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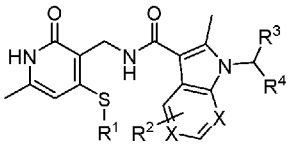
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(54) Title: MODULATORS OF METHYL MODIFYING ENZYMES, COMPOSITIONS AND USES THEREOF



(I)

(57) Abstract: Provided are compounds of Formula (I): and pharmaceutically acceptable salts and compositons thereof, which are useful for treating a variety of conditions associated with methyl modifying enzymes.

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MODULATORS OF METHYL MODIFYING ENZYMES, COMPOSITIONS AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisonal Application No. 62/583,737, filed November 9, 2017, the entire contents of which are incorporated herein by reference.

BACKGROUND

[0002] Eukaryotic chromatin is composed of macromolecular complexes called nucleosomes. A nucleosome has 147 base pairs of DNA wrapped around a protein octamer having two subunits of each of histone protein H2A, H2B, H3, and H4. Histone proteins are subject to post-translational modifications which in turn affect chromatin structure and gene expression. One type of post-translational modification found on histones is methylation of lysine and arginine residues. Histone methylation plays a critical role in the regulation of gene expression in eukaryotes. Methylation affects chromatin structure and has been linked to both activation and repression of transcription (Zhang and Reinberg, Genes Dev. 15:2343-2360, 2001). Enzymes that catalyze attachment and removal of methyl groups from histones are implicated in gene silencing, embryonic development, cell proliferation, and other processes.

[0003] One class of histone methylases is characterized by the presence of a SET domain, comprising about 130 amino acids. EZH2 is an example of a human SET-domain containing methylase. EZH2 associates with EED (Embryonic Ectoderm Development) and SUZ12 (suppressor of zeste 12 homolog) to form a complex known as PRC2 (Polycomb Group Repressive Complex 2) having the ability to tri-methylate histone H3 at lysine 27 (Cao and Zhang, Mol. Cell 15:57-67, 2004). PRC2 complexes can also include RBAP46 and RBAP48 subunits. Another example is the related methylase EZH1.

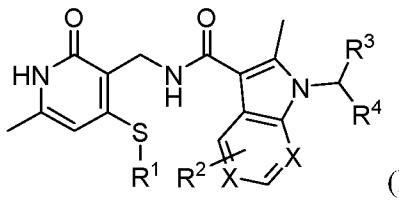
[0004] The oncogenic activities of EZH2 have been shown by a number of studies in various different cancer types. ~15-20% GCB-DLBCLs harbor a gain-of-function mutation in EZH2 (Y641 residue) and these cells are hypersensitive to EZH2 inhibition both *in vitro* and *in vivo* (McCabe et al, 2012; Bradley et al, 2014). In cell line experiments, over-expression of EZH2 induces cell invasion, growth in soft agar, and motility, while knockdown of EZH2 inhibits cell proliferation and cell invasion (Kleer et al., 2003, Proc. Nat. Acad. Sci. USA 100:11606-11611; Varambally et al., (2002), "The polycomb group protein EZH2 is involved in progression of prostate cancer," Nature 419, 624-629). It has been shown that EZH2

represses the expression of several tumor suppressors, including E-cadherin, DAB2IP and RUNX3 among others. In xenograft models, EZH2 knockdown inhibits tumor growth and metastasis. It has been shown that down modulation of EZH2 in murine models blocks prostate cancer metastasis (Min et al., "An oncogene-tumor suppressor cascade drives metastatic prostate cancer by coordinately activating Ras and nuclear factor- kappaB," Nat Med. 2010 Mar; 16(3):286-94). Recently, it was demonstrated that EZH2 is over-expressed in neuroendocrine tumors and inhibition of EZH2 in mouse tumors restore androgen dependence (Ku et al, Science, 355, 2017). EZH2 overexpression is associated with aggressiveness of certain cancers such as breast cancer (Kleer et al., Proc. Nat. Acad. Sci. USA 100:11606-11611, 2003). Recent studies also suggest that prostate cancer specific oncogenic fusion gene TMPRSS2-ERG induces repressive epigenetic programs via direct activation of EZH2 (Yu et al., "An Integrated Network of Androgen Receptor, Polycomb, and TMPRSS2-ERG Gene Fusions in Prostate Cancer Progression," Cancer Cell. 2010 May 18;17(5):443-454).

[0005] Given their role in the regulation of diverse biological processes, methyl modifying enzymes, in particular EZH2 and mutant forms thereof, are attractive targets for modulation.

SUMMARY

[0006] Disclosed herein are compounds and pharmaceutically acceptable compositions thereof that are modulators of EZH2 (See e.g., **Table 1**). Such compounds include those of structural formula **I**:



(I);

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^3, and R^4 are defined and described herein.

[0007] In one aspect, introducing a thiol group (-SR^1) on the methyl pyridinone of the disclosed compounds was found to have a profound effect on the residence time. See e.g., **Table 3**, where replacement of a methoxy, methyl or chlorine for -SCH_3 resulted in over a 17 fold increase in residence time, and afforded compounds with improved cellular activity.

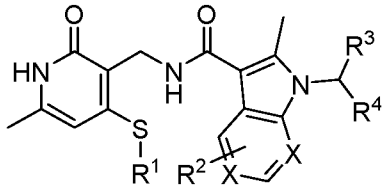
[0008] The disclosed compounds, pharmaceutically acceptable salts, and pharmaceutically acceptable compositions, are useful for treating a variety of conditions

associated with methyl modifying enzymes. These conditions include e.g., one or more cancers.

DETAILED DESCRIPTION

1. *General Description of Compounds*

[0009] In certain embodiments, the present disclosure provides a compound of Formula **I**:



(**I**);

or a pharmaceutically acceptable salt thereof, wherein

each X is independently CH or N;

R^1 is $(C_1\text{-}C_4)$alkyl, -$(C_3\text{-}C_5)$cycloalkyl, or $(C_1\text{-}C_4)$haloalkyl;

R^2 is hydrogen, halo, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy, or -CN;

R^3 is $(C_1\text{-}C_4)$alkyl or halo$(C_1\text{-}C_4)$alkyl;

R^4 is $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkoxy, -$(C_1\text{-}C_4)$alkylOH, -$(C_1\text{-}C_4)$alkylO$(C_1\text{-}C_4)$alkyl, phenyl, 5-6 membered heteroaryl, monocyclic $(C_3\text{-}C_7)$cycloalkyl, bridged bicyclic $(C_5\text{-}C_8)$cycloalkyl, or 4-7 membered monocyclic heterocyclyl, wherein said phenyl, heteroaryl, monocyclic cycloalkyl, bridged bicyclic cycloalkyl, and heterocyclyl are each optionally substituted with 1 to 3 groups selected from R^5;

R^5 is selected from $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, halo$(C_3\text{-}C_6)$cycloalkyl, -$(C_1\text{-}C_4)$alkylOH, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy, halo, nitrile, amide, urea, carbamate, sulfonamide, hydroxyl, oxo, OR^6, -OC(O)$(C_1\text{-}C_4)$alkyl, -C(O)$(C_1\text{-}C_4)$alkyl, -C(O)$(C_1\text{-}C_4)$alkylOH, -C(O)$(C_1\text{-}C_4)$alkylNH$(C_1\text{-}C_4)$alkyl, -C(O)$(C_1\text{-}C_4)$alkylN(($C_1\text{-}C_4$)alkyl)$_2$, -C(O)$(C_1\text{-}C_4)$alkylNH$_2$, -SO$_2$$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkyl-O-$(C_1\text{-}C_4)$alkyl, substituted phenyl, 5-6 membered heteroaryl, 4-7 membered heterocyclyl, and NR^AR^B, , wherein said cycloalkyl for R^5 is optionally substituted with -O$(C_1\text{-}C_4)$alkyl;

R^A is hydrogen, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, 4-7 membered heterocyclyl, or $(C_1\text{-}C_4)$alkyl-O-$(C_1\text{-}C_4)$alkyl;

R^B is hydrogen, $(C_1\text{-}C_4)$alkyl, -$(C_3\text{-}C_5)$cycloalkyl, or 4-7 membered heterocyclyl, wherein said $(C_1\text{-}C_4)$alkyl for R^B is optionally substituted with 1 to 3 groups selected from halo, phenyl, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, and OH and wherein said heterocyclyl, -$(C_3$-

C_5)cycloalkyl for R^B is optionally substituted with 1 to 3 groups selected from (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, -O(C_1-C_4)alkyl, and -C(=O)O(C_1-C_4)alkyl; or

R^A and R^B taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclyl optionally substituted with 1 to 3 groups selected from halo,(C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, oxo, halo(C_1-C_4)alkoxy, 5-6 membered heteroaryl, (C_3-C_6)cycloalkyl, -SO_2(C_1-C_4)alkyl, NMe_2, hydroxy, cyano, spirooxetanyl and (C_1-C_4)cycloalkoxy optionally substituted with (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, or (C_1-C_4)alkoxy; and

R^6 is (C_3-C_6)cycloalkyl, 4-7 membered heterocyclyl, or 5-6 membered heteroaryl, -O(C_1-C_4)alkyl, wherein said 4-7 membered heterocyclyl for R^6 is optionally substituted with 1 or 2 (C_1-C_4)alkyl groups.

2. Definitions

[0010] The terms "halo" and "halogen" as used herein refer to an atom selected from fluorine (fluoro, -F), chlorine (chloro, -Cl), bromine (bromo, -Br), and iodine (iodo, -I).

[0011] The term "alkyl," as used herein, refers to a monovalent saturated, straight- or branched-chain hydrocarbon radical, having unless otherwise specified, 1-8 carbon atoms. Examples of alkyl radicals include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, sec-pentyl, iso-pentyl, tert-butyl, n-pentyl, neopentyl, n-hexyl, sec-hexyl, and the like.

[0012] The term "alkoxy," as used herein, refers to an alkyl group which is attached to another moiety via an oxygen atom (–O(alkyl)). Non-limiting examples include e.g., methoxy, ethoxy, propoxy, and butoxy.

[0013] The term "haloalkyl" includes mono, poly, and perhaloalkyl groups where the halogens are independently selected from fluorine, chlorine, bromine, and iodine.

[0014] "Haloalkoxy" is a haloalkyl group which is attached to another moiety via an oxygen atom such as, e.g., but are not limited to –$OCHCF_2$ or –OCF_3.

[0015] The term "aryl" refers to an aromatic carbocyclic ring system having, unless otherwise specified, a total of 6 to 14 ring members, e.g., phenyl, naphthyl, and the like. The term "aryl" may be used interchangeably with the term "aryl ring", "aryl group", "aryl moiety," or "aryl radical". It will be understood that when specified, optional substituents on an aryl group (e.g., in the case of an optionally substituted aryl or aryl which is optionally substituted) may be present on any substitutable position, i.e., any ring carbon substituted with hydrogen. In one aspect, substituents for a substituted phenyl group include halo, (C_1-

C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy. In other aspect, include halo, (C_1-C_4)alkyl, and halo(C_1-C_4)alkyl.

[0016] The term "carbocyclyl" (also referred to herein as "carbocycle" or "cycloaliphatic", as used herein, means a monocyclic, bicyclic (e.g., a bridged or spiro bicyclic ring), polycyclic (e.g., tricyclic), or fused hydrocarbon ring system that is completely saturated or that contains one or more units of unsaturation, but where there is no aromatic ring. Cycloalkyl is a completely saturated carbocycle. Monocyclic cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Bridged bicyclic cycloalkyl groups include, without limitation, bicyclo[3.2.1]octane, bicyclo[2.2.1]heptane, bicyclo[3.1.0]hexane, bicyclo[1.1.1]pentane, and the like. Spiro bicyclic cycloalkyl groups include, e.g., spiro[3.6]decane, spiro[4.5]decane, and the like. Fused cycloalkyl rings include, e.g., decahydronaphthalene, octahydropentalene, and the like. It will be understood that when specified, optional substituents on a carbocyclyl (e.g., in the case of an optionally substituted carbocyclyl or carbocyclyl which is optionally substituted) may be present on any substitutable position and, include, *e.g.*, the position at which the carbocyclyl group is attached.

[0017] The term "oxo" means the group "=O".

[0018] The term "amide" means the group $-C(O)NR^xR^y$, where R^x and R^y are each independently hydrogen or (C_1-C_4)alkyl.

[0019] The term "urea" means the group $-NR^xC(O)NR^xR^y$, where R^x and R^y are each independently hydrogen or (C_1-C_4)alkyl.

[0020] The term "carbamate" means the group $-OC(O)NR^xR^y$, where R^x and R^y are each independently hydrogen or (C_1-C_4)alkyl.

[0021] The term "sulfonamide" means the group $-S(O)_2NR^xR^y$, where R^x and R^y are each independently hydrogen or (C_1-C_4)alkyl.

[0022] The term "heteroaryl" used alone or as part of a larger moiety as in "heteroarylalkyl", "heteroarylalkoxy", or "heteroarylaminoalkyl", refers to a 5-10 -membered aromatic radical containing 1-4 heteroatoms selected from N, O, and S, and includes, for example, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring", "heteroaryl group", or "heteroaromatic". The terms "heteroaryl" also include groups in which a heteroaromatic ring is fused to one or more aromatic rings, where the radical or point of attachment is on the

heteroaromatic ring. Nonlimiting examples include indolyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, quinazolinyl, and quinoxalinyl. It will be understood that when specified, optional substituents on a heteroaryl group may be present on any substitutable position (carbon and nitrogen).

[0023] The term "heterocyclyl" means a 3-12 membered (e.g., a 4-, 5-, 6- and 7-membered) saturated or partially unsaturated heterocyclic ring containing 1 to 4 heteroatoms independently selected from N, O, and S. It can be mononcyclic, bicyclic (e.g., a bridged, fused, or spiro bicyclic ring), or tricyclic. The terms "heterocycle", "heterocyclyl", "heterocyclyl ring", "heterocyclic group", "heterocyclic moiety", and "heterocyclic radical", are used interchangeably herein. A heterocyclyl ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothienyl, terahydropyranyl, pyrrolidinyl, pyridinonyl, pyrrolidonyl, piperidinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, morpholinyl, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl, oxetanyl, azetidinyl and tetrahydropyrimidinyl. A heterocyclyl group may be mono- or bicyclic. The term "heterocyclyl" also includes, e.g., unsaturated heterocyclic radicals fused to another unsaturated heterocyclic radical or aryl or heteroaryl ring, such as for example, tetrahydronaphthyridine, indolinone, dihydropyrrolotriazole, imidazopyrimidine, quinolinone, dioxaspirodecane. It will also be understood that when specified, optional substituents on a heterocyclyl group may be present on any substitutable position and, include, *e.g.*, the position at which the heterocyclyl is attached (e.g., in the case of an optionally substituted heterocyclyl or heterocyclyl which is optionally substituted).

[0024] The term "spiro" refers to two rings that shares one ring atom (e.g., carbon).

[0025] The term "fused" refers to two rings that share two adjacent ring ring atoms with one another.

[0026] The term "bridged" refers to two rings that share three ring atoms with one another.

[0027] Structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers, if present. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures

of the present compounds are within the scope of the present disclosure. Tautomeric forms of the compounds are also included.

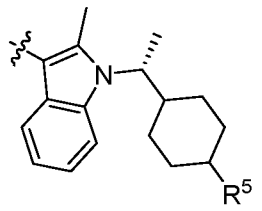
[0028] "Geometric isomer" means isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring, or to a bridged bicyclic system. Atoms (other than H) on each side of a carbon-carbon double bond may be in an E (substituents are on opposite sides of the carbon-carbon double bond) or Z (substituents are oriented on the same side) configuration. "R," "S," "S*," "R*," "E," "Z," "cis," and "trans," indicate configurations relative to the core molecule. When a disclosed compound is named or depicted by structure without indicating a particular geometric isomer form, it is to be understood that the name or structure encompasses one geometric isomer free of other geometric isomers, mixtures of geometric isomers, or mixtures of all geometric isomers.

[0029] Unless otherwise specified, when the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight pure relative to all of the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight optically pure. Percent optical purity by weight is the ratio of the weight of the enantiomer over the weight of the enantiomer plus the weight of its optical isomer. Enantiomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts which may be separated, for example, by crystallization; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, supercritical fluid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or supercritical fluid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. Specific enantiomers may also be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

[0030] Unless otherwise specified, when a disclosed compound is named or depicted by structure without indicating the stereochemistry, and the compound has at least one chiral center, the name or structure encompasses one enantiomer of compound free from the corresponding optical isomer, a racemic mixture of the compound and mixtures enriched in one enantiomer relative to its corresponding optical isomer.

[0031] Unless otherwise specified, when a disclosed compound is named or depicted by structure without indicating the stereochemistry and has at least two chiral centers, the name or structure encompasses a diastereomer free of other diastereomers, a pair of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s) and mixtures of diastereomeric pairs in which one diastereomeric pair is enriched relative to the other diastereomeric pair(s), for example, by a molar excess of at least 60%, 70%, 80%, 90%, 99% or 99.9%. Diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated.

[0032] Unless otherwise specified, when only some of the stereochemical centers in a disclosed compound are depicted or named by structure, the named or depicted configuration is enriched relative to the remaining configurations, for example, by a molar excess of at least 60%, 70%, 80%, 90%, 99% or 99.9%. For example, the substructure:



means that that the configuration about the chiral carbon is stereochemically enriched as R (e.g., by a molar excess of at least 60%, 70%, 80%, 90%, 99% or 99.9%) and that the geometry about the cyclohexyl may be cis or trans, or a mixture thereof.

[0033] Unless otherwise specified, when referred to as part of the structure or name, isomer 1 and isomer 2 refer to *cis* and *trans* isomers of the 1,4-disubstituted cyclohexane or a 1,3-disubstituted cyclobutene. Isomer 1 is either the product eluting with the shortest retention time when isolated from a chiral column chromatography purification or regular phase chromatography purification or it is the product with the higher Rf when isolated via prep-TLC. In some cases, only one of the *cis* or *trans* isomers is isolated during the synthesis. These products have been referred to as single isomers rather than isomer 1 or isomer 2 because their counterpart was not synthesized as a relative reference.

[0034] The term "patient," as used herein, means an animal, such as a mammal, and such as a human. The terms "subject" and "patient" may be used interchangeably.

[0035] The term "pharmaceutically acceptable carrier" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with

which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions described herein include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0036] The terms "treatment," "treat," and "treating" refer to reversing, alleviating, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. Treatment may also be continued after symptoms have resolved, for example to delay recurrence.

[0037] The term "effective amount" or "therapeutically effective amount" refers to an amount of a compound described herein that will elicit a biological or medical response of a subject e.g., a dosage of between 0.01 - 100 mg/kg body weight/day.

3. Compounds

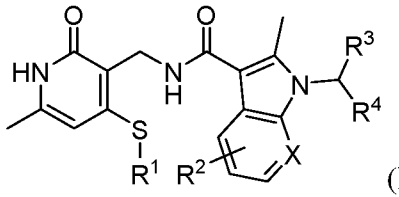
[0038] In a first embodiment, provided herein is a compound of Formula **I**, wherein

R^5 is selected from $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, halo$(C_3\text{-}C_6)$cycloalkyl, -$(C_1\text{-}C_4)$alkylOH, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy, halo, nitrile, amide, urea, carbamate, sulfonamide, hydroxyl, oxo, $(C_1\text{-}C_4)$alkyl-O-$(C_1\text{-}C_4)$alkyl, substituted phenyl, 5-6 membered heteroaryl and NR^AR^B;

R^B is hydrogen, $(C_1\text{-}C_4)$alkyl or 4-7 membered heterocyclyl, wherein said $(C_1\text{-}C_4)$alkyl for R^B is optionally substituted with 1 to 3 groups selected from halo, phenyl, $(C_1\text{-}C_4)$alkoxy, and OH and wherein said heterocyclyl for R^B is optionally substituted with 1 to 3 groups selected from $(C_1\text{-}C_4)$alkyl, -O$(C_1\text{-}C_4)$alkyl, and -C(=O)O$(C_1\text{-}C_4)$alkyl; or

R^A and R^B taken together with the nitrogen atom to which they are attached form a 4-7 membered heterocyclyl optionally substituted with 1 to 3 groups selected from halo,$(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, oxo, halo$(C_1\text{-}C_4)$alkoxy, and $(C_1\text{-}C_4)$cycloalkoxy optionally substituted with $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, or $(C_1\text{-}C_4)$alkoxy; and the remaining variables are as described above.

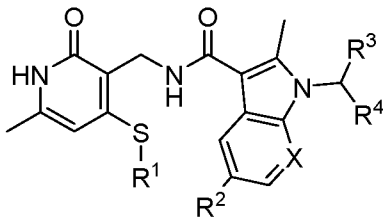
[0039] In a second embodiment, the compound of Formula **I** is of the Formula **Ia**:



(**Ia**);

or a pharmaceutically acceptable salt thereof, wherein the variables are as described above for Formula **I** or the first embodiment.

[0040] In a third embodiment, the compound of Formula **I** is of the Formula **Ia'**:

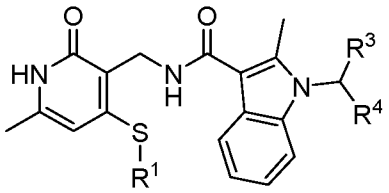


(**Ia'**);

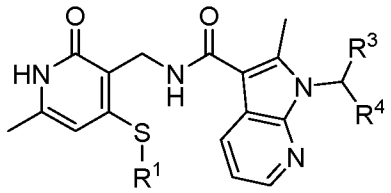
or a pharmaceutically acceptable salt thereof, wherein the variables are as described above for Formula **I** or the first embodiment.

[0041] In a fourth embodiment, R^2 in the compound of Formula **I**, **Ia**, or **Ia'** is hydrogen or fluorine, wherein the variables are as described above for Formula **I** or the first embodiment.

[0042] In a fifth embodiment, the compound of Formula **I** is of the Formula **II** or **IIa**:



(**II**); or



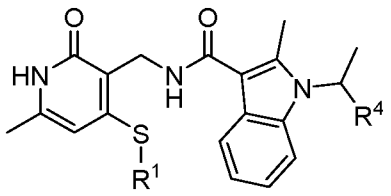
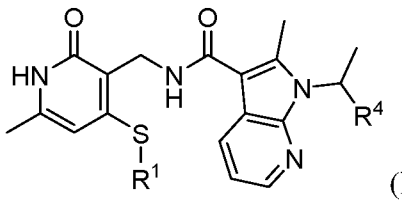
(**IIa**);

or a pharmaceutically acceptable salt thereof, wherein the variables are as described above for Formula **I** or the first embodiment.

[0043] In a sixth embodiment, R^3 in the compound of Formula **I**, **Ia**, **Ia'**, **II**, or **IIa** is (C_1-C_4)alkyl; R^4 is -(C_1-C_4)alkylOH, -(C_1-C_4)alkylO(C_1-C_4)alkyl, monocyclic (C_3-C_6)cycloalkyl, bridged bicyclic (C_5-C_8)cycloalkyl, or 4-7 membered heterocyclyl, wherein said cycloalkyl and heterocyclyl are each optionally substituted with 1 to 2 groups selected from R^5; R^5 is selected from (C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, hydroxyl, (C_1-C_4)alkoxy, halo, -(C_1-C_4)alkylOH, halo(C_1-C_4)alkyl, and NR^AR^B; and R^B is hydrogen, (C_1-C_4)alkyl or 4-7 membered heterocyclyl, wherein said (C_1-C_4)alkyl for R^B is optionally substituted with 1 to 3 groups selected from halo, phenyl, and OH and wherein said heterocyclyl for R^B is optionally substituted with 1 to 3 groups selected from (C_1-C_4)alkyl, -O(C_1-C_4)alkyl, and -C(=O)O(C_1-

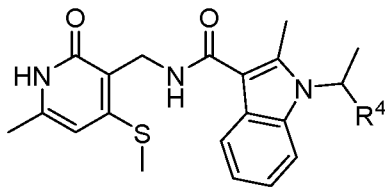
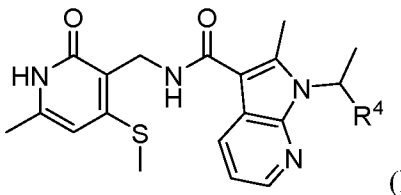
C_4)alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached form a 4-7 membered heterocyclyl optionally substituted with 1 or 2 groups selected from (C_1-C_4)alkyl, halo(C_1-C_4)alkoxy, halo, and (C_1-C_4)alkoxy, wherein the variables are as described above for Formula **I** or the first embodiment.

[0044] In a seventh embodiment, the compound of Formula **I**, **Ia**, **Ia'**, **II**, or **IIa** is of the Formula **III** or **IIIa**:


(**III**); or

(**IIIa**);

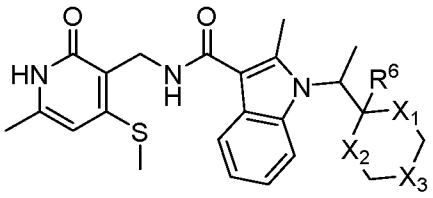
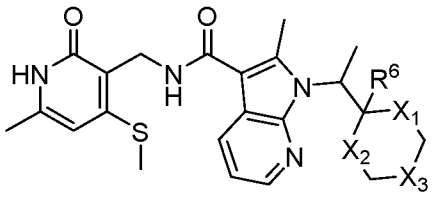
or a pharmaceutically acceptable salt thereof, wherein the remaining variables are as described for Formula **I** or the first or sixth embodiment.

[0045] In an eighth embodiment, the compound of any one of Formulae **I** to **IIIa** is of the Formula **IV** or **IVa**:


(**IV**); or

(**IVa**);

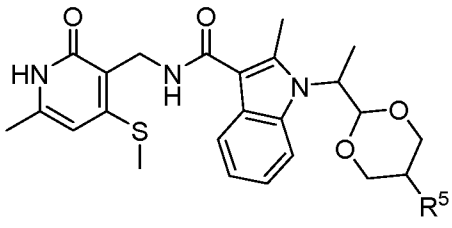
or a pharmaceutically acceptable salt thereof, wherein the remaining variables are as described for Formula **I** or the first or sixth embodiment.

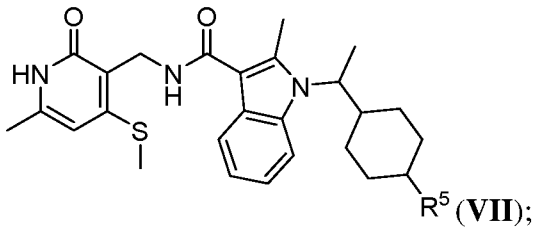
[0046] In a ninth embodiment, the compound of any one of Formulae **I** to **IVa** is of the Formula **V** or **Va**:

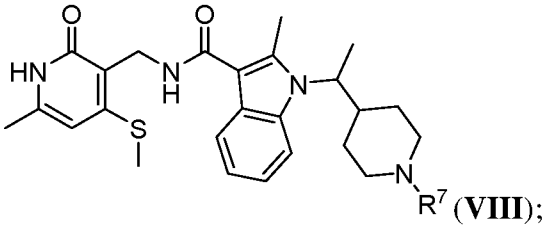

(**V**); or

(**Va**);

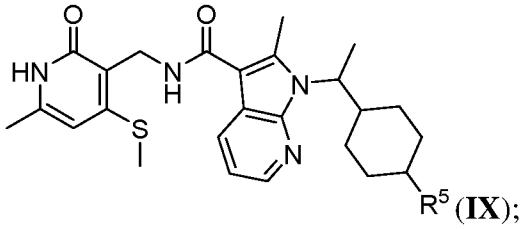
or a pharmaceutically acceptable salt thereof, wherein X_1 and X_2 are each independently absent, O, or CH_2; X_3 is O, NH, -NR^7, CH_2, or CHR^5; R^6 is hydrogen or R^6 and X_3 taken together with their intervening ring atoms form a bridged bicyclic (C_5-C_8)cycloalkyl; and R^7 is (C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, -(C_1-C_4)alkylOH, or halo(C_1-C_4)alkyl; provided that X_3 is not O, NH, or NR^7 when X_1 and X_2 are each O, wherein the remaining variables are as described for Formula **I** or the first or sixth embodiment.

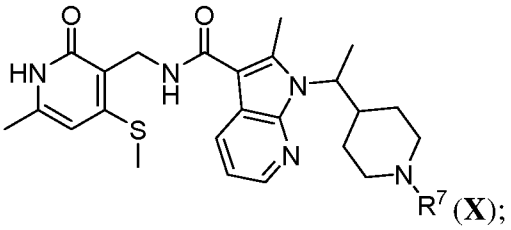
[0047] In a tenth embodiment, the compound of any one of Formulae **I** to **V** is of the Formula **VI**, **VII**, **VIII**, **IX**, **X**, or **XI**:

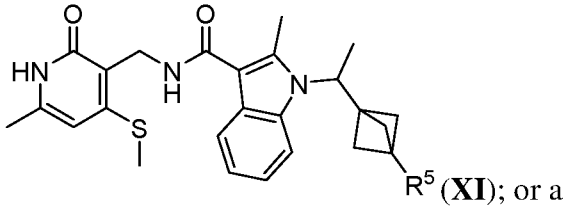

(VI);

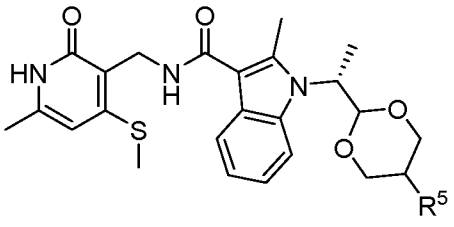

(VII);

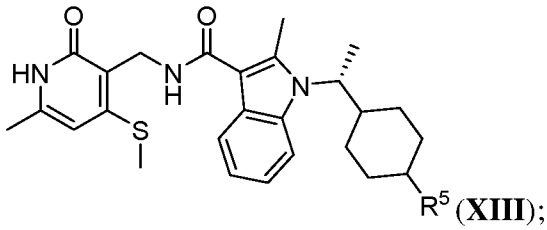

(VIII);

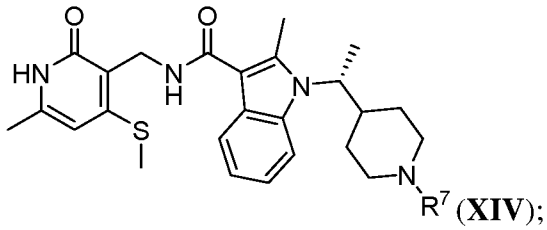

(IX);

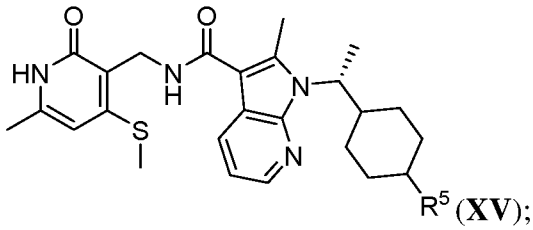

(X);

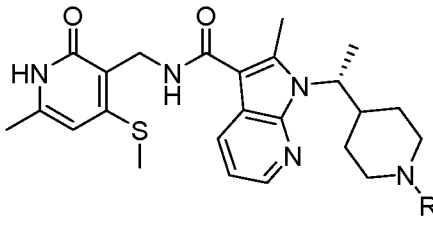

(XI); or a pharmaceutically acceptable salt thereof, wherein the remaining variables are as described for Formula **I** or the first, sixth, or ninth embodiment. Alternatively, the compound of any one of Formulae **I** to **V** is of the Formula **XII**, **XIII**, **XIV**, **XV**, **XVI**, or **XVII**:

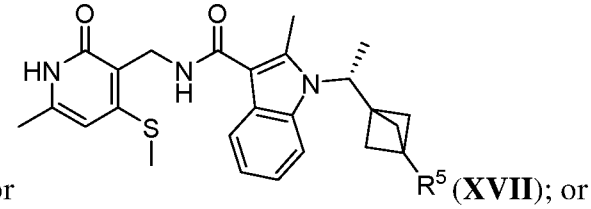

(XII);


(XIII);

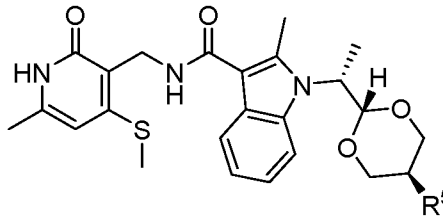

(XIV);


(XV);

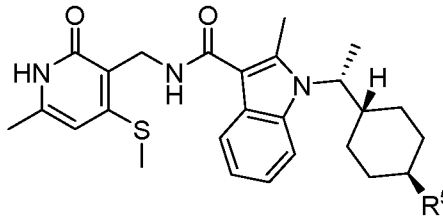

(XVI); or


(XVII); or a

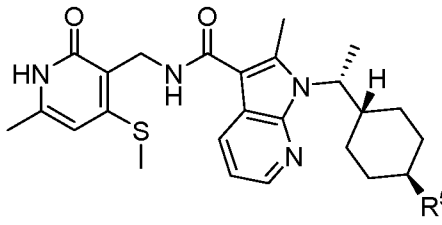
pharmaceutically acceptable salt thereof, wherein the remaining variables are as described for Formula **I** or the first, sixth, or ninth embodiment. In another alternative, the compound of any one of Formulae **I** to **V** is of the Formula **XVIII**, **XIX**, or **XX**:



(R^5 (**XVIII**);

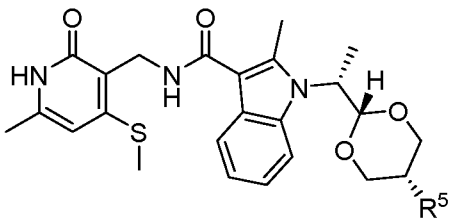


R^5 (**XIX**); or

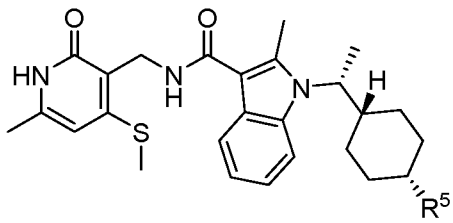


R^5 (**XX**); or a

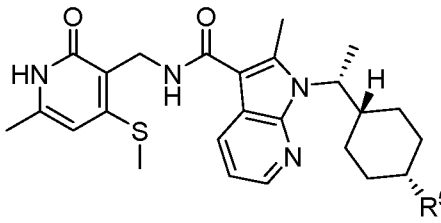
pharmaceutically acceptable salt thereof, wherein the remaining variables are as described for Formula **I** or the first, sixth, or ninth embodiment. In an eleventh embodiment, R^5 in the compound of any one of Formulae **I** to **VII**, **IX**, **XI**, **XII**, **XIII**, **XV**, **XVII**, **XVIII**, **XIX**, and **XX** is halo(C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, or NR^AR^B, wherein the remaining variables are as described for Formula **I** or the first, sixth, or ninth embodiment. In another alternative, the compound of any one of Formulae **I** to **V** is of the Formula **XVIII'**, **XIX'**, or **XX'**:



(R^5 (**XVIII'**);



R^5 (**XIX'**); or



R^5 (**XX'**); or a

pharmaceutically acceptable salt thereof, wherein the remaining variables are as described for Formula **I** or the first, sixth, or ninth embodiment.

[0048] In a twelfth embodiment, R^7 in the compound of Formula **VIII**, **X**, **XIV**, or **XVI** is halo(C_1-C_4)alkyl, -(C_1-C_4)alkylOH, or (C_3-C_6)cycloalkyl, wherein the remaining variables are as described for Formula **I** or the first, sixth, or ninth embodiment.

[0049] In a thirteenth embodiment, R^B in the compound of any one of Formulae **I** to **VII**, **IX**, **XI**, **XII**, **XIII**, **XV**, **XVII**, **XVIII**, **XVIII'**, **XIX**, **XIX'**, **XX** and **XX'** is (C_1-C_4)alkyl or a

monocyclic 4- to 6- membered heterocyclyl, wherein said (C_1-C_4)alkyl for R^B is optionally substituted with 1 to 3 groups selected from halo and O(C_1-C_4)alkyl and wherein said heterocyclyl for R^B is optionally substituted with 1 to 2 (C_1-C_4)alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached form a monocyclic 4- to 6-membered heterocyclyl optionally substituted with 1 or 2 groups selected from (C_1-C_4)alkyl, halo, halo(C_1-C_4)alkoxy, and (C_1-C_4)alkoxy, wherein the remaining variables are as described for Formula **I** or the first, fourth, sixth, ninth, or twelfth embodiment.

[0050] In a fourteenth embodiment, R^B in the compound of any one of Formulae **I** to **VII**, **IX**, **XI**, **XII**, **XIII**, **XV**, **XVII**, **XVIII**, **XVIII'**, **XIX**, **XIX'**, **XX** and **XX'** is (C_1-C_4)alkyl or oxetanyl, wherein said (C_1-C_4)alkyl for R^B is optionally substituted with 1 to 3 groups selected from halo and -O(C_1-C_4)alkyl and wherein said oxetanyl for R^B is optionally substituted with 1 to 2 (C_1-C_4)alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached form an azetidinyl or oxetanyl, each of which are optionally substituted with 1 or 2 groups selected from (C_1-C_4)alkyl, halo, halo(C_1-C_4)alkoxy, and (C_1-C_4)alkoxy, wherein the remaining variables are as described for Formula **I** or the first, fourth, sixth, ninth, twelfth, or thirteenth embodiment.

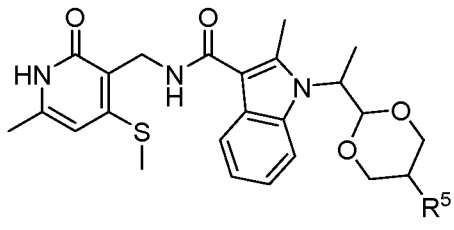
[0051] In a fifteenth embodiment, R^A in the compound of any one of Formulae **I** to **VII**, **IX**, **XI**, **XII**, **XIII**, **XV**, **XVII**, **XVIII**, **XVIII'**, **XIX**, **XIX'**, **XX** and **XX'** is hydrogen, halo(C_1-C_4)alkyl, or (C_1-C_4)alkyl, wherein the remaining variables are as described for Formula **I** or the first, fourth, sixth, ninth, twelfth, or thirteenth embodiment.

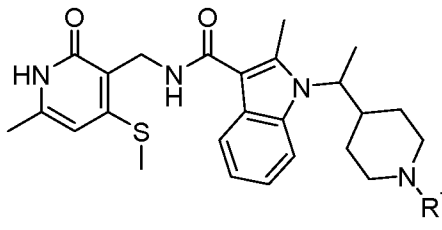
[0052] In a sixteenth embodiment, R^A in the compound of any one of Formulae **I** to **VII**, **IX**, **XI**, **XII**, **XIII**, **XV**, **XVII**, **XVIII**, **XVIII'**, **XIX**, **XIX'**, **XX** and **XX'** is hydrogen, halo(C_1-C_4)alkyl, or (C_1-C_4)alkyl; R^B is (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, or oxetanyl, wherein said oxetanyl is optionally substituted with (C_1-C_4)alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached form an azetidinyl optionally substituted with 1 or 2 groups selected from (C_1-C_4)alkoxy, halo, and halo(C_1-C_4)alkoxy, wherein the remaining variables are as described for Formula **I** or the first, fourth, sixth, ninth, twelfth, thirteenth, or fourteenth embodiment.

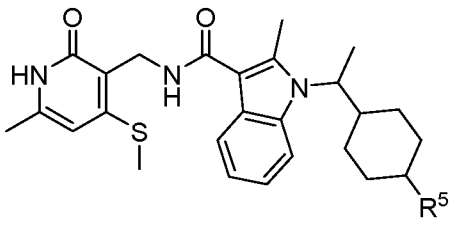
[0053] In a seventeenth embodiment, R^A in the compound of any one of Formulae **I** to **VII**, **IX**, **XI**, **XII**, **XIII**, **XV**, **XVII**, **XVIII**, **XVIII'**, **XIX**, **XIX'**, **XX** and **XX'** is hydrogen or methyl; R^B is (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, or oxetanyl, wherein said oxetanyl is optionally substituted with methyl; or R^A and R^B taken together with the nitrogen atom to which they are attached form an azetidinyl optionally substituted with methoxy, trifluoromethoxy, difluoromethoxy, difluoromethyl, or one or two fluoro wherein the remaining variables are as

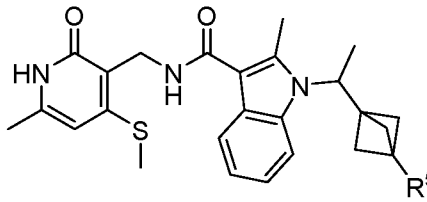
described for Formula **I**, wherein the remaining variables are as described for Formula **I** or the first, fourth, sixth, ninth, twelfth, thirteenth, fourteenth, or fifteenth embodiment.

[0054] In an eighteenth embodiment, the compound of Formula **I** is of the Formula **XXI**, **XXII**, **XXIII**, or **XXIV**:


(XXI);


(XXII);


(XXIII); or


(XXIV);

or a pharmaceutically acceptable salt thereof, wherein

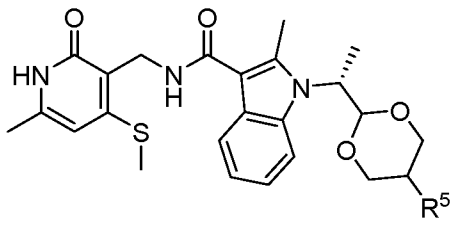
R^5 is hydroxyl, $(C_1\text{-}C_4)$alkoxy, or NR^AR^B;

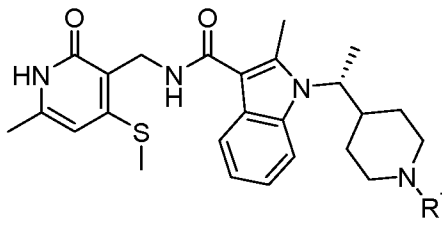
R^A is hydrogen, $(C_1\text{-}C_4)$alkyl, or halo$(C_1\text{-}C_4)$alkyl;

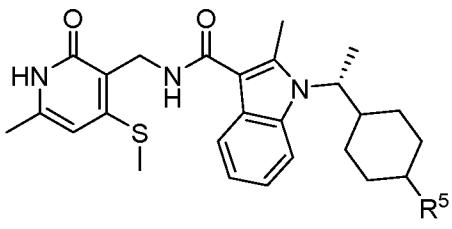
R^B is $(C_1\text{-}C_4)$alkyl or monocyclic 4- to 6- membered heterocyclyl optionally substituted with 1 or 2 $(C_1\text{-}C_4)$alkyl; or

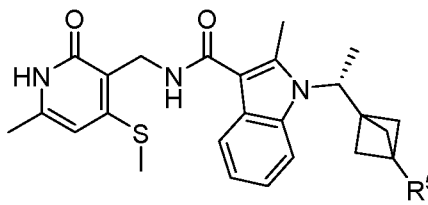
R^A and R^B taken together with the nitrogen atom to which they are attached form a monocyclic 4- to 6- membered heterocyclyl optionally substituted with halo, $(C_1\text{-}C_4)$alkoxy or halo$(C_1\text{-}C_4)$alkoxy.

[0055] In a ninteenth embodiment, the compound of Formula **I** is of the Formula **XXV**, **XXVI**, **XXVII**, or **XXVIII**:


(XXV);

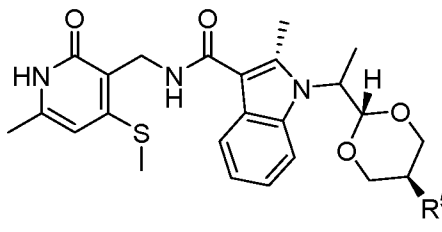

(XXVI);

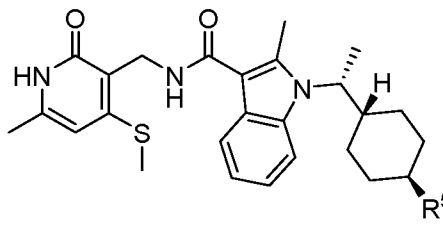

(XXVII); or


(XXVIII);

or a pharmaceutically acceptable salt thereof, wherein the variables are as described above in the eigthteenth embodiment.

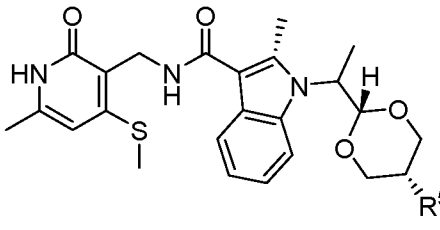
[0056] In a twentieth embodiment, the compound of Formula **I** is of the Formula **XXIX** or **XXX**:

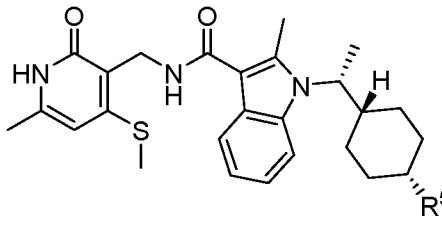

(**XXIX**); or


(**XXX**);

or a pharmaceutically acceptable salt thereof, wherein the variables are as described above in the eighteenth embodiment.

[0057] In a twenty-first embodiment, the compound of Formula **I** is of the Formula **XXXI** or **XXXII**:


(**XXXI**); or

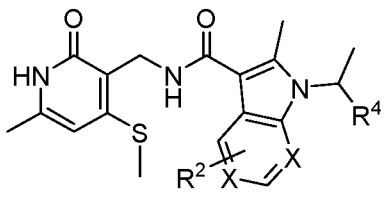

(**XXXII**);

or a pharmaceutically acceptable salt thereof, wherein the variables are as described above in the eighteenth embodiment.

[0058] In a twenty-second embodiment, R^A in the compound of the Formula **XXI**, **XXIII**, **XXIV**, **XXV**, **XXVII**, **XXVIII**, **XXIX**, **XXX**, **XXXI**, and **XXXII** is hydrogen, (C_1-C_4)alkyl, or halo(C_1-C_4)alkyl; R^B is (C_1-C_4)alkyl or oxetanyl optionally substituted with (C_1-C_4)alkyl; or R^A and R^B taken together with the nitrogen atom to which they are attached form an azetidinyl optionally substituted with halo, (C_1-C_4)alkoxy or halo(C_1-C_4)alkoxy. Alternatively, R^A is hydrogen, methyl, or 2,2,2-trifluoroethyl; R^B is methyl or oxetanyl optionally substituted with methyl; or R^A and R^B taken together with the nitrogen atom to which they are attached form an azetidinyl optionally substituted with methoxy, difluoromethoxy, or fluoro.

[0059] In a twenty-third embodiment, R^7 in the compound of the Formula **XXII** or **XXVI** is halo(C_1-C_4)alkyl or -(C_1-C_4)alkylOH.

[0060] In a twenty-fourth embodiment, the compound of Formula **I** is of the Formula **XXXIII**:


(**XXXIII**);

or a pharmaceutically acceptable salt thereof, wherein

R^2 is hydrogen or halo;

R^4 is cyclohexyl, piperidinyl or dioxanyl, each of which being optionally and independently substituted with 1 to 3 groups selected from R^5;

R^5 is selected from halo, $(C_3\text{-}C_6)$cycloalkyl, OR^6, $-OC(O)(C_1\text{-}C_4)$alkyl, $-C(O)(C_1\text{-}C_4)$alkylOH, $-C(O)(C_1\text{-}C_4)$alkylN$((C_1\text{-}C_4)\text{alkyl})_2$, $-SO_2(C_1\text{-}C_4)$alkyl, 4-7 membered heterocyclyl, and NR^AR^B, wherein said cycloalkyl for R^5 is optionally substituted with $-O(C_1\text{-}C_4)$alkyl;

R^A is hydrogen;

R^B is $(C_3\text{-}C_5)$cycloalkyl or 4-7 membered heterocyclyl, wherein said heterocyclyl or cycloalkyl for R^B is optionally substituted with 1 to 3 groups selected from $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, and hydroxy$(C_1\text{-}C_4)$alkyl; or

R^A and R^B taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclyl optionally substituted with 1 to 3 groups selected from halo, hydroxyl, cyano, $(C_1\text{-}C_4)$alkyl, hydroxy$(C_1\text{-}C_4)$alkyl, NMe_2, $-SO_2(C_1\text{-}C_4)$alkyl, 5-6 membered heteroaryl, and $(C_3\text{-}C_6)$cycloalkyl; and

R^6 is $(C_3\text{-}C_6)$cycloalkyl, 4-7 membered heterocyclyl, 5-6 membered heteroaryl, or $-O(C_1\text{-}C_4)$alkyl, wherein said 4-7 membered heterocyclyl and said 5-6 membered heteroaryl for R^6 are each optionally and independently substituted with 1 or 2 $(C_1\text{-}C_4)$alkyl groups.

[0061] In a twenty-fifth embodiment, R^5 in the Compound of Formula **XXXIII** is selected from halo, $(C_3\text{-}C_6)$cycloalkyl, OR^6, $-OC(O)(C_1\text{-}C_4)$alkyl, $-C(O)(C_1\text{-}C_4)$alkylOH, $-C(O)(C_1\text{-}C_4)$alkylN$((C_1\text{-}C_4)\text{alkyl})_2$, $-SO_2(C_1\text{-}C_4)$alkyl, 4-7 membered heterocyclyl, and NR^AR^B, wherein said cycloalkyl for R^5 is optionally substituted with $-O(C_1\text{-}C_4)$alkyl;

R^A is hydrogen;

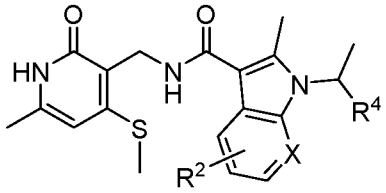
R^B is $(C_3\text{-}C_5)$cycloalkyl or 4-7 membered heterocyclyl, wherein said heterocyclyl or cycloalkyl for R^B are each optionally and independently substituted with 1 to 3 groups selected from $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, and hydroxy$(C_1\text{-}C_4)$alkyl; or

R^A and R^B taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclyl optionally substituted with 1 to 3 groups selected from halo, hydroxyl, cyano, $(C_1\text{-}C_4)$alkyl, NMe_2, hydroxy$(C_1\text{-}C_4)$alkyl, $-SO_2(C_1\text{-}C_4)$alkyl, 5-6 membered heteroaryl, and $(C_3\text{-}C_6)$cycloalkyl; and

R^6 is $(C_3\text{-}C_6)$cycloalkyl, 4-7 membered heterocyclyl, 5-6 membered heteroaryl, or $-O(C_1\text{-}C_4)$alkyl, wherein said 4-7 membered heterocyclyl and said 5-6 membered heteroaryl

for R^6 are each optionally and independently substituted with 1 or 2 $(C_1\text{-}C_4)$alkyl groups, wherein the remaining variables are as described in the twenty-fourth embodiment.

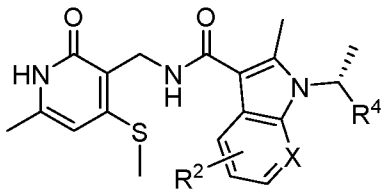
[0062] In a twenty-sixth embodiment, the compound of Formula **XXXIII** is of the Formula **XXXIV**:



(**XXXIV**);

or a pharmaceutically acceptable salt thereof, wherein the remaining variables are as described for Formula **XXXIII** or the twenty-fifth embodiment.

[0063] In a twenty-sixth embodiment, the compound of Formula **XXXIII** is of the Formula **XXXV**:



(**XXXV**);

or a pharmaceutically acceptable salt thereof, wherein the remaining variables are as described for Formula **XXXIII** or the twenty-fifth embodiment.

[0064] In a twenty-seventh embodiment, R^2 in the compounds of Formula **XXXIII** to **XXXV** is hydrogen or fluorine, wherein the remaining variables are as described for Formula **XXXIII** or the twenty-fifth embodiment.

[0065] In a twenty eighth embodiment, R^5 in the compounds of Formula **XXXIII** to **XXXV** is selected from halo, $(C_3\text{-}C_6)$cycloalkyl, $-OC(O)(C_1\text{-}C_4)$alkyl, $-C(O)(C_1\text{-}C_4)$alkylOH, $-C(O)(C_1\text{-}C_4)$alkylN$((C_1\text{-}C_4)\text{alkyl})_2$, $-SO_2(C_1\text{-}C_4)$alkyl, and NR^AR^B wherein said cycloalkyl for R^5 is optionally substituted with $-O(C_1\text{-}C_4)$alkyl;

R^B is $(C_3\text{-}C_5)$cycloalkyl or 4-7 membered heterocyclyl each optionally and independently substituted with 1 to 3 groups selected from $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, and hydroxy$(C_1\text{-}C_4)$alkyl; or

R^A and R^B taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclyl optionally substituted with 1 to 3 groups selected from halo, hydroxyl, cyano, $(C_1\text{-}C_4)$alkyl, NMe_2, $-SO_2(C_1\text{-}C_4)$alkyl, 5-6 membered heteroaryl, and $(C_3\text{-}C_6)$cycloalkyl; and

R^6 is 4-7 membered heterocyclyl or 5-6 membered heteroaryl, wherein said 4-7 membered heterocyclyl and said 5-6 membered heteroaryl for R^6 are each optionally and

independently substituted with (C_1-C_4)alkyl, wherein the remaining variables are as described for Formula **XXXIII** or the twenty-fifth or twenty-seventh embodiment.

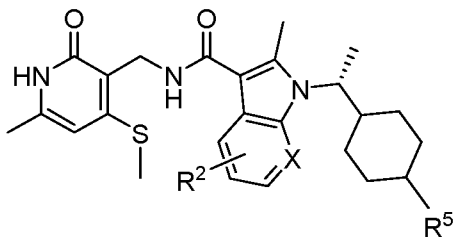
[0066] In a twenty-ninth embodiment, R^5 in the compounds of Formula **XXXIII** to **XXXV** is selected from halo, cyclobutyl, -OC(O)(C_1-C_4)alkyl, -C(O)(C_1-C_4)alkylOH, -C(O)(C_1-C_4)alkylN((C_1-C_4)alkyl)$_2$, -SO_2(C_1-C_4)alkyl, and NR^AR^B wherein said cyclobutyl for R^5 is optionally substituted with -O(C_1-C_4)alkyl;

R^B is tetrahydrofuranyl, cyclopropyl, or oxatanyl, each optionally and independently substituted with 1 to 3 groups selected from (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, and hydroxy(C_1-C_4)alkyl; or

R^A and R^B taken together with the nitrogen atom to which they are attached form an azetidinyl, oxaazaspirohexanyl, oxaazaspiroheptanyl, each of which are optionally and independently substituted with 1 to 3 groups selected from halo, hydroxyl, cyano, (C_1-C_4)alkyl, NMe_2, -SO_2(C_1-C_4)alkyl, triazolyl, and cyclopropyl; and

R^6 is an oxetanyl, azetidinyl, pyrazolyl, 4-7 membered heterocyclyl or 5-6 membered heteroaryl, wherein said 4-7 membered heterocyclyl and said 5-6 membered heteroaryl for R^6 are each optionally and independently substituted with (C_1-C_4)alkyl, wherein the remaining variables are as described for Formula **XXXIII** or the twenty-fifth, twenty-seventh, or twenty-eighth embodiment.

[0067] In a thirtieth embodiment, the compound of Formula **XXXIII** is of the Formula **XXXVI**:



(**XXXV**);

[0068] or a pharmaceutically acceptable salt thereof, wherein the remaining variables are as described for Formula **XXXIII** or the twenty-fifth, twenty-seventh, or twenty-eighth embodiment.

[0069] Specific examples of compounds are provided in the EXEMPLIFICATION section and are included as part of a thirteenth embodiment herein. Pharmaceutically acceptable salts as well as the neutral forms of these compounds are also included.

4. Uses, Formulation and Administration

[0070] In some embodiments, the present disclosure provides a composition comprising a compound described herein or a pharmaceutically acceptable derivative thereof and a

pharmaceutically acceptable carrier. The amount of compound in a provided composition is such that is effective to measurably modulate a histone methyl modifying enzyme, or a mutant thereof, in a biological sample or in a patient.

[0071] In certain embodiments, a composition described herein is formulated for administration to a patient in need of such composition. Compositions described herein may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. In some embodiments, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions described herein may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents.

[0072] In some embodiments, the compositions are administered orally.

[0073] A specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound described herein in the composition will also depend upon the particular compound in the composition.

[0074] The compounds described herein may be present in the form of pharmaceutically acceptable salts. For use in medicines, the salts of the compounds of the invention refer to non-toxic “pharmaceutically acceptable salts.” Pharmaceutically acceptable salt forms include pharmaceutically acceptable acidic/anionic or basic/cationic salts. Suitable pharmaceutically acceptable acid addition salts of the compounds described herein include e.g., salts of inorganic acids (such as hydrochloric acid, hydrobromic, phosphoric, nitric, and sulfuric acids) and of organic acids (such as, acetic acid, benzenesulfonic, benzoic, methanesulfonic, and p-toluenesulfonic acids). Compounds of the present teachings with acidic groups such as carboxylic acids can form pharmaceutically acceptable salts with pharmaceutically acceptable base(s). Suitable pharmaceutically acceptable basic salts include e.g., ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts). Compounds with a quaternary ammonium group also contain a counteranion such as chloride, bromide, iodide, acetate, perchlorate and the like. Other examples of such salts include hydrochlorides,

hydrobromides, sulfates, methanesulfonates, nitrates, benzoates and salts with amino acids such as glutamic acid.

[0075] Compounds and compositions described herein are generally useful for the modulating of activity of one or more enzymes involved in epigenetic regulation and in particular EZH1 and EZH2 and, even more specifically EZH2 and mutant forms thereof. In some embodiments, compounds described herein down-regulate or suppress the activity of EZH2. In some embodiments, compounds described herein are antagonists of EZH2 activity. In some embodiments, compounds described herein down-regulate or suppress the activity of EZH1. In some embodiments, compounds described herein are antagonists of EZH1 activity.

[0076] In some embodiments, compounds and compositions described herein are useful in treating diseases and/or disorders associated with overexpression of EZH1 or EZH2 and/or expression of a mutant form of EZH2, such as those mutant forms that alter EZH2 substrate activity. The study of EZH2 deletions, missense and frameshift mutations suggest that EZH2 functions as a tumor suppressor in blood disorders such as myelodysplastic syndromes (MDS) and myeloid malignancies (Ernst et al., Nat Genet. 2010 Aug; 42(8):722-6; Nikoloski et al., Nat Genet. 2010 Aug; 42(8):665-7). In some embodiments, compounds and compositions described herein are useful in treating diseases and/or disorders associated with the presence of EZH2 having a Y641N, Y641C, Y641F, Y641H, Y641S, A677G, or A687 mutation. In a particular aspect of this embodiment, the EZH2 has a Y641N mutation.

[0077] In some embodiments, the present disclosure provides a method of treating a subject suffering from a disease and/or disorder associated with overexpression of EZH1 or EZH2 and/or expression of a mutant form of EZH2 comprising the step of administering a compound described herein, or a pharmaceutically acceptable salt or composition thereof. In some embodiments, the above method additionally comprises the preliminary step of determining if the subject is overexpressing EZH2 or expressing a mutant form of EZH2.

[0078] In some embodiments, the disease or disorder associated with the presence of a mutant form of EZH2 is a human B cell lymphoma. In some embodiments, the disease and/or disorder associated with the presence of Y641N EZH2 is follicular lymphoma or diffuse large-B-cell lymphoma. In some embodiments, compounds or compositions described herein are useful in treating blood disorders, such as myelodysplastic syndromes, leukemia, anemia and cytopenia. Sneeringer et al., "Coordinated activities of wild-type plus mutant EZH2 drive tumor-associated hypertrimethylation of lysine 27 on histone H3 (H3K27) in human B-cell lymphomas," Sneeringer et al., Proc. Natl Acad. Sci. 2010 Dec; 109(48):20980-20985.

[0079] In some embodiments, compounds and compositions described herein are useful in treating diseases and/or disorders associated with cellular proliferation. In some embodiments, compounds and compositions described herein are useful in treating diseases and/or disorders associated with misregulation of cell cycle or DNA repair. In some embodiments, compounds and compositions described herein are useful in treating cancer.

[0080] In one aspect, cancers that may be treated by the compounds, compositions and methods described herein include, but are not limited to Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, clear cell carcinoma,

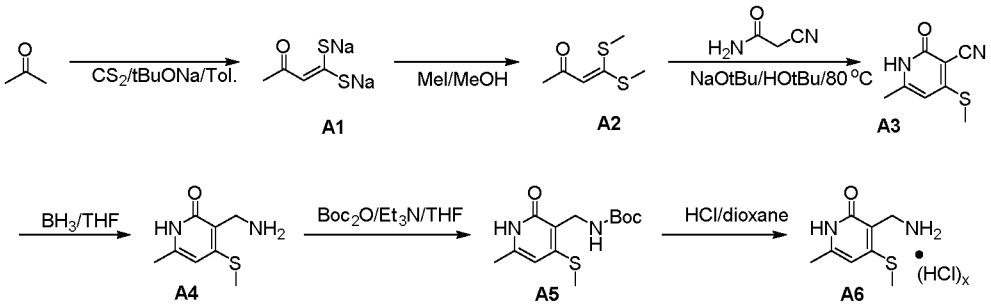
unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma.

[0081] In one aspect, the cancer treated by the compounds, compositions, and methods described herein are selected from breast cancer, prostate cancer, colon cancer, renal cell carcinoma, glioblastoma multiforme cancer, bladder cancer, melanoma, bronchial cancer, lymphoma and liver cancer.

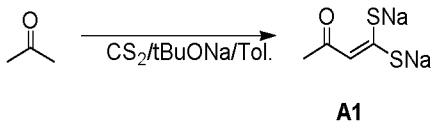
EXEMPLIFICATION

[0082] The representative examples that follow are intended to help illustrate the present disclosure, and are not intended to, nor should they be construed to, limit the scope of the invention.

Synthesis of Intermediate A6: 3-(aminomethyl)-6-methyl-4-(methylthio)pyridin-2(1H)-one



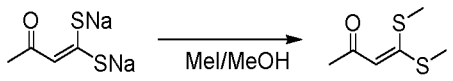
[0083] **Step 1: Synthesis of sodium 3-oxobut-1-ene-1,1-bis(thiolate) (A1)**



[0084] A mixture of t-BuONa (16.6 g, 172 mmol, 2.0 equiv) in toluene (30 mL) was degassed and purged with N_2 3 times, and then acetone (5.0 g, 86 mmol, 1.0 equiv) was

added at 0 °C. Then CS_2 (6.6 g, 86 mmol, 1.0 equiv) was added slowly. The resulting mixture was stirred at 0 °C for 4 h. The reaction mixture was filtered, and the filter cake was dried to give **A1**, sodium 3-oxobut-1-ene-1,1-bis(thiolate) (15.4 g, crude), as a yellow solid, which was used directly in the next step without further purification.

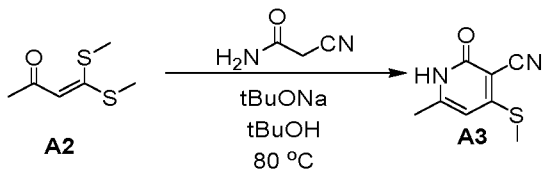
[0085] Step 2: 4,4-bis(methylthio)but-3-en-2-one(A2)



A1 **A2**

[0086] To a solution of **A1** (15.4 g, 86.4 mmol, 1.0 equiv) in methanol (90 mL) was added MeI (24.5 g, 173 mmol, 2.0 equiv) slowly. The mixture was stirred at 70 °C for 1 h. The reaction mixture was then concentrated and water (30 mL) was added to the reaction mixture. The mixture was extracted with ethyl acetate (60 mL * 3). The organic layer was dried over sodium sulfate and concentrated to give a **A2**, 4,4-bis(methylthio)but-3-en-2-one (6.8 g, 36 mmol, 42% yield) was obtained as a brown oil. LCMS $[M+H]^+$ m/z: calc'd 163.02; found 163.0. ^1H NMR (400 MHz, $CDCl_3$) δ 6.02 (s, 1H), 2.45 (s, 3H), 2.43 (s, 3H), 2.15 (s, 3H).

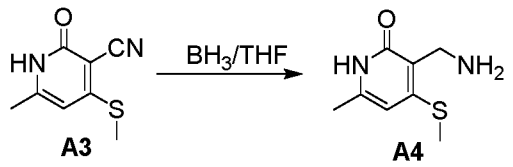
[0087] Step 3: Synthesis of 6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridine-3-carbonitrile (A3)



A2 **A3**

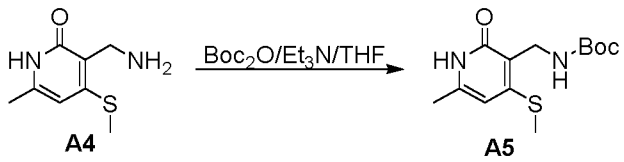
[0088] To a solution of 4,4-bis(methylthio)but-3-en-2-one (2.9 g, 18 mmol, 1.0 equiv) and 2-cyanoacetamide (1.5 g, 18 mmol, 1.0 equiv) in 2-methylpropan-2-ol (50 mL) was added *t*-BuONa (1.9 g, 20 mmol, 1.1 equiv). The mixture was stirred at 80 °C for 12 h. Two batches of the reaction were performed and combined at this stage. Water (20 mL) was added and the pH was adjusted to 5-6 with 10% HCl solution. Then the resulting mixture was filtered, and the filter cake was washed with petroleum ether (petroleum ether) (20 mL * 2) to give crude **A3**, 6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridine-3-carbonitrile (4.8 g, 27 mmol, 74% yield), as an off-white solid. LCMS $[M+H]^+$ m/z: calc'd 181.04; found 181.0. ^1H NMR (400 MHz, DMSO-d_6) δ 6.27 (s, 1H), 2.56 (s, 3H), 2.25 (s, 3H).

