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(54) Title: LACTAMS FOR USE AS SARM1 INHIBITORS

(57) Abstract: This invention relates to lactam compounds of Formula (I), as further detailed herein, which are used for inhibition of SARM1 proteins, as well as compositions comprising these compounds and methods of treatment by their administration.

LACTAMS FOR USE AS SARM1 INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 63/588,206 filed on October 5, 2023 and U.S. Provisional Patent Application No. 63/679,941 filed on August 6, 2024, the contents of both which are incorporated herein by reference in their entirety.

FIELD OF THE DISCLOSURE

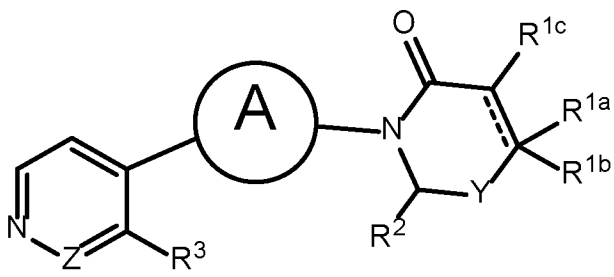
This invention relates to lactam compounds of Formula (I), as further detailed herein, which are used for inhibition of SARM1 (selective androgen receptor modulator 1) proteins, as well as compositions comprising these compounds and methods of treatment by their administration.

BACKGROUND OF THE DISCLOSURE

Axonal degeneration is a hallmark of several neurological disorders including peripheral neuropathy, traumatic brain injury, and neurodegenerative diseases (See, for example, Gerdts et al., SARM1 activation triggers axon degeneration locally via NAD(+) destruction. Science 3482016, pp.453-457 and Krauss et al., (2020) Trends Pharmacol. Sci.41, 281, each of which is hereby incorporated by reference in its entirety). Neurodegenerative diseases and injuries are devastating to both patients and caregivers. Costs associated with these diseases currently exceed several hundred billion dollars annually in the Unites States alone. Since the incidence of many of these diseases and disorders increases with age, their incidence is rapidly increasing as demographics change.

BRIEF DESCRIPTION OF THE DISCLOSURE

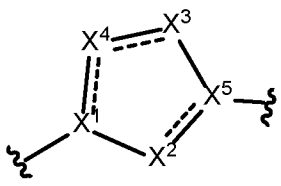
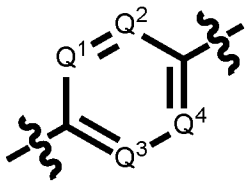
In one aspect, the present disclosure is directed to a compound of Formula (I):



I,

or pharmaceutically acceptable salts thereof;

wherein:

Ring A is  ; or  ;

X^1 is CR^7 or N;

X^2 is CR^4, CHR^4, or N;

X^3 is absent, CH, CH_2, NH, or S;

X^4 is N, CH_2, CH, NH, O, or S;

X^5 is CR^8;

Y is absent, CR^5R^6, or CH_2CH_2, wherein R^5 and R^6 are independently H, OH, CN, halo, C_{1-6} alkyl, or C_{1-6} cycloalkyl, or R^5 and R^6, taken together with the carbon to which they are bonded, form a C_{3-6} cycloalkyl;

Z is CH or N;

one of Q^1 and Q^2 is N and the other is CR^4;

one of Q^3 and Q^4 is N and the other is CR^4; or Q^3 and Q^4 are CR^4;

R^{1a} is H or C_{1-6} alkyl;

R^{1b} is selected from C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, bicyclo[1.1.1]pentan-1-yl, and C_{1-6} alkyl substituted with C_{6-10} aryl or C_{1-6} haloalkoxy; wherein each aryl, heteroaryl, cycloalkyl, and bicyclo[1.1.1]pentan-1-yl is optionally substituted with one to four substituents, wherein each substituent is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{3-6} cycloalkyl; or

R^{1a} and R^{1b} taken together with the carbon to which they are bonded, form a C_{3-6} cycloalkyl;

R^{1c} is H, F, or C_{1-6} alkyl;

R^2 is H, OH, CN, oxo or C_{1-6} alkyl;

R^3 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, and 5- to 10-membered heteroaryl;

R^4 is H, halo, cyano, C_{1-6} haloalkyl, or C_{1-6} hydroxyalkyl;

R^7 and R^8 are either absent, or form a -CH_2- bridge between the carbon atoms to which they are attached;

〰 represents the point of attachment to the rest of the compound; and

==== represents a single or double bond.

Also provided are methods of using the compounds for treatment of SARM1-mediated diseases and indications and methods of making the compounds.

DETAILED DESCRIPTION OF THE DISCLOSURE

DEFINITIONS

The term “halogen” or “halo” refers to F, Cl, Br or I. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl.

The term "alkyl" refers to a saturated linear or branched-chain monovalent hydrocarbon radical. In one example, the alkyl radical is one to eighteen carbon atoms (C_{1-18}). In other examples, the alkyl radical is C_{1-12}, C_{1-10}, C_{1-8}, C_{1-6}, C_{1-5}, C_{1-4}, or C_{1-3}. Examples of alkyl groups include methyl (Me, $–CH_3$), ethyl (Et, $–CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $–CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $–CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $–CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $–CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $–CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $–C(CH_3)_3$), 1-pentyl (n-pentyl, $–CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($–CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($–CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($–CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($–CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($–CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($–CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($–CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($–CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($–C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($–CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($–CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($–C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($–CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($–C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($–CH(CH_3)C(CH_3)_3$, 1-heptyl and 1-octyl.

The terms “cyano” or “nitrile” refers to –C≡N or –CN.

The term "haloalkoxy" refers to –O–haloalkyl.

The term "hydroxy" refers to –OH.

The term "hydroxyalkyl" refers to alkyl substituted with one hydroxy substituent.

The term “alkoxy” refers to –O–alkyl.

The term “aryl” refers to a carbocyclic aromatic group, whether or not fused to one or more groups, having the number of carbon atoms designated, or if no number is designated, up to 14 carbon atoms. One example includes aryl groups having 6-14 carbon atoms. Another example includes aryl groups having 6-10 carbon atoms. Examples of aryl groups include phenyl, naphthyl, biphenyl, phenanthrenyl, naphthacenyl, 1,2,3,4-tetrahydronaphthalenyl, 1H-indenyl, 2,3-dihydro-1H-indenyl,

and the like (see, e.g., Lang's Handbook of Chemistry (Dean, J. A., ed.) 13th ed. Table 7-2 [1985]). A particular aryl is phenyl.

The term "cycloalkyl" refers to a saturated hydrocarbon ring group. Cycloalkyl encompasses mono-, bi-, tricyclic, spiro and bridged, saturated ring systems. In one example, the cycloalkyl group is 3 to 12 carbon atoms (C_{3-12}). In other examples, cycloalkyl is C_{3-7}, C_{3-8}, C_{3-10}, or C_{5-10}. In other examples, the cycloalkyl group, as a monocycle, is C_{3-8}, C_{3-6}, or C_{5-6}. In another example, the cycloalkyl group, as a bicycle, is C_7-C_{12}. In another example, the cycloalkyl group, as a spiro system, is C_{5-12}. Examples of monocyclic cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl and cyclododecyl. Exemplary arrangements of bicyclic cycloalkyls having 7 to 12 ring atoms include, but are not limited to, [4,4], [4,5], [5,5], [5,6] or [6,6] ring systems. Exemplary bridged bicyclic cycloalkyls include, but are not limited to, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane and bicyclo[3.2.2]nonane. Examples of spirocycloalkyl include, spiro[2.2]pentane, spiro[2.3]hexane, spiro[2.4]heptane, spiro[2.5]octane and spiro[4.5]decane.

The term "heteroaryl" refers to any mono-, bi-, or tricyclic aromatic ring system containing from 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulfur, and in an example embodiment, at least one heteroatom is nitrogen. See, for example, Lang's Handbook of Chemistry (Dean, J. A., ed.) 13th ed. Table 7-2 [1985]. Included in the definition are any bicyclic groups where any of the above heteroaryl rings are fused to an aryl ring, wherein the aryl ring or the heteroaryl ring is joined to the remainder of the molecule. In one embodiment, heteroaryl includes 5-6 membered monocyclic aromatic groups where one or more ring atoms is nitrogen, sulfur or oxygen. Example heteroaryl groups include thienyl, furyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, thiatriazolyl, oxatriazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, tetrazinyl, tetrazolo[1,5-b]pyridazinyl, imidazol[1,2-a]pyrimidinyl and purinyl, as well as benzo-fused derivatives, for example benzoxazolyl, benzofuryl, benzothiazolyl, benzothiadiazolyl, benzotriazolyl, benzoimidazolyl, indazolyl and indolyl.

In particular embodiments, a heteroaryl group is attached at a carbon atom of the heteroaryl group. By way of example, carbon bonded heterocyclyl groups include bonding arrangements at position 2, 3, 4, 5, or 6 of a pyridine ring, position 3, 4, 5, or 6 of a pyridazine ring, position 2, 4, 5, or 6 of a pyrimidine ring, position 2, 3, 5, or 6 of a pyrazine ring, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole ring, position 2, 4, or 5 of an oxazole, imidazole or thiazole ring, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole ring, position 2 or 3 of an aziridine ring, position 2, 3, or 4 of an azetidine ring, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline ring or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline ring.

In certain embodiments, the heteroaryl group is N-attached. By way of example, nitrogen bonded heterocyclyl or heteroaryl groups include bonding arrangements at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of an isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline.

"Fused" refers to any ring structure described herein that shares one or more atoms (e.g., carbon or nitrogen atoms) with an existing ring structure in the compounds of the invention.

The term "haloalkyl" refers to an alkyl chain in which one or more hydrogen has been replaced by a halogen. Examples of haloalkyls are trifluoromethyl, difluoromethyl, and fluoromethyl.

The terms "compound(s) of the invention," and "compound(s) of the present invention" and the like, unless otherwise indicated, include compounds of Formula (I), Formula (II), Formula (III), Formula (IV), Formulas (IIa)-(IIg), Formulas (IIIa)-(IIIc), Formulas (IVa)-(IVc), Formulas (IIa-1), (IIa-2) (IIa-3), (IIa-4), (IIa-5), (IIa-6), (IIb-1), (IIb-2), (IIb-3), (IIb-4), (IIb-5), (IIb-6), (IIc-1), (IIc-2), (IIc-3), (IIc-4), (IIc-5), (IIc-6), (IId-1), (IId-2), (IId-3), (IId-4), (IId-5), (IId-6), (IIe-1), (IIe-2), (IIe-3), (IIe-4), (IIe-5), (IIe-6), (IIf-1), (IIf-2), (IIf-3), (IIf-4), (IIf-5), (IIf-6), (IIg-1), (IIg-2), (IIg-3), (IIg-4), (IIg-5), and (IIg-6), and the compounds listed in the Tables herein, including stereoisomers (including atropisomers), geometric isomers, tautomers, isotopes, and salts (e.g., pharmaceutically acceptable salts) thereof.

The term "optionally substituted" unless otherwise specified means that a group may be unsubstituted or substituted by one or more (e.g., 0, 1, 2, 3, 4, or 5 or more, or any range derivable therein) of the substituents listed for that group in which said substituents may be the same or different. In an embodiment, an optionally substituted group has 1 substituent. In another embodiment an optionally substituted group has 2 substituents. In another embodiment an optionally substituted group has 3 substituents. In another embodiment an optionally substituted group has 4 substituents. In another embodiment an optionally substituted group has 5 substituents.

As used herein a wavy line "" that intersects a bond in a chemical structure indicate the point of attachment of the atom to which the wavy bond is connected in the chemical structure to the remainder of a molecule, or to the remainder of a fragment of a molecule.

As used herein, "" represents a single or double bond in a chemical structure.

In certain embodiments, divalent groups are described generically without specific bonding configurations. It is understood that the generic description is meant to include both bonding configurations, unless specified otherwise. For example, in the group R^1–R^2–R^3, if the group R^2 is

described as $-CH_2C(O)-$, then it is understood that this group can be bonded both as $R^1-CH_2C(O)-R^3$, and as $R^1-C(O)CH_2-R^3$, unless specified otherwise.

The term "pharmaceutically acceptable" refers to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, such as, for example, a human, as appropriate.

Compounds of the invention may be in the form of a salt, such as a pharmaceutically acceptable salt. "Pharmaceutically acceptable salts" include both acid and base addition salts. "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid and the like, and organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

The term "pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particular base addition salts are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, tromethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particular organic non-toxic bases include isopropylamine, diethylamine, ethanolamine, tromethamine, dicyclohexylamine, choline, and caffeine.

In some embodiments, a salt is selected from a hydrochloride, hydrobromide, trifluoroacetate, sulfate, phosphate, acetate, fumarate, maleate, tartrate, lactate, citrate, pyruvate, succinate, oxalate, methanesulfonate, p-toluenesulfonate, bisulfate, benzenesulfonate, ethanesulfonate, malonate, xinafoate, ascorbate, oleate, nicotinate, saccharinate, adipate, formate, glycolate, palmitate, L-lactate, D-lactate, aspartate, malate, L-tartrate, D-tartrate, stearate, furoate (e.g., 2-furoate or 3-furoate),

napadisylate (naphthalene-1,5-disulfonate or naphthalene-1-(sulfonic acid)-5-sulfonate), edisylate (ethane-1,2-disulfonate or ethane-1-(sulfonic acid)-2-sulfonate), isothionate (2-hydroxyethylsulfonate), 2-mesitylenesulfonate, 2-naphthalenesulfonate, 2,5-dichlorobenzenesulfonate, D-mandelate, L-mandelate, cinnamate, benzoate, adipate, esylate, malonate, mesitylate (2-mesitylenesulfonate), napsylate (2-naphthalenesulfonate), camsylate (camphor-10-sulfonate, for example (1S)-(+)-10-camphorsulfonic acid salt), glutamate, glutarate, hippurate (2-(benzoylamino)acetate), orotate, xylate (p-xylene-2-sulfonate), and pamoic (2,2'-dihydroxy-1,1'-dinaphthylmethane-3,3'-dicarboxylate).

A "sterile" formulation is aseptic or free from all living microorganisms and their spores.

The term "stereoisomers" refer to compounds that have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space. Stereoisomers include diastereomers, enantiomers, conformers and the like.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g., melting points, boiling points, spectral properties or biological activities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography such as HPLC.

The term "enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or *R* and *S,* are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur

where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

"Atropisomers" are stereoisomers arising because of hindered rotation around a single bond, where energy differences due to steric strain or other contributors create a barrier to rotation that is high enough to allow for isolation of individual conformers.

The invention described herein also embraces isotopically-labeled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. All isotopes of any particular atom or element as specified are contemplated within the scope of the compounds of the invention, and their uses. Exemplary isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I. Certain isotopically-labeled compounds of the present invention (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (^{3}H) and carbon-14 (^{14}C) isotopes are useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Isotopically labeled compounds of the present invention can generally be prepared by following procedures analogous to those disclosed in the Examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

Compounds of the invention may contain one or more asymmetric carbon atoms. Accordingly, the compounds may exist as diastereomers, enantiomers or mixtures thereof. The syntheses of the compounds may employ racemates, diastereomers or enantiomers as starting materials or as intermediates. Mixtures of particular diastereomeric compounds may be separated, or enriched in one or more particular diastereomers, by chromatographic or crystallization methods.

Similarly, enantiomeric mixtures may be separated, or enantiomerically enriched, using the same techniques or others known in the art. Each of the asymmetric carbon or nitrogen atoms may be in the R or S configuration and both of these configurations are within the scope of the invention.

In the structures shown herein, where the stereochemistry of any particular chiral atom is not specified, then all stereoisomers are contemplated and included as the compounds of the invention. Where stereochemistry is specified by a solid wedge or dashed line representing a particular configuration, then that stereoisomer is so specified and defined. Unless otherwise specified, if solid wedges or dashed lines are used, relative stereochemistry is intended.

A "subject," "individual," or "patient" is a vertebrate. In certain embodiments, the vertebrate is a mammal. Mammals include, but are not limited to, farm animals (such as cows), sport animals, pets (such as guinea pigs, cats, dogs, rabbits and horses), primates, mice and rats. In certain embodiments, a mammal is a human. In embodiments comprising administration of a compound of to a patient, the patient is typically in need thereof.

The terms "inhibiting" and "reducing," or any variation of these terms, includes any measurable decrease or complete inhibition to achieve a desired result. For example, there may be a decrease of about, at most about, or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more, or any range derivable therein, reduction of activity compared to normal.

A "therapeutically effective amount" means an amount of a compound of the present invention, such as a compound of Formula (I), Formula (II), Formula (III), or Formula (IV), or any other Formula specified herein, or a pharmaceutically acceptable salt thereof, that (i) treats or prevents the particular disease, condition or disorder, or (ii) attenuates, ameliorates or eliminates one or more symptoms of the particular disease, condition, or disorder, and optionally (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition or disorder described herein.

"Treatment" (and variations such as "treat" or "treating") refers to clinical intervention in an attempt to alter the natural course of the individual or cell being treated, and can be performed either for prophylaxis or during the course of clinical pathology. Desirable effects of treatment include preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, stabilized (i.e., not worsening) state of disease, decreasing the rate of disease progression, amelioration or palliation of the disease state, prolonging survival as compared to expected survival if not receiving treatment and remission or improved prognosis. In some embodiments, compounds of the invention, are used to delay development of a disease or disorder or to slow the progression of a disease or disorder. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or

disorder, (for example, through a genetic mutation) or those in which the condition or disorder is to be prevented.

A "therapeutic effect," as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described above. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

The term "co-administration," "administered in combination with," and their grammatical equivalents, as used herein, encompass administration of two or more agents to an animal, including humans, so that both agents and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which both agents are present.

The terms "antagonist" and "inhibitor" are used interchangeably, and they refer to a compound having the ability to inhibit a biological function of a target protein, whether by inhibiting the activity or expression of the protein, such as SARM1. Accordingly, the terms "antagonist" and "inhibitors" are defined in the context of the biological role of the target protein. While preferred antagonists herein specifically interact with (e.g., bind to) the target, compounds that inhibit a biological activity of the target protein by interacting with other members of the signal transduction pathway of which the target protein is a member are also specifically included within this definition. A preferred biological activity inhibited by an antagonist is associated with the development, growth, or spread of a tumor.

The term "agonist" as used herein refers to a compound having the ability to initiate or enhance a biological function of a target protein, whether by inhibiting the activity or expression of the target protein. Accordingly, the term "agonist" is defined in the context of the biological role of the target polypeptide. While preferred agonists herein specifically interact with (e.g., bind to) the target, compounds that initiate or enhance a biological activity of the target polypeptide by interacting with other members of the signal transduction pathway of which the target polypeptide is a member are also specifically included within this definition.

Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. Exemplary isotopes that can be incorporated into compounds of the invention, include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. Isotopically-labeled compounds (e.g., those labeled with ^{3}H and ^{14}C) can be useful in compound or substrate tissue distribution assays. Tritiated

(i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes can be useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements). In some embodiments, in compounds of the invention, one or more carbon atoms are replaced by ^{13}C- or ^{14}C-enriched carbon. Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C, and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Isotopically labeled compounds can generally be prepared by following procedures analogous to those disclosed in the Schemes or in the Examples herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

It is specifically contemplated that any limitation discussed with respect to one embodiment of the invention may apply to any other embodiment of the invention. Furthermore, any compound or composition of the invention may be used in any method of the invention, and any method of the invention may be used to produce or to utilize any compound or composition of the invention.

The use of the term "or" is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternative are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or."

Throughout this application, the term "about" is used to indicate that a value includes the standard deviation of error for the device or method being employed to determine the value.

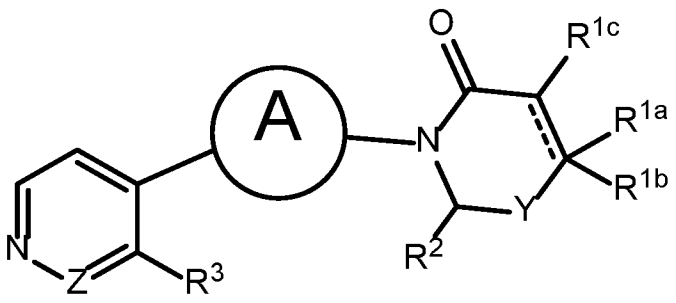
As used herein, "a" or "an" means one or more, unless clearly indicated otherwise. As used herein, "another" means at least a second or more.

Headings used herein are intended only for organizational purposes.

SARM1 INHIBITORS

In an aspect, the invention provides compounds which are capable of selectively binding to and/or modulating a SARM1 protein.

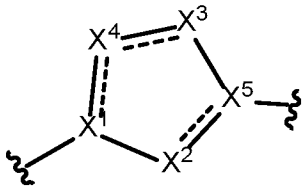
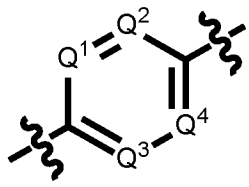
As noted, one aspect of the invention includes a compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof;

wherein:

Ring A is  ; or  ;

X^1 is CR^7 or N;

X^2 is CR^4, CHR^4, or N;

X^3 is absent, CH, CH_2, NH, or S;

X^4 is N, CH_2, CH, NH, O, or S;

X^5 is CR^8;

Y is absent, CR^5R^6, or CH_2CH_2, wherein R^5 and R^6 are independently H, OH, CN, halo, C_{1-6} alkyl, or C_{1-6} cycloalkyl, or R^5 and R^6, taken together with the carbon to which they are bonded, form a C_{3-6} cycloalkyl;

Z is CH or N;

one of Q^1 and Q^2 is N and the other is CR^4;

one of Q^3 and Q^4 is N and the other is CR^4; or Q^3 and Q^4 are CR^4;

R^{1a} is H or C_{1-6} alkyl;

R^{1b} is selected from C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, bicyclo[1.1.1]pentan-1-yl, and C_{1-6} alkyl substituted with C_{6-10} aryl or C_{1-6} haloalkoxy; wherein each aryl, heteroaryl, cycloalkyl, and bicyclo[1.1.1]pentan-1-yl is optionally substituted with one to four substituents, wherein each substituent is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{3-6} cycloalkyl; or

R^{1a} and R^{1b} taken together with the carbon to which they are bonded, form a C_{3-6} cycloalkyl;

R^{1c} is H, F, or C_{1-6} alkyl;

R^2 is H, OH, CN, oxo or C_{1-6} alkyl;

R^3 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, and 5- to 10-membered heteroaryl;

R^4 is H, halo, cyano, C_{1-6} haloalkyl, or C_{1-6} hydroxyalkyl;

R^7 and R^8 are either absent, or form a -CH_2- bridge between the carbon atoms to which they are attached;

〰 represents the point of attachment to the rest of the compound; and

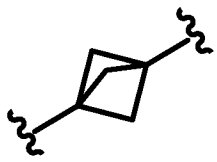
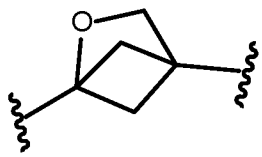
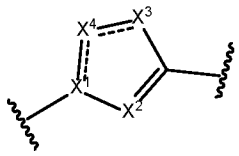
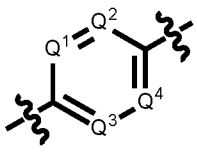
═══ represents a single or double bond.

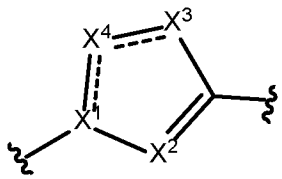
According to some embodiments of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, X^1 is CR^7; X^2 is CHR^4; X^3 is absent or CH_2; X^4 is CH_2 or O; X^5 is CR^8; and R^7 and R^8 form a -CH_2- bridge between the carbon atoms to which they are attached. In one such embodiment, R^4 is H.

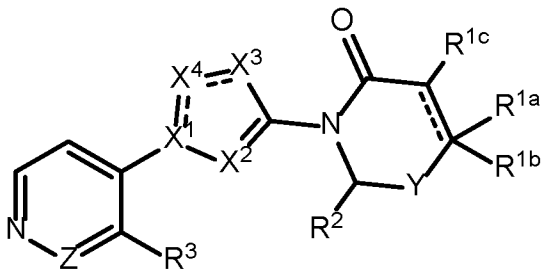
According to some embodiments of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, X^1 is CR^7; X^2 is CHR^4; X^3 is absent; X^4 is CH_2; X^5 is CR^8; and R^7 and R^8 form a -CH_2- bridge between the carbon atoms to which they are attached. In one such embodiment, R^4 is H.

According to some embodiments of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, X^1 is CR^7; X^2 is CHR^4; X^3 is CH_2; X^4 is O; X^5 is CR^8; and R^7 and R^8 form a -CH_2- bridge between the carbon atoms to which they are attached. In one such embodiment, R^4 is H.

According to some embodiments of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, Ring A is selected from

 ,  ,  , and  wherein X^1, X^2, X^3, X^4, Q^1, Q^2, Q^3 and Q^4 are as defined above. In some such embodiments, X^1 is C or N; X^2 is CR^4 or N; X^3 is CH, NH, or S; and X^4 is N, CH, NH, or S. In some embodiments Q1 is N and Q^2, Q^3 and Q^4 are CR^4. In one such embodiment, R^4 is H.

According to some embodiments of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, Ring A is  , and the compound has Formula (II):



(II),

wherein Z, Y, X^1, X^2, X^3, X4, R^{1a}, R^{1b}, R^{1c}, R^2, and R^3 are as defined for Formula (I).

According to some embodiments of the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof, X^1 is C; X^2 is N; X^3 is NH; and X^4 is N.

According to some embodiments of the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof, X^1 is C; X^2 is CR^4; X^3 is NH; and X^4 is N, wherein R^4 is as defined for Formula (I). In one such embodiment, R^4 is H.

According to some embodiments of the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof, X^1 is N; X^2 is CR^4; X^3 is CH; and X^4 is N, wherein R^4 is as defined for Formula (I). In one such embodiment, R^4 is H.

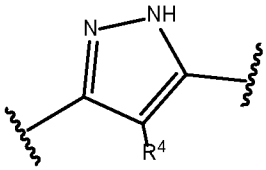
According to some embodiments of the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof, X^1 is C; X^2 is CR^4; X^3 is S; and X^4 is N, wherein R^4 is as defined for Formula (I). In one such embodiment, R^4 is H.

According to some embodiments of the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof, X^1 is N; X^2 is N; X^3 is CH; and X^4 is N.

According to some embodiments of the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof, X^1 is N; X^2 is N; X^3 is CH; and X^4 is CH.

According to some embodiments of the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof, X^1 is C; X^2 is N; X^3 is NH; and X^4 is CH.

According to some embodiments of the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof, Ring A is selected from



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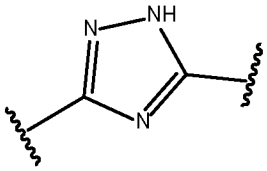

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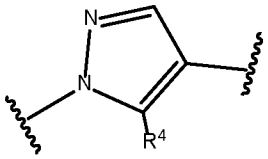

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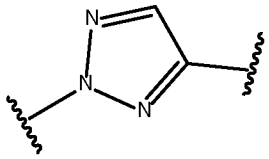

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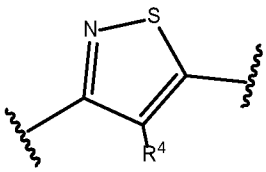

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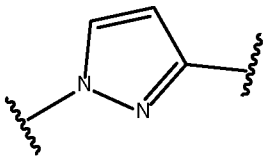

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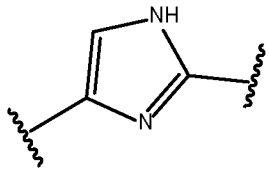
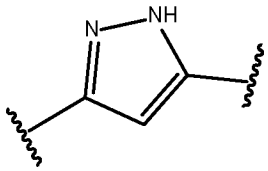
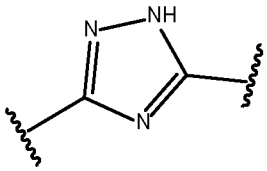
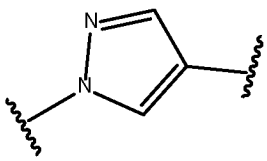
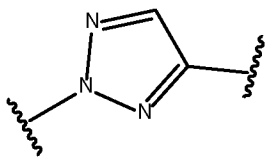
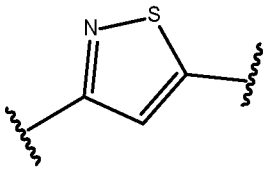
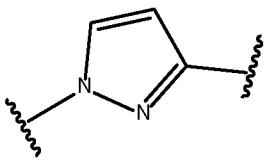
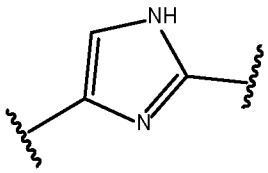


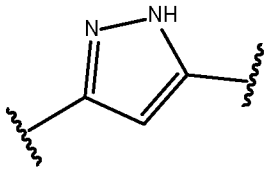
,

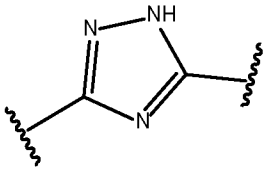
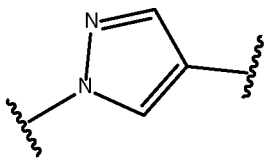
wherein R^4 is as defined for Formula (I). In one such embodiment, R^4 is H, halo, or C_{1-6} hydroxyalkyl. In one such embodiment, R^4 is H.

According to some embodiments of the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof, Ring A is selected from

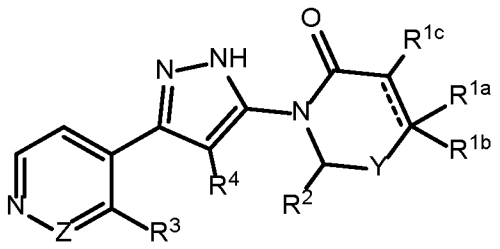
 ,  ,  ,  ,

 ,  , and  .

According to some embodiments of the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof, Ring A is selected from  ,

 , and  .

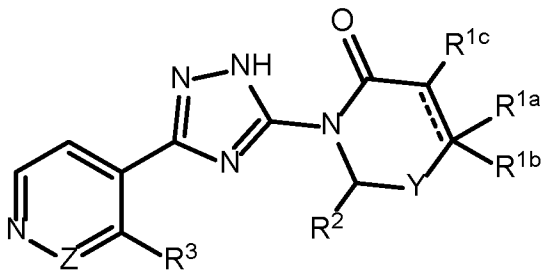
According to some embodiments of the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof, the compound has Formula (IIa):



(IIa),

wherein Z, Y, R^{1a}, R^{1b}, R^{1c}, R^2, R^3, and R^4 are as defined for Formula (I). In one such embodiment, R^4 is H.

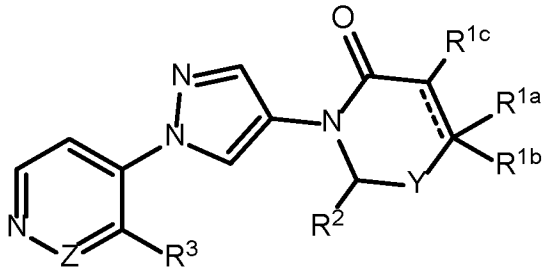
According to some embodiments of the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof, the compound has Formula (IIb):



(IIb),

wherein Z, Y, R^{1a}, R^{1b}, R^{1c}, R^2, and R^3 are as defined for Formula (I).

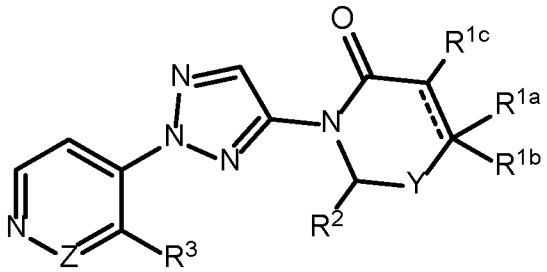
According to some embodiments of the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof, the compound has Formula (IIc):



(IIc),

wherein Z, Y, R^{1a}, R^{1b}, R^{1c}, R^2, and R^3 are as defined for Formula (I).

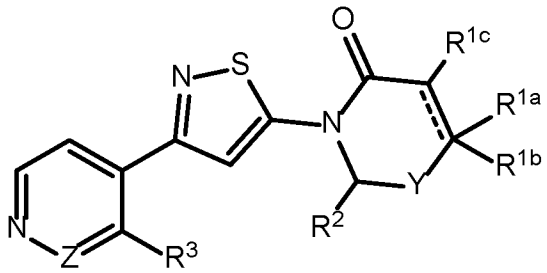
According to some embodiments of the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof, the compound has Formula (IId):



(IId),

wherein Z, Y, R^{1a}, R^{1b}, R^{1c}, R^2, and R^3 are as defined for Formula (I).

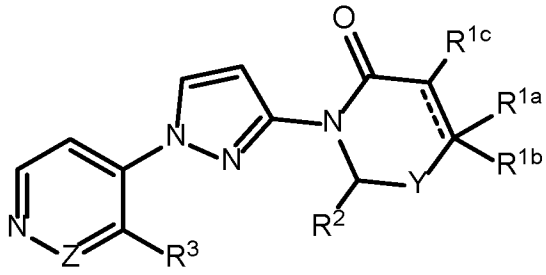
According to some embodiments of the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof, the compound has Formula (IIe):



(IIe),

wherein Z, Y, R^{1a}, R^{1b}, R^{1c}, R^2, and R^3 are as defined for Formula (I).

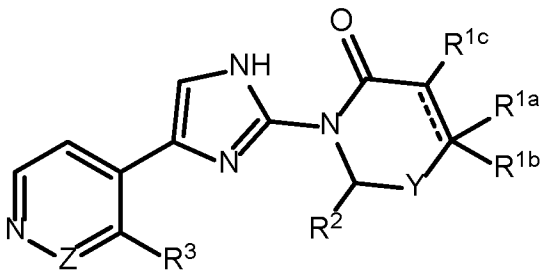
According to some embodiments of the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof, the compound has Formula (IIf):



(IIf),

wherein Z, Y, R^{1a}, R^{1b}, R^{1c}, R^2, and R^3 are as defined for Formula (I).

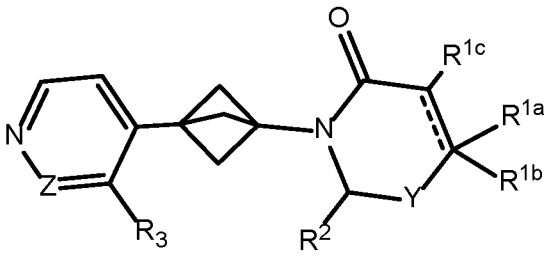
According to some embodiments of the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof, the compound has Formula (IIg):



(IIg),

wherein Z, Y, R^{1a}, R^{1b}, R^{1c}, R^2, and R^3 are as defined for Formula (I).

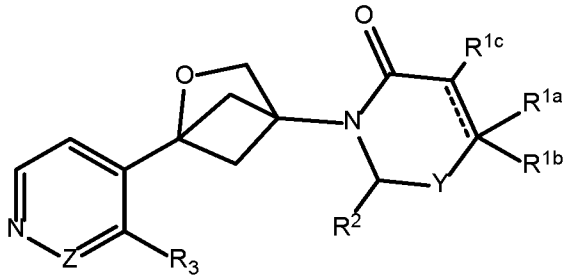
According to some embodiments of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, the compound has Formula (III):



(III),

wherein Z, Y, R^{1a}, R^{1b}, R^{1c}, R^2, and R^3 are as defined for Formula I.

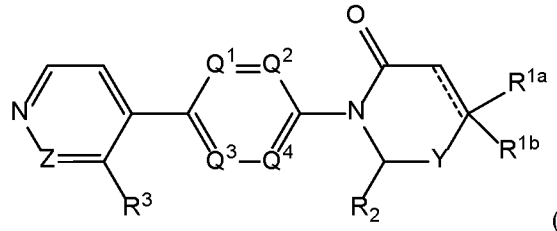
A ccording to some embodiments of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, the compound has Formula (IV):



(IV),

wherein Z, Y, R^{1a}, R^{1b}, R^{1c}, R^2, and R^3 are as defined for Formula I.

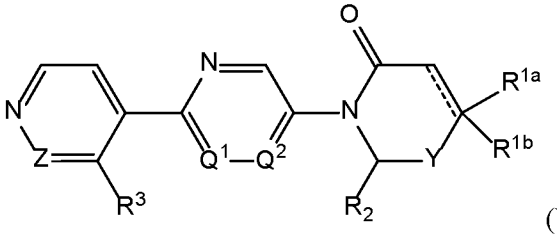
According to some embodiments of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, the compound has Formula (V)



(V)

wherein Z, Y, Q^1, Q^2, Q^3, Q^4, R^{1a}, R^{1b}, R^2, and R^3 are as defined herein.

A According to some embodiments of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, the compound has Formula (Va)



(Va)

wherein Z, Y, Q^3, Q^4, R^{1a}, R^{1b}, R^2, and R^3 are as defined herein.

According to some embodiments of the compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), Formula (IIf), Formula (IIg), or a pharmaceutically acceptable salt thereof, Z is N.

According to some embodiments of the compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), Formula (IIf), Formula (IIg), or a pharmaceutically acceptable salt thereof, Z is CH.

According to some embodiments of the compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), Formula (IIf), Formula (IIg), or a pharmaceutically acceptable salt thereof, R^3 is H, cyclopropyl, phenyl, or pyridinyl. In one such embodiment, R^3 is H.

According to some embodiments of the compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), Formula (IIf), Formula (IIg), or a pharmaceutically acceptable salt thereof, Y is absent.

According to some embodiments of the compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), Formula (IIf), Formula (IIg), or a pharmaceutically acceptable salt thereof, Y is CH_2CH_2.

According to some embodiments of the compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), Formula (IIf), Formula (IIg), or a pharmaceutically acceptable salt thereof, Y is CR^5R^6, wherein R^5 and R^6 are as defined for Formula (I). In one such embodiment, R^5 and R^6 are independently H, OH, CN, or halo. In one such embodiment, R^5 and R^6 are H. In one such embodiment, R^5 is H and R^6 is OH or CN.

According to some embodiments of the compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), Formula (IIf), Formula (IIg), or a pharmaceutically acceptable salt thereof, R^2 is H, OH, CN, oxo or methyl. In some such embodiments, R^2 is H.

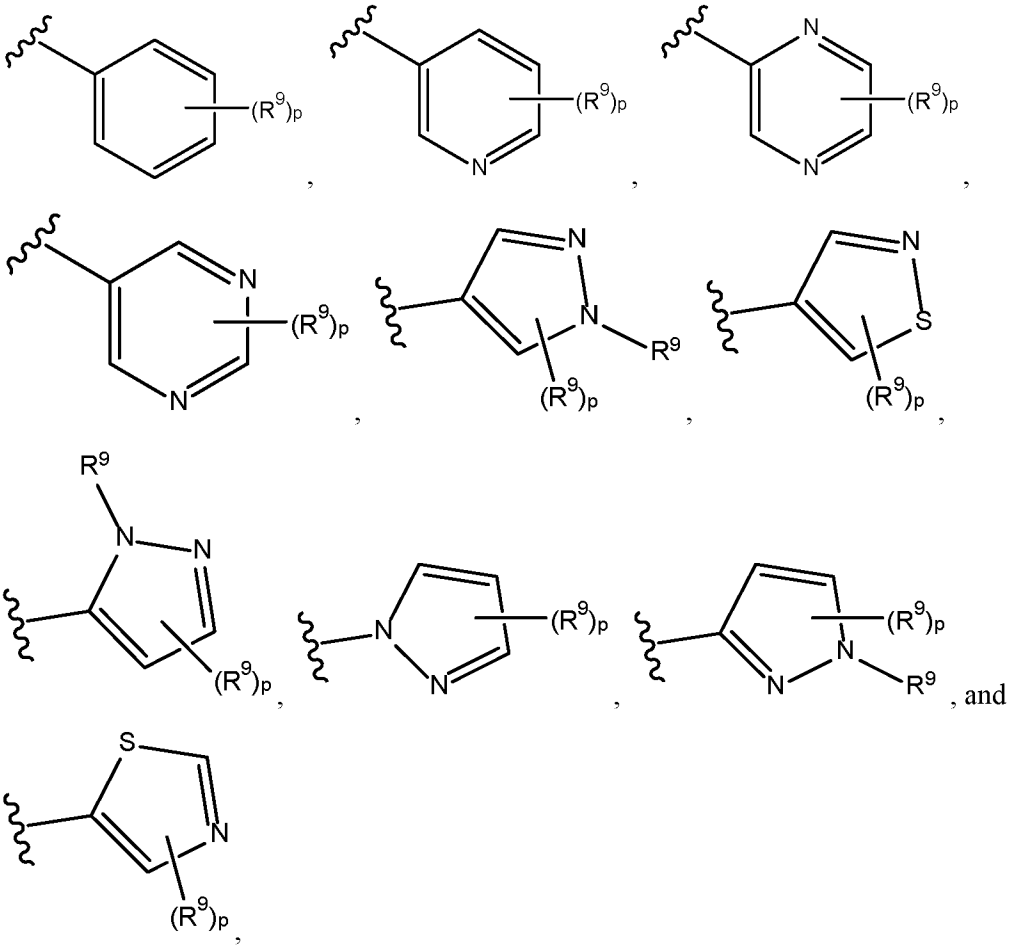
According to some embodiments of the compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), Formula (IIf), Formula (IIg), or a pharmaceutically acceptable salt thereof, R^{1a} is H or methyl. In some such embodiments, R^{1a} is H.

According to some embodiments of the compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), Formula (IIf), Formula (IIg), or a pharmaceutically acceptable salt thereof, R^{1a} and R^{1b} taken together with the carbon to which they are bonded, form a C_{3-6} cycloalkyl.

According to some embodiments of the compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), Formula (IIf), Formula (IIg), or a pharmaceutically acceptable salt thereof, R^{1b} is selected from C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, and C_{1-6} alkyl substituted with C_{6-10} aryl or C_{1-6} haloalkoxy; wherein each aryl or heteroaryl is optionally substituted with one to four substituents, wherein each substituent is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{3-6} cycloalkyl.

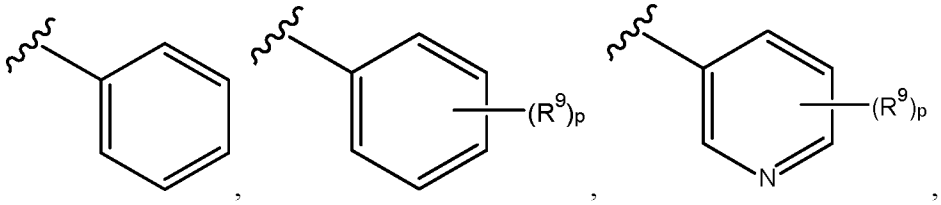
According to some embodiments of the compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), Formula (IIf), Formula (IIg), or a pharmaceutically acceptable salt thereof, R^{1b} is selected from C_{6-10} aryl and 5- to 10-membered heteroaryl, wherein each aryl or heteroaryl is optionally substituted with one to four substituents, wherein each substituent is independently selected from C_{1-6} alkyl, halo, C_{1-6} alkoxy, and C_{1-6} haloalkyl.

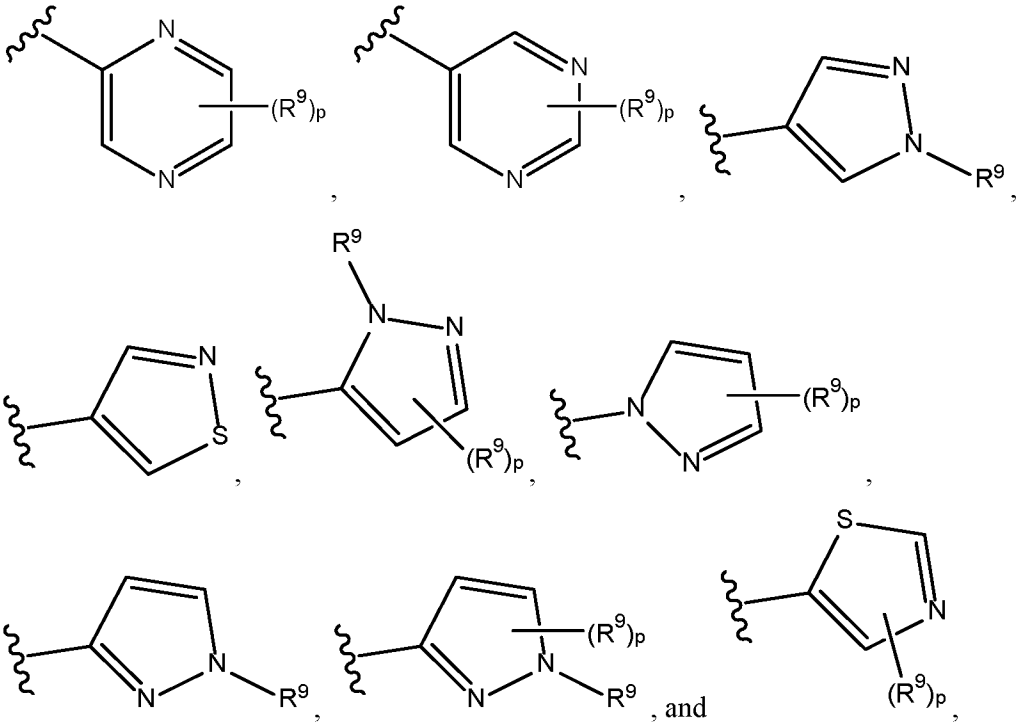
According to some embodiments of the compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), Formula (IIf), Formula (IIg), or a pharmaceutically acceptable salt thereof, R^{1b} is selected from



wherein each R^9 is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{3-6} cycloalkyl; and p is 0, 1, 2, 3, or 4. In some such embodiments, each R^9 is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, and C_{1-6} alkoxy. In some such embodiments, each R^9 is independently selected from methyl, halo, C_1 haloalkyl and methoxy.

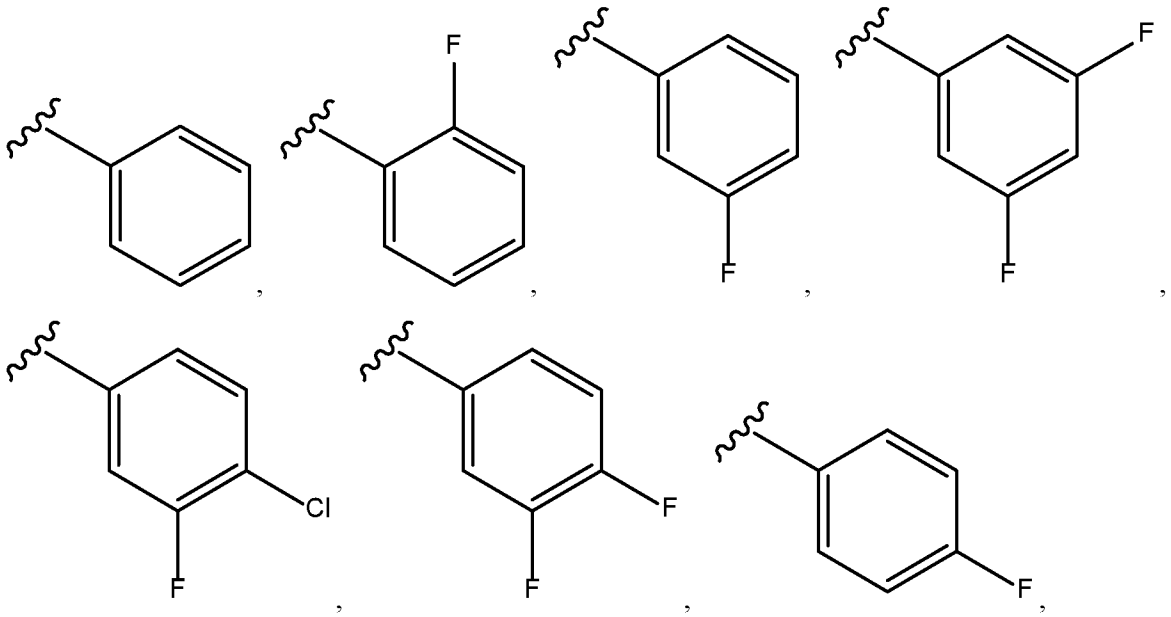
According to some embodiments of the compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), Formula (IIf), Formula (IIg), or a pharmaceutically acceptable salt thereof, R^{1b} is selected from

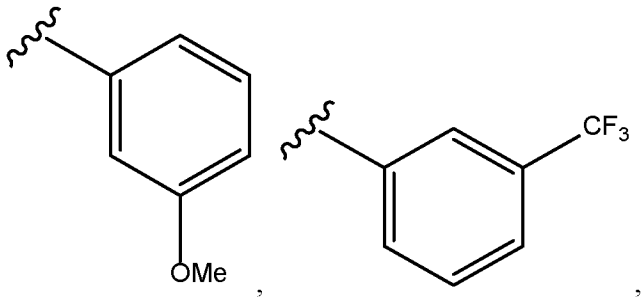


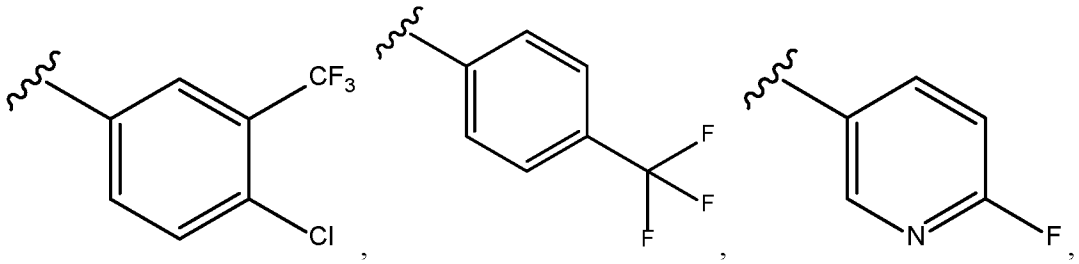


wherein p is 1 or 2. In some such embodiments, each R^9 is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl and C_{1-6} alkoxy. In some such embodiments, each R^9 is independently selected from methyl, halo, C_1 haloalkyl, and methoxy.

According to some embodiments of the compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), Formula (IIf), Formula (IIg), or a pharmaceutically acceptable salt thereof, R^{1b} is selected from




OMe
CF3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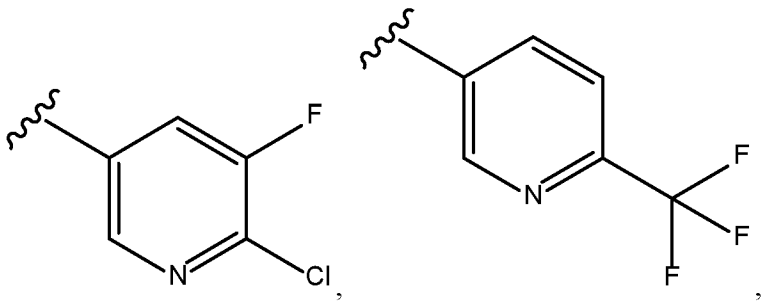
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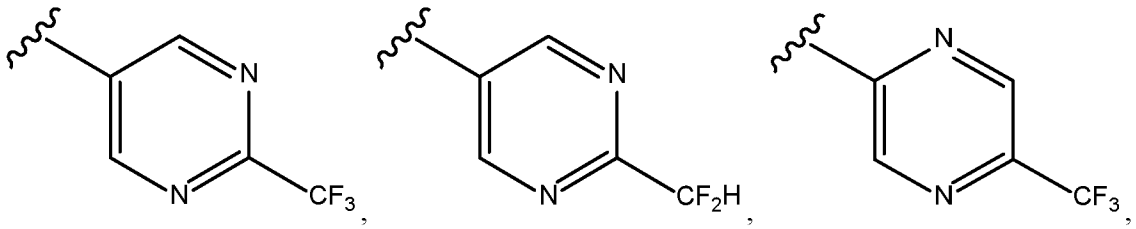
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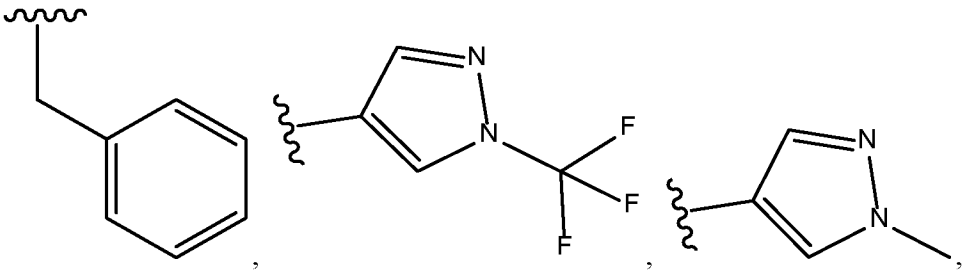
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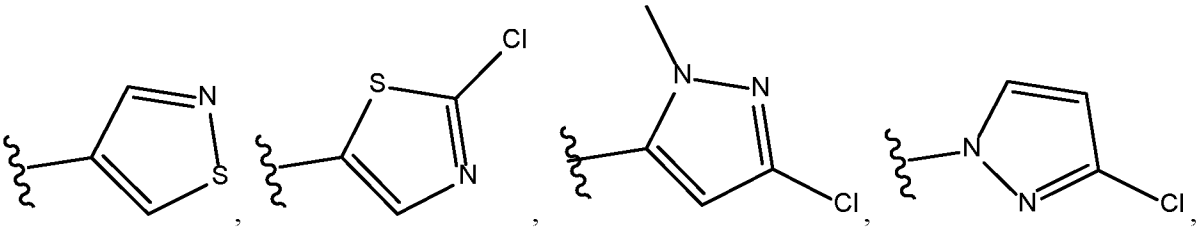
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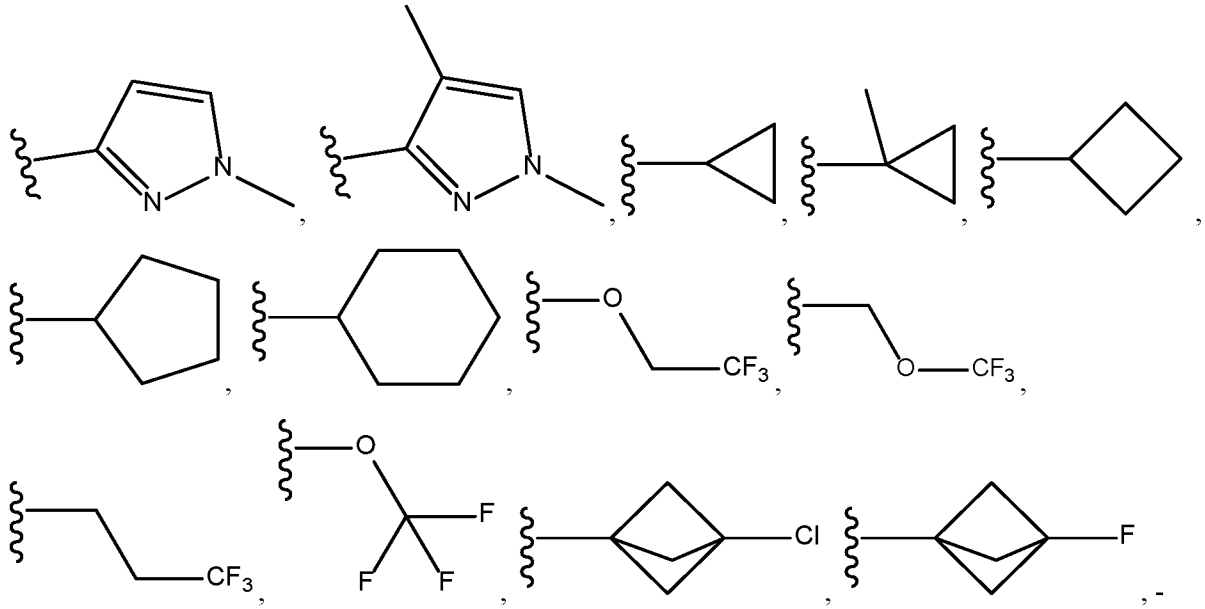
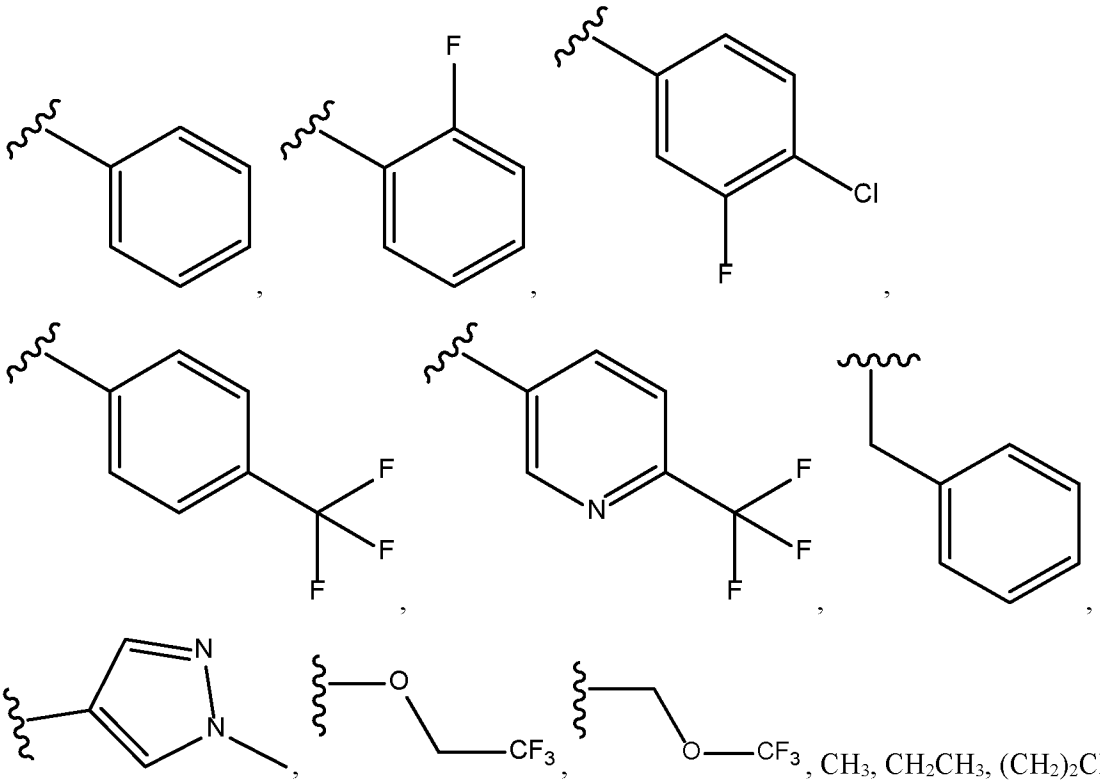


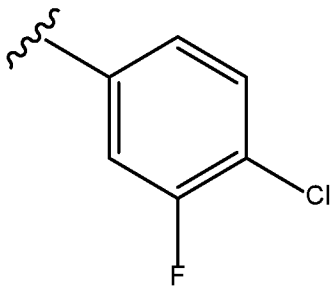
CH_3, -CH_2CH_3, -$(CH_2)_2CH_3$, CH_2CF_3, and CF_3.

According to some embodiments of the compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), Formula (IIf), Formula (IIg), or a pharmaceutically acceptable salt thereof, R^{1b} is selected from



, CH_3, CH_2CH_3, $(CH_2)_2CH_3$, and CF_3.

According to some embodiments of the compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), Formula (IIf), Formula (IIg), or a pharmaceutically acceptable salt thereof, R^{1b} is

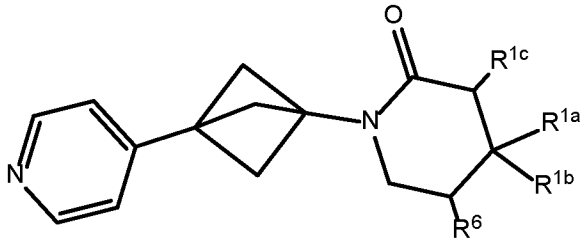


.

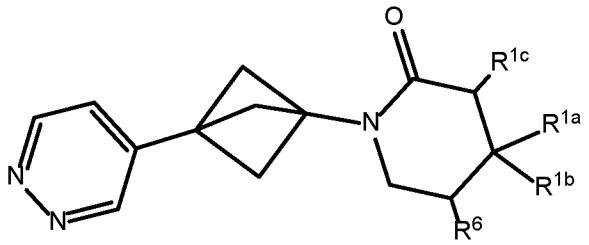
According to some embodiments of the compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), Formula (IIf), Formula (IIg), or a pharmaceutically acceptable salt thereof, R^{1c} is H.

According to some embodiments of the compound of Formula (I), Formula (II), Formula (III), Formula (IV), Formula (IIa), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe), Formula (IIf), Formula (IIg), or a pharmaceutically acceptable salt thereof, R^{1c} is F.

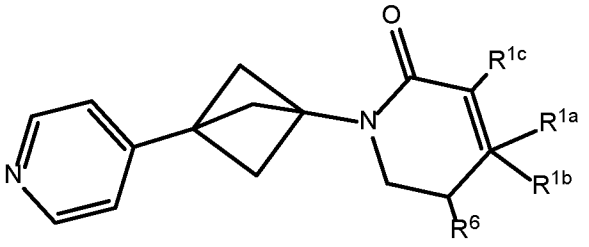
According to some embodiments of the compound of Formula (I) or Formula (III), or a pharmaceutically acceptable salt thereof, the compound has Formula (IIIa), Formula (IIIb), or Formula (IIIc):



(IIIa)



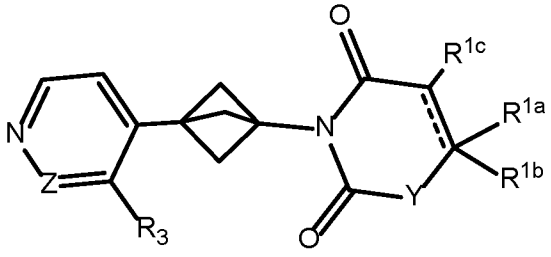
(IIIb)



(IIIc),

wherein R^6 is H, OH, or CN, and R^{1a}, R^{1b}, and R^{1c} are as defined for Formula (I). In one such embodiment, wherein R^{1a} is H and R^{1b} is selected from C_{6-10} aryl and 5- to 10-membered heteroaryl, wherein each aryl or heteroaryl is optionally substituted with one to four substituents, wherein each substituent is independently selected from C_{1-6} alkyl, halo, and C_{1-6} haloalkyl. In one such embodiment, each aryl or heteroaryl is optionally substituted with one to four substituents, wherein each substituent is independently halo.

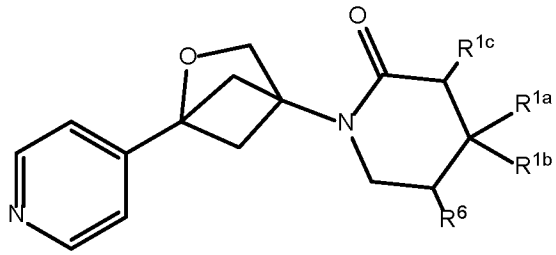
According to some embodiments of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, the compound has Formula (IIId):



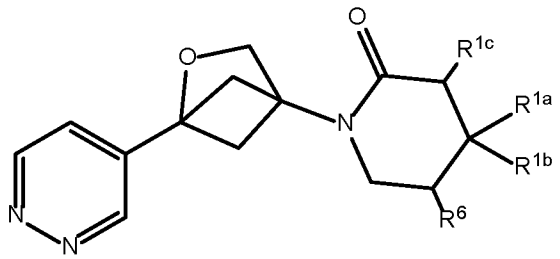
(IIId),

wherein Z, Y, R^{1a}, R^{1b}, R^{1c} and R^3 are as defined for Formula I.

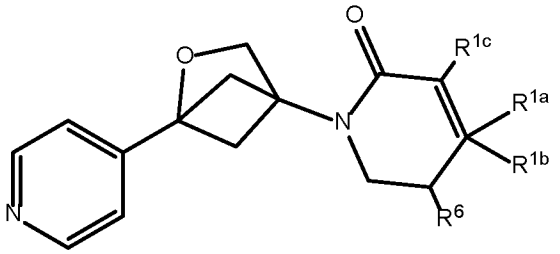
According to some embodiments of the compound of Formula (I) or Formula (IV), or a pharmaceutically acceptable salt thereof, the compound has Formula (IVa), Formula (IVb), or Formula (IVc):



(IVa)



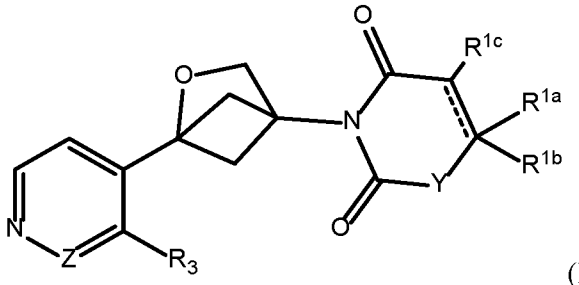
(IVb)



(IVc),

wherein R^6 is H, OH, or CN, and R^{1a}, R^{1b}, and R^{1c} are as defined for Formula (I). In one such embodiment, wherein R^{1a} is H and R^{1b} is selected from C_{6-10} aryl and 5- to 10-membered heteroaryl, wherein each aryl or heteroaryl is optionally substituted with one to four substituents, wherein each substituent is independently selected from C_{1-6} alkyl, halo, and C_{1-6} haloalkyl. In one such embodiment, each aryl or heteroaryl is optionally substituted with one to four substituents, wherein each substituent is independently halo.

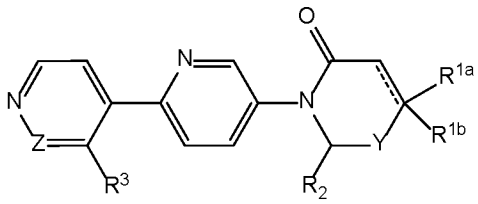
According to some embodiments of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, the compound has Formula (IVd):



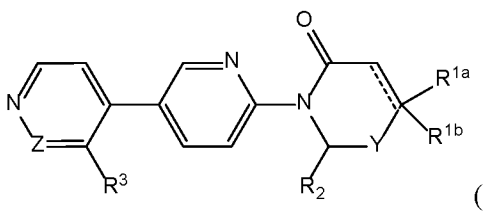
(IVd),

wherein Z, Y, R^{1a}, R^{1b}, R^{1c} and R^3 are as defined for Formula I.

According to some embodiments of the compound of Formula (I) or Formula (V), the compound has Formula (Va), (Vb), (Vc), (Vd), (Ve) or (Vf)



(Va)



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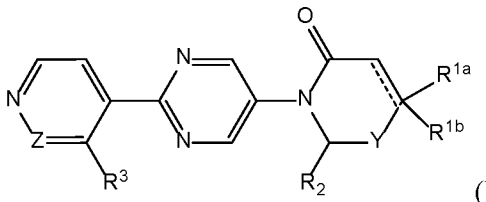
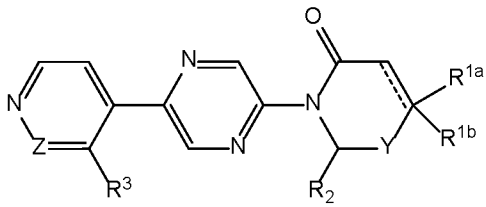
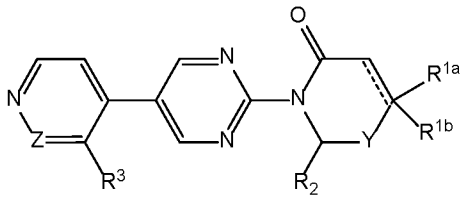


Vb)

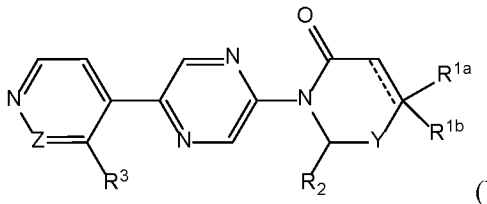
(Vc)



(Vd)

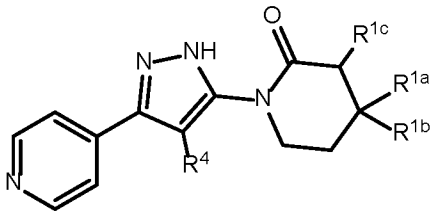


(Ve)

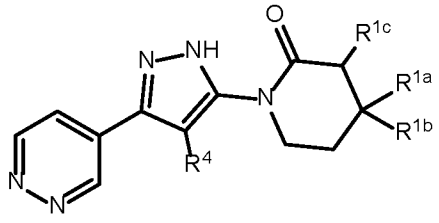


(Vf).

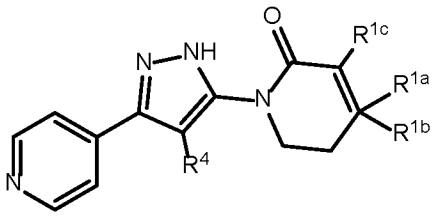
According to some embodiments of the compound of Formula (I) , Formula (II), Formula (IIa), or a pharmaceutically acceptable salt thereof, the compound has Formula (IIa-1), Formula (IIa-2), Formula (IIa-3), Formula (IIa-4), Formula (IIa-5), or Formula (IIa-6):



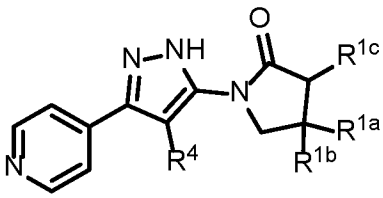
(IIa-1),



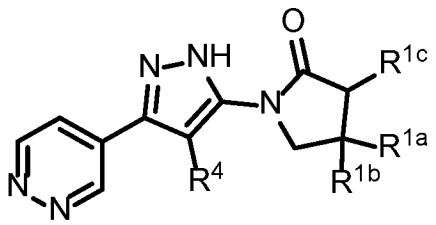
(IIa-2),



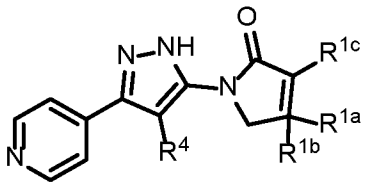
(IIa-3),



(IIa-4),



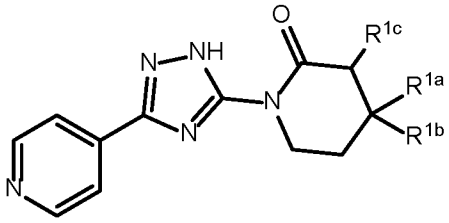
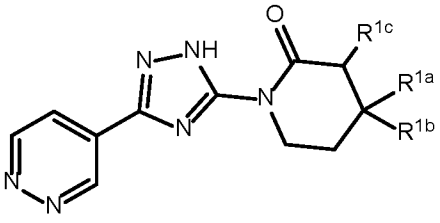
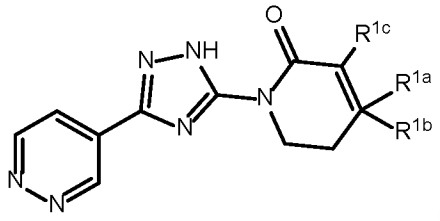
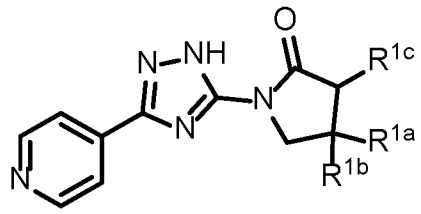
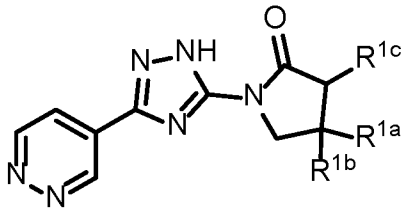
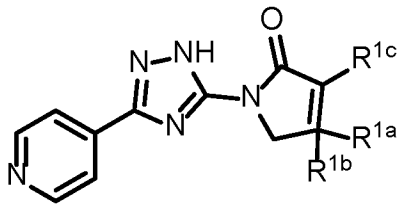
(IIa-5), and



(IIa-6),

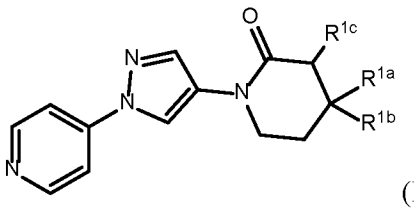
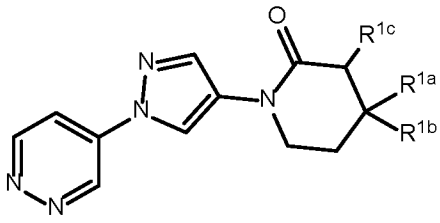
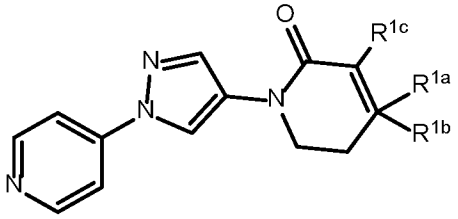
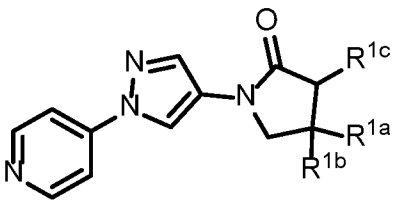
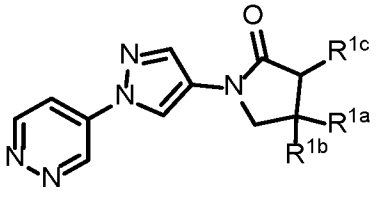
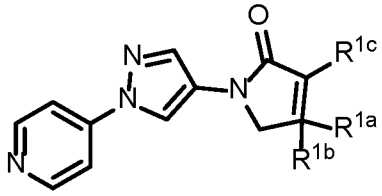
wherein R^{1a}, R^{1b}, R^{1c}, and R^4 are as defined for Formula (I). In one such embodiment, R^4 is H. In one such embodiment, R^{1c} is H or F.

According to some embodiments of the compound of Formula (I), Formula (II), Formula (IIb), or a pharmaceutically acceptable salt thereof, the compound has Formula (IIb-1), Formula (IIb-2), Formula (IIb-3), Formula (IIb-4), Formula (IIb-5), or Formula (IIb-6):


(IIb-1),

(IIb-2),

(IIb-3),

(IIb-4),

(IIb-5), and

(IIb-6)

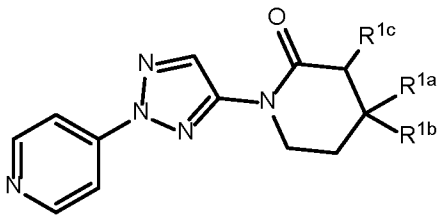
wherein R^{1a}, R^{1b}, and R^{1c} are as defined for Formula (I).

According to some embodiments of the compound of Formula (I) , Formula (II), Formula (IIc), or a pharmaceutically acceptable salt thereof, the compound has Formula (IIc-1), Formula (IIc-2), Formula (IIc-3), Formula (IIc-4), Formula (IIc-5), or Formula (IIc-6):

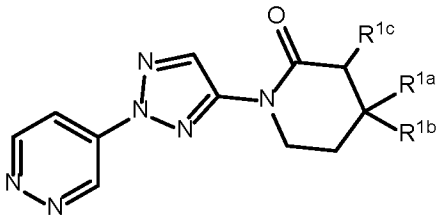

(IIc-1),

(IIc-2),

(IIc-3),

(IIc-4),

(IIc-5), and

(IIc-6),

wherein R^{1a}, R^{1b}, and R^{1c} are as defined for Formula (I).

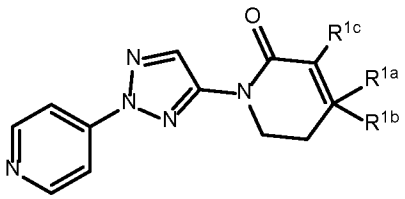
According to some embodiments of the compound of Formula (I), Formula (II), Formula (IId), or a pharmaceutically acceptable salt thereof, the compound has Formula (IId-1), Formula (IId-2), Formula (IId-3), Formula (IId-4), Formula (IId-5), or Formula (IId-6):



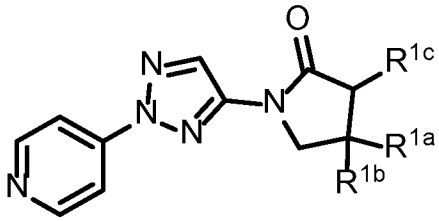
(IId-1),



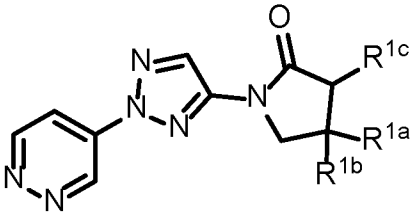
(IId-2),



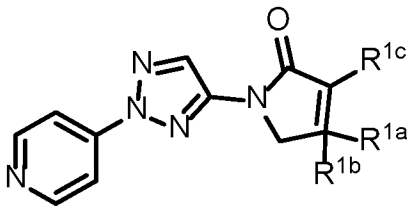
(IId-3),



(IId-4),



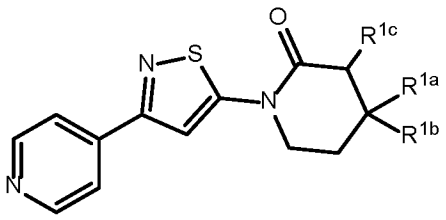
(IId-5), and



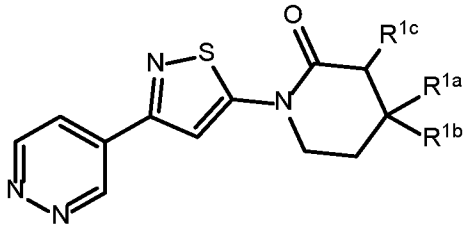
(IId-6),

wherein R^{1a}, R^{1b}, and R^{1c} are as defined for Formula (I).

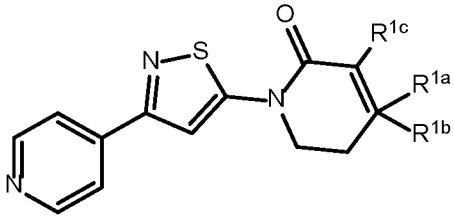
According to some embodiments of the compound of Formula (I), Formula (II), Formula (IIe), or a pharmaceutically acceptable salt thereof, the compound has Formula (IIe-1), Formula (IIe-2), Formula (IIe-3), Formula (IIe-4), Formula (IIe-5), or Formula (IIe-6):



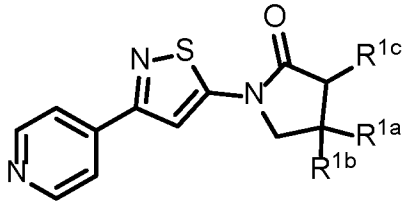
(IIe-1),



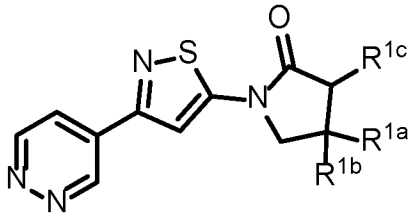
(IIe-2),



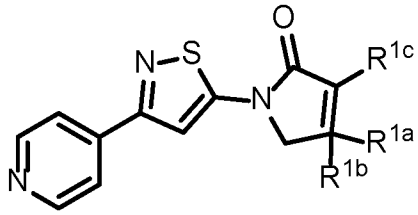
(IIe-3),



(IIe-4),



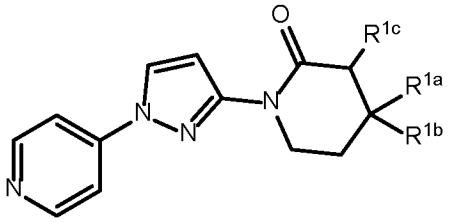
(IIe-5), and



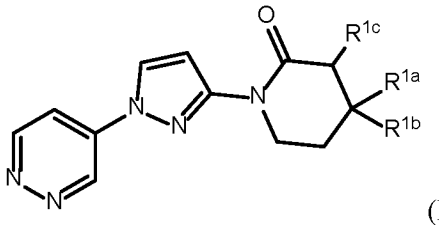
(IIe-6),

wherein R^{1a}, R^{1b}, and R^{1c} are as defined for Formula (I).

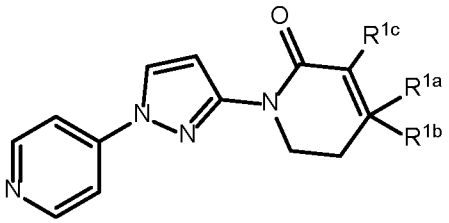
According to some embodiments of the compound of Formula (I), Formula (II), Formula (IIf), or a pharmaceutically acceptable salt thereof, the compound has Formula (IIf-1), Formula (IIf-2), Formula (IIf-3), Formula (IIf-4), Formula (IIf-5), or Formula (IIf-6):



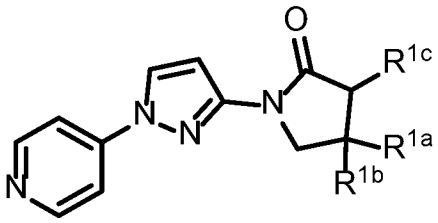
(IIf-1),



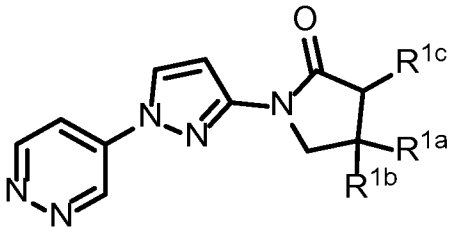
(IIf-2),



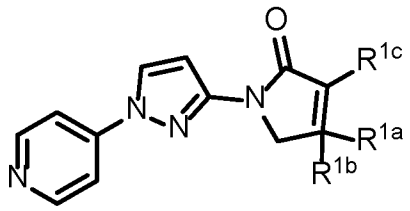
(IIf-3),



(IIf-4),



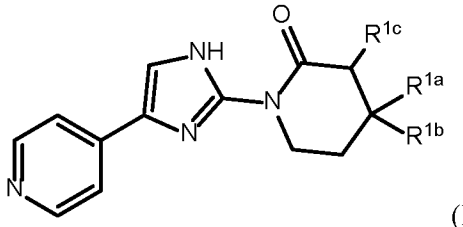
(IIf-5), and



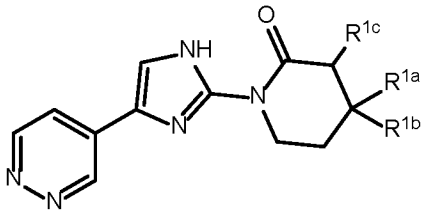
(IIf-6),

wherein R^{1a}, R^{1b}, and R^{1c} are as defined for Formula (I).

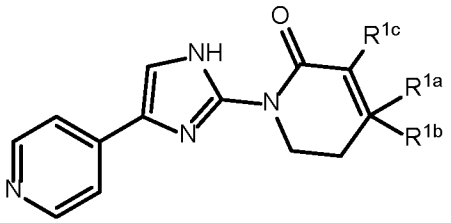
According to some embodiments of the compound of Formula (I), Formula (II), Formula (IIg), or a pharmaceutically acceptable salt thereof, the compound has Formula (IIg-1), Formula (IIg-2), Formula (IIg-3), Formula (IIg-4), Formula (IIg-5), or Formula (IIg-6):



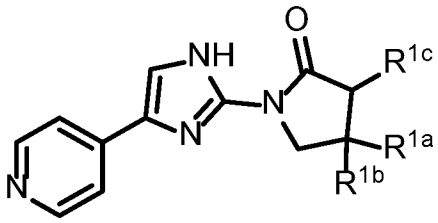
(IIg-1),



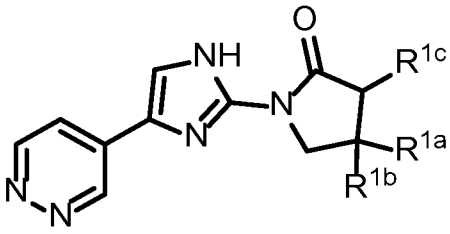
(IIg-2),



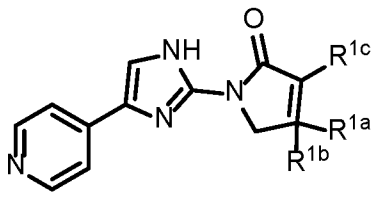
(IIg-3),



(IIg-4),



(IIg-5), and

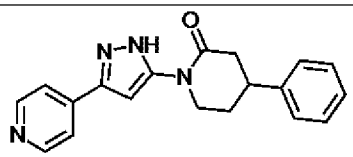
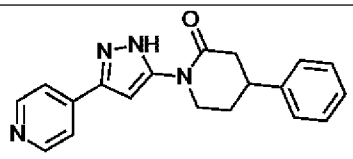
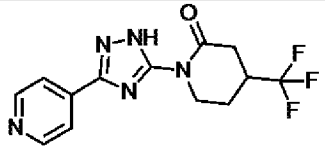


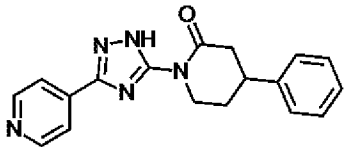
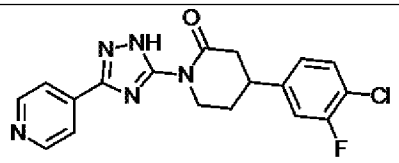
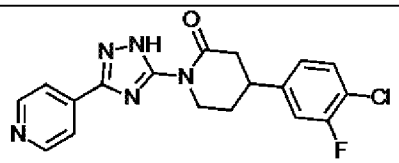
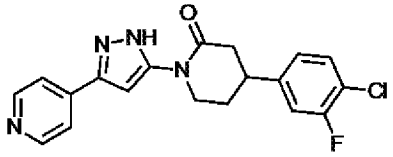
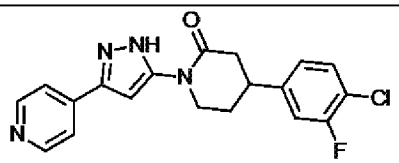
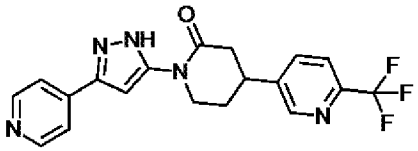
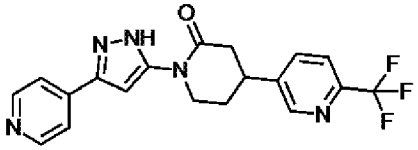
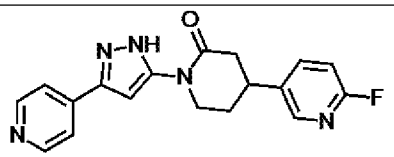
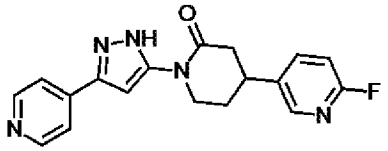
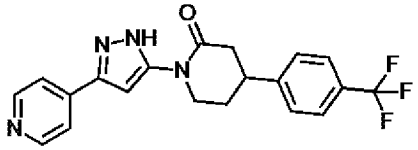
(IIg-6),

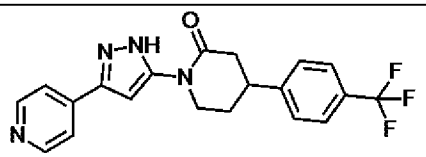
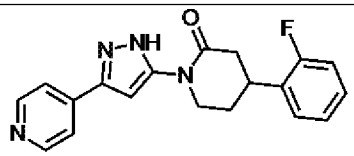
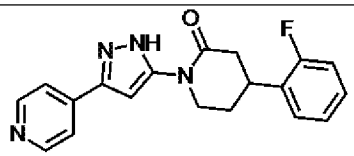
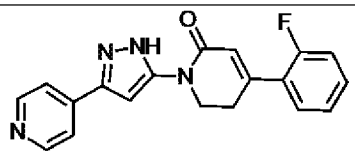
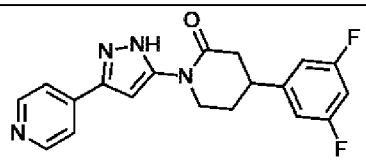
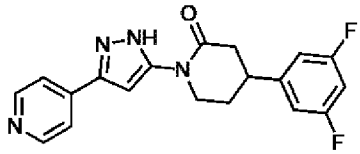
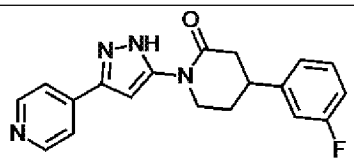
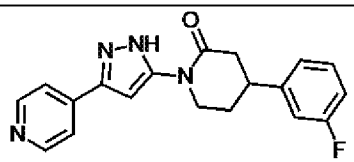
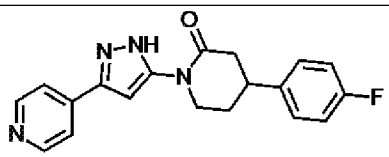
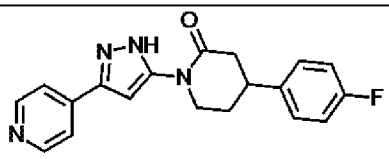
wherein R^{1a}, R^{1b}, and R^{1c} are as defined for Formula (I).

