

GPR52 MODULATORS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 63/598,722, filed November 14, 2023, which is hereby incorporated by reference in its entirety for all purposes.

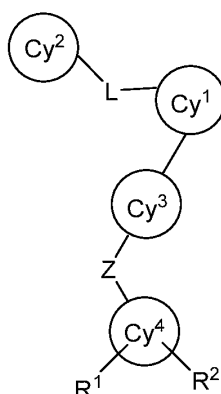
BACKGROUND

[0002] The basal ganglia, particularly the striatum, plays a pivotal role in the regulation of motor functions, the modulation of reward processing, and various aspects of learning. Within this complex neural network, the orphan G-protein coupled receptor GPR52 emerges as a key player. Medium spiny neurons (MSNs) constitute the major population of neurons in the mammalian striatum and are commonly divided into D1 and D2 subtypes. The excitatory (i.e., G-coupled) GPR52 receptor is prominently expressed on D2 MSNs, which are the mediators of the indirect (or inhibitory) pathway in striatal output. This expression profile of GPR52 suggests that the receptor may functionally regulate cAMP signaling to oppose the activity of inhibitory (i.e., Gi-coupled) dopamine D2 receptors. Positive modulation of the constitutive activity of GPR52 holds promise for treating several psychiatric diseases in addition to deficits in motor control. Thus, there is a need for the development of novel GPR52 positive modulators.

SUMMARY OF THE DISCLOSURE

[0003] The present disclosure provides compounds that are modulators of the G protein-coupled receptor 52 (GPR52) as well as pharmaceutical compositions and uses thereof in treating diseases or disorders that are treatable by administration of a GPR52 modulators.

[0004] In embodiments, the present disclosure provides compounds of Formula (I),



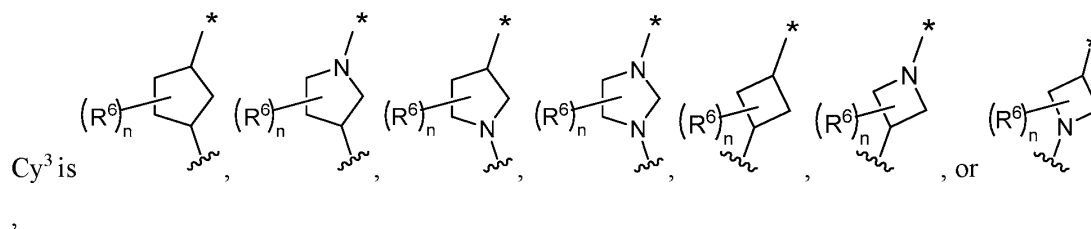
Formula (I)

or a pharmaceutically acceptable salt thereof,

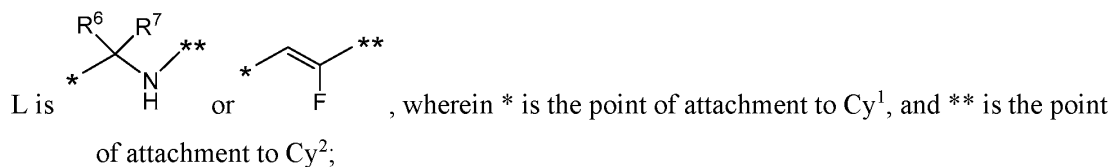
wherein

Cy¹ is a nitrogen-containing heterocyclylene or a nitrogen-containing heteroarylene, wherein
 when the heterocyclylene contains two nitrogen atoms, the nitrogen atoms are adjacent to each other, and
 when the heteroarylene contains two nitrogen atoms, the nitrogen atoms are adjacent to each other or the heteroarylene is pyrimidine;

Cy² is a nitrogen-containing 4-8 membered heterocyclyl, heteroaryl, spiroheterocyclyl, or bicyclic heterocyclyl;



wherein * is the point of attachment to Cy¹, and wherein is the point of attachment to Z;
 Cy⁴ is aryl or nitrogen-containing heteroaryl;



Z is -O- or -CR⁴R⁵-

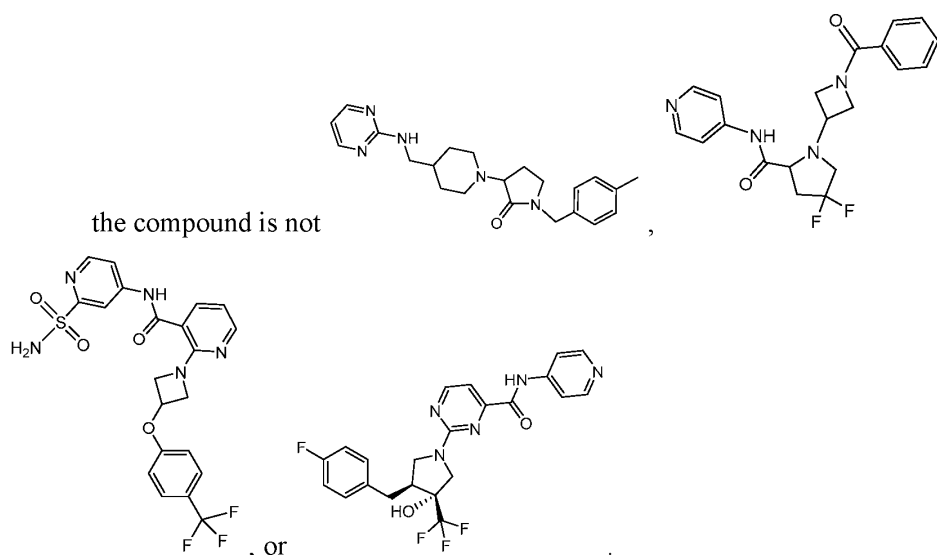
R¹ and R² are each independently hydrogen, halogen, alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, -CF₃, -CN, or -OCF₃;

R⁴ and R⁵ are each independently hydrogen, halogen, alkyl, alkoxy, -OH, -CF₃, -CHF₂, -CH₂CF₃, -CN, -C(=O)CH₃, -S(=O)₂CH₃, cycloalkyl, heterocyclyl, aryl, heteroaryl, or R⁴ and R⁵ together form =O;

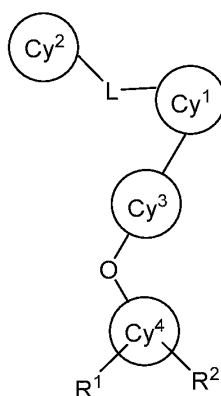
R⁶ and R⁷ are each independently hydrogen, alkyl, halogen, -OH, -CF₃, or -CHF₂, R⁶ and R⁷ together with the carbon to which they are attached form =O, carbocyclyl, or heterocyclyl; or two R⁶ attached to the same carbon atom form =O;

n is 0, 1, 2, or 3; and

wherein Cy¹ is not 1,2,5 thiadiazole, Cy² is not thiazole or thiadiazole, and



[0005] In embodiments, the present disclosure provides compounds having Formula (Ia)



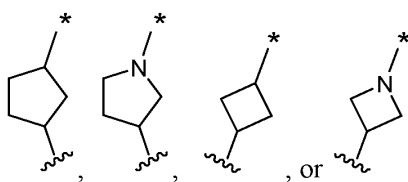
Formula (Ia)

or a pharmaceutically acceptable salt thereof,

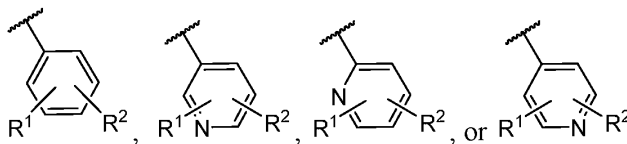
wherein

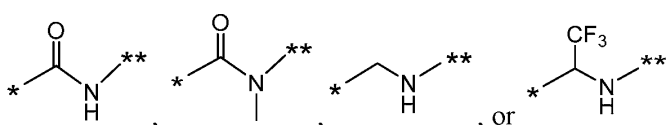
Cy¹ is a nitrogen-containing heterocyclylene or a nitrogen-containing heteroarylene, wherein
 when the heterocyclylene contains two nitrogen atoms, the nitrogen atoms are adjacent to each other, and
 when the heteroarylene contains two nitrogen atoms, the nitrogen atoms are adjacent to each other or the heteroarylene is pyrimidine;

Cy² is a nitrogen-containing 4-8 membered heterocyclyl, heteroaryl, spiroheterocyclyl, or bicyclic heterocyclyl;

Cy³ is , wherein * is the point of attachment to

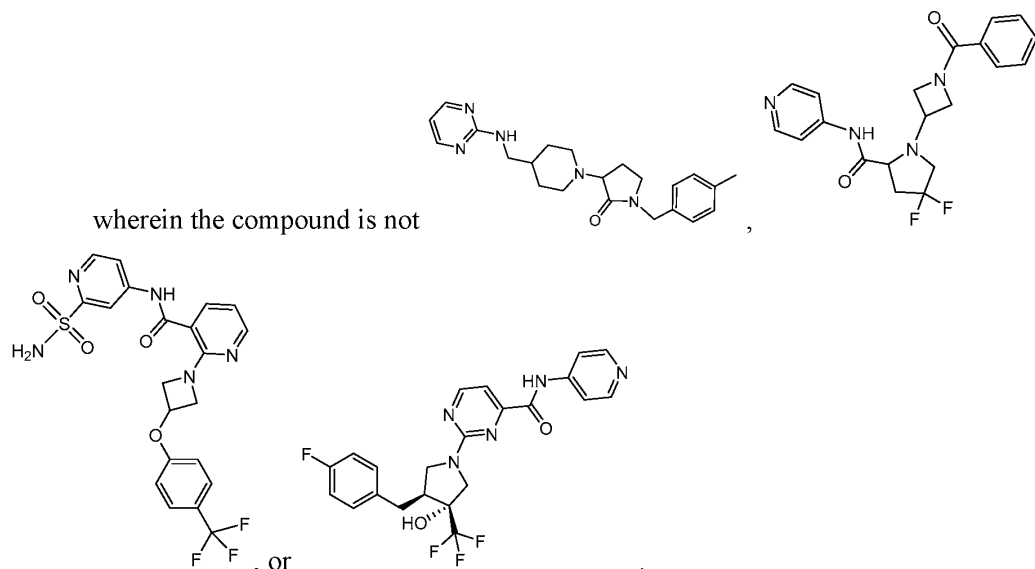
Cy¹, and wherein  is the point of attachment to O;

Cy⁴ is ; or R¹ is the point of attachment to

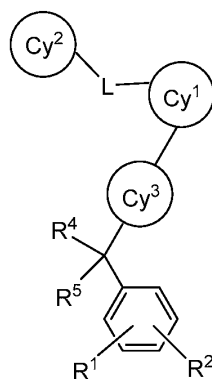
L is , wherein * is the point of attachment to Cy¹, and ** is the point of attachment to Cy²;

R¹ and R² are each independently hydrogen, halogen, alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, -CF₃, -CN, or -OCF₃; and

wherein Cy¹ is not 1,2,5 thiadiazole, wherein Cy² is not thiazole or thiadiazole, and



[0006] In embodiments, the present disclosure provides compounds having Formula (Ib)



Formula (Ib)

or a pharmaceutically acceptable salt thereof,

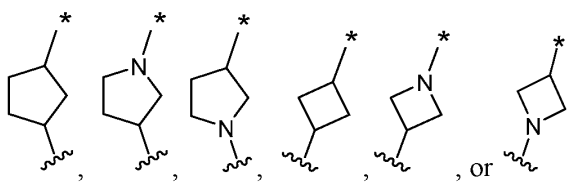
wherein

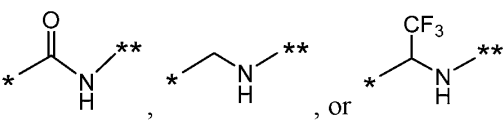
Cy¹ is a nitrogen-containing heterocyclylene or a nitrogen-containing heteroarylene, wherein

when the heterocyclylene contains two nitrogen atoms, the nitrogen atoms are adjacent to each other, and

when the heteroarylene contains two nitrogen atoms, the nitrogen atoms are adjacent to each other or the heteroarylene is pyrimidine;

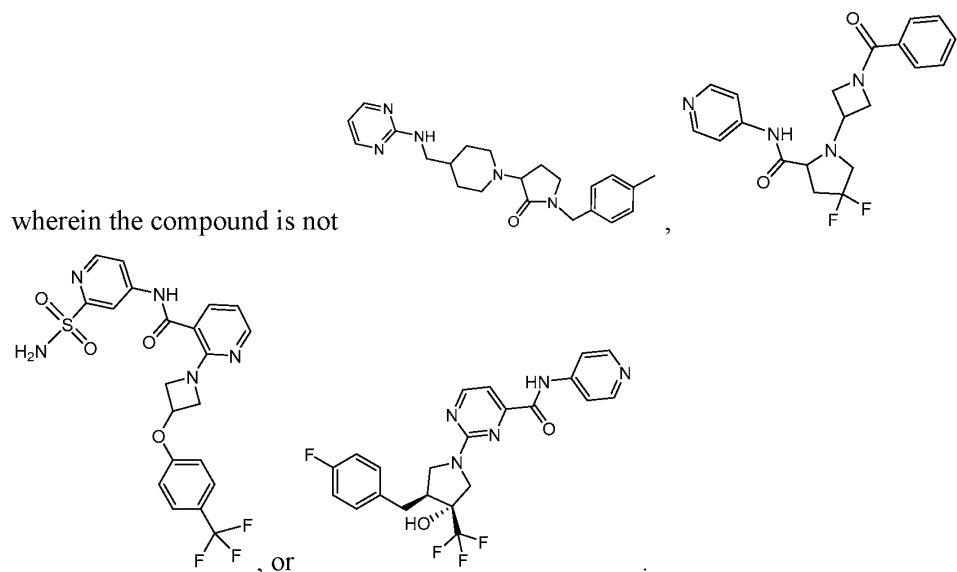
Cy² is a nitrogen-containing 4-8 membered heterocyclyl, heteroaryl, spiroheterocyclyl, or bicyclic heterocyclyl;

Cy³ is , wherein * is the point of attachment to Cy¹;

L is , wherein * is the point of attachment to Cy¹, and ** is the point of attachment to Cy²;

R¹ and R² are each independently hydrogen, halogen, alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, -CF₃, -CN, or -OCF₃;

R⁴ and R⁵ are each independently hydrogen, C₁-C₃ alkyl, -F, or R⁴ and R⁵ together form =O; wherein Cy¹ is not 1,2,5 thiadiazole, wherein Cy² is not thiazole or thiadiazole, and



DETAILED DESCRIPTION

[0007] Throughout this disclosure, various patents, patent applications and publications are referenced. The disclosures of these patents, patent applications and publications in their entireties are incorporated into this disclosure by reference for all purposes in order to more fully describe the state of the art as known to those skilled therein as of the date of this disclosure. This disclosure

will govern in the instance that there is any inconsistency between the patents, patent applications and publications cited and this disclosure.

Definitions

[0008] For convenience, certain terms employed in the specification, examples and claims are collected here. Unless defined otherwise, all technical and scientific terms used in this disclosure have the same meanings as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0009] The term "about" when immediately preceding a numerical value means a range (e.g., plus or minus 10% of that value). For example, "about 50" can mean 45 to 55, "about 25,000" can mean 22,500 to 27,500, etc., unless the context of the disclosure indicates otherwise, or is inconsistent with such an interpretation. For example, in a list of numerical values such as "about 49, about 50, about 55, ... ", "about 50" means a range extending to less than half the interval(s) between the preceding and subsequent values, e.g., more than 49.5 to less than 50.5. Furthermore, the phrases "less than about" a value or "greater than about" a value should be understood in view of the definition of the term "about" provided herein. Similarly, the term "about" when preceding a series of numerical values or a range of values (e.g., "about 10, 20, 30" or "about 10-30") refers, respectively to all values in the series, or the endpoints of the range.

[0010] The terms "administer," "administering" or "administration" as used herein refer to administering a compound or pharmaceutically acceptable salt of the compound or a composition comprising the compound or pharmaceutically acceptable salt of the compound to a patient.

[0011] The term "pharmaceutically acceptable salts" includes both acid and base addition salts. Pharmaceutically acceptable salts include those obtained by reacting the active compound functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methanesulfonic acid, camphorsulfonic acid, oxalic acid, maleic acid, succinic acid, citric acid, formic acid, hydrobromic acid, benzoic acid, tartaric acid, fumaric acid, salicylic acid, mandelic acid, carbonic acid, etc. Base addition salts include but are not limited to, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chlorprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris-(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, triethylamine, dibenzylamine, ephenamine,

dehydroabietylamine, N-ethylpiperidine, benzylamine, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, ethylamine, basic amino acids, e. g., lysine and arginine dicyclohexylamine and the like. Examples of metal salts include lithium, sodium, potassium, magnesium, calcium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methylammonium, dimethylammonium, trimethylammonium, ethylammonium, hydroxyethylammonium, diethylammonium, butylammonium, tetramethylammonium salts and the like. Examples of organic bases include lysine, arginine, guanidine, diethanolamine, choline and the like. Those skilled in the art will further recognize that acid addition salts may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods.

[0012] The term "treating" as used herein with regard to a patient, refers to improving at least one symptom of the patient's disorder. Treating can be improving, or at least partially ameliorating a disorder or an associated symptom of a disorder.

[0013] The terms "effective amount" and "therapeutically effective amount" are used interchangeably in this disclosure and refer to an amount of a compound, or a salt thereof, (or pharmaceutical composition containing the compound or salt) that, when administered to a patient, is capable of performing the intended result. The "effective amount" will vary depending on the active ingredient, the state, disorder, or condition to be treated and its severity, and the age, weight, physical condition and responsiveness of the mammal to be treated.

[0014] The term "therapeutically effective" applied to dose or amount refers to that quantity of a compound or pharmaceutical composition that is sufficient to result in a desired clinical benefit after administration to a patient in need thereof.

[0015] The term "carrier" or "vehicle" as used interchangeably herein encompasses carriers, excipients, adjuvants, and diluents or a combination of any of the foregoing, meaning a material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material involved in carrying or transporting a pharmaceutical agent from one organ, or portion of the body, to another organ or portion of the body. In addition to the adjuvants, excipients and diluents known to one skilled in the art, the carrier includes nanoparticles of organic and inorganic nature.

[0016] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, “C₁-C₆ alkyl” is intended to encompass C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅, and C₅₋₆ alkyl.

[0017] “Alkyl” or “alkyl group” refers to a fully saturated, straight or branched hydrocarbon chain having from one to twelve carbon atoms, and which is attached to the rest of the molecule by a single bond. Alkyls comprising any number of carbon atoms from 1 to 12 are included. An alkyl comprising up to 12 carbon atoms is a C₁-C₁₂ alkyl, an alkyl comprising up to 10 carbon atoms is a C₁-C₁₀ alkyl, an alkyl comprising up to 6 carbon atoms is a C₁-C₆ alkyl and an alkyl comprising up to 5 carbon atoms is a C₁-C₅ alkyl. A C₁-C₅ alkyl includes C₅ alkyls, C₄ alkyls, C₃ alkyls, C₂ alkyls and C₁ alkyl (*i.e.*, methyl). A C₁-C₆ alkyl includes all moieties described above for C₁-C₅ alkyls but also includes C₆ alkyls. A C₁-C₁₀ alkyl includes all moieties described above for C₁-C₅ alkyls and C₁-C₆ alkyls, but also includes C₇, C₈, C₉ and C₁₀ alkyls. Similarly, a C₁-C₁₂ alkyl includes all the foregoing moieties, but also includes C₁₁ and C₁₂ alkyls. Non-limiting examples of C₁-C₁₂ alkyl include methyl, ethyl, *n*-propyl, *i*-propyl, *sec*-propyl, *n*-butyl, *i*-butyl, *sec*-butyl, *t*-butyl, *n*-pentyl, *t*-amyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl, *n*-undecyl, and *n*-dodecyl. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[0018] “Alkylene” or “alkylene chain” refers to a fully saturated, straight or branched divalent hydrocarbon chain radical, and having from one to twelve carbon atoms. Non-limiting examples of C₁-C₁₂ alkylene include methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to a radical group (e.g., those described herein) through a single bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkylene chain can be optionally substituted.

[0019] “Alkenyl” or “alkenyl group” refers to a straight or branched hydrocarbon chain having from two to twelve carbon atoms and having one or more carbon-carbon double bonds. Each alkenyl group is attached to the rest of the molecule by a single bond. Alkenyl group comprising any number of carbon atoms from 2 to 12 are included. An alkenyl group comprising up to 12 carbon atoms is a C₂-C₁₂ alkenyl, an alkenyl comprising up to 10 carbon atoms is a C₂-C₁₀ alkenyl, an alkenyl group comprising up to 6 carbon atoms is a C₂-C₆ alkenyl and an alkenyl comprising

up to 5 carbon atoms is a C₂-C₅ alkenyl. A C₂-C₅ alkenyl includes C₅ alkenyls, C₄ alkenyls, C₃ alkenyls, and C₂ alkenyls. A C₂-C₆ alkenyl includes all moieties described above for C₂-C₅ alkenyls but also includes C₆ alkenyls. A C₂-C₁₀ alkenyl includes all moieties described above for C₂-C₅ alkenyls and C₂-C₆ alkenyls, but also includes C₇, C₈, C₉ and C₁₀ alkenyls. Similarly, a C₂-C₁₂ alkenyl includes all the foregoing moieties, but also includes C₁₁ and C₁₂ alkenyls. Non-limiting examples of C₂-C₁₂ alkenyl include ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), isopropenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 4-octenyl, 5-octenyl, 6-octenyl, 7-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 4-nonenyl, 5-nonenyl, 6-nonenyl, 7-nonenyl, 8-nonenyl, 1-decenyl, 2-decenyl, 3-decenyl, 4-decenyl, 5-decenyl, 6-decenyl, 7-decenyl, 8-decenyl, 9-decenyl, 1-undecenyl, 2-undecenyl, 3-undecenyl, 4-undecenyl, 5-undecenyl, 6-undecenyl, 7-undecenyl, 8-undecenyl, 9-undecenyl, 10-undecenyl, 1-dodecenyl, 2-dodecenyl, 3-dodecenyl, 4-dodecenyl, 5-dodecenyl, 6-dodecenyl, 7-dodecenyl, 8-dodecenyl, 9-dodecenyl, 10-dodecenyl, and 11-dodecenyl. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[0020] “Alkenylene” or “alkenylene chain” refers to an unsaturated, straight or branched divalent hydrocarbon chain radical having one or more olefins and from two to twelve carbon atoms. Non-limiting examples of C₂-C₁₂ alkenylene include ethenylene, propenylene, *n*-butenylene, and the like. The alkenylene chain is attached to the rest of the molecule through a single bond and to a radical group (e.g., those described herein) through a single bond. The points of attachment of the alkenylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkenylene chain can be optionally substituted.

[0021] “Alkynyl” or “alkynyl group” refers to a straight or branched hydrocarbon chain having from two to twelve carbon atoms, and having one or more carbon-carbon triple bonds. Each alkynyl group is attached to the rest of the molecule by a single bond. Alkynyl group comprising any number of carbon atoms from 2 to 12 are included. An alkynyl group comprising up to 12 carbon atoms is a C₂-C₁₂ alkynyl, an alkynyl comprising up to 10 carbon atoms is a C₂-C₁₀ alkynyl, an alkynyl group comprising up to 6 carbon atoms is a C₂-C₆ alkynyl and an alkynyl comprising up to 5 carbon atoms is a C₂-C₅ alkynyl. A C₂-C₅ alkynyl includes C₅ alkynyls, C₄ alkynyls, C₃

alkynyls, and C₂ alkynyls. A C₂-C₆ alkynyl includes all moieties described above for C₂-C₅ alkynyls but also includes C₆ alkynyls. A C₂-C₁₀ alkynyl includes all moieties described above for C₂-C₅ alkynyls and C₂-C₆ alkynyls, but also includes C₇, C₈, C₉ and C₁₀ alkynyls. Similarly, a C₂-C₁₂ alkynyl includes all the foregoing moieties, but also includes C₁₁ and C₁₂ alkynyls. Non-limiting examples of C₂-C₁₂ alkenyl include ethynyl, propynyl, butynyl, pentynyl and the like. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[0022] “Alkynylene” or “alkynylene chain” refers to an unsaturated, straight or branched divalent hydrocarbon chain radical having one or more alkynes and from two to twelve carbon atoms. Non-limiting examples of C₂-C₁₂ alkynylene include ethynylene, propynylene, *n*-butynylene, and the like. The alkynylene chain is attached to the rest of the molecule through a single bond and to a radical group (e.g., those described herein) through a single bond. The points of attachment of the alkynylene chain to the rest of the molecule and to the radical group can be through any two carbons within the chain having a suitable valency. Unless stated otherwise specifically in the specification, an alkynylene chain can be optionally substituted.

[0023] “Alkoxy” refers to a group of the formula -OR_a where R_a is an alkyl, alkenyl or alkynyl as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkoxy group can be optionally substituted.

[0024] “Aryl” refers to a hydrocarbon ring system comprising hydrogen, 6 to 18 carbon atoms and at least one aromatic ring, and which is attached to the rest of the molecule by a single bond. For purposes of this disclosure, the aryl can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems. Aryls include, but are not limited to, aryls derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, the “aryl” can be optionally substituted.

[0025] “Carbocyclyl,” “carbocyclic ring” or “carbocycle” refers to a rings structure, wherein the atoms which form the ring are each carbon, and which is attached to the rest of the molecule by a single bond. Carbocyclic rings can comprise from 3 to 20 carbon atoms in the ring. Carbocyclic rings include aryls and cycloalkyl, cycloalkenyl, and cycloalkynyl as defined herein. Unless stated otherwise specifically in the specification, a carbocyclyl group can be optionally substituted.

[0026] “Cycloalkyl” refers to a stable non-aromatic monocyclic or polycyclic fully saturated hydrocarbon consisting solely of carbon and hydrogen atoms, which can include fused, bridged, or spirocyclic ring systems, having from three to twenty carbon atoms (e.g., having from three to ten carbon atoms) and which is attached to the rest of the molecule by a single bond. Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls include, for example, adamantyl, norbornyl, decaliny, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, a cycloalkyl group can be optionally substituted.

[0027] “Cycloalkenyl” refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon consisting solely of carbon and hydrogen atoms, having one or more carbon-carbon double bonds, which can include fused or bridged ring systems, having from three to twenty carbon atoms, preferably having from three to ten carbon atoms, and which is attached to the rest of the molecule by a single bond. Monocyclic cycloalkenyls include, for example, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like. Polycyclic cycloalkenyls include, for example, bicyclo[2.2.1]hept-2-enyl and the like. Unless otherwise stated specifically in the specification, a cycloalkenyl group can be optionally substituted.

[0028] “Haloalkyl” refers to an alkyl, as defined above, that is substituted by one or more halo radicals, e.g., trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. Unless stated otherwise specifically in the specification, a haloalkyl group can be optionally substituted.

[0029] “Heterocyclyl”, “heterocyclic ring”, or “heterocycle” refers to a stable saturated, unsaturated, or aromatic 3- to 20-membered ring which consists of two to nineteen carbon atoms and from one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and which is attached to the rest of the molecule by a single bond. Heterocyclyl or heterocyclic rings include heteroaryls, heterocyclylalkyls, heterocyclylalkenyls, and heterocyclylalkynyls. Unless stated otherwise specifically in the specification, the heterocyclyl can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused, bridged, or spirocyclic ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl can be optionally oxidized; the nitrogen atom can be optionally quaternized; and the heterocyclyl can be partially or fully saturated. Examples of such heterocyclyl include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazoliny, imidazolidiny, isothiazolidiny,

isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, a heterocyclyl or heterocyclylene group can be optionally substituted. “Heterocyclylene” refers to a divalent radical derived from “heterocyclyl”, “heterocyclic ring”, or “heterocycle”.

[0030] “Heteroaryl” refers to a 5- to 20-membered ring system comprising hydrogen atoms, one to nineteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, at least one aromatic ring, including compounds with aromatic resonance structures (e.g., 2-pyridone), and which is attached to the rest of the molecule by a single bond. For purposes of this disclosure, the heteroaryl can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl can be optionally oxidized; the nitrogen atom can be optionally quaternized. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzofuranyl, benzooxazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4 benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnoliny, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indoliziny, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinoliny, quinuclidinyl, isoquinoliny, tetrahydroquinoliny, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e. thienyl). Unless stated otherwise specifically in the specification, a heteroaryl group can be optionally substituted. “Heteroarylene” refers to a divalent radical derived from “heteroaryl”.

[0031] The term “substituted” used herein means any of the groups described herein (e.g., alkyl, alkenyl, alkynyl, alkoxy, aryl, aralkyl, carbocyclyl, cycloalkyl, cycloalkenyl, cycloalkynyl, haloalkyl, heterocyclyl, and/or heteroaryl) wherein at least one hydrogen atom is replaced by a

bond to a non-hydrogen atoms such as, but not limited to: a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, and ester groups; a sulfur atom in groups such as thiol groups, thioalkyl groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as trialkylsilyl groups, dialkylarylsilyl groups, alkyl diarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. "Substituted" also means any of the above groups in which one or more hydrogen atoms are replaced by a higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; and nitrogen in groups such as imines, oximes, hydrazones, and nitriles. For example, "substituted" includes any of the above groups in which one or more hydrogen atoms are replaced with $-NR_gR_h$, $-NR_gC(=O)R_h$, $-NR_gC(=O)NR_gR_h$, $-NR_gC(=O)OR_h$, $-NR_gSO_2R_h$, $-OC(=O)NR_gR_h$, $-OR_g$, $-SR_g$, $-SOR_g$, $-SO_2R_g$, $-OSO_2R_g$, $-SO_2OR_g$, $=NSO_2R_g$, and $-SO_2NR_gR_h$. "Substituted" also means any of the above groups in which one or more hydrogen atoms are replaced with $-C(=O)R_g$, $-C(=O)OR_g$, $-C(=O)NR_gR_h$, $-CH_2SO_2R_g$, $-CH_2SO_2NR_gR_h$. In the foregoing, R_g and R_h are the same or different and independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl. "Substituted" further means any of the above groups in which one or more hydrogen atoms are replaced by a bond to an amino, cyano, hydroxyl, imino, nitro, oxo, thioxo, halogen, alkyl, alkenyl, alkynyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl group. In embodiments, "substituted" further means any alkyl, cycloalkyl or heterocyclylalkyl in which one or more hydrogen atoms is replaced by an isotope e.g., deuterium. In addition, each of the foregoing substituents can also be optionally substituted with one or more of the above substituents.

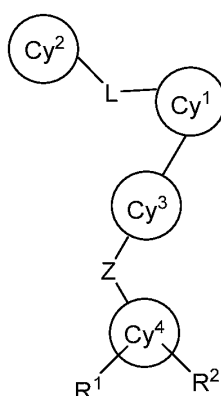
[0032] The compounds of the present disclosure may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example deuterium (2H), tritium (3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present

disclosure, whether radioactive or not, are intended to be encompassed within the scope of the disclosure.

Compounds

[0033] The present disclosure provides compounds that are modulators of the G protein-coupled receptor 52 (GPR52) as well as pharmaceutical compositions thereof and uses thereof in treating various diseases and disorders.

[0034] In embodiments, the present disclosure provides a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof,

wherein

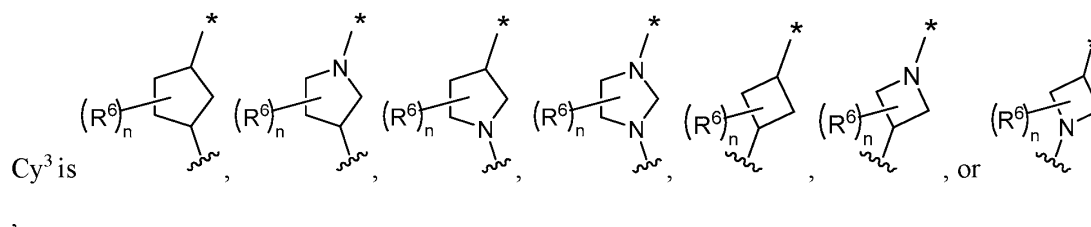
Cy¹ is a nitrogen-containing heterocyclylene or a nitrogen-containing heteroarylene, wherein

when the heterocyclylene contains two nitrogen atoms, the nitrogen atoms are adjacent to each other, and

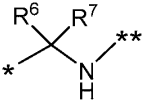
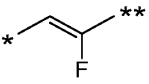
when the heteroarylene contains two nitrogen atoms, the nitrogen atoms are adjacent to each other or the heteroarylene is pyrimidine;

Cy² is a nitrogen-containing 4-8 membered heterocyclyl, heteroaryl, spiroheterocyclyl, or

bicyclic heterocyclyl;



wherein * is the point of attachment to Cy¹, and wherein ζ is the point of attachment to Z;
Cy⁴ is aryl or nitrogen-containing heteroaryl;

L is  or , wherein * is the point of attachment to Cy¹, and ** is the point of attachment to Cy²;

Z is -O- or -CR⁴R⁵-

R¹ and R² are each independently hydrogen, halogen, alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, -CF₃, -CN, or -OCF₃;

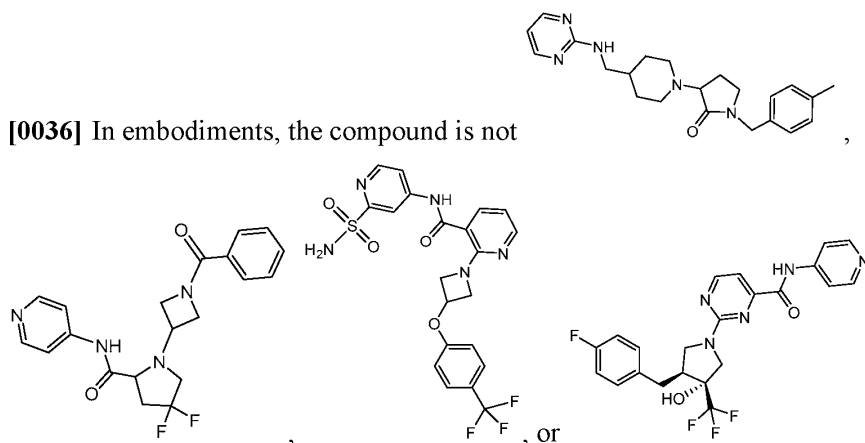
R⁴ and R⁵ are each independently hydrogen, halogen, alkyl, alkoxy, -OH, -CF₃, -CHF₂, -CH₂CF₃, -CN, -C(=O)CH₃, -S(=O)₂CH₃, cycloalkyl, heterocyclyl, aryl, heteroaryl, or R⁴ and R⁵ together form =O;

R⁶ and R⁷ are each independently hydrogen, alkyl, halogen, -OH, -CF₃, or -CHF₂, R⁶ and R⁷ together with the carbon to which they are attached form =O, carbocyclyl, or heterocyclyl; or two R⁶ attached to the same carbon atom form =O; and

n is 0, 1, 2, or 3.

[0035] In embodiments, Cy¹ is not 1,2,5 thiadiazole. In embodiments, Cy² is not thiazole or thiadiazole.

[0036] In embodiments, the compound is not



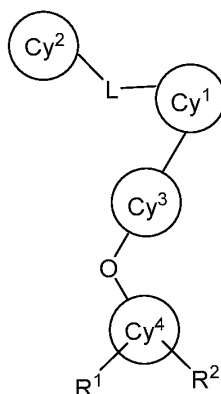
[0037] In embodiments, Z is -O-.

[0038] In embodiments, Z is -CR⁴R⁵-. In embodiments, R⁴ and R⁵ are each independently hydrogen, halogen, alkyl, -CHF₂, -CH₂CF₃, -CN, -C(=O)CH₃, -S(=O)₂CH₃, cycloalkyl, heterocyclyl, aryl, heteroaryl, or R⁴ and R⁵ together form =O. In embodiments, R⁴ and R⁵ are each

independently hydrogen, halogen, alkyl, or R^4 and R^5 together form $=O$. In embodiments, R^4 and R^5 are halogen. In embodiments, R^4 and R^5 are hydrogen or C_1 - C_5 alkyl.

[0039] In embodiments, Z is $-CH_2-$, $-C(=O)-$, $-CHF-$, $-CHCH_3$, or $-CF_2$. In embodiments, Z is $-CH_2-$. In embodiments, Z is $-C(=O)-$. In embodiments, Z is $-CHF-$. In embodiments, Z is $-CHCH_3$. In embodiments, Z is $-CF_2$.

[0040] In embodiments, the present disclosure provides a compound having Formula (Ia)



Formula (Ia)

or a pharmaceutically acceptable salt thereof,

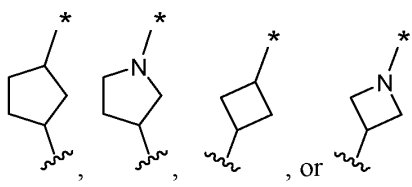
wherein

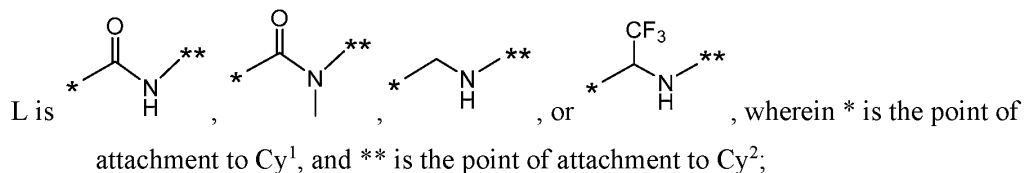
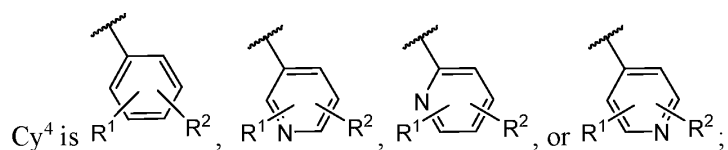
Cy^1 is a nitrogen-containing heterocyclylene or a nitrogen-containing heteroarylene, wherein

when the heterocyclylene contains two nitrogen atoms, the nitrogen atoms are adjacent to each other, and

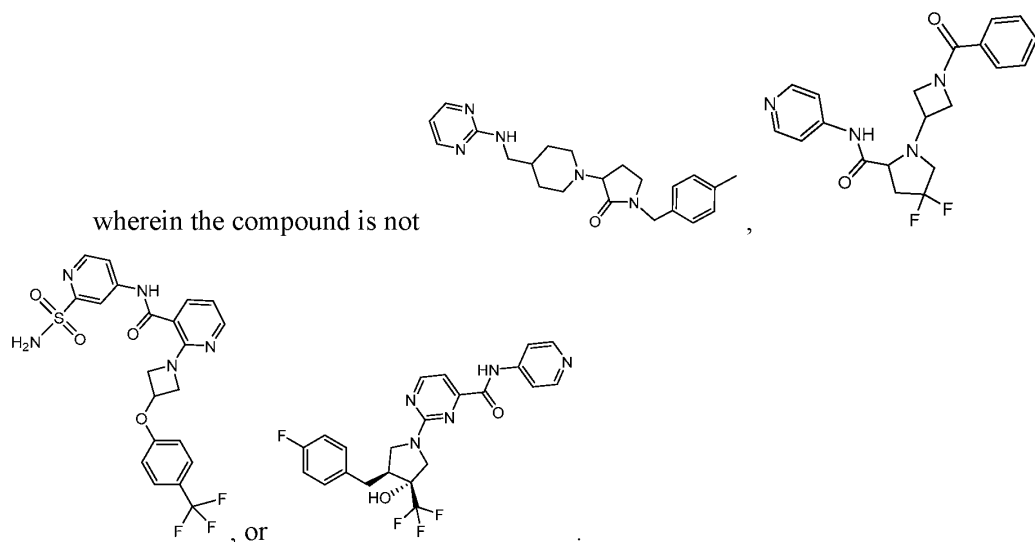
when the heteroarylene contains two nitrogen atoms, the nitrogen atoms are adjacent to each other or the heteroarylene is pyrimidine;

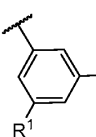
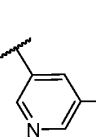
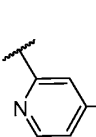
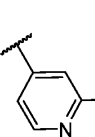
Cy^2 is a nitrogen-containing 4-8 membered heterocyclyl, heteroaryl, spiroheterocyclyl, or bicyclic heterocyclyl;

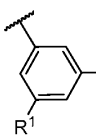
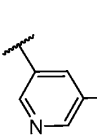
Cy^3 is , wherein * is the point of attachment to Cy^1 , and wherein  is the point of attachment to O;

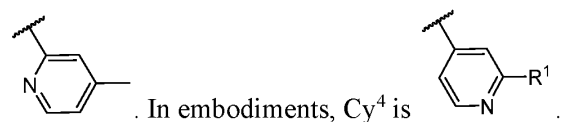


R¹ and R² are each independently hydrogen, halogen, alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, -CF₃, -CN, or -OCF₃; and wherein Cy¹ is not 1,2,5 thiadiazole, wherein Cy² is not thiazole or thiadiazole, and



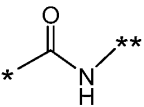
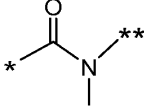
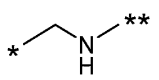
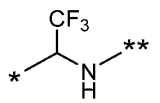
[0041] In embodiments, Cy⁴ is , , , or . In

embodiments, Cy⁴ is . In embodiments, Cy⁴ is . In embodiments, Cy⁴ is

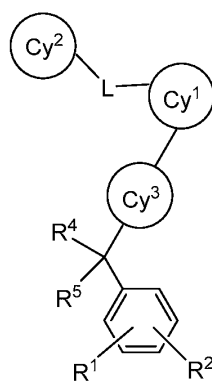


[0042] In embodiments, R^1 is hydrogen, halogen, C_1 - C_3 alkyl, alkoxy, cycloalkyl, $-CF_3$, $-CN$, or $-OCF_3$. In embodiments, R^1 is hydrogen, cyclopropyl, $-F$, $-Cl$, $-CF_3$, $-CH_3$, or $-C(CH_3)_2$. In embodiments, R^1 is hydrogen. In embodiments, R^1 is alkyl. In embodiments, R^1 is C_1 - C_3 alkyl. In embodiments, R^1 is alkoxy. In embodiments, R^1 is cycloalkyl. In embodiments, R^1 is $-CF_3$. In embodiments, R^1 is $-CN$. In embodiments, R^1 is $-OCF_3$. In embodiments, R^1 is cyclopropyl. In embodiments, R^1 is $-F$. In embodiments, R^1 is $-Cl$. In embodiments, R^1 is $-CF_3$. In embodiments, R^1 is $-CH_3$. In embodiments, R^1 is $-C(CH_3)_2$.

[0043] In embodiments, R^2 is hydrogen, halogen, alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-CF_3$, $-CN$, or $-OCF_3$. In embodiments, R^2 is hydrogen. In embodiments, R^2 is halogen. In embodiments, R^2 is alkyl. In embodiments, R^2 is C_1 - C_3 alkyl. In embodiments, R^2 is alkoxy. In embodiments, R^2 is heterocyclyl. In embodiments, R^2 is aryl. In embodiments, R^2 is heteroaryl. In embodiments, R^2 is $-CF_3$. In embodiments, R^2 is $-CN$. In embodiments, R^2 is $-OCF_3$.

[0044] In embodiments, L is . In embodiments, L is . In embodiments, L is . In embodiments, L is .

[0045] In embodiments, the present disclosure provides a compound having Formula (Ib)



Formula (Ib)

or a pharmaceutically acceptable salt thereof,

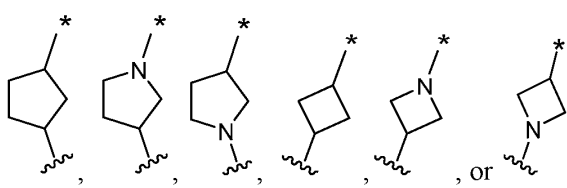
wherein

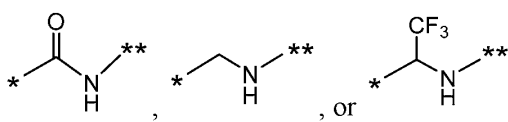
Cy^1 is a nitrogen-containing heterocyclylene or a nitrogen-containing heteroarylene, wherein

when the heterocyclylene contains two nitrogen atoms, the nitrogen atoms are adjacent to each other, and

when the heteroarylene contains two nitrogen atoms, the nitrogen atoms are adjacent to each other or the heteroarylene is pyrimidine;

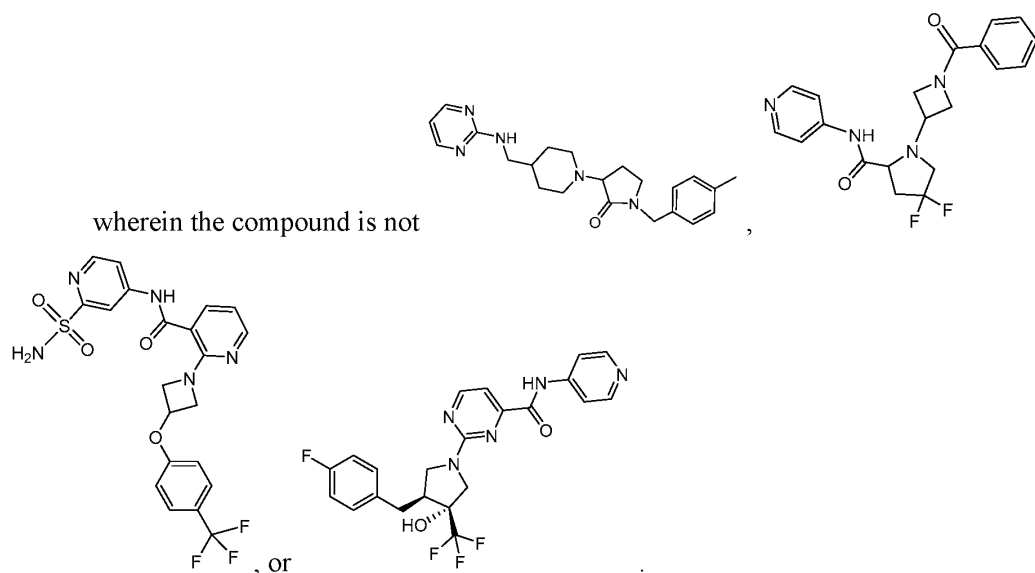
Cy² is a nitrogen-containing 4-8 membered heterocyclyl, heteroaryl, spiroheterocyclyl, or bicyclic heterocyclyl;

Cy³ is , wherein * is the point of attachment to Cy¹;

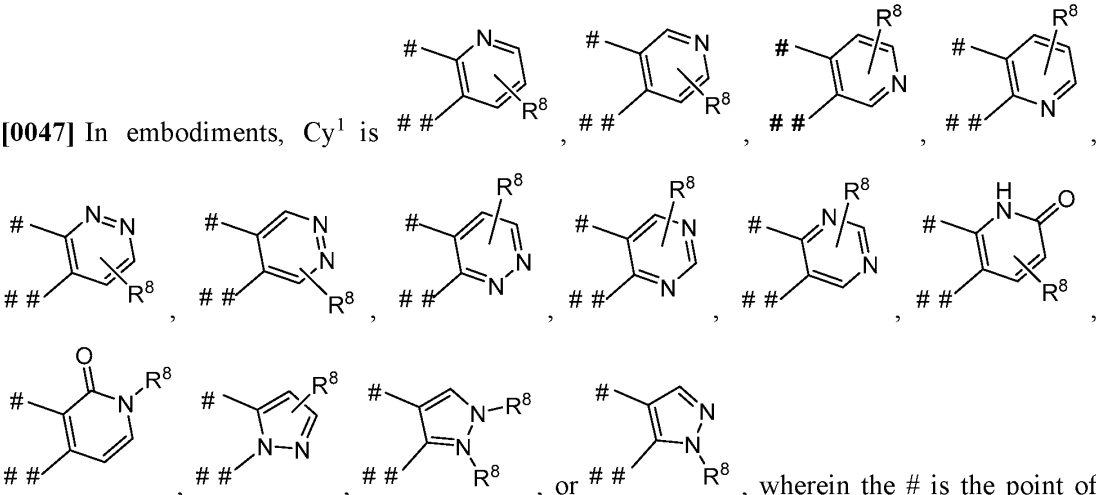
L is , wherein * is the point of attachment to Cy¹, and ** is the point of attachment to Cy²;

R¹ and R² are each independently hydrogen, halogen, alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, -CF₃, -CN, or -OCF₃;

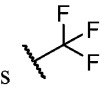
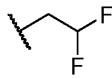
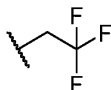
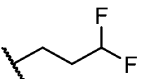
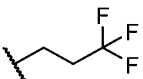
R⁴ and R⁵ are each independently hydrogen, C₁-C₃ alkyl, -F, or R⁴ and R⁵ together form =O; and wherein Cy¹ is not 1,2,5 thiadiazole, wherein Cy² is not thiazole or thiadiazole, and



[0046] In embodiments, Cy¹ is a 4-6 membered N-heteroarylene. In embodiments, Cy¹ is a 4-6 membered N-heterocyclylene. In embodiments, Cy¹ is pyridinyl, pyridinonyl, pyridazinyl, pyrimidinyl, or pyrazolyl. In embodiments, Cy¹ is pyridinyl. In embodiments, Cy¹ is pyridinonyl. In embodiments, Cy¹ is pyridazinyl. In embodiments, Cy¹ is pyrimidinyl. In embodiments, Cy¹ is pyrazolyl.

[0047] In embodiments, Cy¹ is , wherein the # is the point of attachment to L, and ## is the point of attachment to Cy³.

[0048] In embodiments, each R⁸ is independently C₁-C₅ alkyl, C₁-C₅ haloalkyl, C₁-C₅ alkoxy, cycloalkyl, heterocyclyl, -CH₂OH, -CH₂CH₂OH, -CC(=O)NH₂, -CC(=O)NHCH₃, -CCOOH, or -CC(=O)N(CH₃)₂. In embodiments, R⁸ is C₁-C₅ alkyl. In embodiments, R⁸ is C₁-C₅ haloalkyl. In embodiments, R⁸ is C₁-C₅ alkoxy. In embodiments, R⁸ is cycloalkyl. In embodiments, R⁸ is heterocyclyl. In embodiments, R⁸ is -CH₂OH. In embodiments, R⁸ is -CH₂CH₂OH. In embodiments, R⁸ is -CC(=O)NH₂. In embodiments, R⁸ is -CC(=O)NHCH₃. In embodiments, R⁸ is -CCOOH. In embodiments, R⁸ is -CC(=O)N(CH₃)₂. In embodiments, R⁸ is -CH₃. In embodiments, R⁸ is -CH₂CH₃. In embodiments, R⁸ is -CH₂CH₂CH₃.

[0049] In embodiments, R⁸ is C₁-C₃ haloalkyl. In embodiments, R⁸ is . In embodiments, R⁸ is . In embodiments, R⁸ is . In embodiments, R⁸ is . In embodiments, R⁸ is . In embodiments, R⁸ is . In embodiments, R⁸ is .

[0050] In embodiments, R⁸ is C₃-C₆ cycloalkyl. In embodiments, R⁸ is C₃-C₆ heterocyclyl. In

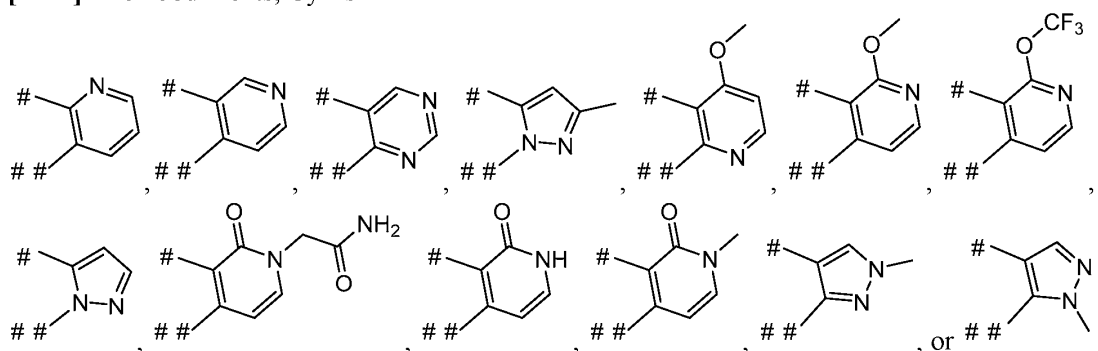
embodiments, R⁸ is cyclopropyl. In embodiments, R⁸ is . In embodiments, R⁸ is .

In embodiments, R^8 is . In embodiments, R^8 is . In embodiments, R^8 is .

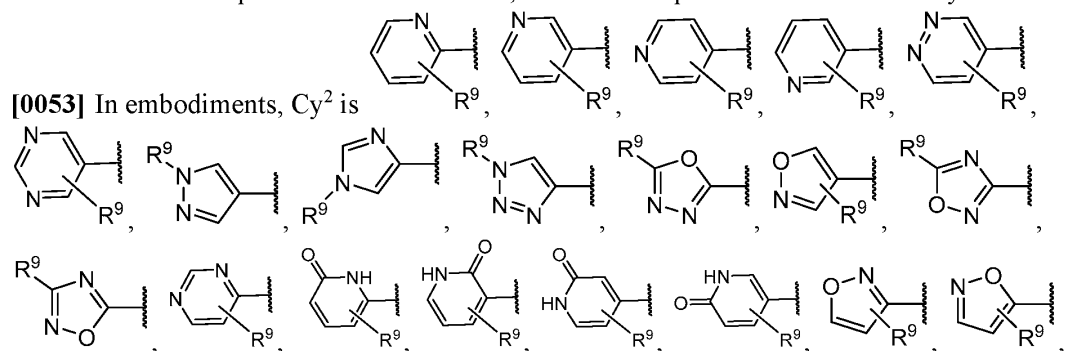
In embodiments, R^8 is . In embodiments, R^8 is . In embodiments, R^8 is . In embodiments, R^8 is .

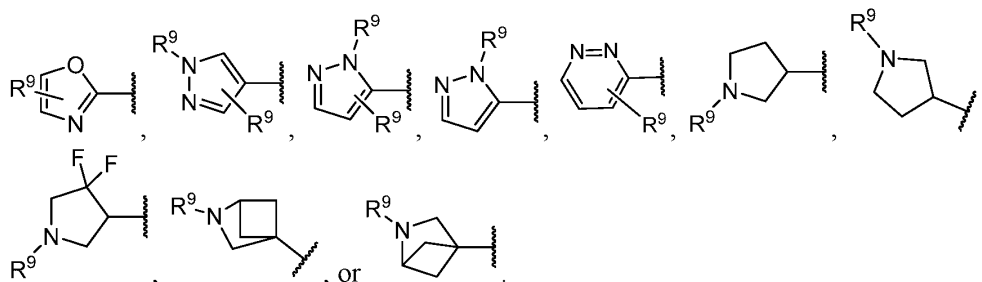
[0051] In embodiments, R⁸ is C₁-C₅ alkoxy (e.g., C₁, C₂, C₃, C₄, or C₅ alkoxy). In embodiments, R⁸ is -OCH₃. In embodiments, R⁸ is -OCF₃. In embodiments, R⁸ is -CC(=O)NH₂. In embodiments, R⁸ is -CC(=O)N(CH₃)₂. In embodiments, R⁸ is . In embodiments, R⁸ is .