[0089] Step 4: Synthesis 3-(aminomethyl)-6-methyl-4-(methylthio)pyridin-2(1H)-one (A4)



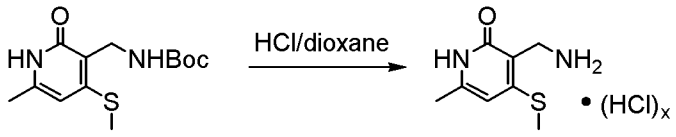
[0090] A mixture of 6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridine-3-carbonitrile (3.6 g, 20 mmol, 1.0 equiv) in tetrahydrofuran (50 mL) was degassed and purged with N_2 3 times at 0 °C, and then BH_3-Me_2S (10 M, 8.0 mL, 4.0 equiv) was added slowly. The reaction mixture was warmed to 70 °C and was stirred for 2 h. Methanol (15 mL) was slowly added at 0 °C to quench the reaction before the mixture was concentrated to give **A4**, 3-(aminomethyl)-6-methyl-4-(methylthio)pyridin-2(1H)-one (3.8 g, crude), as a light yellow solid and used directly in the next step. LCMS $[M+H]^+$ m/z: calc'd 185.07; found 185.0.

[0091] Step 5: Synthesis of tert-butyl ((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamate (A5)



[0092] To a solution of 3-(aminomethyl)-6-methyl-4-methylsulfanyl-1H-pyridin-2-one (3.6 g, 20 mmol, 1.0 equiv) in tetrahydrofuran (80 mL) was added triethylamine (5.9 g, 59 mmol, 3.0 equiv). The mixture was stirred at 25 °C for 0.5 h. Then $(Boc)_2O$ (6.4 g, 29 mmol, 1.5 equiv) was added and the reaction was stirred at 25 °C for 12 h. The reaction mixture was then concentrated, the residue washed with water (35 mL) and the desired product extracted with a 5:1 mixture of petroleum ether/ethyl acetate (30 mL * 3). **A5**, tert-butyl ((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamate (5.8 g, crude) was obtained as a white solid. LCMS $[M+H]^+$ m/z: calc'd 285.12; found 284.9. ^1H NMR (400 MHz, DMSO-d_6) δ 6.05 (s, 1H), 4.03 - 4.00 (m, 2H), 2.42 (s, 3H), 2.15 (s, 3H), 1.39 (s, 9H).

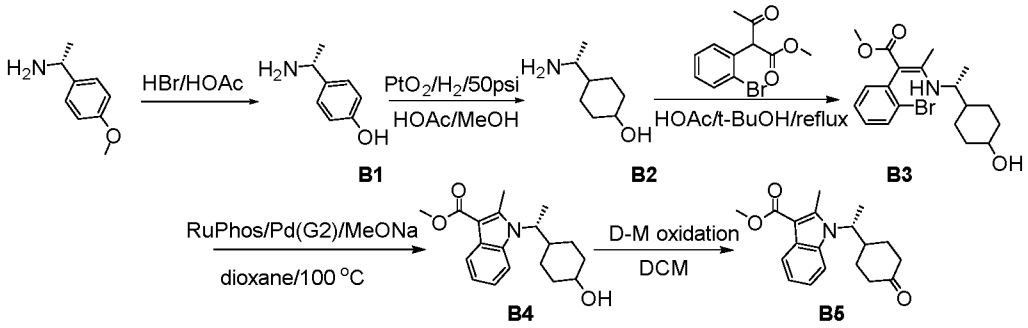
[0093] Step 6: 3-(aminomethyl)-6-methyl-4-(methylthio)pyridin-2(1H)-one hydrochloride (A6)



A5 **A6**

[0094] tert-butyl ((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamate (5.0 g, 17.6 mmol, 1.0 equiv) was added to a HCl solution (100 mL, 4 M in 1,4-dioxane). The reaction mixture was stirred at 25 °C for 2 h then concentrated under reduced pressure. The residue was washed with dichloromethane (30 mL * 2) and ethyl acetate (30 mL * 1). **A6**, 3-(aminomethyl)-6-methyl-4-(methylthio)pyridin-2(1H)-one hydrochloride (4.5 g, crude, HCl salt) was obtained as a yellow solid and was used directly in the next step without further purification. LCMS $[M+H]^+$ m/z: calc'd 185.07; found 185.0. ^1H NMR (400 MHz, D_2O) δ 6.31 (s, 1H), 4.03 (s, 2H), 2.41 (s, 3H), 2.18 (s, 3H).

Synthesis of methyl (R)-2-methyl-1-(1-(4-oxocyclohexyl)ethyl)-1H-indole-3-carboxylate (B5)

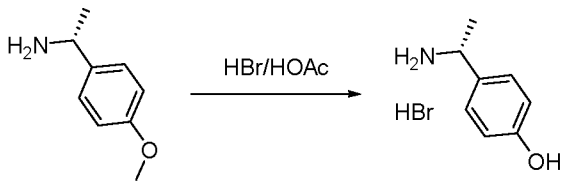


B1 **B2** **B3**

B4 **B5**

[0095]

[0096] Step 1: Synthesis of 4-[(1R)-1-aminoethyl]phenol;hydrobromide (B1)

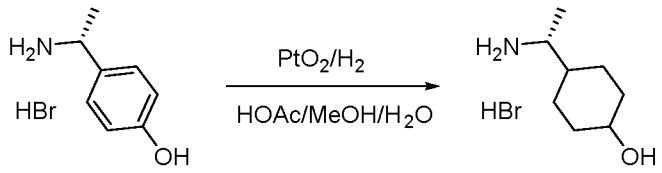


B1

[0097] The mixture of (1R)-1-(4-methoxyphenyl)ethanamine (20 g, 132.27 mmol, 1 equiv) in HBr 35% in acetic acid (170 mL, 1.03 mol, 7.81 equiv) was stirred at 0 °C for 1 h then stirred at 20 °C for 47 hours. The reaction was concentrated and acetonitrile (200 mL) was added to the residue. The mixture was stirred at 0 °C for 1 h, then filtered. The filter cake was washed with acetonitrile (50 mL) and ethylacetate (150 mL), then dried under in

vacuum. The desired compound, 4-[(1R)-1-aminoethyl]phenol hydrobromide salt (24 g, 110.05 mmol, 83.20% yield) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.57 (br s, 1H), 8.18 (br s, 3H), 7.32 - 7.26 (m, J = 8.5 Hz, 2H), 6.82 - 6.76 (m, J = 8.5 Hz, 2H), 4.30 (td, J = 5.8, 11.9 Hz, 1H), 1.46 (d, J = 6.8 Hz, 3H).

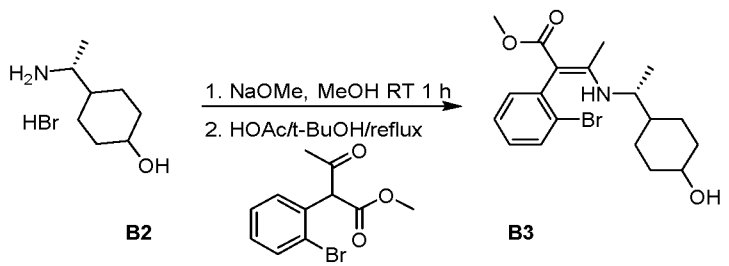
[0098] Step 2: Synthesis of 4-[(1R)-1-aminoethyl]cyclohexanol (B2)



B1 B2

[0099] To a solution of 4-[(1R)-1-aminoethyl]phenol hydrobromide salt (20 g, 92 mmol, 1 equiv) in methanol (250 mL) was added acetic acid (12 mL), water (12 mL) and PtO_2 (2.0 g, 8.8 mmol, 0.1 equiv) under a nitrogen atmosphere. The suspension was degassed (several under vacuum and hydrogen refill cycles). The reaction was stirred under hydrogen atmosphere (55 psi) at 20 °C for 48 hours (Four batches were run in parallel). The batches were combined, filtered and concentrated under reduced pressure. The residue was dissolved in methanol (200 mL) and potassium carbonate (50 g) was added. The mixture was stirred at 20 °C for 1 h, then filtered and concentrated under reduced pressure. The residue was dissolved in a 10:1 mixture of dichloromethane:methanol (200 mL) and filtered. The filtrate was concentrated under reduced pressure to the desired compound, 4-[(1R)-1-aminoethyl]cyclohexanol (80 g, crude) as a white solid. It was used in the next step without further purification.

[00100] Step 3: The synthesis of methyl 2-(2-bromophenyl)-3-(((1R)-1-(4-hydroxycyclohexyl)ethyl)amino)but-2-enoate (B3)

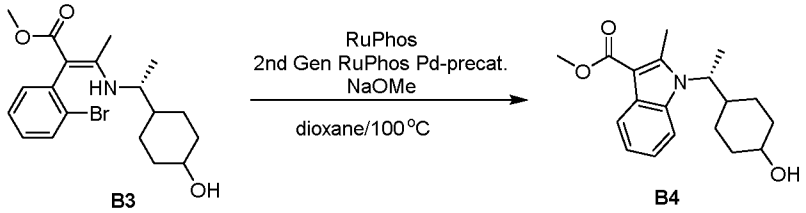


B2 B3

[00101] A mixture of crude (R)-4-(1-aminoethyl)cyclohexan-1-ol (10.0 g, 44.6 mmol, 1.0 equiv, HBr salt) and NaOMe (2.65 g, 49.1 mmol, 1.1 equiv) in methanol (20.0 mL) was stirred at 25 °C for 1 h under N_2. Then the reaction mixture was filtered, and the filtrate was concentrated to give (R)-4-(1-aminoethyl)cyclohexan-1-ol free base. Then methyl 2-(2-

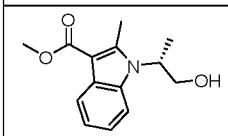
bromophenyl)-3-oxo-butanoate (13.3 g, 49.1 mmol, 1.1 equiv), *t*-BuOH (100 mL) and acetic acid (3.48 g, 58.0 mmol, 1.3 equiv) were added. The resulting mixture was stirred at 85 °C for 12 h and then concentrated under vacuum and quenched with saturated sodium bicarbonate (80 mL). The mixture was extracted with ethyl acetate (160 mL * 3). The organic layer was dried by anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude was purified by flash silica gel chromatography to give **B3**, methyl 2-(2-bromophenyl)-3-(((1R)-1-(4-hydroxycyclohexyl)ethyl)amino)but-2-enoate (2.0 g, 3.4 mmol, 8% yield), as a brown gum. LCMS $[M+Na]^+$ m/z: calc'd 418.11; found 418.0.

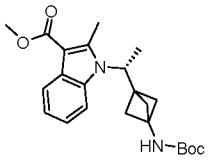
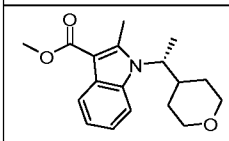
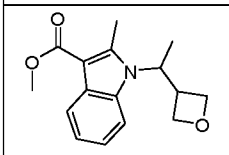
[00102] Step 4: The synthesis of methyl 1-((1R)-1-(4-hydroxycyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxylate (B4)



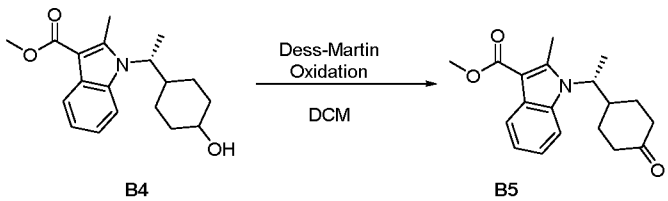
[00103] A mixture of methyl 2-(2-bromophenyl)-3-(((1R)-1-(4-hydroxycyclohexyl)ethyl)amino)but-2-enoate (2.5 g, 6.3 mmol, 1.0 equiv), sodium methoxide (510 mg, 9.5 mmol, 1.5 equiv), RuPhos (294 mg, 631 umol, 0.1 equiv) and 2nd Gen RuPhos precatalyst (490 mg, 631 umol, 0.1 equiv) in 1,4-dioxane (100 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 100 °C for 13 h under N_2. The reaction mixture was concentrated and then water (30 mL) was added. The desired product was extracted with dichloromethane (60 mL * 3) and the organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude was purified by flash silica gel chromatography to give **B4**, methyl 1-((1R)-1-(4-hydroxycyclohexyl)ethyl)-2-methyl-indole-3-carboxylate (3.70 g, 11.1 mmol, 88% yield), as a yellow solid. LCMS $[M+H]^+$ m/z: calc'd 316.41; found 315.9.

[00104] The following intermediates were synthesized using similar conditions as those described in Steps 3 and 4, above, along with appropriate starting materials.

Structure	Name	Intermediate	LCMS
	methyl (R)-1-(1-hydroxypropan-2-yl)-2-methyl-1H-indole-3-carboxylate	C1	LCMS $[M+H]^+$ m/z: calc'd 248.12; found 247.9.

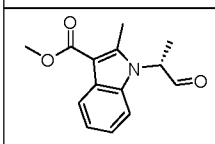
	methyl (R)-1-(1-(3-((tert-butoxycarbonyl)amino)bicyclo[1.1.1]pentan-1-yl)ethyl)-2-methyl-1H-indole-3-carboxylate	D8	LCMS $[M+H]^+$ m/z: calc'd 399.22; found 399.2.
	methyl (R)-2-methyl-1-(1-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-indole-3-carboxylate	F1	LCMS $[M+H]^+$ m/z: calc'd 302.17; found 301.9.
	methyl 2-methyl-1-(1-(oxetan-3-yl)ethyl)-1H-indole-3-carboxylate	G1	LCMS $[M+H]^+$ m/z: calc'd 274.14; found 273.9.

[00105] Step 5: The synthesis of methyl (R)-2-methyl-1-(1-(4-oxocyclohexyl)ethyl)-1H-indole-3-carboxylate (B5)

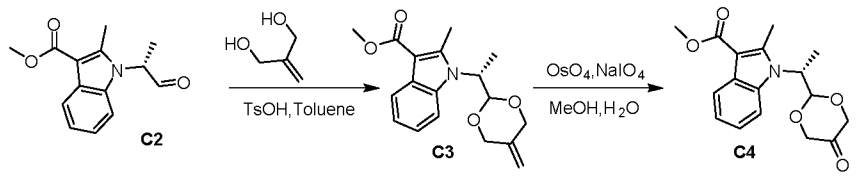


[00106] To the solution of methyl 1-((1R)-1-(4-hydroxycyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxylate (180 mg, 571 umol, 1.0 equiv) in dichloromethane (8 mL) was added Dess-Martin periodinane (484 mg, 1.10 mmol, 0.35 mL, 2.0 equiv) in portions at 10 °C. The mixture was stirred at 10 °C for 16 h. The reaction was quenched with saturated sodium bicarbonate (30 mL) and the desired product was extracted with dichloromethane (20 mL * 3). The organic layers were washed with saturated sodium thiosulfate (50 mL), dried over sodium sulfate and concentrated under vacuum. The crude was purified by silica gel chromatography to give **B5**, methyl (R)-2-methyl-1-(1-(4-oxocyclohexyl)ethyl)-1H-indole-3-carboxylate (150 mg, 441 umol, 77 % yield), as a light yellow oil. LCMS $[M+Na]^+$ m/z: calc'd 336.17; found 336.2.

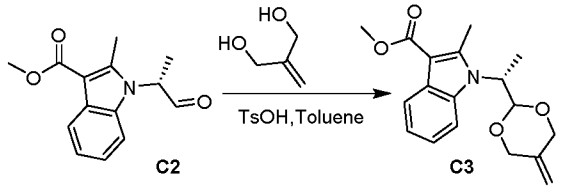
[00107] The following intermediates were synthesized using similar conditions as those described in Step 5, above, along with appropriate starting materials.

Structure	Name	Intermediate	LCMS
	(R)-methyl 2-methyl-1-(1-oxopropan-2-yl)-1H-indole-3-carboxylate	C2	LCMS ($[M+H_2O]^+$) m/z: calc'd 264.12; found 263.9.

Synthesis of methyl (R)-2-methyl-1-(1-(5-oxo-1,3-dioxan-2-yl)ethyl)-1H-indole-3-carboxylate (C4)

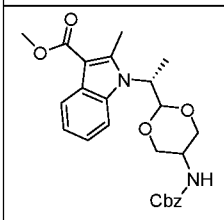


[00108] Step 1: Synthesis of methyl (R)-2-methyl-1-(1-(5-methylene-1,3-dioxan-2-yl)ethyl)-1H-indole-3-carboxylate (C3)

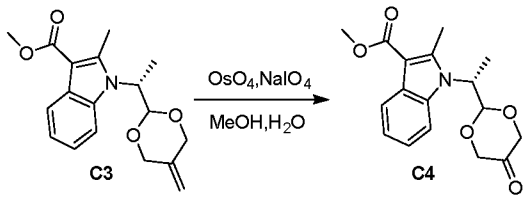


[00109] The mixture of (R)-methyl 2-methyl-1-(1-oxopropan-2-yl)-1H-indole-3-carboxylate (4.1 g, 17 mmol, 1 equiv), 2-methylenepropane-1,3-diol (5.9 g, 67 mmol, 5.5 mL, 4 equiv) and TsOH (864 mg, 5.01 mmol, 0.3 equiv) in toluene (50 mL) was stirred at 120 °C for 17 h. The mixture was concentrated and to the residue was added saturated aqueous Na_2CO_3 (30 mL). The desired product was extracted with ethyl acetate (35 mL * 3). The combined organic layer was washed with brine (35 mL*3), dried over sodium sulfate, filtered and concentrated. The crude was purified by silica-gel column chromatography to give **C3**, methyl (R)-2-methyl-1-(1-(5-methylene-1,3-dioxan-2-yl)ethyl)-1H-indole-3-carboxylate (3.3 g, 10 mmol, 63% yield) as a yellow oil. LCMS $[M+H]^+$ m/z: calc'd 316.15; found 316.0.

[00110] The following intermediate(s) were synthesized using similar conditions as those described in Step 1, above, along with appropriate starting materials.

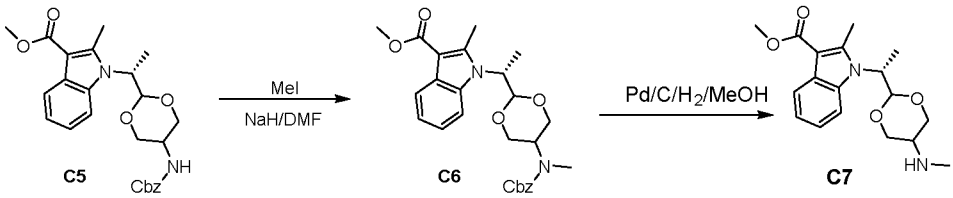
Structure	Name	Intermediate	LCMS
	methyl (R)-1-(1-(5-(((benzyloxy)carbonyl)amino)-1,3-dioxan-2-yl)ethyl)-2-methyl-1H-indole-3-carboxylate	C5	LCMS $[M+Na]^+$ m/z: calc'd 475.19; found 475.0.

[00111] Step 2: Synthesis of methyl (R)-2-methyl-1-(1-(5-oxo-1,3-dioxan-2-yl)ethyl)-1H-indole-3-carboxylate (C4)

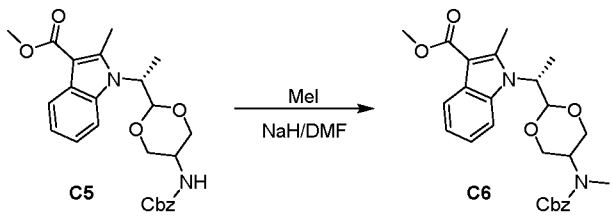


[00112] The mixture of methyl (R)-2-methyl-1-(1-(5-methylene-1,3-dioxan-2-yl)ethyl)-1H-indole-3-carboxylate (2.0 g, 6.4 mmol, 1 equiv), $NaIO_4$ (5.4 g, 25 mmol, 1.4 mL, 4 equiv) and OsO_4 (8.0 g, 31 mmol, 1.6 mL, 5 equiv) was stirred in methanol (48 mL) and water (32 mL) at 25 °C for 17 h. The mixture was extracted with ethyl acetate (60 mL *4), washed with saturated sodium chloride (50 mL * 2), dried with sodium sulfate, concentrated under vacuum. The crude was purified by siliga-gel column chromatography to give **C5**, methyl (R)-2-methyl-1-(1-(5-oxo-1,3-dioxan-2-yl)ethyl)-1H-indole-3-carboxylate (1.3 g, 4.1 mmol, 65% yield), as a yellow oil. LCMS ($[M+H_2O]^+$) m/z: calc'd 336.13; found 335.9.

Synthesis of methyl (R)-2-methyl-1-(1-(5-(methylamino)-1,3-dioxan-2-yl)ethyl)-1H-indole-3-carboxylate (C7)



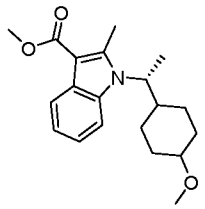
[00113] Step 1: Synthesis of methyl (R)-1-(1-(5-(((benzyloxy)carbonyl)(methyl)amino)-1,3-dioxan-2-yl)ethyl)-2-methyl-1H-indole-3-carboxylate (C6)



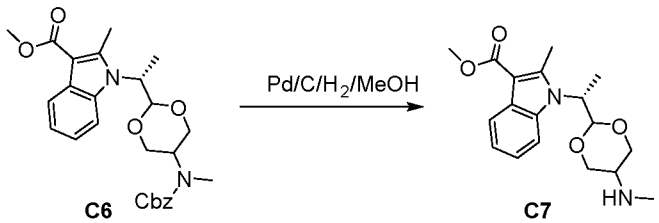
[00114] To a mixture of methyl (R)-1-(1-(5-(((benzyloxy)carbonyl)amino)-1,3-dioxan-2-yl)ethyl)-2-methyl-1H-indole-3-carboxylate (400 mg, 884 umol, 1 equiv) in N,N-dimethylformamide (2 mL) was added sodium hydride (42 mg, 1.1 mmol, 60% in mineral oil, 1.2 equiv) at 0°C under N_2 atmosphere. The mixture was stirred at 20 °C for 0.3 h. To the reaction was added methyl iodide (2.15 g, 15.1 mmol, 17.1 equiv). The mixture was stirred at 20 °C for 4 hours. To the mixture was diluted with ethyl acetate (10 mL). The reaction was quenched by addition water (10 mL) at 0 °C. The desired product was extracted with ethyl

acetate (5 mL* 3). The organic phases were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel flash chromatography (0 to 20% ethyl acetate in petroleum ether). **C6**, methyl (R)-1-(1-(5-(((benzyloxy)carbonyl)(methyl)amino)-1,3-dioxan-2-yl)ethyl)-2-methyl-1H-indole-3-carboxylate (396 mg, 603 umol, 68% yield), was obtained as a yellow solid.

[00115] The following intermediate(s) were synthesized using similar conditions as those described in Step 1, above, along with appropriate starting materials.

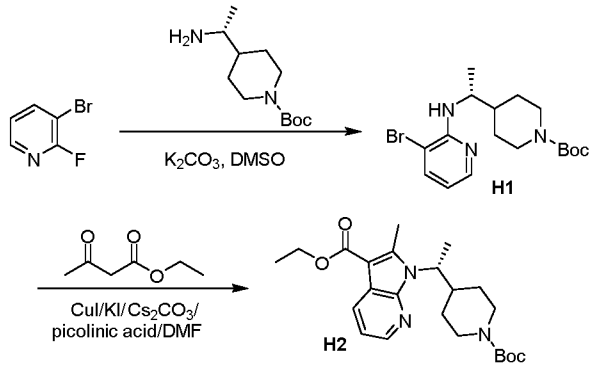
Structure	Name	Intermediate	LCMS
	methyl (R)-1-(1-(4-methoxycyclohexyl) ethyl)-2-methyl-1H-indole-3-carboxylate	B6	LCMS $[M+H]^+$ m/z: calc'd 330.20; found 330.0.

Step 2: Synthesis of methyl (R)-2-methyl-1-(1-(5-(methylamino)-1,3-dioxan-2-yl)ethyl)-1H-indole-3-carboxylate (C7)

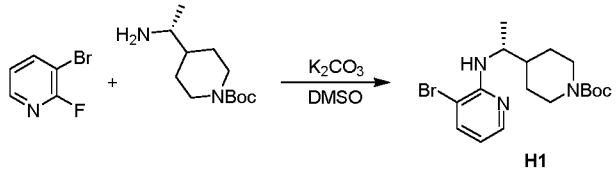


[00116] A mixture of methyl (R)-1-(1-(5-(((benzyloxy)carbonyl)(methyl)amino)-1,3-dioxan-2-yl)ethyl)-2-methyl-1H-indole-3-carboxylate (600 mg, 1.3 mmol, 1.0 equiv) and Pd/C (150 mg, 1.3 mmol, 10% w/w, 1 equiv) in methanol (3 mL) (caution: methanol can catch fire in contact with Pd/C) was degassed and purged with H_2 3 times, and then the mixture was stirred at 20 °C for 2 h under H_2 atmosphere (15 Psi). The catalyst was removed by filtration through celite and the filtrate concentrated under reduced pressure. **C7**, methyl (R)-2-methyl-1-(1-(5-(methylamino)-1,3-dioxan-2-yl)ethyl)-1H-indole-3-carboxylate (460 mg, 1.27 mmol, 99% yield), was obtained as a yellow solid. LCMS $[M+Na]^+$ m/z: calc'd 333.17; found 332.9.

Synthesis of ethyl (R)-1-(1-(1-(tert-butoxycarbonyl)piperidin-4-yl)ethyl)-2-methyl-1H-pyrrolo[2,3-b]pyridine-3-carboxylate (H2)

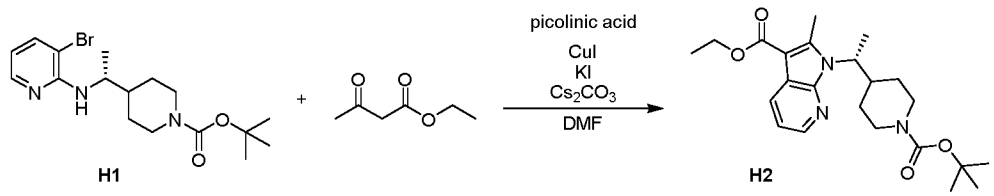


[00117] Step 1: Synthesis of tert-butyl (R)-4-(1-((3-bromopyridin-2-yl)amino)ethyl)piperidine-1-carboxylate (H1)



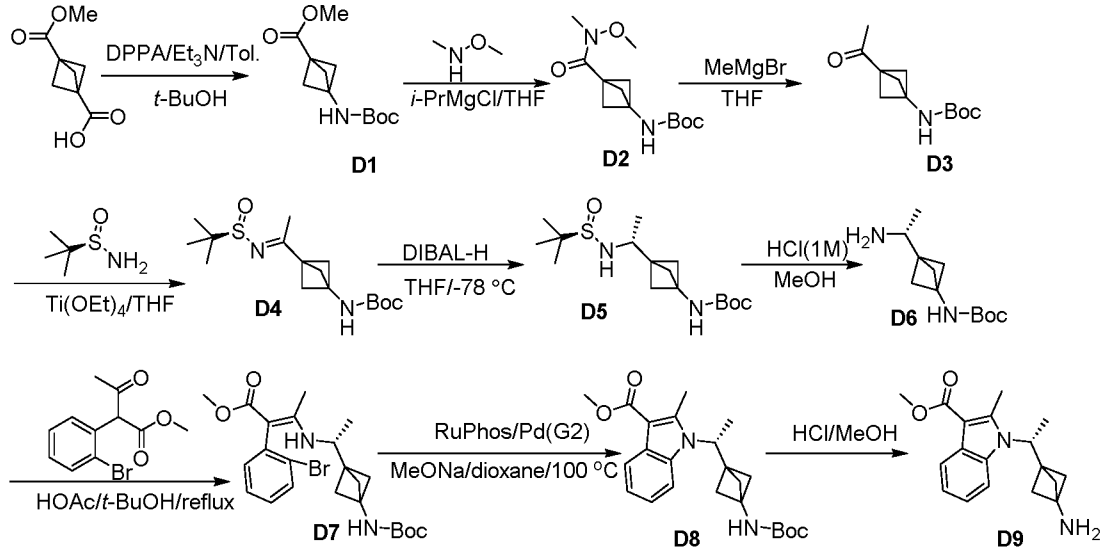
[00118] A mixture of tert-butyl 4-[(1R)-1-aminoethyl]piperidine-1-carboxylate (1.0 g, 4.4 mmol, 1 equiv) , 3-bromo-2-fluoro-pyridine (800 mg, 4.6 mmol, 1 equiv) , and potassium carbonate (1.8 g, 13 mmol, 3.0 equiv) in dimethyl sulfoxide (15 mL) was degassed and purged with N_2 3 times. The reaction was stirred at 120 °C for 18 hr under N_2 atmosphere, then quenched with water (20 mL) after cooling to 25 °C. The desired product was extracted with ethyl acetate (20 mL * 3) and the combined organic layers were washed with brine (20 mL * 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 20/1 to 5/1). Compound **H1**, tert-butyl (R)-4-(1-((3-bromopyridin-2-yl)amino)ethyl)piperidine-1-carboxylate (1.0 g, 2.6 mmol, 59% yield) was obtained as a colorless oil. LCMS $[M+H]^+$ m/z: calc'd 384.12; found 384.0. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 7.58 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.43 - 6.40 (m, 1H), 4.81 (d, J = 8.4 Hz, 1H), 4.19 - 4.09 (m, 1H), 2.66 (br s, 2H), 1.78 - 1.76 (m, 2H), 1.69 - 1.57 (m, 2H), 1.44 (s, 9H), 1.33 - 1.23 (m, 3H), 1.18 (d, J = 6.8 Hz, 3H).

[00119] Step 2: Synthesis of ethyl (R)-1-(1-(1-(tert-butoxycarbonyl)piperidin-4-yl)ethyl)-2-methyl-1H-pyrrolo[2,3-b]pyridine-3-carboxylate (H2)

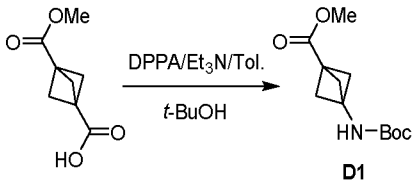


[00120] A mixture of tert-butyl (R)-4-(1-((3-bromopyridin-2-yl)amino)ethyl)piperidine-1-carboxylate (500 mg, 1.3 mmol, 1 equiv), ethyl 3-oxobutanoate (680 mg, 5.2 mmol, 4 equiv), picolinic acid (130 mg, 1.1 mmol, 0.8 equiv), CuI (25 mg, 131 umol, 0.1 equiv), KI (325 mg, 2.0 mmol, 1.5 equiv) and cesium carbonate (1.27 g, 3.9 mmol, 3 equiv) in N,N-dimethylformamide (6 mL) was degassed and purged with N_2 for 3 times and then the mixture was stirred at 150 °C for 1 h under N_2 atmosphere. The reaction mixture was quenched by addition water (15 mL) at 25°C, and then the desired product extracted with ethyl acetate (20 mL * 2). The combined organic layers were washed with brine (20 mL * 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 20/1-5/1). Compound **H2**, ethyl (R)-1-(1-(1-(tert-butoxycarbonyl)piperidin-4-yl)ethyl)-2-methyl-1H-pyrrolo[2,3-b]pyridine-3-carboxylate (200 mg, 399 umol, 31% yield) was obtained as a colorless oil. LCMS $[M+H]^+$ m/z: calc'd 416.25; found 416.1. ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.0 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 7.15 (dd, *J* = 8.0 Hz, 4.0 Hz, 1H), 4.40 (d, *J* = 8.0 Hz, 2H), 4.26 - 4.17 (m, 1H), 4.07 - 3.91 (m, 2H), 2.80 (br s, 3H), 2.02 - 1.97 (m, 1H), 1.89 - 1.85 (m, 1H), 1.59 (d, *J* = 6.8 Hz, 3H), 1.45 (t, *J* = 8.0 Hz, 3H), 1.43 (s, 9H), 1.29 - 1.11 (m, 3H), 0.95 - 0.84 (m, 2H).

Synthesis of methyl (R)-1-(1-(3-aminobicyclo[1.1.1]pentan-1-yl)ethyl)-2-methyl-1H-indole-3-carboxylate (D9)

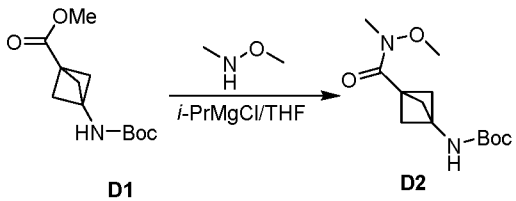


[00121] Step 1: Synthesis of methyl 3-((tert-butoxycarbonyl)amino)bicyclo[1.1.1]pentane-1-carboxylate (D1)`



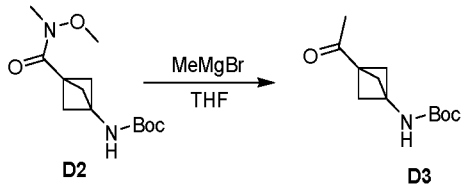
[00122] To a mixture of 3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (10 g, 59 mmol, 1.0 equiv), diphenylphosphoryl azide (DPPA) (19.4 g, 70.5 mmol, 15.3 mL, 1.2 equiv) and triethylamine (7.1 g, 71 mmol, 9.8 mL, 1.2 equiv) in toluene (150 mL) was added *t*-BuOH (8.70 g, 118 mmol, 11.2 mL, 2.0 equiv). The mixture was stirred at 110 °C for 12 h. The reaction was cooled to 25 °C and concentrated. The residue was diluted with water (50 mL) and the desired product extracted with ethyl acetate (100 mL * 3). The combined organic layer was washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated. The crude was purified by column chromatography on silica gel to give **D1**, methyl 3-((tert-butoxycarbonyl)amino)bicyclo[1.1.1]pentane-1-carboxylate (10.5 g, 43.5 mmol, 74% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (br s, 1H), 3.68 (s, 3H), 2.28 (s, 6H), 1.44 (s, 9H).

[00123] Step 2: Synthesis of tert-butyl (3-(methoxy(methyl)carbamoyl)bicyclo[1.1.1]pentan-1-yl)carbamate (D2)



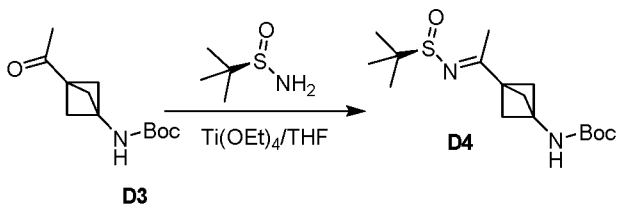
[00124] To a solution of methyl 3-((tert-butoxycarbonyl)amino)bicyclo[1.1.1]pentane-1-carboxylate (10.5 g, 43.5 mmol, 1.0 equiv) and N-methoxymethanamine (6.4 g, 65 mmol, 1.5 equiv, HCl salt) in tetrahydrofuran (100 mL) was added *i*-PrMgCl (2 M in Et_2O, 87 mL, 4 equiv) dropwise at 0 °C. The mixture was stirred at 0 °C for 4 h then poured into cooled saturated NH_4Cl (50 mL) and diluted with water (20 mL), and extracted with ethyl acetate (100 mL*3). The combined organic layer was washed with brine (100 mL), dried over sodium sulfate, filtered and concentrated. The crude was purified by column chromatography on silica gel to give **D2**, tert-butyl (3-(methoxy(methyl)carbamoyl)bicyclo[1.1.1]pentan-1-yl)carbamate (10 g, 37 mmol, 85% yield) as a white solid. LCMS $[M+H]^+$ m/z: calc'd 270.16; found 270.9. ^1H NMR (400 MHz, $CDCl_3$) δ 5.05 (br s, 1H), 3.65 (s, 3H), 3.17 (s, 3H), 2.33 (s, 6H), 1.43 (s, 9H).

[00125] **Step 3: Synthesis of tert-butyl (3-acetylbicyclo[1.1.1]pentan-1-yl)carbamate (D3)**



[00126] To a solution of tert-butyl (3-(methoxy(methyl)carbamoyl)bicyclo[1.1.1]pentan-1-yl)carbamate (10 g, 37 mmol, 1.0 equiv) in tetrahydrofuran (100 mL) was added MeMgBr (3 M, 99 mL, 8.0 equiv) dropwise at 0 °C. The mixture was stirred at 0 °C for 4 h. The mixture was poured into saturated NH_4Cl (30 mL), diluted with water (10 mL), and extracted with ethyl acetate (80 mL * 3). The combined organic layer was washed with brine (100 mL), dried over sodium sulfate, filtered and concentrated. The crude was purified by column chromatography on silica to give **D3**, tert-butyl (3-acetylbicyclo[1.1.1]pentan-1-yl)carbamate (4.50 g, 18.8 mmol, 51% yield,), as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 4.99 (br s, 1H), 2.26 (s, 6H), 2.14 (s, 3H), 1.44 (s, 9H).

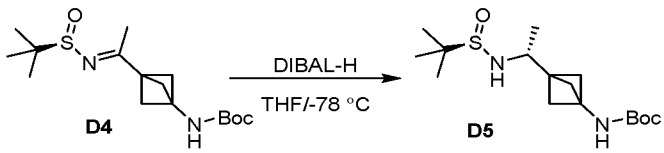
[00127] **Step 4: Synthesis of tert-butyl (R,E)-(3-(1-((tert-butylsulfinyl)imino)ethyl)bicyclo[1.1.1]pentan-1-yl)carbamate (D4)**



[00128] To a solution of tert-butyl (3-acetylbicyclo[1.1.1]pentan-1-yl)carbamate (4.5 g, 20 mmol, 1.0 equiv) and 2-methylpropane-2-sulfinamide (3.6 g, 30 mmol, 1.5 equiv) in

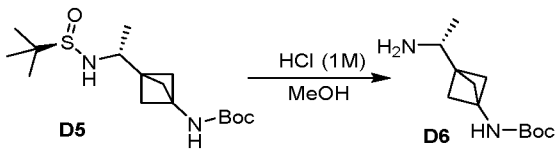
tetrahydrofuran (80 mL) was added $Ti(OEt)_4$ (9.1 g, 40 mmol, 2.0 equiv). The mixture was stirred at 85 °C for 12 h. The mixture was cooled to 25 °C, and then water (15 mL) was added to the mixture resulting in formation of a white precipitate. The mixture was diluted with dichloromethane (80 mL) and filtered. The filtrate was washed with brine (30 mL). The filter cake was washed with dichloromethane (80 mL*2). The combined filtrate was concentrated. The crude was purified by column chromatography on silica gel to give **D4**, tert-butyl (R,E)-(3-(1-((tert-butylsulfinyl)imino)ethyl)bicyclo[1.1.1]pentan-1-yl)carbamate (3.60 g, 10.6 mmol, 53% yield) as a white solid.

[00129] Step 5: Synthesis of tert-butyl (3-((R)-1-(((R)-tert-butylsulfinyl)amino)ethyl)bicyclo[1.1.1]pentan-1-yl)carbamate(D5)



[00130] To a solution of tert-butyl (R,E)-(3-(1-((tert-butylsulfinyl)imino)ethyl)bicyclo[1.1.1]pentan-1-yl)carbamate (7.0 g, 21 mmol, 1.0 equiv) in tetrahydrofuran (80 mL) was added DIBAL-H (1 M in toluene, 43 mL, 2.0 equiv) dropwise at -78 °C. The mixture was stirred at -78 °C for 2 h. The reaction was quenched with methanol (20 mL), and then diluted with water (20 mL) and ethyl acetate (50 mL). The mixture was filtered and the filtrate was washed with brine (30 mL). The filter cake was washed with ethyl acetate (50 mL * 3). The combined filtrate was dried over sodium sulfate, filtered and concentrated. The crude was purified by column chromatography on silica gel to give **D5**, tert-butyl (3-((R)-1-(((R)-tert-butylsulfinyl)amino)ethyl)bicyclo[1.1.1]pentan-1-yl)carbamate (5.70 g, 13.5 mmol, 63% yield,), as a white solid. ^1H NMR (400MHz, $CDCl_3$) δ 4.96 (br s, 1H), 3.55 - 3.49 (m, 1H), 3.02 (s, 1H), 2.04 - 1.87 (m, 6H), 1.44 (s, 9H), 1.18 (s, 9H), 1.12 (d, J = 6.8 Hz, 3H).

[00131] Step 6: Synthesis of tert-butyl (R)-(3-(1-aminoethyl)bicyclo[1.1.1]pentan-1-yl)carbamate (D6)

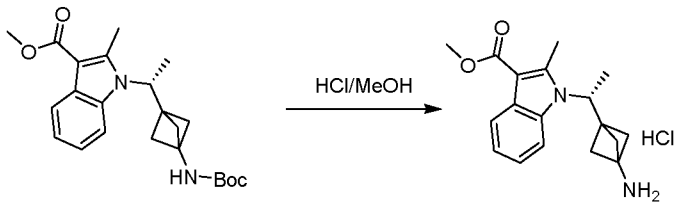


[00132] To a solution of tert-butyl (3-((R)-1-(((R)-tert-butylsulfinyl)amino)ethyl)bicyclo[1.1.1]pentan-1-yl)carbamate (3.3 g, 10 mmol, 1.0 equiv) in methanol (15 mL) was added HCl (1 M in methanol, 10 mL, 1.0 equiv) at 15 °C. The mixture was stirred at 15 °C for 30 min after which the pH was adjusted to 7~8 with saturated sodium

bicarbonate solution and concentrated to dryness. The residue was washed with dichloromethane (100 mL) and filtered. The filter cake was washed with dichloromethane (100 mL * 2). The combined filtrate was concentrated to give **D6**, tert-butyl (R)-(3-(1-aminoethyl)bicyclo[1.1.1]pentan-1-yl)carbamate (2.0 g, crude) as a white solid. LCMS $[M+H]^+$ m/z: calc'd 227.17; found 227.0. ^1H NMR (400 MHz, $CDCl_3$) δ 5.30 (br s, 1H), 3.21 - 3.16 (m, 1H), 1.96 - 1.92 (m, 6H), 1.44 (s, 9H), 1.13 (d, J = 6.4 Hz, 3H).

[00133] Steps 7 and 8: Synthesis of intermediate D8 from intermediate D6 was performed using the procedures described previously.

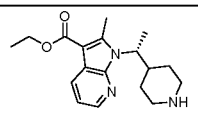
[00134] Step 9: Synthesis of methyl (R)-1-(1-(3-aminobicyclo[1.1.1]pentan-1-yl)ethyl)-2-methyl-1H-indole-3-carboxylate (D9)



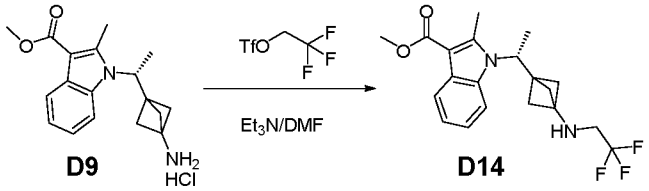
D8 D9

[00135] A mixture of methyl (R)-1-(1-(3-((tert-butoxycarbonyl)amino)bicyclo[1.1.1]pentan-1-yl)ethyl)-2-methyl-1H-indole-3-carboxylate (200 mg, 0.502 mmol, 1.0 equiv) in a solution of HCl (4 M in methanol, 5.0 mL, 40 equiv) was stirred at 15 °C for 30 min. The mixture pH was adjusted to 7-8 with saturated sodium bicarbonate and concentrated. The solid was washed with dichloromethane (20 mL * 3) and filtered. The filtrate was concentrated to give **D9**, methyl (R)-1-(1-(3-aminobicyclo[1.1.1]pentan-1-yl)ethyl)-2-methyl-1H-indole-3-carboxylate (0.14 g, crude), as white solid. LCMS $[M+H]^+$ m/z: calc'd 299.17; found 299.0.

[00136] The following intermediate(s) were synthesized using similar conditions as those described in Step 9, above, along with appropriate starting materials.

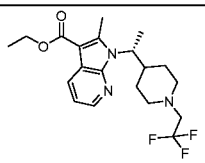
Structure	Name	Intermediate	LCMS
	ethyl (R)-2-methyl-1-(1-(piperidin-4-yl)ethyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxylate	H3	LCMS $[M+H]^+$ m/z: calc'd 316.19; found 315.9.

Synthesis methyl (R)-2-methyl-1-(1-(3-((2,2,2-trifluoroethyl)amino)bicyclo[1.1.1]pentan-1-yl)ethyl)-1H-indole-3-carboxylate (D14)

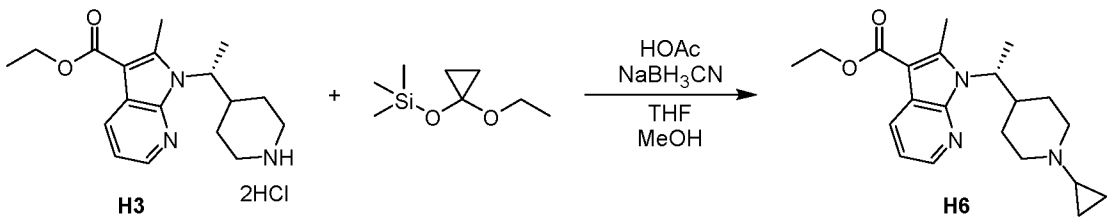


[00137] To a mixture of methyl (R)-1-(1-(3-aminobicyclo[1.1.1]pentan-1-yl)ethyl)-2-methyl-1H-indole-3-carboxylate (180 mg, 537 umol, 1 equiv, HCl salt) and triethylamine (218 mg, 2.20 mmol, 299 uL, 4 equiv) in N,N-dimethylformamide (8 mL) was added 2,2,2-trifluoroethyltriflate (211 mg, 1.1 mmol, 144 uL, 2 equiv). The mixture was stirred at 100 °C for 16 h. The mixture was cooled to 15 °C and concentrated. The residue was diluted with water (15 mL) and the desired product extracted with ethyl acetate (40 mL*3). The combined organic layer was dried over sodium sulfate, filtered and concentrated. The crude was purified by flash silica gel chromatography to give **D14**, methyl (R)-2-methyl-1-(1-(3-((2,2,2-trifluoroethyl)amino)bicyclo[1.1.1]pentan-1-yl)ethyl)-1H-indole-3-carboxylate (120 mg, 300 umol, 56% yield) as a yellow oil. LCMS $[M+H]^+$ m/z: calc'd 381.17; found 381.1.

[00138] The following intermediate(s) were synthesized using similar conditions as those described in the step above, along with appropriate starting materials.

Structure	Name	Intermediate	LCMS
	ethyl (R)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxylate	H4	LCMS $[M+H]^+$ m/z: calc'd 398.20; found 398.0.

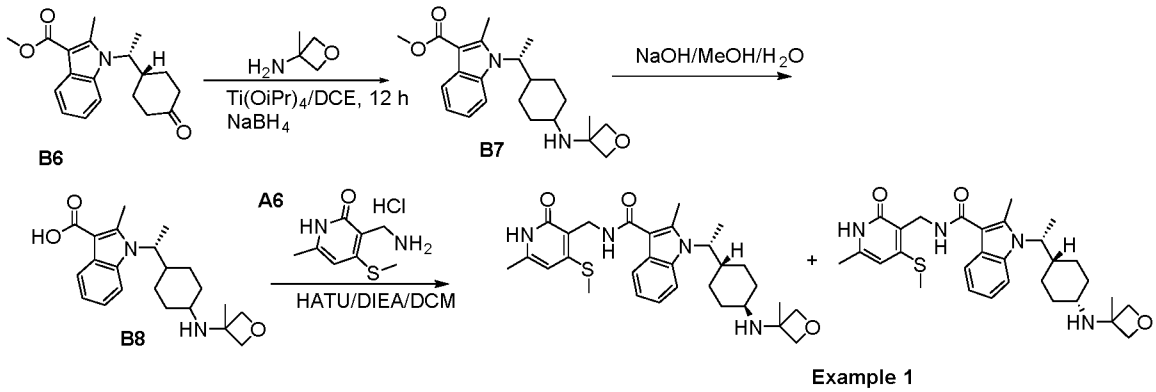
Synthesis of 1-[(1R)-1-(1-cyclopropyl-4-piperidyl)ethyl]-2-methyl-pyrrolo[2,3-*b*] pyridine-3-carboxylate (H6)



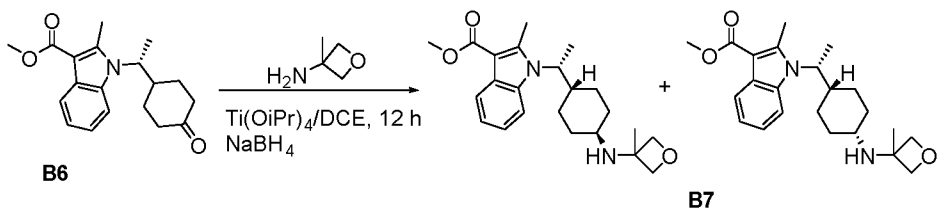
[00139] A solution of ethyl 2-methyl-1-[(1R)-1-(4-piperidyl)ethyl]pyrrolo[2,3-*b*]pyridine-3-carboxylate dihydrochloride salt (250 mg, 0.64 mmol, 1 equiv) in saturated aqueous $NaHCO_3$ (10 mL) was extracted with ethyl acetate (10 mL × 3) and the combined organic

layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to give the free amine. To a solution of the free amine and (1-ethoxycyclopropoxy)-trimethyl-silane (230 mg, 1.3 mmol, 265 uL, 2 equiv) in THF (3 mL) and MeOH (0.2 mL) were added AcOH (79 mg, 1.3 mmol, 75 uL, 2 equiv) and $NaBH_3CN$ (60 mg, 0.96 mmol, 1.5 equiv). The reaction was stirred at 60 °C for 16 hours then quenched with saturated aqueous NH_4Cl (5 mL). The desired product was extracted with ethyl acetate (10 mL × 3) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to dryness. The residue was purified by prep-TLC (SiO_2, petroleum ether:ethyl acetate, 1:1). The title compound, ethyl 1-[(1R)-1-(1-cyclopropyl-4-piperidyl)ethyl]-2-methyl-pyrrolo[2,3-*b*] pyridine-3-carboxylate (105 mg, 0.274 mmol, 43% yield, 93% purity), was obtained as yellow oil. LCMS $[M+H]^+$ m/z: calc'd 356.2; found 356.1.

Synthesis of (R)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(4-((3-methyloxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxamide (Example 1, isomer 1 and isomer 2)



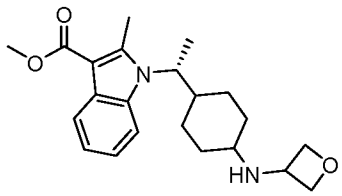
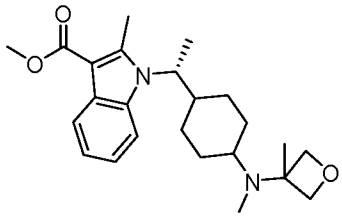
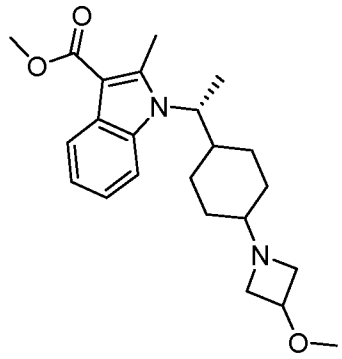
[00140] Step 1: Synthesis of methyl (R)-2-methyl-1-(1-(4-((3-methyloxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxylate (B6)

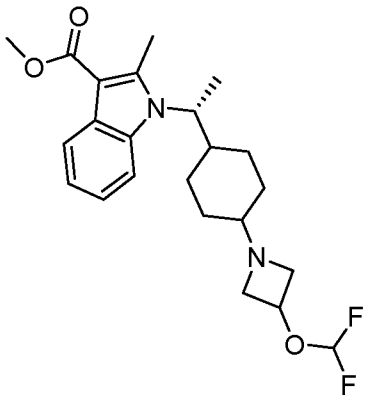
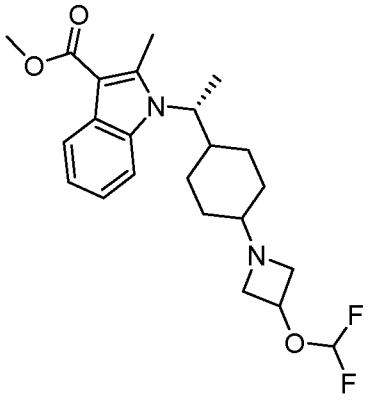
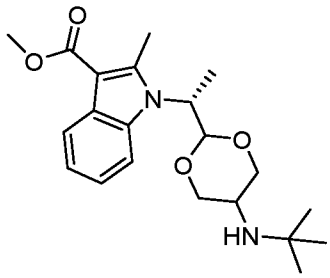
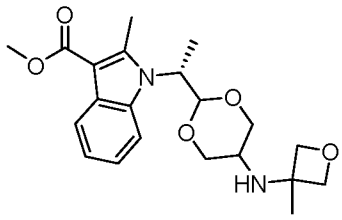


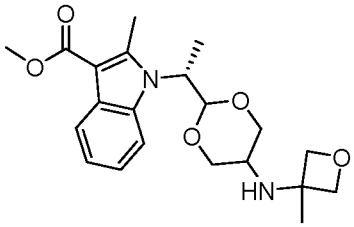
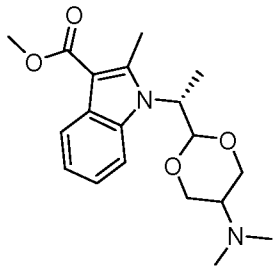
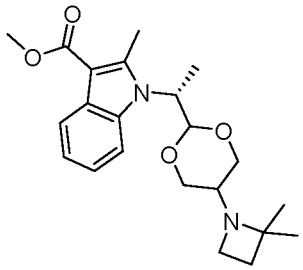
[00141] To a solution of methyl (R)-2-methyl-1-(1-(4-oxocyclohexyl)ethyl)-1H-indole-3-carboxylate (300 mg, 957 umol, 1 equiv) and 3-methyloxetan-3-amine (250 mg, 2.9 mmol, 3 equiv) in dichloroethane (10 mL) was added Ti(Oi-Pr)$_4$ (816 mg, 2.9 mmol, 847 uL, 3 equiv). The mixture was stirred at 15 °C for 13 h. Sodium borohydride (217 mg, 5.7 mmol, 6 equiv) was then added to the mixture and stirred at 15 °C for 2 h. The mixture was then diluted with saturated sodium bicarbonate (15 mL) and water (10 mL), extracted with dichloromethane

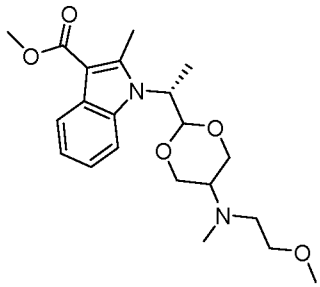
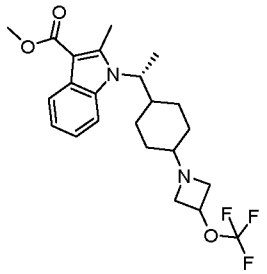
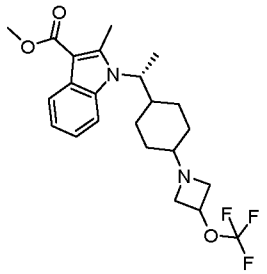
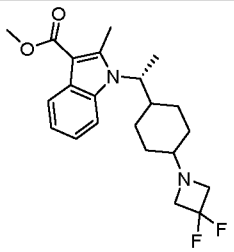
(40 mL*3). The combined organic layer was washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated. The crude was purified by column chromatography on silica gel to give **B7** as a mixture of cis/trans isomers, methyl (R)-2-methyl-1-(1-(4-((3-methyloxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxylate (300 mg, 749 μmol, 78% yield) as a white solid. LCMS $[M+H]^+$ m/z: calc'd 385.24; found 385.1.

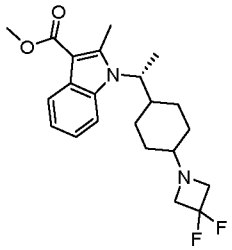
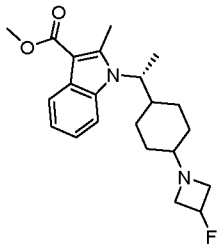
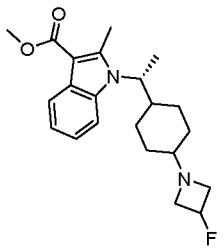
[00142] The following intermediates were synthesized using similar conditions as those described in Step 1, above, along with appropriate starting materials and reagents.

Structure and Name	Intermediate	Cis/trans Isomer Separation Method and Retention Time (if any)	LCMS
 methyl 2-methyl-1-((1R)-1-(4-(oxetan-3-ylamino)cyclohexyl)ethyl)-1H-indole-3-carboxylate	B9		LCMS $[M+H]^+$ m/z: calc'd 371.23; found 371.1.
 methyl (R)-2-methyl-1-(1-(4-(methyl(3-methyloxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxylate	B10		LCMS $[M+H]^+$ m/z: calc'd 399.26; found 399.1.
 methyl 1-((1R)-1-(4-(3-methoxyazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxylate	B11		LCMS $[M+H]^+$ m/z: calc'd 385.24; found 385.1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 7.6 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.21 - 7.15 (m, 2H), 4.28 - 4.04 (m, 2H), 3.93 (s, 3H), 3.66 - 3.58 (m, 2H), 3.25 (s, 3H), 2.95 - 2.77 (m, 5H), 2.29 - 2.05 (m, 3H), 1.72 - 1.41 (m, 6H), 1.17 - 0.79 (m, 4H).

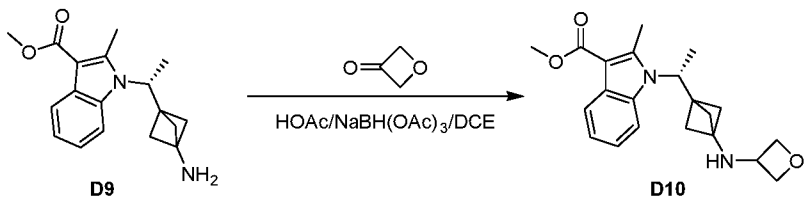
 methyl (R)-1-(1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxylate	B12 Isomer 1 (1st eluting isomer)	Cis-trans isomers separated by silica-gel column chromatography Eluent of 0~60% Ethyl acetate/Petroleum ether gradient @ 30mL/min	LCMS $[M+H]^+$ m/z: calc'd 421.22; found 421.1.
 methyl (R)-1-(1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxylate	B12 Isomer 2 (2nd eluting isomer)	Cis-trans isomers separated by silica-gel column chromatography Eluent of 0~60% Ethyl acetate/Petroleum ether gradient @ 30mL/min	LCMS $[M+H]^+$ m/z: calc'd 421.22; found 421.1.
 methyl (R)-1-(1-(5-(tert-butylamino)-1,3-dioxan-2-yl)ethyl)-2-methyl-1H-indole-3-carboxylate	C8		LCMS $[M+H]^+$ m/z: calc'd 375.22; found 375.1.
 methyl (R)-2-methyl-1-(1-(5-	C9 Isomer 1 (1st eluting isomer)	Cis-trans isomers separated by silica-gel column chromatography (Petroleum ether/Ethyl acetate = 10/1 - 1/2).	LCMS $[M+Na]^+$ m/z: calc'd: 411.20.; found 411.1. ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (br d, J = 7.2 Hz, 1H), 7.50 (br d, J = 7.2 Hz, 1H), 7.24 - 7.16 (m, 2H), 4.94 (br d, J = 5.0 Hz,

((3-methyloxetan-3-yl)amino)-1,3-dioxan-2-yl)ethyl)-1H-indole-3-carboxylate			1H), 4.64 - 4.53 (m, 1H), 4.37 (s, 2H), 4.35 (s, 2H), 4.14 (br d, *J* = 12.4 Hz, 1H), 3.93 (s, 3H), 3.92 - 3.84 (m, 2H), 3.30 (br t, *J* = 9.6 Hz, 1H), 3.04 (br d, *J* = 4.8 Hz, 2H), 2.80 (br s, 3H), 1.66 (br d, *J* = 7.2 Hz, 3H), 1.47 (s, 3H)
 methyl (R)-2-methyl-1-(1-(5-((3-methyloxetan-3-yl)amino)-1,3-dioxan-2-yl)ethyl)-1H-indole-3-carboxylate	C9 Isomer 2 (2nd eluting isomer)	Cis-trans isomers separated by silica-gel column chromatography (Petroleum ether/Ethyl acetate = 10/1 - 1/2).	LCMS ([M+Na]$^+$) m/z: calc'd: 411.20; found 411.1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (br d, *J* = 7.6 Hz, 1H), 7.55 (br d, *J* = 7.2 Hz, 1H), 7.24 - 7.15 (m, 2H), 5.07 (br d, *J* = 5.2 Hz, 1H), 4.71 - 4.59 (m, 1H), 4.47 (br d, *J* = 6.0 Hz, 2H), 4.41 - 4.36 (m, 2H), 3.93 (s, 3H), 3.91 - 3.80 (m, 2H), 3.73 - 3.59 (m, 2H), 2.83 (s, 3H), 2.67 (br s, 1H), 1.70 (d, *J* = 7.2 Hz, 3H), 1.46 (s, 3H)
 methyl (R)-1-(1-(5-(dimethylamino)-1,3-dioxan-2-yl)ethyl)-2-methyl-1H-indole-3-carboxylate	C10		LCMS [M+H]$^+$ m/z: calc'd 347.19; found 346.9
 methyl (R)-1-(1-(5-(2,2-dimethylazetidin-1-yl)-1,3-dioxan-2-yl)ethyl)-2-methyl-1H-indole-3-carboxylate	C11		LCMS [M+H]$^+$ m/z: calc'd 387.22; found 387.0

 methyl (R)-1-(1-(5-((2-methoxyethyl)(methyl)amino)-1,3-dioxan-2-yl)ethyl)-2-methyl-1H-indole-3-carboxylate	C12		LCMS $[M+H]^+$ m/z: calc'd 391.22; found 391.0
 methyl (R)-2-methyl-1-(1-(4-(3-(trifluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-1H-indole-3-carboxylate	B13 Isomer 1 (1st eluting isomer)	Cis-trans isomers separated by silica-gel preparative thin-layer chromatography (Petroleum ether/Ethyl acetate = 3/1).	LCMS $[M+H]^+$ calc'd. 439.21; found 439.0.
 methyl (R)-2-methyl-1-(1-(4-(3-(trifluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-1H-indole-3-carboxylate	B13 Isomer 2 (2nd eluting isomer)	Cis-trans isomers separated by silica-gel preparative thin-layer chromatography (Petroleum ether/Ethyl acetate = 3/1).	LCMS $[M+H]^+$ calc'd. 439.21; found 439.0.
 methyl (R)-1-(1-(4-(3,3-difluoroazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxylate	B14 Isomer 1 (1st eluting isomer)	Cis-trans isomers separated by silica-gel preparative thin-layer chromatography (Petroleum ether/Ethyl acetate = 5/0 - 5/2).	LCMS $[M+H]^+$ m/z: calc'd 391.21; found 391.0

 methyl (R)-1-(1-(4-(3,3-difluoroazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxylate	B14 Isomer 2 (2nd eluting isomer)	Cis-trans isomers separated by silica-gel preparative thin-layer chromatography (Petroleum ether/Ethyl acetate = 5/0 - 5/2).	LCMS $[M+H]^+$ m/z: calc'd 391.21; found 391.0
 methyl (R)-1-(1-(4-(3-fluoroazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxylate	B15 Isomer 1 (1st eluting isomer)	Cis-trans isomers separated by silica-gel preparative thin-layer chromatography (Petroleum ether/Ethyl acetate = 5/0 - 5/5).	LCMS $[M+H]^+$ m/z: calc'd 373.22; found 373.1.
 methyl (R)-1-(1-(4-(3-fluoroazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxylate	B15 Isomer 2 (2nd eluting isomer)	Cis-trans isomers separated by silica-gel preparative thin-layer chromatography (Petroleum ether/Ethyl acetate = 5/0 - 5/5).	LCMS $[M+H]^+$ m/z: calc'd 373.22; found 373.1.

[00143] Step 10: Synthesis methyl (R)-2-methyl-1-(1-(3-(oxetan-3-ylamino)bicyclo[1.1.1]pentan-1-yl)ethyl)-1H-indole-3-carboxylate (D10)

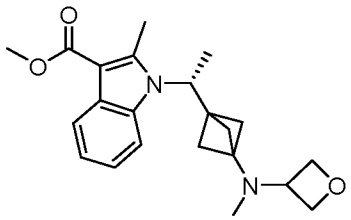
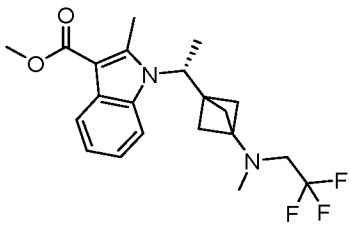


D9 D10

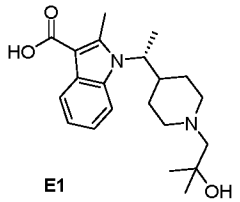
[00144] To a solution of **D9**, methyl (R)-1-(1-(3-aminobicyclo[1.1.1]pentan-1-yl)ethyl)-2-methyl-1H-indole-3-carboxylate (170 mg, 570 umol, 1.0 equiv) and oxetan-3-one (123 mg, 1.7 mmol, 3.0 equiv) in dichloroethane (3.0 mL) was added AcOH (34 mg, 570 umol, 33 uL, 1.0 equiv). The mixture was stirred at 15 °C for 12 h. $NaBH(OAc)_3$ (604 mg, 2.90 mmol, 5.0

equiv) was added into the flask. The mixture was stirred at 15 °C for 2 h. TLC (ethyl acetate) showed new spots formed. The mixture was diluted with saturated sodium bicarbonate (3 mL) and water (10 mL), extracated with dichloromethane (20 mL*3). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by preperative-TLC (ethyl acetae). methyl (R)-2-methyl-1-(1-(3-(oxetan-3-ylamino)bicyclo[1.1.1]pentan-1-yl)ethyl)-1H-indole-3-carboxylate (60 mg, 168 umol, 29% yield) was obtained as white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.13 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.21- 7.13 (m, 2H), 4.79 - 4.70 (m, 3H), 4.36 - 4.33 (m, 2H), 3.95 - 3.92 (m, 4H), 2.84 - 2.76 (m, 3H), 1.72 - 1.65 (m, 9H).

[00145] The following intermediates were synthesized using similar reductive mination conditions as those described above, along with appropriate starting materials and reagents.

