 37 °C, 5% CO_2 for 2 hours. Following compound treatment, cells were washed with ice-cold Dulbecco's phosphate-buffered saline, no Ca^{2+} or Mg^{2+} (ThermoFisher Scientific 14190144), and then lysed in RIPA buffer (50 mM Tris-HCl pH 7.5, 1% Igepal, 0.5% sodium deoxycholate, 150 mM NaCl, and 0.5% sodium dodecyl sulfate) containing protease inhibitors (Roche 4693132001) and phosphatase inhibitors (Roche 4906837001). Phosphorylation of ERK1/2 in compound-treated lysates was assayed using Phospho-ERK1/2 Whole Cell Lysate kits (Meso Scale Discovery K151DWD) according to the manufacturer's protocol. Assay plates were read on a Meso Scale Discovery Sector Imager 6000, and data were analyzed using a 4-parameter logistic model to calculate IC_{50} values.

AsPC-1 and SW620 CTG Assay Protocols

[00460] AsPC-1 (human pancreatic adenocarcinoma; ATCC CRL-1682) or SW620 (human colon adenocarcinoma; ATCC CCL-227) cells were cultured in RPMI 1640 medium containing 10% fetal bovine serum and 1x penicillin/streptomycin/L-glutamine. Cells were

seeded in 384-well plates at a density of 3.33E+04 cells/mL and incubated at 37 °C, 5% CO_2, overnight. Serially-diluted compound or DMSO was added to the cells, and plates were incubated at 37 °C, 5% CO_2 for 72 h. Cell viability was measured using a CellTiter-Glo® Luminescent Cell Viability Assay kit (Promega) according to the manufacturer's protocol. The luminescence signal of treated samples was normalized to DMSO control, and data were analyzed using a 4-parameter logistic model to calculate IC_{50} values.

Table 3:

Example #	MS *m/z* (ESI): $(M+H)^+$	G12D Coupled Exchange (μM)	AsPC-1 p-ERK (μM)	AsPC-1 CTG (μM)	SW620 CTG (μM)
1.001	673.9	<0.001	0.0069	NT	0.016
1.002	678.0	0.003	0.0005	0.004	0.0003
1.003	634.0	0.003	0.0039	0.067	0.004
1.004	678.0	0.003	0.144	1.12	NT
1.005	680.1	0.003	0.287	2.24	NT
1.006	634.0	0.182	NT	NT	NT
1.007	622.3	0.002	0.0213	0.303	NT
1.008	666.0	0.008	0.0165	0.203	0.01
1.009	666.0	0.005	0.105	NT	NT
1.010	666.0	0.002	0.0016	0.02	0.001
1.011	646.0	0.002	0.0142	0.211	0.007
1.012	622.2	0.002	0.0302	0.474	NT
1.013	669.3	0.001	0.0029	0.007	0.0004
1.014	645.0	0.004	0.0016	0.006	0.0004
1.015	663.0	0.032	0.0193	NT	0.006
1.018	693.2	0.002	0.0009	0.009	0.001
1.019	666.3	0.001	0.001	0.045	NT
1.020	672.3	0.002	0.0015	0.02	NT
1.021	666.3	0.002	0.0042	0.083	0.001
1.022	662.3	0.001	0.0054	0.104	NT
1.024	672.1	0.002	0.0116	0.106	0.008
1.025	632.3	0.001	0.0422	0.431	NT
1.027	660.3	0.003	0.0749	0.67	NT
1.028	663.3	0.002	0.0928	1.61	NT
1.029	662.3	0.115	NT	NT	NT
1.030	663.3	0.073	NT	NT	NT
1.032	636.0	0.001	0.033	0.306	NT
1.033	692.2	0.002	0.0004	0.008	0.001
1.034	664.0	0.003	0.0009	0.004	0.0003
1.035	662.0	0.003	0.0014	0.016	NT
1.036	692.2	0.001	0.0688	0.913	NT
1.037	691.8	0.003	0.225	5	NT
1.038	674.8	0.002	0.0005	0.009	0.001

1.039	682.2	0.002	0.0021	0.03	NT
1.040	658.2	0.003	0.0032	0.021	0.002
1.041	676.2	0.007	0.0106	0.066	0.012
1.042	674.0	0.003	0.0131	NT	NT
1.043	692.0	0.002	0.0159	0.257	0.03
1.044	652.2	0.002	0.0282	0.379	NT
1.045	680.0	0.002	0.0371	0.29	NT
1.046	652.2	0.009	0.213	2.632	NT
1.047	655.2	0.002	0.0015	0.007	0.003
1.048	674.8	0.066	NT	NT	NT
1.049	658.2	0.057	NT	NT	NT
1.050	690.2	0.004	0.0008	NT	0.001
1.051	690.9	0.002	0.0009	0.011	NT
1.052	692.2	0.003	0.0015	0.019	NT
1.053	691.0	0.002	0.002	0.007	< 0.001
1.054	718.1	0.004	0.0023	0.028	NT
1.055	706.2	0.006	0.0071	0.08	0.015
1.056	693.1	0.003	0.0087	0.086	0.004
1.057	667.9	0.002	0.0316	0.471	0.003
1.058	674.9	0.002	0.0321	0.437	NT
1.059	694.2	0.005	0.0649	0.539	NT
1.061	644.2	0.002	0.0081	0.149	NT
1.062	689.4	0.003	0.0528	0.625	NT
1.065	665.2	0.003	0.0401	NT	NT
1.066	691.3	0.007	0.0519	0.938	NT
1.067	664.2	0.01	NT	0.429	NT
1.068	718.0	0.003	0.0013	0.026	NT
1.069	718.0	0.003	0.012	0.184	NT
1.070	694.1	0.005	1.0	5.0	NT
1.071	694.1	< 0.001	0.0049	0.042	NT
1.072	707.1	0.003	0.0033	0.027	NT
1.073	689.4	0.034	NT	NT	NT
1.074	720.4	0.018	0.0023	0.005	NT
1.075	720.4	0.775	0.0121	0.052	NT
1.076	750.1	0.587	0.123	0.675	NT
1.077	708.3	0.17	0.0284	0.309	NT
1.078	693	0.003	0.0017	0.004	NT
1.079	693	0.002	9.0031	0.006	NT
1.080	673	0.003	0.0068	0.028	0.002
1.081	662	0.024	0.571	>5	NT
1.082	670	0.005	0.0069	0.157	NT
1.083	670	0.003	0.0041	0.071	NT
1.084	662.3	0.002	0.001	0.03	0.003
1.085	664.0	0.003	0.0012	0.015	0.002
1.086	662.3	0.018	0.69	>5	NT
1.087	680	0.221	NT	NT	NT
1.088	680	0.002	0.0108	0.248	NT
1.089	704	0.004	0.0118	0.059	NT

1.090	680	0.004	0.0058	0.064	NT
1.091	634.3	0.01	0.0089	0.156	NT

[00461] The results presented in **Table 3** have been generated with the in vitro assays described above. These assays may be used to test any other compound described herein to assess and characterize a compound's biological activity. In view of the disclosure provided herein, compounds not specifically tested would be expected to have similar results.

[00462] Compounds showing activity in the coupled exchange assay are useful in the methods provided herein (see Section "METHODS OF USE").