[0052] In embodiments, Cy¹ is

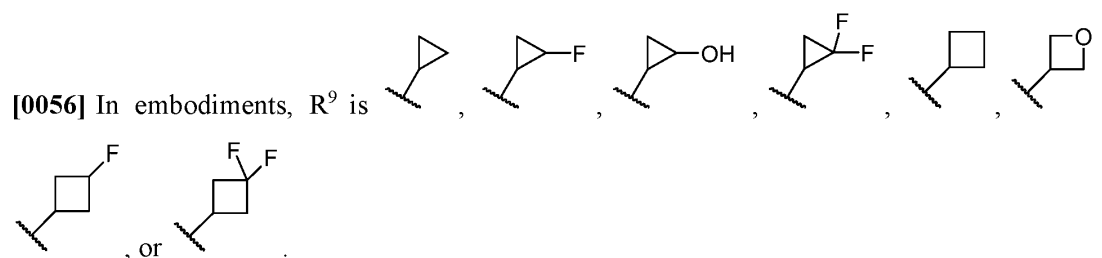
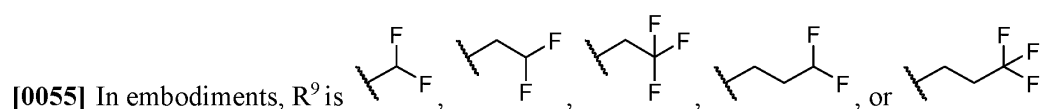


wherein the # is the point of attachment to L, and ## is the point of attachment to Cy³.

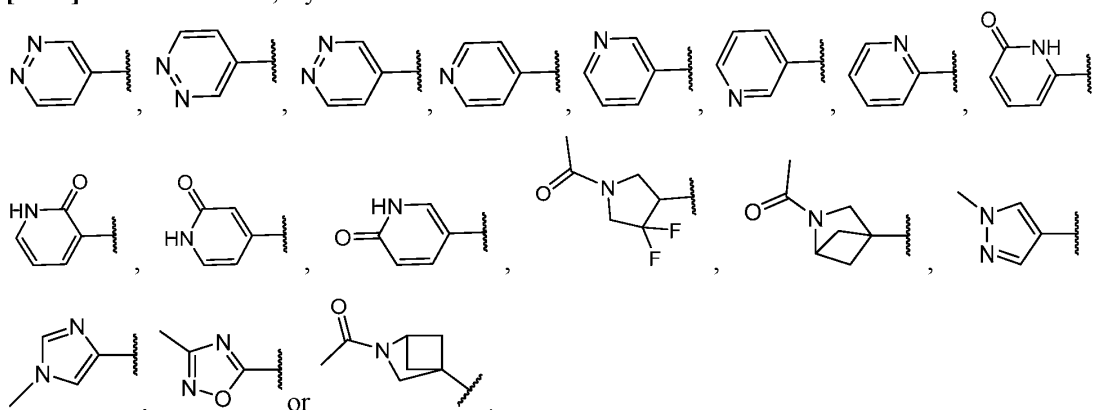


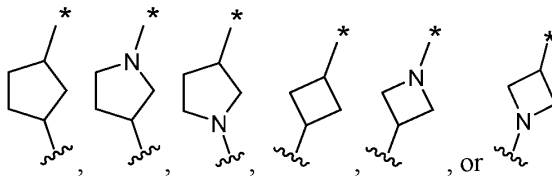


[0054] In embodiments, each R⁹ is independently hydrogen, halogen, CF₃, C₁-C₃ alkyl, C₁-C₅ haloalkyl, cycloalkyl, C(=O)CH₃, or SO₂CH₃. In embodiments, R⁹ is hydrogen. In embodiments, R⁹ is -F, -Cl, -Br, or -I. In embodiments, R⁹ is -CF₃. In embodiments, R⁹ is C₁-C₃ alkyl. In embodiments, R⁹ is C₁-C₅ haloalkyl. In embodiments, R⁹ is cycloalkyl. In embodiments, R⁹ is C(=O)CH₃. In embodiments, R⁹ is SO₂CH₃. In embodiments, R⁹ is -Cl. In embodiments, R⁹ is -CH₃. In embodiments, R⁹ is -C(=O)CH₃.

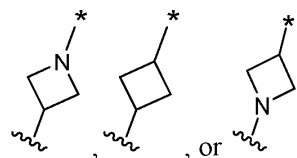


[0057] In embodiments, Cy² is

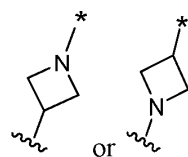




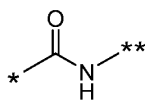
[0058] In embodiments, Cy^3 is , , , , or , wherein * is the point of attachment to Cy^1 .



[0059] In embodiments, Cy^3 is , or .

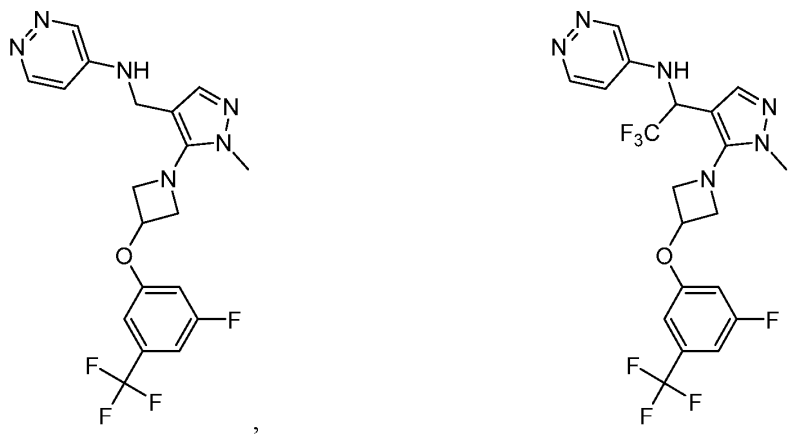


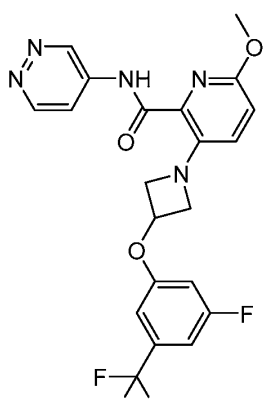
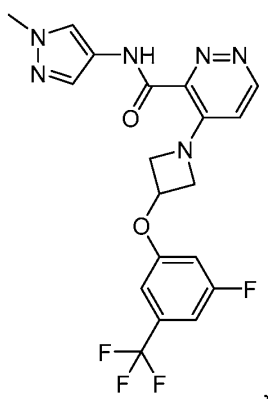
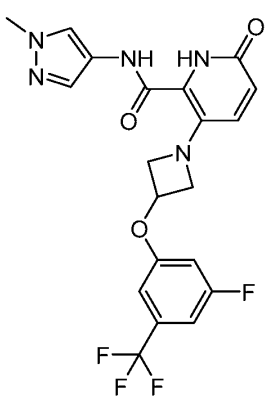
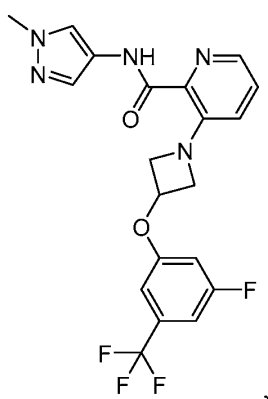
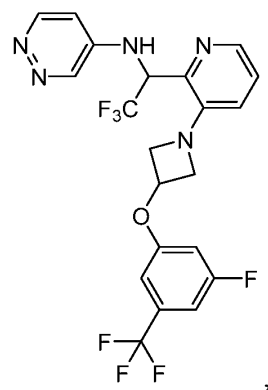
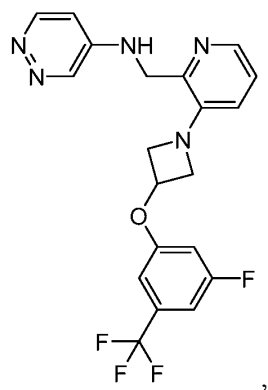
[0060] In embodiments, Cy^3 is or .

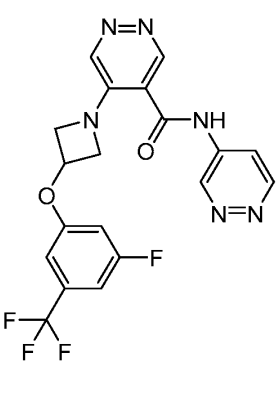
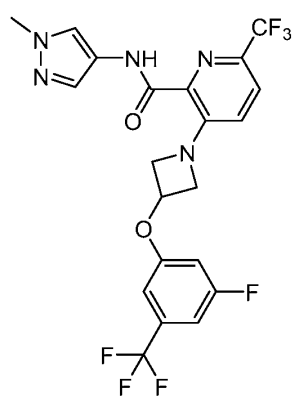
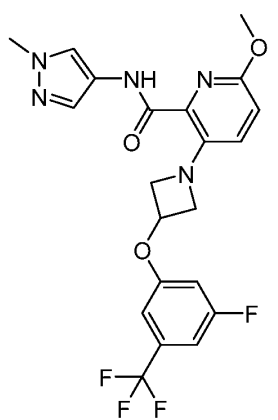
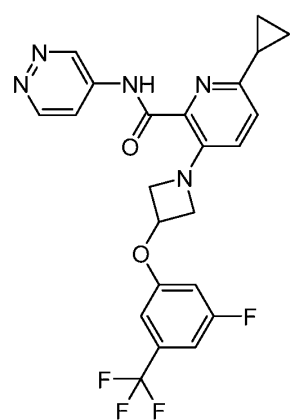
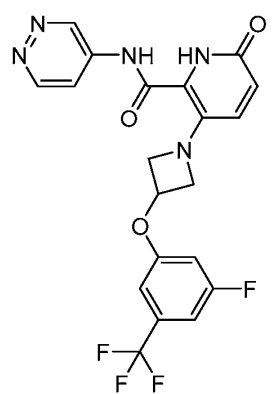
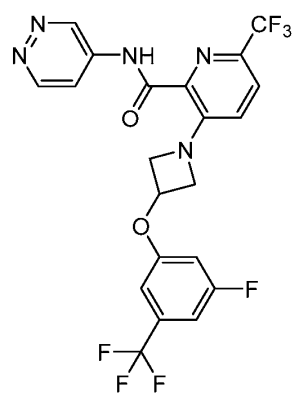


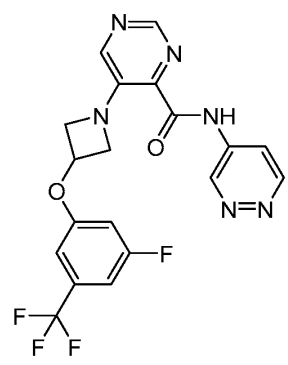
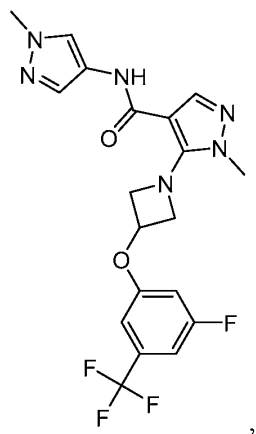
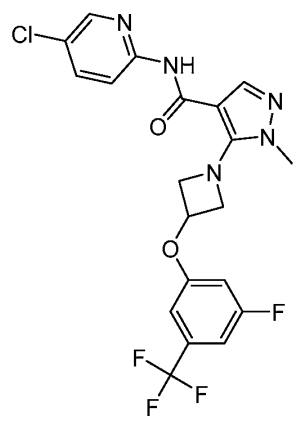
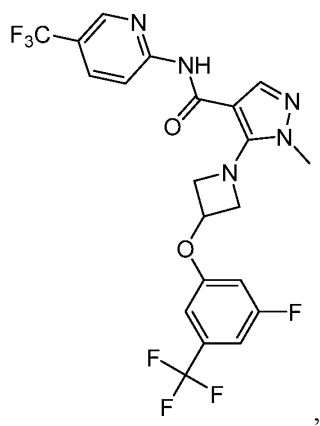
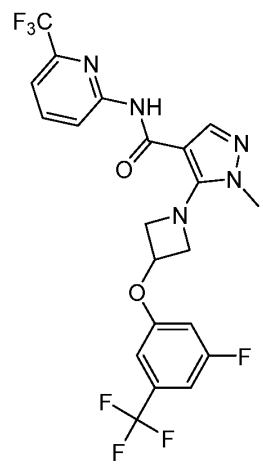
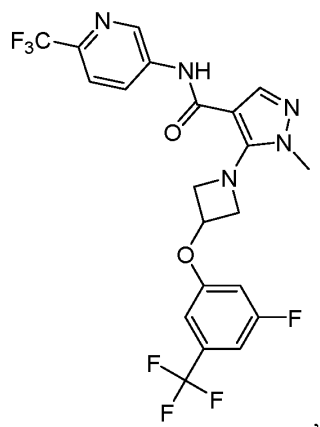
[0061] In embodiments, L is .

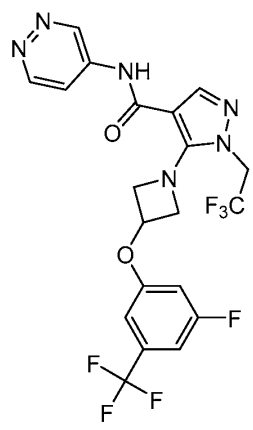
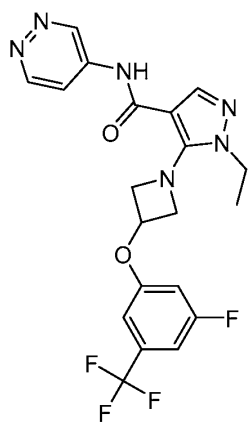
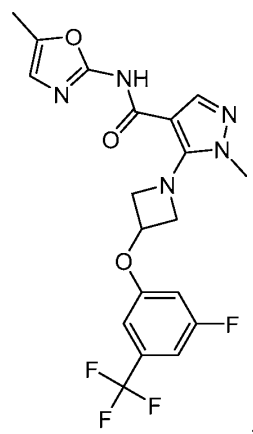
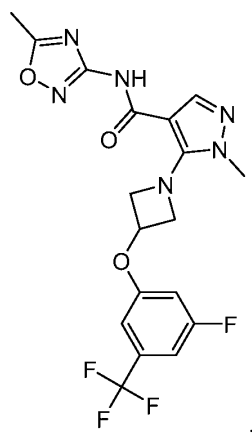
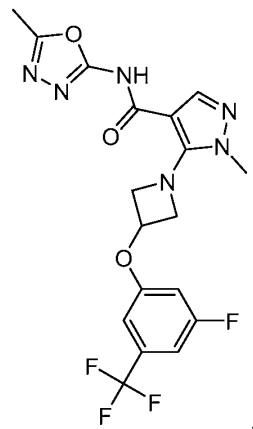
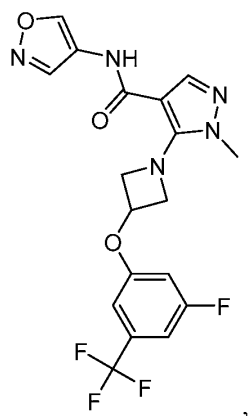
[0062] In embodiments, a compound of Formula (I), (Ia), or (Ib) is selected from:

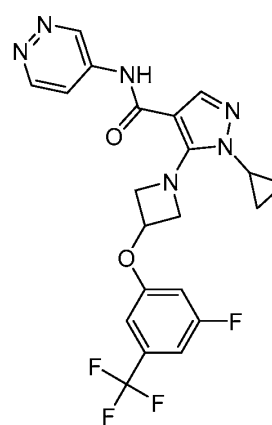
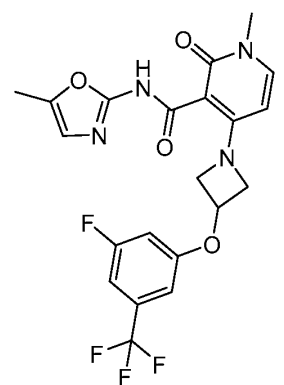
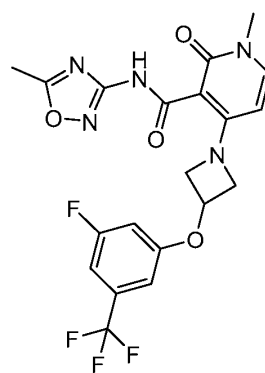
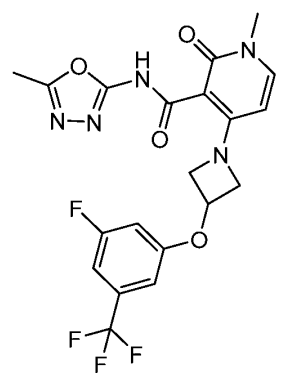
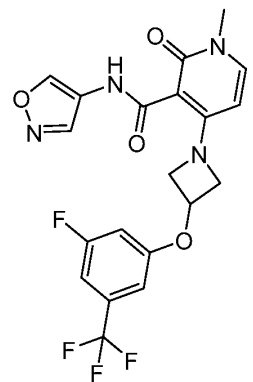
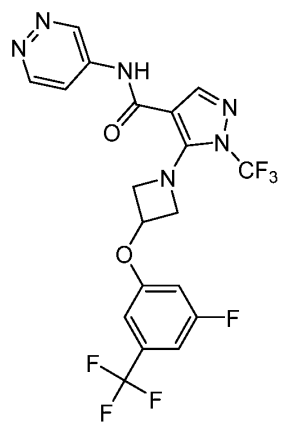


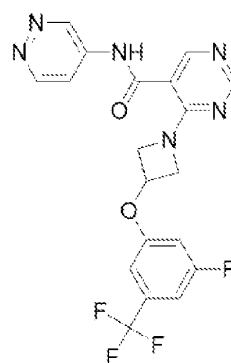
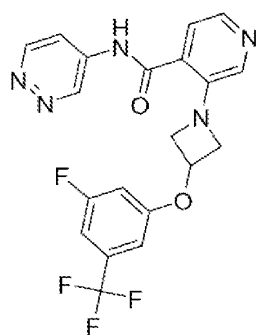
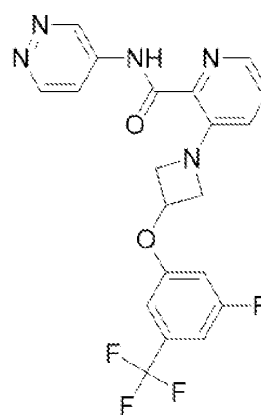
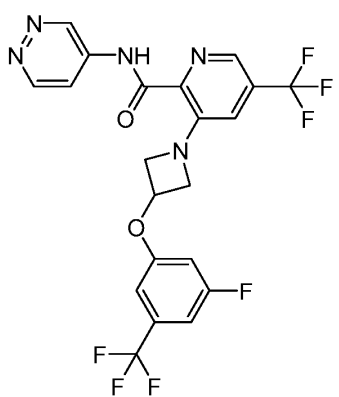
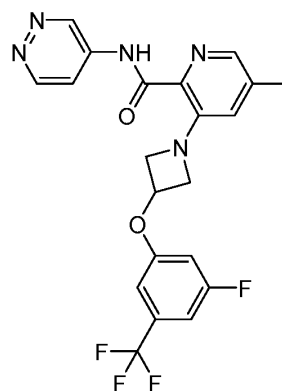
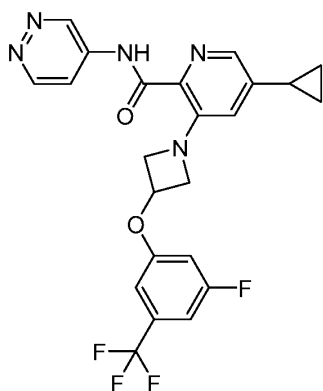


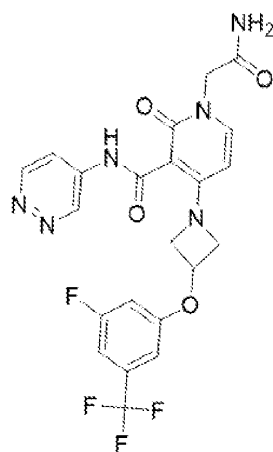
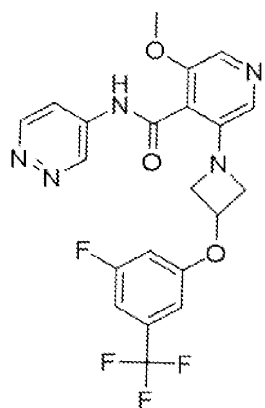
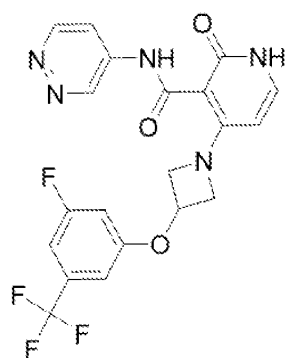
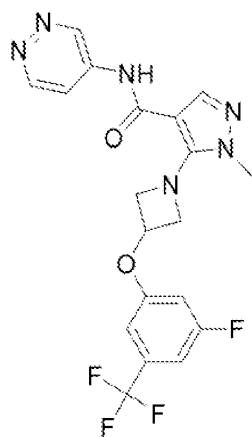
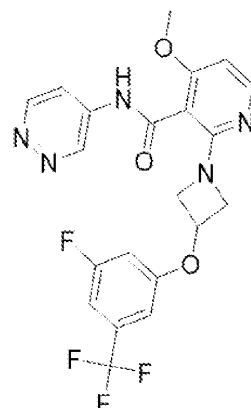
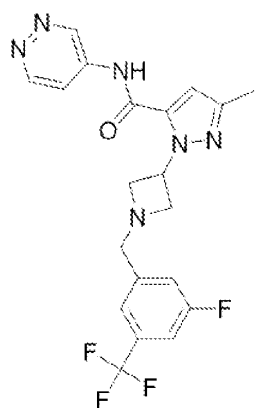


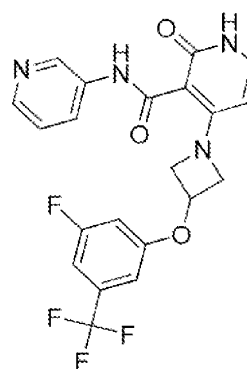
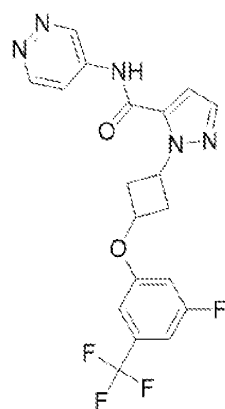
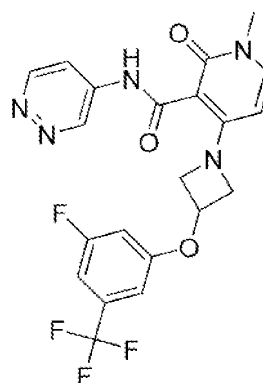
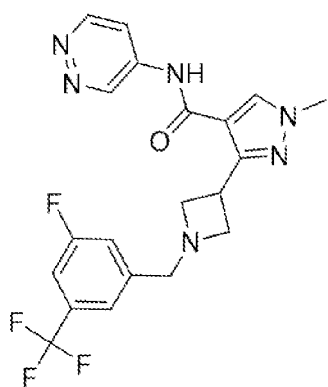
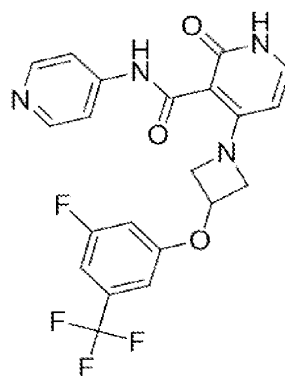
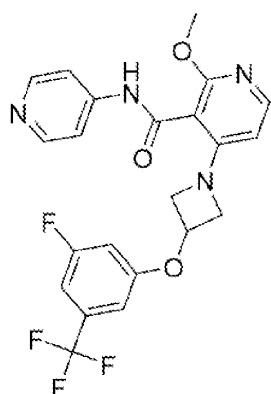


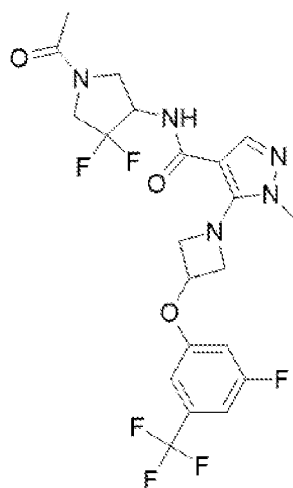
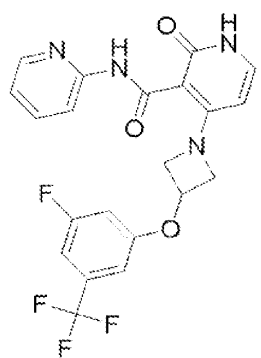
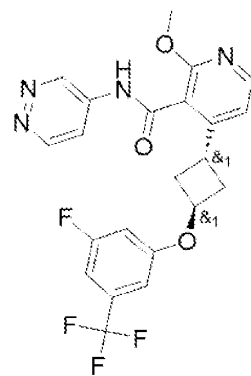
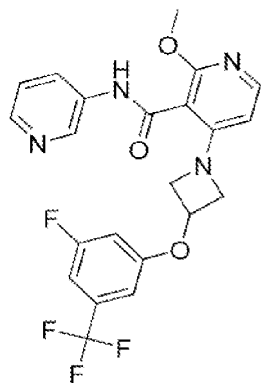
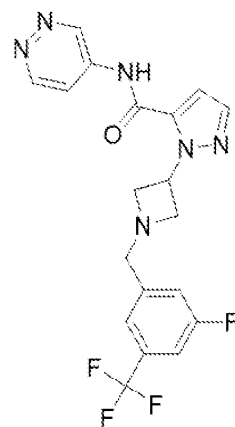
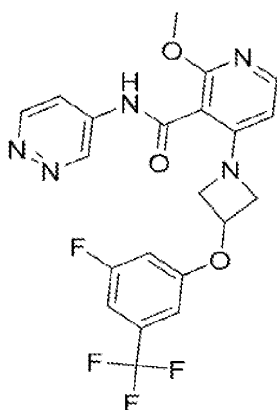


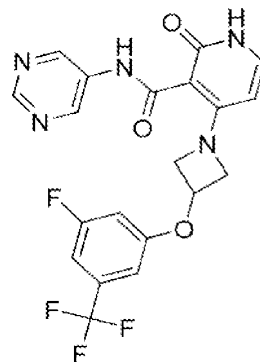
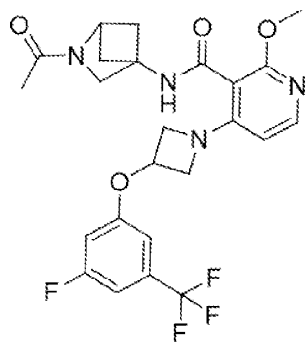
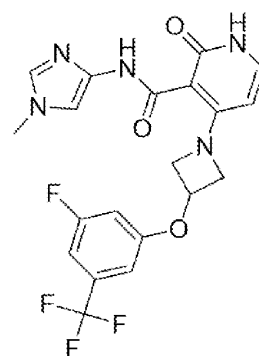
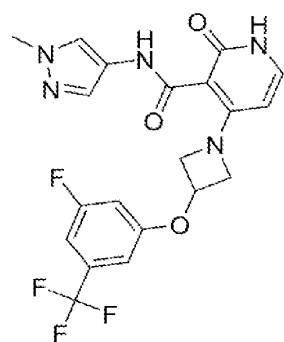
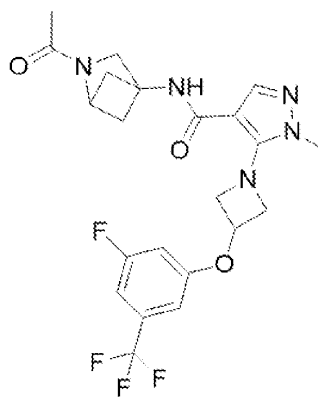
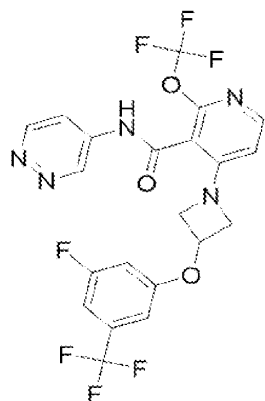


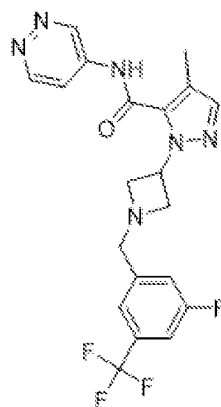
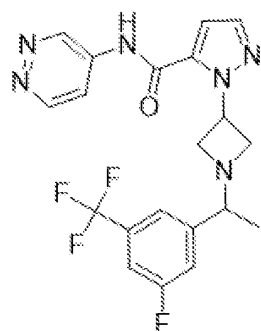
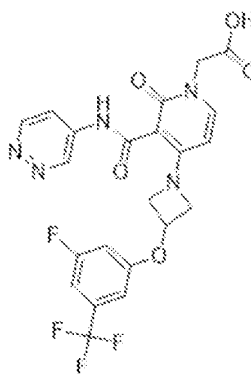
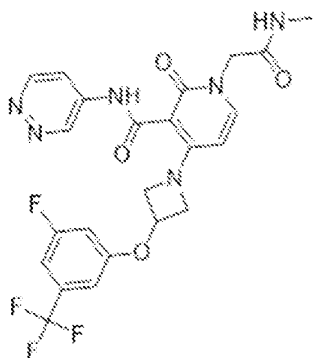
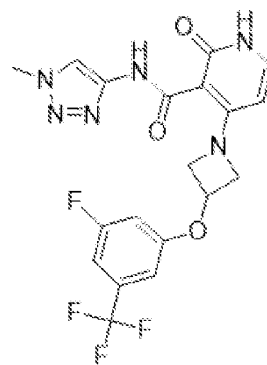
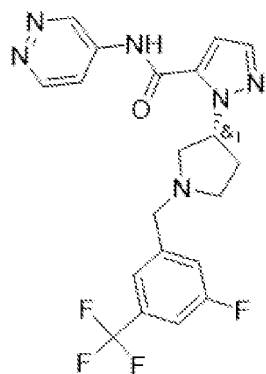


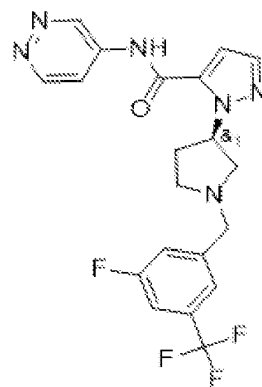
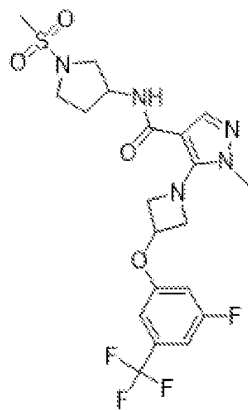
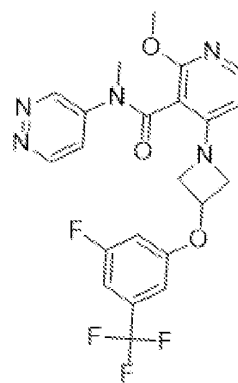
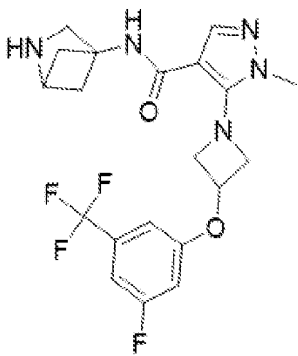
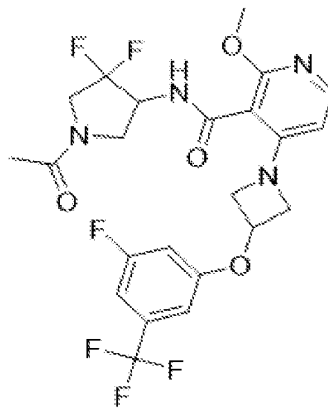
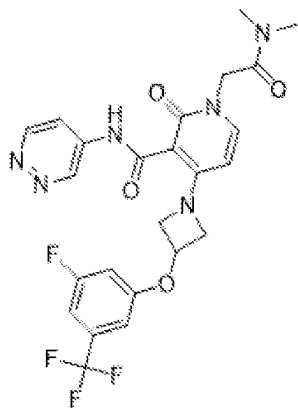


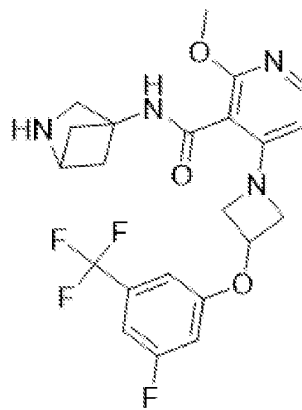
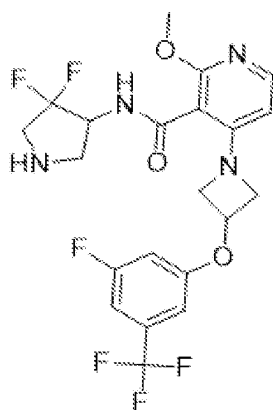
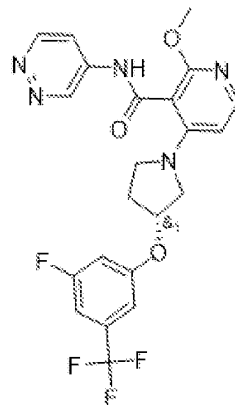
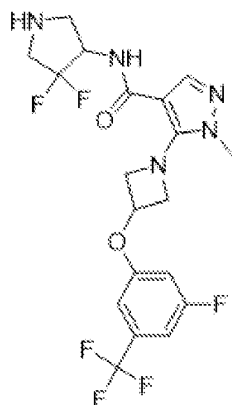
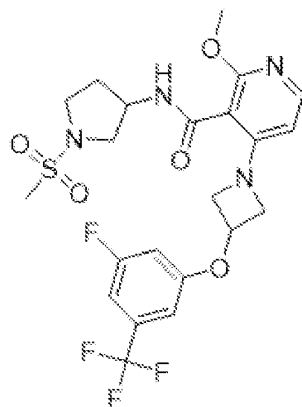
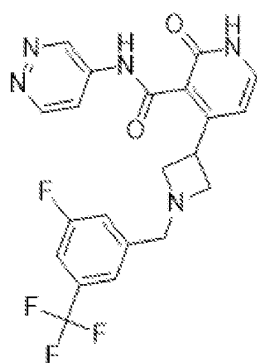


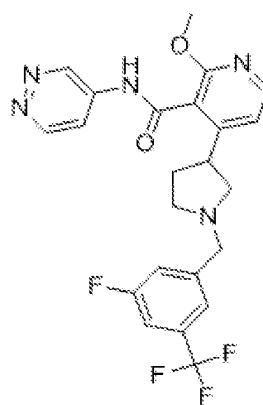
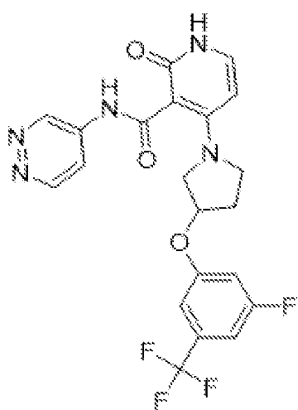
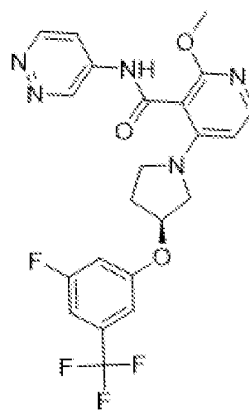
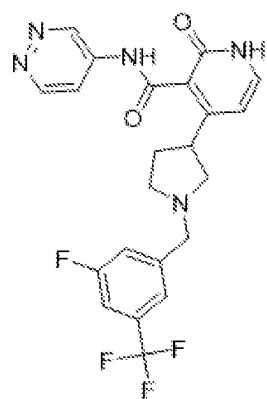
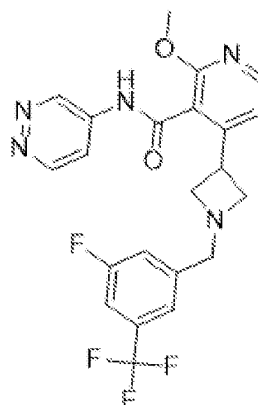
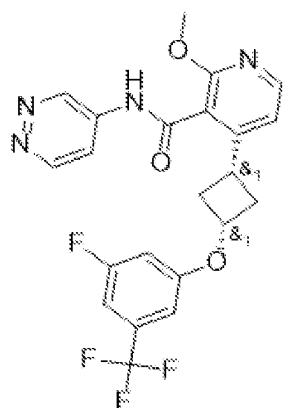


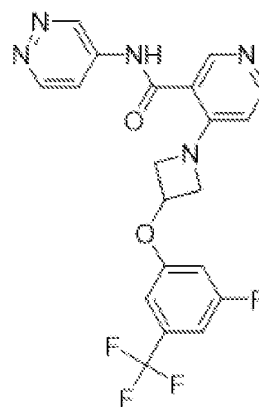
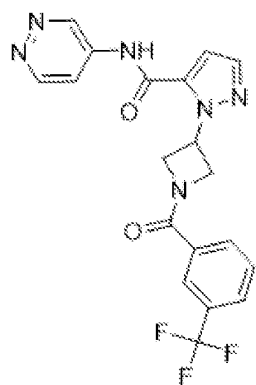
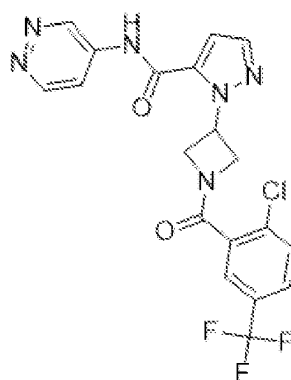
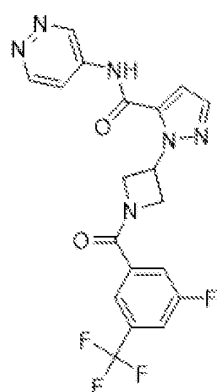
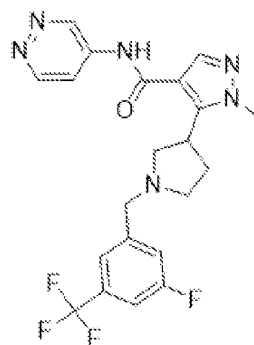
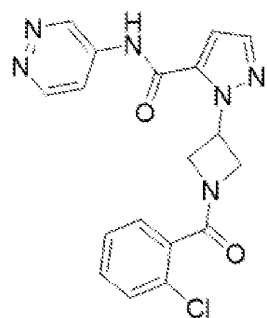


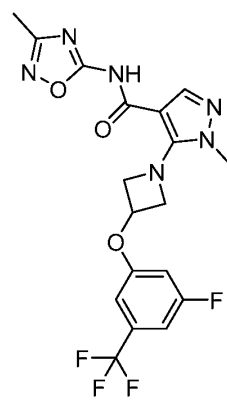
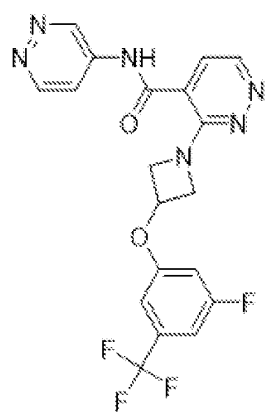
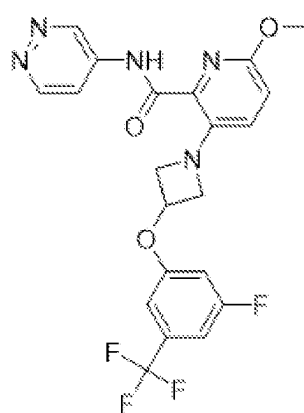
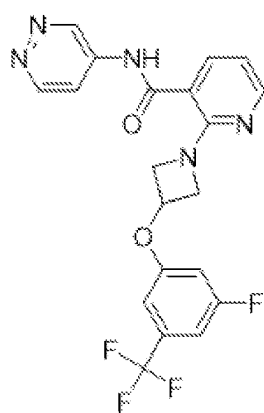
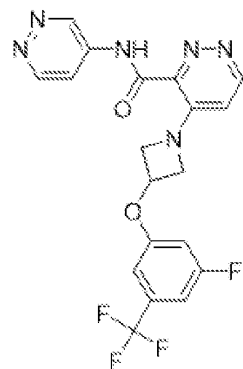
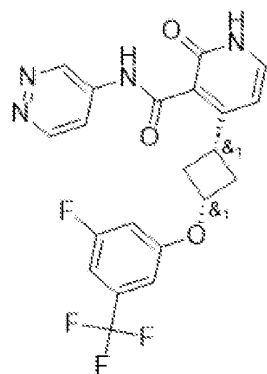


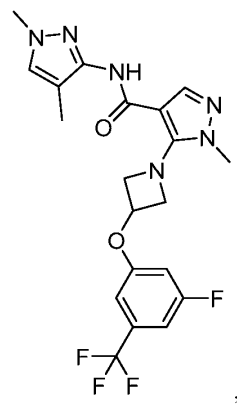
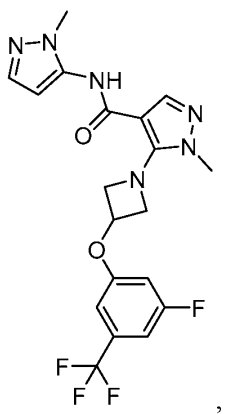
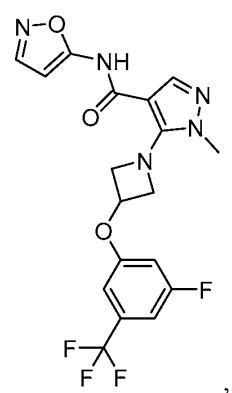
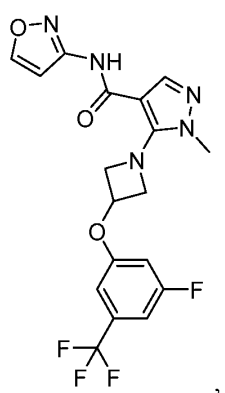
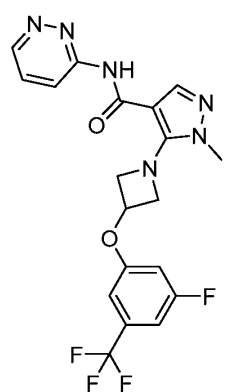
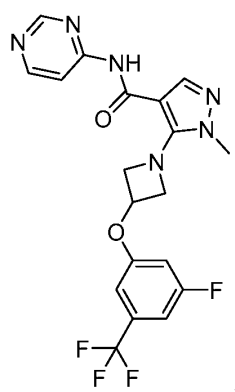


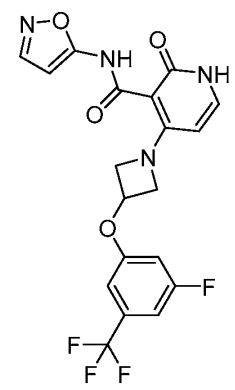
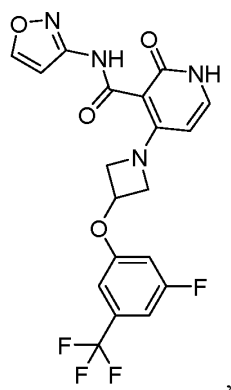
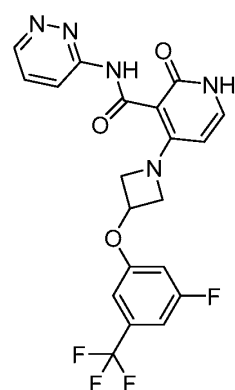
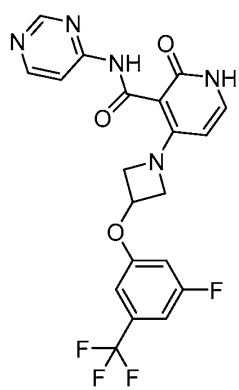
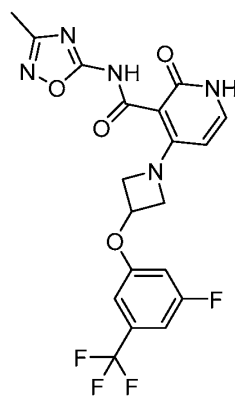
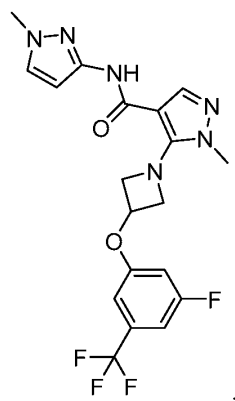


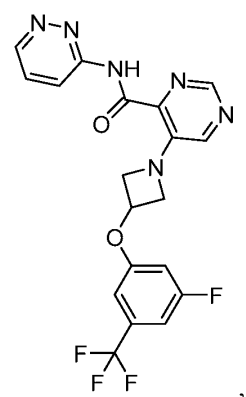
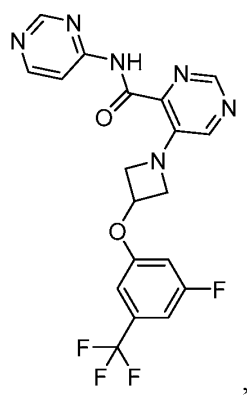
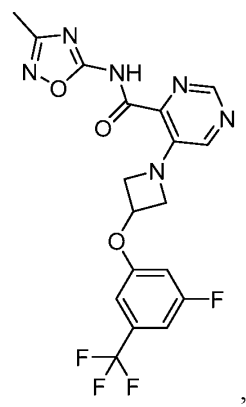
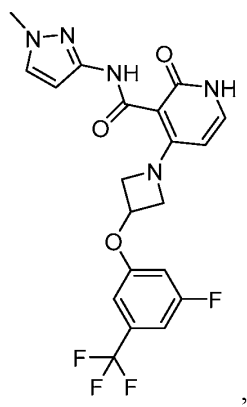
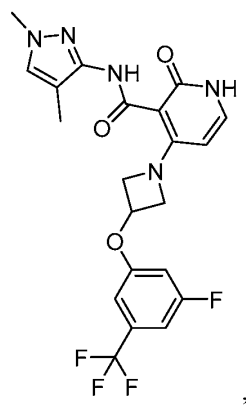
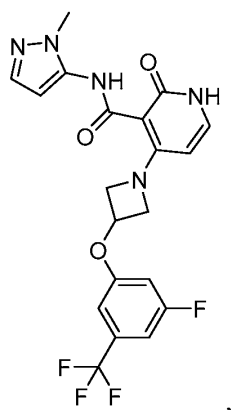


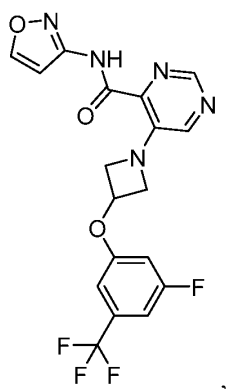




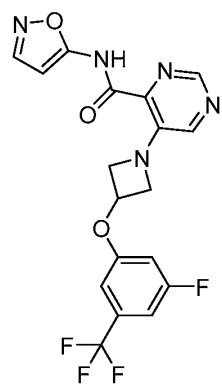




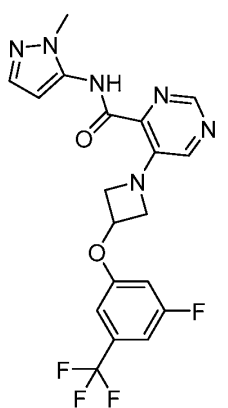




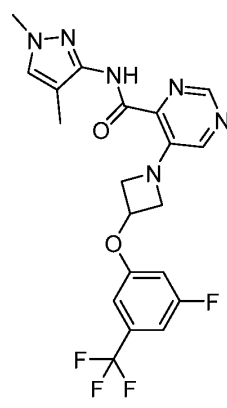
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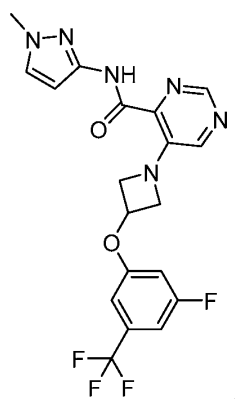
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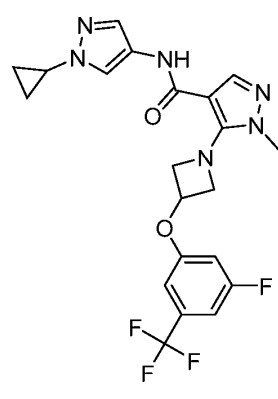
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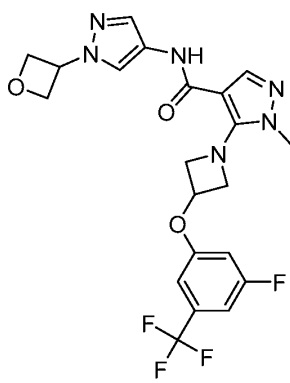
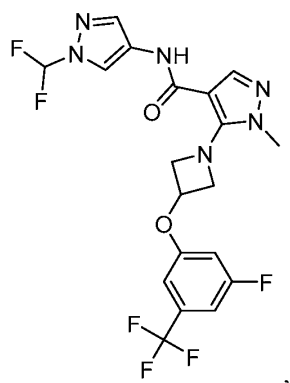
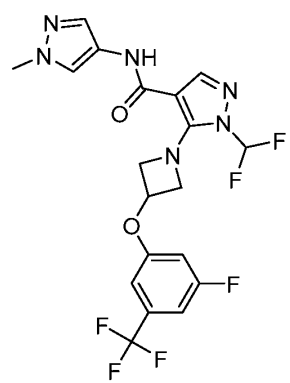
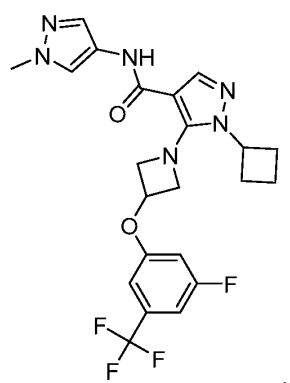
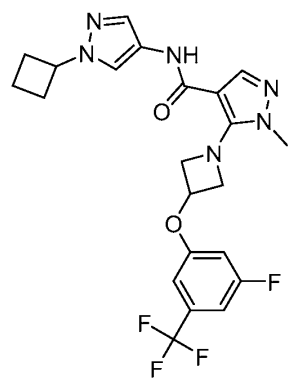
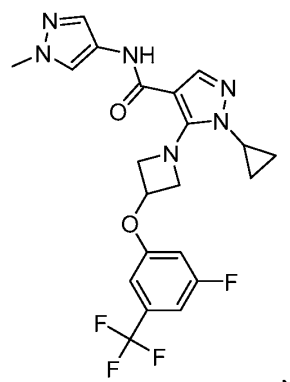
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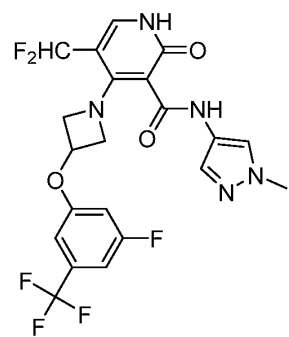
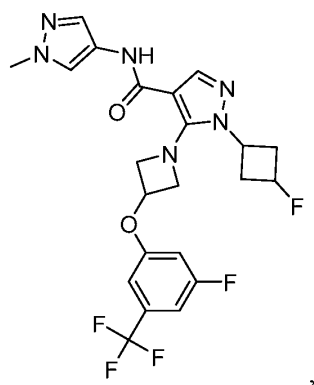
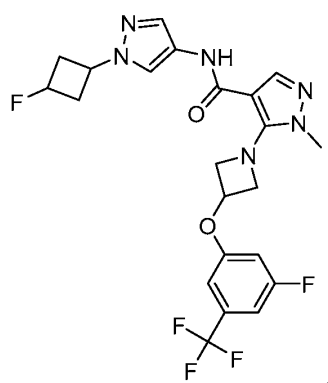
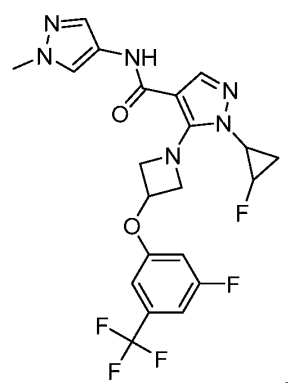
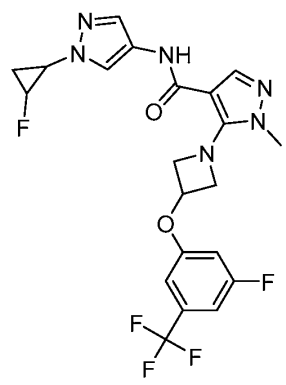
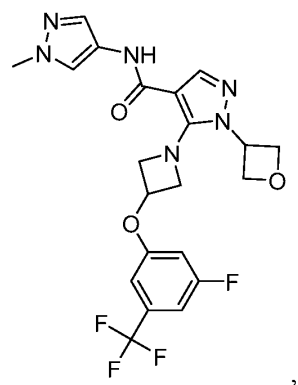