Structure and Name	Intermediate	Isomer Separation Method and Retention Time (if any)	LCMS
 methyl (R)-2-methyl-1-(1-(3-(methyl(oxetan-3-yl)amino)bicyclo[1.1.1]pentan-1-yl)ethyl)-1H-indole-3-carboxylate	D11		LCMS $[M+H]^+$ m/z: calc'd 369.21; found 369.1
 methyl (R)-2-methyl-1-(1-(3-(methyl(2,2,2-trifluoroethyl)amino)bicyclo[1.1.1]pentan-1-yl)ethyl)-1H-indole-3-carboxylate	D12		LCMS $[M+H]^+$ m/z: calc'd 395.19; found 395.0.

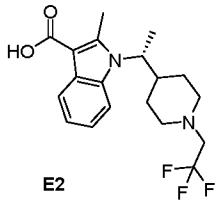
Synthesis of methyl (R)-1-(1-(1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)ethyl)-2-methyl-1H-indole-3-carboxylate (E1)



E1

[00146] **E1**, methyl (R)-1-(1-(1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)ethyl)-2-methyl-1H-indole-3-carboxylate was prepared according to the procedure reported in WO2015/023915. LCMS $[M+H]^+$ m/z: calc'd 372.24, found 373.1.

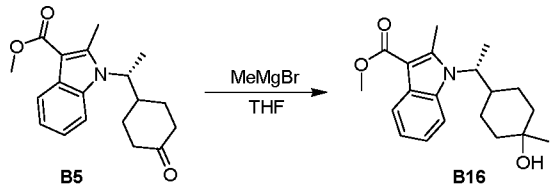
Synthesis of methyl (R)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxylate (E2)



E2

[00147] **E2**, methyl (R)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxylate was prepared according to the procedure reported in WO2015/023915.

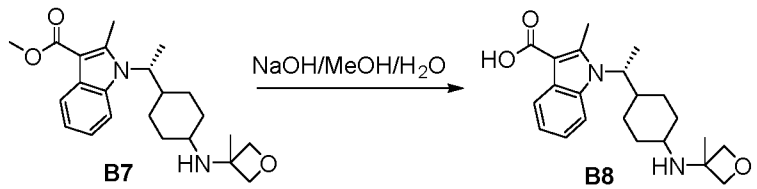
Synthesis of methyl (R)-1-(1-(4-hydroxy-4-methylcyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxylate (B16)



B5 B16

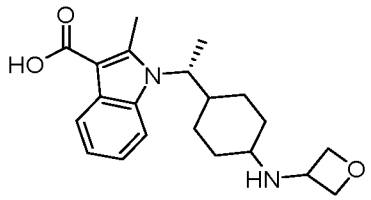
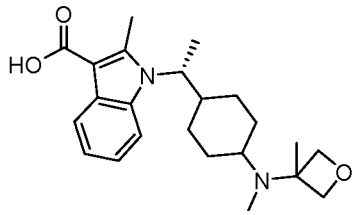
[00148] To a solution of methyl (R)-2-methyl-1-(1-(4-oxocyclohexyl)ethyl)-1H-indole-3-carboxylate (200 mg, 638 umol, 1 equiv) in THF (10 mL) was added MeMgBr (3 M, 700 uL, 3.3 equiv) at -78 °C under N2 atmosphere. The mixture was stirred at -78 °C for 1 h under N2 atmosphere. The reaction mixture was quenched by addition of saturated NH_4Cl 20 mL at 0 °C. The mixture was extracted with ethyl acetate 60 mL (20 mL * 3). The combined organic layers were washed with brine 60 mL (20 mL * 3), dried over sodium sulfate, filtered and concentrated under reduced pressure to give **B16**, methyl (R)-1-(1-(4-hydroxy-4-methylcyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxylate (210 mg, 484 umol) in 76 % yield as a yellow solid. LCMS ($[M + H]^+$) m/z: calc'd: 330.20.; found 330.3.

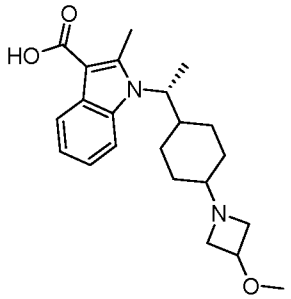
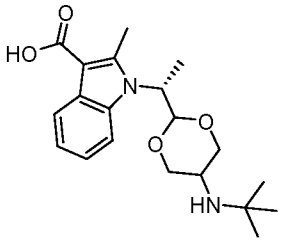
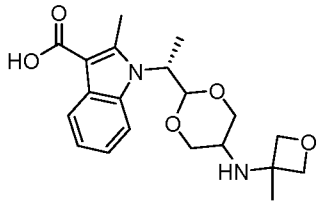
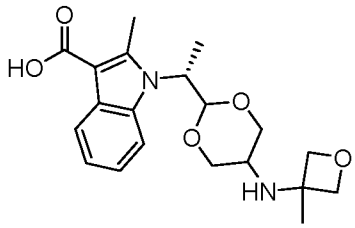
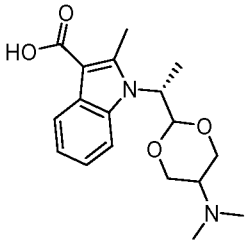
[00149] Step 2: (R)-2-methyl-1-(1-(4-((3-methyloxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxylic acid (B8)

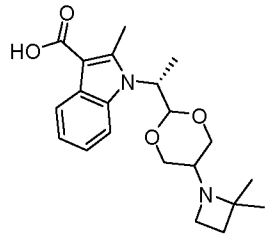
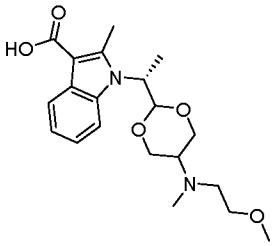
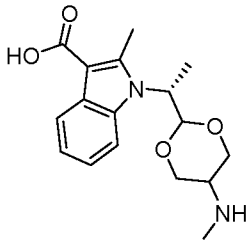
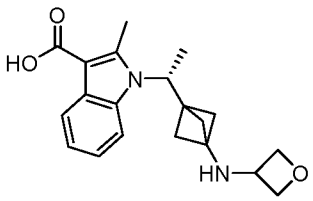
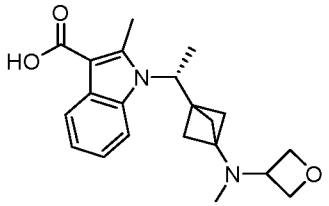


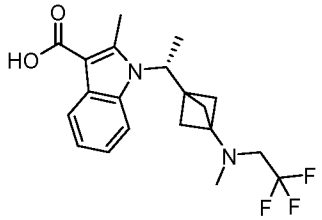
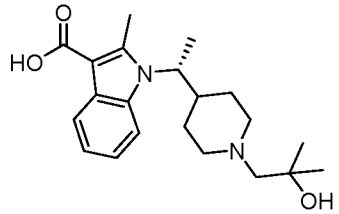
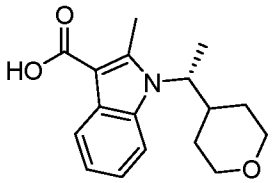
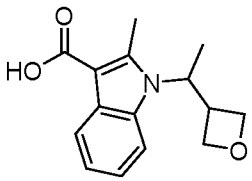
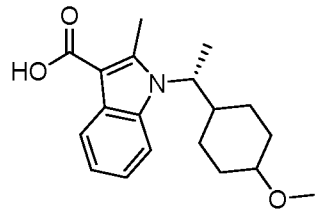
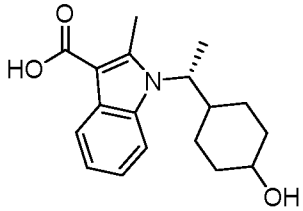
[00150] To a solution of methyl (R)-2-methyl-1-(1-(4-((3-methyloxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxylate (150 mg, 390 umol, 1.0 equiv, cis/trans mixture) in methanol (3 mL) and water (1.5 mL) was added NaOH (156 mg, 3.9 mmol, 10 equiv). The mixture was stirred at 80 °C for 12 h. The reaction mixture was concentrated. dichloromethane (15 mL) and water (10 mL) were added. The mixture was adjusted to pH = 5 - 6 with HCl (1 M) solution. The mixture was extracted with dichloromethane (20 mL * 3). The organic layer was dried by anhydrous sodium sulfate, filtered and concentrated under vacuum to give **B7**, (R)-2-methyl-1-(1-(4-((3-methyloxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxylic acid (160.0 mg, crude), as a white solid. LCMS $[M+H]^+$ m/z: calc'd 371.23; found 371.1.

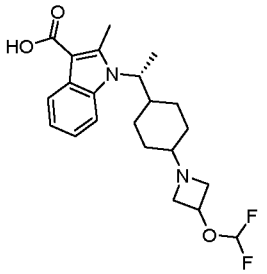
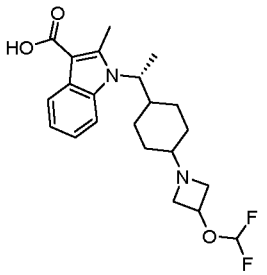
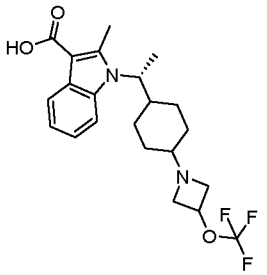
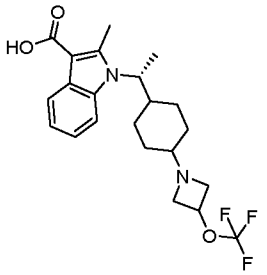
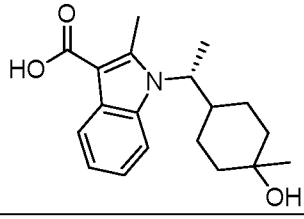
[00151] The following intermediates were synthesized using similar conditions as those described above, along with appropriate starting materials.

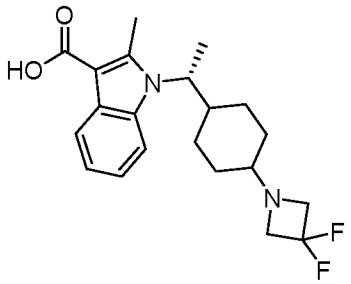
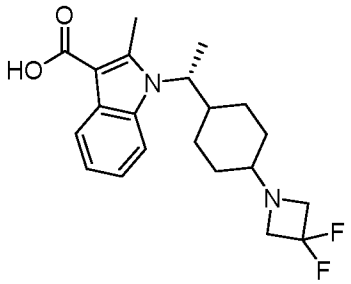
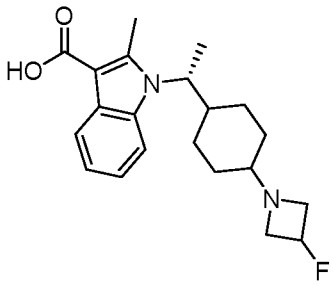
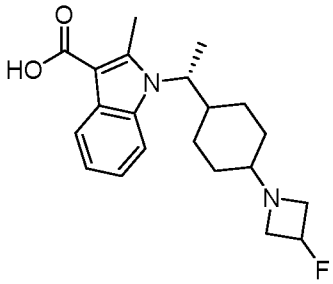
Structure and Name	Intermediate	LCMS
 2-methyl-1-((1R)-1-(4-(oxetan-3-ylamino)cyclohexyl)ethyl)-1H-indole-3-carboxylic acid	B17	LCMS $[M+H]^+$ m/z: calc'd 357.21; found 357.0.
 (R)-2-methyl-1-(1-(4-(methyl(3-methyloxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxylic acid	B18	LCMS $[M+H]^+$ m/z: calc'd 385.24; found 385.0.

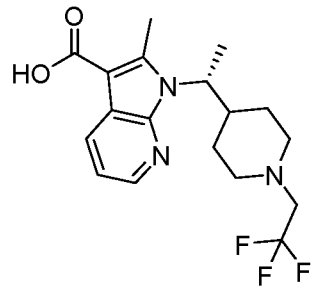
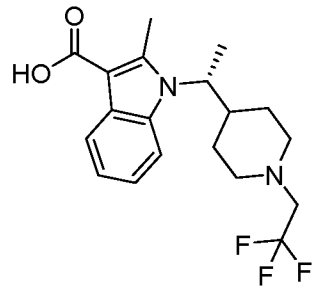
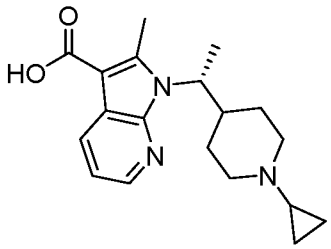
 1-((1R)-1-(4-(3-methoxyazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxylic acid	B19	LCMS $[M+H]^+$ m/z: calc'd 371.23; found 371.1.
 (R)-1-(1-(5-(tert-butylamino)-1,3-dioxan-2-yl)ethyl)-2-methyl-1H-indole-3-carboxylic acid	C14	LCMS $[M+H]^+$ m/z: calc'd 361.21; found 361.1.
 (R)-2-methyl-1-(1-(5-((3-methyloxetan-3-yl)amino)-1,3-dioxan-2-yl)ethyl)-1H-indole-3-carboxylic acid	C15 isomer 1 [From C9 isomer 1]	LCMS $[M+H]^+$ m/z: calc'd 397.18; found 397.1
 (R)-2-methyl-1-(1-(5-((3-methyloxetan-3-yl)amino)-1,3-dioxan-2-yl)ethyl)-1H-indole-3-carboxylic acid	C15 isomer 2 (From C9 isomer 2)	LCMS m/z: calc'd 397.18 $[M+Na]^+$; found 397.1
 (R)-1-(1-(5-(dimethylamino)-1,3-dioxan-2-yl)ethyl)-2-methyl-1H-indole-3-carboxylic acid	C16	LCMS $[M+H]^+$ m/z: calc'd 333.17; found 332.9

 (R)-1-(1-(5-(2,2-dimethylazetidin-1-yl)-1,3-dioxan-2-yl)ethyl)-2-methyl-1H-indole-3-carboxylic acid	C17	LCMS $[M+H]^+$ m/z: calc'd 373.20; found 373.0
 (R)-1-(1-(5-((2-methoxyethyl)(methyl)amino)-1,3-dioxan-2-yl)ethyl)-2-methyl-1H-indole-3-carboxylic acid	C18	LCMS $[M+H]^+$ m/z: calc'd 377.22; found 377.0
 (R)-2-methyl-1-(1-(5-(methylamino)-1,3-dioxan-2-yl)ethyl)-1H-indole-3-carboxylic acid	C19	LCMS $[M+H]^+$ m/z: calc'd 319.16; found 318.9
 (R)-2-methyl-1-(1-(3-(oxetan-3-ylamino)bicyclo[1.1.1]pentan-1-yl)ethyl)-1H-indole-3-carboxylic acid	D14	LCMS $[M+H]^+$ m/z: calc'd 341.18; found 340.9
 (R)-2-methyl-1-(1-(3-(methyl(oxetan-3-yl)amino)bicyclo[1.1.1]pentan-1-yl)ethyl)-1H-indole-3-carboxylic acid	D15	LCMS $[M+H]^+$ m/z: calc'd 355.19; found 355.1

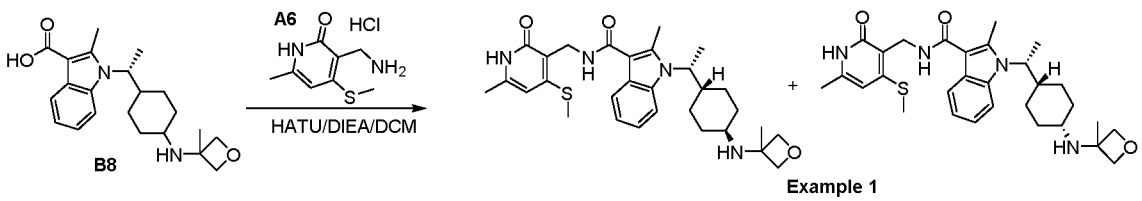
 (R)-2-methyl-1-(1-(3-(methyl(2,2,2-trifluoroethyl)amino)bicyclo[1.1.1]pentan-1-yl)ethyl)-1H-indole-3-carboxylic acid	D16	LCMS $[M+H]^+$ m/z: calc'd 381.17; found 381.1
 (R)-1-(1-(1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)ethyl)-2-methyl-1H-indole-3-carboxylic acid	E3	LCMS $[M+H]^+$ m/z: calc'd 359.23, found 359.1
 (R)-2-methyl-1-(1-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-indole-3-carboxylic acid	F2	LCMS $[M+H]^+$ m/z: calc'd 288.15; found 287.9
 2-methyl-1-(1-(oxetan-3-yl)ethyl)-1H-indole-3-carboxylic acid	G2	LCMS $[M+H]^+$ m/z: calc'd 260.12; found 259.9
 (R)-1-(1-(4-methoxycyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxylic acid	B20	LCMS $[M+H]^+$ m/z: calc'd 316.18; found 316.0
 (R)-1-(1-(4-hydroxycyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxylic acid	B21	LCMS $[M+H]^+$ m/z: calc'd 302.17; found 301.9

 (R)-1-(1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxylic acid	B22 Isomer 1 (From B12 isomer 1)	LCMS $[M+H]^+$ m/z: calc'd 407.21; found 407.1
 (R)-1-(1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxylic acid	B22 Isomer 2 (From B12 isomer 2)	LCMS $[M+H]^+$ m/z: calc'd 407.21; found 407.1
 (R)-2-methyl-1-(1-(4-(3-(trifluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-1H-indole-3-carboxylic acid	B23 Isomer 1 (From B13 isomer 1)	LCMS $[M+H]^+$ calc'd. 425.2; found 425.1
 (R)-2-methyl-1-(1-(4-(3-(trifluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-1H-indole-3-carboxylic acid	B23 Isomer 2 (From B13 isomer 2)	LCMS $[M+H]^+$ calc'd. 425.2; found 425.1
	B24	LCMS $[M+H]^+$ m/z: calc'd: 316.18.; found 316.0

(R)-1-(1-(4-hydroxy-4-methylcyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxylic acid		
 (R)-1-((R)-1-(4-(3,3-difluoroazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-1H-1l4-indole-3-carboxylic acid	B25 Isomer 1 (From B14 isomer 1)	LCMS $[M+H]^+$ m/z: calc'd: 377.2.; found 377.0
 (R)-1-((R)-1-(4-(3,3-difluoroazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-1H-1l4-indole-3-carboxylic acid	B25 Isomer 2 (From B14 isomer 2)	LCMS $[M+H]^+$ m/z: calc'd: 377.2.; found 377.0
 (R)-1-(1-(4-(3-fluoroazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxylic acid	B26 Isomer 1 (From B15 isomer 1)	LCMS $[M+H]^+$ m/z: calc'd 359.21; found 359.0
 (R)-1-(1-(4-(3-fluoroazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxylic acid	B26 Isomer 2 (From B15 isomer 2)	LCMS $[M+H]^+$ m/z: calc'd 359.21; found 359.0

 (R)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxylic acid	H5	LCMS $[M+H]^+$ m/z: calc'd 370.17; found 370.1
 (R)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxylic acid	E4	LCMS $[M+H]^+$ m/z: calc'd 357.21; found 357.2
 (R)-1-(1-(1-cyclopropylpiperidin-4-yl)ethyl)-2-methyl-1H-pyrrolo[2,3-b]pyridine-3-carboxylic acid	H7	LCMS $[M+H]^+$ m/z: calc'd 328.19; found 328.0.

[00152] Step 3: Synthesis of (R)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(4-((3-methyloxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxamide (Example 1, isomer 1 and isomer 2)



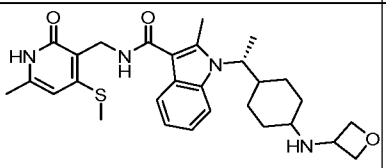
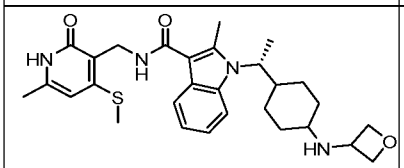
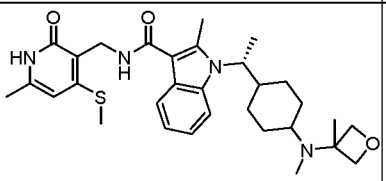
[00153] To a solution of (R)-2-methyl-1-(1-(4-((3-methyloxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxylic acid (90 mg, 243 umol, 1.0 equiv, cis/trans mixture) and 3-(aminomethyl)-6-methyl-4-methylsulfanyl-1H-pyridin-2-one (215

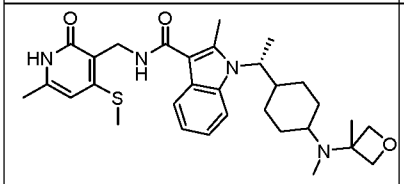
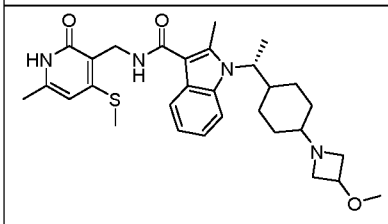
mg, 972 umol, 4 equiv, HCl salt) in dichloromethane (2 mL) was added HATU (111 mg, 292 umol, 1.2 equiv) and diisopropyethylamine (157 mg, 1.2 mmol, 5 equiv). The mixture was stirred at 25 °C for 2 h. The reaction was diluted with water (5 mL) and extracted with dichloromethane (10 mL * 3). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum before being purified by prep-HPLC (column: Waters Xbridge 150×25mm 5um; mobile phase A [water (0.05% ammonia hydroxide v/v)] and B [acetonitrile]; gradient B: 35%-65% over 10min). The cis and trans isomers were separated via SFC. Isomer 1 was purified on a Chiralpak AS-3 100×4.6mm I.D., 3um column. The mobile phase A [CO_2] and B [ethanol (0.05% diethylamine)]. The gradient was a ramp from 5% to 40% of B in 4.5 min and held at 40% for 2.5 min, and then 5% of B for 1 min at a flow rate of 2.8 mL/min and a column temperature of 40 °C. The retention time of **Isomer 1** is 3.86 min. Isomer 2 was further purified on a Chiralcel OD-3 100×4.6mm I.D., 3um column. The mobile phase A [CO_2] and B [ethanol (0.05% diethylamine)]. The column gradient was a ramp from 5% to 40% of B in 4.5 min and held at 40% for 2.5 min, and then 5% of B for 1 min at a flow rate of 2.8 mL/min and a column temperature of 40 °C. The retention time of **Isomer 2** is 5.27 min.

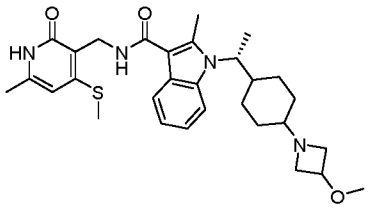
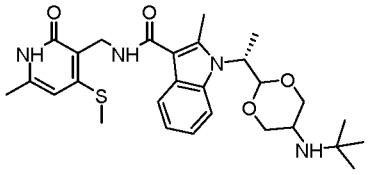
[00154] **Isomer 1:** (R)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(4-((3-methyloxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxamide (0.0354 g, 63.3 umol, 26.1% yield) was obtained as a white solid. LCMS $[M+H]^+$ m/z: calc'd 537.28; found 537.1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.64 (br s, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.35 - 7.32 (m, 1H), 7.09 - 7.02 (m, 2H), 6.00 (s, 1H), 4.72 - 4.71 (m, 2H), 4.46 - 4.33 (m, 4H), 4.05 - 4.03 (m, 1H), 2.72 (s, 3H), 2.54 (br s, 1H), 2.49 (s, 3H), 2.21 (s, 3H), 2.10 - 1.89 (m, 3H), 1.60 (d, J = 7.2 Hz, 3H), 1.49 (s, 3H), 1.19 - 0.79 (m, 5H).

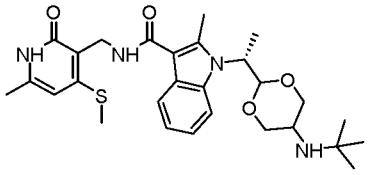
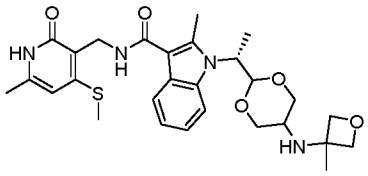
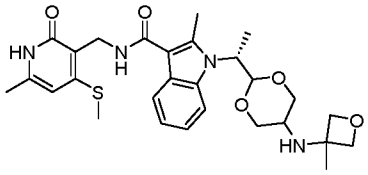
[00155] **Isomer 2:** (R)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(4-((3-methyloxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxamide (0.0072 g, 12.7 umol, 5.3% yield) was obtained as a white solid. LCMS $[M+H]^+$ m/z: calc'd 537.28; found 537.1. ^{1}H NMR (400 MHz, $CDCl_3$) δ12.67 (br s, 1H), 7.84 (d, J = 7.2 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.33 - 7.32 (m, 1H), 7.10 - 7.02 (m, 2H), 6.01 (s, 1H), 4.75 - 4.70 (m, 2H), 4.52 - 4.24 (m, 5H), 3.01 - 2.77 (m, 4H), 2.48 (s, 3H), 2.22 (s, 3H), 2.20 - 1.64 (m, 4H), 1.59 (d, J = 6.8 Hz, 3H), 1.48 (s, 3H), 1.33 - 1.05 (m, 5H).

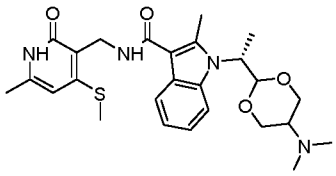
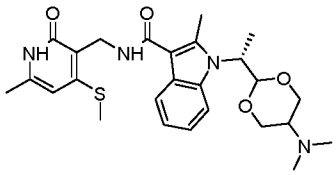
[00156] The following examples were synthesized using the amide coupling procedure described above and using appropriate starting materials.

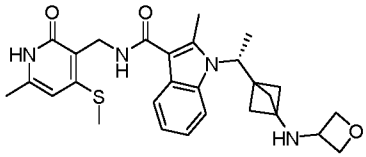
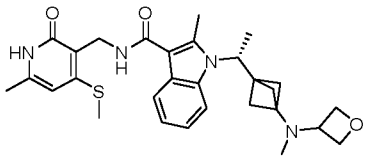
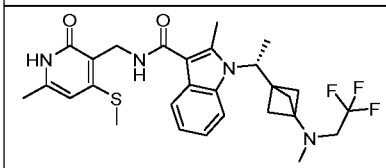
Name and Structure	Ex. #	Isomer Separation Method and Retention Time (if any)	LCMS + HNMR
 (R)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(4-(oxetan-3-ylamino)cyclohexyl)ethyl)-1H-indole-3-carboxamide	2 Isomer 1	Column: Chiralpak AD-3 100×4.6mm I.D., 3um Mobile phase: 40% of ethanol (0.05% diethylamine) in CO_2 Flow rate: 2.8 mL/min Column temperature: 40 °C Retention Time = 5.06 min	LCMS $[M+H]^+$ m/z: calc'd 523.27; found 523.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.76 (br. s., 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.35 - 7.32 (m, 1H), 7.09 - 7.02 (m, 2H), 6.00 (s, 1H), 4.80 - 4.76 (m, 4H), 4.40 - 4.34 (m, 2H), 4.04 - 4.02 (m, 2H), 2.71 (s, 3H), 2.48 (s, 3H), 2.37 (br s, 1H), 2.21 (s, 3H), 2.18 - 1.91 (m, 2H), 1.59 (d, *J* = 6.8 Hz, 6H), 1.13 - 0.79 (m, 5H).
 (R)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(4-(oxetan-3-ylamino)cyclohexyl)ethyl)-1H-indole-3-carboxamide	2 Isomer 2	Column: Chiralpak AD-3 100×4.6mm I.D., 3um Mobile phase: 40% of ethanol (0.05% diethylamine) in CO_2 Flow rate: 2.8 mL/min Column temperature: 40 °C Retention Time = 2.95 min	LCMS $[M+H]^+$ m/z: calc'd 523.27; found 523.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.90 (br. s., 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.32 (br s, 1H), 7.09 - 7.01 (m, 2H), 6.01 (s, 1H), 4.83 - 4.75 (m, 4H), 4.45 - 4.41 (m, 2H), 4.00 - 3.98 (m, 2H), 2.84 (s, 3H), 2.48 (s, 3H), 2.29 (br s, 1H), 2.21 (s, 3H), 1.77 - 1.55 (m, 7H), 1.32 - 0.86 (m, 5H).
 2-methyl-1-((1R)-1-(4-	3 Isomer 1	Column: Chiralpak AS-3 100×4.6mm I.D., 3um Mobile phase: A: CO_2 B:ethanol (0.05% diethylamine) Gradient: from 5% to	LCMS $[M+H]^+$ m/z: calc'd 551.30; found 551.1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.43 (br s, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.32 (s,

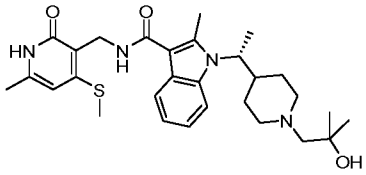
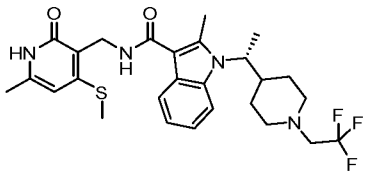
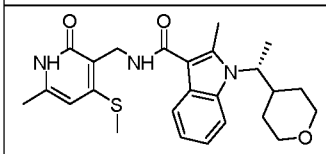
(methyl(3-methyloxetan-3-yl)amino)cyclohexyl)ethyl)-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide		40% of B in 4.5 min and hold 40% for 2.5 min, then 5% of B for 1 min Flow rate: 2.8 mL/min Column temperature: 40 °C Retention Time = 3.83 min	1H), 7.10 - 7.04 (m, 2H), 6.00 (s, 1H), 4.73 - 4.72 (m, 2H), 4.60 (d, J = 5.2 Hz, 1H), 4.56 (d, J = 5.6 Hz, 1H), 4.14 - 4.07 (m, 3H), 2.83 - 2.71 (m, 3H), 2.48 (s, 3H), 2.20 - 2.10 (m, 6H), 2.02 (s, 3H), 1.82 - 1.79 (m, 1H), 1.63 - 1.57 (m, 3H), 1.42 - 1.39 (m, 5H), 1.05 - 1.02 (m, 3H), 0.78 - 0.74 (m, 1H).
 2-methyl-1-((1R)-1-(4-(methyl(3-methyloxetan-3-yl)amino)cyclohexyl)ethyl)-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	3 Isomer 2	Column: Chiralcel OD-3 100×4.6mm I.D., 3um Mobile phase: A: CO_2 B:ethanol (0.05% diethylamine) Gradient: from 5% to 40% of B in 4.5 min and hold 40% for 2.5 min, then 5% of B for 1 min Flow rate: 2.8 mL/min Column temperature: 40 °C Retention Time = 5.27 min	LCMS $[M+Na]^+$ m/z: calc'd 573.30; found 573.1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.22 (br s, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.30 - 7.26 (m, 1H), 7.09 - 7.04 (m, 2H), 6.00 (s, 1H), 4.76 - 4.63 (m, 4H), 4.40 - 4.38 (m, 1H), 4.13 - 4.07 (m, 2H), 2.84 - 2.79 (m, 3H), 2.48 (s, 4H), 2.31- 2.30 (m, 1H), 2.21 (s, 3H), 1.97 (s, 3H), 1.78 - 1.76 (m, 1H), 1.57 - 1.53 (m, 4H), 1.39 - 1.25 (m, 6H), 1.16 - 1.09 (m, 2H), 1.01 - 0.97 (m, 1H).
 1-((1R)-1-(4-(3-methoxyazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-	4 Isomer 1	Column: Chiralpak AD-3 100×4.6mm I.D., 3um Mobile phase: 40% of ethanol (0.05% diethylamine) in CO_2 Flow rate: 2.8 mL/min Column temperature: 40 °C Retention Time = 3.35 min	LCMS $[M+H]^+$ m/z: calc'd 537.28; found 537.1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.70 (br s, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.37 (s, 1H), 7.10 - 7.02 (m, 2H), 6.00 (s, 1H), 4.78 - 4.71 (m, 2H), 4.03 - 3.98 (m, 2H), 3.59 - 3.52 (m, 2H), 3.24 (s,

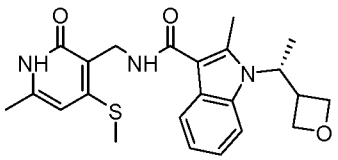
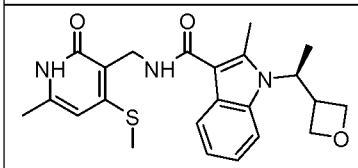
yl)methyl)-1H-indole-3-carboxamide			3H), 2.87 - 2.80 (m, 2H), 2.72 (s, 3H), 2.48 (s, 3H), 2.18 - 2.06 (m, 4H), 1.91 - 1.58 (m, 6H), 1.07 - 0.73 (m, 5H).
 1-((1R)-1-(4-(3-methoxyazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	4 Isomer 2	Column: Chiralpak AD-3 100×4.6mm I.D., 3um Mobile phase: 40% of ethanol (0.05% diethylamine) in CO_2 Flow rate: 2.8 mL/min Column temperature: 40 °C Retention Time = 1.77 min	LCMS $[M+H]^+$ m/z: calc'd 537.28; found 537.2. ^1H NMR (400 MHz, $CDCl_3$) δ 12.50 (br s, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 7.2 Hz, 1H), 7.31 (s, 1H), 7.13 - 7.01 (m, 2H), 6.00 (s, 1H), 4.80 - 4.70 (m, 2H), 4.02 - 4.00 (m, 2H), 3.58 - 3.47 (m, 2H), 3.25 (s, 3H), 2.79 - 2.71 (m, 5H), 2.48 (s, 3H), 2.20 (s, 3H), 1.63 - 1.38 (m, 10H), 1.13 - 0.74 (m, 3H).
 1-((1R)-1-(5-(tert-butylamino)-1,3-dioxan-2-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	5 Isomer 1	Column: Chiralcel OD-3 100×4.6mm I.D., 3um Mobile phase: A: CO_2 B: ethanol (0.05% diethylamine) Gradient: from 5% to 40% of B in 4.5 min and hold 40% for 2.5 min, then 5% of B for 1 min Flow rate: 2.8 mL/min Column temperature: 40 °C Retention Time = 4.92 min	LCMS $[M+H]^+$ m/z: calc'd 526.26; found 527.1. ^1H NMR (400 MHz, CD_3OD) δ 7.73-7.72 (d, *J* = 7.6 Hz, 1H), 7.59 (br s, 1H), 7.13 - 7.05 (m, 2H), 6.29 (s, 1H), 5.03 (br s, 1H), 4.61 (s, 2H), 4.60 - 4.58 (m, 1H), 4.13 (d, *J* = 8.0 Hz, 1H), 3.91 (d, *J* = 7.6 Hz, 1H), 3.42 (t, *J* = 10.8 Hz, 1H), 3.33 - 3.32 (m, 1H), 2.97 - 2.94 (m, 1H), 2.63 (s, 3H), 2.53 (s, 3H), 2.31 (s, 3H), 1.64 (d, *J* = 7.2 Hz, 3H), 1.08 (s, 9H).

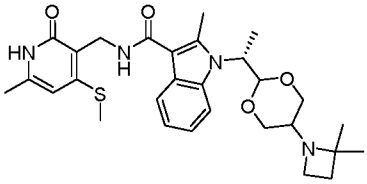
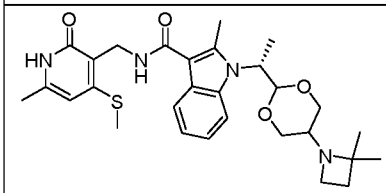
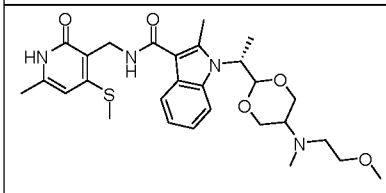
 1-((1R)-1-(5-(tert-butylamino)-1,3-dioxan-2-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	5 Isomer 2	Column: Chiralcel OD-3 100×4.6mm I.D., 3um Mobile phase: A: CO_2 B: ethanol (0.05% diethylamine) Gradient: from 5% to 40% of B in 4.5 min and hold 40% for 2.5 min, then 5% of B for 1 min Flow rate: 2.8 mL/min Column temperature: 40 °C Retention Time = 4.39 min	LCMS $[M+H]^+$ m/z: calc'd 526.26; found 527.1. ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (d, *J* = 7.6 Hz, 1H), 7.62 (br s, 1H), 7.15 - 7.07 (m, 2H), 6.32 (s, 1H), 5.13 (br s, 1H), 4.62 (s, 2H), 4.60 - 4.58 (m, 1H), 4.34 (d, J = 11.6 Hz, 1H), 4.12 (d, *J* = 6.4 Hz,1H), 3.75 - 3.70 (m, 1H), 3.45 (br s, 2H), 2.63 (s, 3H), 2.59 (s, 3H), 2.32 (s, 3H), 1.68 (d, *J* = 7.2 Hz, 3H), 1.29 (s, 9H).
 2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((1R)-1-(5-((3-methyloxetan-3-yl)amino)-1,3-dioxan-2-yl)ethyl)-1H-indole-3-carboxamide	6 Isomer 1 (From C15isomer 1)	N/A	LCMS $[M+H]^+$ m/z: calc'd 541.24; found 541.1. ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (d, *J* = 7.46 Hz, 1H), 7.61 (br s, 1H), 7.06 - 7.15 (m, 2H), 6.32 (s, 1H), 5.02 (m, 1H), 4.62 (s, 2H), 4.58 (br s, 1H), 4.44 (dd, *J* = 9.8, 6.0 Hz, 2H), 4.28 - 4.33 (m, 2H), 4.07 - 4.13 (m, 1H), 3.89 (br dd, *J* = 11.0, 2.5 Hz, 1H), 3.35 - 3.50 (m, 1H), 3.13 - 3.30 (m, 1H), 2.98 (tt, *J* = 10.4, 5.0 Hz, 1H), 2.63 (br s, 3H), 2.55 (s, 3H), 2.32 (s, 3H), 1.65 (d, *J* = 7.2 Hz, 3H), 1.31 (s, 3H).
 2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-	6 Isomer 2 (From C15 isomer 2)	N/A	LCMS $[M+H]^+$ m/z: calc'd 541.24; found 541.1. ^{1}H NMR (400 MHz, CD_3OD) δ 7.70 - 7.81 (m, 2H), 7.05 - 7.15 (m, 2H), 6.29 (s, 1H), 5.09 - 5.14 (m, 1H), 4.52 - 4.67 (m, 3H), 4.00 - 4.16 (m,

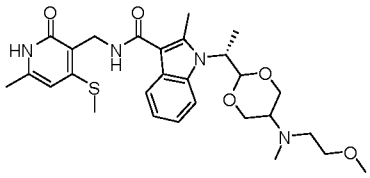
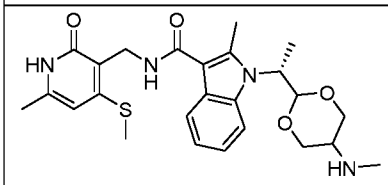
yl)methyl)-1-((1R)-1-(5-((3-methyloxetan-3-yl)amino)-1,3-dioxan-2-yl)ethyl)-1H-indole-3-carboxamide			3H), 3.79 - 3.93 (m, 3H), 3.67 (br dd, *J* = 11.29, 1.0 Hz, 1H), 3.51 - 3.6 (m, 1H), 2.56 - 2.65 (m, 4H), 2.52 - 2.55 (m, 3H), 2.28 - 2.33 (m, 3H), 1.73 (br d, *J* = 7.8 Hz, 3H), 1.32 (s, 3H).
 1-((1R)-1-(5-(dimethylamino)-1,3-dioxan-2-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	7 Isomer 1	Column: Chiralcel OD-3 100×4.6mm I.D., 3um Mobile phase: A: CO_2 B: ethanol (0.05% diethylamine) Gradient: from 5% to 40% of B in 4.5 min and hold 40% for 2.5 min, then 5% of B for 1 min Flow rate: 2.8 mL/min Column temperature: 40 °C Retention Time = 5.23 min	LCMS $[M+H]^+$ m/z: calc'd 499.2; found 498.2. ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (d, J = 8.0 Hz, 1H), 7.62 (br s, 1H), 7.21 - 7.14 (m, 2H), 6.99 (s, 1H), 5.13 (br s, 1H), 4.65 - 4.63 (m. 1H), 4.62 (s, 2H), 4.51 (d, *J* = 9.6 Hz, 1H), 4.29 (br s, 1H), 3.89 (t, *J* = 10.8 Hz, 1H), 3.62 (br s, 1H), 2.75 (s, 6H), 2.71 (s, 3H), 2.56 (s, 3H), 2.33 (s, 3H), 2.05 (br s, 1H), 1.68 (d, *J* = 7.2 Hz, 3H).
 1-((1R)-1-(5-(dimethylamino)-1,3-dioxan-2-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	7 Isomer 2	Column: Chiralcel OD-3 100×4.6mm I.D., 3um Mobile phase: A: CO_2 B: ethanol (0.05% diethylamine) Gradient: from 5% to 40% of B in 4.5 min and hold 40% for 2.5 min, then 5% of B for 1 min Flow rate: 2.8 mL/min Column temperature: 40 °C Retention Time = 4.66 min	LCMS $[M+H]^+$ m/z: calc'd 499.2; found 498.2. ^{1}H NMR (400 MHz, CD_3OD) δ 7.71 (d, *J* = 7.6 Hz, 1H), 7.62 (br s, 1H), 7.13 - 7.08 (m, 2H), 6.33 (s, 1H), 5.10 (br s, 1H), 4.62 (s, 2H), 4.60 (m, 1H), 4.46 (br s, 1H), 4.26 (d, *J* = 8.2 Hz, 1H), 3.82 (t, *J* = 10.4 Hz, 1H), 3.54 (br s, 1H), 3.10 (br s, 1H), 2.62 (s, 9H), 2.56 (s, 3H), 2.33 (s, 3H), 1.68 (d, *J* = 5.6 Hz, 3H).

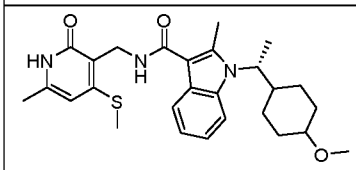
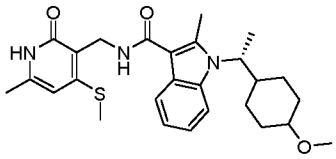
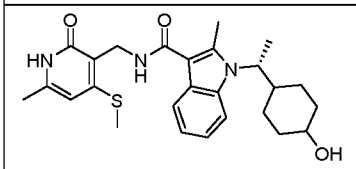
 (R)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(3-(oxetan-3-ylamino)bicyclo[1.1.1]pentan-1-yl)ethyl)-1H-indole-3-carboxamide	8	N/A	LCMS $[M+H]^+$ m/z: calc'd 507.24; found 507.0. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.12 (br s, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.33 - 6.99 (m, 3H), 5.99 (s, 2H), 4.76 - 4.63 (m, 5H), 4.32 (t, J = 6.8 Hz, 2H), 3.92 - 3.91(m, 1H), 2.78 - 2.69 (m, 3H), 2.47 (s, 3H), 2.19 (s, 3H), 1.82 - 1.68 (m, 2H), 1.66 - 1.61 (m, 7H).
 (R)-2-methyl-1-(1-(3-(methyl(oxetan-3-yl)amino)bicyclo[1.1.1]pentan-1-yl)ethyl)-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	9	N/A	LCMS $[M+H]^+$ m/z: calc'd 521.25; found 521.1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.52 (br s, 1H), 7.84 (d, *J* = 6.8 Hz, 1H), 7.45 (d, *J* = 7.2 Hz, 1H), 7.34 - 7.28 (m, 1H), 7.08 - 7.05 (m, 2H), 6.02 (s, 1H), 4.93 - 4.67 (m, 3H), 4.59 - 4.57 (m, 4H), 3.69 - 3.63 (m, 1H), 2.83 - 2.73 (m, 3H), 2.50 (s, 3H), 2.24 (s, 3H), 2.07 (s, 3H), 1.70 - 1.60 (m, 9H).
 (R)-2-methyl-1-(1-(3-(methyl(2,2,2-trifluoroethyl)amino)bicyclo[1.1.1]pentan-1-yl)ethyl)-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	10	N/A	LCMS $[M+H]^+$ m/z: calc'd 547.23; found 547.0. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.46 (br s, 1H), 7.83 (d, *J* = 8Hz, 1H), 7.45 (d, *J* = 8Hz, 1H), 7.33 (s, 1H), 7.30 - 7.03 (m, 2H), 6.0 (s, 1H), 4.75 - 4.68 (m, 3H), 2.94 - 2.82 (m, 2H), 2.72 (s, 3H), 2.48 (s, 3H), 2.34 (s, 3H), 2.21(s, 3H), 1.72 - 1.60 (m, 9H).

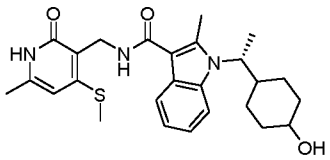
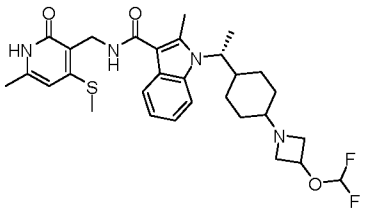
 (R)-1-(1-(1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	11	N/A	LCMS $[M+H]^+$ m/z: calc'd 524.28, found 525.1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.99 (s, 1H), 7.86 - 7.84 (d, J = 7.6 Hz, 1H), 7.46 - 7.44 (d, J = 7.6 Hz, 1H), 7.30 (s, 1H), 7.09 - 7.04 (m, 2H), 6.00 (s, 1H), 4.75 - 4.70 (m, 2H), 4.14 - 4.11 (m, 1H), 3.02 - 2.99 (m, 1H), 2.74 (s, 3H), 2.70 - 2.67 (m, 1H), 2.46 (s, 3H), 2.38 - 2.30 (m, 1H), 2.26 - 2.25 (m, 2H), 2.22 (s, 3H), 2.17 (m, 1H), 2.10 - 2.08 (m, 1H), 1.96 - 1.92 (m, 1H), 1.65 (s, 3H), 1.42 - 1.39 (m, 1H), 1.13 (s, 3H), 1.11 (s, 3H), 0.93 - 0.89 (m, 1H).
 (R)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide	12	N/A	LCMS $[M+H]^+$ m/z: calc'd 535.23; found 535.1. ^{1}H NMR (400 MHz, CD_3OD) δ 7.77 (d, J = 7.2 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.23 - 7.16 (m, 2H), 7.12 (s, 1H), 4.66 (s, 2H), 4.39 - 4.23 (m, 3H), 3.81 - 3.78 (m, 1H), 3.51 - 3.38 (m, 1H), 3.31 - 3.30 (m, 5H), 2.75 (s, 3H), 2.70 (s, 3H), 2.56 (s, 3H), 2.37 - 2.33 (m, 1H), 1.90 - 1.87 (m, 1H), 1.69 - 1.58 (m, 4H), 1.12 - 1.09 (m, 1H).
 (R)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-	13	N/A	LCMS $[M+H]^+$ m/z: calc'd 454.21; found 454.0. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 7.6Hz, 1H), 7.46 (d, J = 8.4Hz,

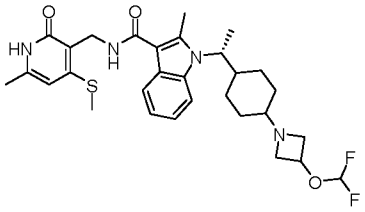
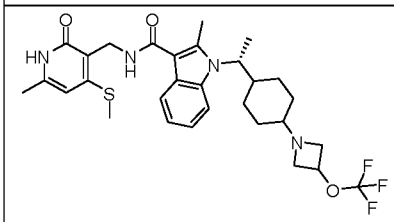
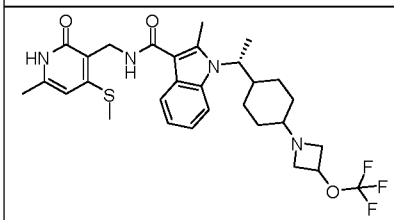
dihydropyridin-3-yl)methyl)-1-(1-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-indole-3-carboxamide			1H), 7.33-7.01 (m, 3H), 6.00 (s, 1H), 4.76 - 4.67 (m, 2H), 4.11-4.04 (m, 2H), 3.77 - 3.74 (m, 1H), 3.44 - 3.41 (m, 1H), 2.86 - 2.72 (m, 3H), 2.48 - 2.42 (m, 4H), 2.20 (s, 3H), 1.90 - 1.87 (m, 1H), 1.60 (d, *J* = 6.8Hz, 3H), 1.44 - 1.43 (m, 1H), 1.13 - 1.09 (m, 1H), 0.85 - 0.82 (m, 1H).
 (R)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(oxetan-3-yl)ethyl)-1H-indole-3-carboxamide	14 Isomer 1	Chiralpak AD-3 100×4.6mm I.D., 3um. Mobile phase: A: CO_2 B: ethanol (0.05% diethylamine). Gradient: from 5% to 40% of B in 4.5 min and hold 40% for 2.5 min, then 5% of B for 1 min. Flow rate: 2.8 mL/min Column temperature: 40 °C. Retention time = 6.53 min	LCMS $[M+H]^+$ m/z: calc'd 426.18; found 426.0. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.14 (br s, 1H), 7.82 (br d, *J* = 7.8 Hz, 1H), 7.34 (br s, 2H), 7.13 - 6.98 (m, 2H), 6.00 (s, 1H), 4.94 (t, *J* = 6.9 Hz, 2H), 4.79 - 4.64 (m, 2H), 4.49 (br t, *J* = 5.9 Hz, 2H), 4.09 (t, *J* = 6.1 Hz, 1H), 3.93 (br s, 1H), 2.85 (br s, 3H), 2.48 (s, 3H), 2.19 (s, 3H), 1.51 (br d, *J* = 6.5 Hz, 3H).
 (S)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(oxetan-3-yl)ethyl)-1H-indole-3-carboxamide	14 Isomer 2	Chiralpak AD-3 100×4.6mm I.D., 3um. Mobile phase: A: CO_2 B:ethanol (0.05% diethylamine). Gradient: from 5% to 40% of B in 4.5min and hold 40% for 2.5 min, then 5% of B for 1 min. Flow rate: 2.8 mL/min Column temperature: 40 °C. Retention time = 5.97 min	LCMS $[M+H]^+$ m/z: calc'd 426.18; found 426.0. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.79 (br s, 1H), 7.82 (br d, *J* = 7.8 Hz, 1H), 7.35 (br d, *J* = 8.3 Hz, 2H), 7.16 - 6.99 (m, 2H), 6.00 (s, 1H), 4.94 (dd, *J* = 6.5, 7.3 Hz, 2H), 4.82 - 4.64 (m, 2H), 4.49 (br t, *J* = 5.9 Hz, 2H), 4.10 - 4.05 (m, 1H), 3.94 (br s, 1H), 2.86 (br s, 3H), 2.48 (s, 3H), 2.20 (s, 3H), 1.54 - 1.43 (m, 3H).

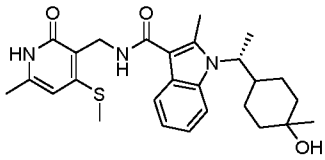
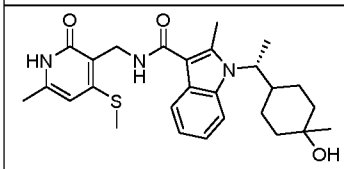
 (R)-1-(1-(5-(2,2-dimethylazetidin-1-yl)-1,3-dioxan-2-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	15 Isomer 1 (2nd eluting isomer)	column: Waters Xbridge 150*25 5u;mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN];B%: 45%-70%, 8min, Column Temp: 30 °C	LCMS $[M+H]^+$ m/z: calc'd 539.26; found 539.1. ^{1}H NMR (400 MHz, CD_3OD) δ 7.69 (d, *J* = 7.5 Hz, 1H), 7.58 (br s, 1H), 7.14 - 7.02 (m, 2H), 6.30 (s, 1H), 5.07 - 5.01 (m, 1H), 4.60 (br s, 3H), 4.10 (br d, *J* = 10.8 Hz, 1H), 3.88 (br d, *J* = 9.5 Hz, 1H), 3.43 (t, *J* = 10.5 Hz, 1H), 3.15 (br d, *J* = 12.5 Hz, 1H), 3.07 (t, *J* = 7.2 Hz, 2H), 2.86 (tt, *J* = 4.9, 10.0 Hz, 1H), 2.61 (br s, 3H), 2.54 (s, 3H), 2.31 (s, 3H), 1.83 (t, *J* = 7.0 Hz, 2H), 1.63 (d, *J* = 7.3 Hz, 3H), 1.23 (s, 3H), 1.22 (s, 3H)
 (R)-1-(1-(5-(2,2-dimethylazetidin-1-yl)-1,3-dioxan-2-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	15 Isomer 2 (1st eluting isomer)	column: Waters Xbridge 150*25 5u;mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN];B%: 45%-70%,8min, Column Temp: 30 °C	LCMS $[M+H]^+$ m/z: calc'd 539.26; found 539.1.^{1}H NMR (400 MHz, CD_3OD) δ 7.71 (br d, *J* = 7.3 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.16 - 7.01 (m, 2H), 6.31 (s, 1H), 5.21 (br d, *J* = 6.8 Hz, 1H), 4.61 (s, 3H), 4.05 - 3.97 (m, 1H), 3.96 - 3.88 (m, 1H), 3.74 (br d, *J* = 12.3 Hz, 1H), 3.60 - 3.49 (m, 1H), 3.31 - 3.30 (m, 1H), 3.26 - 3.13 (m, 2H), 2.67 (s, 3H), 2.54 (s, 3H), 2.31 (s, 3H), 1.91 (br s, 2H), 1.63 (br d, *J* = 7.0 Hz, 3H), 1.31 (s, 3H), 1.28 (s, 3H)
	16 Isomer 1	Chiralpak AD-3 100×4.6mm I.D., 3um. Mobile phase: 40% ethanol (0.05% diethylamine) in	LCMS $[M+H]^+$ m/z: calc'd 543.3; found 543.1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8 Hz, 1H), 7.61

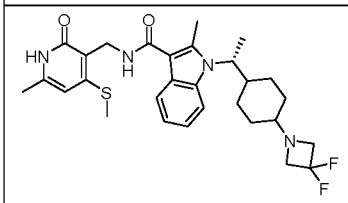
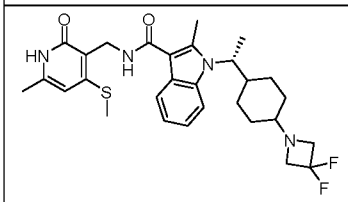
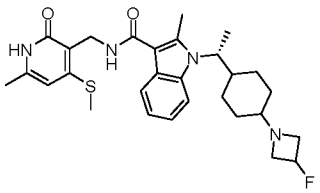
(R)-1-(1-(5-((2-methoxyethyl)(methyl)amino)-1,3-dioxan-2-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide		CO_2. Flow rate: 2.8 mL/min Column temperature: 40 °C. Retention time = 2.19 min	(s, 1H), 7.14 - 7.06 (m, 2H), 6.30 (s, 1H), 5.02 (d, *J* = 16 Hz, 1H), 4.62 (s, 3H), 4.31 (d, *J* = 12 Hz, 1H), 4.09 (d, *J* = 8 Hz, 1H), 3.72 - 3.45 (m, 1H), 3.43 - 3.42 (m, 3H), 3.34 - 3.31 (m, 3H), 2.78 - 2.76 (m, 1H), 2.65 - 2.63 (m, 5H), 2.55 (s, 3H), 2.32 - 2.28 (m, 6H), 1.66 (d, *J* = 8 Hz, 3H)
 (R)-1-(1-(5-((2-methoxyethyl)(methyl)amino)-1,3-dioxan-2-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	16 Isomer 2	Chiralpak AD-3 100×4.6mm I.D., 3um. Mobile phase: 40% ethanol (0.05% diethylamine) in CO_2. Flow rate: 2.8 mL/min Column temperature: 40 °C. Retention time = 1.53 min	LCMS $[M+H]^+$ m/z: calc'd 543.26; found 543.1. ^1H NMR (400 MHz, CD_3OD) δ 7.73 (d, *J* = 8 Hz, 1H), 7.61 (s, 1H), 7.14 - 7.06 (m, 2H), 6.31 (s, 1H), 5.03(d, *J* = 4 Hz, 1H), 4.63 (s, 3H), 4.31 (d, *J* = 8 Hz, 1H), 4.09 (d, *J* = 8Hz, 1H), 3.72 - 3.45 (m, 1H), 3.44 - 3.43 (m, 3H), 3.34 - 3.32 (m, 3H), 2.80 - 2.73 (m, 1H), 2.67 - 2.63 (m, 5H), 2.55 (s, 3H), 2.32 - 2.28 (m, 6H), 1.66 (d, *J* = 8 Hz, 3H).
 (R)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(5-(methylamino)-1,3-dioxan-2-yl)ethyl)-1H-indole-3-carboxamide	17	Chiralpak AD-3 100×4.6mm I.D., 3um. Mobile phase: A: CO_2 B:ethanol (0.05% diethylamine). Gradient: from 5% to 40% of B in 4.5 min and hold 40% for 2.5 min, then 5% of B for 1 min. Flow rate: 2.8 mL/min Column temperature: 40 °C. Retention time = 6.3 min	LCMS $[M+H]^+$ m/z: calc'd 485.21: found 485.0. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.0 Hz , 1H), 7.48(s, 1H), 7.27(s, 1H), 7.11-7.02 (m, 2H), 6.00 (s, 1H), 4.90 (s, 1H), 4.72 (d, *J* = 8.0 Hz, 2H), 4.55 (s, 1H), 4.31 - 4.28 (m, 1H), 4.10 - 4.07 (m, 1H), 3.31 (t, *J* = 8.0 Hz, 1H), 3.09 (m, 1H), 2.85-2.79 (m, 1H), 2.74 (s, 3H), 2.48 (s,

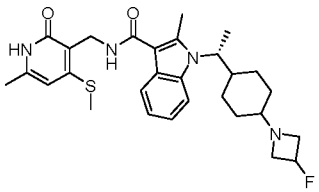
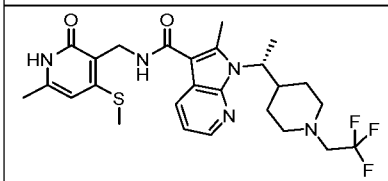
			3H), 2.41 (s, 3H), 2.21 (s, 3H), 1.66 - 1.61 (m, 4H), 1.31 - 1.26 (m, 1H).
 1-((R)-1-((1r,4R)-4-methoxycyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	18 Isomer 1	Column: Chiralpak AD-3 50×3 mm I.D., 3 um Column: Chiralpak AD-3 50×3mm I.D., 3 um. Mobile phase: 40% of ethanol (0.05% diethylamine) in CO_2. Flow rate: 2 mL/min Column temperature: 40 °C Retention time = 1.15 min	LCMS $[M+H]^+$ m/z: calc'd 482.24; found 482.2. ^1H NMR (400 MHz, $CDCl_3$) δ 12.77 (br s, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.36 (br s, 1H), 7.11 - 7.02 (m, 2H), 6.00 (s, 1H), 4.75 - 4.68 (m, 2H), 4.08 - 4.03 (m, 1H), 3.31 (s, 3H), 3.06 (s, 1H), 2.85 - 2.72 (m, 3H), 2.48 (s, 3H), 2.19 - 2.10 (m, 5H), 1.87 - 1.84 (m, 1H), 1.59 (d, *J* = 6.8 Hz, 3H), 1.59 - 0.76 (m, 6H).
 1-((R)-1-((1r,4R)-4-methoxycyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	18 Isomer 2	Column: Chiralpak AD-3 50×3 mm I.D., 3 um Column: Chiralpak AD-3 50×3mm I.D., 3 um. Mobile phase: 40% of ethanol (0.05% diethylamine) in CO_2. Gradient from 5% to 40% of B in 2.5 min and hold 40% for 0.35 min, then from 40% to 5% of B for 0.15 min. Flow rate: 2.5mL/min Column temperature: 40 °C Retention time = 2.41 min	LCMS $[M+H]^+$ m/z: calc'd 482.24; found 482.2. ^1H NMR (400 MHz, $CDCl_3$) δ 12.44 (br s, 1H), 7.84 (d, *J* = 6.8 Hz, 1H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.29 (br s, 1H), 7.08 - 7.03 (m, 2H), 6.00 (s, 1H), 4.76 - 4.60 (m, 2H), 4.14 (s, 1H), 3.3 - 3.27 (m, 4H), 2.85 - 2.73 (m, 3H), 2.48 (s, 3H), 2.21 (s, 3H), 2.03 - 2.01 (m, 2H), 1.59 - 1.43 (m, 6H), 1.12 - 0.80 (m, 4H).
 (R)-1-(1-(4-hydroxycyclohexyl)ethyl)-	19 Isomer 1	Column: Chiralpak AD-3 50×3 mm I.D., 3 um Column: Chiralpak AD-3 50×3mm I.D., 3um Mobile phase: 40%	LCMS $[M+H]^+$ m/z: calc'd 468.22: found 468.0. ^1H NMR (400 MHz, $CDCl_3$) δ 12.90 (s, 1H), 7.82 (d, *J* = 8.0, 1H), 7.46 - 7.44

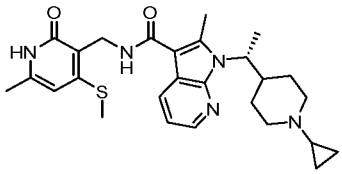
2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide		of ethanol (0.05% diethylamine) in CO_2. Flow rate: 2 mL/min Column temperature: 40 °C Retention time = 2.1 min	(m, 1H), 7.36 - 7.35 (m, 1H), 7.10 - 7.00 (m, 2H), 6.00 (s, 1H), 4.84 - 4.60 (m, 2H), 4.03 - 4.00 (m, 1H), 3.48 (s, 1H), 2.83 - 2.69 (m, 3H), 2.48 (s, 3H), 2.19 (s, 3H), 2.08 - 2.03 (m, 2H), 1.60 - 1.58 (m, 3H), 1.32 - 1.27 (m, 3H), 1.10 - 1.07 (m, 1H), 1.00 - 0.97 (m, 2H), 0.77 - 0.73 (m, 1H).
 (R)-1-(1-(4-hydroxycyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	19 Isomer 2	Column: Chiralpak AD-3 50×3 mm I.D., 3 um. Mobile phase: 40% of ethanol (0.05% diethylamine) in CO_2. Flow rate: 2 mL/min. Column temperature: 40 °C Retention time: 0.99 min	LCMS $[M+H]^+$ m/z: calc'd 468.22: found 468.0. ^1H NMR (400 MHz, $CDCl_3$) δ 13.00 (s, 1H), 7.83 (d, *J* = 8.0, 1H), 7.46 (d, *J* = 8.0, 1H), 7.31 (s, 1H), 7.10-7.00 (m, 2H), 6.00 (s, 1H), 4.78 - 4.67 (m, 2H), 4.17 - 4.13 (m, 1H), 4.00 (s, 1H), 2.84 - 2.72 (m, 3H), 2.48 (s, 3H), 2.24 - 2.20 (m, 4H), 1.85 - 1.80 (m, 2H), 1.62 - 1.53 (m, 6H), 1.29 - 1.20 (m, 3H), 0.83 - 0.80 (m, 1H).
 (R)-1-(1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	20 Isomer 1 (From B22 isomer 1)	Column: Chiralcel OD-3 100×4.6mm I.D., 3 um. Mobile phase: A:CO_2 B:ethanol (0.05% diethylamine) Gradient: from 5% to 40% of B in 4.5 min and hold 40% for 2.5 min, then 5% of B for 1 min. Flow rate: 2.8 mL/min. Column temperature: 40 °C Retention time: 4.7 min	LCMS $[M+H]^+$ m/z: calc'd 573.26; found 573.1. ^1H NMR (400 MHz, $CDCl_3$) δ 12.72 (br s, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.35 - 7.34 (m, 1H), 7.10 - 7.02 (m, 2H), 6.16 (t, *J* = 73.6 Hz, 1H), 6.00 (s, 1H), 4.76 - 4.70 (m, 3H), 4.05 - 4.03 (m, 1H), 3.67 - 3.57 (m, 2H), 3.04 - 2.97 (m, 2H), 2.72 (s, 3H), 2.48 (s, 3H), 2.19 - 1.88 (m, 7H), 1.59 (d,