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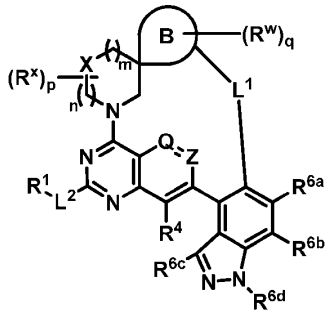
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What is claimed is:

1. A compound of Formula (**I**):



(**I**)

or a pharmaceutically acceptable salt thereof, wherein;

X is -CH_2- or -O-

Z is C-H, C-halogen, C-CN, C-C_{1-4} alkyl, C-C_{1-4} haloalkyl, C-C_{1-4} alkoxy, C-C_{1-4} haloalkoxy, C-C_{3-7} cycloalkyl or N;

Q is CH, C-halogen, C-C_{1-4} alkyl, C-C_{1-4} haloalkyl or N;

B is a C_{3-7} cycloalkyl or 3-7 membered heterocycloalkyl;

n is 0, 1 or 2;

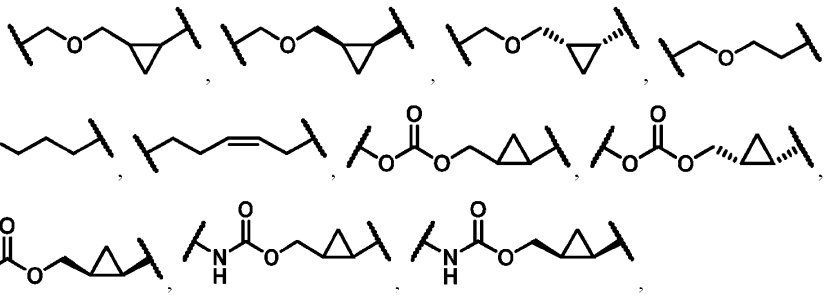
m is 0, 1 or 2;

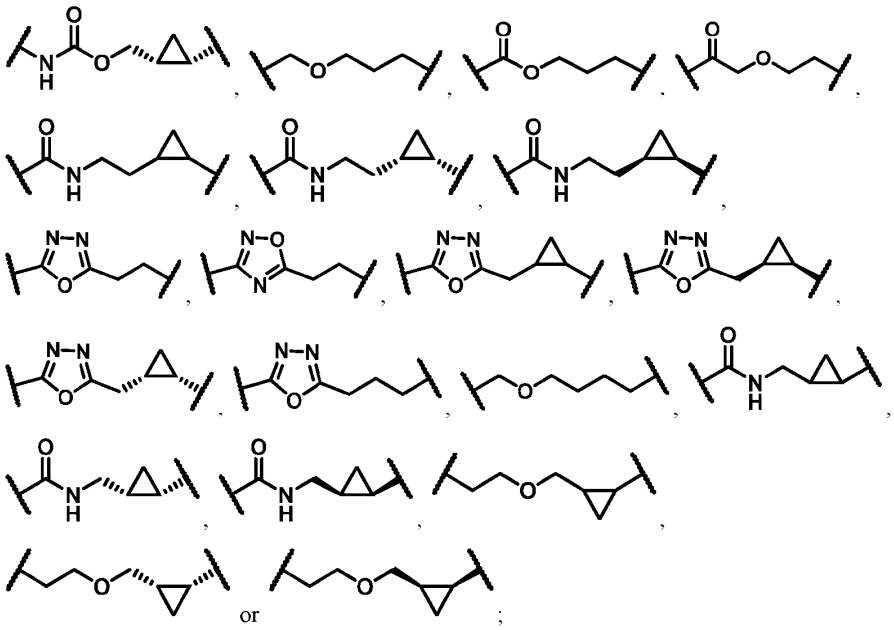
p is 0, 1 or 2;

q is 0, 1 or 2;

each R^x independently is hydroxyl, halogen, oxo, cyano, -$N(R^z)_2$, C_{1-4} alkyl, C_{1-4} deuteroalkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{1-4} hydroxyalkylene, 5-7 membered heteroaryl, -$S(O)_2$-C_{1-4}alkyl, -$S(O)_2N(R^z)_2$, -$C(O)R^z$, -$C(O)OR^z$, -$C(O)N(R^z)_2$, -C_{1-4} alkylene-C(O)-C_{1-4}alkyl, -C_{1-4} alkylene-$C(O)N(R^z)_2$, C_{1-4} alkylene-$S(O)_2$-C_{1-4}alkyl, or -S-C_{1-4}alkyl;

L^2 is a bond, C_{1-6} alkylene, -O-C_{1-6} alkylene, -S-C_{1-6} alkylene, NR^z, O or S, wherein each C_{1-6} alkylene, -O-C_{1-6} alkylene and -S-C_{1-6} alkylene chain is substituted with 0-2 occurrences of R^2;

L^1 is 



or ;

R^1 is hydrogen, hydroxyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-8} cycloalkyl or 4-15 membered heterocycloalkyl, wherein each aryl, heteroaryl, cycloalkyl or heterocycloalkyl is substituted with 0-3 occurrences of R^5;

each R^2 independently is halogen, deuterium, hydroxyl or C_{1-4} alkyl;

wherein two geminal R^2 groups, together with the atom to which they are attached form a spiro-C_{3-7} cycloalkyl group substituted with 0-2 occurrences of R^w; or wherein two adjacent R^2 groups, together with the atoms to which they are attached form a fused-C_{3-7} cycloalkyl group substituted with 0-2 occurrences of R^w;

R^4 is hydrogen, hydroxyl, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl or cyano;

each R^5 independently is halogen, cyano, oxo, -T-R^y, hydroxyl, -N(R^z)$_2$, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy or -O-C_{2-4} alkynyl;

each R^{6a}, R^{6b} and R^{6c} independently is hydrogen, halogen, hydroxyl, cyano, -N(R^z)$_2$, -C(O)R^z, -C(O)OR^z, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{2-4} alkynyl or C_{3-6} cycloalkyl or R^{6a} and R^{6b}, together with the atom to which they are attached form a fused C_{3-7} cycloalkyl;

R^{6d} is hydrogen, -C(O)-C_{1-8} alkyl or -C(O)-OC_{1-8} alkyl;

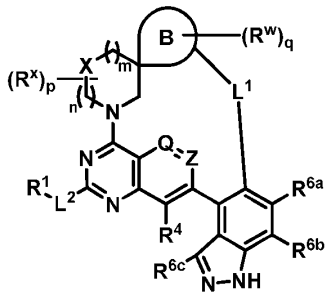
each R^w independently is C_{1-4} alkyl, C_{1-4} alkoxy, -C(O)-C_{1-4} alkyl, -C(O)-O-C_{1-4} alkyl, halogen, hydroxyl or C_{1-4} haloalkyl;

T is C_{1-4} alkylene, -S(O)$_2$-, -C(O)-, -C_{1-4} alkylene-C(O)-, C_{1-4} alkylene-S(O)$_2$- or -S-;

R^y is halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyl, cyano or -N(R^z)$_2$; and

each R^z independently is hydrogen or C_{1-4} alkyl.

2. The compound of claim 1, wherein the compound is a compound of Formula (**I-B**):



(**I-B**)

or a pharmaceutically acceptable salt thereof, wherein;

X is $-CH_2-$ or -O-

Z is C-H, C-halogen, C-CN, C-C_{1-4} alkyl, C-C_{1-4} haloalkyl, C-C_{1-4} alkoxy, C-C_{1-4} haloalkoxy, C-C_{3-7} cycloalkyl or N;

Q is CH, C-halogen, C-C_{1-4} alkyl, C-C_{1-4} haloalkyl or N;

B is a C_{3-7} cycloalkyl or 3-7 membered heterocycloalkyl;

n is 0, 1 or 2;

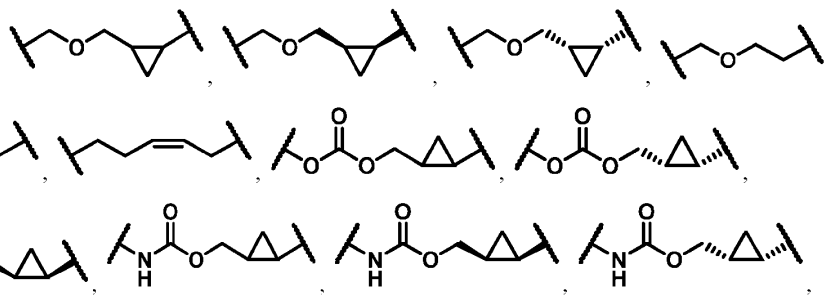
m is 0, 1 or 2;