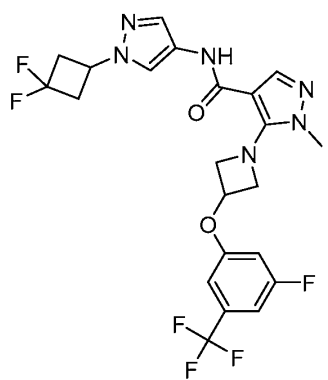
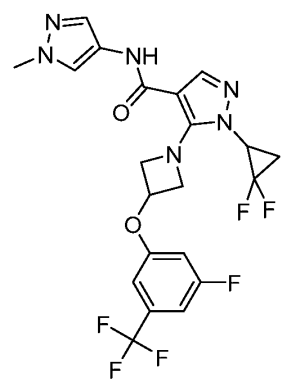
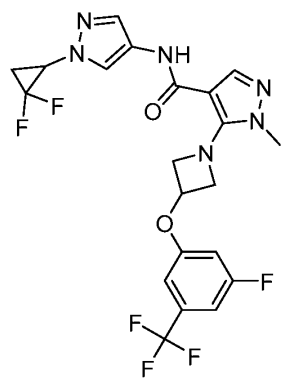
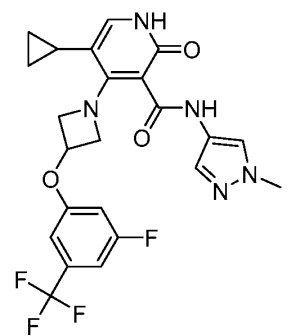
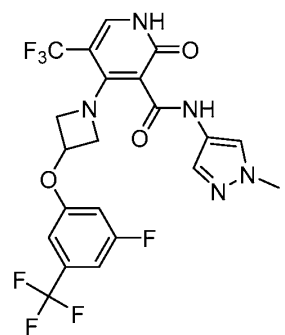
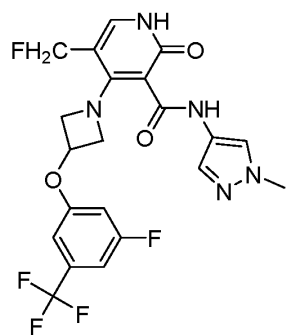
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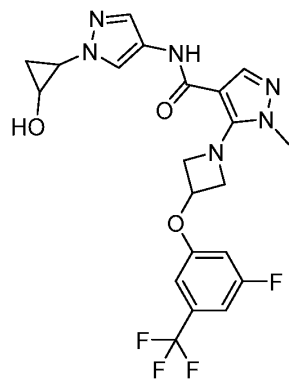
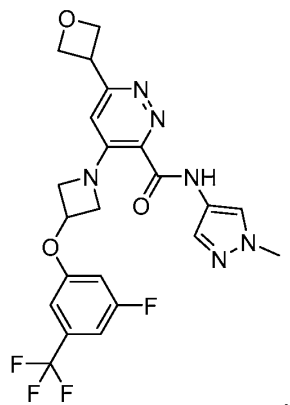
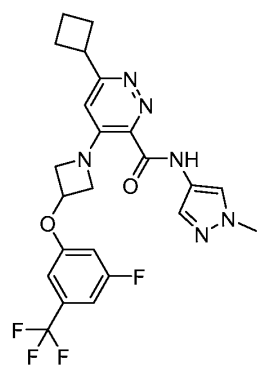
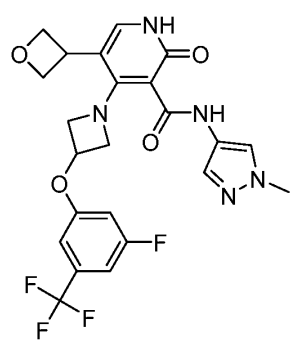
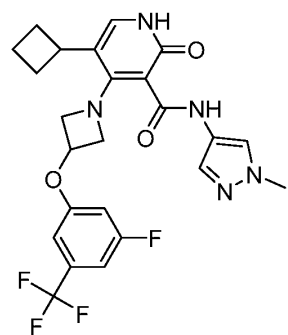
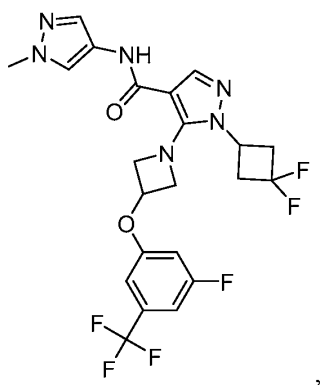


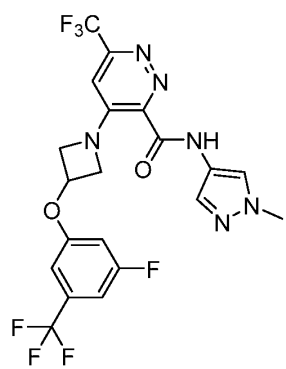
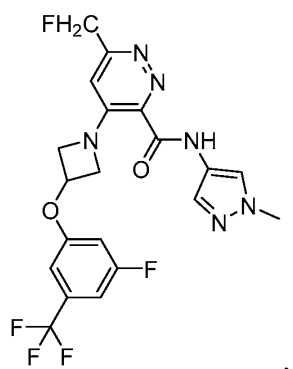
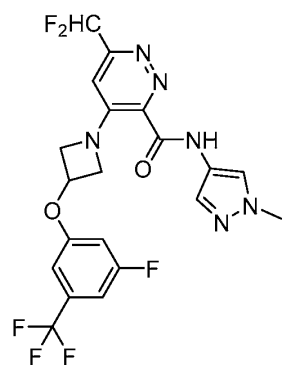
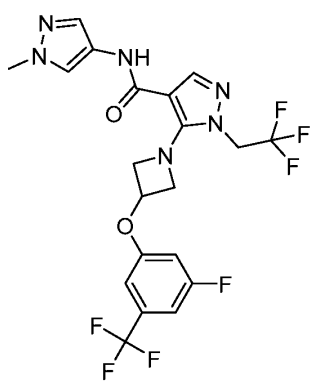
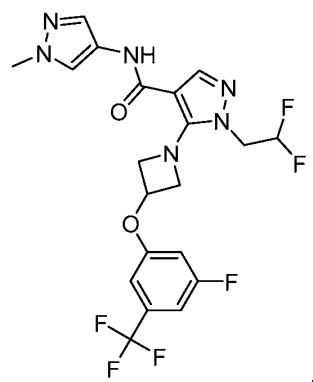
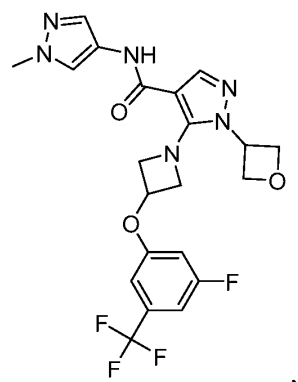
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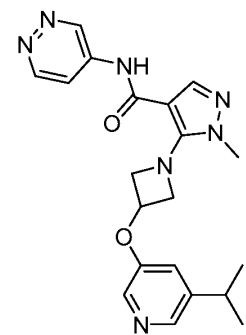
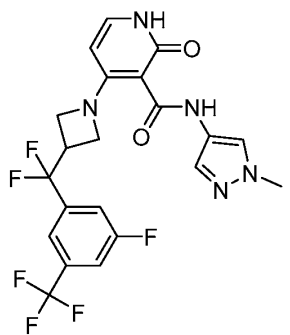
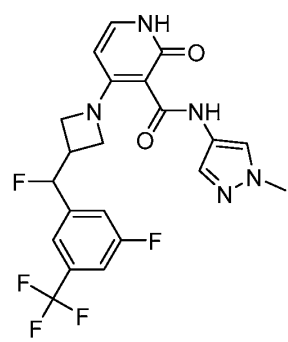
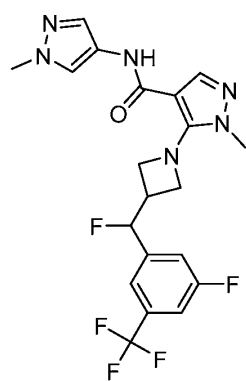
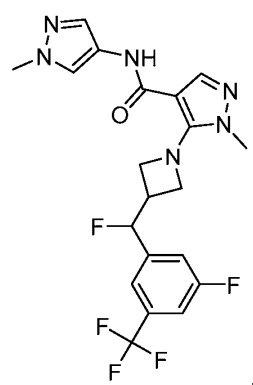
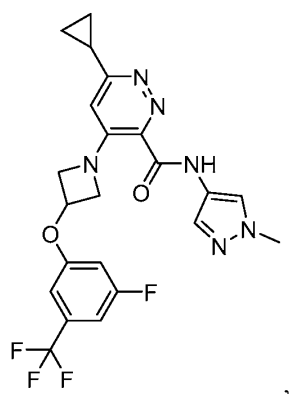


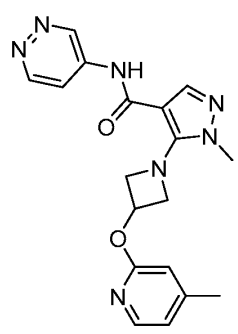
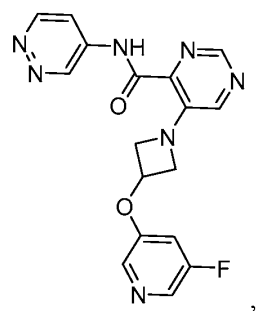
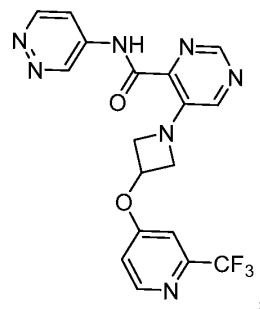
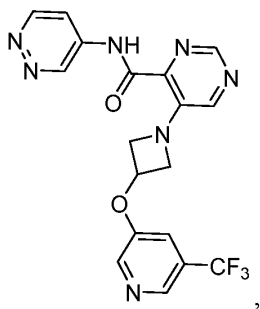
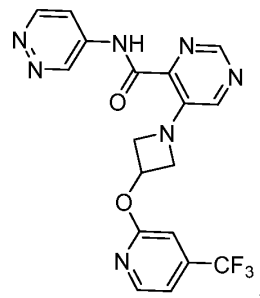
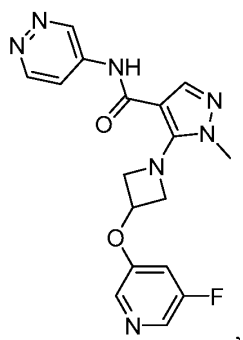
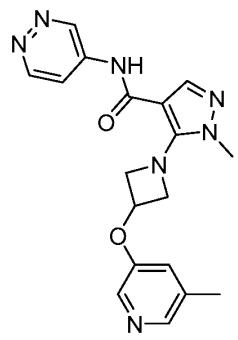
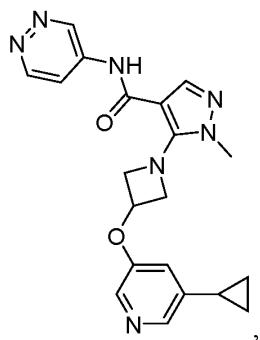


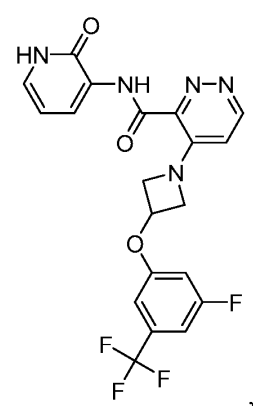
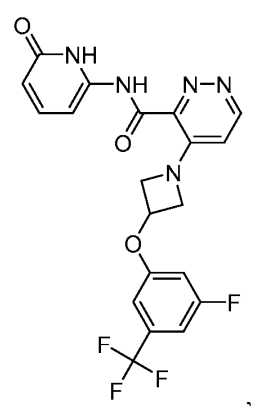
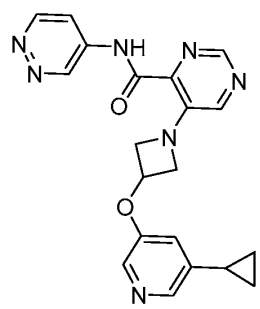
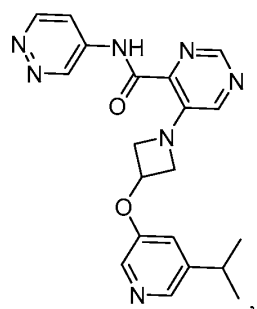
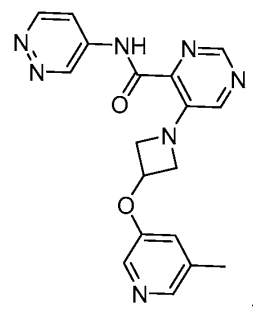
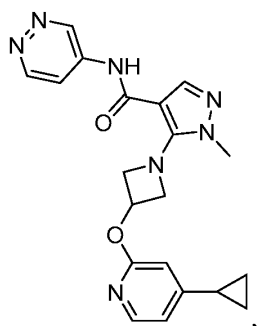
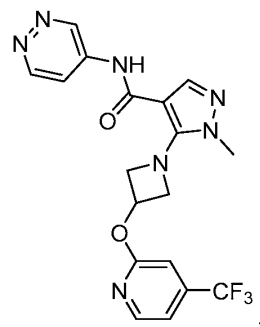
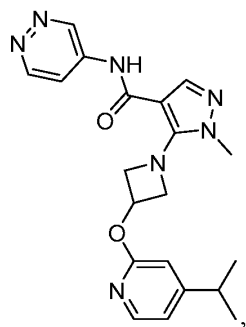


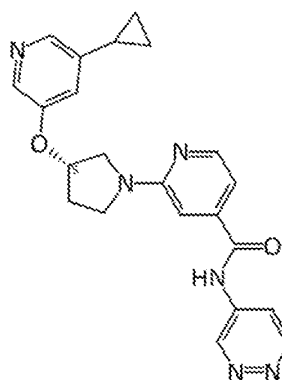
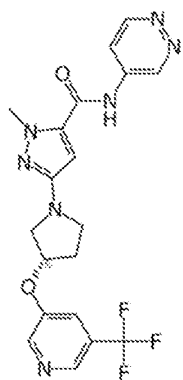
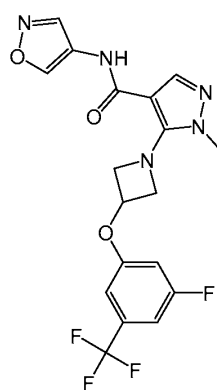
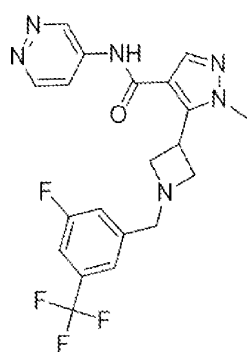


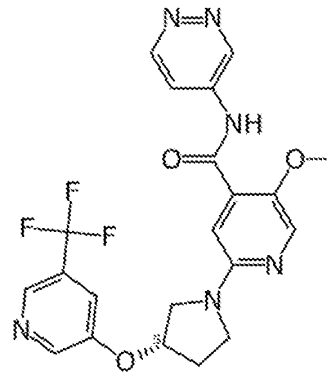
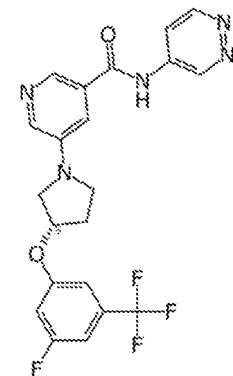
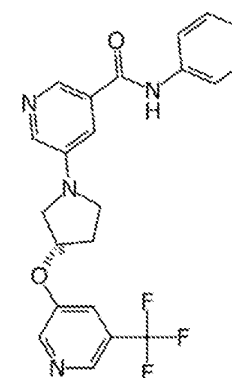
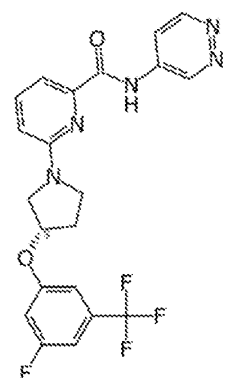
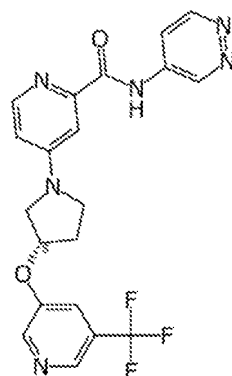
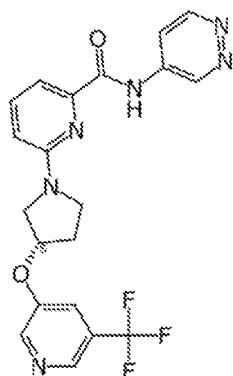


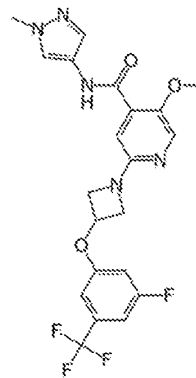
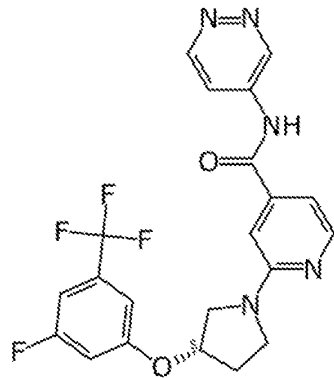
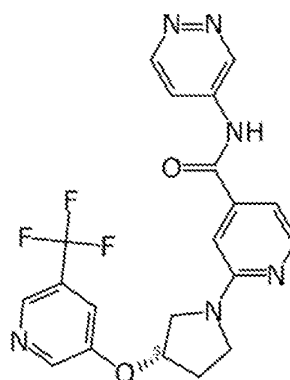
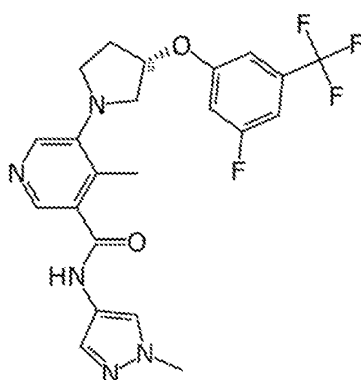
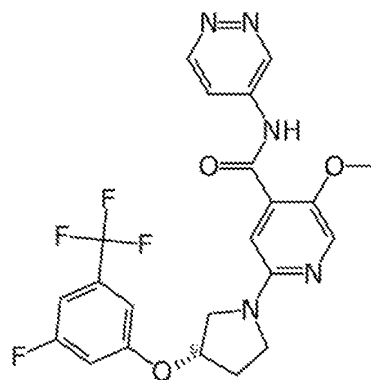
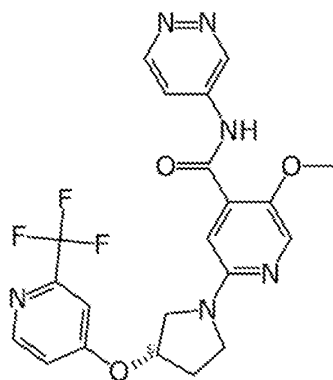


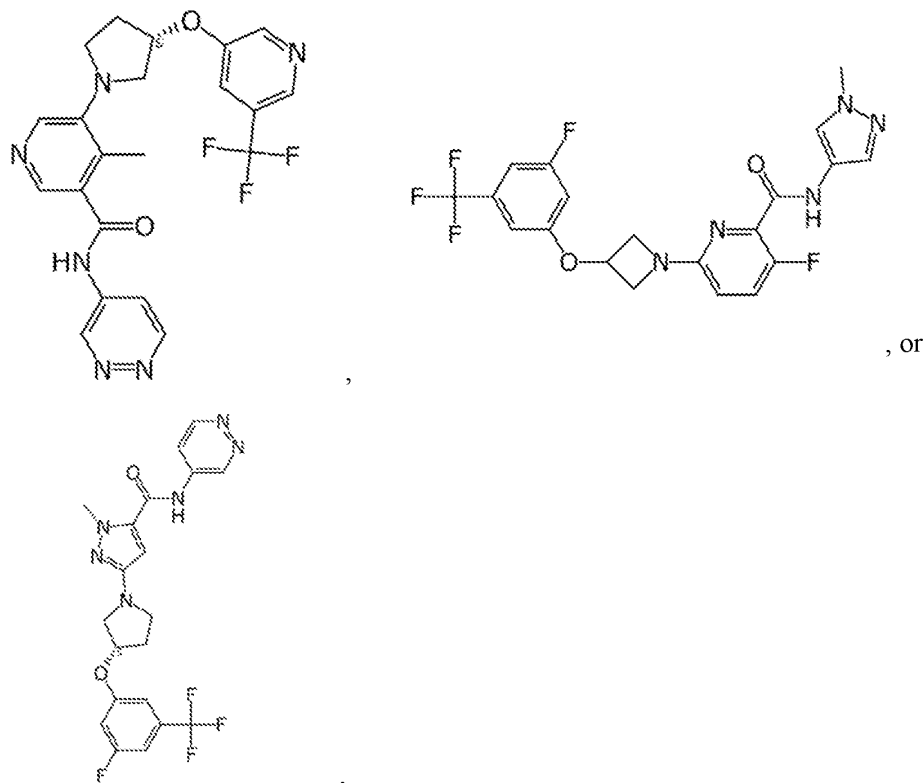












or a pharmaceutically acceptable salt or stereoisomer thereof.

Compositions

[0063] The present disclosure provides pharmaceutical compositions for providing a compound of the present disclosure to a patient in need thereof. In embodiments, a pharmaceutical composition comprises one or more compounds of the present disclosure (e.g., a compound of Formula (I), (Ia), (Ib), or Table 1) or a pharmaceutically acceptable salt or stereoisomer thereof.

[0064] In embodiments of the present disclosure, a pharmaceutical composition comprises a therapeutically effective amounts of one or more compounds of the present disclosure (e.g., a compound of Formula (I), (Ia), (Ib), or Table 1) or a pharmaceutically acceptable salt or stereoisomer thereof.

[0065] In embodiments, a pharmaceutical composition, as described herein, comprises one or more compounds selected from Table 1, or a pharmaceutically acceptable salt or stereoisomer thereof.

[0066] In embodiments of the present disclosure, a pharmaceutical composition comprising one or more compounds of the present disclosure (e.g., a compound of Formula (I), (Ia), (Ib), or Table 1) or a pharmaceutically acceptable salt or stereoisomer thereof, and a pharmaceutically acceptable excipient or adjuvant is provided. The pharmaceutically acceptable excipients and adjuvants are added to the composition for a variety of purposes. In embodiments, a pharmaceutical composition comprising one or more compounds disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, further comprise a pharmaceutically acceptable carrier. In embodiments, a pharmaceutically acceptable carrier includes a pharmaceutically acceptable excipient, binder, and/or diluent. In embodiments, suitable pharmaceutically acceptable carriers include, but are not limited to, inert solid fillers or diluents and sterile aqueous or organic solutions. In embodiments, suitable pharmaceutically acceptable excipients include, but are not limited to, water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylase, magnesium stearate, talc, silicic acid, viscous paraffin, and the like.

[0067] In embodiments, the compounds of the present disclosure can be formulated for administration by a variety of means including orally, parenterally, by inhalation spray, topically, or rectally in compositions containing pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used here includes subcutaneous, intravenous, intramuscular, and intraarterial injections with a variety of infusion techniques. Intraarterial and intravenous injection as used herein includes administration through catheters.

[0068] In embodiments, the compounds of the present disclosure are administered in a therapeutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound-administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

Methods of Treatment

[0069] In embodiments, the compounds of the present disclosure modulate G protein-coupled receptor (GPR52) activity in a patient in need thereof.

[0070] In embodiments, the present disclosure provides a method of treating a neurological and/or psychiatric disorder in a patient in need thereof, comprising administering a compound of the present disclosure to a patient in need thereof. In embodiments, the neurological or psychiatric

disorder comprises Parkinson's disease, Huntington's disease, attention deficit hyperactivity disorder (ADHD), mood disorders, bipolar disorder, epilepsy, Alzheimer's disease, anxiety, depression, dyskinesia, and schizophrenia.

[0071] In embodiments, the compounds of the present disclosure are administered in combination with one or more other compounds used for treating neurological or psychiatric disorder.

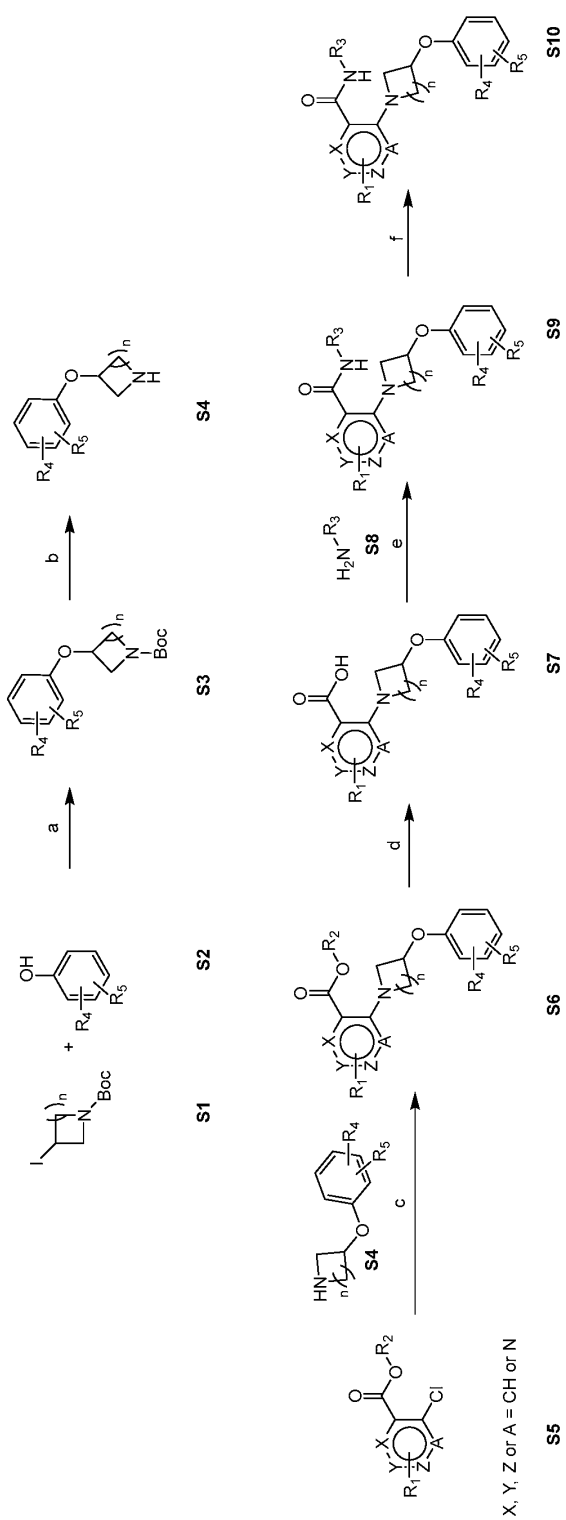
EXAMPLES

[0072] The disclosure now being generally described, it will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present disclosure and are not intended to limit the invention.

[0073] The compounds of the present disclosure can be synthesized using the methods as hereinafter described below, together with synthetic methods known in the art of synthetic organic chemistry or variations thereon as appreciated by those skilled in the art.

[0074] Preparation of compounds can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Greene and Wuts, *Protective Groups in Organic Synthesis*, 4th. Ed., Wiley & Sons, 2006, as well as in Jerry March, *Advanced Organic Chemistry*, 4th edition, John Wiley & Sons, publisher, New York, 1992 which are incorporated herein by reference in their entirety.

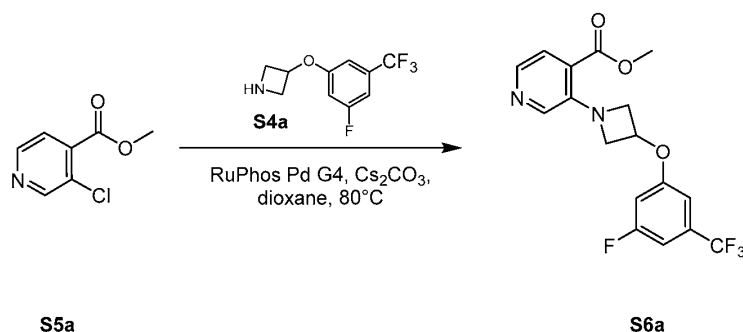
Scheme 1:



Reagents and conditions: (a) i) Cs_2CO_3 , DMF, 100°C , 12 h, or ii) RuPhos Pd G4, Cs_2CO_3 , dioxane, 80°C , or iii) DIEA, EtOH, 80°C , 12 h (b) HCl/1,4-dioxane, 25°C , 16 h (c) **S5**, TEA, DMA, 25°C , 1 h (d) LiOH, THF/MeOH/water, 25°C , 5 h (e) i) NH_2R^2 , HATU, DIPEA, DMF, 25°C , 2 h ii) TFA/DCM, 25°C , 2 h f) additional modifications (not in all cases).

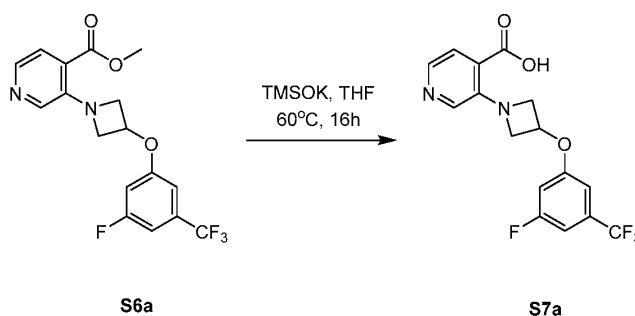
Example 1. Scheme 1. 3-(3-(3-fluoro-5-(trifluoromethyl)phenoxy)azetidin-1-yl)-N-(pyridazin-4-yl)isonicotinamide

[0075] Step c. methyl 3-[3-[3-fluoro-5-(trifluoromethyl)phenoxy]azetidin-1-yl]pyridine-4-carboxylate (S6a):



[0076] A mixture of **S5a** (300 mg, 1.75 mmol, 1 eq), **S4a** (616 mg, 2.6 mmol, 1.5 eq), Cs₂CO₃ (1.42 g, 4.4 mmol, 2.5 eq) and RuPhos Pd G4 (149 mg, 175 μmol, 0.1 eq) in dioxane (10 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80 °C for 3 h under N₂ atmosphere. LC-MS showed **S5a** was consumed completely and desired mass was detected. The reaction mixture was filtered. The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 85/15). **S6a** (523 mg, 80.83% yield) was obtained as a yellow solid.

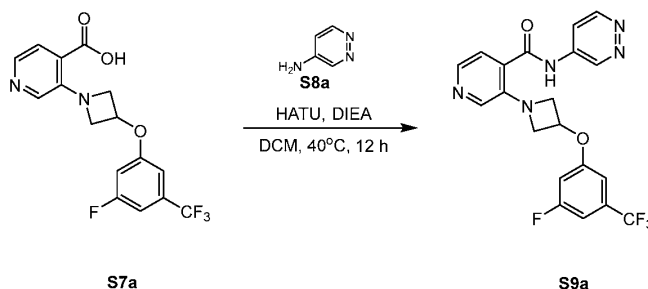
[0077] Step d. 3-[3-[3-fluoro-5-(trifluoromethyl)phenoxy]azetidin-1-yl]pyridine-4-carboxylic acid (S7a):



[0078] [To a solution of **S6a** (430 mg, 1.2 mmol, 1 eq) in THF (8 mL) was added TMSOK (372 mg, 2.9 mmol, 2.5 eq). The mixture was stirred at 60 °C for 1 h. LC-MS showed **S6a** was consumed completely and desired mass was detected. The reaction mixture was concentrated

under reduced pressure to give a residue. The crude product was used for next step directly without purification. **S7a** (546 mg, 99.09% yield, 75% purity) was obtained as a white solid.

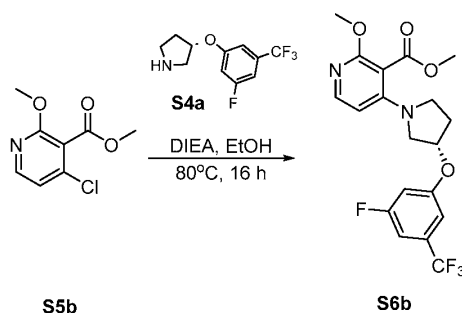
[0079] Step e. 3-[3-[3-fluoro-5-(trifluoromethyl)phenoxy]azetidin-1-yl]-N-pyridazin-4-yl-pyridine-4-carboxamide (**S9a**):



[0080] To a solution of **S7a** (200 mg, 561 μ mol, 1 eq) in DMF (5 mL) was added HATU (256 mg, 674 μ mol, 1.2 eq) and DIEA (181 mg, 1.40 mmol, 2.5 eq) was degassed and purged with N₂ for 3 times. The mixture was stirred at 25°C for 30 min. And then **S8a** (81 mg, 842 μ mol, 1.5 eq) was added the mixture. The mixture was stirred at 25°C for 1 h. LC-MS showed **S7a** was consumed completely and desired mass was detected. The reaction mixture was quenched by addition water 1 mL at 25 °C, and the reaction was concentrated under reduced pressure to remove DMF. The residue was diluted with ACN 5 mL. The mixture was filtered. The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Neutral condition; column: Waters Xbridge BEH C18 150×25mm×5 μ m; mobile phase: [water(NH₄HCO₃)-ACN]; gradient: 30%-60% B over 10 min). **S9a** (67 mg, 155 μ mol, 28% yield) was obtained as a yellow solid.

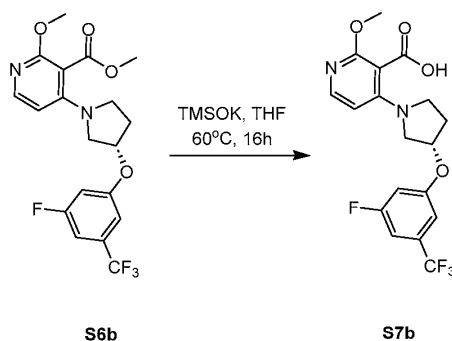
Example 2. Scheme 1. (S)-4-(3-(3-fluoro-5-(trifluoromethyl)phenoxy)pyrrolidin-1-yl)-2-methoxy-N-(pyridazin-4-yl)nicotinamide

[0081] Step c. methyl (S)-4-(3-(3-fluoro-5-(trifluoromethyl)phenoxy)pyrrolidin-1-yl)-2-methoxynicotinate (**S6b**):



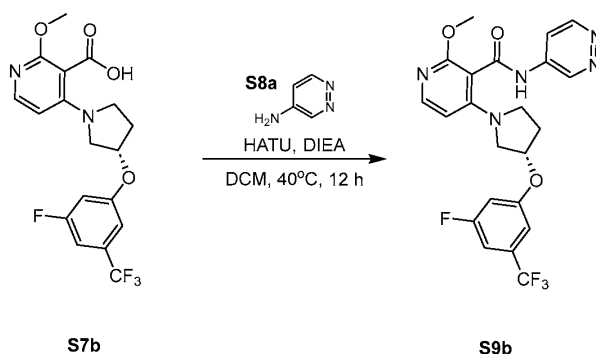
[0082] To a solution of **S5b** (1 g, 5.00 mmol, 1 eq) and **S4b** (1.75 g, 7.44 mmol, 1.5 eq) in EtOH (20 mL) was added DIEA (1.9 g, 14.9 mmol, 3 eq). The mixture was stirred at 80°C for 16 h. LCMS showed **S5b** was consumed completely and one main peak with desired m/z was detected. The reaction mixture was concentrated under reduced pressure to remove EtOH. The mixture was adjusted to pH = 7 with 1 M HCl and extracted with EtOAc 150 mL (50 mL × 3). The combined organic layers were washed with brine 60 mL (20 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/3 to 10/4). **S6b** (2 g, >99% yield) was obtained as a yellow solid.

[0083] Step d. (S)-4-(3-(3-fluoro-5-(trifluoromethyl)phenoxy)pyrrolidin-1-yl)-2-methoxynicotinic acid (**S7b**):



[0084] Compound **S7b** was synthesized following the procedure described in **Example 1 - Step d** and was obtained as a yellow solid (1.5 g, 3.9 mmol, 83% yield).

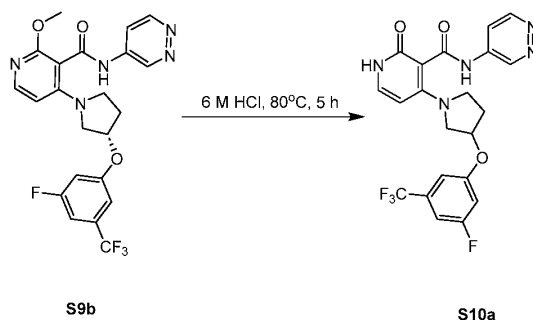
[0085] Step e. (S)-4-(3-(3-fluoro-5-(trifluoromethyl)phenoxy)pyrrolidin-1-yl)-2-methoxy-N-(pyridazin-4-yl)nicotinamide (**S9b**):



[0086] Compound **S9b** was synthesized following the procedure described in **Example 1 - Step d** and was obtained as a yellow solid (42.6 mg, 92 μ mol, 18% yield).

Example 3. Scheme 1. 4-(1-(3-fluoro-5-(trifluoromethyl)benzyl)azetidin-3-yl)-2-oxo-N-(pyridazin-4-yl)-1,2-dihydropyridine-3-carboxamide

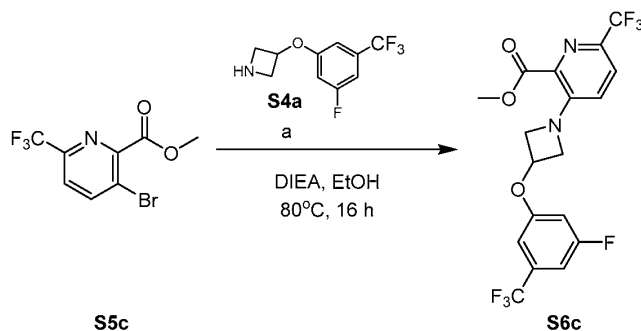
[0087] Step f. 4-(1-(3-fluoro-5-(trifluoromethyl)benzyl)azetidin-3-yl)-2-oxo-N-(pyridazin-4-yl)-1,2-dihydropyridine-3-carboxamide (**S10a**):



[0088] To a solution of **S9b** (300 mg, 1.13 mmol) was added HCl (6 M, 3.00 mL). The mixture was stirred at 80°C for 5 h. After the reaction completed (detected by LCMS) the reaction mixture was lyophilized to give directly to give pure **S10a** (32 mg, 69 μ mol, 22% yield) as a white solid.

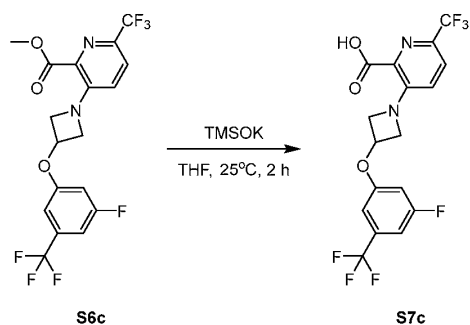
Example 4. Scheme 1. (S)-4-(3-(3-fluoro-5-(trifluoromethyl)phenoxy)pyrrolidin-1-yl)-2-methoxy-N-(pyridazin-4-yl)nicotinamide

[0089] Step c. methyl 3-(3-(3-fluoro-5-(trifluoromethyl)phenoxy)azetidin-1-yl)-6-(trifluoromethyl)picolinate (**S6c**):



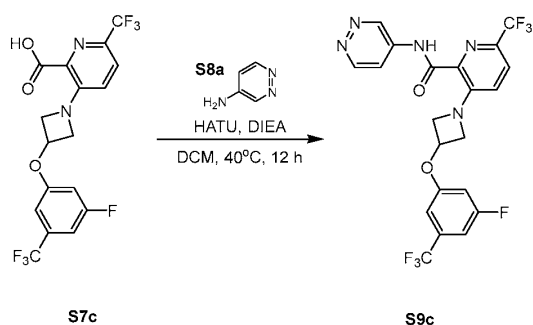
[0090] Compound **S6c** was synthesized following the procedure described in **Example 2 - Step c** and was obtained as a yellow solid (2 g, >99% yield).

[0091] Step d. 3-(3-(3-fluoro-5-(trifluoromethyl)phenoxy)azetidin-1-yl)-6-(trifluoromethyl)picolinic acid (**S7c**):



[0092] Compound **S7c** was synthesized following the procedure described in **Example 2 - Step d** and was obtained as a yellow solid (1.5 g, 83% yield).

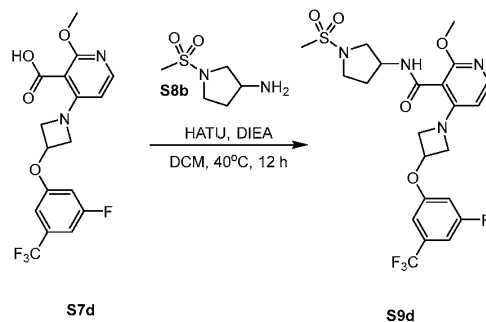
[0093] Step e. 3-(3-(3-fluoro-5-(trifluoromethyl)phenoxy)azetidin-1-yl)-N-(pyridazin-4-yl)-6-(trifluoromethyl)picolinamide (**S9c**):



[0094] Compound **S8c** was synthesized following the procedure described in **Example 2 - Step e** and was obtained as a yellow solid (43 mg, 18% yield).

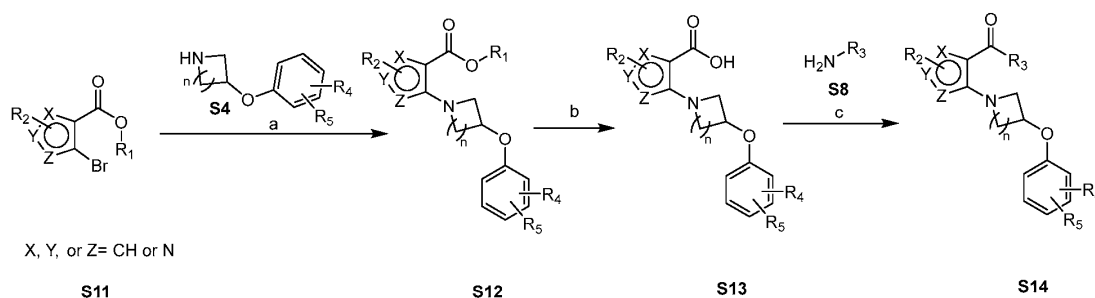
Example 5. Scheme 1. 4-(3-(3-fluoro-5-(trifluoromethyl)phenoxy)azetidin-1-yl)-2-methoxy-N-(1-(methylsulfonyl)pyrrolidin-3-yl)nicotinamide (S9d)

[0095] Step e. 4-(3-(3-fluoro-5-(trifluoromethyl)phenoxy)azetidin-1-yl)-2-methoxy-N-(1-(methylsulfonyl)pyrrolidin-3-yl)nicotinamide (S9c):



[0096] Compound S9d was synthesized following the procedure described in **Example 1 - Step e** and was obtained as a yellow solid (70 mg, 25% yield)

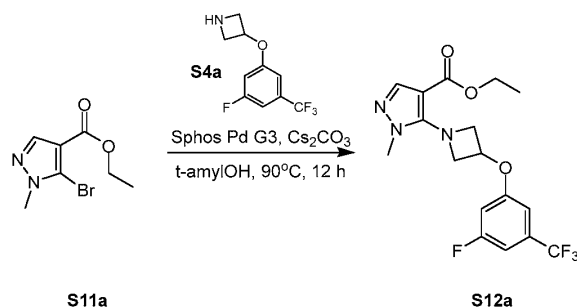
Scheme 2:



[0097] Reagents and conditions: (a) S4, Sphos Pd G3, Cs₂CO₃, t-amylOH, 90°C, 12 h (b) LiOH, THF/MeOH/water, 40°C, 2 h (c) i) NH₂R³, HATU, DIPEA, DMF, 25°C, 2 h ii) TFA/DCM, 25°C, 2 h

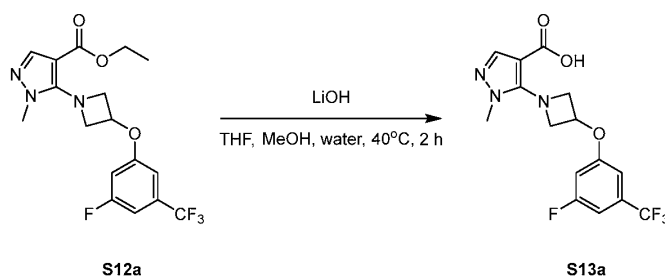
Example 6. Scheme 2. 5-(3-(3-fluoro-5-(trifluoromethyl)phenoxy)azetidin-1-yl)-1-methyl-N-(pyridazin-4-yl)-1H-pyrazole-4-carboxamide

[0098] Step a. Ethyl 5-(3-(3-fluoro-5-(trifluoromethyl)phenoxy)azetidin-1-yl)-1-methyl-1H-pyrazole-4-carboxylate (S9a):



[0099] A mixture of **S11a** (500 mg, 2.15 mmol), **S4a** (504 mg, 2.15 mmol), cesium carbonate (1.40 g, 4.29 mmol) and (2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl) [2-(2'-amino-1,1'-biphenyl)]palladium (II) methanesulfonate (272 mg, 321 μmol) in 2-methylbutan-2-ol (10 mL) was degassed and purged with N_2 for 3 times and then the mixture was stirred at 90°C for 12 h under N_2 atmosphere. LC-MS showed **S11a** was consumed completely and one main peak with desired m/z was detected. Then the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was diluted with water (5 mL) and extracted with ethyl acetate (3×3 mL). The combined organic layers were washed with brine (4 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by silica gel chromatography (petroleum ether: ethyl acetate = 10: 1 to 0:1) to give **S12a** (270 mg, 29% yield) as white solid.

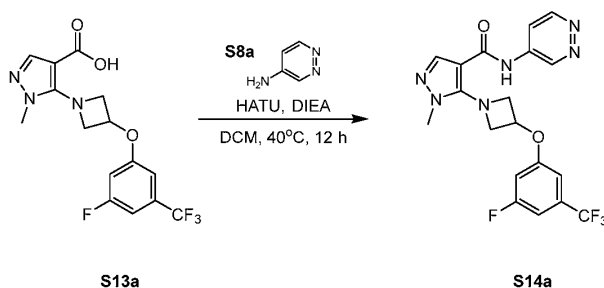
[0100] Step b. 5-(3-(3-fluoro-5-(trifluoromethyl)phenoxy)azetidin-1-yl)-1-methyl-1H-pyrazole-4-carboxylic acid (**S10a**):



[0101] A mixture of **S12a** (220 mg, 568 μmol) and lithium hydroxide monohydrate (143 mg, 3.41 mmol) in water (0.7 mL), methanol (0.7 mL) and tetrahydrofuran (0.7 mL) was degassed and purged with N_2 for 3 times, then the mixture was stirred at 40°C for 2 h under N_2 atmosphere. LC-MS showed **S12a** was consumed completely and one main peak with desired m/z was detected. Then the reaction mixture was combined with a 50 mg scale reaction for work-up. The resulting mixtures were diluted with water (5 mL) and acidified by a mixture solution (saturated aqueous

citric acid monohydrate solution: saturated aqueous ammonium chloride solution = 1: 1) to pH = 3. Then the reaction mixture was extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give **S13a** (140 mg, yield 53%) as a white solid which was used for next step without purification.

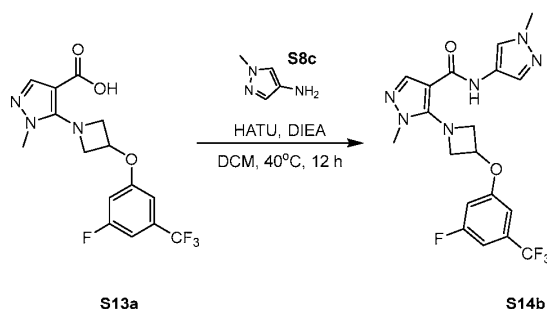
[0102] Step c. *5-(3-(3-fluoro-5-(trifluoromethyl)phenoxy)azetidin-1-yl)-1-methyl-N-(pyridazin-4-yl)-1H-pyrazole-4-carboxamide (S14a)*:



[0103] A mixture of **S13a** (70 mg, 195 μ mol), HATU (88.9 mg, 234 μ mol), DIEA (75.5 mg, 585 μ mol) and pyridazin-4-amine (92.7 mg, 974 μ mol) in dichloromethane (1.4 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 40°C for 12 h under N₂ atmosphere. LC-MS showed **S13a** was consumed completely and one main peak with desired m/z was detected. The resulting mixtures were diluted with water (5 mL) and extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with brine (4 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. Then the crude product was purified by pre-HPLC to give **S14a** (yield 42%) as a white solid.

Example 7. Scheme 2. 5-(3-(3-fluoro-5-(trifluoromethyl)phenoxy)azetidin-1-yl)-1-methyl-N-(pyridazin-4-yl)-1H-pyrazole-4-carboxamide (S14b)

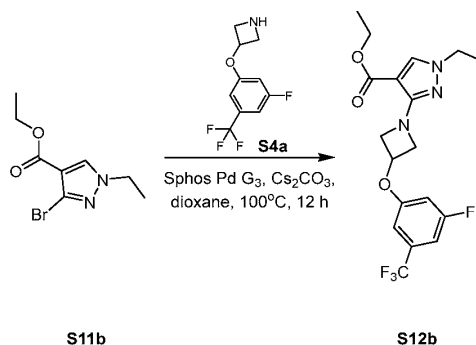
[0104] Step c. *5-(3-(3-fluoro-5-(trifluoromethyl)phenoxy)azetidin-1-yl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazole-4-carboxamide (S14b)*:



[0105] Compound **S14b** was synthesized following the procedure described in **Example 6**, **Scheme 2 – Step c** and was obtained as a white solid (45 mg, 37% yield).

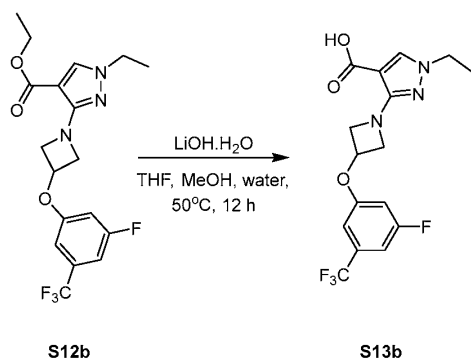
Example 8. Scheme 2. (S)-4-(3-(3-fluoro-5-(trifluoromethyl)phenoxy)pyrrolidin-1-yl)-2-methoxy-N-(pyridazin-4-yl)nicotinamide

[0106] Step a. ethyl 1-ethyl-3-(3-(3-fluoro-5-(trifluoromethyl)phenoxy)azetidin-1-yl)-1H-pyrazole-4-carboxylate (**14b**):



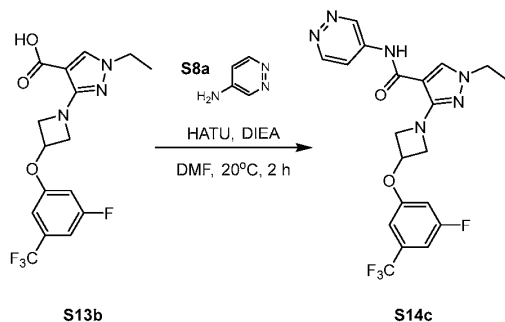
[0107] Compound **S12b** was synthesized following the procedure described in **Example 6**, **Scheme 2 - Step a** and was obtained as a yellow solid (2 g, >99% yield).

[0108] Step b. 1-ethyl-3-(3-(3-fluoro-5-(trifluoromethyl)phenoxy)azetidin-1-yl)-1H-pyrazole-4-carboxylic acid (**S13b**):



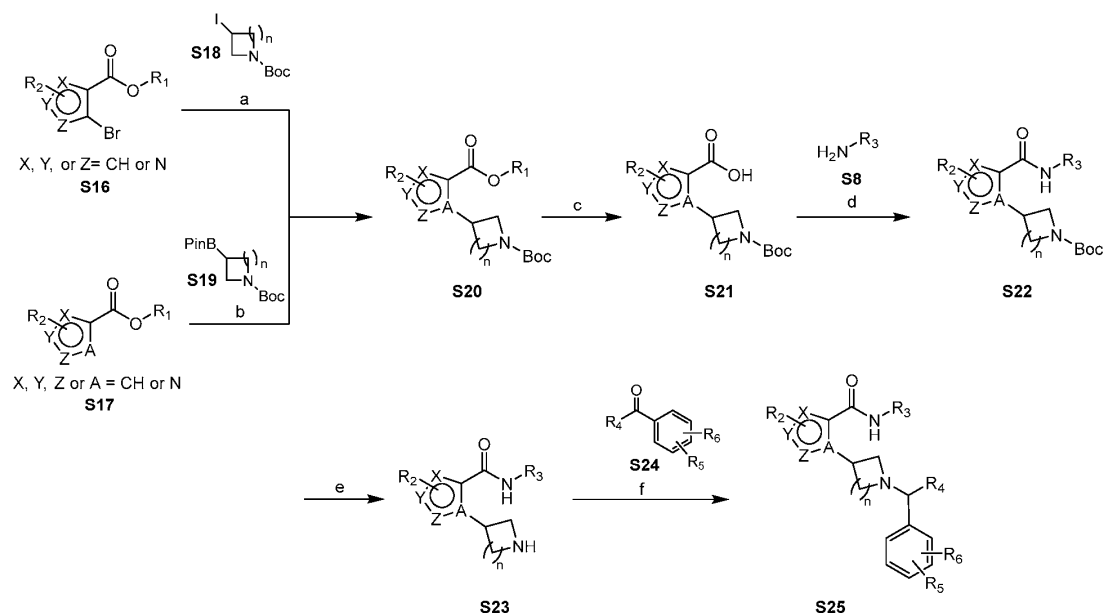
[0109] Compound **S13b** was synthesized following the procedure described in **Example 6**, **Scheme 2 - Step b** and was obtained as a yellow solid (1.5 g, 83% yield).

[0110] Step c. 3-(3-(3-fluoro-5-(trifluoromethyl)phenoxy)azetidin-1-yl)-N-(pyridazin-4-yl)-6-(trifluoromethyl)picolinamide (**S14c**):



[0111] Compound **S14c** was synthesized following the procedure described in **Example 6**, **Scheme 2 - Step c** and was obtained as a yellow solid (43 mg, 18% yield).

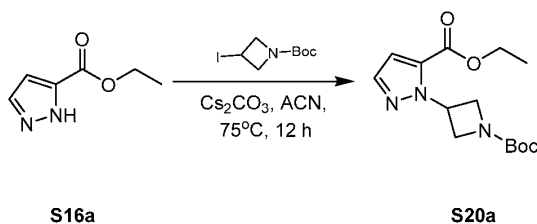
Scheme 3



[0112] Reagents and conditions: (a) halide **S18**, Cs_2CO_3 , ACN, 75°C , 12 h or (b) boronic acid or boronate ester **S19**, $\text{Pd}(\text{dppf})\text{Cl}_2$, K_3PO_4 , dioxane/ H_2O , 60°C , 2 h ii) Pd/C , H_2 , 25°C , 2 h (15 Psi) (c) LiOH , THF/ MeOH/water , 25°C , 5 h (d) **S8**, HATU, DIPEA, DMF, 25°C , 2 h (e) $\text{HCl}/1,4\text{-dioxane}$, 25°C , 2 h i) (f) **S24**, $\text{NaBH}(\text{OAc})_3$, TEA, DCE, 25°C , 12 h.