			J = 7.2 Hz, 3H), 1.08 - 0.74 (m, 5H).
 (R)-1-(1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	20 Isomer 2 (From B22 isomer 2)	Column: Chiralcel OD-3 100×4.6 mm I.D., 3 um Mobile phase: A:CO_2 B:ethanol (0.05% diethylamine) Gradient: from 5% to 40% of B in 4.5 min and hold 40% for 2.5 min, then 5% of B for 1 min. Flow rate: 2.8 mL/min Column temperature: 40 °C Retention time: 4.4 min	LCMS $[M+H]^+$ m/z: calcd 573.26; found 573.1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.28 (brs, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.28 - 7.01 (m, 3H), 6.35 - 5.98 (m, 2H), 4.78 - 4.66 (m, 3H), 4.19 (br s, 1H), 3.63 - 3.54 (m, 2H), 2.92 - 2.74 (m, 5H), 2.48 (s, 3H), 2.25 - 2.21 (m, 4H), 1.58 - 0.74 (m, 11H).
 (R)-1-(1-(4-(3-(trifluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	21 Isomer 1 (From B23 isomer 1)	N/A	LCMS $[M+H]^+$ calc'd. 591.2; found 591.1. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.82 (br d, J = 7.5 Hz, 1H), 7.44 (br d, J = 8.0 Hz, 1H), 7.36 - 7.30 (m, 1H), 7.14 - 7.00 (m, 2H), 6.00 (s, 1H), 4.80 - 4.65 (m, 3H), 4.20 - 3.94 (m, 1H), 3.71 - 3.55 (m, 2H), 3.05 (td, J = 7.0, 13.7 Hz, 2H), 2.71 (s, 3H), 2.48 (s, 3H), 2.19 (s, 3H), 2.07 (br s, 2H), 1.99 - 1.86 (m, 2H), 1.82 - 1.76 (m, 1H), 1.58 (br d, J = 7.0 Hz, 3H), 1.55 - 1.44 (m, 1H), 1.15 - 0.96 (m, 3H), 0.75 (br t, J = 9.3 Hz, 2H).
 (R)-1-(1-(4-(3-(trifluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-2-	21 Isomer 2 (From B23 isomer 2)	N/A	LCMS $[M+H]^+$ calc'd. 591.2; found 591.1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (br d, J = 7.5 Hz, 1H), 7.44 (br d, J = 8.0 Hz, 1H), 7.29 (br s, 1H), 7.16 - 6.99 (m, 2H), 5.99 (s, 1H), 4.86 - 4.58 (m, 3H), 4.16 (br s, 1H),

methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide			3.64 (br s, 1H), 3.60 - 3.46 (m, 1H), 3.12 - 2.88 (m, 2H), 2.86 - 2.63 (m, 3H), 2.48 (s, 3H), 2.27 (br s, 1H), 2.23 - 2.15 (m, 3H), 1.76 - 1.64 (m, 4H), 1.56 (br d, *J* = 7.0 Hz, 3H), 1.51 - 1.25 (m, 3H), 1.24 - 0.98 (m, 2H), 0.72 (br s, 1H).
 (R)-1-(1-(4-hydroxy-4-methylcyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	22 Isomer 1 (2nd eluting isomer)	column: Waters X bridge 150 * 25 5u; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 32%-57%, 7.8 min. Temp: 30 °C	LCMS $[M+H]^+$ m/z: calc'd: 482.24; found 482.1. ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (br d, *J* = 7.6 Hz, 1H), 7.56 (br d, *J* = 7.6 Hz, 1H), 7.16 - 6.99 (m, 2H), 6.30 (s, 1H), 4.61 (s, 2H), 4.25 - 4.07 (m, 1H), 2.62 (s, 2H), 2.53 (s, 3H), 2.30 (s, 3H), 2.21 (br d, *J* = 11.2 Hz, 1H), 1.91 - 1.82 (m, 1H), 1.74 (br d, *J* = 10.4 Hz, 1H), 1.62 (br d, *J* = 6.8 Hz, 3H), 1.54 - 1.39 (m, 3H), 1.34 - 1.25 (m, 1H), 1.24 - 1.17 (m, 1H), 1.14 (s, 3H), 1.11 - 1.05 (m, 1H), 0.70 (br d, *J* = 12.0 Hz, 1H)
 (R)-1-(1-(4-hydroxy-4-methylcyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	22 Isomer 2 (1st eluting isomer)	column: Waters X bridge 150 * 25 5u; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 32%-57%, 7.8 min. Temp: 30 °C	LCMS $[M+H]^+$ m/z: calc'd: 482.24; found 482.1. ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (br d, *J* = 7.6 Hz, 1H), 7.56 (br d, *J* = 7.6 Hz, 1H), 7.17 - 7.02 (m, 2H), 6.30 (s, 1H), 4.61 (s, 2H), 4.27 - 4.14 (m, 1H), 2.61 (s, 2H), 2.53 (s, 3H), 2.30 (s, 4H), 2.04 (br d, *J* = 10.8 Hz, 1H), 1.76 (br d, *J* = 10.8 Hz, 1H), 1.61 (br d, *J* = 6.8 Hz, 3H), 1.58 - 1.49 (m,

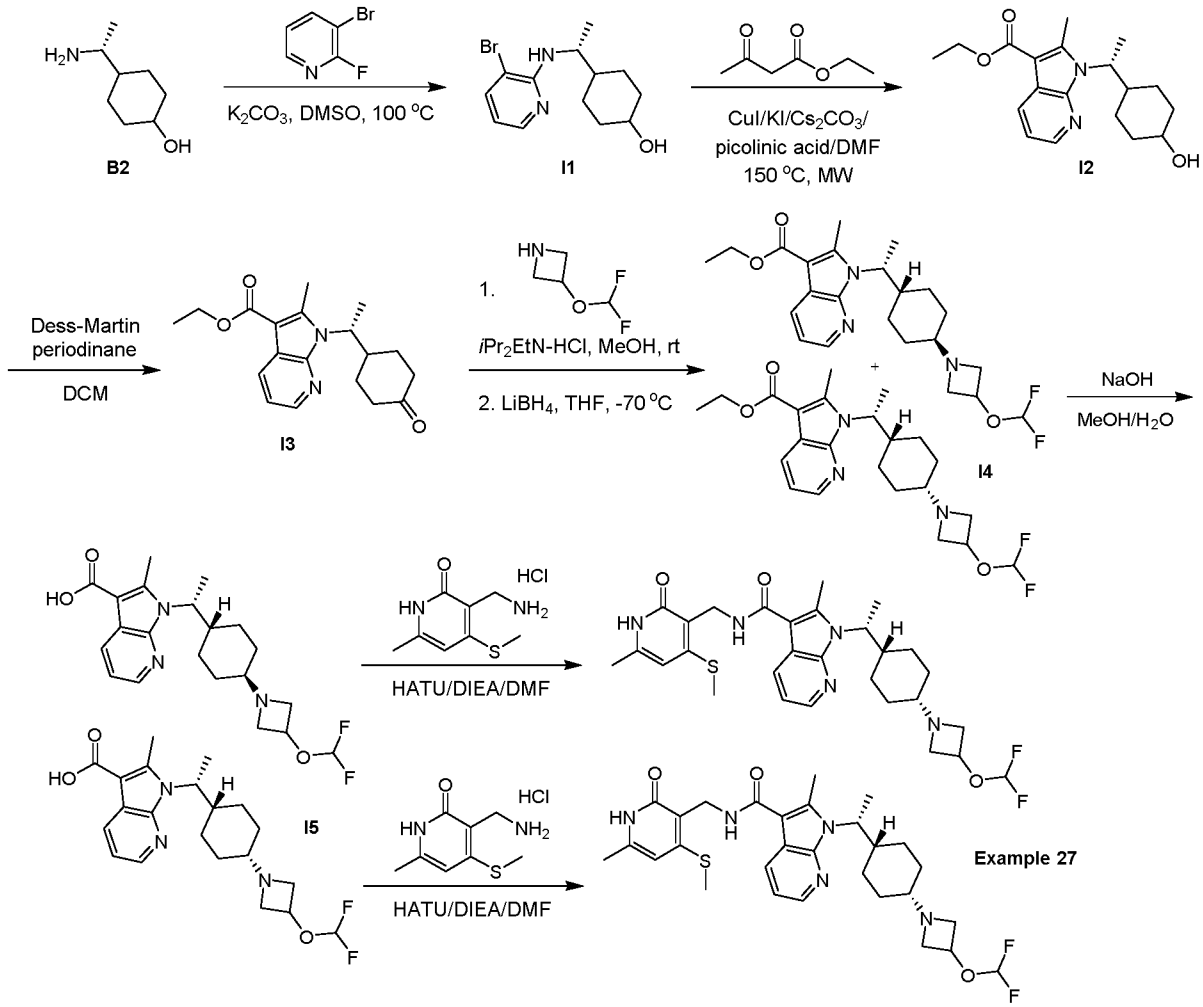
			1H), 1.45 (br d, *J* = 11.2 Hz, 1H), 1.28 (br d, *J* = 12.0 Hz, 2H), 1.20 (s, 4H), 1.00 - 0.87 (m, 2H)
 (R)-1-(1-(4-(3,3-difluoroazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	23 Isomer 1 (From B25 isomer 1)	Column: Chiralpak AS-3 100×4.6 mm I.D., 3 um. Mobile phase: A: CO_2 B:ethanol (0.05% diethylamine). Gradient: from 5% to 40% of B in 4.5 min and hold 40% for 2.5 min, then 5% of B for 1 min. Flow rate: 2.8 mL/min Column temperature: 40 °C Retention time = 3.61 min	LCMS $[M+H]^+$ m/z: calc'd 543.25: found 543.1. ^1H NMR (400 MHz, $CDCl_3$) δ 12.13 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.32 (s, 1H), 7.11-7.04 (m, 2H), 6.00 (s, 1H), 4.77 - 4.71 (m, 2H), 4.08 - 4.06 (m, 1H), 3.51 (t, *J* = 12.0 Hz, 4H), 2.83 -2 .71 (m, 3H), 2.49 (s, 3H), 2.16 - 2.11 (m, 4H), 2.08 (m, 1H), 2.00 (s, 1H), 1.86 (m, 3H), 1.27 (m, 1H), 1.17 - 1.05 (m, 3H), 0.83 - 0.74 (m, 2H).
 (R)-1-(1-(4-(3,3-difluoroazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	23 Isomer 2 (From B25 isomer 2)	Column: Chiralpak AD-3 150×4.6 mm I.D., 3 um. Mobile phase: A: CO_2 B:ethanol (0.05% diethylamine). Gradient: from 5% to 40% of B in 5.5 min and hold 40% for 3.0 min, then 5% of B for 1.5 min. Flow rate: 2.5 mL/min. Column temperature: 40 °C Retention time = 6.16 min	LCMS $[M+H]^+$ m/z: calcd 543.25; found 543.1. ^1H NMR (400 MHz, $CDCl_3$) δ 12.58 (s,1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.31 (s,1H), 7.11 - 7.04 (m, 2H), 6.02 (s,1H), 4.81 - 4.71 (m,2H), 4.22 - 4.17 (m,1H), 3.49 - 3.43 (m, 4H), 2.85 - 2.76 (m, 3H), 2.50 (s, 3H), 2.34 (s,1H), 2.23 (s, 4H), 1.73 (s, 1H), 1.60 - 1.37 (m, 7H), 1.18 - 1.16 (m, 2H), 0.75 (s, 1H).
 (R)-1-(1-(4-(3-	24 Isomer 1 (From B26 Isomer 2)	Column: Chiralpak AS-3 100×4.6 mm I.D., 3 um. Mobile phase: A: CO_2 B:ethanol (0.05% diethylamine). Gradient: from 5% to	LCMS $[M+H]^+$ m/z: calc'd 524.3; found 525.1. ^1H NMR (400 MHz, $CDCl_3$) δ 12.73 - 12.64 (m, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.45 - 7.26 (m, 1H),

fluoroazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide		40% of B in 4.5 min and hold 40% for 2.5 min, then 5% of B for 1 min. Flow rate: 2.8mL/min. Column temperature: 40 °C. Retention time = 3.54 min	7.08 - 7.01 (m, 2H), 6.00 (s, 1H), 5.16 - 5.01 (m, 1H), 4.74 - 4.70 (m, 2H), 4.05 - 4.04 (m, 1H), 3.66 - 3.61 (m, 2H), 3.11 - 3.06 (m, 2H), 3.05 - 2.71 (m, 3H), 2.48 (s, 3H), 2.18 (s, 3H), 2.09 – 2.07 (m, 1H), 1.90 - 1.87 (m, 2H), 1.59 - 1.57 (m, 4H), 1.08 - 1.04 (m, 3H), 0.78 - 0.73 (m, 2H).
 (R)-1-(1-(4-(3-fluoroazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	24 Isomer 2 (From B26 Isomer 1)	Chiralcel OD-3 100×4.6 mm I.D., 3 um. Mobile phase: A: CO_2 B:ethanol (0.05% diethylamine). Gradient: from 5% to 40% of B in 4.5 min and hold 40% for 2.5 min, then 5% of B for 1 min. Flow rate: 2.8 mL/min Column temperature: 40 °C Retention time = 4.62 min	LCMS $[M+H]^+$ m/z: calcd 525.26; found 525.1. ^1H NMR (400 MHz, $CDCl_3$) δ 12.44 (s, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.31 - 7.28 (m, 1H), 7.08 - 7.01 (m, 2H), 5.99 (s, 1H), 5.16 - 5.01 (m, 1H), 4.75 - 4.68 (m, 2H), 4.17 - 4.15 (m, 1H), 3.62 - 3.52 (m, 2H), 3.00 - 2.95 (m, 2H), 2.81 - 2.71 (m, 3H), 2.47 (s, 3H), 2.26 - 2.20 (m, 5H), 1.66 - 1.55 (m, 4H), 1.38 - 1.35 (m, 4H), 1.12 - 1.06 (m, 2H), 0.72 - 0.70 (m, 1H).
 (R)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	25	N/A	LCMS $[M+H]^+$ m/z: calc'd 536.22; found 536.1. ^1H NMR (400 MHz, CD_3OD) δ 8.20 (d, *J* = 4.0 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.14 - 7.11 (m, 1H), 6.32 (s, 1H), 4.62 (s, 3H), 4.18 - 4.13 (m, 1H), 3.11 - 3.06 (m, 1H), 3.05 - 2.97 (m, 2H), 2.81 - 2.78 (m, 1H), 2.69 (br s, 3H), 2.56 (s, 3H), 2.43

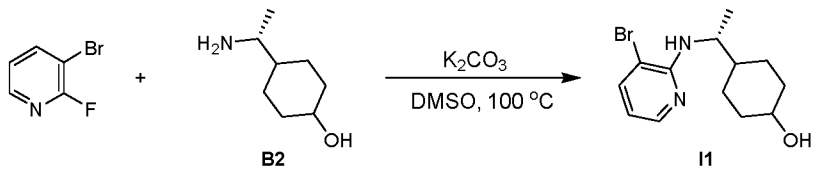
			- 2.38 (m, 1H), 2.33 (s, 3H), 2.14 - 2.10 (m, 1H), 2.04 - 2.00 (m, 1H), 1.68 (br s, 3H), 1.50 - 1.44 (m, 1H), 1.19 - 1.15 (m, 1H), 0.88 - 0.85 (m, 1H).
 (R)-1-(1-(1-cyclopropylpiperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	26	N/A	LCMS $[M+H]^+$ m/z: calcd 494.25; found 494.4. ^{1}H NMR (400MHz, CD_3OD) δ 8.20 (dd, *J* = 5.2, 1.2 Hz, 1H), 8.10 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.14 - 7.11 (m, 1H), 6.32 (s, 1H), 4.62 (s, 2H), 4.17 - 4.11 (m, 1H), 3.18 - 3.15 (m, 1H), 2.88 - 2.85 (m, 2H), 2.68 (br s, 3H), 2.58 (s, 3H), 2.33 (s, 3H), 2.29 - 2.26 (m, 1H), 2.06 - 1.99 (m, 2H), 1.69 (br s, 3H), 1.64 - 1.59 (m, 1H), 1.41 - 1.31 (m, 1H), 1.14 - 1.03 (m, 1H), 0.91-0.87 (m, 1H), 0.52 - 0.36 (m, 4H).

N/A = not applicable

Synthesis of (R)-1-(1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide (Example 27, Isomer 1)



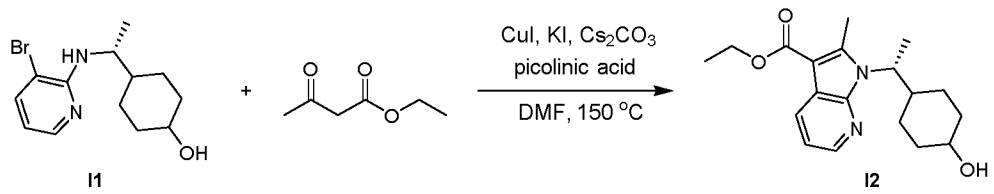
[00157] Step 1: Synthesis of 4-[(1R)-1-[(3-bromo-2-pyridyl)amino]ethyl]cyclohexanol (I1)



[00158] To a mixture of 3-bromo-2-fluoro-pyridine (8.0 g, 45 mmol, 1.0 equiv) and 4-[(1R)-1-aminoethyl]cyclohexanol (18.5 g, 129 mmol, 2.84 equiv) in DMSO (150 mL) was added potassium carbonate (12.6 g, 90.9 mmol, 2 equiv). The reaction was stirred at 100 °C for 17 hours (two batches were run in parallel). After combining the batches, the reaction was quenched with water (150 mL) and the desired product was extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (70 mL × 3), dried over sodium sulfate, filtered and concentrated to dryness under reduced pressure. The residue was

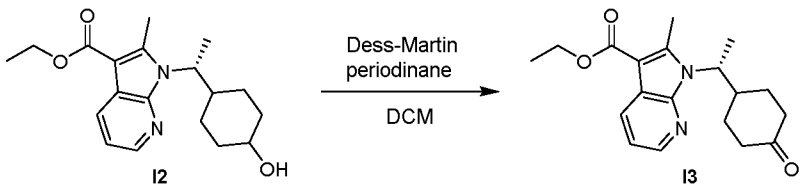
purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate, 50:1 to 1:1). The title compound, 4-[(1R)-1-[(3-bromo-2-pyridyl)amino]ethyl]cyclohexanol (6.7 g, 16 mmol, 18% yield, 73% purity), was obtained as a yellow oil. LCMS $[M+H]^+$ m/z: calc'd 299.07; found 299.2

[00159] Step 2: Synthesis of ethyl 1-[(1R)-1-(4-hydroxycyclohexyl)ethyl]-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylate (I2)



[00160] 4-[(1R)-1-[(3-bromo-2-pyridyl)amino]ethyl]cyclohexanol (1.0 g, 3.3 mmol, 1 equiv), ethyl 3-oxobutanoate (2.27 g, 17.4 mmol, 2.20 mL, 5.21 equiv), pyridine-2-carboxylic acid (204 mg, 1.66 mmol, 0.5 equiv), potassium iodide (832 mg, 5.01 mmol, 1.5 equiv), cesium carbonate (2.18 g, 6.68 mmol, 2 equiv), copper(I) iodide (320 mg, 1.68 mmol, 0.5 equiv) and dimethylformamide (15 mL) were charged into a microwave tube and the reaction was heated using microwave irradiation at 150 °C for 2 h under nitrogen atmosphere (eight batches were prepared in parallel). The combined batches were quenched with water (150 mL) and the desired product was extracted with ethyl acetate (40 mL × 3). The combined organic layers were washed with brine (50 mL × 3), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, petroleum ether:ethyl acetate, 20:1 to 1:1). The title compound, ethyl 1-[(1R)-1-(4-hydroxycyclohexyl)ethyl]-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylate (4.0 g, 7.9 mmol, 29% yield, 65% purity), was obtained as a yellow oil. LCMS $[M+H]^+$ m/z: calc'd 331.19; found 331.4

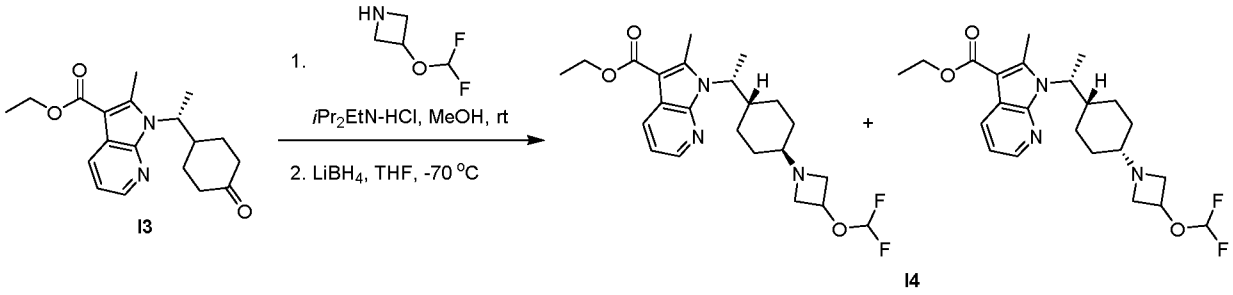
[00161] Step 3: Synthesis of ethyl 2-methyl-1-[(1R)-1-(4-oxocyclohexyl)ethyl]pyrrolo[2,3-b]pyridine-3-carboxylate (I3)



[00162] To a solution of ethyl 1-[(1R)-1-(4-hydroxycyclohexyl)ethyl]-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylate (2.0 g, 6.1 mmol, 1 equiv) in dichloromethane (20 mL) was added Dess-Martin periodinane (3.08 g, 7.26 mmol, 1.2 equiv) at 0 °C and the reaction was stirred at 0 °C for 40 min (two batches were prepared in parallel). The combined batches

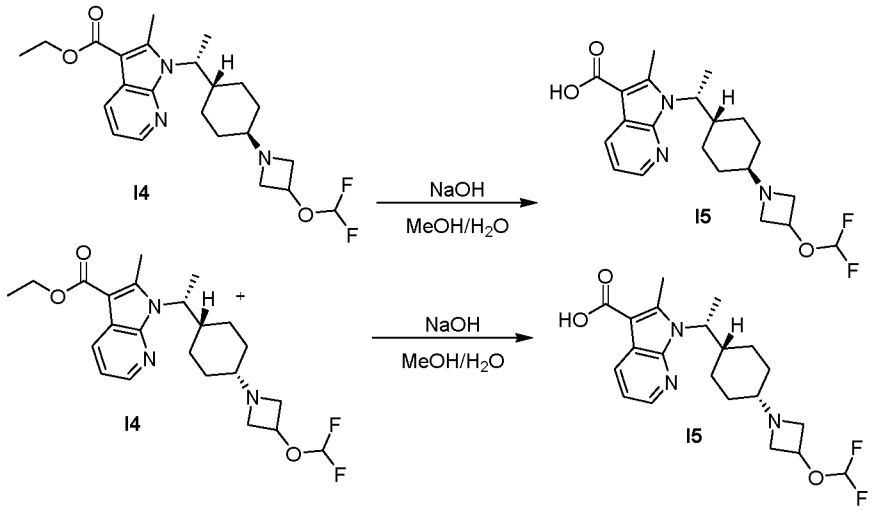
were quenched with saturated Na_2SO_3 (150 mL) and the desired product was extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with saturated sodium bicarbonate (100 mL) and brine (70 mL × 3), dried over sodium sulfate, filtered and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography (SiO_2, petroleum ether:ethyl acetate, 20:1 to 3:1). The title compound, ethyl 2-methyl-1-[(1R)-1-(4-oxocyclohexyl)ethyl]pyrrolo[2,3-b]pyridine-3-carboxylate (1.7 g, 5.1 mmol, 42% yield, 98% purity), was obtained as a yellow oil. LCMS $[M+H]^+$ m/z: calc'd 329.18; found 329.4

[00163] Step 4: Synthesis of ethyl 1-[(1R)-1-[4-[3-(difluoromethoxy)azetidin-1-yl]cyclohexyl]ethyl]-2-methyl-pyrrolo[2,3-*b*]pyridine-3-carboxylate (I4)



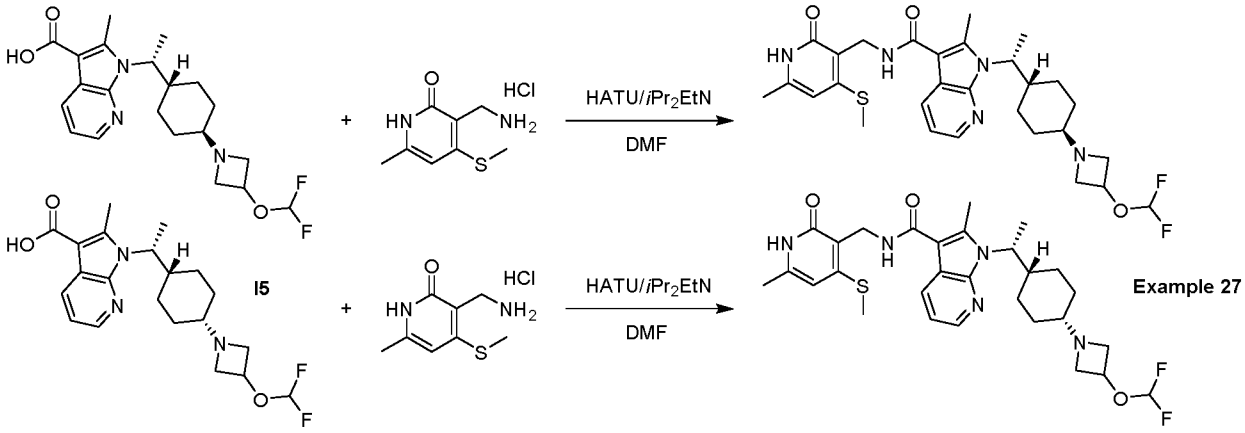
[00164] A mixture of 3-(difluoromethoxy)azetidine (140 mg, 1.14 mmol, 2.5 equiv) and N,N-diisopropylethylammonium chloride (590 mg, 4.57 mmol, 795 uL, 10 equiv) in methanol (2 mL) was stirred at 25 °C for 1 hour, then added to a solution of ethyl 2-methyl-1-[(1R)-1-(4-oxocyclohexyl)ethyl]pyrrolo[2,3-*b*]pyridine-3-carboxylate (150 mg, 457 umol, 1 equiv) in tetrahydrofuran (1 mL). This new mixture was stirred at 25 °C for 1.5 hours, then cooled to -70 °C. $LiBH_4$ (15 mg, 689 umol, 1.5 equiv) was added at -70 °C, and the reaction was stirred at -70 °C for 30 mins under a nitrogen atmosphere. The reaction was quenched with hydrochloric acid (1 M, 5 mL) and the mixture was stirred for 10 minutes at rt. The mixture was neutralized with saturated aqueous sodium bicarbonate until pH = 8. The desired product was extracted with ethyl acetate (10 mL × 3) and the combined organic layers were dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by preparative TLC (SiO_2, petroleum ether:ethyl acetate, 1:1) to give two isomers of the title compound, ethyl 1-[(1R)-1-[4-[3-(difluoromethoxy)azetidin-1-yl]cyclohexyl]ethyl]-2-methyl-pyrrolo[2,3-*b*]pyridine-3-carboxylate, as yellow oil. **Isomer 1** (major): 90 mg, 165 umol, 36% yield, 80% purity. LCMS $[M+H]^+$ m/z: calc'd 436.23; found 436.1. **Isomer 2** (minor): LCMS $[M+H]^+$ m/z: calc'd 436.23; found 436.1.

[00165] Step 5: Synthesis of 1-[(1R)-1-[4-[3-(difluoromethoxy)azetidin-1-yl]cyclohexyl]ethyl]-2-methyl-pyrrolo[2,3-*b*]pyridine-3-carboxylic acid (I5)



[00166] To a solution of the ethyl 1-[(1R)-1-[4-[3-(difluoromethoxy)azetidin-1-yl]cyclohexyl]ethyl]-2-methyl-pyrrolo[2,3-*b*]pyridine-3-carboxylate major isomer from Step 4 (140 mg, 322 umol, 1 equiv) in methanol (2 mL) was added sodium hydroxide (260 mg, 6.50 mmol, 20 equiv) in water (0.4 mL). The mixture was stirred at 70 °C for 14 h under an nitrogen atmosphere. The reaction mixture was concentrated under vacuum and the residue was neutralized at 0 °C by adding a solution of citric acid dropwise until pH = 4. The desired product was extracted with ethylacetate (10 mL× 3) and the combined organic layers were dried over sodium sulfate, filtered and concentrated to dryness under vacuum to give **Isomer 1** of the title compound, 1-[(1R)-1-[4-[3-(difluoromethoxy)azetidin-1-yl]cyclohexyl]ethyl]-2-methyl-pyrrolo[2,3-*b*]pyridine-3-carboxylic acid (120 mg, crude) as yellow oil. LCMS ($M+H^+$) m/z: calcd 408.20; found 408.1. Similar conditions using the minor isomer from Step 4 afforded **Isomer 2** of the title compound. LCMS $[M+H]^+$ m/z: calcd 408.20; found 408.0.

[00167] Step 6: Synthesis of (R)-1-(1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide (Example 27)

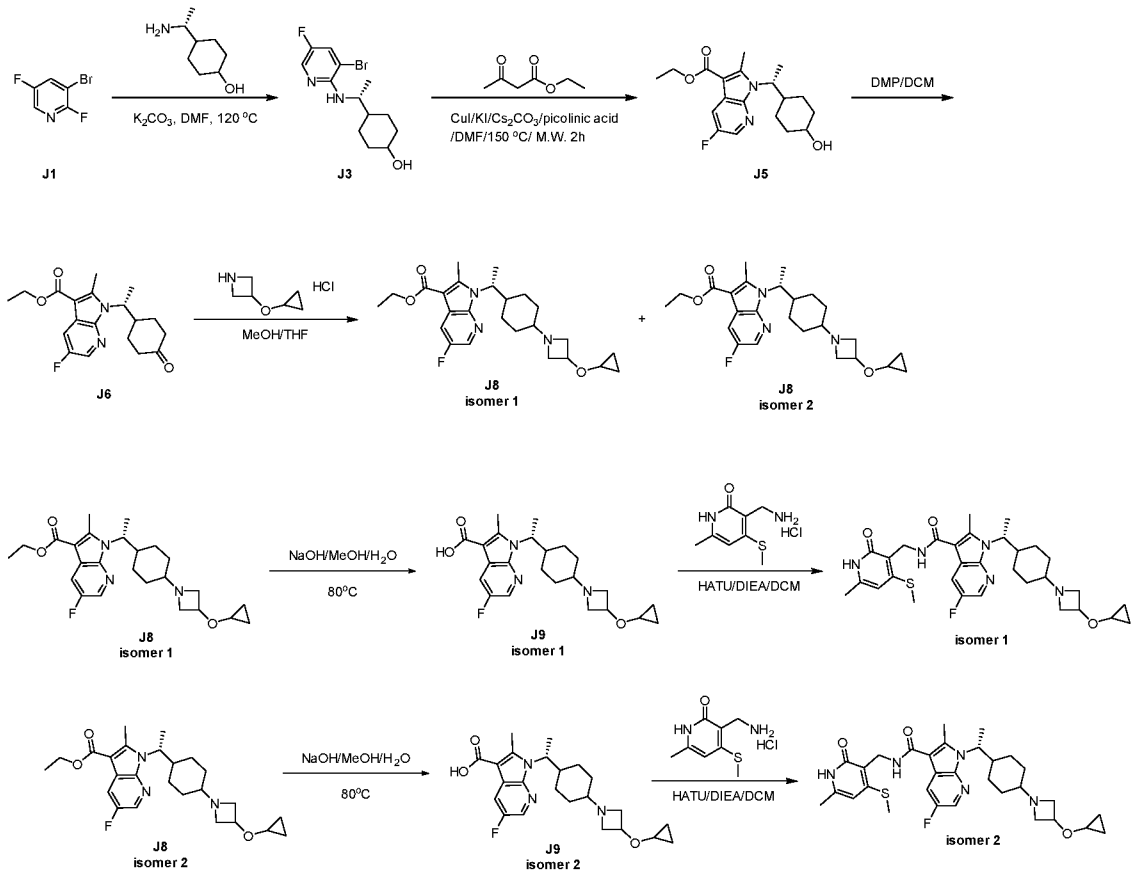


[00168] A solution of 1-[(1R)-1-[4-[3-(difluoromethoxy)azetidin-1-yl]cyclohexyl]ethyl]-2-methyl-pyrrolo[2,3-*b*]pyridine-3-carboxylic acid, Isomer 1 from Step 5 (35 mg, 86 umol, 1 equiv), 3-(aminomethyl)-6-methyl-4-methylsulfanyl-1H-pyridin-2-one hydrochloride salt (25 mg, 113 umol, 1.3 equiv), HATU (40 mg, 105 umol, 1.2 equiv), N,N-diisopropylethylamine (75 uL, 431 umol, 5 equiv) in dimethylformamide (2 mL) was degassed (three vacuum and nitrogen refill cycles), and then stirred at 25 °C for 14 h under a nitrogen atmosphere. The reaction was diluted with ethyl acetate (10 mL) and washed with brine (10 mL × 3). The organic phase was concentrated under vacuum and the residue was purified by preparative HPLC [column type: Xtimate C18 150×25mm, 5um, column temperature: 30 °C; mobile phase: water (0.05% ammonia hydroxide v/v) -acetonitrile; gradient acetonitrile: 40% to 80%, over 6.5min] to give the title compound, (R)-1-(1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide, **Isomer 1** (31 mg, 54 umol, 62% yield, 100% purity) as a white solid. LCMS $[M+H]^+$ m/z: calc'd 574.26; found 574.1 . ^{1}H NMR (400MHz, CD_3OD) δ 8.20 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.13 – 7.10 (m, 1H), 6.39 (t, *J* = 72 Hz, 1H), 6.32 (s, 1H), 5.20 (br s, 1H), 4.74 – 4.68 (m, 1H), 4.62 (s, 3H), 3.67 – 3.58 (m, 2H), 3.15 – 3.08 (m, 2H), 2.68 (s, 3H), 2.55 (s, 3H), 2.32 (s, 3H), 2.23 – 1.93 (m, 4H), 1.68 – 1.62 (m, 4H), 1.11 – 1.05 (m, 1H), 0.96 – 0.91 (m, 3H).

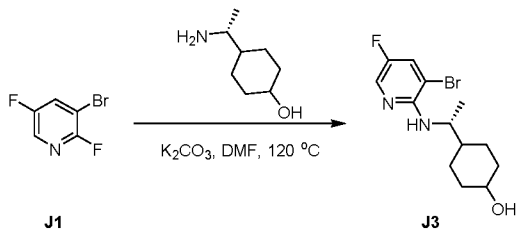
[00169] Isomer 2 of Example 27 was formed using a similar procedure to the above, except starting with **Isomer 2** from Step 5. LCMS $[M+H]^+$ m/z: calcd 574.26; found 574.1. ^{1}H NMR (400 MHz, CD_3OD) δ 8.20 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.13 – 7.10 (m, 1H), 6.39 (t, *J* = 72 Hz, 1H), 6.32 (s, 1H), 5.38 – 5.35 (m, 1H), 4.62 (m, 4H), 3.67 – 3.60

(m, 2H), 2.71 (s, 3H), 2.56 (s, 3H), 2.33 (s, 3H), 2.21 (t, J = 8.0 Hz, 2H), 2.06 – 2.03 (m, 4H), 1.66 – 1.61 (m, 4H), 0.94 – 0.91 (m, 4H).

Synthesis of 1-((R)-1-(4-(3-cyclopropoxyazetidin-1-yl)cyclohexyl)ethyl)-5-fluoro-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide (Example 28, Isomer 1 and 2)



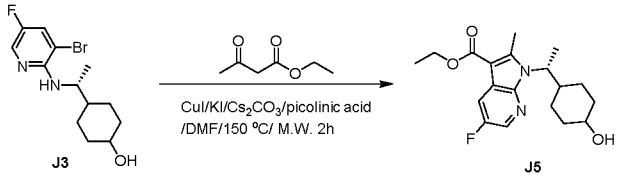
Step 1: 4-[(1R)-1-[(3-Bromo-5-fluoro-2-pyridyl)amino]ethyl]cyclohexanol



To a solution of 4-[(1R)-1-aminoethyl]cyclohexanol hydrochloride (5.6 g, 30.9 mmol, 1.2 *eq*) in DMF (25 mL) was added K_2CO_3 (10.7 g, 77.3 mmol, 3 *eq*). The mixture was stirred at 15°C for 0.5h. 3-Bromo-2,5-difluoro-pyridine (5 g, 25.8 mmol, 1 *eq*) was added and the mixture was stirred at 120°C for 8h. LCMS detected desired compound. The reaction mixture was concentrated to dryness, H_2O (100mL) was added, and extracted with ethyl

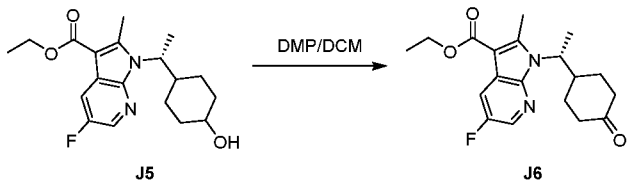
acetate (180mL x 3). The combined organic layer was washed with brine (80mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, eluent of 0~45% ethyl acetate/Petroleum ether gradient @ 60 mL/min). 4-[(1R)-1-[(3-Bromo-5-fluoro-2-pyridyl)amino]ethyl]cyclohexanol (5.2 g, 16.23 mmol, 62.96% yield, 99% purity) was obtained as yellow oil. LCMS ($M+H^+$) m/z: calcd 317.06; found 317.1.

Step 2: Ethyl 5-fluoro-1-[(1R)-1-(4-hydroxycyclohexyl)ethyl]-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylate



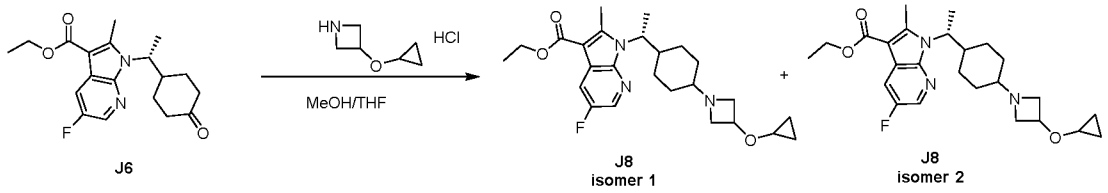
4-[(1R)-1-[(3-Bromo-5-fluoro-2-pyridyl)amino]ethyl]cyclohexanol (1 g, 3.2 mmol, 1 *eq*), ethyl 3-oxobutanoate (2.1 g, 15.8 mmol, 2.0 mL, 5 *eq*), KI (785.0 mg, 4.7 mmol, 1.5 *eq*), picolinic acid (194.1 mg, 1.6 mmol, 0.5 *eq*), Cs_2CO_3 (2.1 g, 6.3 mmol, 2 *eq*) and CuI (300.2 mg, 1.6 mmol, 0.5 *eq*) in DMF (10 mL) were combined in a microwave tube. The mixture was degassed and purged with N_2 (3x). The sealed tube was heated at 150 °C for 1 hour under microwave irradiation. LCMS detected desired compound. The reaction was repeated 5 times at the same scale. The five batches were combined and concentrated to dryness. H_2O (50mL) was added to the residue, extracted with ethyl acetate (100mL x 3). The combined organic phase was washed with brine (50mL) and concentrated to dryness. The residue was dissolved in DCM (10mL), and aqueous HCl (50mL, 1N) was added into the mixture and stirred at 15°C for 1h. The mixture was extracted with ethyl acetate (80mL x 3). The combined organic phase was washed with brine (50mL) and dried (Na_2SO_4), filtered and concentrated to give ethyl 5-fluoro-1-[(1R)-1-(4-hydroxycyclohexyl)ethyl]-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylate (3.3 g, crude) as a black brown oil. LCMS ($M+H^+$) m/z: calcd 349.18; found 349.1

Step 3: Ethyl 5-fluoro-2-methyl-1-[(1R)-1-(4-oxocyclohexyl)ethyl]pyrrolo[2,3-b]pyridine-3-carboxylate



To a solution of ethyl 5-fluoro-1-[(1R)-1-(4-hydroxycyclohexyl)ethyl]-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylate (3.3 g, 9.5 mmol, 1 *eq*) in DCM (30 mL) was added DMP (6.0 g, 14.2 mmol, 4.4 mL, 1.5 *eq*). The mixture was stirred at 15°C for 1.5h. LCMS detected desired compound. The mixture was diluted with DCM (50mL) and washed with sat.$Na_2S_2O_3$ (30mL x 2). The organic phase was washed with $NaHCO_3$ (30mL x 2) and brine (30mL). The combined aqueous phase was extracted with ethyl acetate (250mL x 2). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, eluent of 0~28% ethyl acetate/petroleum ether gradient @ 60 mL/min). Ethyl 5-fluoro-2-methyl-1-[(1R)-1-(4-oxocyclohexyl)ethyl]pyrrolo[2,3-b]pyridine-3-carboxylate (460 mg, 1.1 mmol, 11.9% yield, 85% purity) was obtained as yellow oil. LCMS ($M+H^+$) m/z: calcd 347.17; found 347.0.

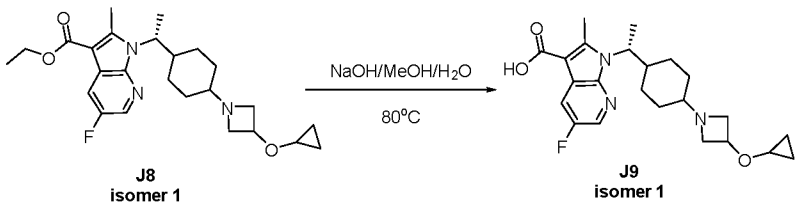
Step 4: Ethyl 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-5-fluoro-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylate (isomer 1 and isomer 2)



To a solution of 3-(cyclopropoxy)azetidine (933.0 mg, 6.2 mmol, 4 *eq*, HCl salt) in MeOH (4 mL) was added DIEA (705.2 mg, 5.5 mmol, 950.4 uL, 3.5 *eq*). The mixture was stirred at 15°C for 1h. ethyl 5-fluoro-2-methyl-1-[(1R)-1-(4-oxocyclohexyl)ethyl]pyrrolo[2,3-b]pyridine-3-carboxylate (540.0 mg, 1.6 mmol, 1 *eq*) in THF (4 mL) was added into the mixture. The mixture was stirred at 15°C for 1.5h. $LiBH_4$ (169.8 mg, 7.8 mmol, 5 *eq*) was added into the mixture at -70°C. The mixture was stirred at -70°C for 0.5h. LCMS detected the desired compound. TLC (PE/EA=2/1 and DCM/MeOH=20/1) showed new spots formed. The reaction was quenched with water (20 mL), extracted with ethyl acetate (50 mL

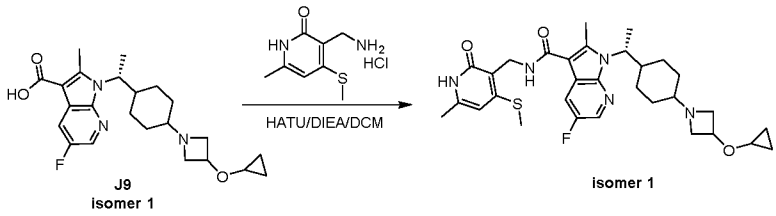
x 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep-TLC (DCM/MeOH=20/1) to give the pure *cis* and *trans* isomers separately. Ethyl 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-5-fluoro-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylate isomer 1 (350.0 mg, 789.1 umol, 50.6% yield, 100% purity) was obtained as a yellow gum; LCMS ($M+H^+$) m/z: calcd 444.26; found 444.2. Ethyl 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-5-fluoro-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylate isomer 2 (70.0 mg, 140.5 umol, 9.0% yield, 89% purity) was obtained as a yellow gum. LCMS ($M+H^+$) m/z: calcd 444.26; found 444.2.

Step 5: 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-5-fluoro-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylic acid isomer 1



To a solution of ethyl 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-5-fluoro-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylate isomer 1 (210.0 mg, 473.5 umol, 1 *eq*) in EtOH (6 mL) was added NaOH (189.4 mg, 4.7 mmol, 10 *eq*) in H_2O (1.5 mL). The mixture was stirred at 80°C for 12h. LCMS detected the desired compound. The mixture was cooled to 25°C and concentrated. The residue was diluted with water (20 mL), adjusted to pH=6~7 with saturated citric acid and extracted with ethyl acetate (40 mL x 3). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-5-fluoro-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylic acid isomer 1 (230.0 mg, crude) was obtained as blue gum. LCMS ($M+H^+$) m/z: calcd 416.23; found 416.2.

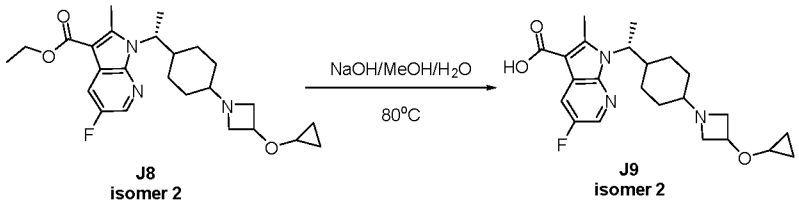
Step 6: 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-5-fluoro-2-methyl-N-[(6-methyl-4-methylsulfanyl-2-oxo-1H-pyridin-3-yl)methyl]pyrrolo[2,3-b]pyridine-3-carboxamide isomer 1



To a mixture of 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-5-fluoro-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylic acid isomer 1 (230.0 mg, 553.6 umol, 1 *eq*) and HATU (378.9 mg, 996.4 umol, 1.8 *eq*) in DCM (15 mL) was added DIEA (286.2 mg, 2.2 mmol, 385.7 uL, 4 *eq*). The mixture was stirred at 30°C for 0.5h. 3-(Aminomethyl)-6-methyl-4-methylsulfanyl-1H-pyridin-2-one (183.3 mg, 830.3 umol, 1.5 *eq*, HCl salt) was added into the mixture. The mixture was stirred at 30°C for 12h. LCMS detected the desired compound. The mixture was diluted with water (20 mL), extracted with DCM (40 mL x 3). The combined organic layer was washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep-TLC (DCM/MeOH=10/1). To give 250 mg (purity: 94%) of the desired compound product. The product was re-purified by prep-HPLC (column: Waters Xbridge 150 x 25 5u; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN];B%: 33%-63%,7.8min). 1-[(1R)-1-[4-[3-(Cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-5-fluoro-2-methyl-N-[(6-methyl-4-methylsulfanyl-2-oxo-1H-pyridin-3-yl)methyl]pyrrolo[2,3-b]pyridine-3-carboxamide isomer 1 (211.8 mg, 100% purity) was obtained as white solid. LCMS ($M+H^+$) m/z: calcd 582.28; found 582.1.

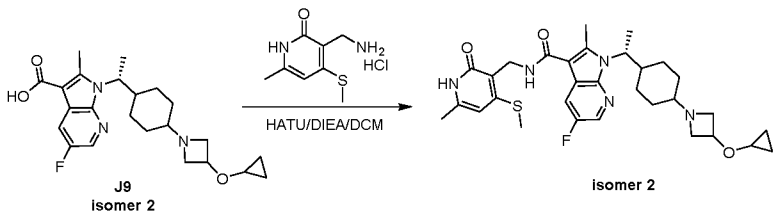
^1H NMR (400MHz, CDCl3) δ 12.72 (s, 1H), 8.07 (s, 1H), 7.89 (d, J = 8.8Hz, 1H), 7.36 - 7.33 (m, 1H), 6.05 (s, 1H), 4.72 (d, J = 4.4Hz, 2H), 4.22 - 4.19 (m, 1H), 3.63 - 3.57 (m, 2H), 3.22 - 3.20 (m, 1H), 2.87 - 2.79 (m, 5H), 2.51 (s, 3H), 2.28 (s, 3H), 2.09 - 2.07 (m, 1H), 1.89 - 1.87 (m, 2H), 1.75 (s, 1H), 1.64 - 1.57 (m, 4H), 1.05 - 0.96 (m, 3H), 0.77 (s, 2H), 0.58 - 0.54 (m, 2H), 0.47 - 0.42 (m, 2H).

Step 7: 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-5-fluoro-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylic acid isomer 2



To a solution of ethyl 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-5-fluoro-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylate isomer 2 (70.0 mg, 157.8 umol, 1 *eq*) in EtOH (3 mL) was added NaOH (63.1 mg, 1.6 mmol, 10 *eq*) in H_2O (1 mL). The mixture was stirred at 80°C for 12h. LCMS detected the desired compound. The mixture was concentrated. The residue was diluted with water (10 mL), adjusted to pH = 6~7 with saturated citric acid, extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-5-fluoro-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylic acid isomer 2 (70 mg, crude) was obtained as blue solid. LCMS ($M+H^+$) m/z: calcd 416.23; found 416.0.

Step 8: 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-5-fluoro-2-methyl-N-[(6-methyl-4-methylsulfanyl-2-oxo-1H-pyridin-3-yl)methyl]pyrrolo[2,3-b]pyridine-3-carboxamide isomer 2

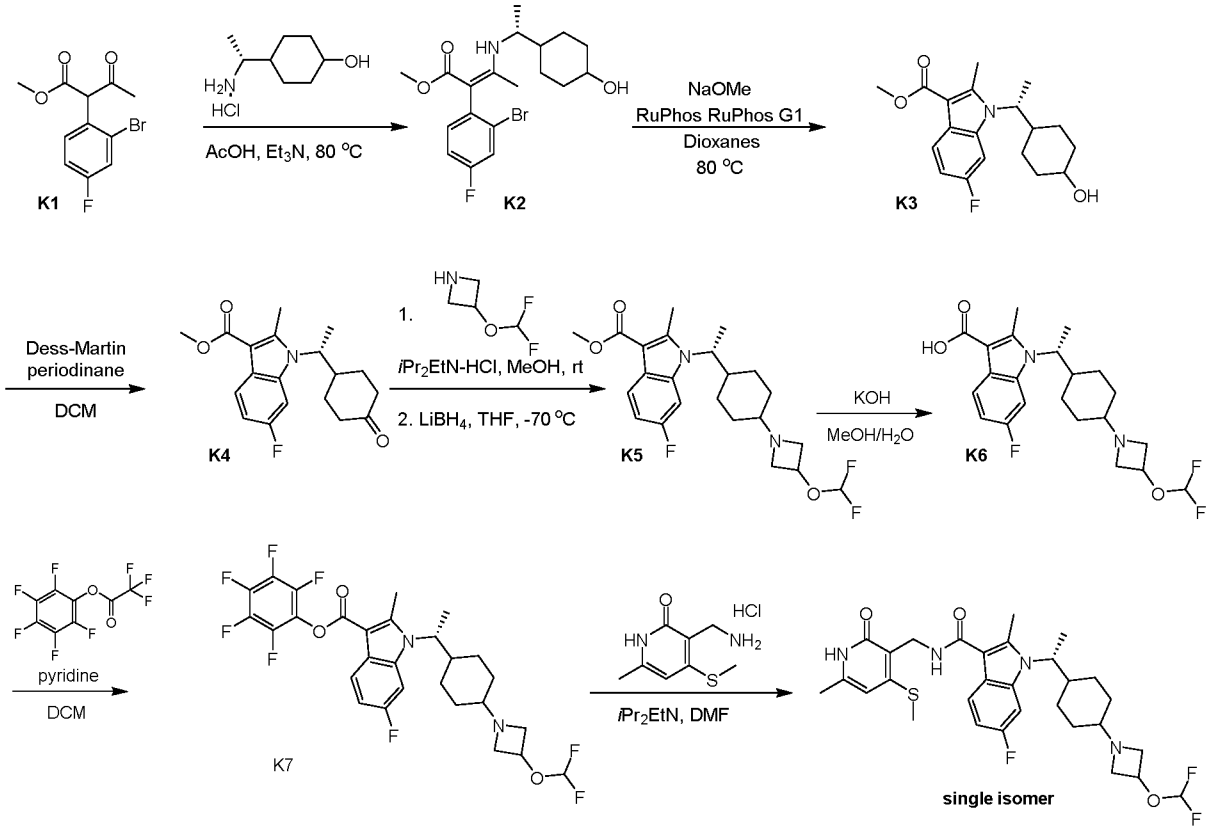


To a mixture of 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-5-fluoro-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylic acid isomer 2 (70.0 mg, 168.5 umol, 1 *eq*) and HATU (76.9 mg, 202.2 umol, 1.2 *eq*) in DCM (4 mL) was added DIEA (108.9 mg, 842.4 umol, 146.72 uL, 5 *eq*). The mixture was stirred at 30°C for 0.5h. 3-(Aminomethyl)-6-methyl-4-methylsulfanyl-1H-pyridin-2-one (55.8 mg, 252.7 umol, 1.5 *eq*, HCl salt) was added into the mixture. The mixture was stirred at 30°C for 12h. LCMS detected the desired compound. The mixture was diluted with water (20 mL), extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered

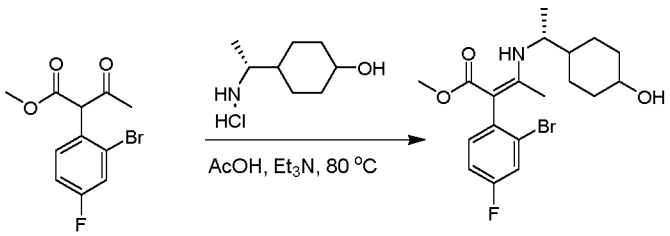
and concentrated. The residue was purified by prep-HPLC (column: Waters Xbridge 150 x 25 5u; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN];B%: 40%-70%,7.8min). 1-[(1R)-1-[4-[3-(Cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-5-fluoro-2-methyl-N-[(6-methyl-4-methylsulfanyl-2-oxo-1H-pyridin-3-yl)methyl]pyrrolo[2,3-b]pyridine-3-carboxamide isomer 2 (53.9 mg, 91.7 umol, 54.5% yield, 99% purity) was obtained as white solid. LCMS ($M+H^+$) m/z: calcd 582.28; found 582.1.

^{1}H NMR (400MHz, CDCl3) δ 12.71 (s, 1H), 8.04 (s, 1H), 7.86 (dd, J = 2.4 Hz, 9.6Hz, 1H), 7.28 (s, 1H), 6.03 (s, 1H), 4.70 (s, 2H), 4.20 - 4.17 (m, 2H), 3.58 (s, 1H), 3.50 (s, 1H), 3.22 - 3.19 (m, 1H), 2.76 - 2.72 (m, 5H), 2.49 (s, 3H), 2.27 (s, 3H), 2.18 (s, 1H), 1.70 (s, 3H), 1.47 - 1.34 (m, 3H), 1.13 - 1.07 (m, 2H), 0.69 (s, 1H), 0.54 - 0.53 (m, 2H), 0.45 - 0.43 (m, 2H).

Synthesis of 1-((R)-1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-6-fluoro-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide (Example 29, single isomer)

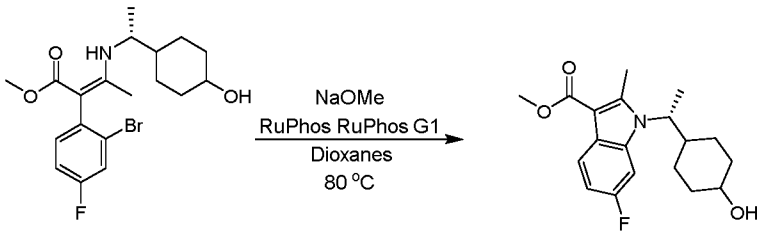


Step 1: Synthesis of methyl (R,Z)-2-(2-bromo-4-fluorophenyl)-3-((1-(4-hydroxycyclohexyl)ethyl)amino)but-2-enoate



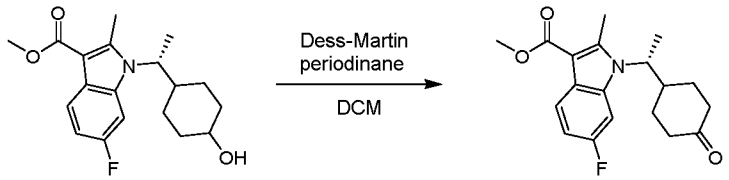
To a round bottom ed flask was added (R)-4-(1-aminoethyl)cyclohexan-1-ol (0.707 g, 3.94 mmol, 1.0 equiv), t-BuOH (13 mL), triethylamine (0.552 mL, 27.3 mmol, 23 equiv), and methyl 2-(2-bromo-4-fluorophenyl)-3-oxobutanoate (1.14 g, 3.94 mmol, 1.0 equiv) [prepared according to the procedure reported in WO2013120104]. To this solution was added AcOH (0.49 ml, 8.7 mmol, 2.2 equiv) and the reaction was heated overnight at 85 °C before cooling to room temperature and concentrating. The crude residue was purified via silica gel chromatography to afford methyl (R,Z)-2-(2-bromo-4-fluorophenyl)-3-((1-(4-hydroxycyclohexyl)ethyl)amino)but-2-enoate **X#** (1.42 g, 3.42 mmol, 87%). LCMS $[M+H]^+$ m/z: calc'd 414.11; found 414.2.

Step 2: Synthesis of methyl (R)-6-fluoro-1-(1-(4-hydroxycyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxylate



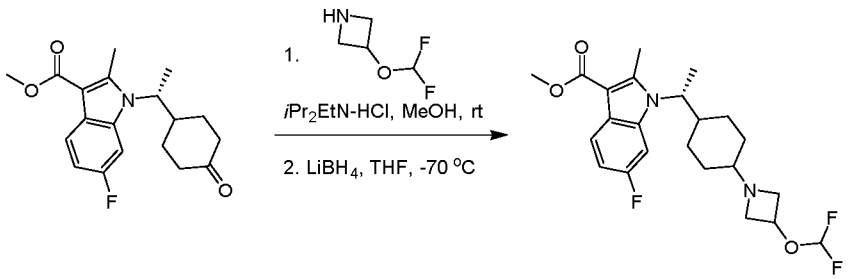
To a resealable vial was added Ruphos (79.7 mg, 171 µmol, 0.05 equiv), Pd-precat. RuPhos G1 (111 mg, 136 µmol, 0.04 equiv), and methyl (2Z)-2-(2-bromo-4-fluorophenyl)-3-{[(1R)-1-(4-hydroxycyclohexyl)ethyl]amino}but-2-enoate (1420 mg, 3.42 mmol, 1.0 equiv) dissolved in dioxanes (11.4 mL). To this solution was added sodium methoxide (277 mg, 5.13 mmol, 1.5 equiv) and the reaction was evacuated/backfilled with nitrogen (3X) before heating to reflux overnight. The solution was cooled to room temperature and diluted with ethyl acetate. The precipitate was filtered off and the filtrate concentrated. The crude residue was purified by flash chromatography to afford methyl 6-fluoro-1-[(1R)-1-(4-hydroxycyclohexyl)ethyl]-2-methyl-1H-indole-3-carboxylate (1033 mg, 90%). LCMS $[M+H]^+$ m/z: calc'd 334.18; found 334.3.

Step 3: Synthesis of methyl (R)-6-fluoro-2-methyl-1-(1-(4-oxocyclohexyl)ethyl)-1H-indole-3-carboxylate



To the mixture of methyl 6-fluoro-1-[(1R)-1-(4-hydroxycyclohexyl)ethyl]-2-methyl-1H-indole-3-carboxylate (890 mg, 2.66 mmol, 1.0 equiv) in dichloromethane (10.6 mL) was added Dess-Martin periodinane (1.35 g, 3.19 mmol, 1.2 equiv) at 0 °C and stirred at 0 °C for 2 h. The reaction was then quenched with isopropanol and warmed to room temperature. The mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with saturated sodium bicarbonate (100 mL) and brine (70 mL × 3), dried over sodium sulfate, filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=20/1 to 3:1) to give methyl (R)-6-fluoro-2-methyl-1-(1-(4-oxocyclohexyl)ethyl)-1H-indole-3-carboxylate (513 mg, 58%) as a clear oil. LCMS $[M+H]^+$ m/z: calc'd 332.17; found 332.2

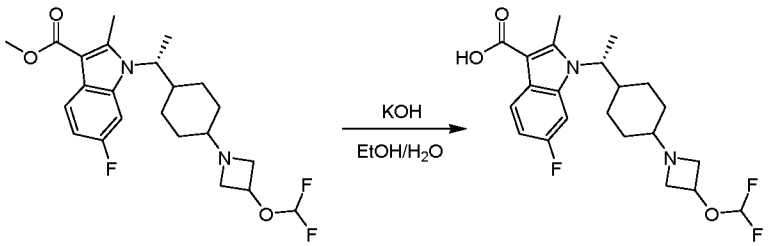
Step 4: Synthesis of methyl 1-((R)-1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-6-fluoro-2-methyl-1H-indole-3-carboxylate (single isomer)



A mixture of 3-(difluoromethoxy)azetidine (132 mg, 1.08 mmol, 4.5 equiv) and N,N-diisopropylethylammonium chloride (174 mg, 1.26 mmol, 5.3 equiv) in methanol (1 mL) was stirred at 25 °C for 1 hour, then added to a solution of methyl (R)-6-fluoro-2-methyl-1-(1-(4-oxocyclohexyl)ethyl)-1H-indole-3-carboxylate (80 mg, 0.241 mmol, 1 equiv) in tetrahydrofuran (1 mL). This new mixture was stirred at 25 °C for 1.5 hours, then cooled to -70 °C. $LiBH_4$ (2M in THF) (0.168 mL, 0.337 mmol, 1.4 equiv) was added at -70 °C, and the reaction was stirred at -70 °C for 30 min under a nitrogen atmosphere. The reaction was quenched with hydrochloric acid (1 M, 5 mL) and the mixture was stirred for 10 min at rt. The mixture was neutralized with saturated aqueous sodium bicarbonate until pH = 8. The desired product was extracted with ethyl acetate (10 mL × 3) and the combined organic layers

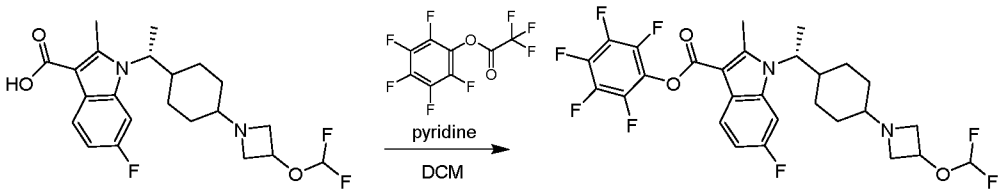
were dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified via silica gel chromatography to afford methyl 1-((R)-1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-6-fluoro-2-methyl-1H-indole-3-carboxylate (single isomer) (56 mg, 0.127 mmol, 53%). LCMS $[M+H]^+$ m/z: calc'd 439.2; found 439.2.

Step 5: Synthesis of 1-((R)-1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-6-fluoro-2-methyl-1H-indole-3-carboxylic acid (single isomer)



To a solution of methyl 1-((R)-1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-6-fluoro-2-methyl-1H-indole-3-carboxylate single isomer (76 mg, 0.173 mmol, 1.0 equiv) in ethanol (1.3 mL) and water (0.40 mL) was added KOH (58 mg, 1.0 mmol, 6 equiv). The mixture was stirred at 80 °C for 2 h. The reaction mixture was concentrated, and dichloromethane (15 mL) and water (10 mL) were added. The mixture was adjusted to pH = 5 - 6 with hydrochloric acid (1 M) solution. The mixture was extracted with dichloromethane (20 mL * 3). The organic layer was dried by anhydrous sodium sulfate, filtered and concentrated under vacuum to give 1-((R)-1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-6-fluoro-2-methyl-1H-indole-3-carboxylic acid (90 mg, crude), as a solid. LCMS $[M+H]^+$ m/z: calc'd 425.21; found 425.2.

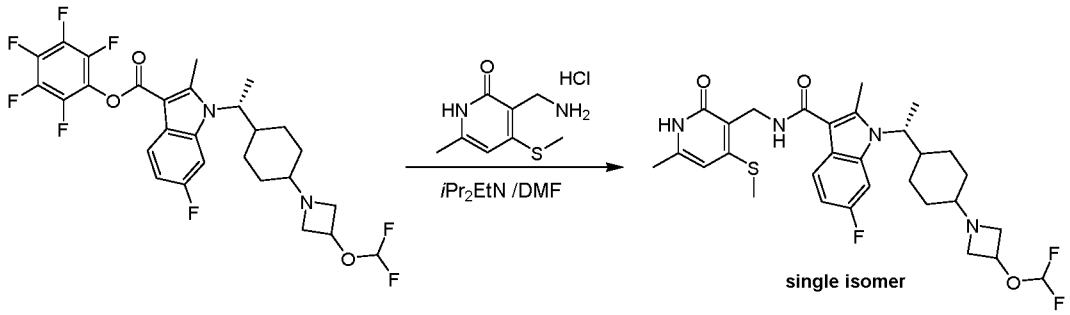
Step 6: Synthesis of perfluorophenyl 2-methyl-1-((R)-1-(4-((3-(trifluoromethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxylate



To a stirred solution of 1-((R)-1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-6-fluoro-2-methyl-1H-indole-3-carboxylic acid (70 mg, 164 µmol, 1.0 equiv) in dichloromethane (0.66 mL) was added pyridine (33 µL, 0.41 mmol, 2.5 equiv) followed by dropwise addition of 2,3,4,5,6-pentafluorophenyl 2,2,2-trifluoroacetate (43 µL, 0.248 mmol,

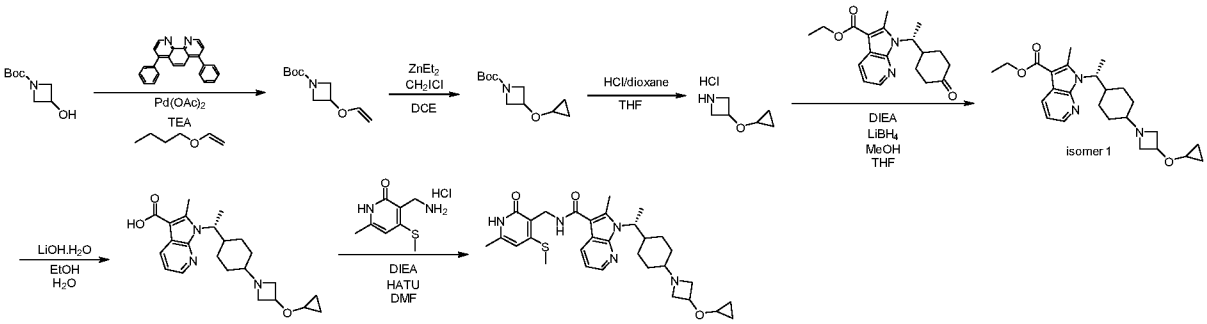
1.5 equiv). This mixture was stirred for 30 min at which time the starting material was consumed. The reaction was then concentrated under reduced pressure. The crude product was directly used in the next step (59 mg, crude). LCMS $[M+H]^+$ m/z: calc'd 591.19; found 591.2.