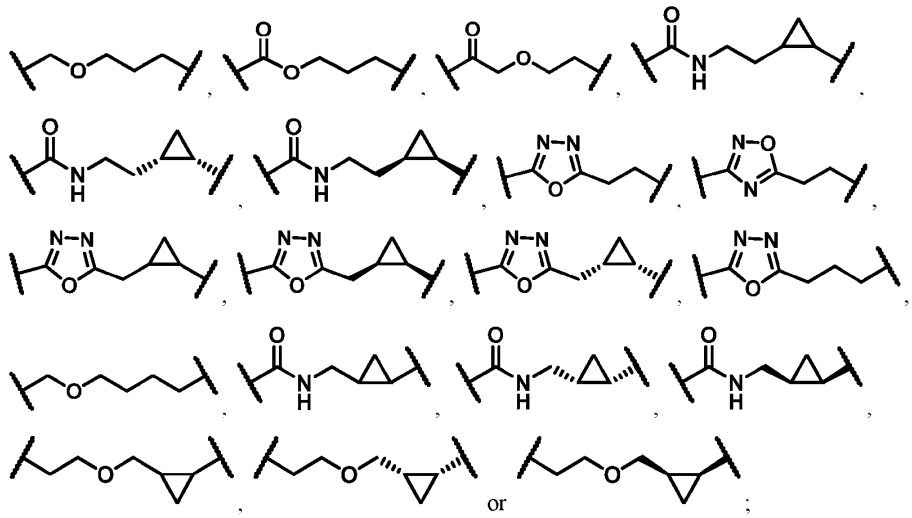
p is 0, 1 or 2;

q is 0, 1 or 2;

each R^x independently is hydroxyl, halogen, oxo, cyano, $-N(R^z)_2$, C_{1-4} alkyl, C_{1-4} deuteroalkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{1-4} hydroxyalkylene, 5-7 membered heteroaryl, $-S(O)_2-C_{1-4}$alkyl, $-S(O)_2N(R^z)_2$, $-C(O)R^z$, $-C(O)OR^z$, $-C(O)N(R^z)_2$, $-C_{1-4}$ alkylene-C(O)-C_{1-4}alkyl, $-C_{1-4}$ alkylene-$C(O)N(R^z)_2$, C_{1-4} alkylene-$S(O)_2-C_{1-4}$alkyl, or -S-C_{1-4}alkyl;

L^2 is a bond, C_{1-6} alkylene, -O-C_{1-6} alkylene, -S-C_{1-6} alkylene, NR^z, O or S, wherein each C_{1-6} alkylene, -O-C_{1-6} alkylene and -S-C_{1-6} alkylene chain is substituted with 0-2 occurrences of R^2;

L^1 is 



or ;

R^1 is hydrogen, hydroxyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-8} cycloalkyl or 4-15 membered heterocycloalkyl, wherein each aryl, heteroaryl, cycloalkyl or heterocycloalkyl is substituted with 0-3 occurrences of R^5;

each R^2 independently is halogen, deuterium, hydroxyl or C_{1-4} alkyl;

wherein two geminal R^2 groups, together with the atom to which they are attached form a spiro-C_{3-7} cycloalkyl group substituted with 0-2 occurrences of R^w; or wherein two adjacent R^2 groups, together with the atoms to which they are attached form a fused-C_{3-7} cycloalkyl group substituted with 0-2 occurrences of R^w; R^4 is hydrogen, hydroxyl, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl or cyano;

each R^5 independently is halogen, cyano, oxo, -T-R^y, hydroxyl, -$N(R^z)_2$, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy or -O-C_{2-4} alkynyl;

each R^{6a}, R^{6b} and R^{6c} independently is hydrogen, halogen, hydroxyl, cyano, -$N(R^z)_2$, -$C(O)R^z$, -$C(O)OR^z$, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{2-4} alkynyl or C_{3-6} cycloalkyl or R^{6a} and R^{6b}, together with the atom to which they are attached form a fused C_{3-7} cycloalkyl;

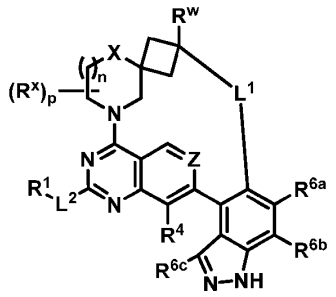
T is C_{1-4} alkylene, -$S(O)_2$-, -C(O)-, -C_{1-4} alkylene-C(O)-, C_{1-4} alkylene-$S(O)_2$- or -S-;

each R^w independently is C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxyl or C_{1-4} haloalkyl;

R^y is halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, hydroxyl, cyano or -$N(R^z)_2$; and

each R^z independently is hydrogen or C_{1-4} alkyl.

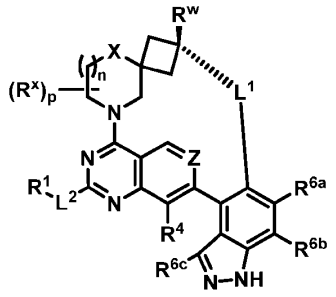
3. The compound or salt of claim 2, wherein the compound is a compound of Formula **(II-B)**:



(II-B)

or a pharmaceutically acceptable salt of said compound, wherein X, Z, p, n, R^x, L^2, L^1, R^1, R^2, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^w, T, R^y and R^z are as defined for Formula **(I-B)**.

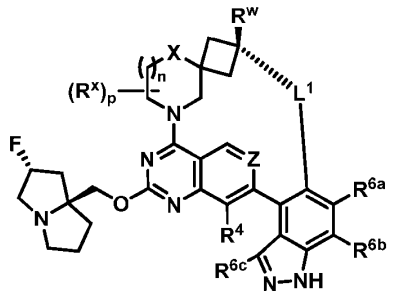
4. The compound or salt of claim 2, wherein the compound is a compound of Formula **(III-B)**:



(III-B)

or a pharmaceutically acceptable salt of said compound, wherein X, Z, p, n, R^x, L^2, L^1, R^1, R^2, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^w, T, R^y and R^z are as defined for Formula **(I-B)**.

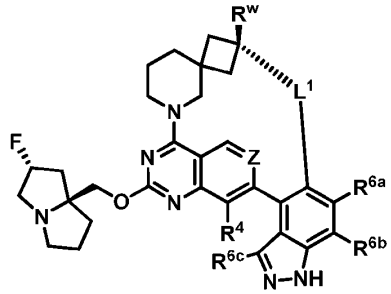
5. The compound or salt of claim 2, wherein the compound is a compound of Formula **(IV-B)**:



(IV-B)

or a pharmaceutically acceptable salt of said compound, wherein X, Z, p, n, R^x, L^1, R^4, R^{6a}, R^{6b}, R^{6c}, R^w, T, R^y and R^z are as defined for Formula (**I-B**).

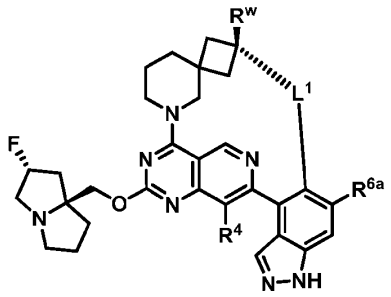
6. The compound or salt of claim 2, wherein the compound is a compound of Formula (**V-B**):



(V-B)

or a pharmaceutically acceptable salt of said compound, wherein Z, L^1, R^4, R^{6a}, R^{6b}, R^{6c}, R^w, T, R^y and R^z are as defined for Formula (**I-B**).

7. The compound or salt of claim 2, wherein the compound is a compound of Formula (**VI-B**):



(VI-B)

or a pharmaceutically acceptable salt of said compound, wherein L^1, R^{6a}, R^{6b}, R^{6c}, R^w, T, R^y and R^z are as defined for Formula **(I-B)**.

8. The compound or salt of any of claims 1-2, wherein Z is N and Q is CH.

9. The compound or salt of any of claims 1-2, wherein Z is N and Q is N.

10. The compound or salt of any of claims 1-9, wherein L^2 is -O-methylene or -O-ethylene substituted with 0-2 occurrences of R^2.

11. The compound or salt of any of claims 1-10, wherein L^2 is -O-methylene substituted with 0 occurrences of R^2.

12. The compound or salt of claim 11, wherein R^1 is 7a-(hexahydro-1H-pyrrolizinyl), 2-azetidinyl or 2-pyrrolidinyl substituted with 0-3 occurrences of R^5.