Example 9. Scheme 1. 1-(1-(3-fluoro-5-(trifluoromethyl)benzyl)azetidin-3-yl)-N-(pyridazin-4-yl)-1H-pyrazole-5-carboxamide

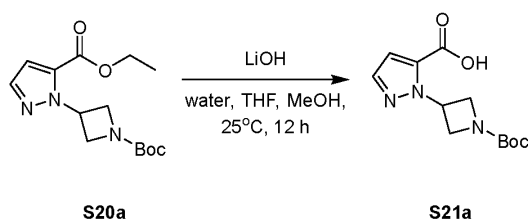
[0113] Step a. Ethyl 1-(1-(tert-butoxycarbonyl)azetidin-3-yl)-1H-pyrazole-5-carboxylate (S20a**):**



[0114] A mixture of **S16a** (2.0 g, 14.3 mmol) in acetonitrile (100 mL) was added **S18a** tert-butyl 3-iodoazetidine-1-carboxylate (4.0 g, 14.0 mmol) and cesium carbonate (9.3 g, 28.5 mmol). Then the mixture was degassed and purged with N_2 for 3 times, and then the stirred at 75°C for 12 h under N_2 atmosphere. LCMS showed **S16a** was consumed completely and one main peak with desired m/s. The reaction mixture was filtered and the filtrate was concentrated under reduced

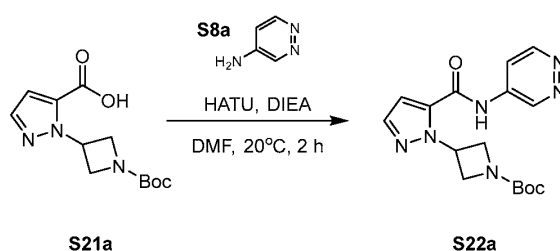
pressure to give a residue. The residue diluted with water (20 mL) and extracted with ethyl acetate 60 mL (20 mL $\times$ 3). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel chromatography (petroleum ether: ethyl acetate = 10: 1 to 0:1) to give **S20a** (1 g, yield 23%) as a yellow oil.

[0115] Step c. 1-(1-(tert-butoxycarbonyl)azetidin-3-yl)-1H-pyrazole-5-carboxylic acid (**S21a**):



[0116] A mixture of **S20a** (800 mg, 2.71 mmol) in tetrahydrofuran (4 mL), water (4 mL) and methanol (4 mL) was added lithium hydroxide hydrate (389 mg, 16.3 mmol). Then the mixture was stirred at 25°C for 12 h under N₂ atmosphere. LCMS showed **S20a** was consumed completely and one main peak with desired m/s. The reaction mixture was combined with a 200 mg scale reaction. The residue was diluted with water (5 mL) and was acidified by adding saturated aqueous citric acid solution to pH = 3. Then the reaction mixture was extracted with ethyl acetate 30 mL (10 mL $\times$ 3). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give **S21a** (720 mg, yield 76%) as a white solid. The crude product was used for next step directly without purification.

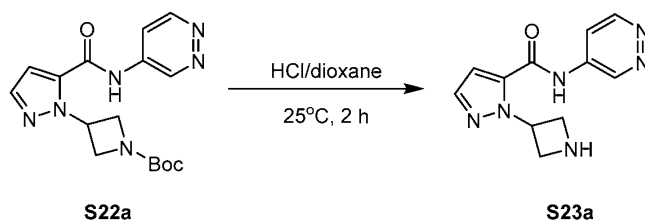
[0117] Step d. Tert-butyl 3-(5-(pyridazin-4-ylcarbamoyl)-1H-pyrazol-1-yl)azetidine-1-carboxylate (**S22a**):



[0118] To a solution of **S21a** (470 mg, 1.76 mmol) in dimethylformamide (4 mL) was added HATU (802 mg, 2.1 mmol), N-ethyl-N-isopropyl-propan-2-amine (682 mg, 5.30 mmol) and pyridazin-4-amine (251 mg, 2.64 mmol). The mixture was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 20°C for 2 h under N₂ atmosphere. LCMS showed **S21a**

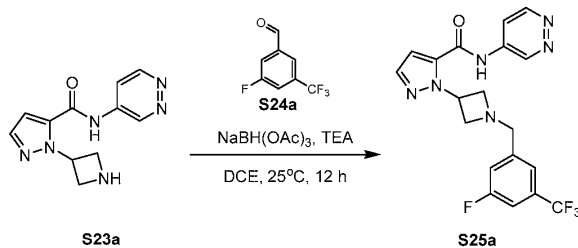
was consumed completely and one main peak with desired m/s was detected. The residue was diluted with water (20 mL) and extracted with ethyl acetate 9 mL (10 mL $\times$ 3). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (petroleum ether: ethyl acetate = 3:1 to 0:1) to give **S22a** (310 mg, yield 39%) as a yellow oil.

[0119] Step e. 1-(azetidin-3-yl)-N-(pyridazin-4-yl)-1H-pyrazole-5-carboxamide (**S23a**):



[0120] A solution of **S22a** (310 mg, 900 μ mol) in HCl/dioxane (3 mL, 4 M) was stirred at 25°C for 2 h. LCMS showed **S22a** was consumed completely and one main peak with desired m/s was detected. The reaction mixture was concentrated under reduced pressure to give **S23a** (220 mg, yield 85%) as a white solid. The crude product was used for next step directly without purification.

[0121] Step f. 1-(1-(3-fluoro-5-(trifluoromethyl)benzyl)azetidin-3-yl)-N-(pyridazin-4-yl)-1H-pyrazole-5-carboxamide (**S25a**):

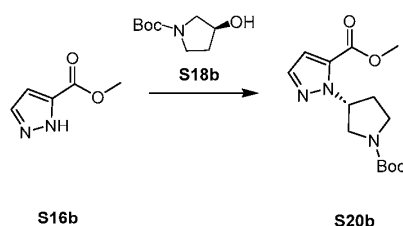


[0122] To a solution of **S23a** (220 mg, 900 μ mol) and **S24a** (207 mg, 1.08 mmol) in dichloroethane (2.2 mL) was added NaBH(OAc)₃ (286 mg, 1.35 mmol) and triethylamine (100 mg, 991 μ mol). The mixture was stirred at 25°C for 12 h. LCMS showed **S23a** was consumed completely and one main peak with desired m/s was detected. The reaction mixture was quenched by water (20 mL), extracted with dichloromethane 90 mL (30 mL $\times$ 3). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18

150*40mm*10um; mobile phase: [water(NH₄HCO₃)-ACN]; gradient: 30%-60% B over 8 min) to give **S25a** (110 mg, yield 20%) as a white solid.

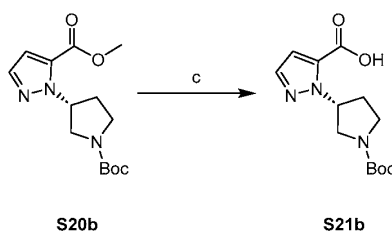
Example 10. Scheme 3. (R)-1-(1-(3-fluoro-5-(trifluoromethyl)benzyl)pyrrolidin-3-yl)-N-(pyridazin-4-yl)-1H-pyrazole-5-carboxamide

Step a. Methyl (R)-1-(1-(tert-butoxycarbonyl)pyrrolidin-3-yl)-1H-pyrazole-5-carboxylate (**S20b**).



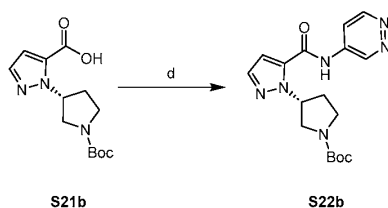
[0123] A mixture of **S16b** (1.00 g, 7.93 mmol, 1 eq), **S18b** tert-butyl (3S)-3-hydroxypyrrolidine-1-carboxylate (1.78 g, 9.52 mmol, 1.2 eq) and PPh₃ (3.12 g, 11.9 mmol, 1.5 eq) in toluene (20 mL) was degassed and purged with N₂ for 3 times, and then the mixture was added DIAD (2.41 g, 11.9 mmol, 2.31 mL, 1.5 eq) at 0°C for 3 h under N₂ atmosphere. LCMS showed Reactant 1 was consumed completely and desired mass was detected. The reaction mixture was diluted with water 120 mL and extracted with ethyl acetate 120 mL (40 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=3/1 to 1/1). **S20b** (2.50 g, crude) was obtained as a yellow oil.

[0124] Step c. (R)-1-(1-(tert-butoxycarbonyl)pyrrolidin-3-yl)-1H-pyrazole-5-carboxylic acid (**S21b**).



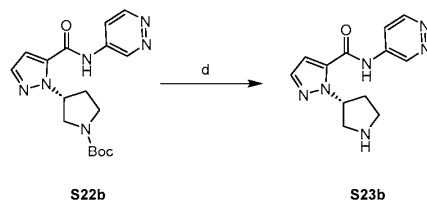
[0125] Compound **S21b** was synthesized following the procedure described in **Example 9 - Step c** and was obtained as a crude white solid without further purification.

[0126] Step d. tert-butyl (R)-3-(5-(pyridazin-4-ylcarbamoyl)-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate (**S22b**).



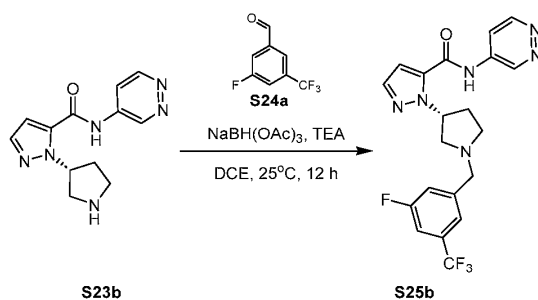
[0127] Compound **S22b** was synthesized following the procedure described in **Example 9 – Step d** and was obtained as a white solid (200 mg, 20% yield).

[0128] Step e. (R)-N-(pyridazin-4-yl)-1-(pyrrolidin-3-yl)-1H-pyrazole-5-carboxamide (S23b).



[0129] Compound **S23b** was synthesized following the procedure described in **Example 9 – Step e** and was obtained as a crude white solid without further purification.

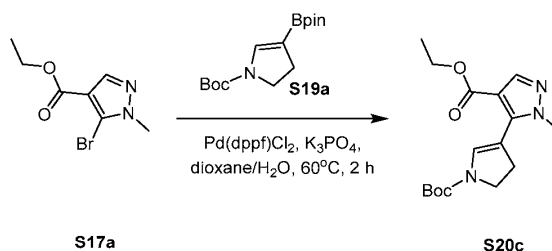
[0130] Step f. (R)-1-(1-(3-fluoro-5-(trifluoromethyl)benzyl)pyrrolidin-3-yl)-N-(pyridazin-4-yl)-1H-pyrazole-5-carboxamide (S25b).



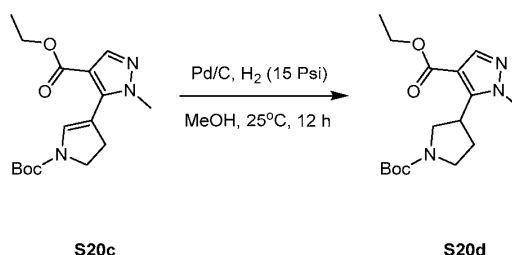
[0131] Compound **S25b** was synthesized following the procedure described in **Scheme 3 – Step 7** and (30 mg, 10% yield) was obtained as a yellow solid.

Example 11. Scheme 3. 5-[1-[[3-fluoro-5-(trifluoromethyl)phenyl]methyl]pyrrolidin-3-yl]-1-methyl-N-pyridazin-4-yl-pyrazole-4-carboxamide

[0132] Step b. Ethyl 5-(1-tert-butoxycarbonylpyrrolidin-3-yl)-1-methyl-pyrazole-4-carboxylate (S20d):

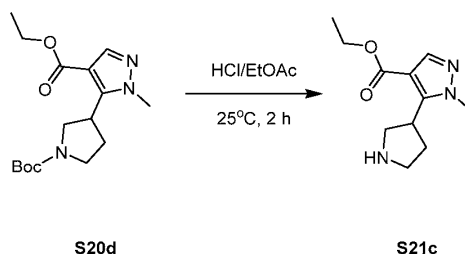


[0133] i) To a solution of **S17a** (2.53 g, 8.58 mmol, 2 *eq*) and **S19a** (1 g, 4.29 mmol, 1 *eq*) in dioxane (12 mL) and H₂O (3 mL) was added Pd(dppf)Cl₂ (313.95 mg, 429 μmol, 0.1 *eq*) and K₃PO₄ (2.73 g, 12.9 mmol, 3 *eq*). The mixture was stirred at 60°C for 2 h under N₂ atmosphere. LCMS showed the reaction was completed, and ~52% of desired compound was detected. The reaction was cooled to room temperature and poured in water (20 mL), and then extracted with EtOAc (20 mL × 3). The organic phase was washed with brine (20 mL × 1), dried over Na₂SO₄, and then concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=20/1 to 3/1) to give **S20c** (1.3 g, 94% yield) as a brown solid.



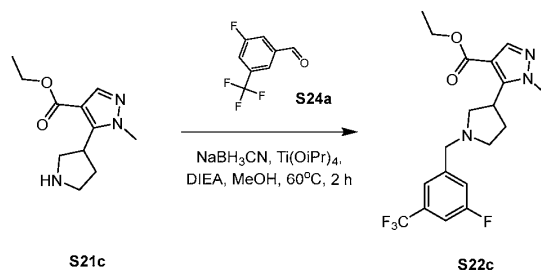
[0134] ii) To a solution of **S20c** (400 mg, 1.24 mmol, 1 *eq*) in MeOH (10 mL) was added Pd/C (265 mg, 249 μmol, 10% purity, 0.2 *eq*) and H₂ (125.71 mg, 62.23 mmol, 50 *eq*). The mixture was stirred at 25°C for 12 h under H₂ (15 *Psi*) atmosphere. LCMS showed the reaction was completed, and ~97% of desired compound was detected. The reaction was filtered and concentrated in vacuum to give **S20d** (310 mg, crude) as light yellow oil.

[0135] Step e. Ethyl 1-methyl-5-pyrrolidin-3-yl-pyrazole-4-carboxylate (S21c**):**



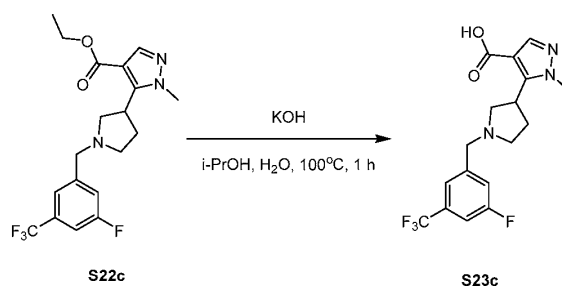
[0136] Compound **S21c** was synthesized following the procedure described in **Example 9 - Step e** and was obtained as a crude yellow solid without further purification.

[0137] Step f. 5-[1-[[3-fluoro-5-(trifluoromethyl)phenyl]methyl]pyrrolidin-3-yl]-1-methyl-pyrazole-4-carboxylate (**S22c**):



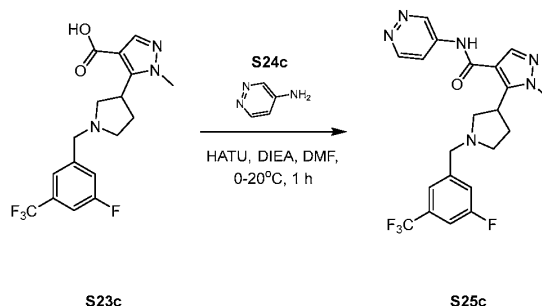
[0138] Compound **S22c** was synthesized following the procedure described in **Scheme 3- Step 7** and (160 mg, 36% yield) was obtained as a yellow oil.

[0139] Step c. 5-[1-[[3-fluoro-5-(trifluoromethyl)phenyl]methyl]pyrrolidin-3-yl]-1-methyl-pyrazole-4-carboxylate (**S23c**):



[0140] To a solution of **S22c** (100 mg, 250 μmol , 1 *eq*) in propan-2-ol (1 mL) and H_2O (0.2 mL) was added KOH (70.2 mg, 1.25 mmol, 5.0 *eq*). The mixture was stirred at 100°C for 1 h. LCMS showed the reaction was completed, and ~88% of desired compound was detected. The residue was adjusted to pH=6 with 1M HCl. The aqueous phase was extracted with ethyl acetate (2 mL $\times$ 3). The combined organic phase was washed with brine (2 mL $\times$ 1), dried with anhydrous Na_2SO_4 , filtered and concentrated in vacuum to give **S23c** (90 mg, crude) as yellow oil. This residue was without further purification and used to the next step directly.

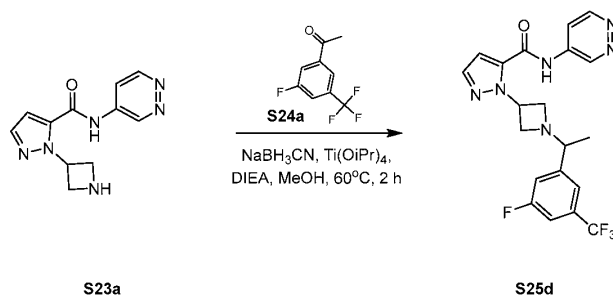
[0141] Step d. 5-[1-[[3-fluoro-5-(trifluoromethyl)phenyl]methyl]pyrrolidin-3-yl]-1-methyl-N-pyridazin-4-yl-pyrazole-4-carboxamide (**24c**):



[0142] Compound **S25c** was synthesized following the procedure described in **Example 9 – Step d** and was obtained as a white solid (25.1 mg, 53.51 μ mol, 25% yield, 96% purity).

Example 12. Scheme 3. 5-[1-[[3-fluoro-5-(trifluoromethyl)phenyl]methyl]pyrrolidin-3-yl]-1-methyl-N-pyridazin-4-yl-pyrazole-4-carboxamide

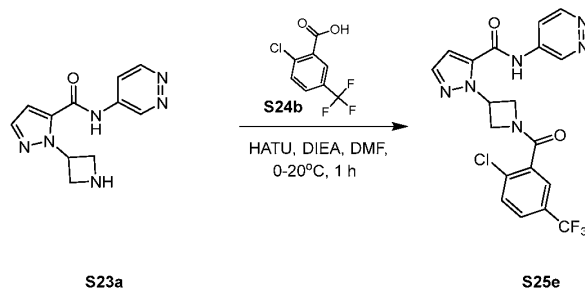
[0143] Step d. 5-[1-[[3-fluoro-5-(trifluoromethyl)phenyl]methyl]pyrrolidin-3-yl]-1-methyl-N-pyridazin-4-yl-pyrazole-4-carboxamide (S25d):



[0144] Compound **S22c** was synthesized following the procedure described in **Example 9 - Step 7** and was obtained as a white solid (34 mg, 9.5% yield).

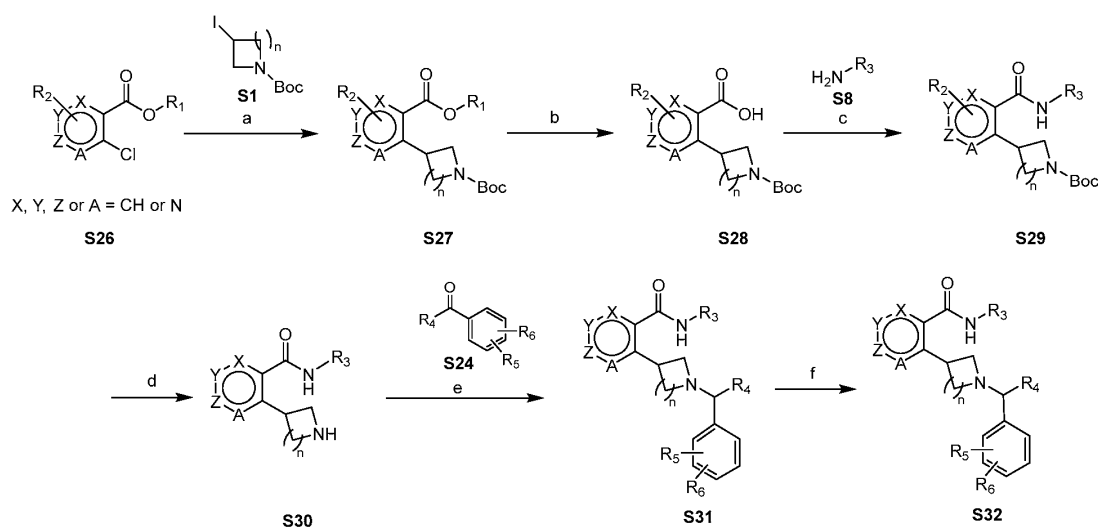
Example 13. Scheme 3. 1-(1-(2-chloro-5-(trifluoromethyl)benzoyl)azetidin-3-yl)-N-(pyridazin-4-yl)-1H-pyrazole-5-carboxamide

[0145] Step f. 1-(1-(2-chloro-5-(trifluoromethyl)benzoyl)azetidin-3-yl)-N-(pyridazin-4-yl)-1H-pyrazole-5-carboxamide (S23e):



[0146] To a solution of **S23a** (0.2 g, 819 μ mol, 1 eq) and **S24b** (169 mg, 819 μ mol, 1 eq) in DMF (2 mL) was added $\text{NaBH}(\text{OAc})_3$ (521 mg, 2.46 mmol, 3 eq). The mixture was stirred at 20 °C for 2 hr. LC-MS showed 13% of Reactant 1 remained. The mixture was diluted with water 6 mL and extracted with EtOAc 6 mL (2 mL $\times$ 3). The combined organic layers were washed with brine 6 mL (2 mL $\times$ 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition: column: Waters xbridge 150*25mm 10um; mobile phase: [water (NH_4HCO_3)-ACN]; gradient: 35%-65% B over 10 min) to give **S25e** (34 mg, 9.4% yield) obtained as white solid.

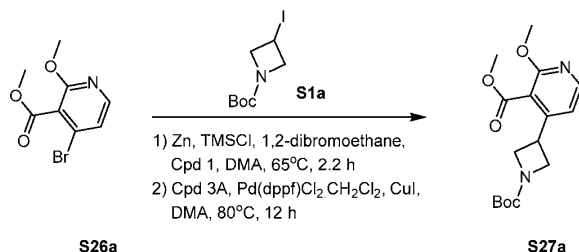
Scheme 4:



Reagents and conditions: (a) (b) LiOH , THF/MeOH/water, 25°C, 5 h (c) NH_2R^2 , HATU, DIPEA, DMF, 25°C, 2 h (d) $\text{HCl}/1,4\text{-dioxane}$, 25°C, 2 h (e) benzaldehyde, $\text{NaBH}(\text{OAc})_3$, TEA, DCE, 25 °C, 12 h (f) additional modifications (not in all cases)

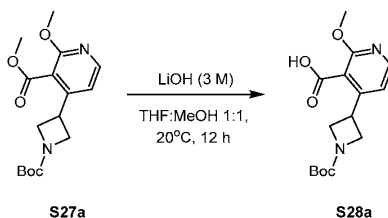
Example 15. Scheme 4. 4-(1-(3-fluoro-5-(trifluoromethyl)benzyl)azetidin-3-yl)-2-methoxy-N-(pyridazin-4-yl)nicotinamide

[0147] Step a. methyl 4-(1-(tert-butoxycarbonyl)azetidin-3-yl)-2-methoxynicotinate (S27a):



[0148] N₂ atmosphere, to a suspension of Zn (2.4 g, 37 mmol) in DMA (16 mL) and the resulting suspension was heated to 65°C. Then it was added TMSCl (0.56 mL, 4.6 mmol) and 1,2-dibromoethane (0.4 mL, 4.5 mmol). The mixture was stirred at 65°C for 40 min. A solution of S26a (12 g, 28 mmol) in DMA (16 mL) was then added dropwise to the reaction mixture over 0.5 h. The resultant suspension was stirred at 65°C for 1 h and allowed to cool to room temperature. After decantation, the supernatant was collected by syringe and added to a mixture of S1a (2 g, 7 mmol) Pd(dppf)Cl₂·CH₂Cl₂ (278 mg, 341 μmol, CuI (130 mg, 682 μmol) in DMA (20 mL) under N₂ atmosphere. The reaction mixture was sealed under N₂ atmosphere and heated at 80°C for 12 h. LCMS showed the reaction was completed, and 32% of desired compound was detected. The mixture was cooled to 0°C and slowly dropwise saturated ammonium chloride (100 mL), the mixture was stirred at 0°C for 30 min. The residue was diluted with water (100 mL) and extracted with acetate ethyl 300 mL (100 mL × 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether: Ethyl acetate = 20 : 1 to 3 : 1) to give S27a (1.5 g, 63% yield) as yellow oil.

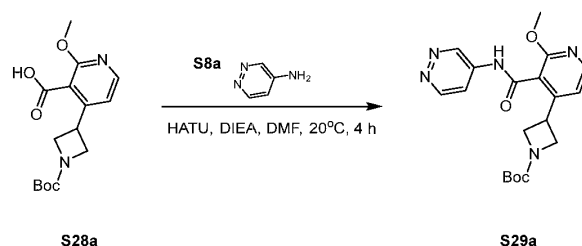
[0149] Step b. 4-(1-(tert-butoxycarbonyl)azetidin-3-yl)-2-methoxynicotinic acid (S28a):



[0150] To a solution of S27a (1.4 g, 4.3 mmol) in tetrahydrofuran (14 mL) and methanol (14 mL) was added LiOH (3 M, 14 mL). The mixture was stirred at 20°C for 12 h. LCMS showed

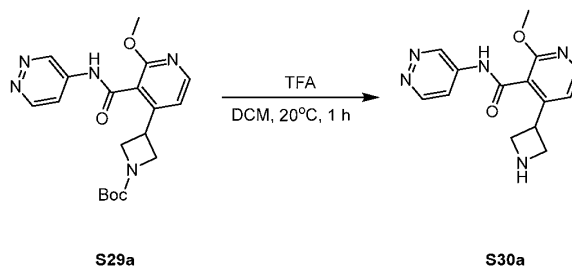
the reaction was completed, and 90% of desired compound was detected. The mixture acidified by adding 1 M HCl dropwise at 0°C to pH = 6 and was bubbled with N₂ flow to remove tetrahydrofuran. The mixture was lyophilized to give **S28a** (0.8 g, 55% yield) as a white solid. The crude product was used into the next step without further purification.

[0151] Step c. 5-[1-[[3-fluoro-5-(trifluoromethyl)phenyl]methyl]pyrrolidin-3-yl]-1-methyl-pyrazole-4-carboxylate (**S29a**):



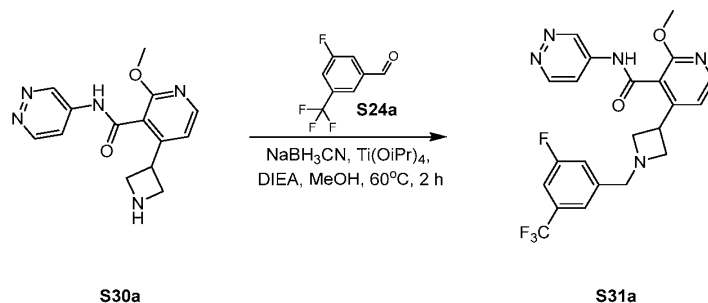
[0152] To a solution of **S28a** (0.8 g, 2.59 mmol) in DMF (10 mL) was added DIEA (1.01 g, 7.78 mmol) HATU (1.18 g, 3.11 mmol) and pyridazin-4-amine (370.13 mg, 3.89 mmol). The mixture was stirred at 20°C for 4 h. LCMS showed the reaction was completed, and 21% of desired compound was detected. The reaction mixture was partitioned between water (50 mL) and ethyl acetate (50 mL). The organic phase was separated, washed with brine 100 mL (50 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether: Ethyl acetate = 10:1 to 0:1) to give **S29a** (0.8 g, 72.00% yield) as an orange solid.

[0153] Step d. 4-(azetidin-3-yl)-2-methoxy-N-(pyridazin-4-yl)nicotinamide (**S30a**):



[0154] To a solution of **S29a** (600 mg, 1.56 mmol) in dichloromethane (6 mL) was added trifluoroacetic acid (1.20 mL). The mixture was stirred at 20°C for 1 h. LCMS showed the reaction was completed, and 86% of desired compound was detected. The mixture was concentrated under reduced pressure to give **S30a** (350 mg, 71% yield). The crude product was used into the next step without further purification.

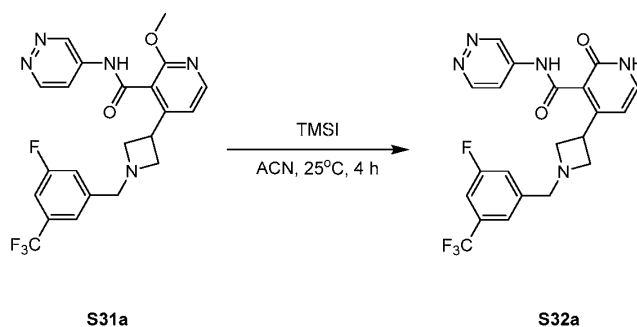
[0155] Step e. *4-(1-(3-fluoro-5-(trifluoromethyl)benzyl)azetidin-3-yl)-2-methoxy-N-(pyridazin-4-yl)nicotinamide (S31a)*:



[0156] To a solution of **S30a** (350 mg, 1.23 mmol) and 3-fluoro-5-(trifluoromethyl)benzaldehyde (236 mg, 1.23 mmol) in methanol (3 mL) was added DIEA (666 mg, 5.15 mmol), tetrakisopropoxytitanium (1.1 g, 3.7 mmol) and NaBH_3CN (231.28 mg, 3.68 mmol). The mixture was stirred at 60°C for 2 h. LCMS showed the reaction was completed, and 43% of desired compound was detected. The mixture was added water (5 mL) and filtered by celite, the filter cake was rinsed by ethyl acetate (10 mL) and the filtrate was concentrated under high vacuum to give crude product. The residue was purified by prep-HPLC (FA condition, column: Phenomenex luna C^{18} $100 \times 40 \text{ mm} \times 5 \mu\text{m}$; mobile phase: $[\text{H}_2\text{O} (0.2\% \text{FA}) - \text{ACN}]$; gradient: 1% - 40% B over 8.0 min) to give **S31a** (200 mg, 33% yield) as a yellow solid.

Example 16. Scheme 4. (S32a)

[0157] Step f. *4-(1-(3-fluoro-5-(trifluoromethyl)benzyl)azetidin-3-yl)-2-oxo-N-(pyridazin-4-yl)-1,2-dihydropyridine-3-carboxamide (S32a)*:

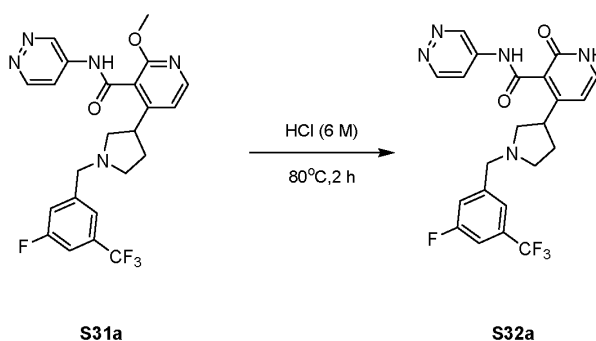


[0158] To a solution of **S31a** (180 mg, 390 μmol) in acetonitrile (2 mL) was added TMSI (156 mg, 780 μmol). The mixture was stirred at 25°C for 4 h. LCMS showed the reaction was completed, and 72% of desired compound was detected. The mixture was added water (0.5 mL)

and the residue was purified by prep-HPLC (NH₄HCO₃ condition, column: Waters Xbridge Prep OBD C¹⁸ 150 × 40 mm × 10 μm; mobile phase: [H₂O (0.05% NH₃H₂O+10 mM NH₄HCO₃) - ACN]; gradient: 20% - 55% B over 8.0 min) to give **S32a** as a white solid (200 mg, 33% yield).

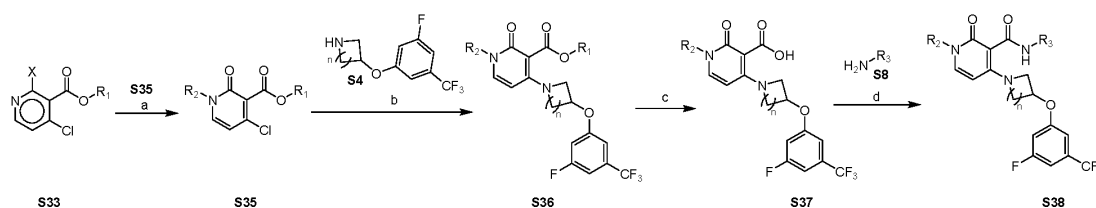
Example 17. Scheme 4. (**S33a**)

[0159] Step f. *4-(1-(3-fluoro-5-(trifluoromethyl)benzyl)azetidin-3-yl)-2-oxo-N-(pyridazin-4-yl)-1,2-dihydropyridine-3-carboxamide (**S33a**)*:



[0160] To a solution of **S32a** (36 mg, 76 μmol, 1 eq) in HCl (6 M, 1 mL, 79 eq). The mixture was stirred at 80°C for 2 h. LC-MS showed **S32a** was consumed completely and 86% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C¹⁸ 75 × 30 mm × 3 μm; mobile phase: [H₂O (0.2% FA)-ACN]; gradient: 1%-40% B over 8.0 min) to give **S33a** (7.4 mg, 21% yield) as a white solid.

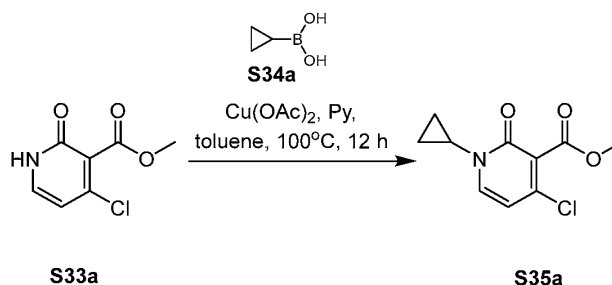
Scheme 5:



[0161] Reagents and conditions: (a) Cu(OAc)₂, Py, toluene, 100°C, 12 h; (b) K₂CO₃, NMP, 80°C, 12 h; (c) KOH, IPA, 60°C, 12 h; (d) HATU, DIEA, DMF, 20°C, 2 h.

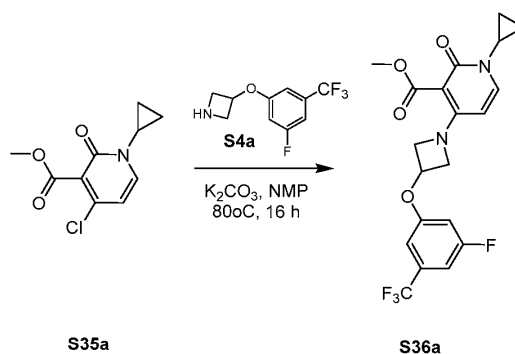
Example 18. Scheme 5. 1-cyclopropyl-4-[3-[3-fluoro-5-(trifluoromethyl)phenoxy]azetidin-1-yl]-N-(1-methylpyrazol-4-yl)-2-oxo-pyridine-3-carboxamide (S38a)

[0162] Step a. *Methyl 4-chloro-1-cyclopropyl-2-oxo-1,2-dihydropyridine-3-carboxylate (S35a)*



[0163] To a solution of **S33a** (1.00 g, 5.33 mmol, 1 eq) in toluene (30 mL) was added **S34a** (916 mg, 10.6 mmol, 2 eq), $\text{Cu}(\text{OAc})_2$ (968 mg, 5.33 mmol, 1 eq) and Py (2.11 g, 26.7 mmol, 5 eq) under O_2 . The mixture was stirred at 100°C for 12 h under O_2 atmosphere. LC-MS showed **S33a** was consumed completely and new peaks were shown on LC-MS and ~80% of desired compound was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate = 0/1 to 1/0) to give **S33a** (0.60 g, 49% yield) as a yellow solid.

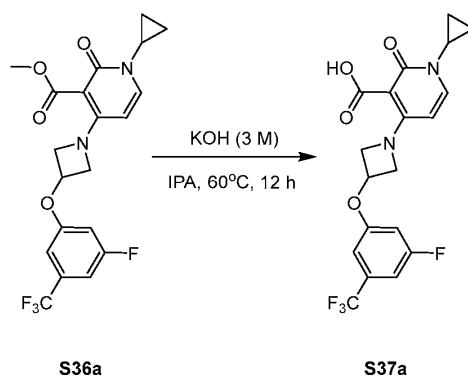
[0164] Step b. *Methyl 1-cyclopropyl-4-[3-[3-fluoro-5-(trifluoromethyl)phenoxy]azetidin-1-yl]-2-oxo-pyridine-3-carboxylate (S36a)*



[0165] To a solution of **S35a** (0.60 g, 2.6 mmol, 1 eq) and **S4a** (1.24 g, 5.27 mmol, 2 eq) in 1-methylpyrrolidin-2-one (6 mL) was added K_2CO_3 (1.09 g, 7.91 mmol, 3 eq). The mixture was stirred at 80°C for 12 h. LC-MS showed **S35a** was consumed completely and new peaks were shown on LC-MS and ~62% of desired compound was detected. The reaction mixture was partitioned between water 30 mL and Ethyl acetate (EtOAc) 50 mL. The organic phase was

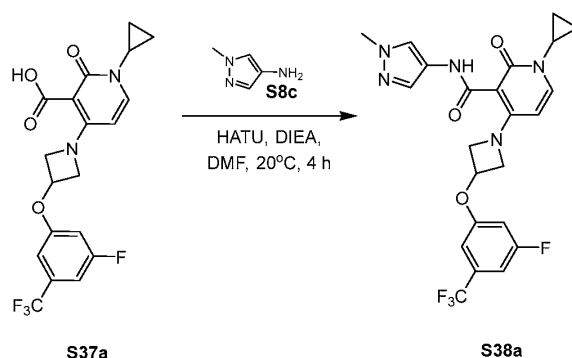
separated, washed with brine 30 mL (10 mL $\times$ 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 1/0 to 0/1) to give **S36a** (0.40 g, 36% yield) as a yellow solid

[0166] Step c. *1-cyclopropyl-4-[3-[3-fluoro-5-(trifluoromethyl)phenoxy]azetidin-1-yl]-2-oxo-pyridine-3-carboxylic acid (S37a)*



[0167] To a solution of **S36a** (3.00 g, 14.88 mmol, 1 eq) in THF (120 mL) was added TMSOK (5.73 g, 44.6 mmol, 3 eq). The mixture was stirred at 25°C for 1 h. LC-MS showed the reaction was completed. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was triturated with EtOH at 25°C for 30 min. **S37a** (3.00 g, 74% yield) was obtained as a yellow solid.

[0168] Step d. *1-cyclopropyl-4-[3-[3-fluoro-5-(trifluoromethyl)phenoxy]azetidin-1-yl]-N-(1-methylpyrazol-4-yl)-2-oxo-pyridine-3-carboxamide (S38a)*

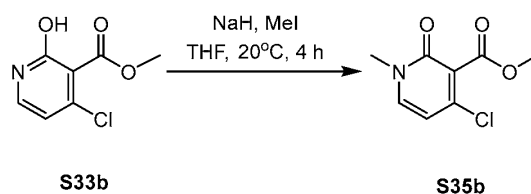


[0169] To a solution of **S37a** (300 mg, 728 μ mol, 1 eq) in DMF (3 mL) was added HATU (415 mg, 1.09 mmol, 1.5 eq) and DIEA (282 mg, 2.18 mmol, 3 eq). The mixture was stirred at 20°C

for 5 min. Then 1-methylpyrazol-4-amine (141 mg, 1.46 mmol, 2 eq) was added to the mixture. The mixture was stirred at 20°C for 2 h. LC-MS showed **S37a** was consumed completely and new peaks were shown on LC-MS and ~54% of desired compound was detected. The reaction mixture was partitioned between water 20 mL and EtOAc 60 mL. The organic phase was separated, washed with brine 30 mL (10 mL × 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition: column: Waters xbridge 150 * 25 mm 10 um; mobile phase: [water (NH₄HCO₃) - ACN]; gradient: 30% - 60% B over 10 min) to give **S38a** (161 mg, 45% yield) as a white solid.

Example 19. Scheme 5. Methyl 4-chloro-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (S35b)

[0170] Step a. Methyl 4-chloro-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (S35b)

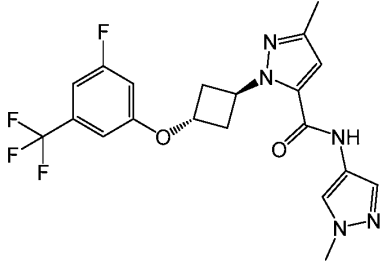
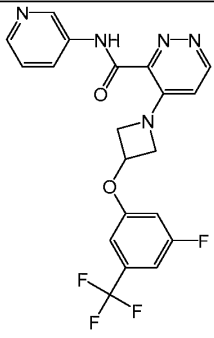
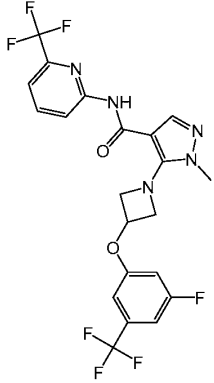


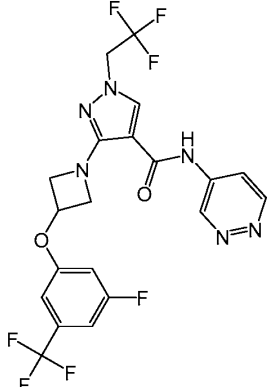
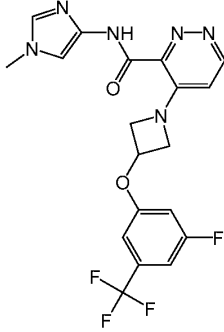
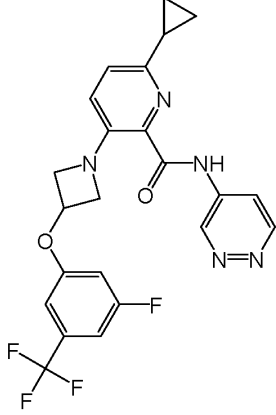
[0171] To a solution of **S33a** (13.0 g, 69.0 mmol, 1 eq) in THF (260 mL) was added NaH (4.16 g, 104 mmol, 60% purity, 1.5 eq) in portions and the reaction mixture was stirred at 0°C for 1 h. And then MeI (**S34a**, 29.5 g, 208 mmol, 3 eq) was added to the mixture. The mixture was stirred at 20°C for 3 h. LC-MS showed the reaction was completed and desired mass was detected. The reaction mixture was quenched by addition NH₄Cl 100 mL under N₂. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Basic condition: column: Daisogel C18 250×70mm×10um; mobile phase: [water (ammonia hydroxide v/v)-ACN]; gradient: 5%-35% B over 23 min). **S35a** (7.0 g, 50% yield) was obtained as a white solid.

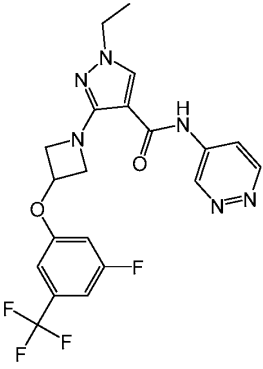
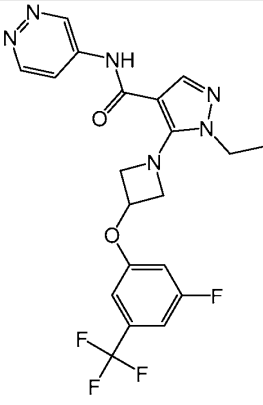
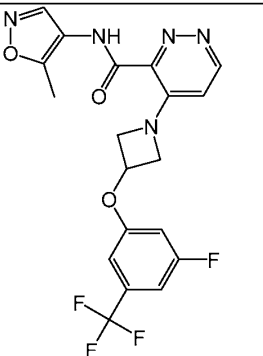
Example 20. Characterization of the compounds

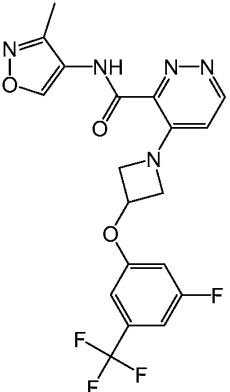
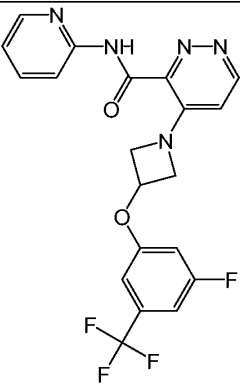
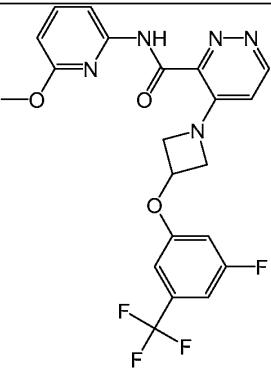
[0172] The characterization of the compounds of the present disclosure is summarized in **Table 1**. The GPR52 EC₅₀ data was obtained using the protocol as described in **Example 21**.

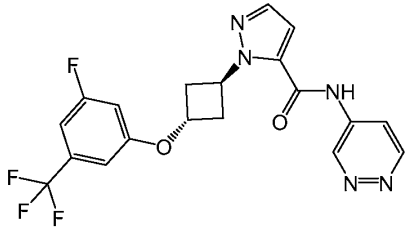
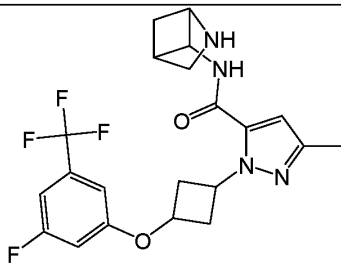
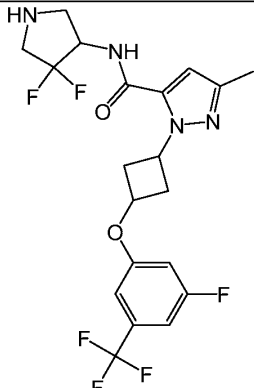
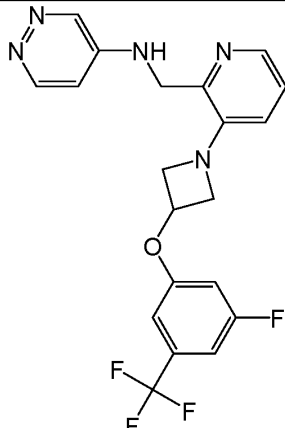
Table 1. Characterization for compounds of the present disclosure

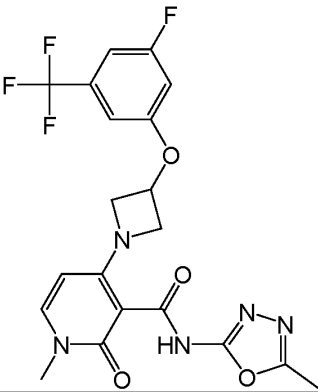
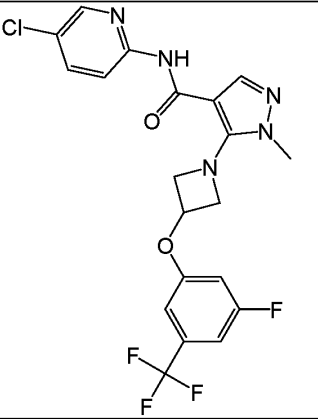
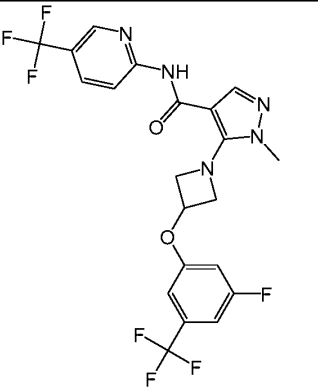
Compound	GPR52 EC50	¹ H NMR	MS [M+1]
 or a diastereomer	****	¹ H NMR (METHANOL-d ₄ , 400 MHz) δ 7.97 (s, 1H), 7.58 (s, 1H), 7.0-7.0 (m, 2H), 6.91 (br d, 1H, J=10.5 Hz), 6.64 (s, 1H), 5.8-6.0 (m, 1H), 5.09 (tt, 1H, J=3.4, 6.8 Hz), 3.86 (s, 3H), 3.0-3.1 (m, 2H), 2.6-2.8 (m, 2H), 2.32 (s, 3H)	438.150
	****	¹ H NMR (CHLOROFORM-d, 400 MHz) δ 10.10 (br s, 1H), 8.91 (br s, 1H), 8.7-8.8 (m, 1H), 8.42 (br s, 1H), 8.26 (br d, 1H, J=8.3 Hz), 7.37 (br d, 1H, J=2.8 Hz), 7.02 (br d, 1H, J=8.9 Hz), 6.84 (s, 1H), 6.68 (br d, 1H, J=9.8 Hz), 6.5-6.6 (m, 1H), 5.0-5.2 (m, 1H), 4.6-4.9 (m, 2H), 4.2-4.5 (m, 2H)	434.120
	**	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 10.69 (s, 1H), 8.31 (d, 1H, J=8.5 Hz), 8.00 (t, 1H, J=8.0 Hz), 7.84 (s, 1H), 7.53 (d, 1H, J=7.4 Hz), 7.27 (br d, 1H, J=8.6 Hz), 7.1-7.2 (m, 1H), 7.09 (s, 1H), 5.1-5.2 (m, 1H), 4.64 (dd, 2H, J=6.1, 9.4 Hz), 4.19 (dd, 2H, J=3.6, 9.6 Hz), 3.67 (s, 3H)	504.120

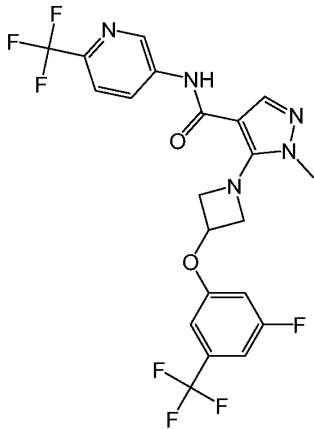
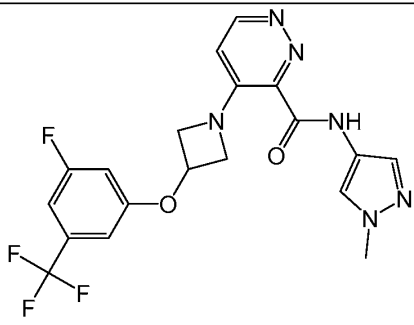
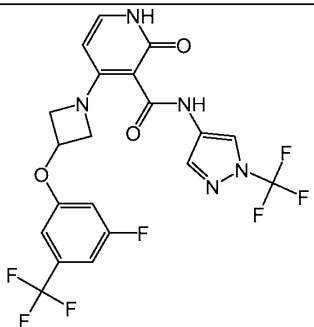
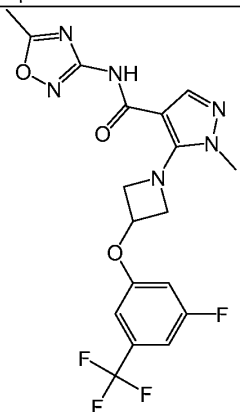
	****	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 10.1-10.6 (m, 1H), 9.36 (d, 1H, J=1.9 Hz), 8.9-9.0 (m, 1H), 8.40 (s, 1H), 7.97 (dd, 1H, J=2.7, 5.9 Hz), 7.26 (br d, 1H, J=8.4 Hz), 7.0-7.2 (m, 2H), 5.2-5.3 (m, 1H), 5.0-5.2 (m, 2H), 4.42 (dd, 2H, J=6.2, 9.6 Hz), 3.90 (dd, 2H, J=3.7, 9.7 Hz)	505.110
	****	¹ H NMR (CHLOROFORM-d, 400 MHz) δ 8.74 (d, 1H, J=6.4 Hz), 7.41 (s, 1H), 7.33 (s, 1H), 7.01 (br d, 1H, J=8.4 Hz), 6.83 (s, 1H), 6.6-6.7 (m, 1H), 6.54 (d, 1H, J=6.4 Hz), 5.09 (br t, 1H, J=3.7 Hz), 4.7-4.8 (m, 2H), 4.2-4.3 (m, 2H), 3.71 (s, 3H)	437.130
	****	¹ H NMR (CHLOROFORM-d, 400 MHz) δ 10.29 (s, 1H), 9.23 (d, 1H, J=2.4 Hz), 9.07 (d, 1H, J=5.9 Hz), 8.22 (dd, 1H, J=2.6, 5.9 Hz), 7.24 (d, 1H, J=8.6 Hz), 7.0-7.0 (m, 2H), 6.84 (s, 1H), 6.68 (td, 1H, J=2.1, 9.9 Hz), 5.0-5.1 (m, 1H), 4.61 (dd, 2H, J=6.3, 9.8 Hz), 4.04 (dd, 2H, J=4.0, 9.9 Hz), 2.0-2.2 (m, 1H), 1.0-1.1 (m, 2H), 0.9-1.0 (m, 2H)	474.150

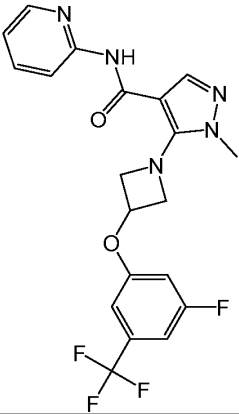
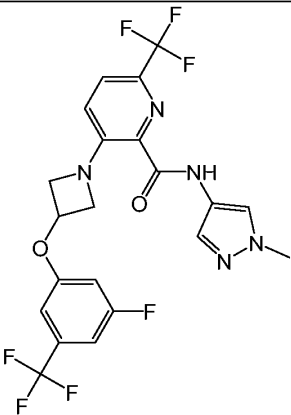
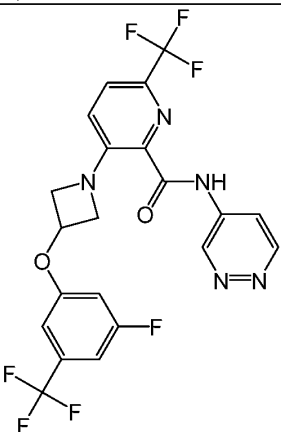
	****	¹ H NMR (CHLOROFORM-d, 400 MHz) δ 9.99 (br s, 1H), 9.34 (br s, 1H), 9.03 (d, 1H, J=6.0 Hz), 8.28 (dd, 1H, J=1.9, 5.9 Hz), 8.10 (s, 1H), 7.0-7.0 (m, 1H), 6.87 (s, 1H), 6.7-6.8 (m, 1H), 5.1-5.2 (m, 1H), 4.45 (dd, 2H, J=6.3, 9.6 Hz), 4.1-4.2 (m, 4H), 1.52 (t, 3H, J=7.3 Hz)	451.140
	****	¹ H NMR (CHLOROFORM-d, 400 MHz) δ 9.42 (d, 1H, J=2.4 Hz), 9.03 (d, 1H, J=6.1 Hz), 8.91 (br s, 1H), 8.3-8.3 (m, 1H), 7.91 (s, 1H), 7.00 (br d, 1H, J=7.9 Hz), 6.86 (s, 1H), 6.70 (td, 1H, J=2.2, 9.9 Hz), 5.1-5.2 (m, 1H), 4.68 (dd, 2H, J=6.7, 8.7 Hz), 4.28 (dd, 2H, J=4.1, 9.0 Hz), 4.12 (q, 2H, J=7.2 Hz), 1.44 (t, 3H, J=7.3 Hz)	451.140
	****	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 10.63 (s, 1H), 8.7-8.8 (m, 2H), 7.30 (br d, 1H, J=8.3 Hz), 7.18 (br d, 1H, J=10.5 Hz), 7.10 (s, 1H), 6.79 (d, 1H, J=6.3 Hz), 5.2-5.3 (m, 1H), 4.5-4.6 (m, 2H), 4.0-4.1 (m, 2H), 2.42 (s, 3H)	438.110