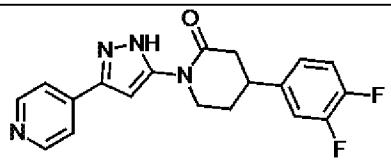
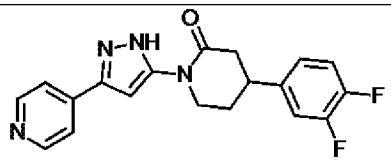
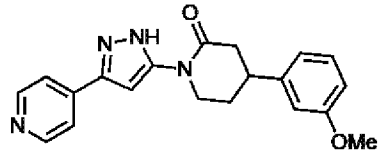
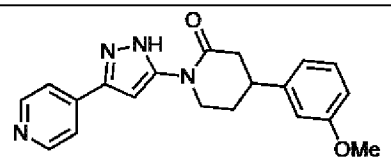
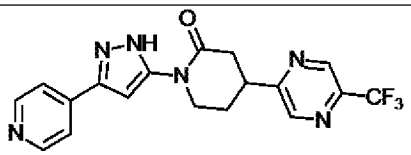
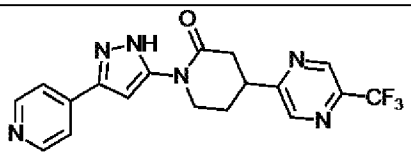
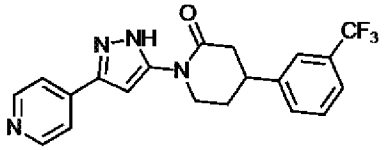
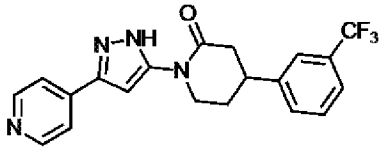
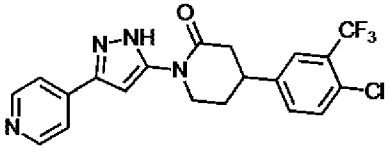
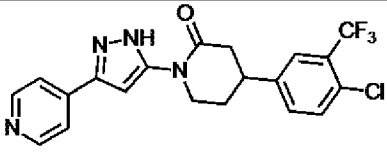
According to some embodiments of the compound of Formula (I), Formula (II), Formula (III), Formula (IV), or a pharmaceutically acceptable salt thereof, the compound is selected from the compounds in Table 1, shown below, or a pharmaceutically acceptable salt thereof.

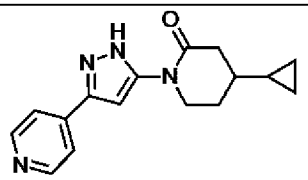
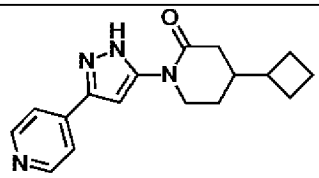
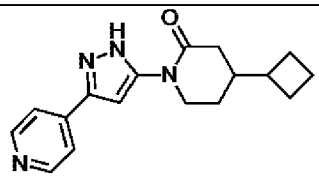
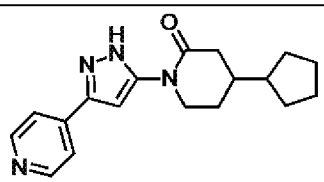
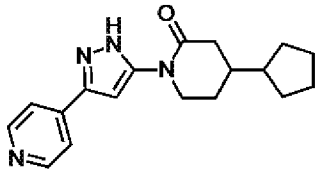
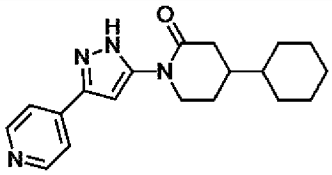
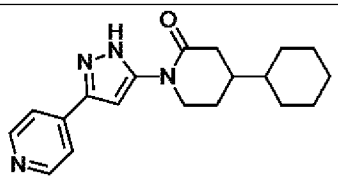
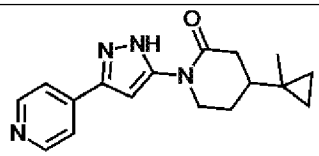
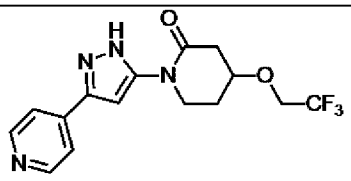
Table 1. Exemplary compounds of the present disclosure. Salts of such compounds are also contemplated. See the Examples section for preparation of such compounds. Compounds that do not have preparation details explicitly described in the Examples may be prepared by modifying the preparation details for other compounds provided herein, using methods generally known in the art.

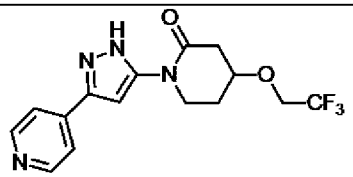
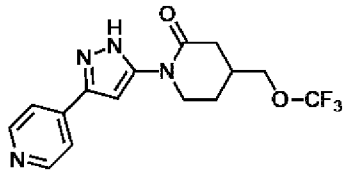
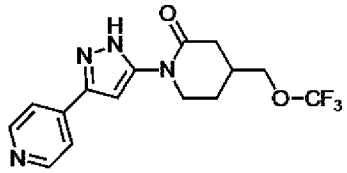
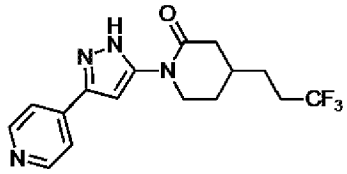
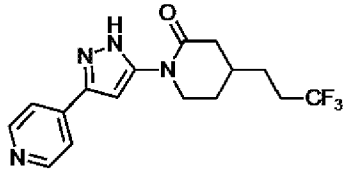
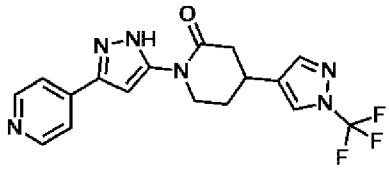
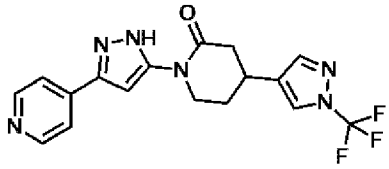
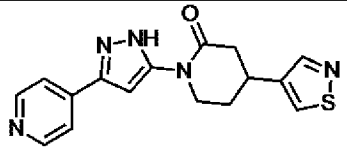
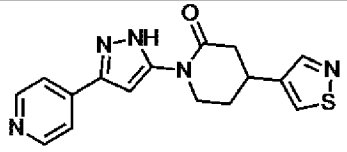
Ex	Structure	IUPAC
1a		4-phenyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
1b		4-phenyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
2		1-(3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5-yl)-4-(trifluoromethyl)piperidin-2-one

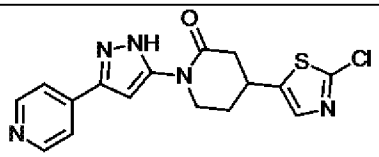
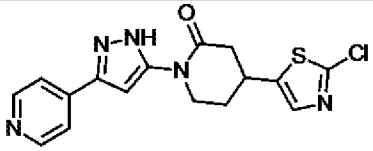
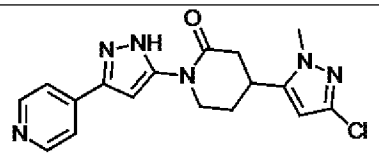
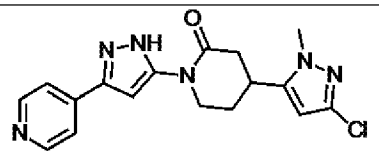
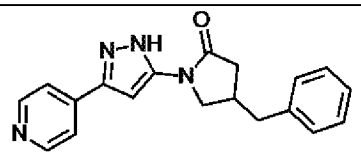
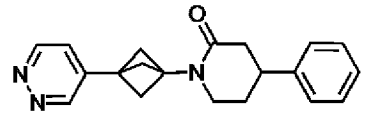
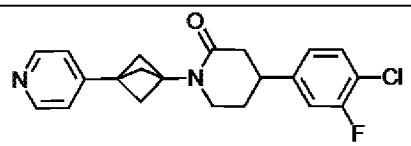
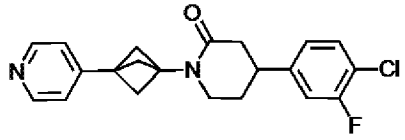
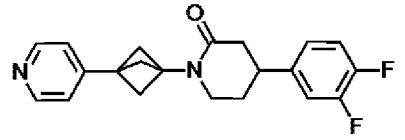
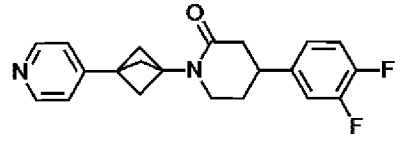
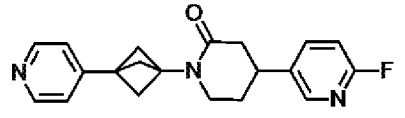
3		4-phenyl-1-(3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5-yl)piperidin-2-one
4a		4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5-yl)piperidin-2-one
4b		4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5-yl)piperidin-2-one
5a		4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
5b		4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
6a		1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)piperidin-2-one
6b		1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)piperidin-2-one
7a		4-(6-fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
7b		4-(6-fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
8a		1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(4-(trifluoromethyl)phenyl)piperidin-2-one

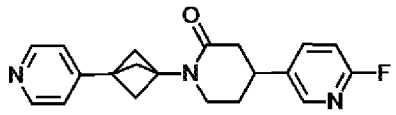
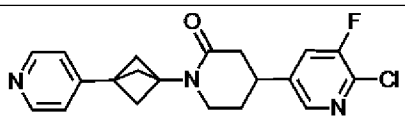
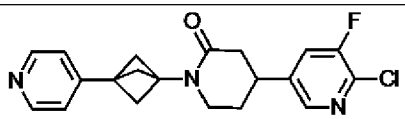
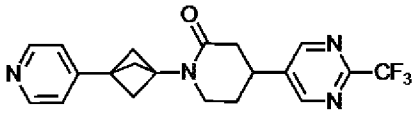
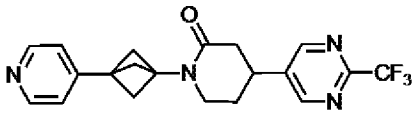
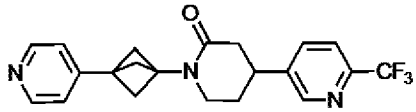
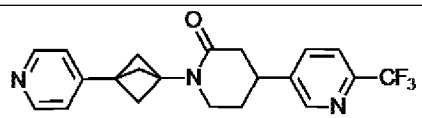
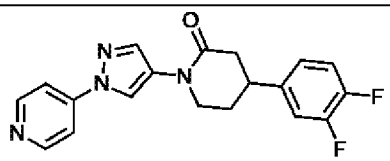
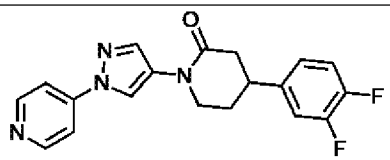
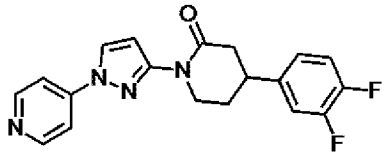
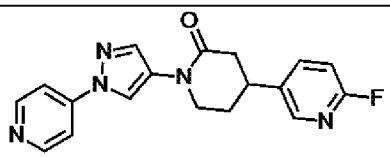
8b		1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(4-(trifluoromethyl)phenyl)piperidin-2-one
9a		4-(2-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
9b		4-(2-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
10		4-(2-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-5,6-dihydropyridin-2(1*H*)-one
11a		4-(3,5-difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
11b		4-(3,5-difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
12a		4-(3-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
12b		4-(3-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
13a		4-(4-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
13b		4-(4-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one

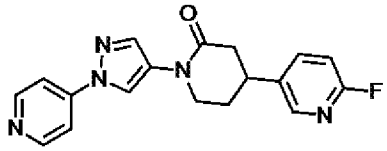
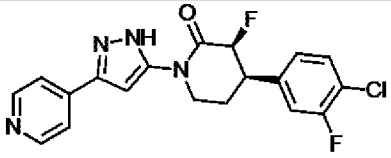
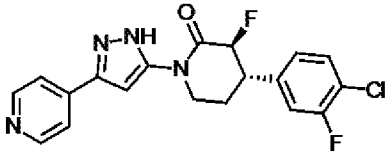
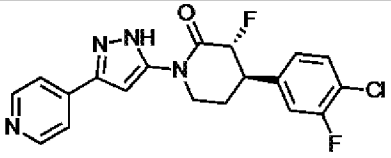
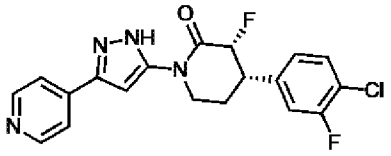
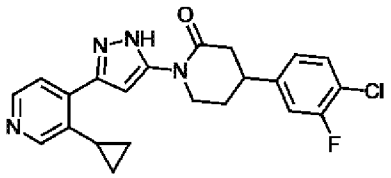
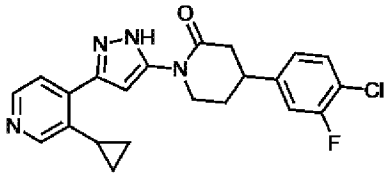
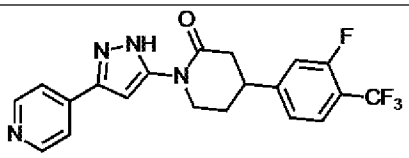
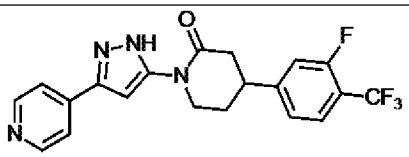
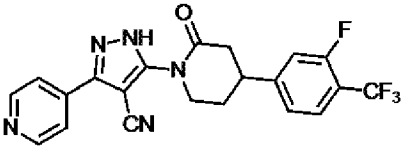
14a		4-(3,4-difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
14b		4-(3,4-difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
15a		4-(3-methoxyphenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
15b		4-(3-methoxyphenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
16a		1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(5-(trifluoromethyl)pyrazin-2-yl)piperidin-2-one
16b		1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(5-(trifluoromethyl)pyrazin-2-yl)piperidin-2-one
17a		1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(3-(trifluoromethyl)phenyl)piperidin-2-one
17b		1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(3-(trifluoromethyl)phenyl)piperidin-2-one
18a		4-(4-chloro-3-(trifluoromethyl)phenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
18b		4-(4-chloro-3-(trifluoromethyl)phenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one

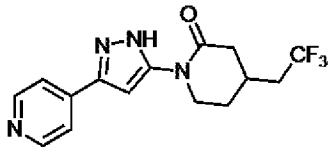
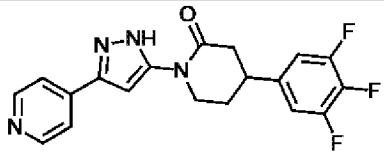
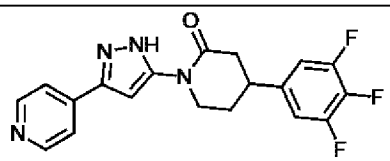
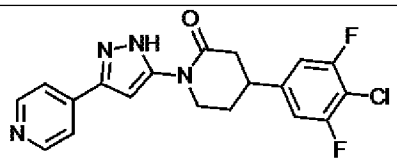
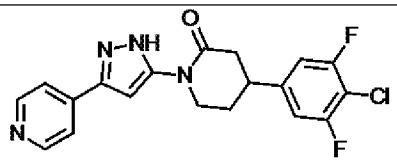
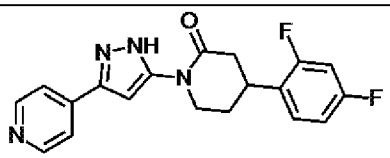
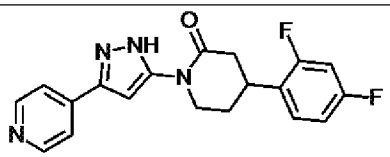
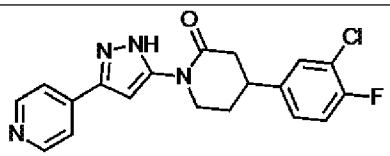
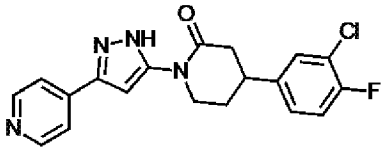
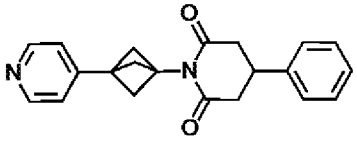
19		4-cyclopropyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
20a		4-cyclobutyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
20b		4-cyclobutyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
21a		4-cyclopentyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
21b		4-cyclopentyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
22a		4-cyclohexyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
22b		4-cyclohexyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
23		4-(1-methylcyclopropyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
24a		1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(2,2,2-trifluoroethoxy)piperidin-2-one

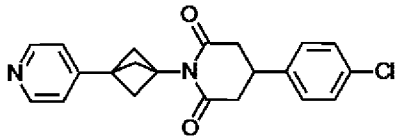
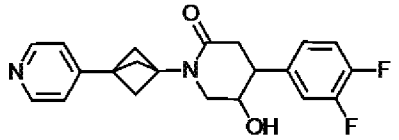
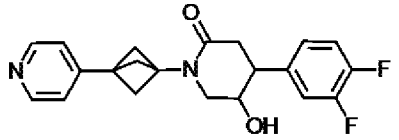
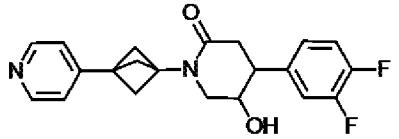
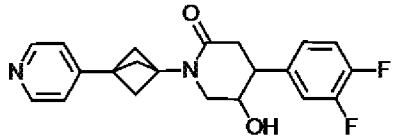
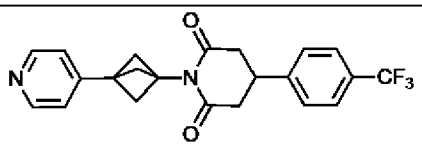
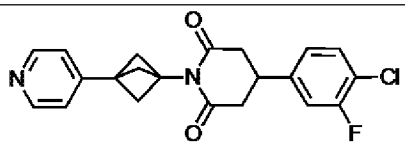
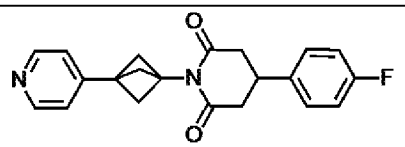
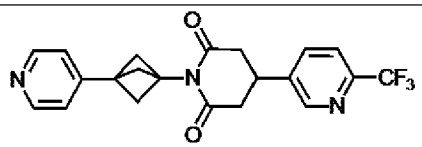
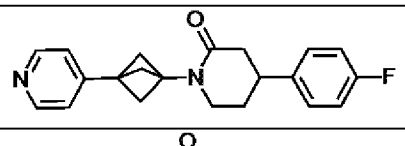
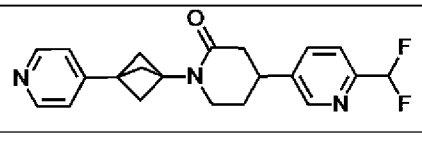
24b		1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(2,2,2-trifluoroethoxy)piperidin-2-one
25a		1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-((trifluoromethoxy)methyl)piperidin-2-one
25b		1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-((trifluoromethoxy)methyl)piperidin-2-one
26a		1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(3,3,3-trifluoropropyl)piperidin-2-one
26b		1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(3,3,3-trifluoropropyl)piperidin-2-one
27a		1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(1-(trifluoromethyl)-1*H*-pyrazol-4-yl)piperidin-2-one
27b		1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(1-(trifluoromethyl)-1*H*-pyrazol-4-yl)piperidin-2-one
28a		4-(isothiazol-4-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
28b		4-(isothiazol-4-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one

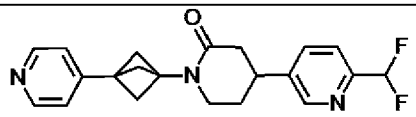
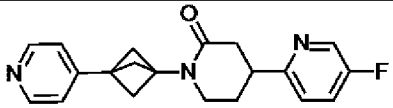
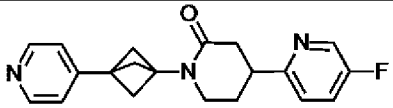
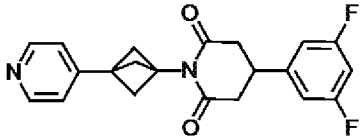
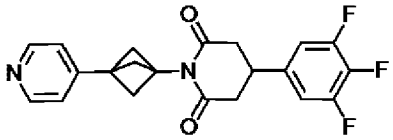
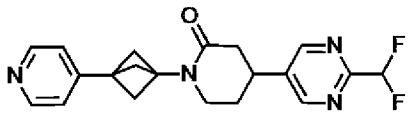
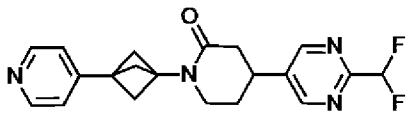
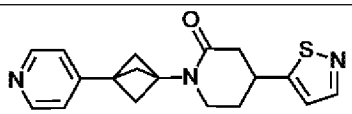
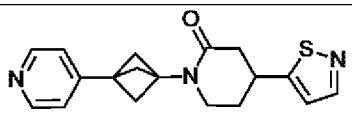
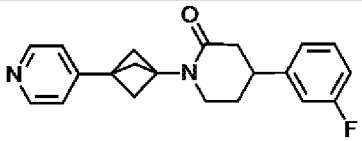
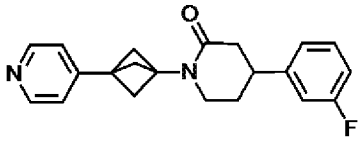
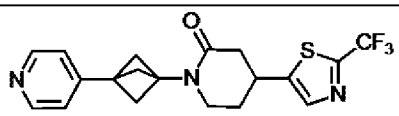
29a		4-(2-chlorothiazol-5-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
29b		4-(2-chlorothiazol-5-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
30a		4-(3-chloro-1-methyl-1*H*-pyrazol-5-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
30b		4-(3-chloro-1-methyl-1*H*-pyrazol-5-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
31		4-benzyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)pyrrolidin-2-one
32		4-phenyl-1-(3-(pyridazin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
33a		4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
33b		4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
34a		4-(3,4-difluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
34b		4-(3,4-difluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
35a		4-(6-fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one

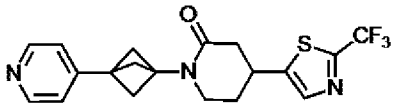
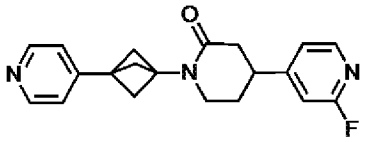
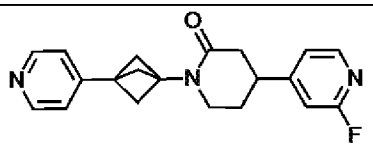
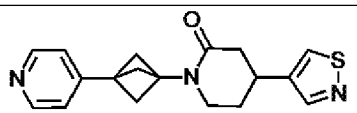
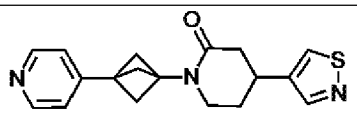
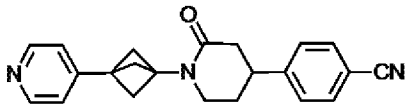
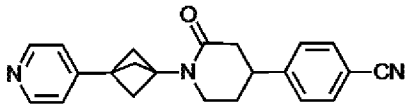
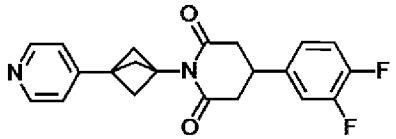
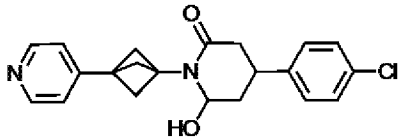
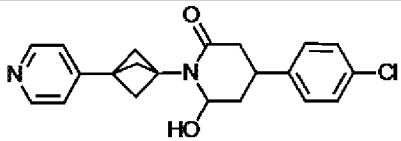
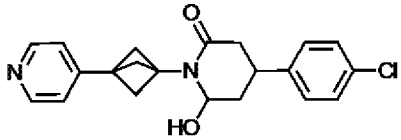
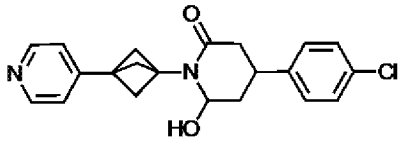
35b		4-(6-fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
36a		4-(6-chloro-5-fluoro-3-pyridyl)-1-[3-(4-pyridyl)-1-bicyclo[1.1.1]pentanyl]piperidin-2-one
36b		4-(6-chloro-5-fluoro-3-pyridyl)-1-[3-(4-pyridyl)-1-bicyclo[1.1.1]pentanyl]piperidin-2-one
37a		1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(2-(trifluoromethyl)pyrimidin-5-yl)piperidin-2-one
37b		1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(2-(trifluoromethyl)pyrimidin-5-yl)piperidin-2-one
38a		1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)piperidin-2-one
38b		1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)piperidin-2-one
39a		4-(3,4-difluorophenyl)-1-(1-(pyridin-4-yl)-1*H*-pyrazol-4-yl)piperidin-2-one
39b		4-(3,4-difluorophenyl)-1-(1-(pyridin-4-yl)-1*H*-pyrazol-4-yl)piperidin-2-one
40		4-(4-chloro-3-fluorophenyl)-1-(1-(pyridin-4-yl)-1*H*-pyrazol-3-yl)piperidin-2-one
41a		4-(6-fluoropyridin-3-yl)-1-(1-(pyridin-4-yl)-1*H*-pyrazol-4-yl)piperidin-2-one

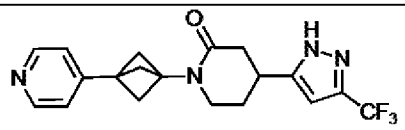
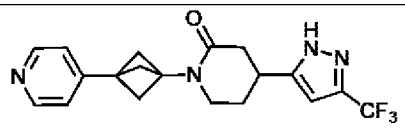
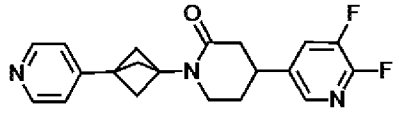
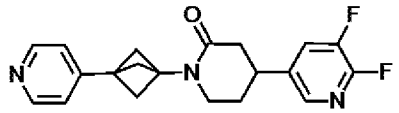
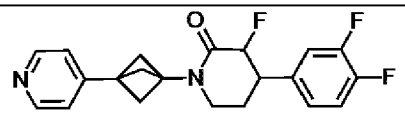
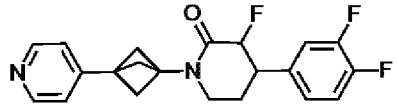
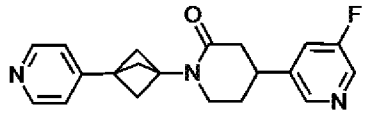
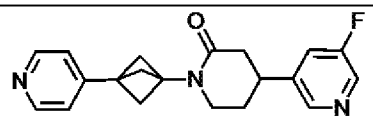
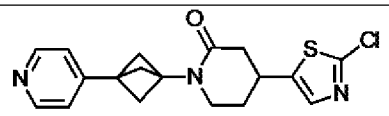
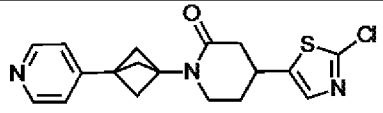
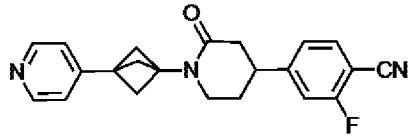
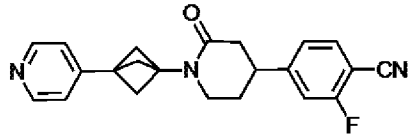
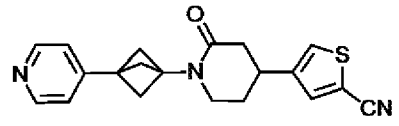
41b		4-(6-fluoropyridin-3-yl)-1-(1-(pyridin-4-yl)-1*H*-pyrazol-4-yl)piperidin-2-one
42a		4-(4-chloro-3-fluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
42b		4-(4-chloro-3-fluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
42c		4-(4-chloro-3-fluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
42d		4-(4-chloro-3-fluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
43a		4-(4-chloro-3-fluorophenyl)-1-(3-(3-cyclopropylpyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
43b		4-(4-chloro-3-fluorophenyl)-1-(3-(3-cyclopropylpyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
44a		4-(3-fluoro-4-(trifluoromethyl)phenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
44b		4-(3-fluoro-4-(trifluoromethyl)phenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
45		5-(4-(4-chloro-3-fluorophenyl)-2-oxopiperidin-1-yl)-3-(pyridin-4-yl)-1*H*-pyrazole-4-carbonitrile

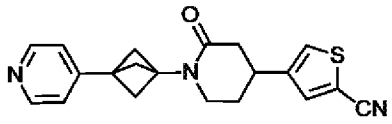
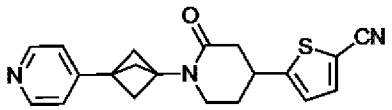
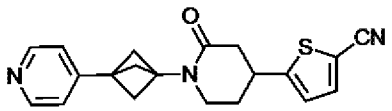
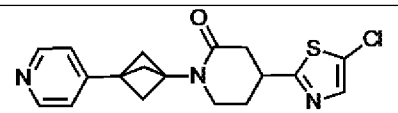
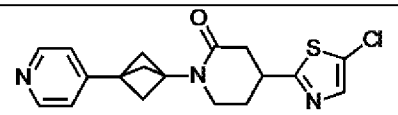
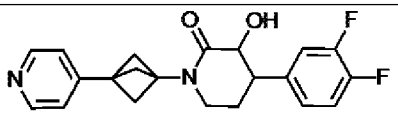
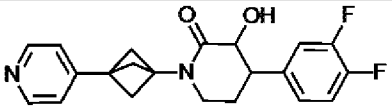
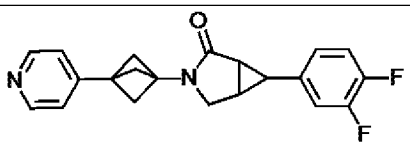
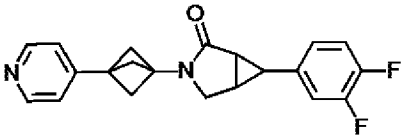
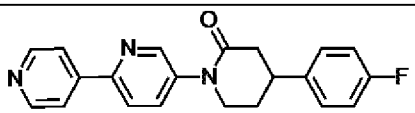
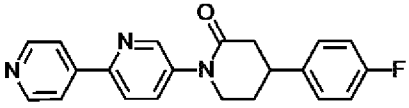
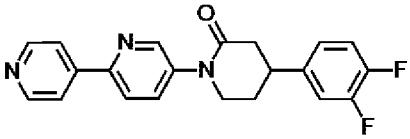
46		1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)-4-(2,2,2-trifluoroethyl)piperidin-2-one
47a		1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(3,4,5-trifluorophenyl)piperidin-2-one
47b		1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(3,4,5-trifluorophenyl)piperidin-2-one
48a		4-(4-chloro-3,5-difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
48b		4-(4-chloro-3,5-difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
49a		4-(2,4-difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
49b		4-(2,4-difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
50a		4-(3-chloro-4-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
50b		4-(3-chloro-4-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one
51		4-phenyl-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidine-2,6-dione

52		4-(4-chlorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidine-2,6-dione
53a		*trans*-4-(3,4-difluorophenyl)-5-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
53b		*trans*-4-(3,4-difluorophenyl)-5-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
53c		*cis*-4-(3,4-difluorophenyl)-5-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
53d		*cis*-4-(3,4-difluorophenyl)-5-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
54		1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(4-(trifluoromethyl)phenyl)piperidine-2,6-dione
55		4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidine-2,6-dione
56		4-(4-fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidine-2,6-dione
57		1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)piperidine-2,6-dione
58		4-(4-fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
59a		4-(6-(difluoromethyl)pyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one

59b		4-(6-(difluoromethyl)pyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
60a		4-(5-fluoropyridin-2-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
60b		4-(5-fluoropyridin-2-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
61		4-(3,5-difluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidine-2,6-dione
62		1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(3,4,5-trifluorophenyl)piperidine-2,6-dione
63a		4-(2-(difluoromethyl)pyrimidin-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
63b		4-(2-(difluoromethyl)pyrimidin-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
64a		4-(isothiazol-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
64b		4-(isothiazol-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
65a		4-(3-fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
65b		4-(3-fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
66a		1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(2-(trifluoromethyl)thiazol-5-yl)piperidin-2-one

66b		1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(2-(trifluoromethyl)thiazol-5-yl)piperidin-2-one
67a		4-(2-fluoropyridin-4-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
67b		4-(2-fluoropyridin-4-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
68a		4-(isothiazol-4-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
68b		4-(isothiazol-4-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
69a		4-(2-oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)benzonitrile
69b		4-(2-oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)benzonitrile
70		4-(3,4-difluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidine-2,6-dione
71a		4-(4-chlorophenyl)-6-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
71b		4-(4-chlorophenyl)-6-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
71c		4-(4-chlorophenyl)-6-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
71d		4-(4-chlorophenyl)-6-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one

72a		1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)piperidin-2-one
72b		1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)piperidin-2-one
73a		4-(5,6-difluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
73b		4-(5,6-difluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
74a		4-(3,4-difluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
74b		4-(3,4-difluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
75a		4-(5-fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
75b		4-(5-fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
76a		4-(2-chlorothiazol-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
76b		4-(2-chlorothiazol-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
77a		2-fluoro-4-(2-oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)benzonitrile
77b		2-fluoro-4-(2-oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)benzonitrile
78a		4-(2-oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)thiophene-2-carbonitrile

78b		4-(2-oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)thiophene-2-carbonitrile
79a		5-(2-oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)thiophene-2-carbonitrile
79b		5-(2-oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)thiophene-2-carbonitrile
80a		4-(5-chlorothiazol-2-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
80b		4-(5-chlorothiazol-2-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
81a		4-(3,4-difluorophenyl)-3-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
81b		4-(3,4-difluorophenyl)-3-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one
82a		(*Rel* 1*S*,5*R*,6*R*)-6-(3,4-difluorophenyl)-3-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-3-azabicyclo[3.1.0]hexan-2-one
82b		(*Rel* 1*R*,5*S*,6*S*)-6-(3,4-difluorophenyl)-3-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-3-azabicyclo[3.1.0]hexan-2-one
83a		1-([2,4'-bipyridin]-5-yl)-4-(4-fluorophenyl)piperidin-2-one
83b		1-([2,4'-bipyridin]-5-yl)-4-(4-fluorophenyl)piperidin-2-one
84a		1-([2,4'-bipyridin]-5-yl)-4-(3,4-difluorophenyl)piperidin-2-one

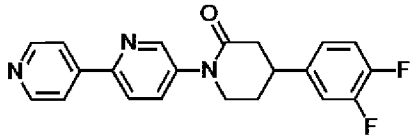
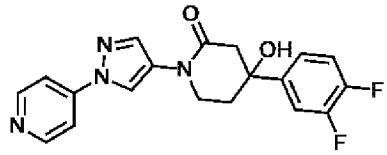
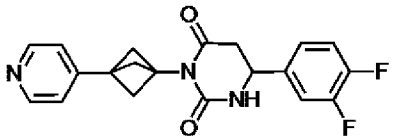
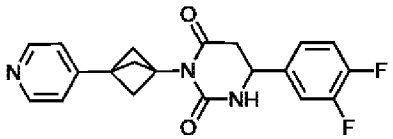
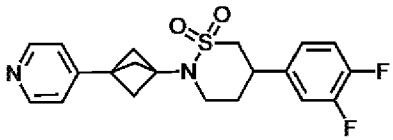
84b		1-([2,4'-bipyridin]-5-yl)-4-(3,4-difluorophenyl)piperidin-2-one
85		4-(3,4-difluorophenyl)-4-hydroxy-1-(1-(pyridin-4-yl)-1*H*-pyrazol-4-yl)piperidin-2-one
86a		6-(3,4-difluorophenyl)-3-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione
86b		6-(3,4-difluorophenyl)-3-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione
87		5-(3,4-difluorophenyl)-2-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-1,2-thiazinane 1,1-dioxide

Table 1

In another embodiment of the compound of Formula (I), (II), (III), or (IV), the compound is a compound corresponding to Compound of Formula IIa-1 or Compound of Formula IIIa, or a pharmaceutically acceptable salt thereof. In another embodiment of the compound of Formula (I) or Formula (III), the compound is a compound corresponding to Compound 73, Compound 74, Compound 41a or Compound 41b, or a pharmaceutically acceptable salt thereof. In another embodiment of the compound of Formula (I) or Formula (II), the compound is a compound corresponding to Compound 5a, Compound 5b, Compound 14a, Compound 14b, or Compound 50, or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound is Compound 50. In one embodiment, the compound is Compound 73. In one embodiment, the compound is Compound 74. In one embodiment, the compound is Compound 5a. In one embodiment, the compound is Compound 5b. In one embodiment, the compound is Compound 14a. In one embodiment, the compound is Compound 14b. In one embodiment, the compound is Compound 41a. In one embodiment, the compound is Compound 41b.

The compounds of the invention (e.g., compounds of Formula (I), (II), (III), or (IV)), or their pharmaceutically acceptable salts may contain one or more asymmetric centers and may thus give rise

to enantiomers, diastereomers, and other stereoisomeric forms that are defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids. Embodiments thus include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (R)- and (S)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

Embodiments of the present invention include all manner of rotamers and conformationally restricted states of a compound of the invention. Atropisomers, which are stereoisomers arising because of hindered rotation about a single bond, where energy differences due to steric strain or other contributors create a barrier to rotation that is high enough to allow for isolation of individual conformers, are also included. As an example, certain compounds of the invention may exist as mixtures of atropisomers or purified or enriched for the presence of one atropisomer.

In some embodiments, the compound of Formula (I), Formula (II), Formula (III), or Formula (IV) is a mixture of enantiomers. In other embodiments, the compound of Formula (I), Formula (II), Formula (III), or Formula (IV) is a substantially purified enantiomerr. In some embodiments, the compound of Formula (I), Formula (II), Formula (III), or Formula (IV) is a substantially purified R-enantiomer. In some other embodiments, the compound of Formula (I), Formula (II), Formula (III), or Formula (IV) is a substantially purified S- enantiomer.

SYNTHESIS OF SARM1 INHIBITORS

Compounds of the present disclosure can be made by a variety of methods depicted in the illustrative synthetic reaction schemes shown and described below. The starting materials and reagents used in preparing these compounds generally are either available from commercial suppliers, such as Aldrich Chemical Co., or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's *Reagents for Organic Synthesis*; Wiley & Sons: New York, vol. 1-21; R. C. LaRock, *Comprehensive Organic Transformations*, 2nd edition Wiley-VCH, New York 1999; *Comprehensive Organic Synthesis*, B. Trost and I. Fleming (Eds.) vol. 1-9 Pergamon, Oxford, 1991; *Comprehensive Heterocyclic Chemistry*, A. R. Katritzky and C. W. Rees (Eds.) Pergamon, Oxford 1984, vol. 1-9; *Comprehensive Heterocyclic Chemistry II*, A. R. Katritzky and C. W. Rees (Eds) Pergamon, Oxford 1996, vol. 1-11; and *Organic Reactions*, Wiley &

Sons: New York, 1991, vol. 1-40. The following synthetic reaction schemes are merely illustrative of some methods by which the compounds of the present invention can be synthesized, and various modifications to these synthetic reaction schemes can be made and will be suggested to one skilled in the art having referred to the disclosure contained herein.

For illustrative purposes, reaction Schemes below provide routes for synthesizing the compounds of the invention as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used. Although some specific starting materials and reagents are depicted in the Schemes and discussed below, other starting materials and reagents can be substituted to provide a variety of derivatives or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

The starting materials and the intermediates of the synthetic reaction schemes can be isolated and purified if desired using conventional techniques, including but not limited to, filtration, distillation, crystallization, chromatography, and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

Unless specified to the contrary, the reactions described herein preferably are conducted under an inert atmosphere at atmospheric pressure at a reaction temperature range of from about −78 °C to about 150 °C, more preferably from about 0 °C to about 125 °C, and most preferably and conveniently at about room (or ambient) temperature, or, about 20 °C.

Some compounds in following schemes are depicted with generalized substituents; however, one skilled in the art will immediately appreciate that the nature of the substituents can varied to afford the various compounds contemplated in this invention. Moreover, the reaction conditions are exemplary and alternative conditions are well known. The reaction sequences in the following examples are not meant to limit the scope of the invention as set forth in the claims.

Persons skilled in the art will recognize that the chemical reactions described may be readily adapted to prepare other compounds of the present invention. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the invention.

METHODS OF TREATMENT WITH AND USES OF SARM1 INHIBITORS

The present disclosure provides a variety of uses and applications for compounds and/or compositions as described herein, for example in light of their activities and/or characteristics as described herein. In some embodiments, such uses may include therapeutic and/or diagnostic uses. Alternatively, in some embodiments such uses may include research, production, and/or other technological uses.

In one aspect, the present disclosure provides methods comprising administering one or more compounds of Formula (I) to an individual, e.g., to treat, prevent, or reduce the risk of developing one or more conditions characterized by axonal degeneration. In some such embodiments, the compound of Formula (I) is a SARM1 inhibitor.

For instance, in one aspect, the present disclosure provides a method of treating or preventing axonal degeneration comprising administering to an individual in need thereof a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the compound of Formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient. In one aspect, the individual is a human. In one aspect, the individual has a condition characterized by axonal degeneration or is at risk of developing a condition characterized by axonal degeneration.

Another embodiment of the present disclosure relates to a method of inhibiting SARM1 activity in an individual in need thereof, comprising steps of administering to said individual a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

Inhibition of enzymes in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to biological assays, gene expression studies, and biological target identification.

In certain embodiments, the present disclosure relates to a method of treating axonal degeneration in a biological sample or inhibiting SARM1 in a biological sample comprising the step of contacting said biological sample with a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient. In some embodiments, one or more compounds and/or pharmaceutical compositions as described herein are useful, for example as a method of for inhibiting the degradation of neurons derived from a subject. In some embodiments, one or more compounds and/or pharmaceutical compositions as described herein, are useful for inhibiting the degeneration of a neuron, or portion thereof, cultured in vitro. In some

embodiments, one or more compounds and/or pharmaceutical compositions as described herein, are useful as stabilizing agents to promote in vitro neuronal survival.

In some embodiments, the compounds and/or pharmaceutical compositions of the present disclosure inhibit NADase activity of SARM1. Alternatively, or additionally, in some embodiments, the compounds or pharmaceutical compositions of the present disclosure alleviate one or more attributes of neurodegeneration. In some embodiments, the present disclosure provides methods of treating a neurodegenerative disease or disorder comprising administering to an individual in need thereof a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient. In one aspect, the neurodegenerative disease is associated with axonal degeneration. In one aspect, the neurodegenerative disease is selected from amyotrophic lateral sclerosis (ALS), chemotherapy-induced peripheral neuropathy (CIPN), peripheral neuropathy, and multiple sclerosis (MS).

In some embodiments, one or more compounds and/or pharmaceutical compositions as described herein are useful, for example, in the practice of medicine. In some embodiments, one or more compounds and/or pharmaceutical compositions as described herein are useful, for example, to treat, prevent, or ameliorate axonal degeneration (e.g., one or more features or characteristics thereof). In some embodiments, one or more compounds and/or pharmaceutical compositions as described herein are useful, for example to inhibit axonal degeneration, including axonal degeneration that results from reduction or depletion of NAD+. In some embodiments, one or more compounds and/or compositions as described herein are useful, for example to prevent the axon distal to an axonal injury from degenerating.

In some embodiments, one or more compounds and/or pharmaceutical compositions as described herein are useful, for example as a method for inhibiting the degradation of a peripheral nervous system neuron or a portion thereof. In some embodiments, one or more compounds and/or pharmaceutical compositions as described herein are useful, for example as a method for inhibiting or preventing degeneration of a central nervous system (neuron) or a portion thereof. In some embodiments, one or more compounds and/or pharmaceutical compositions as described herein is characterized that, when administered to a population of individuals, reduces one or more symptoms or features of neurodegeneration. For example, in some embodiments, a relevant symptom or feature may be selected from extent, rate, and/or timing of neuronal disruption.

In certain embodiments, the present disclosure provides compounds that are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present disclosure. Compounds provided by this disclosure are also useful for the study of

SARM1 activity in biological and pathological phenomena and the comparative evaluation of new SARM1 activity inhibitors in vitro or in vivo. In certain embodiments, the present disclosure provides assays for identifying and/or characterizing compounds and/or compositions provided herein. In some embodiments, provided assays utilize particular reagents and/or systems (e.g., certain vector constructs and/or polypeptides) useful in assaying SARM1 activity. For example, in some embodiments, provided assays may utilize, for example, a SAM-TIR in which the SARM1 N-terminal auto-inhibitory domain is deleted, and/or one or more tagged versions of a TIR domain.

In some embodiments, one or more compounds and/or pharmaceutical compositions as described herein are useful, for example as a method of for inhibiting the degradation of neurons derived from a subject. In some embodiments, one or more compounds and/or pharmaceutical compositions as described herein, are useful for inhibiting the degeneration of a neuron, or portion thereof, cultured in vitro. In some embodiments, one or more compounds and/or pharmaceutical compositions as described herein, are useful as stabilizing agents to promote in vitro neuronal survival.

In some embodiments, one or more compounds and/or pharmaceutical compositions as described herein are useful, for example in affecting biomarkers associated with neurodegeneration. In some embodiments, changes in biomarkers can be detected systemically or with a sample of CSF, plasma, serum, and/or tissue from a subject. In some embodiments, one or more compounds and/or compositions can be used to affect a change in the concentration of NF-L and/or NF-H contained the CSF of a subject. In some embodiments, one or more compounds and/or pharmaceutical compositions as described herein can affect constitutive NAD and/or cADPR levels in neurons and/or axons.

In some embodiments, one or more biomarkers of neurodegeneration comprises: concentration of NF-L in one or more of: a CSF sample, a blood sample, and a plasma sample from the subject; concentration of NF-H in one or more of: a CSF sample, a blood sample, and a plasma sample from the subject; concentration of Ubiquitin C-terminal Hydrolase L1 (UCH-L1) in one or more of: a CSF sample, a blood sample, and a plasma sample from the subject; concentration of alpha-synuclein in one or more of: a CSF sample, a blood sample, and a plasma sample from the subject; constitutive NAD+ levels in neurons and/or axons of the subject; constitutive cADPR levels in neurons and/or axons of the subject; levels of albumin, amyloid-β (Aβ)38, Aβ40, Aβ42, GFAP, hFABP, MCP)-1, neurogranin, NSE, sAPPα, sAPPβ, sTREM 2, phospho-tau, or total-tau in one or more of: a CSF sample, a blood sample, a plasma sample, skin biopsy sample, a nerve biopsy sample, and a brain biopsy sample from the subject; and levels of C-C Motif Chemokine Ligand (CCL)2, CCL7, CCL12, colony stimulating factor (CSF)1, or Interleukin (IL)6 in one or more of: a

cerebrospinal fluid (CSF) sample, a blood sample, a plasma sample, skin biopsy sample, a nerve biopsy sample, and a brain biopsy sample from the subject.

In some embodiments, one or more compounds and/or pharmaceutical compositions as described herein can affect a detectable change in the levels of one or more neurodegeneration-associated proteins in a subject. Such proteins include, but are not limited to, albumin, amyloid-β (Aβ)38, Aβ40, Aβ42, GFAP, hFABP, MCP-1, neurogranin, NSE, sAPPα, sAPPβ, sTREM 2, phospho-tau, and/or total-tau. In some embodiments, one or more compounds and/or compositions as described herein can affect a change in cytokines and/or chemokines, including, but not limited to, Ccl2, Ccl7, Ccl12, Csf1, and/or Il6.

In some embodiments, compounds and/or compositions as described herein may be administered to individuals suffering from one or more diseases, disorders, or conditions. In some embodiments, the one or more diseases, disorders, or conditions are mediated by SARM1.

In some embodiments, a neurodegenerative disease or disorder comprises an acute or chronic disease or disorder of the peripheral nervous system (PNS), an acute or chronic disease or disorder of the central nervous system (CNS), or a disease associated with neurodegeneration.

In some embodiments, a neurodegenerative disease or disorder comprises an acute disease or disorder of the PNS. In some embodiments, an acute disease or disorder of the PNS is the result of a mechanical injury, thermal injury, or injury from a chemical agent or chemotherapy. In some embodiments, a mechanical injury comprises a compression or entrapment injury or a pressure injury. In some embodiments, a compression or entrapment injury comprises carpal tunnel syndrome, direct trauma, a penetrating injury, a contusion, a fracture or a dislocated bone. In some embodiments, a pressure injury comprises pressure involving superficial nerves, pressure from a tumor or increased intraocular pressure. In some embodiments, a chemical agent or chemotherapy comprises a cytotoxic anticancer agent, thalidomide, an epothilone, a taxane, a vinca alkaloid, a proteasome inhibitor, a platinum-based drug or an auristatin. In some embodiments, an epothilone is ixabepilone. In some embodiments, a taxane is paclitaxel or docetaxel. In some embodiments, a vinca alkaloid is vinblastine, vinorelbine, vincristine, or vindesine. In some embodiments, a proteasome inhibitor is bortezomib. In some embodiments, a platinum-based drug is cisplatin, oxaliplatin, or carboplatin. In some embodiments, an auristatin is conjugated monomethyl auristatin E.

In some embodiments, a neurodegenerative disease or disorder comprises a chronic disease or disorder of the PNS. In some embodiments, a chronic disease or disorder of the PNS comprises a systemic disorder, a pain disorder, or a metabolic disease or disorder.

In some embodiments, a chronic disease or disorder of the PNS comprises inherited neuropathies, Charcot-Marie-Tooth disease, hereditary sensory and autonomic neuropathy (HSAN),

chronic inflammatory demyelinating polyneuropathy (CIDP), idiopathic neuropathies or other peripheral neuropathies.

In some embodiments, a systemic disorder comprises diabetes, uremia, AIDS, leprosy, a nutritional deficiency, atherosclerosis, an enteric neuropathy, an axonopathy, Guillain-Barre syndrome, severe acute motor axonal neuropathy (AMAN), systemic lupus erythematosus, scleroderma, sarcoidosis, rheumatoid arthritis, or polyarteritis nodosa.

In some embodiments, a pain disorder comprises chronic pain, fibromyalgia, spinal pain, carpal tunnel syndrome, pain from cancer, arthritis, sciatica, headaches, pain from surgery, muscle spasms, back pain, visceral pain, pain from injury, dental pain, neurogenic pain, neuropathic pain, nerve inflammation, nerve damage, shingles, herniated disc, torn ligament, or diabetes.

In some embodiments, a metabolic disease or disorder comprises diabetes mellitus, hypoglycemia, uremia, hypothyroidism, hepatic failure, polycythemia, amyloidosis, acromegaly, porphyria, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), disorders of lipid/glycolipid metabolism, a nutritional deficiency, a vitamin deficiency, or a mitochondrial disorder.

In some embodiments, a neurodegenerative disease or disorder comprises an acute disease or disorder of the CNS. In some embodiments, an acute disease or disorder of the CNS comprises an ischemia, a traumatic CNS injury, injury from a chemical agent, thermal injury, or viral encephalitis.

In some embodiments, an ischemia comprises cerebral ischemia, hypoxic demyelination, ischemic demyelination, ischemic optic neuropathy, or non-arteritic anterior ischemic optic neuropathy.

In some embodiments, a traumatic CNS injury comprises a spinal cord injury, a TBI, a mechanical injury to the head and/or spine, a traumatic injury to the head and/or spine, blunt force trauma, closed head injury, open head injury, exposure to a concussive and/or explosive force, a penetrating injury to the CNS, increased intraocular pressure, or damage from a force which causes axons to deform, stretch, crush or sheer.

In some embodiments, a viral encephalitis comprises enterovirus encephalitis, arbovirus encephalitis, herpes simplex virus (HSV) encephalitis, West Nile virus encephalitis, La Crosse encephalitis, Bunyavirus encephalitis, pediatric viral encephalitis, or HIV encephalopathy (HIV-associated dementia).

In some embodiments, a neurodegenerative disease or disorder comprises a chronic disease or disorder of the CNS.

In some embodiments, a chronic disease or disorder of the CNS comprises Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease), multiple sclerosis (MS), Huntington's disease (HD), senile dementia, Pick's disease, Gaucher's disease, Hurler syndrome, progressive multifocal leukoencephalopathy, Alexander's disease, congenital hypomyelination, encephalomyelitis, acute disseminated encephalomyelitis, central pontine myelinolysis, osmotic hyponatremia, Tay-Sachs disease, motor neuron disease, ataxia, spinal muscular atrophy (SMA), Niemann-Pick disease, acute hemorrhagic leukoencephalitis, trigeminal neuralgia, Bell's palsy, cerebral ischemia, multiple system atrophy, Pelizaeus Merzbacher disease, periventricular leukomalacia, a hereditary ataxia, noise-induced hearing loss, congenital hearing loss, age-related hearing loss, Creutzfeldt-Jakob disease, transmissible spongiform encephalopathy, Lewy Body Dementia, frontotemporal dementia, amyloidosis, diabetic neuropathy, globoid cell leukodystrophy (Krabbe's disease), Bassen-Kornzweig syndrome, transverse myelitis, motor neuron disease, a spinocerebellar ataxia, pre-eclampsia, hereditary spastic paraplegias, spastic paraparesis, familial spastic paraplegia, French settlement disease, Strumpell-Lorrain disease, non-alcoholic steatohepatitis (NASH), adrenomyeloneuropathy, progressive supra nuclear palsy (PSP), Friedrich's ataxia, or spinal cord injury.

In some embodiments, a chronic disease or disorder of the CNS comprises an optic nerve disorder, a traumatic CNS injury, or a metabolic disease or disorder.

In some embodiments, an optic nerve disorder comprises an acute optic neuropathy (AON), a genetic or idiopathic retinal condition, Leber congenital amaurosis (LCA), Leber hereditary optic neuropathy (LHON), primary open-angle glaucoma (POAG), acute angle-closure glaucoma (AACG), autosomal dominant optic atrophy, retinal ganglion degeneration, retinitis pigmentosa, an outer retinal neuropathy, optic nerve neuritis, optic nerve degeneration associated with multiple sclerosis, Kjer's optic neuropathy, an ischemic optic neuropathy, a deficiency in vitamin B12, a deficiency in folic acid (vitamin B9), isolated vitamin E deficiency syndrome, non-arteritic anterior ischemic optic neuropathy, exposure to ethambutol, or exposure to cyanide.

In some embodiments, a traumatic CNS injury comprises a traumatic brain injury (TBI), a spinal cord injury, traumatic axonal injury or chronic traumatic encephalopathy (CTE).

In some embodiments, a metabolic disease or disorder comprises diabetes mellitus, hypoglycemia, Bassen-Kornzweig syndrome, uremia, hypothyroidism, hepatic failure, polycythemia, amyloidosis, acromegaly, porphyria, disorders of lipid/glycolipid metabolism, nutritional/vitamin deficiencies, and mitochondrial disorders.

In some embodiments, a neurodegenerative disease or disorder comprises a disease associated with neurodegeneration. In some embodiments, a neurodegenerative disease or disorder results from blood clotting issues, inflammation, obesity, aging, stress, cancer, or diabetes.

In some embodiments, the condition is an acute peripheral neuropathy. Chemotherapy-induced peripheral neuropathy (CIPN) is an example of an acute peripheral neuropathy. CIPN can be associated with various drugs, such as, but not limited to, thalidomide, epothilones (e.g., ixabepilone), taxanes (e.g., paclitaxel and docetaxel), vinca alkaloids (e.g., vinblastine, vinorelbine, vincristine, and vindesine), proteasome inhibitors (e.g., bortezomib), platinum-based drugs (e.g., cisplatin, oxaliplatin, and carboplatin).

In some embodiments, one or more compounds and/or pharmaceutical compositions as described herein are useful, for example, to treat one or more neurodegenerative diseases, disorders or conditions selected from neuropathies or axonopathies. In some embodiments, one or more compounds and/or compositions as described herein are useful, for example to treat a neuropathy or axonopathy associated with axonal degeneration. In some embodiments, a neuropathy associated with axonal degeneration is a hereditary or congenital neuropathy or axonopathy. In some embodiments, a neuropathy associated with axonal degeneration results from a de novo or somatic mutation. In some embodiments, a neuropathy associated with axonal degeneration is selected from a list contained herein. In some embodiments, a neuropathy or axonopathy is associated with axonal degeneration, including, but not limited to Parkinson's disease, non-Parkinson's disease, Alzheimer's disease, Herpes infection, diabetes, amyotrophic lateral sclerosis, a demyelinating disease, ischemia or stroke, chemical injury, thermal injury, and AIDS.

In some embodiments, one or more compounds or pharmaceutical compositions as described herein is characterized that, when administered to a population of subjects, reduces one or more symptoms or features of neurodegeneration. For example, in some embodiments, a relevant symptom or feature may be selected from extent, rate, and/or timing of neuronal disruption. In some embodiments, neuronal disruption may be or comprise axonal degradation, loss of synapses, loss of dendrites, loss of synaptic density, loss of dendritic arborization, loss of axonal branching, loss of neuronal density, loss of myelination, loss of neuronal cell bodies, loss of synaptic potentiation, loss of action-potential potentiation, loss of cytoskeletal stability, loss of axonal transport, loss of ion channel synthesis and turnover, loss of neurotransmitter synthesis, loss of neurotransmitter release and reuptake capabilities, loss of axon-potential propagation, neuronal hyperexitability, and/or neuronal hypoexcitability. In some embodiments, neuronal disruption is characterized by an inability to maintain an appropriate resting neuronal membrane potential. In some embodiments, neuronal disruption is characterized by the appearance of inclusion bodies, plaques, and/or neurofibrillary

tangles. In some embodiments, neuronal disruption is characterized by the appearance of stress granules. In some embodiments, neuronal disruption is characterized by the intracellular activation of one or more members of the cysteine-aspartic protease (Caspase) family. In some embodiments, neuronal disruption is characterized by a neuron undergoing programed cell death (e.g., apoptosis, pyroptosis, ferroapoptosis, and/or necrosis) and/or inflammation.

In some embodiments, the neurodegenerative or neurological disease or disorder is associated with axonal degeneration, axonal damage, axonopathy, a demyelinating disease, a central pontine myelinolysis, a nerve injury disease or disorder, a metabolic disease, a mitochondrial disease, metabolic axonal degeneration, axonal damage resulting from a leukoencephalopathy or a leukodystrophy. In some embodiments, the neurodegenerative or neurological disease or disorder is selected from spinal cord injury, stroke, multiple sclerosis, progressive multifocal leukoencephalopathy, congenital hypomyelination, encephalomyelitis, acute disseminated encephalomyelitis, central pontine myelolysis, osmotic hyponatremia, hypoxic demyelination, ischemic demyelination, adrenoleukodystrophy, Alexander's disease, Niemann-Pick disease, Pelizaeus Merzbacher disease, periventricular leukomalacia, globoid cell leukodystrophy (Krabbe's disease), Wallerian degeneration, optic neuritis, transverse myelitis, amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease), Huntington's disease, Alzheimer's disease, Parkinson's disease, Tay-Sacks disease, Gaucher's disease, Hurler Syndrome, traumatic brain injury, post radiation injury, neurologic complications of chemotherapy (chemotherapy induced neuropathy; CIPN), neuropathy, acute ischemic optic neuropathy, vitamin B12 deficiency, isolated vitamin E deficiency syndrome, Bassen-Kornzweig syndrome, Glaucoma, Leber's hereditary optic atrophy (neuropathy), Leber congenital amaurosis, neuromyelitis optica, metachromatic leukodystrophy, acute hemorrhagic leukoencephalitis, trigeminal neuralgia, Bell's palsy, cerebral ischemia, multiple system atrophy, traumatic glaucoma, tropical spastic paraparesis human T-lymphotropic virus 1 (HTLV-1) associated myelopathy, west Nile virus encephalopathy, La Crosse virus encephalitis, Bunyavirus encephalitis, pediatric viral encephalitis, essential tremor, Charcot-Marie-Tooth disease, motor neuron disease, SMA, HSAN, adrenomyeloneuropathy, PSP, Friedrich’s ataxia, hereditary ataxias, noise induced hearing loss, congenital hearing loss, Lewy Body Dementia, frontotemporal dementia, amyloidosis, diabetic neuropathy, HIV neuropathy, enteric neuropathies and axonopathies, Guillain-Barre syndrome, AMAN, Creutzfeldt-Jakob disease, transmissible spongiform encephalopathy, spinocerebellar ataxias, pre-eclampsia, hereditary spastic paraplegias, spastic paraparesis, familial spastic paraplegia, French settlement disease, Strumpell-Lorrain disease, and NASH.

In some embodiments, the present disclosure provides inhibitors of SARM1 activity for treatment of neurodegenerative or neurological diseases or disorders that involve axon degeneration

or axonopathy. The present disclosure also provides methods of using inhibitors of SARM1 activity to treat, prevent or ameliorate axonal degeneration, axonopathies and neurodegenerative or neurological diseases or disorders that involve axonal degeneration.

In some embodiments, the present disclosure provides methods of treating neurodegenerative or neurological diseases or disorders related to axonal degeneration, axonal damage, axonopathies, demyelinating diseases, central pontine myelinolysis, nerve injury diseases or disorders, metabolic diseases, mitochondrial diseases, metabolic axonal degeneration, axonal damage resulting from a leukoencephalopathy or a leukodystrophy.

In some embodiments, neuropathies and axonopathies include any disease or condition involving neurons and/or supporting cells, such as for example, glia, muscle cells or fibroblasts, and, in particular, those diseases or conditions involving axonal damage. Axonal damage can be caused by traumatic injury or by non-mechanical injury due to diseases, conditions, or exposure to toxic molecules or drugs. The result of such damage can be degeneration or dysfunction of the axon and loss of functional neuronal activity. Disease and conditions producing or associated with such axonal damage are among a large number of neuropathic diseases and conditions. Such neuropathies can include peripheral neuropathies, central neuropathies, and combinations thereof. Furthermore, peripheral neuropathic manifestations can be produced by diseases focused primarily in the central nervous systems and central nervous system manifestations can be produced by essentially peripheral or systemic diseases.

In some embodiments, a peripheral neuropathy can involve damage to the peripheral nerves, and/or can be caused by diseases of the nerves or as the result of systemic illnesses. Some such diseases can include diabetes, uremia, infectious diseases such as AIDs or leprosy, nutritional deficiencies, vascular or collagen disorders such as atherosclerosis, and autoimmune diseases such as systemic lupus erythematosus, scleroderma, sarcoidosis, rheumatoid arthritis, and polyarteritis nodosa. In some embodiments, peripheral nerve degeneration results from traumatic (mechanical) damage to nerves as well as chemical or thermal damage to nerves. Such conditions that injure peripheral nerves include compression or entrapment injuries such as glaucoma, carpal tunnel syndrome, direct trauma, penetrating injuries, contusions, fracture or dislocated bones; pressure involving superficial nerves (ulna, radial, or peroneal) which can result from prolonged use of crutches or staying in one position for too long, or from a tumor; intraneural hemorrhage; ischemia; exposure to cold or radiation or certain medicines or toxic substances such as herbicides or pesticides. In particular, the nerve damage can result from chemical injury due to a cytotoxic anticancer agent such as, for example, taxol, cisplatinin, a proteasome inhibitor, or a vinca alkaloid such as vincristine. Typical symptoms of such peripheral neuropathies include weakness, numbness, paresthesia

(abnormal sensations such as burning, tickling, pricking or tingling) and pain in the arms, hands, legs and/or feet. In some embodiments, a neuropathy is associated with mitochondrial dysfunction. Such neuropathies can exhibit decreased energy levels, i.e., decreased levels of NAD and ATP.

In some embodiments, peripheral neuropathy is a metabolic and endocrine neuropathy which includes a wide spectrum of peripheral nerve disorders associated with systemic diseases of metabolic origin. These diseases include, for example, diabetes mellitus, hypoglycemia, uremia, hypothyroidism, hepatic failure, polycythemia, amyloidosis, acromegaly, porphyria, disorders of lipid/glycolipid metabolism, nutritional/vitamin deficiencies, and mitochondrial disorders, among others. The common hallmark of these diseases is involvement of peripheral nerves by alteration of the structure or function of myelin and axons due to metabolic pathway dysregulation.

In some embodiments, neuropathies include optic neuropathies such as glaucoma; retinal ganglion degeneration such as those associated with retinitis pigmentosa and outer retinal neuropathies; optic nerve neuritis and/or degeneration including that associated with multiple sclerosis; traumatic injury to the optic nerve which can include, for example, injury during tumor removal; hereditary optic neuropathies such as Kjer's disease and Leber's hereditary optic neuropathy; ischemic optic neuropathies, such as those secondary to giant cell arteritis; metabolic optic neuropathies such as neurodegenerative diseases including Leber's neuropathy mentioned earlier, nutritional deficiencies such as deficiencies in vitamins B12 or folic acid, and toxicities such as due to ethambutol or cyanide; neuropathies caused by adverse drug reactions and neuropathies caused by vitamin deficiency. Ischemic optic neuropathies also include non-arteritic anterior ischemic optic neuropathy.

In some embodiments neurodegenerative diseases that are associated with neuropathy or axonopathy in the central nervous system include a variety of diseases. Such diseases include those involving progressive dementia such as, for example, Alzheimer's disease, senile dementia, Pick's disease, and Huntington's disease; central nervous system diseases affecting muscle function such as, for example, Parkinson's disease, motor neuron diseases and progressive ataxias such as amyotrophic lateral sclerosis; demyelinating diseases such as, for example multiple sclerosis; viral encephalitides such as, for example, those caused by enteroviruses, arboviruses, and herpes simplex virus; and prion diseases. Mechanical injuries such as glaucoma or traumatic injuries to the head and spine can also cause nerve injury and degeneration in the brain and spinal cord. In addition, ischemia and stroke as well as conditions such as nutritional deficiency and chemical toxicity such as with chemotherapeutic agents can cause central nervous system neuropathies.

In some embodiments, the present disclosure provides a method of treating a neuropathy or axonopathy associated with axonal degeneration. In some such embodiments, a neuropathy or

axonopathy associated with axonal degeneration can be any of a number of neuropathies or axonopathies such as, for example, those that are hereditary or congenital or associated with Parkinson's disease, Alzheimer's disease, Herpes infection, diabetes, amyotrophic lateral sclerosis, a demyelinating disease, ischemia or stroke, chemical injury, thermal injury, and AIDS. In addition, neurodegenerative diseases not mentioned above as well as a subset of the above-mentioned diseases can also be treated with the methods of the present disclosure. Such subsets of diseases can include Parkinson's disease or non-Parkinson's diseases, or Alzheimer's disease.

In some embodiments, compounds and/or pharmaceutical compositions as described herein are administered to individuals suffering from or susceptible to a disease, disorder or condition as described herein; in some embodiments, such a disease, disorder or condition is characterized by axonal degeneration, such as one of the conditions mentioned herein.

In some embodiments, an individual to whom a compound or pharmaceutical composition is administered as described herein exhibits one or more signs or symptoms associated with axonal degeneration; in some embodiments, the subject does not exhibit any signs or symptoms of neurodegeneration.

In some embodiments, provided methods comprise administering a compound of Formula (I) to an individual in need thereof. In some such embodiments, the individual is at risk of developing a condition characterized by axonal degeneration. In some embodiments, the individual has a condition characterized by axonal degeneration. In some embodiments, the patient has been diagnosed with a condition characterized by axonal degeneration.

In some embodiments, provided methods comprise administering a composition as described herein to a population of individuals in need thereof. In some embodiments, the population is drawn from individuals who engage in activities where the potential for traumatic neuronal injury is high. In some embodiments, the population is drawn from athletes who engage in contact sports or other high-risk activities.

In some embodiments, the individual is at risk of developing a condition characterized by axonal degeneration. In some embodiments, the individual is identified as being at risk of axonal degeneration, e.g., based on the individual's genotype, a diagnosis of a condition associated with axonal degeneration, and/or exposure to an agent and/or a condition that induces axonal degeneration.

In some embodiments, the individual is at risk of developing a neurodegenerative disorder. In some embodiments the individual is elderly. In some embodiments, the individual is known to have a genetic risk factor for neurodegeneration. In some embodiments, the individual has a family history of neurodegenerative disease. In some embodiments, the individual expresses one or more copies of a known genetic risk factor for neurodegeneration. In some embodiments, the individual is drawn from

a population with a high incidence of neurodegeneration. In some embodiments, the individual has a hexanucleotide repeat expansion in chromosome 9 open reading frame 72. In some embodiments, the individual has one or more copies of the ApoE4 allele.

In some embodiments, individuals to which a compound or pharmaceutical composition as described herein is administered may be or comprise individuals suffering from or susceptible to a neurodegenerative disease, disorder or condition. In some embodiments, a neurodegenerative disease, disorder or condition may be or comprise a traumatic neuronal injury. In some embodiments, a traumatic neuronal injury is blunt force trauma, a closed-head injury, an open head injury, exposure to a concussive and/or explosive force, a penetrating injury into the brain cavity or innervated region of the body. In some embodiments, a traumatic neuronal injury is a force which causes the axons to deform, stretch, crush or sheer.

In some embodiments, the individual engages in an activity identified as a risk factor for neuronal degradation, e.g., a subject that engages in contact sports or occupations with a high chance for traumatic neuronal injury.

For example, the individual may be a patient who is receiving, or is prescribed, a chemotherapy associated with peripheral neuropathy. Examples of chemotherapeutic agents include, but not limited to, thalidomide, epothilones (e.g., ixabepilone), taxanes (e.g., paclitaxel and docetaxel), vinca alkaloids (e.g., vinblastine, vinorelbine, vincristine, and vindesine), proteasome inhibitors (e.g., bortezomib), platinum-based drugs (e.g., cisplatin, oxaliplatin, and carboplatin).

In some embodiments, provided methods comprise administering a pharmaceutical composition as described herein to an individual or population of individuals based on the presence or absence of one or more biomarkers. In some embodiments, provided methods further comprise monitoring the level of a biomarker in an individual or population of individuals and adjusting the dosing regimen accordingly.

DOSAGE AND ADMINISTRATION

The present invention provides pharmaceutical compositions or medicaments containing a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof and at least one therapeutically inert excipient, as well as methods of using the compounds of the invention to prepare such compositions and medicaments.

An embodiment, therefore, includes a pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof. A further embodiment includes a pharmaceutical composition comprising a

therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable excipient.

In one example, a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof, with the desired degree of purity may be formulated by mixing with physiologically acceptable excipients, *i.e.*, excipients that are non-toxic to recipients at the dosages and concentrations employed into a dosage form at ambient temperature and at the appropriate pH. The pH of the formulation depends mainly on the particular use and the concentration of compound, but typically ranges anywhere from about 3 to about 8. In another embodiment, compound of the present invention, or a pharmaceutically acceptable salt thereof is sterile. The compound of the present invention, or a pharmaceutically acceptable salt thereof may be stored, for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution.

Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the severity of the disorder, the particular patient being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The "therapeutically effective amount" of the compound of the present invention, or a pharmaceutically acceptable salt thereof to be administered will be governed by such considerations, and is the minimum amount necessary to inhibit SARM1 activity. Typically, such amount may be below the amount that is toxic to normal cells, or the patient as a whole.

The pharmaceutical composition (or formulation) for application may be packaged in a variety of ways depending upon the method used for administering the drug. Generally, an article for distribution includes a container having deposited therein the pharmaceutical formulation in an appropriate form. Suitable containers are well-known to those skilled in the art and include materials such as bottles (plastic and glass), sachets, ampoules, plastic bags, metal cylinders, and the like. The container may also include a tamper-proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container may have deposited thereon a label that describes the contents of the container. The label may also include appropriate warnings.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof, which matrices are in the form of shaped articles, *e.g.,* films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides, copolymers of L-glutamic acid and

gamma-ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid.

A dose to treat human patients may range from about 0.01 mg to about 1000 mg of a compound of the present invention, or a pharmaceutically acceptable salt thereof. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician. A dose may be administered once a day (QD), twice per day (BID), or more frequently, depending on the pharmacokinetic and pharmacodynamic properties, including absorption, distribution, metabolism, and excretion of the particular compound. In addition, toxicity factors may influence the dosage and administration regimen. When administered orally, the pill, capsule, or tablet may be ingested daily or less frequently for a specified period of time. The regimen may be repeated for a number of cycles of therapy.

A therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof may be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal, epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

A therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof may be administered in any convenient administrative form, *e.g.*, tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain components conventional in pharmaceutical preparations, *e.g.*, diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

A typical formulation is prepared by mixing a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof and an excipient. Suitable excipients include carriers (for example microcrystalline cellulose, lactose, mannitol), solvents (e.g., liquid polyethylene glycols), emulsifiers and dispersants or wetting agents (for example sodium dodecyl sulphate, polyoxysorbitan oleate), binders (for example polyvinylpyrrolidone), synthetic and natural polymers (for example albumin), stabilizers (e.g., antioxidants, for example ascorbic acid), colorants (e.g., inorganic pigments, for example iron oxides) and taste and/or odour correctants, and are well known to those skilled in the art and are described in detail in, *e.g.*, Ansel, H. C., *et al.*, Ansel's *Pharmaceutical Dosage Forms and Drug Delivery Systems*. Philadelphia:

Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., *et al. Remington: The Science and Practice of Pharmacy*. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, R. C., *Handbook of Pharmaceutical Excipients*, Chicago, Pharmaceutical Press, 2005. The formulations may also include one or more buffers, surfactants, lubricating agents, suspending agents, preservatives, opaquing agents, glidants, processing aids, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (*i.e.*, a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (*i.e.*, medicament).

In certain embodiments, pharmaceutical preparations for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. In specific embodiments, disintegrating agents are optionally added. Disintegrating agents include, by way of example only, cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

In one embodiment, dosage forms, such as dragee cores and tablets, are provided with one or more suitable coating. In specific embodiments, concentrated sugar solutions are used for coating the dosage form. The sugar solutions, optionally contain additional components, such as by way of example only, gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs and/or pigments are also optionally added to the coatings for identification purposes. Additionally, the dyestuffs and/or pigments are optionally utilized to characterize different combinations of active compound doses.

In certain embodiments, therapeutically effective amounts of at least one of the compounds described herein are formulated into other oral dosage forms. Oral dosage forms include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In specific embodiments, push-fit capsules contain the active ingredients in admixture with one or more filler. Fillers include, by way of example only, lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In other embodiments, soft capsules, contain one or more active compound that is dissolved or suspended in a

suitable liquid. Suitable liquids include, by way of example only, one or more fatty oil, liquid paraffin, or liquid polyethylene glycol. In addition, stabilizers are optionally added.

In other embodiments, therapeutically effective amounts of at least one of the compounds described herein are formulated for buccal or sublingual administration. Formulations suitable for buccal or sublingual administration include, by way of example only, tablets, lozenges, or gels. In still other embodiments, the compounds described herein are formulated for parental injection, including formulations suitable for bolus injection or continuous infusion. In specific embodiments, formulations for injection are presented in unit dosage form (e.g., in ampoules) or in multi-dose containers. Preservatives are, optionally, added to the injection formulations. In still other embodiments, the pharmaceutical compositions are formulated in a form suitable for parenteral injection as sterile suspensions, solutions or emulsions in oily or aqueous vehicles. Parenteral injection formulations optionally contain formulatory agents such as suspending, stabilizing and/or dispersing agents. In specific embodiments, pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. In additional embodiments, suspensions of the compound of the present invention, or a pharmaceutically acceptable salt thereof are prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles for use in the pharmaceutical compositions described herein include, by way of example only, fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. In certain specific embodiments, aqueous injection suspensions contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension contains suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, in other embodiments, the active ingredient is in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

In certain embodiments, pharmaceutical compositions are formulated in any conventional manner using one or more physiologically acceptable excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any pharmaceutically acceptable techniques and excipients are optionally used as suitable. Pharmaceutical compositions comprising a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof are manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

Pharmaceutical compositions include at least one pharmaceutically acceptable excipient and a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof, described herein as an active ingredient. The active ingredient is in free-acid or freebase form, or in a pharmaceutically acceptable salt form. In addition, the methods and pharmaceutical compositions described herein include the use of N-oxides, crystalline forms (also known as polymorphs), as well as active metabolites of these compounds having the same type of activity. All tautomers of the compounds described herein are included within the scope of the compounds presented herein. Additionally, the compounds described herein encompass unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein. In addition, the pharmaceutical compositions optionally include other medicinal or pharmaceutical agents, excipients, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, buffers, and/or other therapeutically valuable substances.

Methods for the preparation of compositions comprising a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof described herein include formulating the compound of the present invention, or a pharmaceutically acceptable salt thereof with one or more inert, pharmaceutically acceptable excipients to form a solid, semi-solid or liquid. Solid compositions include, but are not limited to, powders, tablets, dispersible granules, capsules, cachets, and suppositories. Liquid compositions include solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein. Semi-solid compositions include, but are not limited to, gels, suspensions and creams. The form of the pharmaceutical compositions described herein include liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. These compositions also optionally contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and so forth.

In some embodiments, pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof illustratively takes the form of a liquid where the agents are present in solution, in suspension or both. Typically, when the composition is administered as a solution or suspension a first portion of the agent is present in solution and a second portion of the agent is present in particulate form, in suspension in a liquid matrix. In some embodiments, a liquid composition includes a gel formulation. In other embodiments, the liquid composition is aqueous.

In certain embodiments, useful aqueous suspensions contain one or more polymers as suspending agents. Useful polymers include water-soluble polymers such as cellulosic polymers, e.g., hydroxypropyl methylcellulose, and water-insoluble polymers such as cross-linked carboxyl-containing polymers. Certain pharmaceutical compositions described herein comprise a mucoadhesive polymer, selected for example from carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

Useful pharmaceutical compositions also, optionally, include solubilizing agents to aid in the solubility of a compound of the present invention, or a pharmaceutically acceptable salt thereof. The term "solubilizing agent" generally includes agents that result in formation of a micellar solution or a true solution of the agent. Certain acceptable nonionic surfactants, for example polysorbate 80, are useful as solubilizing agents, as are ophthalmically acceptable glycols, polyglycols, e.g., polyethylene glycol 400, and glycol ethers.

Furthermore, useful pharmaceutical compositions optionally include one or more pH adjusting agents or buffering agents, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

Additionally, useful compositions also, optionally, include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

Other useful pharmaceutical compositions optionally include one or more preservatives to inhibit microbial activity. Suitable preservatives include mercury-containing substances such as merfen and thiomersal; stabilized chlorine dioxide; and quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride.

Still other useful compositions include one or more surfactants to enhance physical stability or for other purposes. Suitable nonionic surfactants include polyoxyethylene fatty acid glycerides and vegetable oils, e.g., polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, e.g., octoxynol 10, octoxynol 40.

Still other useful compositions include one or more antioxidants to enhance chemical stability where required. Suitable antioxidants include, by way of example only, ascorbic acid and sodium metabisulfite.

In certain embodiments, aqueous suspension compositions are packaged in single-dose non-reclosable containers. Alternatively, multiple-dose reclosable containers are used, in which case it is typical to include a preservative in the composition.

In alternative embodiments, other delivery systems for hydrophobic pharmaceutical compounds are employed. Liposomes and emulsions are examples of delivery vehicles or excipients useful herein. In certain embodiments, organic solvents such as N-methylpyrrolidone are also employed. In additional embodiments, the compounds described herein are delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials are useful herein. In some embodiments, sustained-release capsules release the compounds for a few weeks up to over 100 days.

The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary excipient therefore. Veterinary excipients are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered parenterally, orally or by any other desired route.

ARTICLES OF MANUFACTURE

In another embodiment of the invention, an article of manufacture, or "kit", containing materials useful for the treatment of the diseases and disorders described above is provided. In one embodiment, the kit comprises a container comprising compound of the present invention, or a pharmaceutically acceptable salt thereof. The kit may further comprise a label or package insert on or associated with the container. The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products. Suitable containers include, for example, bottles, vials, syringes, blister pack, etc. The container may be formed from a variety of materials such as glass or plastic. The container may hold a compound of the present invention, or a pharmaceutically acceptable salt thereof or a formulation thereof which is effective for treating the condition and may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is a compound of the present invention, or a pharmaceutically acceptable salt thereof. Alternatively, or additionally, the

article of manufacture may further comprise a second container comprising a pharmaceutical diluent, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution or dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

In another embodiment, the kits are suitable for the delivery of solid oral forms of a compound of the present invention, or a pharmaceutically acceptable salt thereof, such as tablets or capsules. Such a kit can include a number of unit dosages. An example of such a kit is a "blister pack". Blister packs are well known in the packaging industry and are widely used for packaging pharmaceutical unit dosage forms.

EXAMPLES

The following examples illustrate the preparation and biological evaluation of compounds within the scope of the invention. These examples and preparations which follow are provided to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

Abbreviations

The following abbreviations are used in the Examples:

CDI: 1,1-carbonyldiimidazole

DCE: dichloroethane

DCM: dichloromethane

DEA: diethylamine

DIPEA: N,N-diisopropylethylamine

DMAP: 4-dimethylaminopyridine

DMDACH: (1S,2S)-(+)-N,N'-Dimethylcyclohexane-1,2-diamine

DMEDA: 1,2-dimethylethylenediamine

DMF: dimethylformamide

DMSO: dimethylsulfoxide

EE: EtOAc / EtOH

EtOAc: ethyl acetate

EtOH: ethanol

HFIP: 1,1,3,3,-hexafluoro-2-propanol

HOAc: acetic acid

HPLC: high performance liquid chromatography

i-PrOH: isopropanol

LCMS: liquid chromatography-mass spectrometry

MeOH: methanol

MeCN: Acetonitrile

MsCl: methanesulfonyl chloride

MTBE: methyl tert-butyl ether

n-BuOH: n-butanol

NMR: nuclear magnetic resonance

TBAF: tetra-n-butylammonium fluoride

TBSCl: tert-butyldimethylsilyl chloride

TEA: triethylamine

TFA: trifluoroacetic acid

THF: tetrahydrofuran

TLC: thin layer chromatography

prep-TLC: preparative thin layer chromatography

SEM-Cl: 2-(trimethylsilyl)ethoxymethyl chloride

SFC: supercritical fluid chromatography

ANALYTICAL PROCEDURES

CHIRAL ANALYTICAL SEPARATION METHODS:

Chiral analytical separation methods (e.g., supercritical fluid chromatography (SFC), and high performance liquid chromatography (HPLC)) used in the following synthetic examples are summarized in the table below. For compounds purified by column chromatography (C.C.), refer to synthetic experimental procedures.

	Column	**Mobile Phase**	**Flow Type**	**Flow Rate**
A	PIC 200 Chiral	A = Supercritical CO_2 B = MeOH + 0.1% NH_4OH	A / B = 65 / 35	70 mL/min

B	Reverse phase chromatography	A = MeCN B = 0.05% NH_4OH + 10 mM NH_4HCO_3	Gradient: 13-43%	
C	Reverse phase chromatography	A = MeCN B = 0.05% NH_4OH + 10 mM NH_4HCO_3	Gradient: 33-66%	
D	Chiralcel OJ	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 55 / 45	80 ml/min
E	Chiralpak IG	A = Supercritical CO_2 B = *i*-PrOH + 0.1% NH_4OH	A / B = 40 / 60	80 ml/min
F	Chiralpak IC	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 55 / 45	100 ml/min
G	Chiralpak IC	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 60 / 40	80 ml/min
H	Chiralpak AS	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 75 / 25	150 ml/min
I	Chiralpak IC	A = Supercritical CO_2 B = MeOH + 0.1% NH_4OH	A / B = 75 / 25	50 ml/min
J	Chiralpak IG	A = Supercritical CO_2 B = *i*-PrOH + 0.1% NH_4OH	A / B = 40 / 60	60 ml/min
K	Chiralpak AD	A = Supercritical CO_2 B = *i*-PrOH + 0.1% NH_4OH	A / B = 45 / 55	80 ml/min
L	Cellulose-2	A = Supercritical CO_2 B = MeOH + 0.1% NH_4OH	A / B = 65 / 35	150 ml/min
M	Chiralpak AD	A = Supercritical CO_2 B = *i*-PrOH + 0.1% NH_4OH	A / B = 60 / 40	80 ml/min
N	Chiralcel OD	A = Supercritical CO_2 B = MeOH + 0.1% NH_4OH	A / B = 60 / 40	80 ml/min
O	Chiralpak IC	A = Supercritical CO_2 B = MeOH + 0.1% NH_4OH	A / B = 40 / 60	80 ml/min
P	Chiralpak IG	A = Supercritical CO_2 B = *i*-PrOH + 0.1% NH_4OH	A / B = 50 / 50	80 ml/min
Q	Chiralpak IC	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 60 / 40	60 ml/min
R	Reverse phase chromatography	A = MeCN B = 0.05% NH_4OH + 10 mM NH_4HCO_3	Gradient: 28-58%	
S	Chiralpak IH	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 65 / 35	100 ml/min

T	Chiralpak IH	A = Supercritical CO_2 B = MeOH + 0.1% NH_4OH	A / B = 55 / 45	150 ml/min
U	Reverse phase chromatography	A = MeCN B = 0.05% NH_4OH + 10 mM NH_4HCO_3	Gradient: 40-70%	
V	Chiralpak AD	A = Supercritical CO_2 B = *i*-PrOH + 0.1% NH_4OH	A / B = 40 / 60	80 ml/min
W	Chiralpak AD	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 60 / 40	80 ml/min
X	Chiralpak AD	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 45 / 55	80 ml/min
Y	Chiralpak IG	A = Supercritical CO_2 B = *i*-PrOH + 0.1% NH_4OH	A / B = 60 / 40	80 ml/min
Z	Chiralpak IH	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 55 / 45	100 ml/min
AA	Chiralpak AS	A = Supercritical CO_2 B = *i*-PrOH + 0.1% NH_4OH	A / B = 50 / 50	150 ml/min
AB	Chiralcel OJ	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 60 / 40	80 ml/min
AC	XSelect CSH Prep C18	A = MeCN B = 0.1% NaOH in H_2O	Gradient: 20-60%	60 ml/min
AD	Column Chromatography	A = DCM B = MeOH	Gradient: 0-10%	
AE	Chiralpak IG	A = Supercritical CO_2 B = *i*-PrOH + 0.1% NH_4OH	A / B = 55 / 45	80 ml/min
AF	Chiralpak AY	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 85 / 15	150 ml/min
AG	Chiralpak AD	A = Supercritical CO_2 B = MeOH + 0.1% NH_4OH	A / B = 65 / 35	80 ml/min
AH	Cellulose-2	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 50 / 50	150 ml/min
AI	Chiralpak AD	A = Supercritical CO_2 B = MeOH + 0.1% NH_4OH	A / B = 70 / 30	70 ml/min
AJ	Chiralpak IC	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 75 / 25	50 ml/min
AK	Reverse phase chromatography	A = MeCN B = 0.05% NH_4OH + 10 mM NH_4HCO_3	Gradient: 47-77%	

AL	Chiralpak IH	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 50 / 50	100 ml/min
AM	Chiralpak IC	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 55 / 45	80 ml/min
AN	Reverse phase chromatography	A = MeCN B = 0.05% NH_4OH + 10 mM NH_4HCO_3	Gradient: 48-78%	
AO	Chiralcel OJ	A = Supercritical CO_2 B = *i*-PrOH + 0.1% NH_4OH	A / B = 55 / 45	80 ml/min
AP	Chiralpak IG	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 40 / 60	80 ml/min
AQ	Chiralpak AD	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 40 / 60	80 ml/min
AR	Reverse phase chromatography	A = MeCN B = 0.05% NH_4OH + 10 mM NH_4HCO_3	Gradient: 23-53%	
AS	Reverse phase chromatography	A = MeCN B = 0.05% NH_4OH + 10 mM NH_4HCO_3	Gradient: 34-64%	
AT	Chiralpak AD	A = Supercritical CO_2 B = *i*-PrOH + 0.1% NH_4OH	A / B = 50 / 50	80 ml/min
AU	Chiralpak AD	A = Supercritical CO_2 B = *i*-PrOH + 0.1% NH_4OH	A / B = 45 / 55	80 ml/min
AV	Chiralcel OD	A = Supercritical CO_2 B = *i*-PrOH + 0.1% NH_4OH	A / B = 65 / 35	150 ml/min
AW	XSelect CSH Prep C18	A = MeCN B = 0.1% CH_2O_2 in H_2O	Gradient: 5-85%	60 ml/min
AX	XSelect CSH Prep C18	A = MeCN B = 0.1% NaOH in H_2O	Gradient: 30-70%	60 ml/min
AY	Chiralpak IA	A = Supercritical CO_2 B = MeOH + 0.1% NH_4OH	Isocratic 20%	70 ml/min
AZ	Chiralpak IK	A = Supercritical CO_2 B = MeOH + 0.1% NH_4OH	Isocratic 25%	70 ml/min
BA	Triart C18	A = MeCN B = 0.1% CH_2O_2 in H_2O	Gradient: 20-60%	60 ml/min
BB	Gemini-NX C18	A = MeCN B = 0.1% CH_2O_2 in H_2O	Gradient: 5-85%	60 ml/min
BC	XSelect CSH Prep C18	A = MeCN B = 0.1% CH_2O_2 in H_2O	Gradient: 5-50%	60 ml/min

BD	Reverse phase chromatography	A = MeCN B = 0.05% NH_4OH + 10 mM NH_4HCO_3	Gradient: 46-76%	
BE	Chiralpak AD	A = Supercritical CO_2 B = MeOH + 0.1% NH_4OH	A / B = 60 / 40	80 ml/min
BF	Chiralpak AD	A = Supercritical CO_2 B = MeOH + 0.1% NH_4OH	A / B = 55 / 45	80 ml/min
BG	Cellulose-2	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 45 / 55	150 ml/min
BH	Chiralpak AD	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 70 / 30	80 ml/min
BI	Chiralcel IC	A = Supercritical CO_2 B = *i*-PrOH + 0.1% NH_4OH	A / B = 55 / 45	80 ml/min
BJ	Chiralpak AD	A = Supercritical CO_2 B = MeOH + 0.1% NH_4OH	A / B = 40 / 60	80 ml/min
BK	XSelect CSH Prep C18	A = MeCN B = 0.1% NaOH in H_2O	Gradient: 5-85%	60 ml/min
BL	Chiralpak IG	A = Supercritical CO_2 B = MeOH + 0.1% NH_4OH	A / B = 60 / 40	70 ml/min
BM	Chiralcel OD	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 80 / 20	150 ml/min
BN	Regis (S,S) whelk-01	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 40 / 60	80 ml/min
BO	Chiralcel OD	A = Supercritical CO_2 B = MeOH + 0.1% NH_4OH	A / B = 70 / 30	80 ml/min
BP	Chiralpak IC	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 40 / 60	80 ml/min
BQ	Chiralpak AS	A = Supercritical CO_2 B = MeOH + 0.1% NH_4OH	A / B = 70 / 30	80 ml/min
BR	Chiralpak AD	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 60 / 40	150 ml/min
BS	Chiralpak AD	A = Supercritical CO_2 B = MeOH + 0.1% NH_4OH	A / B = 30 / 70	150 ml/min
BT	Chiralpak AD	A = Supercritical CO_2 B = MeOH + 0.1% NH_4OH	A / B = 60 / 40	150 ml/min
BU	Chiralcel OD	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 60 / 40	80 ml/min

BV	Chiralpak AY	A = Supercritical CO_2 B = EtOH + 0.1% NH_4OH	A / B = 55 / 45	100 ml/min
BW	Reverse phase chromatography	A = MeCN B = 10 mM NH_4HCO_3 in H_2O	Gradient: 45-75%	
BX	Chiralpak AD	A = Supercritical CO_2 B = MeOH + 0.1% NH_4OH	A / B = 70 / 30	150 ml/min
BY	Reverse phase chromatography	A = MeCN B = 0.05% NH_4OH + 10 mM NH_4HCO_3	Gradient: 35-65%	

LCMS Analytical Methods

Agilent 10-min: Experiments were performed on an Agilent 1290 UHPLC coupled with Agilent MSD (6140) mass spectrometer using ESI as ionization source. The LC separation was using a Phenomenex XB-C18, 1.7mm, 50 × 2.1 mm column at a flow rate of 0.4 ml / minute. MPA (mobile phase A) was water with 0.1% FA and MPB (mobile phase B) was acetonitrile with 0.1% FA. The gradient started at 2% MPB and ended at 98% MPB over 7 min and held at 98%B for 1.5 min following equilibration for 1.5 min. LC column temperature was 40 °C. UV absorbance was collected by a DAD detector and mass spec full scan was applied to all experiments.