13. The compound or salt of claim 12, wherein R^1 is 7a-(hexahydro-1H-pyrrolizinyl), 2-azetidinyl or 2-pyrrolidinyl substituted with one occurrence of R^5.

14. The compound or salt of claim 13, wherein R^5 is fluorine or methyl.

15. The compound or salt of claim 12, wherein R^1 is 2-pyrrolidinyl substituted with two occurrences of R^5.

16. The compound or salt of claim 15, wherein R^5 is independently fluorine, ethyl or methyl.

17. The compound or salt of any of claims 1-10, wherein L^2 is -O-methylene substituted with 2 occurrences of R^2.

18. The compound or salt of claim 17, wherein both R^2 are deuterium.

19. The compound or salt of claim 18, wherein R^1 is 7a-(hexahydro-1H-pyrrolizinyl) substituted with one occurrence of R^5.

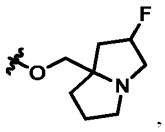
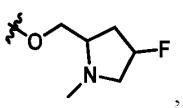
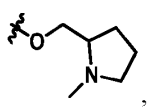
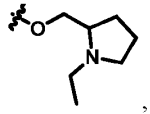
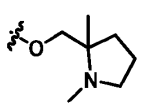
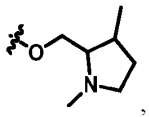
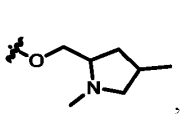
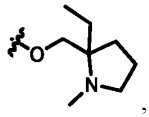
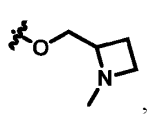
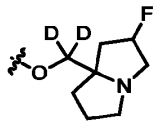
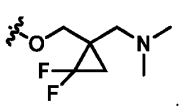
20. The compound or salt of claim 19, wherein R^5 is halogen.

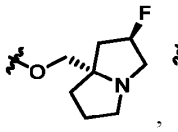
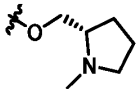
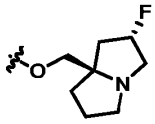
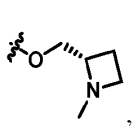
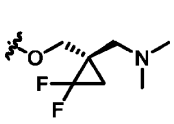
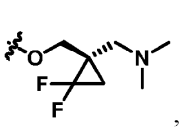
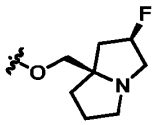
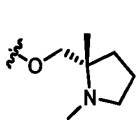
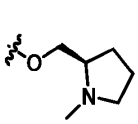
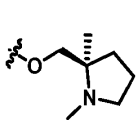
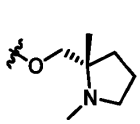
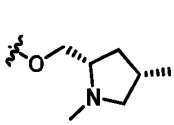
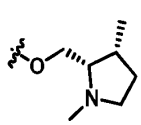
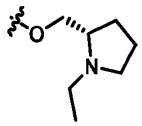
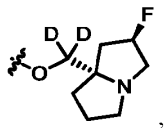
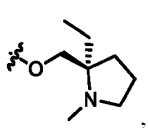
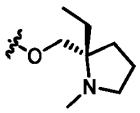
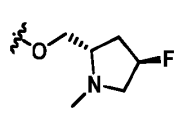
21. The compound or salt of any of claims 1-10, wherein L^2 is -O-*n*-propylene substituted with two occurrences of R^2.

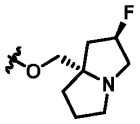
22. The compound or salt of claim 21, wherein two geminal R^2 groups, together with the atom to which they are attached form a spiro-cyclopropyl substituted with two occurrences of R^w.

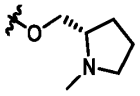
23. The compound or salt of claim 22, wherein both R^w are halogen.

24. The compound or salt of claim 23, wherein R^1 is $-N(R^z)_2$ and both R^z are methyl.

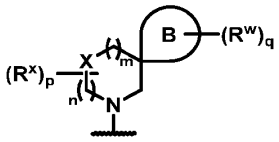
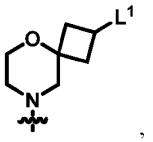
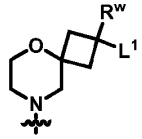
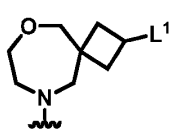
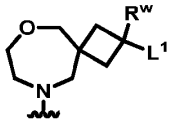
25. The compound or salt of any of claims 1-10, wherein $-L^2-R^1$ is , , , , , , , , , , or .

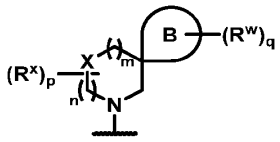
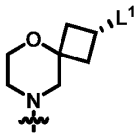
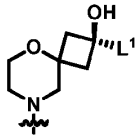
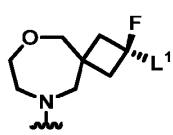
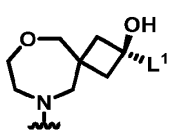
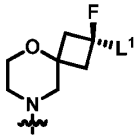
26. The compound or salt of claim 25, wherein -L^2-R^1 is  ,  ,  , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  or .

27. The compound or salt of claim 26, wherein -L^2-R^1 is  .

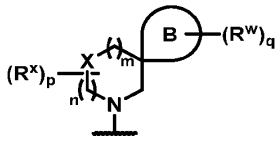
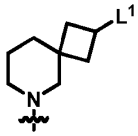
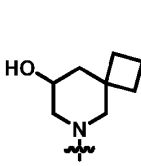
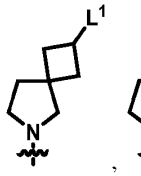
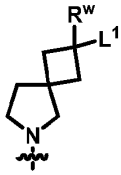
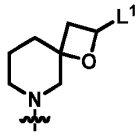
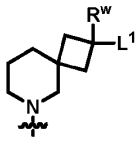
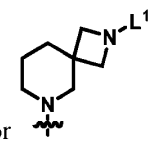
28. The compound or salt of claim 26, wherein -L^2-R^1 is  .

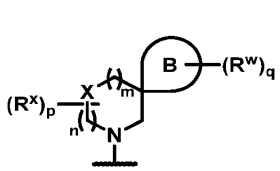
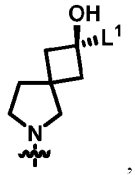
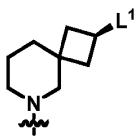
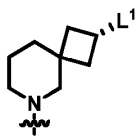
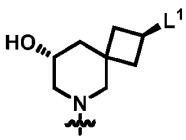
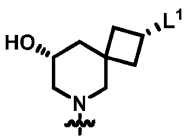
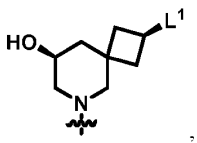
29. The compound or salt of any of claims 1-28, wherein X is O.

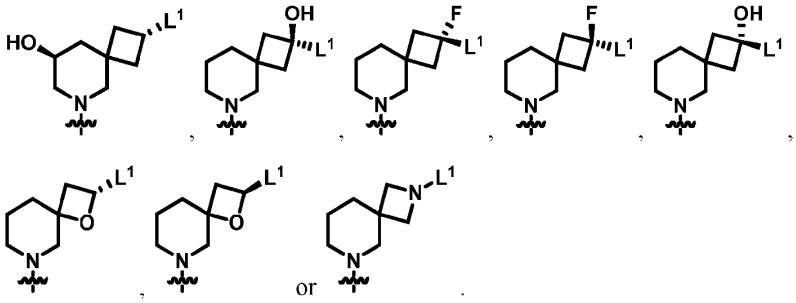
30. The compound or salt of claim 29, wherein  is  ,  ,  or  .

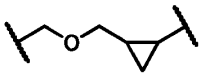
31. The compound or salt of claim 30, wherein  is  ,  ,  ,  or  .