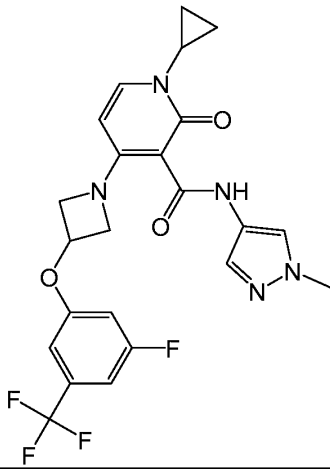
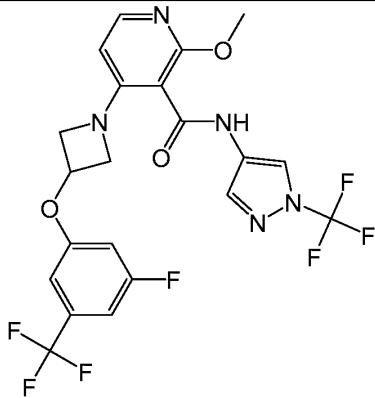
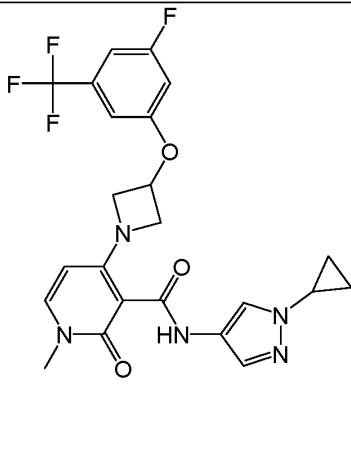
	****	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 10.64 (br s, 1H), 9.16 (s, 1H), 8.77 (d, 1H, J=6.2 Hz), 7.29 (br d, 1H, J=8.5 Hz), 7.16 (br d, 1H, J=10.6 Hz), 7.09 (s, 1H), 6.78 (d, 1H, J=6.3 Hz), 5.2-5.3 (m, 1H), 4.5-4.5 (m, 2H), 4.0-4.1 (m, 2H), 2.31 (s, 3H)	438.110
	****	¹ H NMR (CHLOROFORM-d, 400 MHz) δ 10.30 (br s, 1H), 8.78 (d, 1H, J=6.3 Hz), 8.3-8.4 (m, 1H), 8.30 (d, 1H, J=8.3 Hz), 7.7-7.8 (m, 1H), 7.1-7.1 (m, 1H), 7.01 (br d, 1H, J=8.1 Hz), 6.83 (s, 1H), 6.6-6.7 (m, 1H), 6.52 (d, 1H, J=6.3 Hz), 5.1-5.1 (m, 1H), 4.70 (br s, 2H), 4.28 (br d, 2H, J=8.1 Hz)	434.120
	****	¹ H NMR (CHLOROFORM-d, 400 MHz) δ 10.15 (br s, 1H), 8.77 (d, 1H, J=6.3 Hz), 7.84 (d, 1H, J=7.9 Hz), 7.62 (t, 1H, J=7.9 Hz), 7.01 (br d, 1H, J=8.3 Hz), 6.83 (s, 1H), 6.6-6.7 (m, 1H), 6.5-6.6 (m, 2H), 5.1-5.1 (m, 1H), 4.71 (br s, 2H), 4.29 (br d, 2H, J=8.4 Hz), 3.90 (s, 3H)	464.130
	****	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 10.6-11.0 (m, 1H), 9.46 (d, 1H, J=2.1 Hz), 9.08 (d, 1H, J=5.9 Hz), 8.04 (dd, 1H, J=2.6, 5.9 Hz), 7.74 (d, 1H, J=1.9 Hz), 7.24 (br d, 1H, J=8.5 Hz), 7.16 (d, 1H, J=2.0 Hz), 7.12 (br d, 1H, J=10.8 Hz)	422.120

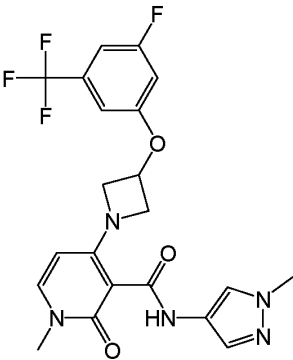
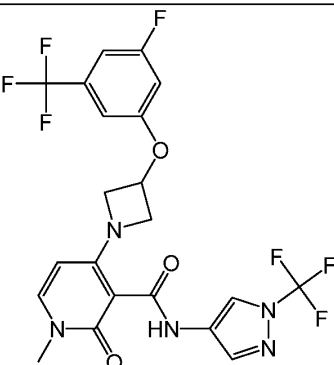
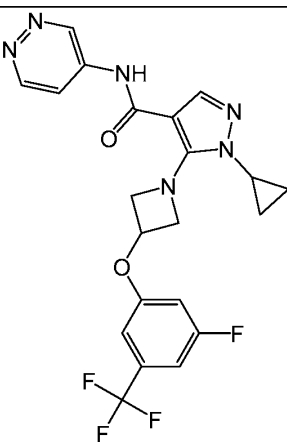
 or a diastereomer		Hz), 7.08 (s, 1H), 5.81 (br t, 1H, J=7.1 Hz), 5.12 (td, 1H, J=3.4, 6.5 Hz), 3.0-3.1 (m, 2H), 2.6-2.7 (m, 2H)	
	***	¹ H NMR (METHANOL-d ₄ , 400 MHz) δ 7.02 (br d, 1H, J=8.4 Hz), 6.98 (s, 1H), 6.91 (dd, 1H, J=2.0, 10.5 Hz), 6.59 (s, 1H), 5.8-5.9 (m, 1H), 5.08 (tt, 1H, J=3.3, 6.8 Hz), 4.19 (s, 1H), 3.48 (s, 2H), 3.0-3.1 (m, 2H), 2.67 (ddd, 2H, J=3.3, 8.7, 13.8 Hz), 2.35 (br d, 2H, J=5.6 Hz), 2.30 (s, 3H), 2.0-2.1 (m, 2H)	439.200
	***	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 9.55 (br s, 1H), 8.76 (br d, 1H, J=8.4 Hz), 7.24 (br d, 1H, J=8.5 Hz), 7.1-7.1 (m, 1H), 7.06 (s, 1H), 6.75 (s, 1H), 5.80 (quin, 1H, J=7.7 Hz), 5.09 (td, 1H, J=3.4, 6.3 Hz), 4.9-5.0 (m, 1H), 3.6-4.0 (m, 4H), 2.9-3.1 (m, 2H), 2.5-2.6 (m, 2H), 2.25 (s, 3H)	463.200
	**	¹ H NMR (ACETONITRILE-d ₃ , 400 MHz) Shift 8.2-8.8 (m, 3H), 7.91 (br s, 1H), 7.18 (br d, 1H, J=3.3 Hz), 7.11 (br d, 1H, J=8.3 Hz), 7.01 (br s, 2H), 6.92 (br d, 1H, J=10.4 Hz), 5.46 (br s, 2H), 5.17 (br s, 1H), 4.47 (br s, 2H), 3.99 (br d, 2H, J=3.9 Hz)	420.140

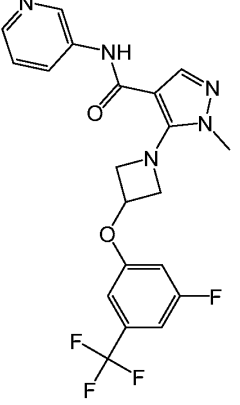
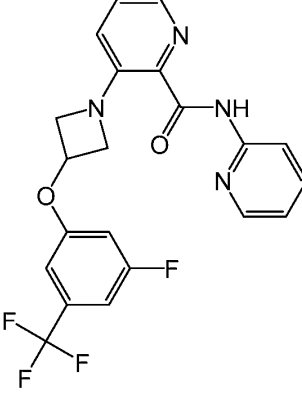
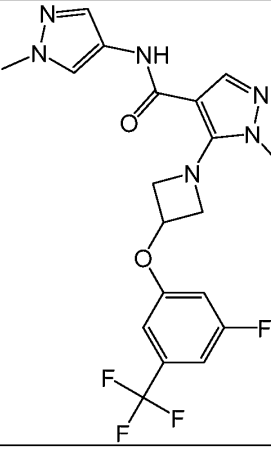
	***	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 13.05 (br s, 1H), 7.69 (d, 1H, J=7.8 Hz), 7.30 (br d, 1H, J=8.5 Hz), 7.2-7.2 (m, 1H), 7.11 (s, 1H), 5.90 (d, 1H, J=7.8 Hz), 5.21 (td, 1H, J=3.0, 6.3 Hz), 4.54 (br dd, 2H, J=6.3, 10.3 Hz), 4.13 (br dd, 2H, J=1.9, 11.1 Hz), 3.39 (s, 3H), 2.43 (s, 3H)	468.100
	***	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 10.47 (s, 1H), 8.35 (d, 1H, J=2.6 Hz), 8.10 (d, 1H, J=8.9 Hz), 7.8-7.9 (m, 2H), 7.28 (br d, 1H, J=8.4 Hz), 7.1-7.2 (m, 2H), 5.1-5.2 (m, 1H), 4.64 (dd, 2H, J=6.3, 9.3 Hz), 4.19 (dd, 2H, J=3.6, 9.4 Hz), 3.68 (s, 3H)	470.090
	**	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 10.74 (br s, 1H), 8.69 (dd, 1H, J=0.8, 1.5 Hz), 8.26 (d, 1H, J=8.9 Hz), 8.12 (dd, 1H, J=2.4, 9.0 Hz), 7.86 (s, 1H), 7.28 (br d, 1H, J=8.6 Hz), 7.0-7.2 (m, 2H), 5.1-5.3 (m, 1H), 4.66 (dd, 2H, J=6.3, 9.4 Hz), 4.21 (dd, 2H, J=3.6, 9.6 Hz), 3.69 (s, 3H)	504.120

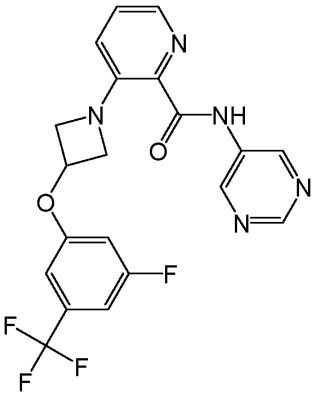
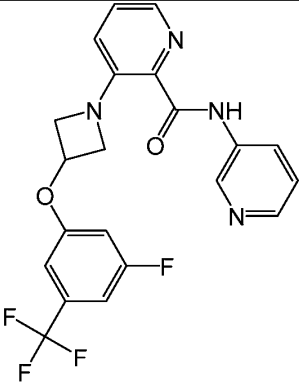
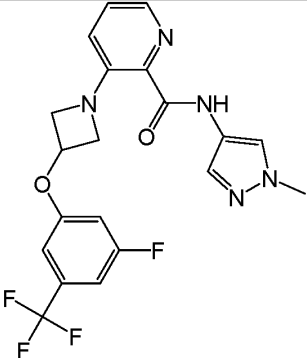
	***	¹H NMR (DMSO-d₆, 400 MHz) δ 10.26 (s, 1H), 8.94 (d, 1H, J=2.3 Hz), 8.37 (dd, 1H, J=2.2, 8.7 Hz), 7.7-7.9 (m, 2H), 7.28 (br d, 1H, J=8.5 Hz), 7.1-7.2 (m, 2H), 5.20 (br t, 1H, J=3.4 Hz), 4.67 (dd, 2H, J=6.3, 9.3 Hz), 4.20 (dd, 2H, J=3.6, 9.4 Hz), 3.70 (s, 3H)	504.120
	****	¹H NMR (DMSO-d₆, 400 MHz) δ 10.94 (s, 1H), 8.76 (d, 1H, J=6.1 Hz), 8.03 (s, 1H), 7.59 (s, 1H), 7.31 (br d, 1H, J=8.3 Hz), 7.18 (br d, 1H, J=10.6 Hz), 7.11 (s, 1H), 6.76 (d, 1H, J=6.3 Hz), 5.2-5.3 (m, 1H), 4.4-4.5 (m, 2H), 4.0-4.1 (m, 2H), 3.82 (s, 3H)	437.130
	***	¹H NMR (DMSO-d₆, 400 MHz) δ 11.47 (s, 1H), 11.20 (br s, 1H), 8.51 (s, 1H), 8.08 (s, 1H), 7.2-7.3 (m, 2H), 7.15 (br d, 1H, J=10.6 Hz), 7.09 (s, 1H), 5.75 (d, 1H, J=7.5 Hz), 5.1-5.2 (m, 1H), 4.4-4.6 (m, 2H), 4.11 (br dd, 2H, J=2.2, 10.8 Hz)	506.100
	***	¹H NMR (CHLOROFORM-d, 400 MHz) δ 7.88 (br s, 1H), 7.84 (s, 1H), 7.01 (br d, 1H, J=8.0 Hz), 6.86 (br s, 1H), 6.69 (br d, 1H, J=9.8 Hz), 5.12 (br d, 1H, J=4.0 Hz), 4.78 (br t, 2H, J=7.4 Hz), 4.39 (br dd, 2H, J=3.8, 8.1 Hz), 3.80 (s, 3H), 2.36 (br s, 3H)	441.120

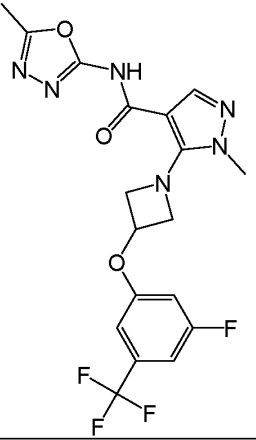
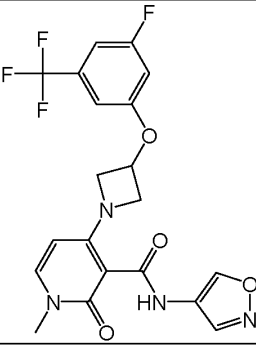
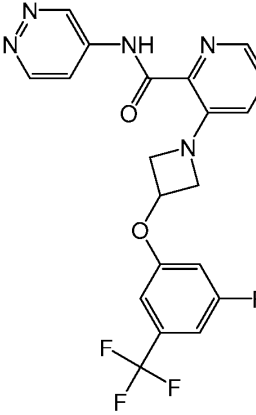
	***	¹H NMR (DMSO-d₆, 400 MHz) δ 10.25 (s, 1H), 8.3-8.4 (m, 1H), 8.05 (d, 1H, J=8.4 Hz), 7.83 (s, 1H), 7.7-7.8 (m, 1H), 7.28 (br d, 1H, J=8.4 Hz), 7.1-7.2 (m, 1H), 7.0-7.1 (m, 2H), 5.2-5.2 (m, 1H), 4.6-4.7 (m, 2H), 4.1-4.2 (m, 2H), 3.68 (s, 3H)	436.130
	***	¹H NMR (DMSO-d₆, 400 MHz) δ 10.56 (s, 1H), 8.02 (s, 1H), 7.78 (d, 1H, J=8.8 Hz), 7.55 (s, 1H), 7.29 (br d, 1H, J=8.5 Hz), 7.1-7.2 (m, 2H), 7.10 (s, 1H), 5.25 (tt, 1H, J=3.3, 6.2 Hz), 4.43 (dd, 2H, J=6.3, 9.8 Hz), 3.99 (dd, 2H, J=3.0, 9.9 Hz), 3.82 (s, 3H)	504.120
	****	¹H NMR (DMSO-d₆, 400 MHz) δ 11.10 (br s, 1H), 9.50 (dd, 1H, J=0.8, 2.6 Hz), 9.09 (dd, 1H, J=0.9, 5.9 Hz), 8.09 (dd, 1H, J=2.8, 5.9 Hz), 7.86 (d, 1H, J=8.9 Hz), 7.3-7.3 (m, 2H), 7.17 (td, 1H, J=2.1, 10.5 Hz), 7.10 (s, 1H), 5.2-5.3 (m, 1H), 4.49 (dd, 2H, J=6.3, 10.1 Hz), 4.04 (dd, 2H, J=3.1, 10.1 Hz)	502.100

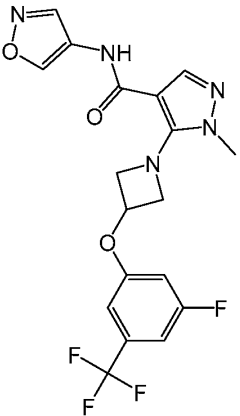
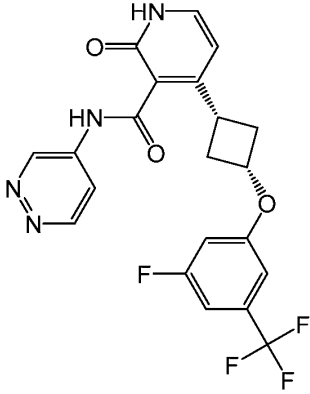
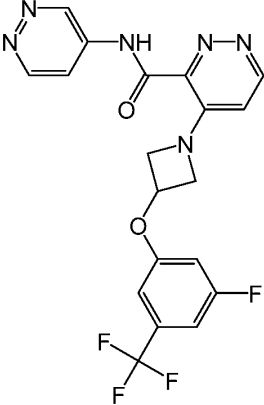
	****	¹H NMR (DMSO-d₆, 400 MHz) δ 10.79 (s, 1H), 7.94 (s, 1H), 7.45 (s, 1H), 7.41 (d, 1H, J=7.8 Hz), 7.29 (br d, 1H, J=8.6 Hz), 7.15 (br d, 1H, J=10.8 Hz), 7.08 (s, 1H), 5.70 (d, 1H, J=7.8 Hz), 5.1-5.2 (m, 1H), 4.44 (br dd, 2H, J=6.6, 10.1 Hz), 4.03 (dd, 2H, J=2.4, 10.5 Hz), 3.78 (s, 3H), 3.1-3.2 (m, 1H), 0.9-1.0 (m, 2H), 0.7-0.8 (m, 2H)	492.160
	***	¹H NMR (DMSO-d₆, 400 MHz) δ 10.85 (s, 1H), 8.51 (s, 1H), 7.94 (s, 1H), 7.85 (d, 1H, J=6.0 Hz), 7.25 (br d, 1H, J=8.5 Hz), 7.13 (br d, 1H, J=10.6 Hz), 7.03 (s, 1H), 6.22 (d, 1H, J=6.0 Hz), 5.2-5.3 (m, 1H), 4.42 (dd, 2H, J=6.4, 9.4 Hz), 3.90 (dd, 2H, J=3.1, 9.6 Hz), 3.80 (s, 3H)	520.110
	****	¹H NMR (DMSO-d₆, 400 MHz) δ 10.78 (s, 1H), 7.97 (s, 1H), 7.56 (d, 1H, J=7.6 Hz), 7.45 (s, 1H), 7.28 (br d, 1H, J=8.5 Hz), 7.15 (br d, 1H, J=10.5 Hz), 7.08 (s, 1H), 5.75 (d, 1H, J=7.6 Hz), 5.1-5.2 (m, 1H), 4.45 (br dd, 2H, J=6.4, 10.0 Hz), 4.02 (br dd, 2H, J=2.4, 10.5 Hz), 3.66 (td, 1H, J=3.5, 7.3 Hz), 3.34 (s, 3H), 1.0-1.0 (m, 2H), 0.9-0.9 (m, 2H)	492.150

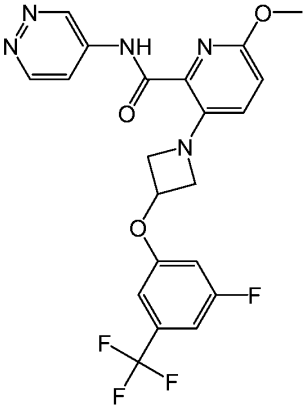
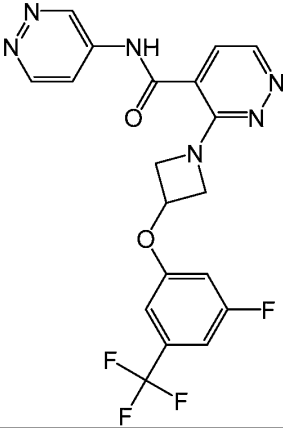
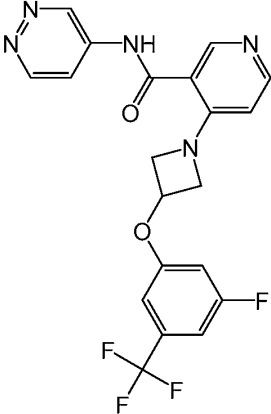
	****	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 10.76 (s, 1H), 7.93 (s, 1H), 7.56 (d, 1H, J=7.6 Hz), 7.43 (s, 1H), 7.28 (br d, 1H, J=8.5 Hz), 7.15 (br d, 1H, J=10.6 Hz), 7.08 (s, 1H), 5.75 (d, 1H, J=7.6 Hz), 5.18 (br s, 1H), 4.44 (br dd, 2H, J=6.3, 10.3 Hz), 4.02 (dd, 2H, J=2.7, 10.7 Hz), 3.78 (s, 3H), 3.34 (s, 3H)	466.140
	***	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 11.27 (s, 1H), 8.50 (s, 1H), 8.06 (s, 1H), 7.61 (d, 1H, J=7.6 Hz), 7.29 (br d, 1H, J=8.5 Hz), 7.1-7.2 (m, 1H), 7.08 (s, 1H), 5.79 (d, 1H, J=7.6 Hz), 5.18 (tt, 1H, J=3.3, 6.3 Hz), 4.47 (br dd, 2H, J=6.1, 10.4 Hz), 4.05 (dd, 2H, J=2.5, 10.6 Hz), 3.36 (s, 3H)	520.110
	****	¹ H NMR (METHANOL-d ₄ , 400 MHz) δ 9.38 (d, 1H, J=2.4 Hz), 9.09 (d, 1H, J=6.6 Hz), 8.50 (dd, 1H, J=2.6, 6.6 Hz), 7.79 (s, 1H), 7.08 (br d, 1H, J=8.5 Hz), 7.01 (s, 1H), 6.95 (br d, 1H, J=10.4 Hz), 5.1-5.2 (m, 1H), 4.9-4.9 (m, 2H), 4.44 (dd, 2H, J=3.6, 9.8 Hz), 3.5-3.6 (m, 1H), 1.1-1.2 (m, 4H)	463.140

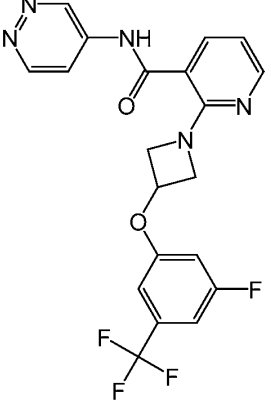
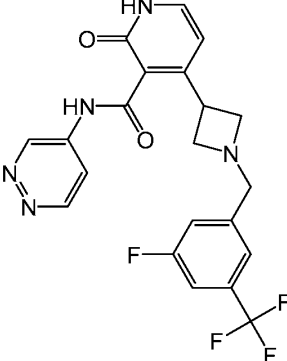
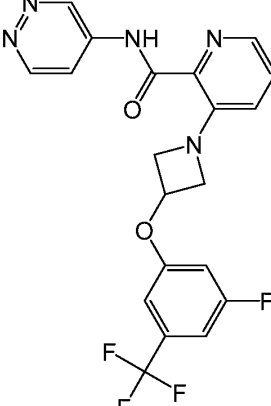
	****	¹H NMR (CHLOROFORM-d, 400 MHz) δ 8.64 (d, 1H, J=2.0 Hz), 8.35 (d, 1H, J=4.6 Hz), 8.22 (br d, 1H, J=8.9 Hz), 7.94 (s, 1H), 7.69 (s, 1H), 7.31 (dd, 1H, J=4.8, 8.3 Hz), 6.98 (br d, 1H, J=8.2 Hz), 6.85 (s, 1H), 6.68 (br d, 1H, J=9.9 Hz), 5.1-5.1 (m, 1H), 4.7-4.7 (m, 2H), 4.27 (dd, 2H, J=4.1, 8.9 Hz), 3.80 (s, 3H)	436.130
	****	¹H NMR (METHANOL-d₄, 400 MHz) δ 8.3-8.3 (m, 2H), 8.08 (dd, 1H, J=0.9, 4.3 Hz), 7.84 (dt, 1H, J=1.9, 7.9 Hz), 7.43 (dd, 1H, J=4.3, 8.5 Hz), 7.19 (dd, 1H, J=0.9, 8.6 Hz), 7.1-7.2 (m, 1H), 7.07 (br d, 1H, J=8.4 Hz), 7.00 (s, 1H), 6.94 (td, 1H, J=2.1, 10.3 Hz), 5.1-5.2 (m, 1H), 4.49 (dd, 2H, J=6.3, 9.6 Hz), 4.11 (dd, 2H, J=3.1, 9.6 Hz)	433.120
	****	¹H NMR (DMSO-d₆, 400 MHz) δ 9.79 (s, 1H), 7.89 (s, 1H), 7.65 (s, 1H), 7.41 (s, 1H), 7.29 (br d, 1H, J=8.5 Hz), 7.1-7.2 (m, 1H), 7.10 (s, 1H), 5.2-5.2 (m, 1H), 4.6-4.7 (m, 2H), 4.1-4.2 (m, 2H), 3.77 (s, 3H), 3.66 (s, 3H)	439.140

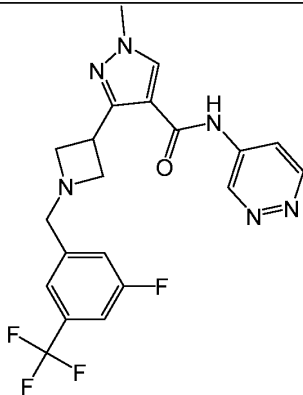
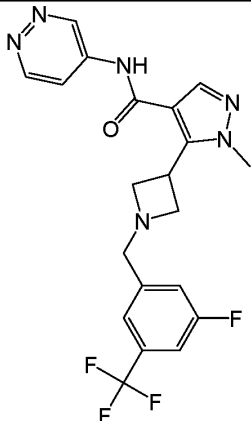
	****	¹H NMR (CHLOROFORM-d, 400 MHz) δ 10.06 (s, 1H), 9.18 (s, 2H), 8.98 (s, 1H), 8.09 (dd, 1H, J=0.9, 4.2 Hz), 7.39 (dd, 1H, J=4.3, 8.5 Hz), 7.04 (dd, 1H, J=0.9, 8.6 Hz), 6.98 (br d, 1H, J=8.3 Hz), 6.84 (s, 1H), 6.68 (td, 1H, J=2.1, 9.9 Hz), 5.10 (tt, 1H, J=4.2, 6.2 Hz), 4.66 (dd, 2H, J=6.3, 9.9 Hz), 4.09 (dd, 2H, J=4.0, 9.9 Hz)	434.120
	****	¹H NMR (CHLOROFORM-d, 400 MHz) δ 10.00 (br s, 1H), 8.77 (d, 1H, J=2.0 Hz), 8.3-8.4 (m, 2H), 8.08 (d, 1H, J=3.9 Hz), 7.34 (ddd, 2H, J=4.6, 8.3, 18.3 Hz), 7.00 (br dd, 2H, J=8.2, 18.9 Hz), 6.84 (s, 1H), 6.67 (br d, 1H, J=9.9 Hz), 5.0-5.1 (m, 1H), 4.64 (dd, 2H, J=6.4, 9.3 Hz), 4.08 (dd, 2H, J=4.0, 9.6 Hz), 2.4-2.4 (m, 1H)	433.120
	****	¹H NMR (CHLOROFORM-d, 400 MHz) δ 9.64 (s, 1H), 8.0-8.1 (m, 2H), 7.3-7.4 (m, 1H), 7.27 (s, 1H), 6.9-7.0 (m, 2H), 6.84 (s, 1H), 6.67 (br d, 1H, J=10.0 Hz), 5.0-5.1 (m, 1H), 4.6-4.7 (m, 2H), 4.0-4.1 (m, 2H), 3.91 (s, 3H)	436.130

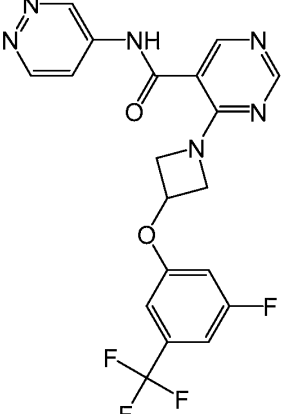
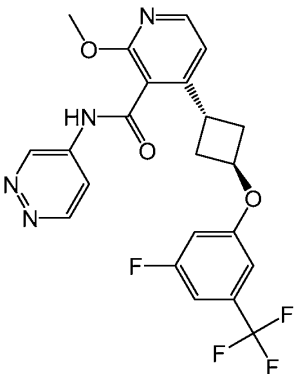
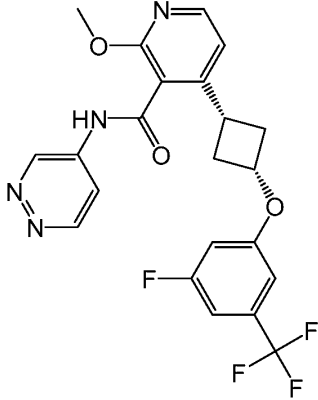
	***	¹H NMR (METHANOL-d₄, 400 MHz) Shift 7.75 (s, 1H), 7.06 (br d, 1H, J=8.4 Hz), 6.99 (s, 1H), 6.93 (td, 1H, J=2.1, 10.4 Hz), 5.17 (tt, 1H, J=3.9, 6.3 Hz), 4.74 (dd, 2H, J=6.6, 9.3 Hz), 4.33 (dd, 2H, J=3.8, 9.6 Hz), 3.75 (s, 3H), 2.49 (s, 3H)	441.120
	***	¹H NMR (DMSO-d₆, 400 MHz) δ 11.20 (br s, 1H), 9.16 (s, 1H), 8.74 (s, 1H), 7.61 (br d, 1H, J=7.4 Hz), 7.28 (br d, 1H, J=8.1 Hz), 7.0-7.2 (m, 2H), 5.80 (br d, 1H, J=7.5 Hz), 5.18 (br s, 1H), 4.46 (br s, 2H), 4.06 (br d, 2H, J=9.6 Hz), 3.36 (br s, 3H)	453.110
	****	¹H NMR (CHLOROFORM-d, 400 MHz) δ 10.20 (br s, 1H), 9.33 (d, 1H, J=2.4 Hz), 9.12 (d, 1H, J=6.0 Hz), 8.69 (s, 1H), 8.33 (s, 1H), 8.22 (dd, 1H, J=2.8, 6.0 Hz), 7.02 (br d, 1H, J=8.4 Hz), 6.85 (s, 1H), 6.70 (td, 1H, J=2.1, 9.7 Hz), 5.1-5.2 (m, 1H), 4.77 (dd, 2H, J=6.3, 9.9 Hz), 4.29 (dd, 2H, J=3.8, 10.3 Hz)	435.110

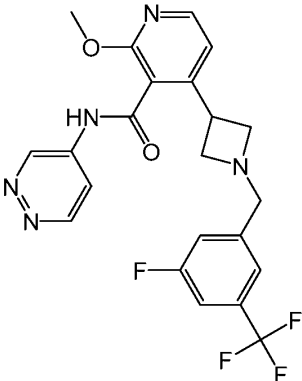
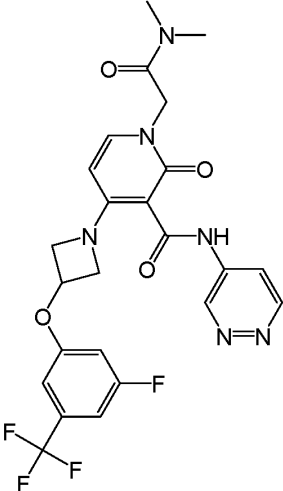
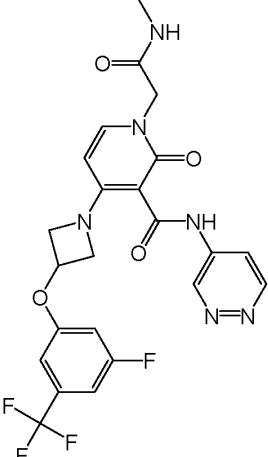
	****	¹H NMR (DMSO-d₆, 400 MHz) δ 10.07 (s, 1H), 9.08 (s, 1H), 8.60 (s, 1H), 7.69 (s, 1H), 7.28 (br d, 1H, J=8.5 Hz), 7.15 (td, 1H, J=2.0, 10.6 Hz), 7.10 (s, 1H), 5.1-5.2 (m, 1H), 4.66 (dd, 2H, J=6.3, 9.4 Hz), 4.21 (dd, 2H, J=3.8, 9.5 Hz), 3.68 (s, 3H)	426.110
 or a diastereomer	***	¹H NMR (DMSO-d₆, 400 MHz) δ 12.0-12.2 (m, 1H), 11.3-11.4 (m, 1H), 9.34 (d, 1H, J=1.9 Hz), 9.06 (d, 1H, J=5.9 Hz), 8.02 (dd, 1H, J=2.5, 5.6 Hz), 7.56 (d, 1H, J=6.8 Hz), 7.21 (br d, 1H, J=8.1 Hz), 7.11 (br d, 1H, J=10.9 Hz), 7.05 (s, 1H), 6.40 (d, 1H, J=6.8 Hz), 4.8-4.9 (m, 1H), 3.3-3.3 (m, 1H), 2.8-2.9 (m, 2H), 2.1-2.2 (m, 2H)	449.120
	****	¹H NMR (400 MHz, DMSO-d₆) δ = 11.44 (br s, 1H), 9.56 (s, 1H), 9.07 (d, J = 5.8 Hz, 1H), 8.81 (d, J = 6.4 Hz, 1H), 8.18 - 8.10 (m, 1H), 7.29 (br d, J = 8.8 Hz, 1H), 7.17 (br d, J = 10.5 Hz, 1H), 7.10 (s, 1H), 6.84 (d, J = 6.3 Hz, 1H), 5.29 - 5.23 (m, 1H), 4.58 - 4.50 (m, 2H), 4.14 - 4.06 (m, 2H) ¹H NMR (DMSO-d₆, 400 MHz) δ 11.49 (br s, 1H), 9.58 (d, 1H, J=2.3 Hz), 9.08 (d, 1H, J=5.9 Hz), 8.82 (d, 1H, J=6.3 Hz), 8.1-8.2 (m, 1H), 7.30 (br d, 1H, J=8.8 Hz), 7.17 (br	435.110

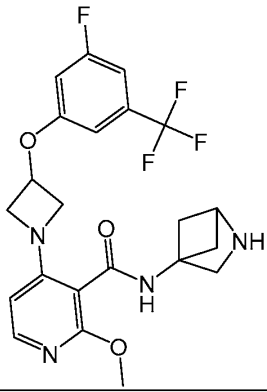
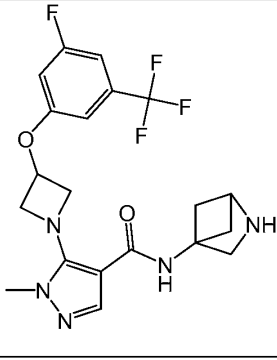
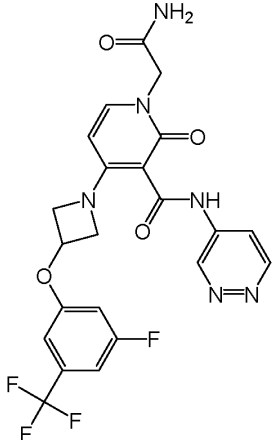
		d, 1H, J=10.6 Hz), 7.11 (s, 1H), 6.85 (d, 1H, J=6.4 Hz), 5.2-5.3 (m, 1H), 4.5-4.6 (m, 2H), 4.1-4.1 (m, 2H)	
	****	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 10.69 (s, 1H), 9.51 (d, 1H, J=1.8 Hz), 9.04 (d, 1H, J=5.8 Hz), 8.11 (dd, 1H, J=2.4, 5.8 Hz), 7.2-7.3 (m, 2H), 7.15 (br d, 1H, J=10.5 Hz), 7.09 (s, 1H), 7.02 (d, 1H, J=8.9 Hz), 5.21 (br s, 1H), 4.33 (br dd, 2H, J=6.3, 9.2 Hz), 3.8-4.0 (m, 5H)	464.130
	****	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 11.27 (br s, 1H), 9.35 (s, 1H), 9.10 (d, 1H, J=6.1 Hz), 8.81 (d, 1H, J=4.8 Hz), 7.9-8.1 (m, 1H), 7.64 (d, 1H, J=4.6 Hz), 7.27 (br d, 1H, J=8.8 Hz), 7.16 (br d, 1H, J=10.5 Hz), 7.09 (s, 1H), 5.2-5.4 (m, 1H), 4.5-4.7 (m, 2H), 4.0-4.1 (m, 2H)	435.110
	****	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 11.14 (s, 1H), 9.3-9.5 (m, 1H), 9.07 (d, 1H, J=5.9 Hz), 8.47 (s, 1H), 8.27 (d, 1H, J=6.0 Hz), 8.03 (dd, 1H, J=2.8, 5.9 Hz), 7.28 (br d, 1H, J=8.5 Hz), 7.16 (br d, 1H, J=10.6 Hz), 7.09 (s, 1H), 6.60 (d, 1H, J=6.0 Hz), 5.1-5.4 (m, 1H), 4.48 (dd, 2H, J=6.3, 10.1 Hz), 4.00 (dd, 2H, J=2.7, 10.3 Hz)	434.120

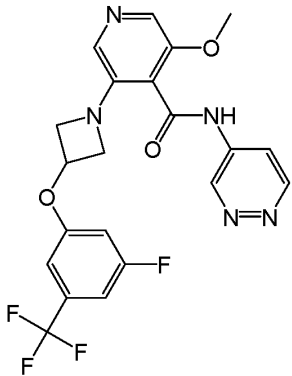
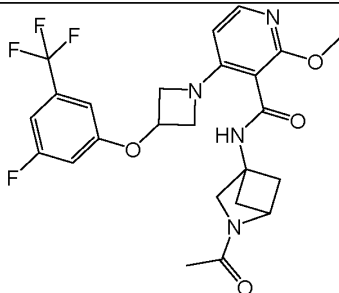
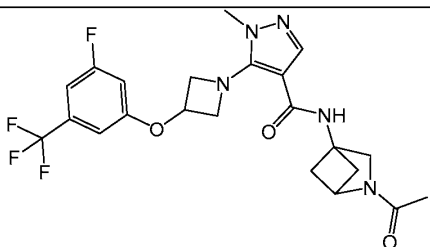
	****	¹H NMR (CHLOROFORM-d, 400 MHz) δ 9.83 (s, 1H), 9.3-9.4 (m, 1H), 8.96 (d, 1H, J=5.9 Hz), 8.38 (dd, 1H, J=1.7, 4.8 Hz), 8.27 (dd, 1H, J=2.8, 5.9 Hz), 7.99 (dd, 1H, J=1.8, 7.6 Hz), 6.97 (br d, 1H, J=8.3 Hz), 6.91 (dd, 1H, J=4.9, 7.6 Hz), 6.80 (s, 1H), 6.65 (td, 1H, J=2.1, 9.8 Hz), 5.06 (ddd, 1H, J=2.2, 4.0, 6.2 Hz), 4.52 (dd, 2H, J=6.4, 10.0 Hz), 4.15 (dd, 2H, J=3.8, 10.2 Hz)	434.120
	***	¹H NMR (DMSO-d₆, 400 MHz) δ 11.9-12.6 (m, 1H), 11.34 (br s, 1H), 9.31 (d, 1H, J=2.0 Hz), 9.04 (d, 1H, J=5.8 Hz), 8.00 (dd, 1H, J=2.6, 5.8 Hz), 7.61 (d, 1H, J=6.8 Hz), 7.4-7.6 (m, 3H), 6.59 (d, 1H, J=6.9 Hz), 3.8-3.9 (m, 1H), 3.68 (s, 2H), 3.56 (br t, 2H, J=7.5 Hz), 3.16 (br t, 2H, J=6.9 Hz)	448.130
	****	¹H NMR (CHLOROFORM-d, 400 MHz) δ 10.33 (br s, 1H), 9.3-9.3 (m, 1H), 9.07 (d, 1H, J=6.0 Hz), 8.25 (dd, 1H, J=2.8, 5.9 Hz), 8.10 (dd, 1H, J=1.1, 4.2 Hz), 7.41 (dd, 1H, J=4.2, 8.6 Hz), 7.05 (dd, 1H, J=1.0, 8.5 Hz), 7.00 (br d, 1H, J=8.3 Hz), 6.85 (s, 1H), 6.69 (td, 1H, J=2.1, 9.9 Hz), 5.10 (tt, 1H, J=4.1, 6.3 Hz), 4.65 (dd, 2H, J=6.3, 9.8 Hz), 4.12 (dd, 2H, J=4.1, 10.1 Hz) ¹H NMR (CHLOROFORM-d, 400	434.120

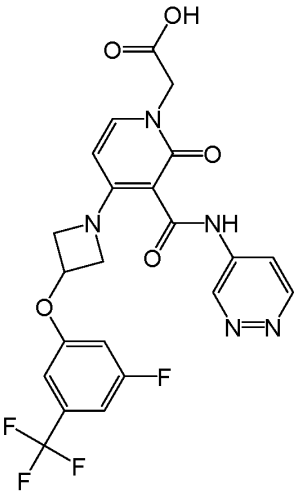
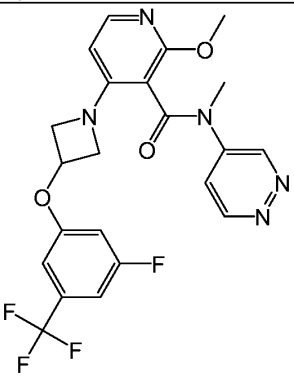
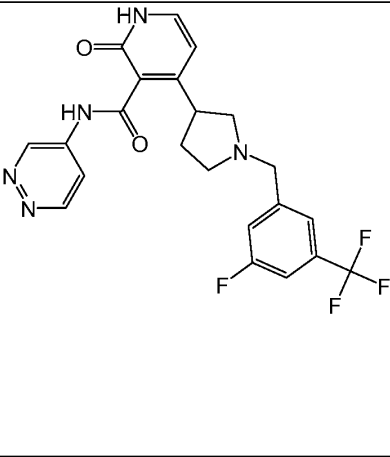
		MHz) δ 10.32 (s, 1H), 9.29 (d, 1H, J=2.6 Hz), 9.07 (d, 1H, J=6.0 Hz), 8.24 (dd, 1H, J=2.8, 5.9 Hz), 8.1-8.1 (m, 1H), 7.41 (dd, 1H, J=4.2, 8.6 Hz), 7.0-7.1 (m, 1H), 7.00 (br d, 1H, J=8.1 Hz), 6.85 (s, 1H), 6.69 (td, 1H, J=2.1, 9.8 Hz), 5.1-5.1 (m, 1H), 4.65 (dd, 2H, J=6.4, 9.8 Hz), 4.12 (dd, 2H, J=4.1, 9.8 Hz)	
	****	¹ H NMR (METHANOL-d ₄ , 400 MHz) δ 9.35 (dd, 1H, J=0.9, 2.8 Hz), 8.96 (dd, 1H, J=0.9, 6.0 Hz), 8.24 (s, 1H), 8.17 (dd, 1H, J=2.8, 6.0 Hz), 7.50 (s, 1H), 7.37 (br t, 2H, J=10.6 Hz), 4.21 (t, 1H, J=7.9 Hz), 3.94 (s, 3H), 3.8-3.8 (m, 4H), 3.48 (t, 2H, J=7.9 Hz)	435.150
	****	¹ H NMR (CHLOROFORM-d, 400 MHz) δ 9.65 (br s, 1H), 9.32 (br s, 1H), 9.01 (d, 1H, J=5.9 Hz), 8.23 (dd, 1H, J=2.4, 5.8 Hz), 7.99 (s, 1H), 7.40 (s, 1H), 7.29 (br s, 1H), 7.24 (br d, 1H, J=8.5 Hz), 4.24 (br t, 1H, J=8.1 Hz), 3.9-4.0 (m, 7H), 3.68 (br t, 2H, J=7.6 Hz)	435.150

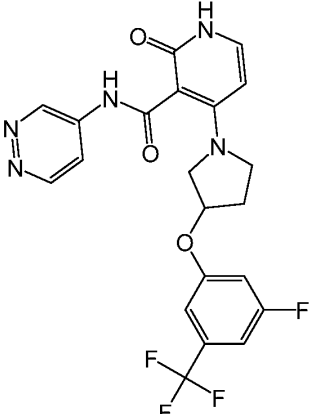
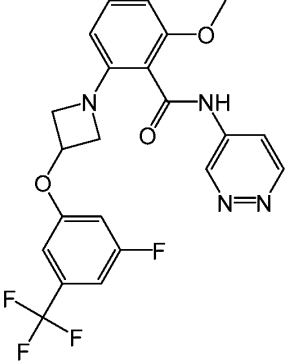
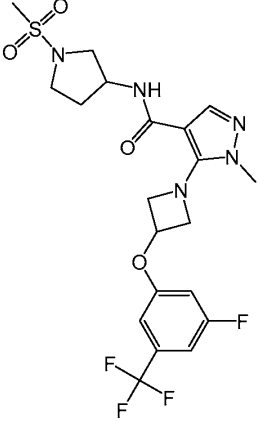
	****	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 9.37 (dd, 1H, J=0.9, 2.7 Hz), 9.08 (dd, 1H, J=0.9, 5.9 Hz), 8.64 (s, 1H), 8.57 (s, 1H), 8.01 (dd, 1H, J=2.7, 5.9 Hz), 7.28 (br d, 1H, J=8.5 Hz), 7.15 (td, 1H, J=2.1, 10.5 Hz), 7.09 (s, 1H), 5.2-5.3 (m, 1H), 4.58 (br dd, 2H, J=6.4, 10.5 Hz), 4.05 (dd, 2H, J=2.8, 10.8 Hz)	435.110
 or a diastereomer	****	¹ H NMR (CHLOROFORM-d, 400 MHz) δ 9.7-9.9 (m, 1H), 9.48 (br d, 1H, J=1.3 Hz), 9.01 (d, 1H, J=6.1 Hz), 8.53 (br dd, 1H, J=2.8, 3.9 Hz), 8.3-8.4 (m, 1H), 7.0-7.1 (m, 1H), 6.92 (br d, 1H, J=8.3 Hz), 6.8-6.9 (m, 1H), 6.6-6.7 (m, 1H), 4.8-4.9 (m, 1H), 4.1-4.2 (m, 1H), 4.04 (s, 3H), 2.6-2.8 (m, 4H)	463.130
 or a diastereomer	**	¹ H NMR (CHLOROFORM-d, 400 MHz) δ 9.3-9.5 (m, 2H), 9.02 (br d, 1H, J=5.3 Hz), 8.42 (br d, 1H, J=3.8 Hz), 8.29 (d, 1H, J=5.4 Hz), 7.05 (d, 1H, J=5.4 Hz), 6.92 (br d, 1H, J=7.9 Hz), 6.85 (s, 1H), 6.69 (br d, 1H, J=10.4 Hz), 4.67 (quin, 1H, J=7.0 Hz), 4.04 (s, 3H), 3.6-3.7 (m, 1H), 2.9-3.0 (m, 2H), 2.2-2.4 (m, 2H)	463.130

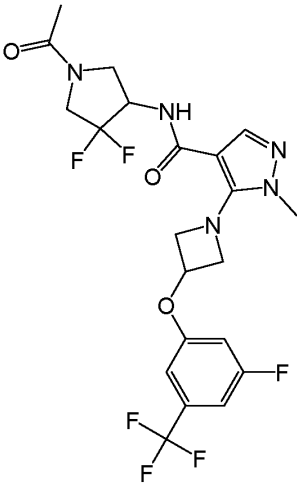
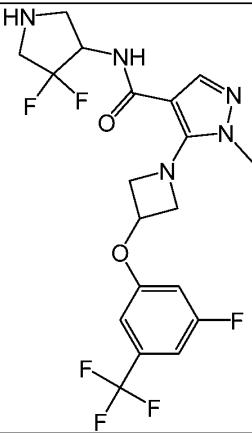
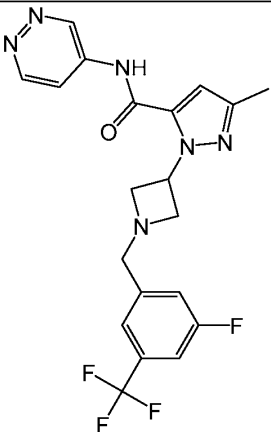
	**	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 11.13 (s, 1H), 9.31 (d, 1H, J=2.0 Hz), 9.08 (d, 1H, J=5.9 Hz), 8.31 (d, 1H, J=5.4 Hz), 8.01 (dd, 1H, J=2.7, 5.8 Hz), 7.4-7.6 (m, 3H), 7.30 (d, 1H, J=5.4 Hz), 3.89 (s, 3H), 3.74 (br s, 3H), 3.61 (br t, 2H, J=7.1 Hz), 3.28 (br s, 2H)	462.150
	***	¹ H NMR (DMSO-d ₆ , 400 MHz) Shift 12.48 (br s, 1H), 9.41 (br s, 1H), 9.17 (br d, 1H, J=6.1 Hz), 8.39 (br d, 1H, J=4.1 Hz), 7.55 (br d, 1H, J=7.5 Hz), 7.30 (br d, 1H, J=8.3 Hz), 7.17 (br d, 1H, J=10.4 Hz), 7.11 (br s, 1H), 5.94 (br d, 1H, J=7.6 Hz), 5.25 (br s, 1H), 4.77 (br s, 2H), 4.59 (br s, 2H), 4.19 (br d, 2H, J=10.9 Hz), 3.05 (s, 3H), 2.85 (s, 3H)	535.470
	***	¹ H NMR (DMSO-d ₆ , 400 MHz) Shift 11.66 (s, 1H), 9.32 (br s, 1H), 8.97 (d, 1H, J=5.9 Hz), 8.07 (br d, 1H, J=4.1 Hz), 8.01 (br d, 1H, J=3.6 Hz), 7.56 (br d, 1H, J=7.6 Hz), 7.29 (br d, 1H, J=8.3 Hz), 7.17 (br d, 1H, J=10.4 Hz), 7.11 (s, 1H), 5.88 (br d, 1H, J=7.6 Hz), 5.22 (br s, 1H), 4.55 (br s, 2H), 4.47 (s, 2H), 4.13 (br d, 2H, J=10.9 Hz), 2.61 (br d, 3H, J=4.1 Hz)	521.440

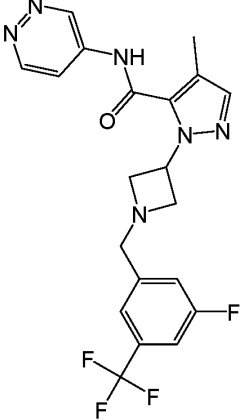
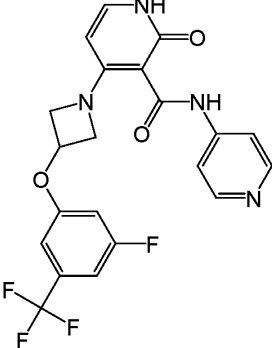
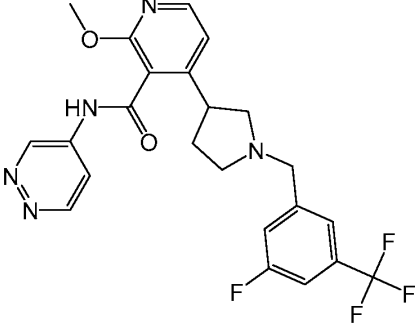
	**	¹ H NMR (METHANOL-d ₄ , 400 MHz) δ 7.76 (d, 1H, J=6.0 Hz), 7.09 (br d, 1H, J=8.4 Hz), 6.9-7.0 (m, 2H), 6.17 (d, 1H, J=6.0 Hz), 5.2-5.3 (m, 1H), 4.52 (dd, 2H, J=6.4, 9.1 Hz), 4.07 (dd, 2H, J=3.5, 9.5 Hz), 3.86 (s, 3H), 3.62 (s, 1H), 3.03 (s, 2H), 2.0-2.2 (m, 2H), 1.76 (dd, 2H, J=1.6, 4.4 Hz)	467.160
	***	¹ H NMR (METHANOL-d ₄ , 400 MHz) δ 7.57 (s, 1H), 7.07 (br d, 1H, J=8.3 Hz), 7.00 (s, 1H), 6.93 (br d, 1H, J=10.1 Hz), 5.1-5.2 (m, 1H), 4.63 (dd, 2H, J=6.7, 8.4 Hz), 4.22 (dd, 2H, J=4.0, 8.9 Hz), 3.70 (s, 3H), 3.66 (s, 1H), 3.06 (s, 2H), 2.0-2.2 (m, 2H), 1.80 (br d, 2H, J=4.5 Hz)	441.170
	*****	¹ H NMR (DMSO-d ₆ , 400 MHz) Shift 12.34 (s, 1H), 9.39 (d, 1H, J=2.0 Hz), 9.14 (d, 1H, J=6.3 Hz), 8.32 (dd, 1H, J=2.5, 6.3 Hz), 7.5-7.7 (m, 2H), 7.30 (br d, 1H, J=8.3 Hz), 7.1-7.2 (m, 2H), 7.12 (s, 1H), 5.92 (d, 1H, J=7.8 Hz), 5.2-5.3 (m, 1H), 4.57 (br s, 2H), 4.48 (s, 2H), 4.1-4.2 (m, 2H)	507.130