Step 7: Synthesis of 1-((R)-1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-6-fluoro-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide

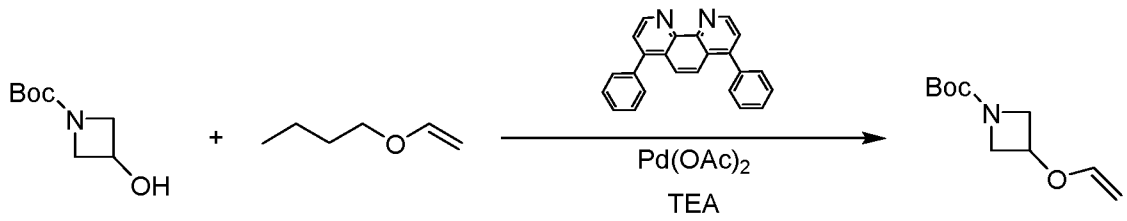


To a solution of perfluorophenyl 1-((R)-1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-6-fluoro-2-methyl-1H-indole-3-carboxylate (40 mg, 61 µmol, 1.0 equiv) in dimethyl formamide (166 µL) was added 3-(aminomethyl)-6-methyl-4-(methylsulfanyl)-1,2-dihydropyridin-2-one (34 mg, 182 µmol, 3.0 equiv) followed by diisopropylethylamine (21 µL, 120 µmol, 2.0 equiv). The reaction was stirred at 60 °C for 1 h. The reaction was then diluted with water (10 mL), extracted with dichloromethane (20 mL*4). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. The crude mixture was purified by column chromatography on silica gel to give 1-((R)-1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-6-fluoro-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide (6.0 mg, 10 µmol, 17% yield) as a white solid. LCMS $[M+H]^+$ m/z: calc'd 591.26; found 591.3. 1H NMR (400MHz, CDCl3) δ 12.15 (br. s., 1 H), 7.75 (dd, J = 5.4, 8.8 Hz, 1 H), 7.31 (br. s., 1 H), 7.12 (d, J = 10.3 Hz, 1 H), 6.81 (dt, J = 2.4, 9.0 Hz, 1 H), 6.37 - 5.95 (m, 2 H), 4.73 (td, J = 5.7, 11.6 Hz, 2 H), 4.03 (br. s., 1 H), 3.74 - 3.61 (m, 2 H), 3.09 - 3.00 (m, 2 H), 2.72 - 2.66 (m, 2 H), 2.49 (s, 3 H), 2.20 (s, 3 H), 2.08 (d, J = 7.8 Hz, 1 H), 2.00 (br. s., 1 H), 1.90 (d, J = 10.3 Hz, 1 H), 1.57 (d, J = 6.8 Hz, 3 H), 1.15 - 1.02 (m, 3 H), 0.92 - 0.71 (m, 3 H).

The synthesis of 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-2-methyl-N-[(6-methyl-4-methylsulfanyl-2-oxo-1H-pyridin-3-yl)methyl]pyrrolo[2,3-b]pyridine-3-carboxamide (Example 30, single isomer)



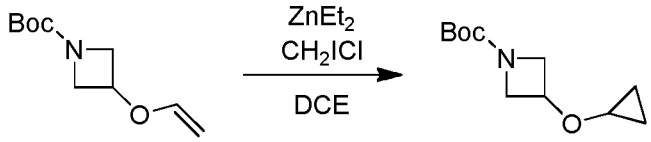
Step 1: tert-Butyl 3-vinyloxyazetidine-1-carboxylate



To a solution of tert-butyl 3-hydroxyazetidine-1-carboxylate (1.5 g, 8.66 mmol, 1 *eq*) in 1-vinyloxybutane (13.08 g, 130.61 mmol, 16.79 mL, 15.08 *eq*) was added TEA (381.68 mg, 3.77 mmol, 525 uL, 0.44 *eq*), 4,7-diphenyl-1,10-phenanthroline (120 mg, 361 umol, 0.04 *eq*) and $Pd(OAc)_2$ (90 mg, 400.87 umol, 0.046 *eq*). The mixture was purged with N_2 for 5 min and stirred at 80 °C for 2 hours under microwave irradiation. TLC showed desired compound was detected. The reaction was repeated 3 times, and the three batches were combined, the mixture was filtered and concentrated under reduced pressure to give a crude residue which was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, eluent of 0~20% ethyl acetate/petroleum ether gradient @ 50 mL/min). tert-Butyl 3-vinyloxyazetidine-1-carboxylate (3.5 g, 17.57 mmol, 67.61% yield) was obtained as colorless oil.

^1H NMR (400 MHz, $CDCl_3$) δ 6.37 (dd, *J* = 14.4, 6.8 Hz, 1H), 4.59 (tt, *J* = 6.4, 4.0 Hz, 1H), 4.17 (dd, *J* = 10.4, 6.4 Hz, 2H), 4.05 - 4.10 (m, 1H), 3.96 (dd, *J* = 14.4, 2.4 Hz, 1H), 3.90 (dd, *J* = 10.4, 4.4 Hz, 2H), 1.44 (s, 9H).

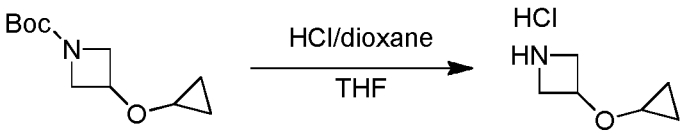
Step 2: tert-Butyl 3-(cyclopropoxy)azetidine-1-carboxylate



A solution of tert-butyl 3-vinyloxyazetidine-1-carboxylate (1.5 g, 7.53 mmol, 1 *eq*) and chloro(iodo)methane (4.42 g, 25.05 mmol, 1.82 mL, 3.33 *eq*) in DCE (20 mL) was cooled to -5 °C. Diethylzinc (1 M in toluene, 12.12 mL, 1.61 *eq*) was added to the solution dropwise at -5 °C, and the reaction mixture was stirred at 25 °C for 0.5 hour. The reaction was quenched with NH_4Cl solution (10 mL) at 0 °C, concentrated NH_4OH solution (20 mL) was added, and the mixture was extracted with MTBE 45 mL (15mL x 3). The organic layers were washed with NH_4Cl solution (15mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, eluent of 0~20% ethyl acetate/petroleum ether gradient @ 12 mL/min). tert-Butyl 3-(cyclopropoxy)azetidine-1-carboxylate (220 mg, 1.03 mmol, 13.70% yield) was obtained as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (tt, *J* = 6.4, 4.4 Hz, 1H), 4.03 - 4.15 (m, 2H), 3.85 (dd, *J* = 10.0, 4.4 Hz, 2H), 3.24 (tt, *J* = 6.0, 2.8 Hz, 1H), 1.43 (s, 9H), 0.55 - 0.64 (m, 2H), 0.44 - 0.52 (m, 2H).

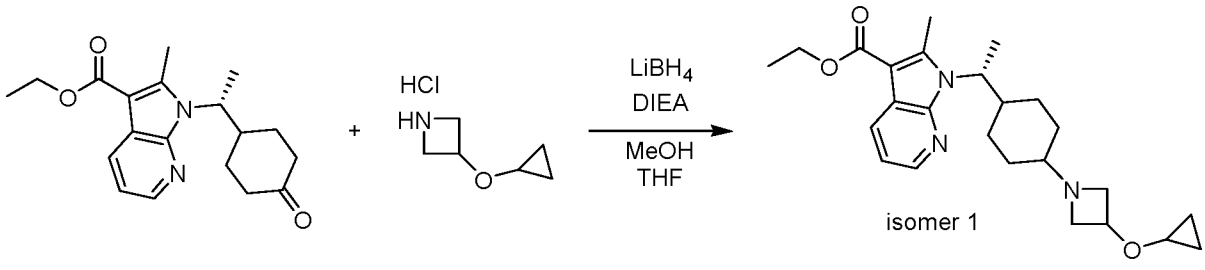
Step 3: 3-(Cyclopropoxy)azetidine hydrochloride



HCl/dioxane (4 M, 4.80 mL, 13.65 *eq*) was added dropwise at 0 °C to a solution of tert-butyl 3-(cyclopropoxy)azetidine-1-carboxylate (300 mg, 1.41 mmol, 1 *eq*) in THF (2 mL). The reaction was stirred at 25 °C for 3 hours, diluted with *i*-PrOH (20 mL) and concentrated under reduced pressure to give 3-(cyclopropoxy)azetidine hydrochloride (200 mg, crude) as a yellow oil.

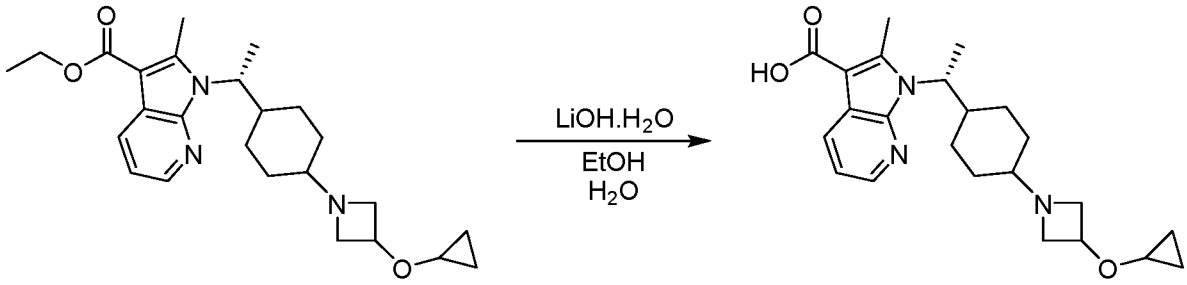
^{1}H NMR (400 MHz, CD_3OD) δ 4.39 - 4.54 (m, 1H), 4.19 (br dd, *J* = 11.2, 6.8 Hz, 2H), 3.89 (br dd, *J* = 10.8, 5.2 Hz, 2H), 3.25 - 3.33 (m, 1H), 0.46 - 0.55 (m, 2H), 0.37 - 0.46 (m, 2H).

Step 4: Ethyl 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylate



A mixture of 3-(cyclopropoxy)azetidine hydrochloride (850 mg, 5.68 mmol, 3.73 *eq*) and DIEA (816 mg, 6.32 mmol, 1.1 mL, 4.15 *eq*) in MeOH (6 mL) was stirred at 20°C for 1hr. Ethyl 2-methyl-1-[(1R)-1-(4-oxocyclohexyl)ethyl]pyrrolo[2,3-b]pyridine-3-carboxylate (500 mg, 1.52 mmol, 1 *eq*) in THF (2 mL) was added, and the mixture stirred at 20°C for 1.5h. To the reaction mixture was added $LiBH_4$ (73 mg, 3.35 mmol, 2.2 *eq*) at -78 °C and stirring continued at -78 °C for 30 min. LCMS showed desired compound. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (100 mL) and extracted with EtOAc (30 mL x2).The organic phase was washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=1/1 to 0:1) to give ethyl 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylate isomer 1 (450 mg, 1.06 mmol, 69.45% yield, 100% purity) as yellow oil [LCMS ($M+H^+$) calcd. 462.2; found 462.1] and ethyl 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylate isomer 2 (40 mg, 62.04 umol, 4.07% yield, 66% purity) as yellow oil [LCMS ($M+H^+$) calcd. 462.2; found 462.1].

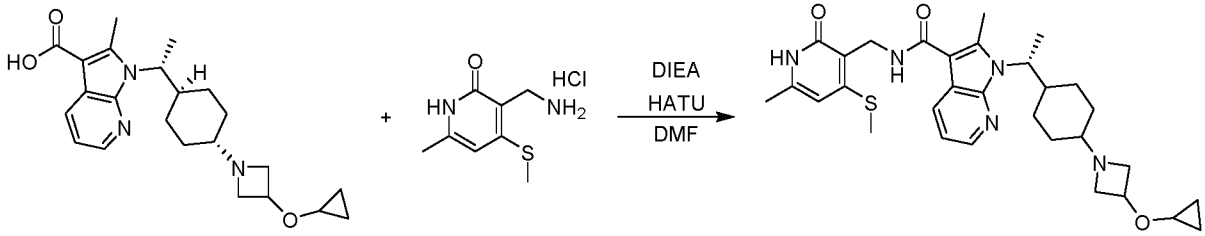
Step 5: 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylic acid (single isomer)



To a solution of ethyl 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylate isomer 1 (120 mg, 281.98 umol, 1 *eq*) in EtOH (1 mL) was added $LiOH.H_2O$ (112.5 mg, 2.68 mmol, 9.51 *eq*) in H_2O (0.2 mL). The mixture was stirred at 80 °C for 16 hours. The mixture was concentrated, diluted with H_2O (5 mL) and pH adjusted to 6 with citric acid. The solution was extracted with DCM (10 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylic acid single isomer (100 mg, crude) as a yellow oil.

LCMS ($M+H^+$) m/z: calcd 398.24; found 398.1.

Step 6: 1-[(1R)-1-[4-[3-(Cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-2-methyl-N-[(6-methyl-4-methylsulfanyl-2-oxo-1H-pyridin-3-yl)methyl]pyrrolo[2,3-b]pyridine-3-carboxamide (single isomer)

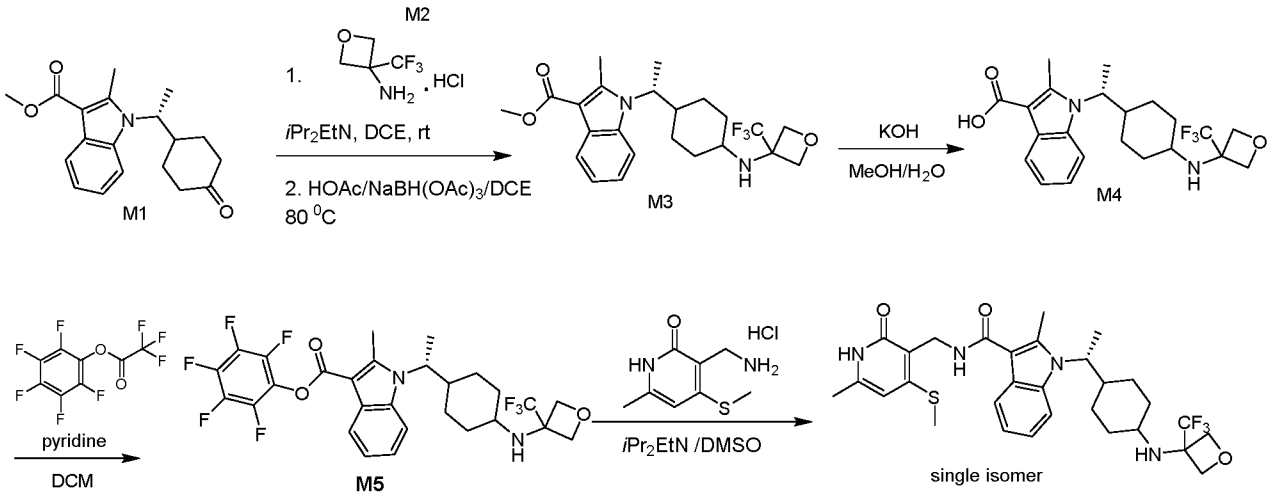


To a solution of 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-2-methyl-pyrrolo[2,3-b]pyridine-3-carboxylic acid (100 mg, 251.57 umol, 1 *eq*) in DMF (2 mL) was added DIEA (163 mg, 1.26 mmol, 220 uL, 5.02 *eq*) and HATU (115 mg, 302.45 umol, 1.2 *eq*). The mixture was stirred at 25 °C for 0.5 hour. 3-(Aminomethyl)-6-methyl-4-methylsulfanyl-1H-pyridin-2-one hydrochloride (85 mg, 385.10 umol, 1.53 *eq*) was added to the mixture and stirred at 25 °C for 2 hours. The reaction mixture was filtered and the filtrate was purified by prep-HPLC (column: Waters Xbridge 150*25 5u; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 38%-68%, 6.5min. Column Temp: 30 °C) to give 1-[(1R)-1-[4-[3-(cyclopropoxy)azetidin-1-yl]cyclohexyl]ethyl]-2-methyl-N-[(6-methyl-4-methylsulfanyl-2-oxo-1H-pyridin-3-yl)methyl]pyrrolo[2,3-b]pyridine-3-carboxamide single isomer (53.3 mg, 94.55 umol, 37.58% yield, 100% purity) as a white solid.

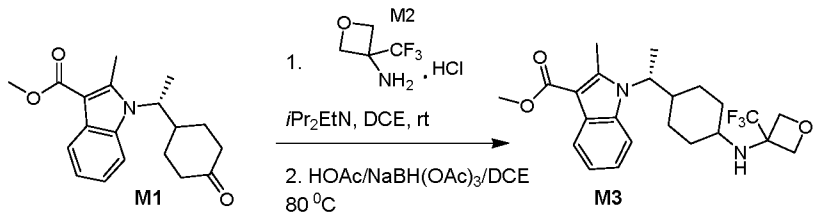
^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (br d, *J* = 4.0 Hz, 1H), 8.10 (br d, *J* = 7.6 Hz, 1H), 7.12 (br dd, *J* = 7.2, 4.8 Hz, 1H), 6.32 (s, 1H), 4.61 (s, 2H), 4.20 (m, 1H), 4.09 (br s, 1H), 3.62 (br t, *J* = 6.8 Hz, 1H), 3.56 (br t, *J* = 6.8 Hz, 1H), 3.24 - 3.31 (m, 1H), 2.91 - 3.03 (m, 2H), 2.72 - 2.75 (m, 1H), 2.67 (br s, 3H), 2.55 (s, 3H), 2.32 (s, 3H), 2.14 (br d, *J* = 12.0 Hz, 1H), 2.05 (br s, 1H), 1.94 (br d, *J* = 9.6 Hz, 1H), 1.57 - 1.74 (m, 4H), 1.03 - 1.18 (m, 2H), 0.95 (br s, 1H), 0.71 - 0.92 (m, 2H), 0.49 - 0.56 (m, 2H), 0.42 - 0.48 (m, 2H).

LCMS ($M+H^+$) m/z: calcd 564.29; found 564.3.

Synthesis of 2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((R)-1-(4-((3-(trifluoromethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxamide (single isomer) (Example 130)

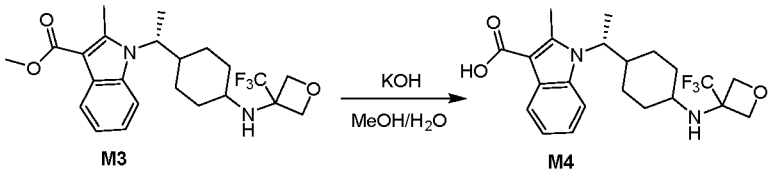


Step 1: Synthesis of methyl 2-methyl-1-((R)-1-(4-((3-(trifluoromethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxylate (single isomer)



A mixture of [3-(trifluoromethyl)oxetan-3-yl]amine hydrochloride (735 mg, 4.14 mmol) and diisopropylethylamine (754 µL, 4.34 mmol) in dichloroethane (10.3 mL) was stirred at 25 °C for 0.5 h under nitrogen atmosphere. To the reaction was added methyl 2-methyl-1-[(1R)-1-(4-oxocyclohexyl)ethyl]-1H-indole-3-carboxylate (650 mg, 2.07 mmol) and acetic acid (236 µL, 4.14 mmol). This mixture was then stirred at 80 °C for 45 min (mixture now clear light yellow). Then sodium triacetoxyborohydride (438 mg, 2.07 mmol) was added into the reaction mixture and stirred at 80 °C. The mixture was diluted with saturated sodium bicarbonate (3 mL) and water (10 mL), extracted with dichloromethane (20 mL x 3). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. The crude was purified by column chromatography on silica gel to give methyl 2-methyl-1-((R)-1-(4-((3-(trifluoromethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxylate (single isomer) (651 mg, 1.17 mmol, 57% yield) as a white solid. LCMS $[M+H]^+$ m/z: calc'd 438.22; found 439.2.

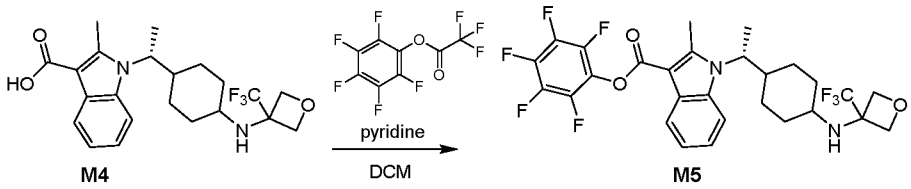
Step 2: Synthesis of 2-methyl-1-((R)-1-(4-((3-(trifluoromethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxylic acid (single isomer)



M3 M4

To a solution of methyl 2-methyl-1-((R)-1-(4-((3-(trifluoromethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxylate single isomer (651 mg, 1.17 mmol, 1.0 equiv) in methanol (3 mL) and water (1.5 mL) was added KOH (786 mg, 14.0 mmol, 12 equiv). The mixture was stirred at 80 °C for 12 h. The reaction mixture was concentrated. Dichloromethane (15 mL) and water (10 mL) were added, and the mixture was adjusted to pH = 5 - 6 with hydrochloric acid (1 M) solution. The mixture was extracted with dichloromethane (20 mL * 3). The organic layer was dried by anhydrous sodium sulfate, filtered and concentrated under vacuum to give 2-methyl-1-((R)-1-((1r,4R)-4-((3-(trifluoromethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxylic acid (500 mg, crude), as a white solid. LCMS $[M+H]^+$ m/z: calc'd 425.21; found 425.3.

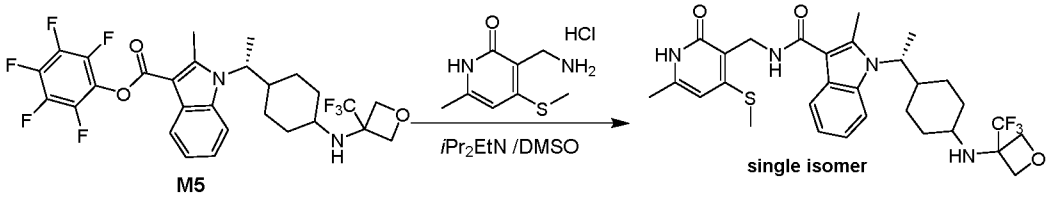
Step 3: Synthesis of perfluorophenyl 2-methyl-1-((R)-1-(4-((3-(trifluoromethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxylate (single isomer)



M4 M5

To a stirred solution of 2-methyl-1-[(1R)-1-[4-{[3-(trifluoromethyl)oxetan-3-yl]amino}cyclohexyl]ethyl]-1H-pyrrolo[2,3-b]pyridine-3-carboxylic acid single isomer (500 mg, 1178 µmol, 1.0 equiv) in dichloromethane (4.68 mL) was added pyridine (236 µL, 2.94 mmol, 2.5 equiv) followed by dropwise addition of 2,3,4,5,6-pentafluorophenyl 2,2,2-trifluoroacetate (403 µL, 2.35 mmol, 2.0 equiv). This mixture was stirred for 30 min at which time the starting material was consumed. The reaction was stopped by concentration under reduced pressure. The crude product was directly used in the next step. LCMS $[M+H]^+$ m/z: calc'd 591.19; found 591.14.

Step 4: Synthesis of 2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((R)-1-(4-((3-(trifluoromethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxamide (single isomer)



To a solution of 2,3,4,5,6-pentafluorophenyl 2-methyl-1-[(1R)-1-(4-{[3-(trifluoromethyl)oxetan-3-yl]amino}cyclohexyl)ethyl]-1H-indole-3-carboxylate single isomer (758 mg, 1158 µmol, 1.0 equiv) in dimethyl sulfoxide (5 mL) was added 3-(aminomethyl)-6-methyl-4-(methylsulfanyl)-1,2-dihydropyridin-2-one (755 mg, 4.10 mmol, 3.5 equiv) followed by ethylbis(propan-2-yl)amine (218 µL, 1.27 mmol, 1.1 equiv). The reaction was stirred overnight at room temperature, followed by heating at 50 °C for 1 h. The reaction was then diluted with water (10 mL), extracted with dichloromethane (20 mL x 4). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. The crude mixture was purified by column chromatography on silica gel to give 2-methyl-N-{[6-methyl-4-(methylsulfanyl)-2-oxo-1,2-dihydropyridin-3-yl]methyl}-1-[(1R)-1-(4-{[3-(trifluoromethyl)oxetan-3-yl]amino}cyclohexyl)ethyl]-1H-indole-3-carboxamide (single isomer) (415 mg, 0.703 mmol, 61% yield) as a white solid. LCMS $[M+H]^+$ m/z: calc'd 591.26; found 591.3. 1H NMR (400MHz, CDCl3) δ 12.78 (br. s., 1 H), 7.84 (d, J = 7.8 Hz, 1 H), 7.45 (d, J = 8.3 Hz, 1 H), 7.33 (br. s., 1 H), 7.14 - 6.98 (m, 2 H), 6.01 (s, 1 H), 4.81 - 4.62 (m, 4 H), 4.49 (t, J = 7.8 Hz, 2 H), 4.11 - 3.97 (m, 1 H), 2.65 (d, J = 9.8 Hz, 1 H), 2.48 (s, 3 H), 2.21 (s, 3 H), 2.09 (d, J = 12.2 Hz, 1 H), 1.95 (d, J = 11.7 Hz, 1 H), 1.66 - 1.55 (m, 6 H), 1.31 - 1.18 (m, 2 H), 1.18 - 1.09 (m, 1 H), 1.04 (d, J = 13.2 Hz, 1 H), 0.98 - 0.90 (m, 1 H), 0.90 - 0.75 (m, 2 H).

The following examples were synthesized using substantially similar procedures as described above, and using appropriate starting materials.

Name	Ex. #	LCMS	^{1}H-NMR
Name	Example #	LCMS	NMR
(R)-1-(1-hydroxypropan-2-yl)-2-methyl-N-((6-methyl-4-(methylthio)-2-	31	(M + H+) m/z: calcd 400.51,	1H NMR (400MHz ,METHANOL-d4) δ = 7.73 (d, J = 7.3 Hz, 1 H), 7.54 (d, J = 7.8 Hz, 1

oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide		found 400.3.	H), 7.20 - 7.02 (m, 2 H), 6.47 (s, 1 H), 4.70 (br dd, J =7.1, 14.4 Hz, 1 H), 4.62 (s, 2 H), 4.21 - 4.09 (m, 1 H), 3.88 (dd, J = 5.4, 11.7 Hz, 1 H), 2.67 (s, 3 H), 2.58 (s, 3 H), 2.36 (s, 3 H), 1.59 (d, J = 7.3 Hz, 3 H)
(R)-1-(1-methoxypropan-2-yl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	32	(M + H+) m/z: calcd 414.53, found 414.2.	1H NMR (400MHz ,DMSO-d6) δ = 11.78 - 11.57 (m, 1 H), 7.73 (d, J = 7.8 Hz, 1 H), 7.68 (br s, 1 H), 7.58 (d, J = 7.8 Hz, 1 H), 7.12 - 7.00 (m, 2 H), 6.14 (s, 1 H), 4.77 (br d, J = 5.4 Hz, 1 H), 4.40 (br d, J = 2.9 Hz, 2 H), 3.91 (br t, J = 9.5 Hz, 1 H), 3.79 (br s, 2 H), 3.67 (dd, J = 5.1, 10.0 Hz, 1 H), 3.16 (s, 3 H), 2.61 (s, 3 H), 2.48 (s, 3 H), 2.19 (s, 3 H), 1.52 (d, J = 7.3 Hz, 3 H)
(R)-1-(1-ethoxypropan-2-yl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	33	(M + H+) m/z: calcd 528.56, found 428.2.	1H NMR (400MHz ,METHANOL-d4) δ = 7.79 - 7.68 (m, 1 H), 7.53 (d, J = 8.3 Hz, 1 H), 7.17 - 6.95 (m, 2 H), 6.34 (s, 1 H), 4.82 - 4.74 (m, 2 H), 4.61 (s, 2 H), 4.00 (t, J = 9.3 Hz, 1 H), 3.79 (dd, J = 4.9, 10.3 Hz, 1 H), 3.48 - 3.37 (m, 1 H), 2.91 - 2.77 (m, 1 H), 2.65 (s, 3 H), 2.54 (s, 3 H), 2.31 (s, 3 H), 1.60 (d, J = 7.3 Hz, 3 H), 1.01 (t, J = 6.8 Hz, 3 H)
(S)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(2-methylpyrimidin-5-yl)ethyl)-1H-indole-3-carboxamide	34	(M+H+) m/z: calcd 462.19; found 462.3	1H NMR (400MHz, CDCl3) δ 12.52 (brs, 1H), 8.40 (s, 2H), 7.84 (d, J = 7.6 Hz, 1H), 7.44 - 7.43 (m, 1H), 7.04 - 6.97 (m, 2H), 6.91 (d, J = 8.0 Hz, 1H), 6.01 (s, 1H), 5.84 - 5.79 (m, 1H), 4.75 - 4.74 (m, 2H), 2.77 (s, 3H), 2.71 (s, 3H), 2.45 (s, 3H), 2.20 (s, 3H), 1.98 (d, J = 7.2 Hz, 3H).
(R)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(2-methylpyrimidin-5-yl)ethyl)-1H-indole-3-carboxamide	35	(M+H+) m/z: calcd 462.19; found 462.3	1H NMR (400MHz, CDCl3) δ 12.68 (brs, 1H), 8.40 (s, 2H), 7.84 (d, J = 8.0 Hz, 1H), 7.43 - 7.42 (m, 1H), 7.03 - 6.97 (m, 2H), 6.90 (d, J = 8.0 Hz, 1H), 6.01 (s, 1H), 5.84 - 5.79 (m, 1H), 4.74 (d, J = 4.0 Hz, 2H), 2.77 (s, 3H), 2.71 (s, 3H), 2.49 (s, 3H), 2.19 (s, 3H), 1.98 (d, J = 7.2 Hz, 3H).
1-((R)-1-(4-hydroxycyclohexyl)ethyl)-	36 isomer 1	(M + H+) m/z: calcd:	1H NMR (400MHz, CD3OD) δ 8.18 (dd, J = 1.6, 4.4 Hz, 1H), 8.08

2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide		469.22.; found 469.1	(d, J = 7.6 Hz, 1H), 7.10 (dd, J = 4.0, 7.6 Hz, 1H), 6.29 (s, 1H), 4.63 (br s, 2H), 4.06 (br s, 1H), 3.51 - 3.38 (m, 1H), 2.83 - 2.70 (m, 1H), 2.65 (br s, 3H), 2.53 (s, 3H), 2.30 (s, 3H), 2.13 - 1.89 (m, 2H), 1.75 - 1.59 (m, 4H), 1.37 - 1.25 (m, 1H), 1.22 - 1.10 (m, 1H), 1.08 - 0.81 (m, 3H)
1-((R)-1-(4-hydroxycyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	36 isomer 2	(M + H+) m/z: calcd: 469.22.; found 469.1	1H NMR (400MHz, CD3OD) δ 8.16 (d, J = 3.6 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.08 (dd, J = 4.8, 7.6 Hz, 1H), 6.28 (s, 1H), 4.58 (s, 2H), 4.28 - 4.03 (m, 1H), 3.86 (br s, 1H), 2.87 (br d, J = 16.8 Hz, 1H), 2.70 - 2.60 (m, 3H), 2.52 (s, 3H), 2.29 (s, 3H), 1.86 - 1.72 (m, 2H), 1.64 (br s, 3H), 1.59 - 1.44 (m, 3H), 1.42 - 1.07 (m, 2H), 0.72 (br s, 1H)
1-((R)-1-((3R,4R)-3-fluoropiperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	37	(M+H+) m/z: calcd 471.22; found 471.3.	1H NMR (400MHz, CD3OD) δ 7.75 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.19 - 7.06 (m, 2H), 6.32 (s, 1H), 4.62 - 4.42 (m, 3H), 3.28 (br d, J = 6.3 Hz, 2H), 2.78 - 2.66 (m, 2H), 2.65 - 2.59 (m, 4H), 2.56 (s, 3H), 2.33 (s, 4H), 1.76 (dd, J = 2.6, 6.9 Hz, 3H), 1.03 (br s, 2H)
1-((1R)-1-((3S)-3-fluoropiperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	38	(M+H+) m/z: calcd 471.22; found 471.2.	1H NMR (400 MHz, MeOD) δ 7.78 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.24 - 7.10 (m, 2H), 5.41 - 5.29 (m, 1H), 4.66 - 4.60 (m, 3H), 4.00 - 3.73 (m, 2H), 3.50 - 3.42 (m, 2H), 3.21 - 3.18 (m, 2H), 3.21 - 3.18 (m, 2H), 3.04 - 2.81 (m, 3H), 2.74 - 2.71 (m, 3H), 2.56 (s, 3H), 1.78 - 1.66 (m, 3H), 1.40 - 1.29 (m, 2H), 0.95 - 0.90 (m, 1H)
(R)-1-(1-(1-cyanopiperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	39	(M+H+) m/z: calcd 478.23; found 478.1	1H NMR (400 MHz, CD3OD) δ 7.73 (br d, J = 7.5 Hz, 1H), 7.50 - 7.50 (m, 1H), 7.58 (br d, J = 7.5 Hz, 1H), 7.17 - 7.05 (m, 2H), 6.30 (s, 1H), 4.63 - 4.60 (m, 2H), 4.23 (br dd, J = 7.0, 10.5 Hz, 1H), 3.58 - 3.33 (m, 1H), 3.25 - 3.08 (m, 1H), 3.10 - 3.07 (m, 1H), 2.81 (br t, J = 11.5 Hz, 1H), 2.62 (s, 3H), 2.54 (s, 3H), 2.44 (br d, J = 11.5 Hz, 1H), 2.31 (s, 3H), 2.19 - 1.99 (m, 1H),

			1.63 (br d, J = 7.0 Hz, 3H), 1.59 - 1.38 (m, 1H), 1.33 - 1.09 (m, 1H), 0.88 (br d, J = 14.5 Hz, 1H).
1-((1R)-1-(4-hydroxycyclohexyl)ethyl)-2,6-dimethyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	40	(M + H+) m/z: calcd 483.62, found 483.3.	1H NMR (400MHz ,METHANOL-d4) δ = 8.93 - 8.84 (m, 1 H), 8.65 (tt, J = 1.5, 7.8 Hz, 1 H), 8.14 - 8.08 (m, 1 H), 8.07 - 7.87 (m, 1 H), 7.04 (br d, J = 4.9 Hz, 1 H), 6.43 (s, 1 H), 6.26 (s, 1 H), 4.59 (s, 1 H), 4.44 (s, 1 H), 3.88 (br s, 1 H), 3.55 - 3.40 (m, 1 H), 2.65 (s, 4 H), 2.61 - 2.55 (m, 4 H), 2.51 (s, 1 H), 2.34 (s, 2 H), 2.29 (s, 1 H), 2.24 - 1.95 (m, 2 H), 1.92 - 1.48 (m, 5 H), 1.46 - 0.79 (m, 4 H)
7-((R)-1-(4-methoxycyclohexyl)ethyl)-6-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide	41 isomer 1	(M+H+) m/z: calcd 484.23; found 484.2	1H NMR (400 MHz, CD3OD) δ 9.02 (s, 1H), 8.72 (s, 1H), 6.31 (s, 1H), 4.60 (s, 2H), 4.17 (br s, 1H), 3.31 (s, 3H), 3.20 - 3.07 (m, 1H), 2.69 (br s, 3H), 2.60 - 2.52 (m, 3H), 2.31 (s, 3H), 2.21 - 2.10 (m, 2H), 1.88 (br s, 1H), 1.68 (br d, J = 6.5 Hz, 3H), 1.34 - 1.16 (m, 3H), 0.96 (br s, 3H).
7-((R)-1-(4-methoxycyclohexyl)ethyl)-6-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide	41 isomer 2	(M+H+) m/z: calcd 484.23; found 484.2	1H NMR (400 MHz, CD3OD) δ 9.02 (s, 1H), 8.70 (s, 1H), 6.31 (s, 1H), 4.63 - 4.57 (m, 2H), 4.22 (br s, 1H), 3.42 (br s, 1H), 3.27 (s, 3H), 2.69 (s, 3H), 2.54 (s, 3H), 2.31 (s, 3H), 2.02 (br d, J = 14.6 Hz, 1H), 1.85 - 1.78 (m, 1H), 1.77 - 1.71 (m, 1H), 1.67 (br d, J = 6.6 Hz, 3H), 1.56 - 1.40 (m, 2H), 1.35 - 1.05 (m, 3H), 0.69 (br d, J = 11.8 Hz, 1H).
1-((R)-1-((3R,4R)-3-fluoro-1-methylpiperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	42	(M+H+) m/z: calcd 485.23; found 485.4.	1H NMR (400MHz, CD3OD) δ 7.76 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.23 - 7.10 (m, 2H), 6.33 (s, 1H), 4.68 (br d, J = 5.0 Hz, 2H), 4.58 - 4.51 (m, 1H), 3.17 (br dd, J = 5.3, 10.5 Hz, 2H), 2.88 - 2.72 (m, 1H), 2.65 (s, 2H), 2.56 (m, 6H), 2.33 (s, 3H), 2.29 (s, 3H), 2.14 (br dd, J = 6.0, 10.5 Hz, 1H), 1.76 (dd, J = 2.8, 7.0 Hz, 3H), 1.21 - 1.02 (m, 2H).
1-((1R)-1-((3S)-3-fluoro-1-methylpiperidin-4-yl)ethyl)-2-methyl-N-((6-	43	(M+H+) m/z: calcd 485.23;	1H NMR (400 MHz, CDCl3) δ 12.47 (brs, 1H), 7.88 - 7.85 (m, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.14

methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide		found 485.1.	- 7.05 (m, 2H), 6.01 (s, 1H), 5.01 - 4.68 (m, 2H), 4.57 - 4.56 (m, 1H), 3.31 - 2.83 (m, 2H), 2.71 (s, 3H), 2.49 (s, 3H), 2.31 - 2.22 (m, 8H), 1.86 - 1.53 (m, 7H).
6-fluoro-1-((R)-1-(4-hydroxycyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	44 isomer 1	(M + H+) m/z: calcd: 486.22; found 486.2.	1H NMR (400MHz, CDCl3) δ 7.68 (dd, J = 5.6, 8.6 Hz, 1 H), 7.15 (d, J = 9.8 Hz, 1 H), 6.92 (dt, J = 2.0, 9.0 Hz, 1 H), 6.76 (br. s., 1 H), 6.41 (s, 1 H), 4.72 (d, J = 10.3 Hz, 2 H), 4.11 - 3.96 (m, 1 H), 3.60 - 3.46 (m, 1 H), 2.66 (s, 2 H), 2.56 (s, 3 H), 2.46 (s, 3 H), 2.09 (d, J = 8.3 Hz, 3 H), 1.78 (d, J = 10.3 Hz, 1 H), 1.58 (d, J = 7.3 Hz, 3 H), 1.40 - 1.24 (m, 1 H), 1.17 - 1.01 (m, 3 H), 0.90 - 0.75 (m, 1 H).
6-fluoro-1-((R)-1-(4-hydroxycyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	44 isomer 2	(M + H+) m/z: calcd: 486.22; found 486.2.	1H NMR (400MHz, CDCl3) δ 7.70 - 7.60 (m, 1 H), 7.16 (d, J = 10.3 Hz, 1 H), 6.93 (d, J = 2.4 Hz, 1 H), 6.72 (br. s., 1 H), 6.48 (s, 1 H), 4.72 (br. s., 2 H), 4.19 - 4.09 (m, 1 H), 4.04 (br. s., 1 H), 2.72 - 2.62 (m, 2 H), 2.57 (s, 3 H), 2.50 (s, 3 H), 2.21 - 2.05 (m, 2 H), 1.93 - 1.75 (m, 3 H), 1.64 - 1.49 (m, 4 H), 1.40 - 1.28 (m, 1 H), 1.25 - 1.12 (m, 1 H), 1.12 - 1.03 (m, 0 H), 0.85 - 0.75 (m, 1 H).
(R)-1-(1-(4,4-difluorocyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	45	(M + H+) m/z: calcd 488.21: found 488.0	1HNMR (400MHz, CDCl3) δ 12.01(s, 1H), 7.83(d, J = 8.0, 1H), 7.72(d, J = 8.0, 1H), 7.28(s, 1H), 7.08-7.02(m, 2H), 5.98(s, 1H), 4.75-4.64(m, 2H), 4.11(m, 1H), 2.83-2.70(m, 3H), 2.46(s, 3H), 2.29(m, 1H), 2.20(s, 3H), 2.08-2.05(m, 2H), 1.85-1.80(m, 2H), 1.61-1.60(m, 4H), 1.23-1.18(m, 2H), 1.10-1.04(m, 2H)
(R)-1-(1-(4-(dimethylamino)phenyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	46	(M+H+) m/z: calcd 489.22; found 489.1.	1H NMR (400 MHz, CDCl3) δ 7.74 (d, J = 8.0 Hz, 1H), 7.27-7.25 (m,1H), 6.97-6.87 (m, 5H), 6.56 (d, J = 8.8 Hz, 2H), 5.93 (s,1H), 5.73-5.67 (m,1H), 4.67-4.65 (m,2H), 2.84(s,6H), 2.66 (s,3H), 2.40 (s,3H), 2.13 (s,3H), 1.80 (d, J = 6.8 Hz,3H)
(S)-1-(1-(4-(dimethylamino)phenyl)ethyl)-2-methyl-N-((6-	47	(M+H+) m/z: calcd 489.22;	1H NMR (400 MHz, CDCl3) δ 7.74 (d, J = 6.8Hz,1H), 7.29-7.26 (m,1H), 6.98-6.87 (m,5H),6.57-

methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide		found 489.1.	6.55 (m,2H), 5.92 (s,1H), 5.72-5.67 (m,1H), 4.67-4.62 (m,2H), 2.83 (s, 6H), 2.66 (s,3H), 2.40 (s,3H), 2.17-2.12 (m,3H), 1.81-1.79 (m,3H).
(R)-1-(1-(1-cyclopropylpiperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	48	(M + H+) m/z: calcd 493.26, found 493.3	1H NMR (400MHz ,DMSO-d6) δ = 11.65 (br. s., 2 H), 8.90 (br. s., 2 H), 7.85 - 7.43 (m, 3 H), 7.20 - 6.90 (m, 2 H), 6.12 (s, 1 H), 4.64 - 4.46 (m, 0H), 4.38 (d, J= 2.0 Hz, 2 H), 4.26 - 4.04 (m, 1 H), 3.68 - 3.45 (m, 1 H), 3.29 (d, J = 11.7 Hz, 1 H), 3.22 - 2.84 (m, 2 H), 2.83 - 2.61 (m, 2 H), 2.56 (s, 2 H), 2.46 (s, 2 H), 2.35 - 2.22 (m, 0 H), 2.22 - 2.09 (m, 3 H), 2.06 - 1.89 (m, 0 H), 1.56 (d, J = 6.4 Hz, 3 H), 1.32 - 1.02 (m, 1 H), 1.01 - 0.64 (m, 4 H)
2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((R)-1-(3-(oxetan-3-ylamino)cyclobutyl)ethyl)-1H-indole-3-carboxamide	49 single isomer	(M+H+) m/z: calcd 495.24; found 495.1	1H NMR (400 MHz, CD3OD) δ 7.72 (br d, J = 8.0 Hz, 1H), 7.61 - 7.50 (m, 1H), 7.09 (br d, J = 5.0 Hz, 2H), 6.33 (s, 1H), 5.36 (br t, J = 4.5 Hz, 1H), 4.81 - 4.70 (m, 2H), 4.68 - 4.64 (m, 2H), 4.54 - 4.41 (m, 2H), 3.98 - 3.88 (m, 1H), 2.77 - 2.68 (m, 3H), 2.56 (s, 3H), 2.52 - 2.47 (m, 1H), 2.33 (s, 3H), 2.30 (br d, J = 3.0 Hz, 1H), 2.21 (t, J = 7.5 Hz, 1H), 2.18 - 2.12 (m, 1H), 2.05 (br d, J = 5.0 Hz, 1H), 1.92 - 1.89 (m, 1H), 1.60 - 1.52 (m, 3H)
(R)-7-(1-(1-cyclopropylpiperidin-4-yl)ethyl)-6-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide	50	(M+H+) m/z: calcd 495.25; found 495.5.	1H NMR (400MHz, CD3OD) δ 9.05 (s, 1H), 8.74 (s, 1H), 6.33 (s, 1H), 4.63 (br s, 1H), 4.61 (s, 2H), 3.42 - 3.34 (m, 4H), 3.17 - 2.89 (m, 1H), 2.72 (br s, 3H), 2.57 (s, 3H), 2.33 (s, 3H), 2.23 (br s, 1H), 1.73 (br d, J=6.8 Hz, 3H), 1.55 (br s, 1H), 1.35 - 0.92 (m, 3H), 0.79 (br s, 4H).
1-((R)-1-(4-(dimethylamino)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	51 isomer 1	(M+H+) m/z: calcd 496.27; found 496.3	1H NMR (400 MHz, CD3OD) δ 8.19 (dd, J = 1.5, 4.8 Hz, 1H), 8.09 (br d, J = 8.0 Hz, 1H), 7.11 (dd, J = 4.8, 8.0 Hz, 1H), 6.31 (s, 1H), 4.61 (s, 2H), 4.10 (br s, 1H), 3.34 (br d, J = 1.6 Hz, 1H), 2.67 (br s, 3H), 2.55 (s, 3H), 2.32 (s, 3H), 2.27 (s, 6H), 2.24 - 2.15 (m, 2H), 2.11 - 2.01 (m, 1H), 1.79 - 1.60 (m, 4H), 1.40 - 1.26 (m, 1H), 1.17 (br d, J =

			11.6 Hz, 1H), 1.03 (br d, J = 12.8 Hz, 2H), 0.89 (br d, J = 12.0 Hz, 1H)
1-((R)-1-(4-(dimethylamino)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	51 isomer 2	(M+H+) m/z: calcd 496.27; found 496.3	1H NMR (400 MHz, CD3OD) δ 8.17 (br s, 1H), 8.08 (d, J = 7.6 Hz, 1H), 7.09 (br s, 1H), 6.30 (s, 1H), 4.60 (s, 2H), 4.37 (br s, 1H), 3.33 - 3.32 (m, 1H), 2.71 (br s, 3H), 2.53 (s, 3H), 2.30 (s, 3H), 2.27 (s, 6H), 2.24 - 2.06 (m, 1H), 1.86 - 1.49 (m, 8H), 1.43 - 1.26 (m, 1H), 1.07 (br s, 1H), 0.92 (br s, 1H)
(R)-1-(1-(1-(2-hydroxyethyl)piperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	52	(M+H+) m/z: calcd 497.25; found 497.1.	1H NMR (400MHz, CDCl3) δ 12.44 (brs, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.29 - 7.24 (m, 1H), 7.06 - 7.00 (m, 2H), 5.98 (s, 1H), 4.78 - 4.62 (m, 2H), 4.11 - 4.07 (m, 1H), 3.54 (s, 2H), 3.01 - 2.98 (m, 1H), 2.82 - 2.65 (m, 4H), 2.46 - 2.44 (m, 5H), 2.19 (s, 4H), 2.09 - 2.03 (m, 1H), 1.97 - 1.94 (m, 1H), 1.80 - 1.75 (m, 2H), 1.58 - 1.57 (m, 3H), 1.38 - 1.35 (m, 1H), 1.03 - 0.95 (m, 2H).
5-chloro-1-((R)-1-(4-hydroxycyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	53 isomer 1	(M + Na+) m/z: calcd 503.18: found 503.1	1H NMR (400MHz, CDCl3) δ 11.92(s, 1H), 8.13(d, J = 10.8Hz, 2H), 7.32(s, 1H), 6.05-6.02(m, 1H), 4.71(m, 2H), 3.51(m, 1H), 2.74(m, 2H), 2.52-2.46(m, 3H), 2.29-2.26 (m, 3H), 2.07 (m, 2H), 1.75-1.73 (m, 1H), 1.63-1.59(m, 3H), 1.43 (m, 1H), 1.31(m, 1H), 1.05-0.97(m, 3H), 0.94-0.81(m, 1H).
5-chloro-1-((R)-1-(4-hydroxycyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	53 isomer 2	(M + Na+) m/z: calcd 503.18: found 503.1	1H NMR (400MHz, CDCl3) δ 11.49(s, 1H), 8.14(d, J = 15.6Hz, 2H), 7.34-7.32(m, 1H), 6.02(s, 1H), 4.68(s, 2H), 3.99(s, 2H), 2.76(s, 3H), 2.50(s, 3H), 2.29-2.27(m, 3H), 1.81(m, 2H), 1.63-1.61(m, 3H), 1.33-1.12(m, 4H), 0.74(m, 1H).
(R)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(1-(2,2,2-trifluoroethyl)azetidin-3-yl)ethyl)-1H-indole-3-carboxamide	54	(M+H+) m/z: calcd 507.20; found 507.1.	1H NMR (400MHz, CD3OD) δ 7.69 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.08 – 7.04 (m, 2H), 6.28 (s, 1H), 5.32 (s, 1H), 4.59 (s, 2H), 3.36 (s, 2H), 3.12 – 3.05 (m, 4H), 2.83 – 2.80 (m, 1H), 2.69 (s, 3H), 2.52 (s, 3H), 2.29 (s, 3H), 1.52 (d, J = 8.0 Hz, 3H).

(S)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(1-(2,2,2-trifluoroethyl)azetidin-3-yl)ethyl)-1H-indole-3-carboxamide	55	(M+H+) m/z: calcd 507.20; found 507.3.	1H NMR (400MHz, CD3OD) δ 7.69 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.09 – 7.04 (m, 2H), 6.28 (s, 1H), 5.32 (s, 1H), 4.59 (s, 2H), 3.36 (s, 2H), 3.12 – 3.05 (m, 4H), 2.83 – 2.80 (m, 1H), 2.69 (s, 3H), 2.52 (s, 3H), 2.29 (s, 3H), 1.52 (d, J = 8.0 Hz, 3H)
1-((R)-1-((3S,4R)-1-cyclopropyl-3-fluoropiperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	56	(M+H+) m/z: calcd 571.27; found 571.1	1H NMR (400 MHz, CDCl3) δ 13.00 (s, 1H), 7.88-7.85 (m, 1H), 7.40-7.32 (m, 2H), 7.11-7.02 (m, 2H), 6.00 (s, 1H), 4.98-4.55 (m, 3H), 3.86-2.84 (m, 3H), 2.70 (s, 3H), 2.48 (s, 3H), 2.42-2.38(m, 1H), 2.20 (s, 3H), 2.10-1.82 (m, 2H), 1.65 (d, J = 7.2 Hz, 3H), 1.59-1.26 (m, 2H), 0.85-0.80 (m, 1H), 0.50-0.39 (m, 4H).
(R)-1-(1-(1-cyclopropylpiperidin-4-yl)ethyl)-6-fluoro-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	57	(M + H+) m/z: calcd: 511.25; found 511.3.	1H NMR (400MHz, CDCl3) δ 12.96 - 12.73 (m, 1 H), 7.76 (dd, J = 5.4, 8.8 Hz, 1 H), 7.35 - 7.28 (m, 1 H), 7.14 (d, J = 10.3 Hz, 1 H), 6.80 (t, J = 8.1 Hz, 1 H), 6.02 (s, 1 H), 4.80 - 4.63 (m, 2 H), 4.07 (dd, J = 6.8, 10.3 Hz, 1 H), 3.14 (d, J = 11.2 Hz, 1 H), 2.84 (d, J = 11.7 Hz, 1 H), 2.65 (s, 2 H), 2.49 (s, 3 H), 2.24 - 2.14 (m, 4 H), 1.99 - 1.88 (m, 2 H), 1.59 - 1.49 (m, 4 H), 1.40 - 1.22 (m, 2 H), 1.11 - 0.97 (m, 1 H), 0.92 (d, J = 12.7 Hz, 1 H), 0.49 - 0.36 (m, 3 H).
(R)-1-(1-(1-cyclopropylpiperidin-4-yl)ethyl)-5-fluoro-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	58	(M + H+) m/z: calcd 512.66, found 512.3.	1H NMR (400MHz ,METHANOL-d4) δ = 8.08 (s, 1 H), 7.83 (dd, J = 2.7, 9.5 Hz, 1 H), 6.30 (s, 1 H), 4.58 (s, 2 H), 3.13 (br d, J = 11.7 Hz, 1 H), 2.85 (br d, J = 12.2 Hz, 1 H), 2.66 (s, 3 H), 2.54 (s, 3 H), 2.31 (s, 2 H), 2.29 - 2.21 (m, 1 H), 2.07 - 1.90 (m, 2 H), 1.73 - 1.54 (m, 4 H), 1.42 - 1.24 (m, 2 H), 1.06 (dq, J = 4.2, 12.3 Hz, 1 H), 0.86 (br d, J = 13.2 Hz, 1 H), 0.54 - 0.28 (m, 4 H)
(R)-1-(1-(1-(2,2-difluoroethyl)piperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-	59	(M + H+) m/z: calcd: 518.23.; found 518.1	1H NMR (400MHz, CD3OD) δ 8.16 (d, J = 3.6 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.08 (dd, J = 4.8, 8.0 Hz, 1H), 6.28 (s, 1H), 6.10 - 5.74 (m, 1H), 4.58 (s, 2H), 4.11 (br s, 1H), 3.05 (br d, J = 11.6 Hz,

pyrrolo[2,3-b]pyridine-3-carboxamide			1H), 2.78 - 2.70 (m, 2H), 2.68 - 2.64 (m, 3H), 2.54 - 2.45 (m, 3H), 2.29 (s, 3H), 2.26 - 2.18 (m, 1H), 2.05 - 1.90 (m, 2H), 1.65 (br s, 3H), 1.41 (br d, J = 10.8 Hz, 1H), 1.14 - 1.06 (m, 3H), 0.84 (br d, J = 13.2 Hz, 1H)
1-((R)-1-(4-(difluoromethoxy)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	60 isomer 1	(M+H+) m/z: calcd 518.22; found 518.4.	1H NMR (400MHz, CDCl3) δ 12.52 (brs, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.30 (s, 1H), 7.09 - 7.02 (m, 2H), 6.20 (t, J = 75.6 Hz, 1H), 6.00 (s, 1H), 4.77 - 4.671 (m, 2H), 4.36 (s, 1H), 4.16 - 4.11 (m, 1H), 2.84 - 2.73 (m, 3H), 2.47 (s, 3H), 2.26 - 2.20 (m, 4H), 2.04 - 2.01 (m, 1H), 1.88 - 1.85 (m, 1H), 1.73 - 1.69 (m, 1H), 1.60 - 1.59 (m, 3H), 1.53 - 1.49 (m, 2H), 1.26 - 1.17 (m, 2H), 0.87 - 0.84 (m, 1H).
1-((R)-1-(4-(difluoromethoxy)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	60 isomer 2	(M+H+) m/z: calcd 518.2; found 518.1.	1H NMR (400MHz, MeOD) δ 7.73 (d, J = 6.4Hz, 1H), 7.59 (d, J = 8Hz, 1H), 7.14 - 7.06 (m, 2H), 6.53 - 6.15 (m, 2H), 4.62 (s, 1H), 4.17 - 4.14 (m, 1H), 3.98 - 3.97 (m, 1H), 2.69 - 2.57 (m, 5H), 2.33 (s, 3H), 2.33 - 2.13 (m, 1H), 2.13 - 2.11 (m, 2H), 1.81 (d, J = 9.2Hz, 1H), 1.62 (d, J = 7.2Hz, 3H), 1.48 - 1.38 (m, 1H), 1.31 - 1.28 (m, 3H), 1.25 - 1.24 (m, 1H), 0.95 - 0.90 (m, 2H).
(R)-1-(1-(4-(tert-butylamino)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	61	(M + H+) m/z: calcd 523.30, found 523.2.	1H NMR (400MHz, CDCl3) δ 7.79-7.77 (d, J=7.6 Hz, 1H), 7.44-7.42 (d, J=7.2 Hz, 1H), 7.10-7.03 (m, 2H), 6.01 (s, 1H), 4.78-4.65 (m, 2H), 4.06-4.01 (m, 1H), 2.70 (s, 3H), 2.49(s, 3H), 2.46(s, 1H), 2.22 (s, 3H), 2.17-1.95 (m, 2H), 1.58-1.56 (m, 5H), 1.12 (s, 11H), 0.95-0.81 (m, 3H).
2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((R)-1-(4-(oxetan-3-ylamino)cyclohexyl)ethyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	62 isomer 1	(M+H+) m/z: calcd 524.26; found 524.5.	1H NMR (400 MHz, CDCl3) δ 8.12 (d, J = 4.0 Hz, 1H), 8.03 (d, J = 7.6 Hz, 1H), 7.29 (m, 1H), 6.91 (dd, J = 4.8, 7.6 Hz, 1H), 5.95 (s, 1H), 4.78 - 4.58 (m, 4H), 4.37 - 4.24 (m, 2H), 3.95 (m, 1H), 2.99 - 2.46 (m, 4H), 2.42 (s, 3H), 2.28 (m, 1H), 2.15 (s, 3H), 2.07 - 1.95 (m, 1H), 1.82 (br d, J = 11.6 Hz, 1H), 1.69 - 1.43 (m, 7H), 1.20 -

			0.96 (m, 2H), 0.90 (br d, J = 12.4 Hz, 1H), 0.84 - 0.66 (m, 2H).
2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((R)-1-(4-(oxetan-3-ylamino)cyclohexyl)ethyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	62 isomer 2	(M+H+) m/z: calcd 524.26; found 524.5.	1H NMR (400 MHz, CDCl3) δ 8.13 (br s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.27 (br s, 1H), 6.91 (m, 1H), 5.95 (s, 1H), 4.78 - 4.57 (m, 4H), 4.43 - 4.26 (m, 2H), 3.97 - 3.87 (m, 1H), 3.65 (q, J = 7.2 Hz, 1H), 2.85 - 2.56 (m, 4H), 2.42 (s, 3H), 2.16 (s, 3H), 1.63 - 1.38 (m, 9H), 1.31 - 1.12 (m, 3H), 1.05 - 0.92 (m, 1H), 0.77 (br s, 1H).
6-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-7-((R)-1-(4-(oxetan-3-ylamino)cyclohexyl)ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide	63 single isomer	(M+H+) calcd. 525.2; found 525.1.	1H NMR (400MHz, CD3OD) δ 9.03 (s, 1H), 8.72 (s, 1H), 6.32 (s, 1H), 5.00 - 4.92 (m, 1H), 4.87 - 4.73 (m, 3H), 4.61 (s, 2H), 4.47 (td, J = 6.4, 11.0 Hz, 2H), 4.06 (quin, J = 6.8 Hz, 1H), 2.75 - 2.65 (m, 3H), 2.56 (s, 3H), 2.39 (br d, J = 3.4 Hz, 1H), 2.35 - 2.24 (m, 3H), 2.19 - 1.99 (m, 1H), 1.99 - 1.90 (m, 1H), 1.69 (br d, J = 6.5 Hz, 4H), 1.25 - 1.06 (m, 2H), 1.00 - 0.85 (m, 3H)
(R)-1-(1-(1-(3-fluorocyclobutyl)piperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	64 isomer 1	(M + H+) m/z: calcd 525.27, found 525.3	
1-((R)-1-(1-(3-fluorocyclobutyl)piperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	64 isomer 2	(M + H+) m/z: calcd 525.27, found 525.3	
1-((R)-1-(4-(3-fluoroazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	65 single isomer	(M+H+) m/z: calcd 526.27; found 526.4	1H NMR (400 MHz, CD3OD) δ 8.17 (d, J = 3.5 Hz, 1H), 8.08 (br d, J = 8.0 Hz, 1H), 7.10 (br dd, J = 4.8, 7.8 Hz, 1H), 6.30 (s, 1H), 5.17 - 4.97 (m, 1H), 4.60 (br s, 2H), 4.07 (br s, 1H), 3.63 - 3.52 (m, 2H), 3.25 - 3.14 (m, 2H), 2.67 (m, 3H), 2.53 (s, 3H), 2.30 (s, 3H), 2.14 - 2.07 (m, 2H), 1.94 - 1.91 (m, 1H), 1.65 - 1.60 (m, 4H), 1.13 -

			1.11 (m, 3H), 1.07 - 1.04 (m, 1H), 0.94 - 0.86 (m, 2H)
(R)-1-(1-(1-(3-fluorocyclobutyl)piperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	66	(M+H+) m/z: calcd 526.26; found 526.2	1H NMR (400 MHz, CD3OD) δ 8.18 (d, J = 4.0 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.12 - 7.09 (m, 1H), 6.30 (s, 1H), 5.15 - 4.99 (m, 1H), 4.60 (s, 2H), 4.17 - 4.10 (m, 1H), 3.03 - 2.98 (m, 2H), 2.74 - 2.67 (m, 4H), 2.54 (s, 3H), 2.31 (s, 3H), 2.26 - 2.24 (m, 2H), 2.21 - 2.17 (m, 1H), 2.08 - 2.02 (m, 1H), 1.90 - 1.84 (m, 1H), 1.67 (br s, 3H), 1.43 - 1.30 (m, 4H), 1.14 - 1.06 (m, 1H), 0.93 - 0.88 (m, 1H).
1-((R)-1-(4-(2-methoxyethoxy)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	67 isomer 1	(M+H+) m/z: calcd 526.27; found 526.3	1H NMR (400 MHz, CDCl3) δ 13.10(br, 1H), 7.82(d, J = 7.6Hz, 1H), 7.46(d, J = 8.0Hz, 1H), 7.31(s, 1H), 7.06-6.99(m, 2H), 4.77-4.67(m, 2H), 4.16-4.12(m, 1H), 3.51(s, 5H), 3.38(s, 3H), 2.84-2.72(m, 3H), 2.47(s, 3H), 2.22-2.18(m, 4H), 2.00(s, 1H), 1.75-1.71(m, 2H), 1.57(d, J = 6.8Hz, 3H), 1.47-0.79(m, 6H).
1-((R)-1-(4-(2-methoxyethoxy)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	67 isomer 2	(M+H+) m/z: calcd 526.27; found 526.2	1H NMR (400 MHz, CDCl3) δ 13.00 (s,1H), 7.75 (d, J = 8Hz,1H), 7.38 (d, J = 8.4Hz,1H), 7.32-7.30 (m,1H), 7.03-6.93 (m,2H), 5.92 (s,1H), 4.70-4.62 (m,2H), 3.99-3.97 (m,1H), .3.52-3.49 (m,2H), 3.44-3.42 (m,2H), 3.41 (s,3H), 3.30-3.29 (m,1H), 3.12-2.64 (m,3H), 2.41 (s,3H), 2.09-2.05 (m,6H), 1.79-1.76 (m,1H), 1.52-1.51 (m,3H), 1.02-1.00 (m,1H), 0.97-0.95 (m,3H), 0.72-0.69 (m,1H).
7-((R)-1-(4-(3-fluoroazetidin-1-yl)cyclohexyl)ethyl)-6-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide	68 single isomer	(M + H+) m/z: calcd: 527.25.; found 527.6	1H NMR (400MHz, CD3OD) δ 9.00 (s, 1H), 8.68 (s, 1H), 6.29 (s, 1H), 5.16 - 4.97 (m, 1H), 4.57 (s, 3H), 3.67 - 3.49 (m, 2H), 3.26 - 3.13 (m, 2H), 2.67 (br s, 3H), 2.53 (s, 3H), 2.29 (s, 3H), 2.17 - 2.03 (m, 2H), 1.92 (br d, J = 12.0 Hz, 1H), 1.70 - 1.59 (m, 4H), 1.35 - 0.97 (m, 3H), 0.95 - 0.70 (m, 3H)
(R)-5-chloro-1-(1-(1-cyclopropylpiperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-	69	(M+H+) m/z: calcd 528.21; found 528.2	1H NMR (400 MHz, CDCl3) δ 12.65 (br, 1H), 8.15-8.11(m, 2H), 7.36(s, 1H), 6.03 (s, 1H), 4.71-4.68 (m, 2H), 3.97 (s, 2H), 3.12-3.09

oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide			(m, 1H), 2.82-2.71 (m, 4H), 2.49 (s, 3H), 2.25-2.20 (m, 4H), 1.95-1.90 (m, 2H), 1.63-1.51 (m, 2H), 1.30-1.25 (m, 3H), 0.88-0.36 (m, 6H).
1-((R)-1-((R)-1-cyclopropyl-3,3-difluoropiperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	70	(M+H+) m/z: calcd 530.23; found 530.1.	1H NMR (400MHz, CD3OD) δ 8.25 - 8.20 (m, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.14 (dd, J = 4.6, 7.9 Hz, 1H), 6.32 (s, 1H), 4.65 (br s, 1H), 4.61 (s, 2H), 3.31 - 3.21 (m, 2H), 2.87 - 2.78 (m, 1H), 2.66 (s, 3H), 2.60 - 2.45 (m, 4H), 2.33 (s, 3H), 2.07 (br t, J = 12.3 Hz, 1H), 1.84 (br d, J = 4.8 Hz, 3H), 1.70 (br s, 1H), 1.32 - 1.20 (m, 1H), 0.88 (br s, 1H), 0.55 - 0.35 (m, 4H)
1-((R)-1-((S)-1-cyclopropyl-3,3-difluoropiperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	70	(M+H+) m/z: calcd 530.23; found 530.2.	1H NMR (400MHz, CD3OD) δ 8.19 (d, J = 3.5 Hz, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.10 (dd, J = 4.9, 7.9 Hz, 1H), 6.32 (s, 1H), 4.86 - 4.83 (m, 1H), 4.62 (s, 2H), 3.21 - 3.14 (m, 1H), 3.04 (dt, J = 4.4, 11.5 Hz, 1H), 2.71 (s, 3H), 2.56 (s, 3H), 2.44 - 2.25 (m, 5H), 2.17 (br d, J = 13.9 Hz, 1H), 1.75 - 1.65 (m, 4H), 1.63 - 1.52 (m, 1H), 1.45 - 1.29 (m, 1H), 0.54 - 0.44 (m, 3H), 0.40 - 0.32 (m, 1H).
2-methyl-1-((R)-1-((2S,4S)-1-methyl-2-(trifluoromethyl)piperidin-4-yl)ethyl)-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	71	(M+H+) calcd.535.1; found 535.2	1H NMR (400MHz, CD3OD) δ 7.75 (br d, J = 7.8 Hz, 1H), 7.60 (br d, J = 7.5 Hz, 1H), 7.19 - 7.06 (m, 2H), 6.32 (s, 1H), 4.63 (s, 2H), 4.26 (br dd, J = 7.3, 10.3 Hz, 1H), 2.82 (br d, J = 7.8 Hz, 1H), 2.77 (br s, 1H), 2.63 (s, 3H), 2.55 (s, 3H), 2.46 (br d, J = 11.0 Hz, 1H), 2.37 (s, 3H), 2.32 (s, 3H), 2.10 (br t, J = 12.2 Hz, 1H), 1.66 (br d, J = 6.8 Hz, 3H), 1.53 - 1.28 (m, 1H), 1.22 - 1.16 (m, 1H), 1.13 (br s, 1H), 0.84 (br d, J = 13.6 Hz, 1H)
2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((R)-1-(4-(2-oxopyrrolidin-1-yl)cyclohexyl)ethyl)-1H-indole-3-carboxamide	72 single isomer	(M+H+) m/z: calcd: 535.27; found 535.1	1H NMR (400 MHz, CD3OD) δ 7.73 (br d, J = 7.6 Hz, 1H), 7.54 (br d, J = 8.0 Hz, 1H), 7.14 - 7.01 (m, 2H), 6.27 - 6.20 (m, 1H), 4.58 (d, J = 2.0 Hz, 2H), 4.16 - 4.08 (m, 1H), 3.81 - 3.70 (m, 1H), 3.36 - 3.31 (m, 1H), 3.28 - 3.20 (m, 1H), 2.58 (s, 3H), 2.49 (s, 3H), 2.33 - 2.27 (m, 2H), 2.26 (s, 3H), 2.23 -