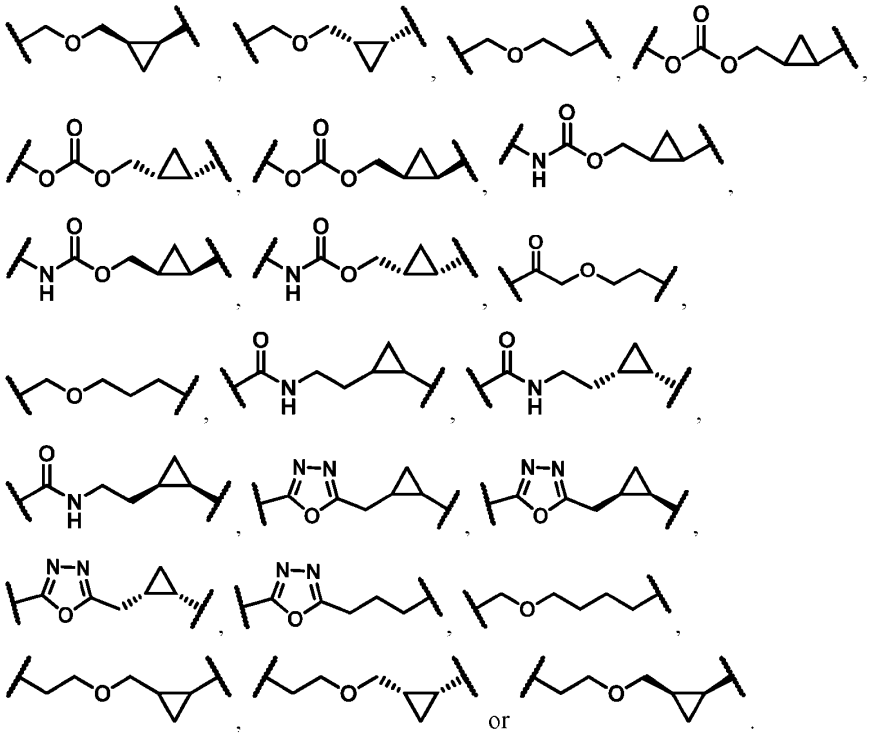
32. The compound or salt of any of claims 1-28, wherein X is -CH_2-.

33. The compound or salt of claim 32, wherein  is  ,  ,  ,  ,  ,  or  .

34. The compound or salt of claim 33, wherein  is  ,  ,  ,  ,  ,  ,



35. The compound or salt of any of claims 1-34, wherein L^1 is ,



36. The compound or salt of any of claims 1-35, wherein R^4 is hydrogen, hydroxyl, halogen, C_{1-4} alkyl or C_{1-4} alkoxy.

37. The compound or salt of claim 36, wherein R^4 is fluorine.

38. The compound or salt of any of claims 1-37, wherein R^{6a}, R^{6b} and R^{6c} are each independently hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy or C_{1-4} haloalkyl.

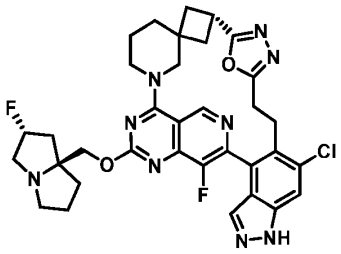
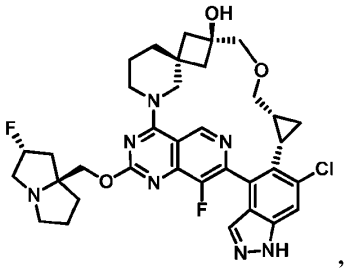
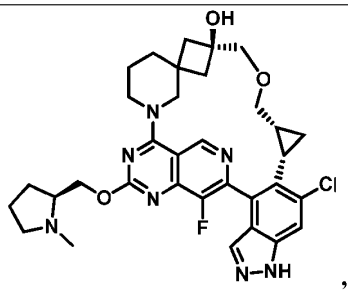
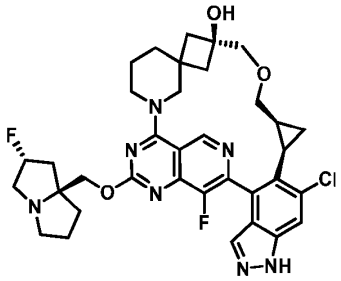
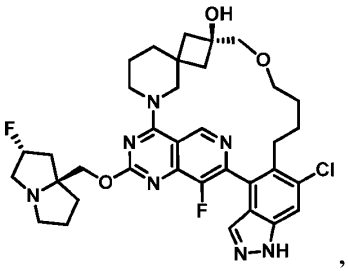
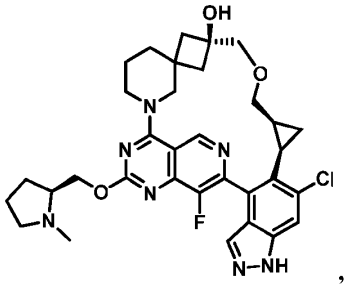
39. The compound or salt of claim 38, wherein R^{6b} and R^{6c} are each hydrogen and R^{6a} is chlorine.

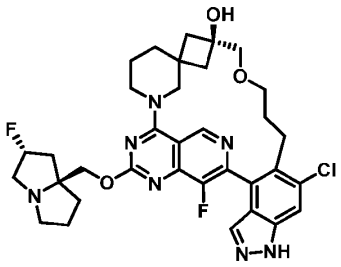
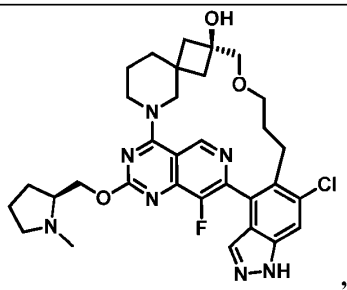
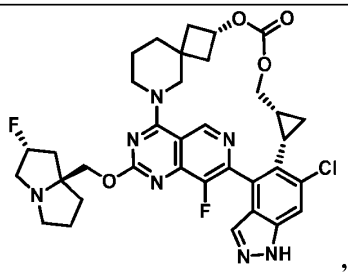
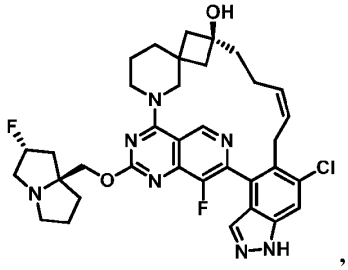
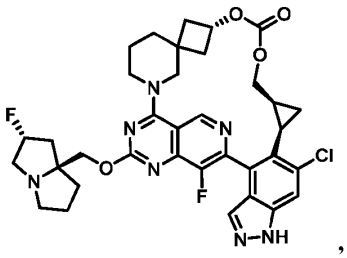
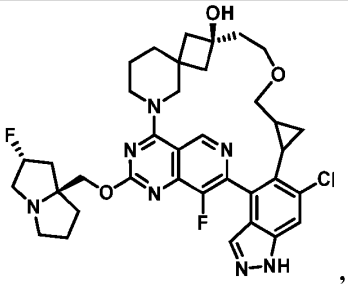
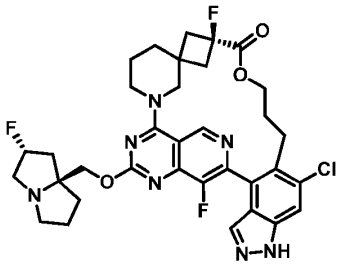
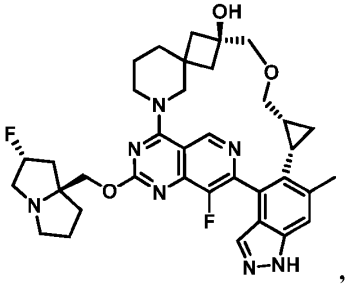
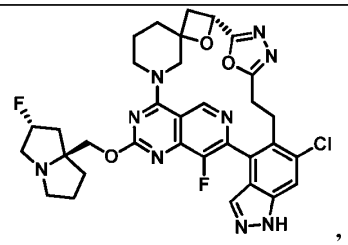
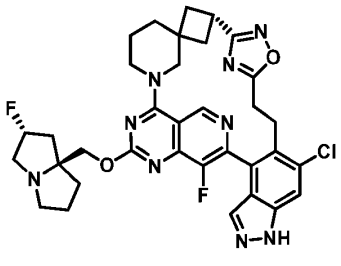
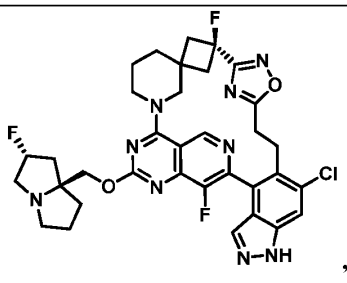
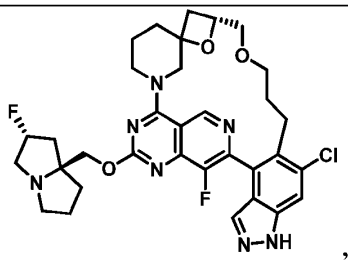
40. The compound or salt of claim 38, wherein R^{6b} and R^{6c} are each hydrogen and R^{6a} is methyl.