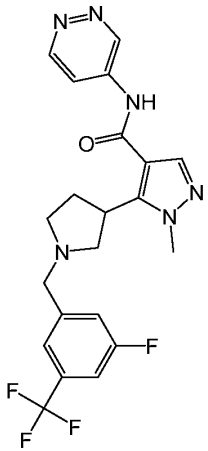
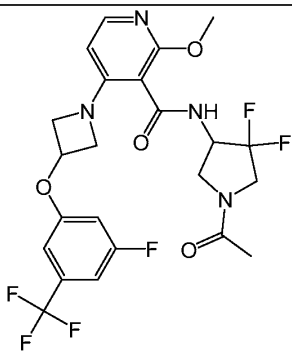
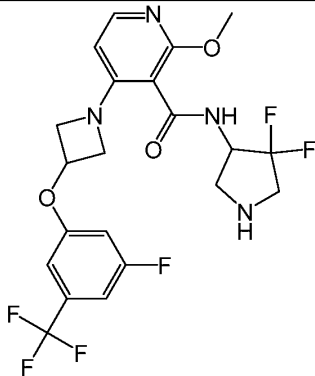
	****	¹H NMR (DMSO-d₆, 400 MHz) Shift 11.22 (br s, 1H), 9.32 (d, 1H, J=1.9 Hz), 9.08 (d, 1H, J=5.9 Hz), 8.02 (dd, 1H, J=2.6, 5.8 Hz), 7.91 (s, 1H), 7.69 (s, 1H), 7.26 (br d, 1H, J=8.5 Hz), 7.14 (br d, 1H, J=10.6 Hz), 7.05 (s, 1H), 5.23 (br s, 1H), 4.41 (br dd, 2H, J=6.7, 8.2 Hz), 3.89 (br dd, 2H, J=3.4, 8.9 Hz), 3.85 (s, 3H))	463.130
	***	¹H NMR (DMSO-d₆, 400 MHz) δ 9.01 (d, 1H, J=13.8 Hz), 7.78 (br d, 1H, J=5.8 Hz), 7.29 (br d, 1H, J=8.0 Hz), 7.17 (br d, 1H, J=10.4 Hz), 7.08 (s, 1H), 6.14 (dd, 1H, J=2.8, 5.8 Hz), 5.25 (br d, 1H, J=2.8 Hz), 4.4-4.5 (m, 3H), 3.9-4.0 (m, 2H), 3.77 (s, 3H), 3.54 (s, 1H), 2.26 (br s, 1H), 2.09 (br s, 1H), 1.94 (s, 2H), 1.88 (s, 2H), 1.70 (br dd, 2H, J=2.9, 19.9 Hz)	509.170
	****	¹H NMR (CHLOROFORM-d, 400 MHz) δ 7.49 (d, 1H, J=4.6 Hz), 6.99 (br d, 1H, J=7.9 Hz), 6.85 (s, 1H), 6.68 (br d, 1H, J=10.1 Hz), 6.2-6.4 (m, 1H), 5.0-5.1 (m, 1H), 4.6-4.7 (m, 2H), 4.2-4.2 (m, 2H), 3.75 (s, 3H), 3.70 (s, 1H), 3.60 (s, 1H), 2.4-2.5 (m, 1H), 2.08 (s, 3H), 2.03 (s, 2H), 1.9-2.0 (m, 2H)	482.170

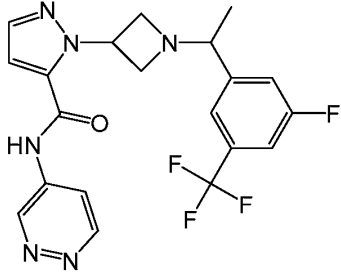
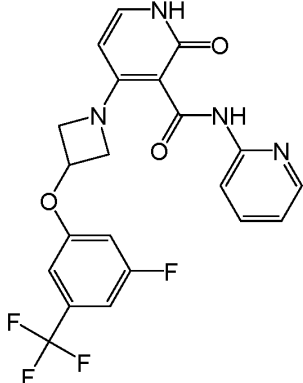
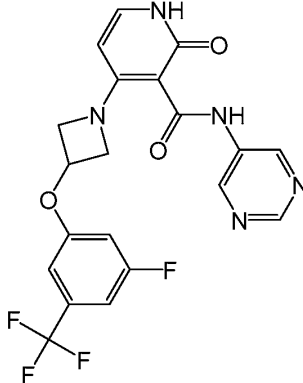
	***	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 11.74 (br s, 1H), 9.33 (br s, 1H), 8.97 (br d, 1H, J=5.6 Hz), 8.00 (br d, 1H, J=3.0 Hz), 7.59 (br d, 1H, J=7.6 Hz), 7.29 (br d, 1H, J=8.1 Hz), 7.16 (br d, 1H, J=10.5 Hz), 7.10 (br s, 1H), 5.87 (br d, 1H, J=7.6 Hz), 5.22 (br s, 1H), 4.4-4.6 (m, 4H), 4.13 (br d, 2H, J=10.6 Hz)	508.120
	***	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 9.23 (br s, 1H), 9.11 (br d, 1H, J=5.4 Hz), 7.77 (br s, 1H), 7.60 (br d, 1H, J=3.4 Hz), 7.22 (br d, 1H, J=8.3 Hz), 7.0-7.2 (m, 2H), 6.15 (br d, 1H, J=5.1 Hz), 5.30 (br s, 1H), 4.53 (br d, 2H, J=6.5 Hz), 4.02 (br s, 2H), 3.70 (br s, 3H), 3.09 (br s, 3H)	478.140
	**	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 11.96 (br s, 1H), 11.09 (s, 1H), 9.31 (d, 1H, J=2.1 Hz), 9.05 (d, 1H, J=5.9 Hz), 8.00 (dd, 1H, J=2.5, 5.9 Hz), 7.5-7.6 (m, 4H), 6.46 (d, 1H, J=6.9 Hz), 3.7-3.8 (m, 2H), 2.78 (dt, 1H, J=4.1, 8.3 Hz), 2.7-2.7 (m, 1H), 2.59 (dd, 1H, J=5.3, 9.5 Hz), 2.5-2.5 (m, 1H), 2.46 (br s, 1H), 2.1-2.2 (m, 1H), 1.76 (br dd, 1H, J=6.6, 12.9 Hz)	462.150

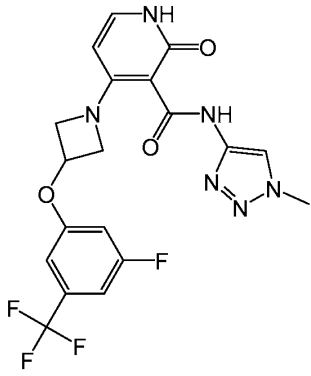
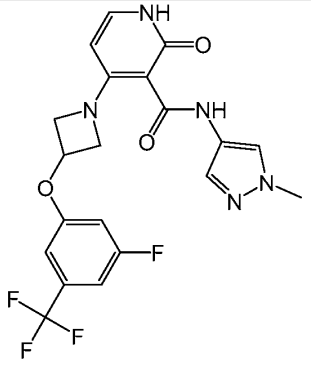
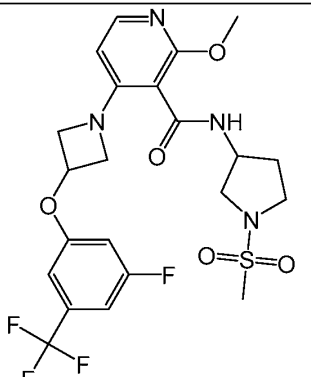
	**	¹H NMR (METHANOL-d₄, 400 MHz) δ 9.32 (d, 1H, J=1.9 Hz), 8.97 (d, 1H, J=5.5 Hz), 8.15 (dd, 1H, J=2.8, 6.0 Hz), 7.30 (d, 1H, J=7.8 Hz), 7.0-7.1 (m, 3H), 6.23 (d, 1H, J=7.6 Hz), 5.2-5.2 (m, 1H), 3.99 (dd, 1H, J=4.3, 12.8 Hz), 3.8-3.8 (m, 1H), 3.6-3.6 (m, 1H), 3.45 (d, 1H, J=12.9 Hz), 2.3-2.3 (m, 2H)	464.130
	****	¹H NMR (DMSO-d₆, 400 MHz) δ 11.03 (br s, 1H), 9.32 (br s, 1H), 9.03 (br d, 1H, J=5.6 Hz), 8.03 (br d, 1H, J=3.0 Hz), 7.2-7.3 (m, 2H), 7.13 (br d, 1H, J=10.6 Hz), 7.04 (s, 1H), 6.50 (br d, 1H, J=8.3 Hz), 6.20 (br d, 1H, J=8.4 Hz), 5.18 (br s, 1H), 4.30 (br t, 2H, J=7.3 Hz), 3.8-3.8 (m, 2H), 3.73 (s, 3H)	463.200
	***	¹H NMR (DMSO-d₆, 400 MHz) Shift 7.95 (d, 1H, J=6.4 Hz), 7.57 (s, 1H), 7.29 (br d, 1H, J=8.4 Hz), 7.1-7.2 (m, 1H), 7.09 (s, 1H), 5.1-5.2 (m, 1H), 4.58 (dd, 2H, J=6.2, 9.3 Hz), 4.33 (sxt, 1H, J=6.3 Hz), 4.12 (dd, 2H, J=3.9, 9.4 Hz), 3.63 (s, 3H), 3.48 (dd, 1H, J=6.7, 10.2 Hz), 3.4-3.4 (m, 1H), 3.27 (dd, 1H, J=2.4, 6.8 Hz), 3.10 (dd, 1H, J=5.3, 10.3 Hz), 2.89 (s, 3H), 2.11 (qd, 1H, J=6.5, 13.2 Hz), 1.8-2.0 (m, 1H)	506.200

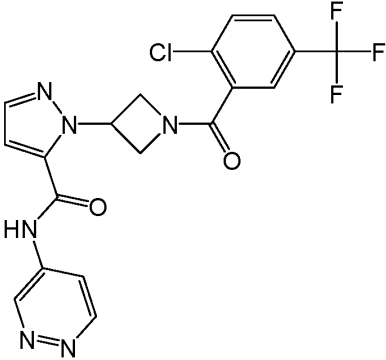
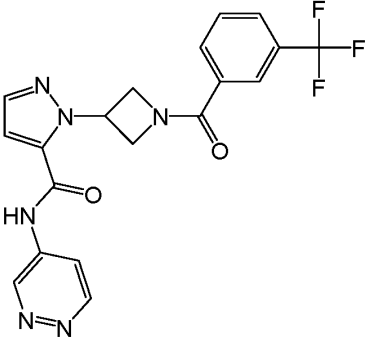
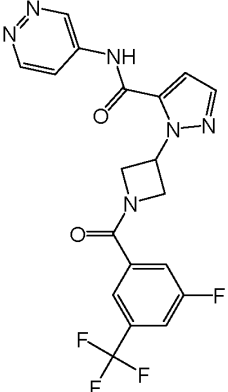
	****	¹H NMR (METHANOL-d₄, 400 MHz) Shift 7.33 (s, 1H), 6.76 (br d, 1H, J=8.4 Hz), 6.68 (s, 1H), 6.62 (br d, 1H, J=10.4 Hz), 4.8-4.9 (m, 1H), 4.6-4.8 (m, 1H), 4.3-4.4 (m, 2H), 3.9-4.0 (m, 2H), 3.6-3.8 (m, 2H), 3.5-3.6 (m, 1H), 3.41 (s, 3H), 3.1-3.3 (m, 1H), 1.76 (d, 3H, J=4.5 Hz)	506.200
	***	¹H NMR (DMSO-d₆, 400 MHz) Shift 7.87 (br d, 1H, J=8.6 Hz), 7.59 (s, 1H), 7.28 (br d, 1H, J=8.5 Hz), 7.1-7.2 (m, 1H), 7.09 (s, 1H), 5.1-5.2 (m, 1H), 4.58 (dd, 2H, J=6.3, 9.0 Hz), 4.4-4.5 (m, 1H), 4.12 (td, 2H, J=4.4, 8.9 Hz), 3.64 (s, 3H), 3.1-3.3 (m, 2H), 2.9-3.0 (m, 1H), 2.7-2.9 (m, 2H)	464.200
	****	¹H NMR (ACETONITRILE-d₃, 400 MHz) δ 9.35 (dd, 1H, J=0.9, 2.6 Hz), 9.25 (br s, 1H), 8.99 (dd, 1H, J=0.8, 5.9 Hz), 8.01 (dd, 1H, J=2.8, 5.9 Hz), 7.48 (s, 1H), 7.3-7.4 (m, 2H), 6.76 (s, 1H), 5.60 (quin, 1H, J=7.0 Hz), 3.78 (s, 2H), 3.7-3.8 (m, 2H), 3.6-3.6 (m, 2H), 2.29 (s, 3H)	435.200

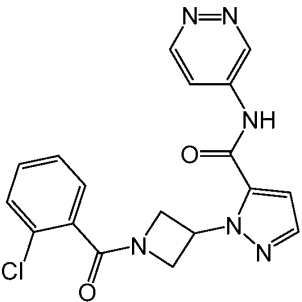
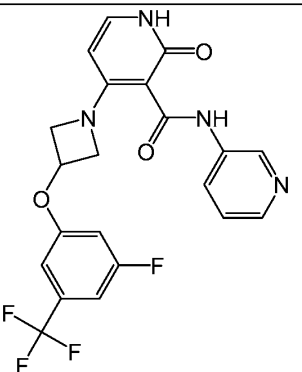
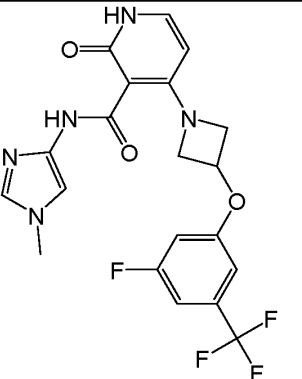
	***	¹ H NMR (DMSO-d ₆ , 400 MHz) Shift 10.91 (s, 1H), 9.39 (d, 1H, J=2.5 Hz), 9.10 (d, 1H, J=5.9 Hz), 7.98 (dd, 1H, J=2.6, 5.9 Hz), 7.4-7.6 (m, 4H), 5.26 (quin, 1H, J=7.1 Hz), 3.79 (s, 2H), 3.73 (t, 2H, J=7.4 Hz), 3.52 (t, 2H, J=7.3 Hz), 2.17 (s, 3H)	435.200
	****	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 11.69 (s, 1H), 11.22 (br s, 1H), 8.38 (br d, 2H, J=4.9 Hz), 7.58 (d, 2H, J=6.0 Hz), 7.29 (br dd, 2H, J=8.0, 13.5 Hz), 7.15 (br d, 1H, J=10.5 Hz), 7.09 (s, 1H), 5.76 (d, 1H, J=7.5 Hz), 5.20 (td, 1H, J=3.0, 6.1 Hz), 4.52 (br dd, 2H, J=6.3, 10.3 Hz), 4.11 (dd, 2H, J=2.4, 10.8 Hz)	449.116
	**	¹ H NMR (CHLOROFORM-d, 400 MHz) δ 9.18 (d, 1H, J=2.0 Hz), 9.00 (d, 1H, J=5.9 Hz), 8.76 (br s, 1H), 8.2-8.3 (m, 2H), 7.46 (s, 1H), 7.37 (br d, 1H, J=8.5 Hz), 7.24 (br d, 2H, J=5.5 Hz), 4.00 (s, 3H), 3.8-3.9 (m, 1H), 3.7-3.8 (m, 2H), 3.03 (br s, 1H), 2.8-3.0 (m, 2H), 2.65 (br d, 1H, J=8.4 Hz), 2.4-2.5 (m, 1H), 1.95 (br d, 1H, J=5.8 Hz)	476.163

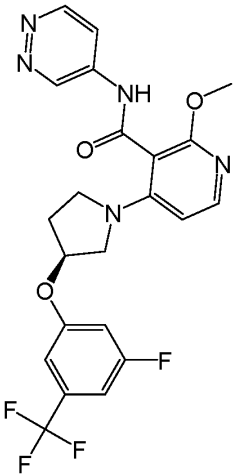
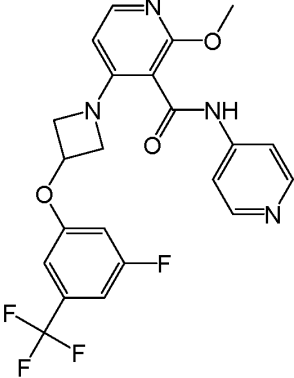
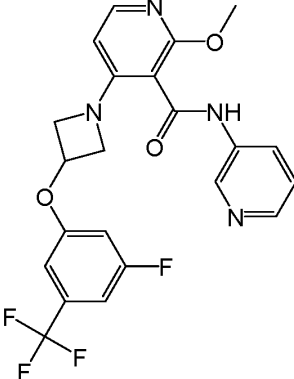
	**	¹ H NMR (CHLOROFORM-d, 400 MHz) δ 9.1-9.3 (m, 2H), 9.05 (d, 1H, J=5.9 Hz), 8.17 (dd, 1H, J=2.4, 5.6 Hz), 7.93 (s, 1H), 7.40 (br s, 1H), 7.25 (br s, 1H), 4.22 (br dd, 1H, J=6.5, 7.7 Hz), 4.08 (br d, 1H, J=11.6 Hz), 3.99 (s, 3H), 3.6-3.8 (m, 1H), 3.28 (br d, 1H, J=4.6 Hz), 2.79 (br s, 3H), 2.3-2.5 (m, 1H), 2.1-2.3 (m, 1H)	449.163
	***	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 8.8-8.9 (m, 1H), 7.81 (br d, 1H, J=5.8 Hz), 7.29 (br d, 1H, J=8.3 Hz), 7.14 (br d, 1H, J=10.4 Hz), 7.06 (br s, 1H), 6.17 (br d, 1H, J=5.8 Hz), 5.28 (br s, 1H), 4.8-5.0 (m, 1H), 4.4-4.5 (m, 2H), 3.9-4.1 (m, 4H), 3.78 (s, 3H), 3.7-3.8 (m, 1H), 3.26 (br dd, 1H, J=8.0, 10.9 Hz), 1.94 (br d, 3H, J=7.6 Hz)	533.150
	**	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 8.52 (br d, 1H, J=8.6 Hz), 7.79 (br d, 1H, J=5.9 Hz), 7.28 (br d, 1H, J=8.4 Hz), 7.13 (br d, 1H, J=10.5 Hz), 7.05 (br s, 1H), 6.15 (br d, 1H, J=5.9 Hz), 5.26 (br s, 1H), 4.5-4.6 (m, 1H), 4.43 (br t, 2H, J=7.3 Hz), 3.9-4.0 (m, 2H), 3.76 (s, 3H), 3.1-3.3 (m, 2H), 2.8-3.0 (m, 2H), 2.69 (br t, 1H, J=9.9 Hz)	491.140

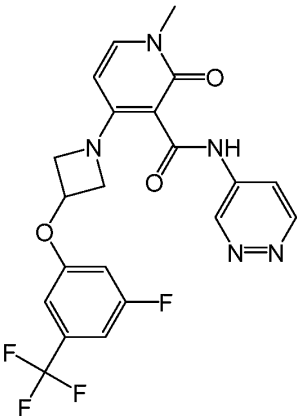
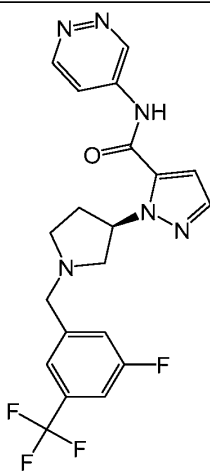
	***	¹H NMR (CHLOROFORM-d, 400 MHz) δ 9.86 (s, 1H), 9.32 (d, 1H, J=2.5 Hz), 8.99 (d, 1H, J=6.0 Hz), 8.29 (dd, 1H, J=2.7, 5.9 Hz), 7.59 (d, 1H, J=1.9 Hz), 7.41 (s, 1H), 7.29 (br d, 1H, J=9.3 Hz), 7.20 (br d, 1H, J=8.3 Hz), 6.97 (d, 1H, J=2.0 Hz), 5.72 (quin, 1H, J=7.1 Hz), 3.96 (t, 1H, J=7.1 Hz), 3.72 (t, 1H, J=7.2 Hz), 3.65 (br t, 1H, J=7.1 Hz), 3.56 (q, 1H, J=6.4 Hz), 3.47 (t, 1H, J=7.2 Hz), 1.27 (d, 3H, J=6.5 Hz)	435.150
	****	¹H NMR (CHLOROFORM-d, 400 MHz) δ 12.1-12.2 (m, 1H), 11.47 (br d, 1H, J=2.3 Hz), 8.4-8.5 (m, 1H), 8.35 (br d, 1H, J=4.4 Hz), 7.7-7.8 (m, 1H), 7.5-7.5 (m, 1H), 7.0-7.1 (m, 2H), 6.82 (s, 1H), 6.6-6.7 (m, 1H), 5.7-5.8 (m, 1H), 5.0-5.1 (m, 1H), 4.6-4.7 (m, 2H), 4.2-4.4 (m, 2H)	449.116
	***	¹H NMR (CHLOROFORM-d, 400 MHz) δ 12.28 (br d, 1H, J=1.0 Hz), 9.3-9.4 (m, 1H), 9.27 (s, 2H), 8.97 (s, 1H), 7.2-7.2 (m, 1H), 7.02 (br d, 1H, J=8.9 Hz), 6.83 (s, 1H), 6.67 (br d, 1H, J=10.3 Hz), 5.76 (d, 1H, J=7.6 Hz), 5.06 (br dd, 1H, J=3.8, 6.0 Hz), 4.6-4.9 (m, 2H), 4.2-4.4 (m, 2H)	450.111

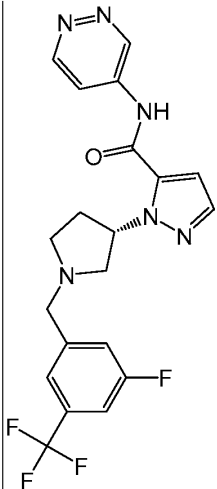
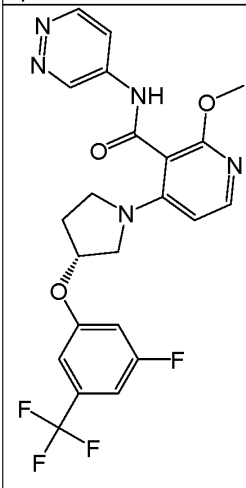
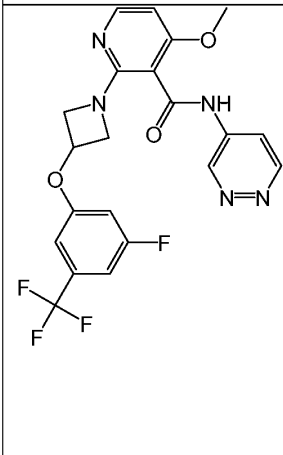
	***	¹ H NMR (CHLOROFORM-d, 400 MHz) δ 12.08 (br s, 1H), 11.6-11.7 (m, 1H), 8.12 (s, 1H), 7.46 (br d, 1H, J=5.5 Hz), 7.0-7.0 (m, 1H), 6.82 (s, 1H), 6.66 (br d, 1H, J=10.0 Hz), 5.79 (d, 1H, J=7.5 Hz), 5.0-5.1 (m, 1H), 4.66 (br dd, 2H, J=6.2, 10.2 Hz), 4.2-4.4 (m, 2H), 4.11 (s, 3H)	453.122
	*****	¹ H NMR (CHLOROFORM-d, 400 MHz) δ 11.3-11.5 (m, 1H), 10.0-10.2 (m, 1H), 8.11 (s, 1H), 7.85 (br s, 1H), 7.2-7.2 (m, 1H), 7.0-7.0 (m, 1H), 6.82 (s, 1H), 6.6-6.7 (m, 1H), 5.74 (d, 1H, J=7.5 Hz), 5.02 (br t, 1H, J=3.3 Hz), 4.67 (br dd, 2H, J=4.1, 7.9 Hz), 4.29 (br d, 2H, J=9.0 Hz), 3.99 (s, 3H)	452.127
	***	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 8.58 (br d, 1H, J=6.3 Hz), 7.78 (br d, 1H, J=5.8 Hz), 7.29 (br d, 1H, J=8.3 Hz), 7.17 (br d, 1H, J=10.5 Hz), 7.10 (br s, 1H), 6.14 (br d, 1H, J=5.8 Hz), 5.25 (br s, 1H), 4.44 (br t, 2H, J=7.4 Hz), 4.3-4.4 (m, 1H), 3.92 (br d, 2H, J=8.8 Hz), 3.76 (s, 3H), 3.5-3.5 (m, 1H), 3.3-3.4 (m, 1H), 3.2-3.3 (m, 1H), 3.12 (br dd, 1H, J=4.2, 9.9 Hz), 2.89 (s, 3H), 2.12 (qd, 1H, J=6.6, 12.8 Hz), 1.8-1.9 (m, 1H)	533.140

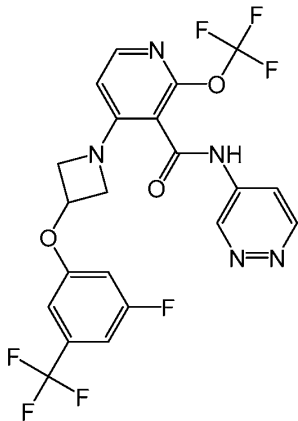
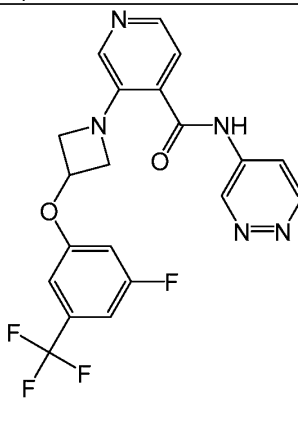
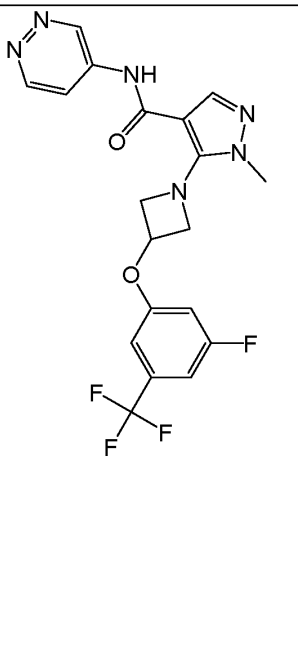
	*	¹H NMR (CHLOROFORM-d, 400 MHz) δ 10.06 (br s, 1H), 9.41 (d, 1H, J=2.6 Hz), 9.03 (d, 1H, J=6.0 Hz), 8.23 (dd, 1H, J=2.7, 5.9 Hz), 7.69 (d, 1H, J=1.6 Hz), 7.6-7.7 (m, 1H), 7.5-7.6 (m, 2H), 7.04 (d, 1H, J=2.0 Hz), 5.9-6.1 (m, 1H), 4.68 (d, 2H, J=6.8 Hz), 4.57 (dd, 1H, J=5.4, 9.5 Hz), 4.4-4.5 (m, 1H)	451.080
	*	¹H NMR (CHLOROFORM-d, 400 MHz) δ 10.60 (br s, 1H), 9.43 (d, 1H, J=2.3 Hz), 8.98 (d, 1H, J=5.9 Hz), 8.24 (dd, 1H, J=2.6, 5.9 Hz), 7.91 (s, 1H), 7.84 (br d, 1H, J=7.8 Hz), 7.74 (br d, 1H, J=7.8 Hz), 7.5-7.6 (m, 2H), 7.06 (d, 1H, J=1.9 Hz), 6.03 (quin, 1H, J=6.7 Hz), 4.7-4.9 (m, 2H), 4.6-4.7 (m, 2H)	417.120
	*	¹H NMR (CHLOROFORM-d, 400 MHz) δ 10.53 (br s, 1H), 9.42 (br s, 1H), 9.00 (br d, 1H, J=5.8 Hz), 8.27 (br d, 1H, J=3.5 Hz), 7.72 (s, 1H), 7.5-7.6 (m, 2H), 7.46 (br d, 1H, J=7.8 Hz), 7.06 (s, 1H), 6.05 (quin, 1H, J=6.5 Hz), 4.6-5.0 (m, 4H)	435.110

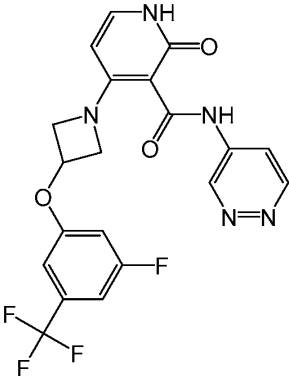
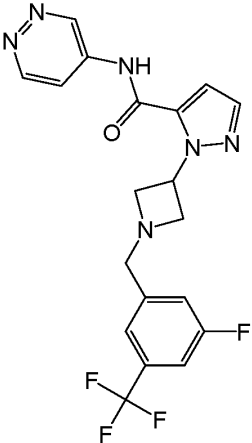
	**	¹H NMR (CHLOROFORM-d, 400 MHz) δ 10.53 (br s, 1H), 9.44 (br s, 1H), 8.98 (br s, 1H), 8.19 (br s, 1H), 7.52 (d, 1H, J=1.8 Hz), 7.3-7.4 (m, 4H), 7.03 (d, 1H, J=1.9 Hz), 5.98 (quin, 1H, J=6.7 Hz), 4.63 (br d, 2H, J=6.6 Hz), 4.53 (dd, 1H, J=5.4, 9.6 Hz), 4.4-4.5 (m, 1H)	383.090
	*****	¹H NMR (DMSO-d₆, 400 MHz) δ 11.45 (s, 1H), 11.17 (br s, 1H), 8.75 (d, 1H, J=2.3 Hz), 8.23 (dd, 1H, J=1.4, 4.7 Hz), 8.0-8.1 (m, 1H), 7.2-7.4 (m, 3H), 7.0-7.2 (m, 2H), 5.75 (d, 1H, J=7.4 Hz), 5.20 (tt, 1H, J=3.2, 6.2 Hz), 4.52 (br dd, 2H, J=7.0, 10.4 Hz), 4.10 (dd, 2H, J=2.3, 10.8 Hz)	449.120
	*****	¹H NMR (DMSO-d₆, 400 MHz) δ 11.64 (s, 1H), 10.9-11.4 (m, 1H), 7.0-7.5 (m, 6H), 5.76 (d, 1H, J=7.5 Hz), 5.1-5.3 (m, 1H), 4.48 (br s, 2H), 4.0-4.3 (m, 2H), 3.60 (s, 3H)	452.130

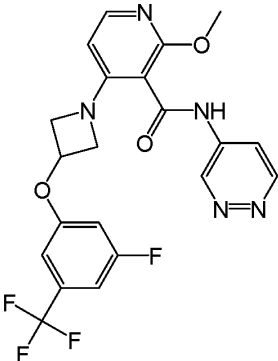
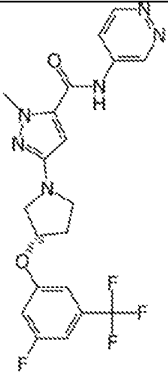
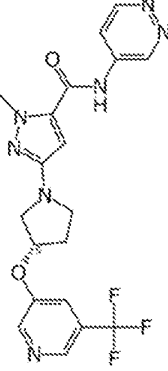
 or an enantiomer	**	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 11.07 (s, 1H), 9.28 (d, 1H, J=2.1 Hz), 9.04 (d, 1H, J=5.9 Hz), 7.97 (dd, 1H, J=2.8, 5.9 Hz), 7.85 (d, 1H, J=6.1 Hz), 7.1-7.2 (m, 2H), 7.08 (s, 1H), 6.45 (d, 1H, J=6.3 Hz), 5.25 (br s, 1H), 3.78 (s, 3H), 3.74 (dd, 1H, J=4.2, 11.7 Hz), 3.4-3.5 (m, 3H), 2.1-2.3 (m, 2H)	478.140
	****	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 10.79 (s, 1H), 8.4-8.5 (m, 2H), 7.86 (d, 1H, J=6.0 Hz), 7.6-7.7 (m, 2H), 7.27 (br d, 1H, J=8.6 Hz), 7.14 (br d, 1H, J=10.6 Hz), 7.06 (s, 1H), 6.23 (d, 1H, J=5.9 Hz), 5.2-5.3 (m, 1H), 4.4-4.5 (m, 2H), 3.91 (dd, 2H, J=3.3, 9.6 Hz), 3.80 (s, 3H)	463.130
	****	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 10.63 (s, 1H), 8.81 (d, 1H, J=2.4 Hz), 8.29 (dd, 1H, J=1.4, 4.6 Hz), 8.12 (td, 1H, J=1.8, 8.5 Hz), 7.85 (d, 1H, J=5.9 Hz), 7.36 (dd, 1H, J=4.7, 8.3 Hz), 7.27 (br d, 1H, J=8.4 Hz), 7.1-7.2 (m, 1H), 7.06 (s, 1H), 6.22 (d, 1H, J=6.0 Hz), 5.2-5.3 (m, 1H), 4.45 (dd, 2H, J=6.4, 9.4 Hz), 3.93 (dd, 2H, J=3.3, 9.5 Hz), 3.80 (s, 3H)	463.130

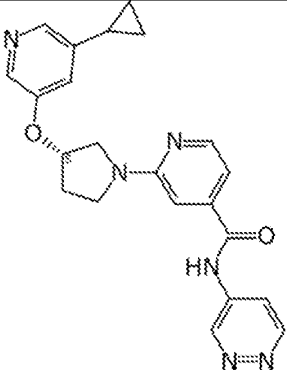
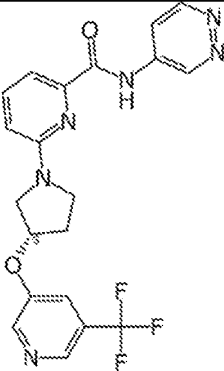
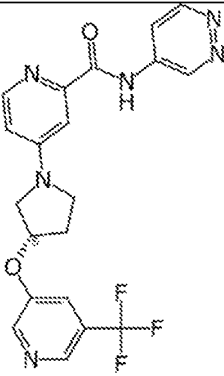
	****	1H NMR (DMSO-d₆, 400 MHz) δ 11.74 (s, 1H), 9.33 (d, 1H, J=2.0 Hz), 8.98 (d, 1H, J=5.9 Hz), 8.00 (dd, 1H, J=2.6, 5.9 Hz), 7.65 (d, 1H, J=7.6 Hz), 7.28 (br d, 1H, J=8.5 Hz), 7.1-7.2 (m, 1H), 7.09 (s, 1H), 5.84 (d, 1H, J=7.8 Hz), 5.20 (tt, 1H, J=3.3, 6.2 Hz), 4.51 (br dd, 2H, J=6.1, 10.5 Hz), 4.09 (dd, 2H, J=2.3, 10.9 Hz), 3.38 (s, 3H) 1H NMR (DMSO-d₆, 400 MHz) δ 11.74 (s, 1H), 9.33 (d, 1H, J=1.8 Hz), 8.98 (d, 1H, J=5.8 Hz), 8.00 (dd, 1H, J=2.4, 5.6 Hz), 7.65 (d, 1H, J=7.6 Hz), 7.28 (br d, 1H, J=8.3 Hz), 7.15 (br d, 1H, J=10.5 Hz), 7.09 (s, 1H), 5.84 (d, 1H, J=7.8 Hz), 5.20 (br s, 1H), 4.51 (br s, 2H), 4.09 (br d, 2H, J=8.9 Hz), 3.38 (s, 3H)	464.130
 or an enantiomer	***	1H NMR (DMSO-d₆, 400 MHz) δ 10.82 (br s, 1H), 9.48 (br s, 1H), 9.08 (br d, 1H, J=5.6 Hz), 8.05 (br d, 1H, J=3.3 Hz), 7.66 (s, 1H), 7.56 (br s, 1H), 7.50 (br d, 2H, J=9.0 Hz), 7.13 (s, 1H), 5.70 (br s, 1H), 3.7-3.8 (m, 2H), 3.09 (br t, 1H, J=8.4 Hz), 2.7-2.8 (m, 3H), 2.2-2.4 (m, 2H)	435.150

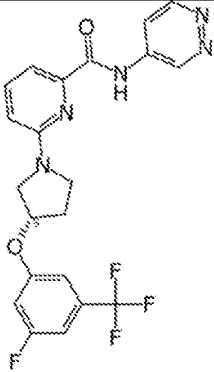
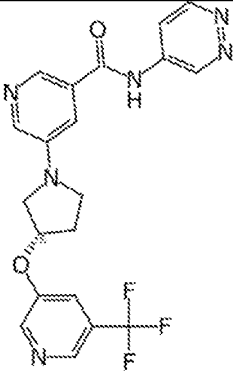
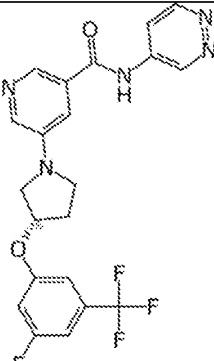
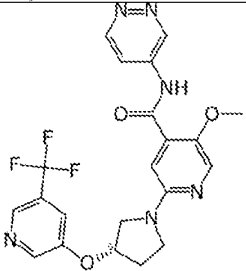
	***	¹H NMR (DMSO-d₆, 400 MHz) δ 10.78 (br s, 1H), 9.46 (d, 1H, J=2.3 Hz), 9.08 (d, 1H, J=5.9 Hz), 8.03 (dd, 1H, J=2.6, 5.9 Hz), 7.66 (d, 1H, J=1.9 Hz), 7.5-7.6 (m, 3H), 7.10 (d, 1H, J=2.0 Hz), 5.6-5.8 (m, 1H), 3.7-3.8 (m, 2H), 3.09 (t, 1H, J=8.5 Hz), 2.7-2.8 (m, 3H), 2.2-2.4 (m, 2H)	435.150
	**	¹H NMR (DMSO-d₆, 400 MHz) δ 11.06 (s, 1H), 9.28 (d, 1H, J=2.5 Hz), 9.04 (d, 1H, J=5.8 Hz), 7.96 (dd, 1H, J=2.6, 5.9 Hz), 7.85 (d, 1H, J=6.1 Hz), 7.1-7.2 (m, 2H), 7.08 (s, 1H), 6.45 (d, 1H, J=6.1 Hz), 5.2-5.2 (m, 1H), 5.2-5.2 (m, 1H), 5.25 (br s, 1H), 3.78 (s, 3H), 3.74 (dd, 1H, J=4.2, 11.7 Hz), 3.51 (br dd, 2H, J=4.6, 9.2 Hz), 3.46 (br d, 1H, J=11.8 Hz), 2.1-2.3 (m, 2H)	478.140
	****	¹H NMR (DMSO-d₆, 400 MHz) δ 11.08 (s, 1H), 9.32 (d, 1H, J=1.8 Hz), 9.06 (d, 1H, J=5.9 Hz), 8.13 (d, 1H, J=5.9 Hz), 8.02 (dd, 1H, J=2.6, 5.9 Hz), 7.24 (br d, 1H, J=8.5 Hz), 7.12 (br d, 1H, J=10.6 Hz), 7.04 (s, 1H), 6.62 (d, 1H, J=5.9 Hz), 5.1-5.2 (m, 1H), 4.41 (dd, 2H, J=6.3, 9.4 Hz), 3.88 (dd, 2H, J=3.6, 9.6 Hz), 3.82 (s, 3H)	464.130

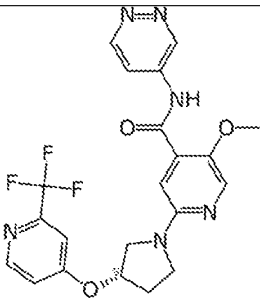
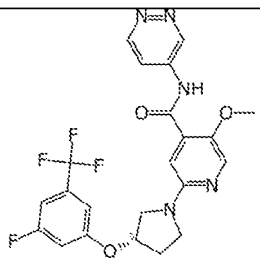
	****	¹H NMR (DMSO-d₆, 400 MHz) δ 11.3-11.4 (m, 1H), 9.32 (br s, 1H), 9.11 (br d, 1H, J=5.9 Hz), 8.01 (dd, 1H, J=2.5, 5.6 Hz), 7.98 (d, 1H, J=5.9 Hz), 7.28 (br d, 1H, J=8.6 Hz), 7.15 (br d, 1H, J=10.5 Hz), 7.07 (s, 1H), 6.56 (d, 1H, J=5.9 Hz), 5.25 (tt, 1H, J=3.2, 6.3 Hz), 4.53 (dd, 2H, J=6.6, 9.6 Hz), 4.01 (dd, 2H, J=3.3, 10.0 Hz)	518.100
	****	¹H NMR (DMSO-d₆, 400 MHz) δ 10.8-11.5 (m, 1H), 9.38 (d, 1H, J=2.0 Hz), 9.08 (d, 1H, J=5.9 Hz), 8.0-8.1 (m, 2H), 8.03 (dd, 1H, J=2.6, 5.9 Hz), 7.37 (d, 1H, J=4.9 Hz), 7.26 (br d, 1H, J=8.5 Hz), 7.15 (br d, 1H, J=10.6 Hz), 7.08 (s, 1H), 5.26 (td, 1H, J=2.8, 6.0 Hz), 4.41 (dd, 2H, J=6.3, 9.1 Hz), 3.92 (dd, 2H, J=3.3, 9.3 Hz)	434.120
	****	¹H NMR (CHLOROFORM-d, 400 MHz) δ 9.25 (d, 1H, J=2.6 Hz), 9.0-9.1 (m, 1H), 8.3-8.4 (m, 1H), 8.16 (dd, 1H, J=2.8, 5.9 Hz), 7.7-7.8 (m, 1H), 7.00 (br d, 1H, J=8.3 Hz), 6.85 (s, 1H), 6.6-6.7 (m, 1H), 5.1-5.1 (m, 1H), 4.72 (dd, 2H, J=6.5, 9.0 Hz), 4.31 (dd, 2H, J=4.3, 9.3 Hz), 3.82 (s, 3H) ¹H NMR (CHLOROFORM-d, 400 MHz) δ 9.59 (br d, 1H, J=1.9 Hz), 9.4-9.5 (m, 1H), 9.01 (d, 1H, J=6.3 Hz), 8.4-8.5 (m, 1H), 7.98 (s, 1H), 7.0-7.0 (m, 1H),	437.130

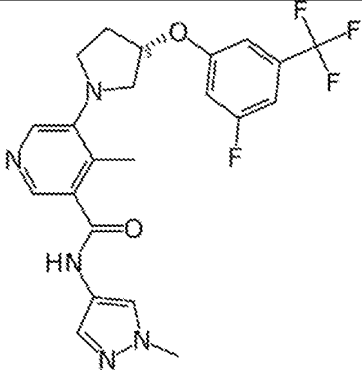
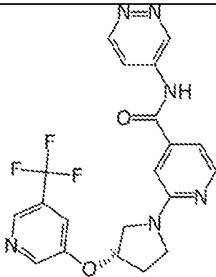
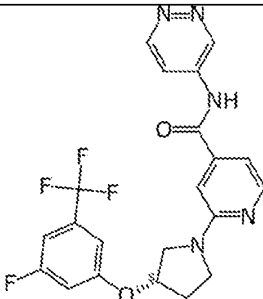
		6.85 (s, 1H), 6.69 (br d, 1H, J=9.8 Hz), 5.1-5.1 (m, 1H), 4.73 (dd, 2H, J=6.4, 8.7 Hz), 4.3-4.4 (m, 2H), 3.81 (s, 3H)	
	****	1H NMR (DMSO-d₆, 400 MHz) δ 11.98 (s, 1H), 11.2-11.3 (m, 1H), 9.31 (d, 1H, J=2.0 Hz), 8.97 (d, 1H, J=5.9 Hz), 7.99 (dd, 1H, J=2.7, 5.9 Hz), 7.3-7.4 (m, 2H), 7.1-7.2 (m, 2H), 5.79 (d, 1H, J=7.5 Hz), 5.20 (br s, 1H), 4.5-4.6 (m, 2H), 4.13 (br dd, 2H, J=2.3, 11.1 Hz)	450.111
	****	1H NMR (CHLOROFORM-d, 400 MHz) δ 9.32 (br s, 1H), 9.07 (d, 1H, J=5.8 Hz), 8.17 (dd, 1H, J=2.8, 5.9 Hz), 7.62 (s, 1H), 7.47 (br s, 1H), 7.3-7.4 (m, 1H), 7.2-7.3 (m, 1H), 6.96 (br s, 1H), 5.8-6.0 (m, 1H), 4.0-4.1 (m, 2H), 3.9-4.0 (m, 2H), 3.8-3.9 (m, 2H) 1H NMR (CHLOROFORM-d, 400 MHz) δ 9.30 (d, 1H, J=2.3 Hz), 9.13 (br s, 1H), 9.04 (d, 1H, J=5.9 Hz), 8.23 (dd, 1H, J=2.8, 5.9 Hz), 7.63 (d, 1H, J=2.0 Hz), 7.41 (s, 1H), 7.29 (br d, 1H, J=9.2 Hz), 7.23 (br d, 1H, J=8.3 Hz), 6.95 (d, 1H, J=2.0 Hz), 5.81 (quin, 1H, J=6.9 Hz), 3.94 (br t, 2H, J=7.7 Hz), 3.85 (s, 2H), 3.74 (t, 2H, J=7.5 Hz)	421.130

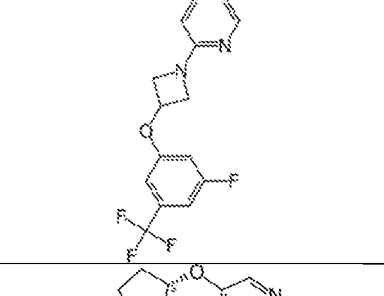
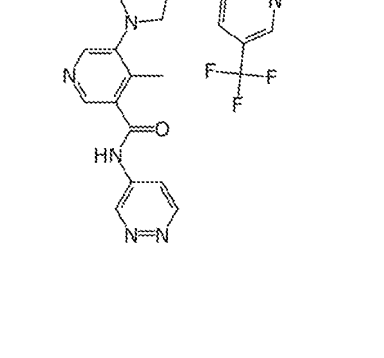
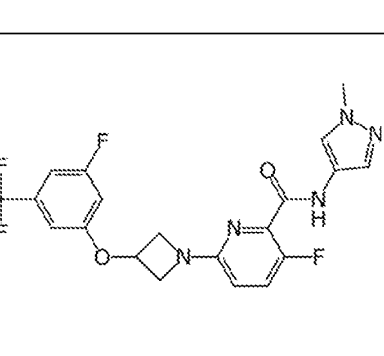
	****	¹H NMR (DMSO-d₆, 400 MHz) δ 11.08 (s, 1H), 9.33 (d, 1H, J=2.0 Hz), 9.06 (d, 1H, J=5.8 Hz), 8.02 (dd, 1H, J=2.8, 5.9 Hz), 7.87 (d, 1H, J=5.9 Hz), 7.27 (br d, 1H, J=8.5 Hz), 7.14 (br d, 1H, J=10.6 Hz), 7.06 (s, 1H), 6.25 (d, 1H, J=6.0 Hz), 5.2-5.3 (m, 1H), 4.44 (dd, 2H, J=6.4, 9.4 Hz), 3.91 (dd, 2H, J=3.3, 9.5 Hz), 3.81 (s, 3H)	464.130
	***	¹H NMR (DMSO-d₆, 400 MHz) δ 10.59 (s, 1H), 9.47 (dd, 1H, J=0.9, 2.7 Hz), 9.07 (dd, 1H, J=0.9, 5.9 Hz), 8.04 (dd, 1H, J=2.8, 5.9 Hz), 7.2-7.3 (m, 2H), 7.15 (s, 1H), 6.41 (s, 1H), 5.28 (br t, 1H, J=4.9 Hz), 3.93 (s, 3H), 3.66 (dd, 1H, J=4.8, 11.3 Hz), 3.3-3.4 (m, 3H), 2.3-2.4 (m, 1H), 2.15 (br dd, 1H, J=6.1, 7.2 Hz)	451.14
	***	¹H NMR (DMSO-d₆, 400 MHz) δ 10.60 (s, 1H), 9.47 (dd, 1H, J=0.8, 2.7 Hz), 9.07 (dd, 1H, J=0.8, 6.0 Hz), 8.5-8.7 (m, 2H), 8.04 (dd, 1H, J=2.7, 5.9 Hz), 7.83 (s, 1H), 6.42 (s, 1H), 5.38 (br t, 1H, J=4.9 Hz), 3.93 (s, 3H), 3.67 (dd, 1H, J=4.8, 11.3 Hz), 3.4-3.4 (m, 3H), 2.3-2.4 (m, 1H), 2.1-2.2 (m, 1H)	434.15

	***	¹ H NMR (CHLOROFORM-d, 400 MHz) δ 9.3-9.3 (m, 1H), 9.14 (br s, 1H), 9.08 (d, 1H, J=5.9 Hz), 8.31 (d, 1H, J=5.3 Hz), 8.25 (dd, 1H, J=2.8, 6.0 Hz), 8.06 (d, 1H, J=1.8 Hz), 8.01 (d, 1H, J=2.6 Hz), 6.93 (dd, 1H, J=1.3, 5.3 Hz), 6.87 (s, 1H), 6.83 (t, 1H, J=2.2 Hz), 5.08 (br d, 1H, J=2.4 Hz), 3.6-3.8 (m, 4H), 2.2-2.5 (m, 2H), 1.8-1.9 (m, 1H), 1.0-1.1 (m, 2H), 0.7-0.8 (m, 2H)	403.18
	***	¹ H NMR (CHLOROFORM-d, 400 MHz) δ 10.12 (s, 1H), 9.24 (d, 1H, J=2.6 Hz), 9.10 (d, 1H, J=5.9 Hz), 8.5-8.6 (m, 2H), 8.24 (dd, 1H, J=2.8, 5.9 Hz), 7.7-7.8 (m, 1H), 7.61 (d, 1H, J=7.3 Hz), 7.45 (s, 1H), 6.69 (d, 1H, J=8.4 Hz), 5.26 (br s, 1H), 3.7-4.0 (m, 4H), 2.3-2.6 (m, 2H)	431.14
	****	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 11.19 (br s, 1H), 9.70 (d, 1H, J=1.9 Hz), 9.08 (d, 1H, J=5.8 Hz), 8.5-8.7 (m, 2H), 8.29 (d, 1H, J=5.8 Hz), 8.22 (dd, 1H, J=2.5, 5.9 Hz), 7.87 (br s, 1H), 7.28 (d, 1H, J=1.8 Hz), 6.79 (dd, 1H, J=2.1, 5.6 Hz), 5.48 (br s, 1H), 3.82 (br dd, 1H, J=4.1, 11.7 Hz), 3.5-3.6 (m, 3H), 2.2-2.4 (m, 2H)	431.14

	***	¹ H NMR (CHLOROFORM-d, 400 MHz) δ 10.32 (br s, 1H), 9.32 (s, 1H), 9.12 (d, 1H, J=5.9 Hz), 8.37 (br d, 1H, J=4.0 Hz), 7.7-7.8 (m, 1H), 7.59 (d, 1H, J=7.3 Hz), 6.9-7.0 (m, 2H), 6.84 (br d, 1H, J=9.9 Hz), 6.69 (d, 1H, J=8.4 Hz), 5.17 (br s, 1H), 3.7-4.0 (m, 4H), 2.3-2.5 (m, 2H)	448.13
	****	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 10.8-11.0 (m, 1H), 9.5-9.5 (m, 1H), 9.1-9.1 (m, 1H), 8.63 (d, 1H, J=2.6 Hz), 8.58 (s, 1H), 8.41 (d, 1H, J=1.8 Hz), 8.21 (d, 1H, J=2.9 Hz), 8.1-8.1 (m, 1H), 7.85 (s, 1H), 7.3-7.4 (m, 1H), 5.49 (br s, 1H), 3.8-3.8 (m, 1H), 3.5-3.6 (m, 3H), 2.3-2.4 (m, 1H), 2.2-2.3 (m, 1H)	448.13
	****	¹ H NMR (DMSO-d ₆ , 400 MHz) δ 10.87 (br s, 1H), 9.5-9.5 (m, 1H), 9.0-9.2 (m, 1H), 8.41 (d, 1H, J=1.3 Hz), 8.20 (d, 1H, J=2.6 Hz), 8.0-8.1 (m, 1H), 7.4-7.4 (m, 1H), 7.2-7.3 (m, 2H), 7.18 (s, 1H), 5.40 (br s, 1H), 3.7-3.8 (m, 1H), 3.5-3.6 (m, 3H), 2.2-2.4 (m, 2H)	448.13
	****	¹ H NMR (400 MHz, METHANOL-d ₄) δ = 9.42 - 9.39 (m, 1H), 9.06 (d, J = 6.1 Hz, 1H), 8.53 (d, J = 2.4 Hz, 1H), 8.48 (s, 1H), 8.24 (dd, J = 2.8, 6.1 Hz, 1H), 8.04 (s, 1H), 7.74 (s, 1H), 6.94 (s, 1H), 5.37 (br t, J = 4.5 Hz, 1H), 4.59 (s, 2H), 3.98 (s, 3H), 3.89 -	461.15

		3.74 (m, 2H), 3.72 - 3.58 (m, 2H)	
	***	¹H NMR (400 MHz, DMSO-d₆) δ = 10.92 (s, 1H), 9.38 (d, J = 2.0 Hz, 1H), 9.09 (d, J = 5.9 Hz, 1H), 8.58 (d, J = 5.7 Hz, 1H), 8.08 (s, 1H), 8.04 (dd, J = 2.7, 5.9 Hz, 1H), 7.46 (d, J = 2.2 Hz, 1H), 7.33 (dd, J = 2.4, 5.6 Hz, 1H), 6.72 (s, 1H), 5.44 (br s, 1H), 3.83 (s, 3H), 3.81 - 3.74 (m, 1H), 3.67 - 3.56 (m, 2H), 3.52 - 3.46 (m, 1H), 2.45 - 2.31 (m, 1H), 2.28 - 2.19 (m, 1H)	430.14
	****	¹H NMR (400 MHz, DMSO-d₆) δ = 12.89 (br s, 1H), 9.67 (d, J = 2.5 Hz, 1H), 9.42 (d, J = 6.5 Hz, 1H), 8.61 (dd, J = 2.6, 6.5 Hz, 1H), 7.75 (s, 1H), 7.41 (s, 1H), 7.30 (br d, J = 10.8 Hz, 1H), 7.25 (br d, J = 8.5 Hz, 1H), 7.19 (s, 1H), 5.45 (br s, 1H), 4.00 - 3.92 (m, 1H), 3.86 (s, 4H), 3.84 - 3.81 (m, 1H), 3.75 - 3.65 (m, 1H), 2.46 - 2.27 (m, 2H)	478.14

	***	¹H NMR (400 MHz, DMSO-d₆) δ = 11.21 (s, 1H), 8.44 (s, 1H), 8.27 (s, 1H), 8.04 (s, 1H), 7.57 (s, 1H), 7.27 (br d, J = 10.8 Hz, 1H), 7.21 (br d, J = 8.4 Hz, 1H), 7.15 (s, 1H), 5.32 (br s, 1H), 3.96 (br dd, J = 4.4, 11.3 Hz, 1H), 3.83 (s, 3H), 3.74 - 3.64 (m, 1H), 3.56 - 3.43 (m, 2H), 2.55 - 2.50 (m, 3H), 2.40 - 2.26 (m, 1H), 2.18 (br s, 1H)	464.17
	****	¹H NMR (400 MHz, CHLOROFORM-d) δ = 9.39 - 9.36 (m, 1H), 9.10 (d, J = 5.9 Hz, 1H), 8.68 (br s, 1H), 8.53 (s, 1H), 8.49 (d, J = 2.7 Hz, 1H), 8.36 - 8.32 (m, 1H), 8.27 (dd, J = 2.8, 5.9 Hz, 1H), 7.41 (s, 1H), 6.98 - 6.93 (m, 2H), 5.23 - 5.15 (m, 1H), 3.92 (d, J = 2.8 Hz, 2H), 3.84 - 3.67 (m, 2H), 2.51 - 2.33 (m, 2H)	431.14
	****	¹H NMR (400 MHz, DMSO-d₆) δ = 9.49 (d, J = 1.9 Hz, 1H), 9.11 (d, J = 5.9 Hz, 1H), 8.27 (d, J = 5.1 Hz, 1H), 8.08 (dd, J = 2.6, 5.9 Hz, 1H), 7.33 - 7.22 (m, 2H), 7.18 (s, 1H), 7.03 (d, J = 5.1 Hz, 1H), 6.94 (s, 1H), 5.37 (br s, 1H), 3.85 - 3.79 (m, 1H), 3.74 - 3.66 (m, 2H), 3.60 - 3.52 (m, 2H), 2.41 - 2.22 (m, 2H)	448.14

	****	¹H NMR (CHLOROFORM-d, 400 MHz) δ 9.69 (br s, 1H), 8.06 (br d, 2H, J=6.5 Hz), 7.49 (br s, 1H), 7.20 (br s, 1H), 6.98 (br d, 1H, J=7.6 Hz), 6.84 (br s, 1H), 6.69 (br d, 1H, J=9.5 Hz), 5.10 (br s, 1H), 4.49 (br t, 2H, J=6.8 Hz), 4.0-4.1 (m, 5H), 3.91 (br s, 3H)	466.14
	****	¹H NMR (DMSO-d₆, 400 MHz) δ 11.31 (s, 1H), 9.40 (d, 1H, J=2.5 Hz), 9.16 (d, 1H, J=6.0 Hz), 8.5-8.7 (m, 2H), 8.36 (d, 2H, J=15.1 Hz), 8.14 (dd, 1H, J=2.6, 6.0 Hz), 7.83 (s, 1H), 5.39 (br s, 1H), 3.86 (dd, 1H, J=4.9, 11.1 Hz), 3.61 (q, 1H, J=8.4 Hz), 3.43 (br s, 1H), 3.3-3.3 (m, 1H), 2.3-2.5 (m, 4H), 2.1-2.2 (m, 1H).	445.15
	****	¹H NMR (DMSO-d₆, 400 MHz) δ 10.29 (s, 1H), 8.03 (s, 1H), 7.66 (t, 1H, J=9.6 Hz), 7.59 (s, 1H), 7.30 (br d, 1H, J=8.4 Hz), 7.18 (br d, 1H, J=10.5 Hz), 7.12 (s, 1H), 6.74 (dd, 1H, J=2.6, 8.9 Hz), 5.3-5.4 (m, 1H), 4.53 (dd, 2H, J=6.3, 9.4 Hz), 4.03 (dd, 2H, J=3.5, 9.6 Hz), 3.8-3.8 (m, 3H)	454.12

 $<0.1 \mu\text{M} = ****$ $\geq 0.1 \text{ } \mu\text{M to } < 1.0 \text{ } \mu\text{M} = ***$ $\geq 1.0 \mu\text{M}$ to $< 30 \mu\text{M}$ = ** $\geq 30 \mu\text{M} = *$

Example 21. GPR52 Agonist Functional cAMP Assay

[0001] CHO cells stably expressing GPR52 receptor were dissociated from cell culture flasks, counted to have 1e6 cells/mL (4.5e6 cells needed/384-well plate), washed once in D-PBS and finally suspended in assay buffer (Stimulation Buffer with 1X HBSS, 5mM HEPES, in the presence of 0.1 % BSA and 150 μ M of Ro 20-1724 Phosphodiesterase inhibitor; pH adjusted to 7.4 with 1N NaOH).