Agilent 30-min: Experiments were performed on an Agilent 1290 HPLC coupled with Agilent MSD (6140) mass spectrometer using ESI as ionization source. The LC separation was done on an Agilent Zorbax Eclipse XDB-C18, 3.5 um, 100 × 3.0 mm column at a flow rate of 0.7 ml/minute. MPA (mobile phase A) was water with 0.1% FA and MPB (mobile phase B) was acetonitrile with 0.1% FA. The gradient started at 2% MPB and ended at 98% MPB over 25.5 min and held at 98%B for 2.5 min following equilibration for 1.5 min. LC column temperature was 40 °C. UV absorbance was collected by a DAD detector and mass spec full scan was applied to all experiments.

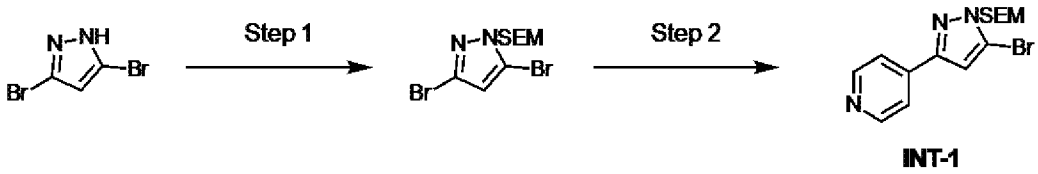
Thermo qE 10-min: The samples were analyzed on a Dionex Ultimate 3000 coupled with Thermo Scientific Q Exactive HRMS using ESI as ionization source. The LC separation was done on a Phenomenex XB-C18, 1.7µm, 50 × 2.1 mm column at a flow rate of 0.4 ml / minute. MPA (mobile phase A) was water with 0.1% FA and MPB (mobile phase B) was acetonitrile with 0.1% FA. The gradient started at 2 % MPB and ended at 98% MPB over 7 min and held at 98% MPB for 1.5 min following an equilibration for 1.5 min. LC column temperature was 40 °C. UV absorbance was collected by a DAD detector and mass spec full scan was applied to all experiments.

Thermo qE 30-min: The samples were analyzed on a Dionex Ultimate 3000 coupled with Thermo Scientific Q Exactive HRMS using ESI as ionization source. The LC separation was done

on an Agilent Zorbax Eclipse XDB-C18, 3.5 um, 100 × 3.0 mm column at a flow rate of 0.7 ml/minute. MPA (mobile phase A) was water with 0.1% FA and MPB (mobile phase B) was acetonitrile with 0.1% FA. The gradient started at 2% MPB and ended at 98% MPB over 25.5 min and held at 98%B for 2.5 min following equilibration for 1.5 min. LC column temperature was 40 °C. UV absorbance was collected by a DAD detector and mass spec full scan was applied to all experiments.

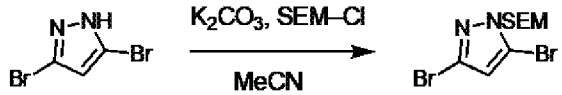
Experimental Procedures:

Intermediate 1: 3,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole



INT-1

Step 1: *Synthesis of 3,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole*

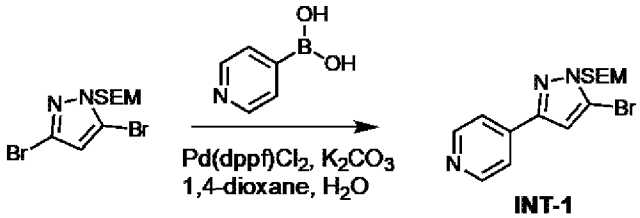


A mixture of 3,5-dibromo-1H-pyrazole (50.0 g, 221 mmol) and K_2CO_3 (91.8 g, 664 mmol) in MeCN (350 mL) was stirred at 25 °C for 0.5 h under nitrogen atmosphere. Then SEM-Cl (40.6 g, 244 mmol, 43.1 mL) was added dropwise at 25 °C for 16 hr. The mixture was refluxed at 80 °C for 3.5 hrs. LCMS showed the starting material was consumed completely. The reaction mixture was filtered and the filtrate was concentrated in vacuum to give a crude product. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=100/1 to 10/1). 3,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (50.5 g, 142 mmol, 64.1% yield) was obtained as a colorless oil.

LCMS: (ESI, m/z) $[M+H]^+$ = 357, RT = 0.640 min.

^{1}H NMR: (400 MHz, $CDCl_3$) δ ppm -0.04 - 0.12 (m, 9 H) 0.87 - 0.98 (m, 2 H) 3.56 - 3.73 (m, 2 H) 5.44 (s, 2 H) 6.38 (s, 1 H).

Step 2: *Synthesis of 3,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (INT-1)*

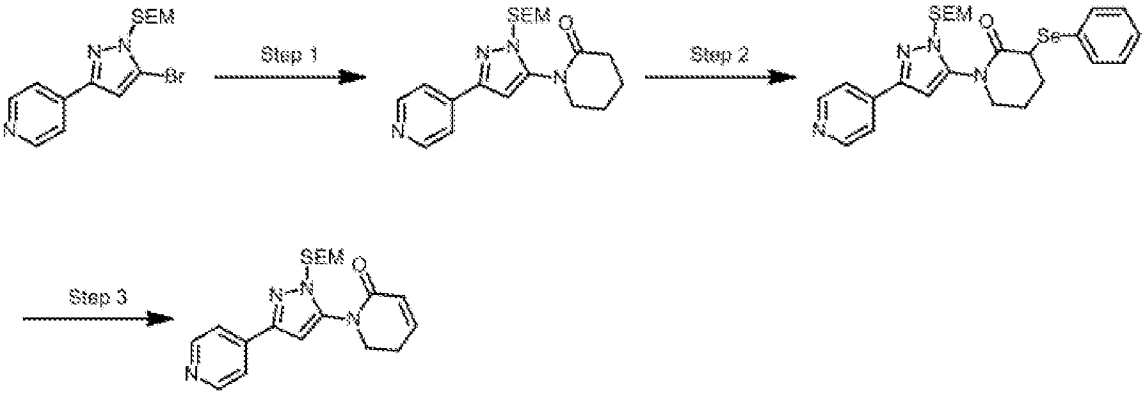


INT-1

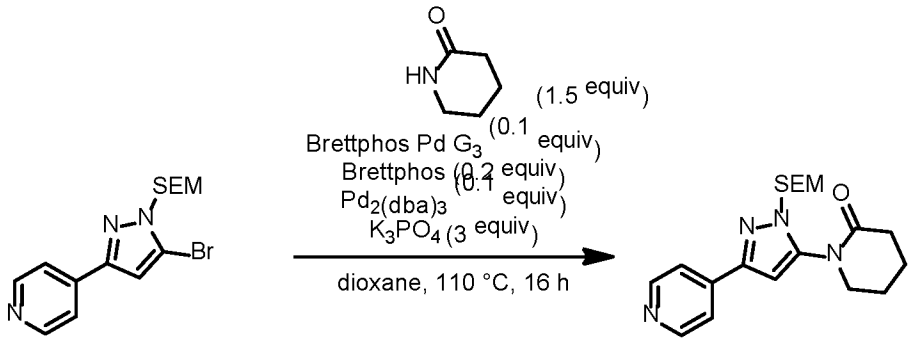
To a mixture of 3,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (200 g, 562 mmol), pyridin-4-ylboronic acid (75.9 g, 617 mmol) and K_2CO_3 (233 g, 1.68 mol) in dioxane (1000 mL) and H_2O (400 mL) was added $Pd(dppf)Cl_2$ (20.6 g, 28.1 mmol). The reaction mixture was stirred at 100 °C for 45 min under nitrogen atmosphere. LCMS showed the starting material was consumed completely. After cooling to room temperature, the reaction mixture was partitioned between EtOAc (500 mL) and brine (800 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (800 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=3/1). *3,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole* **INT-1** (260 g, 734 mmol, 43.6% yield) was obtained as a yellow oil.

^{1}H NMR: (400 MHz, $CDCl_3$) δ ppm -0.05 - 0.09 (m, 8 H) 0.86 - 1.06 (m, 2 H) 3.62 - 3.91 (m, 2 H) 5.36 - 5.63 (m, 2 H) 6.52 - 6.80 (m, 1 H) 7.53 - 7.72 (m, 2 H) 8.62 - 8.79 (m, 2 H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 355, RT = 0.468 min.

Intermediate 2

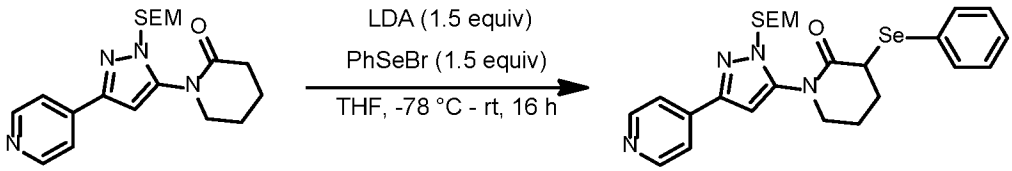


Step 1: *Synthesis of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)piperidin-2-one*



To a mixture of 4-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)pyridine (2.0 g, 5.64 mmol), piperidin-2-one (840 mg, 8.47 mmol), and K_3PO_4 (3.6 g, 17 mmol) in 1,4-dioxane (30 mL) was added Brettphos Pd G3 (511 mg, 0.56 mmol), Brettphos (606 mg, 1.13 mmol) and $Pd_2(dba)_3$ (513 mg, 0.56 mmol). The mixture was stirred at 110 °C for 16 hours under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified flash column chromatography (SiO_2, 50% EtOAc in petroleum ether) to afford 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one (1 g, 48% yield) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.69 (d, J = 6.0 Hz, 2H), 7.60 (d, J = 6.0 Hz, 2H), 7.18 (s, 1H), 5.38 (s, 2H), 3.94 (t, J = 6.0 Hz, 2H), 3.75 (t, J = 8.0 Hz, 2H), 2.60 (t, J = 6.4 Hz, 2H), 1.98 - 1.89 (m, 4H), 0.965 (t, J = 8.4 Hz, 2H), 0.01 (s, 9H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 529.1

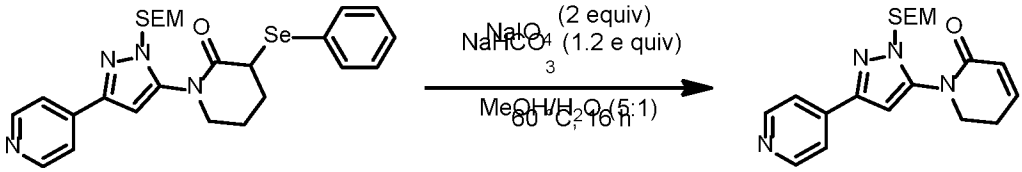
***Step 2**: Synthesis of 3-(phenylselanyl)-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)piperidin-2-one*



To a solution of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one (5.0 g, 13.42 mmol) in THF (50 mL) added LDA (10.07 mL, 20.13 mmol) dropwise at -78 °C under nitrogen atmosphere. After stirring at -78 °C for 1 hour, a solution of benzeneselenenyl bromide (4.75 g, 20.13 mmol) in THF (50 mL) was added. The mixture was stirred at -78 °C for 1 hour and then was stirred at room temperature for 16 hours. The reaction mixture was quenched with NH_4Cl (10 mL), and the residue was dissolved in DCM (200 mL). The organic phase was washed with water (50 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (SiO_2, 0-50% ethyl acetate in petroleum ether) to afford 3-(phenylselanyl)-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one (2.8 g, 40% yield) as a yellow oil. **LCMS**: (ESI, m/z) $[M+H]^+$ =

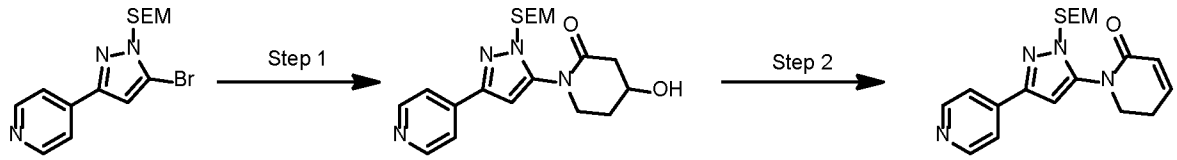
373.1

***Step 3**: Synthesis of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)-5,6-dihydropyridin-2(1H)-one (INT-2)*

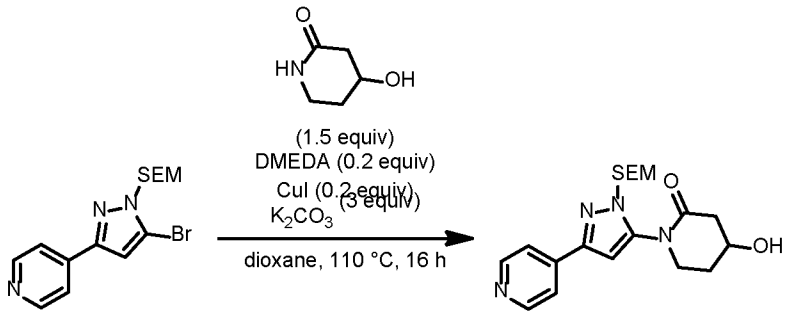


To a mixture of 3-(phenylselanyl)-1-(3-(pyridin- 4 -yl)-1-((2-(trimethylsilyl) ethoxy) methyl)-1*H*-pyrazol-5-yl) piperidin-2-one (5.0 g, 9.48 mmol) and $NaHCO_3$ (0.96 g, 11.37 mmol) in methyl alcohol (160 mL) and water (32 mL) was added $NaIO_4$ (4.05 g, 18.95 mmol). Then the mixture was stirred at 60 °C for 16 h. After cooling to room temperature, the resulting mixture was quenched by $NaHCO_3$ (20 mL) and extracted with DCM (300 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 0-25% petroleum ether in (Ethyl acetate / ethanol = 3:1)) to afford 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-5,6-dihydropyridin-2(1*H*)-one (Intermediate 2, 2.4 g, 68% yield) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.70 (d, J = 6.0 Hz, 2H), 7.61 (d, J = 6.0 Hz, 2H), 7.21 (s, 1H), 6.81 - 6.73 (m, 1H), 6.11 - 6.04 (m, 1H), 5.38 (s, 2H), 4.18 (t, J = 6.8 Hz, 2H), 3.79 - 3.71 (m, 2H), 2.58 - 2.44 (m, 2H), 1.01 - 0.93 (m, 2H), 0.02 (s, 9H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 371.1

Intermediate 3



***Step 1:** Synthesis of 4-hydroxy-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)piperidin-2-one*

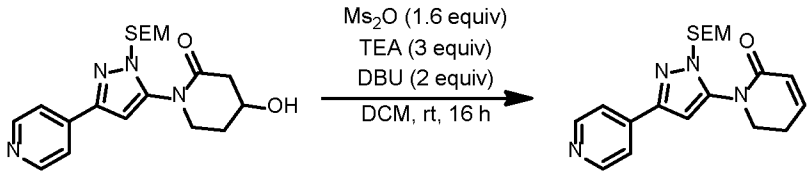


To a mixture of 4-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)pyridine (10.0 g, 28 mmol), 4-hydroxypiperidin-2-one (4.87 g, 42 mmol) and K_2CO_3 (11.7 g, 84 mmol) in 1,4-

dioxane (120 mL) was added CuI (0.19 mL, 5.64 mmol) and DMEDA (0.61 mL, 5.64 mmol). The mixture was stirred at 110 ℃ for 16 hours under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified flash column chromatography (SiO_2, 30% EE (EtOAc / EtOH = 3/1) in petroleum ether) to afford 4-hydroxy-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one (4.8 g, 44% yield) as a yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.69 (d, J = 6.0 Hz, 2H), 7.60 (d, J = 6.0 Hz, 2H), 7.17 (s, 1H), 5.38 (s, 2H), 4.39 - 4.27 (m, 1H), 4.20 - 4.11 (m, 1H), 3.99 - 3.88 (m, 1H), 3.75 (t, J = 8.0 Hz, 2H), 2.98 - 2.81 (m, 1H), 2.68 - 2.60 (m, 1H), 2.27 - 2.12 (m, 2H), 2.09 - 2.02 (m, 1H), 0.97 (t, J = 8.4 Hz, 2H), 0.01 (s, 9H). LCMS: (ESI, m/z) $[M+H]^+$ = 289.3

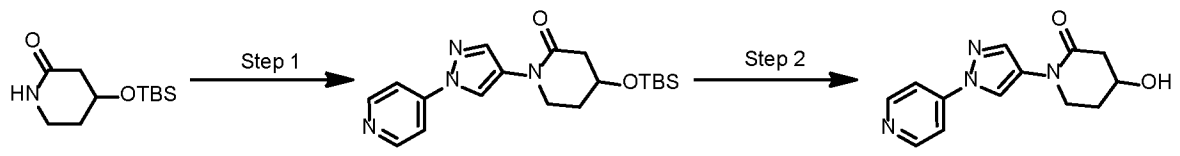
Step 2: *Synthesis of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)-5,6-dihydropyridin-2(1H)-one (INT-3)*



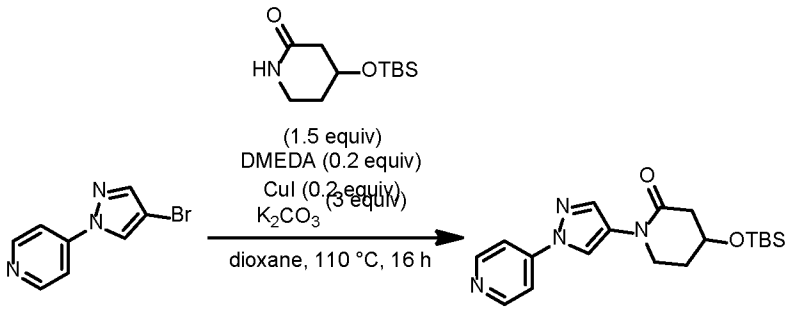
To a solution of 4-hydroxy-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one (4.8 g, 12 mmol) and TEA (5 mL, 37 mmol) in DCM (100 mL) was added Ms_2O (3.44 g, 19 mmol). The reaction mixture was stirred at room temperature for 5 hours. Then DBU (3.7 mL, 24 mmol) was added and the mixture was still stirred at room temperature for 16 hours. The reaction was quenched with saturated aqueous NH_4Cl solution (50 mL). The organic phase was separated, and the aqueous phase was extracted with DCM (50 mL x 2). The combined the organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 20% EE (EtOAc /EtOH =3/1) in petroleum ether) to afford 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-5,6-dihydropyridin-2(1*H*)-one (**INT-3**, 4 g, 79% yield) as a yellow oil.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.69 (d, J = 5.6 Hz, 2H), 7.72 - 7.58 (m, 2H), 7.09 (s, 1H), 6.93 - 6.84 (m, 1H), 6.01 - 5.89 (m, 1H), 5.43 (s, 2H), 4.05 (t, J = 6.8 Hz, 2H), 3.62 (t, J = 6.8 Hz, 2H), 0.95 - 0.71 (m, 2H), -0.07 (s, 9H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 371.3

Intermediate 4



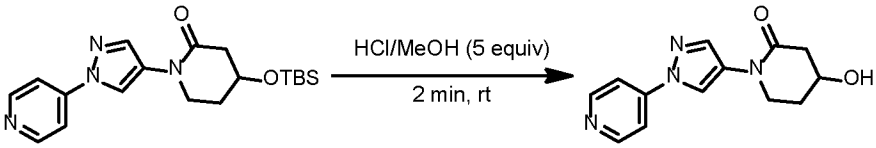
Step 1: *Synthesis of 4-((tert-butyldimethylsilyl)oxy)-1-(1-(pyridin-4-yl)-1H-pyrazol-4-yl)piperidin-2-one*



To a solution of 4-(4-bromo-1*H*-pyrazol-1-yl)pyridine (500 mg, 2.23 mmol), 4-((*tert*-butyldimethylsilyl)oxy)piperidin-2-one (767 mg, 3.35 mmol) in 1,4-dioxane (10 mL) was added DMEDA (0.05 mL, 0.45 mmol), K_2CO_3 (925 mg, 6.69 mmol) and CuI (85 mg, 0.45 mmol). The mixture was stirred at 110 °C for 16 hours under nitrogen atmosphere. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 50% EtOAc in petroleum ether) to afford 4-((*tert*-butyldimethylsilyl)oxy)-1-(1-(pyridin-4-yl)-1*H*-pyrazol-4-yl)piperidin-2-one (360 mg, 43% yield) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.80 - 8.59 (m, 3H), 7.90 (s, 1H), 7.81 - 7.73 (m, 2H), 4.33 - 4.25 (m, 1H), 4.03 - 3.92 (m, 1H), 3.75 - 3.65 (m, 1H), 2.81 - 2.71 (m, 1H), 2.66 - 2.56 (m, 1H), 2.18 - 2.02 (m, 2H), 0.89 (s, 9H), 0.11 (d, J = 2.0 Hz, 6H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 373.1

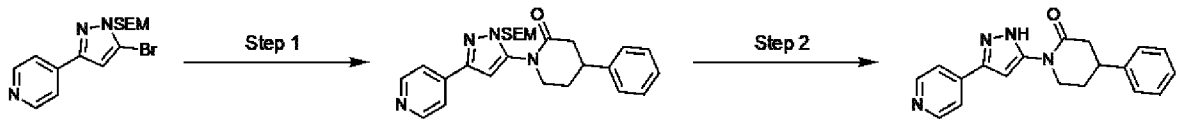
Step 2: *Synthesis of 4-hydroxy-1-(1-(pyridin-4-yl)-1H-pyrazol-4-yl)piperidin-2-one (INT-4)*



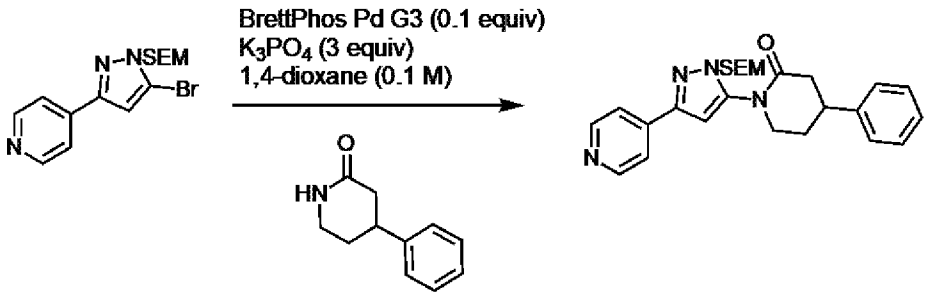
A solution of 4-((*tert*-butyldimethylsilyl)oxy)-1-(1-(pyridin-4-yl)-1*H*-pyrazol-4-yl)piperidin-2-one (1.0 g, 2.68 mmol) in HCl/MeOH (6 mL, 13 mmol) slowly at room temperature. The mixture was clear, and then became cloudy over the course of 2 minutes. The mixture was concentrated and added $NaHCO_3$ saturated solution to adjust pH = 8, then the mixture was concentrate and purified by flash column chromatography (SiO_2, 6% MeOH in DCM) to afford 4-hydroxy-1-(1-(pyridin-4-yl)-1*H*-pyrazol-4-yl)piperidin-2-one (560 mg, 81% yield) as a white solid.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.83 (s, 1H), 8.70 - 8.60 (m, 2H), 8.22 (s, 1H), 7.92 - 7.81 (m, 2H), 5.11 (d, J = 3.6 Hz, 1H), 4.14 - 4.05 (m, 1H), 3.87 - 3.77 (m, 1H), 3.69 - 3.61 (m, 1H), 2.72 - 2.64 (m, 1H), 2.40 - 2.31 (m, 1H), 2.14 - 2.00 (m, 1H), 1.94 - 1.85 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 259.1

Examples 1a and 1b

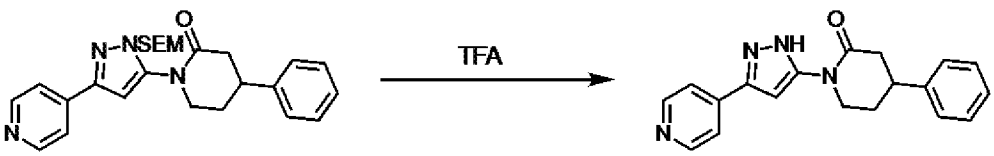


Step 1: Synthesis of (4-phenyl-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)piperidin-2-one)



To a vial equipped with a stir bar was added INT-1 (50 mg, 1 equiv, 0.14 mmol), 4-phenylpiperidin-2-one (74.2 mg, 3.0 equiv, 0.42 mmol), BrettPhos Pd G3 (13.45 mg, 0.1 equiv, 0.014 mmol), and K_3PO_4 (94.5 mg, 3.0 equiv, 0.42 mmol). The reaction was placed under nitrogen and diluted with anhydrous 1,4-dioxane (1.4 mL, 0.1 M). The reaction was stirred at 110 °C for 16 h under nitrogen. After cooling to room temperature, the mixture was diluted with water and extracted with DCM/MeOH (3 x 5 mL). The combined organics were dried with $MgSO_4$, filtered, and rotovaped. The crude material (4-phenyl-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one) was taken to the next step without further purification. LCMS: (ESI, m/z) $[M+H]^+$ = 449.1

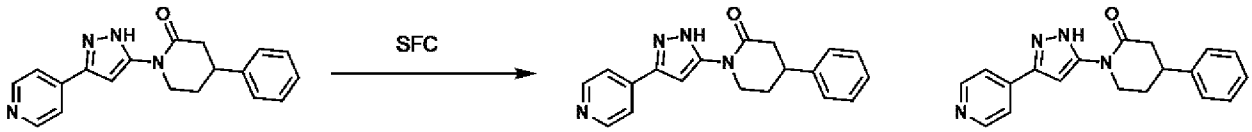
Step 2: Synthesis of 4-phenyl-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one



To a vial equipped with a stir bar and 4-phenyl-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one was added TFA (1 mL). The reaction was stirred at room temperature for 1 hour upon which no residual starting material was observed by LCMS. The TFA was evaporated and the material was purified by prep HPLC (XSelect CSH Prep C18, 50 mm x 30 mm, 5 μm), 0.1% Ammonium hydroxide in water / acetonitrile using a gradient of

20% to 60% acetonitrile; 60 mL/min, 25 °C) to yield 4-phenyl-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one as a white solid (30.1 mg, 67% yield). LCMS: (ESI, m/z) $[M+H]^+$ = 319.10

Step 3: Chiral separation of 4-phenyl-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Ex. 1a & 1b)

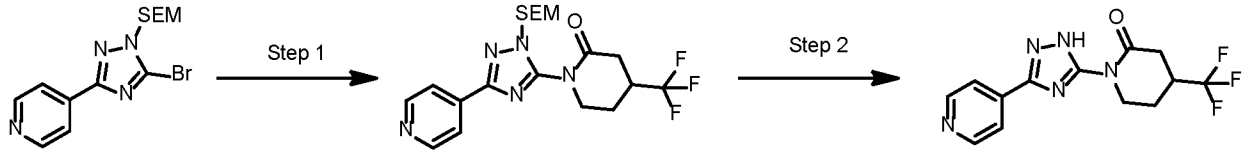


4-phenyl-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (30 mg, 0.094 mmol) was separated by chiral SFC (PIC 200 Chiral (150 mm x 21.2 mm, 5 um), Supercritical CO_2 / MeOH + 0.1% NH_4OH = 65/35; 70 mL/min, 40 °C) to afford 4-phenyl-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Example 1a, peak 1, 12.1 mg) and 4-phenyl-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Example 1b, peak 2, 8.87 mg) both as white solid.

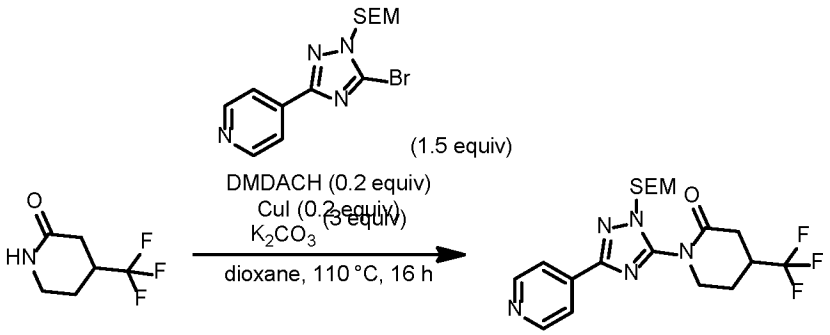
Example 1a: **^{1}H NMR** (400 MHz, DMSO) δ 8.63 (s, 1H), 7.72 (d, J = 5.4 Hz, 2H), 7.35 (m, 4H), 7.25 (tt, J = 6.3, 3.1 Hz, 2H), 4.03 (s, 1H), 3.82 (td, J = 4.81, 11.8, 1H), 3.23 (m, 1H), 2.78 – 2.61 (m, 2H), 2.2–2.03 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 319.10

Example 1b: **^{1}H NMR** (400 MHz, DMSO) δ 13.32 (s, 1H), 8.63 (d, J = 4.8 Hz, 2H), 7.73 (d, J = 5.6 Hz, 2H), 7.35 (d, J = 5.4 Hz, 4H), 7.30 – 7.20 (m, 2H), 4.02 (bs, 1H), 3.82 (td, J = 11.8, 4.8 Hz, 1H), 2.78 – 2.61 (m, 2H), 2.22 – 2.04 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 319.10

Example 2

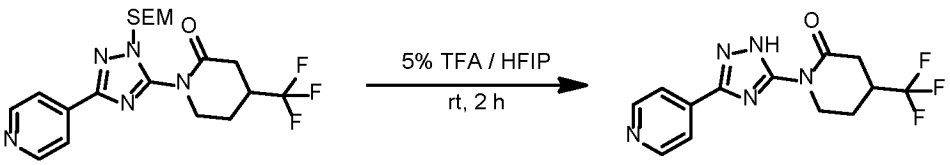


Step 1: Synthesis of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazol-5-yl)-4-(trifluoromethyl)piperidin-2-one



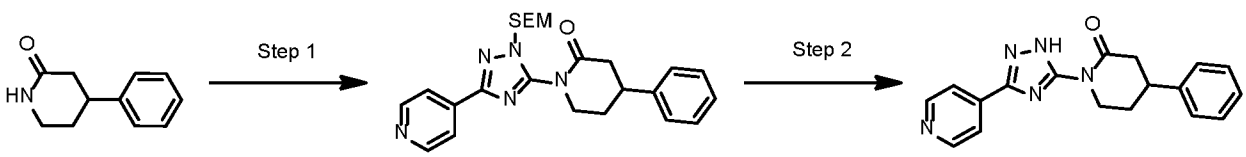
To a mixture of 4-(trifluoromethyl)piperidin-2-one (400 mg, 2.39 mmol), 4-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-1,2,4-triazol-3-yl)pyridine (1.27 g, 3.59 mmol) in 1,4-dioxane (20 mL) was added DMDACH (0.08 mL, 0.48 mmol), CuI (92 mg, 0.48 mmol) and K_2CO_3 (248 mg, 1.8 mmol). The mixture was stirred at 110 °C for 16 hours under nitrogen atmosphere. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 40-70%/0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to give 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-1,2,4-triazol-5-yl)-4-(trifluoromethyl)piperidin-2-one (30 mg, 6% yield) as a yellow oil. **LCMS**: (ESI, m/z) $[M+H]^+$ = 442.1

Step 2: Synthesis of 1-(3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)-4-(trifluoromethyl)piperidin-2-one (Ex 2)

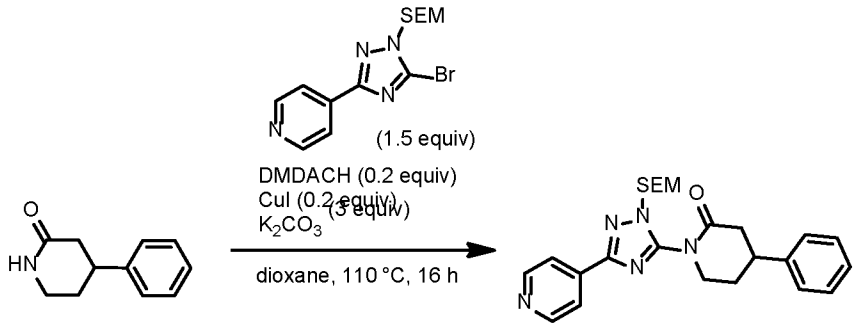


A mixture of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-1,2,4-triazol-5-yl)-4-(trifluoromethyl)piperidin-2-one (60 mg, 0.14 mmol) in 5% TFA/HFIP solution (6 mL) was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure. The residue was dissolved in DCM (5 mL), and then was adjusted pH = 8 with saturated $NaHCO_3$ solution. The organic phase was separated, and the aqueous phase was extracted with DCM (5 mL x 2). The combines organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 13-43% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to afford 1-(3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5-yl)-4-(trifluoromethyl)piperidin-2-one (12.7 mg, 30% yield) as a white solid. **^{1}H NMR** (DMSO-d_6, 400 MHz): δ 13.96 (s, 1H), 8.68 (d, J = 6.0 Hz, 2H), 7.90 (d, J = 5.6 Hz, 2H), 4.34 - 4.25 (m, 1H), 3.95 - 3.86 (m, 1H), 3.20 - 3.10 (m, 1H), 2.85 - 2.75 (m, 1H), 2.72 - 2.60 (m, 1H), 2.29 - 2.20 (m, 1H), 2.04 - 1.85 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 311.9.

Example 3

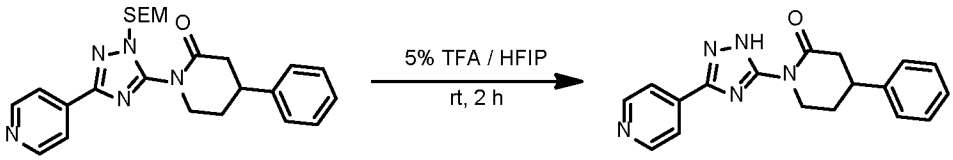


Step 1: *Synthesis of 4-phenyl-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazol-5-yl)piperidin-2-one*



To a mixture of 4-phenylpiperidin-2-one (329 mg, 1.88 mmol) and 4-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-1,2,4-triazol-3-yl)pyridine (1.0 g, 2.82 mmol) in 1,4-dioxane (5 mL) was added DMDACH (53 mg, 0.38 mmol), CuI (71 mg, 0.38 mmol) and K_2CO_3 (778 mg, 5.63 mmol). The resulting mixture was stirred at 110 °C for 16 hrs under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 0-5% methanol in ethyl acetate) to afford 200 mg crude, which was further purified by preparative-TLC (10% methanol in dichloromethane) to afford 4-phenyl-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-1,2,4-triazol-5-yl)piperidin-2-one (45 mg, 5% yield) as a yellow solid.

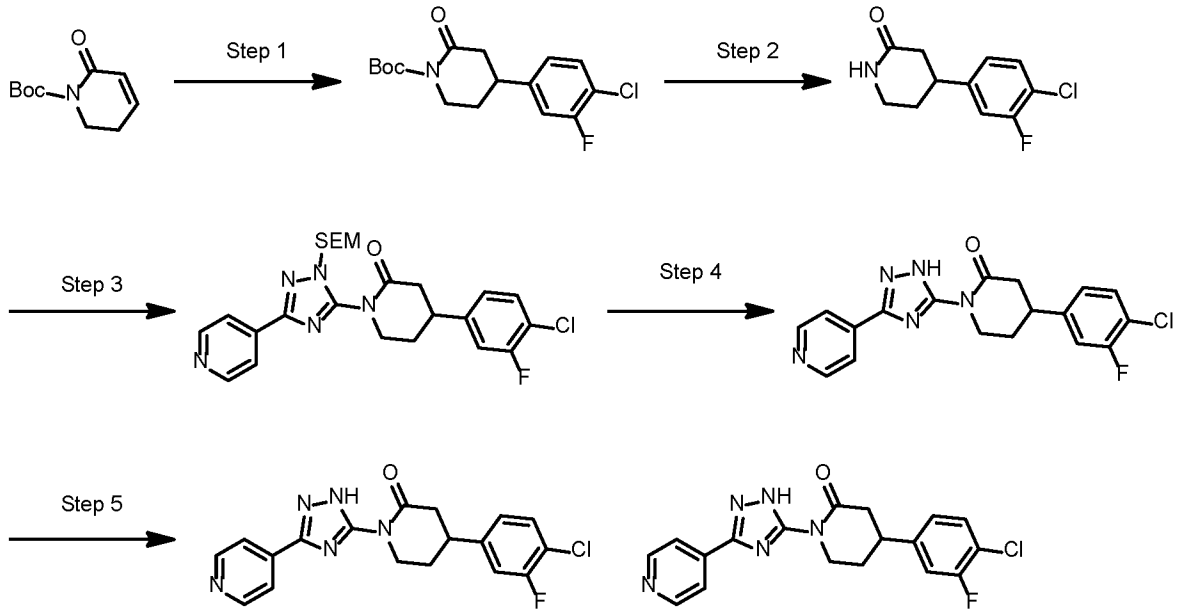
Step 2: *Synthesis of 4-phenyl-1-(3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)piperidin-2-one*



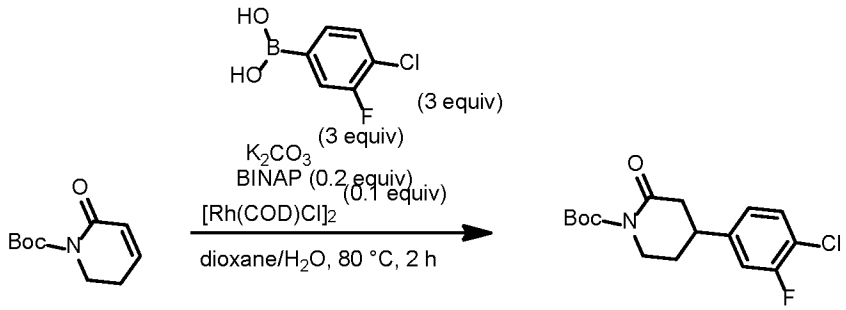
A solution of 4-phenyl-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-1,2,4-triazol-5-yl)piperidin-2-one (95 mg, 0.21 mmol) in 5% TFA / HFIP solution (5 mL) was stirred at room temperature for 2 hours. The reaction was concentrated, the residue was dissolved in DCM (3 mL), and the pH was adjusted to 8 with saturated $NaHCO_3$ solution. The mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile: 36-66% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to afford 4-phenyl-1-(3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5-yl)piperidin-2-one (27 mg, 39% yield) as a white solid.

^{1}H NMR (DMSO-*d*6, 400 MHz): δ 8.67 - 8.62 (m, 2H), 7.92 - 7.86 (m, 2H), 7.39 - 7.33 (m, 4H), 7.29 - 7.22 (m, 1H), 4.24 - 4.12 (m, 1H), 3.98 - 3.86 (m, 1H), 3.25 - 3.20 (m, 1H), 2.81 - 2.74 (m, 2H), 2.24 - 2.07 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 320.0.

Examples 4a and 4b



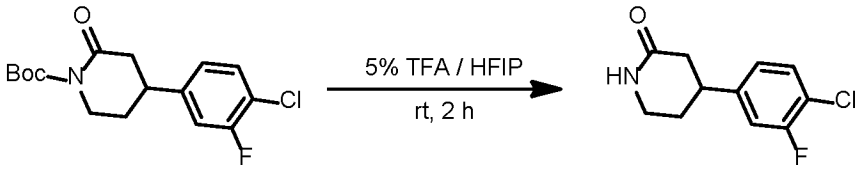
Step 1: Synthesis of tert-butyl 4-(4-chloro-3-fluoro-phenyl)-2-oxo-piperidine-1-carboxylate



To a mixture of *tert*-butyl 2-oxo-5,6-dihydropyridine-1(2*H*)-carboxylate (2.0 g, 10.14 mmol) in 1,4-dioxane (40 mL) and water (4 mL) was added 4-chloro-3-fluorophenylboronicacid (5.3 g, 30.42 mmol), K_2CO_3 (4.2 g, 30.42 mmol), BINAP (1.26 g, 2.03 mmol), chloro(1,5-cyclooctadiene)rhodium(I)dimer (0.5 g, 1.01 mmol). The reaction mixture was stirred at 80 °C for 2 hours under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was filtered and diluted with water (50 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (50 mL x 2). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, 20% ethyl acetate in petroleum ether) to afford *tert*-butyl 4-(4-chloro-3-fluoro-phenyl)-2-oxo-piperidine-1-carboxylate (2.4 g, 72% yield) as a white solid. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.37 (t, J = 8.0 Hz, 1H), 7.01 (m, J = 6.0 Hz, 1H), 6.96 - 6.92 (m, 1H), 3.93 - 3.85 (m, 1H), 3.66 - 3.57 (m, 1H), 3.18 - 3.06 (m, 1H), 2.88 - 2.79 (m, 1H), 2.62 - 2.52 (m,

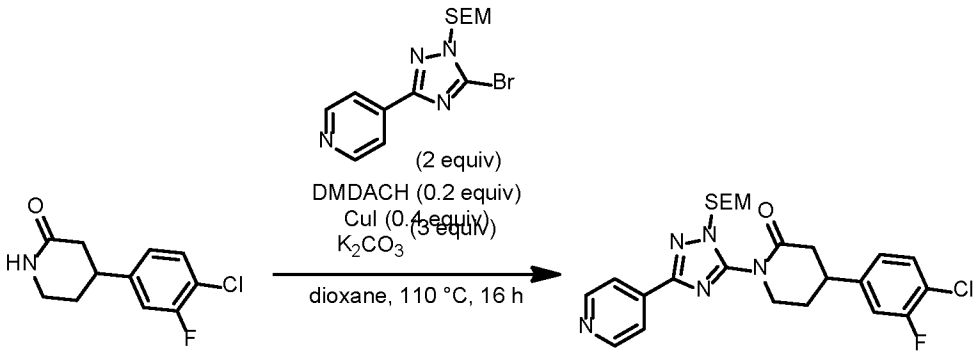
1H), 2.25 - 2.15 (m, 1H), 1.98 - 1.87 (m, 1H), 1.55 (s, 9H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 254.1

Step 2: Synthesis of 4-(4-chloro-3-fluorophenyl)piperidin-2-one



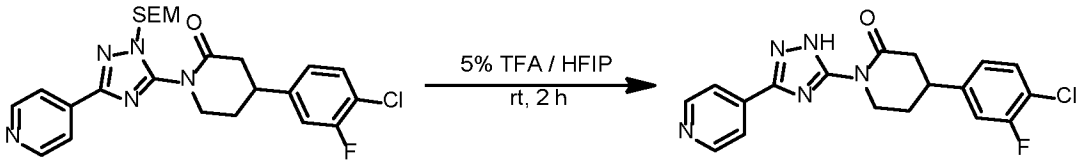
A mixture of *tert*-butyl 4-(4-chloro-3-fluoro-phenyl)-2-oxo-piperidine-1-carboxylate (3.0 g, 9.15 mmol) in 5% TFA/HFIP solution (30 mL) was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure. The residue was dissolved in DCM (10 mL), and then treated with aqueous saturated $NaHCO_3$ until pH = 8. The organic phase was separated, and the aqueous phase was extracted with DCM (10 mL x 2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford 4-(4-chloro-3-fluorophenyl)piperidin-2-one (1.3 g, 62% yield) as a white solid. **^{1}H NMR** (DMSO-d_6, 400 MHz): δ 7.58 (s, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.40 - 7.35 (m, , 1H), 7.20 - 7.15 (m, 1H), 3.26 - 3.16 (m, 2H), 3.13 - 3.04 (m, 1H), 2.43 - 2.25 (m, 2H), 1.93 - 1.76 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 228.1

Step 3: Synthesis of 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazol-5-yl)piperidin-2-one



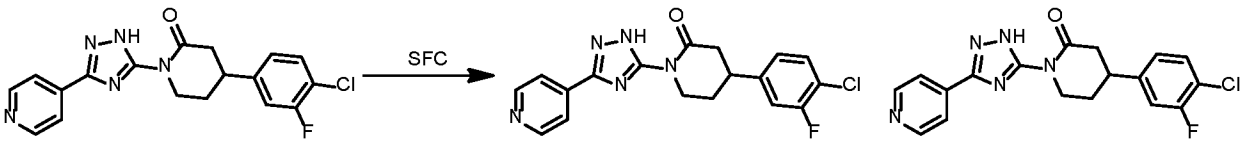
To a mixture of 4-(4-chloro-3-fluoro-phenyl)piperidin-2-one (390 mg, 1.71 mmol), 4-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-1,2,4-triazol-3-yl)pyridine (1.22 g, 3.43 mmol) in 1,4-dioxane (10 mL) was added DMDACH (48 mg, 0.34 mmol), CuI (130 mg, 0.69 mmol) and K_2CO_3 (710 mg, 5.14 mmol). The mixture was stirred at 110 °C for 16 hours under nitrogen atmosphere. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 100% ethyl acetate in petroleum ether) to afford 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-1,2,4-triazol-5-yl)piperidin-2-one (100 mg, 12% yield) as a yellow solid. **LCMS**: (ESI, m/z) $[M+H]^+$ = 502.1

Step 4: Synthesis of 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)piperidin-2-one



A mixture of 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-1,2,4-triazol-5-yl)piperidin-2-one (140 mg, 0.28 mmol) in 5% TFA/HFIP solution (8 mL) was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure. The residue was dissolved in DCM (5 mL), and then treated with aqueous saturated $NaHCO_3$ until pH = 8. The organic phase was separated, and the aqueous phase was extracted with DCM (5 mL x 2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5-yl)piperidin-2-one (100 mg, 96%) as a white solid.

Step 5: Chiral Separation of 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)piperidin-2-one (Ex. 4a & 4b)

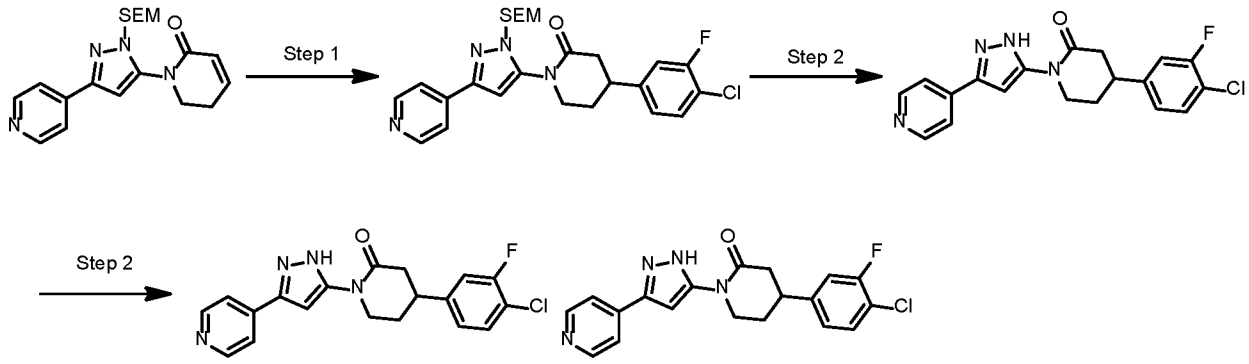


4-(4-Chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5-yl)piperidin-2-one (130 mg, 0.35 mmol) was separated by chiral SFC (Chiralcel OJ (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 55/45; 80 mL/min) to afford 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5-yl)piperidin-2-one (**Example 4a**, peak 1, Rt = 1.890 min, 31.2 mg, 24% yield) and 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5-yl)piperidin-2-one (**Example 4b**, peak 2, Rt = 2.417 min, 25 mg, 19% yield) both as white solid.

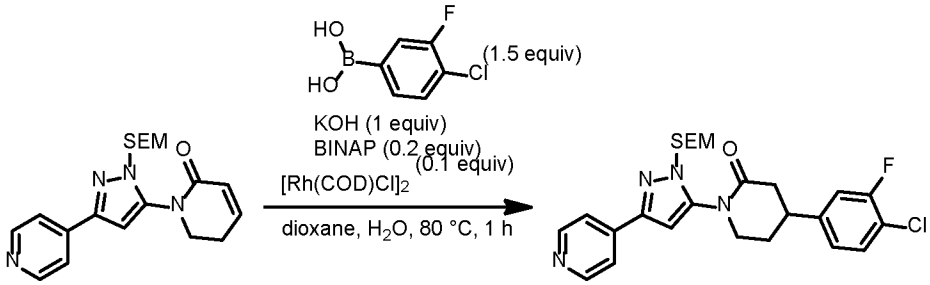
Example 4a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ = 13.98 (s, 1H), 8.67 (d, J = 6.0 Hz, 2H), 7.90 (d, J = 6.0 Hz, 2H), 7.57 (t, J = 8.0 Hz, 1H), 7.46 (d, J = 9.2 Hz, 1H), 7.26 - 7.20 (m, 1H), 4.30 - 4.21 (m, 1H), 3.99 - 3.84 (m, 1H), 3.38 - 3.35 (m, 1H), 2.84 - 2.77 (m, 2H), 2.25 - 2.06 (m, 2H). LCMS: (ESI, m/z) $[M+H]^+$ = 372.0.

Example 4b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ = 13.98 (s, 1H), 8.67 (d, J = 6.0 Hz, 2H), 7.89 (d, J = 6.0 Hz, 2H), 7.57 (t, J = 8.0 Hz, 1H), 7.50 - 7.42 (m, 1H), 7.26 - 7.20 (m, 1H), 4.32 - 4.20 (m, 1H), 3.98 3.86 (m, 1H), 3.38 - 3.35 (m, 1H), 2.87 - 2.74 (m, 2H), 2.26 - 2.06 (m, 2H). LCMS: (ESI, m/z) $[M+H]^+$ = 372.0.

Examples 5a and 5b

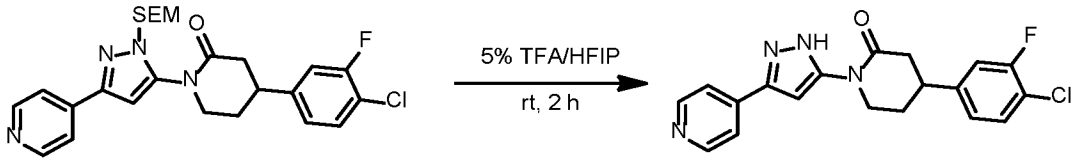


Step 1: Synthesis of 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)piperidin-2-one



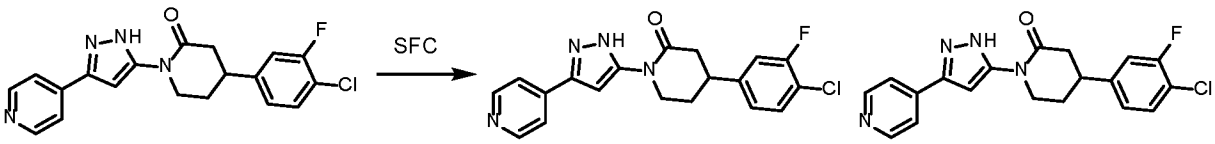
To a solution of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-5,6-dihydropyridin-2(1*H*)-one (1 g, 2.7 mmol) in dioxane (20 mL) and water (2 mL) was added (4-chloro-3-fluorophenyl)boronic acid (705 mg, 4.05 mmol), BINAP (336 mg, 0.54 mmol), KOH (151 mg, 2.7 mmol) and $[Rh(COD)Cl]_2$ (133 mg, 0.27 mmol). The reaction mixture was stirred at 80 °C for 16 hrs under nitrogen atmosphere. After cooling to room temperature, ethyl acetate (30 mL) and water (30 mL) were added. The organic layer was separated and washed with brine (20 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (SiO_2, 70% ethyl acetate in petroleum ether) to afford 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one (420 mg, 31% yield) as a brown solid. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.71 (d, J = 6.0 Hz, 2H), 7.61 (d, J = 6.0 Hz, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.21 (s, 1H), 7.06 (d, J = 10.0 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 5.39 (s, 2H), 4.25 - 4.17 (m, 1H), 3.95 - 3.84 (m, 1H), 3.76 (t, J = 8.4 Hz, 2H), 3.29 - 3.16 (m, 1H), 2.99 - 2.88 (m, 1H), 2.74 - 2.64 (m, 1H), 2.35 - 2.25 (m, 1H), 2.14 - 2.06 (m, 1H), 0.97 (t, J = 8.4 Hz, 2H), 0.01 (s, 9H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 501.1.

Step 2: Synthesis of 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one



A solution of 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)piperidin-2-one (370 mg, 0.74 mmol) in 5% TFA/HFIP (8 mL) was stirred at room temperature for 2 hours. The reaction mixture was concentrated and under reduced pressure. The residue was dissolved in ethyl acetate (10 mL) and $NaHCO_3$ solution (10 mL) were added. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 38-68%/0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to afford 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (140 mg, 51% yield) as a white solid. **LCMS**: (ESI, m/z) $[M+H]^+$ = 371.0.

Step 3: Chiral Separation of 4-(4-Chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Ex. 5a & 5b)

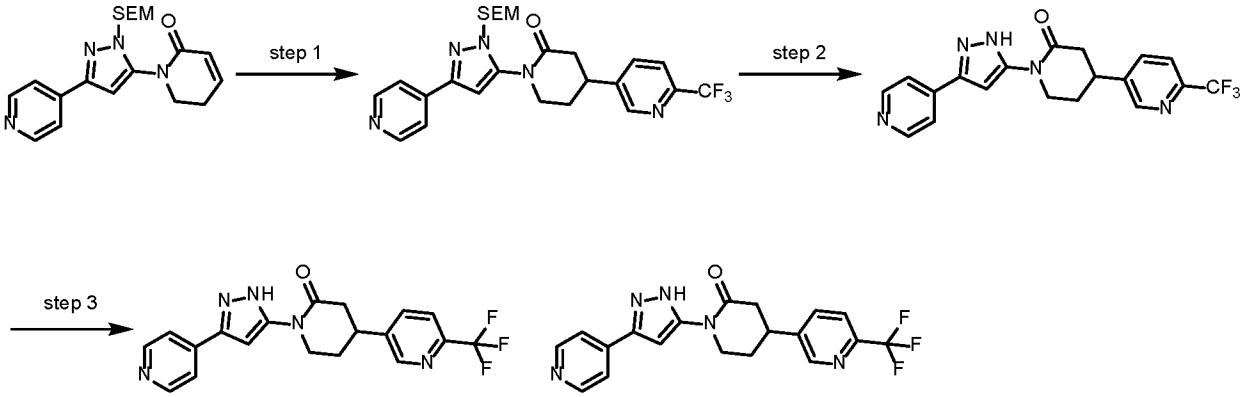


4-(4-Chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (140 mg) was separated by chiral SFC (Chiralpak IG (250 mm x 30 mm, 10 um), Supercritical CO_2 / *i*-PrOH + 0.1% NH_4OH = 40/60; 80 mL/min) to afford 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Example 5a**, peak 1, Rt = 2.293 min, 35.3 mg, 25% yield) and 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Example 5b**, peak 2, Rt = 3.226 min, 43.5 mg, 31% yield) both as white solid.

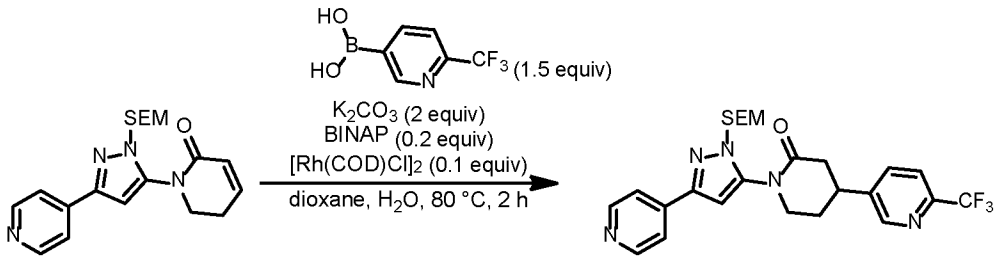
Example 5a: **^{1}H NMR** (DMSO-d_6, 400 MHz): δ = 13.34 (s, 1H), 8.64 (d, J = 6.0 Hz, 2H), 7.73 (d, J = 6.0 Hz, 2H), 7.57 (t, J = 8.0 Hz, 1H), 7.46 (dd, J = 11.2, 2.0 Hz, 1H), 7.28 - 7.15 (m, 2H), 4.12 - 3.99 (m, 1H), 3.87 - 3.75 (m, 1H), 3.30 - 3.22 (m, 1H), 2.79 - 2.64 (m, 2H), 2.23 - 2.04 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 371.0.

Example 5b: ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 13.32 (s, 1H), 8.66 - 8.58 (m, 2H), 7.76 - 7.69 (m, 2H), 7.56 (t, J = 8.0 Hz, 1H), 7.45 (dd, J = 10.8, 2.0 Hz, 1H), 7.27 - 7.14 (m, 2H), 4.09 - 3.98 (m, 1H), 3.86 - 3.75 (m, 1H), 3.28 - 3.24 (m, 1H), 2.77 - 2.68 (m, 2H), 2.22 - 2.02 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 371.0.

Examples 6a and 6b

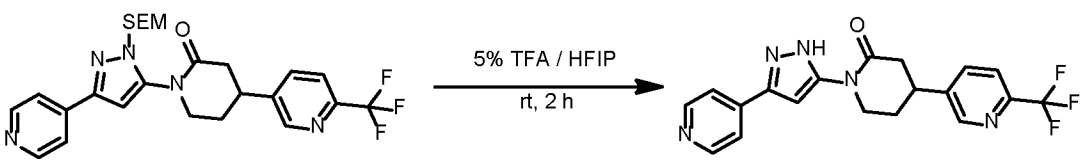


Step 1: Synthesis of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)piperidin-2-one



To a mixture of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-5,6-dihydropyridin-2(1*H*)-one (700 mg, 1.89 mmol) and (6-(trifluoromethyl)pyridin-3-yl)boronic acid (546 mg, 2.86 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was added $[Rh(COD)Cl]_2$ (98 mg, 0.20 mmol), K_2CO_3 (525 mg, 3.8 mmol) and BINAP (238 mg, 0.38 mmol). The mixture was stirred at 80 °C for 2 hours under nitrogen protection. After cooling to room temperature, ethyl acetate (30 mL) and water (30 mL) were added. The organic layer was separated, washed with brine (20 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrated was concentrated and the residue was purified by flash column chromatography (SiO_2, 0-30% (EtOAc/EtOH = 3/1) in petroleum ether) to afford 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)piperidin-2-one (700 mg crude) as a yellow oil. **LCMS**: (ESI, m/z) $[M+H]^+ = 518.3$

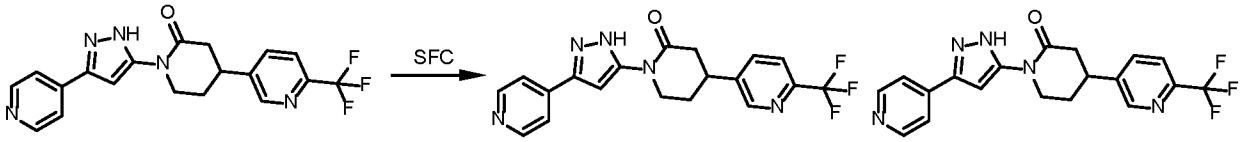
Step 2: Synthesis of 1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)piperidin-2-one



A solution of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-4-(6

(trifluoromethyl)pyridin-3-yl)piperidin-2-one (700 mg crude) in 5% TFA/HFIP (8 mL). The reaction was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (10 mL) and $NaHCO_3$ solution (10 mL) were added. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 41-71% / 0.1% NH_4OH in water) to afford 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)piperidin-2-one (42 mg, 6% yield over 2 steps) as a white solid. **LCMS**: (ESI, m/z) $[M+H]^+$ = 388.0.

Step 3: Chiral Separation of 1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)piperidin-2-one (Ex 6a & 6b)

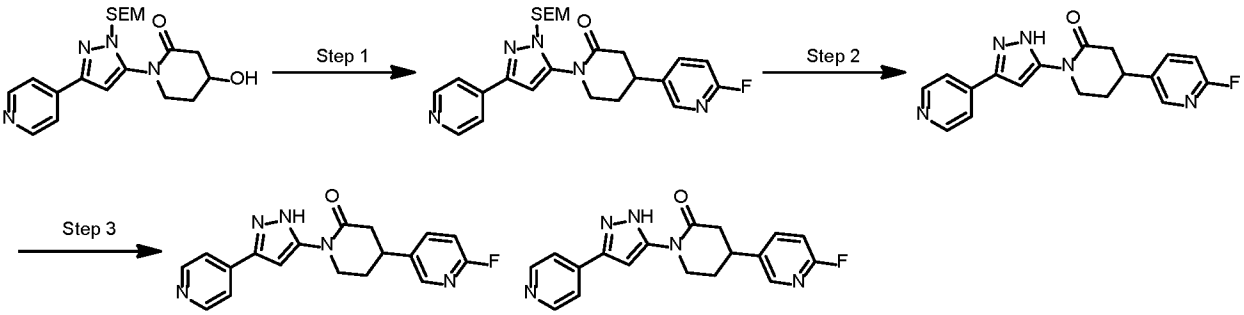


1-(3-(Pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)piperidin-2-one (50 mg, 0.13 mmol) was separated by chiral SFC (Chiralpak IC (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 55/45; 100 mL/min) to afford 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)piperidin-2-one (**Example 6a**, peak 1, Rt = 1.606 min, 11 mg, 22% yield) and 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)piperidin-2-one (**Example 6b**, peak 2, Rt = 2.070 min, 12 mg, 24%) both as white solid.

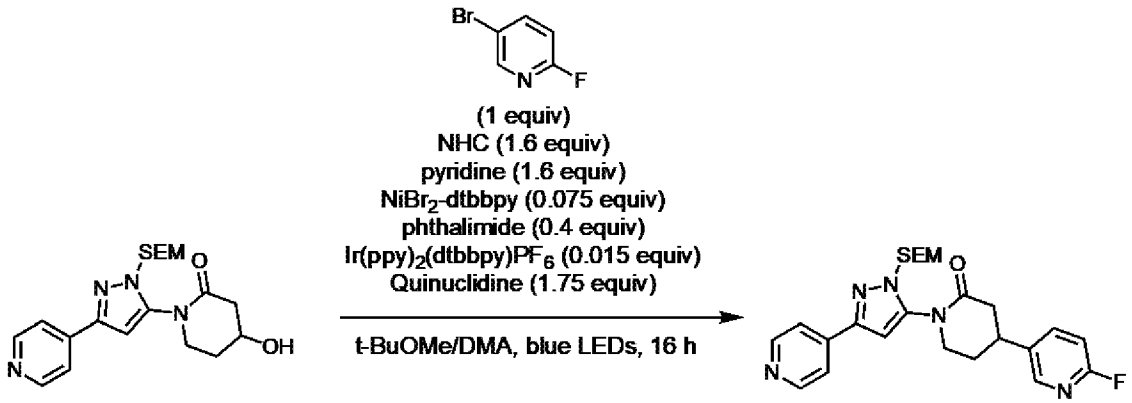
Example 6a: ^{1}**H NMR** (400 MHz, DMSO-d_6): δ = 13.37 (s, 1H), 8.79 (s, 1H), 8.68 - 8.59 (m, 2H), 8.08 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.77 - 7.68 (m, 2H), 7.29 (s, 1H), 4.16 - 4.05 (m, 1H), 3.89 - 3.79 (m, 1H), 3.46 - 3.42 (m, 1H), 2.85 - 2.74 (m, 2H), 2.29 - 2.13 (m, 2H). LCMS: (ESI, m/z) $[M+H]^+$ = 388.0.

Example 6b: ^{1}**H NMR** (400 MHz, DMSO-d_6): δ = 13.37 (s, 1H), 8.79 (s, 1H), 8.68 - 8.59 (m, 2H), 8.08 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.77 - 7.68 (m, 2H), 7.29 (s, 1H), 4.16 - 4.05 (m, 1H), 3.89 - 3.78 (m, 1H), 3.46 - 3.42 (m, 1H), 2.85 - 2.73 (m, 2H), 2.29 - 2.13 (m, 2H). LCMS: (ESI, m/z) $[M+H]^+$ = 388.0.

Examples 7a and 7b



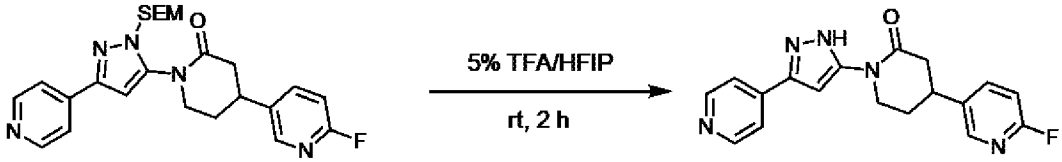
Step 1: *Synthesis of 4-(6-fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)piperidin-2-one*



A solution of 4-bromo-1-methyl-1*H*-pyrazole with 5-bromo-2-fluoropyridine (1.0 g, 2.57 mmol) and 5,7-di-*tert*-butyl-3-phenylbenzo[*d*]oxazol-3-ium tetrafluoroborate (NHC, 1.63 g, 4.12 mmol) in *t*-BuOMe (15 mL) was stirred at room temperature for 5 minutes under nitrogen atmosphere. Then pyridine (0.33 mL, 4.12 mmol) in *t*-BuOMe (5 mL) was added dropwise at room temperature over 5 minutes. The resulting solution was stirred at room temperature for 20 minutes under nitrogen atmosphere. A pink solid precipitated out during this time. Then the solution was filtered and the filtrate was added into another mixture of 4-bromo-1-methyl-1*H*-pyrazole (400 mg, 2.48 mmol), $NiBr_2$·dtbbpy (60 mg, 0.12 mmol), phthalimide (146 mg, 0.99 mmol), quinuclidine (483 mg, 4.34 mmol) and $Ir(ppy)_2(dtbbpy)PF_6$ (34 mg, 0.04 mmol) in DMA (8 mL) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 16 hours under 450 nm LED modules at 100% light intensity with maximum fan speed of 1500 rpm stirring rate in a Pennoc Integrated Photoreactor. The reaction was diluted in water (10 mL) and extracted with ethyl acetate (10 mL x 2). The organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography

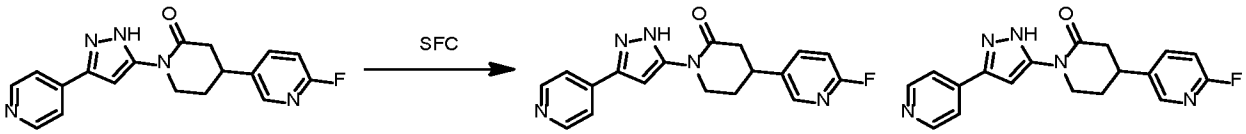
(40% EE (ethyl acetate/ethanol=3/1) in petroleum ether) to yield 4-(6-fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one.

Step 2: Synthesis of 4-(6-Fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one



A mixture of 4-(1-methyl-1*H*-pyrazol-4-yl)-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one (700 mg, 1.55 mmol) in 5% TFA / HFIP solution (20 mL) was stirred at room temperature for 3 hours. The mixture was concentrated under reduced pressure. The residue was dissolved in DCM (5 mL), and then treated with aqueous saturated $NaHCO_3$ until pH = 8. The organic phase was separated, and the aqueous phase was extracted with DCM (10 mL x 2). The combines organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 17-47% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to afford 4-(6-Fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one as a white solid.

Step 3: *Chiral Separation of 4-(6-Fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Ex. 7a & 7b)*

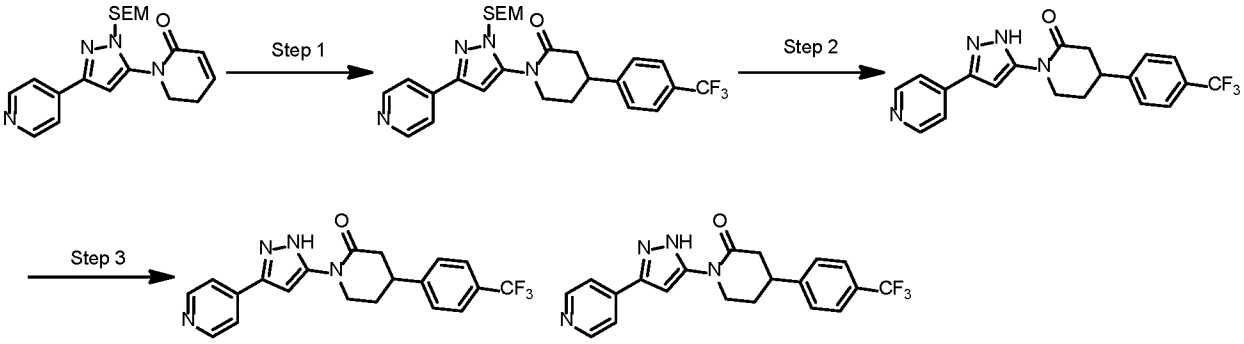


4-(6-Fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (150 mg, 0.44 mmol) was separated by chiral SFC (Chiralpak IC (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 60/40; 80 mL/min) to afford 4-(6-fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 7a**, peak 1, Rt = 2.315 min, 58.2 mg, 38%) and 4-(6-fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 7b**, peak 2, Rt = 3.073 min, 54.7 mg, 36% yield) both as white solid.

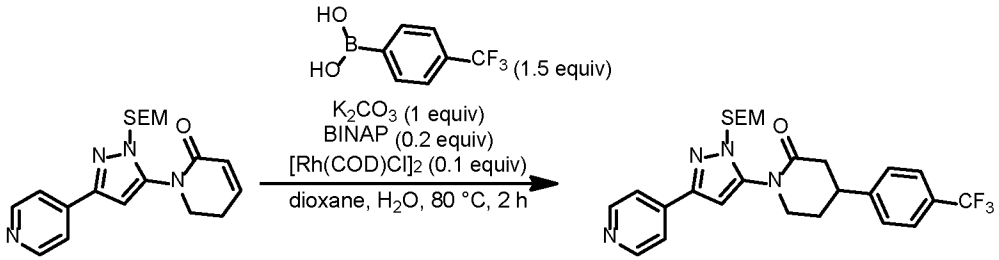
Example 7a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.34 (br s, 1H), 8.63 (d, J = 4.0 Hz, 2H), 8.22 (d, J = 2.0 Hz, 1H), 8.06 - 7.96 (m, 1H), 7.73 (d, J = 4.8 Hz, 2H), 7.29 (s, 1H), 7.18 (dd, J = 2.8, 8.4 Hz, 1H), 4.15 - 4.00 (m, 1H), 3.87 - 3.73 (m, 1H), 3.40 - 3.34 (m, 1H), 2.80 - 2.68 (m, 2H), 2.24 - 2.02 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 338.0

Example 7b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.35 (br s, 1H), 8.63 (d, J = 5.6 Hz, 2H), 8.22 (d, J = 2.4 Hz, 1H), 8.06 - 7.95 (m, 1H), 7.73 (d, J = 6.0 Hz, 2H), 7.29 (s, 1H), 7.18 (dd, J = 2.8, 8.4 Hz, 1H), 4.15 - 4.01 (m, 1H), 3.87 - 3.78 (m, 1H), 3.44 - 3.36 (m, 1H), 2.77 - 2.70 (m, 2H), 2.23 - 2.02 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 338.1

Examples 8a and 8b

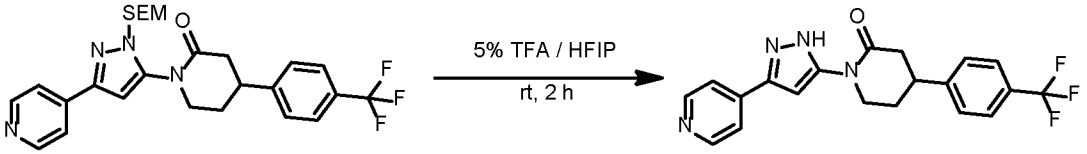


Step 1: Synthesis of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)-4-(4-(trifluoromethyl)phenyl)piperidin-2-one



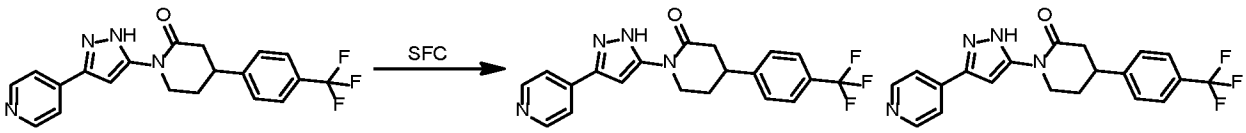
To a mixture of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-5,6-dihydropyridin-2(1*H*)-one (1.00 g, 2.70 mmol) and (4-(trifluoromethyl)phenyl)boronic acid (768 mg, 4.05 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was added $[Rh(COD)Cl]_2$ (133 mg, 0.30 mmol), K_2CO_3 (373 mg, 2.70 mmol) and BINAP (336 mg, 0.54 mmol). The mixture was stirred at 80 °C for 2 hours under nitrogen protection. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 30% ethyl acetate in petroleum ether) to afford 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-4-(4-(trifluoromethyl)phenyl)piperidin-2-one (240 mg crude) as a yellow solid, which was used directly in next step without further purification. **LCMS**: (ESI, m/z) $[M+H]^+$ = 517.2

Step 2: Synthesis of 1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)-4-(4-(trifluoromethyl)phenyl)piperidin-2-one



A solution of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-4-(4-(trifluoromethyl)phenyl)piperidin-2-one (240 mg crude) in 5% TFA/HFIP (4 mL). The reaction was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (10 mL) and $NaHCO_3$ solution (10 mL) were added. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 45-75% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to afford 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(4-(trifluoromethyl)phenyl)piperidin-2-one (80 mg, 7% yield over 2 steps) as a white solid. **LCMS**: (ESI, m/z) $[M+H]^+ = 387.1$

Step 3: Chiral Separation of 1-(3-(Pyridin-4-yl)-1H-pyrazol-5-yl)-4-(4-(trifluoromethyl)phenyl)piperidin-2-one (Ex. 8a & 8b)

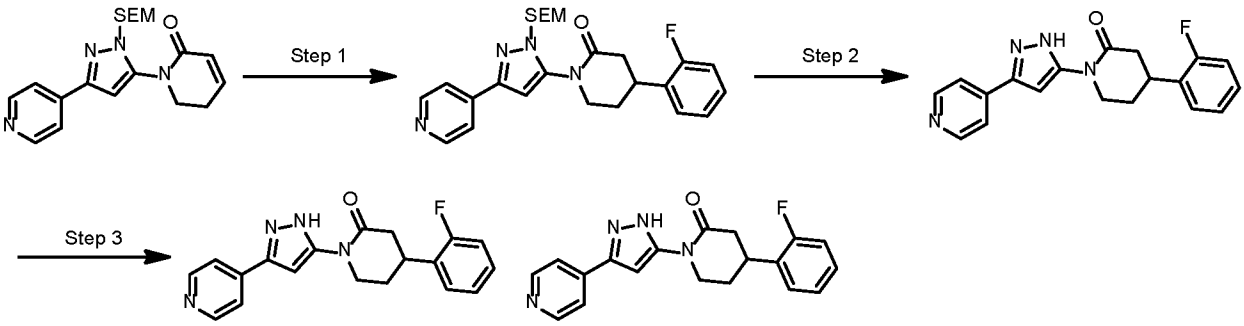


1-(3-(Pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(4-(trifluoromethyl)phenyl)piperidin-2-one (80 mg, 0.21 mmol) was separated by chiral SFC (Chiralpak AS (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 75/25; 150 mL/min) to afford 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(4-(trifluoromethyl)phenyl)piperidin-2-one (**Example 8a**, peak 1, Rt = 3.717 min, 35.4 mg, 44% yield) and 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(4-(trifluoromethyl)phenyl)piperidin-2-one (**Example 8b**, peak 2, Rt = 4.260 min, 33.1 mg, 41% yield) both as white solid.

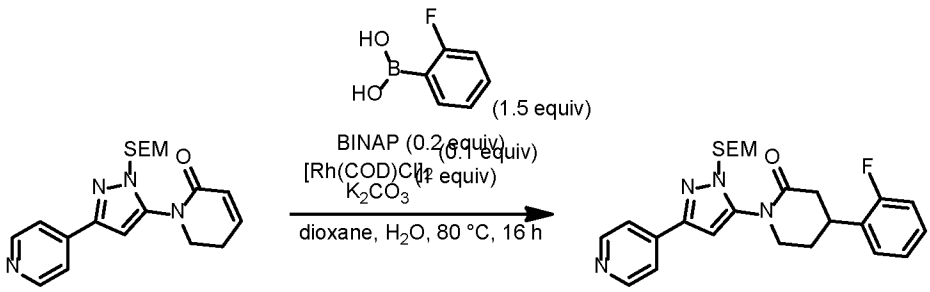
Example 8a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ = 13.34 (s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.79 - 7.66 (m, 4H), 7.58 (d, J = 8.4 Hz, 2H), 7.24 (s, 1H), 4.06 - 3.95 (m, 1H), 3.91 - 3.77 (m, 1H), 3.42 - 3.36 (m, 1H), 2.80 - 2.65 (m, 2H), 2.25 - 2.06 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+ = 387.0$

Example 8b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ = 13.33 (s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.79 - 7.66 (m, 4H), 7.59 (d, J = 8.4 Hz, 2H), 7.25 (s, 1H), 4.06 - 3.95 (m, 1H), 3.91 - 3.77 (m, 1H), 3.42 - 3.36 (m, 1H), 2.80 - 2.65 (m, 2H), 2.25 - 2.06 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+ = 387.0$.

Examples 9a and 9b



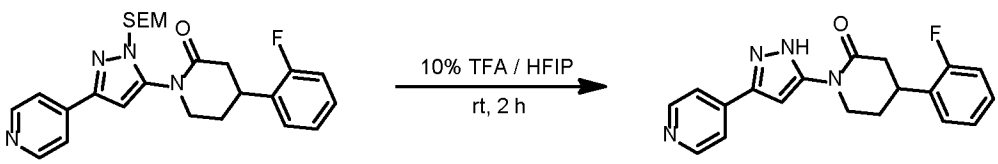
Step 1: *Synthesis of 4-(2-fluorophenyl)-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)piperidin-2-one*



To a mixture of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-5,6-dihydropyridin-2(1*H*)-one (300 mg, 0.81 mmol) and (2-fluorophenyl)boronic acid (170 mg, 1.21 mmol) in 1,4-dioxane (3 mL) and water (0.3 mL) was added K_2CO_3 (112 mg, 0.81 mmol), BINAP (101 mg, 0.16 mmol), $[Rh(COD)Cl]_2$ (40 mg, 0.08 mmol). The reaction mixture was stirred at 80 °C for 16 hours under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was filtered and diluted with water (20 mL). The resulting mixture was extracted with ethyl acetate (30 mL x 2). The combined organic phases were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, 30-60% ethyl acetate in petroleum ether) to afford 4-(2-fluorophenyl)-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one (280 mg, 59% yield) as yellow oil.

LCMS: (ESI, m/z) $[M+H]^+ = 467.1$

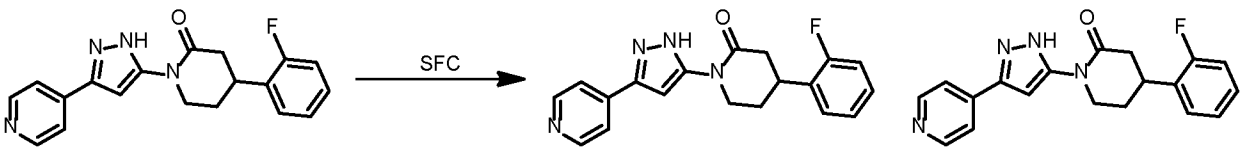
Step 2: *Synthesis of 4-(2-fluorophenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one*



A mixture of 4-(2-fluorophenyl)-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one (280 mg, 0.6 mmol) in 10% TFA / HFIP solution (30 mL) was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (2 mL), and then treated with aqueous saturated $NaHCO_3$ until pH = 8. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (10 mL x 2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 37-67% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to afford 4-(2-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (130 mg, 64% yield) as a white solid.

LCMS: (ESI, m/z) $[M+H]^+$ = 337.0.

Step 3: *Chiral separation of 4-(2-Fluorophenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Ex. 9a & 9b)*

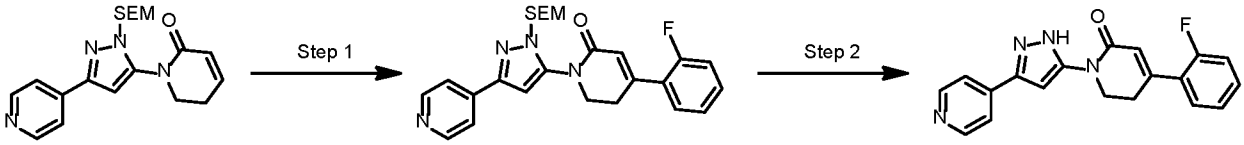


4-(2-Fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (100 mg, 0.30 mmol) was separated by chiral SFC (Chiralpak IC (250 mm x 30 mm, 10 um), Supercritical CO_2 / MeOH + 0.1% NH_4OH = 75/25; 50 mL/min) to afford (2-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 9a**, peak 1, Rt = 1.448 min, 45.5 mg, 45% yield) and (2-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 9b**, peak 2, Rt =1.691 min, 39.5 mg, 39% yield) both as white solids.

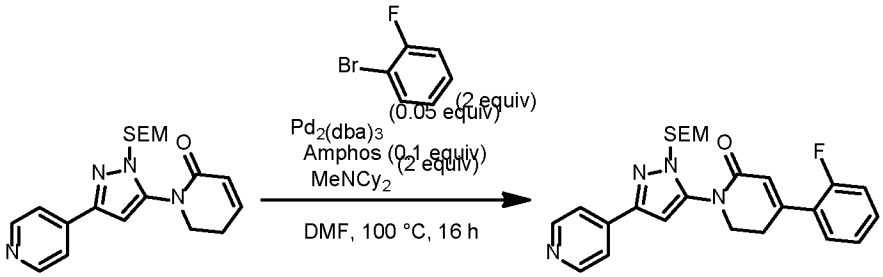
Example 9a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.34 (s, 1H), 8.63 (d, J = 6.4 Hz, 2H), 7.74 - 7.70 (m, 2H), 7.44 - 7.37 (m, 1H), 7.35 - 7.29 (m, 1H), 7.28 - 7.13 (m, 3H), 4.06 - 3.95 (m, 1H), 3.90 - 3.79 (m, 1H), 3.57 - 3.47 (m, 1H), 2.76 - 2.66 (m, 2H), 2.22 - 2.09 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 337.0

Example 9b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.34 (s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.72 (d, J = 6.0 Hz, 2H), 7.44 - 7.37 (m, 1H), 7.35 - 7.29 (m, 1H), 7.28 - 7.13 (m, 3H), 4.08 - 3.98 (m, 1H), 3.90 - 3.80 (m, 1H), 3.58 - 3.46 (m, 1H), 2.74 - 2.68 (m, 2H), 2.20 - 2.11 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 337.0

Example 10



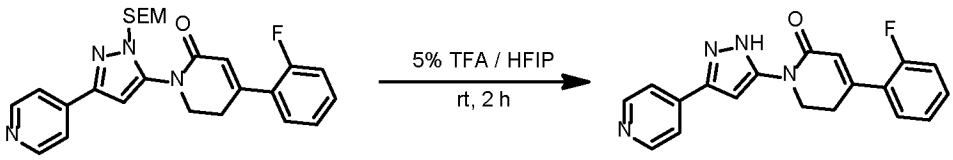
Step 1: *Synthesis of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)-5,6-dihydropyridin-2(1H)-one*



To a solution of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-5,6-dihydropyridin-2(1*H*)-one (300 mg, 0.81 mmol) and 1-bromo-2-fluorobenzene (284 mg, 1.62 mmol) in DMF (5 mL) was added $Pd_2(dba)_3$ (37 mg, 0.04 mmol), Amphos (22 mg, 0.08 mmol), *N*-Methyldicyclohexylamine (0.35 mL, 1.62 mmol) under nitrogen atmosphere. The reaction mixture was heated at 100 °C for 16 hours. After cooling to room temperature, the mixture was diluted with water (5 mL), and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 0-30% EE (25% ethanol in ethyl acetate) in petroleum ether) to afford 4-(2-fluorophenyl)-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-5,6-dihydropyridin-2(1*H*)-one (210 mg, 56% yield) as colorless oil.

LCMS: (ESI, m/z) $[M+H]^+$ = 465.3

Step 2: *Synthesis of 4-(2-fluorophenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)-5,6-dihydropyridin-2(1H)-one*

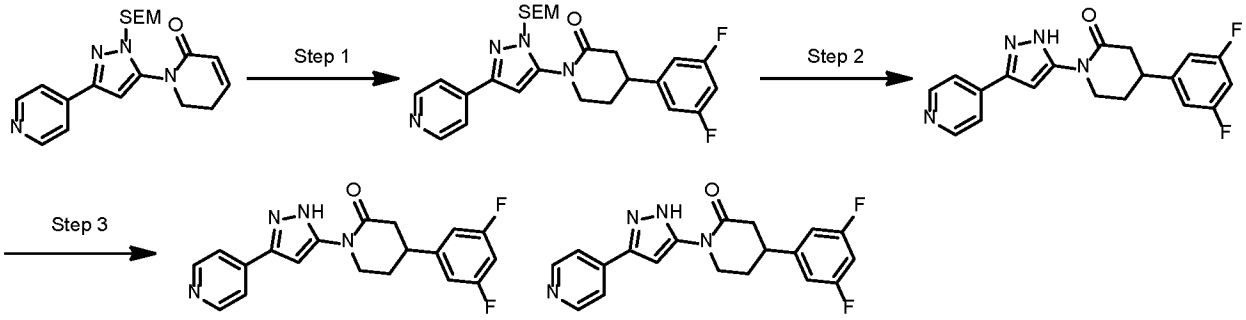


A solution of 4-(2-fluorophenyl)-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-5,6-dihydropyridin-2(1*H*)-one (210 mg, 0.45 mmol) in 5% TFA in HFIP (8 mL). After stirring at room temperature for 2 hours, the reaction mixture was concentrated under reduced pressure to remove TFA. Then the residue was poured into aq. $NaHCO_3$ (5 mL), and extracted with DCM (10 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 35-65% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water)

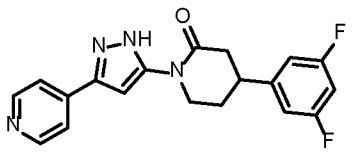
to give 4-(2-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-5,6-dihydropyridin-2(1*H*)-one (**Ex 10**, 22.5 mg, 15% yield) as a white solid.