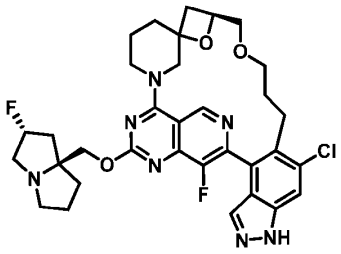
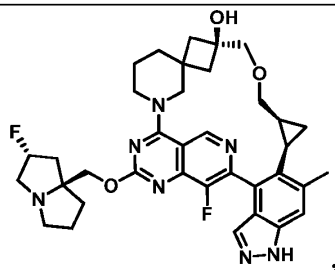
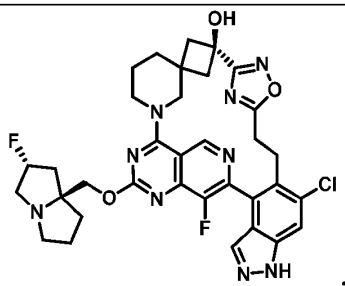
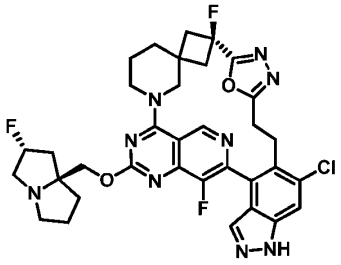
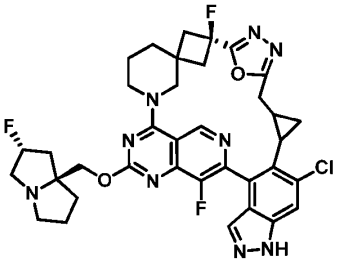
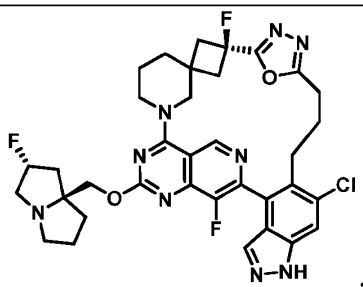
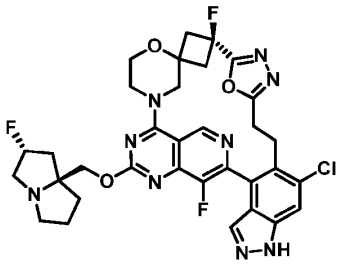
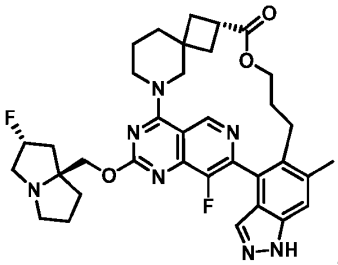
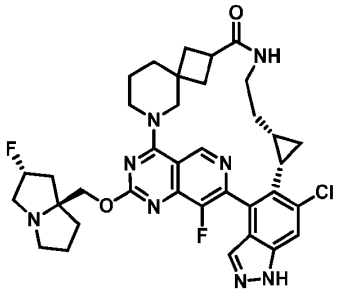
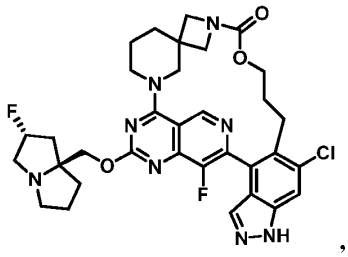
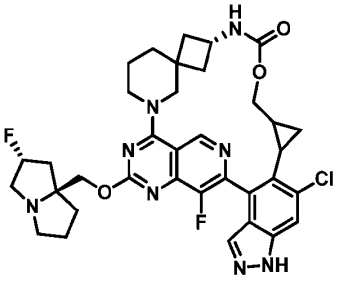
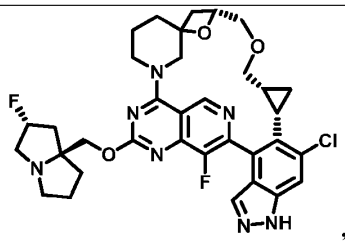
41. The compound or salt of any of claims 1-40, wherein R^{6d} is hydrogen or -C(O)-C_{1-8} alkyl.

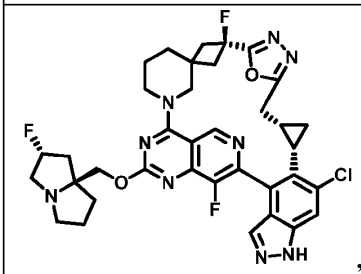
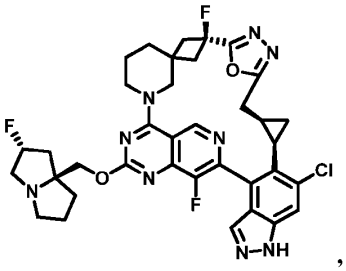
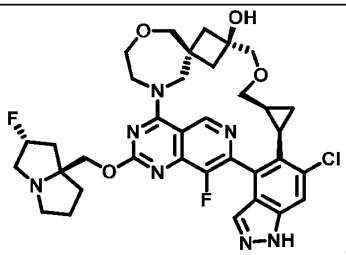
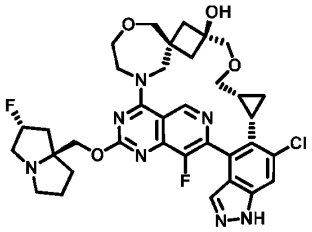
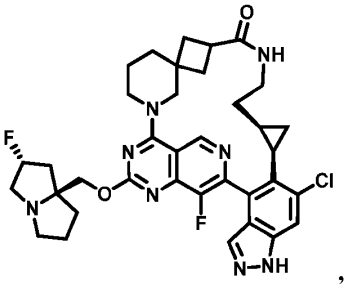
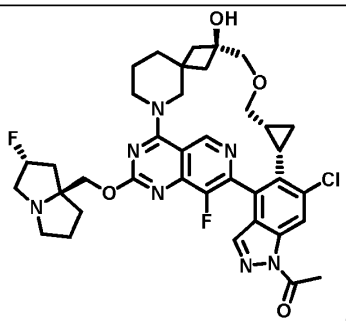
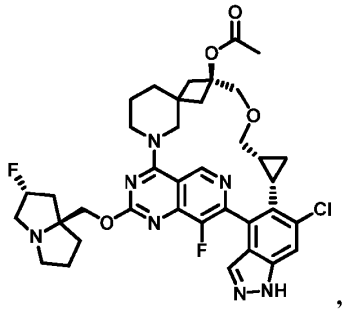
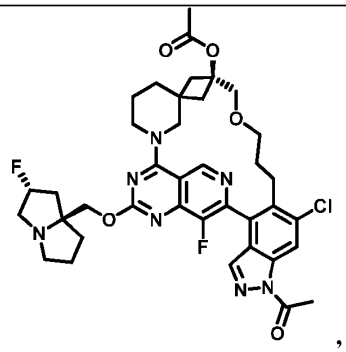
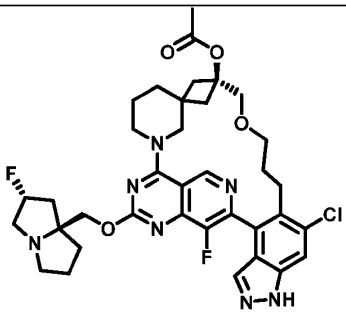
42. The compound or salt of claim 41, wherein R^{6d} is hydrogen.