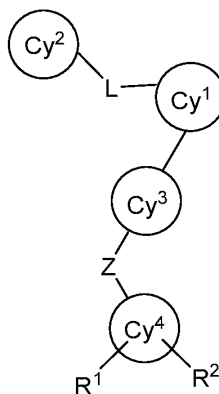
[0002] Cells in suspension from above were plated in 384-well white Optiplate (PerkinElmer) at 10,000 cells/well/10 μ L, briefly centrifuged prior direct addition of compounds (50 nL/well) in 10 mM DMSO using a Tecan D300e Digital Dispenser, final DMSO in each well was normalized to 0.1%. Cells were incubated in the presence of compounds for 45min at 37°C in a humidified incubator.

[0003] To measure cAMP levels, LANCE® Ultra cAMP assay (Perkin Elmer), a homogeneous time-resolved fluorescence resonance energy transfer (TR-FRET) immunoassay was used following manufacturer's recommendations. Plates were shaken for 1h at room temperature before reading on a Tecan InfiniteF200Pro multi-mode plate reader using standard FRET settings (Excitation 340 nm, Emission at 615 nm). FRET values were reported as readings obtained at 665 nm. Data were normalized to DMSO (0.1%) and reference compounds (100%) and fit to a 4-parameter logistical fit to generate antagonist IC50s.

CLAIMS

What is claimed is

1. A compound of Formula (I):



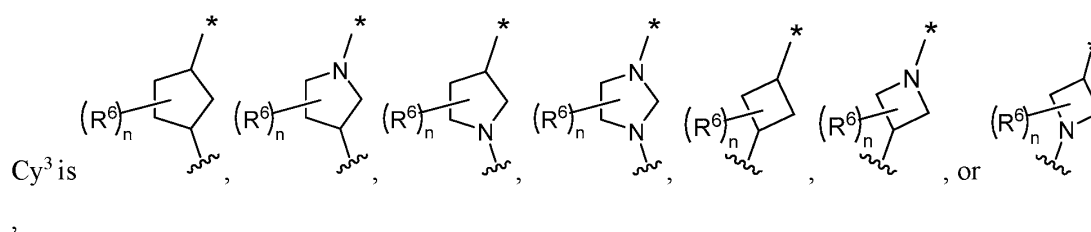
Formula (I)

or a pharmaceutically acceptable salt thereof,

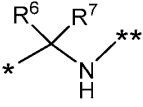
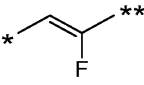
wherein

Cy¹ is a nitrogen-containing heterocyclylene or a nitrogen-containing heteroarylene, wherein
 when the heterocyclylene contains two nitrogen atoms, the nitrogen atoms are adjacent to each other, and
 when the heteroarylene contains two nitrogen atoms, the nitrogen atoms are adjacent to each other or the heteroarylene is pyrimidine;

Cy² is a nitrogen-containing 4-8 membered heterocyclyl, heteroaryl, spiroheterocyclyl, or bicyclic heterocyclyl;



wherein * is the point of attachment to Cy¹, and wherein  is the point of attachment to Z;
 Cy⁴ is aryl or nitrogen-containing heteroaryl;

L is  or , wherein * is the point of attachment to Cy¹, and ** is the point of attachment to Cy²;

Z is -O- or -CR⁴R⁵;

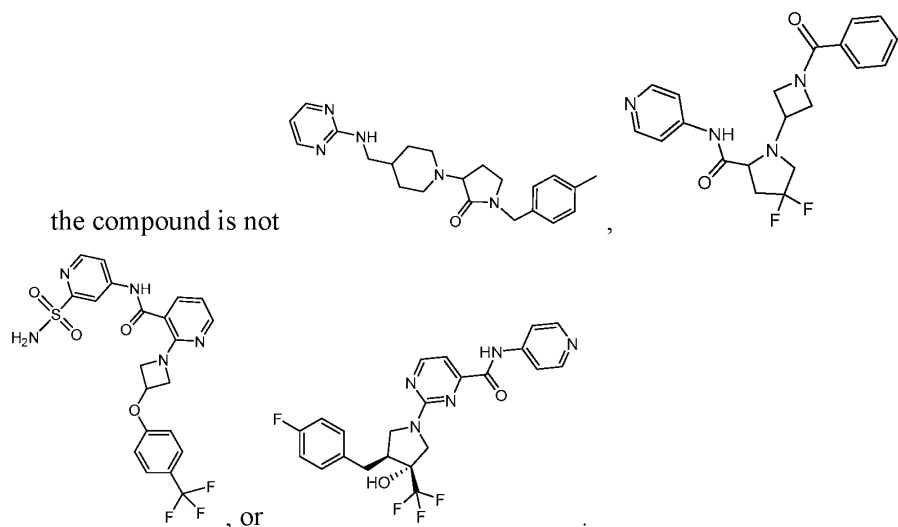
R¹ and R² are each independently hydrogen, halogen, alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, -CF₃, -CN, or -OCF₃;

R⁴ and R⁵ are each independently hydrogen, halogen, alkyl, alkoxy, -OH, -CF₃, -CHF₂, -CH₂CF₃, -CN, -C(=O)CH₃, -S(=O)₂CH₃, cycloalkyl, heterocyclyl, aryl, heteroaryl, or R⁴ and R⁵ together form =O;

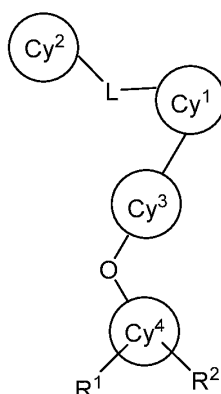
R⁶ and R⁷ are each independently hydrogen, alkyl, halogen, -OH, -CF₃, or -CHF₂, R⁶ and R⁷ together with the carbon to which they are attached form =O, carbocyclyl, or heterocyclyl; or two R⁶ attached to the same carbon atom form =O; and

n is 0, 1, 2, or 3; and

wherein Cy¹ is not 1,2,5 thiadiazole, Cy² is not thiazole or thiadiazole, and



2. The compound of claim 1, wherein Z is -O-.
3. The compound of claim 1, wherein Z is -CR⁴R⁵.
4. The compound of claim 3, wherein Z is -CH₂-, -C(=O)-, -CHF-, -CHCH₃, or -CF₂.
5. The compound of claim 1, having Formula (Ia)



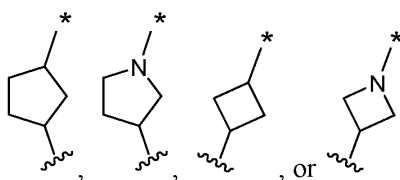
Formula (Ia)

or a pharmaceutically acceptable salt thereof,

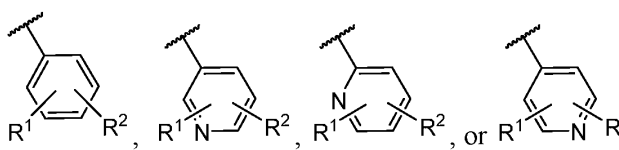
wherein

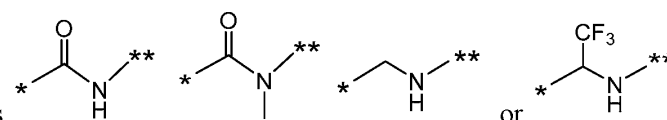
Cy¹ is a nitrogen-containing heterocyclylene or a nitrogen-containing heteroarylene, wherein
 when the heterocyclylene contains two nitrogen atoms, the nitrogen atoms are adjacent to each other, and
 when the heteroarylene contains two nitrogen atoms, the nitrogen atoms are adjacent to each other or the heteroarylene is pyrimidine;

Cy² is a nitrogen-containing 4-8 membered heterocyclyl, heteroaryl, spiroheterocyclyl, or bicyclic heterocyclyl;

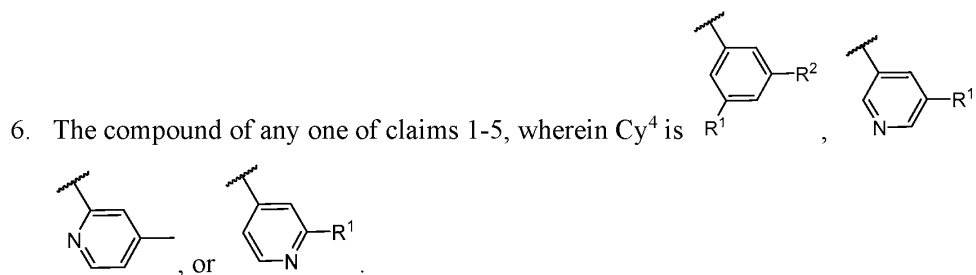
Cy³ is , wherein * is the point of attachment to Cy¹, and

wherein  is the point of attachment to O;

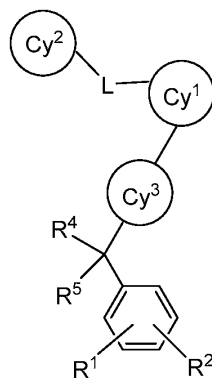
Cy⁴ is ; or R¹ and R² are both hydrogen;

L is , wherein * is the point of attachment to Cy¹, and ** is the point of attachment to Cy²; and

R^1 and R^2 are each independently hydrogen, halogen, alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-CF_3$, $-CN$, or $-OCF_3$.



7. The compound of claim 6, wherein R^1 is hydrogen, halogen, C_1 - C_3 alkyl, alkoxy, cycloalkyl, $-CF_3$, $-CN$, or $-OCF_3$.
8. The compound of claim 6 or 7, wherein R^1 is hydrogen, cyclopropyl, $-F$, $-Cl$, $-CF_3$, $-CH_3$, or $-C(CH_3)_2$.
9. The compound of any one of claims 6-8, wherein R^2 is $-CF_3$.
10. The compound of claim 1, having Formula (Ib)



Formula (Ib)

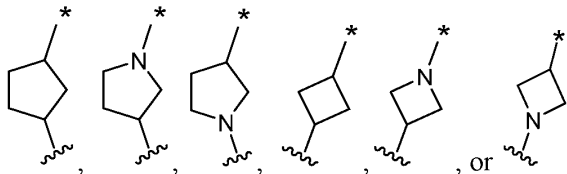
or a pharmaceutically acceptable salt thereof,

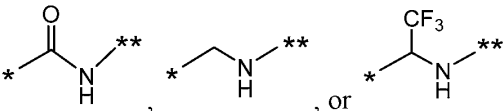
wherein

Cy^1 is a nitrogen-containing heterocyclylene or a nitrogen-containing heteroarylene, wherein when the heterocyclylene contains two nitrogen atoms, the nitrogen atoms are adjacent to each other, and

when the heteroarylene contains two nitrogen atoms, the nitrogen atoms are adjacent to each other or the heteroarylene is pyrimidine;

Cy² is a nitrogen-containing 4-8 membered heterocyclyl, heteroaryl, spiroheterocyclyl, or bicyclic heterocyclyl;

Cy³ is , wherein * is the point of attachment to Cy¹;

L is , wherein * is the point of attachment to Cy¹, and ** is the point of attachment to Cy²;

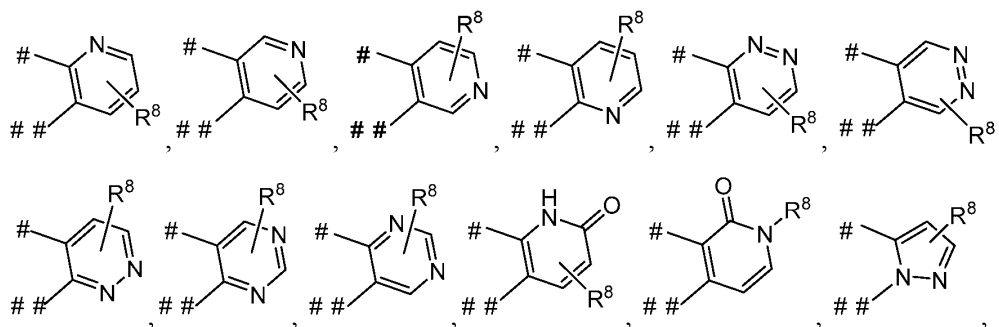
R¹ and R² are each independently hydrogen, halogen, alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, -CF₃, -CN, or -OCF₃; and

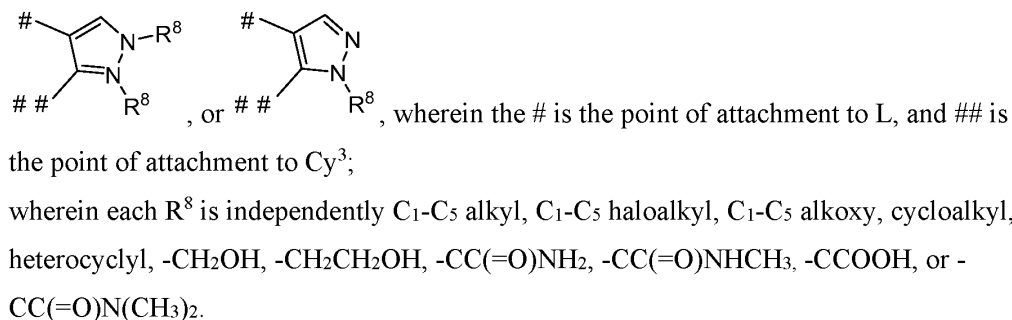
R⁴ and R⁵ are each independently hydrogen, C₁-C₃ alkyl, -F, or R⁴ and R⁵ together form =O.

11. The compound of any one of claims 1-10, wherein Cy¹ is a 4-6 membered N-heteroarylene or N-heterocyclylene.

12. The compound of any one of claims 1-11, wherein Cy¹ is pyridinyl, pyridinonyl, pyridazinyl, pyrimidinyl, or pyrazolyl.

13. The compound of any one of claims 1-12, wherein Cy¹ is

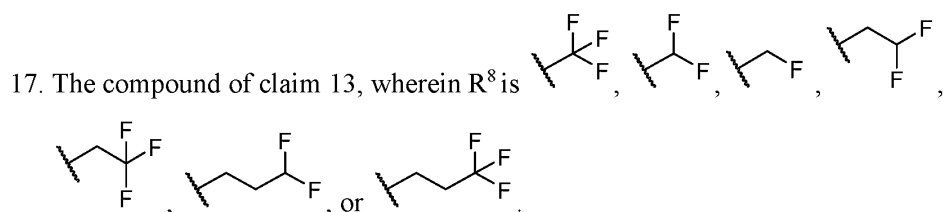




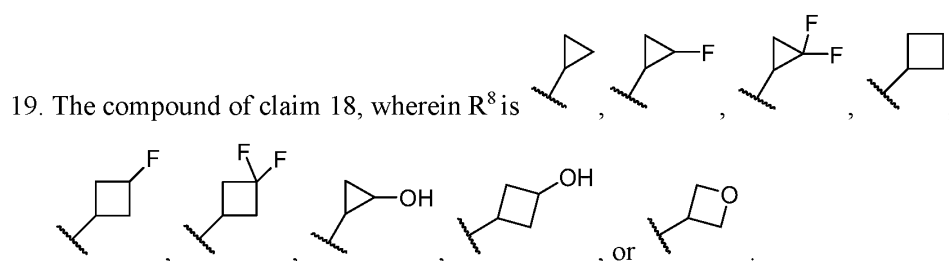
14. The compound of claim 13, wherein R⁸ is C₁-C₃ alkyl.

15. The compound of claim 13, wherein R⁸ is -CH₃.

16. The compound of claim 13, wherein R⁸ is C₁-C₃ haloalkyl.



18. The compound of claim 13, wherein R⁸ is C₃-C₆ cycloalkyl or heterocyclyl.



20. The compound of claim 18, wherein R⁸ is cyclopropyl.

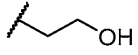
21. The compound of claim 13, wherein R⁸ is C₁-C₅ alkoxy.

22. The compound of claim 21, wherein R⁸ is -OCH₃.

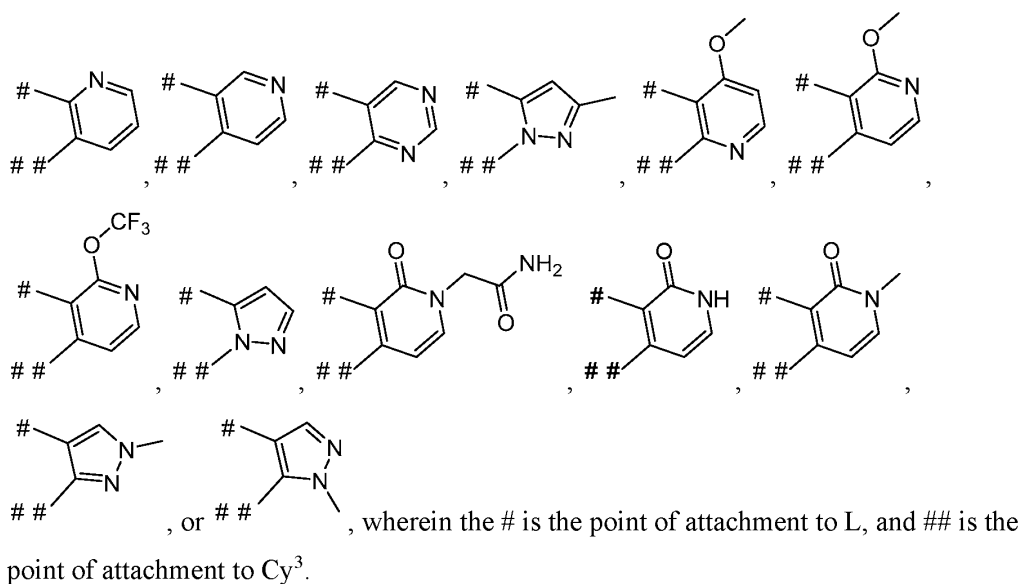
23. The compound of claim 21, wherein R^8 is $-OCF_3$.

24. The compound of claim 13, wherein R^8 is $-CC(=O)NH_2$.

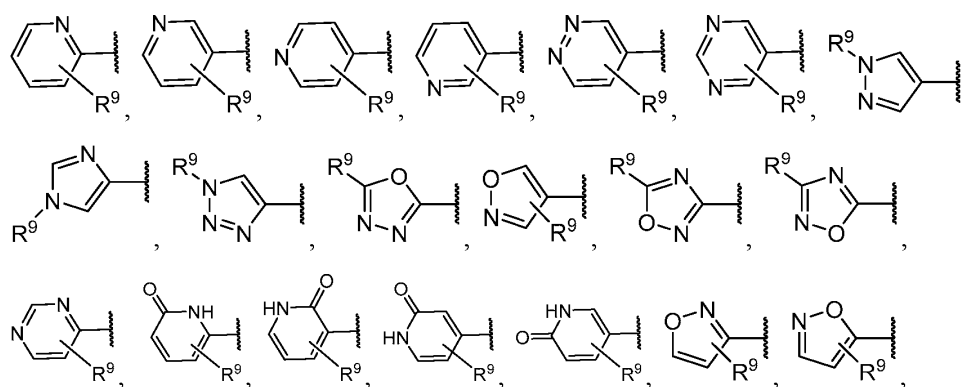
25. The compound of claim 13, wherein R^8 is $-CC(=O)N(CH_3)_2$.

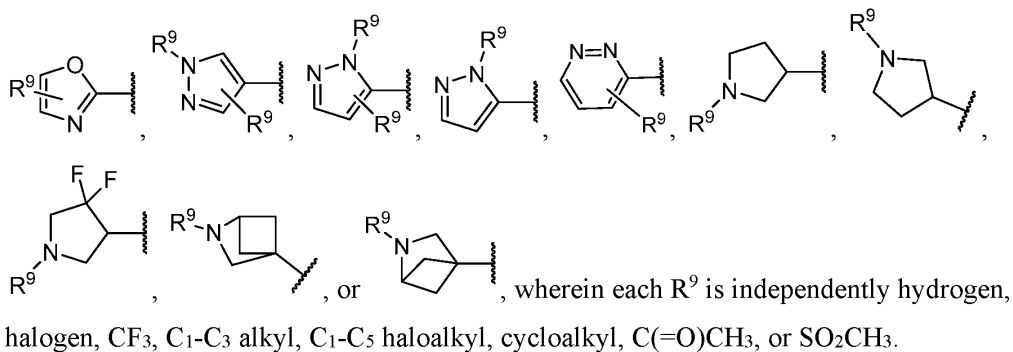
26. The compound of claim 13, wherein R^8 is  or .

27. The compound of any one of claims 1-13, wherein Cy^1 is



28. The compound of any one of claims 1-27, wherein Cy^2 is





29. The compound of claim 28, wherein R^9 is hydrogen.

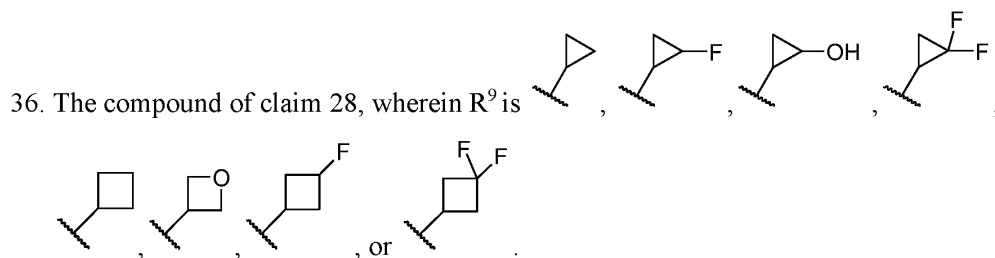
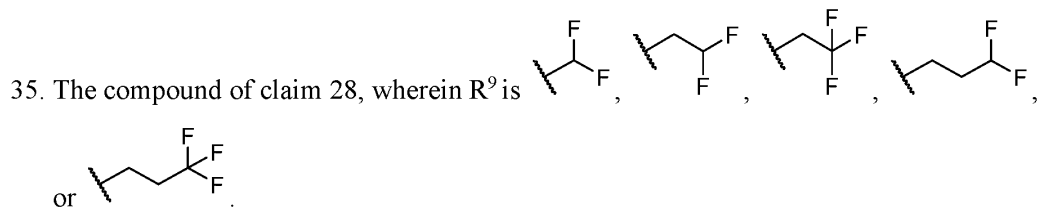
30. The compound of claim 28, wherein R^9 is $-Cl$.

31. The compound of claim 28, wherein R^9 is $-CF_3$.

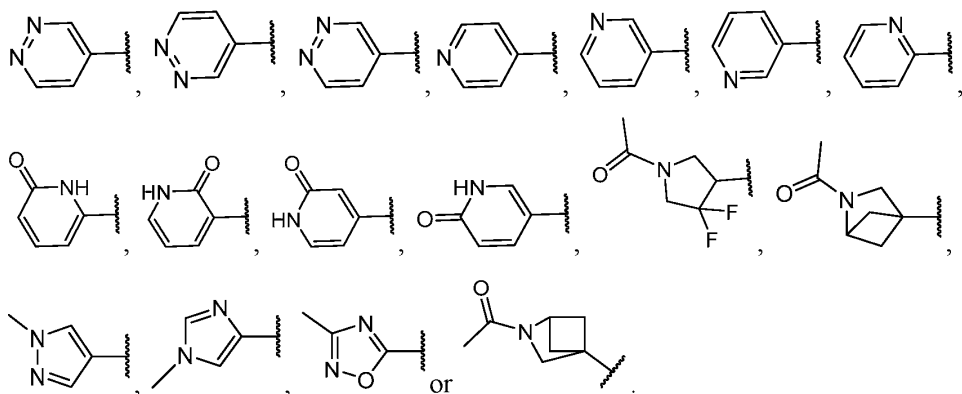
32. The compound of claim 28, wherein R^9 is C_1 - C_3 alkyl.

33. The compound of claim 28, wherein R^9 is $-CH_3$.

34. The compound of claim 28, wherein R^9 is $-C(=O)CH_3$.



37. The compound of claim 28, wherein Cy^2 is

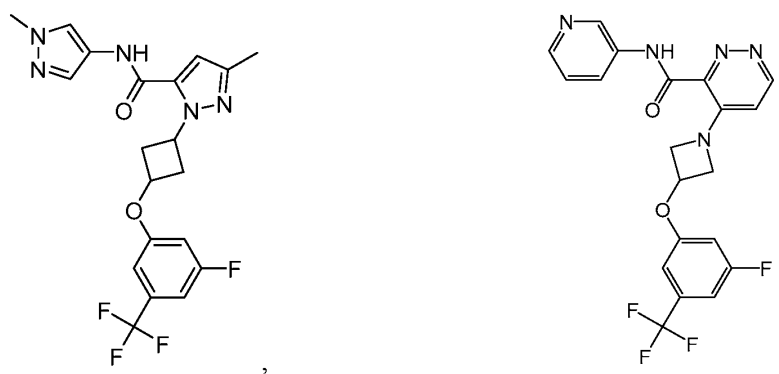


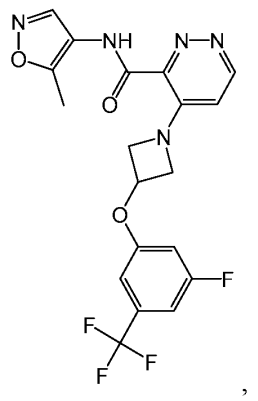
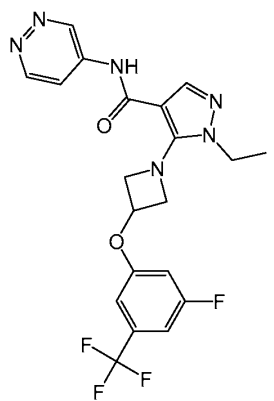
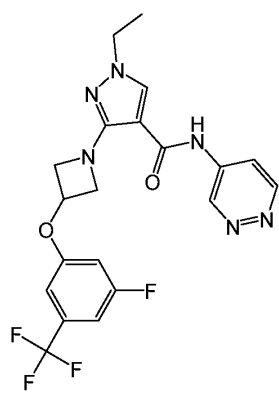
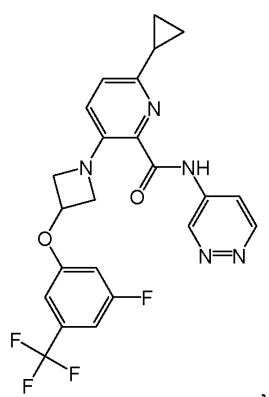
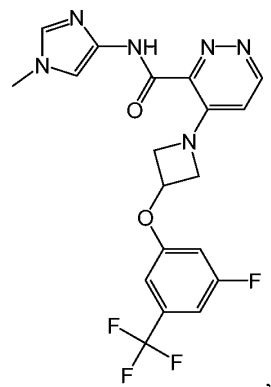
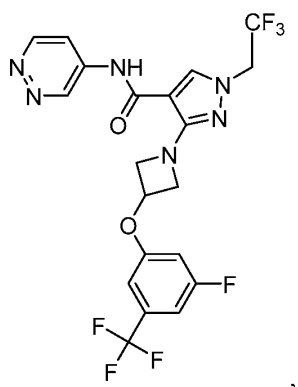
38. The compound of any one of claims 1-37, wherein Cy^3 is , or .

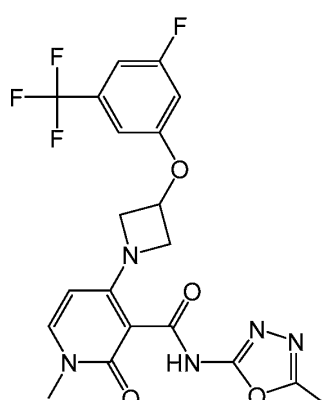
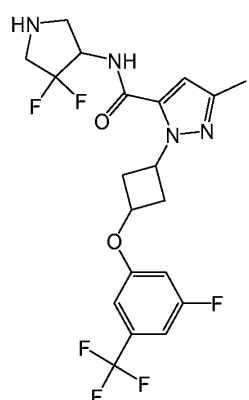
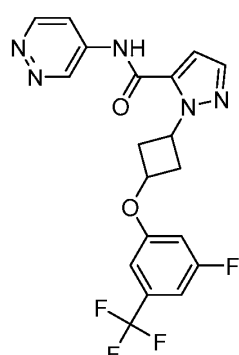
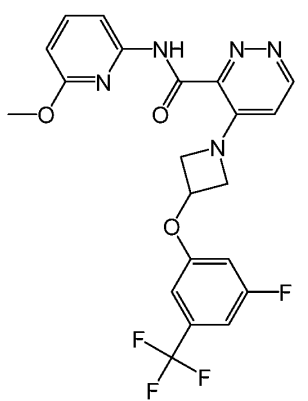
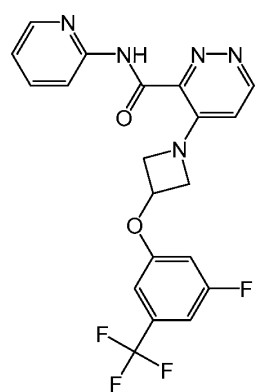
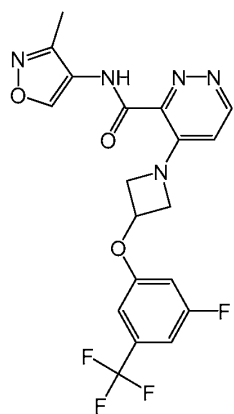
39. The compound of any one of claims 1-38, wherein Cy^3 is or .

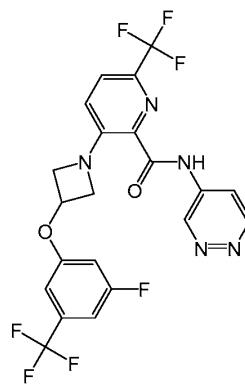
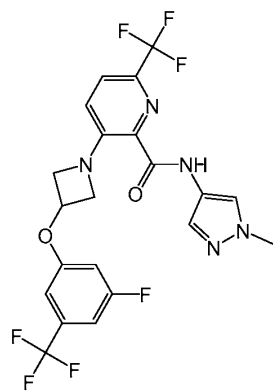
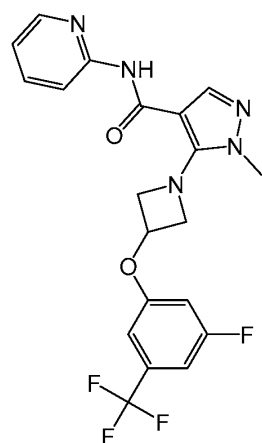
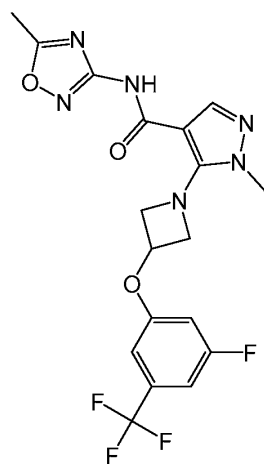
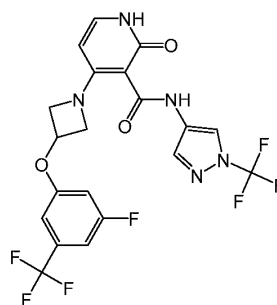
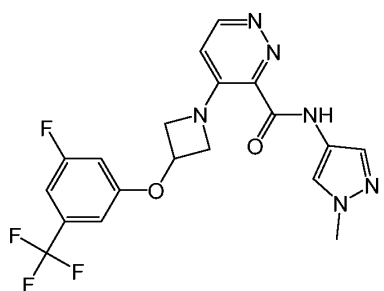
40. The compound of any one of claims 1-39, wherein L is .

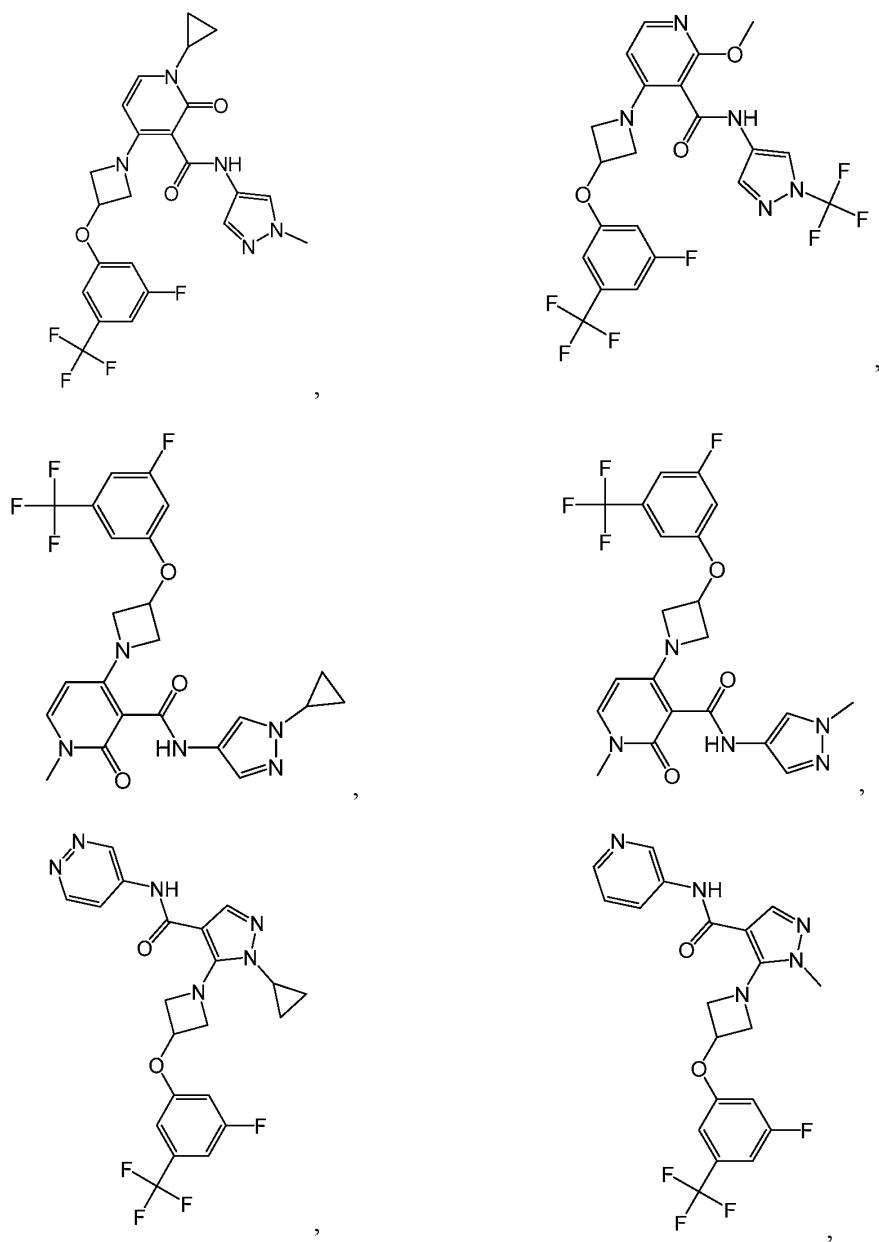
41. The compound of claim 1, having the structure:

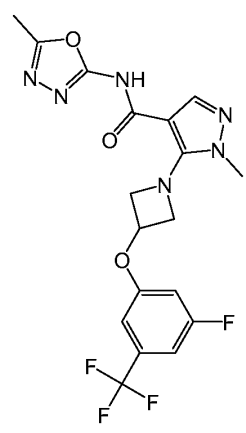
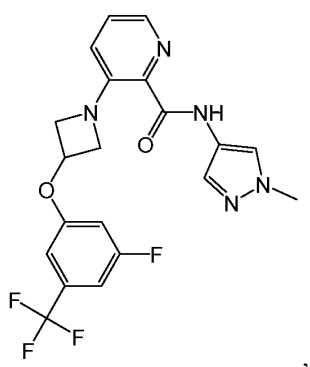
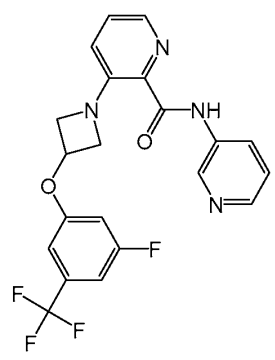
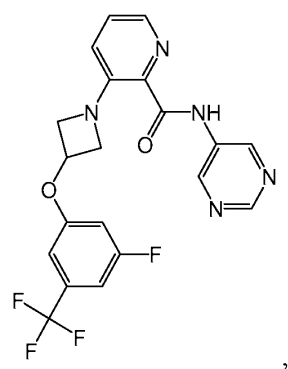
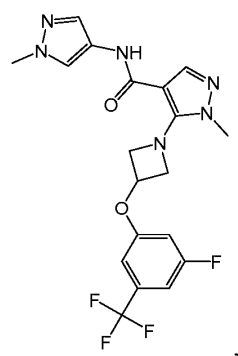
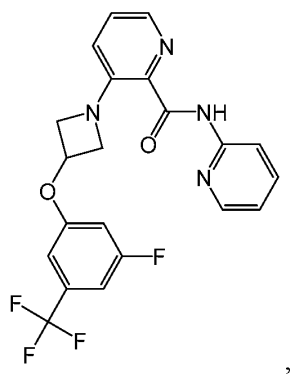


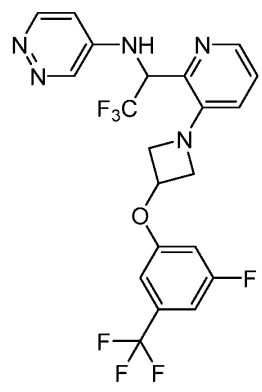
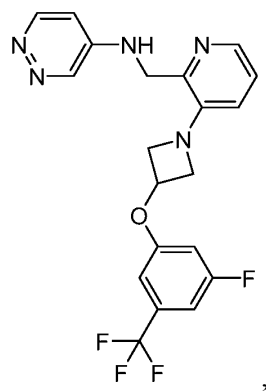
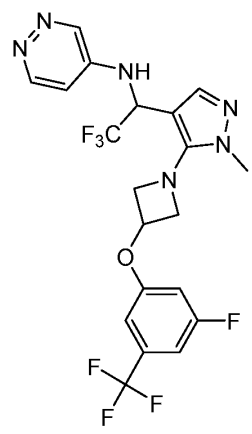
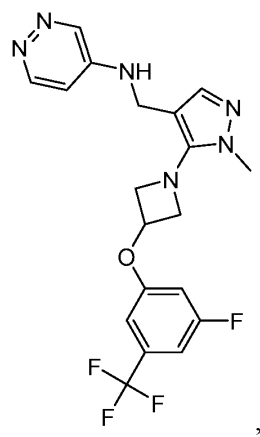
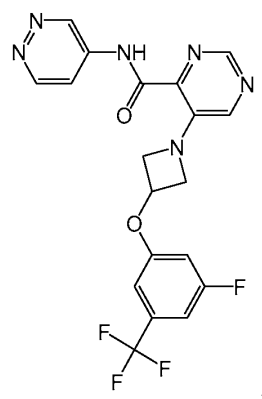
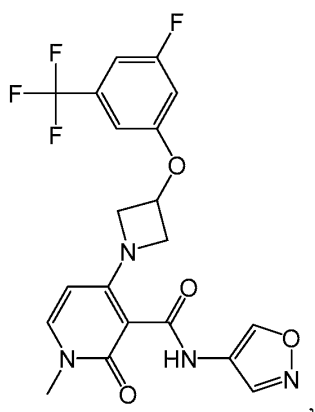


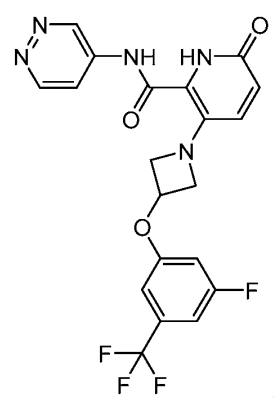
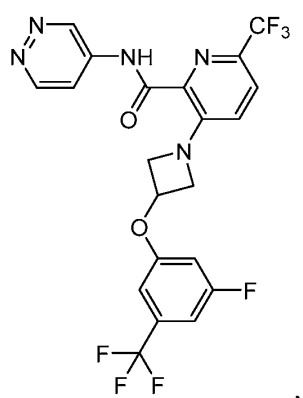
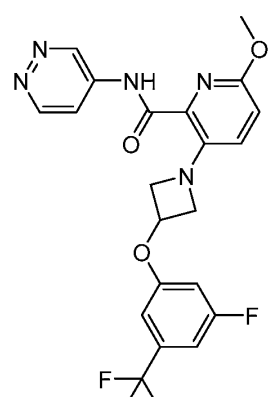
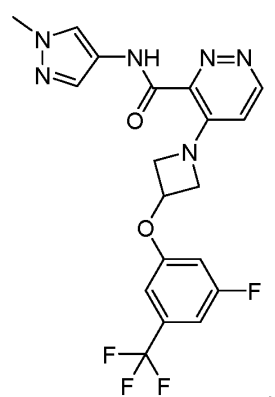
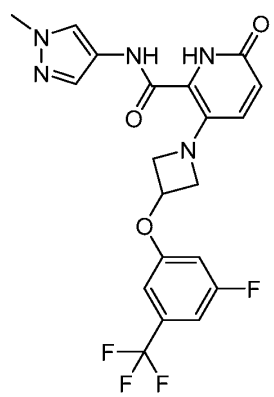
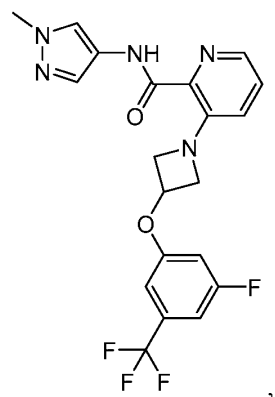


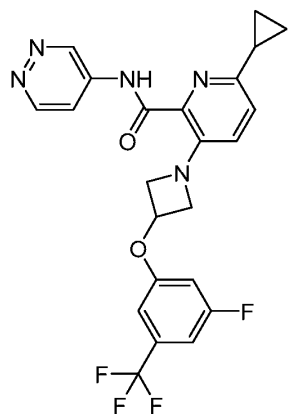




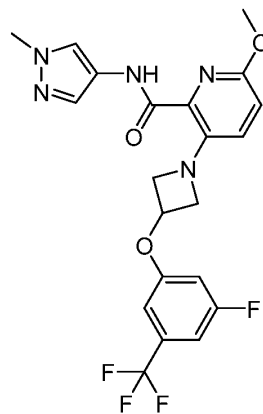




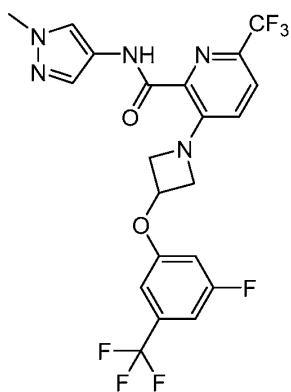




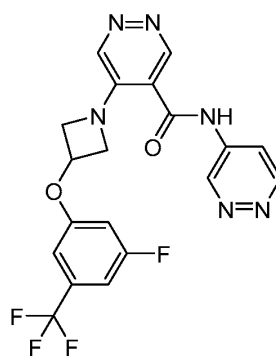
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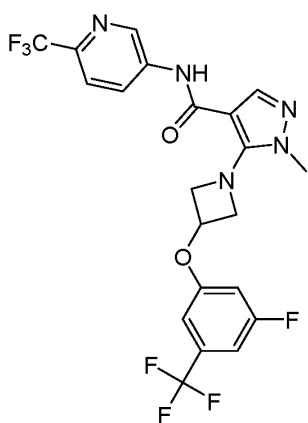
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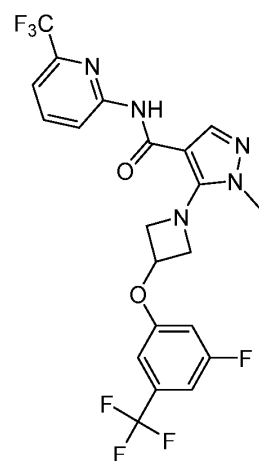
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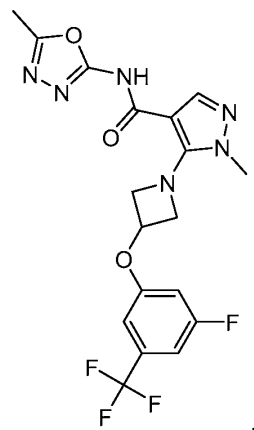
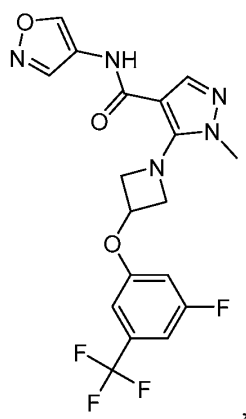
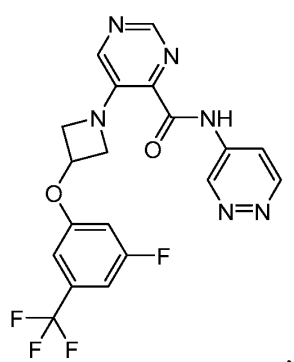
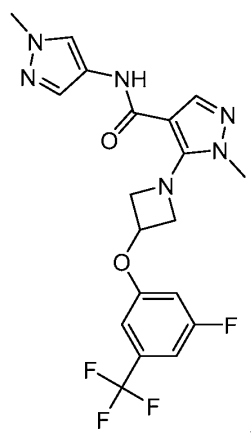
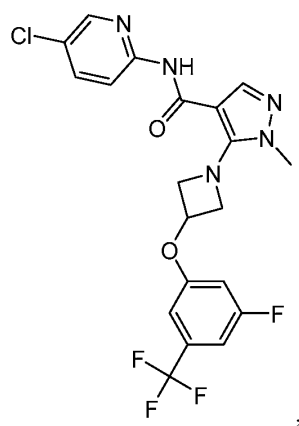
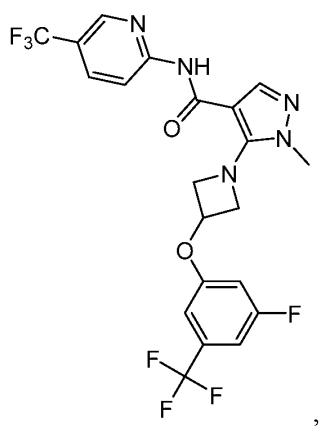
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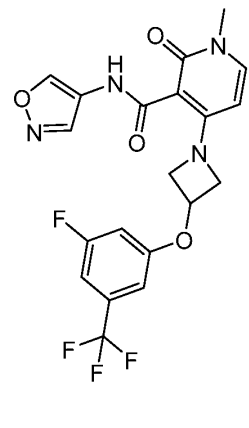
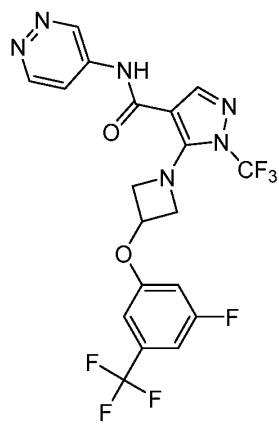
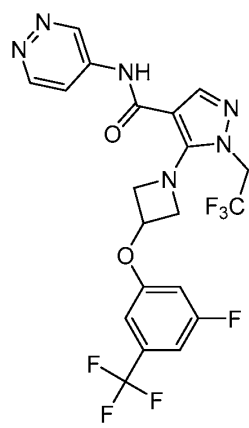
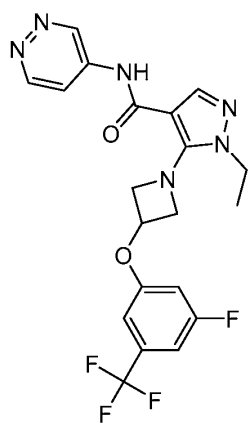
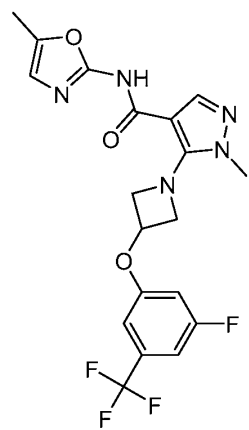
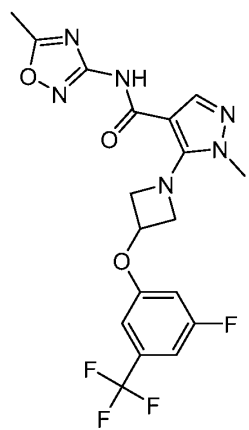


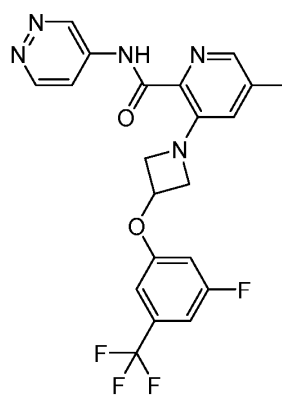
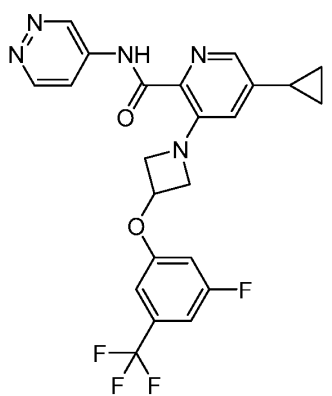
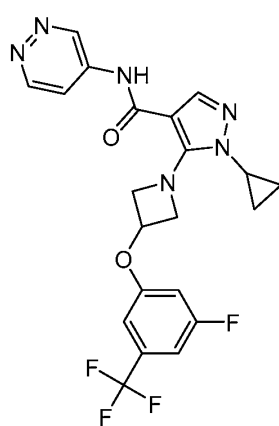
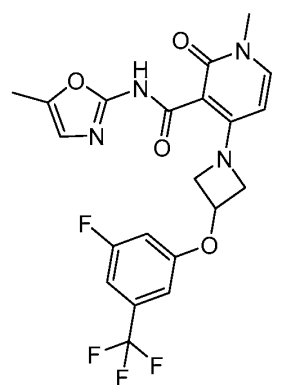
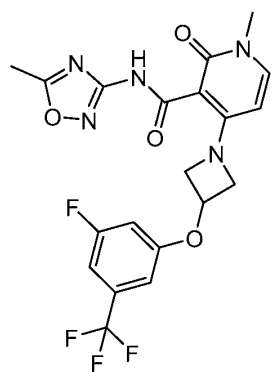
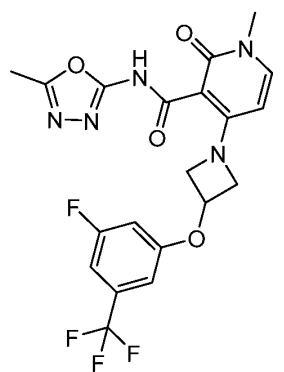
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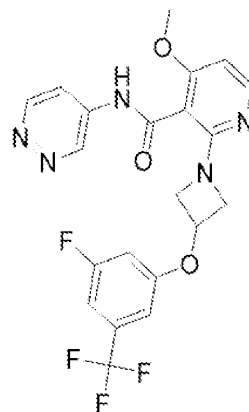
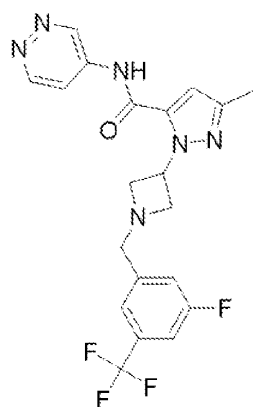
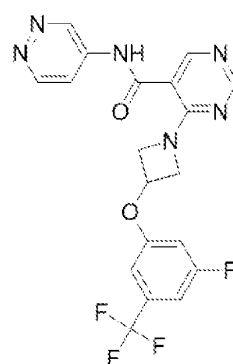
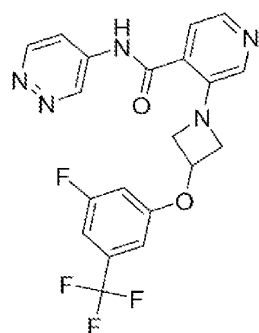
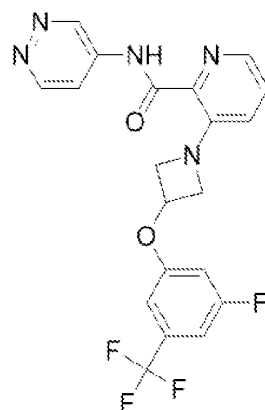
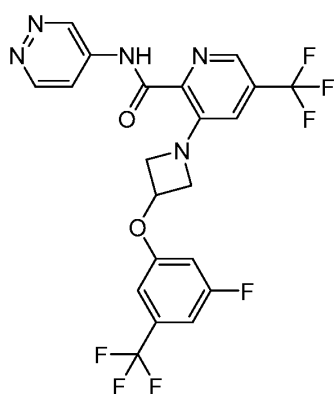