			2.09 (m, 2H), 2.02 - 1.83 (m, 3H), 1.73 (br d, J = 12.0 Hz, 1H), 1.58 (br d, J = 7.2 Hz, 3H), 1.39 (br d, J = 12 Hz, 1H), 1.28 - 1.12 (m, 2H), 0.94 (br s, 2H)
(R)-6-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-7-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide	73	(M+H+) m/z: calcd 537.22; found 537.1	1H NMR (400MHz, CD3OD) δ 9.02 (s, 1H), 8.71 (s, 1H), 6.31 (s, 1H), 4.59 (s, 2H), 3.08 (br d, J = 11.6 Hz, 1H), 3.02 - 2.94 (m, 2H), 2.86 - 2.71 (m, 2H), 2.69 (s, 3H), 2.54 (s, 3H), 2.43 - 2.34 (m, 1H), 2.31 (s, 3H), 2.21 - 2.07 (m, 1H), 1.99 (br d, J = 12.4 Hz, 1H), 1.68 (br d, J = 6.8 Hz, 3H), 1.44 (dq, J = 4.1, 12.4 Hz, 1H), 1.36 - 1.25 (m, 2H), 1.22 - 1.12 (m, 1H), 0.84 (br d, J = 12.4 Hz, 1H).
2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((R)-1-(4-(2-oxooxazolidin-3-yl)cyclohexyl)ethyl)-1H-indole-3-carboxamide	74 single isomer	(M + H+) m/z: calcd: 537.25; found 537.2	1H NMR (400MHz, CD3OD) δ 7.72 (br d, J = 7.6 Hz, 1H), 7.60 - 7.48 (m, 1H), 7.15 - 6.99 (m, 2H), 6.26 (s, 1H), 4.58 (br d, J = 1.6 Hz, 2H), 4.35 - 4.08 (m, 3H), 3.59 - 3.38 (m, 3H), 2.70 - 2.55 (m, 3H), 2.50 (s, 3H), 2.27 (s, 3H), 2.24 - 2.08 (m, 2H), 1.89 - 1.79 (m, 1H), 1.59 (br d, J = 7.2 Hz, 3H), 1.56 - 1.44 (m, 2H), 1.30 - 1.12 (m, 2H), 1.02 - 0.88 (m, 2H)
2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((R)-1-(4-morpholinocyclohexyl)ethyl)-1H-indole-3-carboxamide	75 isomer 1	(M+H+) m/z: calcd 537.28; found 537.1.	1H NMR (400 MHz, CDCl3) δ 12.56 (brs, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.34 - 7.31 (m, 1H), 7.10 - 7.02 (m, 2H), 6.01 (s, 1H), 4.79 - 4.68 (m, 2H), 4.08 - 4.06 (m, 1H), 3.70 (t, J = 4.0 Hz, 4H), 2.84 - 2.71 (m, 3H), 2.53 - 2.49 (m, 7H), 2.21 - 2.03 (m, 7H), 1.59 (d, J = 7.2 Hz, 3H), 1.32 - 1.26 (m, 2H), 1.11 - 0.77 (m, 4H).
2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((R)-1-(4-morpholinocyclohexyl)ethyl)-1H-indole-3-carboxamide	75 isomer 2	(M+H+) m/z: calcd 537.28; found 537.1.	1H NMR (400 MHz, CDCl3) δ 12.39 (brs, 1H), 7.83 (d, J = 7.2 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.32 - 7.29 (m, 1H), 7.10 - 7.04 (m, 2H), 6.00 (s, 1H), 4.80 - 4.65 (m, 2H), 4.29 - 4.25 (m, 1H), 3.72 (s, 4H), 2.84 - 2.76 (m, 3H), 2.48 (s, 3H), 2.42 (s, 4H), 2.22 - 1.87 (m, 6H), 1.56 (d, J = 8.4 Hz, 3H), 1.29 - 0.82 (m, 6H).
1-((R)-1-(4-(3-methoxyazetidin-1-	76 isomer 1	(M+H+) m/z: calcd	1H NMR (400MHz, CD3OD) δ 8.19 (br d, J = 4.0 Hz, 1H), 8.10

yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide		538.28; found 538.1	(br d, J = 7.6 Hz, 1H), 7.16 - 7.09 (m, 1H), 6.32 (s, 1H), 4.89 - 4.81 (m, 1H), 4.62 (s, 3H), 4.00 (m, 1H), 3.63 - 3.49 (m, 2H), 3.25 (s, 3H), 2.95 (m, 2H), 2.67 (br s, 3H), 2.56 (s, 3H), 2.32 (s, 3H), 2.14 (br d, J = 12.8 Hz, 1H), 2.05 (br d, J = 3.2 Hz, 1H), 1.99 - 1.89 (m, 1H), 1.75 - 1.59 (m, 3H), 1.75 - 1.59 (m, 1H), 1.15 - 0.70 (m, 5H).
1-((R)-1-(4-(3-methoxyazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	76 isomer 2	(M+H+) m/z: calcd 538.28; found 538.5.	1H NMR (400MHz, CD3OD) δ 8.19 (br d, J = 4.3 Hz, 1H), 8.09 (dd, J = 1.4, 7.9 Hz, 1H), 7.11 (dd, J = 4.8, 8.0 Hz, 1H), 6.32 (s, 1H), 4.89 - 4.87 (m, 1H), 4.62-4.28 (s, 3H), 4.06 - 3.98 (m, 1H), 3.64 - 3.52 (m, 2H), 3.26 (s, 3H), 2.88 (br s, 2H), 2.71 (br s, 3H), 2.56 (s, 3H), 2.33 (s, 3H), 2.26 (br s, 1H), 1.81 - 1.53 (m, 7H), 1.38 (br s, 1H), 1.33 - 1.21 (m, 1H), 1.17 - 1.03 (m, 1H), 0.80 (br s, 1H).
7-((R)-1-(4-(3-methoxyazetidin-1-yl)cyclohexyl)ethyl)-6-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide	77 single isomer	(M+H+) m/z: calcd 539.27; found 539.1.	1H NMR (400MHz, CD3OD) δ 9.04 (s, 1H), 8.72 (s, 1H), 6.33 (s, 1H), 4.61 (s, 2H), 4.08 (quin, J = 5.6 Hz, 1H), 3.86 - 3.76 (m, 2H), 3.28 (s, 3H), 2.70 (br s, 3H), 2.60 - 2.56 (m, 3H), 2.43 - 2.28 (m, 5H), 2.24 - 2.14 (m, 1H), 2.08 - 2.00 (m, 1H), 1.77 - 1.66 (m, 4H), 1.37 - 1.29 (m, 3H), 1.23 - 1.11 (m, 2H), 1.03 - 0.87 (m, 3H).
1-((R)-1-(5-(3,3-dimethylazetidin-1-yl)-1,3-dioxan-2-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	78 isomer 1	(M+H+) m/z: calcd 539.26; found 539.1	1H NMR (400MHz, CD3OD) δ 7.69 (br d, J = 7.8 Hz, 1H), 7.58 (br s, 1H), 7.15 - 7.00 (m, 2H), 6.29 (s, 1H), 5.06 - 5.00 (m, 1H), 4.60 (s, 3H), 4.10 (br d, J = 8.3 Hz, 1H), 3.90 (br d, J = 9.0 Hz, 1H), 3.38 (br t, J = 10.7 Hz, 1H), 3.12 (br s, 1H), 3.01 (s, 4H), 2.65 - 2.55 (m, 4H), 2.53 (s, 3H), 2.30 (s, 3H), 1.63 (br d, J = 7.0 Hz, 3H), 1.18 (s, 6H)
1-((R)-1-(5-(3,3-dimethylazetidin-1-yl)-1,3-dioxan-2-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-	78 isomer 2	(M+H+) m/z: calcd 539.26; found 539.1	1H NMR (400MHz, CD3OD) δ 7.74 - 7.51 (m, 2H), 7.15 - 7.00 (m, 2H), 6.30 (s, 1H), 5.34 (br s, 1H), 4.61 (br s, 3H), 4.10 (br d, J = 8.3 Hz, 1H), 3.90 (br d, J = 8.3 Hz, 1H), 3.42 - 3.34 (m, 1H), 3.13 (br s, 1H), 3.02 (s, 4H), 2.61 (br s,

carboxamide			4H), 2.54 (s, 3H), 2.31 (s, 3H), 1.63 (br d, J = 7.0 Hz, 3H), 1.18 (s, 6H)
1-((R)-1-(4-((R)-3-fluoropyrrolidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	79 isomer 1	(M+H+) m/z: calcd 539.28; found 539.2	1H NMR (400 MHz, CDCl3) δ 12.63(br, 1H), 7.81(d, J = 7.6Hz, 1H), 7.44(d, J = 8.0Hz, 1H), 7.35-7.34(m, 1H), 7.09-7.01(m, 2H), 5.99 (s, 1H), 5.21-5.05 (m, 1H), 4.77-4.70(m, 2H), 4.21-4.02(m, 1H), 2.97-2.71 (m, 6H), 2.48-2.32 (m, 4H), 2.10-1.99(m, 9H), 1.58(d, J = 6.7Hz, 3H), 1.30-0.78(m, 4H
1-((R)-1-(4-((R)-3-fluoropyrrolidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	79 isomer 2	(M+H+) m/z: calcd 539.28; found 539.2	1H NMR (400 MHz, CDCl3) δ 12.70 (br, 1H), 7.82(d, J =8.0Hz, 1H), 7.46(d, J = 8.0Hz, 1H), 1.16(s, 1H), 7.08-7.01(m, 2H), 5.99(s, 1H), 5.22-5.08(m, 1H), 4.79-4.65(m, 2H), 4.25-4.21(m, 1H), 2.84-2.47(m, 6H), 2.47(s, 3H), 2.20-2.01(m, 9H), 1.86-1.84(m, 1H), 1.56(d, J = 6.8Hz, 3H), 1.25-0.80(m, 4H).
1-((R)-1-(4-(3-fluoro-3-methylazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	80 single isomer	(M+H+) calcd. 540.2; found 540.1.	1H NMR (400MHz, CD3OD) δ 8.19 (d, J = 3.8 Hz, 1H), 8.10 (br d, J = 7.5 Hz, 1H), 7.12 (t, J = 6.0 Hz, 1H), 6.32 (s, 1H), 4.62 (s, 2H), 4.09 (br s, 1H), 3.34 (br s, 2H), 3.32 - 3.22 (m, 3H), 2.68 (br s, 3H), 2.56 (s, 3H), 2.32 (s, 3H), 2.19 - 2.03 (m, 2H), 1.94 (br d, J = 9.8 Hz, 1H), 1.75 - 1.59 (m, 4H), 1.57 - 1.49 (d, J = 20 Hz ,3H), 1.23 - 1.06 (m, 2H), 0.96 (br s, 1H), 0.91 - 0.68 (m, 2H).
(R)-1-(1-(1-(3,3-difluorocyclobutyl)piperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	81	(M + H+) m/z: calcd 543.26, found 543.3	1H NMR (400MHz ,DMSO-d6) δ = 11.64 (br. s., 1 H), 7.72 (d, J= 7.3 Hz, 1 H), 7.67 - 7.45 (m, 2 H), 7.17 - 6.93 (m, 2 H), 6.11 (s, 1 H), 4.37 (d, J=3.4 Hz, 2 H), 4.13 (br. s., 1 H), 2.99 (d, J = 5.9 Hz, 2 H), 2.85 (br. s., 1 H), 2.75 - 2.51 (m, 4 H), 2.46 (s, 3 H), 2.39 - 2.08 (m, 6 H), 1.89 (br. s., 2H), 1.83 - 1.61 (m, 2 H), 1.59 - 1.44 (m, 4 H), 1.43 - 1.19 (m, 2 H), 1.07 - 0.60 (m, 4 H)
7-fluoro-1-((R)-1-(4-(3-fluoroazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-	82 single isomer	(M+H+) m/z: calcd 543.25; found 543.1.	1H NMR (400MHz, MeOD) δ 12.95 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.32 - 7.31 (m, 1H), 6.87 - 6.73 (m, 2H), 5.93 (s, 1H), 5.08 - 4.92 (m, 1H), 4.65 - 4.63 (m, 2H),

dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide			4.00 - 3.97 (m, 1H), 3.58 - 3.52 (m, 2H), 2.99 - 2.96 (m, 2H), 2.71 - 2.63 (m, 3H), 2.41(s, 3H), 2.07(s, 3H), 1.95 - 1.79 (m, 4H), 1.53 - 1.42 (m, 3H), 0.98 - 0.95 (m, 3H), 0.70 - 0.68 (m, 2H).
(R)-6-fluoro-1-(1-(4-(3-fluoroazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	83 single isomer	(M + H+) m/z: calcd: 543.26; found 543.3.	1H NMR (500MHz, CDCl3) δ 12.49 - 12.31 (m, 1 H), 7.75 (dd, J = 5.4, 8.8 Hz, 1 H), 7.31 (br. s., 1 H), 7.12 (d, J = 9.8 Hz, 1 H), 6.81 (dt, J = 2.2, 8.9 Hz, 1 H), 6.03 (s, 1 H), 5.24 - 4.97 (m, 1 H), 4.79 - 4.48 (m, 2 H), 4.03 (br. s., 1 H), 3.80 - 3.64 (m, 1 H), 3.15 (br. s., 1 H), 2.68 (s, 2 H), 2.49 (s, 2 H), 2.23 (s, 3 H), 2.08 (d, J = 10.3 Hz, 2 H), 1.92 (d, J = 11.7 Hz, 1 H), 1.65 - 1.51 (m, 3 H), 1.32 - 1.20 (m, 2 H), 1.16 - 1.01 (m, 2 H), 0.93 - 0.70 (m, 2 H).
5-fluoro-1-((R)-1-(4-(3-fluoroazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	84 isomer 1	(M+H+) m/z: calcd 518.22; found 518.4.	1H NMR (400MHz, MeOD) δ 8.15 (s, 1H), 7.84 (dd, J = 9.2 Hz, 2.4 Hz, 1H), 6.94 (s, 1H), 5.49 - 5.30 (m, 1H), 4.65 - 4.23 (m,7H), 3.27 - 3.15 (m, 1H), 2.94 - 2.71 (m, 8H), 2.52 (s, 3H), 2.28 - 2.16 (m, 2H), 1.90 - 1.87 (m, 1H), 1.70 (d, J = 5.6 Hz, 3H), 1.32 - 1.24 (m, 2H), 1.06 (s, 3H).
5-fluoro-1-((R)-1-(4-(3-fluoroazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	84 isomer 2	(M+H+) m/z: calcd 518.22; found 518.4.	1H NMR (400MHz, MeOD) δ 8.14 (s, 1H), 7.84 (dd, J = 9.2 Hz, 2.4 Hz, 1H), 6.85 (s, 1H), 5.44 - 5.30 (m, 1H), 4.64 - 4.23 (m,7H), 3.26 - 3.15 (m, 1H), 2.92 - 2.66 (m, 8H), 2.59 - 2.49 (m, 3H), 2.27 - 2.25 (m, 2H), 1.90 - 1.84 (m, 1H), 1.69 (d, J = 5.6 Hz, 3H), 1.34 - 1.24 (m, 2H), 1.04 - 1.01 (s, 3H).
1-((R)-1-(5-(3,3-difluoroazetidin-1-yl)-1,3-dioxan-2-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	85 isomer 1	(M+H+) m/z: calcd 547.21; found 547.0	1H NMR (400MHz, CDCl3) δ 7.79 (d, J = 7.2 Hz, 1H), 7.47 (brs, 1H), 7.22 (brs, 1H), 7.10 - 7.01 (m, 2H), 6.04 (s, 1H), 4.87 (s, 1H), 4.69 (s, 2H), 4.53 (s, 1H), 4.09 - 4.06 (m, 1H), 3.87 (d, J = 9.2 Hz, 1H), 3.57 (t, J = 11.2 Hz, 4H), 3.40 (t, J = 10.4 Hz, 1H), 3.19 (t, J = 10.4 Hz, 1H), 2.71 - 2.62 (m, 5H), 2.48 (s, 3H), 2.25 (s, 3H), 1.61 (d, J = 7.2 Hz, 3H).

1-((R)-1-(5-(3,3-difluoroazetidin-1-yl)-1,3-dioxan-2-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	85 isomer 2	(M+H+) m/z: calcd 547.21; found 547.0	1H NMR (400MHz, CDCl3) δ 7.81 (d, J = 7.6 Hz, 1H), 7.47 (brs, 1H), 7.22 (brs, 1H), 7.10 - 7.02 (m, 2H), 6.02 (s, 1H), 4.89 - 4.86 (m, 1H), 4.69 (s, 2H), 4.53 (s, 1H), 4.09 - 4.06 (m, 1H), 3.87 (d, J = 9.3 Hz, 1H), 3.57 (t, J = 11.2 Hz, 4H), 3.40 (t, J = 10.4 Hz, 1H), 3.19 (t, J = 10.4 Hz, 1H), 2.72 - 2.63 (m, 5H), 2.48 (s, 3H), 2.23 (s, 3H), 1.61 (d, J = 7.2 Hz, 3H).
(R)-N-((4-(ethylthio)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide	86	(M + H+) m/z: calcd 549.24; found 549.1.	1H NMR (400MHz, DMSO) δ 11.67 (s, 1H), 7.75 – 7.74(d, J = 4.0 Hz, 1H), 7.64 - 7.59 (m, 2H), 7.09 - 7.02 (m, 2H), 6.15 (s, 1H), 4.39 (s, 2H), 4.18 - 4.14 (m, 1H), 3.10 – 2.98 (m, 5H), 2.69 (s, 2H), 2.59 (s, 3H), 2.35 (m,1H), 2.18 (s, 4H), 2.02 (m, 1H), 1.99 (m, 1H), 1.54 - 1.53 (m, 3H), 1.41 - 1.38 (m,1H), 1.29 – 1.26 (m, 4H), 1.06 (m, 1H), 0.68 - 0.65 (m, 1H)
(R)-2,4-dimethyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide	87	(M+H+) m/z: calcd 549.2; found 549.1.	1H NMR (400MHz, CDCCl3) δ 12.59 - 12.51 (m, 1H), 7.23 (s, 1H), 7.00 - 6.96 (m, 1H), 6.82 (d, J = 6.8Hz, 1H), 6.68 - 6.67 (m, 1H), 5.98 (s, 1H), 4.73 - 4.63 (m, 1H), 3.99 - 3.97 (m, 1H), 3.06 (d, J = 43.6Hz, 1H), 2.92 - 2.87 (m, 2H), 2.74 (d, J = 12Hz, 1H), 2.51 - 2.47 (m, 6H), 2.41 - 2.36 (m, 3H), 2.19 - 2.11 (m, 4H), 1.96 (d, J = 14.8Hz, 1H), 1.44 - 1.42 (m, 1H) 1.30 - 1.26 (m, 3H) 1.25 - 1.01 (m, 1H) 1.00 - 1.00 (m, 1H).0.88 - 0.86 (m, 1H).
(R)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(1-(3,3,3-trifluoropropyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide	88	(M + H+) m/z: calcd 549.67, found 549.3.	1H NMR (400MHz ,DMSO-d6) δ = 11.65 (br s, 1 H), 7.74 (br d, J = 7.3 Hz, 1 H), 7.64 (br t, J = 4.6 Hz, 1 H), 7.59 (br d, J = 7.8 Hz, 1 H), 7.14 - 6.95 (m, 2 H), 6.12 (s, 1 H), 4.43 - 4.37 (m, 2 H), 4.33 (t, J = 5.1 Hz, 1 H), 4.21 - 4.09 (m, 1 H), 2.95 (br d, J = 10.8 Hz, 1 H), 2.66 (br d, J = 11.2 Hz, 1 H), 2.54 (s, 3 H), 2.48 (s, 3 H), 2.46 - 2.39 (m, 3 H), 2.23 - 2.15 (m, 4 H), 1.98 - 1.88 (m, 2 H), 1.63 (br t, J = 10.8 Hz, 1 H), 1.54 (br d, J = 6.8 Hz, 3

			H), 1.38 - 1.27 (m, 1 H), 0.68 (br d, J = 13.2 Hz, 1 H)
6-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-7-((R)-1-(4-((2,2,2-trifluoroethyl)amino)cyclohexyl)ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide	89 single isomer	(M+H+) m/z: calcd 551.23; found 551.1.	1H NMR (400MHz, CD3OD) δ 8.92 (s, 1H), 8.61 (s, 1H), 6.21 (s, 1H), 4.50 (s, 3H), 3.14 – 3.07 (q, J = 10.0 Hz, 2H), 2.59 (s, 3H), 2.45 (s, 3H), 2.37 (s, 1H), 2.22 (s, 3H), 2.04 – 1.94 (m, 3H), 1.69 – 1.57 (m, 4H), 1.10 – 1.05 (m, 2H), 0.86 – 0.79 (m, 3H).
1-((R)-1-(4-(3-methoxy-3-methylazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	90 isomer 1	(M+H+) m/z: calcd 551.30; found 551.2.	1H NMR (400 MHz, CDCl3) δ 13.09 (br, 1H), 7.81(d, J = 8.0 Hz, 1H), 7.43-7.38 (m, 2H), 7.08-6.99 (m, 2H), 5.99(s, 1H),4.72 (s, 2H), 4.06-4.01 (m, 1H), 3.18-3.11 (m, 5H), 3.01-2.96 (m, 2H), 2.71-2.47 (m, 3H), 2.17-2.15 (m, 6H), 1.90-1.87 (m, 2H), 1.57 (d, J = 6.8Hz, 3H), 1.42 (s, 3H), 1.07-1.04 (m, 3H), 0.77-0.75 (m, 2H)
1-((R)-1-(4-(3-methoxy-3-methylazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	90 isomer 2	(M+H+) m/z: calcd 551.30; found 276.0.	1H NMR (400 MHz, CDCl3) δ 12.50 (br, 1H), 7.82 (d, J = 7.2Hz, 1H), 7.45 (d, J = 7.6Hz, 1H), 7.29-7.26 (m ,1H), 7.08-7.01 (m, 2H),5.99 (s, 1H), 4.79-4.66 (m, 2H), 4.20 (s, 1H), 3.18 (s, 3H), 3.11-3.04 (m, 2H), 2.92-2.86 (m, 2H), 2.74 (s, 3H), 2.47 (m, 3H), 2.20 (s, 5H), 1.57-1.55 (m, 4H), 1.45-1.36 (m, 6H), 1.13-0.72 (m, 4H).
1-((R)-1-(4-(3-ethoxyazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	91 isomer 1	(M+H+) m/z: calcd 552.29; found 552.3	1H NMR (400 MHz, CD3OD) δ 8.17 (d, J = 3.5 Hz, 1H), 8.08 (br d, J = 8.0 Hz, 1H), 7.10 (br dd, J = 4.5, 7.5 Hz, 1H), 6.30 (s, 1H), 4.59 (s, 2H), 4.08 - 4.02 (m, 1H), 3.59 - 3.50 (m, 2H), 3.41 (q, J = 7.0 Hz, 2H), 2.95-2.87 (m, 2H), 2.71 - 2.65 (m, 3H), 2.53 (s, 3H), 2.30 (s, 3H), 2.21 - 2.06 (m, 1H), 2.06 - 1.85 (m, 2H), 1.74 - 1.51 (m, 4H), 1.18 - 1.13 (m, 3H), 1.13 - 1.08 (m, 3H), 1.07 - 0.99 (m, 1H), 0.97 - 0.66 (m, 3H)
1-((R)-1-(4-(3-ethoxyazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-	91 isomer 2	(M+H+) m/z: calcd 552.29; found 552.2	1H NMR (400 MHz, CD3OD) δ 8.17 (br d, J = 4.5 Hz, 1H), 8.07 (dd, J = 1.5, 8.0 Hz, 1H), 7.09 (dd, J = 4.8, 7.8 Hz, 1H), 6.30 (s, 1H), 4.60 (s, 2H), 4.07 (br d, J = 6.0 Hz,

dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide			1H), 3.65 - 3.58 (m, 1H), 3.55 (br s, 1H), 3.43 (q, J = 7.0 Hz, 2H), 2.87 (br s, 2H), 2.69 (br s, 3H), 2.54 (s, 3H), 2.30 (s, 3H), 2.24 – 2.19 (m, 1H), 2.07 - 1.95 (m, 1H), 1.71 (br s, 1H), 1.67 - 1.58 (m, 4H), 1.55 - 1.48 (m, 1H), 1.34 - 1.27 (m, 3H), 1.16 (t, J = 7.0 Hz, 3H), 1.06 (br s, 1H), 0.90 (br t, J = 7.0 Hz, 1H), 0.77 (br s, 1H)
(R)-6-fluoro-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide	92	(M + H+) m/z: calcd: 553.23; found 552.9.	1H NMR (400MHz, CDCl3) δ 12.91 (br. s., 1 H), 7.81 - 7.71 (m, 1 H), 7.12 (d, J = 9.8 Hz, 1 H), 6.80 (t, J = 8.3 Hz, 1 H), 6.02 (s, 1 H), 4.80 - 4.61 (m, 2 H), 4.08 (dd, J = 7.3, 10.3 Hz, 1 H), 3.08 (d, J = 10.8 Hz, 1 H), 2.93 (q, J = 9.8 Hz, 2 H), 2.77 (d, J = 11.7 Hz, 1 H), 2.68 (s, 3 H), 2.49 (s, 3 H), 2.38 (t, J = 11.0 Hz, 1 H), 2.20 (s, 3 H), 2.16 - 2.08 (m, 2 H), 1.95 (d, J = 12.2 Hz, 1 H), 1.74 (br. s., 1 H), 1.57 (d, J = 7.3 Hz, 3 H), 1.49 - 1.37 (m, 1 H), 1.20 - 1.07 (m, 1 H), 0.92 (d, J = 12.7 Hz, 1 H).
N-((4-((fluoromethyl)thio)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((R)-1-(4-(3-methoxyazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxamide	93 single isomer	(M + H+) m/z: calcd 555.73, found 555.3.	1H NMR (400 MHz, DMSO-d6) δ 11.81 (s, 1H), 7.73 (d, J = 6.8 Hz, 1H), 7.63 - 7.55 (m, 2H), 7.10 - 7.00 (m, 2H), 6.25 (s, 1H), 6.13 - 5.97 (m, 1H), 4.40 (dd, J = 2.2, 4.6 Hz, 2H), 4.13 - 4.04 (m, 1H), 3.90 - 3.82 (m, 1H), 3.49 - 3.36 (m, 2H), 3.11 (s, 3H), 2.78 - 2.64 (m, 2H), 2.57 (s, 3H), 2.20 (s, 3H), 2.16 - 2.06 (m, 1H), 2.04 - 1.95 (m, 1H), 1.92 - 1.75 (m, 2H), 1.53 (d, J = 6.8 Hz, 3H), 1.51 - 1.47 (m, 1H), 1.18 - 1.02 (m, 2H), 1.00 - 0.87 (m, 2H), 0.83 - 0.72 (m, 2H), 0.65 - 0.51 (m, 1H)
5-fluoro-1-((R)-1-(4-(3-methoxyazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	94 isomer 1	(M+H+) m/z: calcd 556.27; found 556.2.	1H NMR (400MHz, CDCl3) δ 12.09 - 12.01 (m, 1H), 7.99 (s, 1H), 7.81 (d, J = 9.2Hz, 1H), 7.45 - 7.22(m, 1H), 5.96 (s, 1H), 4.63 - 4.58 (m, 2H), 3.96 - 3.93 (m, 1H), 3.56 – 3.51 (m, 2H), 3.17 (s, 3H), 2.83 - 2.67 (m, 5H), 2.42 (s, 3H), 2.20 (s, 3H), 1.80 - 1.66 (m, 1H), 1.60 - 1.56 (m, 3H), 1.53 - 1.52 (m,

			4H), 1.18 - 1.49 (m, 1H), 0.91 - 0.70 (m, 5H).
5-fluoro-1-((R)-1-(4-(3-methoxyazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	94 isomer 2	(M+H+) m/z: calcd 556.27; found 556.2.	1H NMR (400MHz, CDCl3) δ 11.67 - 11.60 (m, 1H), 7.98 - 7.82 (m, 1H), 7.80 (d, J = 9.6Hz, 1H), 7.19 - 7.16(m, 1H), 5.96 (s, 1H), 4.66 - 4.61 (m, 2H), 4.01 - 3.97 (m, 2H), 3.95 - 3.20 (m, 2H), 3.18 (s, 3H), 2.89 - 2.69 (m, 6H), 2.42 (s, 3H), 2.21 (s, 3H), 1.96 - 1.58 (m, 4H), 1.42 - 1.07 (m, 4H), 0.81 - 0.65 (m, 2H).
1-((R)-1-(4-(3,3-difluoropyrrolidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	95 single isomer	(M+H+) calcd. 557; found 557.1	1H NMR (400MHz, CD3OD) δ 7.74 (br d, J = 7.3 Hz, 1H), 7.58 (br d, J = 8.3 Hz, 1H), 7.18 - 7.01 (m, 2H), 6.32 (s, 1H), 4.63 (s, 2H), 4.15 (m, 1H), 2.97 (br t, J = 13.4 Hz, 2H), 2.87 - 2.69 (m, 2H), 2.62 (s, 2H), 2.56 (s, 3H), 2.33 (s, 3H), 2.31 - 2.15 (m, 3H), 2.10 (br d, J = 10.3 Hz, 3H), 1.78 (br s, 1H), 1.64 (br d, J = 7.0 Hz, 3H), 1.37 - 1.10 (m, 3H), 1.10 - 0.82 (m, 3H).
1-((R)-1-(4-(3-(difluoromethyl)azetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	96 single isomer	(M+H+) m/z: calcd 558.26; found 558.1.	1H NMR (400MHz, CD3OD) δ 8.20 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.14 – 7.10 (m, 1H), 6.32 (s, 1H), 6.01 (t, J = 56.0 Hz, 1H), 4.62 (s, 3H), 3.42 – 3.37 (m, 2H), 3.20 – 3.15 (m, 3H), 2.91 – 2.82 (m, 1H), 2.68 (s, 3H), 2.56 (s, 3H), 2.33 (s, 3H), 2.16 – 1.92 (m, 4H), 1.68 – 1.61 (m, 4H), 1.16 – 1.09 (m, 1H), 0.99 – 0.85 (m, 3H).
(R)-4-cyano-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide	97	(M+H+) m/z: calcd 560.22; found 560.1.	1H NMR (400 MHz, DMSO-d6) δ 11.54 (d, 1H), 7.96 (d, J = 8.4Hz, 2H), 7.49 (d, J = 7.2Hz, 1H), 7.21-7.17 (m, 1H), 6.10 (s, 1H), 4.39-4.34 (m, 2H), 4.17-4.13 (m, 1H), 3.10-2.97 (m, 3H), 2.73-2.70(m, 1H), 2.46 (s, 3H), 2.43-2.34 (m, 4H), 2.17(s, 3H), 2.03-1.87 (m, 2H), 1.53 (d, J = 6.8Hz, 3H), 1.48-0.66 (m, 4H).
5-chloro-1-((R)-1-(4-(3-fluoroazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-	98 single isomer	(M+H+) m/z: calcd 560.2; found 560.3.	1HNMR (400MHz, CDCl3) δ 12.97 - 12.95 (m, 1H), 8.14 (d, J = 12.8Hz, 2H), 7.42 - 7.40 (m, 1H), 6.04 (s, 1H), 5.19 - 5.15 (m, 1H), 5.03 - 5.00 (m, 2H), 3.65- 3.59 (m, 2H), 3.07 - 3.06 (m, 2H), 2.76 (s, 3H), 2.50 (s, 3H), 2.25 (s, 3H),

pyrrolo[2,3-b]pyridine-3-carboxamide			2.07 - 1.86 (m, 4H), 1.62 - 1.55 (m, 4H), 1.06 - 0.96 (m, 3H), 0.78 - 0.76 (m, 2H).
N-((4-(cyclopropylthio)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((R)-1-(4-(3-methoxyazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-1H-indole-3-carboxamide	99 single isomer	(M + H+) m/z: calcd: 563.31; found 563.0.	1H NMR (400MHz, CDCl3) δ 12.88 (br. s., 1 H), 7.83 (d, J = 7.8 Hz, 1 H), 7.44 (d, J = 8.3 Hz, 1 H), 7.36 (br. s., 1 H), 7.12 - 7.00 (m, 2 H), 6.43 (s, 1 H), 4.64 (t, J = 5.4 Hz, 2 H), 4.12 - 3.93 (m, 2 H), 3.65 - 3.47 (m, 2 H), 3.24 (s, 3 H), 2.91 - 2.66 (m, 5 H), 2.18 (s, 3 H), 2.16 - 2.02 (m, 2 H), 1.92 (br. s., 2 H), 1.58 (s, 3 H), 1.20 - 0.97 (m, 5 H), 0.86 - 0.68 (m, 4 H).
1-((R)-1-(4-(3-cyclopropoxyazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	100 single isomer	(M+H+) m/z: calcd 563.30; found 563.1	1H NMR (400MHz, CD3OD) δ 7.62 (d, J = 8.0 Hz, 1H), 7.43 (s, d, J = 8.0 Hz, 1H), 7.00 – 6.93 (m, 2H), 6.17 (s, 1H), 4.50 (s, 2H), 4.08 – 3.99 (m, 2H), 3.49 – 3.40 (m, 2H), 3.15 – 3.13 (m, 1H), 2.86 – 2.79 (m, 2H), 2.49 (s, 3H), 2.42 (s, 3H), 2.18 (s, 3H), 2.11 – 1.79 (m, 4H), 1.49 (d, J = 8.0 Hz, 4H), 1.06 – 0.58 (m, 5H), 0.39 – 0.32 (m, 4H).
(R)-4-methoxy-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide	101	(M + H+) m/z: calcd 565.24: found 565.1.	1HNMR (400MHz, CDCl3) δ 8.33-8.24(m, 1H), 7.11-6.94(m, 2H), 6.53(d, J=8.0, 1H), 5.98(s, 1H), 4.74-4.64(m, 2H), 4.18-4.13(m, 1H), 3.52(s, 3H), 3.07(d, J=8.0, 1H), 3.09-2.91(m, 3H), 2.88-2.74(m, 4H), 2.44(s, 3H), 2.36(m, 1H), 2.25-2.20(m, 4H), 2.09(m, 1H), 1.96-1.93(m, 1H), 1.58-1.56(m, 3H), 1.42(m, 1H), 1.11-1.10(m, 1H), 0.93-0.88(m, 1H).
7-((R)-1-(4-(3-cyclopropoxyazetidin-1-yl)cyclohexyl)ethyl)-6-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide	102 isomer 1	(M+H+) m/z: calcd 565.25; found 565.3.	1H NMR (400 MHz, CD3OD) δ 9.01 (s, 1H), 8.70 (s, 1H), 6.30 (s, 1H), 4.80 - 4.87 (m, 1H), 4.59 (s, 2H), 4.18 (quin, J = 6.0 Hz, 1H), 3.50 - 3.64 (m, 2H), 3.23-3.36 (m, 2H), 2.94 (dt, J = 14.0, 7.2 Hz, 2H), 2.68 (br s, 3H), 2.54 (s, 3H), 2.31 (s, 3H), 2.11 (br d, J = 12.6 Hz, 1H), 2.03 (br t, J = 10. 4 Hz, 1H), 1.93 (br d, J = 12.0 Hz, 1H), 1.58 - 1.73 (m, 4H), 0.98 - 1.20 (m, 2H), 0.84 - 0.97 (m, 2H), 0.76

			(br d, J = 11.4 Hz, 1H), 0.47 - 0.53 (m, 2H), 0.39 - 0.47 (m, 2H).
7-((R)-1-(4-(3-cyclopropoxyazetidin-1-yl)cyclohexyl)ethyl)-6-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide	102 isomer 2	(M+H+) m/z: calcd 565.25; found 565.1.	1H NMR (400 MHz, CD3OD) δ 9.01 (s, 1H), 8.69 (s, 1H), 6.31 (s, 1H), 4.89 (br d, J = 2.4 Hz, 1H), 4.59 (s, 2H), 4.21 (quin, J = 6.0 Hz, 1H), 3.53 - 3.65 (m, 2H), 3.23 - 3.30 (m, 2H), 2.88 (dt, J = 17.2, 6.8 Hz, 2H), 2.72 (s, 3H), 2.54 (s, 3H), 2.31 (s, 3H), 2.25 (br s, 1H), 1.71 (br s, 1H), 1.65 (br d, J = 6.4 Hz, 3H), 1.48 - 1.63 (m, 3H), 1.33 - 1.45 (m, 1H), 1.19 - 1.30 (m, 1H), 1.09 (br d, J = 10.6 Hz, 1H), 0.77 (br s, 1H), 0.49 - 0.55 (m, 2H), 0.39 - 0.47 (m, 2H).
(R)-4-chloro-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide	103	(M+H+) m/z: calcd 569.2; found 569.1.	1H NMR (400MHz, CDCCl3) δ 12.41 - 12.38 (m, 1H), 7.32 (d, J = 8.4Hz, 1H), 7.03 - 6.92 (m, 2H), 5.94 (s, 1H), 4.68 (s, 1H), 4.02 - 3.98 (m, 1H), 3.09 (d, J = 10.8Hz, 1H), 2.95 - 2.88 (m, 2H), 2.78 (d, J = 11.6Hz, 1H), 2.46 - 2.44 (m, 6H), 2.36 - 2.20 (m, 1H), 2.11 - 2.07 (m, 5H), 1.96 (d, J = 12.4Hz, 1H), 1.63 - 1.57 (m, 3H), 1.43 - 1.30 (m, 1H), 1.11 - 1.10 (m, 1H) 0.96 - 0.90 (m, 1H).
1-((R)-1-(4-((3R,4R)-3-fluoro-4-methoxypyrrolidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	104 isomer 1	(M+H+) m/z: calcd 570.28; found 570.4.	1H NMR (400MHz, CD3OD) δ 8.20 (d, J = 3.8 Hz, 1H), 8.10 (br d, J = 8.0 Hz, 1H), 7.12 (br dd, J = 5.1, 7.4 Hz, 1H), 6.32 (s, 1H), 5.00 (br s, 1H), 4.62 (s, 2H), 4.10 (br s, 1H), 3.98 - 3.86 (m, 1H), 3.38 (d, J = 3.0 Hz, 3H), 3.26 - 3.14 (m, 1H), 3.07 - 2.92 (m, 1H), 2.86 - 2.63 (m, 4H), 2.56 (s, 3H), 2.42 - 2.35 (m, 1H), 2.33 (s, 3H), 2.20 - 2.02 (m, 3H), 1.84 - 1.60 (m, 4H), 1.38 - 1.13 (m, 3H), 1.06 - 0.83 (m, 3H).
1-((R)-1-(4-((3R,4R)-3-fluoro-4-methoxypyrrolidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	104 isomer 2	(M+H+) m/z: calcd 570.28; found 570.3.	1H NMR (400MHz, CD3OD) δ 8.19 (br s, 1H), 8.10 (br d, J = 7.8 Hz, 1H), 7.12 (br d, J = 7.3 Hz, 1H), 6.32 (s, 1H), 5.02 (br s, 1H), 4.62 (s, 2H), 4.30 (br s, 1H), 3.95 (br d, J = 18.3 Hz, 1H), 3.40 (br d, J = 2.8 Hz, 3H), 3.24 - 3.11 (m, 1H), 3.01 - 2.91 (m, 1H), 2.72 (br s, 4H), 2.56 (s, 3H), 2.33 (s, 4H), 2.17 (br s, 1H), 1.90 - 1.60 (m,

			8H), 1.33 (br d, J = 10.5 Hz, 1H), 1.20 (br d, J = 6.3 Hz, 2H), 0.85 (br s, 1H)
(R)-N-((4-((difluoromethyl)thio)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide	105	(M + H+) m/z: calcd: 571.21; found 571.1.	1H NMR (400MHz, CD3OD) δ 7.77 (br d, J = 7.5 Hz, 1H), 7.62 - 7.55 (m, 1H), 7.42 (s, 1H), 7.28 (s, 1H), 7.17 - 7.08 (m, 2H), 6.41 (s, 1H), 4.63 (br s, 2H), 4.22 (br s, 1H), 3.16 - 3.08 (m, 1H), 3.06 - 2.96 (m, 2H), 2.80 (br d, J = 11.5 Hz, 1H), 2.63 (s, 3H), 2.46 - 2.38 (m, 1H), 2.32 (s, 4H), 2.15 - 1.98 (m, 2H), 1.64 (d, J = 6.8 Hz, 3H), 1.47 (br d, J = 10.0 Hz, 1H), 1.32 (br s, 1H), 1.16 (br s, 1H), 0.00 - 0.00 (m, 1H)
5-chloro-1-((R)-1-(4-(3-methoxyazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	106 isomer 1	(M + H+) m/z: calcd 572.24: found 572.2	1HNMR (400MHz, CDCl3) δ 8.07-8.04(d, J =10.4Hz, 2H), 7.31-7.29(m, 1H), 5.95(s, 1H), 4.61(s, 1H), 3.94-3.91(m, 1H), 3.52-3.47(m, 2H), 3.16(s, 3H), 2.80-2.68(m, 5H), 2.42(s, 3H), 2.18-2.15(m, 3H), 1.98-1.92(m, 1H), 1.82(m, 2H), 1.19-1.16(m, 5H), 1.01-0.99(m, 2H), 0.89-0.86(m, 1H), 0.73-0.69(m, 3H).
5-chloro-1-((R)-1-(4-(3-methoxyazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	106 isomer 2	(M + H+) m/z: calcd 572.24: found 572.2	1HNMR (400MHz, CDCl3) δ 8.07-8.04(d, J =12 Hz, 2H), 7.25(s, 1H), 5.95(s, 1H), 4.62(s, 2H), 3.93(s, 1H), 3.50-3.40(m, 1H), 3.00(s, 3H), 2.68(m, 5H), 2.42(s, 3H), 2.19-2.13(m, 4H), 1.95-1.92(m, 1H), 1.19(s, 9H), 1.08-1.01(m, 3H), 0.83-0.79(m, 1H), 0.63(m, 1H).
5-chloro-1-((R)-1-(4-((R)-3-fluoropyrrolidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	107 single isomer	(M + H+) m/z: calcd 574.23: found 574.2	1HNMR (400MHz, CDCl3) δ 8.14-8.10(m,, 2H), 7.43-7.40(m, 1H), 6.04(s, 1H), 5.20-5.07(m, 1H), 4.70(s, 2H), 3.95(s, 1H), 2.92-2.76(m, 6H), 2.50(s, 3H), 2.25(s, 3H), 2.10-2.01(m, 5H), 1.76-1.72(m, 2H), 1.62(s, 2H), 1.27(m, 2H), 1.07-0.96(m, 2H), 0.81(m, 1H).
7-((R)-1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-6-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-	108 single isomer	(M+H+) m/z: calcd 575.25; found 575.	1H NMR (400MHz, CD3OD) δ 9.02 (s, 1H), 8.71 (s, 1H), 6.59 - 6.22 (m, 2H), 4.76 (br d, J = 6.0 Hz, 1H), 4.60 (s, 2H), 3.77 - 3.76 (m, 1H), 3.74 (br d, J = 7.0 Hz, 1H), 3.26 (br d, J = 13.6 Hz, 2H),

yl)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide			3.14 (s, 1H), 2.69 (br s, 3H), 2.55 (s, 3H), 2.31 (s, 3H), 2.13 (br s, 1H), 1.99 (br s, 1H), 1.68 (br d, J = 6.5 Hz, 4H), 1.38 (d, J = 7.0 Hz, 3H), 1.19 - 1.08 (m, 2H), 0.96 (br s, 2H)
(R)-N-((4-(cyclobutylthio)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide	109	(M+H+) m/z: calcd 575.26; found 575.1	1H NMR (400 MHz, CDCl3) δ 7.85 (d,J = 6.8 Hz,1H), 7.44 (d,J =7.6 Hz,1H), 7.29 (s,1H), 7.10-7.03 (m,2H), 5.86 (s,1H), 4.741-4.650 (m,2H), 4.13-4.10 (m,1H), 3.97-3.93 (m,1H), 2.95-2.91 (m,3H) ,2.71 (m,3H) 2.55-2.53 (m,2H), 2.22-1.94 (m,10H), 1.60 (m,3H) 1.45 (m,1H), 1.15-1.12 (m,1H), 0.94-0.91 (m,1H).
2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((R)-1-(4-(3-(trifluoromethyl)azetidin-1-yl)cyclohexyl)ethyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	110 single isomer	(M+H+) m/z: calcd 576.25; found 576.3	1H NMR (400MHz, CD3OD) δ 8.19 - 8.15 (m, 1H), 8.08 (br d, J = 7.6 Hz, 1H), 7.16 - 7.02 (m, 1H), 6.30 (s, 1H), 4.60 (s, 3H), 4.08 (br s, 1H), 3.53 - 3.39 (m, 2H), 3.26 - 3.17 (m, 3H), 2.73 - 2.60 (m, 3H), 2.53 (s, 3H), 2.30 (s, 3H), 2.16 - 2.01 (m, 2H), 1.95 - 1.86 (m, 1H), 1.71 - 1.52 (m, 4H), 1.19 - 0.99 (m, 2H), 0.98 - 0.64 (m, 3H)
1-((1R)-1-(4-(3-cyclopropoxypyrrolidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	111 single isomer	(M+H+) m/z: calcd 578.31; found 578.1.	1H NMR (400MHz, CD3OD) δ 8.08 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.01 – 6.98 (m, 1H), 6.19 (s, 1H), 4.50 (s, 2H), 4.05 – 4.01 (m, 1H), 3.17 – 3.15 (m, 1H), 2.71 – 2.56 (m, 7H), 2.43 – 2.38 (m, 4H), 2.20 (s, 3H), 2.04 – 1.89 (m, 4H), 1.73 – 1.68 (m, 2H), 1.56 (s, 3H), 1.24 – 1.02 (m, 3H), 0.88 – 0.74 (m, 3H), 0.40 – 0.33 (m, 4H).
1-((R)-1-(4-(3-(tert-butoxy)azetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	112 isomer 1	(M+H+) m/z: calcd 580.32; found 580.3	1H NMR (400 MHz, CD3OD) δ 8.17 (br d, J = 4.0 Hz, 1H), 8.08 (br d, J = 7.8 Hz, 1H), 7.10 (br dd, J = 4.8, 7.5 Hz, 1H), 6.30 (s, 1H), 4.60 (s, 2H), 4.28 (quin, J = 6.4 Hz, 1H), 4.07 (br s, 1H), 3.66 (br t, J = 6.5 Hz, 1H), 3.59 (br t, J = 5.6 Hz, 1H), 2.98 - 2.84 (m, 2H), 2.66 (br s, 3H), 2.54 (s, 3H), 2.31 (s, 3H), 2.11 (br t, J = 11.4 Hz, 2H), 1.95 (br d, J = 11.0 Hz, 1H), 1.65 (br s, 4H), 1.36 - 1.27 (m, 1H), 1.15 (s, 9H), 1.12 - 1.00 (m, 2H),

			1.00 - 0.91 (m, 1H), 0.91 - 0.69 (m, 2H)
1-((R)-1-(4-(3-(tert-butoxy)azetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	112 isomer 2	(M+H+) m/z: calcd 580.32; found 580.3	1H NMR (400 MHz, CD3OD) δ 8.16 (br d, J = 3.8 Hz, 1H), 8.07 (dd, J = 1.3, 8.0 Hz, 1H), 7.09 (dd, J = 4.8, 8.0 Hz, 1H), 6.30 (s, 1H), 4.60 (s, 2H), 4.36 - 4.21 (m, 2H), 3.69 - 3.49 (m, 2H), 2.80 (br t, J = 6.7 Hz, 1H), 2.77 - 2.65 (m, 4H), 2.54 (s, 3H), 2.30 (s, 3H), 2.24 - 2.16 (m, 1H), 1.72 (br d, J = 3.8 Hz, 1H), 1.62 (br d, J = 13.1 Hz, 4H), 1.54 (br s, 2H), 1.41 - 1.27 (m, 2H), 1.22 (br dd, J = 10.0, 13.6 Hz, 1H), 1.16 (s, 9H), 1.11 - 1.00 (m, 1H), 0.77 (br s, 1H)
1-((R)-1-(4-(3-cyclopropoxyazetidin-1-yl)cyclohexyl)ethyl)-7-fluoro-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	113 isomer 1	(M + H+) m/z: calcd 581.29: found 581.3	1HNMR (400MHz, CDCl3) δ 12.72(s, 1H), 7.61-7.59(m, 1H), 7.39-7.37(m, 1H), 6.95-6.93(m, 1H), 6.86-6.81(m, 1H), 6.00(s, 1H), 4.76-4.71(m, 2H), 4.21-4.18(m, 1H), 4.06(m, 1H), 3.57(m, 2H), 3.21-3.19(m, 1H), 2.85-2.79(m, 2H), 2.71(s, 2H), 2.45(s, 3H), 2.15(s, 3H), 2.06-2.04(m, 2H), 1.89-1.85(m, 2H), 1.74(s, 3H), 1.60-1.58(m, 2H), 1.51-1.49(m, 1H), 1.31-1.29(m, 1H), 1.04-1.02(m, 2H), 0.76-0.74(m, 1H), 0.55(s, 2H), 0.44-0.43(m, 2H).
1-((R)-1-(4-(3-cyclopropoxyazetidin-1-yl)cyclohexyl)ethyl)-7-fluoro-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	113 isomer 2	(M + H+) m/z: calcd 581.29: found 581.3	1HNMR (400MHz, CDCl3) δ12.50(s, 1H), 7.55-7.49(m, 1H), 7.22(m, 1H), 6.90-6.87(m, 1H), 6.78-6.72(m, 1H), 5.92(s, 1H), 4.68-4.59(m, 2H), 4.14(s, 2H), 3.52-3.45(m, 2H), 3.15-3.14(s, 1H), 2.72-2.62(m, 3H), 2.41(s, 3H), 2.09-1.96(m, 4H), 1.62-1.57(m, 4H), 1.49-1.36(m, 2H), 1.33-1.19(m, 2H), 1.05(m, 2H), 0.82-0.78(m, 3H), 0.76(m, 1H), 0.48(m, 2H), 0.38-0.36(m, 2H)
(R)-4-(difluoromethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-	114	(M+H+) m/z: calcd 585.22; found 585.2.	1H NMR (400 MHz, CDCl3) δ 7.49-7.43 (m, 1H), 7.35-7.33 (m,1H), 7.16-7.08 (m,1H), 6.76 (m,1H), 5.94 (s,1H), 5.29-5.27 (m,1H), 4.63-4.60 (m,2H), 3.94 (m,1H), 3.00-2.89 (m,1H), 2.89-2.86 (m,2H), 2.86-2.84 (m,1H),

carboxamide			2.43-2.39 (m,5H), 2.19-2.13 (m,1H), 1.98-1.94 (m,11H), 0.79-0.74 (m,3H).
1-((R)-1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-2,5-dimethyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	115 single isomer	(M + H+) m/z: calcd 588.73, found 588.3.	1H NMR (400MHz ,METHANOL-d4) δ = 8.02 (d, J = 1.5 Hz, 1 H), 7.92 (s, 1 H), 6.55 (s, 1 H), 6.36 (s, 1 H), 6.28 (s, 1 H), 6.18 (s, 1 H), 4.68 (quin, J = 6.0 Hz, 1 H), 4.59 (s, 2 H), 3.61 (br t, J = 6.6 Hz, 1 H), 3.56 (br t, J = 7.1 Hz, 1 H), 3.08 (ddd, J = 5.9, 8.1, 13.9 Hz, 2 H), 2.53 (s, 3 H), 2.39 (s, 3 H), 2.29 (s, 3 H), 2.16 - 2.01 (m, 2 H), 1.95 - 1.86 (m, 1 H), 1.68 - 1.55 (m, 4 H), 1.16 - 1.00 (m, 3 H), 0.99 - 0.91 (m, 1 H), 0.89 - 0.69 (m, 3 H)
1-((R)-1-(4-(3-(2,2-difluoroethoxy)azetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	116 single isomer	(M+H+) m/z: calcd 588.27; found 588.6	1H NMR (400MHz, CD3OD) δ 8.19 (dd, J1 = 4.8 Hz, J2 = 1.2 Hz, 1H), 8.09 (d, J = 7.6 Hz, 1H), 7.13 - 7.10 (m, 1H), 6.32 (s, 1H), 8.19 (tt, J1 = 55.2 Hz, J2 = 4.0 Hz, 1H), 4.93 - 4.82 (m, 2H), 4.62 (s, 2H), 4.21 - 4.15 (m, 1H), 3.67 - 3.53 (m, 4H), 3.03 - 2.96 (m, 2H), 2.68 (br s, 3H), 2.53 (s, 3H), 2.32 (s, 3H), 2.16 - 2.13 (m, 1H), 2.08 - 2.02 (m, 1H), 1.96 - 1.93 (m, 1H), 1.69 - 1.62 (m, 4H), 1.19 - 1.05 (m, 2H), 1.02 - 0.96 (m, 1H), 0.91 - 0.75 (m, 2H).
1-((S)-1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)propyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	117 single isomer	(M+H+) m/z: calcd 588.27; found 588.1.	1H NMR (400MHz, CDCl3) δ 12.56 (s, 1H), 8.22 - 8.09 (m, 2H), 7.41 - 7.34 (m, 1H), 6.99 - 6.96 (m, 1H), 6.15 (t, J = 73.6 Hz, 1H), 6.02 (s, 1H), 4.76 - 4.67 (m, 3H), 3.65 - 3.58 (m, 3H), 3.01 - 2.97 (m, 2H), 2.83 - 2.74 (m, 3H), 2.67 - 2.61 (m, 1H), 2.49 (s, 3H), 2.20 (s, 3H), 2.15 - 1.97 (m, 1H), 1.96 - 1.85 (m, 4H),1.51 (s, 1H), 1.04 - 0.96 (m, 3H), 0.76 - 0.75 (m, 2H), 0.59 - 0.53 (m, 3H).
1-((R)-1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)propyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-	118 single isomer	(M+H+) m/z: calcd 588.27; found 588.1.	1H NMR (400MHz, CDCl3) δ 12.85 (s, 1H), 8.21 - 8.09 (m, 2H), 7.42 - 7.39 (m, 1H), 6.98 - 6.94 (m, 1H), 6.14 (t, J = 73.6Hz, 1H), 6.02 (s, 1H), 4.71 - 4.66 (m, 3H), 3.63 - 3.55 (m, 3H), 3.01 - 2.96 (m, 2H), 2.83 - 2.74 (m, 3H), 2.65 - 2.60 (m,

pyrrolo[2,3-b]pyridine-3-carboxamide			1H), 2.48 (s, 3H), 2.19 - 1.85 (m, 8H), 1.52 (s, 1H), 1.03 - 0.95 (m, 3H), 0.76 - 0.74 (m, 2H), 0.59 - 0.53 (m, 3H).
1-((R)-1-(4-((R)-3-(difluoromethoxy)pyrrolidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	119 single isomer	(M+H+) m/z: calcd 588.27; found 588.1	1H NMR (400MHz, CD3OD) δ 8.17 (dd, J = 1.3, 4.5 Hz, 1H), 8.08 (br d, J = 7.8 Hz, 1H), 7.10 (br dd, J = 4.8, 7.8 Hz, 1H), 6.55-6.17 (t, J = 75.2 Hz, 1H), 6.29 (s, 1H), 4.74 - 4.67 (m, 1H), 4.60 (s, 2H), 4.07 (br s, 1H), 2.87 - 2.74 (m, 4H), 2.72 - 2.60 (m, 3H), 2.53 (s, 3H), 2.51 - 2.45 (m, 1H), 2.30 (s, 3H), 2.24 - 1.98 (m, 4H), 1.95 - 1.83 (m, 1H), 1.78 (br d, J = 12.0 Hz, 1H), 1.66 (br s, 3H), 1.38 - 1.08 (m, 3H), 1.06 - 0.78 (m, 2H)
1-((R)-1-(4-((S)-3-(difluoromethoxy)pyrrolidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	120 single isomer	(M + H+) m/z: calcd: 588.27.; found 588.2	1H NMR (400MHz, CD3OD) δ 8.16 (dd, J = 1.2, 4.8 Hz, 1H), 8.06 (br d, J = 7.6 Hz, 1H), 7.08 (br dd, J = 4.8, 7.6 Hz, 1H), 6.34 (s, 1H), 6.28 (s, 1H), 4.69 (br s, 1H), 4.58 (s, 2H), 4.05 (br s, 1H), 2.88 - 2.72 (m, 3H), 2.72 - 2.57 (m, 3H), 2.51 (s, 3H), 2.49 - 2.43 (m, 1H), 2.28 (s, 3H), 2.23 - 1.97 (m, 4H), 1.93 - 1.83 (m, 1H), 1.77 (br d, J = 10.8 Hz, 1H), 1.73 - 1.47 (m, 3H), 1.47 - 1.14 (m, 2H), 1.13 - 1.01 (m, 1H), 1.00 - 0.65 (m, 3H)
1-((R)-1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-7-fluoro-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	121 isomer 1	(M+H+) m/z: calcd 591.25; found 591.1.	1H NMR (400MHz, CDCl3) δ 13.24 (s, 1H), 7.61 - 7.59 (m, 1H), 7.40-7.27 (m, 1H), 6.94 - 6.80 (m, 2H), 6.34 - 5.97 (m, 2H), 6.36 - 5.99 (m, 2H), 4.73 - 4.64 (m, 3H), 4.06 (s, 1H), 3.65 - 3.58 (m, 2H), 3.01 - 2.95 (m, 2H), 2.70 (s, 3H), 2.48 (s, 3H), 2.13 (s, 3H), 2.05 - 2.02 (m, 2H), 2.00 - 1.90 (m, 2H), 1.60 - 1.50 (m, 3H), 1.04 - 1.02 (m, 3H), 0.76 - 0.74 (m, 2H).
1-((R)-1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-7-fluoro-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	121 isomer 2	(M+H+) m/z: calcd 591.25; found 591.1.	1H NMR (400MHz, CDCl3) δ 12.53 - 12.52 (m, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 6.4 Hz, 1H), 6.96 - 6.94 (m, 1H), 6.86 - 6.80 (m, 1H), 6.36 - 5.99 (m, 2H), 4.78 - 4.65 (m, 3H), 4.20 (s, 1H), 3.63 - 3.50 (m, 2H), 2.92 - 2.88 (m, 2H), 2.73 (s, 3H), 2.47 (s, 3H),

			2.18 - 2.00 (m, 5H), 1.66 - 1.63 (m, 8H), 1.57 - 1.48 (m, 3H), 1.43 - 1.41 (m, 1H), 1.26 - 1.12 (m, 2H), 0.75 - 0.74 (m, 1H).
1-((R)-1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-5-fluoro-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	122 single isomer	(M + H+) m/z: calcd 592.25: found 592.2	1HNMR (400MHz, CDCl3) δ 12.48(s, 1H), 8.56(s, 1H), 7.88(d, J = 8.0 Hz, 1H), 7.34-7.31(m, 1H), 6.34-5.97(m, 2H), 4.71-4.70(m, 2H), 3.95(s, 1H), 3.66-3.59(m, 2H), 3.03-2.95(m, 2H), 2.76(s, 3H), 2.50(s, 3H), 2.28(s, 3H), 2.10-1.93(m, 1H), 1.87-1.85(m, 2H), 1.63-1.54(m, 3H), 1.26(s, 3H), 1.05-0.96(m, 3H), 0.77-0.75(m, 2H).
6-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-7-((R)-1-(4-(3-(trifluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide	123 isomer 1	(M+H+) m/z: calcd 593.24; found 593.0	1H NMR (400MHz, CD3OD) δ 9.01 (s, 1H), 8.70 (s, 1H), 6.30 (s, 1H), 4.93 (br s, 1H), 4.85 - 4.77 (m, 1H), 4.59 (s, 2H), 4.14 (br s, 1H), 3.71 - 3.57 (m, 2H), 3.19 (dt, J = 5.7, 9.0 Hz, 2H), 2.68 (br s, 3H), 2.56 - 2.52 (m, 3H), 2.31 (s, 3H), 2.16 - 2.05 (m, 2H), 1.93 (br d, J = 12.1 Hz, 1H), 1.67 (br d, J = 6.4 Hz, 3H), 1.62 (br s, 1H), 1.21 - 0.99 (m, 2H), 0.98 - 0.84 (m, 2H), 0.77 (br d, J = 11.6 Hz, 1H)
6-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-7-((R)-1-(4-(3-(trifluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide	123 isomer 2	(M+H+) m/z: calcd 593.24; found 593.0	1H NMR (400MHz, CD3OD) δ 9.01 (s, 1H), 8.70 (s, 1H), 6.31 (s, 1H), 4.92 - 4.89 (m, 1H), 4.81 (quin, J = 5.7 Hz, 1H), 4.59 (s, 2H), 4.21 - 3.97 (m, 1H), 3.71 - 3.57 (m, 2H), 3.24 - 3.15 (m, 2H), 2.68 (br s, 3H), 2.54 (s, 3H), 2.31 (s, 3H), 2.16 - 2.05 (m, 2H), 1.98 - 1.86 (m, 1H), 1.67 (br d, J = 6.5 Hz, 3H), 1.62 (br s, 1H), 1.22 - 0.99 (m, 2H), 0.98 - 0.66 (m, 3H)
5-chloro-1-((R)-1-(4-(3-cyclopropoxyazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	124 single isomer	(M+H+) m/z: calcd 598.25; found 598.2.	1H NMR (400MHz, CDCl3) δ 12.02 (s, 1H), 8.14 - 8.11 (m, 2H), 7.38 - 7.16 (m, 1H), 6.02 (s, 1H), 4.69 (d, J = 4.8Hz, 2H), 4.20 - 4.17 (m, 1H), 3.62 - 3.56 (m, 2H), 3.20 - 3.18 (m, 1H), 2.84 - 2.74 (m, 5H), 2.49 (s, 3H), 2.24 (s, 3H), 2.08 - 2.06 (m, 1H), 1.88 - 1.85 (m, 2H), 1.61 - 1.55 (m, 5H), 1.04 - 0.96 (m, 3H), 0.76 - 0.74 (m, 2H), 0.54 - 0.52 (m, 2H), 0.45 - 0.42 (m, 2H).