Example 10: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.37 (br s, 1H), 8.63 (d, J = 5.6 Hz, 2H), 7.76 - 7.71 (m, 2H), 7.65 - 7.60 (m, 1H), 7.52 - 7.46 (m, 1H), 7.36 - 7.28 (m, 3H), 6.29 (s, 1H), 4.28 - 4.09 (m, 2H), 3.03 - 2.87 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 334.9.

Examples 11a and 11b

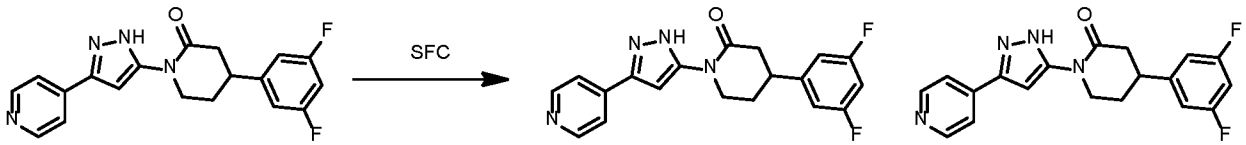


Step 1 – 2: *Synthesis of 4-(3,5-Difluorophenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one*



4-(3,5-Difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **9a and 9b** by replacing (2-fluorophenyl)boronic acid with (3,5-difluorophenyl)boronic acid in Step 1.

Step 3: *Chiral separation of 4-(3,5-Difluorophenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Ex 11a & 11b)*



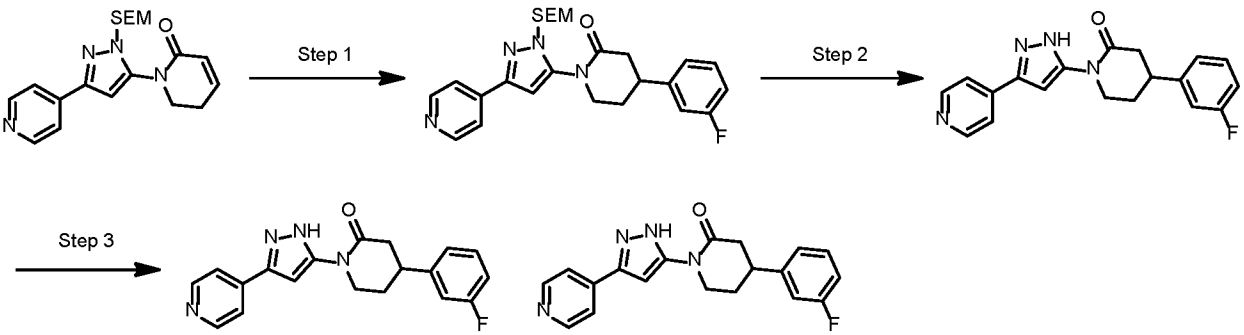
4-(3,5-Difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (135 mg, 0.38 mmol) was separated by chiral SFC (Chiralpak IG (250 mm x 30 mm, 10 um), Supercritical CO_2 / *i*-PrOH + 0.1% NH_4OH = 40/60; 60 mL/min) to afford 30 mg crude of peak 1 and 4-(4-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex. 11b**, peak 2, Rt = 2.267 min, 27.9 mg, 20% yield) both as white solids.

30 mg peak 1 was repurified by reverse phase chromatography (acetonitrile: 42-72% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to afford 4-(3,5-difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 11a)**, peak 1, Rt = 1.552 min, 15.2 mg, 11% yield) as a white solid.

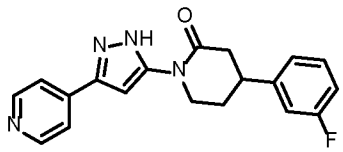
Example 11a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.42 - 13.29 (m, 1H), 8.63 (d, J = 4.0 Hz, 2H), 7.72 (d, J = 4.4 Hz, 2H), 7.28 (s, 1H), 7.15 - 7.06 (m, 3H), 4.13 - 4.00 (m, 1H), 3.83 - 3.76 (m, 1H), 3.31 - 3.25 (m, 1H), 2.80 - 2.63 (m, 2H), 2.22 - 2.03 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 355.0

Example 11b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.40 - 13.18 (m, 1H), 8.69 - 8.54 (m, 2H), 7.72 (d, J = 4.8 Hz, 2H), 7.28 (s, 1H), 7.17 - 7.02 (m, 3H), 4.13 - 4.00 (m, 1H), 3.85 - 3.73 (m, 1H), 3.30 - 3.22 (m, 1H), 2.78 - 2.64 (m, 2H), 2.22 - 2.02 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 355.0

Examples 12a and 12b

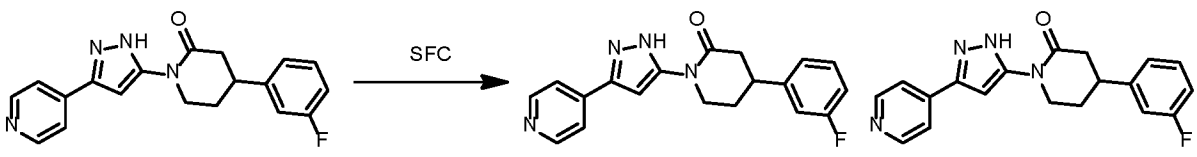


Step 1 — 2: *Synthesis of 4-(3-Fluorophenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one*



4-(3-Fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 9a and 9b** by replacing (2-fluorophenyl)boronic acid with (3-fluorophenyl)boronic acid in Step 1.

Step 3: *Chiral Separation of 4-(3-Fluorophenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Ex 12a & 12b)*

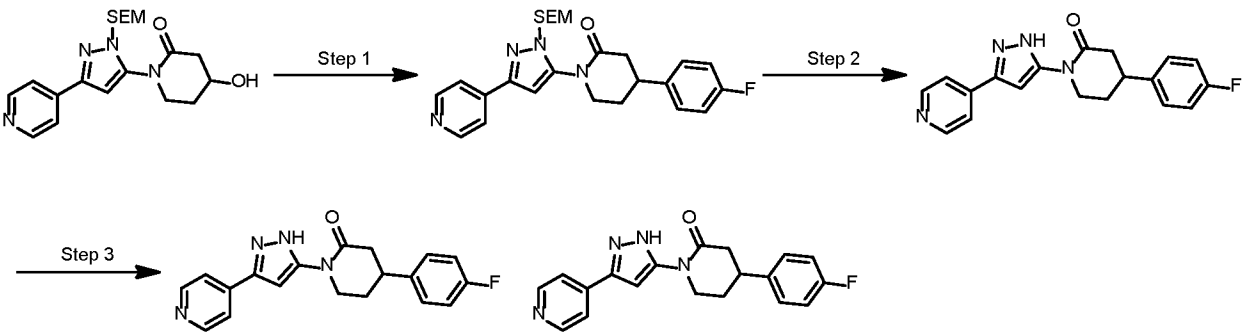


4-(3-Fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (200 mg, 0.59 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / *i*-PrOH + 0.1% NH_4OH = 45/55; 80 mL/min) to afford 4-(3-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex. 12a**, peak 1, Rt = 0.927 min, 70 mg, 35% yield) and 4-(3-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 12b**, peak 2, Rt = 1.250 min, 55 mg, 28% yield) both as white solids.

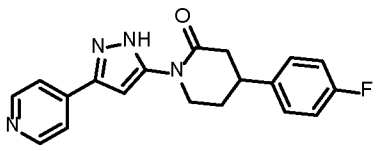
Example 12a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.33 (br s, 1H), 8.67 - 8.59 (m, 2H), 7.76 - 7.69 (m, 2H), 7.45 - 7.32 (m, 1H), 7.26 - 7.15 (m, 3H), 7.09 - 7.04 (m, 1H), 4.08 - 3.95 (m, 1H), 3.84 - 3.77 (m, 1H), 3.28 - 3.20 (m, 1H), 2.78 - 2.61 (m, 2H), 2.23 - 2.01 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 337.0

Example 12b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.35 (br s, 1H), 8.65 (d, J = 6.0 Hz, 2H), 7.89 (d, J = 6.0 Hz, 2H), 7.45 - 7.32 (m, 1H), 7.26 - 7.20 (m, 1H), 4.13 - 3.98 (m, 1H), 3.89 - 3.72 (m, 1H), 3.28 - 3.20 (m, 1H), 2.81 - 2.62 (m, 2H), 2.24 - 2.01 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 337.0

Examples 13a and 13b

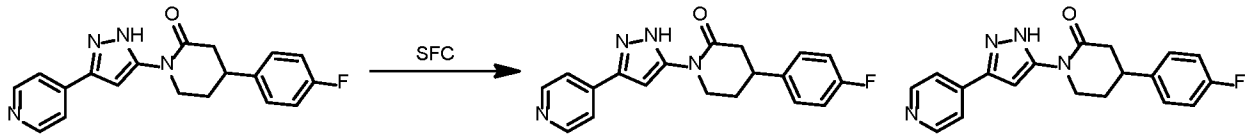


Step 1 — 2: *Synthesis of 4-(4-Fluorophenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one*



4-(4-Fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 9a and 9b** by replacing 4-bromo-1-methyl-1*H*-pyrazole with 1-bromo-4-fluorobenzene in Step 1.

Step 3: *Chiral Separation of 4-(4-Fluorophenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Ex 13a & 13b)*

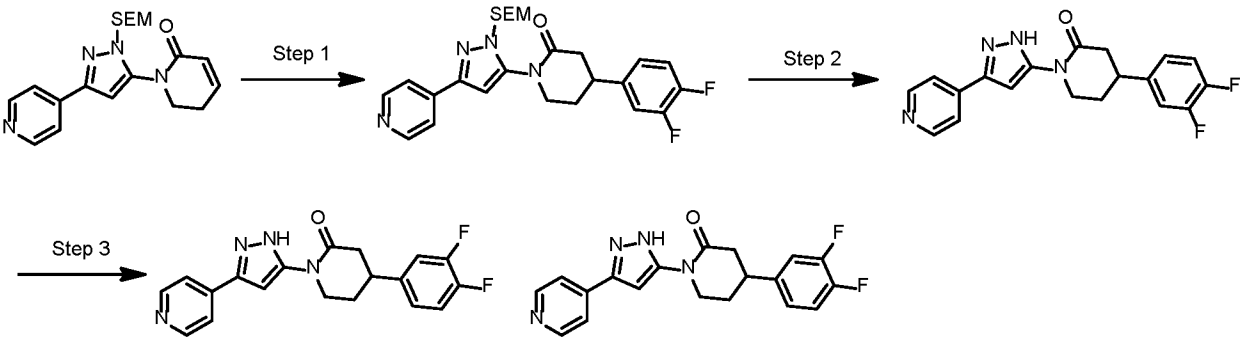


4-(4-Fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (60 mg, 0.18 mmol) was separated by chiral SFC (Cellulose-2 (250 mm x 30 mm, 10 um), Supercritical CO_2 / MeOH + 0.1% NH_4OH = 65/35; 150 mL/min) to afford 4-(4-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 13a**, peak 1, Rt = 4.050 min, 16.2 mg, 27% yield) and 4-(4-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 13b**, peak 2, Rt = 4.538 min, 8.7 mg, 14% yield) both as white solids.

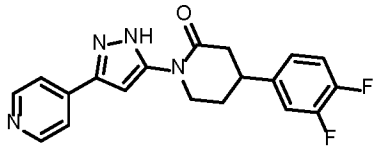
Example 13a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.35 (s, 1H), 8.63 (d, J = 4.0 Hz, 2H), 7.72 (d, J = 4.4 Hz, 2H), 7.38 (dd, J = 5.6, 8.4 Hz, 2H), 7.28 (s, 1H), 7.17 (t, J = 8.8 Hz, 2H), 4.11 - 3.97 (m, 1H), 3.87 - 3.74 (m, 1H), 3.29 - 3.19 (m, 1H), 2.79 - 2.58 (m, 2H), 2.21 - 1.99 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 336.9

Example 13b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.36 (s, 1H), 8.64 (d, J = 3.6 Hz, 2H), 7.73 (d, J = 4.4 Hz, 2H), 7.39 (dd, J = 5.6, 8.4 Hz, 2H), 7.29 (s, 1H), 7.18 (t, J = 8.8 Hz, 2H), 4.11 - 3.98 (m, 1H), 3.89 - 3.74 (m, 1H), 3.29 - 3.20 (m, 1H), 2.78 - 2.61 (m, 2H), 2.22 - 2.02 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 337.0

Examples 14a and 14b

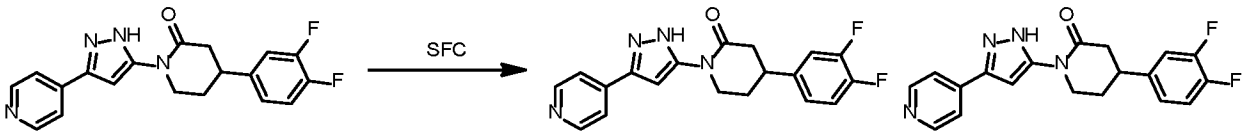


Step 1 — 2: *Synthesis of 4-(3,4-Difluorophenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one*



4-(3,4-Difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 9a and 9b** by replacing (2-fluorophenyl)boronic acid with (3,4-difluorophenyl)boronic acid in Step 1.

Step 3: *Chiral Separation of 4-(3,4-Difluorophenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Ex. 14a & 14b)*

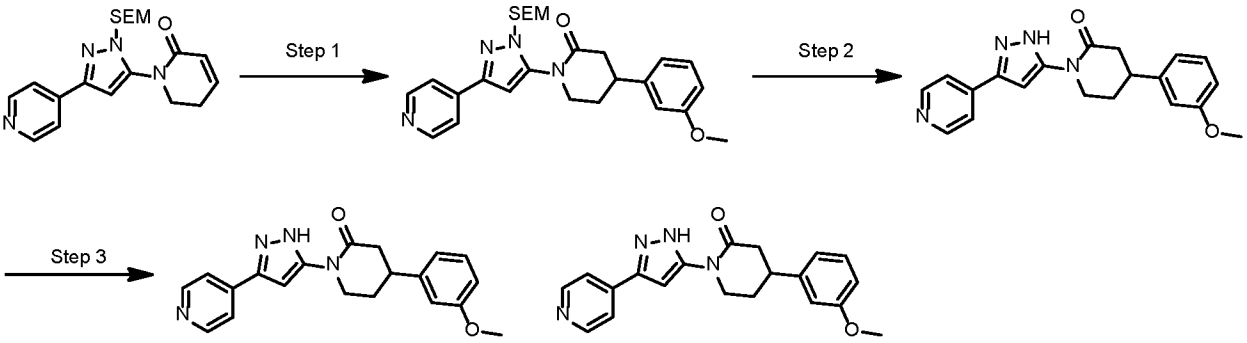


4-(3,4-Difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (170 mg, 0.47 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / *i*-PrOH + 0.1% NH_4OH = 60/40; 80 mL/min) to afford 4-(3,4-difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 14a**, peak 1, Rt = 0.915 min, 51 mg, 30% yield) and 4-(3,4-difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 14b**, peak 2, Rt = 1.290 min, 50 mg, 30% yield) both as white solids.

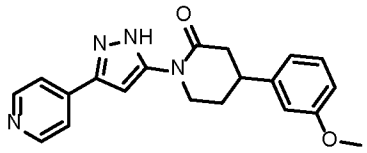
Example 14a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.35 (br s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.72 (d, J = 6.0 Hz, 2H), 7.54 - 7.34 (m, 2H), 7.28 (br s, 1H), 7.22 - 7.17 (m, 1H), 4.11 - 4.01 (m, 1H), 3.84 - 3.72 (m, 1H), 3.30 - 3.20 (m, 1H), 2.79 - 2.64 (m, 2H), 2.22 - 2.01 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 355.0

Example 14b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.36 (s, 1H), 8.64 (d, J = 6.0 Hz, 2H), 7.72 (d, J = 6.0 Hz, 2H), 7.53 - 7.35 (m, 2H), 7.28 (br s, 1H), 7.23 - 7.16 (m, 1H), 4.12 - 4.02 (m, 1H), 3.86 - 3.73 (m, 1H), 3.29 - 3.21 (m, 1H), 2.78 - 2.64 (m, 2H), 2.24 - 2.00 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 355.0

Examples 15a and 15b

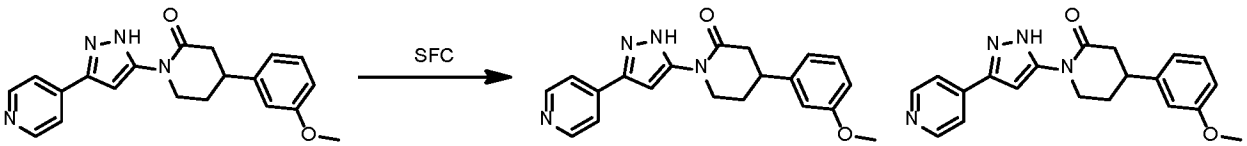


Step 1 — 2: *Synthesis of 4-(3-Methoxyphenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one*



4-(3-Methoxyphenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 9a and 9b** by replacing (2-fluorophenyl)boronic acid with (3-methoxyphenyl)boronic acid in Step 1.

Step 3: *Chiral Separation of 4-(3-Methoxyphenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Ex. 15a & 15b)*



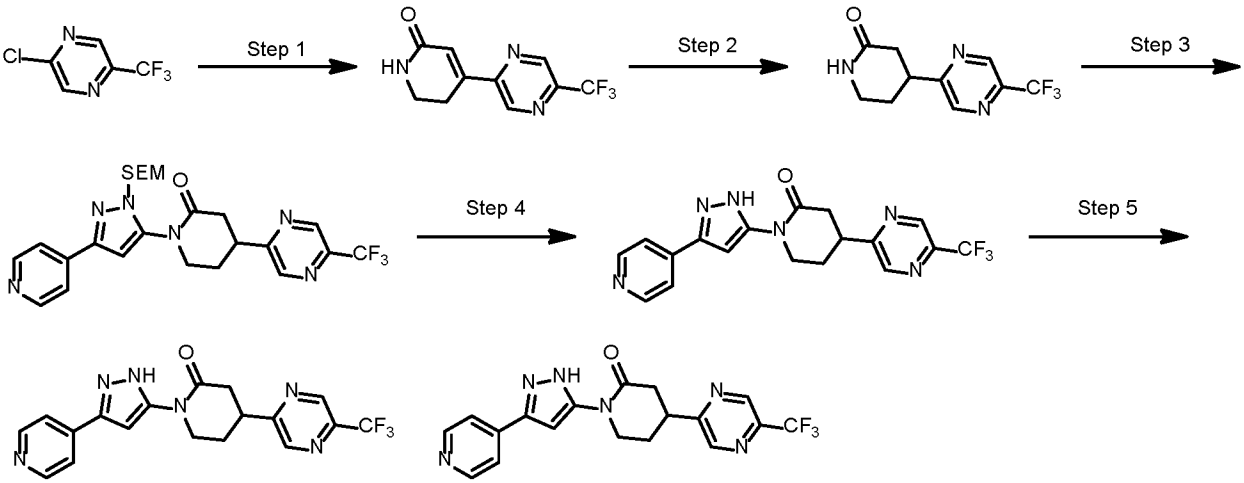
4-(3-Methoxyphenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (140 mg, 0.40) was separated by chiral SFC (Chiralcel OD (250 mm x 30 mm, 10 um), Supercritical CO_2 / MeOH + 0.1% NH_4OH = 60/40; 80 mL/min) to afford 4-(3-methoxyphenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 15a**, peak 1, Rt = 2.502 min, 56.6 mg, 40% yield) and 4-(3-methoxyphenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 15b**, peak 2, Rt = 2.924 min, 62.5 mg, 44% yield) both as white solids.

Example 15a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.32 (br s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.72 (d, J = 6.0 Hz, 2H), 7.31 - 7.12 (m, 2H), 6.94 - 6.87 (m, 2H), 6.84 - 6.78 (m, 1H), 4.08 - 3.95 (m,

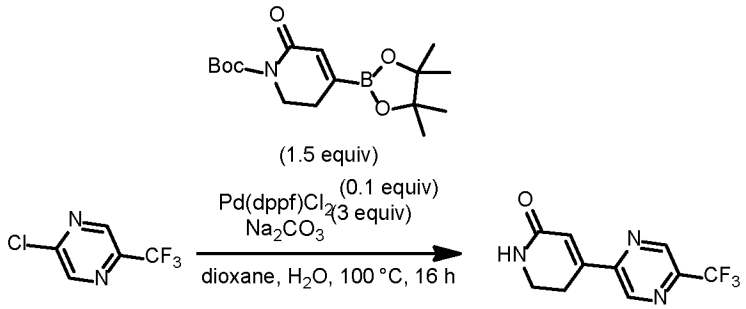
1H), 3.85 - 3.77 (m, 1H), 3.75 (s, 3H), 3.26 - 3.15 (m, 1H), 2.73 - 2.63 (m, 2H), 2.21 - 2.06 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 349.1

Example 15b: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.33 (br s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.72 (d, J = 6.0 Hz, 2H), 7.32 - 7.14 (m, 2H), 6.94 - 6.87 (m, 2H), 6.85 - 6.78 (m, 1H), 4.07 - 3.96 (m, 1H), 3.86 - 3.78 (m, 1H), 3.76 (s, 3H), 3.23 - 3.17 (m, 1H), 2.73 - 2.66 (m, 2H), 2.21 - 2.05 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 349.1

Examples 16a and 16b



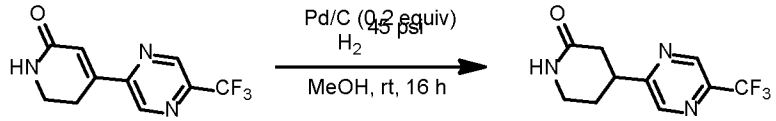
Step 1: *Synthesis of 4-(5-(trifluoromethyl)pyrazin-2-yl)-5,6-dihydropyridin-2(1H)-one*



To a mixture of 2-chloro-5-(trifluoromethyl)pyrazine (2.0 g, 11 mmol), *tert*-butyl 6-oxo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (5.3 g, 16 mmol) in 1,4-dioxane (15 mL) and H_2O (5 mL) was added $Pd(dppf)Cl_2$ (800 mg, 1.1 mmol) and Na_2CO_3 (3.5 g, 33 mmol). The mixture was stirred at 110 °C for 16 hours under nitrogen atmosphere. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 20% EE (Ethyl acetate/ethanol=3/1) in petroleum ether) to afford 4-(5-(trifluoromethyl)pyrazin-2-yl)-5,6-dihydropyridin-2(1*H*)-one (1.4 g, 37% yield) as a yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.02 (s, 1H), 8.98 (s, 1H), 6.78 (d, J = 1.6 Hz, 1H), 6.02 (s, 1H), 3.70 - 3.59 (m, 2H), 3.10 - 2.93 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 243.9

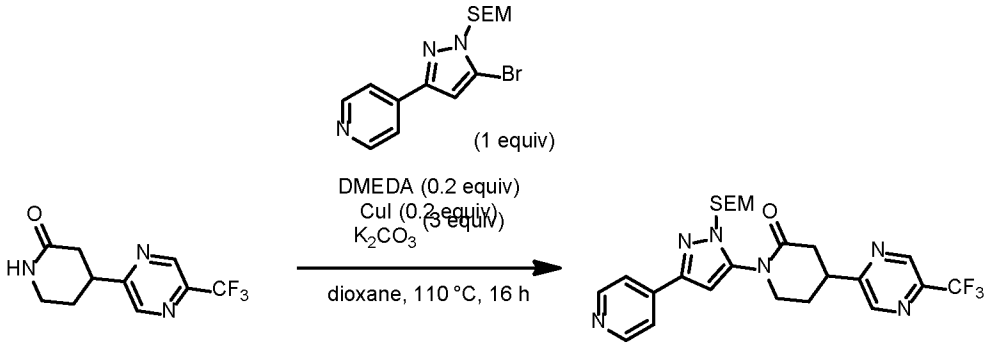
Step 2: *Synthesis of 4-(5-(trifluoromethyl)pyrazin-2-yl)piperidin-2-one*



To a solution of 4-(5-(trifluoromethyl)pyrazin-2-yl)-5,6-dihydropyridin-2(1*H*)-one (1.0 g, 4.11 mmol) in MeOH (20 mL) was added Pd/C (10%, 875 mg, 0.82 mmol). The mixture was stirred at room temperature for 16 hours under H_2 (45 psi). The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 20-50% / 0.225% FA in water) to afford 4-(5-(trifluoromethyl)pyrazin-2-yl)piperidin-2-one (200 mg, 20% yield) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.93 (s, 1H), 8.64 (s, 1H), 5.98 (s, 1H), 3.53 - 3.37 (m, 3H), 2.91 - 2.65 (m, 2H), 2.28 - 2.03 (m, 2H).

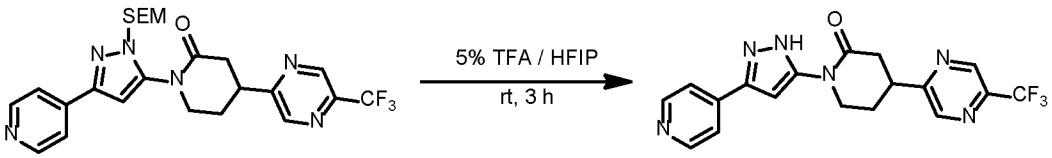
Step 3: *Synthesis of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)-4-(5-(trifluoromethyl)pyrazin-2-yl)piperidin-2-one*



To a mixture of 4-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)pyridine (200 mg, 0.56 mmol), 4-(5-(trifluoromethyl)pyrazin-2-yl)piperidin-2-one (138 mg, 0.56 mmol) in 1,4-dioxane (5 mL) was added DMEDA (0.01 mL, 0.11 mmol), CuI (21 mg, 0.11 mmol) and K_2CO_3 (234 mg, 1.69 mmol). The mixture was stirred at 110 °C for 16 hours under nitrogen atmosphere. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 50% EE (Ethyl acetate/ethanol=3/1) in petroleum ether) to afford 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-4-(5-(trifluoromethyl)pyrazin-2-yl)piperidin-2-one (200 mg, 68% yield) as a yellow oil.

LCMS: (ESI, m/z) $[M+H]^+$ = 519.1

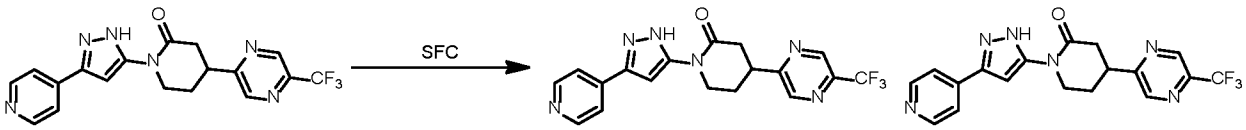
Step 4: *Synthesis of 1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)-4-(5-(trifluoromethyl)pyrazin-2-yl)piperidin-2-one*



A solution of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-4-(5-(trifluoromethyl)pyrazin-2-yl)piperidin-2-one (200 mg, 0.38 mmol) in 5% TFA / HFIP solution (6 mL) was stirred at room temperature for 3 hours. The mixture was concentrated under reduced pressure. The residue was dissolved in DCM (5 mL), and then treated with aqueous saturated $NaHCO_3$ until pH = 8. The organic phase was separated, and the aqueous phase was extracted with DCM (5 mL x 2). The combines organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 29-59% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to afford 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(5-(trifluoromethyl)pyrazin-2-yl)piperidin-2-one (100 mg, 67% yield) as a white solids.

LCMS: (ESI, m/z) $[M+H]^+$ = 389.1

Step 5: *Chiral Separation of 1-(3-(Pyridin-4-yl)-1H-pyrazol-5-yl)-4-(5-(trifluoromethyl)pyrazin-2-yl)piperidin-2-one (Ex 16a & 16b)*

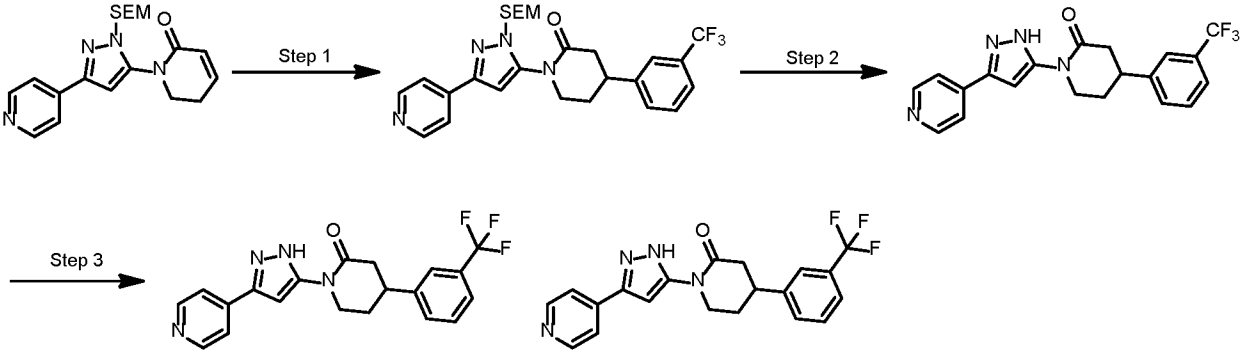


1-(3-(Pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(5-(trifluoromethyl)pyrazin-2-yl)piperidin-2-one (110 mg, 0.30 mmol) was separated by chiral SFC (Chiralpak IC (250 mm x 30 mm, 10 um), Supercritical CO_2 / MeOH + 0.1% NH_4OH = 40/60; 80 mL/min) to give 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(5-(trifluoromethyl)pyrazin-2-yl)piperidin-2-one (**Ex 16a**, peak 1, Rt = 1.901 min, 32.6 mg, 29% yield) and 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(5-(trifluoromethyl)pyrazin-2-yl)piperidin-2-one (**Ex 16b**, peak 2, Rt = 3.743 min, 31.4 mg, 28% yield) both as a white solid.

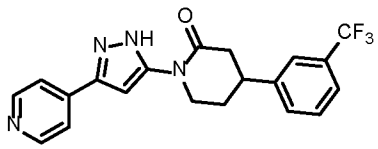
Example 16a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.32 (br s, 1H), 9.16 (s, 1H), 8.95 (s, 1H), 8.63 (d, J = 5.6 Hz, 2H), 7.72 (d, J = 6.0 Hz, 2H), 7.24 (s, 1H), 4.02 - 3.83 (m, 2H), 3.79 - 3.65 (m, 1H), 2.94 - 2.80 (m, 2H), 2.42 - 2.29 (m, 1H), 2.23 - 2.11 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 389.0

Example 16b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.31 (br s, 1H), 9.16 (s, 1H), 8.95 (s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.75 - 7.68 (m, 2H), 7.22 (s, 1H), 4.00 - 3.84 (m, 2H), 3.79 - 3.66 (m, 1H), 2.90 - 2.82 (m, 2H), 2.42 - 2.33 (m, 1H), 2.25 - 2.10 (m, 1H). LCMS: (ESI, m/z) $[M+H]^+$ = 389.0

Examples 17a and 17b

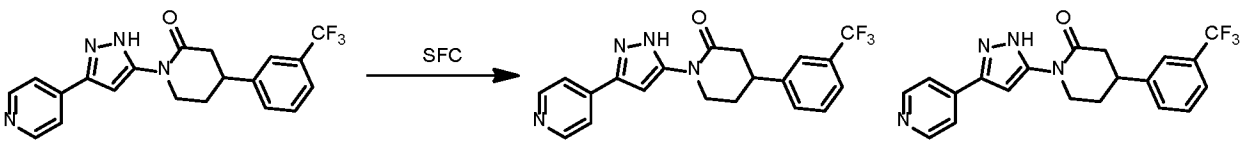


Step 1 — 2: *Synthesis of 1-(3-(Pyridin-4-yl)-1H-pyrazol-5-yl)-4-(3-(trifluoromethyl)phenyl)piperidin-2-one*



1-(3-(Pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(3-(trifluoromethyl)phenyl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 9a and 9b** by replacing (2-fluorophenyl)boronic acid with (3-(trifluoromethyl)phenyl)boronic acid in Step 1.

Step 3: *Chiral Separation of 1-(3-(Pyridin-4-yl)-1H-pyrazol-5-yl)-4-(3-(trifluoromethyl)phenyl)piperidin-2-one (Ex 17a & 17b)*



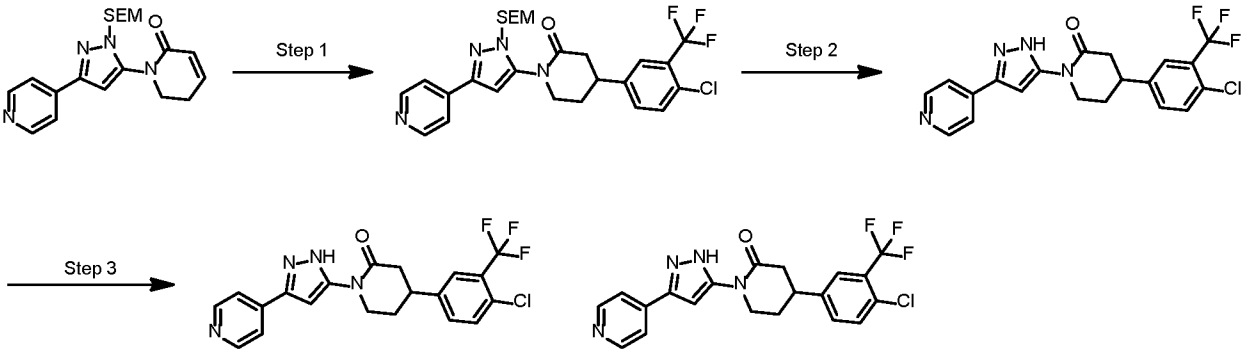
1-(3-(Pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(3-(trifluoromethyl)phenyl)piperidin-2-one (160 mg, 0.41 mmol) was separated by chiral SFC (Chiralpak IG (250 mm x 30 mm, 10 um), Supercritical CO_2 / *i*-PrOH + 0.1% NH_4OH = 50/50; 80 mL/min) to afford 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(3-(trifluoromethyl)phenyl)piperidin-2-one (**Ex 17a**, peak 1, Rt = 3.125 min, 59.5 mg, 37% yield) and 4-

(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 17b**, peak 2, Rt = 4.076 min, 54.1mg, 34% yield) both as white solids.

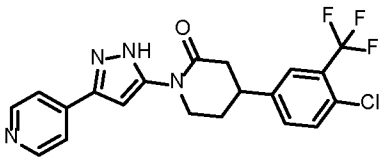
Example 17a: **^{1}H NMR** (DMSO-d_6, 400 MHz): δ 13.36 (br s, 1H), 8.69 - 8.58 (m, 2H), 7.76 - 7.66 (m, 4H), 7.63 - 7.58 (m, 2H), 7.29 (s, 1H), 4.15 - 4.03 (m, 1H), 3.88 - 3.79 (m, 1H), 3.40 - 3.39 (m, 1H), 2.78 - 2.72 (m, 2H), 2.23 - 2.14 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 387.0

Example 17b: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.36 (br s, 1H), 8.69 - 8.58 (m, 2H), 7.76 - 7.66 (m, 4H), 7.63 - 7.58 (m, 2H), 7.29 (s, 1H), 4.15 - 4.00 (m, 1H), 3.89 - 3.77 (m, 1H), 3.40 - 3.39 (m, 1H), 2.80 - 2.71 (m, 2H), 2.23 - 2.10 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 387.0

Examples 18a and 18b

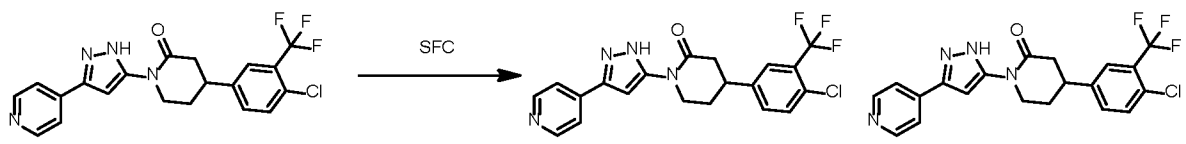


Step 1 — 2: *Synthesis of 4-(4-Chloro-3-(trifluoromethyl)phenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one*



4-(4-Chloro-3-(trifluoromethyl)phenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 9a and 9b** by replacing (2-fluorophenyl)boronic acid with (4-chloro-3-(trifluoromethyl)phenyl)boronic acid in Step 1.

Step 3: Chiral Separation of 4-(4-Chloro-3-(trifluoromethyl)phenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (Ex. 18a & 18b)

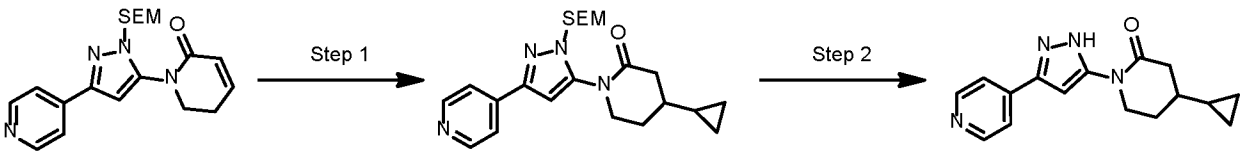


4-(4-Chloro-3-(trifluoromethyl)phenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (155 mg, 0.37 mmol) was separated by chiral SFC (Chiralpak IC (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 60/40; 60 mL/min) to afford 4-(4-chloro-3-(trifluoromethyl)phenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 18a**, peak 1, Rt = 3.435 min, 30.1 mg, 19% yield) and 4-(4-chloro-3-(trifluoromethyl)phenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 18b**, peak 2, Rt = 4.715 min, 45.8 mg, 29% yield) both as white solids.

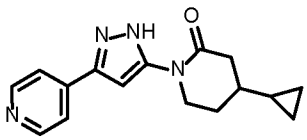
Example 18a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ = 13.37 (s, 1H), 8.65 - 8.63 (m, 2H), 7.83 (s, 1H), 7.78 - 7.66 (m, 4H), 7.29 (s, 1H), 4.11 - 4.01 (m, 1H), 3.85 - 3.75 (m, 1H), 3.40 - 3.35 (m, 1H), 2.80 - 2.70 (m, 2H), 2.20 - 2.04 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 421.0

Example 18b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ = 13.35 (s, 1H), 8.63 (d, J = 4.4 Hz, 2H), 7.83 (s, 1H), 7.78 - 7.66 (m, 4H), 7.28 (s, 1H), 4.11 - 4.01 (m, 1H), 3.85 - 3.75 (m, 1H), 3.45 - 3.38 (m, 1H), 2.80 - 2.70 (m, 2H), 2.20 - 2.05 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 421.0

Example 19



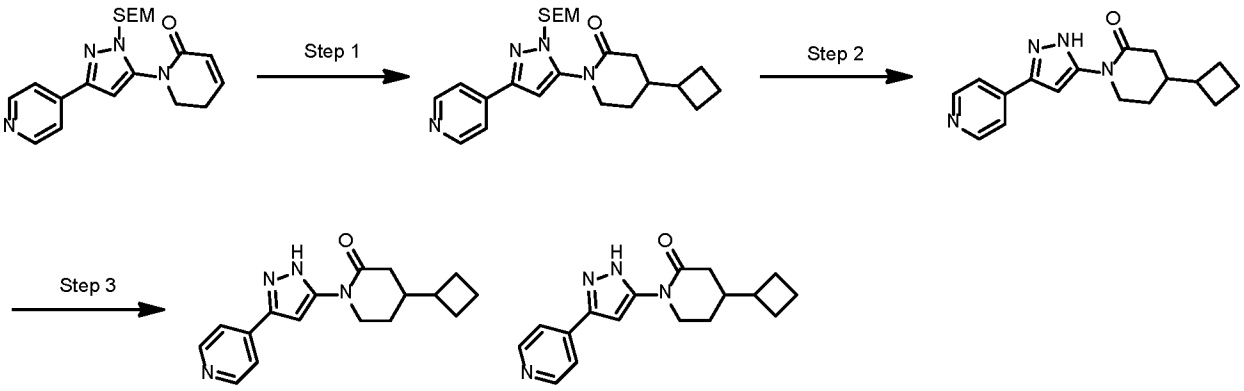
Step 1 – 2: Synthesis of 4-Cyclopropyl-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one



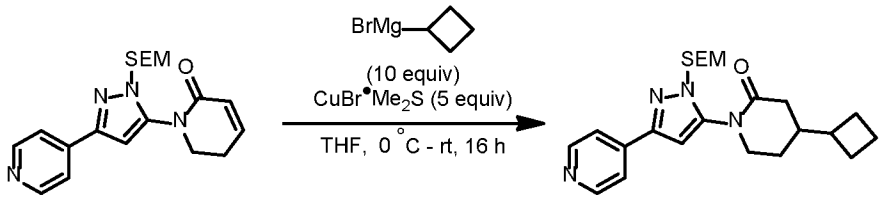
4-Cyclopropyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 19**) was prepared using the general procedure described for the preparation of 4-cyclobutyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 20a** and **Ex 20b**) by replacing cyclobutylmagnesium bromide with cyclopropylmagnesium bromide in Step 1. The title compound was purified by reverse phase chromatography (acetonitrile: 28-58% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to afford 4-cyclopropyl-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (10 mg, 15% yield) as a white solid.

Example 19: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.63 (s, 1H), 8.70 (d, J = 6.0 Hz, 2H), 8.36 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 6.0 Hz, 2H), 7.74 (d, J = 7.2 Hz, 1H), 7.51 - 7.39 (m, 4H), 7.34 (t, J = 7.6 Hz, 1H), 4.77 - 4.46 (m, 3H), 4.13 - 4.02 (m, 1H), 4.01 - 3.98 (m, 1H). **LCMS** (ESI, m/z) $[M+H]^+$ = 282.9

Examples 20a and 20b

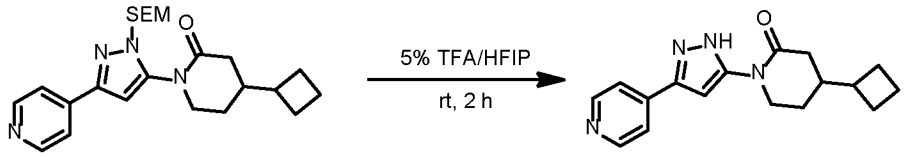


Step 1: Synthesis of 4-cyclobutyl-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)piperidin-2-one



To a solution of copper(I)bromide-dimethylsulfide (2.2 g, 10.8 mmol) in THF (20 mL) cyclobutylmagnesium bromide (0.5 M, 43.2 mL, 21.59 mmol) was added at 0 °C under nitrogen atmosphere. After stirring at 0 °C for 30 minutes, 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-5,6-dihydropyridin-2(1*H*)-one (800 mg, 2.16 mmol) was added. The mixture was stirred at room temperature for 16 hours. The reaction was quenched with saturated aqueous NH_4Cl solution (20 mL) and then extracted by ethyl acetate (20 mL). The organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 0-50% Ethyl acetate in petroleum ether) to afford 4-cyclobutyl-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one (200 mg, 22% yield) as yellow oil. **LCMS**: (ESI, m/z) $[M+H]^+ = 427.3$

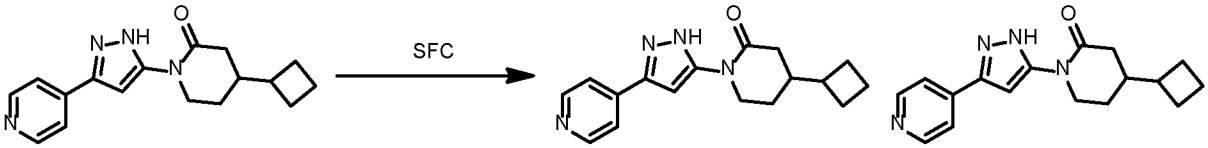
Step 2: Synthesis of 4-cyclobutyl-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one



A solution of 4-cyclobutyl-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one (200 mg, 0.47 mmol) in 5% TFA/HFIP (4 mL) was stirred at room

temperature for 2 hours. The residue was dissolved in DCM (5 mL), and then treated with aqueous saturated $NaHCO_3$ until pH = 8. The organic phase was separated, and the aqueous phase was extracted with DCM (5 mL x 2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 37-67% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to afford 4-cyclobutyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (90 mg, 65% yield) as a white solid. **LCMS**: (ESI, m/z) $[M+H]^+ = 297.2$

Step 3: Chiral Separation of 4-Cyclobutyl-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Ex. 23a & 23b)

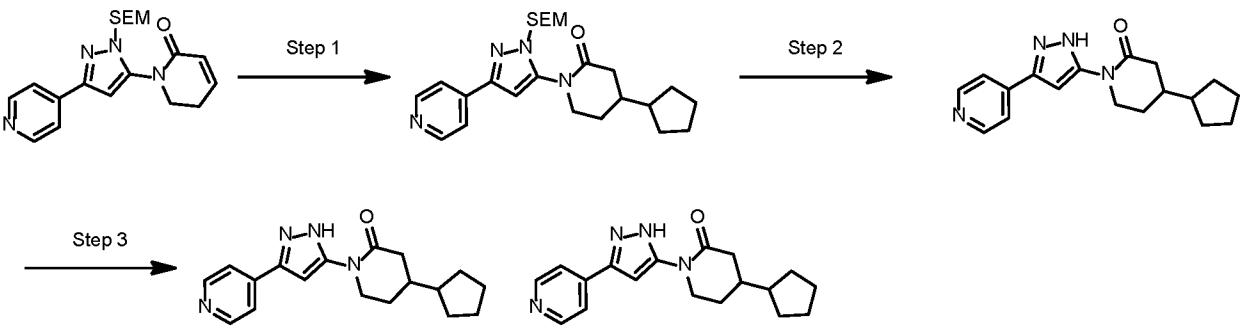


4-Cyclobutyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (90 mg, 0.30 mmol) was separated by chiral SFC (Chiralpak IH (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 65/35; 100 mL/min) to afford 4-cyclobutyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (Example 20a, peak 1, Rt = 3.835 min, 31 mg, 35% yield) and 4-cyclobutyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (Example 20b, peak 2, Rt = 4.109 min, 30 mg, 34% yield) both as white solids.

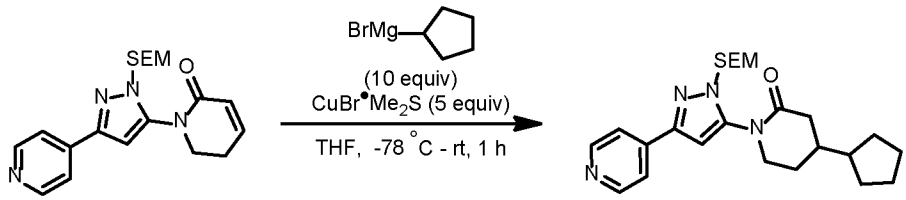
Example 20a: **^{1}H NMR** (DMSO-d_6, 400 MHz): δ 13.29 (s, 1H), 8.61 (d, J = 5.2 Hz, 2H), 7.70 (d, J = 5.2 Hz, 2H), 7.24 (s, 1H), 4.00 - 3.91 (m, 1H), 3.70 - 3.62 (m, 1H), 2.48 - 2.41 (m, 1H), 2.18 - 1.62 (m, 10H), 1.50 - 1.41 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+ = 297.2$

Example 20b: **^{1}H NMR** (DMSO-d_6, 400 MHz): δ 13.28 (s, 1H), 8.61 (d, *J* = 5.2 Hz, 2H), 7.70 (d, *J* = 5.2 Hz, 2H), 7.22 (s, 1H), 4.00 - 3.91 (m, 1H), 3.70 - 3.61 (m, 1H), 2.48 - 2.41 (m, 1H), 2.17 - 1.62 (m, 10H), 1.50 - 1.40 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+ = 297.2$

Examples 21a and 21b



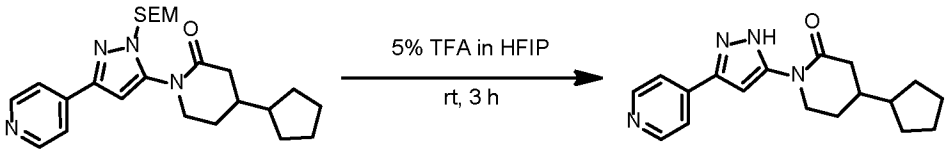
Step 1: *Synthesis of 4-cyclopentyl-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)piperidin-2-one*



To a solution of copper(I)bromide-dimethylsulfide (0.55 g, 2.7 mmol) in THF (8 mL) was added cyclopentylmagnesium bromide (1M in THF, 5.4 mL, 5.4 mmol) at 0 °C under nitrogen atmosphere. After stirring at 0 °C for 30 minutes, a solution of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-5,6-dihydropyridin-2(1*H*)-one (200 mg, 0.54 mmol) in THF (2 mL) was added at -78 °C. The mixture was warmed up to room temperature and stirred at room temperature for 16 hours. The reaction was quenched with saturated aqueous NH_4Cl solution (5 mL) and then extracted by ethyl acetate (20 mL). The organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 0-30% Ethyl acetate in petroleum ether) to afford 4-cyclopentyl-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one (130 mg, 55% yield) as a colorless oil.

LCMS: (ESI, m/z) $[M+H]^+ = 441.3$

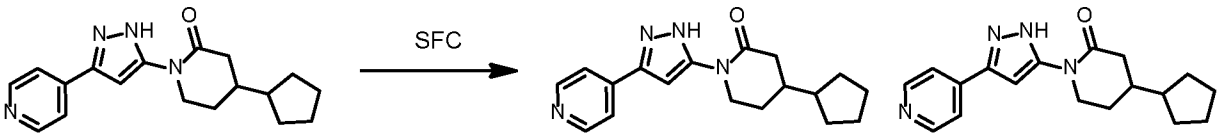
Step 2: *Synthesis of 4-cyclopentyl-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one*



A solution of 4-cyclopentyl-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one (130 mg, 0.3 mmol) in 5% TFA/HFIP (5 mL) was stirred at room temperature for 3 hours. The reaction was concentrated, the residue was dissolved in DCM (5 mL) and the pH was adjusted to 8 with saturated $NaHCO_3$ solution. The organic phase was separated, and the aqueous phase was extracted with DCM (5 mL x 2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford 4-cyclopentyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (90 mg, 98%) as a light yellow solid.

LCMS: (ESI, m/z) $[M+H]^+ = 311.2$

Step 3: *Chiral Separation of 4-Cyclopentyl-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl) piperidin-2-one (Ex 21a & 21b)*

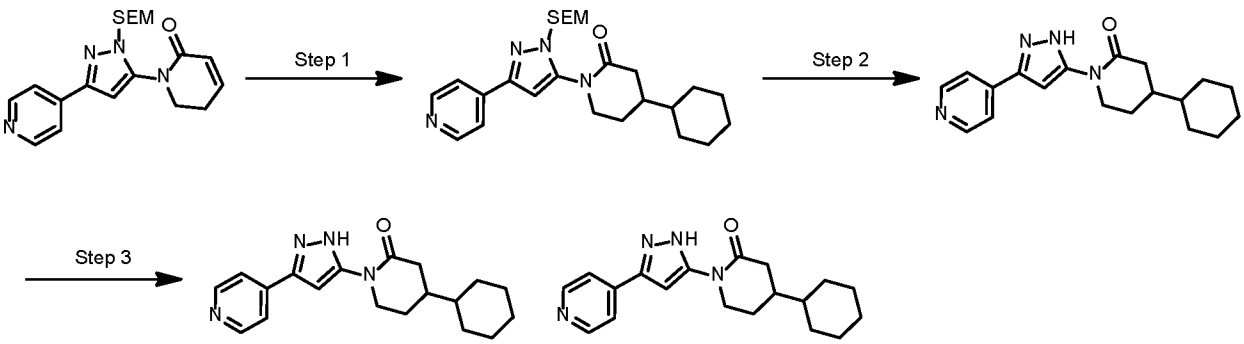


4-Cyclopentyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl) piperidin-2-one (90 mg, 0.29 mmol). was separated by chiral SFC (Chiralpak IH (250 mm x 30 mm, 10 um), Supercritical CO_2 / MeOH + 0.1% NH_4OH = 55/45; 150 mL/min) to afford 4-cyclopentyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl) piperidin-2-one (**Ex 21a**, peak 1, Rt = 2.952 min, 25.8 mg, 29% yield) and 4-cyclobutyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 21b**, peak 2, Rt = 3.338 min, 30 mg, 33% yield) both as white solids.

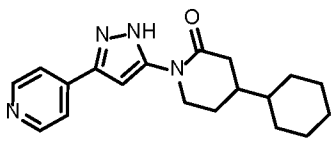
Example 21a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.29 (s, 1H), 8.62 (d, J = 5.2 Hz, 2H), 7.71 (d, J = 5.6 Hz, 2H), 7.24 (s, 1H), 4.05 - 3.95 (m, 1H), 3.71 - 3.61 (m, 1H), 2.25 - 2.16 (m, 1H), 2.08 - 1.99 (m, 1H), 1.79 - 1.51 (m, 10H), 1.21 - 1.12 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 311.0

Example 21b: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.28 (s, 1H), 8.61 (d, J = 4.4 Hz, 2H), 7.71 (d, J = 5.2 Hz, 2H), 7.23 (s, 1H), 4.05 - 3.95 (m, 1H), 3.70 - 3.61 (m, 1H), 2.25 - 2.16 (m, 1H), 2.08 - 1.99 (m, 1H), 1.79 - 1.51 (m, 10H), 1.21 - 1.11 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 311.0

Examples 22a and 22b



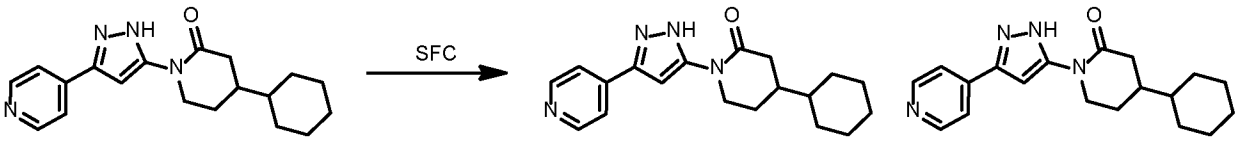
Step 1 — 2: Synthesis of 4-cyclohexyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one



4-cyclohexyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 21a and 21b** by replacing cyclopentylmagnesium bromide with cyclohexylmagnesium bromide in Step 1.

LCMS: (ESI, m/z) $[M+H]^+$ = 325.2

Step 3: *Chiral Separation of 4-Cyclohexyl-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Ex 22a & 22b)*

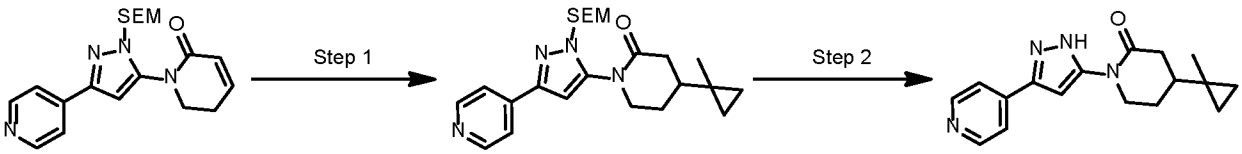


4-Cyclohexyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (110 mg, 0.34 mmol). was separated by chiral SFC (Chiralpak AS (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 75/25; 150 mL/min) to afford 4-cyclohexyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 22a**, peak 1, Rt = 3.384 min, 32.1 mg, 29% yield) and 4-cyclohexyl-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 22b**, peak 2, Rt = 3.678 min, 24.7 mg, 22% yield) both as white solids.

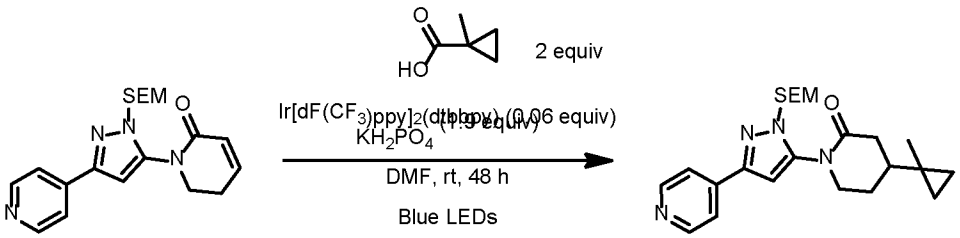
Example 22a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.27 (br s, 1H), 8.61 (d, J = 5.6 Hz, 2H), 7.70 (d, J = 6.0 Hz, 2H), 7.20 (br s, 1H), 4.08 - 3.90 (m, 1H), 3.70 - 3.57 (m, 1H), 2.50 - 2.46 (m, 1H), 2.28 - 2.16 (m, 1H), 2.07 - 1.96 (m, 1H), 1.80 - 1.60 (m, 6H), 1.59 - 1.47 (m, 1H), 1.26 - 1.11 (m, 4H), 1.04 - 0.88 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 325.2

Example 22b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.28 (br s, 1H), 8.61 (d, J = 6.0 Hz, 2H), 7.70 (d, J = 6.0 Hz, 2H), 7.21 (br s, 1H), 4.08 - 3.90 (m, 1H), 3.68 - 3.57 (m, 1H), 2.50 - 2.46 (m, 1H), 2.28 - 2.18 (m, 1H), 2.07 - 1.96 (m, 1H), 1.80 - 1.60 (m, 6H), 1.59 - 1.46 (m, 1H), 1.26 - 1.12 (m, 4H), 1.03 - 0.88 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 325.2

Example 23



Step 1: *Synthesis of 4-(1-methylcyclopropyl)-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)piperidin-2-one*



In a 40 mL vial were added 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-5,6-dihydropyridin-2(1*H*)-one (400 mg, 1.08 mmol), $Ir[dF(CF_3)ppy]_2(dtbbpy)$ (80 mg, 0.07 mmol), 1-methylcyclopropane-1-carboxylic acid (216 mg, 2.16 mmol), KH_2PO_4 (360 mg, 2.07 mmol) in DMF (8mL). The vial was purged with nitrogen and then sealed. The vial was placed in the integrated photoreactor (450 nm LED light) for 48 h. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 66-96% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to give 4-(1-methylcyclopropyl)-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one (45 mg, 9% yield) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.69 (d, J = 5.6 Hz, 2H), 7.60 (d, J = 6.4 Hz, 2H), 7.17 (s, 1H), 5.37 (s, 2H), 4.22 - 4.16 (m, 1H), 3.77 - 3.72 (m, 2H), 3.71 - 3.63 (m, 1H), 2.67 - 2.58 (m, 1H), 2.52 - 2.41 (m, 1H), 2.06 - 1.97 (m, 1H), 1.81 - 1.71 (m, 1H), 1.40 - 1.25 (m, 1H), 1.02 (s, 3H), 0.96 (t, J = 8.0 Hz, 2H), 0.40 - 0.34 (m, 2H), 0.33 - 0.28 (m, 2H), 0.01 (s, 9H). **LCMS** (ESI, m/z) $[M+H]^+$ = 427.1

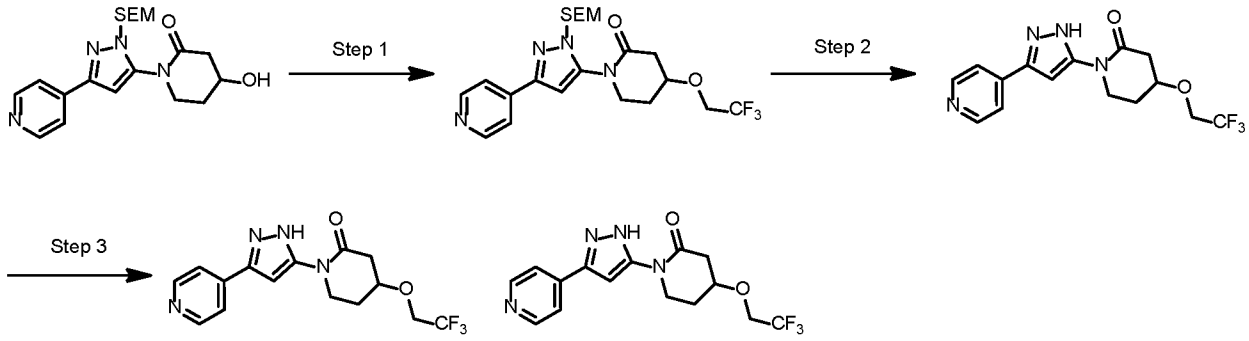
Step 2: *Synthesis of 4-(1-methylcyclopropyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Ex 23)*

A mixture of 4-(1-methylcyclopropyl)-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one (40 mg, 0.09 mmol) in 5% TFA / HFIP solution (1.1 mL) was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure. The residue was dissolved in DCM (10 mL), and then treated with aqueous saturated $NaHCO_3$ until pH = 8. The organic phase was separated, and the aqueous phase was extracted with DCM (10 mL x 2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase

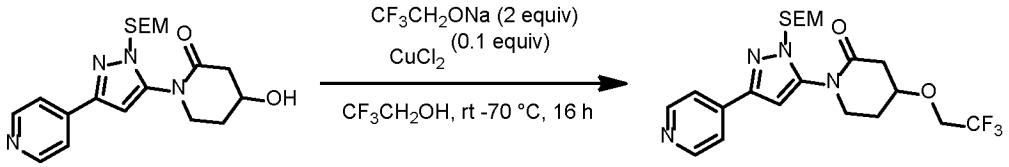
chromatography (acetonitrile: 40-70% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to afford 4-(1-methylcyclopropyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (9.5 mg, 34% yield) both as a white solid.

Example 23: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.35 (s, 1H), 8.71 - 8.53 (m, 2H), 7.78 - 7.64 (m, 2H), 7.22 (br s, 1H), 4.14 - 3.98 (m, 1H), 3.65 - 3.55 (m, 1H), 2.46 - 2.31 (m, 2H), 1.98 - 1.87 (m, 1H), 1.69 - 1.54 (m, 1H), 1.42 - 1.30 (m, 1H), 0.97 (s, 3H), 0.41 - 0.33 (m, 2H), 0.27 - 0.19 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 297.0

Examples 24a and 24b



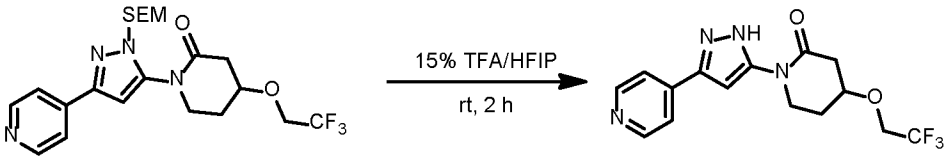
Step 1: *Synthesis of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)-4-(2,2,2-trifluoroethoxy)piperidin-2-one*



To a solution of 4-hydroxy-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one (500 mg, 1.35 mmol) in 2,2,2-trifluoroethanol (2.5 mL) was added sodium 2,2,2-trifluoroethanolate (329 mg, 2.7 mmol) and $CuCl_2$ (18 mg, 0.13 mmol). The reaction mixture was stirred at 70 °C for 16 h. After cooling to room temperature, the reaction was quenched with water (4 mL) and then extracted with ethyl acetate ethyl acetate (4 mL). The organic layer was washed with brine (3 mL) dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and concentrated. The crude was purified by prep-TLC (50% ethyl acetate in petroleum ether) to give 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-4-(2,2,2-trifluoroethoxy)piperidin-2-one (120 mg, 19% yield) as a colorless oil.

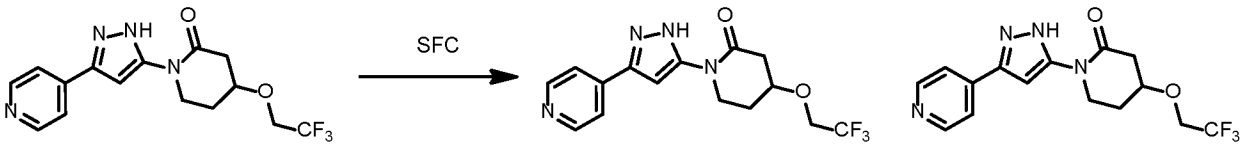
LCMS: (ESI, m/z) $[M+H]^+$ = 471.2

Step 2: *Synthesis of 1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)-4-(2,2,2-trifluoroethoxy)piperidin-2-one*



A mixture of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-4-(2,2,2-trifluoroethoxy)piperidin-2-one (120 mg, 0.26 mmol) in 15% TFA / HFIP solution (8 mL) was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (10 mL), and then treated with aqueous saturated $NaHCO_3$ until pH = 8. The organic phase was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 28-58% / 0.1% NH_4OH in water) to afford 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(2,2,2-trifluoroethoxy)piperidin-2-one (60 mg, 69 % yield) as a white solid.

Step 3: *Chiral Separation of 1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)-4-(2,2,2-trifluoroethoxy)piperidin-2-one (Ex 24a & 24b)*

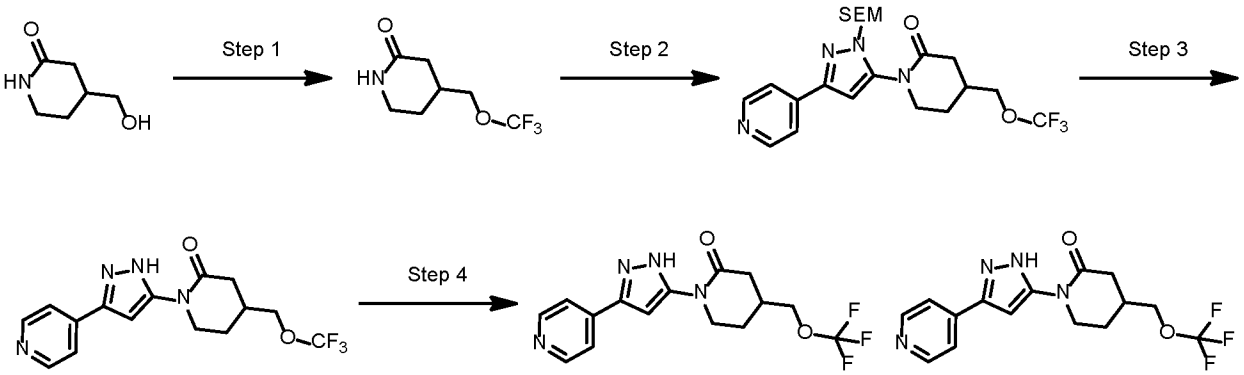


1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(2,2,2-trifluoroethoxy)piperidin-2-one (70 mg, 0.21 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / *i*-PrOH + 0.1% NH_4OH = 40/60; 80 mL/min) to afford 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(2,2,2-trifluoroethoxy)piperidin-2-one (**Ex 24a**, peak 1, Rt = 1.706 min, 22.5 mg, 32% yield) and 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(2,2,2-trifluoroethoxy)piperidin-2-one (**Ex 24b**, peak 2, Rt = 2.254 min, 22.7 mg, 32% yield) both as white solid.

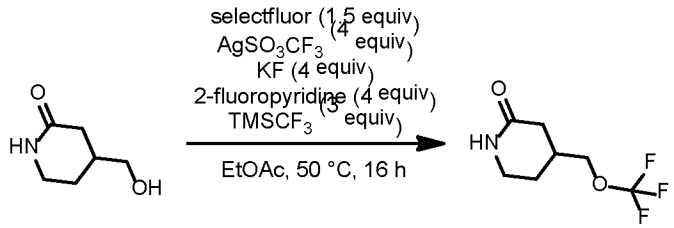
Example 24a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.32 (br s, 1H), 8.62 (d, J = 5.6 Hz, 2H), 7.71 (d, J = 6.0 Hz, 2H), 7.23 (br s, 1H), 4.22 - 4.05 (m, 3H), 3.93 - 3.75 (m, 2H), 2.88 - 2.82 (m, 1H), 2.58 - 2.55 (m, 1H), 2.21 - 2.01 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 341.1

Example 24b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.35 (br s, 1H), 8.62 (d, J = 5.6 Hz, 2H), 7.71 (d, J = 5.6 Hz, 2H), 7.22 (br s, 1H), 4.29 - 4.03 (m, 3H), 3.95 - 3.73 (m, 2H), 2.89 - 2.82 (m, 1H), 2.58 - 2.54 (m, 1H), 2.22 - 1.98 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 340.9

Examples 25a and 25b

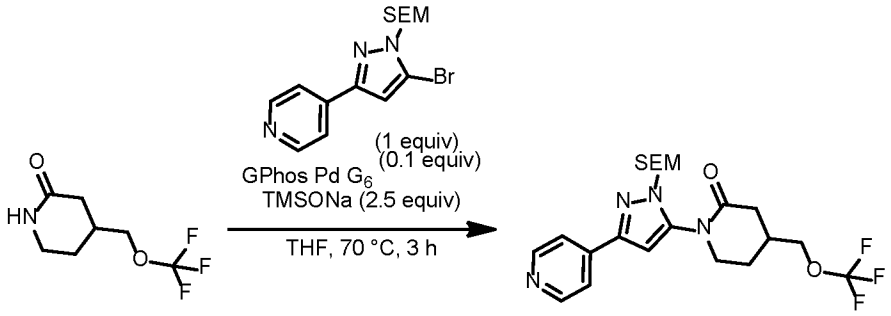


Step 1: Synthesis of 4-(trifluoromethoxymethyl)piperidin-2-one



To a mixture of 4-(hydroxymethyl)piperidin-2-one (4.0 g, 30.97 mmol), 1-fluoro-4-methyl-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate (14.86 g, 46.45 mmol), $AgSO_3CF_3$ (31.83 g, 123.88 mmol) and KF (7.2 g, 123.88 mmol) in ethyl acetate (80 mL) was 2-fluoropyridine (10.66 mL, 123.88 mmol) and trimethyl(trifluoromethyl)silane (13.73 mL, 92.91 mmol). The mixture was stirred at 50 °C for 16 hours under nitrogen condition. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 40%-100% ethyl acetate in petroleum ether) to afford the crude product. The crude product was purified by reverse phase chromatography (acetonitrile: 15-45% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to afford 4-(trifluoromethoxymethyl)piperidin-2-one (1.5 g, 25% yield) as a black solid. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ = 7.52 (s, 1H), 4.05 - 3.93 (m, 2H), 3.22 - 3.06 (m, 2H), 2.27 - 2.11 (m, 2H), 1.99 - 1.88 (m, 1H), 1.87 - 1.77 (m, 1H), 1.47 - 1.31 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 198.1.

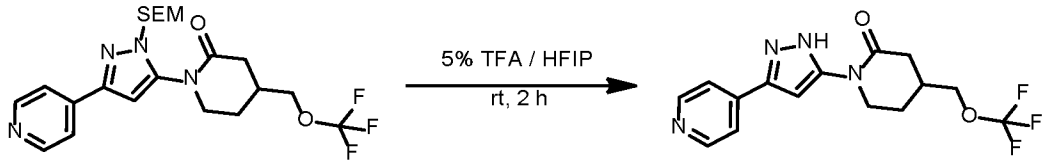
Step 2: Synthesis of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)-4-((trifluoromethoxy)methyl)piperidin-2-one



To a solution of 4-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)pyridine (500 mg, 1.41 mmol) and 4-(trifluoromethoxymethyl)piperidin-2-one (306 mg, 1.55 mmol) in tetrahydrofuran (20 mL) was added sodium trimethyl(oxido)silane (395 mg, 3.53 mmol) and GPhos Pd G6 (133 mg, 0.14 mmol). The mixture was stirred at 70 °C for 3 hours under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 60% ethyl acetate in petroleum ether) to afford 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-4-((trifluoromethoxy)methyl)piperidin-2-one (220 mg, 33% yield) as colorless oil.

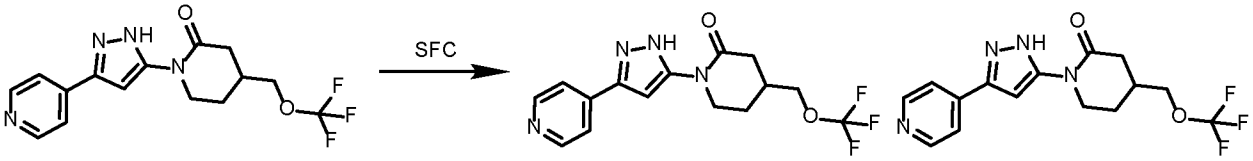
LCMS: (ESI, m/z) $[M+H]^+$ = 471.2.

Step 3: Synthesis of 1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)-4-((trifluoromethoxy)methyl)piperidin-2-one



A solution of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)-4-((trifluoromethoxy)methyl)piperidin-2-one (350 mg, 0.74 mmol) in 5% TFA/HFIP (14 mL) was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure. The residue was dissolved in DCM (5 mL) and then treated with aqueous saturated $NaHCO_3$ until pH = 8. The aqueous phase was extracted with dichloromethane (10 mL x 2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 34-64% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to afford 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-((trifluoromethoxy)methyl)piperidin-2-one (220 mg, 87% yield) as a white solid. **LCMS**: (ESI, m/z) $[M+H]^+$ = 341.1

Step 4: Chiral Separation of 1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)-4-((trifluoromethoxy)methyl)piperidin-2-one (Ex. 25a & 25b)

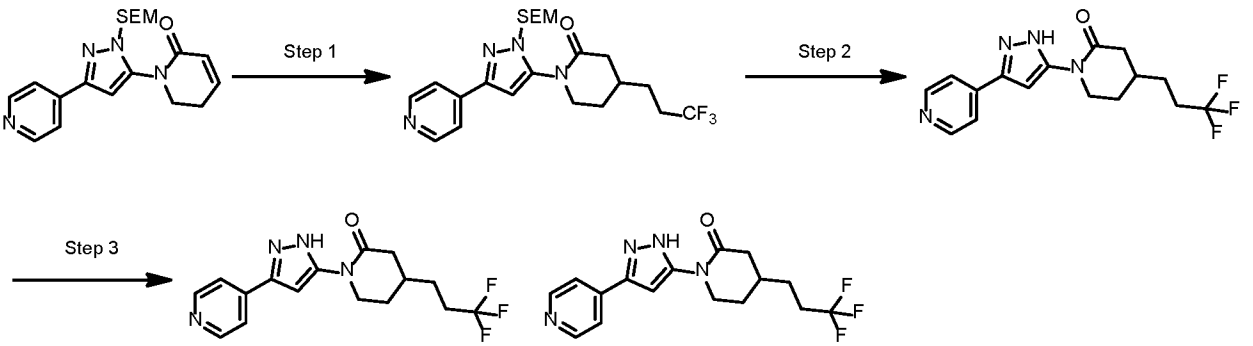


1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-((trifluoromethoxy)methyl)piperidin-2-one (220 mg, 0.59 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 60/40; 80 mL/min) to afford 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-((trifluoromethoxy)methyl)piperidin-2-one (**Ex 25a**, peak 1, Rt = 1.657 min, 78 mg, 35% yield) and 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-((trifluoromethoxy)methyl)piperidin-2-one (**Ex 25b**, peak 2, Rt = 2.256 min, 76 mg, 34% yield) both as white solid.

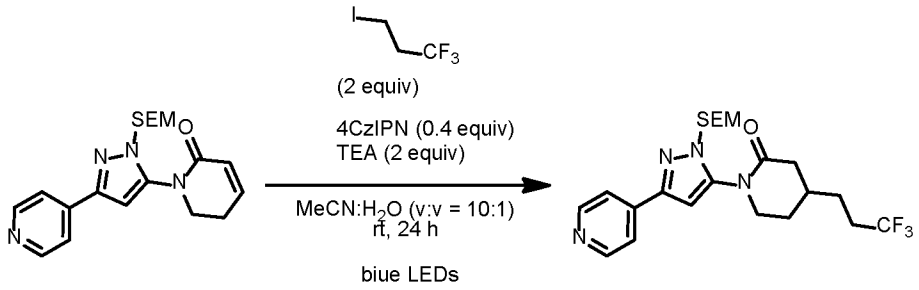
Example 25a: **^{1}H NMR:** (DMSO-d_6, 400 MHz) δ 13.10 (s, 1H), 8.61 (d, J = 4.8 Hz, 2H), 7.69 (d, J = 4.8 Hz, 2H), 7.19 (s, 1H), 4.12 - 3.98 (m, 3H), 3.83 - 3.72 (m, 1H), 2.65 - 2.56 (m, 1H), 2.47 - 2.38 (m, 1H), 2.36 - 2.28 (m, 1H), 2.15 - 2.04 (m, 1H), 1.77 - 1.63 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 341.1

Example 25b: **^{1}H NMR:** (DMSO-d_6, 400 MHz) δ 13.10 (s, 1H), 8.61 (d, J = 5.6 Hz, 2H), 7.69 (d, J = 5.2 Hz, 2H), 7.16 (s, 1H), 4.14 - 3.97 (m, 3H), 3.83 - 3.71 (m, 1H), 2.64 - 2.57 (m, 1H), 2.45 - 2.38 (m, 1H), 2.36 - 2.28 (m, 1H), 2.14 - 2.04 (m, 1H), 1.78 - 1.63 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 341.1

Examples 26a and 26b



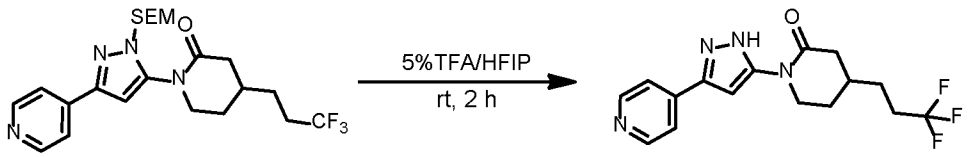
Step 1: *Synthesis of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)-5,6-dihydropyridin-2(1H)-one*



In a 40 mL vial were added 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-5,6-dihydropyridin-2(1*H*)-one (500 mg, 1.35mmol), 1,1,1-trifluoro-3-iodopropane (0.32 mL, 2.7 mmol), TEA (0.39 mL, 2.77 mmol) , 4CzIPN (50 mg, 0.06mmol) in MeCN (12mL) and H_2O(1.2mL). The vial was purged with nitrogen and then sealed. The vial was placed in the integrated photoreactor (450 nm LED light) for 24 h. The mixture was concentrated under concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 15-20%EE (EtOAc/EtOH = 3:1) in petroleum ether) to afford 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-4-(3,3,3-trifluoropropyl)piperidin-2-one (150 mg crude, 60% purity) as a yellow oil.

LCMS: (ESI, m/z) $[M+H]^+$ = 469.0

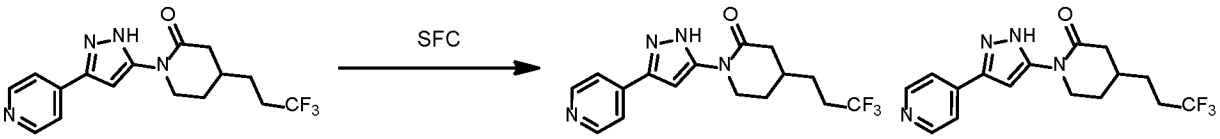
Step 2: *Synthesis of 1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)-4-(3,3,3-trifluoropropyl)piperidin-2-one*



A mixture of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-4-(3,3,3-trifluoropropyl)piperidin-2-one (120 mg crude, 60% purity) in 5% TFA / HFIP solution (2 mL) was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure. Then the reaction residue was poured into saturated $NaHCO_3$ (5 mL), then extracted with DCM (10 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 42-72% / 0.1% NH_4OH in water) to afford to give 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(3,3,3-trifluoropropyl)piperidin-2-one (35 mg, 10% yield over two steps) as a white solid.

LCMS: (ESI, m/z) $[M+H]^+$ =339.0

Step 3: *Chiral Separation of 1-(3-(Pyridin-4-yl)-1H-pyrazol-5-yl)-4-(3,3,3-trifluoropropyl)piperidin-2-one (Ex 26a & 26b)*

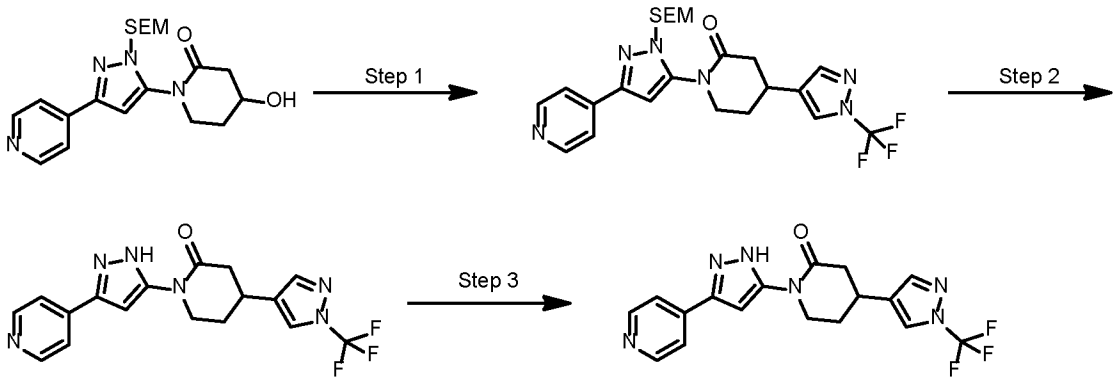


1-(3-(Pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(3,3,3-trifluoropropyl)piperidin-2-one (50 mg, 0.15 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 45/55; 80 mL/min) to afford 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(3,3,3-trifluoropropyl)piperidin-2-one (**Ex 26a**, peak 1, Rt = 1.573 min, 20.2 mg, 40% yield) and 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(3,3,3-trifluoropropyl)piperidin-2-one (**Ex 26b**, peak 2, Rt = 3.031 min, 20.5mg, 41% yield) both as white solids.

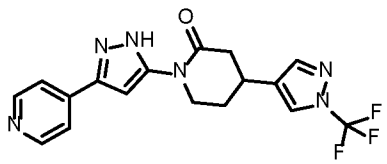
Example 26a: ^{1}**H NMR** (400 MHz, DMSO-d_6): δ 13.31 (s, 1H), 8.62 (d, J = 4.4 Hz, 2H), 7.71 (d, J = 4.8 Hz, 2H), 7.24 (s, 1H), 4.13 - 3.89 (m, 1H), 3.73 - 3.61 (m, 1H), 2.64 - 2.54 (m, 1H), 2.43 - 2.28 (m, 2H), 2.26 - 2.15 (m, 1H), 2.09 - 1.88 (m, 2H), 1.62 - 1.48 (m, 3H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 339.0

Example 26b: ^{1}**H NMR** (400 MHz, DMSO-d_6): δ 13.32 (s, 1H), 8.64 - 8.59 (m, 2H), 7.74 - 7.66 (m, 2H), 7.25 - (s, 1H), 4.07 - 3.95 (m, 1H), 3.72 - 3.58 (m, 1H), 2.64 - 2.54 (m, 1H), 2.39 - 2.29 (m, 2H), 2.26 - 2.15 (m, 1H), 2.07 - 1.92 (m, 2H), 1.59 - 1.48 (m, 3H). **LCMS**: (ESI, m/z) $[M+H]^+$ =339.0

Examples 27a and 27b

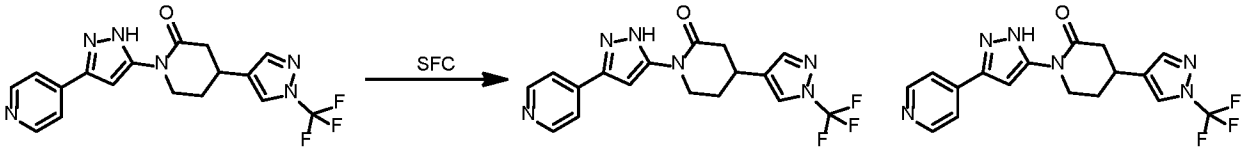


Step 1— 2: *Synthesis of 1-(3-(Pyridin-4-yl)-1H-pyrazol-5-yl)-4-(1-(trifluoromethyl)-1H-pyrazol-4-yl)piperidin-2-one*



1-(3-(Pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(1-(trifluoromethyl)-1*H*-pyrazol-4-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 7a & 7b** by replacing 5-bromo-2-fluoropyridine with 4-bromo-1-(trifluoromethyl)-1*H*-pyrazole in Step 1.

Step 3: *Chiral Separation of 1-(3-(Pyridin-4-yl)-1H-pyrazol-5-yl)-4-(1-(trifluoromethyl)-1H-pyrazol-4-yl)piperidin-2-one (Ex 27a & 27b)*

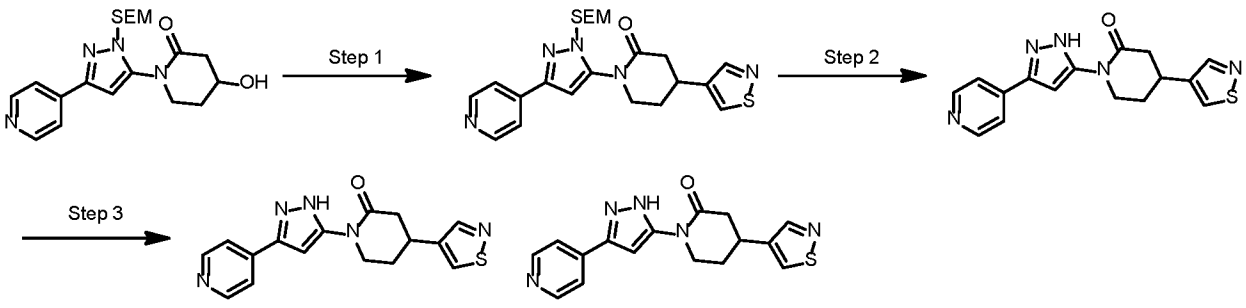


1-(3-(Pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(1-(trifluoromethyl)-1*H*-pyrazol-4-yl)piperidin-2-one (100 mg, 0.27 mmol) was separated by chiral SFC (Chiralpak IG (250 mm x 30 mm, 10 um), Supercritical CO_2 / *i*-PrOH + 0.1% NH_4OH = 60/40; 80 mL/min) to afford 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(1-(trifluoromethyl)-1*H*-pyrazol-4-yl)piperidin-2-one (**Ex 27a**, peak 1, Rt = 0.881 min, 47.3 mg, 46% yield) and 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(1-(trifluoromethyl)-1*H*-pyrazol-4-yl)piperidin-2-one (**Ex 27b**, peak 2, Rt = 2.964 min, 47.2 mg, 46% yield) both as white solids.

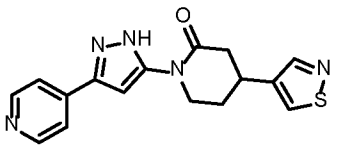
Example 27a: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.33 (s, 1H), 8.66 - 2.58 (m, 2H), 8.41 (s, 1H), 8.01 (s, 1H), 7.72 (d, J = 4.8 Hz, 2H), 7.27 (s, 1H), 4.07 - 3.95 (m, 1H), 3.85 - 3.74 (m, 1H), 3.29 - 3.20 (m, 1H), 2.90 -2.80 (m, 1H), 2.70 - 2.57 (m, 1H), 2.34 - 2.25 (m, 1H), 2.02-1.92 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 377.0

Example 27b: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.32 (s, 1H), 8.62 (d, J = 5.2 Hz, 2H), 8.41 (s, 1H), 8.01 (s, 1H), 7.72 (d, J = 5.6 Hz, 2H), 7.23 (s, 1H), 4.07 - 3.95 (s, 1H), 3.88 - 3.73 (m, 1H), 3.22 - 3.12 (m, 1H), 2.90 -2.80 (m, 1H), 2.70 - 2.57 (m, 1H), 2.34 - 2.25 (m, 1H), 2.01 - 1.90 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 377.0

Examples 28a and 28b

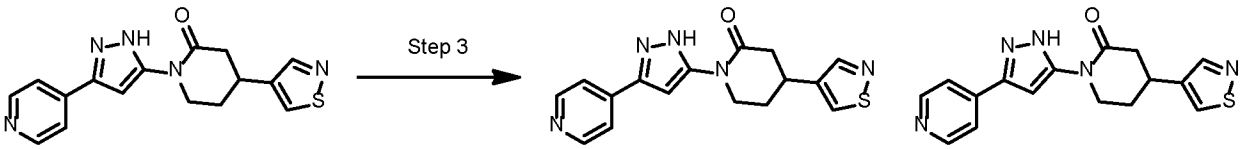


Step 1— 2: *Synthesis of 4-(Isothiazol-4-yl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one*



4-(Isothiazol-4-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 7a and 7b** by replacing 5-bromo-2-fluoropyridine with 4-bromoisothiazole in Step 1.