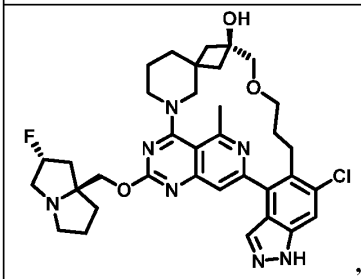
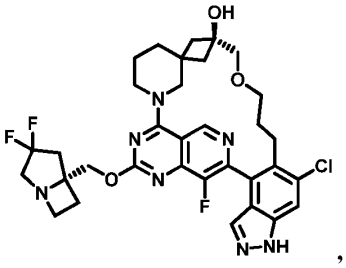
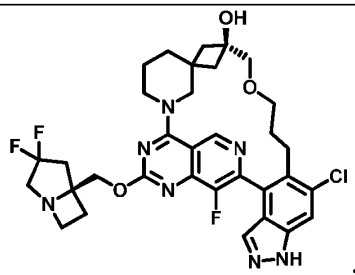
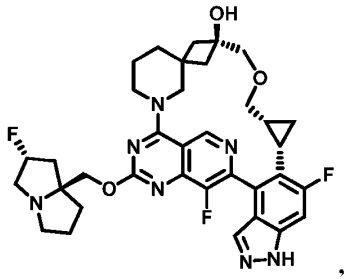
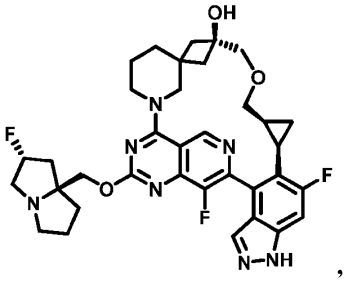
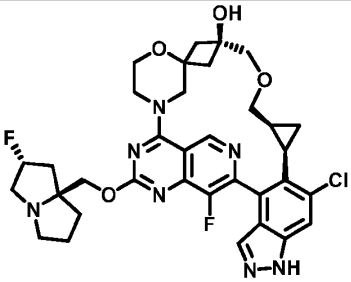
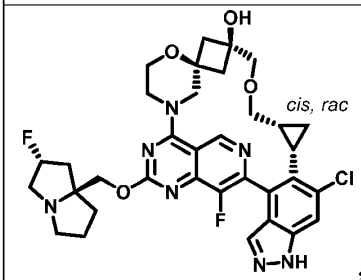
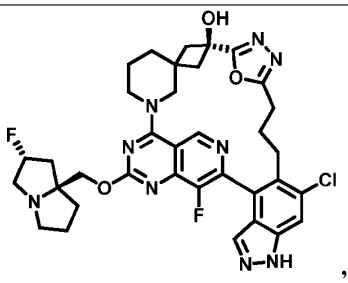
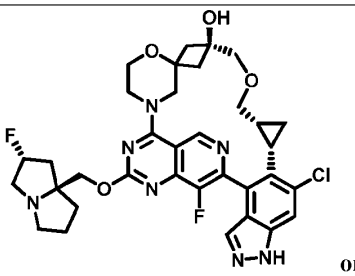
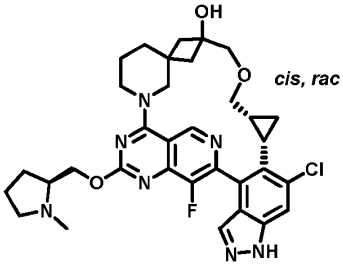
43. The compound or salt of claim 1, wherein the compound is:

Compound	Compound	Compound
 , **1.001**	 , **1.002**	 , **1.003**
 , **1.004**	 , **1.005**	 , **1.006**

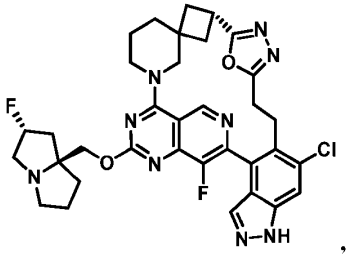
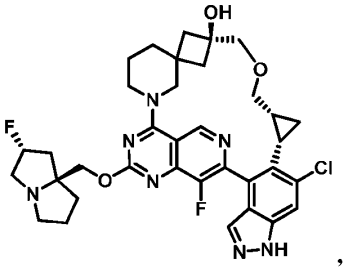
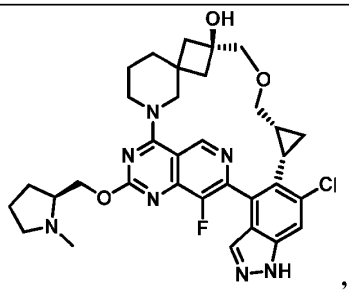
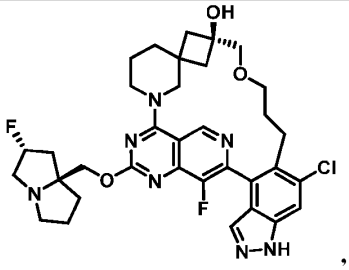
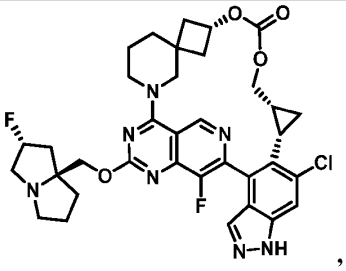
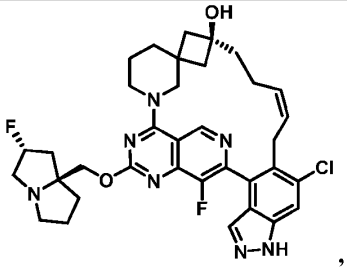
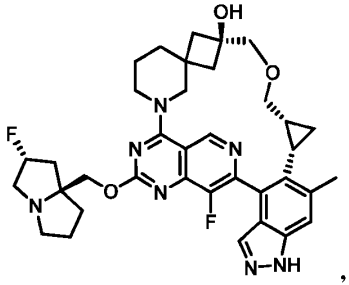
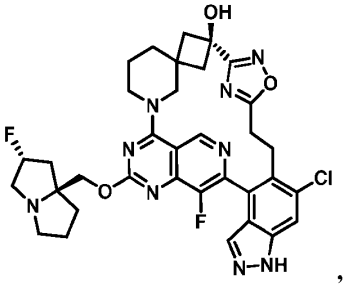
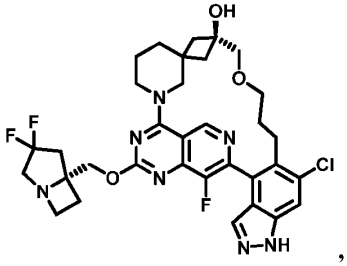
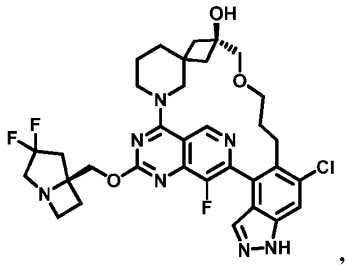
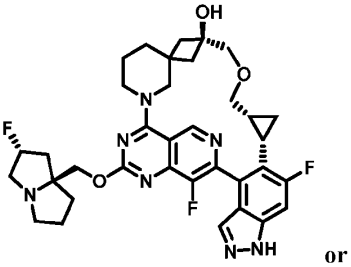
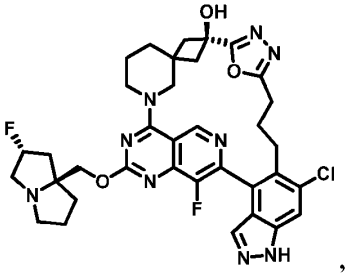
Compound	Compound	Compound
 , 1.010	 , 1.012	 , 1.033
 , 1.035	 , 1.036	 , 1.037
 , 1.039	 , 1.040	 , 1.041
 , 1.042	 , 1.043	 , 1.044

Compound	Compound	Compound
 , 1.046	 , 1.049	 , 1.050
 , 1.052	 , 1.054	 , 1.055
 , 1.059	 , 1.061	 , 1.062
 , 1.065	 , 1.066	 , 1.067