1-((R)-1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-5-methoxy-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	125 isomer 1	(M + H+) m/z: calcd 604.27; found 604.2	1HNMR (400MHz, CDCl3) δ 12.79(s, 1H), 7.94-7.93(m, 1H), 7.69(s, 1H), 7.40(s, 1H), 6.34-5.87(m, 2H), 4.71(s, 3H), 3.81(s, 3H), 3.75-3.57(m, 2H), 3.02-2.94(m, 2H), 2.74(m, 2H), 2.48(s, 3H), 2.20(s, 3H), 1.92(m, 1H), 1.86-1.84(m, 3H), 1.63-1.53(m, 4H), 1.05-0.99(m, 3H), 0.77(s, 2H).
1-((R)-1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-5-methoxy-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	125 isomer 2	(M + H+) m/z: calcd 604.27; found 604.2	1HNMR (400MHz, CDCl3) δ 7.91-7.88 (m, 1H), 7.73-7.71(m, 1H), 7.30 (s, 1H), 6.27-5.90 (m, 2H), 4.68-4.63 (m, 3H), 3.72 (s, 3H), 3.63-3.58 (m, 2H), 3.00-2.83 (m, 2H), 2.67 (s, 3H), 2.42 (s, 3H), 2.17-2.13 (m, 3H), 2.00 (m, 2H), 1.78 (m, 2H), 1.24-1.16 (m, 7H), 0.94-0.91(m, 2H), 0.81-0.71(m, 1H).
5-chloro-1-((R)-1-(4-(3-cyclobutoxyazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	126 single isomer	(M+H+) m/z: calcd 612.27; found 612.4.	1H NMR (400MHz, CD3OD) δ 8.11 (dd, J = 2.0, 16.3 Hz, 2H), 6.31 (s, 1H), 4.86 - 4.81 (m, 1H), 4.58 (s, 2H), 4.04 (br t, J = 6.0 Hz, 1H), 3.91 (quin, J = 7.3 Hz, 1H), 3.61 - 3.45 (m, 2H), 2.96 - 2.85 (m, 2H), 2.65 (br s, 3H), 2.55 (s, 3H), 2.31 (s, 3H), 2.19 - 2.08 (m, 3H), 2.02 (br s, 1H), 1.95 - 1.83 (m, 3H), 1.73 - 1.57 (m, 5H), 1.56 - 1.46 (m, 1H), 1.21 (br s, 1H), 1.13 - 0.98 (m, 2H), 0.94 - 0.68 (m, 3H).
(R)-6-bromo-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide	127	(M+H+) m/z: calcd 615.14; found 615.0	1H NMR (400 MHz, CDCl3) δ 11.87 (s,1H), 7.72-7.70 (m,1H), 7.56-7.52 (s,1H), 7.15 (d,J= 7.6Hz,1H), 6.02 (s,1H), 4.76-4.65 (m,2H), 4.10-4.05(m,1H), 3.08 (d,J=11.6 Hz,1H), 2.97-2.89 (m,2H), 2.80-2.75(m,2H), 2.67 (s,2H),2.49 (s,4H), 2.20 (m,3H), 2.13-2.11 (m,2H),1.96 (d,J=12Hz,1H),1.43-1.40 (m,1H),1.14-1.12 (m,1H), 0.90 (d,J=13.6Hz,1H)
(R)-4-bromo-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-	128	(M+H+) m/z: calcd 615.14; found 615.1.	1H NMR (400 MHz, CDCl3) δ 12.44 (br, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.18 (d, J = 6.8 Hz, 1H), 6.93-6.89 (m, 2H), 5.94 (s, 1H), 4.68 (br, 2H), 4.01-3.97 (m, 1H), 3.07 (d, J = 11.2 Hz, 1H), 2.95-2.88 (m,

yl)ethyl)-1H-indole-3-carboxamide			2H), 2.77 (d, J = 10.8 Hz, 1H), 2.46-2.36 (m, 7H), 2.10-1.92 (m, 6H), 1.56 (d, J = 6.8 Hz, 3H), 1.42-0.97 (m, 4H).
1-((R)-1-(4-(3-(tert-butoxy)azetidin-1-yl)cyclohexyl)ethyl)-5-chloro-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	129 single isomer	(M+H+) m/z: calcd 614.3; found 614.4.	1HNMR (400MHz, CDCl3) δ 13.24 - 13.22 (m, 1H), 8.13 (d, J = 10.4Hz, 2H), 7.43 - 7.40 (m, 1H), 6.03 (s, 1H), 4.70 - 4.69 (m, 2H), 4.27 - 4.23 (m, 1H), 4.22 (s, 1H), 3.62- 3.54 (m, 2H), 2.78 - 2.69 (m, 5H), 2.49 (s, 3H), 2.23 (s, 3H), 2.03 - 2.00 (m, 2H), 1.88 - 1.61 (m, 2H), 1.58 - 1.55 (m, 4H), 1.14 (s, 9H), 1.02 - 0.98 (m, 2H), 0.95 - 0.74 (m, 2H).
(R)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(1-(1-methylcyclopropyl)piperidin-4-yl)ethyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	131	(M+H+) m/z: calcd 508.27; found 508.5	1H NMR (400MHz, CD3OD) δ 8.09 (dd, J1 = 4.8 Hz, J2 = 1.6 Hz, 1H), 7.98 (dd, J1 = 8.0 Hz, J2 = 1.2 Hz, 1H), 7.03 - 6.99 (m, 1H), 6.21 (s, 1H), 4.50 (s, 2H), 4.05 - 3.98 (m, 1H), 2.85 - 2.82 (m, 1H), 2.62 - 2.52 (m, 4H), 2.48 - 2.40 (m, 5H), 2.21 (s, 3H), 2.17 - 2.08 (m, 1H), 1.94 - 1.91 (m, 1H), 1.57 (br s, 3H), 1.24 - 1.20 (m, 1H), 0.97 - 0.89 (m, 4H), 0.81 - 0.75 (m, 1H), 0.49 - 0.45 (m, 1H), 0.41 - 0.38 (m, 1H), 0.28 - 0.20 (m, 2H).
1-((R)-1-(4-cyclopropoxycyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	132 single isomer	(M + H+) m/z: calcd: 508.26; found 508.1	1H NMR (400 MHz, CD3OD) δ 7.70 (br d, J = 7.6 Hz, 1H), 7.53 (br d, J = 8.0 Hz, 1H), 7.14 - 6.98 (m, 2H), 6.27 (s, 1H), 4.62 - 4.53 (m, 2H), 4.11 (br dd, J = 7.2, 10.4 Hz, 1H), 3.40 - 3.31 (m, 2H), 2.62 - 2.53 (m, 3H), 2.51 (s, 3H), 2.27 (s, 3H), 2.24 - 2.05 (m, 3H), 1.83 (br s, 1H), 1.58 (br d, J = 6.8 Hz, 3H), 1.36 - 1.05 (m, 3H), 0.94 - 0.86 (m, 2H), 0.48 - 0.38 (m, 4H)
(R)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(1-(1-(oxetan-3-yl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide	133	(M + H+) m/z: calcd 508.7; found 509.2.	1H NMR (400MHz, CDCl3) δ 12.31 – 12.28 (m 1H), 7.85 – 7.83 (d, J = 8.0Hz, 1H), 7.45 – 7.43(d, J = 8.0Hz, 1H), 7.29 - 7.26 (d, J = 12.0Hz, 1H), 7.10-7.02 (m, 2H), 6.00 (s, 1H), 4.75 – 4.53 (m, 6H), 4.15 – 4.10 (m, 1H), 3.40 – 3.37 (m, 1H), 2.86 – 2.71 (m, 4H), 2.53 – 2.48(m, 4H), 2.21 – 2.17(m, 4H), 2.02 – 1.98 (d, J = 16.0Hz, 1H), 1.90 – 1.83(m, 1H), 1.61 – 1.59

			(m,4H),1.54 – 1.43 (m,1H),1.20 – 1.10(m,1H),0.96 – 0.94 (d, J = 8Hz, 1H).
4-((R)-1-(2-methyl-3-(((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1H-indol-1-yl)ethyl)cyclohexyl acetate	134 isomer 1	(M+H+) m/z: calcd 510.23; found 510.2	1H NMR (400 MHz, CD3OD) δ 7.73 (br d, J = 7.5 Hz, 1H), 7.57 (br d, J = 7.8 Hz, 1H), 7.16 - 7.01 (m, 2H), 6.29 (s, 1H), 4.86 - 4.82 (m, 1H), 4.61 (s, 2H), 4.24 - 4.16 (m, 1H), 2.62 (s, 3H), 2.53 (s, 3H), 2.40 - 2.32 (m, 1H), 2.30 (s, 3H), 2.04 (s, 3H), 2.01 - 1.89 (m, 2H), 1.71 - 1.57 (m, 5H), 1.52 - 1.39 (m, 1H), 1.30 (br t, J = 13.3 Hz, 1H), 1.19 - 1.06 (m, 1H), 0.79 (br d, J = 12.0 Hz, 1H)
4-((R)-1-(2-methyl-3-(((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1H-indol-1-yl)ethyl)cyclohexyl acetate	134 isomer 2	(M+H+) m/z: calcd 510.23; found 510.2	1H NMR (400 MHz, CD3OD) δ 7.73 (br d, J = 7.5 Hz, 1H), 7.57 (br d, J = 7.8 Hz, 1H), 7.17 - 7.02 (m, 2H), 6.30 (s, 1H), 4.67 - 4.56 (m, 3H), 4.21 - 4.11 (m, 1H), 2.78 - 2.57 (m, 3H), 2.53 (s, 3H), 2.30 (s, 3H), 2.29 - 2.23 (m, 1H), 2.19 - 2.03 (m, 2H), 1.96 (s, 3H), 1.76 (br d, J = 11.8 Hz, 1H), 1.62 (br d, J = 7.0 Hz, 3H), 1.51 - 1.38 (m, 1H), 1.35 - 1.20 (m, 1H), 1.17 - 1.05 (m, 1H), 1.01 - 0.89 (m, 2H)
(R)-1-(1-(1-(2-hydroxyacetyl)piperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	135	(M + H+) m/z: calcd 511.65, found 511.3.	1H NMR (400MHz ,METHANOL-d4) δ = 7.74 (br d, J = 7.3 Hz, 1 H), 7.59 (br d, J = 7.8 Hz, 1 H), 7.19 - 6.93 (m, 2 H), 6.39 (br s, 1 H), 4.59 (s, 2H), 4.30 - 4.00 (m, 3 H), 3.77 (br d, J = 13.7 Hz, 1 H), 3.45 (br d, J = 13.2 Hz, 1 H), 3.10 - 2.92 (m, 1 H), 2.78 - 2.63 (m, 2 H), 2.61 - 2.46 (m, 6 H), 2.32 (s, 3 H), 2.11 - 1.96 (m, 1 H), 1.59 (br d, J = 6.8 Hz, 3 H), 1.43 - 1.11 (m, 2 H), 1.10 - 0.74 (m, 2 H)
(R)-1-(1-(4-(3-hydroxyazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	136 single isomer	(M+H+) m/z: calcd 523.27; found 523.2	1H NMR (400 MHz, DMSO-d6) δ 11.68 (br, 1H), 7.74-7.72 (m, 1H), 7.65-7.57 (m, 2H), 7.07-7.01(m, 2H), 6.13(s, 1H), 5.19 (s, 1H), 4.38 (s, 2H), 4.11-4.07 (m, 2H), 2.68 (s, 1H), 2.58 (s, 3H), 2.33 (s, 1H), 2.19-2.13 (m, 5H), 1.84-1.54 (m, 4H), 1.48-0.48 (m, 10H).
2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-	137 isomer 1	(M+H+) m/z: calcd	1H NMR (400 MHz, CDCl3) δ 12.54 (br, 1H), 7.83(d, J = 7.6Hz,

dihydropyridin-3-yl)methyl)-1-((R)-1-(4-(oxetan-3-yloxy)cyclohexyl)ethyl)-1H-indole-3-carboxamide		524.25; found 524.2	1H), 7.44(d, J = 7.6Hz, 1H), 7.30-7.26(m, 1H), 7.08-7.01(m, 2H), 6.00(s, 1H), 4.76-4.55(m, 8H), 4.16-4.15(m, 1H), 3.46(s, 1H), 2.84-2.75(m, 3H), 2.48(s, 3H), 2.21(s, 4H), 1.84-1.79(m, 2H), 1.51-1.46(m, 4H), 1.15-0.81(m, 3H).
2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((R)-1-(4-(oxetan-3-yloxy)cyclohexyl)ethyl)-1H-indole-3-carboxamide	137 isomer 2	(M+H+) m/z: calcd 524.25; found 524.2.	1H NMR (400 MHz, CDCl3) δ 12.36(br, 1H), 7.82(d, J = 7.6Hz, 1H), 7.44(d, J = 8.0Hz, 1H), 7.30-7.26(m, 1H), 7.11-7.00(m, 2H), 5.99(s, 1H), 4.72-4.58(m, 6H), 4.05-4.01(m, 1H), 3.15(s, 1H), 2.75-2.69(m, 3H), 2.48(s, 3H), 2.11-1.98(m, 5H), 1.68-1.65(m, 1H), 1.30-0.77(m, 9H).
1-((R)-1-(4-(3-cyanoazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	138 isomer 1	(M+H+) m/z: calcd 532.27; found 266.5.	1H NMR (400 MHz, CDCl3) δ 7.81 (d, J = 7.2Hz, 1H), 7.43 (d, J = 7.6Hz, 1H), 7.10-7.04 (m, 2H), 6.00 (s, 1H), 4.73-4.69 (m, 2H), 4.05-4.02 (m, 1H), 3.57-3.51 (m, 2H), 3.26-3.18 (m, 3H), 2.71 (s, 3H), 2.48 (s, 3H), 2.22 (s, 3H), 2.06-1.85 (m, 4H), 1.58 (d, J = 7.2Hz, 3H), 1.26-0.74 (m, 7H).
1-((R)-1-(4-(3-cyanoazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	138 isomer 2	(M+H+) m/z: calcd 532.27; found 532.0.	1H NMR (400 MHz, CDCl3) δ 12.29 (br, 1H), 7.82 (d, J = 7.2 Hz, 1H), 7.43 (d, J = 7.2Hz, 1H), 7.15-7.02 (m, 2H), 6.00 (s, 1H), 4.79-4.66 (m, 2H), 4.17-4.12 (m, 1H), 3.51-3.46 (m, 2H), 3.17 (s, 3H), 2.82-2.74 (m, 3H), 2.48 (s, 3H), 2.27-2.21 (m, 5H), 1.57 (d, J = 6.8 Hz, 3H), 1.41-0.70 (m, 7H).
1-((R)-1-(4-(5-oxa-1-azaspiro[2.3]hexan-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	139 isomer 1	(M+H+) m/z: calcd 536.70; found 536.1.	1H NMR (400MHz, CD3OD) δ 8.24 - 8.17 (m, 1H), 8.11 (m, 1H), 7.17 - 7.06 (m, 1H), 6.31 (s, 1H), 5.05 - 4.93 (m, 1H), 4.78 - 4.66 (m, 2H), 4.61 (s, 2H), 4.09 (br s, 1H), 2.89 - 2.59 (m, 4H), 2.55 (d, J = 1.2 Hz, 3H), 2.32 (s, 3H), 2.26 (br d, J = 13.2 Hz, 1H), 2.18 (br d, J = 12.4 Hz, 1H), 1.99 - 1.87 (m, 2H), 1.76 - 1.56 (m, 4H), 1.54 (s, 1H), 1.47 (s, 1H), 1.45 - 1.32 (m, 1H), 1.27 - 0.70 (m, 4H)
1-((R)-1-(4-(5-oxa-1-azaspiro[2.3]hexan-1-yl)cyclohexyl)ethyl)-2-	139 isomer 2	(M+H+) m/z: calcd 536.70;	1H NMR (400MHz, CD3OD) δ 8.22 - 8.16 (m, 1H), 8.14 - 8.05 (m, 1H), 7.11 (m, 1H), 6.31 (s, 1H),

methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide		found 536.1.	5.02 - 4.92 (m, 1H), 4.84 - 4.71 (m, 2H), 4.62 (d, J = 2.4 Hz, 2H), 4.28 (br s, 1H), 2.96 - 2.63 (m, 4H), 2.55 (d, J = 0.8 Hz, 3H), 2.32 (s, 3H), 2.11 - 1.90 (m, 2H), 1.79 (br d, J = 11.2 Hz, 3H), 1.74 - 1.58 (m, 5H), 1.51 (br s, 1H), 1.45 (s, 1H), 1.41 - 1.19 (m, 2H), 0.98 - 0.75 (m, 1H)
(R)-1-(1-(1-(3-methoxycyclobutyl)piperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	140	(M + H+) m/z: calcd 537.29, found 537.3	1H NMR (400MHz ,DMSO-d6) δ= 11.64 (br. s., 1 H), 7.80 - 7.45 (m, 3 H), 7.03 (quin, J = 7.3 Hz, 2 H), 6.11 (s, 1 H), 4.57 - 4.43 (m, 0 H), 4.42 - 4.30 (m, 2 H), 4.20 - 4.05 (m, 1 H), 3.77 (br. s., 0 H), 3.49 (quin, J = 7.0 Hz, 1 H), 3.12 - 3.02 (m, 2 H), 2.94 - 2.78 (m, 1 H), 2.74 - 2.52 (m, 4 H), 2.46 (s, 3 H), 2.37 - 2.07 (m, 5 H), 2.04 - 1.80 (m, 2 H), 1.76 - 1.60 (m, 1 H), 1.58 - 1.19 (m, 6 H), 1.07 - 0.88 (m, 1 H), 0.83 (d, J = 6.4 Hz, 1 H), 0.67 (d, J = 12.2 Hz, 1 H)
(R)-1-(1-(1-(3-methoxycyclobutyl)piperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	141	(M+H+) m/z: calcd 538.28; found 538.1.	1H NMR (400MHz, CD3OD) δ 8.19 (d, J = 4.0 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.12 (dd, J = 4.6, 7.9 Hz, 1H), 6.32 (s, 1H), 5.21 (br s, 1H), 4.73 - 4.64 (m, 1H), 4.61 - 4.55 (m, 2H), 3.69 - 3.59 (m, 1H), 3.23 (s, 3H), 3.06 (br d, J = 8.5 Hz, 1H), 2.82 - 2.66 (m, 4H), 2.56 (s, 3H), 2.53 - 2.36 (m, 3H), 2.33 (s, 3H), 2.12 - 1.92 (m, 2H), 1.83 - 1.61 (m, 6H), 1.44 (br d, J = 18.6 Hz, 1H), 1.13 (br d, J = 10.3 Hz, 1H), 0.93 (br d, J = 12.3 Hz, 1H).
(R)-1-(1-(1-(dimethylglycyl)piperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	142	(M + H+) m/z: calcd 538.72, found 538.4.	1H NMR (400MHz ,METHANOL-d4) δ = 7.73 (br d, J = 7.8 Hz, 1 H), 7.61 (br d, J = 7.3 Hz, 1 H), 7.18 - 7.01 (m, 2 H), 6.41 (d, J = 2.0 Hz, 1 H), 4.61 (s, 2 H), 4.25 (br d, J = 17.6 Hz, 3 H), 3.75 (br d, J = 13.7 Hz, 1 H), 3.43 (br d, J = 13.7 Hz, 1 H), 3.24 - 3.07 (m, 1 H), 2.92 (br d, J = 12.7 Hz, 5 H), 2.84 - 2.68 (m, 2 H), 2.67 - 2.51 (m, 6 H), 2.33 (s, 2 H), 2.10 (br d, J = 12.7 Hz, 1 H), 1.63 (br d, J = 6.8 Hz, 3 H), 1.47 - 1.19 (m, 2 H), 1.15 - 0.86 (m, 2 H)

4-((R)-1-(2-methyl-3-(((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1H-indol-1-yl)ethyl)cyclohexyl butyrate	143 isomer 1	(M + H+) m/z: calcd: 538.27.; found 538.3	1H NMR (400MHz, CD3OD) δ 7.71 (br d, J = 7.6 Hz, 1H), 7.55 (br d, J = 8.0 Hz, 1H), 7.20 - 6.95 (m, 2H), 6.27 (s, 1H), 4.92 (br d, J = 3.2 Hz, 1H), 4.67 - 4.54 (m, 2H), 4.27 - 4.12 (m, 1H), 2.77 - 2.57 (m, 3H), 2.51 (s, 3H), 2.36 - 2.29 (m, 2H), 2.28 - 2.26 (m, 3H), 2.03 - 1.85 (m, 2H), 1.71 - 1.62 (m, 3H), 1.60 (br d, J = 6.8 Hz, 4H), 1.50 - 1.39 (m, 1H), 1.39 - 1.19 (m, 2H), 1.19 - 1.05 (m, 1H), 1.00 - 0.89 (m, 3H), 0.77 (br d, J = 10.8 Hz, 1H)
4-((R)-1-(2-methyl-3-(((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1H-indol-1-yl)ethyl)cyclohexyl butyrate	143 isomer 2	(M + H+) m/z: calcd: 538.27.; found 538.3	1H NMR (400MHz, CD3OD) δ 7.71 (br d, J = 7.6 Hz, 1H), 7.59 - 7.47 (m, 1H), 7.13 - 6.99 (m, 2H), 6.27 (s, 1H), 4.59 (s, 3H), 4.14 (m, 1H), 2.74 - 2.56 (m, 3H), 2.51 (s, 3H), 2.28 (s, 3H), 2.20 (br t, J = 7.2 Hz, 2H), 2.14 - 2.02 (m, 2H), 1.73 (br d, J = 10.8 Hz, 1H), 1.66 - 1.47 (m, 6H), 1.46 - 1.36 (m, 1H), 1.29 - 1.20 (m, 1H), 1.14 - 1.02 (m, 1H), 0.94 (br s, 2H), 0.89 (t, J = 7.6 Hz, 3H)
4-((R)-1-(2-methyl-3-(((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1H-indol-1-yl)ethyl)cyclohexyl isobutyrate	144 isomer 1	(M + H+) m/z: calcd: 538.27.; found 538.3	1H NMR (400MHz, CD3OD) δ 7.71 (br d, J = 7.6 Hz, 1H), 7.54 (br d, J = 8.0 Hz, 1H), 7.13 - 6.98 (m, 2H), 6.25 (s, 1H), 4.94 - 4.88 (m, 1H), 4.58 (d, J = 2.0 Hz, 2H), 4.22 - 4.09 (m, 1H), 2.59 (s, 3H), 2.55 - 2.50 (m, 1H), 2.49 (s, 3H), 2.39 - 2.30 (m, 1H), 2.26 (s, 3H), 1.97 - 1.85 (m, 2H), 1.63 (br s, 1H), 1.59 (br d, J = 6.8 Hz, 3H), 1.49 - 1.39 (m, 1H), 1.35 - 1.19 (m, 2H), 1.14 (d, J = 2.4 Hz, 3H), 1.12 (br d, J = 2.8 Hz, 4H), 0.75 (br d, J = 12.0 Hz, 1H)
4-((R)-1-(2-methyl-3-(((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1H-indol-1-yl)ethyl)cyclohexyl isobutyrate	144 isomer 2	(M + H+) m/z: calcd: 538.27.; found 538.3	1H NMR (400MHz, CD3OD) δ 7.71 (br d, J = 7.6 Hz, 1H), 7.54 (br d, J = 8.0 Hz, 1H), 7.15 - 6.99 (m, 2H), 6.24 (s, 1H), 4.63 - 4.52 (m, 3H), 4.20 - 3.99 (m, 1H), 2.75 - 2.53 (m, 3H), 2.49 (s, 3H), 2.42 (td, J = 6.8, 14.0 Hz, 1H), 2.26 (s, 3H), 2.14 - 1.96 (m, 2H), 1.69 (br d, J = 9.6 Hz, 1H), 1.58 (br d, J = 6.8 Hz, 3H), 1.47 - 1.33 (m, 1H), 1.29 - 1.11 (m, 2H), 1.07 (d, J =

			5.2 Hz, 4H), 1.05 (d, J = 5.2 Hz, 3H), 0.97 - 0.85 (m, 2H)
2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((R)-1-(4-((1-methylazetidin-3-yl)oxy)cyclohexyl)ethyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	145 isomer 1	(M+H+) m/z: calcd 538.28; found 538.2.	1H NMR (400MHz, CDCl3) δ 8.23 -8.01 (m, 2H), 7.41 - 7.35 (m, 2H), 6.99 (s, 1H), 6.03 - 6.01 (m, 1H), 4.71 (s, 2H), 4.15 - 4.05 (m, 2H), 3.71 - 3.67 (m, 5H), 2.92 - 2.86 (m, 4H), 2.80 - 2.49 (m, 12H), 2.23 - 1.83 (m, 4H), 1.25 - 1.15 (m, 4H).
2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((R)-1-(4-((1-methylazetidin-3-yl)oxy)cyclohexyl)ethyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	145 isomer 2	(M+H+) m/z: calcd 538.28; found 577.1.	1H NMR (400MHz, CDCl3) δ 12.70 (s, 1H), 8.20 - 8.10 (m, 2H), 7.38 - 7.35 (m, 1H), 7.00 - 6.97 (m, 1H), 6.03 (s, 1H), 4.72 (s, 2H), 4.37 - 4.33 (m, 1H), 4.16 - 4.14 (m, 2H), 3.60 - 3.50 (m, 3H), 2.89 - 2.81 (m, 6H), 2.49 (s, 3H), 2.24 (s, 3H), 1.84 (d, J = 12.4Hz, 2H), 1.66 - 1.59 (m, 6H), 1.26 - 1.23 (m, 1H), 1.04 (s, 1H), 0.79 - 0.77 (m, 1H).
(R)-1-(1-(1-(ethylsulfonyl)piperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	146	LCMS (M+H+) m/z: calcd 545.23; found 545.1	1H NMR (400 MHz, CD3OD) δ 7.74 (br d, J = 7.5 Hz, 1H), 7.58 (br d, J = 8.0 Hz, 1H), 7.16 - 7.04 (m, 2H), 6.29 (s, 1H), 4.61 (s, 2H), 4.34 - 4.16 (m, 1H), 3.83 (br d, J = 12.0 Hz, 1H), 3.53 (br d, J = 12.0 Hz, 1H), 2.96 (q, J = 7.5 Hz, 2H), 2.86 (dt, J = 2.5, 12.5 Hz, 1H), 2.77 - 2.65 (m, 1H), 2.60 (s, 3H), 2.53 (s, 3H), 2.51 - 2.40 (m, 1H), 2.30 (s, 3H), 2.10 (br d, J = 13.0 Hz, 1H), 1.63 (br d, J = 7.0 Hz, 3H), 1.50 - 1.32 (m, 1H), 1.27 (t, J = 7.5 Hz, 3H), 1.18 - 1.00 (m, 1H), 1.00 - 0.86 (m, 1H)
2-methyl-1-((R)-1-(4-((1-methyl-1H-pyrazol-4-yl)oxy)cyclohexyl)ethyl)-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	147 isomer 1	(M + H+) m/z: calcd 549.26: found 549.2	1HNMR (400MHz, CDCl3) δ 13.00(s, 1H), 8.20-8.19(m, 1H), 8.11-8.09(m, 1H), 7.36(s, 1H), 7.17(s, 1H), 7.02-6.96(m, 2H), 6.02(s, 1H), 4.71(s, 2H), 4.06(s, 2H), 3.79(s, 3H), 2.80(s, 3H), 2.48(s, 3H), 2.21(s, 3H), 2.14-2.11(m, 1H), 1.88-1.80(m, 3H), 1.67-1.54(m, 5H), 1.27-1.16(m, 2H), 0.79-0.76(m, 1H).
2-methyl-1-((R)-1-(4-((1-methyl-1H-pyrazol-4-yl)oxy)cyclohexyl)ethyl)-N-((6-methyl-4-(methylthio)-2-oxo-1,2-	147 isomer 2	(M + H+) m/z: calcd 549.26: found 549.2	1HNMR (400MHz, CDCl3) δ 12.18(s, 1H), 8.22-8.21(m, 1H), 8.12-8.10(m, 1H), 7.39-7.36(m, 1H), 7.16(s, 1H), 7.02-7.00(m, 2H), 6.02(s, 1H), 4.71(s, 2H),

dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide			3.79(s, 3H), 3.74-3.70(m, 1H), 2.77(s, 3H), 2.49(s, 3H), 2.25-2.18(m, 5H), 1.95-1.92(m, 1H), 1.72-1.63(m, 2H), 1.44(m, 1H), 1.32-1.05(m, 5H), 0.89(m, 1H).
1-((R)-1-(4-(3-(dimethylamino)azetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	148 isomer 1	(M + H+) m/z: calcd 550.79, found 550.4.	1H NMR (400MHz ,METHANOL-d4) δ = 7.79 - 7.68 (m, 1 H), 7.54 (br d, J = 7.8 Hz, 1 H), 7.19 - 7.06 (m, 2 H), 6.42 (s, 1 H), 4.61 (s, 2 H), 4.59 - 4.42 (m, 4 H), 4.31 (quin, J = 7.3 Hz, 1 H), 4.18 - 4.07 (m, 1 H), 3.28 - 3.18 (m, 1 H), 2.99 - 2.91 (m, 1 H), 2.86 (s, 6 H), 2.61 - 2.54 (m, 5 H), 2.33 (s, 3 H), 2.28 - 2.07 (m, 4 H), 1.59 (br d, J = 6.8 Hz, 3 H), 1.41 - 1.26 (m, 1 H), 1.23 - 1.10 (m, 1 H), 1.03 - 0.78 (m, 3 H)
1-((1R)-1-(4-(3-(dimethylamino)azetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	148 isomer 2	(M + H+) m/z: calcd 550.79, found 550.4.	1H NMR (400MHz ,METHANOL-d4) δ = 7.73 (br d, J = 7.3 Hz, 1 H), 7.56 (br d, J = 7.8 Hz, 1 H), 7.18 - 7.04 (m, 2 H), 6.39 (s, 1 H), 4.61 (s, 2 H), 4.58 - 4.41 (m, 4 H), 4.27 - 4.10 (m, 2 H), 3.28 - 3.18 (m, 1 H), 2.82 (s, 6 H), 2.74 - 2.67 (m, 1 H), 2.59 (s, 2 H), 2.57 - 2.53 (m, 3 H), 2.33 (s, 3 H), 2.31 - 2.03 (m, 4 H), 1.85 - 1.77 (m, 1 H), 1.62 (br d, J = 6.8 Hz, 3 H), 1.43 - 1.14 (m, 3 H), 1.08 - 0.83 (m, 3 H)
2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((1R)-1-(4-((3-methyltetrahydrofuran-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxamide	149 isomer 1	(M+H+) calcd. 551.3; found 551.2.	1H NMR (400MHz, CDCl3) δ 7.84 (br d, J = 7.0 Hz, 1H), 7.47 (br d, J = 8.0 Hz, 1H), 7.32 (s, 1H), 7.19 - 6.96 (m, 2H), 6.02 (s, 1H), 4.73 (br d, J = 5.5 Hz, 2H), 3.9 (m, 3H), 3.61 - 3.34 (m, 2H), 2.87 - 2.64 (m, 3H), 2.50 (m, 4H), 2.22 (s, 3H), 2.12 - 1.79 (m, 4H), 1.72 - 1.64 (m, 3H), 1.55 - 1.49 (m, 1H), 1.26 (br s, 3H), 1.16 - 0.98 (m, 2H), 0.94 - 0.48 (m, 3H).

2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((1R)-1-(4-((3-methyltetrahydrofuran-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxamide	149 isomer 2		1H NMR (400MHz, CDCl3) δ 7.85 (br d, J = 6.8 Hz, 1H), 7.47 (br d, J = 7.8 Hz, 1H), 7.08 (br d, J = 4.5 Hz, 2H), 6.02 (s, 1H), 4.73 (br d, J = 18.6 Hz, 2H), 4.25 (br s, 1H), 4.01 - 3.82 (m, 2H), 3.60 (br s, 1H), 3.47 (br s, 1H), 2.76 (s, 3H), 2.50 (s, 3H), 2.32 (m, 1H), 2.24 (s, 3H), 2.00 - 1.68 (m, 5H), 1.54 - 1.41 (m, 3H), 1.40 - 1.22 (m, 5H), 1.07 (br s, 2H), 0.91 (br s, 2H).
1-((R)-1-((2s,5S)-5-(6-oxa-1-azaspiro[3.3]heptan-1-yl)-1,3-dioxan-2-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	150 isomer 1	(M + H+) m/z: calcd 553.24: found 553.0.	1HNMR (400MHz, CDCl3) δ 11.80(s, 1H), 7.83(d, J=8.0, 1H), 7.45(d, J=4.0, 1H), 7.22(s, 1H), 7.10-7.04(m, 2H), 5.99(s, 1H), 5.09(m, 1H), 4.90-4.85(m, 2H), 4.73-4.67(m, 5H), 4.26(m, 1H), 3.94-3.91(m, 1H), 3.71-3.68(m, 1H), 3.22-3.20(m, 1H), 3.12-3.10(m, 1H), 2.74(s, 3H), 2.49-2.48(m, 4H), 2.36-2.32(m, 2H), 2.22(s, 3H), 1.26(m, 5H).
1-((R)-1-((2r,5R)-5-(6-oxa-1-azaspiro[3.3]heptan-1-yl)-1,3-dioxan-2-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	150 isomer 2	(M + H+) m/z: calcd 553.24: found 553.0.	1HNMR (400MHz, CDCl3) δ 11.58(s, 1H), 7.82 (d, J=8.0, 1H), 7.52-7.48(m, 1H), 7.23(m, 1H), 7.09-7.05(m, 2H), 5.99(s, 1H), 4.93(m, 1H), 4.82(d, J=8.0 1H), 4.75(m, 1H), 4.72(m, 2H), 4.70(m, 2H), 4.64(m, 1H), 4.42(m, 1H), 4.16(m, 1H), 3.53-3.48(m, 1H), 3.28(m, 1H), 3.01-2.98(m, 3H), 2.74(s, 3H), 2.47(s, 3H), 2.30-2.28(m, 2H), 2.27(s, 3H), 1.26(m, 6H).
1-((S)-1-((2s,5R)-5-(6-oxa-1-azaspiro[3.3]heptan-1-yl)-1,3-dioxan-2-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	151 isomer 1	(M + H+) m/z: calcd 553.24: found 553.0.	1HNMR (400MHz, CDCl3) δ 11.74(s, 1H), 7.84(d, J=4.0, 1H), 7.46(d, J=8.0, 1H), 7.22(s, 1H), 7.12-7.05(m, 2H), 6.02-5.99(m, 1H), 5.10(m, 1H), 4.90-4.85(m, 2H), 4.72-4.69(m, 5H), 4.26(m, 1H), 4.11(m, 1H), 3.94-3.91(m, 1H), 3.62-3.67(m, 1H), 3.22-3.20(m, 1H), 3.12-3.10(m, 1H), 2.74(s, 3H), 2.47(s, 4H), 2.34-2.31(m, 2H), 2.22-2.20(m, 4H), 1.25(m, 5H).
1-((S)-1-((2r,5S)-5-(6-oxa-1-azaspiro[3.3]heptan-1-yl)-	151 isomer 2	(M + H+) m/z: calcd 553.24:	1HNMR (400MHz, CDCl3) δ 11.46-11.41(m, 1H), 7.82(m, 1H), 7.52(m, 1H), 7.09(m, 1H), 7.07(m,

1,3-dioxan-2-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide		found 553.0.	2H), 5.99(s, 1H), 5.39(m, 1H), 4.94(m, 1H), 4.81(m, 1H), 4.76(m, 1H), 4.71(m, 1H), 4.64-4.63(m, 2H), 4.55(m, 1H), 4.40-4.37(m, 1H), 4.12(m, 1H), 3.51(m, 1H), 3.29(m, 1H), 3.00(s, 3H), 2.74(s, 3H), 2.48(s, 3H), 2.28-2.20(m, 5H), 2.02-2.00(m, 1H), 1.26(m, 10H), 0.88-0.86(m, 1H).
1-((R)-1-((3R,4R)-3-fluoro-1-(3-methoxycyclobutyl)piperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	152	(M+H+) m/z: calcd 555.27; found 555.4.	1H NMR (400MHz, CD3OD) δ 7.81 - 7.72 (m, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.19 - 7.09 (m, 2H), 6.32 (s, 1H), 4.71 - 4.63 (m, 2H), 4.58 - 4.49 (m, 1H), 3.68 - 3.59 (m, 1H), 3.26 - 3.12 (m, 4H), 2.75 (s, 1H), 2.67 - 2.58 (m, 4H), 2.56 (s, 3H), 2.54 - 2.36 (m, 4H), 2.33 (s, 3H), 1.99 - 1.90 (m, 1H), 1.78 - 1.60 (m, 6H), 1.18 - 0.99 (m, 2H).
1-((R)-1-((3S,4R)-3-fluoro-1-(3-methoxycyclobutyl)piperidin-4-yl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	153	(M+H+) m/z: calcd 555.27; found 555.1.	1H NMR (400 MHz, CDCl3) δ 7.81-7.78 (m,1H), 7.34-7.24 (m,1H), 7.06-6.97 (m,2H), 5.93 (s,1H), 4.93-4.49 (m,4H), 3.83-3.23 (m,2H), 3.15-3.13 (m,3H), 3.10-2.76 (m,1H), 2.64 (s,4H), 2.41 (s,3H), 2.29-2.27 (m,4H), 2.14 (s,3H), 1.81-1.72 (m,4H), 1.53-1.21 (m,3H), 0.81-0.70 (m,1H).
1-((R)-1-(4-((3-(fluoromethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	154 isomer 1	(M + H+) m/z: calcd: 555.28; found 555.3.	1H NMR (500MHz, CDCl3) δ 7.84 (br d, J = 7.9 Hz, 1 H), 7.45 (br d, J = 8.5 Hz, 1 H), 7.32 (br s, 1 H), 7.09 (br s, 1 H), 7.08 - 7.02 (m, 1 H), 7.12 - 7.00 (m, 2 H), 6.01 (s, 1 H), 4.71 (s, 2 H), 4.62 (s, 1 H), 4.55 (br d, J = 3.1 Hz, 1 H), 4.47 - 4.39 (m, 2 H), 4.27 - 4.17 (m, 1 H), 3.00 (br s, 1 H), 2.31 (br d, J = 9.8 Hz, 1 H), 2.21 (s, 2 H), 2.18 (s, 1 H), 1.84 - 1.76 (m, 1 H), 1.59 (br d, J = 7.3 Hz, 3 H), 1.31 (br d, J = 4.3 Hz, 1 H), 0.94 - 0.83 (m, 1 H).
1-((R)-1-(4-((3-(fluoromethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	154 isomer 2	(M + H+) m/z: calcd: 555.28; found 555.3.	1H NMR (500MHz, CDCl3) δ 12.47 - 12.18 (m, 1 H), 7.90 - 7.78 (m, 1 H), 7.49 - 7.40 (m, 1 H), 7.30 (br s, 1 H), 7.34 - 7.28 (m, 1 H), 7.13 - 7.00 (m, 2 H), 6.01 (s, 1 H), 4.73 (br s, 3 H), 4.63 (br s, 1 H), 4.55 - 4.35 (m, 5 H), 4.10 - 4.00 (m, 1 H), 2.71 (s, 3 H), 2.49 (s, 3

			H), 2.23 - 2.21 (m, 3 H), 2.20 - 2.14 (m, 1 H), 2.11 - 2.06 (m, 1 H), 1.93 - 1.87 (m, 1 H), 1.62 - 1.58 (m, 4 H), 1.27 - 1.19 (m, 2 H), 1.17 - 1.08 (m, 1 H), 1.06 - 1.00 (m, 1 H), 0.95 - 0.77 (m, 2 H).
1-((R)-1-(4-((3-(fluoromethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	155 isomer 1	(M+H+) m/z: calcd 556.71; found 556.3.	1H NMR (400MHz, CD3OD) δ 8.19 (dd, J = 1.2, 4.5 Hz, 1H), 8.10 (br d, J = 7.6 Hz, 1H), 7.12 (dd, J = 4.8, 7.6 Hz, 1H), 6.31 (s, 1H), 4.77 (s, 1H), 4.65 (s, 1H), 4.61 (s, 2H), 4.57 - 4.38 (m, 4H), 4.09 (br s, 1H), 2.78 - 2.51 (m, 8H), 2.32 (s, 3H), 2.12 (br d, J = 11.6 Hz, 1H), 1.88 (br d, J = 11.6 Hz, 1H), 1.75 - 1.50 (m, 4H), 1.31 - 1.11 (m, 2H), 0.93 (br s, 3H)
1-((R)-1-(4-((3-(fluoromethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	155 isomer 2	(M+H+) m/z: calcd 556.71; found 556.3	1H NMR (400MHz, CD3OD) δ 8.20 (br s, 1H), 8.10 (br d, J = 7.2 Hz, 1H), 7.12 (br s, 1H), 6.32 (s, 1H), 4.76 (s, 1H), 4.68 - 4.58 (m, 5H), 4.56 (br s, 1H), 4.48 (d, J = 6.4 Hz, 1H), 4.44 (br d, J = 5.6 Hz, 1H), 2.91 (br s, 1H), 2.74 (br s, 3H), 2.55 (s, 3H), 2.32 (s, 3H), 1.87 - 1.56 (m, 8H), 1.34 (br s, 2H), 1.13 (br d, J = 5.6 Hz, 1H), 0.90 (br s, 1H)
7-((R)-1-(4-((3-(fluoromethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-6-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide	156 isomer 1	(M+H+) m/z: calcd 557.26; found 557.2.	1H NMR (400MHz, CD3OD) δ 9.04 (s, 1H), 8.71 (s, 1H), 6.31 (s, 1H), 4.77 (s, 1H), 4.65 (s, 1H), 4.59 (s, 2H), 4.49-4.55 (m, 2H), 4.43 (dd, J = 6.4, 17.6 Hz, 2H), 4.15 (br s, 1H), 2.79 - 2.51 (m, 8H), 2.32 (s, 3H), 2.11 (br d, J = 10.8 Hz, 1H), 1.88 (br d, J = 11.6 Hz, 1H), 1.73 - 1.49 (m, 4H), 1.31 - 1.10 (m, 2H), 0.93 (br d, J = 5.2 Hz, 3H)
7-((R)-1-(4-((3-(fluoromethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-6-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide	156 isomer 2	(M+H+) m/z: calcd 557.26; found 557.1.	1H NMR (400MHz, CD3OD) δ 9.03 (s, 1H), 8.72 (s, 1H), 6.32 (s, 1H), 4.79 - 4.75 (m, 1H), 4.66 - 4.52 (m, 6H), 4.50 - 4.49 (m, 1H), 4.46 (dd, J = 6.4, 14.0 Hz, 1H), 2.96 - 2.87 (m, 1H), 2.76 (s, 3H), 2.56 (s, 3H), 2.32 (s, 3H), 1.87 - 1.54 (m, 8H), 1.36 (br d, J = 4.4 Hz, 2H), 1.23 - 1.11 (m, 1H), 0.92 (br s, 1H).

1-((R)-1-(4-(3-cyclopropyl-3-fluoroazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	157 single isomer	(M + H+) m/z: calcd: 566.29.; found 566.1	1H NMR (400MHz, CD3OD) δ 8.18 (br d, J = 4.0 Hz, 1H), 8.09 (br d, J = 7.6 Hz, 1H), 7.16 - 7.01 (m, 1H), 6.30 (s, 1H), 4.60 (s, 2H), 4.08 (br s, 1H), 3.28 (br d, J = 5.6 Hz, 2H), 3.25 - 3.20 (m, 2H), 2.67 (br s, 3H), 2.54 (s, 3H), 2.31 (s, 3H), 2.20 - 1.87 (m, 3H), 1.74 - 1.61 (m, 3H),1.59 -1.56 (m, 1H) 1.31 - 1.21 (m, 1H), 1.15 (br d, J = 6.4 Hz, 2H), 1.13 - 1.01 (m, 2H), 0.95 (br s, 1H), 0.89 - 0.80 (m, 1H), 0.56 (br d, J = 8.0 Hz, 2H), 0.48 - 0.36 (m, 2H)
1-((R)-1-(4-(3-hydroxy-3-isopropylazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	158 single isomer	(M + H+) m/z: calcd 566.78, found 566.3.	1H NMR (400MHz ,METHANOL-d4) δ = 8.24 - 8.16 (m, 1 H), 8.11 (br d, J = 7.8 Hz, 1 H), 7.13 (br dd, J = 4.6, 8.1 Hz, 1 H), 6.40 (s, 1 H), 4.61 (s, 2 H), 4.25 (br dd, J = 2.2, 11.0 Hz, 1 H), 4.17 (br dd, J = 2.7, 11.0 Hz, 1 H), 4.05 (d, J = 10.3 Hz, 1 H), 3.97 (d, J = 10.3 Hz, 1 H), 3.89 (dd, J = 5.4, 10.8 Hz, 1 H), 3.85 - 3.77 (m, 1 H), 3.00 (br d, J = 5.9 Hz, 2 H), 2.77 - 2.61 (m, 4 H), 2.56 (s, 3 H), 2.34 (s, 3 H), 2.28 - 2.08 (m, 2 H), 2.02 - 1.78 (m, 3 H), 1.67 (br s, 3 H), 1.41 - 1.17 (m, 3 H), 0.95 (t, J = 7.1 Hz, 3 H), 0.88 (t, J = 6.6 Hz, 3 H)
6-fluoro-1-((R)-1-(4-((3-(hydroxymethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	159 isomer 1	(M + H+) m/z: calcd: 571.28 ; found 571.3.	1H NMR (400MHz, CDCl3) δ 12.35 - 12.07 (m, 1 H), 7.76 (dd, J = 5.6, 8.6 Hz, 1 H), 7.24 (br. s., 1 H), 7.12 (d, J = 10.3 Hz, 1 H), 6.86 - 6.78 (m, 1 H), 6.03 (s, 1 H), 4.81 - 4.61 (m, 2 H), 4.48 (br. s., 2 H), 4.42 - 4.31 (m, 2 H), 4.05 - 3.98 (m, 1 H), 3.86 (br. s., 2 H), 2.66 (s, 2 H), 2.58 (br. s., 1 H), 2.49 (s, 3 H), 2.29 - 2.17 (m, 3 H), 2.07 (d, J = 12.2 Hz, 2 H), 1.93 (d, J = 12.7 Hz, 1 H), 1.57 (s, 3 H), 1.31 (br. s., 1 H), 1.18 - 1.06 (m, 1 H), 1.05 - 0.94 (m, 2 H), 0.90 - 0.68 (m, 2 H).
6-fluoro-1-((R)-1-(4-((3-(hydroxymethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-	159 isomer 2	(M + H+) m/z: calcd: 571.28 ; found 571.3.	1H NMR (400MHz, CDCl3) δ 12.55 - 12.37 (m, 1 H), 7.83 - 7.68 (m, 1 H), 7.12 (d, J = 10.3 Hz, 1 H), 6.82 (t, J = 8.1 Hz, 1 H), 6.03 (s, 1 H), 4.80 - 4.63 (m, 2 H), 4.57

dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide			- 4.42 (m, 2 H), 4.41 - 4.33 (m, 1 H), 4.19 (br. s., 1 H), 3.84 (br. s., 1 H), 2.92 (br. s., 1 H), 2.71 (s, 2 H), 2.49 (s, 3 H), 2.24 (s, 3 H), 2.08 (br. s., 1 H), 1.83 (d, J = 8.8 Hz, 1 H), 1.63 (br. s., 2 H), 1.57 (s, 4 H), 1.15 - 0.79 (m, 4 H).
1-((R)-1-(4-(3-(1H-1,2,3-triazol-1-yl)azetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide	160 single isomer	(M+H+) m/z: calcd 574.29; found 574.3	1H NMR (400 MHz, CD3OD) δ 8.12 (d, J = 0.8 Hz, 1H), 7.76 - 7.71 (m, 2H), 7.55 (br d, J = 7.9 Hz, 1H), 7.13 - 7.03 (m, 2H), 6.28 (s, 1H), 5.26 (quin, J = 6.9 Hz, 1H), 4.61 (d, J = 2.1 Hz, 2H), 4.18 - 4.07 (m, 1H), 3.84 (td, J = 7.7, 19.3 Hz, 2H), 3.64 - 3.55 (m, 2H), 2.61 (s, 3H), 2.52 (s, 3H), 2.29 (s, 3H), 2.23 (br d, J = 10.4 Hz, 2H), 2.13 (br d, J = 10.5 Hz, 1H), 1.96 (br d, J = 10.8 Hz, 1H), 1.66 - 1.57 (m, 4H), 1.21 - 1.07 (m, 2H), 0.98 - 0.74 (m, 3H)
2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((R)-1-(4-((1-(trifluoromethyl)cyclopropyl)amino)cyclohexyl)ethyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	161 single isomer	(M + H+) m/z: calcd: 576.25; found 576.6	1H NMR (400MHz, DMSO-d6) δ 11.67 (s, 1H), 8.18 (d, J = 4.0 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.81 (br t, J = 4.4 Hz, 1H), 7.09 (dd, J = 4.8, 8 Hz, 1H), 6.13 (s, 1H), 4.38 (br d, J = 4.8 Hz, 2H), 4.03 (br s, 1H), 2.65 (br d, J = 16 Hz, 4H), 2.56 (br s, 1H), 2.47 (s, 3H), 2.41 - 2.24 (m, 1H), 2.18 (s, 3H), 2.07 - 1.85 (m, 2H), 1.71 - 1.52 (m, 4H), 1.29 - 1.21 (m, 1H), 1.14 - 0.98 (m, 2H), 0.96 - 0.84 (m, 3H), 0.80 (br s, 3H)
2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((R)-1-(4-(3-(methylsulfonyl)azetidin-1-yl)cyclohexyl)ethyl)-1H-indole-3-carboxamide	162 isomer 1	(M+H+) m/z: calcd 585.25; found 585.1.	1H NMR (400MHz, CD3OD) δ 7.74 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.12 – 7.07 (m, 2H), 6.33 (s, 1H), 5.37 – 5.35 (m, 1H), 4.63 (s, 2H), 4.15 – 4.11 (m, 2H), 3.66 – 3.57 (m, 2H), 3.52 – 3.47 (m, 2H), 2.91 (s, 3H), 2.62 (s, 3H), 2.56 (s, 3H), 2.33 (s, 3H), 2.23 – 2.14 (m, 4H), 2.04 – 2.02 (m, 2H), 1.96 – 1.93 (m, 1H), 1.63 (d, J = 8.0 Hz, 4H), 0.94 – 0.90 (m, 1H).
2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((R)-1-(4-(3-(methylsulfonyl)azetidin-	162 isomer 2	(M+H+) m/z: calcd 585.25; found 585.1.	1H NMR (400MHz, CD3OD) δ 7.74 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.11 – 7.08 (m, 2H), 6.33 (s, 1H), 5.37 – 5.35 (m, 1H), 4.63 (s, 2H), 4.26 (br s, 1H), 4.07 –

1-yl)cyclohexyl)ethyl)-1H-indole-3-carboxamide			4.04 (m, 1H), 3.60 – 3.53 (m, 2H), 3.44 – 3.38 (m, 2H), 2.97 (s, 3H), 2.64 (s, 3H), 2.56 (s, 3H), 2.37 (s, 1H), 2.33 (s, 3H), 2.21 (t, J = 8.0 Hz, 1H), 2.05 (br s, 1H), 1.72 (br s, 2H), 1.62 (d, J = 8.0 Hz, 4H), 1.53 – 1.50 (m, 1H), 1.17 – 1.14 (m, 1H), 0.93 – 0.90 (m, 1H) .
2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((R)-1-(4-((3-(trifluoromethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	163 isomer 1	(M + H+) m/z: calcd: 592.26; found 592.3.	1H NMR (500MHz, CDCl3) δ 12.67 (br. s., 1 H), 8.25 - 8.18 (m, 1 H), 8.11 (dd, J = 1.5, 7.8 Hz, 1 H), 7.36 (br. s., 1 H), 6.99 (dd, J = 4.9, 7.8 Hz, 1 H), 6.03 (s, 1 H), 4.71 (dd, J = 7.1, 8.6 Hz, 4 H), 4.50 (t, J = 7.6 Hz, 2 H), 2.90 - 2.55 (m, 5 H), 2.50 (s, 3 H), 2.22 (s, 3 H), 2.11 (d, J = 9.8 Hz, 1 H), 1.93 (d, J = 11.7 Hz, 1 H), 1.74 - 1.55 (m, 4 H), 1.34 - 1.20 (m, 1 H), 0.99 (q, J = 11.2 Hz, 3 H), 0.83 (d, J = 10.3 Hz, 1 H).
2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((R)-1-(4-((3-(trifluoromethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide	163 isomer 2	(M + H+) m/z: calcd: 592.26; found 592.3.	1H NMR (500MHz, CDCl3) δ 12.75 (br. s., 1 H), 8.21 (br. s., 1 H), 8.17 - 8.04 (m, 1 H), 7.37 (br. s., 1 H), 6.99 (dd, J = 4.9, 7.8 Hz, 1 H), 6.03 (s, 1 H), 4.79 - 4.68 (m, 4 H), 4.58 - 4.47 (m, 2 H), 3.08 - 2.78 (m, 4 H), 2.49 (s, 3 H), 2.23 (s, 3 H), 1.82 (br. s., 1 H), 1.65 (br. s., 6 H), 1.37 (br. s., 2 H), 1.07 (dd, J = 5.1, 13.9 Hz, 1 H), 0.90 (d, J = 9.3 Hz, 1 H).
6-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-7-((R)-1-(4-((3-(trifluoromethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide	164 isomer 1	(M+H+) m/z: calcd 593.24; found 593.1	1H NMR (400MHz, CD3OD) δ 9.03 (s, 1H), 8.84 - 8.55 (m, 1H), 6.32 (s, 1H), 4.68 (dd, J = 7.0, 10.8 Hz, 2H), 4.62 - 4.51 (m, 4H), 4.18 (br s, 1H), 2.69 (br s, 3H), 2.62 (br s, 1H), 2.55 (s, 3H), 2.32 (s, 3H), 2.11 (br d, J = 9.5 Hz, 1H), 1.98 - 1.91 (m, 1H), 1.73 - 1.61 (m, 4H), 1.38 - 1.03 (m, 3H), 1.02 - 0.85 (m, 3H)
6-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-7-((R)-1-(4-((3-(trifluoromethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-7H-pyrrolo[2,3-	164 isomer 2	(M+H+) m/z: calcd 593.24; found 593.1	1H NMR (400MHz, CD3OD) δ 9.01 (s, 1H), 8.70 (s, 1H), 6.30 (s, 1H), 4.71 - 4.64 (m, 2H), 4.61 - 4.54 (m, 4H), 4.42 - 4.21 (m, 1H), 3.01 - 2.90 (m, 1H), 2.73 (s, 3H), 2.54 (s, 3H), 2.30 (s, 3H), 1.81 (br d, J = 8.8 Hz, 1H), 1.67 (br d, J = 6.5 Hz, 6H), 1.49 - 0.98 (m, 4H),

d]pyrimidine-5-carboxamide			0.84 (br s, 1H)

EZH2 Assays

IC$_{50}$ measurements for Inhibitors using EZH2

[00170] *EZH2 biochemical assay* (IC$_{50}$): Compound potencies were assessed through incorporation of ^{3}H-SAM into a biotinylated H3 peptide. Specifically, 30 pM PRC2 containing wt EZH2 (pentameric complex prepared in-house) was pre-incubated with 450 nM SAM, 450 nM ^{3}H-SAM, 2 µM H3K27me3 activating peptide (H_2N-RKQLATKAAR(Kme3)SAPATGGVKKP-amide) and compounds (as 10 point duplicate dose response titrations in DMSO, final assay 0.8% DMSO (v/v)) for 3-5 h in 50 mM Tris (pH 8.5), 1 mM DTT, 0.07 mM Brij-35, 0.1% BSA, and 0.8% DMSO in a total volume of 12.5 µl. Reaction was initiated with biotinylated H3 substrate peptide (H_2N-RKQLATKAAR(Kme1)SAPATGGVKKP-NTPEGBiot) as a 2 µM stock in 12.5 µl of buffer and allowed to react at room temperature for 18-22 h. Quenching was accomplished by addition of 20 µl of STOP solution (50 mM Tris (pH 8.5), 200 mM EDTA, 2 mM SAH). 35 µl of the quenched solution was transferred to streptavidin coated FlashPlates (PerkinElmer), incubated 1-2 h, washed, and read in a TopCount Reader (PerkinElmer). IC$_{50}$s were calculated in Genedata Screener using non-linear least square four parameter fits, where the four parameters were IC$_{50}$, Hill slope, pre-transitional baseline (0% INH), and post-transitional baseline (100% INH).

[00171] **Table 1** shows the activity of selected compounds of this invention in the EZH2 activity inhibition assays. IC$_{50}$ values are reported as follows: "A" indicates an IC$_{50}$ value of less than 0.5 nM; "B" indicates an IC$_{50}$ value of 0.5 nM to 5 nM; "C" indicates an IC$_{50}$ value of greater than 5 nM for each enzyme; and "ND" is not determined.

Table 1: IC$_{50}$ values for selected compounds.

Example	EZH2 (IC$_{50}$)
1 (isomer 1)	**A**
1 (isomer 2)	**A**
2 (isomer 1)	**A**
2 (isomer 2)	**A**
3 (isomer 1)	**A**
3 (isomer 2)	**A**

Example	EZH2 (IC$_{50}$)
16 (isomer 1)	**A**
16 (isomer 2)	**C**
17	**A**
18 (isomer 1)	**A**
18 (isomer 2)	**A**
19 (isomer 1)	**A**

4 (isomer 1)	A
4 (isomer 2)	A
5 (isomer 1)	B
5 (isomer 2)	A
6 (isomer 1)	A
6 (isomer 2)	B
7 (isomer 1)	B
7 (isomer 2)	A
8	A
9	A
10	A
11	A
12	A
13	A
14 (isomer 1)	A
14 (isomer 2)	C
15 (isomer 1)	A
15 (isomer 2)	A

19 (isomer 2)	A
20 (isomer 1)	A
20 (isomer 2)	A
21 (isomer 1)	A
21 (isomer 2)	A
22 (isomer 1)	A
22 (isomer 2)	A
23 (isomer 1)	B
23 (isomer 2)	A
24 (isomer 1)	A
24 (isomer 2)	A
25	A
26	A
27 (isomer 1)	A
27 (isomer 2)	ND

Example	EZH2 (IC_{50})
28 (isomer 1)	A
28 (isomer 2)	A
29	A
30	A
31	C
32	A
33	B
34	C
35	C
36 (isomer 1)	A
36 (isomer 2)	A
37	A
38	A

Example	EZH2 (IC_{50})
102 (isomer 1)	A
102 (isomer 2)	A
103	A
104 (isomer 1)	B
104 (isomer 2)	B
105	B
106 (isomer 1)	A
106 (isomer 2)	A
107	A
108	A
109	A
110	A
111	A

39	A
40	B
41 (isomer 1)	A
41 (isomer 2)	A
42	A
43	A
44 (isomer 1)	A
44 (isomer 2)	A
45	A
46	A
47	B
48	A
49	B
50	A
51 (isomer 1)	A
51 (isomer 2)	A
52	A
53 (isomer 1)	A
53 (isomer 2)	A
54	B
55	B
56	A
57	A
58	A
59	A
60 (isomer 1)	A
60	A
61	A
62 (isomer 1)	A
62	B
63	A
64 (isomer 1)	A
64 (isomer 2)	A
65	A
66	A

112 (isomer 1)	A
112 (isomer 2)	A
113 (isomer 1)	A
113 (isomer 2)	A
114	C
115	A
116	A
117	B
118	A
119	A
120	A
121 (isomer 1)	A
121 (isomer 2)	B
122	A
123 (isomer 1)	A
123 (isomer 2)	A
124	A
125 (isomer 1)	A
125 (isomer 2)	A
126	A
127	A
128	B
129	A
130	A
131	A
132	A
133	A
134 (isomer 1)	A
134 (isomer 2)	A
135	A
136	A
137 (isomer 1)	A
137 (isomer 2)	A
138 (isomer 1)	B
138 (isomer 2)	A

67 (isomer 1)	A
67 (isomer 2)	A
68	A
69	A
70 (isomer 1)	A
70 (isomer 2)	B
71	A
72	A
73	A
74	A
75 (isomer 1)	A
75 (isomer 2)	A
76 (isomer 1)	A
76 (isomer 2)	B
77	A
78 (isomer 1)	A
78 (isomer 2)	C
79 (isomer 1)	A
79 (isomer 2)	A
80	A
81	A
82	A
83	A
84 (isomer 1)	A
84 (isomer 2)	A
85 (isomer 1)	A
85 (isomer 2)	B
86	B
87	B
88	A
89	A
90 (isomer 1)	A
90 (isomer 2)	A
91 (isomer 1)	A
91 (isomer 2)	A

139 (isomer 1)	A
139 (isomer 2)	B
140	A
141	A
142	A
143 (isomer 1)	A
143 (isomer 2)	A
144 (isomer 1)	A
144 (isomer 2)	A
145 (isomer 1)	B
145 (isomer 2)	A
146	A
147 (isomer 1)	A
147 (isomer 2)	A
148 (isomer 1)	A
148 (isomer 2)	A
149 (isomer 1)	A
149 (isomer 2)	A
150 (isomer 1)	B
150 (isomer 2)	A
151 (isomer 1)	B
151 (isomer 2)	C
152	A
153	A
154 (isomer 1)	A
154 (isomer 2)	A
155 (isomer 1)	A
155 (isomer 2)	B
156 (isomer 1)	A
156 (isomer 2)	A
157	A
158	A
159 (isomer 1)	A
159 (isomer 2)	A
160	A

92	**A**
93	**A**
94 (isomer 1)	**A**
94 (isomer 2)	**B**
95	**A**
96	**A**
97	**C**
98	**A**
99	**A**
100	**A**
101	**B**

161	**A**
162 (isomer 1)	**A**
162 (isomer 2)	**B**
163 (isomer 1)	**A**
163 (isomer 2)	**B**
164 (isomer 1)	**A**
164 (isomer 2)	**B**

EC_{50} measurements for Inhibitors in HeLa Cell Assays

[00172] *H3K27me3 Alpha Hela Assay (AlphaLISA).* Ten different doses of each test compound (in a series of 3-fold dilutions) were plated in duplicate 384-well tissue culture treated plates (Catalog # 6007680; Perkin Elmer, Waltham, MA). Hela cells grown in culture were trypsinized and counted using a Countess® cell counter (Catalog # C10281; Life Technologies, Grand Island, NY). Cell were diluted to 67,000 cells per mL in10% DMEM (Catalog # 10569-010 Life Technologies, Grand Island, NY) and 15µL (1,000 cells) were plated into each well using the Biotek MicroFlo™ Select Dispenser (BioTek Instruments, Inc. Vermont, USA),) of the 384-well plate. Plates were incubated at 37°C /5% CO_2 for 72 hrs. One of the duplicate plates was processed for HeLa assay and the other for viability.

[00173] 5µL of Cell-Histone Lysis buffer (1X) (Catalog # AL009F1 Perkin Elmer; Waltham, MA) per well was added to the plate processed for AlphaLISA and the plate was incubated at RT for 30 minutes on a plate shaker with low speed (Model# 4625-Q Thermo Scientific; Waltham, MA). Then, 10µL per well Histone Extraction buffer (catalog # AL009F2; Perkin Elmer; Waltham, MA) was added and the plate further incubated at RT for 20 min on plate shaker with low speed. Next, 10µL of 5X mix of anti-K27me3 acceptor beads plus Biotinylated anti-Histone H3 (C-ter) Antibody (diluted to 3nM final) (Catalog #AL118 Perkin Elmer; Waltham, MA) was added in each well. . Dilution of the acceptor beads and anti-Histone H3 was done in 1X Histone Detection buffer (Catalog # AL009F3 Perkin Elmer; Waltham, MA) which was produced by diluting the 10X stock provided. The plate was sealed with an aluminum plate sealer and incubated at 23°C for 60 min. Next, 10µL 5X solution of Streptavidin Donor beads were added (Catalog #6760002 Perkin Elmer;

Waltham, MA) (20µg/mL final in 1X Histone Detection Buffer), = plate was sealed with Aluminum plate sealer and incubated at 23^{0}C for 30 min. The plates were then read using an EnVision- Alpha Reader (model # 2104 Perkin Elmer; Waltham, MA).

[00174] Cell viability was assayed by adding 15 µL of Cell Titer Glo ((Catalog #G9241 Promega Madison, WI) to each well with cells with media. The plates were incubated at RT for 15 - 20 minutes on a plate shaker at low speed. The plates were then read using an EnVision- Alpha Reader (model # 2104 Perkin Elmer; Waltham, MA).

[00175] Data from both assays was analyzed using Genedata (Basel, Switzerland). Data files were imported to Genedata and assay conditions were specified. A unique Analysis ID was created and the data files analysed to measure dose-dependent inhibition of H3K27me3 mark and cell viability respectively. Readout of DMSO wells were used to normalize the data. Resulting curves were fitted using Smart fit application (Genedata; Basel, Switzerland). The data was checked for quality, validated and integrated in excel format using Stardrop (Optibruim, Cambridge, UK).

[00176] **Table 2** shows the activity of selected compounds of this invention in the HeLa cell assays described above. EC_{50} values are reported as follows: "A" indicates an EC_{50} value of less than 10 nM; "B" indicates an EC_{50} value of 10 nM to 100 nM; "C" indicates an EC_{50} value of greater than 100 nM; and "ND" is not determined.

Table 2. EC_{50} values for selected compounds.