Step 3: *Chiral Separation of 4-(Isothiazol-4-yl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Ex 28a & 28b)*

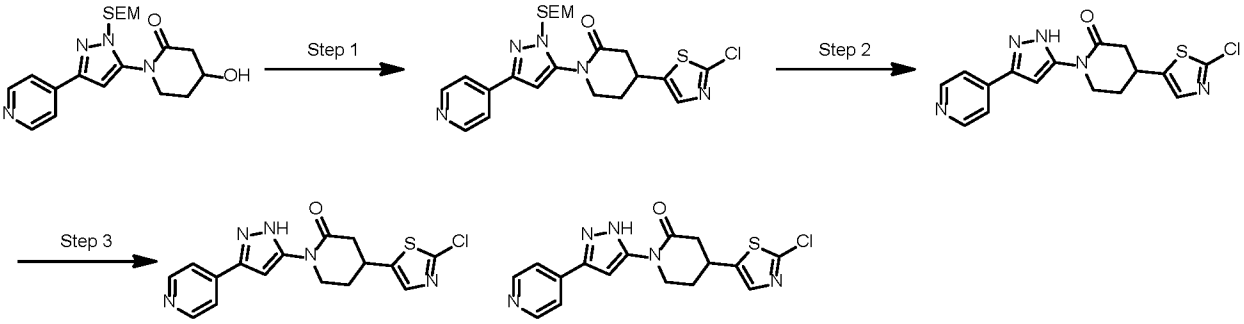


4-(Isothiazol-4-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (100 mg, 0.31 mmol) was separated by chiral SFC (Chiralpak IH (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 55/45; 100 mL/min) to afford 4-(isothiazol-4-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 28a**, peak 1, Rt = 4.528 min, 37.4 mg, 37%) and 4-(isothiazol-4-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 28b**, peak 2, Rt = 4.932 min, 33.6 mg, 34% yield) both as white solids.

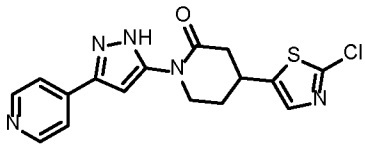
Example 28a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.33 (s, 1H), 8.86 (s, 1H), 8.72 - 8.51 (m, 3H), 7.72 (d, J = 6.0 Hz, 2H), 7.24 (s, 1H), 4.05 - 3.92 (m, 1H), 3.89 - 3.77 (m, 1H), 3.52 - 3.42 (m, 1H), 2.92 - 2.82 (m, 1H), 2.76 - 2.64 (m, 1H), 2.39 - 2.28 (m, 1H), 2.13 - 1.98 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 326.0

Example 28b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.33 (s, 1H), 8.86 (s, 1H), 8.72 - 8.51 (m, 3H), 7.72 (d, J = 5.6 Hz, 2H), 7.25 (s, 1H), 4.05 - 3.92 (m, 1H), 3.89 - 3.77 (m, 1H), 3.52 - 3.42 (m, 1H), 2.92 - 2.82 (m, 1H), 2.76 - 2.64 (m, 1H), 2.38 - 2.26 (m, 1H), 2.15 - 2.00 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 326.0

Examples 29a and 29b

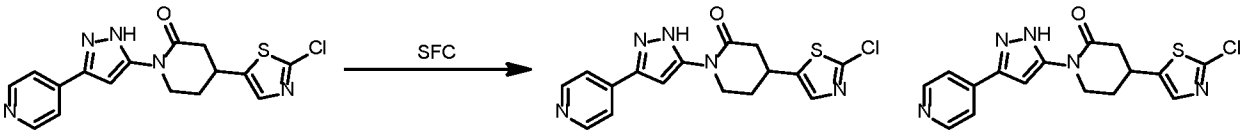


Step 1 — 2: *Synthesis of 4-(2-Chlorothiazol-5-yl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one*



4-(2-Chlorothiazol-5-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 7a and 7b** by replacing 5-bromo-2-fluoropyridine with 5-bromo-2-chlorothiazole in Step 1.

Step 3: *Chiral Separation of 4-(2-Chlorothiazol-5-yl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Ex 29a & 29b)*



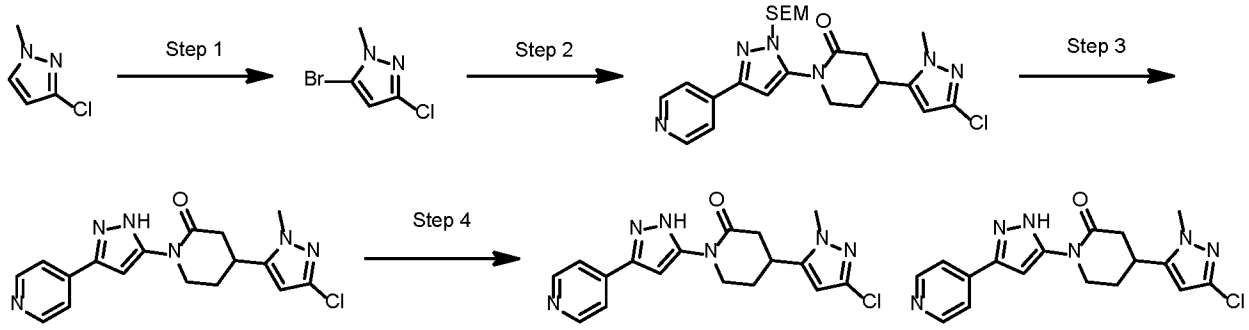
4-(2-Chlorothiazol-5-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (70 mg, 0.19 mmol mmol) was separated by chiral SFC (Chiralpak AS (250 mm x 30 mm, 10 um), Supercritical CO_2 / *i*-PrOH + 0.1% NH_4OH = 50/50; 150 mL/min) to afford 4-(2-chlorothiazol-5-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 29a**, peak 1, Rt = 1.463 min, 20.1 mg, 26% yield) and 4-(2-chlorothiazol-5-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 29b**, peak 2, Rt = 2.378 min, 25.3 mg, 34% yield) both as white solids.

Example 29a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.36 (s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.72 (d, J = 5.6 Hz, 2H), 7.57 (s, 1H), 7.27 (s, 1H), 4.13 - 3.99 (m, 1H), 3.89 - 3.78 (m, 1H), 3.69-3.59

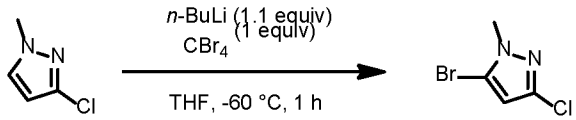
(m, 1H), 2.92 - 2.82 (m, 1H), 2.73 - 2.60 (m, 1H), 2.39 - 2.26 (m, 1H), 2.14 - 2.00 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 360.0

Example 29b: ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 13.33 (s, 1H), 8.62 (d, J = 5.2 Hz, 2H), 7.72 (d, J = 6.0 Hz, 2H), 7.57 (s, 1H), 7.23 (s, 1H), 4.10 - 3.93 (m, 1H), 3.87 - 3.78 (m, 1H), 3.66 - 3.55 (m, 1H), 2.94 - 2.82 (m, 1H), 2.75 - 2.65 (m, 1H), 2.37 - 2.26 (m, 1H), 2.13 - 2.01 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 360.2

Examples 30a and 30b



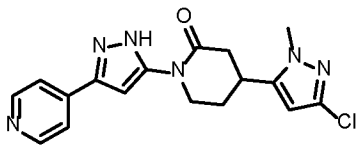
Step 1:



To a solution of 3-chloro-1-methyl-1*H*-pyrazole (4.0 g, 34.3 mmol) in THF (40 mL) was added *n*-BuLi (2.5 M, 15.1 mL, 37.7 mmol) dropwise at -60 °C under nitrogen atmosphere. After stirring at -60 °C for 1 hour, then a solution of CBr_4 (11.3 g, 34.3 mmol) in THF (20 mL) was added dropwise. After stirring at -60 °C for 1 hour under nitrogen atmosphere. The reaction was quenched with water (50 mL) and then extracted with ethyl acetate (80 mL). The organic layer was washed with brine (80 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 5% ethyl acetate in petroleum ether) to afford 5-bromo-3-chloro-1-methyl-1*H*-pyrazole (3 g, 44% yield) as yellow oil.

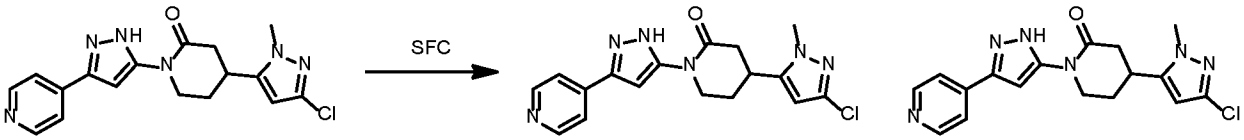
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.22 (s, 1H), 3.83 (s, 3H). LCMS: (ESI, m/z) $[M+H]^+$ = 194.9

Step 2 — 3: *Synthesis of 4-(3-Chloro-1-methyl-1H-pyrazol-5-yl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one*



4-(3-Chloro-1-methyl-1*H*-pyrazol-5-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 7a and 7b** by replacing 5-bromo-2-fluoropyridine with 5-bromo-3-chloro-1-methyl-1*H*-pyrazole in Step 1.

Step 4: *Chiral Separation of 4-(3-Chloro-1-methyl-1H-pyrazol-5-yl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Ex 30a & 30b)*

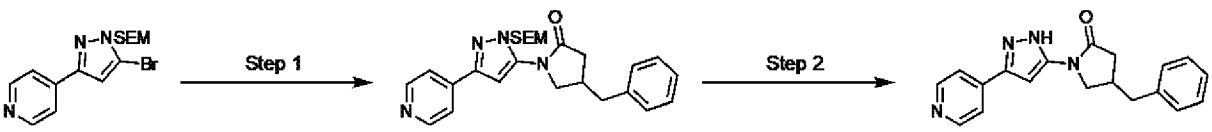


4-(3-Chloro-1-methyl-1*H*-pyrazol-5-yl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (250 mg, 0.70 mmol) was separated by chiral SFC (Chiralcel OJ (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 60/40; 80 mL/min) to afford 4-(3-chloro-1-methyl-1*H*-pyrazol-5-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 30a**, peak 1, Rt = 0.885 min, 91.5 mg, 36% yield) and 4-(3-chloro-1-methyl-1*H*-pyrazol-5-yl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 30b**, peak 2, Rt = 2.182 min, 77.2 mg, 30% yield) both as white solids.

Example 30a: ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 13.36 (br s, 1H), 8.63 (d, J = 5.2 Hz, 2H), 7.72 (d, J = 5.2 Hz, 2H), 7.27 (s, 1H), 6.24 (s, 1H), 4.12 - 3.97 (m, 1H), 3.91 - 3.81 (m, 1H), 3.78 (s, 3H), 3.52 - 3.41 (m, 1H), 2.85 - 2.72 (m, 1H), 2.66 - 2.55 (m, 1H), 2.27 - 2.16 (m, 1H), 2.04 - 1.88 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 357.0

Example 30b: ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 13.35 (br s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.72 (d, J = 6.0 Hz, 2H), 7.26 (s, 1H), 6.24 (s, 1H), 4.11 - 3.94 (m, 1H), 3.91 - 3.81 (m, 1H), 3.78 (s, 3H), 3.52 - 3.41 (m, 1H), 2.83 - 2.73 (m, 1H), 2.66 - 2.55 (m, 1H), 2.27 - 2.15 (m, 1H), 2.02 - 1.89 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 357.1.

Example 31



Step 1 – 2: Synthesis of 4-benzyl-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)pyrrolidin-2-one (Ex 31)

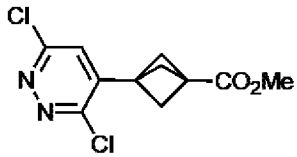
4-benzyl-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)pyrrolidin-2-one was prepared using the general

procedure for Examples 1a and 1b using 4-benzylpyrrolidin-2-one (74.2 mg, 3 equiv, 0.42 mmol) in place of 4-phenylpiperidin-2-one in step 1. The material was purified by prep HPLC (XSelect CSH Prep C18, 50 mm x 30 mm, 5 μm), 0.1% Ammonium hydroxide in water / acetonitrile using a gradient of 20% to 60% acetonitrile; 60 mL/min, 25 °C) to yield 4-benzyl-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)pyrrolidin-2-one as a racemic white solid (15 mg, 33% yield).

Example 31: **^{1}H NMR** (400 MHz, DMSO) δ 13.21 (s, 1H), 8.65 – 8.57 (d, J = 6.2, 2H), 7.75 – 7.69 (d, J = 6.23, 2H), 7.37 – 7.30 (m, 2H), 7.30 – 7.18 (m, 4H), 3.89 (dd, J = 10.0, 7.0 Hz, 1H), 3.57 (dd, J = 10.1, 5.1 Hz, 1H), 2.80 (m, 3H), 2.58 (dd, J = 16.6, 7.7 Hz, 1H), 2.36 – 2.26 (dd, J = 16.6 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 319.1.

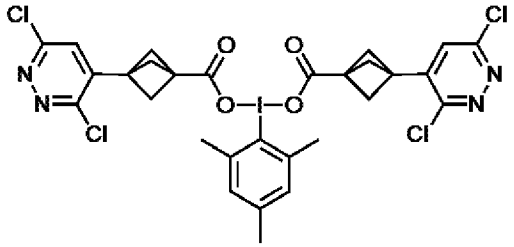
Example 32

Step 1: Synthesis of methyl 3-(3,6-dichloropyridazin-4-yl)bicyclo[1.1.1]pentane-1-carboxylate



To a vial equipped with a stir bar, 1-(1,3-dioxoisoindolin-2-yl) 3-methyl bicyclo[1.1.1]pentane-1,3-dicarboxylate [*prepared via known literature procedure* ref: *Org. Lett.* 2020, 22, 4, 1648–1654] (2000 mg, 6.3 mmol, 1 equiv.), 3,6-dichloropyridazine (2835 mg, 19 mmol, 3 equiv.), and $Ir(ppy)_3$ (42 mg, 0.06 mmol, 0.01 equiv.) were added followed by DMSO (45 mL). The reaction was degassed by sparging with N_2 for 5-10 minutes. The mixture was placed in front of two blue LEDs (without fan, setup reaches about 40 °C). The mixture was stirred until complete consumption of the starting materials was confirmed by LCMS analysis. On completion, the reaction mixture was purified directly by preparative HPLC (30-70% MeCN, 0.1% FA modifier). This afforded methyl 3-(3,6-dichloropyridazin-4-yl)bicyclo[1.1.1]pentane-1-carboxylate (520 mg, 30% Yield) as an off-white semi-solid. **LCMS** (ESI) $[M+H]^+$ = 330.100, 332.100 (5:3). **^{1}H NMR** (400 MHz, MeOD) δ 7.67 (s, 1H), 2.48 (s, 6H), 1.45 (s, 9H).

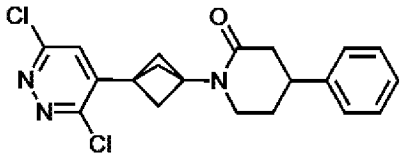
Steps 2 – 3: Synthesis of mesityl-λ^3-iodanediyl bis(3-(3,6-dichloropyridazin-4-yl)bicyclo[1.1.1]pentane-1-carboxylate)



To a vial equipped with a stir bar, methyl 3-(3,6-dichloropyridazin-4-yl)bicyclo[1.1.1]pentane-1-carboxylate (100 mg, 0.37 mmol, 1 equiv.) and THF (1 mL) were added followed by NaOH (1 M, aq) (0.4 mL, 0.4 mmol, 1.1 equiv.). The mixture was stirred until complete consumption of the starting materials was confirmed by LCMS analysis. At this time, citric acid (141 mg, 0.7 mmol, 2.0 equiv.) was added, and the mixture was extracted 5 times with DCM. This afforded 3-(3,6-dichloropyridazin-4-yl)bicyclo[1.1.1]pentane-1-carboxylic acid (90 mg, 0.35 mmol, 95% Yield) as a solid which was used without purification. **LCMS** (ESI) $[M+H]^+$ = 258.852, 260.832 (5:3)

To a vial equipped with a stir bar, 3-(3,6-dichloropyridazin-4-yl)bicyclo[1.1.1]pentane-1-carboxylic acid (90 mg, 0.35 mmol, 2.1 equiv.) and mesityl-λ^3-iodanediyl diacetate (60 mg, 0.16 mmol, 1 equiv.) were added followed by toluene (5 mL). After full dissolution, the mixture was concentrated directly on a rotavap at 50 °C. The sequence was repeated twice more to yield the title compound (113 mg, 0.15 mmol, 90% Yield) as an oil, which was used without further purification.

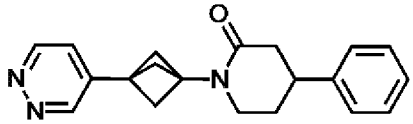
Step 4: Synthesis of 1-(3-(3,6-dichloropyridazin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-phenylpiperidin-2-one



To a vial equipped with a stir bar, tris[2-(2-pyridyl)phenyl]iridium (1.5 mg, 0.002 mmol, 0.02 equiv.), $Cu(acac)_2$ (18 mg, 0.07 mmol, 0.6 equiv.), 4-phenylpiperidin-2-one (20 mg, 0.11 mmol, 1 equiv.), and 1,4-dioxane (2 mL) were added followed by DBU (43 mg, 0.043 mL, 0.29 mmol, 2.5 equiv.). The solution was sparged with N_2 for 5 minutes, then placed in front of blue LEDs and stirred for 1 hour. At this time, the mixture was diluted with iPrOAc and washed three times with brine. The organic fraction were dried over MgSO4, filtered, and concentrated.

Purification via column chromatography gave 1-[3-(3,6-dichloropyridazin-4-yl)-1-bicyclo[1.1.1]pentanyl]-4-phenyl-piperidin-2-one (13 mg, 0.03 mmol, 29% Yield) as a white solid. **LCMS** (ESI) $[M+H]^+$ = 388.100/390.100 (5:3)

Step 5: Synthesis of 4-phenyl-1-(3-(pyridazin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (Ex. 40)



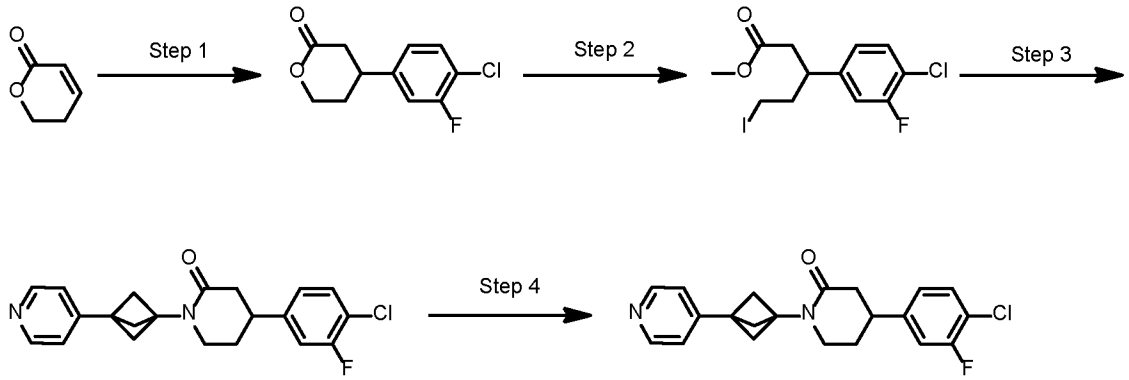
To a vial equipped with a stir bar add, $Pd(dppf)Cl_2$ (4 mg, 0.005 mmol, 0.15 equiv) and THF (0.5 mL) were added. The reaction was degassed with N_2 for 2 minutes, then 1-(3-(3,6-

dichloropyridazin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-phenylpiperidin-2-one (13 mg, 0.03 mmol, 1 equiv), TMEDA (17 uL, 13 mg, 3.4 equiv) and sodium borohydride (4.3 mg, 0.12 mmol, 3.4 equiv) were added. The mixture was strired at room temperature until complete consumption of the starting materials was confirmed by LCMS analysis. Upon completion, the reaction was quenched with sat. aq. NH_4Cl and extracted with DCM (3x). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated.

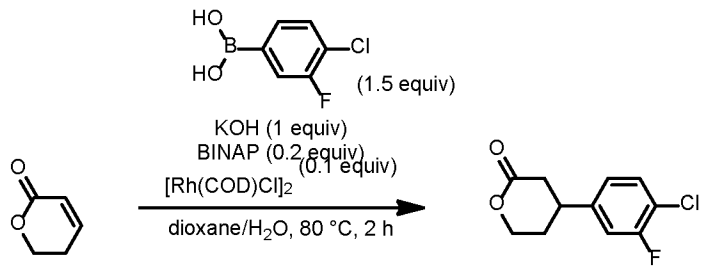
Purification via column chromatography (0 to 10% MeOH in DCM) afforded 4-phenyl-1-(3-pyridazin-4-yl-1-bicyclo[1.1.1]pentanyl)piperidin-2-one (Example 32, 2.7 mg, 0.0085 mmol, 25% Yield) as a white solid. Submitted as the racemate.

Example 32: ^{1}**H NMR** (400 MHz, MeOD) δ 9.14 (s, 1H), 9.09 (d, J = 5.5 Hz, 1H), 7.66 – 7.58 (m, 1H), 7.39 – 7.16 (m, 5H), 3.53 – 3.42 (m, 2H), 3.18 – 3.06 (m, 1H), 2.63 – 2.44 (m, 2H), 2.60 (s, 6H), 2.20 – 2.09 (m, 1H), 2.08 – 1.96 (m, 1H). **LCMS** (ESI) $[M+H]^+$ = 320.2.

Examples 33a and 33b



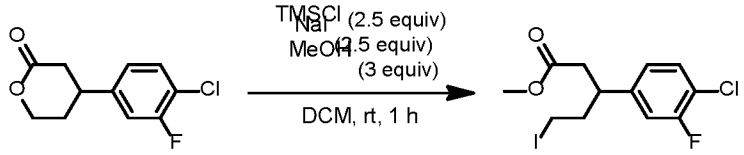
Step 1: Synthesis of 4-(4-chloro-3-fluorophenyl)tetrahydro-2H-pyran-2-one



To a solution of 5,6-dihydro-2*H*-pyran-2-one (4.39 mL, 50.97 mmol), 4-chloro-3-fluorophenylboronicacid (13.33 g, 76.45 mmol), BINAP (6.35 g, 10.19 mmol) and $[Rh(COD)Cl]_2$ (2.51 g, 5.1 mmol) in 1,4-dioxane (100 mL) and water (10 mL) was added KOH (2.86 g, 50.97 mmol) at room temperature. Then the resulting mixture was stirred at 80 °C for 2 hours under nitrogen atmosphere. After cooling to room temperature, the reaction was diluted with brine (50 mL) and extracted with ethyl acetate (100 mL). The organic layer was separated, dried over anhydrous

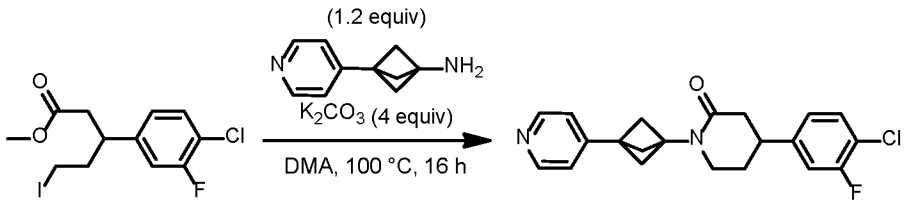
Na2SO4, filtered and concentrated. The residue was purified by flash column chromatography (silica, 15% EtOAc in petroleum ether) to afford 4-(4-chloro-3-fluorophenyl)tetrahydro-2*H*-pyran-2-one (5.1 g, 44% yield) as a white oil. **LCMS**: (ESI, m/z) $[M+H]^+$ = 229.1

Step 2: Synthesis of methyl 3-(4-chloro-3-fluorophenyl)-5-iodopentanoate



To a solution of 4-(4-chloro-3-fluoro-phenyl)tetrahydropyran-2-one (2.50 g, 10.93 mmol) and NaI (4.10 g, 27.33 mmol) in DCM (35 mL) was added TMSCl (3.30 mL, 27.33 mmol) dropwise at 0 °C under nitrogen atmosphere. After stirring at 0 °C for 10 min, to the mixture was added MeOH (1.33 mL, 32.80 mmol) and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 10% ethyl acetate in petroleum ether) to afford methyl 3-(4-chloro-3-fluorophenyl)-5-iodopentanoate (2.1 g, 52% yield) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.35 (t, J = 8.0 Hz, 1H), 7.05 - 6.92 (m, 2H), 3.61 (s, 3H), 3.35 - 3.24 (m, 1H), 3.10 - 3.02 (m, 1H), 2.85 - 2.76 (m, 1H), 2.67 - 2.56 (m, 2H), 2.27 - 1.99 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 370.9

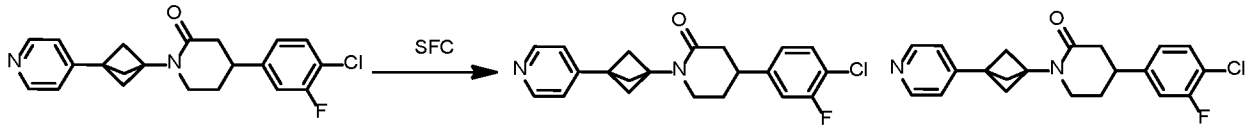
Step 3: Synthesis of 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one



To a solution of methyl 3-(4-chloro-3-fluoro-phenyl)-5-iodo-pentanoate (500 mg, 1.35 mmol) and 3-(4-pyridyl)bicyclo[1.1.1]pentan-1-amine hydrochloride (318 mg, 1.62 mmol) in DMA (5 mL) was added K_2CO_3 (757 mg, 5.40 mmol). The reaction was stirred at 60 °C for 1 h and then heated to 100 °C for 16 hours. After cooling to room temperature, the mixture was quenched with water (30 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed with brine (50 mL x 2), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

The residue was by flash column chromatography (SiO_2, 50% ethyl acetate in petroleum ether) to afford 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (200 mg, 40% yield) as a white solid. **LCMS**: (ESI, m/z) $[M+H]^+ = 371.0$

Step 4: Chiral Separation of 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (Ex. 33a & 33b).

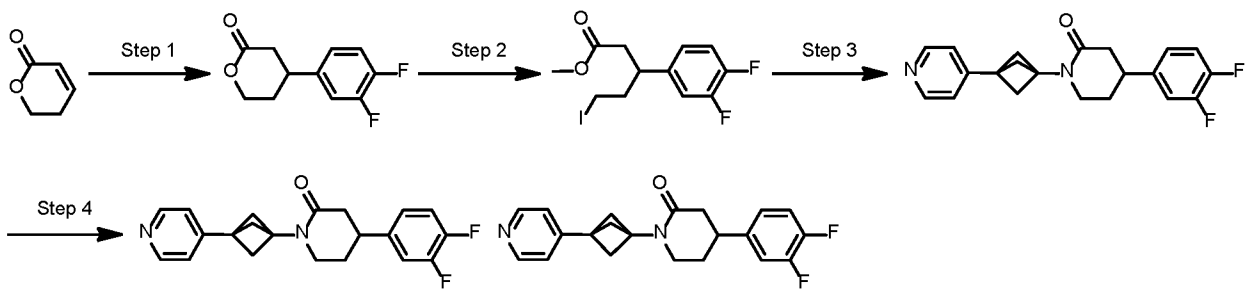


4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (200 mg) was separated by chiral SFC (Chiralpak IG (250 mm x 30 mm, 10 um), Supercritical CO_2 / *i*-PrOH + 0.1% NH_4OH = 55/45; 80 mL/min) to afford 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (Ex. 33a, peak 1, Rt = 3.084 min, 19.7 mg, 10% yield) and 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (Ex. 33b, peak 2, Rt = 3.223 min, 23.8 mg, 12% yield) both as white solids.

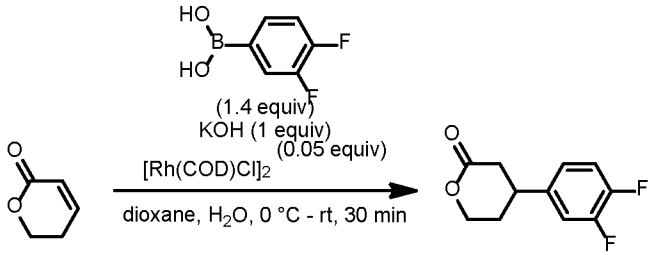
Example 33a: **^{1}H NMR** (DMSO-d_6, 400 MHz): δ 8.50 (d, J = 5.6 Hz, 2H), 7.53 (t, J = 8.0 Hz, 1H), 7.39 -7.32 (m, 1H), 7.26 (d, J = 5.6 Hz, 2H), 7.17 (d, J = 8.4 Hz, 1H), 3.44 - 3.35 (m, 2H), 3.17 - 3.06 (m, 1H), 2.46 - 2.42 (m, 2H), 2.41 (s, 6H), 2.08 - 1.85 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+ = 371.2$

Example 33b: **^{1}H NMR** (DMSO-d_6, 400 MHz): δ 8.49 (d, J = 5.6 Hz, 2H), 7.53 (t, J = 8.0 Hz,, 1H), 7.38 (d, J = 10.8 Hz, 1H), 7.26 (d, J = 5.6 Hz, 2H), 7.17 (d, J = 8.4 Hz, 1H), 3.47 - 3.36 (m, 2H), 3.15 - 3.03 (m, 1H), 2.47 - 2.42 (m, 2H), 2.41 (s, 6H), 2.06 - 1.85 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+ = 371.2$

Examples 34a and 34b



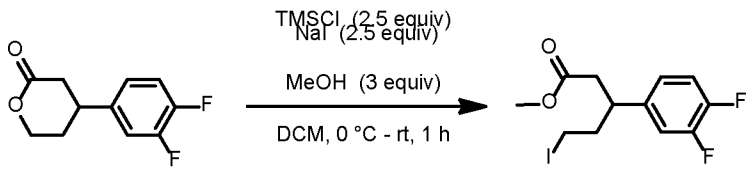
Step 1: *Synthesis of 4-(3,4-difluorophenyl)tetrahydro-2H-pyran-2-one*



To a mixture of (3,4-difluorophenyl)boronic acid (11.27 g, 71.36 mmol), 5,6-dihydro-2*H*-pyran-2-one (5.0 g, 50.97 mmol) and $[Rh(COD)Cl]_2$ (1.26 g, 2.55 mmol) in 1,4-dioxane (100 mL) was added a solution of KOH (2.86 g, 50.97 mmol) in water (10 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 0.5 hours. The mixture was extracted with ethyl Acetate (100 x 3 mL). The combined organic phases were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 25% ethyl acetate in petroleum ether) to give 4-(3,4-difluorophenyl)tetrahydro-2*H*-pyran-2-one (8.4 g, 78% yield) as colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.18 - 7.11 (m, 1H), 7.05 - 7.00 (m, 1H), 6.95 - 6.92 (m, 1H), 4.56 - 4.46 (m, 1H), 4.41 - 4.35 (m, 1H), 3.26 - 3.18 (m, 1H), 2.94 - 2.87 (m, 1H), 2.59 - 2.50 (m, 1H), 2.24 - 2.14 (m, 1H), 2.03 - 1.91 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 213.1

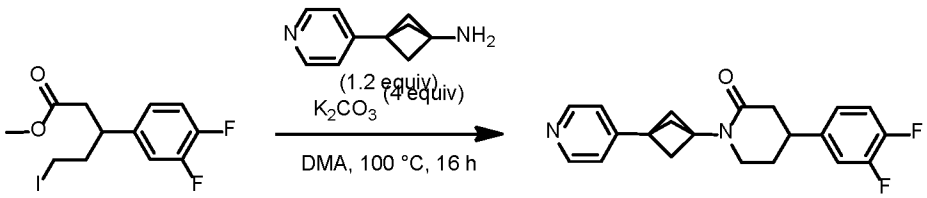
Step 2: *Synthesis of methyl 3-(3,4-difluorophenyl)-5-iodopentanoate*



To a solution of 4-(3,4-difluorophenyl)tetrahydro-2*H*-pyran-2-one (8.4 g, 39.59 mmol) and NaI (14.83 g, 98.97 mmol) in DCM (150 mL) was added TMSCl (11.95 mL, 98.97 mmol) dropwise at 0 °C under nitrogen atmosphere. After stirring at 0 °C for 10 min, to the mixture was added MeOH (4.81 mL, 118.76 mmol) and the mixture was stirred at room temperature for 1 hour. The reaction was quenched with saturated $Na_2S_2SO_3$ solution (30 mL) and extracted with DCM (50 mL x 3), The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 6% ethyl acetate in petroleum ether) to afford methyl 3-(3,4-difluorophenyl)-5-iodopentanoate (8.26 g, 59% yield) as a yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.15 - 7.08 (m, 1H), 7.08 - 7.00 (m, 1H), 6.98 - 6.94 (m, 1H), 3.61 (s, 3H), 3.33 - 3.22 (m, 1H), 3.09 - 3.04 (m, 1H), 2.86 - 2.76 (m, 1H), 2.68 - 2.55 (m, 2H), 2.25 - 2.14 (m, 1H), 2.10 - 1.99 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 355.0

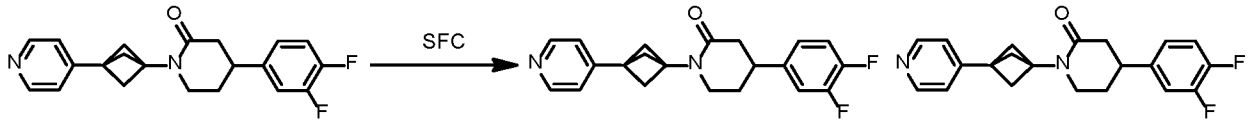
Step 3: *Synthesis of 4-(3,4-difluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one*



To a stirred solution of methyl 3-(3,4-difluorophenyl)-5-iodopentanoate (750 mg, 2.12 mmol) and 3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-amine (617 mg, 2.54 mmol) in DMA (10 mL) was added K_2CO_3 (1.17 g, 8.47 mmol). The mixture was stirred at 100 °C for 16 hours. After cooling to room temperature, the mixture was quenched with water (20 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic phases were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was by flash column chromatography (SiO_2, 20% EE (EtOAc/EtOH = 3:1) in petroleum ether) to yield 4-(3,4-difluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (350 mg, 47% yield) as a yellow solid.

LCMS: (ESI, m/z) $[M+H]^+$ = 355.1

Step 4: *Chiral Separation of 4-(3,4-Difluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (Ex. 34a & 34b)*



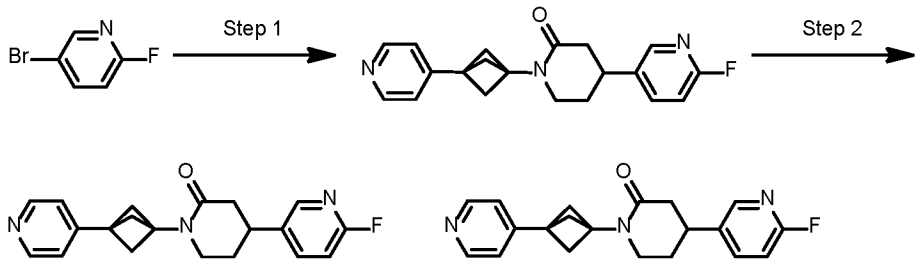
4-(3,4-Difluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (180 mg, 0.51 mmol) was separated by chiral SFC (Chiralpak AY (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 85/15; 150 mL/min) to afford 4-(3,4-difluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex. 34a**, peak 1, Rt = 3.719 min, 32.1 mg, 18% yield) and 4-(3,4-difluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 34b**, peak 2, Rt =3.786 min, 21.2 mg, 12% yield) both as white solids.

Example 34a: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.49 (d, J = 6.0 Hz, 2H), 7.44 - 7.32 (m, 2H), 7.28 - 7.23 (m, 2H), 7.15 - 7.10 (m, 1H), 3.42 - 3.33 (m, 2H), 3.13 - 3.05 (m, 1H), 2.47 - 2.37 (m, 8H), 2.05 - 1.85 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 355.1.

Example 34b: ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.49 (d, J = 4.8 Hz, 2H), 7.43 - 7.33 (m, 2H), 7.28 - 7.23 (m, 2H), 7.16 - 7.10 (m, 1H), 3.42 - 3.34 (m, 2H), 3.14 - 3.04 (m, 1H), 2.44 - 2.35 (m, 8H), 2.04 - 1.85 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 355.1.

Examples 35a and 35b

Step 1: *Synthesis of 4-(6-Fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one*



4-(6-Fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex. 36a and Ex. 36b** by replacing 5-bromo-2-chloro-3-fluoro-pyridine with 5-bromo-2-fluoropyridine in step 1.

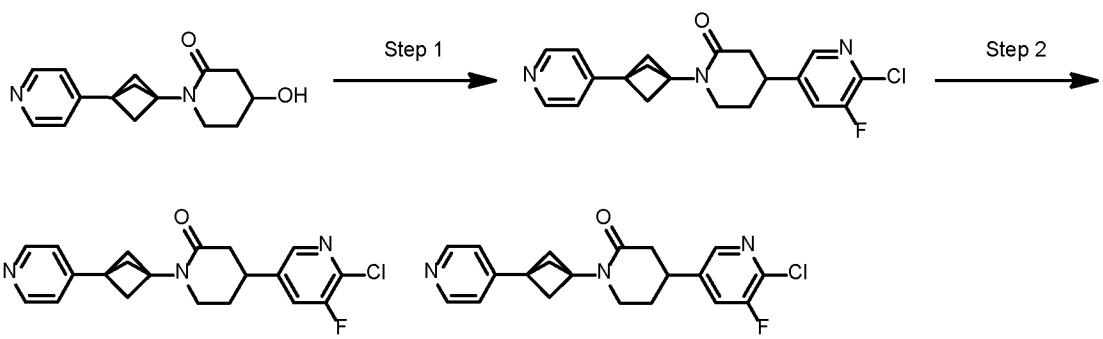
Step 2: *Chiral Separation of 4-(6-Fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (Ex 35a & 35b)*

4-(6-Fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (108 mg, 0.32 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / MeOH + 0.1% NH_4OH = 70/30; 150 mL/min) to give 4-(6-fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 35a**, peak 1, Rt = 1.316 min, 42 mg, 39% yield) and 4-(6-fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 35b**, peak 2, Rt = 1.737 min, 37 mg, 34% yield) both as white solids.

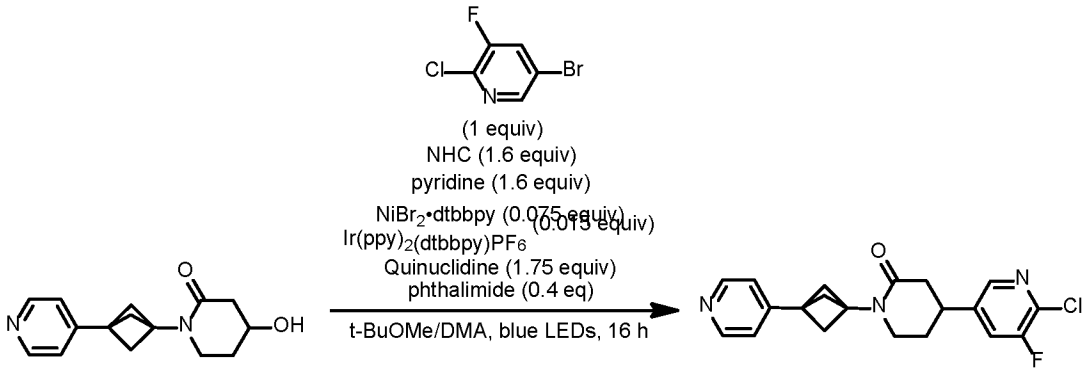
Example 35a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.50 (d, J = 6.0 Hz, 2H), 8.16 (d, J = 2.4 Hz, 1H), 7.98 - 7.91 (m, 1H), 7.31 - 7.23 (m, 2H), 7.18 - 7.13 (m, 1H), 3.44 - 3.35 (m, 2H), 3.22 - 3.11 (m, 1H), 2.48 - 2.38 (m, 8H), 2.07 - 1.90 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 338.2

Example 35b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.54 - 8.46 (m, 2H), 8.16 (d, J = 1.6 Hz, 1H), 7.98 - 7.91 (m, 1H), 7.29 - 7.23 (m, 2H), 7.18 - 7.13 (m, 1H), 3.45 - 3.35 (m, 2H), 3.22 - 3.11 (m, 1H), 2.48 - 2.38 (m, 8H), 2.07 - 1.90 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 338.1

Examples 36a and 36b



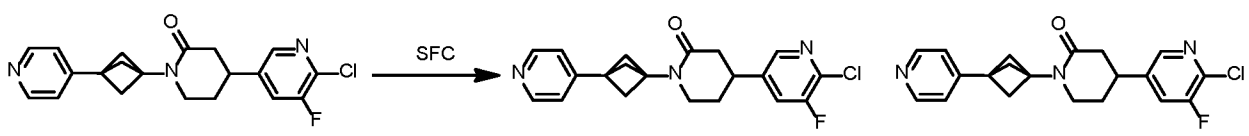
Step 1: *Synthesis of 4-(6-chloro-5-fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one*



A solution of 4-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (200 mg, 0.77 mmol) and 5,7-di-*tert*-butyl-3-phenylbenzo[*d*]oxazol-3-ium tetrafluoroborate (NHC, 490 mg, 1.24 mmol) in t-BuOMe (4 mL) was stirred at room temperature for 5 minutes under nitrogen atmosphere. Then pyridine (0.1 mL, 1.24 mmol) in *t*-BuOMe (2 mL) was added dropwise at room temperature over the course of 5 minutes. The resulting solution was stirred at room temperature for 20 minutes under nitrogen atmosphere, a pink solid precipitated out during this time. Then the solution was filtered and the filtrate was added into another mixture of 5-bromo-2-chloro-3-fluoro-pyridine (155 mg, 0.74 mmol), $NiBr_2$·dtbbpy (27 mg, 0.06 mmol), quinuclidine (144 mg, 1.29 mmol), phthalimide (43 mg, 0.30 mmol) and $Ir(ppy)_2(dtbbpy)PF_6$ (10 mg, 0.01 mmol) in DMA (2 mL) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 16 hours under 450 nm LED modules at 100% light intensity with maxed fan speed of 1500 rpm stirring rate in a PennOC Integrated Photoreactor. The reaction was diluted with water (10 mL) and extracted with ethyl acetate (10 mL x 2). The organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 80 to 100% ethyl acetate in petroleum ether) to afford 4-(6-chloro-5-fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (140 mg, 49% yield) as a yellow solid.

LCMS: (ESI, m/z) $[M+H]^+ = 372.0$

Step 2: *Chiral Separation of 4-(6-Chloro-5-fluoro-3-pyridyl)-1-[3-(4-pyridyl)-1-bicyclo[1.1.1]pentanyl]piperidin-2-one (Ex 36a & 36b)*

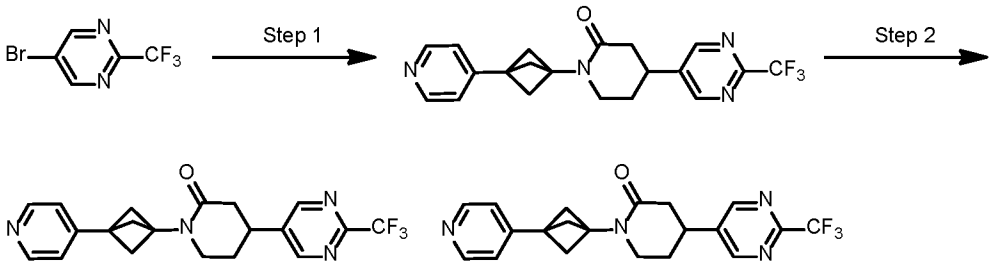


4-(6-Chloro-5-fluoro-3-pyridyl)-1-[3-(4-pyridyl)-1-bicyclo[1.1.1]pentanyl]piperidin-2-one (140 mg, 0.38 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / MeOH + 0.1% NH_4OH = 65/35; 80 mL/min) to afford 4-(6-chloro-5-fluoro-3-pyridyl)-1-[3-(4-pyridyl)-1-bicyclo[1.1.1]pentanyl]piperidin-2-one (**Ex. 36a**, peak 1, Rt = 1.890 min, 35 mg, 24% yield) and 4-(6-chloro-5-fluoro-3-pyridyl)-1-[3-(4-pyridyl)-1-bicyclo[1.1.1]pentanyl]piperidin-2-one (**Ex 36b**, peak 2, Rt = 2.091 min, 38 mg, 27% yield) both as white solids.

Example 36a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.50 (dd, J = 1.6, 4.4 Hz, 2H), 8.26 (d, J = 1.6 Hz, 1H), 7.96 (dd, J = 2.0, 9.6 Hz, 1H), 7.26 (dd, J = 1.6, 4.4 Hz, 2H), 3.47 - 3.36 (m, 2H), 3.27 - 3.16 (m, 1H), 2.49 - 2.46 (m, 2H), 2.41 (s, 6H), 2.10 - 1.90 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 372.1

Example 36b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.50 (dd, J = 1.6, 4.4 Hz, 2H), 8.26 (d, J = 1.6 Hz, 1H), 7.96 (dd, J = 2.0, 9.6 Hz, 1H), 7.26 (dd, J = 1.6, 4.4 Hz, 2H), 3.47 - 3.36 (m, 2H), 3.27 - 3.16 (m, 1H), 2.49 - 2.46 (m, 2H), 2.41 (s, 6H), 2.10 - 1.91 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 372.1

Examples 37a and 37b



Step 1:

1-(3-(Pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(2-(trifluoromethyl)pyrimidin-5-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 36a** and **Ex 36b** by replacing 5-bromo-2-chloro-3-fluoro-pyridine with 5-bromo-2-(trifluoromethyl)pyrimidine in Step 1.

Step 2*: Chiral Separation of 1-(3-(Pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(2-(trifluoromethyl)pyrimidin-5-yl)piperidin-2-one (Ex. 37a & 37b)*

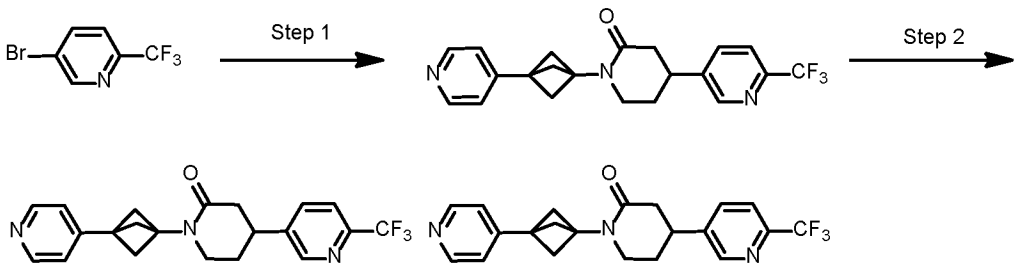
1-(3-(Pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(2-(trifluoromethyl)pyrimidin-5-yl)piperidin-2-one (53 mg, 0.14 mmol) was separated by chiral SFC (Cellulose-2 (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 50/50; 150 mL/min) to afford 1-(3-(pyridin-4-

yl)bicyclo[1.1.1]pentan-1-yl)-4-(2-(trifluoromethyl)pyrimidin-5-yl)piperidin-2-one (**Ex. 37a**, peak 1, Rt = 1.412 min, 25 mg, 47% yield) and 1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(2-(trifluoromethyl)pyrimidin-5-yl)piperidin-2-one (**Ex 37b**, peak 2, Rt = 2.065 min, 22 mg, 41% yield) both as white solids.

Example 37a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 9.04 (s, 2H), 8.50 (d, J = 6.0 Hz, 2H), 7.27 (dd, J = 1.6, 4.4 Hz, 2H), 3.50 - 3.44 (m, 1H), 3.43 - 3.39 (m, 1H), 3.31 - 3.25 (m, 1H), 2.58 (d, J = 8.8 Hz, 2H), 2.46 - 2.39 (m, 6H), 2.18 - 1.97 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 389.2

Example 37b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 9.04 (s, 2H), 8.50 (d, J = 6.0 Hz, 2H), 7.27 (d, J = 6.0 Hz, 2H), 3.50 - 3.43 (m, 1H), 3.42 - 3.39 (m, 1H), 3.31 - 3.26 (m, 1H), 2.58 (d, J = 8.8 Hz, 2H), 2.46 - 2.39 (m, 6H), 2.18 - 1.98 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 389.2

Examples 38a and 38b



Step 1: *Synthesis of 1-(3-(Pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)piperidin-2-one*

1-(3-(Pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex. 36a** and **Ex. 36b** by replacing 5-bromo-2-chloro-3-fluoro-pyridine with 5-bromo-2-(trifluoromethyl)pyridine in Step 1.

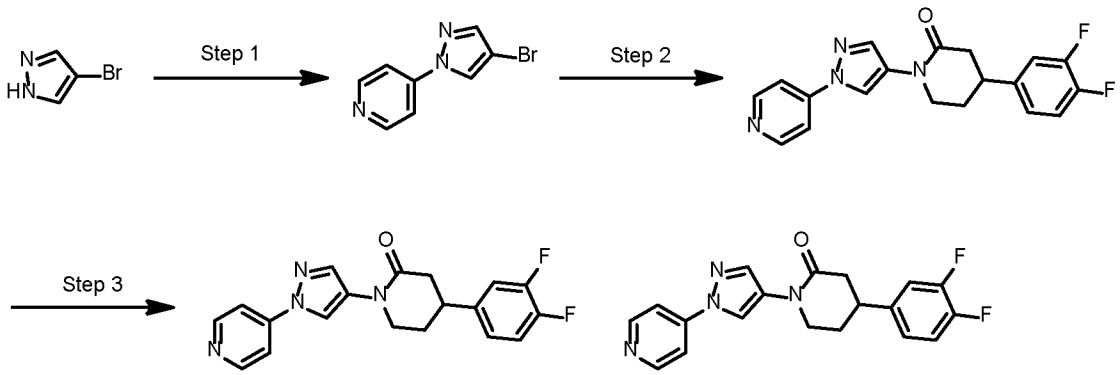
Step 2*: Chiral Separation of 1-(3-(Pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)piperidin-2-one (Ex. 38a & 38b)*

1-(3-(Pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)piperidin-2-one (80 mg, 0.21 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / MeOH + 0.1% NH_4OH = 70/30; 70 mL/min) to afford 1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)piperidin-2-one (**Ex. 38a**, peak 1, Rt = 2.966 min, 21.8 mg, 27% yield) and 1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)piperidin-2-one (**Ex 38b**, peak 2, Rt = 3.210 min, 21 mg, 26% yield) both as white solids.

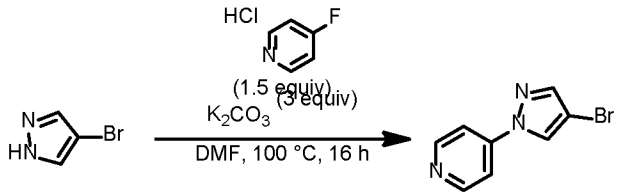
Example 38a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.73 (d, J = 1.6 Hz, 1H), 8.50 (dd, J = 1.6, 4.4 Hz, 2H), 8.02 (dd, J = 1.6, 8.0 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.26 (dd, J = 1.6, 4.4 Hz, 2H), 3.47 - 3.40 (m, 2H), 3.31 - 3.23 (m, 1H), 2.54 - 2.50 (m, 2H), 2.42 (s, 6H), 2.13 - 1.95 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 388.0.

Example 38b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.73 (d, J = 1.6 Hz, 1H), 8.50 (d, J = 6.0 Hz, 2H), 8.02 (dd, J = 1.6, 8.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 4.4 Hz, 2H), 3.47 - 3.36 (m, 2H), 3.30 - 3.23 (m, 1H), 2.57 - 2.51 (m, 2H), 2.45 - 2.38 (m, 6H), 2.12 - 1.96 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 388.1.

Examples 39a and 39b



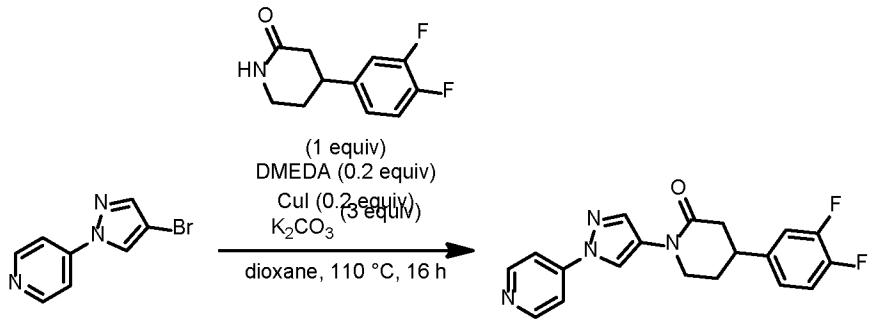
Step 1: *Synthesis of 4-(4-bromopyrazol-1-yl)pyridine*



A solution of 4-bromo-1*H*-pyrazole (5.0 g, 34 mmol) and K_2CO_3 (14.1 g, 102 mmol) in DMF (50 mL) was added 4-fluoropyridine hydrochloride (6.82 g, 51 mmol). The reaction mixture was stirred at 100 °C for 16 hours. After cooling to room temperature, the reaction mixture was poured into H_2O (200 mL) and extracted with ethyl acetate (200 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 0-20% ethyl acetate in petroleum ether) to afford 4-(4-bromopyrazol-1-yl)pyridine (4.8 g, 63% yield) as a white solid.

^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 9.01 (s, 1H), 8.68 - 8.64 (m, 2H), 8.00 (s, 1H), 7.86 - 7.82 (m, 2H).

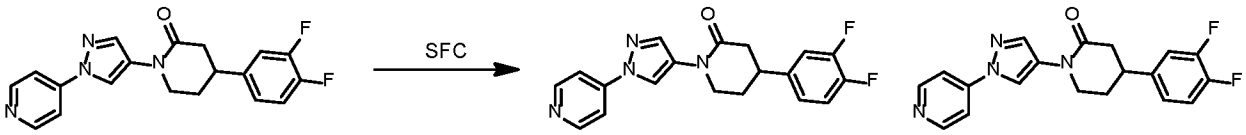
Step 2: *Synthesis of afford 4-(3,4-difluorophenyl)-1-(1-(pyridin-4-yl)-1H-pyrazol-4-yl)piperidin-2-one*



To a mixture of 4-(4-bromopyrazol-1-yl)pyridine (424 mg,1.89 mmol), 4-(3,4-difluorophenyl)piperidin-2-one (400 mg, 1.89 mmol) in 1,4-dioxane (4 mL) was added DMEDA (0.04 mL, 0.38 mmol), CuI (72 mg, 0.38 mmol) and K_2CO_3 (785 mg, 5.68 mmol). The mixture was stirred at 110 °C for 16 hours under nitrogen atmosphere. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 50-70% ethyl acetate in petroleum ether) to afford 4-(3,4-difluorophenyl)-1-(1-(pyridin-4-yl)-1*H*-pyrazol-4-yl)piperidin-2-one (400 mg, 60% yield) as a yellow solid.

LCMS: (ESI, m/z) $[M+H]^+ = 371.0$

Step 3: *Chiral Separation of 4-(3,4-Difluorophenyl)-1-(1-(pyridin-4-yl)-1H-pyrazol-4-yl)piperidin-2-one (Ex. 39a & 39b)*



4-(3,4-Difluorophenyl)-1-(1-(pyridin-4-yl)-1*H*-pyrazol-4-yl)piperidin-2-one (400 mg, mmol) was separated by chiral SFC (Chiralpak IC (250 × 30 mm, 5 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 75/25; 50 mL/min) to give peak 1 (150 mg crude) and peak 2 (150 mg crude).

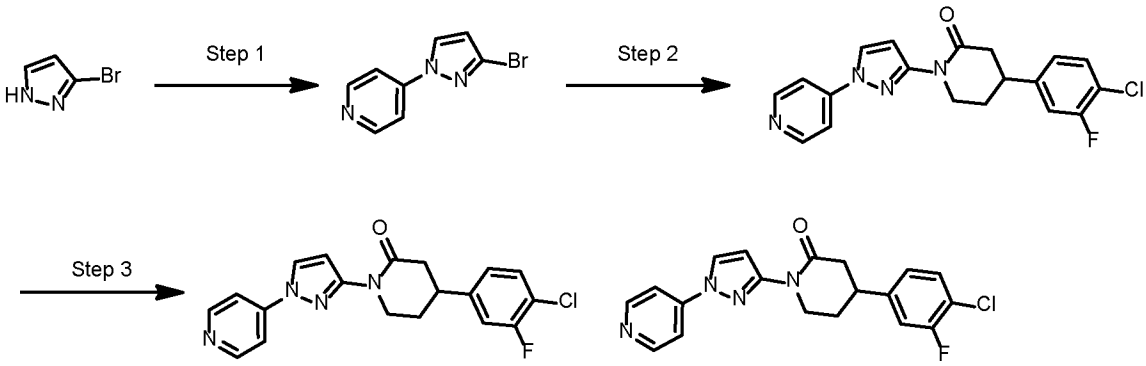
The peak 1 was purified by reverse phase chromatography (acetonitrile: 47-77% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to afford 4-(3,4-difluorophenyl)-1-(1-(pyridin-4-yl)-1*H*-pyrazol-4-yl)piperidin-2-one (**Ex. 39a**, peak 1, Rt = 3.017 min, 96.7 mg, 24% yield) as a white solid.

Example 39a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.87 (s, 1H), 8.65 - 8.61 (m, 2H), 8.26 (s, 1H), 7.88 - 7.84 (m, 2H), 7.51 - 7.36 (m, 2H), 7.21 - 7.16 (m, 1H), 3.85 - 3.75 (m, 2H), 3.28 - 3.22 (m, 1H), 2.72 - 2.64 (m, 2H), 2.20 - 2.09 (m, 2H). **LCMS**: (ESI, m/z) [M+H] = 355.1

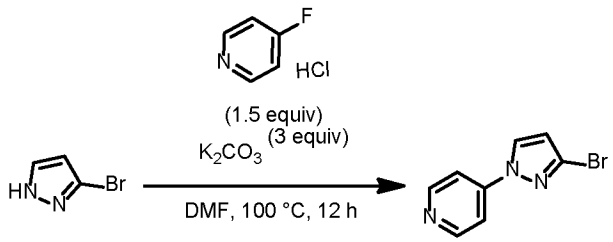
The peak 2 was purified by reverse phase chromatography (acetonitrile: 47-77% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to afford 4-(3,4-difluorophenyl)-1-(1-(pyridin-4-yl)-1*H*-pyrazol-4-yl)piperidin-2-one (**Ex 39b,** peak 2, Rt = 3.567 min, 101.1 mg, 25% yield) as a white solid.

Example 39b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.87 (s, 1H), 8.65 - 8.61 (m, 2H), 8.26 (s, 1H), 7.88 - 7.84 (m, 2H), 7.51 - 7.36 (m, 2H), 7.21 - 7.16 (m, 1H), 3.85 - 3.75 (m, 2H), 3.28 - 3.22 (m, 1H), 2.74 - 2.65 (m, 2H), 2.20 - 2.09 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 355.0

Examples 40a and 40b



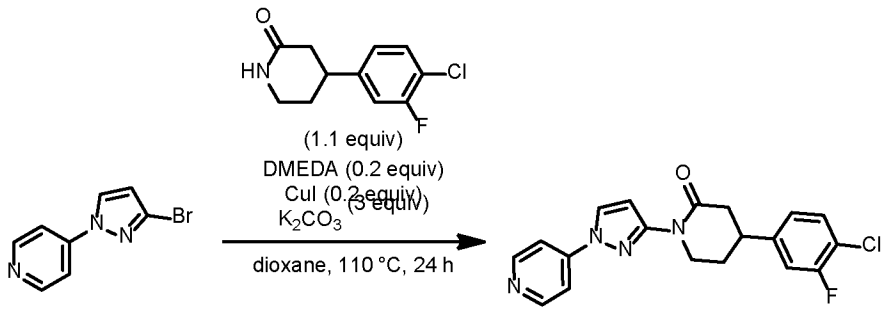
Step 1: *Synthesis of 4-(3-bromopyrazol-1-yl)pyridine*



To a mixture of 3-bromo-1*H*-pyrazole (2.0 g, 13.61 mmol) and K_2CO_3 (5.64 g, 40.82 mmol) in DMF (50 mL) was added and 4-fluoropyridine hydrochloride (2.72 g, 20.41 mmol). The mixture was stirred at 100 °C for 12 hours under nitrogen atmosphere. After cooling to room temperature, the mixture was poured into water (50 mL) and extracted with EtOAc (45 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 20% EtOAc in petroleum ether) to give 4-(3-bromopyrazol-1-yl)pyridine (1.4 g, 46% yield) as a yellow solid.

^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.72 (d, J = 2.4 Hz, 1H), 8.66 (d, J = 5.6 Hz, 2H), 7.82 (d, J = 6.4 Hz, 2H), 6.81 (d, J = 2.8 Hz, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 223.9

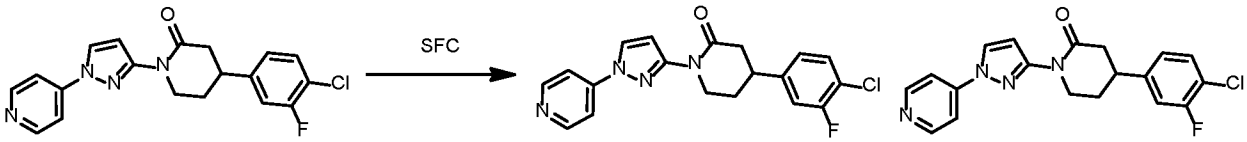
Step 2: *Synthesis of 4-(4-chloro-3-fluorophenyl)-1-(1-(pyridin-4-yl)-1H-pyrazol-3-yl)piperidin-2-one*



To a mixture of 4-(3-bromo-1*H*-pyrazol-1-yl)pyridine (300 mg, 1.34 mmol), 4-(4-chloro-3-fluorophenyl)piperidin-2-one (335 mg, 1.47 mmol) in 1,4-dioxane (8 mL) was added DMEDA (0.03 mL, 0.27 mmol), CuI (51 mg, 0.27 mmol) and K_2CO_3 (555 mg, 4.02 mmol). The mixture was stirred at 110 °C for 24 hours under nitrogen atmosphere. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 43-63% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to give 4-(4-chloro-3-fluorophenyl)-1-(1-(pyridin-4-yl)-1*H*-pyrazol-3-yl)piperidin-2-one (110 mg, 22% yield) as a white solid.

LCMS: (ESI, m/z) $[M+H]^+$ = 371.0

Step 3: *Chiral Separation of 4-(4-Chloro-3-fluorophenyl)-1-(1-(pyridin-4-yl)-1H-pyrazol-3-yl)piperidin-2-one (Ex. 40a & 40b)*

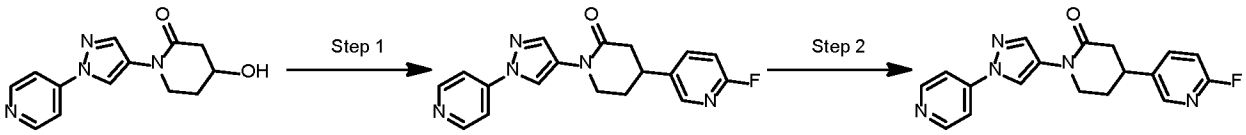


4-(4-Chloro-3-fluorophenyl)-1-(1-(pyridin-4-yl)-1*H*-pyrazol-3-yl)piperidin-2-one (110 mg, 0.30 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 60/40; 80 mL/min) to give 4-(4-chloro-3-fluorophenyl)-1-(1-(pyridin-4-yl)-1*H*-pyrazol-3-yl)piperidin-2-one (**Ex. 40a**, peak 1, Rt = 1.446 min, 32.6 mg, 29% yield) and 4-(4-chloro-3-fluorophenyl)-1-(1-(pyridin-4-yl)-1*H*-pyrazol-3-yl)piperidin-2-one (**Ex. 40b**, peak 2, Rt = 1.969 min, 31.4 mg, 28% yield) both as a white solid. **Ex 40b was inactive in both of the assays.**

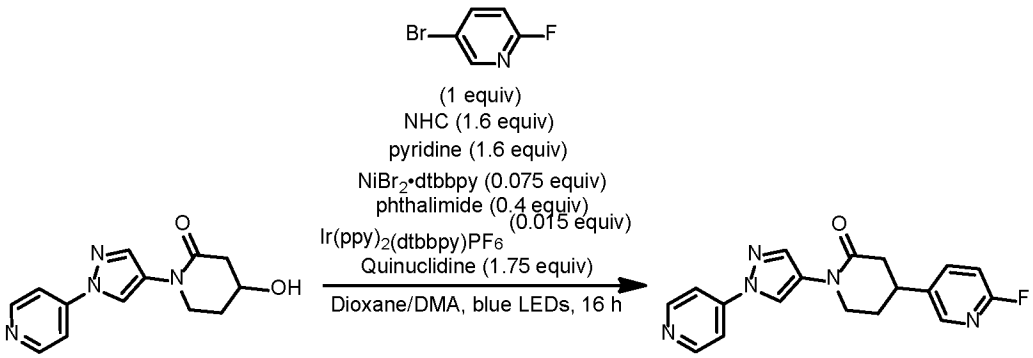
Example 40a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.66 (d, J = 2.8 Hz, 1H), 8.64 - 8.58 (m, 2H), 7.85 - 7.77 (m, 2H), 7.56 (t, J = 8.4 Hz, 1H), 7.46 - 7.43 (m, 1H), 7.23 - 7.21 (m, 1H), 7.08 (d, J = 2.8 Hz, 1H), 4.23 - 4.13 (m, 1H), 3.92 - 3.80 (m, 1H), 3.29 - 3.25 (m, 1H), 2.76 - 2.68 (m, 2H), 2.23 - 2.04 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 371.0

Example 40b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.66 (d, J = 2.8 Hz, 1H), 8.61 (d, J = 6.0 Hz, 2H), 7.86 - 7.77 (m, 2H), 7.56 (t, J = 8.0 Hz, 1H), 7.46 - 7.42 (m, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 2.8 Hz, 1H), 4.25 - 4.13 (m, 1H), 3.89 - 3.82 (m, 1H), 3.32 - 3.25 (m, 1H), 2.79 - 2.67 (m, 2H), 2.25 - 2.05 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 371.0

Examples 41a and 41b



Step 1: *Synthesis of 4-(6-fluoropyridin-3-yl)-1-(1-(pyridin-4-yl)-1H-pyrazol-4-yl)piperidin-2-one*

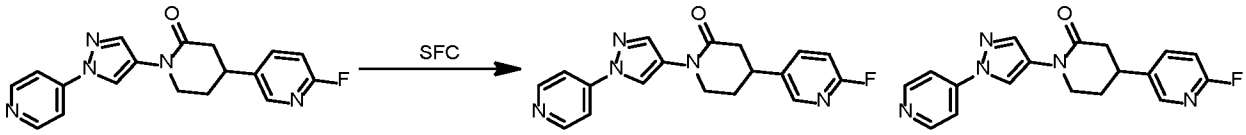


A solution of 4-hydroxy-1-(1-(pyridin-4-yl)-1*H*-pyrazol-4-yl)piperidin-2-one (200 mg, 0.77 mmol) and NHC (490 mg, 1.24 mmol) in dioxane (3 mL) and DMA (0.2 mL) was stirred at room temperature for 5 minutes under nitrogen atmosphere. Then pyridine (0.33 mL, 4.12 mmol) in Dioxane (1 mL) was added dropwise over the course of 5 minutes. The resulting solution was stirred at room temperature for 20 minutes under nitrogen atmosphere. A pink solid precipitated out during this time. Then the solution was filtered and the filtrate was added into another mixture of 5-bromo-2-fluoropyridine (135 mg, 0.77 mmol), $NiBr_2$·dtbbpy (28 mg, 0.06 mmol), phthalimide (45 mg, 0.31 mmol), quinuclidine (149 mg, 1.34 mmol) and $Ir(ppy)_2(dtbbpy)PF_6$ (11 mg, 0.01 mmol) in DMA (2 mL) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 16 hours under 450 nm LED modules at 100% light intensity with maxed fan speed of 1500 rpm stirring rate in a PennOC Integrated Photoreactor. The reaction was diluted with water (10 mL) and extracted with ethyl acetate (10 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 25-55% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water)

to afford 4-(6-fluoropyridin-3-yl)-1-(1-(pyridin-4-yl)-1*H*-pyrazol-4-yl)piperidin-2-one (25 mg, 10% yield) as a white solid.

LCMS: (ESI, m/z) $[M+H]^+ = 338.1$

Step 2: *Chiral Separation of 4-(6-Fluoropyridin-3-yl)-1-(1-(pyridin-4-yl)-1H-pyrazol-4-yl)piperidin-2-one (Ex. 41a & 41b)*

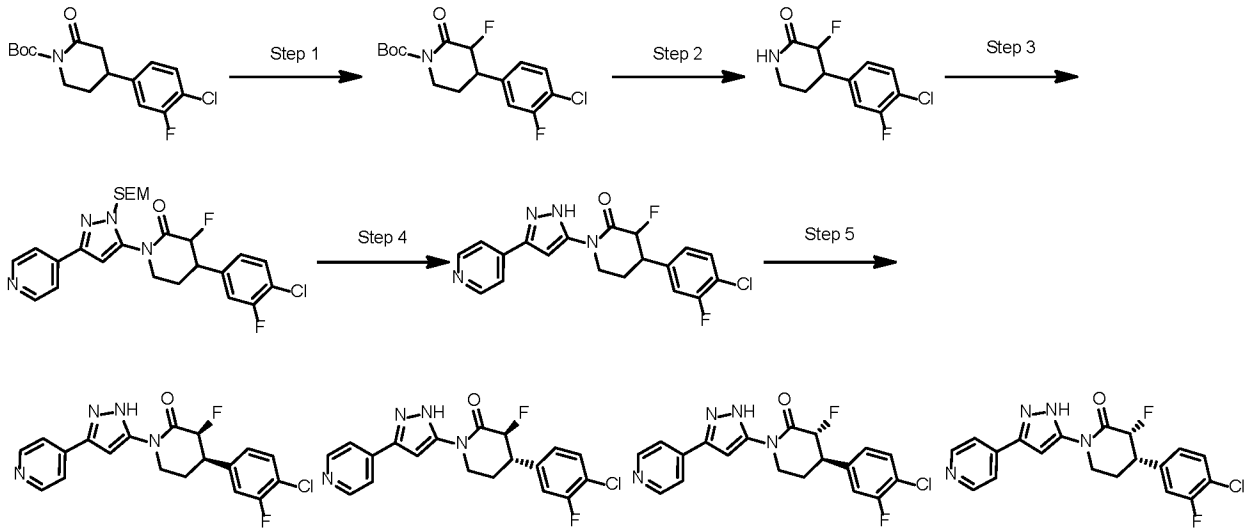


4-(6-Fluoropyridin-3-yl)-1-(1-(pyridin-4-yl)-1*H*-pyrazol-4-yl)piperidin-2-one (45 mg, 0.13 mmol) was separated by chiral SFC (Chiralpak IH (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 50/50; 100 mL/min) to afford 4-(6-fluoropyridin-3-yl)-1-(1-(pyridin-4-yl)-1*H*-pyrazol-4-yl)piperidin-2-one (**Ex. 41a**, peak 1, Rt = 1.460 min, 25.3 mg, 45% yield) and 4-(6-fluoropyridin-3-yl)-1-(1-(pyridin-4-yl)-1*H*-pyrazol-4-yl)piperidin-2-one (**Ex 41b**, peak 2, Rt = 2.095 min, 20.2 mg, 44% yield) both as white solids.

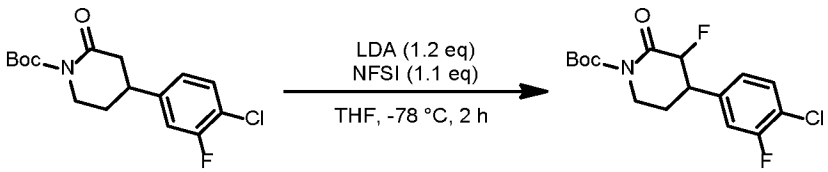
Example 41a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.87 (s, 1H), 8.63 (d, J = 5.6 Hz, 2H), 8.26 (s, 1H), 8.22 (s, 1H), 8.05 - 7.95 (m, 1H), 7.86 (d, J = 5.6 Hz, 2H), 7.18 (dd, J = 2.4, 8.4 Hz, 1H), 3.92 - 3.72 (m, 2H), 3.33 - 3.27 (m, 1H), 2.79 - 2.65 (m, 2H), 2.25 - 2.10 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+ = 338.2$

Example 41b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.87 (s, 1H), 8.63 (d, J = 5.6 Hz, 2H), 8.26 (s, 1H), 8.22 (d, J = 1.6 Hz, 1H), 8.05 - 7.95 (m, 1H), 7.86 (d, J = 6.0 Hz, 2H), 7.18 (dd, J = 2.8, 8.4 Hz, 1H), 3.91 - 3.76 (m, 2H), 3.34 - 3.26 (m, 1H), 2.79 - 2.66 (m, 2H), 2.25 - 2.11 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+ = 338.1$

Examples 42a, 42b, 42c and 42d



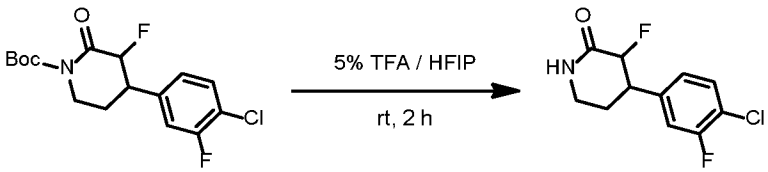
Step 1: *Synthesis of tert-butyl 4-(4-chloro-3-fluoro-phenyl)-3-fluoro-2-oxo-piperidine-1-carboxylate*



To a solution of *tert*-butyl 4-(4-chloro-3-fluoro-phenyl)-2-oxo-piperidine-1-carboxylate (1.0 g, 3.05 mmol) in THF (10 mL) was added LDA (2 M, 1.83 mL, 3.66 mmol) at -78 °C dropwise under nitrogen atmosphere. After stirring at -78 °C for 0.5 hour, a solution of NFSI (1.06 g, 3.36 mmol) in THF (5 mL) was added dropwise at -78 °C. After stirring at -78 °C for 1 hour, the reaction was quenched with saturated ammonium chloride solution (10 mL) and then extracted with ethyl acetate (20 mL x 2). The combined organic phases were washed with brine (20 mL), and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, 20% ethyl acetate in petroleum ether) to afford *tert*-butyl 4-(4-chloro-3-fluoro-phenyl)-3-fluoro-2-oxo-piperidine-1-carboxylate (650 mg, 62% yield) as a white solid.

LCMS: (ESI, m/z) $[M+H-56]^+ = 290.0$

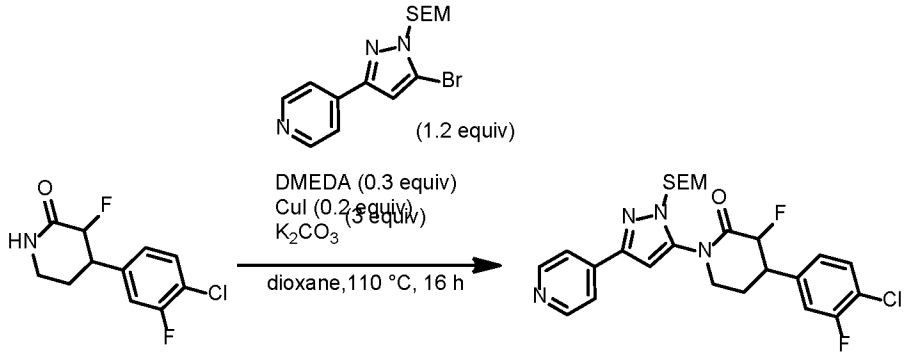
Step 2: *Synthesis of 4-(4-chloro-3-fluoro-phenyl)-3-fluoro-piperidin-2-one*



A solution of *tert*-butyl 4-(4-chloro-3-fluoro-phenyl)-3-fluoro-2-oxo-piperidine-1-carboxylate (650 mg, 1.88 mmol) in 5% TFA / HFIP solution (8 mL) was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in DCM (10 mL), and then was adjusted to pH = 8 with saturated $NaHCO_3$ solution. The aqueous phase was extracted with dichloromethane (10 mL x 2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford 4-(4-chloro-3-fluoro-phenyl)-3-fluoro-piperidin-2-one (450 mg, 97% yield) as a white solid.

LCMS: (ESI, m/z) $[M+H]^+$ = 246.1

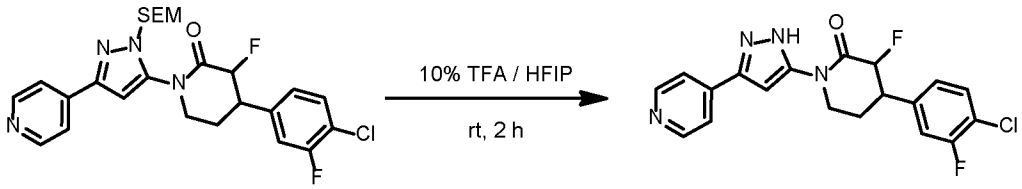
Step 3: *Synthesis of 4-(4-chloro-3-fluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)piperidin-2-one*



To a mixture of 4-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)pyridine (346 mg, 0.98 mmol), 4-(4-chloro-3-fluoro-phenyl)-3-fluoro-piperidin-2-one (200 mg, 0.81 mmol) in 1,4-dioxane (8 mL) was added DMEDA (26 uL, 0.24 mmol), CuI (31 mg, 0.16 mmol) and potassium carbonate (337 mg, 2.44 mmol) was added under nitrogen atmosphere. Then the mixture was stirred at 110 °C for 16 hours. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, 30 to 35% ethyl acetate in petroleum ether) to afford 4-(4-chloro-3-fluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one (347 mg, 82% yield) as a white solid.

LCMS: (ESI, m/z) $[M+H]^+$ = 519.2

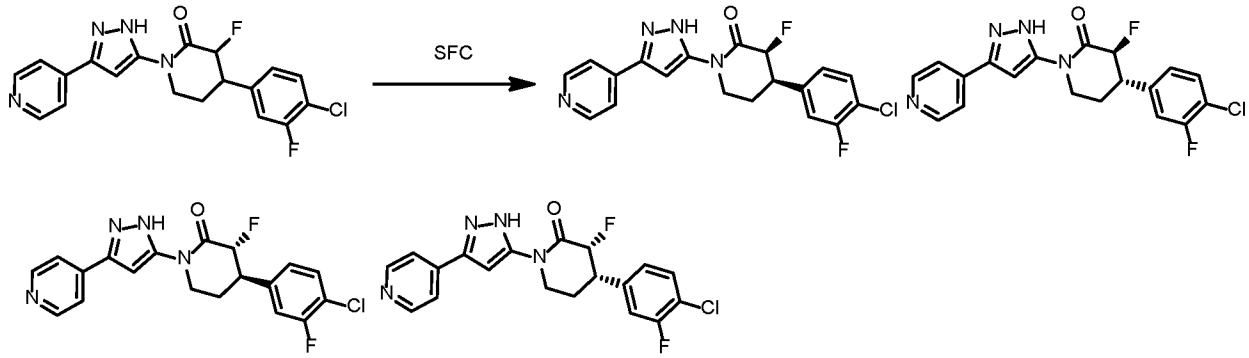
Step 4: *Synthesis of 4-(4-chloro-3-fluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one*



A solution of 4-(4-chloro-3-fluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one (660 mg, 1.27 mmol) in 10% TFA / HFIP solution (10 mL) was stirred at 25 °C for 2 hours. The mixture was concentrated under reduced pressure. The residue was dissolved in DCM (8 mL), and then treated with aqueous saturated $NaHCO_3$ until pH = 8. The organic phase was separated, and the aqueous phase was extracted with DCM (5 mL x 2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced. The crude was purified by reverse phase chromatography (acetonitrile: 45-75% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to afford 4-(4-chloro-3-fluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (350 mg, 70% yield) as a white solid.

LCMS: (ESI, m/z) $[M+H]^+$ = 389.1

Step 5: *Chiral Separation of 4-(4-chloro-3-fluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Ex. 42a, 42b, 42c, & 42d)*



4-(4-chloro-3-fluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (350 mg, 0.90 mmol) was separated by chiral SFC (Chiralpak IC (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 55/45; 80 mL/min) to afford *cis*-4-(4-chloro-3-fluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (peak 1, 40 mg crude) and *trans*-4-(4-chloro-3-fluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex. 42b**, peak 2, Rt = 3.108 min, 113 mg, 32% yield) and a mixture of peak 3 and peak 4 (160 mg) as white solid. The peak 1 was purified by reverse phase chromatography (acetonitrile: 48-78% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to afford *cis*-4-(4-chloro-3-fluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex. 42a**, peak 1, Rt = 1.878 min, 26 mg, 7% yield) as a white solid. The peak 3 was separated by chiral SFC (Chiralcel OJ (250 mm x 30 mm, 10 um),

Supercritical CO_2 / *i*-PrOH + 0.1% NH_4OH = 55/45; 80 mL/min) to afford *trans*-4-(4-chloro-3-fluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 42c**, peak 3, Rt = 3.787 min, 95 mg, 27% yield) as a white solid. The peak 4 was separated by chiral SFC (Chiralpak IC (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 50/50; 80 mL/min) to afford *cis*-4-(4-chloro-3-fluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 42d**, peak 4, Rt = 4.396 min, 20 mg, 6% yield) as a white solid. Their relative configurations were confirmed by 2D NMR.

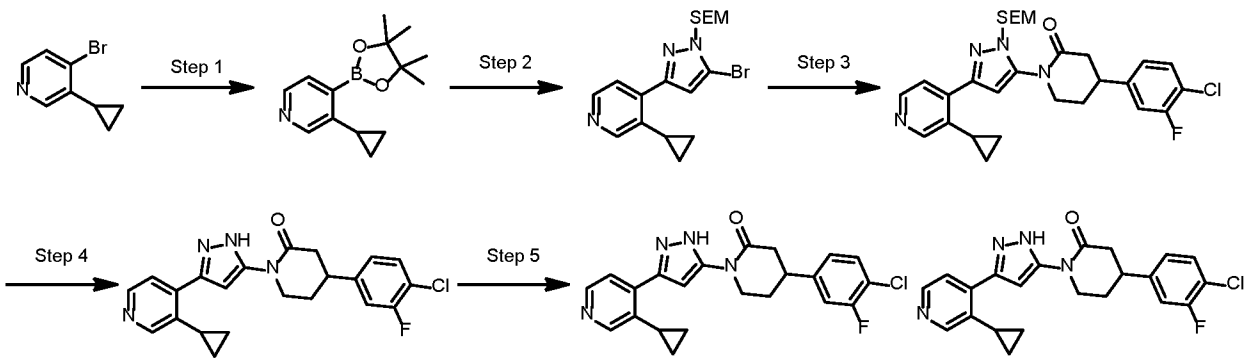
Example 42a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.51 (s, 1H), 8.65 (d, J = 4.4 Hz, 2H), 7.74 (d, J = 5.2 Hz, 2H), 7.60 (t, J = 8.0 Hz, 1H), 7.41 (d, J = 10.4 Hz, 1H), 7.33 (s, 1H), 7.22 (d, J = 8.0 Hz, 1H), 5.22 (dd, J = 3.2, 47.6 Hz, 1H), 4.17 - 4.04 (m, 1H), 3.91 - 3.81 (m, 1H), 3.80 - 3.65 (m, 1H), 2.40 - 2.31 (m, 1H), 2.26 - 2.17 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 389.0

Example 42b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.47 (br s, 1H), 8.65 (d, J = 5.6 Hz, 2H), 7.74 (d, J = 5.6 Hz, 2H), 7.60 (t, J = 8.0 Hz, 1H), 7.53 (d, J = 10.4 Hz, 1H), 7.33 - 7.26 (m, 2H), 5.37 (dd, J = 11.2, 47.6 Hz, 1H), 4.14 - 4.03 (m, 1H), 3.97 - 3.84 (m, 1H), 3.63 - 3.47 (m, 1H), 2.36 - 2.24 (m, 1H), 2.22 - 2.11 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 389.0

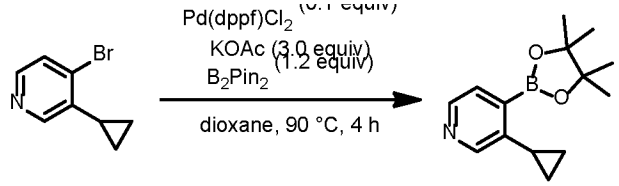
Example 42c: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.47 (br s, 1H), 8.65 (d, J = 5.2 Hz, 2H), 7.74 (d, J = 5.6 Hz, 2H), 7.59 (t, J = 8.0 Hz, 1H), 7.57 - 7.50 (m, 1H), 7.35 - 7.26 (m, 2H), 5.37 (dd, J = 11.2, 47.6 Hz, 1H), 4.15 - 4.03 (m, 1H), 3.95 - 3.84 (m, 1H), 3.61 - 3.48 (m, 1H), 2.34 - 2.24 (m, 1H), 2.20 - 2.11 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 389.0

Example 42d: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.49 (br s, 1H), 8.64 (d, J = 6.0 Hz, 2H), 7.75 (d, J = 6.0 Hz, 2H), 7.60 (t, J = 8.0 Hz, 1H), 7.41 (d, J = 9.2 Hz, 1H), 7.33 (s, 1H), 7.22 (d, J = 8.4 Hz, 1H), 5.22 (dd, J = 3.2, 47.2 Hz, 1H), 4.18 - 4.02 (m, 1H), 3.91 - 3.81 (m, 1H), 3.80 - 3.66 (m, 1H), 2.43 - 2.29 (m, 1H), 2.26 - 2.17 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 389.1

Examples 43a and 43b

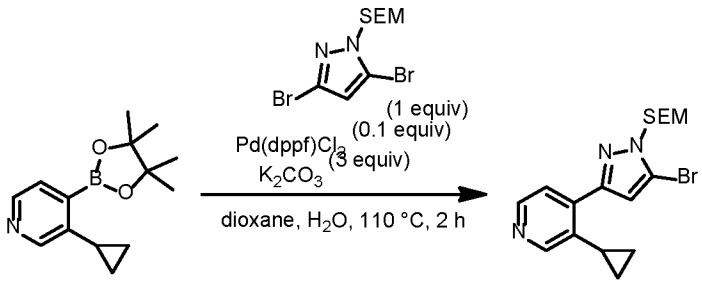


Step 1: *Synthesis of 3-cyclopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine*



A mixture of 4-bromo-3-cyclopropyl-pyridine (5.0 g, 25.2 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (7.7 g, 30.3 mmol), $Pd(dppf)Cl_2$ (1.85 g, 2.5 mmol), KOAc (7.43 g, 75.7 mmol) in 1,4-dioxane (100 mL) was stirred at 90 °C for 4 hours under nitrogen atmosphere. After cooling to room temperature, the resulting mixture was used directly in the next step.

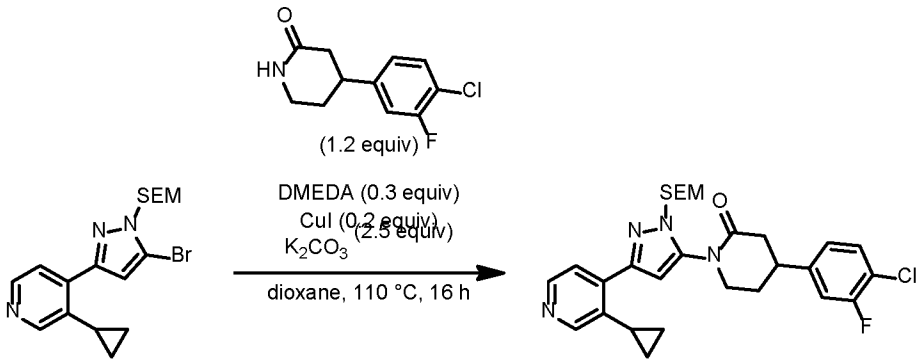
Step 2: *Synthesis of 4-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)-3-cyclopropylpyridine*



To the above solution was added 3,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (8.7 g, 24.5 mmol) in 1,4-dioxane (100 mL) and water (5 mL), K_2CO_3 (10.1 g, 73.4 mmol), $Pd(dppf)Cl_2$ (1.79 g, 2.5 mmol). The mixture was at 110 °C for 2 hours under nitrogen atmosphere. After cooling to room temperature, the was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, filtered and under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 0-17% ethyl acetate in petroleum ether) to give 4-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)-3-cyclopropylpyridine (9 g, 93% yield) as brown liquid.