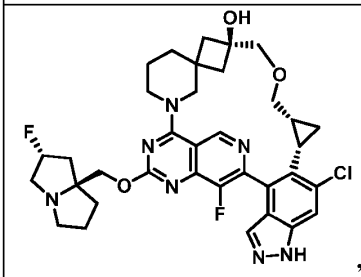
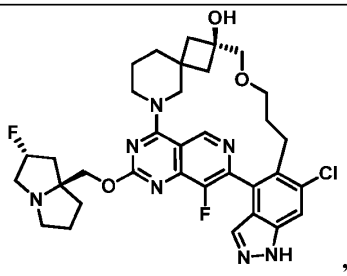
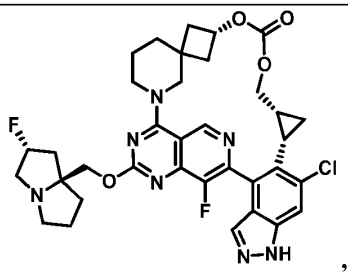
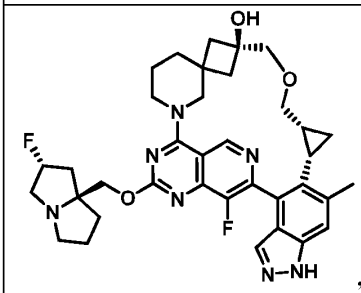
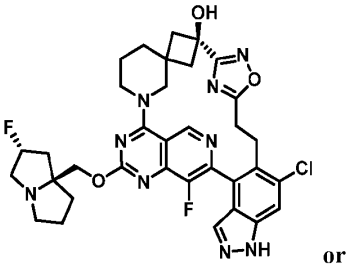
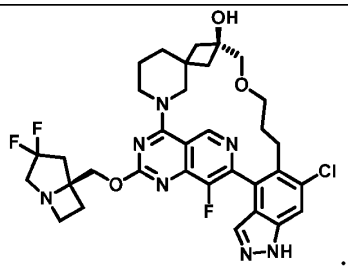
Compound	Compound	Compound
 , 1.068	 , 1.069	 , 1.070
 , 1.071	 , 1.073	 , 1.074
 , 1.075	 , 1.076	 , 1.077

Compound	Compound	Compound
 , 1.081	 , 1.082	 , 1.083
 , 1.084	 , 1.086	 , 1.087
 , 1.088	 , 1.089	 or 1.090
 . 1.091		

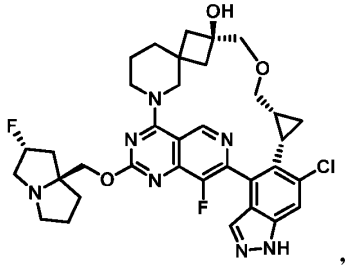
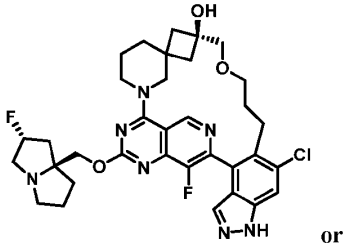
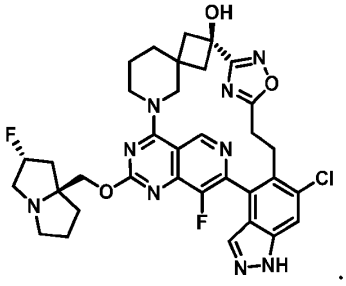
44. The compound or salt of claim 43, wherein the compound is:

Compound	Compound	Compound
 , 1.001	 , 1.002	 , 1.003
 , 1.010	 , 1.033	 , 1.035
 , 1.040	 , 1.050	 , 1.082
 , 1.083	 or 1.084	 , 1.089

45. The compound or salt of claim 44, wherein the compound is:

Compound	Compound	Compound
 , 1.002	 , 1.010	 , 1.033
 , 1.040	 or 1.050	 . 1.083

46. The compound or salt of claim 45, wherein the compound is:

Compound	Compound	Compound
 , 1.002	 or 1.010	 . 1.050

47. A pharmaceutical composition comprising the compound or salt according to any one of claims 1-46 and a pharmaceutically acceptable excipient.

48. A compound or salt according to any one of claims 1-46 or the pharmaceutical composition according to claim 47 for use as a medicament.

49. A compound or salt according to any one of claims 1-46 or the pharmaceutical composition according to claim 47 for use in treating cancer.

50. A compound or salt according to any one of claims 1-46 or the pharmaceutical composition according to claim 47 for use in treating cancer, wherein one or more cells of the cancer express a KRAS G12D, G12V, G12A, G12S, G12R, G13D, Q61H, Q61L, Q61R or G12C mutant protein.

51. The compound, salt or pharmaceutical composition for use of claim 49 or 50, wherein the cancer is pancreatic cancer, colorectal cancer, non-small cell lung cancer, small bowel cancer, appendiceal cancer, cancer of unknown primary, endometrial cancer, mixed cancer types, hepatobiliary cancer, small cell lung cancer, cervical cancer, germ cell cancer, ovarian cancer, gastrointestinal neuroendocrine cancer, bladder cancer, myelodysplastic/myeloproliferative neoplasms, head and neck cancer, esophagogastric cancer, soft tissue sarcoma, mesothelioma, thyroid cancer, leukemia, or melanoma.

52. A use of the compound or salt according to any one of claims 1-46 or the pharmaceutical composition according to claim 47 in the preparation of a medicament for treating cancer.

53. A use of the compound or salt according to any one of claims 1-46 or the pharmaceutical composition according to claim 47 in the preparation of a medicament for treating cancer, wherein one or more cells of the cancer express a KRAS G12D, G12V, G12A, G12S, G12R, G13D, Q61H, Q61L, Q61R or G12C mutant protein.

54. The use according to claim 52 or 53, wherein the cancer is non-small cell lung cancer, small bowel cancer, appendiceal cancer, colorectal cancer, cancer of unknown primary, endometrial cancer, mixed cancer types, pancreatic cancer, hepatobiliary cancer, small cell lung cancer, cervical cancer, germ cell cancer, ovarian cancer, gastrointestinal neuroendocrine cancer, bladder cancer, myelodysplastic/myeloproliferative neoplasms, head and neck cancer, esophagogastric cancer, soft tissue sarcoma, mesothelioma, thyroid cancer, leukemia, or melanoma.

55. A method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound or salt according to any one of claims 1-46 or a pharmaceutical composition according to claim 47.

56. A method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound or salt according to any one of to any one of claims 1-46 or a pharmaceutical composition according to claim 47, wherein one or more cells of the cancer express a KRAS G12D, G12V, G12A, G12S, G12R, G13D, Q61H, Q61L, Q61R or G12C mutant protein.

57. The method according to claim 55 or 56, wherein the cancer is non-small cell lung cancer, small bowel cancer, appendiceal cancer, colorectal cancer, cancer of unknown primary, endometrial cancer, mixed cancer types, pancreatic cancer, hepatobiliary cancer, small cell lung cancer, cervical cancer, germ cell cancer, ovarian cancer, gastrointestinal neuroendocrine cancer, bladder cancer, myelodysplastic/myeloproliferative neoplasms, head and neck cancer, esophagogastric cancer, soft tissue sarcoma, mesothelioma, thyroid cancer, leukemia, or melanoma.

58. The method according to claim 55 or 56, wherein the cancer is non-small cell lung cancer, colorectal cancer, pancreatic cancer, appendiceal cancer, endometrial cancer, esophageal cancer, cancer of unknown primary, ampullary cancer, gastric cancer, small bowel cancer, sinonasal cancer, bile duct cancer, or melanoma.

59. The method according to claim 58, wherein the cancer is non-small cell lung cancer.

60. The method according to claim 58, wherein the cancer is colorectal cancer.

61. The method according to claim 58, wherein the cancer is pancreatic cancer.

62. The method according to anyone of claims 55-61, wherein the subject has a cancer that was determined to have one or more cells expressing the KRAS G12D, G12V, G12A, G12S, G12R, G13D, Q61H, Q61L, Q61R or G12C mutant protein prior to administration of the compound, salt or composition.