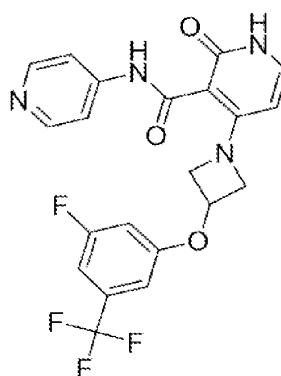
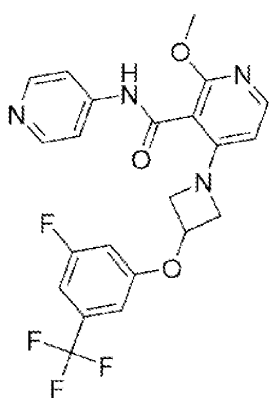
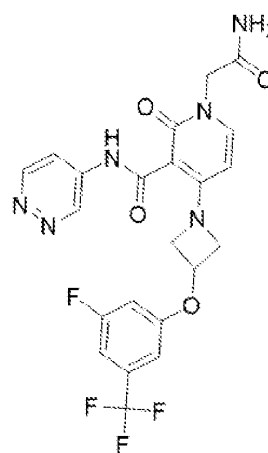
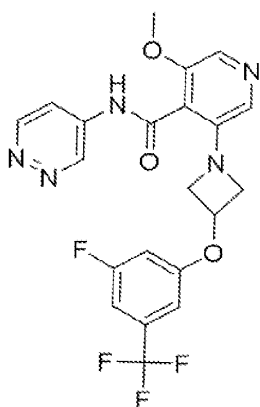
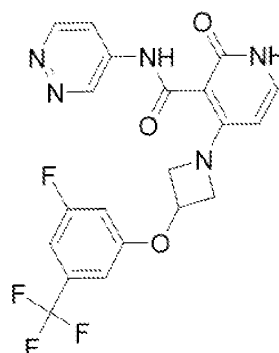
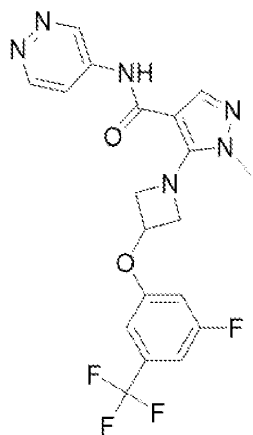
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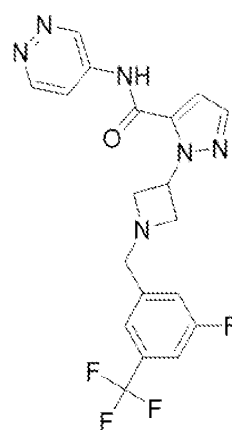
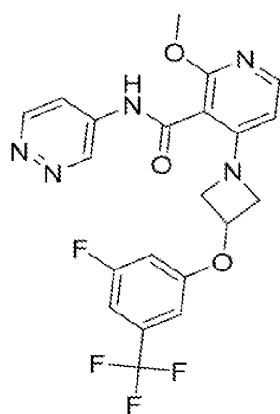
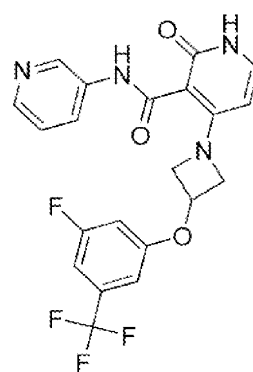
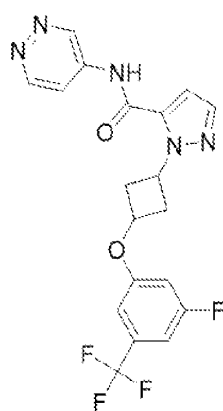
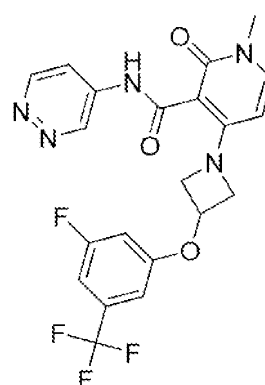
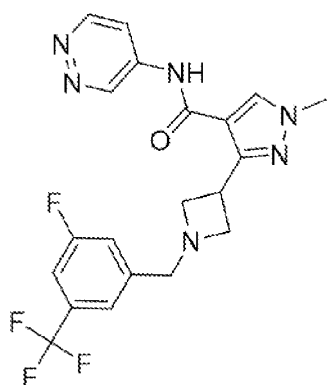


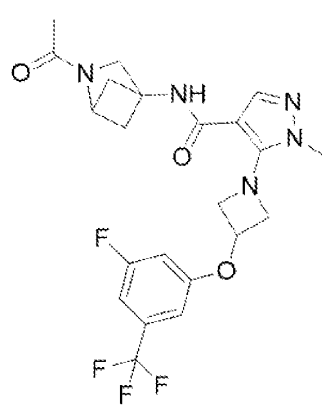
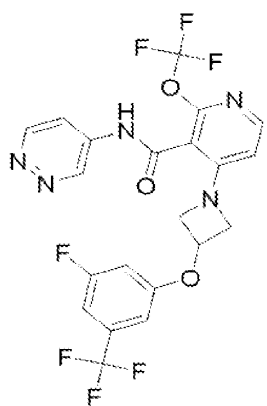
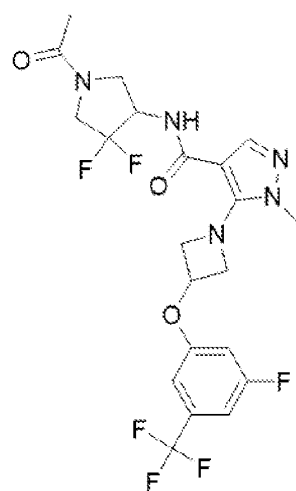
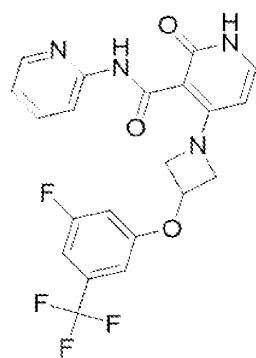
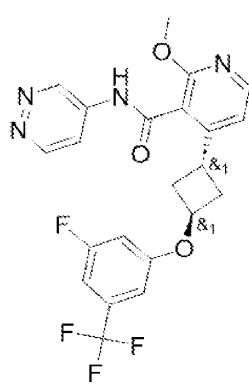
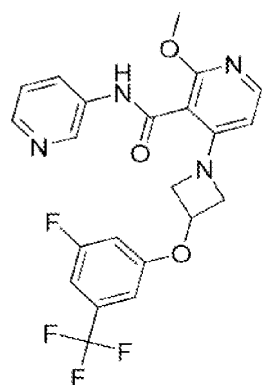


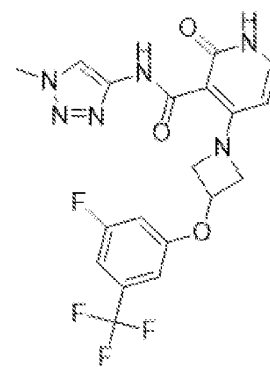
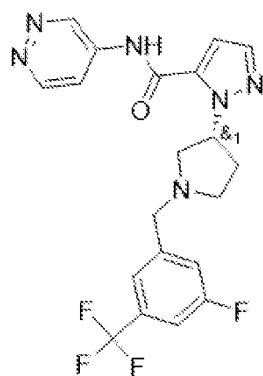
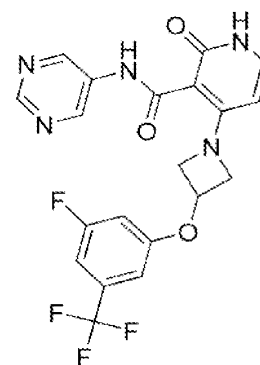
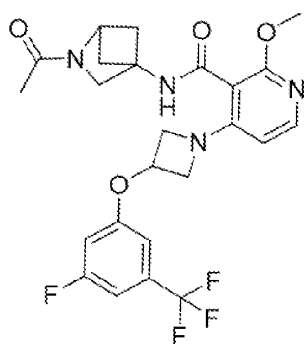
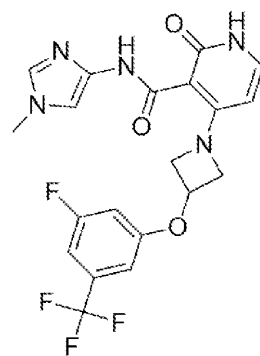
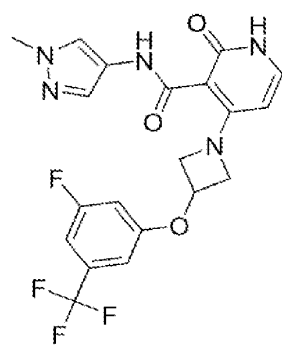


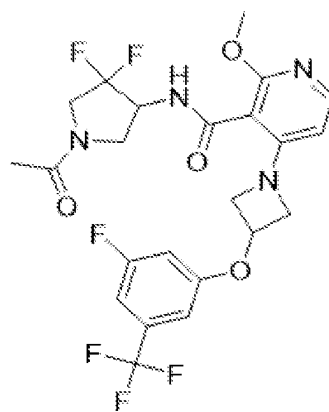
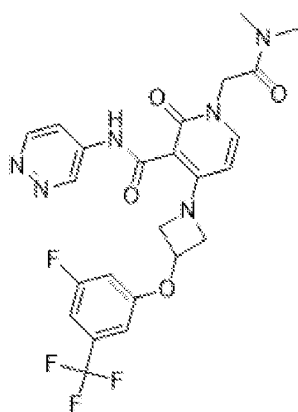
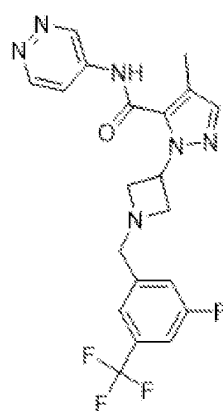
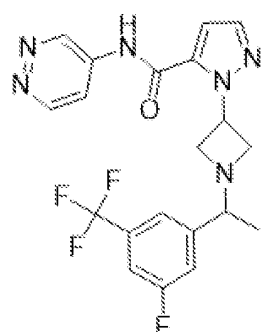
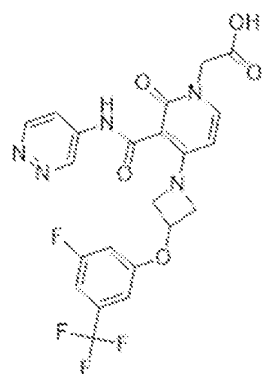
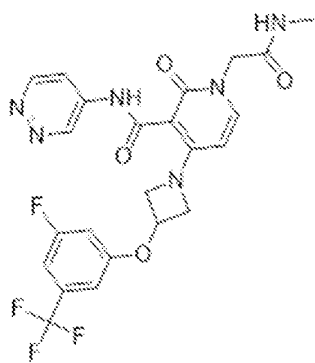


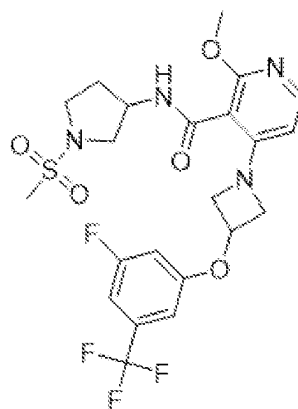
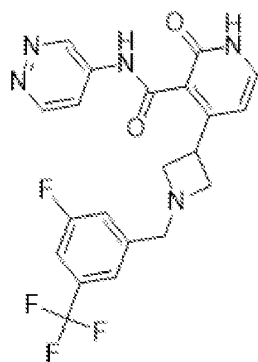
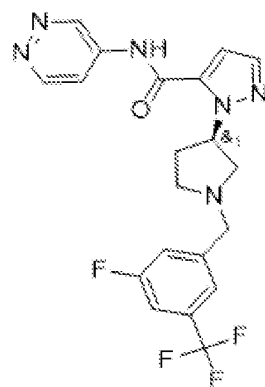
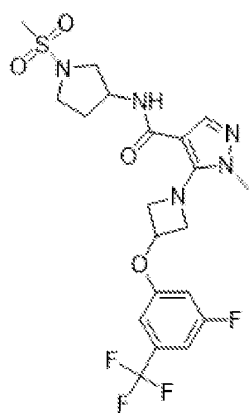
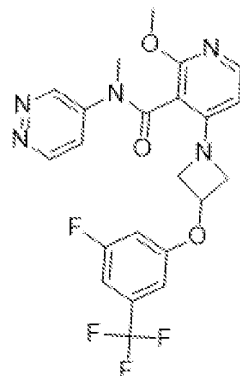
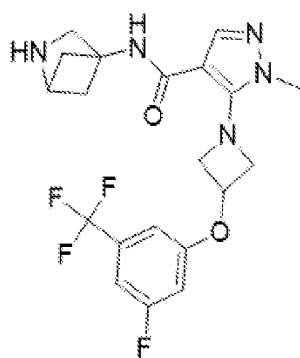


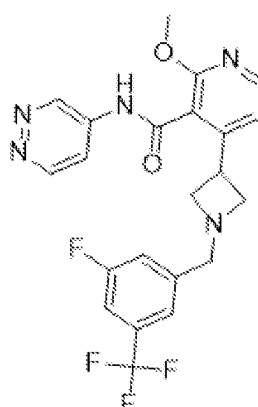
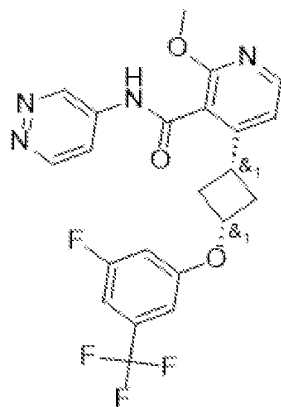
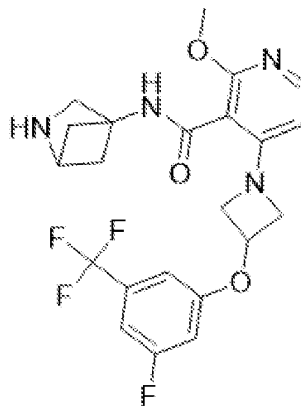
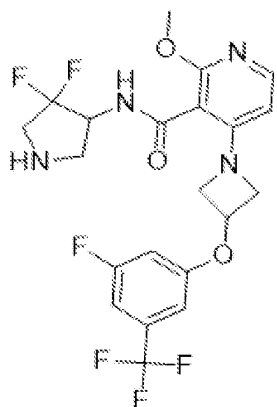
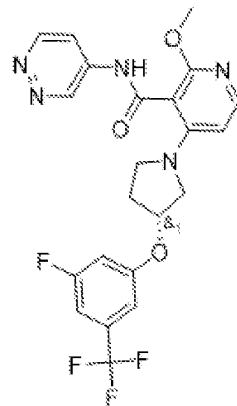
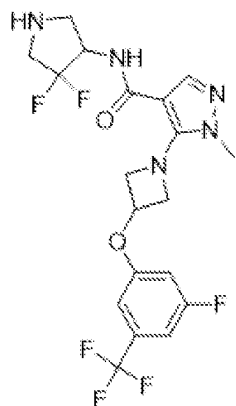


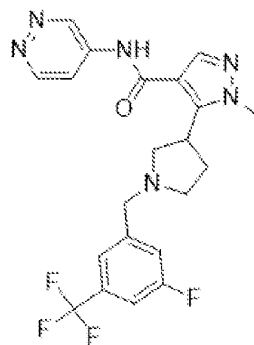
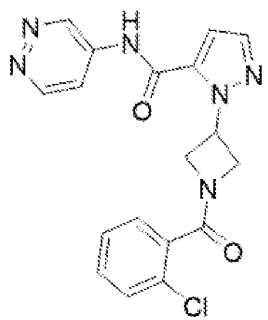
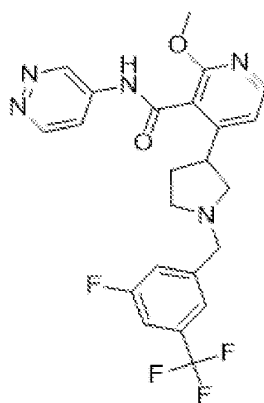
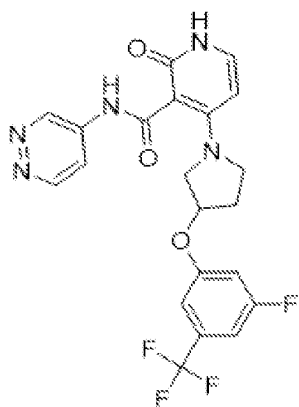
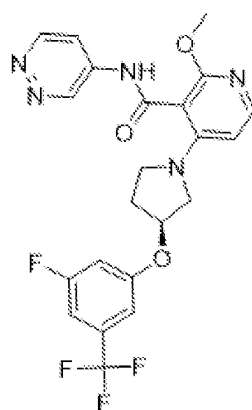
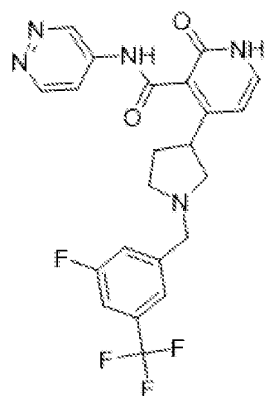


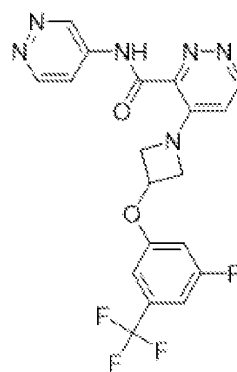
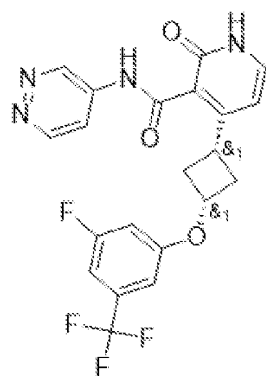
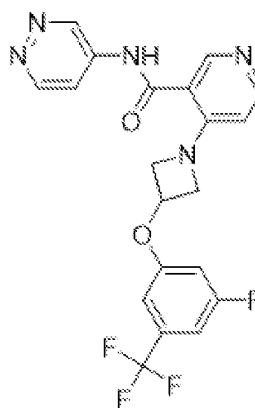
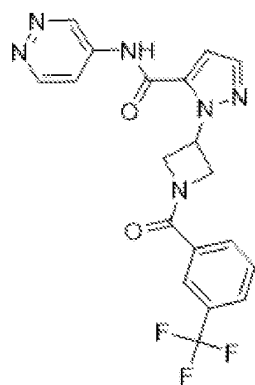
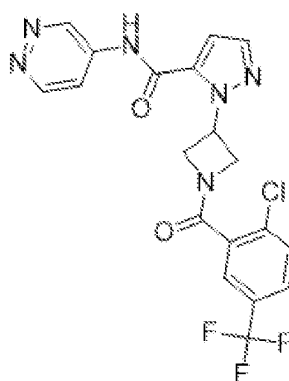
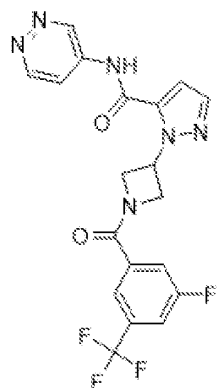


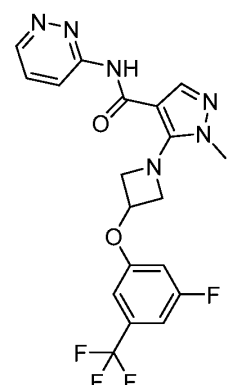
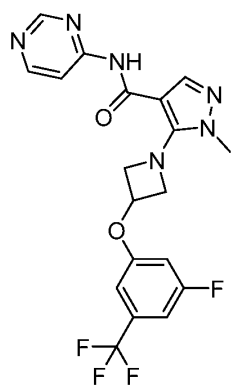
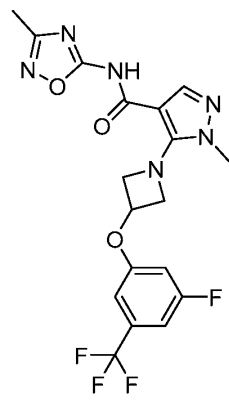
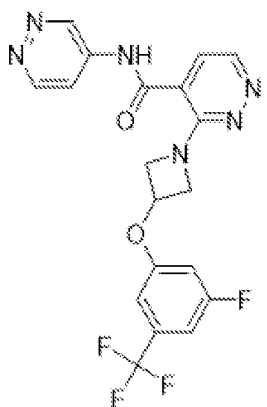
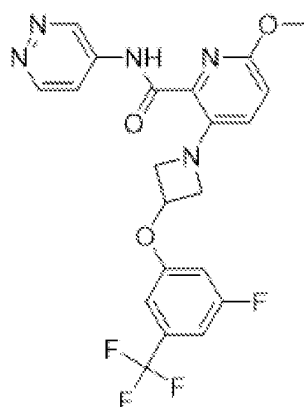
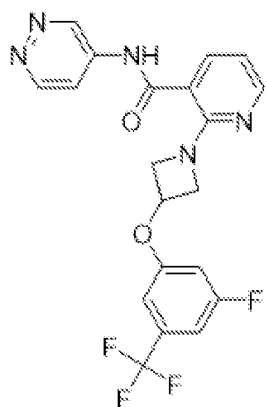


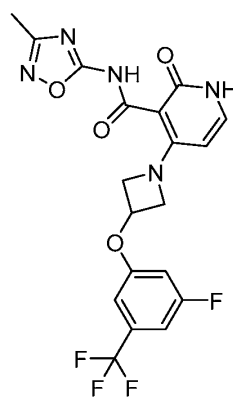
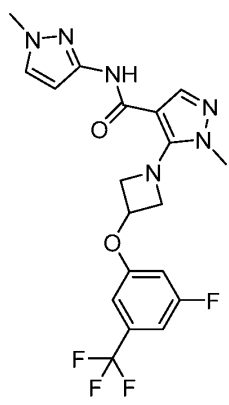
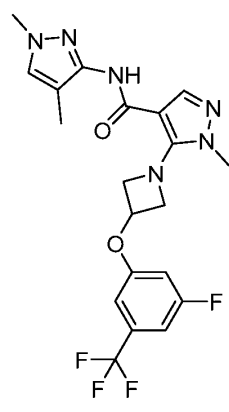
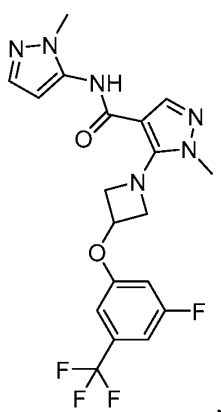
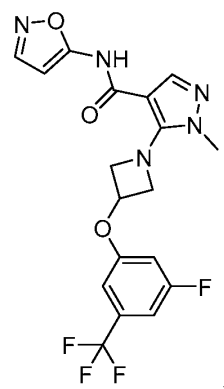
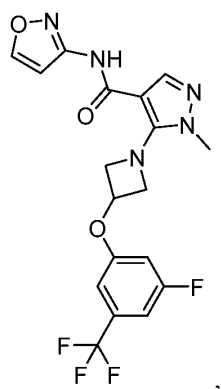


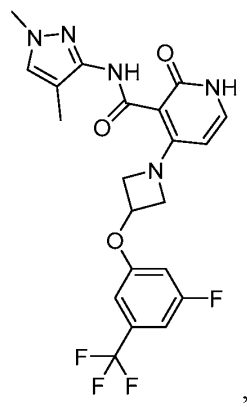
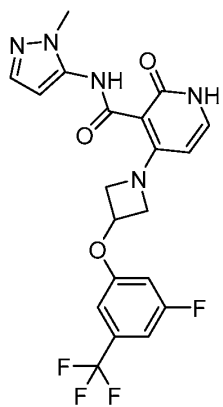
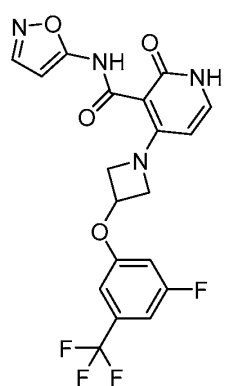
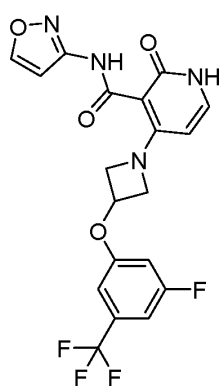
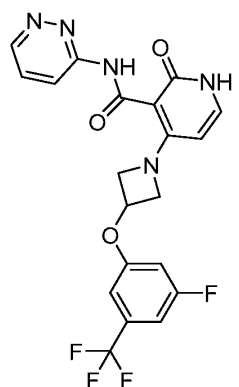
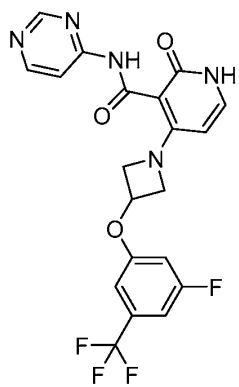


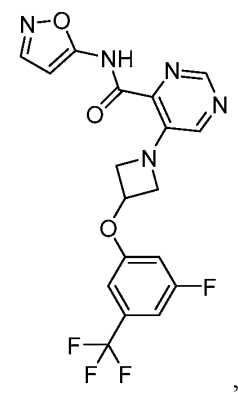
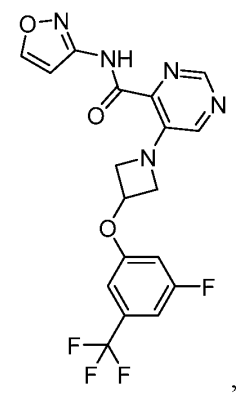
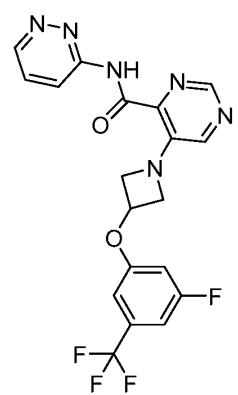
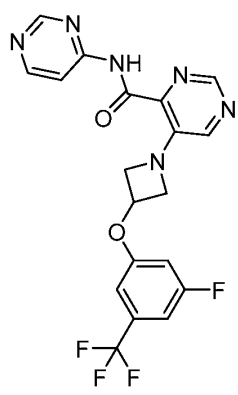
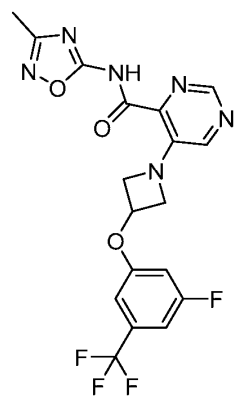
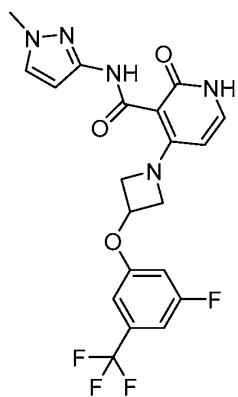


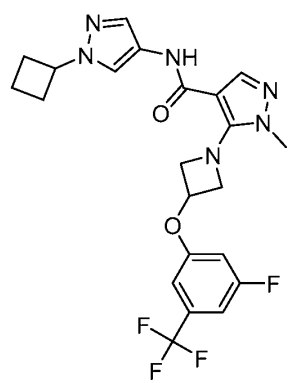
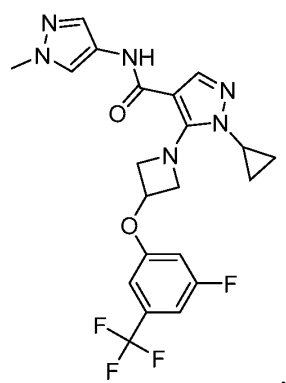
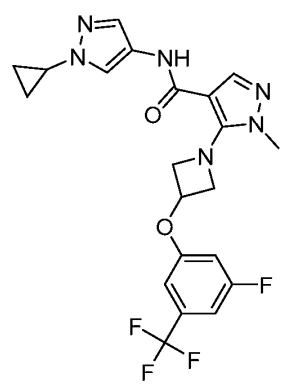
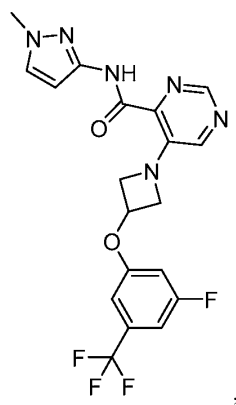
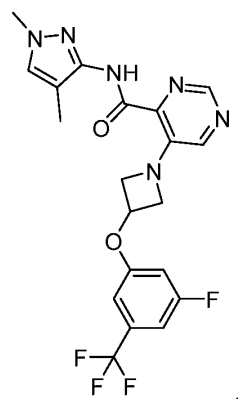
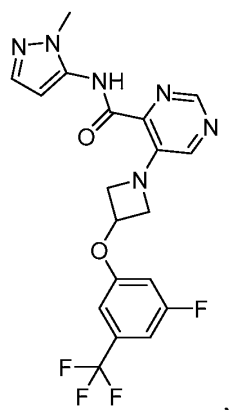


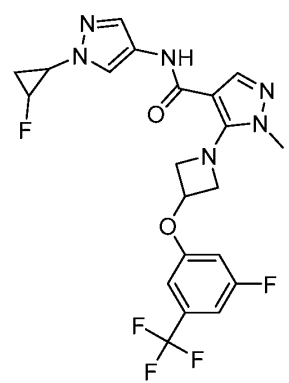
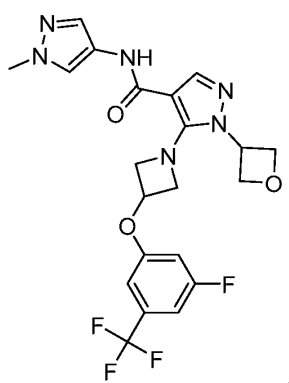
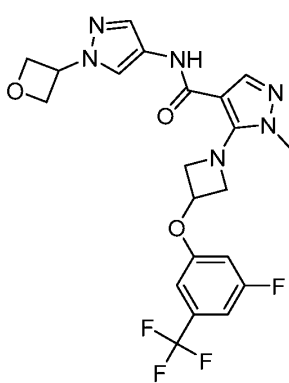
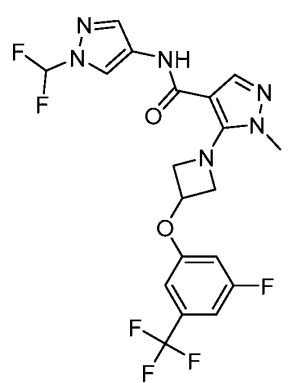
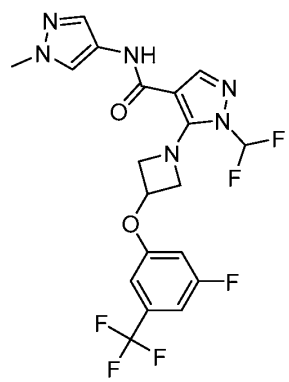
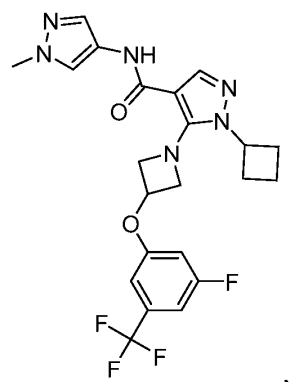


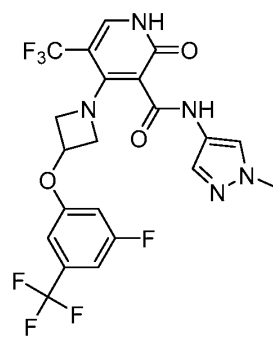
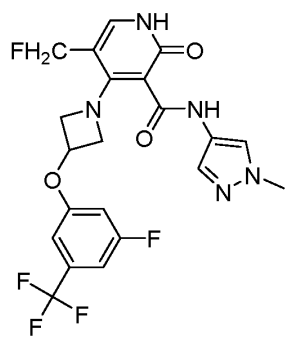
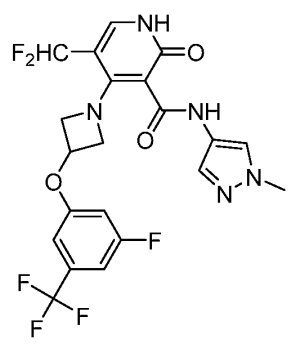
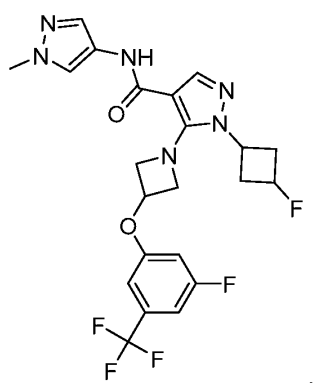
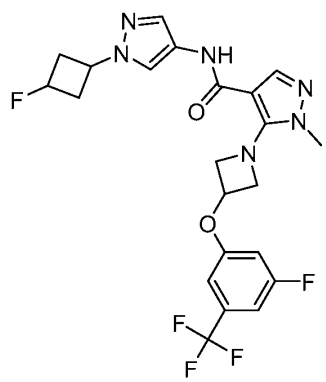
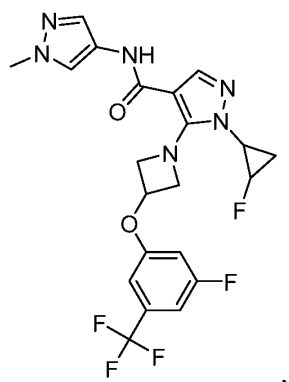


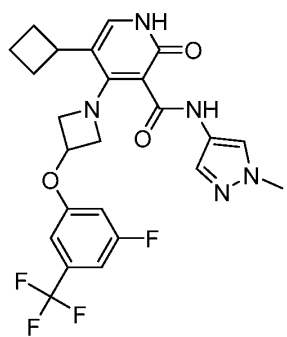
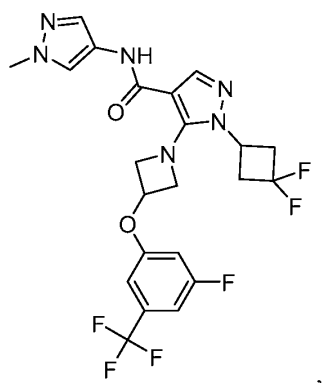
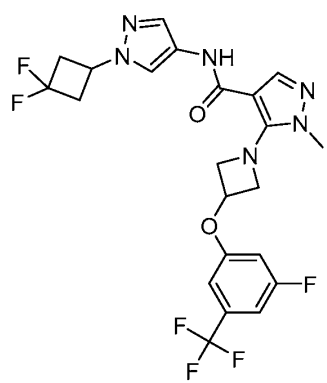
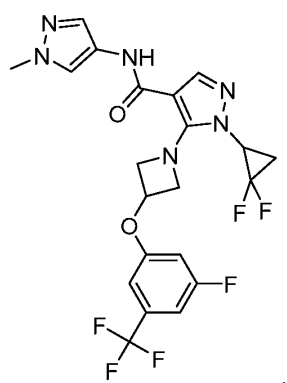
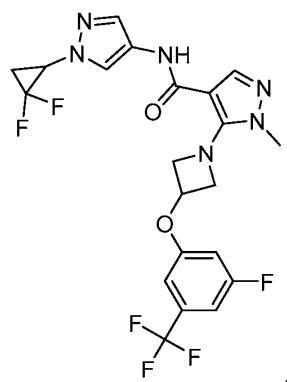
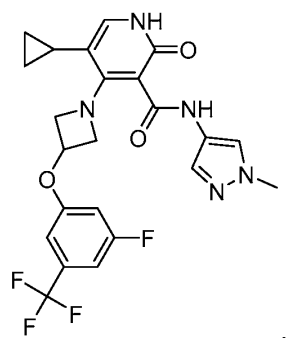


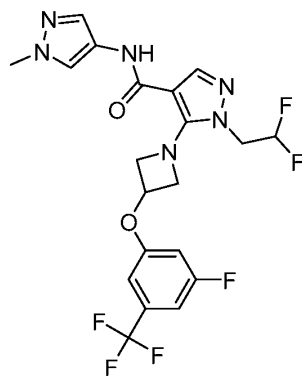
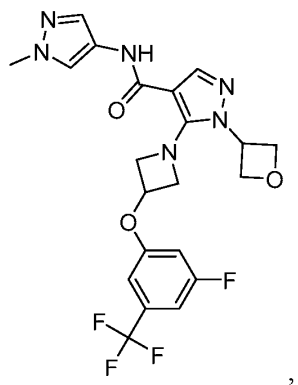
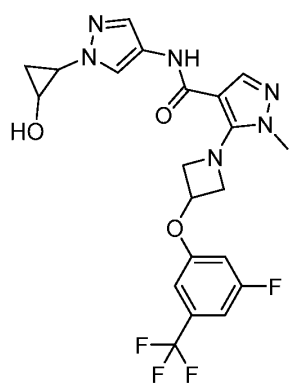
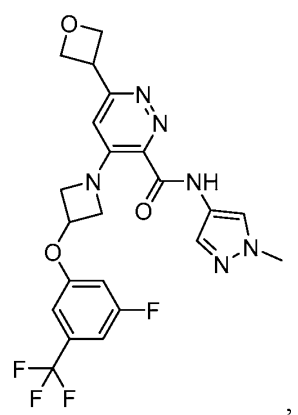
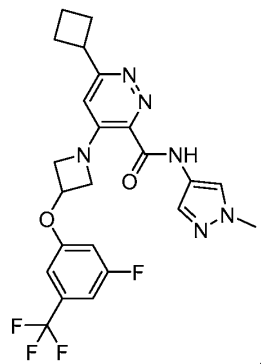
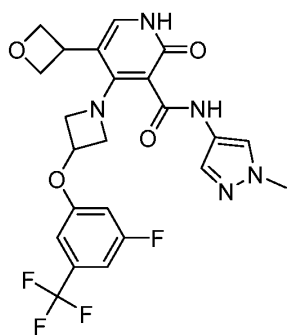


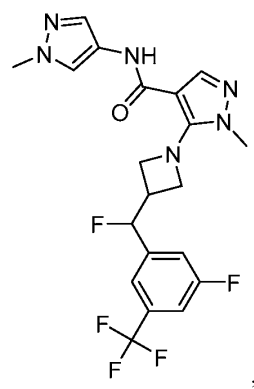
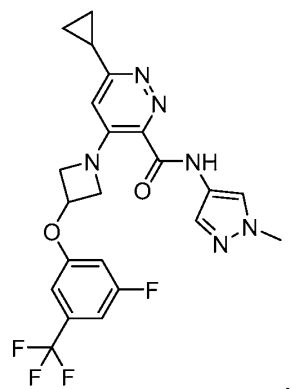
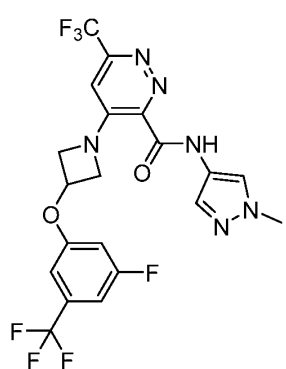
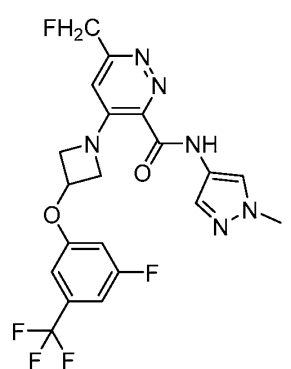
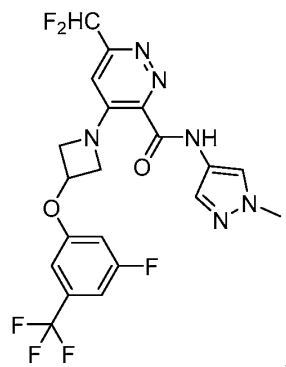
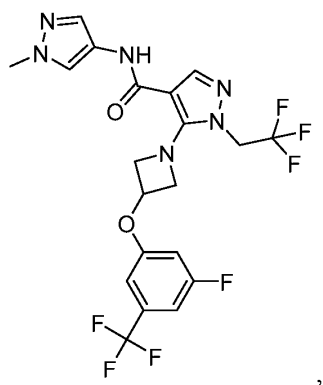


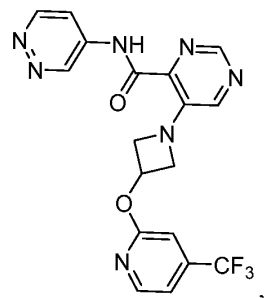
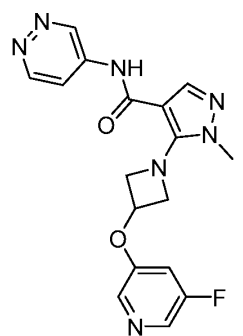
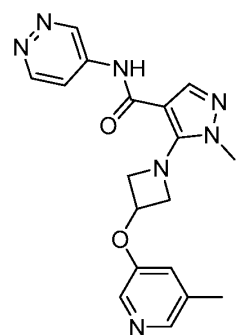
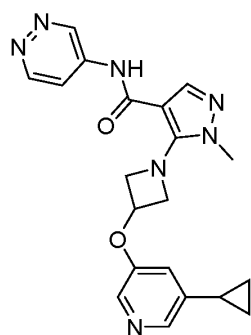
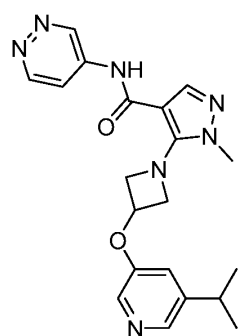
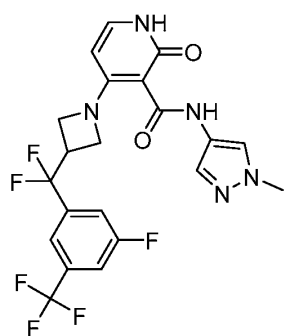
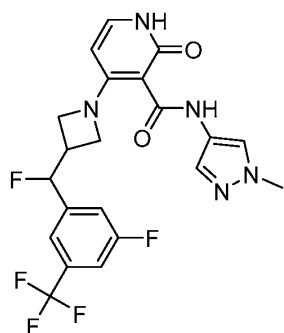
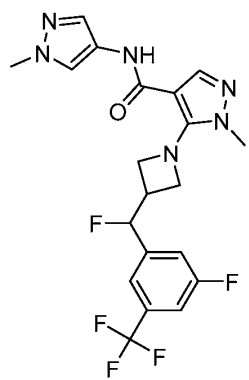


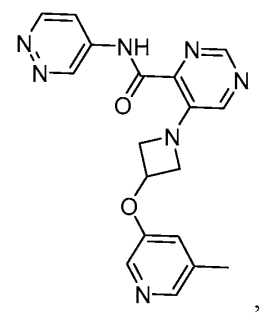
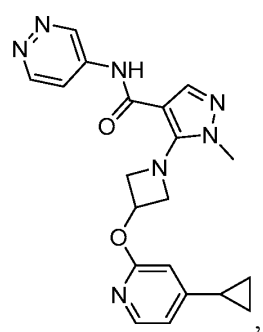
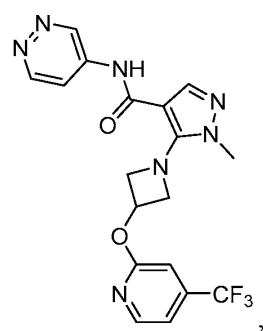
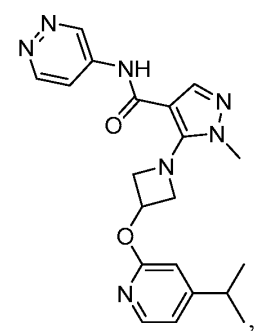
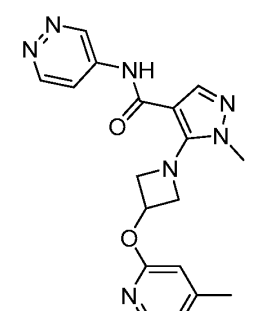
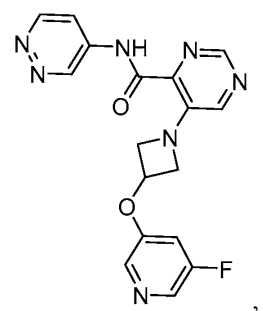
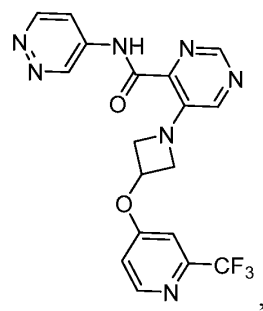
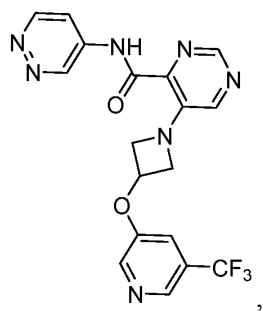


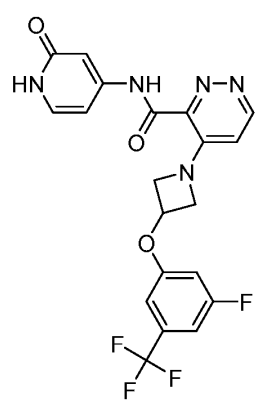
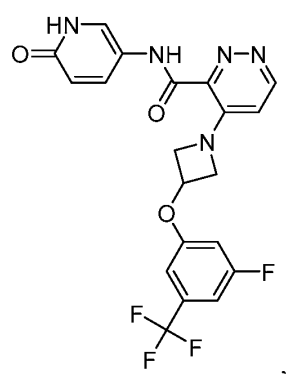
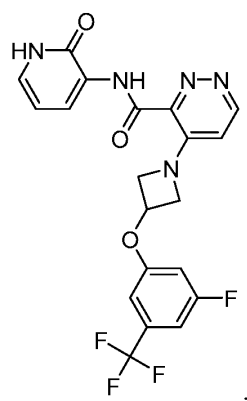
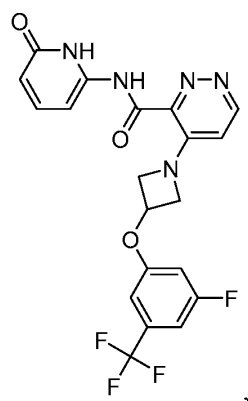
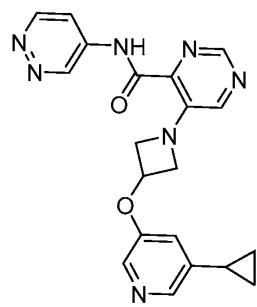
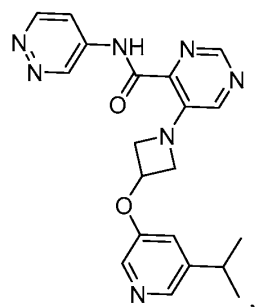


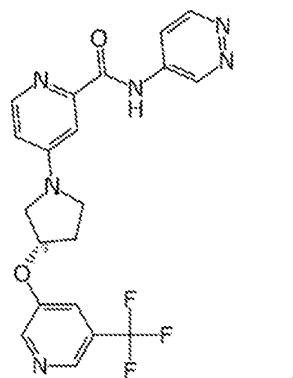
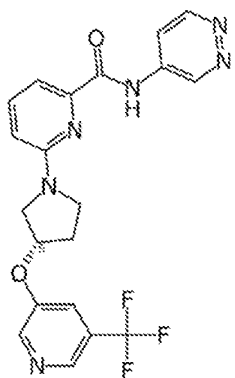
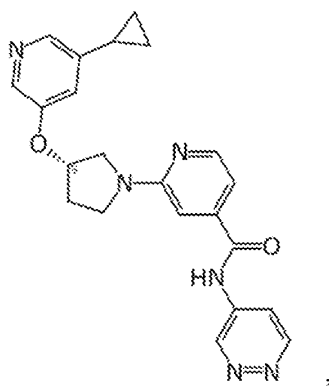
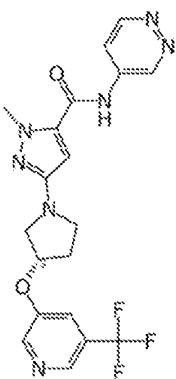
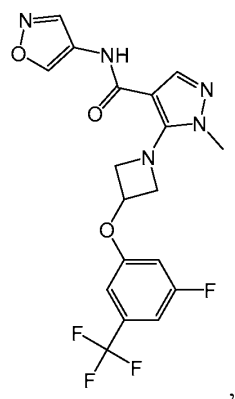
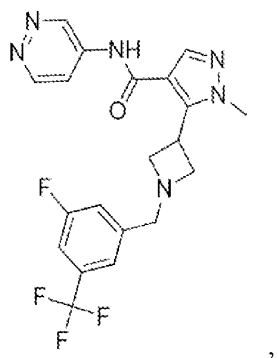


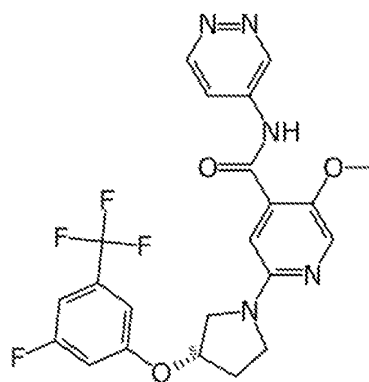
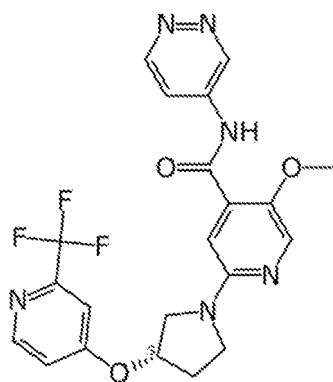
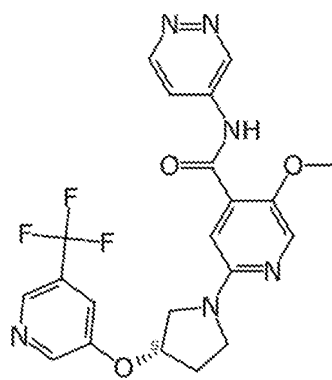
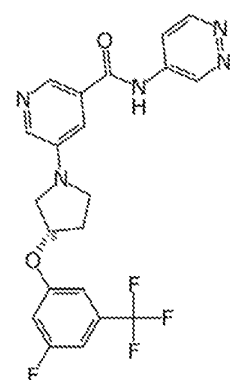
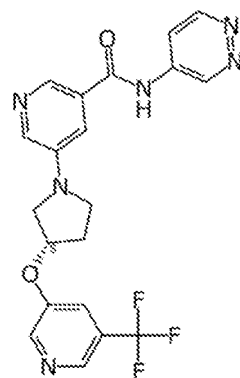
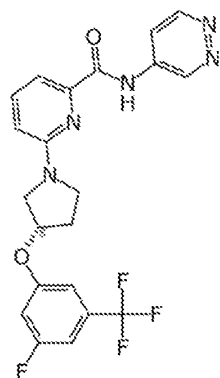


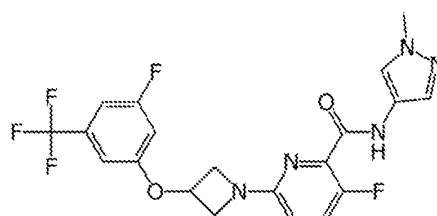
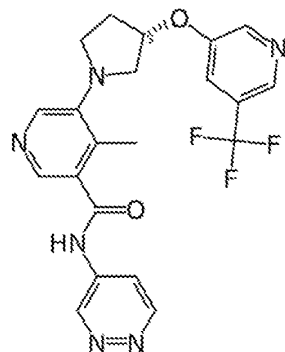
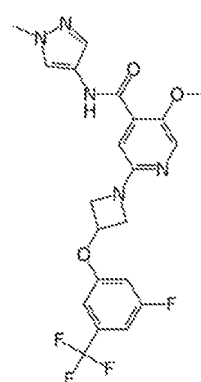
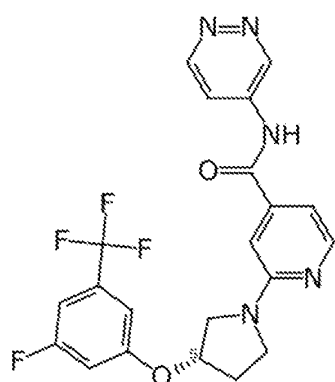
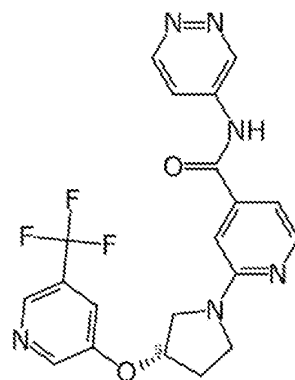
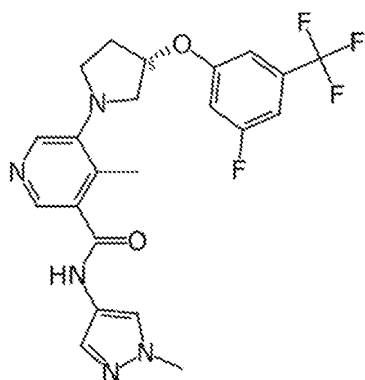












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