LCMS: (ESI, m/z) $[M+H]^+ = 394.1$

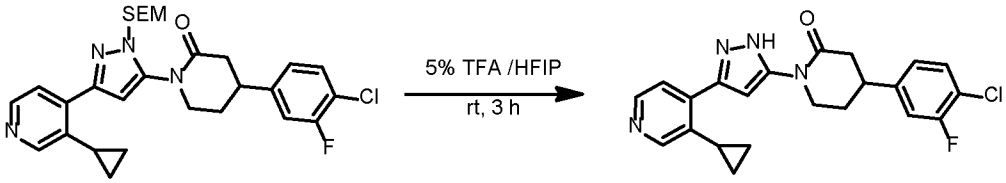
Step 3: *Synthesis of 4-(4-chloro-3-fluorophenyl)-1-(3-(3-cyclopropylpyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)piperidin-2-one*



To a mixture of 4-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)-3-cyclopropylpyridine (600 mg, 1.5 mmol), 4-(4-chloro-3-fluoro-phenyl)piperidin-2-one (416 mg, 1.8 mmol) in 1,4-dioxane (15 mL) was added DMEDA (0.05 mL, 0.5 mmol), CuI (58 mg, 0.3 mmol) and K_2CO_3 (526 mg, 3.8 mmol). Then the mixture was stirred at 110 °C for 16 hours under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was poured into water (5 mL) and extracted with ethyl acetate (10 mL x 2). The combined organic layers were washed with brine (10 mL x 2), dried over anhydrous sodium sulfate, filtered and under reduced pressure. The crude was purified by flash column chromatography (SiO_2, 0-12% EE (25% ethanol in ethyl acetate) in petroleum ether) to afford 4-(4-chloro-3-fluorophenyl)-1-(3-(3-cyclopropylpyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one (250 mg, 30% yield) as a yellow oil.

LCMS: (ESI, m/z) $[M+H]^+ = 541.3$

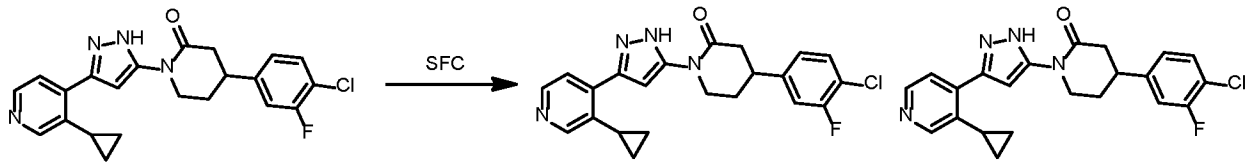
Step 4: *Synthesis of 4-(4-chloro-3-fluorophenyl)-1-(3-(3-cyclopropylpyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one*



A mixture of 4-(4-chloro-3-fluorophenyl)-1-(3-(3-cyclopropylpyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one (270 mg, 0.50 mmol) in 5% TFA / HFIP (10 mL) was stirred at room temperature for 3 hours. The mixture was concentrated and adjust to pH=8 with saturated aqueous $NaHCO_3$ solution. The resulting solution was purified by reverse phase chromatography (acetonitrile: 48-78% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to give 4-(4-chloro-3-fluorophenyl)-1-(3-(3-cyclopropylpyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (60 mg, 29% yield) as white powder.

LCMS: (ESI, m/z) $[M+H]^+ = 411.1$

Step 5: *Chiral Separation of 4-(4-Chloro-3-fluorophenyl)-1-(3-(3-cyclopropylpyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Ex. 43a & 43b)*

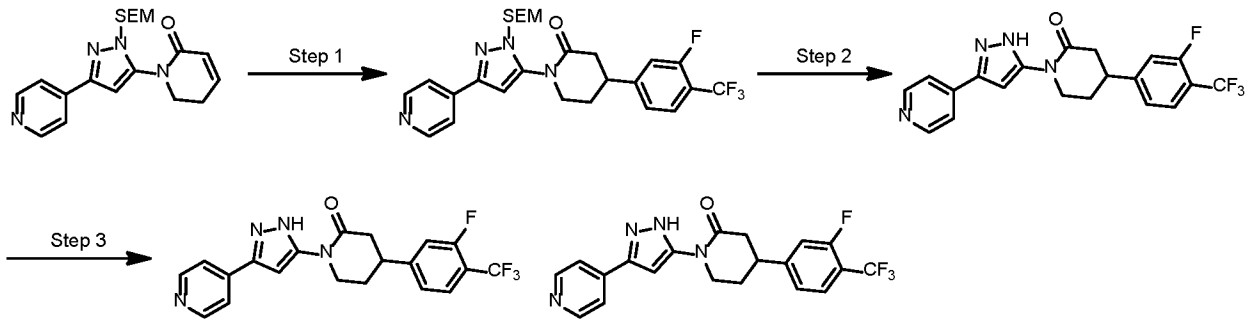


4-(4-Chloro-3-fluorophenyl)-1-(3-(3-cyclopropylpyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (60 mg, 0.15 mmol) was separated by chiral SFC (Chiralpak IG (250 mm x 30 mm, 10 um); Supercritical CO_2 / EtOH + 0.1% NH_4OH = 40/60; 80 mL/min) to give 4-(4-chloro-3-fluorophenyl)-1-(3-(3-cyclopropylpyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex. 43a**, peak 1, Rt = 1.728 min, 17.9 mg, 30% yield) and 4-(4-chloro-3-fluorophenyl)-1-(3-(3-cyclopropylpyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 43b**, peak 2, Rt = 2.397 min, 24.5 mg, 41% yield) both as white solids.

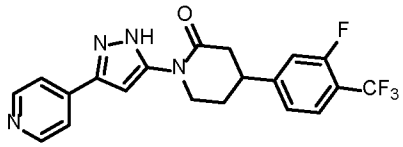
Example 43a: ^{1}**H NMR** (400 MHz, DMSO-d_6): δ 13.07 (s, 1H), 8.47 (d, J = 4.4 Hz, 1H), 8.38 (s, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.51 - 7.39 (m, 2H), 7.29 - 7.18 (m, 2H), 4.15 - 4.03 (m, 1H), 3.86 - 3.78 (m, 1H), 3.29 - 3.25 (m, 1H), 2.76 - 2.65 (m, 2H), 2.22 - 2.03 (m, 3H), 1.02 - 0.95 (m, 2H), 0.84 - 0.77 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 411.1

Example 43b: ^{1}**H NMR** (400 MHz, DMSO-d_6): δ 13.07 (s, 1H), 8.47 (d, J = 4.4 Hz, 1H), 8.38 (s, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.51 - 7.39 (m, 2H), 7.29 - 7.18 (m, 2H), 4.15 - 4.03 (m, 1H), 3.85 - 3.77 (m, 1H), 3.29 - 3.25 (m, 1H), 2.76 - 2.65 (m, 2H), 2.22 - 2.00 (m, 3H), 1.02 - 0.94 (m, 2H), 0.84 - 0.77 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 411.1

Examples 44a and 44b

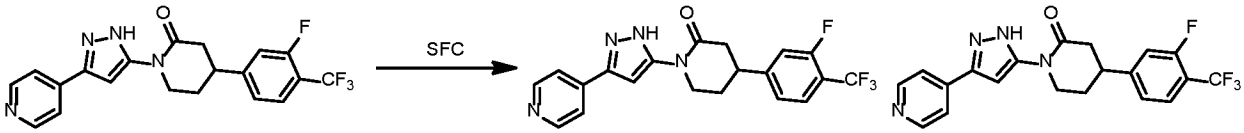


Step 1 — 2: *Synthesis of 4-(3-Fluoro-4-(trifluoromethyl)phenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one*



4-(3-Fluoro-4-(trifluoromethyl)phenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 9a and 9b** by replacing (2-fluorophenyl)boronic acid with (3-fluoro-4-(trifluoromethyl)phenyl)boronic acid in Step 1.

Step 3: *Chiral Separation of 4-(3-Fluoro-4-(trifluoromethyl)phenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Ex. 44a & 44b)*

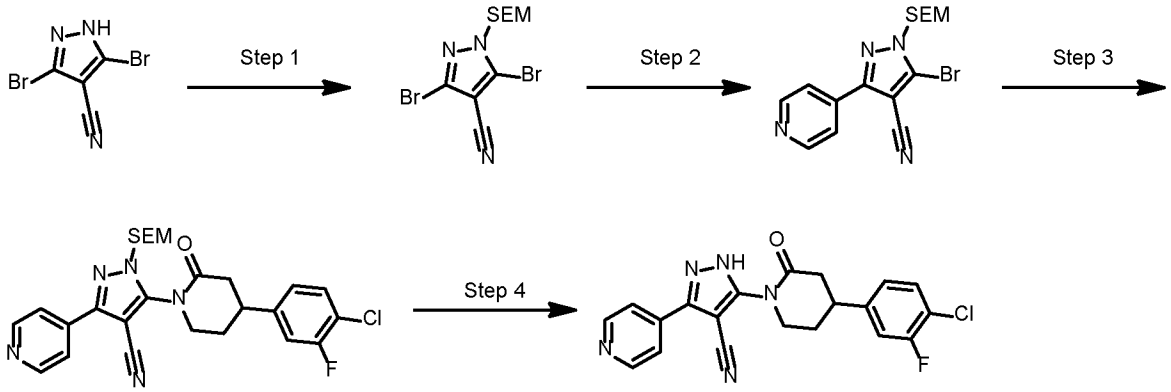


4-(3-Fluoro-4-(trifluoromethyl)phenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (160 mg, 0.40 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 40/60; 80 mL/min) to afford 4-(3-fluoro-4-(trifluoromethyl)phenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 44a**, peak 1, Rt = 1.771 min, 25 mg, 16% yield) and 4-(3-fluoro-4-(trifluoromethyl)phenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 44b**, peak 2, Rt = 2.493 min, 20.1 mg, 13% yield) both as white solids.

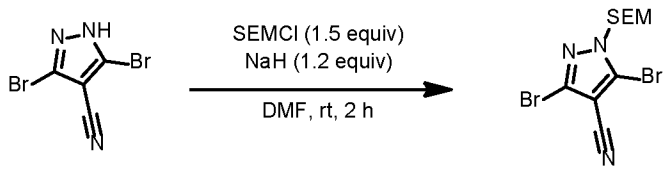
Example 44a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): 13.35 (s, 1H), 8.83 (d, J = 4.4 Hz, 2H), 7.81 - 7.70 (m, 3H), 7.55 (d, J = 12.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.28 (br s, 1H), 4.17 - 3.99 (m, 1H), 3.88 - 3.76 (m, 1H), 3.45 - 3.39 (m, 1H), 2.80 - 2.69 (m, 2H), 2.28 - 2.02 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 405.0

Example 44b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): 13.35 (s, 1H), 8.83 (d, J = 4.4 Hz, 2H), 7.81 - 7.70 (m, 3H), 7.55 (d, J = 12.8 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.28 (br s, 1H), 4.20 - 4.01 (m, 1H), 3.90 - 3.73 (m, 1H), 3.46 - 3.39 (m, 1H), 2.81 - 2.69 (m, 2H), 2.26 - 2.04 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 405.0

Example 45

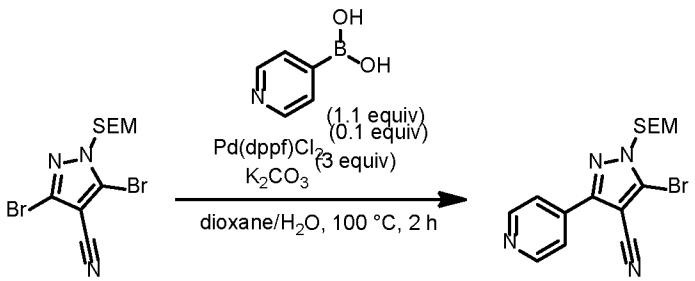


Step 1: *Synthesis of 3,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carbonitrile*



To a stirred solution of 3,5-dibromo-1*H*-pyrazole-4-carbonitrile (2 g, 7.97 mmol) in DMF (20 mL) was added NaH (60% in mineral oil, 229 mg, 9.57 mmol) at 0 °C under nitrogen atmosphere. After stirring at 0 °C for 30 min, SEM-Cl (2 mL, 11.96 mmol) was slowly added. Then the mixture was stirred at room temperature for 2 h. The reaction was quenched with NH_4Cl (10 ml) at 0 °C and diluted with H_2O (10 mL), then extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by by flash column chromatography (SiO_2, 0 - 3% ethyl acetate in petroleum ether) to afford 3,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carbonitrile (2.5 g, 82% yield) as colorless oil.

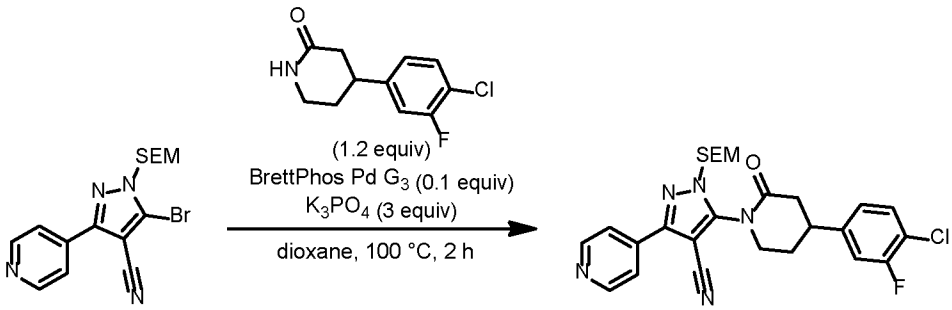
Step 2: *Synthesis of 5-bromo-3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carbonitrile*



To a solution of 3,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carbonitrile (2.35 g, 6.17 mmol) and pyridin-4-ylboronic acid (833 mg, 6.78 mmol) in 1,4-dioxane (20 mL) and water (5 mL) was added $Pd(dppf)Cl_2$ (451 mg, 0.62 mmol) and K_2CO_3 (2.56 g, 18.5 mmol). The mixture was stirred at 100 °C for 2 h under nitrogen atmosphere. The mixture was concentrated in vacuum and the residue was purified by flash column chromatography (SiO_2, 0 - 10% ethyl acetate in petroleum ether) to afford 5-bromo-3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carbonitrile (1.1 g, 47% yield) as a purple solid.

LCMS: (ESI, m/z) $[M+H]^+ = 379.0$

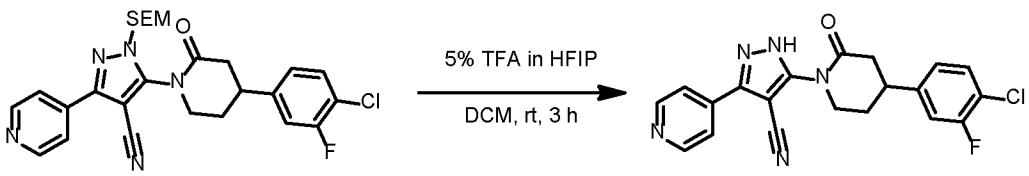
Step 3: *Synthesis of 5-(4-(4-chloro-3-fluorophenyl)-2-oxopiperidin-1-yl)-3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carbonitrile*



To a solution of 5-bromo-3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carbonitrile (500 mg, 1.32 mmol) and 4-(4-chloro-3-fluorophenyl)piperidin-2-one (360 mg, 1.58 mmol) in 1,4-dioxane (8 mL) was added K_3PO_4 (0.33mL, 3.95mmol) and BrettPhos Pd G3 (120 mg, 0.13 mmol). The mixture was stirred at 100 °C for 2 h under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuum. The residue was purified by flash column chromatography (SiO_2, 0-60% ethyl acetate in petroleum ether) to afford 40 mg crude product, which was further purified by pre-TLC (50% ethyl acetate in petroleum ether) to afford 5-(4-(4-chloro-3-fluorophenyl)-2-oxopiperidin-1-yl)-3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carbonitrile (20 mg, 3% yield) as yellow oil.

LCMS: (ESI, m/z) $[M+H]^+ = 526.1$

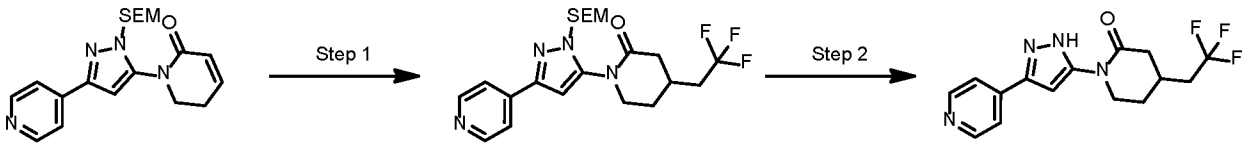
Step 4: *Synthesis of 5-(4-(4-chloro-3-fluorophenyl)-2-oxopiperidin-1-yl)-3-(pyridin-4-yl)-1H-pyrazole-4-carbonitrile (Ex 45)*



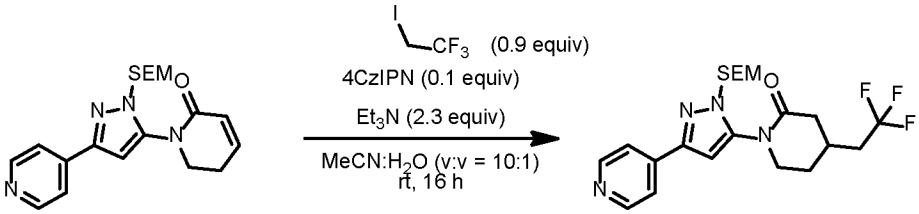
A solution of 5-(4-(4-chloro-3-fluorophenyl)-2-oxopiperidin-1-yl)-3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carbonitrile (20 mg, 0.04 mmol) in 5% TFA in HFIP (2 mL) was stirred at room temperature for 3 h. The mixture was pH adjusted to 8 with saturated $NaHCO_3$ at 0 °C, then extracted by DCM (30 mL x 3). The combined organic layers was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by reverse phase chromatography (acetonitrile: 23-53% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to afford 5-(4-(4-chloro-3-fluorophenyl)-2-oxopiperidin-1-yl)-3-(pyridin-4-yl)-1*H*-pyrazole-4-carbonitrile (6.3 mg, 41% yield) as a white solid.

Example 45: ^{1}**H NMR** (400 MHz, DMSO-d_6) δ 8.80 (d, J = 6.0 Hz, 2H), 7.85 - 7.76 (m, 2H), 7.56 (t, J = 8.4 Hz, 1H), 7.51 -7.45 (m, 1H), 7.28 - 7.24 (m, 1H), 3.95 - 3.77 (m, 2H), 3.37 - 3.41 (m, 1H), 2.78 -2.71 (m, 2H), 2.21 - 2.10 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 396.0

Example 46



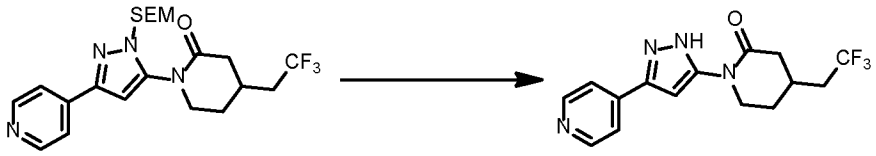
Step 1: *Synthesis of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)-4-(2,2,2-trifluoroethyl)piperidin-2-one*



To a mixture of 1,1,1-trifluoro-2-iodoethane (250 mg, 1.19 mmol), 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-5,6-dihydropyridin-2(1*H*)-one (500 mg, 1.35 mmol) in MeCN (20 mL) and water (2 mL) was added 2,4,5,6-tetra(9*H*-carbazol-9-yl)isophthalonitrile (100 mg, 0.13 mmol) and TEA (0.38 mL, 2.72 mmol). The mixture was purged with nitrogen atmosphere and then sealed. The mixture was placed in the integrated photoreactor (450 nm LED light) for 16 hours. The reaction was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 0 - 30% EE (EtOAc:EtOH = 3:1) in petroleum ether) to afford 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-4-(2,2,2-trifluoroethyl)piperidin-2-one (400 mg crude, 13% purity) as a yellow oil.

LCMS: (ESI, m/z) $[M+H]^+$ = 455.3

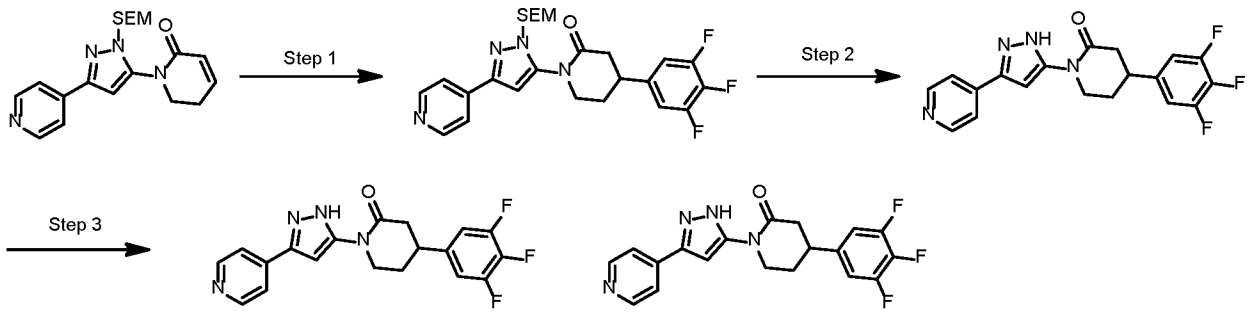
Step 2: *Synthesis of 1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)-4-(2,2,2-trifluoroethyl)piperidin-2-one (Ex. 46)*



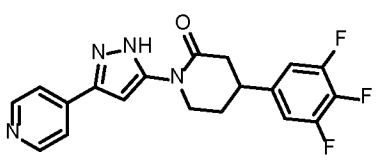
A solution of 1-(3-(pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)-4-(2,2,2-trifluoroethyl)piperidin-2-one (800 mg crued) in 5% TFA / HFIP solution (10 mL) was stirred at room temperature for 12 hours. The reaction mixture was concentrated under reduced pressure to remove TFA. Then the reaction residue was poured into water (5 mL), and then treated with aqueous saturated $NaHCO_3$ until pH = 8. The mixture was extracted with DCM (3 x 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 34-64% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to give 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(2,2,2-trifluoroethyl)piperidin-2-one (20.8 mg, 2% yield over two steps) as a yellow oil.

Example 46: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.31 (s, 1H), 8.62 (d, J = 4.0 Hz, 2H), 7.71 (d, J = 4.4 Hz, 2H), 7.25 (s, 1H), 4.12 - 3.94 (m, 1H), 3.77 - 3.66 (m, 1H), 2.68 - 2.56 (m, 1H), 2.49 - 2.19 (m, 4H), 2.13 - 2.02 (m, 1H), 1.72 (s, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 325.1

Examples 47a and 47b

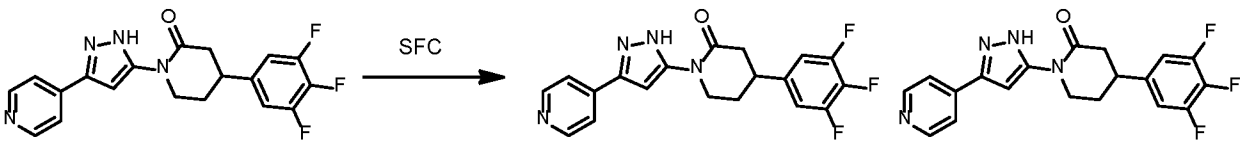


Step 1 — 2: *1-(3-(Pyridin-4-yl)-1H-pyrazol-5-yl)-4-(3,4,5-trifluorophenyl)piperidin-2-one*



1-(3-(Pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(3,4,5-trifluorophenyl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 9a and 9b** by replacing (2-fluorophenyl)boronic acid with (3,4,5-trifluorophenyl)boronic acid in Step 1.

Step 3: *Chiral Separation of 1-(3-(Pyridin-4-yl)-1H-pyrazol-5-yl)-4-(3,4,5-trifluorophenyl)piperidin-2-one (Ex 47a & 47b)*

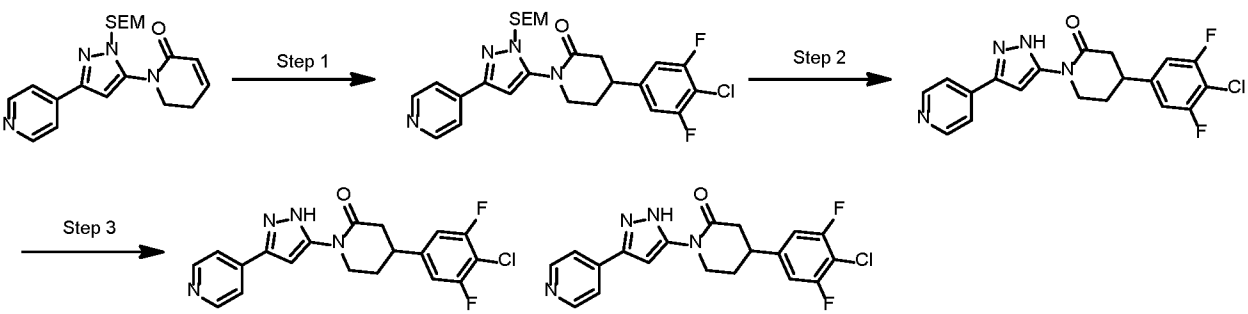


1-(3-(Pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(3,4,5-trifluorophenyl)piperidin-2-one (90 mg, 0.24 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / *i*-PrOH + 0.1% NH_4OH = 50/50; 80 mL/min) to afford 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(3,4,5-trifluorophenyl)piperidin-2-one (**Ex. 47a**, peak 1, Rt = 2.271 min, 26.9 mg, 30% yield) and 1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)-4-(3,4,5-trifluorophenyl)piperidin-2-one (**Ex. 47b**, peak 2, Rt = 2.690 min, 28.0 mg, 31% yield) both as white solid.

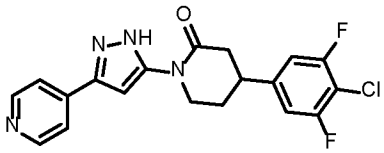
Example 47a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.35 (s, 1H), 8.63 (d, J = 4.0 Hz, 2H), 7.72 (d, J = 4.4 Hz, 2H), 7.36 (dd, J = 9.2, 6.8 Hz, 2H), 7.27 (s, 1H), 4.13 - 4.01 (m, 1 H), 3.82 - 3.70 (m, 1H), 3.29 -3.18 (m, 1H), 2.78 - 2.63 (m, 2H), 2.21 - 1.99 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 373.1

Example 47b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.36 (s, 1H), 8.64 (d, J = 4.0 Hz, 2H), 7.73 (d, J = 4.4 Hz, 2H), 7.37 (dd, J = 9.2, 6.8 Hz, 2H), 7.28 (s, 1H), 4.13 - 4.01 (m, 1 H), 3.83 - 3.71 (m, 1H), 3.29 -3.18 (m, 1H), 2.78 - 2.63 (m, 2H), 2.21 - 1.99 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 373.1

Examples 48a and 48b

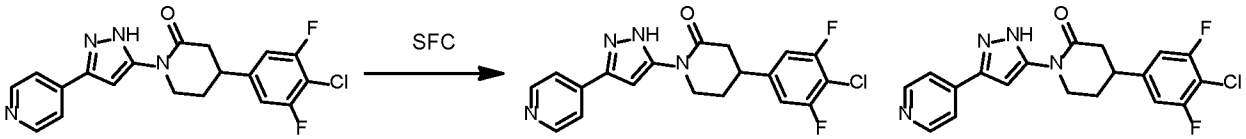


Step 1 — 2: *Synthesis of 4-(4-Chloro-3,5-difluorophenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one*



4-(4-Chloro-3,5-difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 9a** and **Ex 9b** by replacing (2-fluorophenyl)boronic acid with (4-chloro-3,5-difluorophenyl)boronic acid in Step 1.

Step 3: *Chiral Separation of 4-(4-Chloro-3,5-difluorophenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one*

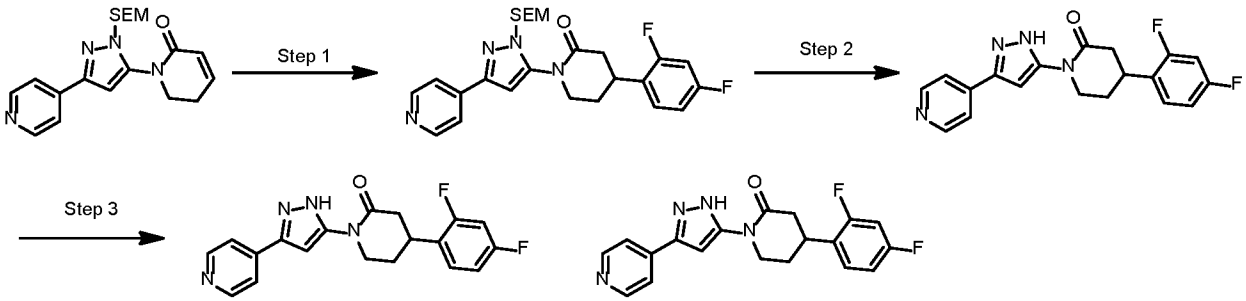


4-(4-Chloro-3,5-difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (160 mg, 0.41 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / *i*-PrOH + 0.1% NH_4OH = 45/55; 80 mL/min) to afford 4-(4-chloro-3,5-difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 48a**, peak 1, Rt = 2.493 min, 40 mg, 25% yield) and 4-(4-chloro-3,5-difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 48b**, peak 2, Rt = 2.944 min, 50.9 mg, 32% yield) both as white solids.

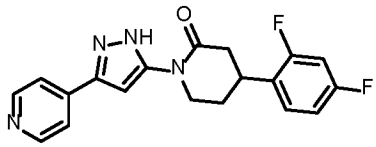
Example 48a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.34 (br s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.77 - 7.69 (m, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.27 (s, 1H), 4.13 - 3.98 (m, 1H), 3.83 - 3.71 (m, Hz, 1H), 2.76 -2.65 (m, 2H), 2.22 - 2.01 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 389.0

Example 48b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.36 (br s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.72 (d, J = 4.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.20 (s, 1H), 4.13 - 4.00 (m, 1H), 3.83 - 3.71 (m, Hz, 1H), 2.73 -2.60 (m, 2H), 2.22 - 2.01 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 389.0

Examples 49a and 49b

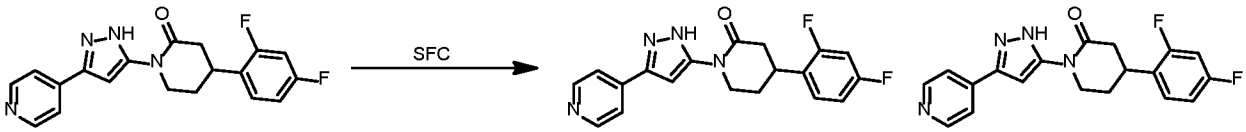


Step 1 — 2: *Synthesis of 4-(2,4-Difluorophenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one*



4-(2,4-Difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 9a and Ex 9b** by replacing (2-fluorophenyl)boronic acid with (2,4-difluorophenyl)boronic acid in Step 1.

Step 3: *Chiral Separation of 4-(2,4-Difluorophenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Ex 48a & 48b)*



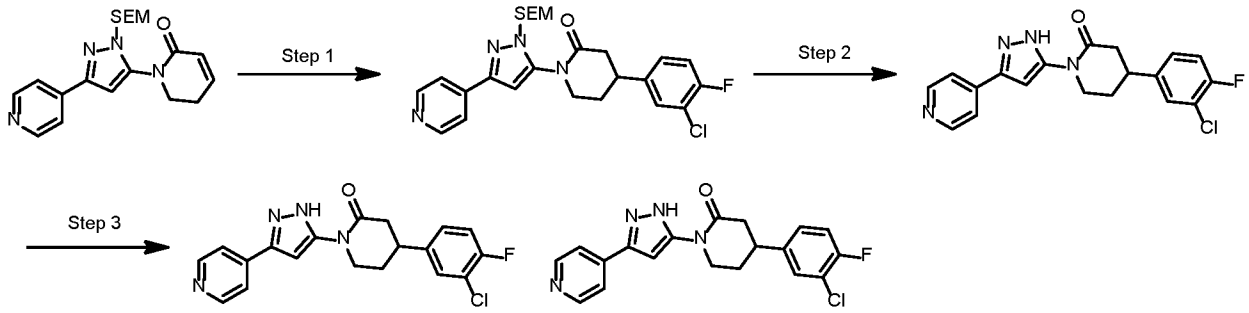
4-(2,4-Difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (47 mg, 0.13 mmol) was separated by chiral SFC (Chiralcel OD (250 mm x 30 mm, 10 um), Supercritical CO_2 / *i*-PrOH + 0.1% NH_4OH = 65/35; 150 mL/min) to 4-(2,4-difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 49a**, peak 1, Rt = 2.341 min, 15 mg, 31% yield) and 4-(2,4-difluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 49b**, peak 2, Rt = 2.808 min, 14 mg, 30% yield) both as white solids.

Example 49a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.36 (br s, 1H), 8.63 (d, J = 5.2 Hz, 2H), 7.73 (d, J = 5.2 Hz, 2H), 7.50 - 7.39 (m, 1H), 7.33 - 7.17 (m, 2H), 7.15 - 7.02 (m, 1H), 4.12 - 3.99 (m, 1H), 3.88 - 3.74 (m, 1H), 3.52 - 3.44 (m, 1H), 2.75 - 2.65 (m, 2H), 2.18 - 2.01 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 355.2

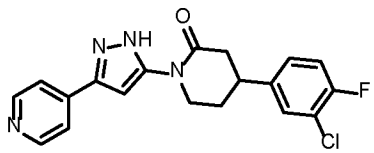
Example 49b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.37 (br s, 1H), 8.63 (d, J = 5.2 Hz, 2H), 7.73 (d, J = 5.6 Hz, 2H), 7.53 - 7.39 (m, 1H), 7.33 - 7.18 (m, 2H), 7.15 - 7.01 (m, 1H), 4.12 - 3.99 (m,

1H), 3.90 - 3.76 (m, 1H), 3.56 - 3.42 (m, 1H), 2.75 - 2.65 (m, 2H), 2.18 - 2.01 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 355.2

Examples 50a and 50b

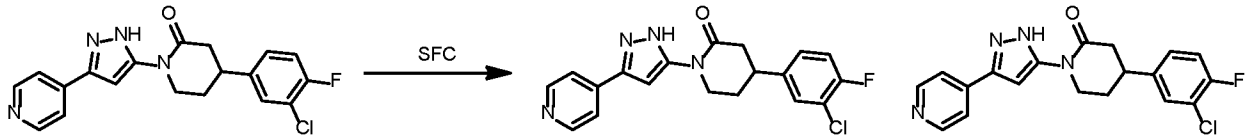


Step 1 — 2: *Synthesis of 4-(3-Chloro-4-fluorophenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one*



4-(3-Chloro-4-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 9a** and **Ex 9b** by replacing (2-fluorophenyl)boronic acid with (3-chloro-4-fluorophenyl)boronic acid in Step 1.

Step 3: *Chiral Separation of 4-(3-Chloro-4-fluorophenyl)-1-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)piperidin-2-one (Ex. 50a & 50b)*



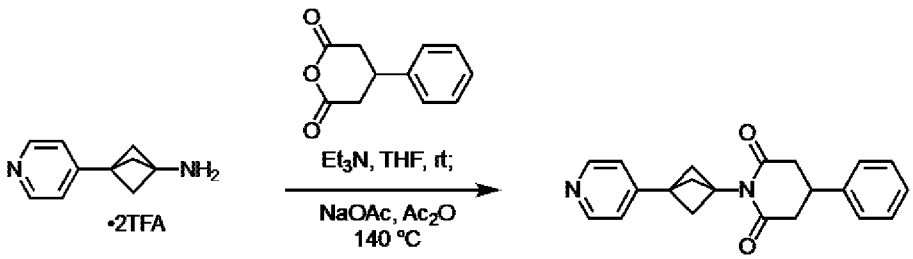
4-(3-Chloro-4-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (50 mg, 0.13 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / *i*-PrOH + 0.1% NH_4OH = 45/55; 80 mL/min) to afford 4-(3-chloro-4-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 50a**, peak 1, Rt = 1.149 min, 12.0 mg, 24% yield) and 4-(3-chloro-4-fluorophenyl)-1-(3-(pyridin-4-yl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 50b**, peak 2, Rt = 1.823 min, 11.7 mg, 23% yield) both as white solids.

Example 50a: **^{1}H NMR** (DMSO-d_6, 400 MHz): δ 13.35 (br s, 1H), 8.62 (d, J = 6.0 Hz, 2H), 7.73 (d, J = 5.6 Hz, 2H), 7.59 (d, J = 7.2 Hz, 1H), 7.43 - 7.33 (m, 2H), 7.28 (s, 1H), 4.14 - 4.02 (m, 1H), 3.86 - 3.73 (m, 1H), 3.31 - 3.22 (m, 1H), 2.77 - 2.65 (m, 2H), 2.22 - 2.03 (m, 2H). **LCMS**: (ESI, m/z) $[M+Na]^+$ = 393.1

Example 50b: **^{1}H NMR** (DMSO-d_6, 400 MHz): δ 13.34 (br s, 1H), 8.62 (d, J = 6.0 Hz, 2H), 7.72 (d, J = 5.6 Hz, 2H), 7.59 (d, J = 8.0 Hz, 1H), 7.43 - 7.33 (m, 2H), 7.23 (s, 1H), 4.11 - 3.97 (m, 1H), 3.86 - 3.73 (m, 1H), 3.31 - 3.22 (m, 1H), 2.76 - 2.64 (m, 2H), 2.22 - 2.03 (m, 2H). **LCMS**: (ESI, m/z) $[M+Na]^+$ = 393.2

Example 51

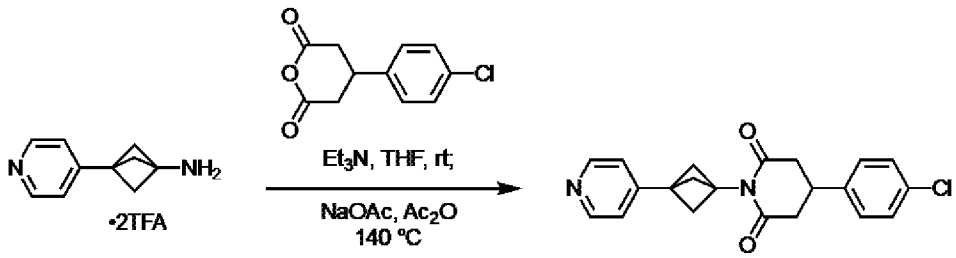
Step 1: *Synthesis of 4-phenyl-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidine-2,6-dione (Ex 51)*



To a solution of 3-(4-pyridyl)bicyclo[1.1.1]pentan-1-amine 2,2,2-trifluoroacetic acid salt (50 mg, 0.13 mmol, 1 equiv.) and 4-phenyloxane-2,6-dione (26 mg, 0.13 mmol, 1.0 equiv.) in tetrahydrofuran (1.3 mL, 0.1 M) was added triethylamine (55 μL, 0.39 mmol, 3.0 equiv.). Resulting solution was stirred at room temperature for 2 hour. The reaction mixture was concentrated under reduced pressure. To the resulting residue was added acetic anhydride (640 uL, 0.2 M) and sodium acetate (14 mg, 0.17 mmol, 1.3 equiv.) and resulting solution was stirred at 140 °C for 2 hour. The product mixture was cooled to room temperature and was added water (3 mL) and stirred in ice bath. To the mixture was slowly added 5N sodium hydroxide solution until pH is neutral. Resulting solution was extracted with isopropyl acetate (5 mL) for 3 times. Organic layers were combined and dried with $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified by prep HPLC (XSelect CSH Prep C18, 50 × 30 mm, 5 μm; 0.1% formic acid in water /acetonitrile using a gradient of 5-85% acetonitrile to; 60 mL/min, 25 °C) to afford 4-phenyl-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidine-2,6-dione (24 mg, 57%) as a colorless solid.
^{1}H NMR (400 MHz, DMSO) δ 8.53 – 8.47 (m, 2H), 7.39 – 7.27 (m, 4H), 7.30 – 7.21 (m, 3H), 3.49 – 3.33 (m, 1H), 2.94 (dd, J = 16.6, 11.7 Hz, 2H), 2.79 (dd, J = 16.6, 4.3 Hz, 2H), 2.60 (s, 6H).
LCMS: (ESI, m/z) $[M+H]^+$ = 333.1601.

Example 52

Step1: *Synthesis of 4-(4-chlorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidine-2,6-dione (Ex 52)*

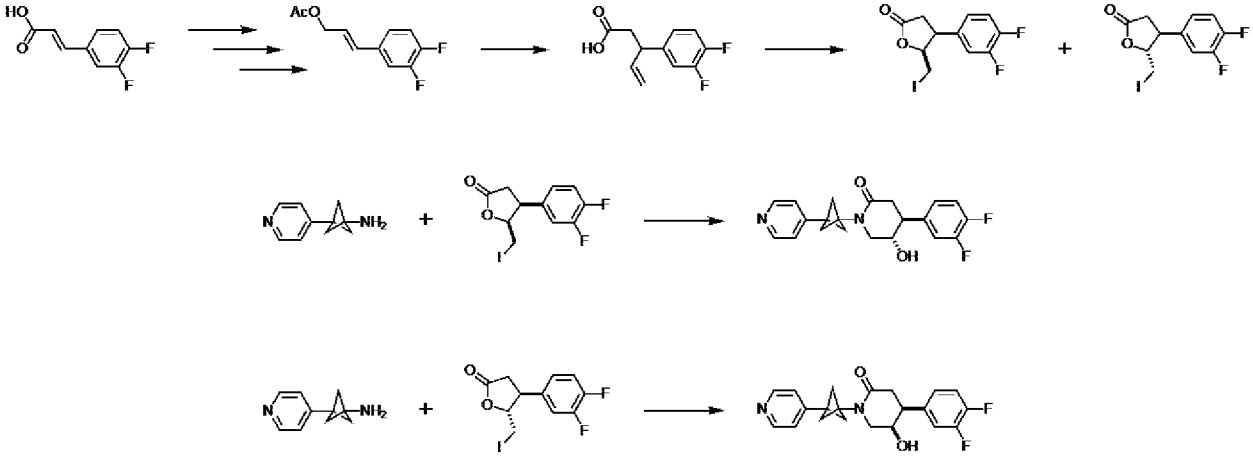


To a solution of 3-(4-pyridyl)bicyclo[1.1.1]pentan-1-amine 2,2,2-trifluoroacetic acid salt (60 mg, 0.22 mmol, 1 equiv.) and 4-(4-chlorophenyl)dihydro-2*H*-pyran-2,6(3*H*)-dione (51 mg, 0.22 mmol, 1.0 equiv.) in tetrahydrofuran (2.2 mL, 0.1 M) was added triethylamine (64 μL, 0.46 mmol, 3.0 equiv.). Resulting solution was stirred at room temperature for 2 hour. The reaction mixture was concentrated under reduced pressure. To the resulting residue was added acetic anhydride (770 uL, 0.2 M) and sodium acetate (16 mg, 0.20 mmol, 1.3 equiv.) and resulting solution was stirred at 140 °C for 2 hours. The product mixture was cooled to room temperature and was added water (3 mL) and stirred in ice bath. To the mixture was slowly added 5N sodium hydroxide solution until pH is neutral. Resulting solution was extracted with isopropyl acetate (5 mL) for 3 times. Organic layers were combined and dried with $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified by prep HPLC (XSelect CSH Prep C18, 50 × 30 mm, 5 μm; 0.1% ammonium hydroxide in water /acetonitrile using a gradient of 30-70% acetonitrileto; 60 mL/min, 25 °C) to afford 4-(4-chlorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidine-2,6-dione (35 mg, 62%) as a colorless solid.

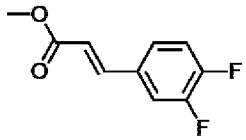
^{1}H NMR (400 MHz, DMSO) δ 8.52 – 8.45 (m, 2H), 7.45 – 7.37 (m, 2H), 7.37 – 7.30 (m, 2H), 7.30 – 7.24 (m, 2H), 3.45 (tt, *J* = 11.7, 4.2 Hz, 1H), 2.93 (dd, *J* = 16.6, 11.8 Hz, 2H), 2.83 – 2.72 (m, 2H), 2.60 (s, 6H).

LCMS: (ESI, m/z) $[M+H]^+$ = 367.1209

Examples 53a, 53b, 53c, and 53d



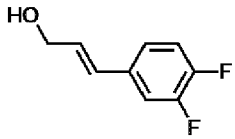
Step 1: *Synthesis of methyl (E)-3-(3,4-difluorophenyl)prop-2-enoate*



To a round bottom flask equipped with a stir bar add (*E*)-3-(3,4-difluorophenyl)prop-2-enoic acid (5000 mg, 27 mmol, 1 equiv.) and MeOH (50 mL) followed by a few drops of sulfuric acid. The mixture was heated to 60 °C. The mixture was stirred until complete consumption of the starting materials was confirmed by LCMS analysis. At this time, the reaction was cooled to room temperature and amberlyst A21 (free base) was added to remove residual acid. The mixture was stirred for 1 hour, then filtered and concentrated. This afforded methyl (*E*)-3-(3,4-difluorophenyl)prop-2-enoate (5130 mg, 26 mmol, 95% Yield) as a white powder which was used without further purification.

^{1}H NMR (400 MHz, CDCl3) δ 7.59 (d, J = 16.0 Hz, 1H), 7.34 (ddd, J = 11.0, 7.6, 2.1 Hz, 1H), 7.25 – 7.11 (m, 2H), 6.35 (d, J = 16.0 Hz, 1H), 3.81 (s, 3H).

Step 2: *Synthesis of (E)-3-(3,4-difluorophenyl)prop-2-en-1-ol*

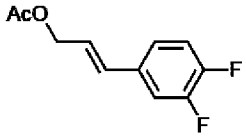


To a round bottom flask equipped with a stir bar add methyl (*E*)-3-(3,4-difluorophenyl)prop-2-enoate (5130 mg, 26 mmol, 1 equiv.) and diethyl ether (50 mL). The flask was cooled to 0 °C and then LAH (2950 mg, 78 mmol, 3 equiv.) was added slowly portion-wise. The mixture was stirred at this temperature until complete consumption of the starting materials was confirmed by LCMS analysis. At this time, the reaction was slowly quenched with aqueous Rochelle salt solution, followed by 1M NaOH (aq). The reaction mixture was diluted with a mixture of heptane and iPrOAc (1:3) and stirred vigorously for 5 minutes after which the reaction was allowed to stand at room temperature overnight. The organic fraction was decanted into an Erlenmeyer flask and the aqueous phase was transferred to a separatory funnel. The aqueous mixture was extracted 3x with 3:1

iPrOAc:heptane. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated. This afforded (*E*)-3-(3,4-difluorophenyl)prop-2-en-1-ol (4370 mg, 26 mmol, 99% yield) as an oil which was used without further purification.

^{1}H NMR (400 MHz, CDCl3) δ 7.23 – 7.14 (m, 1H), 7.14 – 7.03 (m, 2H), 6.54 (d, J = 15.9 Hz, 1H), 6.28 (dt, J = 15.9, 5.5 Hz, 1H), 4.32 (dd, J = 5.5, 1.6 Hz, 2H).

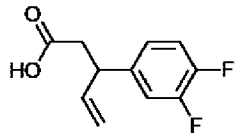
***Step 3**: Synthesis of (E)-3-(3,4-difluorophenyl)allyl acetate*



To a round bottom flask equipped with a stir bar, the crude alcohol from the previous step was added to DCM (100 mL) followed by TEA (2881 mg, 3.97 mL, 28 mmol, 1.1 equiv.). The mixture was cooled to 0 °C and acetyl chloride (2235 mg, 2.03 mL, 28 mmol, 1.1 equiv.) was added slowly dropwise. The mixture was allowed to warm to room temperature. The mixture was then stirred until complete consumption of the starting materials was confirmed by LCMS analysis. At this time, the mixture was washed with sat. aq. NH_4Cl followed by sat. aq. $NaHCO_3$ and brine. The organic fraction was dried over $MgSO_4$, filtered, and concentrated. Purification via column (0-20% iPrOAc in heptane) gave [(*E*)-3-(3,4-difluorophenyl)allyl] acetate (2200 mg, 10.4 mmol, 40% yield) as an oil.

^{1}H NMR (400 MHz, CDCl3) δ 7.20 (ddd, J = 11.1, 7.4, 1.6 Hz, 1H), 7.15 – 7.06 (m, 2H), 6.56 (d, J = 15.9 Hz, 1H), 6.20 (dt, J = 15.9, 6.3 Hz, 1H), 4.74 (d, *J* = 6.3 Hz, 2H), 2.10 (s, 3H).

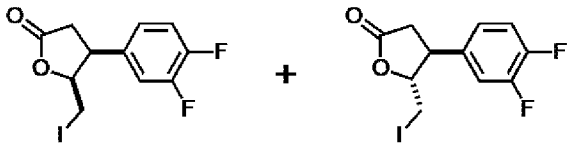
***Step 4:** Synthesis of 3-(3,4-difluorophenyl)pent-4-enoic acid*



In a round bottom flask, the allylic acetate starting material (2200 mg, 10.4 mmol, 1 equiv.) was dissolved in toluene and concentrated to remove water via azeotrope. In the same flask, the dried material was diluted with THF (43 mL) and a stir bar was added. The solution was cooled to -78 °C and then TMSCl (2253 mg, 2.64 mL, 21 mmol, 2 equiv.) was added slowly dropwise. Immediately following this addition, KHMDS (1M in THF) (16000 mg, 17 mL, 15.5 mmol, 1.5 equiv.) was added slowly dropwise. The reaction was stirred at this temperature for 2 hours, then warmed to room temperature and subsequently reflux for 2.5 hours. The reaction was cooled to room temperature and then quenched with sat. aq. $NaHCO_3$ and diluted with diethyl ether. The mixture was extracted three times with 1 M NaOH (aq). The combined aqueous layers were acidified to pH = 2 with 2M HCl (aq) and then extracted four times with DCM. The combined DCM fractions were dried over $MgSO_4$, filtered, and concentrated to afford 3-(3,4-difluorophenyl)pent-4-enoic acid (1800 mg, 8.5 mmol, 82% yield) as a yellow oil which was used without further purification.

^{1}H NMR (400 MHz, CDCl3) δ 7.09 (dt, J = 9.7, 8.3 Hz, 1H), 7.02 (ddd, J = 11.1, 7.6, 2.2 Hz, 1H), 6.98 – 6.89 (m, 1H), 5.99 – 5.82 (m, 1H), 5.18 – 4.99 (m, 2H), 3.83 (q, J = 7.4 Hz, 1H), 2.78 (dd, J = 15.8, 7.5 Hz, 1H), 2.69 (dd, J = 16.1, 8.2 Hz, 1H).

Step 5: *cis*- and *trans*-4-(3,4-difluorophenyl)-5-(iodomethyl)dihydrofuran-2(3*H*)-one



The alkene starting material was split into two portions for iodolactonization following protocols from this reference: ***Org. Biomol. Chem.***, 2013, **11**, 1280-1285

Procedure to favor trans isomer:

To a vial equipped with a stir bar, 3-(3,4-difluorophenyl)pent-4-enoic acid (700 mg, 3.3 mmol, 1 equiv.) and ACN (13 mL) were added followed by iodine (25.13 mg, 9.9 mmol, 3 equiv.). The mixture was protected from light and stirred at room temperature for 3 hours, then added sat. aq. $NaHCO_3$ (7 mL) and stirred an additional hour. On completion, the mixture was diluted with diethyl ether and washed with aq $Na_2S_2O_3$ until the organic layer was colorless. The organic fraction were dried over $MgSO_4$, filtered, and concentrated.

Purification via column (10-50% iPrOAc in heptane gradient) gave *trans*-4-(3,4-difluorophenyl)-5-(iodomethyl)dihydrofuran-2(3*H*)-one (285 mg, 0.84 mmol, 25% yield) and *cis*-4-(3,4-difluorophenyl)-5-(iodomethyl)dihydrofuran-2(3*H*)-one (450 mg, 1.3 mmol, 40% yield).

Note: on this scale the reaction is not selective at room temperature, possibly due to exotherm. Running at smaller scale gave higher selectivity, possibly the reaction must be cooled at this scale.

Procedure to favor cis isomer:

To a vial equipped with a stir bar, 3-(3,4-difluorophenyl)pent-4-enoic acid (700 mg, 3.3 mmol, 1 equiv.) and chloroform (13 mL) were added followed by a solution of sodium bicarbonate (554 mg, 6.6 mmol, 2 equiv.) in water (13 mL). The mixture was cooled to 0 °C while stirring, I_2 (1675 mg, 6.6 mmol, 2 equiv.) was added and the reaction was protected from light. The mixture was stirred until complete consumption of the starting materials was confirmed by LCMS analysis. On completion, the mixture was diluted with ether and washed with aq $Na_2S_2O_3$ until the organic layer was colorless. The organic fraction was dried over $MgSO_4$, filtered, and concentrated.

Purification via column (10-50% iPrOAc in heptane gradient) gave *cis*-4-(3,4-difluorophenyl)-5-(iodomethyl)dihydrofuran-2(3*H*)-one (450 mg, 1.3 mmol, 40% yield) and *trans*-4-(3,4-difluorophenyl)-5-(iodomethyl)dihydrofuran-2(3*H*)-one (166 mg, 0.43 mmol, 13% yield)

Trans isomer:

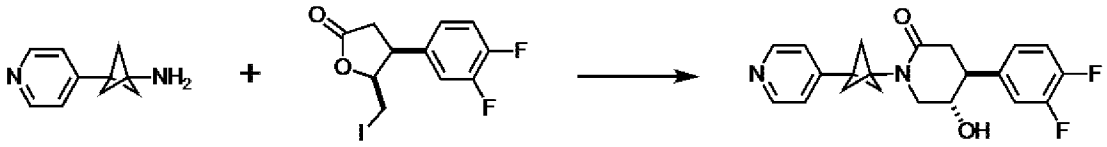
^{1}H NMR (400 MHz, CDCl3) δ 7.19 (dt, J = 9.9, 8.3 Hz, 1H), 7.09 (ddd, J = 10.8, 7.3, 2.3 Hz, 1H), 7.00 (ddt, J = 8.2, 3.8, 1.8 Hz, 1H), 4.29 (dt, J = 6.9, 4.8 Hz, 1H), 3.53 (td, J = 9.1, 6.9 Hz, 1H), 3.46 (dd, J = 11.2, 5.2 Hz, 1H), 3.34 (dd, J = 11.2, 4.2 Hz, 1H), 3.09 (dd, J = 18.0, 9.2 Hz, 1H), 2.74 (dd, J = 18.0, 9.0 Hz, 1H).

Cis Isomer:

^{1}H NMR (400 MHz, CDCl3) δ 7.17 (dt, J = 9.9, 8.3 Hz, 1H), 7.08 (ddd, J = 10.9, 7.3, 2.3 Hz, 1H), 7.01 – 6.91 (m, 1H), 4.92 (dt, J = 8.5, 5.9 Hz, 1H), 3.87 (ddd, J = 8.6, 5.8, 2.8 Hz, 1H), 3.18 (dd, J = 10.3, 5.9 Hz, 1H), 3.09 (dd, J = 17.7, 8.6 Hz, 1H), 2.77 (dd, J = 17.7, 2.8 Hz, 1H), 2.68 (dd, J = 10.3, 8.5 Hz, 1H).

Relative stereochemistry was assigned by analogy to: *Org. Biomol. Chem.*, 2013, **11**, 1280-1285

Step 6A: *trans*-4-(3,4-difluorophenyl)-5-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one



To a vial equipped with a stir bar, *cis*-4-(3,4-difluorophenyl)-5-(iodomethyl)tetrahydrofuran-2-one (450 mg, 1.3 mmol, 1 equiv.), 3-(4-pyridyl)bicyclo[1.1.1]pentan-1-amine dihydrochloride (326 mg, 1.4 mmol, 1.05 equiv.), and K_2CO_3 (736 mg, 5.3 mmol, 4 equiv.) were added followed by MeOH (2.7 mL). The mixture was stirred at 50 °C overnight. At this time 1 mL of MeOH was added and the mixture was heated to 70 °C. After prolonged reaction time the conversion was not improved and the reaction was allowed to cool to room temperature. The mixture was filtered and concentrated, then purified via column (0 to 10% MeOH in DCM) to give the title compound (110 mg, 0.3 mmol, 22% Yield) as a white solid (racemic). Chiral SFC (Chiralpak IA column, 20% MeOH [0.1% NH_4OH modifier] in CO_2 isocratic 20%, flow rate 70 ml/min) afforded 41.9 mg of the fast-eluting enantiomer (**Ex 53a**, 76% recovery) and 37.3 mg of the slow-eluting enantiomer (**Ex 53b**, 68% recovery)

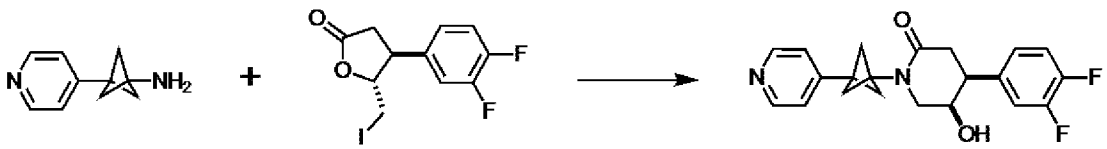
Example 53a: ^{1}H NMR (400 MHz, DMSO) δ 8.53 – 8.47 (m, 2H), 7.42 – 7.30 (m, 2H), 7.29 – 7.23 (m, 2H), 7.14 – 7.07 (m, 1H), 5.16 (d, *J* = 5.6 Hz, 1H), 4.07 – 3.95 (m, 1H), 3.41 (dd, *J* = 11.7, 5.2 Hz, 1H), 3.11 (dd, *J* = 11.7, 8.3 Hz, 1H), 3.02 (td, *J* = 10.1, 6.0 Hz, 1H), 2.58 – 2.43 (m, 2H), 2.40 (s, 6H).

LCMS $[M+H]^+$ = 371.16

Example 53b: ^{1}H NMR (400 MHz, DMSO) δ 8.53 – 8.47 (m, 2H), 7.42 – 7.30 (m, 2H), 7.29 – 7.23 (m, 2H), 7.13 – 7.07 (m, 1H), 5.16 (d, *J* = 5.5 Hz, 1H), 4.07 – 3.95 (m, 1H), 3.41 (dd, *J* = 11.7, 5.2 Hz, 1H), 3.11 (dd, *J* = 11.8, 8.3 Hz, 1H), 3.02 (td, *J* = 10.0, 6.0 Hz, 1H), 2.54 – 2.42 (m, 2H), 2.40 (s, 6H).

LCMS $[M+H]^+$ = 371.16

Step 6B: *cis*-4-(3,4-difluorophenyl)-5-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one



To a vial equipped with a stir bar, *trans*-4-(3,4-difluorophenyl)-5-(iodomethyl)tetrahydrofuran-2-one (450 mg, 1.3 mmol, 1 equiv.), 3-(4-pyridyl)bicyclo[1.1.1]pentan-1-amine dihydrochloride (326 mg, 1.4 mmol, 1.05 equiv.), and K_2CO_3 (736 mg, 5.3 mmol, 4 equiv.) were added followed by MeOH (2.7 mL). The mixture was stirred at 60 °C overnight. At this time the mixture was diluted with DCM and filtered through celite. The filtrate was concentrated and purified via column chromatography (1-10% MeOH in DCM gradient) to afford

cis-4-(3,4-difluorophenyl)-5-hydroxy-1-[3-(4-pyridyl)-1-bicyclo[1.1.1]pentanyl]piperidin-2-one (55 mg, 0.15 mmol, 11% Yield) as a white solid. Chiral SFC (Chiralpak IK column, 25% MeOH [0.1% NH_4OH modifier] in CO_2 isocratic 25%, flow rate 70 ml/min) afforded 8.0 mg of the fast-eluting enantiomer (**Ex 34c**, 29% recovery) and 9.4 mg of the slow-eluting enantiomer (**Ex 53d**, 34% recovery).

Example 53c: ^{1}**H NMR** (400 MHz, DMSO) δ 8.53 – 8.47 (m, 2H), 7.44 – 7.30 (m, 2H), 7.30 – 7.24 (m, 2H), 7.21 – 7.12 (m, 1H), 5.24 (d, J = 3.8 Hz, 1H), 4.08 (s, 1H), 3.55 – 3.37 (m, 1H), 3.1 – 3.3 (m, 2H), 2.70 (dd, J = 16.8, 12.7 Hz, 1H), 2.45 – 2.27 (m, 7H).

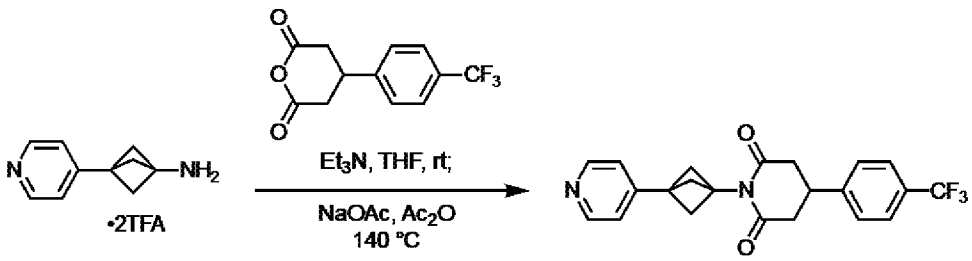
LCMS $[M+H]^+$ = 371.16

Example 53d: ^{1}H NMR (400 MHz, DMSO) δ 8.59 – 8.38 (m, 2H), 7.46 – 7.31 (m, 2H), 7.31 – 7.24 (m, 2H), 7.21 – 7.11 (m, 1H), 5.24 (d, *J* = 3.8 Hz, 1H), 4.08 (s, 1H), 3.51 (dd, *J* = 12.5, 3.1 Hz, 1H), 3.30 – 3.20 (m, 2H), 2.70 (dd, *J* = 16.8, 12.7 Hz, 1H), 2.45 – 2.36 (m, 6H), 2.32 (dd, *J* = 16.9, 5.4 Hz, 1H).

LCMS $[M+H]^+$ = 371.16

Example 54

***Step 1**: Synthesis of 1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(4-(trifluoromethyl)phenyl)piperidine-2,6-dione (Ex. 54)*



To a solution of 3-(4-pyridyl)bicyclo[1.1.1]pentan-1-amine 2,2,2-trifluoroacetic acid salt (50 mg, 0.13 mmol, 1 equiv.) and 4-(4-(trifluoromethyl)phenyl)dihydro-2*H*-pyran-2,6(3*H*)-dione (34 mg, 0.13 mmol, 1.0 equiv.) in tetrahydrofuran (1.3 mL, 0.1 M) was added triethylamine (53 µL, 0.38 mmol, 3.0 equiv.). Resulting solution was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. To the resulting residue was added acetic anhydride (640 uL, 0.2 M) and sodium acetate (14 mg, 0.17 mmol, 1.3 equiv.) and resulting solution was stirred at 140 °C for 2 hours. The product mixture was cooled to room temperature and diluted with water (3 mL) and stirred in ice bath. To the mixture was slowly added 5N sodium hydroxide solution until pH was neutral. Resulting solution was extracted with isopropyl acetate (5 mL) for 3 times. Organic layers were combined and dried with $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified by prep HPLC (XSelect CSH Prep C18, 50 × 30 mm, 5 µm; 0.1%

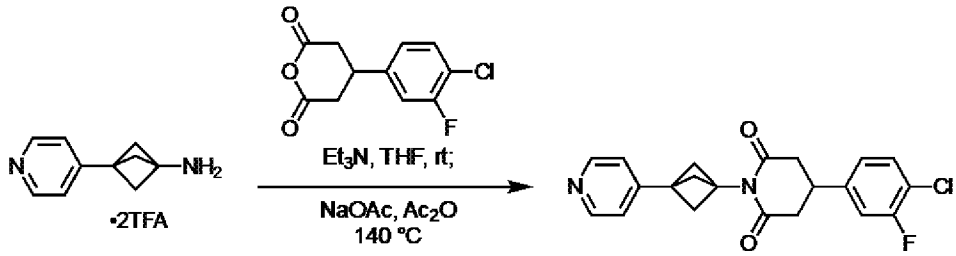
formic acid in water /acetonitrile using a gradient of 5-85%; 60 mL/min, 25 °C) to afford 1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(4-(trifluoromethyl)phenyl)piperidine-2,6-dione (31 mg, 61%) as a colorless solid.

^{1}H NMR (400 MHz, DMSO) δ 8.50 (d, *J* = 5.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 4.9 Hz, 2H), 3.58 (tt, *J* = 11.7, 4.3 Hz, 1H), 2.99 (dd, *J* = 16.6, 12.0 Hz, 2H), 2.83 (dd, *J* = 16.5, 4.3 Hz, 2H), 2.61 (s, 6H).

LCMS: (ESI, m/z) $[M+H]^+$ = 401.1485

Example 55

Step 1: Synthesis of 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidine-2,6-dione (Ex 55)



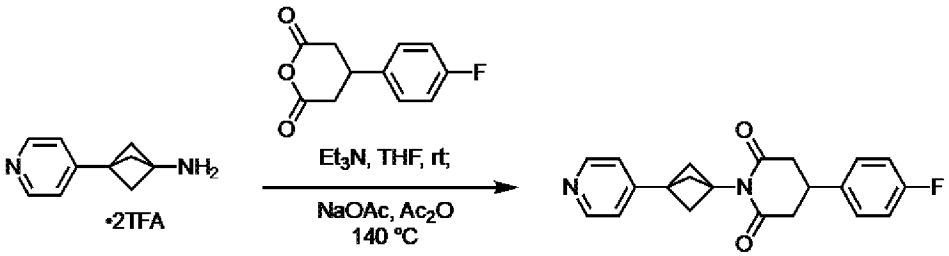
To a solution of 3-(4-pyridyl)bicyclo[1.1.1]pentan-1-amine 2,2,2-trifluoroacetic acid salt (69 mg, 0.18 mmol, 1 equiv.) and 4-(4-chloro-3-fluorophenyl)dihydro-2*H*-pyran-2,6(3*H*)-dione (45 mg, 0.18 mmol, 1.0 equiv.) in tetrahydrofuran (1.8 mL, 0.1 M) was added triethylamine (75 µL, 0.54 mmol, 3.0 equiv.). Resulting solution was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. To the resulting residue was added acetic anhydride (890 uL, 0.2 M) and sodium acetate (19 mg, 0.23 mmol, 1.3 equiv.) and resulting solution was stirred at 140 °C for 2 hours. The product mixture was cooled to room temperature and diluted with water (3 mL) and stirred in ice bath. To the mixture was slowly added 5N sodium hydroxide solution until pH was neutral. Resulting solution was extracted with isopropyl acetate (5 mL) for 3 times. Organic layers were combined and dried with $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified by prep HPLC (Triart C18, 50 × 30 mm, 5 µm; 0.1% formic acid in water /acetonitrile using a gradient of 20-60%; 60 mL/min, 25 °C) to 4-(4-chloro-3-fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidine-2,6-dione (48 mg, 70%) as a colorless solid.

^{1}H NMR (400 MHz, DMSO) δ 8.53 – 8.47 (m, 2H), 7.57 (t, *J* = 8.1 Hz, 1H), 7.52 – 7.32 (m, 1H), 7.30 – 7.24 (m, 2H), 7.22 – 7.11 (m, 1H), 3.49 (tt, *J* = 12.0, 4.3 Hz, 1H), 3.00 – 2.88 (m, 2H), 2.84 – 2.74 (m, 2H), 2.60 (s, 6H).

LCMS: (ESI, m/z) $[M+H]^+$ = 385.1110

Example 56

Step 1: *Synthesis of 4-(4-fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidine-2,6-dione (Ex 56)*



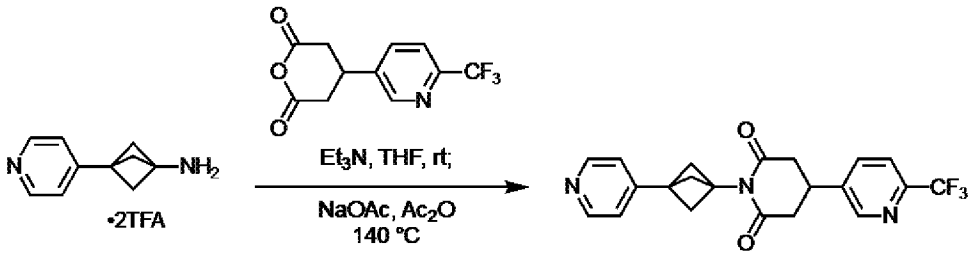
To a solution of 3-(4-pyridyl)bicyclo[1.1.1]pentan-1-amine 2,2,2-trifluoroacetic acid salt (57 mg, 0.15 mmol, 1 equiv.) and 4-(4-fluorophenyl)dihydro-2*H*-pyran-2,6(3*H*)-dione (36 mg, 0.16 mmol, 1.1 equiv.) in tetrahydrofuran (1.5 mL, 0.1 M) was added triethylamine (62 μL, 0.44 mmol, 3.0 equiv.). Resulting solution was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. To the resulting residue was added acetic anhydride (735 uL, 0.2 M) and sodium acetate (16 mg, 0.19 mmol, 1.3 equiv.) and resulting solution was stirred at 140 °C for 2 hours. The product mixture was cooled to room temperature and diluted with water (3 mL) and stirred in ice bath. To the mixture was slowly added 5N sodium hydroxide solution until pH was neutral. Resulting solution was extracted with isopropyl acetate (5 mL) for 3 times. Organic layers were combined and dried with $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified by prep HPLC (Gemini-NX C18, 50 × 30 mm, 5 μm; 0.1% formic acid in water /acetonitrile using a gradient of 5-85%; 60 mL/min, 25 °C) to 4-(4-fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidine-2,6-dione (40 mg, 78%) as a colorless solid.

^{1}H NMR (400 MHz, DMSO) δ 8.53 – 8.47 (m, 2H), 7.35 (qd, *J* = 6.1, 2.5 Hz, 2H), 7.33 – 7.25 (m, 2H), 7.23 – 7.13 (m, 2H), 3.45 (tt, *J* = 12.0, 4.0 Hz, 1H), 2.93 (dd, *J* = 16.6, 11.9 Hz, 2H), 2.78 (dd, *J* = 16.5, 4.3 Hz, 2H), 2.61 (s, 6H).

LCMS: (ESI, m/z) $[M+H]^+$ = 351.1504

Example 57

Step 1: *Synthesis of 1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)piperidine-2,6-dione (Ex 57)*



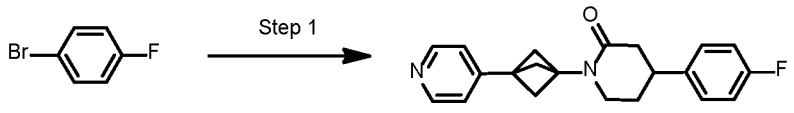
To a solution of 3-(4-pyridyl)bicyclo[1.1.1]pentan-1-amine 2,2,2-trifluoroacetic acid salt (55 mg, 0.14 mmol, 1 equiv.) and 4-(6-(trifluoromethyl)pyridin-3-yl)dihydro-2*H*-pyran-2,6(3*H*)-dione (40 mg, 0.16 mmol, 1.1 equiv.) in tetrahydrofuran (1.4 mL, 0.1 M) was added triethylamine (59 µL, 0.42 mmol, 3.0 equiv.). Resulting solution was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. To the resulting residue was added acetic anhydride (700 uL, 0.2 M) and sodium acetate (15 mg, 0.18 mmol, 1.3 equiv.) and resulting solution was stirred at 140 °C for 2 hours. The product mixture was cooled to room temperature and diluted with water (3 mL) and stirred in ice bath. To the mixture was slowly added 5N sodium hydroxide solution until pH was neutral. Resulting solution was extracted with isopropyl acetate (5 mL) for 3 times. Organic layers were combined and dried with $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified by prep HPLC (XSelect CSH Prep C18, 50 × 30 mm, 5 µm; 0.1% formic acid in water /acetonitrile using a gradient of 5-50%; 60 mL/min, 25 °C) to afford 1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)piperidine-2,6-dione (48 mg, 85%) as a colorless solid.

^{1}H NMR (400 MHz, DMSO) δ 8.76 (d, *J* = 2.2 Hz, 1H), 8.54 – 8.48 (m, 2H), 8.04 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.32 – 7.26 (m, 2H), 3.67 (tt, *J* = 12.3, 4.3 Hz, 1H), 3.04 (ddt, *J* = 17.0, 12.4, 1.3 Hz, 2H), 2.93 – 2.83 (m, 2H), 2.62 (s, 6H).

LCMS: (ESI, m/z) $[M+H]^+$ = 402.1435

Example 58

Step 1: *Synthesis of 4-(4-Fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one*



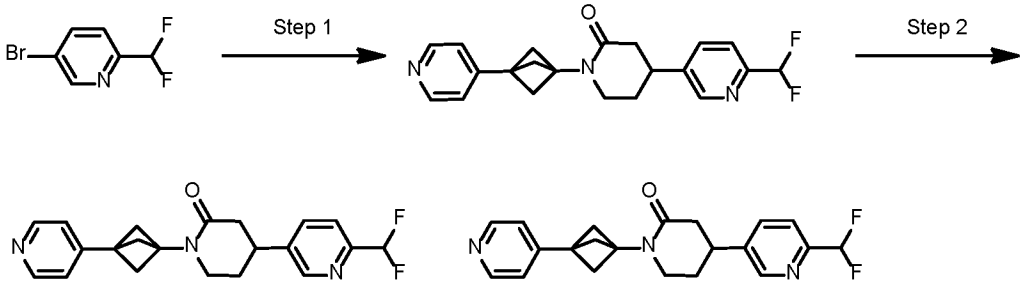
4-(4-Fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 36a** and **Ex 36b** by replacing 5-bromo-2-chloro-3-fluoro-pyridine with 5-bromo-2-(trifluoromethyl)pyridine in Step 1.

The crude was purified by reverse phase chromatography (acetonitrile: 46-76% / 10 mM NH_4HCO3 in water) to obtain 4-(3-fluorophenyl)-1-[3-(4-pyridyl)-1-bicyclo[1.1.1]pentanyl]piperidin-2-one (54 mg, 21% yield) as a white solid.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.50 (dd, J =1.6, 4.4 Hz, 2H), 7.31 (dd, J = 2.8, 8.4 Hz, 2H), 7.28 - 7.23 (m, 2H), 7.14 (t, J = 9.2 Hz, 2H), 3.43 - 3.34 (m, 2H), 3.14 - 3.02 (m, 1H), 2.45 - 2.37 (m, 8H), 2.05 - 1.84 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 337.2

Example 59a and 59b

***Step 1**: Synthesis of 4-(6-(Difluoromethyl)pyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one*



4-(6-(Difluoromethyl)pyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 36a** and **36b** by replacing 5-bromo-2-chloro-3-fluoro-pyridine with 5-bromo-2-(difluoromethyl)pyridine in step 1.

***Step 2**: Chiral Separation of 4-(6-(Difluoromethyl)pyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (Ex 59a & 59b)*

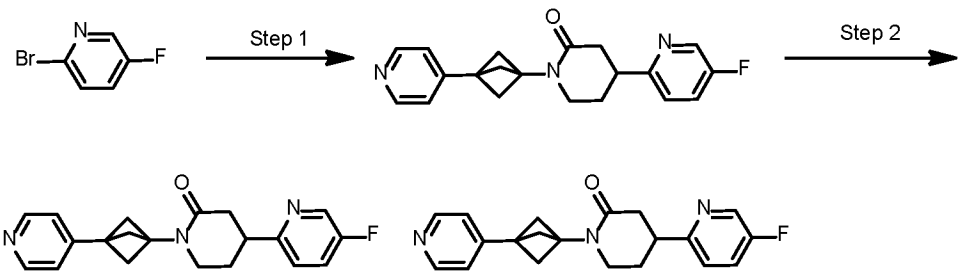
4-(6-(Difluoromethyl)pyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (76 mg, 0.21 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / MeOH + 0.1% NH_4OH = 60/40; 80 mL/min) to afford 4-(6-(difluoromethyl)pyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex. 59a**, peak 1, Rt = 1.753 min, 17.8 mg, 23% yield) and 4-(6-(difluoromethyl)pyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 59b** peak 2, Rt = 2.165 min, 19.7 mg, 26% yield) both as white solids.

Example 59a: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.64 (s, 1H), 8.50 (d, J = 4.8 Hz, 2H), 7.93 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 5.2 Hz, 2H), 6.93 (t, J = 55.2 Hz, 1H), 3.47 - 3.34 (m, 4H), 3.28 - 3.17 (m, 1H), 2.55 - 2.50 (m, 2 H), 2.46 - 2.39 (m, 6H), 2.11 - 1.93 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 370.1

Example 59b: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.64 (s, 1H), 8.50 (d, J = 4.8 Hz, 2H), 7.93 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 5.2 Hz, 2H), 6.93 (t, J = 55.2 Hz, 1H), 3.47 - 3.34 (m, 2H), 3.28 - 3.18 (m, 1H), 2.55 - 2.50 (m, 2 H), 2.46 - 2.38 (m, 6H), 2.12 - 1.94 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 370.1

Examples 60a and 60b

Step 1: *Synthesis of 4-(5-Fluoropyridin-2-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one*



4-(5-Fluoropyridin-2-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 36a** and **36b** by replacing 5-bromo-2-chloro-3-fluoro-pyridine with 2-bromo-5-fluoropyridine in Step 1.

Step 2: *Chiral Separation of 4-(5-Fluoropyridin-2-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (Ex 60a & 60b)*

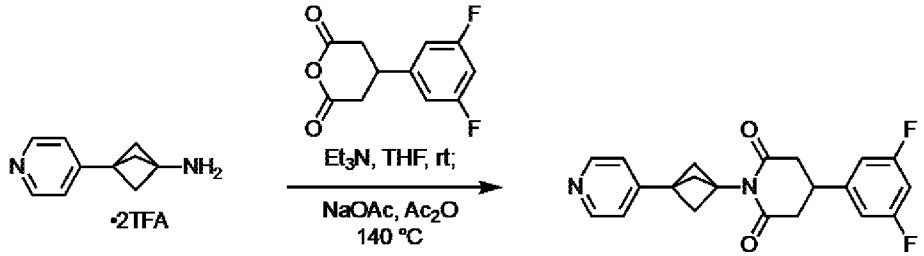
4-(5-Fluoropyridin-2-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (60 mg, 0.18 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / MeOH + 0.1% NH_4OH = 55/45; 80 mL/min) to afford 4-(5-fluoropyridin-2-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 60a**, peak 1, Rt = 1.888 min, 21 mg, 35% yield) and 4-(5-fluoropyridin-2-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 60b**, peak 2, Rt = 2.111 min, 20 mg, 33% yield) both as white solids.

Example 60a: ^{1}**H NMR** (400 MHz, DMSO-d_6) δ 8.55 - 8.45 (m, 3H), 7.72 - 7.66 (m, 1H), 7.43 (dd, J = 4.4, 8.4 Hz, 1H), 7.26 (dd, J = 1.6, 4.4 Hz, 2H), 3.44 - 3.24 (m, 3H), 2.60 - 2.55 (m, 2H), 2.40 (s, 6H), 2.16 - 2.05 (m, 1H), 1.97 - 1.85 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 338.1

Example 60b: ^{1}**H NMR** (400 MHz, DMSO-d_6) δ 8.55 - 8.45 (m, 3H), 7.72 - 7.66 (m, 1H), 7.43 (dd, J = 4.4, 8.8 Hz, 1H), 7.26 (dd, J = 1.6, 4.4 Hz, 2H), 3.44 - 3.22 (m, 3H), 2.56 - 2.52 (m, 2H), 2.40 (s, 6H), 2.15 - 2.06 (m, 1H), 1.96 - 1.85 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 338.1

Examples 61

Step 1: *Synthesis of 4-(3,5-difluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidine-2,6-dione (Ex. 61)*



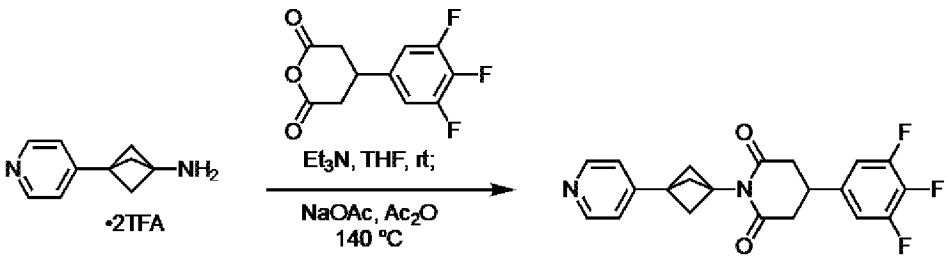
To a solution of 3-(4-pyridyl)bicyclo[1.1.1]pentan-1-amine 2,2,2-trifluoroacetic acid salt (53 mg, 0.14 mmol, 1 equiv.) and 4-(3,5-difluorophenyl)dihydro-2*H*-pyran-2,6(3*H*)-dione (95 mg, 0.41 mmol, 1.1 equiv.) in tetrahydrofuran (1.4 mL, 0.1 M) was added triethylamine (57 µL, 0.41 mmol, 3.0 equiv.). Resulting solution was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. To the resulting residue was added acetic anhydride (680 uL, 0.2 M) and sodium acetate (15 mg, 0.18 mmol, 1.3 equiv.) and resulting solution was stirred at 140 °C for 2 hours. The product mixture was cooled to room temperature and diluted with water (3 mL) and stirred in ice bath. To the mixture was slowly added 5N sodium hydroxide solution until pH was neutral. Resulting solution was extracted with isopropyl acetate (5 mL) for 3 times. Organic layers were combined and dried with $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified by prep HPLC (XSelect CSH Prep C18, 50 × 30 mm, 5 µm; 0.1% ammonium hydroxide in water /acetonitrile using a gradient of 30-70%; 60 mL/min, 25 °C) to afford 4-(3,5-difluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidine-2,6-dione (8 mg, 16%) as a colorless solid.

^{1}H NMR (400 MHz, DMSO) δ 8.53 – 8.47 (m, 2H), 7.31 – 7.25 (m, 2H), 7.18 – 7.08 (m, 2H), 7.11 – 7.05 (m, 1H), 3.50 (tt, *J* = 12.1, 4.3 Hz, 1H), 2.95 (dd, *J* = 16.6, 12.2 Hz, 2H), 2.81 (dd, *J* = 16.7, 4.3 Hz, 2H), 2.61 (s, 6H).

LCMS: (ESI, m/z) $[M+H]^+$ = 369.1416

Example 62

***Step 1**: Synthesis of 1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(3,4,5-trifluorophenyl)piperidine-2,6-dione (Ex 62)*



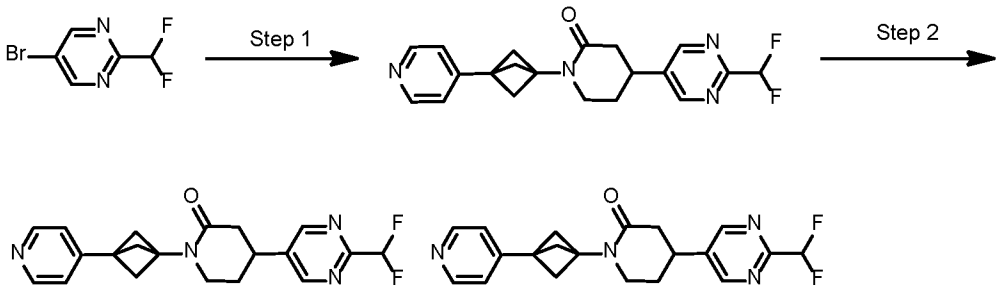
To a solution of 3-(4-pyridyl)bicyclo[1.1.1]pentan-1-amine 2,2,2-trifluoroacetic acid salt (57 mg, 0.15 mmol, 1 equiv.) and 4-(3,4,5-trifluorophenyl)dihydro-2*H*-pyran-2,6(3*H*)-dione (40 mg, 0.16 mmol, 1.1 equiv.) in tetrahydrofuran (1.5 mL, 0.1 M) was added triethylamine (62 µL, 0.44 mmol, 3.0 equiv.). Resulting solution

was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. To the resulting residue was added acetic anhydride (740 uL, 0.2 M) and sodium acetate (16 mg, 0.19 mmol, 1.3 equiv.) and resulting solution was stirred at 140 °C for 2 hours. The product mixture was cooled to room temperature and diluted with water (3 mL) and stirred in ice bath. To the mixture was slowly added 5N sodium hydroxide solution until pH was neutral. Resulting solution was extracted with isopropyl acetate (5 mL) for 3 times. Organic layers were combined and dried with $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified by prep HPLC (XSelect CSH Prep C18, 50 × 30 mm, 5 μm; 0.1% formic acid in water /acetonitrile using a gradient of 5-50%; 60 mL/min, 25 °C) to afford 1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(3,4,5-trifluorophenyl)piperidine-2,6-dione (29 mg, 51%) as a colorless solid.

^{1}H NMR (400 MHz, DMSO) δ 8.53 – 8.47 (m, 2H), 7.39 – 7.24 (m, 4H), 3.49 (tt, *J* = 12.3, 4.3 Hz, 1H), 2.93 (ddt, *J* = 16.9, 12.3, 1.4 Hz, 2H), 2.85 – 2.75 (m, 2H), 2.61 (s, 6H).

LCMS: (ESI, m/z) $[M+H]^+$ = 387.1319

Examples 63a and 63b



***Step 1**: Synthesis of 4-(2-(Difluoromethyl)pyrimidin-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one*

4-(2-(Difluoromethyl)pyrimidin-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 63a** and **Ex 36b** by replacing 5-bromo-2-chloro-3-fluoro-pyridine with 5-bromo-2-(difluoromethyl)pyrimidine in Step 1.

***Step 2**: Chiral Separation of 4-(2-(Difluoromethyl)pyrimidin-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (Ex. 63a & 63b)*

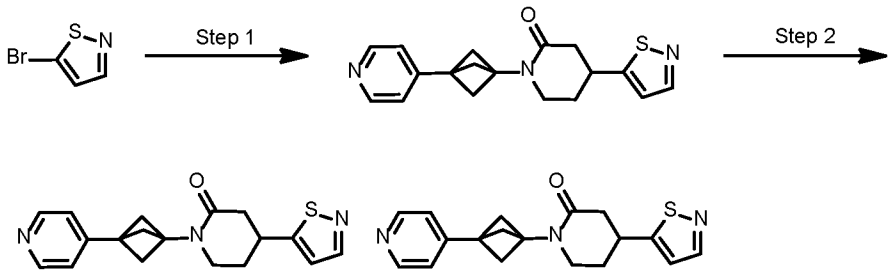
4-(2-(Difluoromethyl)pyrimidin-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (47 mg, 0.13 mmol) was separated by chiral SFC (Cellulose-2 (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 45/55; 150 mL/min) to afford 4-(2-(difluoromethyl)pyrimidin-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 63a**, peak 1, Rt = 2.355 min, 16.7 mg, 36% yield) and 4-(2-(difluoromethyl)pyrimidin-5-yl)-1-(3-

(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 63b**, peak 2, Rt = 3.449 min, 15.8 mg, 34% yield) both as white solids.

Example 63a: ^{1}**H NMR** ($CDCl_3$, 400 MHz): δ 8.76 (s, 2H), 8.54 (d, J = 5.6 Hz, 2H), 7.19 - 7.12 (m, 2H), 6.68 (t, J = 54.4 Hz, 1H), 3.57 - 3.40 (m, 2H), 3.30 - 3.17 (m, 1H), 2.86 - 2.73 (m, 1H), 2.61 - 2.53 (m, 1H), 2.51 (s, 6H), 2.32 - 2.19 (m, 1H), 2.16 - 1.99 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 371.0

Example 63b: ^{1}**H NMR** ($CDCl_3$, 400 MHz): δ 8.76 (s, 2H), 8.55 (d, J = 5.6 Hz, 2H), 7.15 (d, J = 6.0 Hz, 2H), 6.68 (t, J = 54.4 Hz, 1H), 3.57 - 3.40 (m, 2H), 3.30 - 3.18 (m, 1H), 2.86 - 2.73 (m,1H), 2.61 - 2.53 (m, 1H), 2.51 (s, 6H), 2.30 - 2.20 (m, 1H), 2.17 - 2.01 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 371.2

Examples 64a and 64b



***Step 1**: Synthesis of 4-(Isothiazol-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one*

4-(Isothiazol-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 36a** and **Ex 36b** by replacing 5-bromo-2-chloro-3-fluoro-pyridine with 5-bromoisothiazole in step 1.

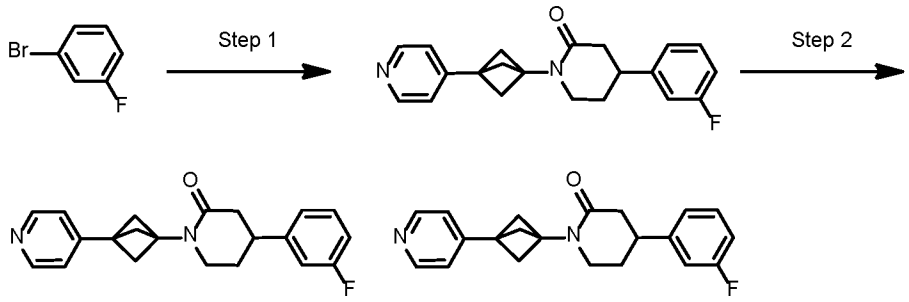
***Step 2**: Chiral Separation of 4-(Isothiazol-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (Ex 64a & 64b)*

4-(Isothiazol-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (100 mg, 0.31 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / MeOH + 0.1% NH_4OH = 60/40; 80 mL/min) to afford 4-(isothiazol-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 64a**, peak 1, Rt = 1.939 min, 18.9 mg, 19% yield) as a white solid and 30 mg crude peak. The crude peak2 was further seperated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / MeOH + 0.1% NH_4OH = 60/40; 80 mL/min) to afford 4-(isothiazol-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 64b**, peak 2, Rt = 2.170 min, 23.8 mg, 24% yield) as a white solid.