Example	EZH2 Cell H3K27me3 Alpha HeLa (EC50 K27me3)
1 (isomer 1)	**A**
1 (isomer 2)	**B**
2 (isomer 1)	**A**
2 (isomer 2)	**B**
3 (isomer 1)	**A**
3 (isomer 2)	**B**
4 (isomer 1)	**A**
4 (isomer 2)	**B**
5 (isomer 1)	**B**
5 (isomer 2)	**A**
6 (isomer 1)	**A**

Example	EZH2 Cell H3K27me3 Alpha HeLa (EC50 K27me3)
16 (isomer 1)	**A**
16 (isomer 2)	**C**
17	**A**
18 (isomer 1)	**A**
18 (isomer 2)	**A**
19 (isomer 1)	**A**
19 (isomer 2)	**A**
20 (isomer 1)	**A**
20 (isomer 2)	**B**
21 (isomer 1)	**A**
21 (isomer 2)	**B**

6 (isomer 2)	C
7 (isomer 1)	C
7 (isomer 2)	A
8	A
9	A
10	A
11	B
12	A
13	A
14 (isomer 1)	B
14 (isomer 2)	C
15 (isomer 1)	A
15 (isomer 2)	C

22 (isomer 1)	A
22 (isomer 2)	A
23 (isomer 1)	B
23 (isomer 2)	A
24 (isomer 1)	A
24 (isomer 2)	A
25	A
26	A
27 (isomer 1)	A
27 (isomer 2)	ND

Example	EZH2 Cell H3K27me3 Alpha HeLa (EC50 K27me3)
28 (isomer 1)	A
28 (isomer 2)	B
29	A
30	A
31	C
32	B
33	B
34	C
35	C
36 (isomer 1)	B
36 (isomer 2)	A
37	B
38	B
39	B
40	C
41 (isomer 1)	A
41 (isomer 2)	A

Example	EZH2 Cell H3K27me3 Alpha HeLa (EC50 K27me3)
102 (isomer 1)	A
102 (isomer 2)	B
103	A
104 (isomer 1)	B
104 (isomer 2)	C
105	B
106 (isomer 1)	A
106 (isomer 2)	B
107	B
108	A
109	B
110	B
111	B
112 (isomer 1)	A
112 (isomer 2)	B
113 (isomer 1)	A
113 (isomer 2)	B

42	A
43	B
44 (isomer 1)	A
44 (isomer 2)	A
45	A
46	B
47	C
48	A
49	C
50	A
51 (isomer 1)	B
51 (isomer 2)	C
52	C
53 (isomer 1)	B
53 (isomer 2)	A
54	B
55	B
56	A
57	A
58	A
59	A
60 (isomer 1)	A
60	A
61	B
62 (isomer 1)	B
62	C
63	B
64 (isomer 1)	B
64 (isomer 2)	B
65	A
66	B
67 (isomer 1)	B
67 (isomer 2)	A
68	A
69	A

114	C
115	A
116	A
117	B
118	A
119	A
120	B
121 (isomer 1)	A
121 (isomer 2)	C
122	A
123 (isomer 1)	A
123 (isomer 2)	A
124	A
125 (isomer 1)	A
125 (isomer 2)	ND
126	A
127	B
128	B
129	A
130	A
131	A
132	A
133	A
134 (isomer 1)	A
134 (isomer 2)	A
135	C
136	C
137 (isomer 1)	A
137 (isomer 2)	A
138 (isomer 1)	B
138 (isomer 2)	B
139 (isomer 1)	B
139 (isomer 2)	B
140	B
141	B

70 (isomer 1)	A
70 (isomer 2)	C
71	A
72	B
73	A
74	B
75 (isomer 1)	B
75 (isomer 2)	B
76 (isomer 1)	A
76 (isomer 2)	C
77	B
78 (isomer 1)	B
78 (isomer 2)	C
79 (isomer 1)	A
79 (isomer 2)	B
80	B
81	B
82	A
83	A
84 (isomer 1)	A
84 (isomer 2)	B
85 (isomer 1)	B
85 (isomer 2)	C
86	B
87	A
88	B
89	B
90 (isomer 1)	B
90 (isomer 2)	C
91 (isomer 1)	A
91 (isomer 2)	B
92	A
93	B
94 (isomer 1)	A
94 (isomer 2)	C

142	C
143 (isomer 1)	A
143 (isomer 2)	A
144 (isomer 1)	A
144 (isomer 2)	A
145 (isomer 1)	C
145 (isomer 2)	C
146	A
147 (isomer 1)	A
147 (isomer 2)	A
148 (isomer 1)	B
148 (isomer 2)	B
149 (isomer 1)	B
149 (isomer 2)	B
150 (isomer 1)	C
150 (isomer 2)	A
151 (isomer 1)	C
151 (isomer 2)	C
152	A
153	A
154 (isomer 1)	B
154 (isomer 2)	A
155 (isomer 1)	A
155 (isomer 2)	B
156 (isomer 1)	A
156 (isomer 2)	B
157	B
158	C
159 (isomer 1)	B
159 (isomer 2)	B
160	A
161	B
162 (isomer 1)	B
162 (isomer 2)	C
163 (isomer 1)	A

95	**A**
96	**A**
97	**C**
98	**A**
99	**B**
100	**A**
101	**B**

163 (isomer 2)	**B**
164 (isomer 1)	**A**
164 (isomer 2)	**B**

Residence Time Measurments

[00177] *EZH2 residence time assay:* Compound residence times were assessed by monitoring the recovery of enzyme activity following a 100-fold dilution of pre-formed enzyme-inhibitor complex (dilution reaction), and comparing it to the activity of an undiluted control with the same final concentrations of all reagents (control reaction). Enzyme activity was measured by incorporation of ^{3}H-SAM into a biotinylated H3 peptide. For the dilution reaction, 20 nM PRC2 containing wt EZH2 (pentameric complex prepared in-house) was pre-incubated with 1 µM activating peptide (H_2N-RKQLATKAAR(Kme3)SAPATGGVKKP-amide) and compound at 600 times its K_i for 2 h in 40 µL of buffer (50 mM Tris pH 8.5, 4 mM DTT, 1 mM $MgCl_2$, 0.07 mM Brij-35, and 0.1 mg/mL BSA), then diluted 100-fold and the reaction initiated by transferring 1.4 µL to a 138.6 µL volume of buffer containing 1 µM activating peptide, 5.05 µM substrate peptide (H_2N-RKQLATKAARKSAPATGGVKKP-NTPEGbiot), 1.01 µM SAM, and 1.01 µM ^{3}H-SAM. For the control reaction, 0.202 nM PRC2 was pre-incubated with 1 µM activating peptide, 1.01 µM SAM, 1.01 µM ^{3}H-SAM, and compound at 6.06 times its Ki for 2 h in 138.6 µL of buffer, then the reaction was initiated by the addition of 1.4 µL 500 µM substrate peptide in water. Reactions were quenched at various time points spanning up to 10 hours, by transferring 8 µL aliquots from the reaction vessel to a plate containing 8 µL per well of STOP solution (50 mM Tris pH 8.5, 200 mM EDTA, 2 mM SAH). After the last time point, 12 µL of the quenched solutions were transferred to a streptavidin coated FlashPlate (PerkinElmer) containing 40 µL per well of STOP solution, incubated 1-8 h, washed, and read in a TopCount plate reader (PerkinElmer). A custom script was used to fit control reaction progress data to a straight line and dilution reaction progress data:

[00178] $$y = v_s t + \frac{v_i - v_s}{k_{obs}}\left(1 - e^{-k_{obs}t}\right) + \boldsymbol{background}$$

[00179] Where $\boldsymbol{y}$ is the product formed, $\boldsymbol{t}$ is the reaction time, $\boldsymbol{v_i}$ is the initial velocity, $\boldsymbol{v_s}$ is the steady state velocity, and $\boldsymbol{k_{obs}}$ is the rate constant for the transition from the initial

velocity phase of the curve to the steady state velocity phase of the curve. In fitting the dilution reaction progress data, v_s was constrained to the slope of the line fitted to the control reaction progress data. The fitted value of k_{obs} was then transformed into residence time:

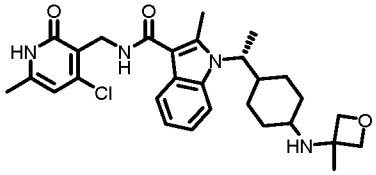
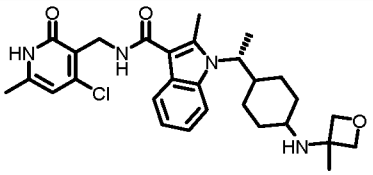
[00180] $$\tau = \frac{[EI] - \frac{1}{K_i}[E][I]}{k_{obs}[EI]}$$

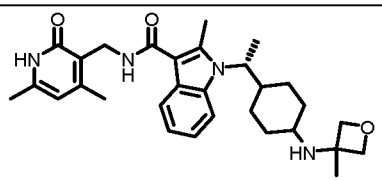
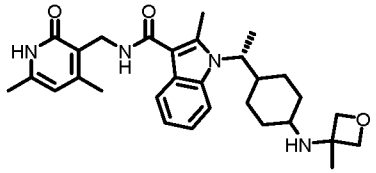
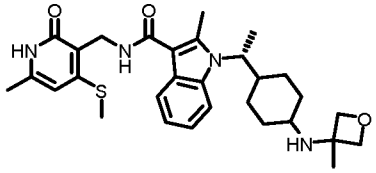
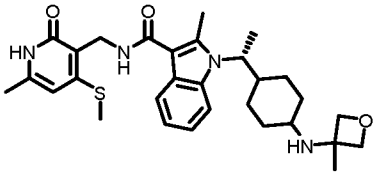
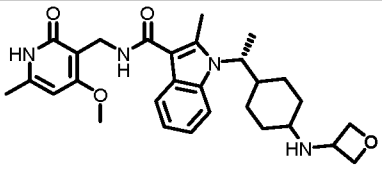
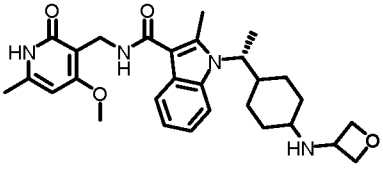
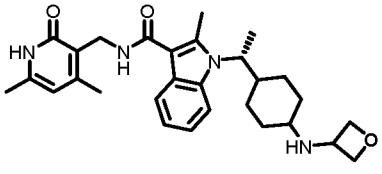
[00181] Where τ is residence time, K_i is the inhibition constant, $[EI]$ is the calculated equilibrium concentration of enzyme-inhibitor complex, $[E]$ is the calculated equilibrium concentration of free enzyme, and $[I]$ is the calculated equilibrium concentration of free inhibitor.

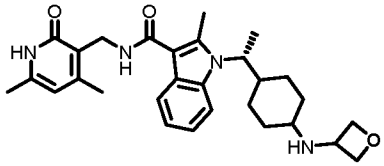
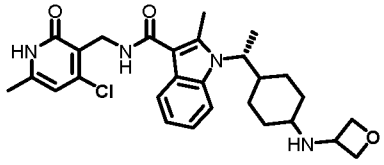
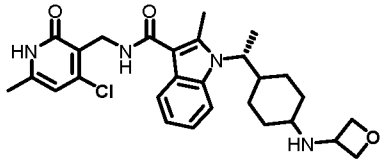
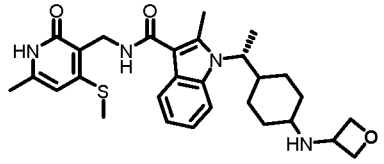
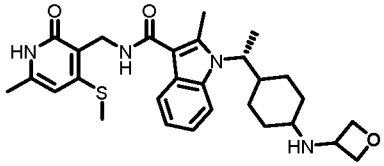
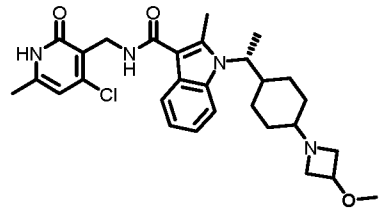
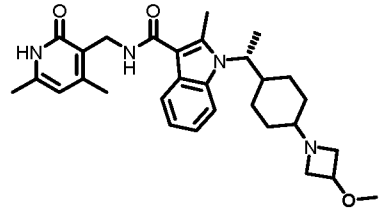
[00182] **Table 3** shows residence time and the activity of values for selected compounds of this invention in the EZH2 residence time assay and in the HeLa cell assays described above.

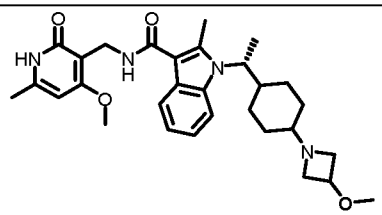
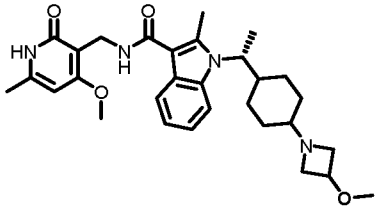
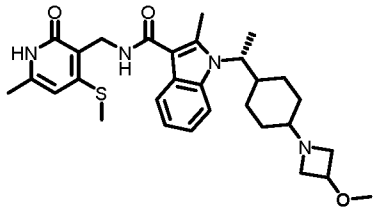
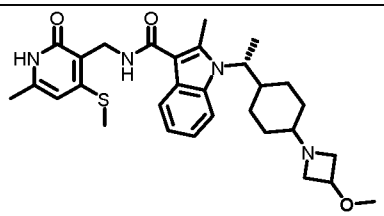
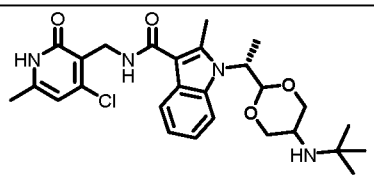
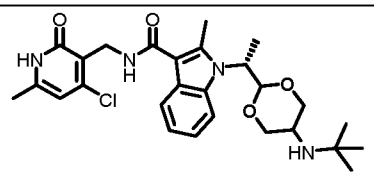
[00183] **Table 3**. Residence time values for selected compounds. Residence time values are reported as follows: "A" indicates a τ value of greater than 35 hours; "B" indicates a τ value of greater than 5 hours but less or equal than 35 hours; "C" indicates a τ value of greater than 0.5 hours but less or equal than 5 hours; "D" indicates a τ value of less or equal than 0.5 hours; and "ND" is not determined. EC_{50} values are reported as follows: "A" indicates an EC_{50} value of less than 5 nM; "B" indicates an EC_{50} value equal or greater than 5 nM but less than 25 nM; "C" indicates an EC_{50} value equal or greater than 25 nM but less than 125 nM; "D" indicates an EC_{50} value of greater than 125 nM; and "ND" is not determined.

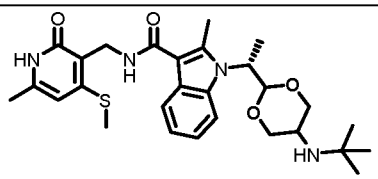
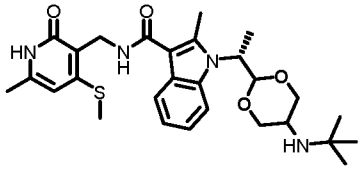
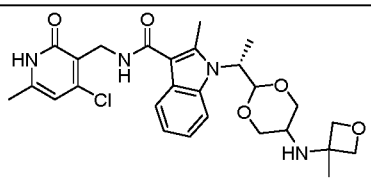
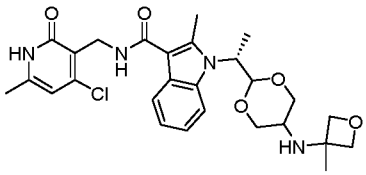
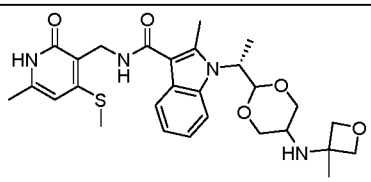
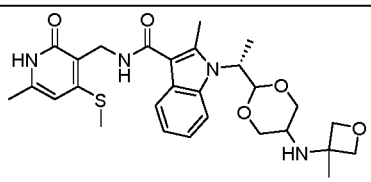
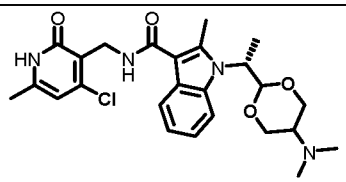
[00184] **Table 3**

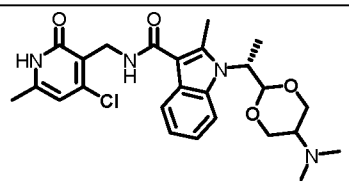
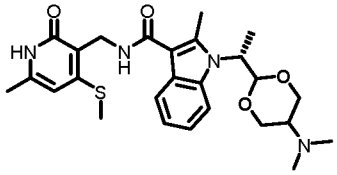
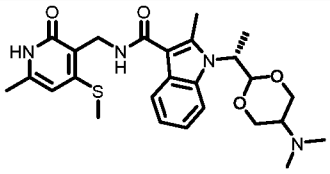
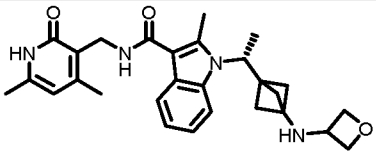
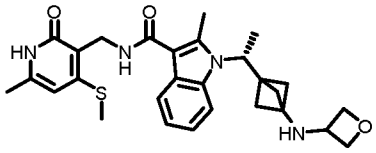
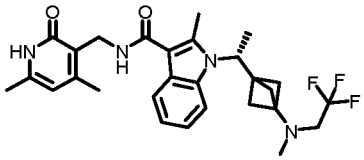
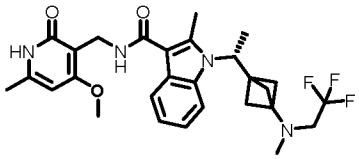
Example	Residence Time	EC_{50} Cellular Activity
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 **Comparator 1 (isomer 2)**	**B**	**B**

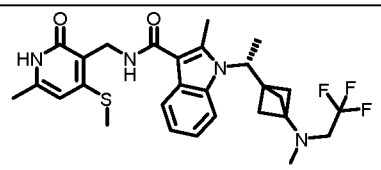
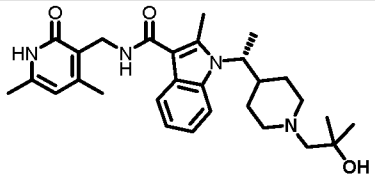
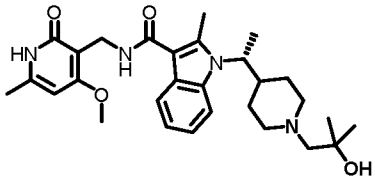
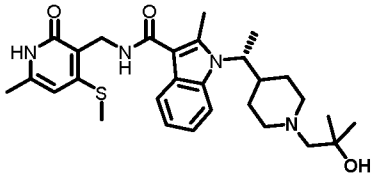
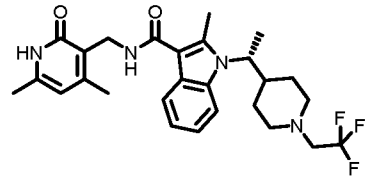
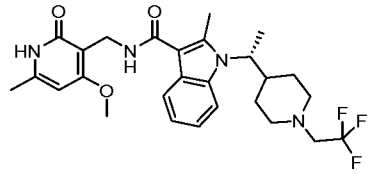
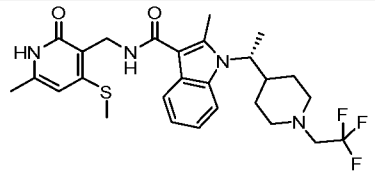
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 Comparator 2 (isomer 2)	B	A
 1 (isomer 1)	A	A
 1 (isomer 2)	B	B
 Comparator 3 (isomer 1)	D	D
 Comparator 3 (isomer 2)	C	C
 Comparator 4 (isomer 1)	D	D

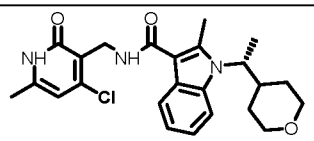
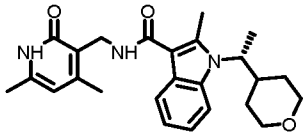
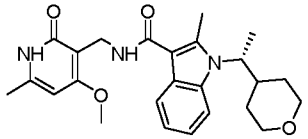
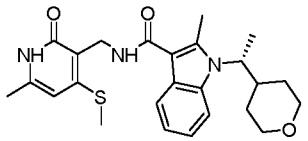
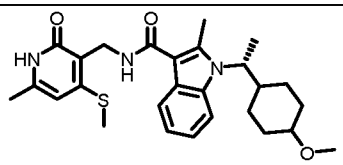
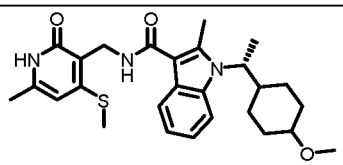
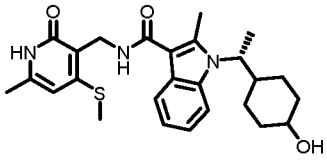
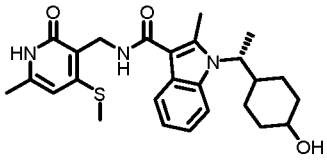
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 Comparator 5 (isomer 1)	D	D
 Comparator 5 (isomer 2)	C	C
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 2 (isomer 2)	C	C
 Comparator 6 (isomer 1)	C	B
 Comparator 21 (isomer 1)	C	B

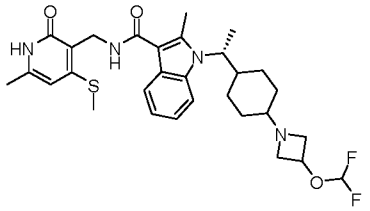
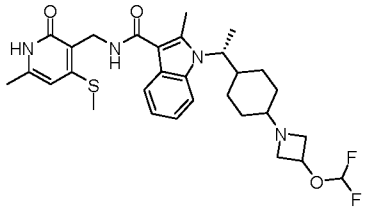
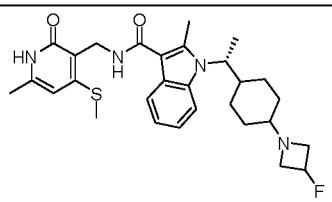
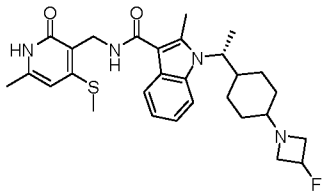
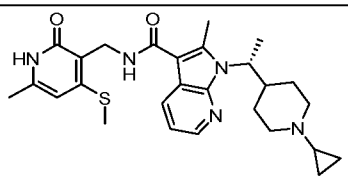
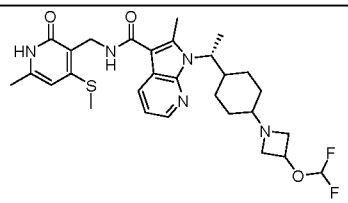
 Comparator 7 (isomer 1)	D	D
 Comparator 7 (isomer 2)	C	D
 4 (isomer 1)	A	A
 4 (isomer 2)	C	B
 Comparator 8 (isomer 1)	C	B
 Comparator 8 (isomer 1)	ND	B

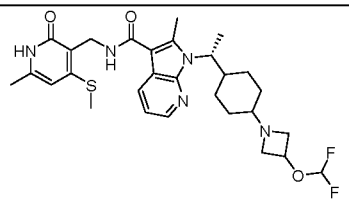
 5 (isomer 1)	D	C
 5 (isomer 2)	A	A
 Comparator 9 (isomer 1)	D	D
 Comparator 9 (isomer 2)	B	B
 6 (isomer 1)	A	A
 6 (isomer 2)	D	D
 Comparator 10 (isomer 1)	D	D

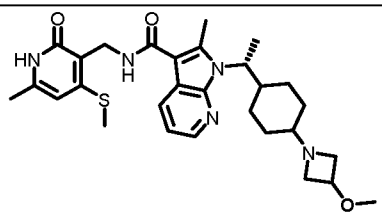
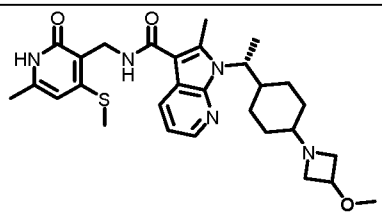
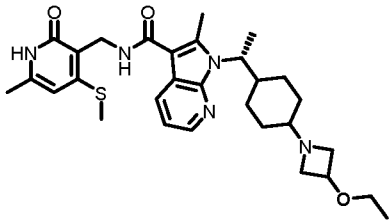
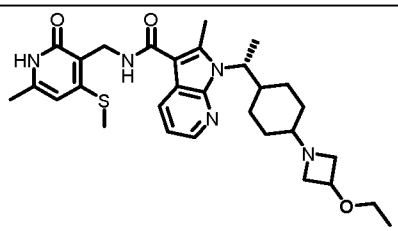
 Comparator 10 (isomer 2)	D	C
 7 (isomer 1)	D	D
 7 (isomer 2)	B	A
 Comparator 11	D	C
 8	B	A
 Comparator 12	D	D
 Comparator 13	C	C

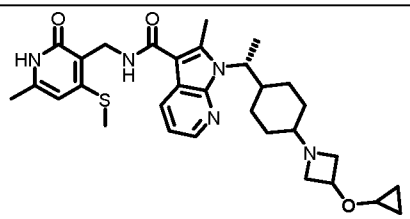
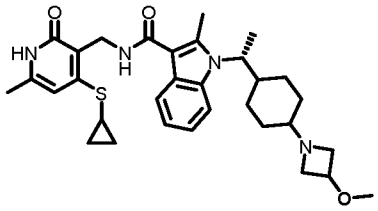
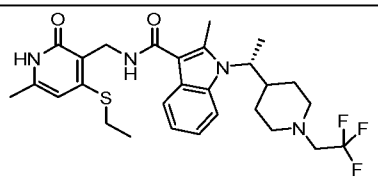
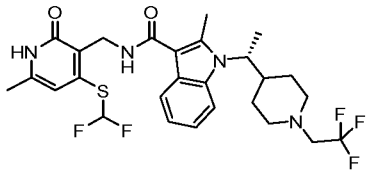
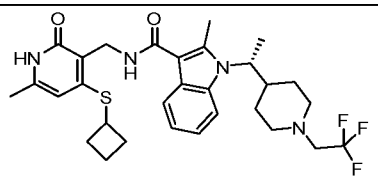
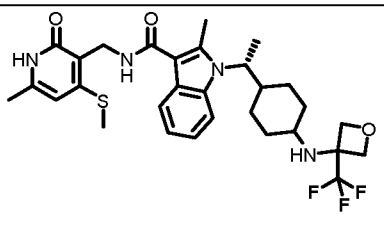
 **10**	**B**	**B**
 **Comparator 14**	**D**	**D**
 **Comparator 15**	**D**	**D**
 **11**	**B**	**C**
 **Comparator 16**	**D**	**C**
 **Comparator 17**	**C**	**B**
 **12**	**B**	**A**

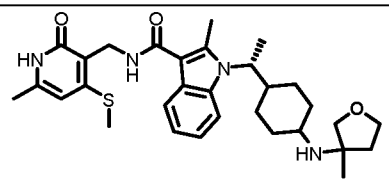
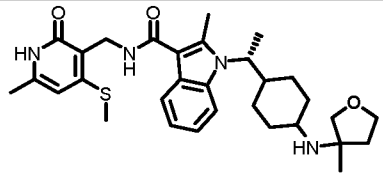
 Comparator 18	D	C
 Comparator 19	D	C
 Comparator 20	C	C
 13	C	A
 18 (isomer 1)	A	A
 18 (isomer 2)	ND	A
 19 (isomer 1)	B	A
 19 (isomer 2)	A	A

 **20 (isomer 1)**	**A**	**A**
 **20 (isomer 2)**	**ND**	**B**
 **24 (isomer 1)**	**A**	**A**
 **24 (isomer 2)**	**C**	**B**
 **26**	**B**	**A**
 **27 (isomer 1)**	**B**	**A**

 27 (isomer 2)	ND	ND

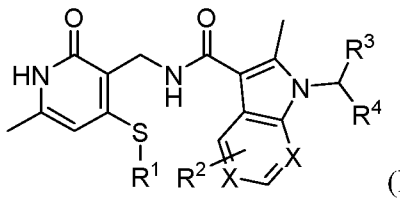
Example	Residence Time	EC_{50} Cellular Activity
 76 (isomer 1)	B	B
 76 (isomer 2)	ND	D
 91 (isomer 1)	B	A
 91 (isomer 2)	ND	C

 **30**	**B**	**A**
 **99**	**B**	**B**
 **86**	**D**	**C**
 **105**	**D**	**C**
 **109**	**C**	**C**
 **130**	**B**	**A**

 **149 (isomer 1)**	**A**	**B**
 **149 (isomer 2)**	**ND**	**C**

Listing of Claims:

1. A compound having the Formula **I**:



(**I**);

or a pharmaceutically acceptable salt thereof, wherein

each X is independently CH or N;

R^1 is $(C_1\text{-}C_4)$alkyl, -$(C_3\text{-}C_5)$cycloalkyl, or $(C_1\text{-}C_4)$haloalkyl;

R^2 is hydrogen, halo, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy, or -CN;

R^3 is $(C_1\text{-}C_4)$alkyl or halo$(C_1\text{-}C_4)$alkyl;

R^4 is $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkoxy, -$(C_1\text{-}C_4)$alkylOH, -$(C_1\text{-}C_4)$alkylO$(C_1\text{-}C_4)$alkyl, phenyl, 5-6 membered heteroaryl, monocyclic $(C_3\text{-}C_7)$cycloalkyl, bridged bicyclic $(C_5\text{-}C_8)$cycloalkyl, or 4-7 membered monocyclic heterocyclyl, wherein said phenyl, heteroaryl, monocyclic cycloalkyl, bridged bicyclic cycloalkyl, and heterocyclyl are each optionally substituted with 1 to 3 groups selected from R^5;

R^5 is selected from $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, halo$(C_3\text{-}C_6)$cycloalkyl, -$(C_1\text{-}C_4)$alkylOH, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy, halo, nitrile, amide, urea, carbamate, sulfonamide, hydroxyl, oxo, OR^6, -OC(O)$(C_1\text{-}C_4)$alkyl, -C(O)$(C_1\text{-}C_4)$alkyl, -C(O)$(C_1\text{-}C_4)$alkylOH, -C(O)$(C_1\text{-}C_4)$alkylNH$(C_1\text{-}C_4)$alkyl, -C(O)$(C_1\text{-}C_4)$alkylN($(C_1\text{-}C_4)$alkyl)$_2$, -C(O)$(C_1\text{-}C_4)$alkylNH$_2$, -SO$_2$$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkyl-O-$(C_1\text{-}C_4)$alkyl, substituted phenyl, 5-6 membered heteroaryl, 4-7 membered heterocyclyl, and NR^AR^B, , wherein said cycloalkyl for R^5 is optionally substituted with -O$(C_1\text{-}C_4)$alkyl;

R^A is hydrogen, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, 4-7 membered heterocyclyl, or $(C_1\text{-}C_4)$alkyl-O-$(C_1\text{-}C_4)$alkyl;

R^B is hydrogen, $(C_1\text{-}C_4)$alkyl, -$(C_3\text{-}C_5)$cycloalkyl, or 4-7 membered heterocyclyl, wherein said $(C_1\text{-}C_4)$alkyl for R^B is optionally substituted with 1 to 3 groups selected from halo, phenyl, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, and OH and wherein said heterocyclyl, -$(C_3\text{-}C_5)$cycloalkyl for R^B is optionally substituted with 1 to 3 groups selected from $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, hydroxy$(C_1\text{-}C_4)$alkyl, -O$(C_1\text{-}C_4)$alkyl, and -C(=O)O$(C_1\text{-}C_4)$alkyl; or

R^A and R^B taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclyl optionally substituted with 1 to 3 groups selected from halo,$(C_1$-

C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, oxo, halo(C_1-C_4)alkoxy, 5-6 membered heteroaryl, (C_3-C_6)cycloalkyl, -SO_2(C_1-C_4)alkyl, NMe_2, hydroxy, cyano, spirooxetanyl and (C_1-C_4)cycloalkoxy optionally substituted with (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, or (C_1-C_4)alkoxy; and

R^6 is (C_3-C_6)cycloalkyl, 4-7 membered heterocyclyl, or 5-6 membered heteroaryl, -O(C_1-C_4)alkyl, wherein said 4-7 membered heterocyclyl and said 5-6 membered heteroaryl for R^6 are each optionally and independently substituted with 1 or 2 (C_1-C_4)alkyl groups.

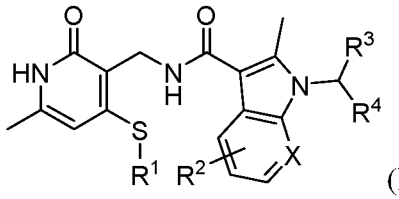
2. The compound of claim 1, wherein

R^5 is selected from (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, halo(C_3-C_6)cycloalkyl, -(C_1-C_4)alkylOH, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, halo, nitrile, amide, urea, carbamate, sulfonamide, hydroxyl, oxo, (C_1-C_4)alkyl-O-(C_1-C_4)alkyl, substituted phenyl, 5-6 membered heteroaryl and NR^AR^B;

R^B is hydrogen, (C_1-C_4)alkyl or 4-7 membered heterocyclyl, wherein said (C_1-C_4)alkyl for R^B is optionally substituted with 1 to 3 groups selected from halo, phenyl, (C_1-C_4)alkoxy, and OH and wherein said heterocyclyl for R^B is optionally substituted with 1 to 3 groups selected from (C_1-C_4)alkyl, -O(C_1-C_4)alkyl, and -C(=O)O(C_1-C_4)alkyl; or

R^A and R^B taken together with the nitrogen atom to which they are attached form a 4-7 membered heterocyclyl optionally substituted with 1 to 3 groups selected from halo,(C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, oxo, halo(C_1-C_4)alkoxy, and (C_1-C_4)cycloalkoxy optionally substituted with (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, or (C_1-C_4)alkoxy.

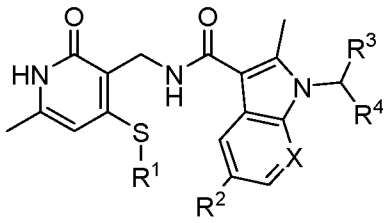
3. The compound of claim 1 or 2, wherein the compound is of the Formula **Ia**:



(**Ia**);

or a pharmaceutically acceptable salt thereof.

4. The compound of any one of claims 1 to 3, wherein the compound is of the Formula **Ia'**:

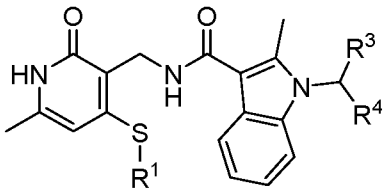


(**Ia'**);

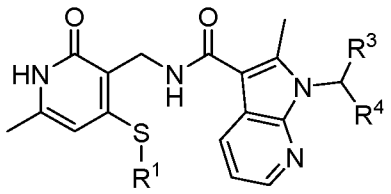
or a pharmaceutically acceptable salt thereof.

5. The compound of any one of claims 1 to 4, wherein R^2 is hydrogen or fluorine.

6. The compound of any one of claims 1 to 5, wherein the compound is of the Formula **II** or **IIa**:



(**II**); or



(**IIa**);

or a pharmaceutically acceptable salt thereof.

7. The compound of any one of claims 1 to 6, wherein

R^3 is $(C_1\text{-}C_4)$alkyl;

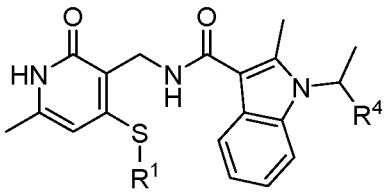
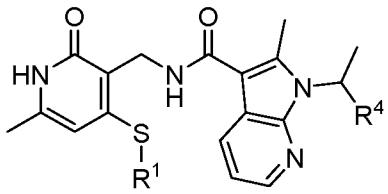
R^4 is -$(C_1\text{-}C_4)$alkylOH, -$(C_1\text{-}C_4)$alkylO$(C_1\text{-}C_4)$alkyl, monocyclic $(C_3\text{-}C_6)$cycloalkyl, bridged bicyclic $(C_5\text{-}C_8)$cycloalkyl, or 4-7 membered heterocyclyl, wherein said cycloalkyl and heterocyclyl are each optionally substituted with 1 to 2 groups selected from R^5; or

R^5 is selected from $(C_1\text{-}C_4)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, hydroxyl, $(C_1\text{-}C_4)$alkoxy, halo, -$(C_1\text{-}C_4)$alkylOH, halo$(C_1\text{-}C_4)$alkyl, and NR^AR^B; and

R^B is hydrogen, $(C_1\text{-}C_4)$alkyl or 4-7 membered heterocyclyl, wherein said $(C_1\text{-}C_4)$alkyl for R^B is optionally substituted with 1 to 3 groups selected from halo, phenyl, and OH and wherein said heterocyclyl for R^B is optionally substituted with 1 to 3 groups selected from $(C_1\text{-}C_4)$alkyl, -O$(C_1\text{-}C_4)$alkyl, and -C(=O)O$(C_1\text{-}C_4)$alkyl; or

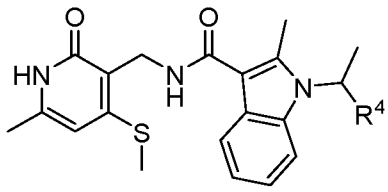
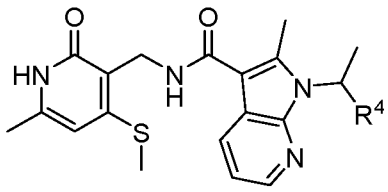
R^A and R^B taken together with the nitrogen atom to which they are attached form a 4-7 membered heterocyclyl optionally substituted with 1 or 2 groups selected from $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkoxy, halo, and $(C_1\text{-}C_4)$alkoxy.

8. The compound of any one of claims 1 to 7, wherein the compound is of the Formula **III** or **IIIa**:


(**III**); or

(**IIIa**);

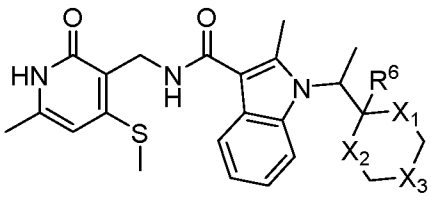
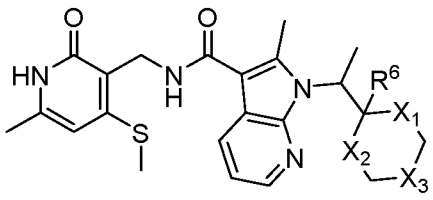
or a pharmaceutically acceptable salt thereof.

9. The compound of any one of claims 1 to 8, wherein the compound is of the Formula **IV** or **IVa**:


(**IV**); or

(**IVa**);

or a pharmaceutically acceptable salt thereof.

10. The compound of any one of claims 1 to 9, wherein the compound is of the Formula **V** or **Va**:


(**V**); or

(**Va**);

or a pharmaceutically acceptable salt thereof, wherein

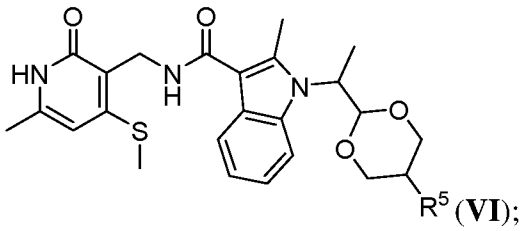
X_1 and X_2 are each independently absent, O, or CH_2;

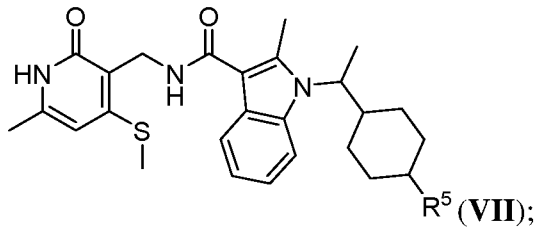
X_3 is O, NH, -NR^7, CH_2, or -CHR^5;

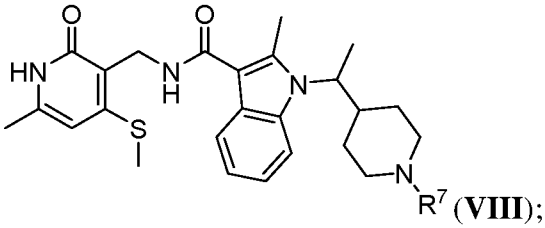
R^6 is hydrogen or R^6 and X_3 taken together with their intervening ring atoms form a bridged bicyclic (C_5-C_8)cycloalkyl; and

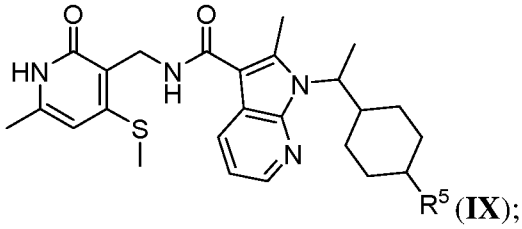
R^7 is (C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, -(C_1-C_4)alkylOH, or halo(C_1-C_4)alkyl; provided that X_3 is not O, NH, or NR^7 when X_1 and X_2 are each O.

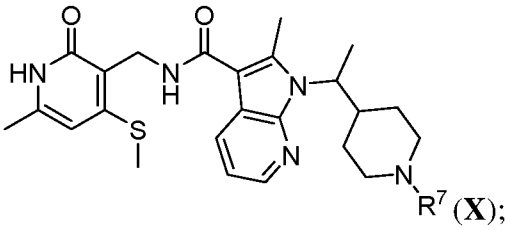
11. The compound of any one of claims 1 to 10, wherein the compound is of the Formula **VI**, **VII**, **VIII**, **IX**, **X**, or **XI**:

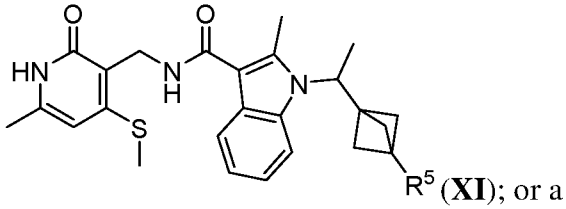

(**VI**);


(**VII**);

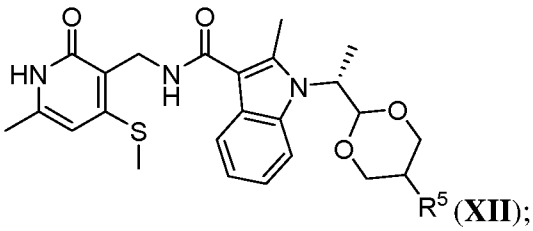

(**VIII**);

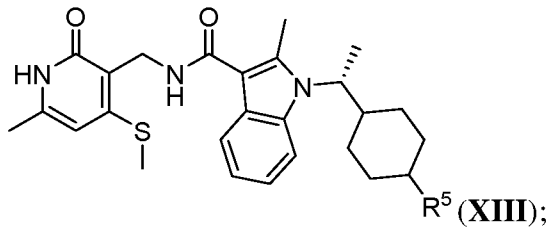

(**IX**);

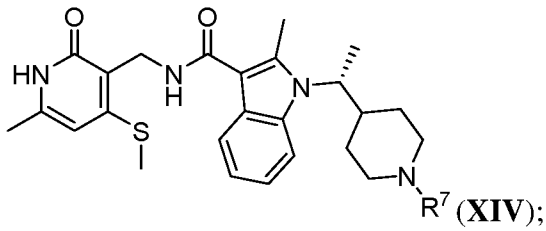

(**X**);

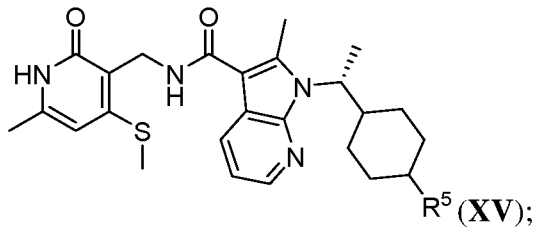

(**XI**); or a pharmaceutically acceptable salt thereof.

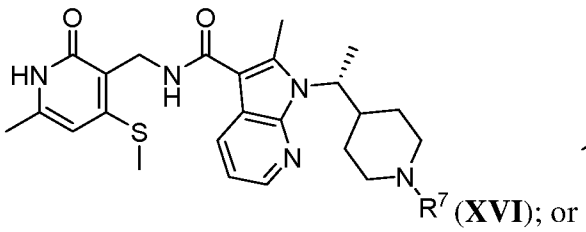
12. The compound of any one of claims 1 to 11, wherein the compound is of the Formula **XII**, **XIII**, **XIV**, **XV**, **XVI**, or **XVII**:

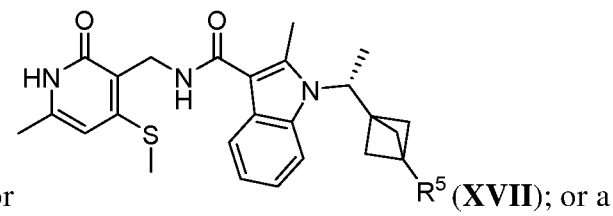

(**XII**);


(**XIII**);

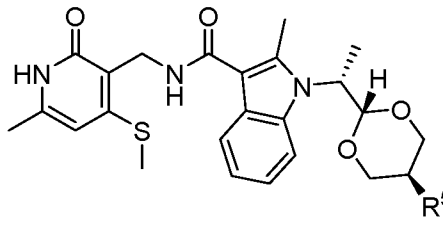

(**XIV**);


(**XV**);

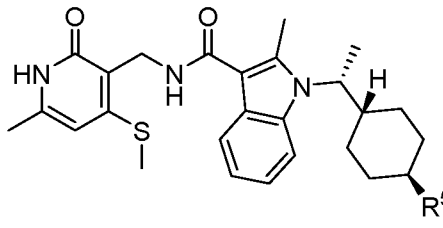

(**XVI**); or


(**XVII**); or a pharmaceutically acceptable salt thereof.

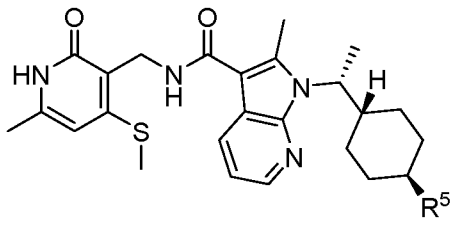
13. The compound of any one of claims 1 to 12, wherein the compound is of the Formula **XVIII**, **XIX**, or **XX**:



(**XVIII**);

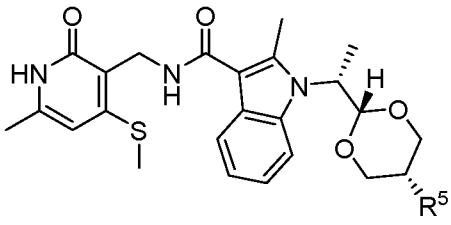


(**XIX**); or

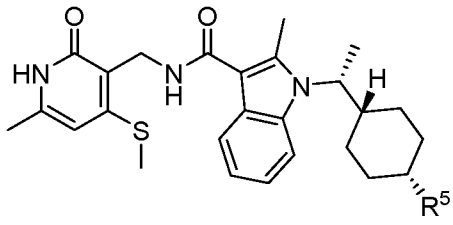


(**XX**) ; or a pharmaceutically acceptable salt thereof.

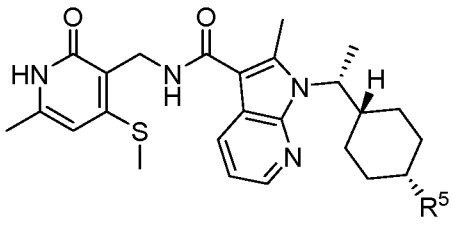
14. The compound of any one of claims 1 to 13, wherein the compound is of the Formula **XVIII'**, **XIX'**, or **XX'**:



(**XVIII'**);



(**XIX'**); or



(**XX'**); or a pharmaceutically acceptable salt thereof.

15. The compound of any one of claims 1 to 14, where R^5 is halo(C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, or NR^AR^B.

16. The compound of any one of claims 1 to 12, where R^7 is halo(C_1-C_4)alkyl, -(C_1-C_4)alkylOH, or (C_3-C_6)cycloalkyl.

17. The compound of any one of claims 1 to 15, wherein

R^B is (C_1-C_4)alkyl or a monocyclic 4- to 6- membered heterocyclyl, wherein said (C_1-C_4)alkyl for R^B is optionally substituted with 1 to 3 groups selected from halo and -O(C_1-C_4)alkyl and wherein said heterocyclyl for R^B is optionally substituted with 1 to 2 (C_1-C_4)alkyl; or

R^A and R^B taken together with the nitrogen atom to which they are attached form a monocyclic 4- to 6- membered heterocyclyl optionally substituted with 1 or 2 groups selected from (C_1-C_4)alkyl, halo, halo(C_1-C_4)alkoxy, and (C_1-C_4)alkoxy.

18. The compound of any one of claims 1 to 15 and 17, wherein

R^B is (C_1-C_4)alkyl or oxetanyl, wherein said (C_1-C_4)alkyl for R^B is optionally substituted with 1 to 3 groups selected from halo and -O(C_1-C_4)alkyl and wherein said oxetanyl for R^B is optionally substituted with 1 or 2 (C_1-C_4)alkyl; or

R^A and R^B taken together with the nitrogen atom to which they are attached form an azetidinyl or oxetanyl, each of which are optionally substituted with 1 or 2 groups selected from (C_1-C_4)alkyl, halo, halo(C_1-C_4)alkoxy, and (C_1-C_4)alkoxy.

19. The compound of any one of claims 1 to 15, 17, and 18, wherein R^A is hydrogen, halo(C_1-C_4)alkyl, or (C_1-C_4)alkyl.

20. The compound of any one of claims 1 to 15 and 17 to 19, wherein

R^A is hydrogen, halo(C_1-C_4)alkyl, or (C_1-C_4)alkyl;

R^B is (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, or oxetanyl, wherein said oxetanyl is optionally substituted with (C_1-C_4)alkyl; or

R^A and R^B taken together with the nitrogen atom to which they are attached form an azetidinyl optionally substituted with 1 or 2 groups selected from (C_1-C_4)alkoxy, halo, and halo(C_1-C_4)alkoxy.

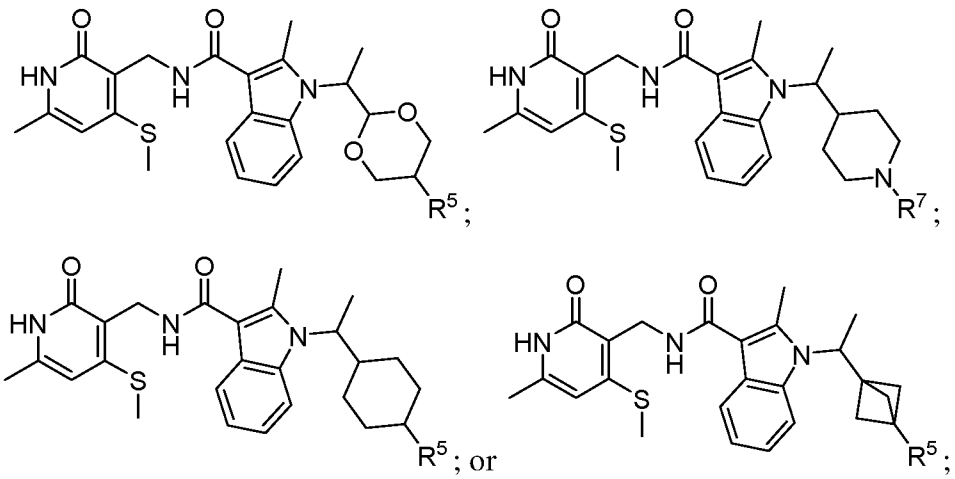
21. The compound of any one of claims 1 to 15 and 17 to 20, wherein

R^A is hydrogen or methyl;

R^B is (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, or oxetanyl, wherein said oxetanyl is optionally substituted with methyl; or

R^A and R^B taken together with the nitrogen atom to which they are attached form an azetidinyl optionally substituted with methoxy, trifluoromethoxy, difluoromethoxy, difluoromethyl, or one or two fluoro.

22. The compound of claim 1, wherein the compound is of the Formula:



or a pharmaceutically acceptable salt thereof, wherein

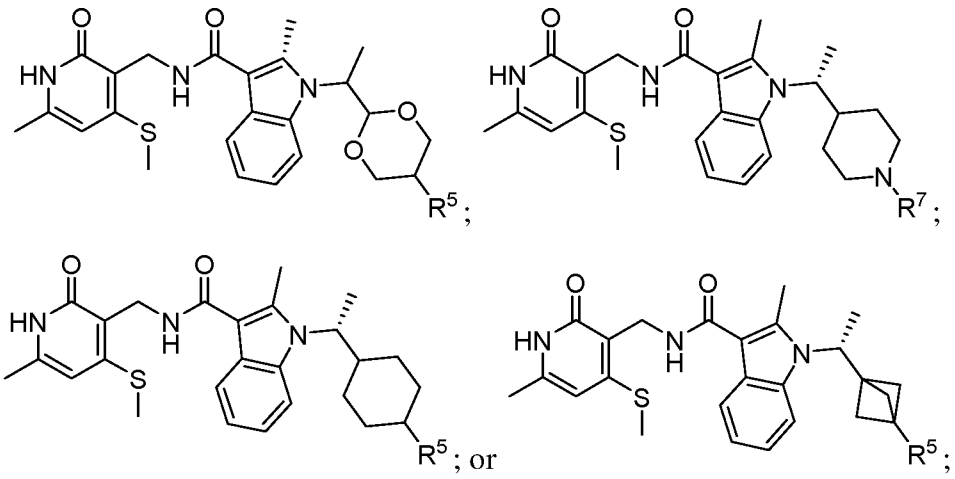
R^5 is hydroxyl, (C_1-C_4)alkoxy, or NR^AR^B;

R^A is hydrogen, (C_1-C_4)alkyl, or halo(C_1-C_4)alkyl;

R^B is (C_1-C_4)alkyl or monocyclic 4- to 6- membered heterocyclyl optionally substituted with 1 or 2 (C_1-C_4)alkyl; or

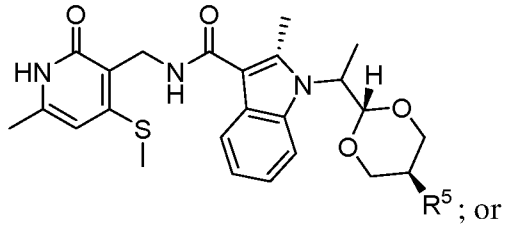
R^A and R^B taken together with the nitrogen atom to which they are attached form a monocyclic 4- to 6- membered heterocyclyl optionally substituted with halo, (C_1-C_4)alkoxy or halo(C_1-C_4)alkoxy.

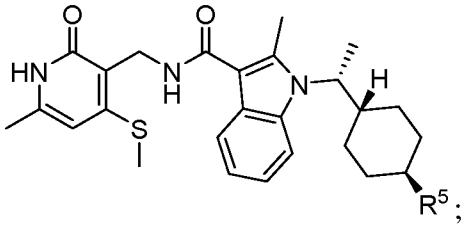
23. The compound of claim 22, wherein the compound is of the Formula:



or a pharmaceutically acceptable salt thereof.

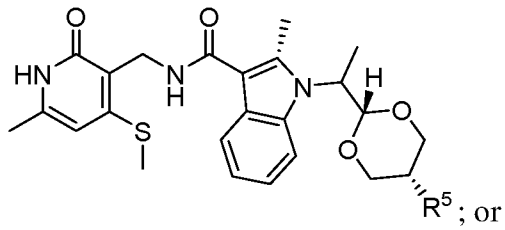
24. The compound of claim 22 or 23, wherein the compound is of the Formula:

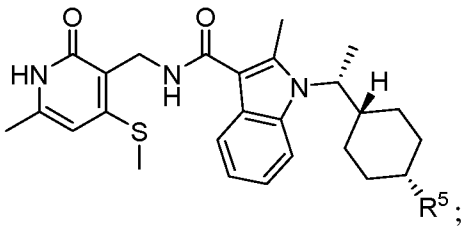

; or


;

or a pharmaceutically acceptable salt thereof.

25. The compound of any one of claims 22 to 24, wherein the compound is of the Formula:


; or


;

or a pharmaceutically acceptable salt thereof.

26. The compound of any one of claims 22 to 25, wherein

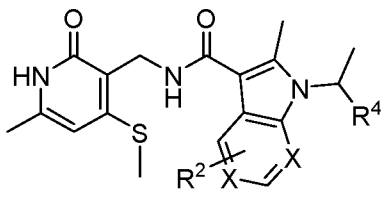
R^A is hydrogen, (C_1-C_4)alkyl, or halo(C_1-C_4)alkyl;

R^B is (C_1-C_4)alkyl or oxetanyl optionally substituted with (C_1-C_4)alkyl; or

R^A and R^B taken together with the nitrogen atom to which they are attached form an azetidinyl optionally substituted with halo, (C_1-C_4)alkoxy or halo(C_1-C_4)alkoxy.

27. The compound of claim 22 or 23, wherein R^7 is halo(C_1-C_4)alkyl or -(C_1-C_4)alkylOH.

28. The compound of claim 1, wherein the compound is of the Formula **XXXIII**:


(**XXXIII**);

or a pharmaceutically acceptable salt thereof, wherein

R^2 is hydrogen or halo;

R^4 is cyclohexyl, piperidinyl or dioxanyl, each of which being optionally and independently substituted with 1 to 3 groups selected from R^5;

R^5 is selected from halo, $(C_3$-$C_6)$cycloalkyl, OR^6, -$OC(O)(C_1$-$C_4)$alkyl, -$C(O)(C_1$-$C_4)$alkylOH, -$C(O)(C_1$-$C_4)$alkyl$N((C_1$-$C_4)alkyl)_2$, -$SO_2(C_1$-$C_4)$alkyl, 4-7 membered heterocyclyl, and NR^AR^B, wherein said cycloalkyl for R^5 is optionally substituted with -$O(C_1$-$C_4)$alkyl;

R^A is hydrogen;

R^B is $(C_3$-$C_5)$cycloalkyl or 4-7 membered heterocyclyl, wherein said heterocyclyl or cycloalkyl for R^B is optionally substituted with 1 to 3 groups selected from $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, and hydroxy$(C_1$-$C_4)$alkyl; or

R^A and R^B taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclyl optionally substituted with 1 to 3 groups selected from halo, hydroxyl, cyano, $(C_1$-$C_4)$alkyl, hydroxy$(C_1$-$C_4)$alkyl, NMe_2, -$SO_2(C_1$-$C_4)$alkyl, 5-6 membered heteroaryl, and $(C_3$-$C_6)$cycloalkyl; and

R^6 is $(C_3$-$C_6)$cycloalkyl, 4-7 membered heterocyclyl, 5-6 membered heteroaryl, or -$O(C_1$-$C_4)$alkyl, wherein said 4-7 membered heterocyclyl and said 5-6 membered heteroaryl for R^6 are each optionally and independently substituted with 1 or 2 $(C_1$-$C_4)$alkyl groups.

29. The compound of claim 28, wherein

R^5 is selected from halo, $(C_3$-$C_6)$cycloalkyl, OR^6, -$OC(O)(C_1$-$C_4)$alkyl, -$C(O)(C_1$-$C_4)$alkylOH, -$C(O)(C_1$-$C_4)$alkyl$N((C_1$-$C_4)alkyl)_2$, -$SO_2(C_1$-$C_4)$alkyl, 4-7 membered heterocyclyl, and NR^AR^B, wherein said cycloalkyl for R^5 is optionally substituted with -$O(C_1$-$C_4)$alkyl;

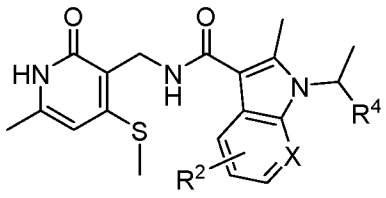
R^A is hydrogen;

R^B is $(C_3$-$C_5)$cycloalkyl or 4-7 membered heterocyclyl, wherein said heterocyclyl or cycloalkyl for R^B are each optionally and independently substituted with 1 to 3 groups selected from $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, and hydroxy$(C_1$-$C_4)$alkyl; or

R^A and R^B taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclyl optionally substituted with 1 to 3 groups selected from halo, hydroxyl, cyano, $(C_1$-$C_4)$alkyl, NMe_2, hydroxy$(C_1$-$C_4)$alkyl, -$SO_2(C_1$-$C_4)$alkyl, 5-6 membered heteroaryl, and $(C_3$-$C_6)$cycloalkyl; and

R^6 is $(C_3$-$C_6)$cycloalkyl, 4-7 membered heterocyclyl, 5-6 membered heteroaryl, or -$O(C_1$-$C_4)$alkyl, wherein said 4-7 membered heterocyclyl and said 5-6 membered heteroaryl for R^6 are each optionally and independently substituted with 1 or 2 $(C_1$-$C_4)$alkyl groups.

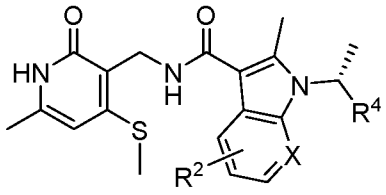
30. The compound of any one of claims 1, 28, and 29, wherein the compound is of the Formula **XXXIV**:



(**XXXIV**);

or a pharmaceutically acceptable salt thereof.

31. The compound of any one of claims 1 and 28 to 30, wherein the compound is of the Formula **XXXV**:



(**XXXV**);

or a pharmaceutically acceptable salt thereof.

32. The compound of any one of claims 1 and 28 to 31, wherein R^2 is hydrogen or fluorine.

33. The compound of any one of claims 1 and 28 to 32, wherein

R^5 is selected from halo, $(C_3\text{-}C_6)$cycloalkyl, $-OC(O)(C_1\text{-}C_4)$alkyl, $-C(O)(C_1\text{-}C_4)$alkylOH, $-C(O)(C_1\text{-}C_4)$alkylN$((C_1\text{-}C_4)\text{alkyl})_2$, $-SO_2(C_1\text{-}C_4)$alkyl, and NR^AR^B wherein said cycloalkyl for R^5 is optionally substituted with $-O(C_1\text{-}C_4)$alkyl;

R^B is $(C_3\text{-}C_5)$cycloalkyl or 4-7 membered heterocyclyl each optionally and independently substituted with 1 to 3 groups selected from $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, and hydroxy$(C_1\text{-}C_4)$alkyl; or

R^A and R^B taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclyl optionally substituted with 1 to 3 groups selected from halo, hydroxyl, cyano, $(C_1\text{-}C_4)$alkyl, NMe_2, $-SO_2(C_1\text{-}C_4)$alkyl, 5-6 membered heteroaryl, and $(C_3\text{-}C_6)$cycloalkyl; and

R^6 is 4-7 membered heterocyclyl or 5-6 membered heteroaryl, wherein said 4-7 membered heterocyclyl and said 5-6 membered heteroaryl for R^6 are each optionally and independently substituted with $(C_1\text{-}C_4)$alkyl.

34. The compound of any one of claims 1 and 28 to 33, wherein

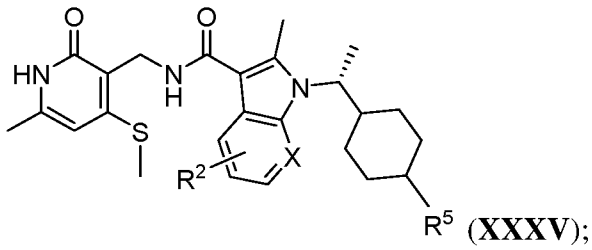
R^5 is selected from halo, cyclobutyl, -OC(O)(C_1-C_4)alkyl, -C(O)(C_1-C_4)alkylOH, -C(O)(C_1-C_4)alkylN((C_1-C_4)alkyl)$_2$, -SO_2(C_1-C_4)alkyl, and NR^AR^B wherein said cyclobutyl for R^5 is optionally substituted with -O(C_1-C_4)alkyl;

R^B is tetrahydrofuranyl, cyclopropyl, or oxatanyl, each optionally and independently substituted with 1 to 3 groups selected from (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, and hydroxy(C_1-C_4)alkyl; or

R^A and R^B taken together with the nitrogen atom to which they are attached form an azetidinyl, oxaazaspirohexanyl, oxaazaspiroheptanyl, each of which are optionally and independently substituted with 1 to 3 groups selected from halo, hydroxyl, cyano, (C_1-C_4)alkyl, NMe_2, -SO_2(C_1-C_4)alkyl, triazolyl, and cyclopropyl; and

R^6 is an oxetanyl, azetidinyl, pyrazolyl, 4-7 membered heterocyclyl or 5-6 membered heteroaryl, wherein said 4-7 membered heterocyclyl and said 5-6 membered heteroaryl for R^6 are each optionally and independently substituted with (C_1-C_4)alkyl.

35. The compound of any one of claims 1 and 28 to 34, wherein the compound is of the Formula:



(**XXXV**);

or a pharmaceutically acceptable salt thereof.

36. The compound of claim 1 or claim 29, wherein the compound is:

1-((R)-1-(4-(3-(difluoromethoxy)azetidin-1-yl)cyclohexyl)ethyl)-6-fluoro-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-indole-3-carboxamide;

2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-((R)-1-(4-((3-(trifluoromethyl)oxetan-3-yl)amino)cyclohexyl)ethyl)-1H-indole-3-carboxamide, or

1-((R)-1-(4-(3-cyclopropoxyazetidin-1-yl)cyclohexyl)ethyl)-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide; or

1-((R)-1-(4-(3-cyclopropoxyazetidin-1-yl)cyclohexyl)ethyl)-5-fluoro-2-methyl-N-((6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide;

or a pharmaceutical acceptable salt thereof.

37. A pharmaceutical composition comprising the compound of any one of claims 1 to 36, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

38. A method for treating cancer in a subject, comprising administering to the subject an effective amount of a compound according to any one of claims 1 to 36, or a pharmaceutically acceptable salt thereof, or the composition of claim 37.

39. The method of claim 38, wherein the cancer is selected from breast cancer, prostate cancer, colon cancer, renal cell carcinoma, glioblastoma multiforme cancer, bladder cancer, melanoma, bronchial cancer, lymphoma, cholangiosarcoma, multiple myeloma, lung cancer, ovarian cancer, and liver cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/059763

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D405/14 C07D401/12 C07D471/04 C07D487/04
A61P35/00 A61K31/4439 A61K31/519 A61K31/454
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2017/217941 A1 (CAMPBELL JOHN EMMERSON [US]) 3 August 2017 (2017-08-03) claims 1, 28-34	1-8, 15-21, 32-34, 37-39
Y	WO 2014/124418 A1 (CONSTELLATION PHARMACEUTICALS INC [US]) 14 August 2014 (2014-08-14) claims 1, 14-16 figure 1	1-8, 15-21, 32-34, 37-39
Y	WO 2013/120104 A2 (CONSTELLATION PHARMACEUTICALS [US]) 15 August 2013 (2013-08-15) cited in the application claims 1, 14-17	1-8, 15-21, 32-34, 37-39

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 February 2019	19/03/2019

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/059763

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2015/023915 A1 (CONSTELLATION PHARMACEUTICALS INC [US]) 19 February 2015 (2015-02-19) cited in the application claims 1, 11, 17, 22-25	1-8, 15-21, 32-34, 37-39
Y	WO 2016/130396 A1 (CONSTELLATION PHARMACEUTICALS INC [US]) 18 August 2016 (2016-08-18) claims 1, 23-27	1-8, 15-21, 32-34, 37-39

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2018/059763

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2017217941 A1	03-08-2017	EP 3160940 A1	03-05-2017
		US 2017217941 A1	03-08-2017
		WO 2015200650 A1	30-12-2015
WO 2014124418 A1	14-08-2014	CL 2015002239 A1	05-02-2016
		CN 105102446 A	25-11-2015
		CR 20150457 A	20-10-2015
		EP 2953941 A1	16-12-2015
		HK 1218648 A1	03-03-2017
		IL 239985 A	29-11-2018
		KR 20150119201 A	23-10-2015
		MA 38341 A1	31-01-2018
		ME 02730 B	20-10-2017
		PE 00442016 A1	11-02-2016
		PH 12015501720 A1	09-11-2015
		PL 2953941 T3	30-11-2017
		SG 11201506077X A	28-08-2015
		SI 2953941 T1	31-08-2017
		TW 201443038 A	16-11-2014
		WO 2014124418 A1	14-08-2014
WO 2013120104 A2	15-08-2013	AR 094755 A1	26-08-2015
		AU 2013216721 A1	04-09-2014
		BR 112015018508 A2	18-07-2017
		CA 2862289 A1	15-08-2013
		CY 1119060 T1	10-01-2018
		DK 2953941 T3	24-07-2017
		EA 201591474 A1	29-01-2016
		EP 2812001 A2	17-12-2014
		ES 2632241 T3	12-09-2017
		HR P20171030 T1	06-10-2017
		JP 5989805 B2	07-09-2016
		JP 5989923 B2	07-09-2016
		JP 2015506985 A	05-03-2015
		JP 2016507573 A	10-03-2016
		LT 2953941 T	11-09-2017
		NZ 628762 A	29-07-2016
		PT 2953941 T	13-07-2017
		UA 117362 C2	25-07-2018
		US 2015011546 A1	08-01-2015
		US 2015259351 A1	17-09-2015
		US 2015368229 A1	24-12-2015
		US 2015376190 A1	31-12-2015
		US 2016333016 A1	17-11-2016
		US 2017056388 A1	02-03-2017
		WO 2013120104 A2	15-08-2013
WO 2015023915 A1	19-02-2015	EP 3033334 A1	22-06-2016
		US 2016185757 A1	30-06-2016
		WO 2015023915 A1	19-02-2015
WO 2016130396 A1	18-08-2016	US 2018037568 A1	08-02-2018
		WO 2016130396 A1	18-08-2016