Example 64a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.53 - 8.45 (m, 3H), 7.30 (s, 1H), 7.28 - 7.23 (m, 2H), 3.67 - 3.56 (m, 1H), 3.41 - 3.35 (m, 2H), 2.72 - 2.64 (m, 1H), 2.48 - 2.42 (m, 1H), 2.41 - 2.36 (s, 6H), 2.28 - 2.17 (m, 1H), 2.00 - 1.87 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 325.9

Example 64b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.56 - 8.45 (m, 3H), 7.30 (d, J = 0.8 Hz, 1H), 7.28 - 7.21 (m, 2H), 3.67 - 3.55 (m, 1H), 3.44 - 3.34 (m, 2H), 2.72 - 2.64 (m, 1H), 2.47 - 2.42 (m, 1H), 2.41 - 2.36 (m, 6H), 2.27 - 2.16 (m, 1H), 2.00 - 1.86 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 326.1

Examples 65a and 65b



Step 1: *Synthesis of 4-(3-Fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one*

4-(3-Fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 36a** and **Ex 36b** by replacing 5-bromo-2-chloro-3-fluoro-pyridine with 1-bromo-3-fluorobenzene in step 1.

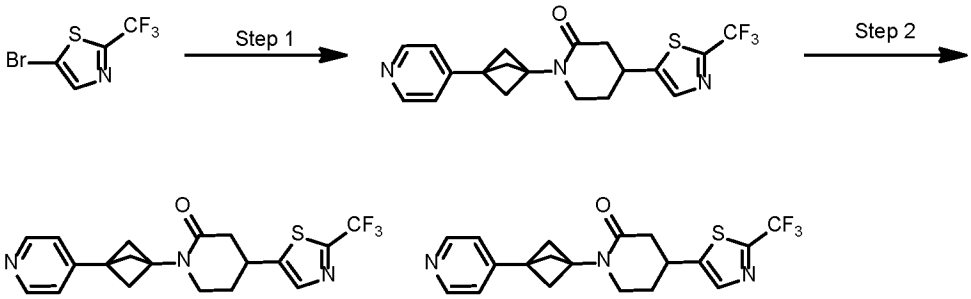
Step 2: *Chiral Separation of 4-(3-Fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (Ex 65a & 65b)*

4-(3-Fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (50 mg, 0.15 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 70/30; 80 mL/min) to afford 4-(3-fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 65a**, peak 1, Rt = 1.794 min, 22 mg, 43% yield) and 4-(3-fluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 65b**, peak 2, Rt = 1.988 min, 20 mg, 40% yield) both as white solid.

Example 65a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.50 (d, J = 6.0 Hz, 2H), 7.41 - 7.32 (m, 1H), 7.29 - 7.23 (m, 2H), 7.19 - 7.10 (m, 2H), 7.08 - 7.01 (m, 1H), 3.42 - 3.37 (m, 2H), 3.17 - 3.04 (m, 1H), 2.47 - 2.36 (m, 8H), 2.07 - 1.86 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 337.2

Example 65b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.49 (d, J = 4.8 Hz, 2H), 7.41 - 7.32 (m, 1H), 7.26 (d, J = 5.2 Hz, 2H), 7.19 - 7.10 (m, 2H), 7.09 - 7.00 (m, 1H), 3.44 - 3.37 (m, 2H), 3.16 - 3.04 (m, 1H), 2.46 - 2.34 (m, 8H), 2.08 - 1.85 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 337.2

Examples 66a and 66b



***Step 1**: Synthesis of 1-(3-(Pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(2-(trifluoromethyl)thiazol-5-yl)piperidin-2-one*

1-(3-(Pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(2-(trifluoromethyl)thiazol-5-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 36a** and **Ex 36b** by replacing 5-bromo-2-chloro-3-fluoro-pyridine with 5-bromo-2-(trifluoromethyl)thiazole in step 1.

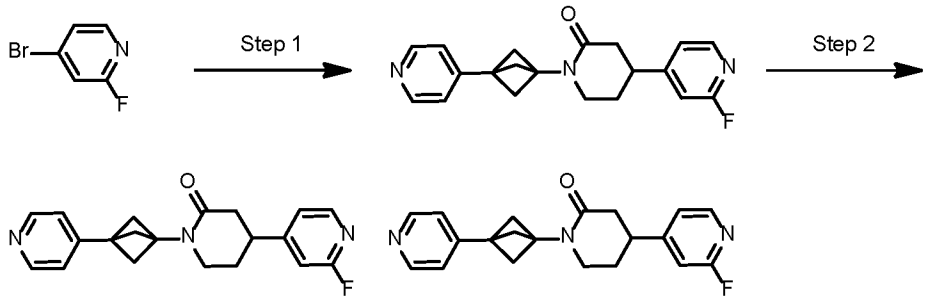
***Step 2**: Chiral Separation of 1-(3-(Pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(2-(trifluoromethyl)thiazol-5-yl)piperidin-2-one (Ex. 66a & 66b)*

1-(3-(Pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(2-(trifluoromethyl)thiazol-5-yl)piperidin-2-one (60 mg, 0.15 mmol) was separated by chiral SFC (Chiralcel IC (250 mm x 30 mm, 10 um), Supercritical CO_2 / *i*-PrOH + 0.1% NH_4OH = 55/45; 80 mL/min) to 1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(2-(trifluoromethyl)thiazol-5-yl)piperidin-2-one (**Ex 66a**, peak 1, Rt = 2.418 min, 17.2 mg, 28% yield) and 1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(2-(trifluoromethyl)thiazol-5-yl)piperidin-2-one (**Ex 66b**, peak 2, Rt = 3.006 min, 20.2 mg, 33%) both as white solids.

Example 66a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.49 (d, J = 5.6 Hz, 2H), 8.00 (s, 1H), 7.26 (d, J = 6.0 Hz, 2H), 3.67 - 3.56 (m, 1H), 3.43 - 3.38 (m, 2H), 2.74 - 2.65 (m, 1H), 2.54 -2.51 (m, 1H), 2.41 (s, 6H), 2.29 - 2.20 (m, 1H), 2.02 - 1.90 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 394.0

Example 66b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.49 (d, J = 6.0 Hz, 2H), 8.00 (s, 1H), 7.28 - 7.24 (m, 2H), 3.67 - 3.56 (m, 1H), 3.43 - 3.38 (m, 2H), 2.74 - 2.66 (m, 1H), 2.54 -2.50 (m, 1H), 2.40 (s, 6H), 2.29 - 2.20 (m, 1H), 2.02 - 1.89 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 394.1.

Examples 67a and 67b



***Step 1**: Synthesis of 4-(2-Fluoropyridin-4-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one*

4-(2-Fluoropyridin-4-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 36a** and **Ex 36b** by replacing 5-bromo-2-chloro-3-fluoro-pyridine with 4-bromo-2-fluoropyridine in step 1.

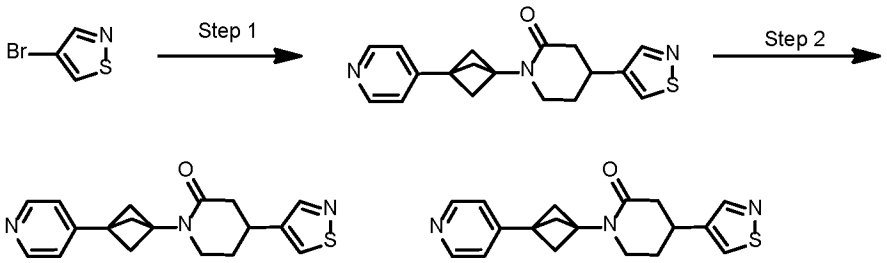
***Step 2**: Chiral Separation of 4-(2-fluoropyridin-4-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (Ex 67a & 67b)*

4-(2-fluoropyridin-4-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (77 mg, 0.23 mmol) was separated by chiral SFC (Chiralpak IC (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 55/45; 80 mL/min) to give 4-(2-fluoropyridin-4-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 67a**, peak 1, Rt = 3.902 min, 26 mg, 33% yield) and 4-(2-fluoropyridin-4-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 67b**, peak 2, Rt = 4.541 min, 26 mg, 33% yield) both as white solids.

Example 67a: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.55 (d, J = 3.6 Hz, 2H), 8.20 (d, J = 5.2 Hz, 1H), 7.17 (d, J = 5.6 Hz, 2H), 7.04 (d, J = 5.2 Hz, 1H), 6.78 (s, 1H), 3.52 - 3.35 (m, 2H), 3.22 - 3.08 (m, 1H), 2.80 - 2.67 (m, 1H), 2.51 (s, 6H), 2.50 - 2.44 (m, 1H), 2.26 - 2.14 (m, 1H), 2.05 - 1.92 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 338.1

Example 67b: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.50 (d, J = 5.6 Hz, 2H), 8.18 (d, J = 4.8 Hz, 1H), 7.31 (d, J = 5.2 Hz, 1H), 7.28 - 7.23 (m, 2H), 7.13 (s, 1H), 3.45 - 3.37 (m, 2H), 3.25 - 3.14 (m, 1H), 2.49 - 2.44 (m, 2H), 2.41 (s, 6H), 2.13 - 2.03 (m, 1H), 2.02 - 1.87 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 338.1

Examples 68a and 68b



***Step 1**: Synthesis of 4-(Isothiazol-4-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one*

4-(Isothiazol-4-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 36a** and **Ex 36b** by replacing 5-bromo-2-chloro-3-fluoro-pyridine with 4-bromoisothiazole in step 1.

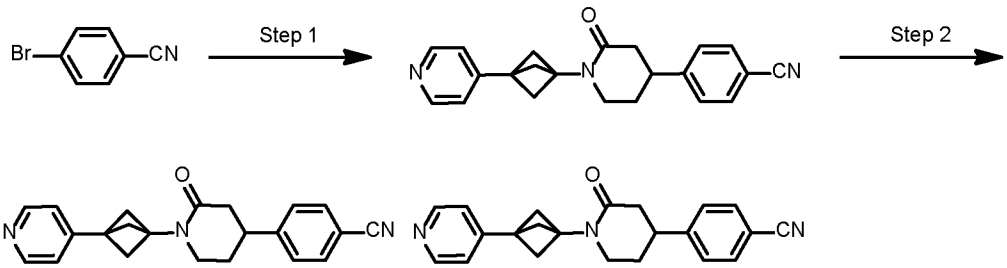
***Step 2**: Chiral Separation of 4-(Isothiazol-4-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (Ex. 68a & 68b)*

4-(Isothiazol-4-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (130 mg, 0.35 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / MeOH + 0.1% NH_4OH = 40/60; 80 mL/min) to give 4-(isothiazol-4-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 68a**, peak 1, Rt = 2.238m min, 35 mg, 23% yield) and 4-(isothiazol-4-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 68b**, peak 2, Rt = 2.902 min, 34 mg, 21% yield) both as white solids.

Example 68a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.79 (s, 1H), 8.58 (s, 1H), 8.49 (d, J = 5.6 Hz, 2H), 7.25 (d, J = 6.0 Hz, 2H), 3.38 - 3.25 (m, 3H), 2.66 - 2.57 (m, 1H), 2.48 - 2.43 (m, 1H), 2.40 (s, 6H), 2.21 - 2.11 (m, 1H), 1.97 - 1.82 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 326.1

Example 68b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.79 (s, 1H), 8.58 (s, 1H), 8.49 (d, J = 5.2 Hz, 2H), 7.26 (d, J = 6.0 Hz, 2H), 3.38 - 3.22 (m, 3H), 2.67 - 2.56 (m, 1H), 2.48 - 2.43 (m, 1H), 2.40 (s, 6H), 2.23 - 2.11 (m, 1H), 1.96 - 1.82 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 325.9

Examples 69a and 69b



Step 1: *Synthesis of 4-(2-Oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)benzonitrile*

4-(2-Oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)benzonitrile was prepared using the general procedure described for the preparation of **Ex 36a** and **Ex 36b** by replacing 5-bromo-2-chloro-3-fluoro-pyridine with 4-bromobenzonitrile in step 1.

Step 2: *Chiral Separation of 4-(2-Oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)benzonitrile (Ex 69a & 69b)*

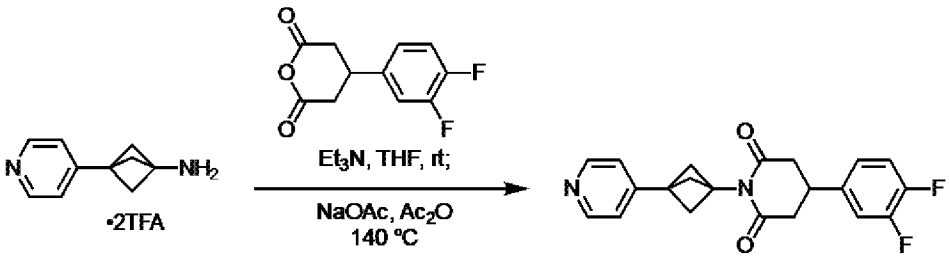
4-(2-Oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)benzonitrile (45 mg, 0.13 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / MeOH + 0.1% NH_4OH = 65/35; 80 mL/min) to give 4-(2-oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)benzonitrile (**Ex 69a**, peak 1, Rt = 2.055 min, 18.1 mg, 40% yield) and 4-(2-oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)benzonitrile (**Ex 69b**, peak 2, Rt = 2.249 min, 20.6 mg, 46% yield) both as white solids.

Example 69a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.55 - 8.45 (m, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.30 - 7.20 (m, 2H), 3.41 - 3.32 (m, 2H), 3.24 - 3.14 (m, 1H), 2.48 - 2.43 (m, 2H), 2.42 - 2.35 (m, 6H), 2.08 - 1.89 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 344.2

Example 69b: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.50 (d, J = 6.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 5.6 Hz, 2H), 3.39 - 3.32 (m, 2H), 3.24 - 3.15 (m, 1H), 2.47 - 2.43 (m, 2H), 2.41 - 2.35 (m, 6H), 2.06 - 1.88 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 344.0

Example 70

Step 1: *Synthesis of 4-(3,4-difluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidine-2,6-dione (Ex 70)*



To a solution of 3-(4-pyridyl)bicyclo[1.1.1]pentan-1-amine 2,2,2-trifluoroacetic acid salt (55 mg, 0.14 mmol, 1 equiv.) and 4-(3,4-difluorophenyl)dihydro-2*H*-pyran-2,6(3*H*)-dione (36 mg, 0.16 mmol, 1.1 equiv.) in tetrahydrofuran (1.4 mL, 0.1 M) was added triethylamine (59 µL, 0.43 mmol, 3.0 equiv.). Resulting solution was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. To the resulting residue was added acetic anhydride (710 uL, 0.2 M) and sodium acetate (15 mg, 0.18 mmol, 1.3 equiv.) and resulting solution was stirred at 140 °C

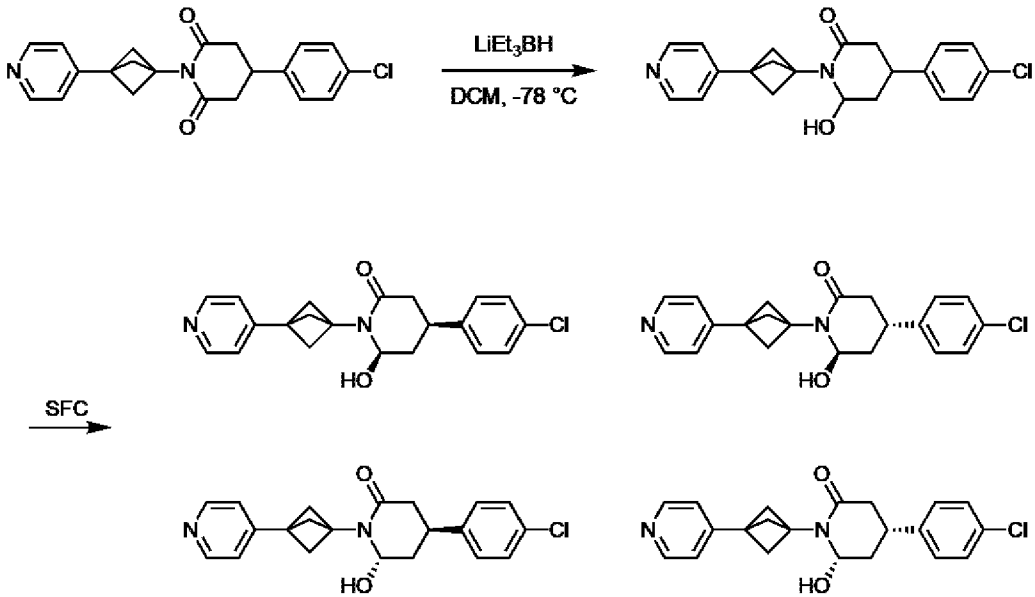
for 2 hours. The product mixture was cooled to room temperature and diluted with water (3 mL) and stirred in ice bath. To the mixture was slowly added 5N sodium hydroxide solution until pH was neutral. Resulting solution was extracted with isopropyl acetate (5 mL) for 3 times. Organic layers were combined and dried with $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified by prep HPLC (XSelect CSH Prep C18, 50 × 30 mm, 5 μm; 0.1% ammonium hydroxide in water /acetonitrile using a gradient of 5-85%; 60 mL/min, 25 °C) to afford 4-(3,4-difluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidine-2,6-dione (20 mg, 38%) as a colorless solid.

^{1}H NMR (400 MHz, DMSO) δ 8.53 – 8.46 (m, 2H), 7.48 – 7.36 (m, 2H), 7.31 – 7.25 (m, 2H), 7.21 – 7.13 (m, 1H), 3.47 (tt, *J* = 11.9, 4.2 Hz, 1H), 2.94 (dd, *J* = 16.6, 12.1 Hz, 2H), 2.79 (dd, *J* = 16.6, 4.4 Hz, 2H), 2.61 (s, 6H).

LCMS: (ESI, m/z) $[M+H]^+$ = 369.1414

Examples 71a, 71b, 71c, and 71d

***Step 1—2**: Synthesis of 4-(4-chlorophenyl)-6-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (Ex 71a, 71b, 71c, and 71d)*



A solution of 4-(4-chlorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidine-2,6-dione (**Ex 52**, 28 mg, 0.077 mmol, 1 equiv.) in dichloromethane (380 μL, 0.2 M) under nitrogen atmosphere was cooled to -78 °C and stirred for 5 min. The solution was then added lithium triethylborohydride (1 M in tetrahydrofuran, 150 μL, 0.15 mmol, 2.0 equiv.) dropwise and resulting solution was stirred at -78 °C for 20 min. The reaction mixture was quenched with dropwise addition of methanol (1 mL) and resulting solution was stirred at -78 °C for 10 min. To the product mixture was added saturated aqueous sodium bicarbonate (1 mL) dropwise and resulting mixture was warmed

up to room temperature. To the solution was added more saturated aqueous sodium bicarbonate (2 mL) and resulting solution was stirred at room temperature for 1 hour and extracted with dichloromethane (4 mL) for 3 times. Organic layers were combined and dried with $MgSO_4$, filtered and concentrated under reduced pressure. Crude mixture was purified and separated by chiral SFC (Chiralpak IG (250 × 21.2 mm, 5 μm), Supercritical CO2 / 0.1% ammonium hydroxide in methanol = 60/40; 70 mL/min) to afford 4-(4-chlorophenyl)-6-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 71a**, peak 1, 2.1 mg, 7.4% yield), 4-(4-chlorophenyl)-6-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 71b**, peak 2, 6.3 mg, 22% yield), 4-(4-chlorophenyl)-6-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 71d**, peak 3, 5.9 mg, 21% yield) and 4-(4-chlorophenyl)-6-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 71c**, peak 2, 2.2 mg, 7.4% yield) as colorless solid. Stereochemistry arbitrarily assigned.

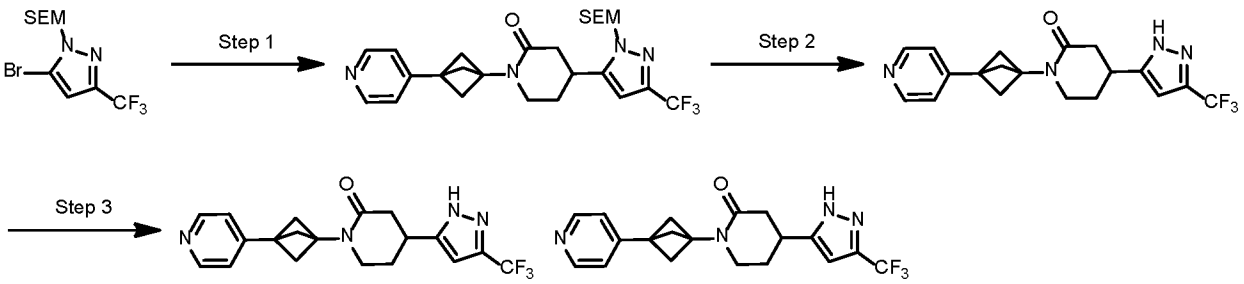
Example 71a: LCMS: (ESI, m/z) $[M+H]^+$ = 369.1362

Example 71b: ^{1}H NMR (400 MHz, DMSO) δ 8.53 – 8.47 (m, 2H), 7.36 (q, *J* = 8.6 Hz, 4H), 7.29 – 7.24 (m, 2H), 5.93 (d, *J* = 5.9 Hz, 1H), 5.12 (dt, *J* = 5.8, 2.8 Hz, 1H), 3.50 (tdd, *J* = 12.4, 5.6, 2.9 Hz, 1H), 2.51 – 2.33 (m, 8H), 2.06 (td, *J* = 13.1, 3.1 Hz, 1H), 1.92 (dq, *J* = 13.2, 2.5 Hz, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 369.1360

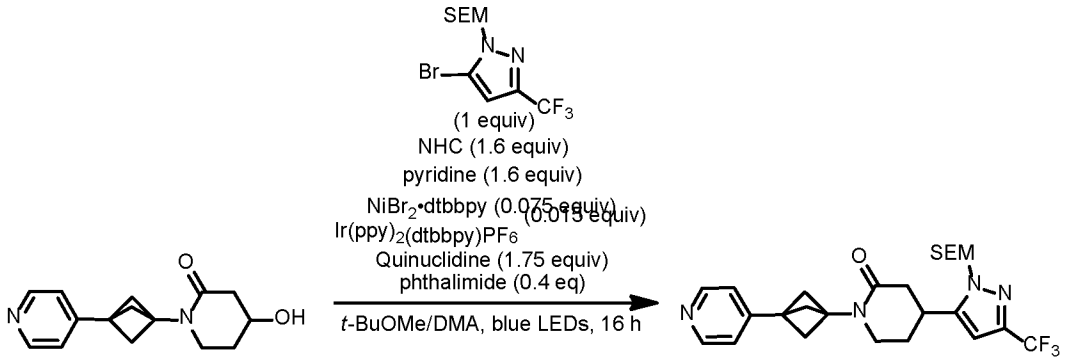
Example 71c: LCMS: (ESI, m/z) $[M+H]^+$ = 369.1360

Example 71d: ^{1}H NMR (400 MHz, DMSO) δ 8.53 – 8.47 (m, 2H), 7.36 (q, *J* = 8.6 Hz, 4H), 7.29 – 7.24 (m, 2H), 5.93 (d, *J* = 5.9 Hz, 1H), 5.12 (dt, *J* = 5.9, 2.8 Hz, 1H), 3.49 (tdt, *J* = 12.3, 6.8, 3.4 Hz, 1H), 2.51 – 2.33 (m, 8H), 2.06 (td, *J* = 13.1, 3.1 Hz, 1H), 1.92 (dq, *J* = 13.2, 2.5 Hz, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 369.1361

Examples 72a and 72b



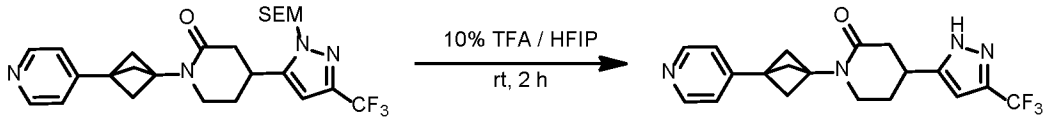
Step 1: *Sythesis of 1-(3-(Pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)piperidin-2-one*



1-(3-(Pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 36a** and **Ex 36b** by replacing 5-bromo-2-chloro-3-fluoro-pyridine with 5-bromo-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole in step 1.

LCMS: (ESI, m/z) $[M+H]^+ = 507.1$

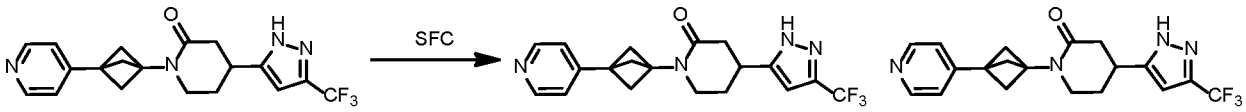
Step 2: *Synthesis of 1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(3-(trifluoromethyl)-1H-pyrazol-5-yl)piperidin-2-one*



A solution of 1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-5-yl)piperidin-2-one (195 mg, 0.38 mmol) in 10% TFA / HFIP solution (5 mL) was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure. The residue was dissolved in DCM (5 mL), and then treated with aqueous saturated $NaHCO_3$ until pH = 8. The organic phase was separated, and the aqueous phase was extracted with DCM (5 mL x 2). The combines organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 40-70% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to afford 1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)piperidin-2-one (80 mg, 55% yield) as a white solid.

LCMS: (ESI, m/z) $[M+H]^+ = 377.2$

Step 3: *Chiral Separation of 1-(3-(Pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(3-(trifluoromethyl)-1H-pyrazol-5-yl)piperidin-2-one (Ex 72a & 72b)*

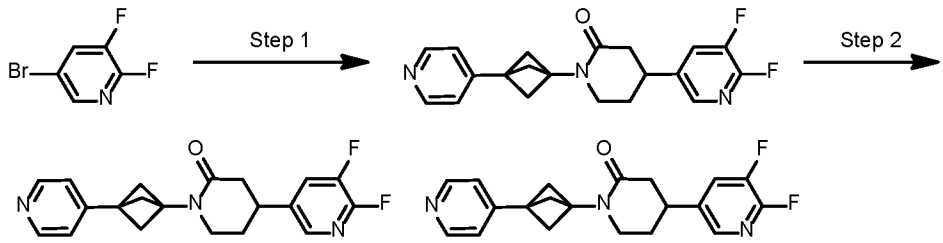


1-(3-(Pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)piperidin-2-one (70 mg, 0.19 mmol) was separated by chiral SFC (Chiralcel OD (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 80/20; 150 mL/min) to give 1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 72a**, peak 1, Rt = 1.234 min, 28 mg, 40% yield) and 1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-4-(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)piperidin-2-one (**Ex 72b**, peak 2, Rt = 1.311 min, 25 mg, 36% yield) both as white solid.

Example 72a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ = 13.47 (br s, 1H), 8.49 (dd, J = 1.6, 6.0 Hz, 2H), 7.25 (dd, J = 2.0, 6.4 Hz, 2H), 6.55 (s, 1H), 3.37 - 3.21 (m, 3H), 2.66 - 2.58 (m, 1H), 2.48 - 2.35 (m, 7H), 2.24 - 2.13 (m, 1H), 1.94 - 1.80 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 377.2

Example 72b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ = 13.47 (br s, 1H), 8.49 (dd, J = 1.6, 4.4 Hz, 2H), 7.31 - 7.21 (m, 2H), 6.55 (s, 1H), 3.38 - 3.15 (m, 1H), 2.65 - 2.58 (m, 1H), 2.47 - 2.36 (m, 7H), 2.25 - 2.12 (m, 1H), 1.93 - 1.80 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 377.2

Examples 73a and 73b



***Step 1**: Synthesis of 4-(5,6-Difluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one*

4-(5,6-Difluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 36a** and **Ex 36b** by replacing 5-bromo-2-chloro-3-fluoro-pyridine with 5-bromo-2,3-difluoropyridine in step 1.

***Step 2**: Chiral Separation of 4-(5,6-Difluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (Ex 73a & 73b)*

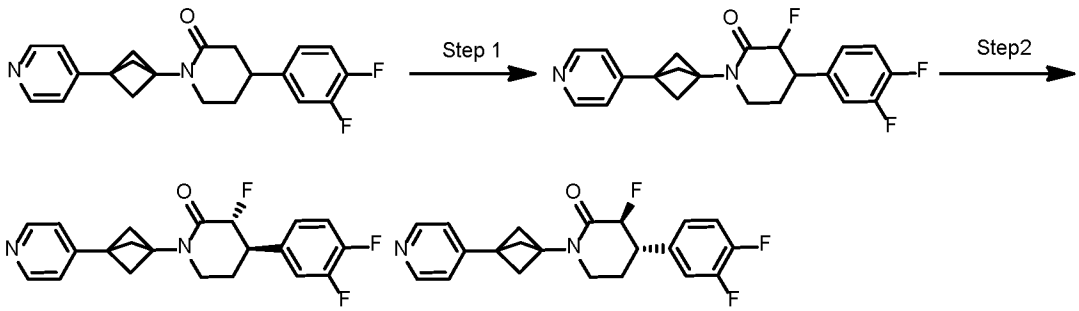
4-(5,6-Difluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (70 mg, 0.19 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical

CO_2 / MeOH + 0.1% NH_4OH = 55/45; 80 mL/min) to give 4-(5,6-difluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 73a**, peak 1, Rt = 1.444 min, 28 mg, 40% yield) and 4-(5,6-difluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 73b**, peak 2, Rt = 2.081 min, 25 mg, 36% yield) both as white solids.

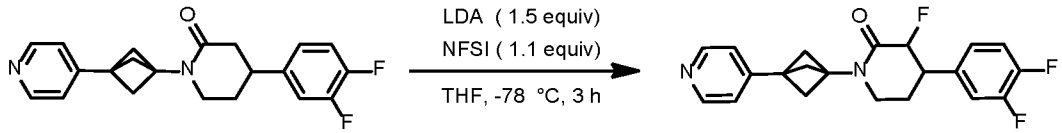
Example 73a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.50 (d, J = 4.8 Hz, 2H), 8.10 - 8.02 (m, 1H), 7.99 (s, 1H), 7.26 (d, J = 6.0 Hz, 2H), 3.46 - 3.37 (m, 2H), 3.25 - 3.15 (m, 1H), 2.49 - 2.45 (m, 2H), 2.41 (s, 6H), 2.08 - 1.90 (m, 2 H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 356.0

Example 73b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.50 (d, J = 4.8 Hz, 2H), 8.10 - 8.02 (m, 1H), 7.99 (s, 1H), 7.26 (d, J = 6.0 Hz, 2H), 3.46 - 3.37 (m, 2H), 3.25 - 3.15 (m, 1H), 2.49 - 2.45 (m, 2H), 2.41 (s, 6H), 2.08 - 1.90 (m, 2 H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 356.2

Examples 74a and 74b



Step 1: *Synthesis of 4-(3,4-difluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one*

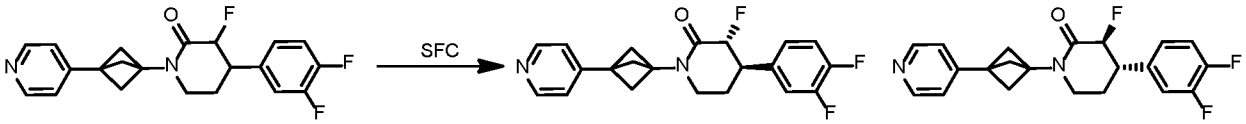


To a stirred solution of 4-(3,4-difluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (500 mg, 1.41 mmol) in THF (7mL) was added LDA (1.1 mL, 2.12 mmol) at -78 °C under nitrogen atmosphere. After stirring at -78 °C for 45 minutes, a solution of NFSI (489 mg, 1.55 mmol) in THF (3 mL) was added dropwise -78 °C. After stirring at -78 °C for 3 hours, the reaction was quenched with saturated NH_4Cl solution (10 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO2, 30% EE (EtOAc/EtOH = 3:1) in petroleum ether) to afford 500 mg crude product, which was further purified by reverse phase chromatography (acetonitrile: 35-55 / 0.05%

NH_4OH + 10 mM NH_4HCO_3 in water) to give 4-(3,4-difluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (70 mg, 13% yield) as a white solid.

LCMS: (ESI, m/z) $[M+H]^+$ = 373.1

Step 2: *Chiral Separation of 4-(3,4-Difluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (Ex 74a & 74b)*



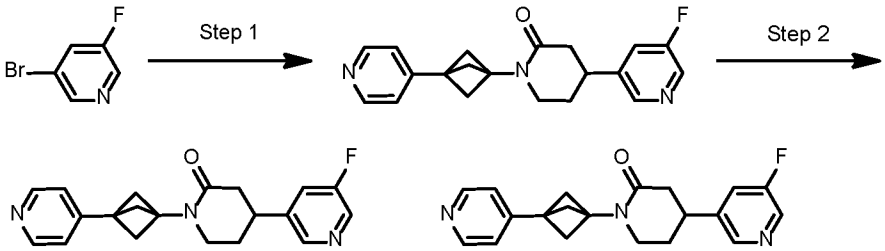
4-(3,4-Difluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (67 mg, 0.18 mmol) was separated by chiral SFC (Regis (S,S) whelk-01 (250 mm x 25 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 40/60; 80 mL/min) to give (3R,4R)-4-(3,4-difluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 74a**, peak 1, Rt = 2.307 min, 18 mg, 27% yield) as a white solid and crude 16 mg crude peak 2. The crude peak 2 (16 mg, 23.9% yield) was further purified by chiral SFC (Chiralcel OD (250 mm x 30mm, 10 um)), Supercritical CO_2 / MeOH + 0.1% NH_4OH = 70/30; 80 mL/min) to give (3S,4S)-4-(3,4-difluorophenyl)-3-fluoro-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 74b**, peak 2, Rt = 3.605 min, 7.1 mg, 11% yield) as a white solid.

The relative configuration was confirmed by 2D NMR. Stereochemistry was arbitrarily assigned to each stereoisomer.

Example 74a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.50 (d, J = 5.6 Hz, 2H), 7.53 - 7.37 (m, 2H), 7.28 (d, J = 5.6 Hz, 2H), 7.24 - 7.19 (m, 1H), 5.08 (dd, J = 11.2, 47.6 Hz, 1H), 3.45 - 3.40 (m, 3H), 2.46 - 2.41 (m, 6H), 2.21 - 2.11 (m, 1H), 2.04 - 1.95 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 373.1

Example 74b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.50 (d, J = 5.6 Hz, 2H), 7.53 - 7.36 (m, 2H), 7.28 (d, J = 6.0 Hz, 2H), 7.24 - 7.19 (m, 1H), 5.08 (dd, J = 11.2, 47.6 Hz, 1H), 3.45 - 3.40 (m, 3H), 2.46 - 2.40 (m, 6H), 2.19 - 2.10 (m, 1H), 2.04 - 1.96 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 373.1

Examples 75a and 75b



Step 1: *Synthesis of 4-(5-Fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one*

4-(5-Fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 36a** and **Ex 36b** by replacing 5-bromo-2-chloro-3-fluoro-pyridine with 3-bromo-5-fluoropyridine in step 1.

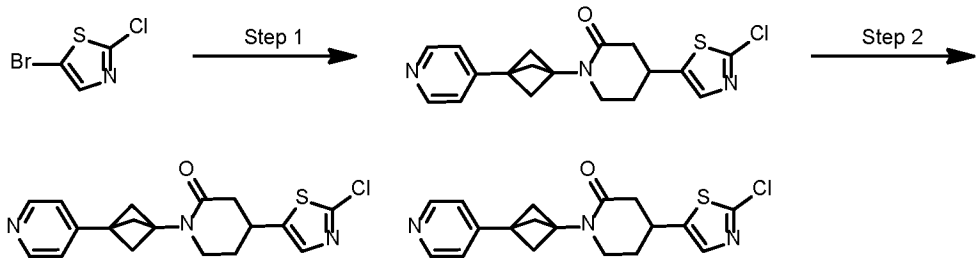
Step 2*: Chiral Separation of 4-(5-Fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one*

4-(5-Fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (86 mg, 0.35 mmol) was separated by chiral SFC (Chiralcel IC (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 40/60; 80 mL/min) to give 4-(5-fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 75a**, peak 1, Rt = 3.626 min, 22 mg, 25% yield) and 4-(5-fluoropyridin-3-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 75b**, peak 2, Rt = 4.874 min, 28 mg, 32% yield) both as white solids.

Example 75a: ^{1}**H NMR** (DMSO-d_6, 400 MHz,): δ 8.49 (dd, J =1.6, 4.8 Hz, 2H), 8.45 (d, J = 2.8 Hz, 1H), 8.42 (s, 1H), 7.72 (dd, J =2.0, 10.4 Hz, 1H), 7.26 (dd, J =1.6, 4.8 Hz, 2H), 3.46 - 3.38 (m, 2H), 3.26 - 3.11 (m, 1H), 2.49 - 2.44 (m, 2H), 2.42 (s, 6H), 2.13 - 1.87 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 338.1

Example 75b: ^{1}H NMR (DMSO-d_6, 400 MHz,): δ 8.50 (d, J = 5.6 Hz, 2H), 8.45 (d, J = 2.4 Hz, 1H), 8.42 (s, 1H), 7.72 (d, J = 10.4 Hz, 1H), 7.26 (d, J = 5.4 Hz, 2H), 3.46 - 3.36 (m, 2H), 3.26 - 3.14 (m, 1H), 2.49 - 2.44 (m, 2H), 2.42 (s, 6H), 2.09 - 1.90 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 338.1.

Examples 76a and 76b



Step 1: *Synthesis of 4-(2-Chlorothiazol-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one*

4-(2-Chlorothiazol-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 36a** and **Ex 36b** by replacing 5-bromo-2-chloro-3-fluoro-pyridine with 5-bromo-2-chlorothiazole in step 1.

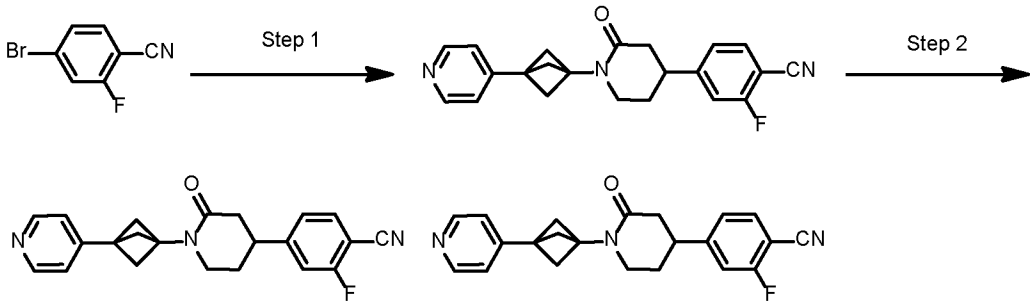
Step 2: *Chiral Separation of 4-(2-Chlorothiazol-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (Ex 76a & 76b)*

4-(2-Chlorothiazol-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (50 mg, 0.14 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / MeOH + 0.1% NH_4OH = 60/40; 80 mL/min) to give 4-(2-chlorothiazol-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 76a**, peak 1, Rt = 2.086 min, 22 mg, 43% yield) and 4-(2-chlorothiazol-5-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 76b**, peak 2, Rt = 2.247 min, 21 mg, 41% yield) both as white solids.

Example 76a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.49 (d, J = 5.2 Hz, 2H), 7.51 (s, 1H), 7.26 (d, J = 5.6 Hz, 2H), 3.51 - 3.38 (m, 3H), 2.66 - 2.58 (m, 1H), 2.46 - 2.37 (m, 7H), 2.23 - 2.12 (m, 1H), 1.95 - 1.81 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 360.1

Example 76b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.49 (d, J = 6.0 Hz, 2H), 7.51 (s, 1H), 7.25 (d, J = 5.6 Hz, 2H), 3.50 - 3.37 (m, 3H), 2.66 - 2.58 (m, 1H), 2.47 - 2.35 (m, 7H), 2.24 - 2.11 (m, 1H), 1.96 - 1.81 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 360.1

Examples 77a and 77b



Step 1: *Synthesis of 2-Fluoro-4-(2-oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)benzonitrile*

2-Fluoro-4-(2-oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)benzonitrile was prepared using the general procedure described for the preparation of **Ex 36a** and **Ex 36b** by replacing 5-bromo-2-chloro-3-fluoro-pyridine with 4-bromo-2-fluorobenzonitrile in step 1.

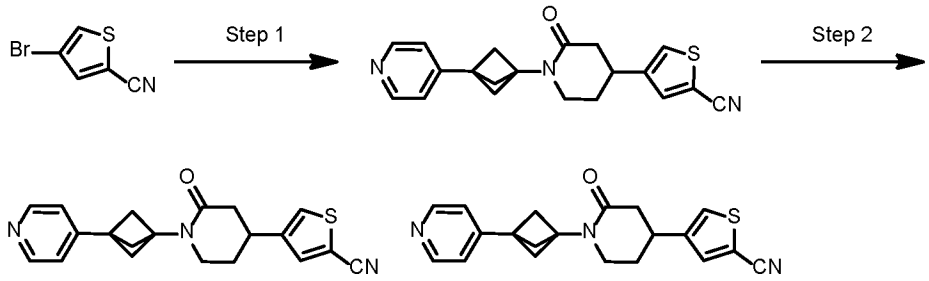
Step 2: *Chiral Separation of 2-Fluoro-4-(2-oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)benzonitrile (Ex. 77a & 77b)*

2-Fluoro-4-(2-oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)benzonitrile (60 mg, 0.17 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / MeOH + 0.1% NH_4OH = 65/35; 80 mL/min) to give 23.9 mg crude peak 1 and 2-fluoro-4-(2-oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)benzonitrile (**Ex 77b**, peak 2, Rt = 2.713 min, 21.6 mg, 36% yield) as a white powder. The crude peak 1 was further purified by chiral SFC (Chiralpak AS (250 mm x 30 mm, 10 um); Supercritical CO_2 / MeOH + 0.1% NH_4OH = 70/30; 80 mL/min) to give 2-fluoro-4-(2-oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)benzonitrile (**Ex 77a**, peak 1, Rt = 2.494 min, 17.2 mg, 29% yield) as a white powder.

Example 77a: ^{1}**H NMR** (400 MHz, DMSO-d_6): δ 8.50 (dd, J = 1.6, 4.4 Hz, 2H), 7.89 (t, J = 7.6 Hz, 1H), 7.52 (d, J = 10.0 Hz, 1H), 7.36 (dd, J = 1.2, 8.0 Hz, 1H), 7.26 (dd, J = 1.6, 4.4 Hz, 1H), 3.44 - 3.38 (m, 2H), 3.26 - 3.17 (m, 1H), 2.50 - 2.44 (m, 2H), 2.41 (s, 6H), 2.08 - 1.91 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 362.1

Example 77b: ^{1}**H NMR** (400 MHz, DMSO-d_6): δ 8.50 (d, J = 5.2 Hz, 2H), 7.89 (t, J = 7.6 Hz, 1H), 7.56 - 7.47 (m, 1H), 7.36 (dd, J = 1.2, 8.0 Hz, 1H), 7.26 (d, J = 6.0 Hz, 2H), 3.44 - 3.38 (m, 2H), 3.27 - 3.16 (m, 1H), 2.50 - 2.44 (m, 2H), 2.43 (s, 6H), 2.07 - 1.88 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 362.1

Examples 78a and 78b



Step 1: *Synthesis of 4-(2-Oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)thiophene-2-carbonitrile*

4-(2-Oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)thiophene-2-carbonitrile was prepared using the general procedure described for the preparation of **Ex 36a** and **Ex 36b** by replacing 5-bromo-2-chloro-3-fluoro-pyridine with 4-bromothiophene-2-carbonitrile in step 1.

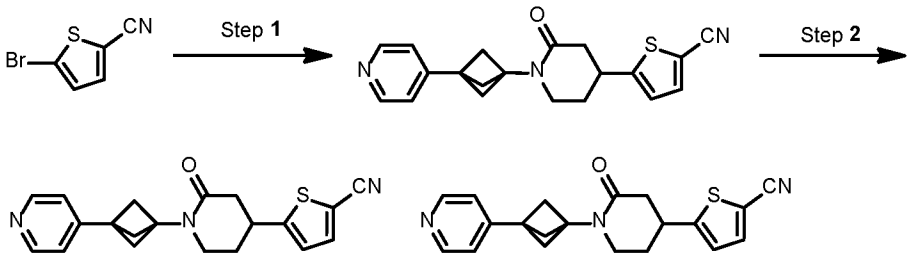
Step 2: *Chiral Separation of 4-(2-Oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)thiophene-2-carbonitrile (Ex 78a & 78b)*

4-(2-Oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)thiophene-2-carbonitrile (93 mg, 0.27 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 60/40; 150 mL/min) to give 4-(2-oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)thiophene-2-carbonitrile (**Ex 78a**, peak 1, Rt = 1.582 min, 33 mg, 35% yield) and 4-(2-oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)thiophene-2-carbonitrile (**Ex 78b**, peak 2, Rt = 2.005 min, 39 mg, 42% yield) both as white solids.

Example 78a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.49 (dd, J = 1.6, 4.4 Hz, 2H), 7.98 (s, 1H), 7.80 (s, 1H), 7.26 (dd, J = 1.6, 4.4 Hz, 2H), 3.38 - 3.33 (m, 2H), 3.24 - 3.13 (m, 1H), 2.59 - 2.56 (m, 1H), 2.44 - 2.35 (m, 7H), 2.16 - 2.07 (m, 1H), 1.92 - 1.78 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 350.1

Example 78b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.49 (dd, J = 1.6, 4.4 Hz, 2H), 7.98 (s, 1H), 7.80 (s, 1H), 7.26 (dd, J = 1.6, 4.4 Hz, 2H), 3.37 - 3.34 (m, 2H), 3.23 - 3.13 (m, 1H), 2.59 - 2.54 (m, 1H), 2.43 - 2.35 (m, 7H), 2.17 - 2.07 (m, 1H), 1.92 - 1.79 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 350.2

Examples 79a and 79b



Step 1: *Synthesis of 5-(2-Oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)thiophene-2-carbonitrile*

5-(2-Oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)thiophene-2-carbonitrile was prepared using the general procedure described for the preparation of **Ex 36a** and **Ex 36b** by replacing 5-bromo-2-chloro-3-fluoro-pyridine with 5-bromothiophene-2-carbonitrile in step 1.

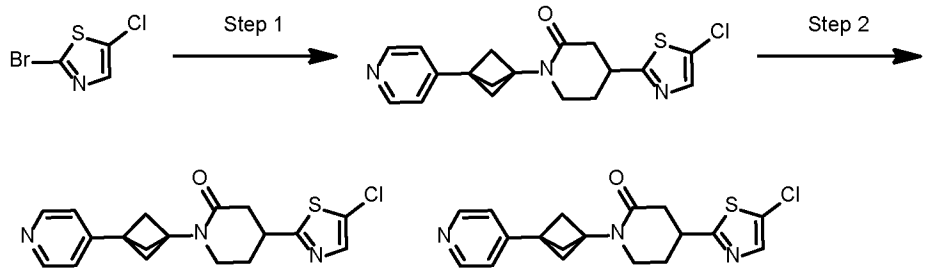
Step 2 : *Chiral Separation of 5-(2-Oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)thiophene-2-carbonitrile (Ex 79a & 79b)*

5-(2-Oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)thiophene-2-carbonitrile (140 mg, 0.4 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / MeOH + 0.1% NH_4OH = 30/70; 150 mL/min) to give 5-(2-oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)thiophene-2-carbonitrile (**Ex 79a**, peak 1, Rt = 2.527 min, 27 mg, 19% yield) and 5-(2-oxo-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-4-yl)thiophene-2-carbonitrile (**Ex 79b**, peak 2, Rt = 2.907 min, 26 mg, 18% yield) both as white solids.

Example 79a: ^{1}**H NMR** ($CDCl_3$, 400 MHz): δ 8.60 - 8.50 (m, 2H), 7.52 (d, J = 4.0 Hz, 1H), 7.16 (d, J = 5.6 Hz, 2H), 6.89 (d, J = 4.0 Hz, 1H), 3.54 - 3.33 (m, 3H), 2.88 - 2.78 (m, 1H), 2.59 - 2.53 (m, 1H), 2.51 - 2.47 (m, 6H), 2.35 - 2.27 (m, 1H), 2.06 - 1.95 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 350.0

Example 79b: ^{1}**H NMR** ($CDCl_3$, 400 MHz): δ 8.57 - 8.51 (m, 2H), 7.52 (d, J = 4.0 Hz, 1H), 7.19 - 7.11 (m, 2H), 6.89 (d, J = 3.6 Hz, 1H), 3.51 - 3.34 (m, 3H), 2.88 - 2.78 (m, 1H), 2.59 - 2.53 (m, 1H), 2.52 - 2.46 (m, 6H), 2.35 - 2.26 (m, 1H), 2.07 - 1.94 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 350.1

Examples 80a and 80b



Step 1: *Synthesis of 4-(5-Chlorothiazol-2-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one*

4-(5-Chlorothiazol-2-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one was prepared using the general procedure described for the preparation of **Ex 36a** and **Ex 36b** by replacing 5-bromo-2-chloro-3-fluoro-pyridine with 2-bromo-5-chlorothiazole in step 1.

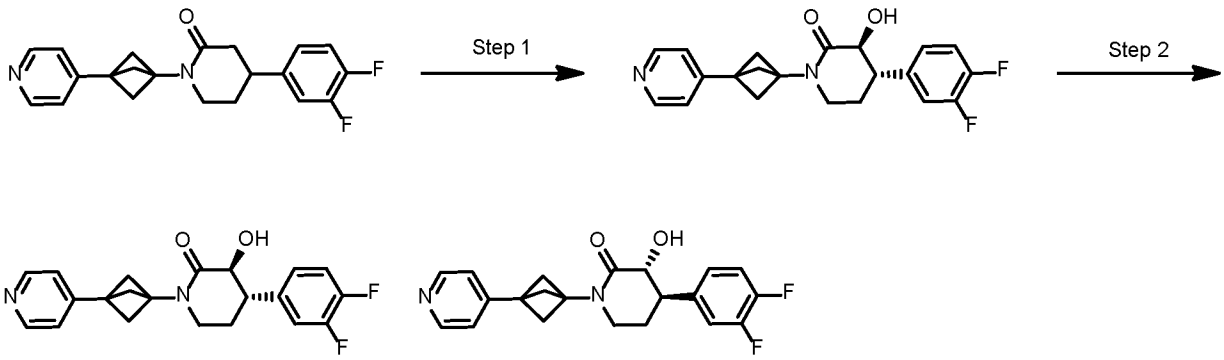
Step 2: *Chiral Separation of 4-(5-Chlorothiazol-2-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (Ex 80a & 80b)*

4-(5-Chlorothiazol-2-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (80 mg, 0.22 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / MeOH + 0.1% NH_4OH = 60/40; 150 mL/min) to give 4-(5-chlorothiazol-2-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 80a**, peak 1, Rt = 4.698 min, 18 mg, 22% yield) and 4-(5-chlorothiazol-2-yl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 80b**, peak 2, Rt = 5.449 min, 24 mg, 30% yield) both as white solids.

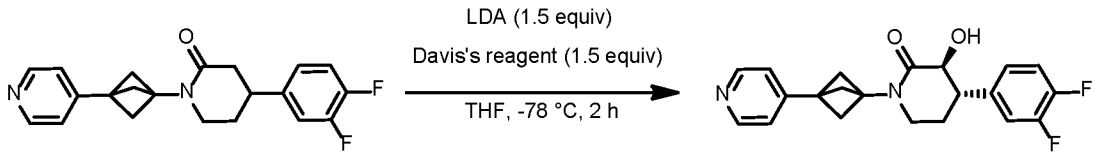
Example 80a: **^{1}H NMR** (DMSO-d_6, 400 MHz): δ 8.52 - 8.45 (m, 2H), 7.75 (s, 1H), 7.28 - 7.22 (m, 2H), 3.61 - 3.51 (m, 1H), 3.41 - 3.40 (m, 1H), 3.33 - 3.30 (m, 1H), 2.69 - 2.61 (m, 1H), 2.57 - 2.53 (m, 1H), 2.38 (s, 6H), 2.29 - 2.20 (m, 1H), 1.99 - 1.87 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 360.1

Example 80b: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.51 - 8.46 (m, 2H), 7.75 (s, 1H), 7.28 - 7.23 (m, 2H), 3.62 - 3.52 (m, 1H), 3.42 - 3.40 (m, 1H), 3.33 - 3.30 (m, 1H), 2.69 - 2.60 (m, 1H), 2.57 - 2.53 (m, 1H), 2.38 (s, 6H), 2.29 - 2.20 (m, 1H), 1.99 - 1.87 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 360.1

Examples 81a and 81b



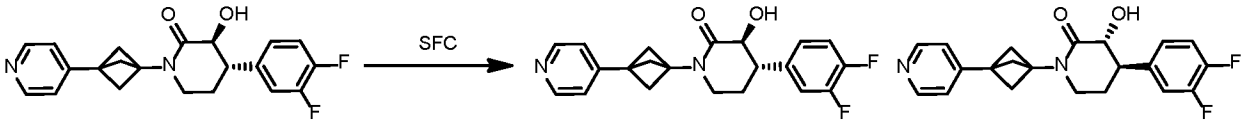
Step 1: *Synthesis of trans-4-(3,4-difluorophenyl)-3-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one*



To a solution of 4-(3,4-difluorophenyl)-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (340 mg, 0.96 mmol) in THF (8 mL) were added LDA (2 M, 0.72 mL, 1.44 mmol) dropwise at -78 °C under nitrogen atmosphere. After stirring at -78 °C for 40 minutes, a solution of 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (376 mg, 1.44 mmol) in THF (2 mL) were added dropwise at -78°C. After stirring at -78 °C for 2 hours, the reaction was quenched with saturated aqueous NH_4Cl solution (15 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 35-65 / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to give *trans*-4-(3,4-difluorophenyl)-3-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (100 mg, 28% yield) as a white solid. The relative configuration was confirmed by 2D NMR.

^{1}H NMR (MeOD-d_4, 400 MHz) δ 8.47 - 8.45 (m, 2H), 7.34 - 7.32 (m, 2H), 7.29 - 7.17 (m, 2H), 7.15 - 7.08 (m, 1H), 4.08 (d, J = 10.8 Hz, 1H), 3.51 - 3.48 (m, 2H), 2.98 - 2.94 (m, 1H), 2.53 (s, 6H), 2.22 - 2.12 (m, 1H), 2.10 - 2.00 (m, 1H). LCMS: (ESI, m/z) $[M+H]^+$ = 371.1.

Step 2: *Chiral Separation of Trans-4-(3,4-difluorophenyl)-3-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (Ex 81a & 81b)*

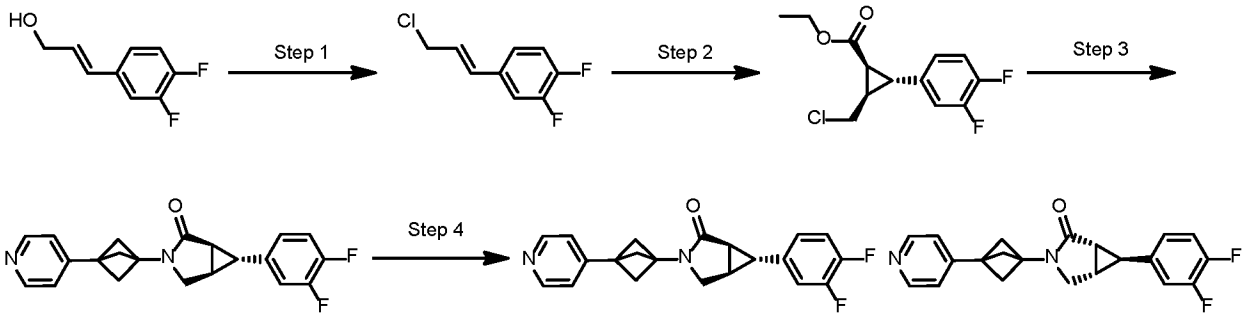


Trans-4-(3,4-difluorophenyl)-3-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (80 mg, 0.22 mmol) was separated by chiral SFC (Chiralcel OD (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 60/40; 80 mL/min) to afford (3*S*,4*S*)-4-(3,4-difluorophenyl)-3-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 81a**, peak 1, Rt = 1.486 min, 34.4 mg, 43% yield) and (3*R*,4*R*)-4-(3,4-difluorophenyl)-3-hydroxy-1-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)piperidin-2-one (**Ex 81b**, peak 2, Rt = 1.667 min, 25.0 mg, 31% yield) both as white solid. Stereochemistry was arbitrarily assigned to each stereoisomer.

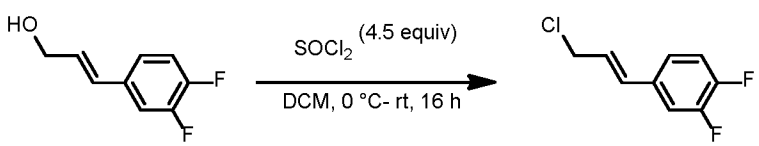
Example 81a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.55 - 8.46 (m, 2H), 7.43 - 7.32 (m, 2H), 7.27 (d, J = 5.6 Hz, 2H), 7.16 - 7.09 (m, 1H), 5.01 (d, J = 4.0 Hz, 1H), 3.99 - 3.96 (m, 1H), 3.40 - 3.35 (m, 2H), 2.99 - 2.88 (m, 1H), 2.43 (s, 6H), 2.17 - 2.04 (m, 1H), 1.95 - 1.90 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 371.1.

Example 81b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.53 (d, J = 5.6 Hz, 2H), 7.43 - 7.33 (m, 2H), 7.33 - 7.30 (m, 2H), 7.16 - 7.10 (m, 1H), 5.01 (br s, 1H), 3.98 (d, J = 10.8 Hz, 1H), 3.48 - 3.37 (m, 2H), 2.99 - 2.87 (m, 1H), 2.44 (s, 6H), 2.14 - 2.04 (m, 1H), 1.95 - 1.90 (m, 1H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 371.1.

Examples 82a and 82b



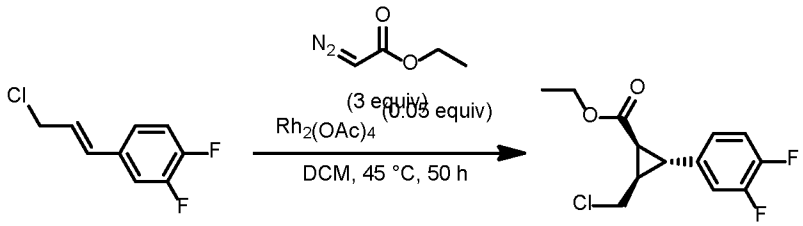
Step 1: *Synthesis of (E)-4-(3-chloroprop-1-en-1-yl)-1,2-difluorobenzene*



To a solution of (*E*)-3-(3,4-difluorophenyl)prop-2-en-1-ol (5.0 g, 39.38 mmol) in DCM (50 mL) was added $SOCl_2$ (9.6 mL, 132.23 mmol) dropwise at 0°C. Then the mixture was stirred at room temperature for 16 hours. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (SiO_2, 3% ethyl acetate in petroleum ether) to afford (*E*)-4-(3-chloroprop-1-en-1-yl)-1,2-difluorobenzene (4.8 g, 86% yield) as colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27 - 7.21 (m, 1H), 7.19 - 7.09 (m, 2H), 6.58 (d, J = 15.6 Hz, 1H), 6.29 - 6.21 (m, 1H), 4.23 (d, J = 7.2 Hz, 2H).

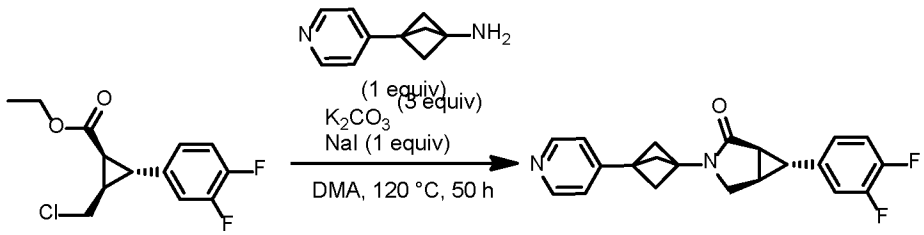
Step 2: *Synthesis of ethyl (1S,2R,3S)-2-(chloromethyl)-3-(3,4-difluorophenyl)cyclopropane-1-carboxylate*



To a solution of (*E*)-4-(3-chloroprop-1-en-1-yl)-1,2-difluorobenzene (2 g, 10.60 mmol) and dirhodium tetraacetate (234 mg, 0.53 mmol) in DCM (10 mL) was added was added ethyl 2-diazoacetate (3.3 mL, 31.81 mmol) dropwise over 30 minutes room temperature. Then the mixture was stirred at 45°C for 50 hours. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (SiO_2, 0-5% ethyl acetate in petroleum ether) to afford ethyl (1*S*,2*R*,3*S*)-2-(chloromethyl)-3-(3,4-difluorophenyl)cyclopropane-1-carboxylate (2.1 g, 75% yield) as colourless oil.

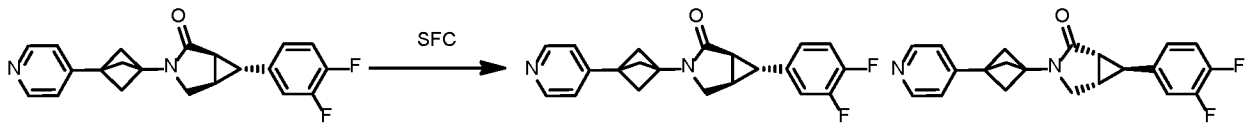
^{1}H NMR($CDCl_3$, 400 MHz): δ 7.12 - 7.06 (m, 1H), 6.96 - 6.91 (m, 1H), 6.89 - 6.84 (m, 1H), 4.29 - 4.17 (m, 2H), 4.03 - 3.98 (m, 1H), 3.87 - 3.82 (m, 1H), 2.66 (t, J = 6.0 Hz, 1H), 2.20 - 2.16 (m, 1H), 2.07 - 1.99 (m, 1H), 1.32 (t, J = 7.2 Hz, 3H).

Step 3: *Synthesis of trans-6-(3,4-difluorophenyl)-3-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-3-azabicyclo[3.1.0]hexan-2-one*



To a solution of 3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-amine (400 mg, 2.03 mmol), methyl ethyl (1*S*,2*R*,3*S*)-2-(chloromethyl)-3-(3,4-difluorophenyl)cyclopropane-1-carboxylate (558 mg, 2.03 mmol) in DMA (5 mL) was added NaI (305 mg, 2.03 mmol) and K_2CO_3 (843 mg, 6.1 mmol). Then the mixture was stirred at 120 °C for 50 hours. After cooling to room temperature, ethyl acetate (50 mL) and water (50 mL) were added. The organic layer was separated, washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 40-80% ethyl acetate in petroleum ether) to afford 180 mg crude product, which was further purified by reverse phase chromatography (acetonitrile: 46-76% / 0.05% NH_4OH in water) to afford *trans*-6-(3,4-difluorophenyl)-3-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-3-azabicyclo[3.1.0]hexan-2-one (120 mg, 17% yield).

Step 4: *Chiral Separation of Trans-6-(3,4-difluorophenyl)-3-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-3-azabicyclo[3.1.0]hexan-2-one (Ex. 82a & 82b)*

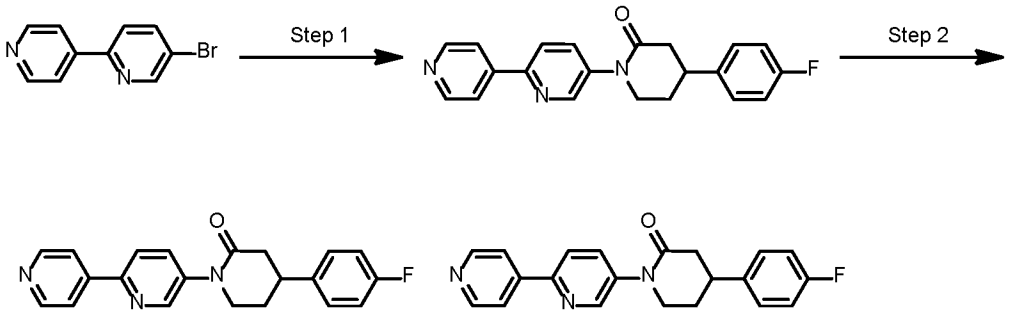


Trans-6-(3,4-difluorophenyl)-3-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-3-azabicyclo[3.1.0]hexan-2-one (120 mg, 0.34 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 70/30; 80 mL/min) to afford (*Rel*-1*S*,5*R*,6*R*)-6-(3,4-difluorophenyl)-3-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-3-azabicyclo[3.1.0]hexan-2-one (**Ex 82a**, peak 1, Rt = 1.601 min, 33 mg, 27% yield) and (*Rel*-1*R*,5*S*,6*S*)-6-(3,4-difluorophenyl)-3-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-3-azabicyclo[3.1.0]hexan-2-one (**Ex 82b**, peak 2, Rt =1.736 min, 36.8 mg, 31% yield) both as white solids. Stereochemistry arbitrarily assigned.

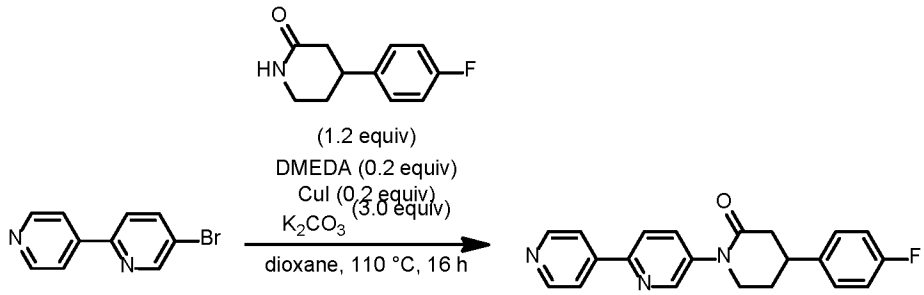
Example 82a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.53 - 8.46 (m, 2H), 7.37 - 7.32 (m, 1H), 7.26 - 7.23 (m, 2H), 7.24 - 7.18 (m, 1H), 7.05 - 6.98 (m, 1H), 3.65 - 3.60 (m, 1H), 3.48 - 3.44 (m, 1H), 2.36 - 2.30 (m, 6H), 2.28 - 2.24 (m, 1H), 2.20 - 2.14 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 353.1

Example 82b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.52 - 8.47 (m, 2H), 7.37 - 7.30 (m, 1H), 7.26 - 7.23 (m, 2H), 7.24 - 7.18 (m, 1H), 7.04 - 6.98 (m, 1H), 3.65 - 3.60 (m, 1H), 3.48 - 3.44 (m, 1H), 2.36 - 2.30 (m, 6H), 2.28 - 2.24 (m, 1H), 2.21 - 2.14 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 353.1

Examples 83a and 83b

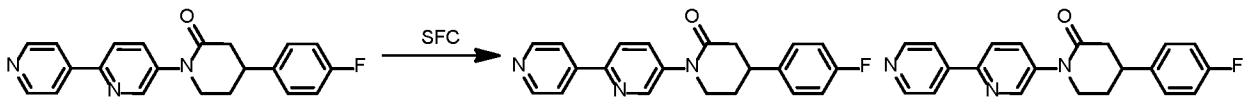


Step 1: Synthesis of 1-([2,4'-bipyridin]-5-yl)-4-(4-fluorophenyl)piperidin-2-one



To a mixture of 4-(4-fluorophenyl)piperidin-2-one (197 mg, 1.0 mmol), 5-bromo-2,4'-bipyridine (200 mg, 0.85 mmol) in 1,4-dioxane (4 mL) was added DMEDA (0.02 mL, 0.2 mmol), K_2CO_3 (353 mg, 2.6 mmol) and CuI (32 mg, 0.2 mmol). The mixture was stirred at 110 °C for 16 h under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 0-26% EE (25% ethanol in ethyl acetate) in petroleum ether) to afford 1-([2,4'-bipyridin]-5-yl)-4-(4-fluorophenyl)piperidin-2-one (200 mg, 68% yield) as a yellow solid.

Step 2: *Chiral Separation of 1-([2,4'-bipyridin]-5-yl)-4-(4-fluorophenyl)piperidin-2-one (Ex. 83a & 83b)*

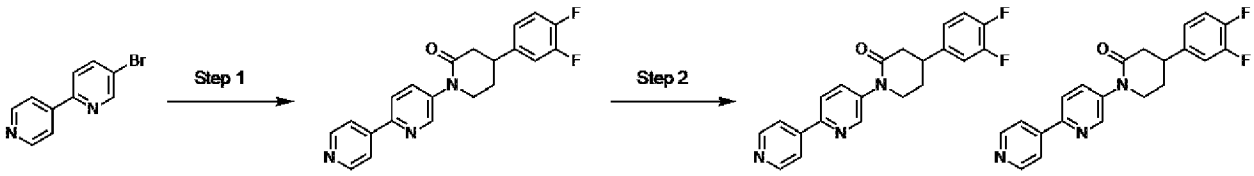


1-([2,4'-bipyridin]-5-yl)-4-(4-fluorophenyl)piperidin-2-one (200 mg, 0.58 mmol) was separated by chiral SFC (Chiralpak AY (250 mm x 30 mm, 10 um), Supercritical CO_2 / *i*-PrOH + 0.1% NH_4OH = 55/45; 100 mL / min) to afford 1-([2,4'-bipyridin]-5-yl)-4-(4-fluorophenyl)piperidin-2-one (**Ex 83a**, peak 1, Rt = 3.810 min, 57.5 mg, 29% yield) and 1-([2,4'-bipyridin]-5-yl)-4-(4-fluorophenyl)piperidin-2-one (**Ex 83b**, peak 2, Rt = 4.102 min, 60.0 mg, 30%) both as a white solids.

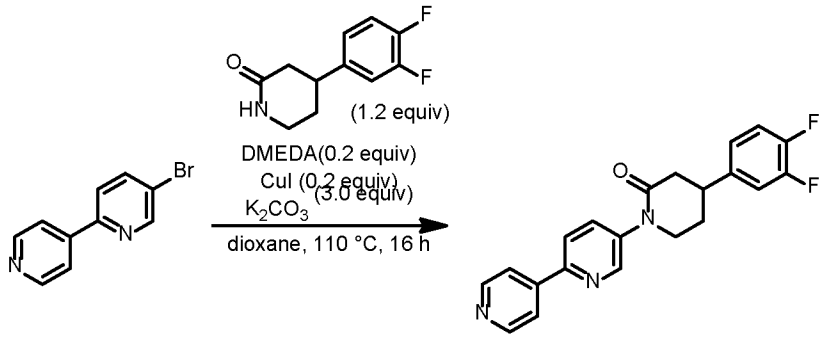
Example 83a: ^{1}**H NMR** (DMSO-d_6, 400 MHz,): δ 8.75 (d, J = 2.40 Hz, 1H), 8.70 (dd, J = 1.6, 4.8 Hz, 2H), 8.18 (d, J = 8.4 Hz, 1H), 8.06 (dd, J = 1.6, 4.8 Hz, 2 H), 7.96 (dd, J = 2.4, 8.4 Hz, 1H), 7.45 - 7.36 (m, 2H), 7.19 (t, J = 8.4 Hz, 2H), 3.99 - 3.89 (m, 1H), 3.74 - 3.67 (m, 1H), 3.38 - 3.33 (m, 1H), 2.72 - 2.63 (m, 2H), 2.19 - 2.09 (m, 2 H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 348.1

Example 83b: ^{1}**H NMR** (DMSO-d_6, 400 MHz,): δ 8.75 (d, J = 2.40 Hz, 1H), 8.70 (dd, J = 2.0, 4.4 Hz, 2H), 8.18 (d, J = 8.4 Hz, 1H), 8.06 (dd, J = 1.6, 4.4 Hz, 2 H), 7.96 (dd, J = 2.4, 8.0 Hz, 1H), 7.45 - 7.36 (m, 2H), 7.19 (t, J = 8.8 Hz, 2H), 3.99 - 3.89 (m, 1H), 3.74 - 3.67 (m, 1H), 3.38 - 3.33 (m, 1H), 2.71 - 2.64 (m, 2H), 2.20 - 2.10 (m, 2 H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 348.0

Examples 84a and 84b

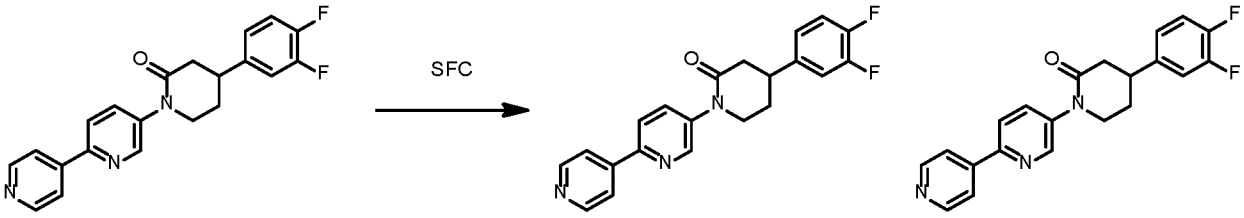


Step 1: *Synthesis of 1-([2,4'-bipyridin]-5-yl)-4-(3,4-difluorophenyl)piperidin-2-one*



To a mixture of 4-(3,4-difluorophenyl)piperidin-2-one (216 mg, 1.02 mmol), 5-bromo-2,4'-bipyridine (200 mg, 0.85 mmol) in 1,4-dioxane (4 mL) was added DMEDA (0.02 mL, 0.2 mmol), K_2CO_3 (353 mg, 2.6 mmol) and CuI (32 mg, 0.2 mmol). The mixture was stirred at 110 °C for 16 h under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 0-36% EE (25% ethanol in ethyl acetate) in petroleum ether) to afford 1-([2,4'-bipyridin]-5-yl)-4-(3,4-difluorophenyl)piperidin-2-one (200 mg, 64% yield) as a white solid.

Step 2: *Chiral Separation of 1-([2,4'-bipyridin]-5-yl)-4-(3,4-difluorophenyl)piperidin-2-one (Ex. 84a & 84b)*

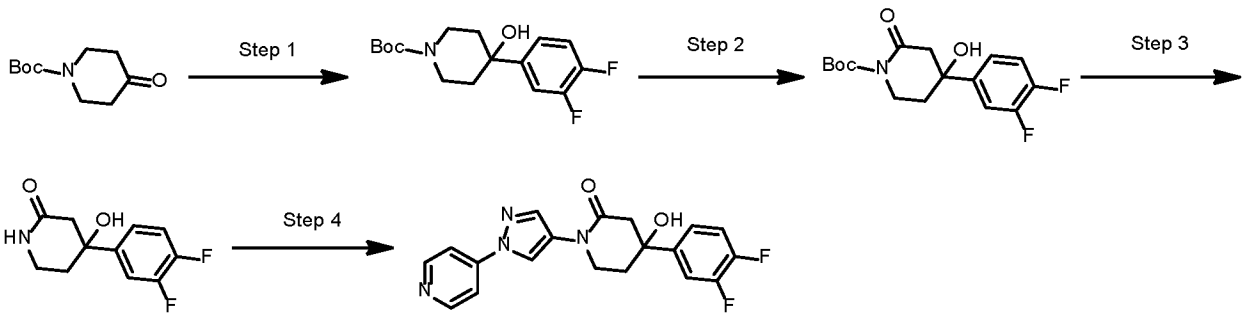


1-([2,4'-bipyridin]-5-yl)-4-(3,4-difluorophenyl)piperidin-2-one (200 mg, 0.55 mmol) was separated by chiral SFC (Cellulose-2 (250 mm x 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% NH_4OH = 50/50; 150 mL / min) to afford 1-([2,4'-bipyridin]-5-yl)-4-(3,4-difluorophenyl)piperidin-2-one (**Ex 81a**, peak 1, Rt = 3.622 min, 57.9 mg, 29% yield) and 1-([2,4'-bipyridin]-5-yl)-4-(3,4-difluorophenyl)piperidin-2-one (**Ex 81b**, peak 2, Rt = 4.371 min, 64.8 mg, 32%) as a white solid.

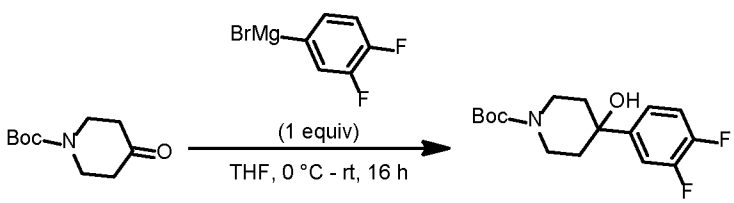
Example 81a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.75 (d, J = 2.4 Hz, 1H), 8.71 (d, J = 4.8 Hz, 2H), 8.18 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 4.8 Hz, 2H), 7.99 - 7.91 (m, 1H), 7.51 - 7.38 (m, 2H), 7.22 - 7.17 (m, 1H), 4.00 - 3.88 (m, 1H), 3.79 - 3.67 (m, 1H), 3.40 - 3.36 (m, 1H), 2.74 - 2.65 (m, 2H), 2.20 - 2.10 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 366.1

Example 81b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.75 (d, J = 2.4 Hz, 1H), 8.70 (d, J = 5.6 Hz, 2H), 8.18 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 6.0 Hz, 2H), 7.99 - 7.91 (m, 1H), 7.51 - 7.36 (m, 2H), 7.22 - 7.17 (m, 1H), 4.00 - 3.88 (m, 1H), 3.79 - 3.67 (m, 1H), 3.40 - 3.36 (m, 1H), 2.74 - 2.65 (m, 2H), 2.20 - 2.10 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 366.1

Example 85



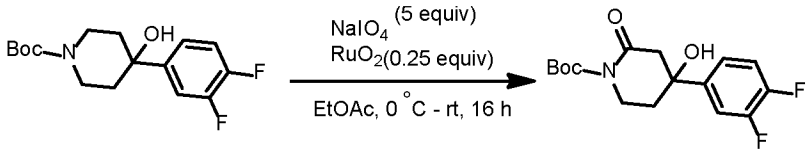
Step 1: *Synthesis of tert-butyl 4-(3,4-difluorophenyl)-4-hydroxypiperidine-1-carboxylate*



To a solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (1.0 g, 5.02 mmol) in THF (10 mL) was added (3, 4-difluorophenyl) magnesium bromide (0.5 M in THF, 10.04 mL, 5.02 mmol) dropwise under nitrogen atmosphere. After addition, the mixture was stirred at room temperature for 16 hours. The reaction mixture was quenched with saturated NH_4Cl solution (1 mL), dried over anhydrous Na_2SO_4, and concentrated to give the product of *tert*-butyl 4-(3,4-difluorophenyl)-4-hydroxypiperidine-1-carboxylate (800 mg crude) as a colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.55 - 7.45 (m, 1H), 7.41 - 7.26 (m, 2H), 5.25 (s, 1H), 3.90 - 3.77 (m, 2H), 3.17 - 3.01 (m, 2H), 1.85 - 1.73 (m, 2H), 1.59 - 1.50 (m, 2H), 1.41 (s, 9H).

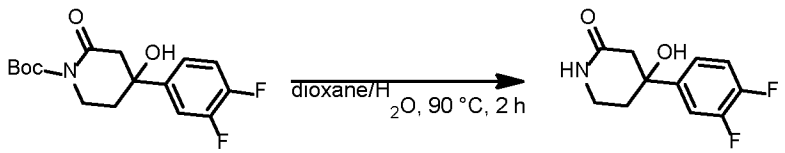
Step 2: *Synthesis of tert-butyl 4-(3,4-difluorophenyl)-4-hydroxy-2-oxopiperidine-1-carboxylate*



To a solution of RuO_2 (541 mg, 4.07 mmol) and *tert*-butyl 4-(3,4-difluorophenyl)-4-hydroxypiperidine-1-carboxylate (5.1 g, 16.28 mmol) in ethyl acetate (50 mL) and water (50 mL) was added $NaIO_4$ (17.41 g, 81.38 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 16 h. The reaction was diluted with water (2 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 36-66% / 0.05% NH_4OH + 10 mM NH_4HCO_3 in water) to give *tert*-butyl 4-(3,4-difluorophenyl)-4-hydroxy-2-oxopiperidine-1-carboxylate (530 mg, 10% yield) as a yellow solid.

LCMS (ESI, m/z) $[M-100+H]^+$ = 272.0

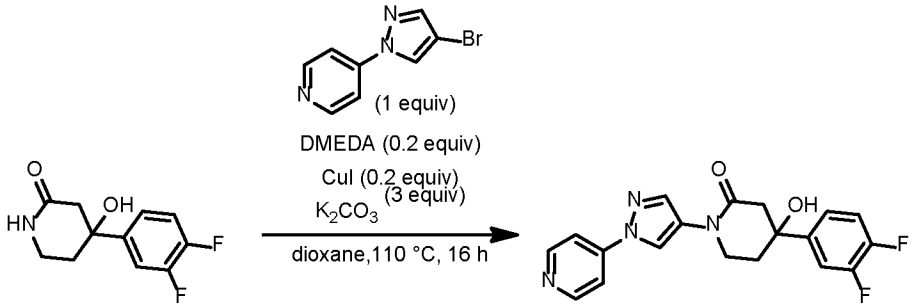
Step 3: *Synthesis of 4-(3,4-difluorophenyl)-4-hydroxypiperidin-2-one*



A solution of *tert*-butyl 4-(3,4-difluorophenyl)-4-hydroxy-2-oxopiperidine-1-carboxylate (530 mg, 1.62mmol) in 1,4-dioxane (5mL) and water (4mL) was heated at 90 °C for 2 hours. After cooling to room temperature, the reaction mixture was filtered and concentrated. The residue was purified by flash column chromatography (SiO_2, 0-10% methanol in dichloromethane) to afford 4-(3,4-difluorophenyl)-4-hydroxypiperidin-2-one (180 mg, 49% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 - 7.30 (m, 1H), 7.21 - 7.13 (m, 2H), 6.08 (s, 1H), 3.70 - 3.63 (m, 1H), 3.32 - 3.26 (m, 1H), 2.83 - 2.75 (m, 1H), 2.66 - 2.58 (m, 1H), 2.15 - 2.09 (m, 1H), 2.05 - 1.95 (m, 1H).

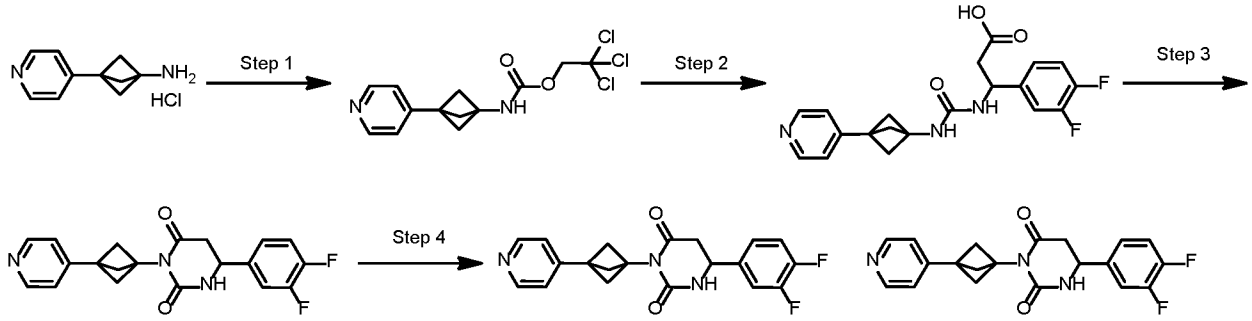
Step 4: *Synthesis of 4-(3,4-difluorophenyl)-4-hydroxy-1-(1-(pyridin-4-yl)-1H-pyrazol-4-yl)piperidin-2-one (Ex 85)*



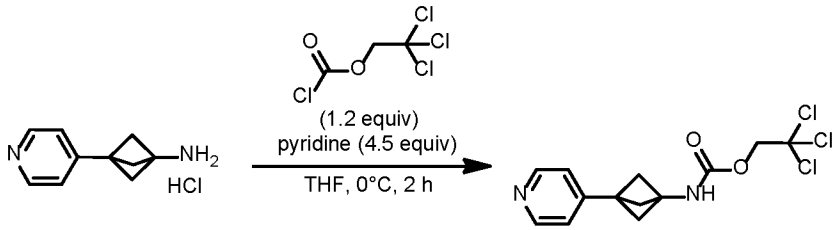
To a mixture of 4-(3,4-difluorophenyl)-4-hydroxypiperidin-2-one (304 mg, 1.34 mmol) and 4-(4-bromopyrazol-1-yl)pyridine (300 mg, 1.34 mmol) in 1,4-dioxane (10 mL) was added DMEDA (24 mg, 0.27 mmol), CuI (51.0 mg, 0.27 mmol) and K_2CO_3 (555 mg, 4.02 mmol). The mixture was stirred at 110 °C for 16 hours under nitrogen atmosphere. After cooling to room temperature, the mixture was diluted with water (5 mL) and extracted with DCM (10 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile 34-64% / 0.1% NH_4OH in water) to afford 4-(3,4-difluorophenyl)-4-hydroxy-1-(1-(pyridin-4-yl)-1*H*-pyrazol-4-yl)piperidin-2-one (**Ex 85**, 34.9 mg, 7% yield) as a white solid.

Example 85: **^{1}H NMR** (DMSO-d_6, 400 MHz): δ 8.89 (s, 1H), 8.64 (d, J = 6.0 Hz, 2H), 8.28 (s, 1H), 7.91 - 7.84 (m, 2H), 7.62 - 7.52 (m, 1H), 7.48 - 7.35 (m, 2H), 5.83 (s, 1H), 3.97 - 3.85 (m, 1H), 3.80 - 3.71 (m, 1H), 3.03 (d, J = 17.2 Hz, 1H), 2.55 - 2.50 (m, 1H), 2.48 - 2.43 (m, 1H), 2.05 - 1.95 (m, 1H). **LCMS** (ESI, m/z) $[M+H]^+$ = 371.0

Examples 86a and 86b



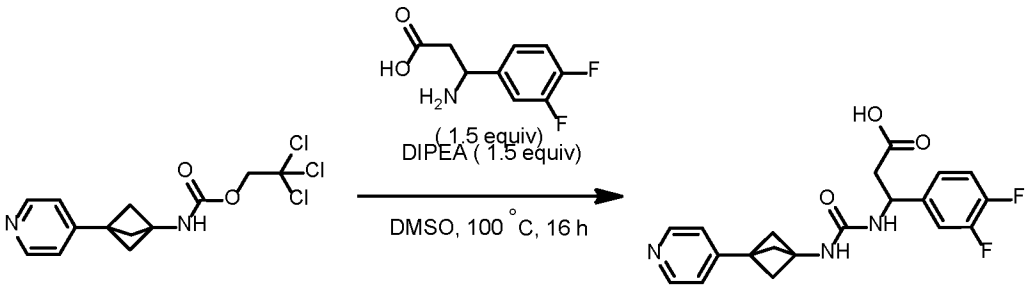
Step 1: *Synthesis of 2,2,2-trichloroethyl (3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)carbamate*



To a solution of 3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-amine hydrochloride (1.17 g, 5.95 mmol) and pyridine (2.92 mL, 26.77 mmol) in anhydrous THF (30 mL) was added 2,2,2-trichloroethyl carbonochloridate (0.98 mL, 7.14 mmol) dropwise in an ice bath under nitrogen atmosphere. After stirring at 0 °C for 2 hours, the reaction was quenched with water (15 mL) and the mixture was extracted with EtOAc (15 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 20-100% EtOAc in petroleum ether) to afford 2,2,2-trichloroethyl (3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)carbamate (1.22 g, 61% yield) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.54 (d, J = 5.6 Hz, 2H), 7.14 (d, J = 5.6 Hz, 2H), 5.78 (br s, 1H), 4.86 - 4.61 (m, 2H), 2.40 (s, 6H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 335.0

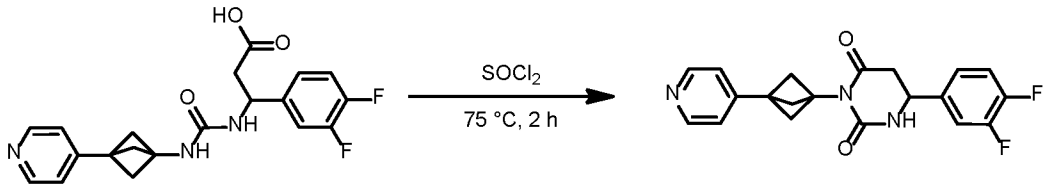
Step 2: *Synthesis of 3-(3,4-difluorophenyl)-3-(3-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)ureido)propanoic acid*



To a solution of 3-amino-3-(3,4-difluorophenyl)propanoic acid (1.1 g, 5.45 mmol) and DIPEA (0.95 mL, 5.45 mmol) in DMSO (20 mL) was added 2,2,2-trichloroethyl (3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)carbamate (1.22 g, 3.64 mmol). The reaction mixture was stirred at 100 °C for 16 hours. After cooling to room temperature, the mixture was concentrated under reduced pressure and the residue was purified by reverse phase chromatography (acetonitrile: 20 - 50% / 0.225% formic acid in water) to afford 3-(3,4-difluorophenyl)-3-(3-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)ureido)propanoic acid (970 mg, 69% yield) as a white solid.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.35 (br s, 1H), 8.47 (d, J = 5.6 Hz, 2H), 7.44 - 7.31 (m, 2H), 7.21 (d, J = 6.0 Hz, 2H), 7.18 - 7.12 (m, 1H), 6.84 (s, 1H), 6.47 (d, J = 8.4 Hz, 1H), 5.00 (q, J = 7.2 Hz, 1H), 2.81 - 2.61 (m, 2H), 2.19 (s, 6H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 388.0

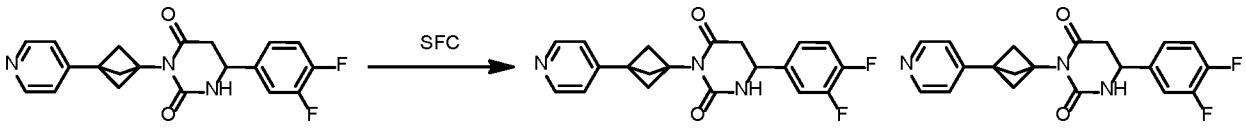
Step 3: *Synthesis of 6-(3,4-difluorophenyl)-3-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)dihydropyrimidine-2,4(1H,3H)-dione*



A solution of 3-(3,4-difluorophenyl)-3-(3-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)ureido)propanoic acid (850 mg, 2.19 mmol) in $SOCl_2$ (22 mL) was heated at 75 °C for 2 hours After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile: 27 - 57% / 0.1% NH_4HCO_3 in wate) to afford 6-(3,4-difluorophenyl)-3-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (500 mg, 61% yield) as a white solid.

LCMS: (ESI, m/z) $[M+H]^+$ = 370.2

Step 4: *Chiral Separation of 6-(3,4-Difluorophenyl)-3-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)dihydropyrimidine-2,4(1H,3H)-dione (Ex 86a & 86b)*

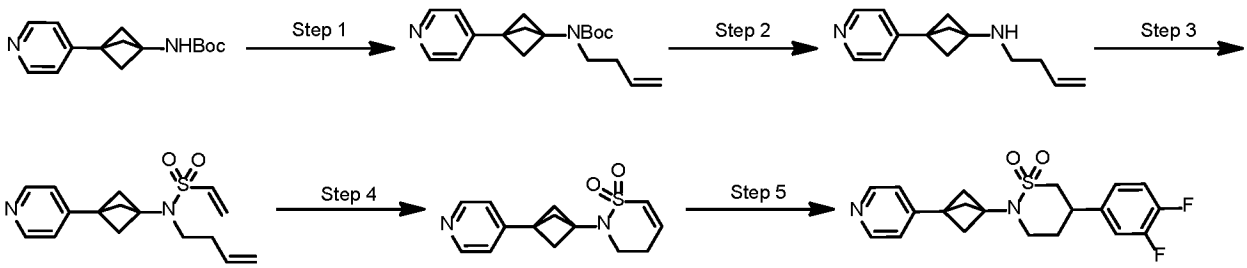


6-(3,4-Difluorophenyl)-3-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (500 mg, 1.35 mmol) was separated by chiral SFC (Chiralpak AD (250 mm x 30 mm, 10 um), Supercritical CO_2 / MeOH + 0.1% NH_4OH = 40/60; 80 mL / min) to afford 6-(3,4-difluorophenyl)-3-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (**Ex 86a**, peak 1, Rt = 1.709 min, 190 mg, 38% yield) and 6-(3,4-difluorophenyl)-3-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (**Ex 86b**, peak 2, Rt = 2.105 min, 201 mg, 40% yield) both as white solid.

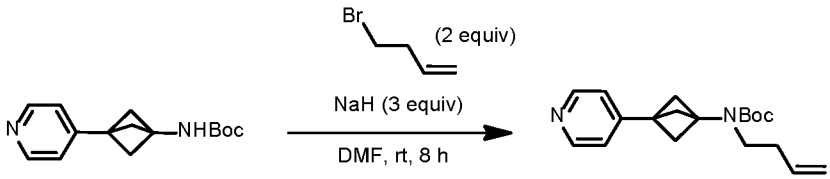
Example 86a: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.48 (d, J = 5.6 Hz, 2H), 8.26 (d, J = 1.6 Hz, 1H), 7.52 - 7.39 (m, 2H), 7.25 (d, J = 6.0 Hz, 2H), 7.21 - 7.15 (m, 1H), 4.75 - 4.56 (m, 1H), 2.97 - 2.88 (m, 1H), 2.87 - 2.78 (m, 1H), 2.54 (s, 6H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 370.1

Example 86b: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.48 (d, J = 5.6 Hz, 2H), 8.27 (d, J = 1.6 Hz, 1H), 7.50 - 7.37 (m, 2H), 7.25 (d, J = 6.0 Hz, 2H), 7.22 - 7.15 (m, 1H), 4.76 - 4.56 (m, 1H), 2.97 - 2.88 (m, 1H), 2.87 - 2.78 (m, 1H), 2.54 (s, 6H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 370.1

Example 87



Step 1: *Synthesis of tert-butyl but-3-en-1-yl(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)carbamate*

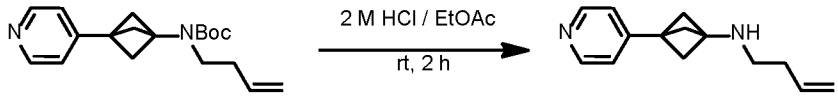


To a solution of *tert*-butyl (3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)carbamate (6 g, 23.2 mmol) in dry DMF (150 ml) was added sodium hydride (60% in mineral oil, 2.8 g, 69.2 mmol) at 0 °C portion wise nitrogen atmosphere. After stirring at 0 °C for 20 minutes, 4-bromobut-1-ene (6.2 g,

46 mmol) was added dropwise at 0 °C. The mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated NH_4Cl solution (50 mL), and then the mixture was extracted with ethyl acetate (200 mL x 2). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 15% EE (ethyl acetate/ethanol = 3/1) in petroleum ether) to afford *tert*-butyl but-3-en-1-yl(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)carbamate (1.6 g, 22% yield) as a yellow solid.

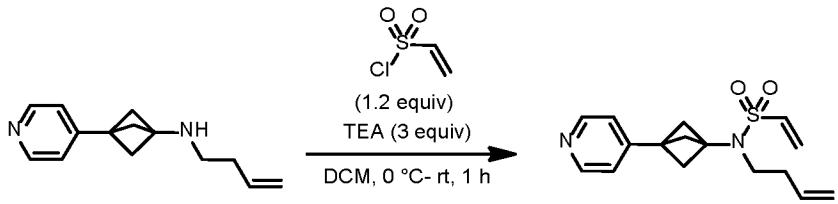
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.51 (d, J = 6.0 Hz, 2H), 7.15 - 7.07 (m, 2H), 5.80 - 5.69 (m, 1H), 5.12 - 4.97 (m, 2H), 3.30 - 3.22 (m, 1H), 2.34 (s, 6H), 2.31 - 2.26 (m, 2H), 1.48 (s, 9H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 315.3

Step 2: *Synthesis of N-(but-3-en-1-yl)-3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-amine*



A solution of *tert*-butyl but-3-en-1-yl(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)carbamate (1.6 g, 5.1 mmol) in 2 M HCl/EtOAc solution (50 mL) was stirred at room temperature for 2 hours. Then the mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (50 mL), and then treated with aqueous saturated $NaHCO_3$ until pH = 8. The organic phase was separated, and the aqueous phase was extracted with EtOAc (50 mL x 2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford *N*-(but-3-en-1-yl)-3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-amine (1.09 g, 98% yield) as a yellow solid. **LCMS**: (ESI, m/z) $[M+H]^+$ = 215.2

Step 3: *Synthesis of N-(but-3-en-1-yl)-N-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)ethenesulfonamide*

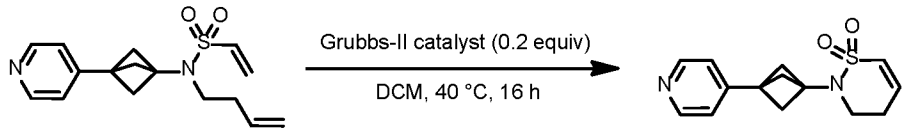


To a solution of *N*-(but-3-en-1-yl)-3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-amine (1.09 g, 5.0 mmol) and TEA (2.0 mL, 15 mmol) in DCM (50 mL) was added ethenesulfonyl chloride (750 mg, 6 mmol) at 0 °C. The mixture was stirred at room temperature for 1 hour, the mixture was quenched with water (50 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (50 mL x 2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered

and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, 30% ethyl acetate in petroleum ether) to afford *N*-(but-3-en-1-yl)-*N*-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)ethenesulfonamide (1.15 g, 75% yield) as a white solid.

LCMS: (ESI, m/z) $[M+H]^+ = 305.2$

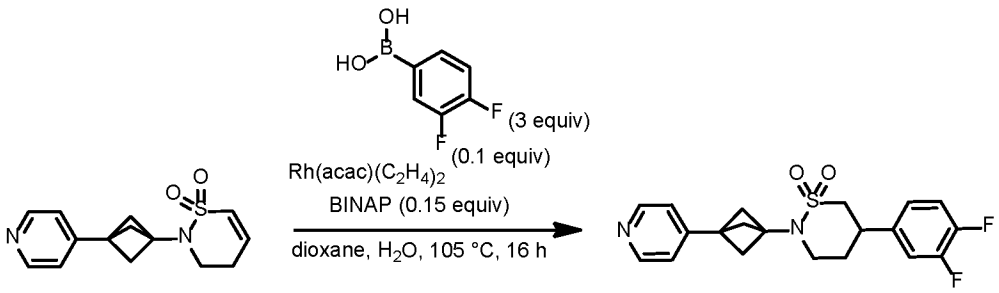
Step 4: *Synthesis of 2-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-3,4-dihydro-2H-1,2-thiazine 1,1-dioxide*



To a solution of *N*-(but-3-en-1-yl)-*N*-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)ethenesulfonamide (1.15 g, 3.7 mmol) in DCM (150 mL) was added Grubbs-II catalyst (612 mg, 0.74 mmoL). The mixture was stirred at 40 °C for 16 hours under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was filtered and diluted with water (100 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (50 mL x 2). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, 30% ethyl acetate in petroleum ether) to afford 2-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-3,4-dihydro-2*H*-1,2-thiazine 1,1-dioxide (70 mg, 7% yield) as a white solid.

LCMS: (ESI, m/z) $[M+H]^+ = 277.2$

Step 5: *Synthesis of 5-(3,4-difluorophenyl)-2-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-1,2-thiazinane 1,1-dioxide (Ex. 87)*



To a solution of 2-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-3,4-dihydro-2*H*-1,2-thiazine 1,1-dioxide (70 mg, 0.25 mmol), (3,4-difluorophenyl)boronic acid (120 mg, 0.75 mmol) in 1,4-dioxane (3 mL) and water (0.3 mL) was added $Rh(acac)(C_2H_4)_2$ (13 mg, 0.03 mmol) and BINAP (25 mg, 0.38 mmol). The mixture was stirred at 105 °C for 16 hours under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was filtered and diluted with water (10 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (10 mL x 2).

The combined organic phases were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by reverse phase chromatography (acetonitrile: 45-75% / 10 mM NH_4HCO_3 in water) to afford 5-(3,4-difluorophenyl)-2-(3-(pyridin-4-yl)bicyclo[1.1.1]pentan-1-yl)-1,2-thiazinane 1,1-dioxide (9.05 mg, 9% yield) as a white solid.

Example 87: ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 8.52 (d, J = 5.2 Hz, 2H), 7.58 - 7.47 (m, 1H), 7.46 - 7.34 (m, 1H), 7.28 (d, J = 5.2 Hz, 2H), 7.25 - 7.18 (m, 1H), 3.52 - 3.38 (m, 4H), 3.31 - 3.21 (m, 1H), 2.48 - 2.35 (m, 6H), 1.85 - 1.71 (m, 2H). **LCMS**: (ESI, m/z) $[M+H]^+$ = 391.0

Characterization Table

Ex	m/z [M+1]	NMR data	Analytical Method
1a	319.10	1H NMR (400 MHz, DMSO) δ 8.63 (s, 1H), 7.72 (d, J = 5.4 Hz, 2H), 7.35 (m, 4H), 7.25 (tt, J = 6.3, 3.1 Hz, 2H), 4.03 (s, 1H), 3.82 (td, J = 4.81, 11.8, 1H), 3.23 (m, 1H), 2.78 – 2.61 (m, 2H), 2.2–2.03 (m, 2H)	Peak 1, Method A
1b	319.10	1H NMR (400 MHz, DMSO) δ 13.32 (s, 1H), 8.63 (d, J = 4.8 Hz, 2H), 7.73 (d, J = 5.6 Hz, 2H), 7.35 (d, J = 5.4 Hz, 4H), 7.30 – 7.20 (m, 2H), 4.02 (bs, 1H), 3.82 (td, J = 11.8, 4.8 Hz, 1H), 2.78 – 2.61 (m, 2H), 2.22 – 2.04 (m, 2H).	Peak 2, Method A
2	311.9	1H NMR (DMSO-d6, 400 MHz): δ 13.96 (s, 1H), 8.68 (d, J = 6.0 Hz, 2H), 7.90 (d, J = 5.6 Hz, 2H), 4.34 - 4.25 (m, 1H), 3.95 - 3.86 (m, 1H), 3.20 - 3.10 (m, 1H), 2.85 - 2.75 (m, 1H), 2.72 - 2.60 (m, 1H), 2.29 - 2.20 (m, 1H), 2.04 - 1.85 (m, 1H).	Method B
3	320.0	1H NMR (DMSO-d6, 400 MHz): δ 8.67 - 8.62 (m, 2H), 7.92 - 7.86 (m, 2H), 7.39 - 7.33 (m, 4H), 7.29 - 7.22 (m, 1H), 4.24 - 4.12 (m, 1H), 3.98 - 3.86 (m, 1H), 3.25 - 3.20 (m, 1H), 2.81 - 2.74 (m, 2H), 2.24 - 2.07 (m, 2H).	Method C
4a	372.0	1H NMR (DMSO-d6, 400 MHz): δ = 13.98 (s, 1H), 8.67 (d, J = 6.0 Hz, 2H), 7.90 (d, J = 6.0 Hz, 2H), 7.57 (t, J = 8.0 Hz, 1H), 7.46 (d, J = 9.2 Hz, 1H), 7.26 - 7.20 (m, 1H), 4.30 - 4.21 (m, 1H), 3.99 - 3.84 (m, 1H), 3.38 - 3.35 (m, 1H), 2.84 - 2.77 (m, 2H), 2.25 - 2.06 (m, 2H).	peak 1, Rt = 1.890 min. Method D

4b	372.0	1H NMR (DMSO-d6, 400 MHz): δ = 13.98 (s, 1H), 8.67 (d, J = 6.0 Hz, 2H), 7.89 (d, J = 6.0 Hz, 2H), 7.57 (t, J = 8.0 Hz, 1H), 7.50 - 7.42 (m, 1H), 7.26 - 7.20 (m, 1H), 4.32 - 4.20 (m, 1H), 3.98 3.86 (m, 1H), 3.38 - 3.35 (m, 1H), 2.87 - 2.74 (m, 2H), 2.26 - 2.06 (m, 2H).	peak 2, Rt = 2.417 min, Method D
5a	371.0	1H NMR (DMSO-d6, 400 MHz): δ = 13.34 (s, 1H), 8.64 (d, J = 6.0 Hz, 2H), 7.73 (d, J = 6.0 Hz, 2H), 7.57 (t, J = 8.0 Hz, 1H), 7.46 (dd, J = 11.2, 2.0 Hz, 1H), 7.28 - 7.15 (m, 2H), 4.12 - 3.99 (m, 1H), 3.87 - 3.75 (m, 1H), 3.30 - 3.22 (m, 1H), 2.79 - 2.64 (m, 2H), 2.23 - 2.04 (m, 2H).	peak 1, Rt = 2.293 min, Method E
5b	371.0	1H NMR (DMSO-d6, 400 MHz): δ = 13.32 (s, 1H), 8.66 - 8.58 (m, 2H), 7.76 - 7.69 (m, 2H), 7.56 (t, J = 8.0 Hz, 1H), 7.45 (dd, J = 10.8, 2.0 Hz, 1H), 7.27 - 7.14 (m, 2H), 4.09 - 3.98 (m, 1H), 3.86 - 3.75 (m, 1H), 3.28 - 3.24 (m, 1H), 2.77 - 2.68 (m, 2H), 2.22 - 2.02 (m, 2H).	peak 2, Rt = 3.226 min, Method E
6a	388.0	1H NMR (400 MHz, DMSO-d6): δ = 13.37 (s, 1H), 8.79 (s, 1H), 8.68 - 8.59 (m, 2H), 8.08 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.77 - 7.68 (m, 2H), 7.29 (s, 1H), 4.16 - 4.05 (m, 1H), 3.89 - 3.79 (m, 1H), 3.46 - 3.42 (m, 1H), 2.85 - 2.74 (m, 2H), 2.29 - 2.13 (m, 2H)	peak 1, Rt = 1.606 min, Method F
6b	388.0	1H NMR (400 MHz, DMSO-d6): δ = 13.37 (s, 1H), 8.79 (s, 1H), 8.68 - 8.59 (m, 2H), 8.08 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.77 - 7.68 (m, 2H), 7.29 (s, 1H), 4.16 - 4.05 (m, 1H), 3.89 - 3.78 (m, 1H), 3.46 - 3.42 (m, 1H), 2.85 - 2.73 (m, 2H), 2.29 - 2.13 (m, 2H).	peak 2, Rt = 2.070 min, Method F
7a	338.0	1H NMR (DMSO-d6, 400 MHz): δ 13.34 (br s, 1H), 8.63 (d, J = 4.0 Hz, 2H), 8.22 (d, J = 2.0 Hz, 1H), 8.06 - 7.96 (m, 1H), 7.73 (d, J = 4.8 Hz, 2H), 7.29 (s, 1H), 7.18 (dd, J = 2.8, 8.4 Hz, 1H), 4.15 - 4.00 (m, 1H), 3.87 - 3.73 (m, 1H), 3.40 - 3.34 (m, 1H), 2.80 - 2.68 (m, 2H), 2.24 - 2.02 (m, 2H)	peak 1, Rt = 2.315 min, Method G
7b	338.1	1H NMR (DMSO-d6, 400 MHz): δ 13.35 (br s, 1H), 8.63 (d, J = 5.6 Hz, 2H), 8.22 (d, J = 2.4 Hz, 1H), 8.06 - 7.95 (m, 1H), 7.73 (d, J = 6.0 Hz, 2H), 7.29 (s, 1H), 7.18 (dd, J = 2.8, 8.4	peak 2, Rt = 3.073 min, Method G

		Hz, 1H), 4.15 - 4.01 (m, 1H), 3.87 - 3.78 (m, 1H), 3.44 - 3.36 (m, 1H), 2.77 - 2.70 (m, 2H), 2.23 - 2.02 (m, 2H).	
8a	387.0	1H NMR (DMSO-d6, 400 MHz): δ = 13.34 (s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.79 - 7.66 (m, 4H), 7.58 (d, J = 8.4 Hz, 2H), 7.24 (s, 1H), 4.06 - 3.95 (m, 1H), 3.91 - 3.77 (m, 1H), 3.42 - 3.36 (m, 1H), 2.80 - 2.65 (m, 2H), 2.25 - 2.06 (m, 2H).	peak 1, Rt = 3.717 min, Method H
8b	387.0	1H NMR (DMSO-d6, 400 MHz): δ = 13.33 (s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.79 - 7.66 (m, 4H), 7.59 (d, J = 8.4 Hz, 2H), 7.25 (s, 1H), 4.06 - 3.95 (m, 1H), 3.91 - 3.77 (m, 1H), 3.42 - 3.36 (m, 1H), 2.80 - 2.65 (m, 2H), 2.25 - 2.06 (m, 2H).	peak 2, Rt = 4.260 min, Method H
9a	337.0	1H NMR (DMSO-d6, 400 MHz): δ 13.34 (s, 1H), 8.63 (d, J = 6.4 Hz, 2H), 7.74 - 7.70 (m, 2H), 7.44 - 7.37 (m, 1H), 7.35 - 7.29 (m, 1H), 7.28 - 7.13 (m, 3H), 4.06 - 3.95 (m, 1H), 3.90 - 3.79 (m, 1H), 3.57 - 3.47 (m, 1H), 2.76 - 2.66 (m, 2H), 2.22 - 2.09 (m, 2H). LCMS: (ESI, m/z) [M+H] + = 337.0	peak 1, Rt = 1.448 min, Method I
9b	337.0	1H NMR (DMSO-d6, 400 MHz): δ 13.34 (s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.72 (d, J = 6.0 Hz, 2H), 7.44 - 7.37 (m, 1H), 7.35 - 7.29 (m, 1H), 7.28 - 7.13 (m, 3H), 4.08 - 3.98 (m, 1H), 3.90 - 3.80 (m, 1H), 3.58 - 3.46 (m, 1H), 2.74 - 2.68 (m, 2H), 2.20 - 2.11 (m, 2H). LCMS: (ESI, m/z) [M+H]+ = 337.0	peak 2, Rt =1.691 min, Method I
10	334.9	^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.37 (br s, 1H), 8.63 (d, J = 5.6 Hz, 2H), 7.76 - 7.71 (m, 2H), 7.65 - 7.60 (m, 1H), 7.52 - 7.46 (m, 1H), 7.36 - 7.28 (m, 3H), 6.29 (s, 1H), 4.28 - 4.09 (m, 2H), 3.03 - 2.87 (m, 2H).	Method BY
11a	355.0	1H NMR (DMSO-d6, 400 MHz): δ 13.42 - 13.29 (m, 1H), 8.63 (d, J = 4.0 Hz, 2H), 7.72 (d, J = 4.4 Hz, 2H), 7.28 (s, 1H), 7.15 - 7.06 (m, 3H), 4.13 - 4.00 (m, 1H), 3.83 - 3.76 (m, 1H), 3.31 - 3.25 (m, 1H), 2.80 - 2.63 (m, 2H), 2.22 - 2.03 (m, 2H)	peak 1, Rt = 1.552 min, Method J
11b	355.0	1H NMR (DMSO-d6, 400 MHz): δ 13.40 - 13.18 (m, 1H), 8.69 - 8.54 (m, 2H), 7.72 (d, J = 4.8 Hz, 2H), 7.28 (s, 1H), 7.17 - 7.02 (m, 3H), 4.13 - 4.00 (m, 1H), 3.85 - 3.73 (m, 1H),	peak 2, Rt = 2.267 min, Method J

		3.30 - 3.22 (m, 1H), 2.78 - 2.64 (m, 2H), 2.22 - 2.02 (m, 2H).	
12a	337.0	1H NMR (DMSO-d6, 400 MHz): δ 13.33 (br s, 1H), 8.67 - 8.59 (m, 2H), 7.76 - 7.69 (m, 2H), 7.45 - 7.32 (m, 1H), 7.26 - 7.15 (m, 3H), 7.09 - 7.04 (m, 1H), 4.08 - 3.95 (m, 1H), 3.84 - 3.77 (m, 1H), 3.28 - 3.20 (m, 1H), 2.78 - 2.61 (m, 2H), 2.23 - 2.01 (m, 2H).	peak 1, Rt = 0.927 min, Method K
12b	337.0	1H NMR (DMSO-d6, 400 MHz): δ 13.35 (br s, 1H), 8.65 (d, J = 6.0 Hz, 2H), 7.89 (d, J = 6.0 Hz, 2H), 7.45 - 7.32 (m, 1H), 7.26 - 7.20 (m, 1H), 4.13 - 3.98 (m, 1H), 3.89 - 3.72 (m, 1H), 3.28 - 3.20 (m, 1H), 2.81 - 2.62 (m, 2H), 2.24 - 2.01 (m, 2H).	peak 2, Rt = 1.250 min, Method K
13a	336.9	1H NMR (DMSO-d6, 400 MHz): δ 13.35 (s, 1H), 8.63 (d, J = 4.0 Hz, 2H), 7.72 (d, J = 4.4 Hz, 2H), 7.38 (dd, J = 5.6, 8.4 Hz, 2H), 7.28 (s, 1H), 7.17 (t, J = 8.8 Hz, 2H), 4.11 - 3.97 (m, 1H), 3.87 - 3.74 (m, 1H), 3.29 - 3.19 (m, 1H), 2.79 - 2.58 (m, 2H), 2.21 - 1.99 (m, 2H).	peak 1, Rt = 4.050 min, Method L
13b	337.0	: 1H NMR (DMSO-d6, 400 MHz): δ 13.36 (s, 1H), 8.64 (d, J = 3.6 Hz, 2H), 7.73 (d, J = 4.4 Hz, 2H), 7.39 (dd, J = 5.6, 8.4 Hz, 2H), 7.29 (s, 1H), 7.18 (t, J = 8.8 Hz, 2H), 4.11 - 3.98 (m, 1H), 3.89 - 3.74 (m, 1H), 3.29 - 3.20 (m, 1H), 2.78 - 2.61 (m, 2H), 2.22 - 2.02 (m, 2H).	peak 2, Rt = 4.538 min, Method L
14a	355.0	1H NMR (DMSO-d6, 400 MHz): δ 13.35 (br s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.72 (d, J = 6.0 Hz, 2H), 7.54 - 7.34 (m, 2H), 7.28 (br s, 1H), 7.22 - 7.17 (m, 1H), 4.11 - 4.01 (m, 1H), 3.84 - 3.72 (m, 1H), 3.30 - 3.20 (m, 1H), 2.79 - 2.64 (m, 2H), 2.22 - 2.01 (m, 2H)	peak 1, Rt = 0.915 min, Method M
14b	355.0	1H NMR (DMSO-d6, 400 MHz): δ 13.36 (s, 1H), 8.64 (d, J = 6.0 Hz, 2H), 7.72 (d, J = 6.0 Hz, 2H), 7.53 - 7.35 (m, 2H), 7.28 (br s, 1H), 7.23 - 7.16 (m, 1H), 4.12 - 4.02 (m, 1H), 3.86 - 3.73 (m, 1H), 3.29 - 3.21 (m, 1H), 2.78 - 2.64 (m, 2H), 2.24 - 2.00 (m, 2H).	peak 2, Rt = 1.290 min, Method M
15a	349.1	1H NMR (DMSO-d6, 400 MHz): δ 13.32 (br s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.72 (d, J = 6.0 Hz, 2H), 7.31 - 7.12 (m, 2H), 6.94 - 6.87 (m, 2H), 6.84 - 6.78 (m, 1H), 4.08 - 3.95 (m, 1H),	peak 1, Rt = 2.502 min, Method N

		3.85 - 3.77 (m, 1H), 3.75 (s, 3H), 3.26 - 3.15 (m, 1H), 2.73 - 2.63 (m, 2H), 2.21 - 2.06 (m, 2H).	
15b	349.1	1H NMR (DMSO-d6, 400 MHz): δ 13.33 (br s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.72 (d, J = 6.0 Hz, 2H), 7.32 - 7.14 (m, 2H), 6.94 - 6.87 (m, 2H), 6.85 - 6.78 (m, 1H), 4.07 - 3.96 (m, 1H), 3.86 - 3.78 (m, 1H), 3.76 (s, 3H), 3.23 - 3.17 (m, 1H), 2.73 - 2.66 (m, 2H), 2.21 - 2.05 (m, 2H).	peak 2, Rt = 2.924 min, Method N
16a	389.0	1H NMR (DMSO-d6, 400 MHz): δ 13.32 (br s, 1H), 9.16 (s, 1H), 8.95 (s, 1H), 8.63 (d, J = 5.6 Hz, 2H), 7.72 (d, J = 6.0 Hz, 2H), 7.24 (s, 1H), 4.02 - 3.83 (m, 2H), 3.79 - 3.65 (m, 1H), 2.94 - 2.80 (m, 2H), 2.42 - 2.29 (m, 1H), 2.23 - 2.11 (m, 1H).	peak 1, Rt = 1.901 min, Method O
16b	389.0	1H NMR (DMSO-d6, 400 MHz): δ 13.31 (br s, 1H), 9.16 (s, 1H), 8.95 (s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.75 - 7.68 (m, 2H), 7.22 (s, 1H), 4.00 - 3.84 (m, 2H), 3.79 - 3.66 (m, 1H), 2.90 - 2.82 (m, 2H), 2.42 - 2.33 (m, 1H), 2.25 - 2.10 (m, 1H).	peak 2, Rt = 3.743 min, Method O
17a	387.0	1H NMR (DMSO-d6, 400 MHz): δ 13.36 (br s, 1H), 8.69 - 8.58 (m, 2H), 7.76 - 7.66 (m, 4H), 7.63 - 7.58 (m, 2H), 7.29 (s, 1H), 4.15 - 4.03 (m, 1H), 3.88 - 3.79 (m, 1H), 3.40 - 3.39 (m, 1H), 2.78 - 2.72 (m, 2H), 2.23 - 2.14 (m, 2H).	peak 1, Rt = 3.125 min, Method P
17b	387.0	1H NMR (DMSO-d6, 400 MHz): δ 13.36 (br s, 1H), 8.69 - 8.58 (m, 2H), 7.76 - 7.66 (m, 4H), 7.63 - 7.58 (m, 2H), 7.29 (s, 1H), 4.15 - 4.00 (m, 1H), 3.89 - 3.77 (m, 1H), 3.40 - 3.39 (m, 1H), 2.80 - 2.71 (m, 2H), 2.23 - 2.10 (m, 2H).	peak 2, Rt = 4.076 min, Method P
18a	421.0	1H NMR (DMSO-d6, 400 MHz): δ = 13.37 (s, 1H), 8.65 - 8.63 (m, 2H), 7.83 (s, 1H), 7.78 - 7.66 (m, 4H), 7.29 (s, 1H), 4.11 - 4.01 (m, 1H), 3.85 - 3.75 (m, 1H), 3.40 - 3.35 (m, 1H), 2.80 - 2.70 (m, 2H), 2.20 - 2.04 (m, 2H).	peak 1, Rt = 3.435 min, Method Q
18b	421.0	1H NMR (DMSO-d6, 400 MHz): δ = 13.35 (s, 1H), 8.63 (d, J = 4.4 Hz, 2H), 7.83 (s, 1H), 7.78 - 7.66 (m, 4H), 7.28 (s, 1H), 4.11 - 4.01 (m, 1H), 3.85 - 3.75 (m, 1H), 3.45 - 3.38 (m, 1H), 2.80 - 2.70 (m, 2H), 2.20 - 2.05 (m, 2H).	peak 2, Rt = 4.715 min, Method Q

19	282.9	1H NMR (DMSO-d6, 400 MHz): δ 13.63 (s, 1H), 8.70 (d, J = 6.0 Hz, 2H), 8.36 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 6.0 Hz, 2H), 7.74 (d, J = 7.2 Hz, 1H), 7.51 - 7.39 (m, 4H), 7.34 (t, J = 7.6 Hz, 1H), 4.77 - 4.46 (m, 3H), 4.13 - 4.02 (m, 1H), 4.01 - 3.98 (m, 1H).	Method R
20a	297.2	1H NMR (DMSO-d6, 400 MHz): δ 13.29 (s, 1H), 8.61 (d, J = 5.2 Hz, 2H), 7.70 (d, J = 5.2 Hz, 2H), 7.24 (s, 1H), 4.00 - 3.91 (m, 1H), 3.70 - 3.62 (m, 1H), 2.48 - 2.41 (m, 1H), 2.18 - 1.62 (m, 10H), 1.50 - 1.41 (m, 1H).	peak 1, Rt = 3.835 min, Method S
20b	297.2	1H NMR (DMSO-d6, 400 MHz): δ 13.28 (s, 1H), 8.61 (d, J = 5.2 Hz, 2H), 7.70 (d, J = 5.2 Hz, 2H), 7.22 (s, 1H), 4.00 - 3.91 (m, 1H), 3.70 - 3.61 (m, 1H), 2.48 - 2.41 (m, 1H), 2.17 - 1.62 (m, 10H), 1.50 - 1.40 (m, 1H).	peak 2, Rt = 4.109 min, Method S
21a	311.0	1H NMR (DMSO-d6, 400 MHz): δ 13.29 (s, 1H), 8.62 (d, J = 5.2 Hz, 2H), 7.71 (d, J = 5.6 Hz, 2H), 7.24 (s, 1H), 4.05 - 3.95 (m, 1H), 3.71 - 3.61 (m, 1H), 2.25 - 2.16 (m, 1H), 2.08 - 1.99 (m, 1H), 1.79 - 1.51 (m, 10H), 1.21 - 1.12 (m, 2H).	peak 1, Rt = 2.952 min, Method T
21b	311.0	1H NMR (DMSO-d6, 400 MHz): δ 13.28 (s, 1H), 8.61 (d, J = 4.4 Hz, 2H), 7.71 (d, J = 5.2 Hz, 2H), 7.23 (s, 1H), 4.05 - 3.95 (m, 1H), 3.70 - 3.61 (m, 1H), 2.25 - 2.16 (m, 1H), 2.08 - 1.99 (m, 1H), 1.79 - 1.51 (m, 10H), 1.21 - 1.11 (m, 2H).	peak 2, Rt = 3.338 min, Method T
22a	325.2	1H NMR (DMSO-d6, 400 MHz): δ 13.27 (br s, 1H), 8.61 (d, J = 5.6 Hz, 2H), 7.70 (d, J = 6.0 Hz, 2H), 7.20 (br s, 1H), 4.08 - 3.90 (m, 1H), 3.70 - 3.57 (m, 1H), 2.50 - 2.46 (m, 1H), 2.28 - 2.16 (m, 1H), 2.07 - 1.96 (m, 1H), 1.80 - 1.60 (m, 6H), 1.59 - 1.47 (m, 1H), 1.26 - 1.11 (m, 4H), 1.04 - 0.88 (m, 2H).	peak 1, Rt = 3.384 min, Method H
22b	325.2	1H NMR (DMSO-d6, 400 MHz): δ 13.28 (br s, 1H), 8.61 (d, J = 6.0 Hz, 2H), 7.70 (d, J = 6.0 Hz, 2H), 7.21 (br s, 1H), 4.08 - 3.90 (m, 1H), 3.68 - 3.57 (m, 1H), 2.50 - 2.46 (m, 1H), 2.28 - 2.18 (m, 1H), 2.07 - 1.96 (m, 1H), 1.80 - 1.60 (m, 6H), 1.59 - 1.46 (m, 1H), 1.26 - 1.12 (m, 4H), 1.03 - 0.88 (m, 2H).	peak 2, Rt = 3.678 min, Method H
23	297.0	1H NMR (DMSO-d6, 400 MHz): δ 13.35 (s, 1H), 8.71 - 8.53 (m, 2H), 7.78 - 7.64 (m, 2H), 7.22 (br s, 1H), 4.14 - 3.98 (m,	Method U

		1H), 3.65 - 3.55 (m, 1H), 2.46 - 2.31 (m, 2H), 1.98 - 1.87 (m, 1H), 1.69 - 1.54 (m, 1H), 1.42 - 1.30 (m, 1H), 0.97 (s, 3H), 0.41 - 0.33 (m, 2H), 0.27 - 0.19 (m, 2H).	
24a	341.1	1H NMR (DMSO-d6, 400 MHz): δ 13.32 (br s, 1H), 8.62 (d, J = 5.6 Hz, 2H), 7.71 (d, J = 6.0 Hz, 2H), 7.23 (br s, 1H), 4.22 - 4.05 (m, 3H), 3.93 - 3.75 (m, 2H), 2.88 - 2.82 (m, 1H), 2.58 - 2.55 (m, 1H), 2.21 - 2.01 (m, 2H).	peak 1, Rt = 1.706 min, Method V
24b	340.9	1H NMR (DMSO-d6, 400 MHz): δ 13.35 (br s, 1H), 8.62 (d, J = 5.6 Hz, 2H), 7.71 (d, J = 5.6 Hz, 2H), 7.22 (br s, 1H), 4.29 - 4.03 (m, 3H), 3.95 - 3.73 (m, 2H), 2.89 - 2.82 (m, 1H), 2.58 - 2.54 (m, 1H), 2.22 - 1.98 (m, 2H).	peak 2, Rt = 2.254 min, Method V
25a	341.1	1H NMR: (DMSO-d6, 400 MHz) δ 13.10 (s, 1H), 8.61 (d, J = 4.8 Hz, 2H), 7.69 (d, J = 4.8 Hz, 2H), 7.19 (s, 1H), 4.12 - 3.98 (m, 3H), 3.83 - 3.72 (m, 1H), 2.65 - 2.56 (m, 1H), 2.47 - 2.38 (m, 1H), 2.36 - 2.28 (m, 1H), 2.15 - 2.04 (m, 1H), 1.77 - 1.63 (m, 1H).	peak 1, Rt = 1.657 min, Method W
25b	341.1	1H NMR: (DMSO-d6, 400 MHz) δ 13.10 (s, 1H), 8.61 (d, J = 5.6 Hz, 2H), 7.69 (d, J = 5.2 Hz, 2H), 7.16 (s, 1H), 4.14 - 3.97 (m, 3H), 3.83 - 3.71 (m, 1H), 2.64 - 2.57 (m, 1H), 2.45 - 2.38 (m, 1H), 2.36 - 2.28 (m, 1H), 2.14 - 2.04 (m, 1H), 1.78 - 1.63 (m, 1H).	peak 2, Rt = 2.256 min, Method W
26a	341.1	1H NMR: (DMSO-d6, 400 MHz) δ 13.10 (s, 1H), 8.61 (d, J = 4.8 Hz, 2H), 7.69 (d, J = 4.8 Hz, 2H), 7.19 (s, 1H), 4.12 - 3.98 (m, 3H), 3.83 - 3.72 (m, 1H), 2.65 - 2.56 (m, 1H), 2.47 - 2.38 (m, 1H), 2.36 - 2.28 (m, 1H), 2.15 - 2.04 (m, 1H), 1.77 - 1.63 (m, 1H).	peak 1, Rt = 1.573 min, Method X
26b	341.1	1H NMR: (DMSO-d6, 400 MHz) δ 13.10 (s, 1H), 8.61 (d, J = 5.6 Hz, 2H), 7.69 (d, J = 5.2 Hz, 2H), 7.16 (s, 1H), 4.14 - 3.97 (m, 3H), 3.83 - 3.71 (m, 1H), 2.64 - 2.57 (m, 1H), 2.45 - 2.38 (m, 1H), 2.36 - 2.28 (m, 1H), 2.14 - 2.04 (m, 1H), 1.78 - 1.63 (m, 1H).	peak 2, Rt = 3.031 min, Method X
27a	377.0	1H NMR (DMSO-d6, 400 MHz): δ 13.33 (s, 1H), 8.66 - 2.58 (m, 2H), 8.41 (s, 1H), 8.01 (s, 1H), 7.72 (d, J = 4.8 Hz, 2H),	peak 1, Rt = 0.881 min,

		7.27 (s, 1H), 4.07 - 3.95 (m, 1H), 3.85 - 3.74 (m, 1H), 3.29 - 3.20 (m, 1H), 2.90 -2.80 (m, 1H), 2.70 - 2.57 (m, 1H), 2.34 - 2.25 (m, 1H), 2.02-1.92 (m, 1H).	Method Y
27b	377.0	1H NMR (DMSO-d6, 400 MHz): δ 13.32 (s, 1H), 8.62 (d, J = 5.2 Hz, 2H), 8.41 (s, 1H), 8.01 (s, 1H), 7.72 (d, J = 5.6 Hz, 2H), 7.23 (s, 1H), 4.07 - 3.95 (s, 1H), 3.88 - 3.73 (m, 1H), 3.22 - 3.12 (m, 1H), 2.90 -2.80 (m, 1H), 2.70 - 2.57 (m, 1H), 2.34 - 2.25 (m, 1H), 2.01 - 1.90 (m, 1H).	peak 2, Rt = 2.964 min, Method Y
28a	326.0	1H NMR (DMSO-d6, 400 MHz): δ 13.33 (s, 1H), 8.86 (s, 1H), 8.72 - 8.51 (m, 3H), 7.72 (d, J = 6.0 Hz, 2H), 7.24 (s, 1H), 4.05 - 3.92 (m, 1H), 3.89 - 3.77 (m, 1H), 3.52 - 3.42 (m, 1H), 2.92 - 2.82 (m, 1H), 2.76 - 2.64 (m, 1H), 2.39 - 2.28 (m, 1H), 2.13 - 1.98 (m, 1H).	peak 1, Rt = 4.528 min, Method Z
28b	326.0	1H NMR (DMSO-d6, 400 MHz): δ 13.33 (s, 1H), 8.86 (s, 1H), 8.72 - 8.51 (m, 3H), 7.72 (d, J = 5.6 Hz, 2H), 7.25 (s, 1H), 4.05 - 3.92 (m, 1H), 3.89 - 3.77 (m, 1H), 3.52 - 3.42 (m, 1H), 2.92 - 2.82 (m, 1H), 2.76 - 2.64 (m, 1H), 2.38 - 2.26 (m, 1H), 2.15 - 2.00 (m, 1H).	peak 2, Rt = 4.932 min, Method Z
29a	360.0	1H NMR (DMSO-d6, 400 MHz): δ 13.36 (s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.72 (d, J = 5.6 Hz, 2H), 7.57 (s, 1H), 7.27 (s, 1H), 4.13 - 3.99 (m, 1H), 3.89 - 3.78 (m, 1H), 3.69-3.59 (m, 1H), 2.92 - 2.82 (m, 1H), 2.73 - 2.60 (m, 1H), 2.39 - 2.26 (m, 1H), 2.14 - 2.00 (m, 1H).	peak 1, Rt = 1.463 min, Method AA
29b	360.2	1H NMR (DMSO-d6, 400 MHz): δ = 13.33 (s, 1H), 8.62 (d, J = 5.2 Hz, 2H), 7.72 (d, J = 6.0 Hz, 2H), 7.57 (s, 1H), 7.23 (s, 1H), 4.10 - 3.93 (m, 1H), 3.87 - 3.78 (m, 1H), 3.66 - 3.55 (m, 1H), 2.94 - 2.82 (m, 1H), 2.75 - 2.65 (m, 1H), 2.37 - 2.26 (m, 1H), 2.13 - 2.01 (m, 1H).	peak 2, Rt = 2.378 min, Method AA
30a	357.0	1H NMR (DMSO-d6, 400 MHz): δ = 13.36 (br s, 1H), 8.63 (d, J = 5.2 Hz, 2H), 7.72 (d, J = 5.2 Hz, 2H), 7.27 (s, 1H), 6.24 (s, 1H), 4.12 - 3.97 (m, 1H), 3.91 - 3.81 (m, 1H), 3.78 (s, 3H), 3.52 - 3.41 (m, 1H), 2.85 - 2.72 (m, 1H), 2.66 - 2.55 (m, 1H), 2.27 - 2.16 (m, 1H), 2.04 - 1.88 (m, 1H).	peak 1, Rt = 0.885 min, Method AB

30b	357.1	1H NMR (DMSO-d6, 400 MHz): δ = 13.35 (br s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.72 (d, J = 6.0 Hz, 2H), 7.26 (s, 1H), 6.24 (s, 1H), 4.11 - 3.94 (m, 1H), 3.91 - 3.81 (m, 1H), 3.78 (s, 3H), 3.52 - 3.41 (m, 1H), 2.83 - 2.73 (m, 1H), 2.66 - 2.55 (m, 1H), 2.27 - 2.15 (m, 1H), 2.02 - 1.89 (m, 1H).	peak 2, Rt = 2.182 min, Method AB
31	319.1	1H NMR (400 MHz, DMSO) δ 13.21 (s, 1H), 8.65 – 8.57 (d, J = 6.2, 2H), 7.75 – 7.69 (d, J = 6.23, 2H), 7.37 – 7.30 (m, 2H), 7.30 – 7.18 (m, 4H), 3.89 (dd, J = 10.0, 7.0 Hz, 1H), 3.57 (dd, J = 10.1, 5.1 Hz, 1H), 2.80 (m, 3H), 2.58 (dd, J = 16.6, 7.7 Hz, 1H), 2.36 – 2.26 (dd, J = 16.6 1H).	Method AC
32	320.2	1H NMR (400 MHz, MeOD) δ 9.14 (s, 1H), 9.09 (d, J = 5.5 Hz, 1H), 7.66 – 7.58 (m, 1H), 7.39 – 7.16 (m, 5H), 3.53 – 3.42 (m, 2H), 3.18 – 3.06 (m, 1H), 2.63 – 2.44 (m, 2H), 2.60 (s, 6H), 2.20 – 2.09 (m, 1H), 2.08 – 1.96 (m, 1H).	Method AD
33a	371.2	1H NMR (DMSO-d6, 400 MHz): δ 8.50 (d, J = 5.6 Hz, 2H), 7.53 (t, J = 8.0 Hz, 1H), 7.39 -7.32 (m, 1H), 7.26 (d, J = 5.6 Hz, 2H), 7.17 (d, J = 8.4 Hz, 1H), 3.44 - 3.35 (m, 2H), 3.17 - 3.06 (m, 1H), 2.46 - 2.42 (m, 2H), 2.41 (s, 6H), 2.08 - 1.85 (m, 2H).	peak 1, Rt = 3.084 min, Method AE
33b	371.2	1H NMR (DMSO-d6, 400 MHz): δ 8.49 (d, J = 5.6 Hz, 2H), 7.53 (t, J = 8.0 Hz,, 1H), 7.38 (d, J = 10.8 Hz, 1H), 7.26 (d, J = 5.6 Hz, 2H), 7.17 (d, J = 8.4 Hz, 1H), 3.47 - 3.36 (m, 2H), 3.15 - 3.03 (m, 1H), 2.47 - 2.42 (m, 2H), 2.41 (s, 6H), 2.06 - 1.85 (m, 2H).	peak 2, Rt = 3.223 min, Method AE
34a	355.1	1H NMR (DMSO-d6, 400 MHz): δ 8.49 (d, J = 6.0 Hz, 2H), 7.44 - 7.32 (m, 2H), 7.28 - 7.23 (m, 2H), 7.15 - 7.10 (m, 1H), 3.42 - 3.33 (m, 2H), 3.13 - 3.05 (m, 1H), 2.47 - 2.37 (m, 8H), 2.05 - 1.85 (m, 2H).	peak 1, Rt = 3.719 min, Method AF
34b	355.1	1H NMR (DMSO-d6, 400 MHz): δ = 8.49 (d, J = 4.8 Hz, 2H), 7.43 - 7.33 (m, 2H), 7.28 - 7.23 (m, 2H), 7.16 - 7.10 (m, 1H), 3.42 - 3.34 (m, 2H), 3.14 - 3.04 (m, 1H), 2.44 - 2.35 (m, 8H), 2.04 - 1.85 (m, 2H)	peak 2, Rt =3.786 min, Method AF
35a	338.2	1H NMR (DMSO-d6, 400 MHz): δ 8.50 (d, J = 6.0 Hz, 2H),	peak 1, Rt =

		8.16 (d, J = 2.4 Hz, 1H), 7.98 - 7.91 (m, 1H), 7.31 - 7.23 (m, 2H), 7.18 - 7.13 (m, 1H), 3.44 - 3.35 (m, 2H), 3.22 - 3.11 (m, 1H), 2.48 - 2.38 (m, 8H), 2.07 - 1.90 (m, 2H).	1.316 min, Method BX
35b	338.1	1H NMR (DMSO-d6, 400 MHz): δ 8.54 - 8.46 (m, 2H), 8.16 (d, J = 1.6 Hz, 1H), 7.98 - 7.91 (m, 1H), 7.29 - 7.23 (m, 2H), 7.18 - 7.13 (m, 1H), 3.45 - 3.35 (m, 2H), 3.22 - 3.11 (m, 1H), 2.48 - 2.38 (m, 8H), 2.07 - 1.90 (m, 2H).	peak 2, Rt = 1.737 min, Method BX
36a	372.1	1H NMR (DMSO-d6, 400 MHz): δ 8.50 (dd, J = 1.6, 4.4 Hz, 2H), 8.26 (d, J = 1.6 Hz, 1H), 7.96 (dd, J = 2.0, 9.6 Hz, 1H), 7.26 (dd, J = 1.6, 4.4 Hz, 2H), 3.47 - 3.36 (m, 2H), 3.27 - 3.16 (m, 1H), 2.49 - 2.46 (m, 2H), 2.41 (s, 6H), 2.10 - 1.90 (m, 2H).	peak 1, Rt = 1.890 min, Method AG
36b	372.1	1H NMR (DMSO-d6, 400 MHz): δ 8.50 (dd, J = 1.6, 4.4 Hz, 2H), 8.26 (d, J = 1.6 Hz, 1H), 7.96 (dd, J = 2.0, 9.6 Hz, 1H), 7.26 (dd, J = 1.6, 4.4 Hz, 2H), 3.47 - 3.36 (m, 2H), 3.27 - 3.16 (m, 1H), 2.49 - 2.46 (m, 2H), 2.41 (s, 6H), 2.10 - 1.91 (m, 2H).	peak 2, Rt = 2.091 min, Method AG
37a	389.2	1H NMR (DMSO-d6, 400 MHz): δ 9.04 (s, 2H), 8.50 (d, J = 6.0 Hz, 2H), 7.27 (dd, J = 1.6, 4.4 Hz, 2H), 3.50 - 3.44 (m, 1H), 3.43 - 3.39 (m, 1H), 3.31 - 3.25 (m, 1H), 2.58 (d, J = 8.8 Hz, 2H), 2.46 - 2.39 (m, 6H), 2.18 - 1.97 (m, 2H).	peak 1, Rt = 1.412 min, Method AH
37b	389.2	1H NMR (DMSO-d6, 400 MHz): δ 9.04 (s, 2H), 8.50 (d, J = 6.0 Hz, 2H), 7.27 (d, J = 6.0 Hz, 2H), 3.50 - 3.43 (m, 1H), 3.42 - 3.39 (m, 1H), 3.31 - 3.26 (m, 1H), 2.58 (d, J = 8.8 Hz, 2H), 2.46 - 2.39 (m, 6H), 2.18 - 1.98 (m, 2H).	peak 2, Rt = 2.065 min, Method AH
38a	388.0	1H NMR (DMSO-d6, 400 MHz): δ 8.73 (d, J = 1.6 Hz, 1H), 8.50 (dd, J = 1.6, 4.4 Hz, 2H), 8.02 (dd, J = 1.6, 8.0 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.26 (dd, J = 1.6, 4.4 Hz, 2H), 3.47 - 3.40 (m, 2H), 3.31 - 3.23 (m, 1H), 2.54 - 2.50 (m, 2H), 2.42 (s, 6H), 2.13 - 1.95 (m, 2H).	peak 1, Rt = 2.966 min, Method AI
38b	388.1	1H NMR (DMSO-d6, 400 MHz): δ 8.73 (d, J = 1.6 Hz, 1H), 8.50 (d, J = 6.0 Hz, 2H), 8.02 (dd, J = 1.6, 8.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 4.4 Hz, 2H), 3.47 - 3.36 (m,	peak 2, Rt = 3.210 min, Method AI

		2H), 3.30 - 3.23 (m, 1H), 2.57 - 2.51 (m, 2H), 2.45 - 2.38 (m, 6H), 2.12 - 1.96 (m, 2H).	
39a	355.1	1H NMR (DMSO-d6, 400 MHz): δ 8.87 (s, 1H), 8.65 - 8.61 (m, 2H), 8.26 (s, 1H), 7.88 - 7.84 (m, 2H), 7.51 - 7.36 (m, 2H), 7.21 - 7.16 (m, 1H), 3.85 - 3.75 (m, 2H), 3.28 - 3.22 (m, 1H), 2.72 - 2.64 (m, 2H), 2.20 - 2.09 (m, 2H).	peak 1, Rt = 3.017 min, Method AJ followed by Method AK
39b	355.0	1H NMR (DMSO-d6, 400 MHz): δ 8.87 (s, 1H), 8.65 - 8.61 (m, 2H), 8.26 (s, 1H), 7.88 - 7.84 (m, 2H), 7.51 - 7.36 (m, 2H), 7.21 - 7.16 (m, 1H), 3.85 - 3.75 (m, 2H), 3.28 - 3.22 (m, 1H), 2.74 - 2.65 (m, 2H), 2.20 - 2.09 (m, 2H).	peak 2, Rt = 3.567 min, Method AJ followed by Method AK
40	371.0	1H NMR (DMSO-d6, 400 MHz): δ 8.66 (d, J = 2.8 Hz, 1H), 8.64 - 8.58 (m, 2H), 7.85 - 7.77 (m, 2H), 7.56 (t, J = 8.4 Hz, 1H), 7.46 - 7.43 (m, 1H), 7.23 - 7.21 (m, 1H), 7.08 (d, J = 2.8 Hz, 1H), 4.23 - 4.13 (m, 1H), 3.92 - 3.80 (m, 1H), 3.29 - 3.25 (m, 1H), 2.76 - 2.68 (m, 2H), 2.23 - 2.04 (m, 2H).	peak 1, Rt = 1.446 min, Method W
41a	338.2	1H NMR (DMSO-d6, 400 MHz): δ 8.87 (s, 1H), 8.63 (d, J = 5.6 Hz, 2H), 8.26 (s, 1H), 8.22 (s, 1H), 8.05 - 7.95 (m, 1H), 7.86 (d, J = 5.6 Hz, 2H), 7.18 (dd, J = 2.4, 8.4 Hz, 1H), 3.92 - 3.72 (m, 2H), 3.33 - 3.27 (m, 1H), 2.79 - 2.65 (m, 2H), 2.25 - 2.10 (m, 2H).	peak 1, Rt = 1.460 min, Method AL
41b	338.1	1H NMR (DMSO-d6, 400 MHz): δ 8.87 (s, 1H), 8.63 (d, J = 5.6 Hz, 2H), 8.26 (s, 1H), 8.22 (d, J = 1.6 Hz, 1H), 8.05 - 7.95 (m, 1H), 7.86 (d, J = 6.0 Hz, 2H), 7.18 (dd, J = 2.8, 8.4 Hz, 1H), 3.91 - 3.76 (m, 2H), 3.34 - 3.26 (m, 1H), 2.79 - 2.66 (m, 2H), 2.25 - 2.11 (m, 2H).	peak 2, Rt = 2.095 min, Method AL
42a	389.0	1H NMR (DMSO-d6, 400 MHz): δ 13.51 (s, 1H), 8.65 (d, J = 4.4 Hz, 2H), 7.74 (d, J = 5.2 Hz, 2H), 7.60 (t, J = 8.0 Hz, 1H), 7.41 (d, J = 10.4 Hz, 1H), 7.33 (s, 1H), 7.22 (d, J = 8.0 Hz, 1H), 5.22 (dd, J = 3.2, 47.6 Hz, 1H), 4.17 - 4.04 (m, 1H), 3.91 - 3.81 (m, 1H), 3.80 - 3.65 (m, 1H), 2.40 - 2.31 (m, 1H), 2.26 - 2.17 (m, 1H).	peak 1, Rt = 1.878 min, Method AM followed by Method AN

42b	389.0	1H NMR (DMSO-d6, 400 MHz): δ 13.47 (br s, 1H), 8.65 (d, J = 5.6 Hz, 2H), 7.74 (d, J = 5.6 Hz, 2H), 7.60 (t, J = 8.0 Hz, 1H), 7.53 (d, J = 10.4 Hz, 1H), 7.33 - 7.26 (m, 2H), 5.37 (dd, J = 11.2, 47.6 Hz, 1H), 4.14 - 4.03 (m, 1H), 3.97 - 3.84 (m, 1H), 3.63 - 3.47 (m, 1H), 2.36 - 2.24 (m, 1H), 2.22 - 2.11 (m, 1H).	peak 2, Rt = 3.108 min, Method AM
42c	389.0	1H NMR (DMSO-d6, 400 MHz): δ 13.47 (br s, 1H), 8.65 (d, J = 5.2 Hz, 2H), 7.74 (d, J = 5.6 Hz, 2H), 7.59 (t, J = 8.0 Hz, 1H), 7.57 - 7.50 (m, 1H), 7.35 - 7.26 (m, 2H), 5.37 (dd, J = 11.2, 47.6 Hz, 1H), 4.15 - 4.03 (m, 1H), 3.95 - 3.84 (m, 1H), 3.61 - 3.48 (m, 1H), 2.34 - 2.24 (m, 1H), 2.20 - 2.11 (m, 1H).	peak 3, Rt = 3.787 min, Method AO
42d	389.1	1H NMR (DMSO-d6, 400 MHz): δ 13.49 (br s, 1H), 8.64 (d, J = 6.0 Hz, 2H), 7.75 (d, J = 6.0 Hz, 2H), 7.60 (t, J = 8.0 Hz, 1H), 7.41 (d, J = 9.2 Hz, 1H), 7.33 (s, 1H), 7.22 (d, J = 8.4 Hz, 1H), 5.22 (dd, J = 3.2, 47.2 Hz, 1H), 4.18 - 4.02 (m, 1H), 3.91 - 3.81 (m, 1H), 3.80 - 3.66 (m, 1H), 2.43 - 2.29 (m, 1H), 2.26 - 2.17 (m, 1H).	peak 4, Rt = 4.396 min, Method AO
43a	411.1	1H NMR (400 MHz, DMSO-d6): δ 13.07 (s, 1H), 8.47 (d, J = 4.4 Hz, 1H), 8.38 (s, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.51 - 7.39 (m, 2H), 7.29 - 7.18 (m, 2H), 4.15 - 4.03 (m, 1H), 3.86 - 3.78 (m, 1H), 3.29 - 3.25 (m, 1H), 2.76 - 2.65 (m, 2H), 2.22 - 2.03 (m, 3H), 1.02 - 0.95 (m, 2H), 0.84 - 0.77 (m, 2H).	peak 1, Rt = 1.728 min, Method AP
43b	411.1	1H NMR (400 MHz, DMSO-d6): δ 13.07 (s, 1H), 8.47 (d, J = 4.4 Hz, 1H), 8.38 (s, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.51 - 7.39 (m, 2H), 7.29 - 7.18 (m, 2H), 4.15 - 4.03 (m, 1H), 3.85 - 3.77 (m, 1H), 3.29 - 3.25 (m, 1H), 2.76 - 2.65 (m, 2H), 2.22 - 2.00 (m, 3H), 1.02 - 0.94 (m, 2H), 0.84 - 0.77 (m, 2H).	peak 2, Rt = 2.397 min, Method AP
44a	405.0	1H NMR (DMSO-d6, 400 MHz): 13.35 (s, 1H), 8.83 (d, J = 4.4 Hz, 2H), 7.81 - 7.70 (m, 3H), 7.55 (d, J = 12.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.28 (br s, 1H), 4.17 - 3.99 (m, 1H), 3.88 - 3.76 (m, 1H), 3.45 - 3.39 (m, 1H), 2.80 - 2.69 (m, 2H), 2.28 - 2.02 (m, 2H).	peak 1, Rt = 1.771 min, Method AQ
44b	405.0	1H NMR (DMSO-d6, 400 MHz): 13.35 (s, 1H), 8.83 (d, J =	peak 2, Rt =

		4.4 Hz, 2H), 7.81 - 7.70 (m, 3H), 7.55 (d, J = 12.8 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.28 (br s, 1H), 4.20 - 4.01 (m, 1H), 3.90 - 3.73 (m, 1H), 3.46 - 3.39 (m, 1H), 2.81 - 2.69 (m, 2H), 2.26 - 2.04 (m, 2H).	2.493 min, Method AQ
45	396.0	1H NMR (400 MHz, DMSO-d6) δ 8.80 (d, J = 6.0 Hz, 2H), 7.85 - 7.76 (m, 2H), 7.56 (t, J = 8.4 Hz, 1H), 7.51 -7.45 (m, 1H), 7.28 - 7.24 (m, 1H), 3.95 - 3.77 (m, 2H), 3.37 - 3.41 (m, 1H), 2.78 -2.71 (m, 2H), 2.21 - 2.10 (m, 2H).	Method AR
46	325.1	1H NMR (DMSO-d6, 400 MHz): δ 13.31 (s, 1H), 8.62 (d, J = 4.0 Hz, 2H), 7.71 (d, J = 4.4 Hz, 2H), 7.25 (s, 1H), 4.12 - 3.94 (m, 1H), 3.77 - 3.66 (m, 1H), 2.68 - 2.56 (m, 1H), 2.49 - 2.19 (m, 4H), 2.13 - 2.02 (m, 1H), 1.72 (s, 1H).	Method AS
47a	373.1	1H NMR (DMSO-d6, 400 MHz): δ 13.35 (s, 1H), 8.63 (d, J = 4.0 Hz, 2H), 7.72 (d, J = 4.4 Hz, 2H), 7.36 (dd, J = 9.2, 6.8 Hz, 2H), 7.27 (s, 1H), 4.13 - 4.01 (m, 1 H), 3.82 - 3.70 (m, 1H), 3.29 -3.18 (m, 1H), 2.78 - 2.63 (m, 2H), 2.21 - 1.99 (m, 2H).	peak 1, Rt = 2.271 min, Method AT
47b	373.1	1H NMR (DMSO-d6, 400 MHz): δ 13.36 (s, 1H), 8.64 (d, J = 4.0 Hz, 2H), 7.73 (d, J = 4.4 Hz, 2H), 7.37 (dd, J = 9.2, 6.8 Hz, 2H), 7.28 (s, 1H), 4.13 - 4.01 (m, 1 H), 3.83 - 3.71 (m, 1H), 3.29 -3.18 (m, 1H), 2.78 - 2.63 (m, 2H), 2.21 - 1.99 (m, 2H).	peak 2, Rt = 2.690 min, Method AT
48a	389.0	1H NMR (DMSO-d6, 400 MHz): δ 13.34 (br s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.77 - 7.69 (m, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.27 (s, 1H), 4.13 - 3.98 (m, 1H), 3.83 - 3.71 (m, Hz, 1H), 2.76 -2.65 (m, 2H), 2.22 - 2.01 (m, 2H).	peak 1, Rt = 2.493 min, Method AU
48b	389.0	1H NMR (DMSO-d6, 400 MHz): δ 13.36 (br s, 1H), 8.63 (d, J = 6.0 Hz, 2H), 7.72 (d, J = 4.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.20 (s, 1H), 4.13 - 4.00 (m, 1H), 3.83 - 3.71 (m, Hz, 1H), 2.73 -2.60 (m, 2H), 2.22 - 2.01 (m, 2H).	peak 2, Rt = 2.944 min, Method AU
49a	355.2	1H NMR (DMSO-d6, 400 MHz): δ 13.36 (br s, 1H), 8.63 (d, J = 5.2 Hz, 2H), 7.73 (d, J = 5.2 Hz, 2H), 7.50 - 7.39 (m, 1H), 7.33 - 7.17 (m, 2H), 7.15 - 7.02 (m, 1H), 4.12 - 3.99 (m, 1H),	peak 1, Rt = 2.341 min, Method AV

		3.88 - 3.74 (m, 1H), 3.52 - 3.44 (m, 1H), 2.75 - 2.65 (m, 2H), 2.18 - 2.01 (m, 2H).	
49b	355.2	1H NMR (DMSO-d6, 400 MHz): δ 13.37 (br s, 1H), 8.63 (d, J = 5.2 Hz, 2H), 7.73 (d, J = 5.6 Hz, 2H), 7.53 - 7.39 (m, 1H), 7.33 - 7.18 (m, 2H), 7.15 - 7.01 (m, 1H), 4.12 - 3.99 (m, 1H), 3.90 - 3.76 (m, 1H), 3.56 - 3.42 (m, 1H), 2.75 - 2.65 (m, 2H), 2.18 - 2.01 (m, 2H).	peak 2, Rt = 2.808 min, Method AV
50a	393.1	1H NMR (DMSO-d6, 400 MHz): δ 13.35 (br s, 1H), 8.62 (d, J = 6.0 Hz, 2H), 7.73 (d, J = 5.6 Hz, 2H), 7.59 (d, J = 7.2 Hz, 1H), 7.43 - 7.33 (m, 2H), 7.28 (s, 1H), 4.14 - 4.02 (m, 1H), 3.86 - 3.73 (m, 1H), 3.31 - 3.22 (m, 1H), 2.77 - 2.65 (m, 2H), 2.22 - 2.03 (m, 2H).	peak 1, Rt = 1.149 min, Method AU
50b	393.2	1H NMR (DMSO-d6, 400 MHz): δ 13.34 (br s, 1H), 8.62 (d, J = 6.0 Hz, 2H), 7.72 (d, J = 5.6 Hz, 2H), 7.59 (d, J = 8.0 Hz, 1H), 7.43 - 7.33 (m, 2H), 7.23 (s, 1H), 4.11 - 3.97 (m, 1H), 3.86 - 3.73 (m, 1H), 3.31 - 3.22 (m, 1H), 2.76 - 2.64 (m, 2H), 2.22 - 2.03 (m, 2H).	peak 2, Rt = 1.823 min, Method AU
51	333.1	1H NMR (400 MHz, DMSO) δ 8.53 – 8.47 (m, 2H), 7.39 – 7.27 (m, 4H), 7.30 – 7.21 (m, 3H), 3.49 – 3.33 (m, 1H), 2.94 (dd, J = 16.6, 11.7 Hz, 2H), 2.79 (dd, J = 16.6, 4.3 Hz, 2H), 2.60 (s, 6H).	Method AW
52	367.1	1H NMR (400 MHz, DMSO) δ 8.52 – 8.45 (m, 2H), 7.45 – 7.37 (m, 2H), 7.37 – 7.30 (m, 2H), 7.30 – 7.24 (m, 2H), 3.45 (tt, J = 11.7, 4.2 Hz, 1H), 2.93 (dd, J = 16.6, 11.8 Hz, 2H), 2.83 – 2.72 (m, 2H), 2.60 (s, 6H).	Method AX
53a	371.16	1H NMR (400 MHz, DMSO) δ 8.53 – 8.47 (m, 2H), 7.42 – 7.30 (m, 2H), 7.29 – 7.23 (m, 2H), 7.14 – 7.07 (m, 1H), 5.16 (d, J = 5.6 Hz, 1H), 4.07 – 3.95 (m, 1H), 3.41 (dd, J = 11.7, 5.2 Hz, 1H), 3.11 (dd, J = 11.7, 8.3 Hz, 1H), 3.02 (td, J = 10.1, 6.0 Hz, 1H), 2.58 – 2.43 (m, 2H), 2.40 (s, 6H).	Peak 1, Method AY
53b	371.16	1H NMR (400 MHz, DMSO) δ 8.53 – 8.47 (m, 2H), 7.42 – 7.30 (m, 2H), 7.29 – 7.23 (m, 2H), 7.13 – 7.07 (m, 1H), 5.16 (d, J = 5.5 Hz, 1H), 4.07 – 3.95 (m, 1H), 3.41 (dd, J = 11.7,	Peak 2, Method AY

		5.2 Hz, 1H), 3.11 (dd, J = 11.8, 8.3 Hz, 1H), 3.02 (td, J = 10.0, 6.0 Hz, 1H), 2.54 – 2.42 (m, 2H), 2.40 (s, 6H).	
53c	371.16	1H NMR (400 MHz, DMSO) δ 8.53 – 8.47 (m, 2H), 7.44 – 7.30 (m, 2H), 7.30 – 7.24 (m, 2H), 7.21 – 7.12 (m, 1H), 5.24 (d, J = 3.8 Hz, 1H), 4.08 (s, 1H), 3.55 – 3.37 (m, 1H), 3.1 – 3.3 (m, 2H), 2.70 (dd, J = 16.8, 12.7 Hz, 1H), 2.45 – 2.27 (m, 7H).	Peak 1, Method AZ
53d	371.16	1H NMR (400 MHz, DMSO) δ 8.59 – 8.38 (m, 2H), 7.46 – 7.31 (m, 2H), 7.31 – 7.24 (m, 2H), 7.21 – 7.11 (m, 1H), 5.24 (d, J = 3.8 Hz, 1H), 4.08 (s, 1H), 3.51 (dd, J = 12.5, 3.1 Hz, 1H), 3.30 – 3.20 (m, 2H), 2.70 (dd, J = 16.8, 12.7 Hz, 1H), 2.45 – 2.36 (m, 6H), 2.32 (dd, J = 16.9, 5.4 Hz, 1H).	Peak 2, Method AZ
54	401.1	1H NMR (400 MHz, DMSO) δ 8.50 (d, J = 5.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 4.9 Hz, 2H), 3.58 (tt, J = 11.7, 4.3 Hz, 1H), 2.99 (dd, J = 16.6, 12.0 Hz, 2H), 2.83 (dd, J = 16.5, 4.3 Hz, 2H), 2.61 (s, 6H).	Method AW
55	385.1	1H NMR (400 MHz, DMSO) δ 8.53 – 8.47 (m, 2H), 7.57 (t, J = 8.1 Hz, 1H), 7.52 – 7.32 (m, 1H), 7.30 – 7.24 (m, 2H), 7.22 – 7.11 (m, 1H), 3.49 (tt, J = 12.0, 4.3 Hz, 1H), 3.00 – 2.88 (m, 2H), 2.84 – 2.74 (m, 2H), 2.60 (s, 6H).	Method BA
56	351.1	1H NMR (400 MHz, DMSO) δ 8.53 – 8.47 (m, 2H), 7.35 (qd, J = 6.1, 2.5 Hz, 2H), 7.33 – 7.25 (m, 2H), 7.23 – 7.13 (m, 2H), 3.45 (tt, J = 12.0, 4.0 Hz, 1H), 2.93 (dd, J = 16.6, 11.9 Hz, 2H), 2.78 (dd, J = 16.5, 4.3 Hz, 2H), 2.61 (s, 6H)	Method BB
57	402.1	1H NMR (400 MHz, DMSO) δ 8.76 (d, J = 2.2 Hz, 1H), 8.54 – 8.48 (m, 2H), 8.04 (dd, J = 8.3, 2.2 Hz, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.32 – 7.26 (m, 2H), 3.67 (tt, J = 12.3, 4.3 Hz, 1H), 3.04 (ddt, J = 17.0, 12.4, 1.3 Hz, 2H), 2.93 – 2.83 (m, 2H), 2.62 (s, 6H)	Method BC
58	337.2	1H NMR (DMSO-d6, 400 MHz): δ 8.50 (dd, J =1.6, 4.4 Hz, 2H), 7.31 (dd, J = 2.8, 8.4 Hz, 2H), 7.28 - 7.23 (m, 2H), 7.14 (t, J = 9.2 Hz, 2H), 3.43 - 3.34 (m, 2H), 3.14 - 3.02 (m, 1H), 2.45 - 2.37 (m, 8H), 2.05 - 1.84 (m, 2H).	Method BD

59a	370.1	1H NMR (DMSO-d6, 400 MHz): δ 8.64 (s, 1H), 8.50 (d, J = 4.8 Hz, 2H), 7.93 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 5.2 Hz, 2H), 6.93 (t, J = 55.2 Hz, 1H), 3.47 - 3.34 (m, 4H), 3.28 - 3.17 (m, 1H), 2.55 - 2.50 (m, 2 H), 2.46 - 2.39 (m, 6H), 2.11 - 1.93 (m, 2H)	peak 1, Rt = 1.753 min, Method BE
59b	370.1	1H NMR (DMSO-d6, 400 MHz): δ 8.64 (s, 1H), 8.50 (d, J = 4.8 Hz, 2H), 7.93 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 5.2 Hz, 2H), 6.93 (t, J = 55.2 Hz, 1H), 3.47 - 3.34 (m, 2H), 3.28 - 3.18 (m, 1H), 2.55 - 2.50 (m, 2 H), 2.46 - 2.38 (m, 6H), 2.12 - 1.94 (m, 2H)	peak 2, Rt = 2.165 min, Method BE
60a	338.1	1H NMR (400 MHz, DMSO-d6) δ 8.55 - 8.45 (m, 3H), 7.72 - 7.66 (m, 1H), 7.43 (dd, J = 4.4, 8.4 Hz, 1H), 7.26 (dd, J = 1.6, 4.4 Hz, 2H), 3.44 - 3.24 (m, 3H), 2.60 - 2.55 (m, 2H), 2.40 (s, 6H), 2.16 - 2.05 (m, 1H), 1.97 - 1.85 (m, 1H).	peak 1, Rt = 1.888 min, Method BF
60b	338.1	1H NMR (400 MHz, DMSO-d6) δ 8.55 - 8.45 (m, 3H), 7.72 - 7.66 (m, 1H), 7.43 (dd, J = 4.4, 8.8 Hz, 1H), 7.26 (dd, J = 1.6, 4.4 Hz, 2H), 3.44 - 3.22 (m, 3H), 2.56 - 2.52 (m, 2H), 2.40 (s, 6H), 2.15 - 2.06 (m, 1H), 1.96 - 1.85 (m, 1H).	peak 2, Rt = 2.111 min, Method BF
61	369.1	1H NMR (400 MHz, DMSO) δ 8.53 – 8.47 (m, 2H), 7.31 – 7.25 (m, 2H), 7.18 – 7.08 (m, 2H), 7.11 – 7.05 (m, 1H), 3.50 (tt, J = 12.1, 4.3 Hz, 1H), 2.95 (dd, J = 16.6, 12.2 Hz, 2H), 2.81 (dd, J = 16.7, 4.3 Hz, 2H), 2.61 (s, 6H)	Method AX
62	387.1	1H NMR (400 MHz, DMSO) δ 8.53 – 8.47 (m, 2H), 7.39 – 7.24 (m, 4H), 3.49 (tt, J = 12.3, 4.3 Hz, 1H), 2.93 (ddt, J = 16.9, 12.3, 1.4 Hz, 2H), 2.85 – 2.75 (m, 2H), 2.61 (s, 6H)	Method BC
63a	371.0	1H NMR (CDCl3, 400 MHz): δ 8.76 (s, 2H), 8.54 (d, J = 5.6 Hz, 2H), 7.19 - 7.12 (m, 2H), 6.68 (t, J = 54.4 Hz, 1H), 3.57 - 3.40 (m, 2H), 3.30 - 3.17 (m, 1H), 2.86 - 2.73 (m, 1H), 2.61 - 2.53 (m, 1H), 2.51 (s, 6H), 2.32 - 2.19 (m, 1H), 2.16 - 1.99 (m, 1H).	peak 1, Rt = 2.355 min, Method BG
63b	371.2	1H NMR (CDCl3, 400 MHz): δ 8.76 (s, 2H), 8.55 (d, J = 5.6 Hz, 2H), 7.15 (d, J = 6.0 Hz, 2H), 6.68 (t, J = 54.4 Hz, 1H), 3.57 - 3.40 (m, 2H), 3.30 - 3.18 (m, 1H), 2.86 - 2.73 (m,1H),	peak 2, Rt = 3.449 min, Method BG

		2.61 - 2.53 (m, 1H), 2.51 (s, 6H), 2.30 - 2.20 (m, 1H), 2.17 - 2.01 (m, 1H).	
64a	325.9	1H NMR (DMSO-d6, 400 MHz): δ 8.53 - 8.45 (m, 3H), 7.30 (s, 1H), 7.28 - 7.23 (m, 2H), 3.67 - 3.56 (m, 1H), 3.41 - 3.35 (m, 2H), 2.72 - 2.64 (m, 1H), 2.48 - 2.42 (m, 1H), 2.41 - 2.36 (s, 6H), 2.28 - 2.17 (m, 1H), 2.00 - 1.87 (m, 1H).	peak 1, Rt = 1.939 min, Method BE
64b	326.1	1H NMR (DMSO-d6, 400 MHz): δ 8.56 - 8.45 (m, 3H), 7.30 (d, J = 0.8 Hz, 1H), 7.28 - 7.21 (m, 2H), 3.67 - 3.55 (m, 1H), 3.44 - 3.34 (m, 2H), 2.72 - 2.64 (m, 1H), 2.47 - 2.42 (m, 1H), 2.41 - 2.36 (m, 6H), 2.27 - 2.16 (m, 1H), 2.00 - 1.86 (m, 1H).	peak 2, Rt = 2.170 min, Method BE
65a	337.2	1H NMR (DMSO-d6, 400 MHz): δ 8.50 (d, J = 6.0 Hz, 2H), 7.41 - 7.32 (m, 1H), 7.29 - 7.23 (m, 2H), 7.19 - 7.10 (m, 2H), 7.08 - 7.01 (m, 1H), 3.42 - 3.37 (m, 2H), 3.17 - 3.04 (m, 1H), 2.47 - 2.36 (m, 8H), 2.07 - 1.86 (m, 2H).	peak 1, Rt = 1.794 min, Method BH
65b	337.2	1H NMR (DMSO-d6, 400 MHz): δ 8.49 (d, J = 4.8 Hz, 2H), 7.41 - 7.32 (m, 1H), 7.26 (d, J = 5.2 Hz, 2H), 7.19 - 7.10 (m, 2H), 7.09 - 7.00 (m, 1H), 3.44 - 3.37 (m, 2H), 3.16 - 3.04 (m, 1H), 2.46 - 2.34 (m, 8H), 2.08 - 1.85 (m, 2H).	peak 2, Rt = 1.988 min, Method BH
66a	394.0	1H NMR (DMSO-d6, 400 MHz): δ 8.49 (d, J = 5.6 Hz, 2H), 8.00 (s, 1H), 7.26 (d, J = 6.0 Hz, 2H), 3.67 - 3.56 (m, 1H), 3.43 - 3.38 (m, 2H), 2.74 - 2.65 (m, 1H), 2.54 -2.51 (m, 1H), 2.41 (s, 6H), 2.29 - 2.20 (m, 1H), 2.02 - 1.90 (m, 1H).	peak 1, Rt = 2.418 min, Method BI
66b	394.1	1H NMR (DMSO-d6, 400 MHz): δ 8.49 (d, J = 6.0 Hz, 2H), 8.00 (s, 1H), 7.28 - 7.24 (m, 2H), 3.67 - 3.56 (m, 1H), 3.43 - 3.38 (m, 2H), 2.74 - 2.66 (m, 1H), 2.54 -2.50 (m, 1H), 2.40 (s, 6H), 2.29 - 2.20 (m, 1H), 2.02 - 1.89 (m, 1H).	peak 2, Rt = 3.006 min, Method BI
67a	338.1	1H NMR (CDCl3, 400 MHz): δ 8.55 (d, J = 3.6 Hz, 2H), 8.20 (d, J = 5.2 Hz, 1H), 7.17 (d, J = 5.6 Hz, 2H), 7.04 (d, J = 5.2 Hz, 1H), 6.78 (s, 1H), 3.52 - 3.35 (m, 2H), 3.22 - 3.08 (m, 1H), 2.80 - 2.67 (m, 1H), 2.51 (s, 6H), 2.50 - 2.44 (m, 1H), 2.26 - 2.14 (m, 1H), 2.05 - 1.92 (m, 1H).	peak 1, Rt = 3.902 min, Method AM
67b	338.1	: 1H NMR (DMSO-d6, 400 MHz): δ 8.50 (d, J = 5.6 Hz, 2H), 8.18 (d, J = 4.8 Hz, 1H), 7.31 (d, J = 5.2 Hz, 1H), 7.28 - 7.23	peak 2, Rt = 4.541 min,

		(m, 2H), 7.13 (s, 1H), 3.45 - 3.37 (m, 2H), 3.25 - 3.14 (m, 1H), 2.49 - 2.44 (m, 2H), 2.41 (s, 6H), 2.13 - 2.03 (m, 1H), 2.02 - 1.87 (m, 1H).	Method AM
68a	326.1	1H NMR (DMSO-d6, 400 MHz): δ 8.79 (s, 1H), 8.58 (s, 1H), 8.49 (d, J = 5.6 Hz, 2H), 7.25 (d, J = 6.0 Hz, 2H), 3.38 - 3.25 (m, 3H), 2.66 - 2.57 (m, 1H), 2.48 - 2.43 (m, 1H), 2.40 (s, 6H), 2.21 - 2.11 (m, 1H), 1.97 - 1.82 (m, 1H).	peak 1, Rt = 2.238m min, Method BJ
68b	325.9	1H NMR (DMSO-d6, 400 MHz): δ 8.79 (s, 1H), 8.58 (s, 1H), 8.49 (d, J = 5.2 Hz, 2H), 7.26 (d, J = 6.0 Hz, 2H), 3.38 - 3.22 (m, 3H), 2.67 - 2.56 (m, 1H), 2.48 - 2.43 (m, 1H), 2.40 (s, 6H), 2.23 - 2.11 (m, 1H), 1.96 - 1.82 (m, 1H).	peak 2, Rt = 2.902 min, Method BJ
69a	344.2	1H NMR (DMSO-d6, 400 MHz): δ 8.55 - 8.45 (m, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.30 - 7.20 (m, 2H), 3.41 - 3.32 (m, 2H), 3.24 - 3.14 (m, 1H), 2.48 - 2.43 (m, 2H), 2.42 - 2.35 (m, 6H), 2.08 - 1.89 (m, 2H).	peak 1, Rt = 2.055 min, Method AG
69b	344.0	1H NMR (DMSO-d6, 400 MHz): δ 8.50 (d, J = 6.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 5.6 Hz, 2H), 3.39 - 3.32 (m, 2H), 3.24 - 3.15 (m, 1H), 2.47 - 2.43 (m, 2H), 2.41 - 2.35 (m, 6H), 2.06 - 1.88 (m, 2H).	peak 2, Rt = 2.249 min, Method AG
70	369.1	1H NMR (400 MHz, DMSO) δ 8.53 – 8.46 (m, 2H), 7.48 – 7.36 (m, 2H), 7.31 – 7.25 (m, 2H), 7.21 – 7.13 (m, 1H), 3.47 (tt, J = 11.9, 4.2 Hz, 1H), 2.94 (dd, J = 16.6, 12.1 Hz, 2H), 2.79 (dd, J = 16.6, 4.4 Hz, 2H), 2.61 (s, 6H).	Method BK
71a	369.1		Peak 1, Method BL
71b	369.1	1H NMR (400 MHz, DMSO) δ 8.53 – 8.47 (m, 2H), 7.36 (q, J = 8.6 Hz, 4H), 7.29 – 7.24 (m, 2H), 5.93 (d, J = 5.9 Hz, 1H), 5.12 (dt, J = 5.8, 2.8 Hz, 1H), 3.50 (tdd, J = 12.4, 5.6, 2.9 Hz, 1H), 2.51 – 2.33 (m, 8H), 2.06 (td, J = 13.1, 3.1 Hz, 1H), 1.92 (dq, J = 13.2, 2.5 Hz, 1H).	Peak 2, Method BL
71c	369.1		Peak 3, Method BL

71d	369.1	1H NMR (400 MHz, DMSO) δ 8.53 – 8.47 (m, 2H), 7.36 (q, J = 8.6 Hz, 4H), 7.29 – 7.24 (m, 2H), 5.93 (d, J = 5.9 Hz, 1H), 5.12 (dt, J = 5.9, 2.8 Hz, 1H), 3.49 (tdt, J = 12.3, 6.8, 3.4 Hz, 1H), 2.51 – 2.33 (m, 8H), 2.06 (td, J = 13.1, 3.1 Hz, 1H), 1.92 (dq, J = 13.2, 2.5 Hz, 1H).	Peak 4, Method BL
72a	377.2	1H NMR (DMSO-d6, 400 MHz): δ = 13.47 (br s, 1H), 8.49 (dd, J = 1.6, 6.0 Hz, 2H), 7.25 (dd, J = 2.0, 6.4 Hz, 2H), 6.55 (s, 1H), 3.37 - 3.21 (m, 3H), 2.66 - 2.58 (m, 1H), 2.48 - 2.35 (m, 7H), 2.24 - 2.13 (m, 1H), 1.94 - 1.80 (m, 1H).	peak 1, Rt = 1.234 min, Method BM
72b	377.2	1H NMR (DMSO-d6, 400 MHz): δ = 13.47 (br s, 1H), 8.49 (dd, J = 1.6, 4.4 Hz, 2H), 7.31 - 7.21 (m, 2H), 6.55 (s, 1H), 3.38 - 3.15 (m, 1H), 2.65 - 2.58 (m, 1H), 2.47 - 2.36 (m, 7H), 2.25 - 2.12 (m, 1H), 1.93 - 1.80 (m, 1H).	peak 2, Rt = 1.311 min, Method BM
73a	356.0	1H NMR (DMSO-d6, 400 MHz): δ 8.50 (d, J = 4.8 Hz, 2H), 8.10 - 8.02 (m, 1H), 7.99 (s, 1H), 7.26 (d, J = 6.0 Hz, 2H), 3.46 - 3.37 (m, 2H), 3.25 - 3.15 (m, 1H), 2.49 - 2.45 (m, 2H), 2.41 (s, 6H), 2.08 - 1.90 (m, 2 H).	peak 1, Rt = 1.444 min, Method BF
73b	356.2	1H NMR (DMSO-d6, 400 MHz): δ 8.50 (d, J = 4.8 Hz, 2H), 8.10 - 8.02 (m, 1H), 7.99 (s, 1H), 7.26 (d, J = 6.0 Hz, 2H), 3.46 - 3.37 (m, 2H), 3.25 - 3.15 (m, 1H), 2.49 - 2.45 (m, 2H), 2.41 (s, 6H), 2.08 - 1.90 (m, 2 H).	peak 2, Rt = 2.081 min, Method BF
74a	373.1	1H NMR (DMSO-d6, 400 MHz): δ 8.50 (d, J = 5.6 Hz, 2H), 7.53 - 7.37 (m, 2H), 7.28 (d, J = 5.6 Hz, 2H), 7.24 - 7.19 (m, 1H), 5.08 (dd, J = 11.2, 47.6 Hz, 1H), 3.45 - 3.40 (m, 3H), 2.46 - 2.41 (m, 6H), 2.21 - 2.11 (m, 1H), 2.04 - 1.95 (m, 1H).	peak 1, Rt = 2.307 min, Method BN
74b	373.1	1H NMR (DMSO-d6, 400 MHz): δ 8.50 (d, J = 5.6 Hz, 2H), 7.53 - 7.36 (m, 2H), 7.28 (d, J = 6.0 Hz, 2H), 7.24 - 7.19 (m, 1H), 5.08 (dd, J = 11.2, 47.6 Hz, 1H), 3.45 - 3.40 (m, 3H), 2.46 - 2.40 (m, 6H), 2.19 - 2.10 (m, 1H), 2.04 - 1.96 (m, 1H).	peak 2, Rt = 3.605 min, Method BN followed by Method BO
75a	338.1	1H NMR (DMSO-d6, 400 MHz,): δ 8.49 (dd, J =1.6, 4.8 Hz, 2H), 8.45 (d, J = 2.8 Hz, 1H), 8.42 (s, 1H), 7.72 (dd, J =2.0, 10.4 Hz, 1H), 7.26 (dd, J =1.6, 4.8 Hz, 2H), 3.46 - 3.38 (m,	peak 1, Rt = 3.626 min, Method BP

		2H), 3.26 - 3.11 (m, 1H), 2.49 - 2.44 (m, 2H), 2.42 (s, 6H), 2.13 - 1.87 (m, 2H).	
75b	338.1	1H NMR (DMSO-d6, 400 MHz,): δ 8.50 (d, J = 5.6 Hz, 2H), 8.45 (d, J = 2.4 Hz, 1H), 8.42 (s, 1H), 7.72 (d, J = 10.4 Hz, 1H), 7.26 (d, J = 5.4 Hz, 2H), 3.46 - 3.36 (m, 2H), 3.26 - 3.14 (m, 1H), 2.49 - 2.44 (m, 2H), 2.42 (s, 6H), 2.09 - 1.90 (m, 2H).	peak 2, Rt = 4.874 min, Method BP
76a	360.1	1H NMR (DMSO-d6, 400 MHz): δ 8.49 (d, J = 5.2 Hz, 2H), 7.51 (s, 1H), 7.26 (d, J = 5.6 Hz, 2H), 3.51 - 3.38 (m, 3H), 2.66 - 2.58 (m, 1H), 2.46 - 2.37 (m, 7H), 2.23 - 2.12 (m, 1H), 1.95 - 1.81 (m, 1H).	peak 1, Rt = 2.086 min, Method BE
76b	360.1	1H NMR (DMSO-d6, 400 MHz): δ 8.49 (d, J = 6.0 Hz, 2H), 7.51 (s, 1H), 7.25 (d, J = 5.6 Hz, 2H), 3.50 - 3.37 (m, 3H), 2.66 - 2.58 (m, 1H), 2.47 - 2.35 (m, 7H), 2.24 - 2.11 (m, 1H), 1.96 - 1.81 (m, 1H).	peak 2, Rt = 2.247 min, Method BE
77a	362.1	1H NMR (400 MHz, DMSO-d6): δ 8.50 (dd, J = 1.6, 4.4 Hz, 2H), 7.89 (t, J = 7.6 Hz, 1H), 7.52 (d, J = 10.0 Hz, 1H), 7.36 (dd, J = 1.2, 8.0 Hz, 1H), 7.26 (dd, J = 1.6, 4.4 Hz, 1H), 3.44 - 3.38 (m, 2H), 3.26 - 3.17 (m, 1H), 2.50 - 2.44 (m, 2H), 2.41 (s, 6H), 2.08 - 1.91 (m, 2H).	peak 1, Rt = 2.494 min, Method AG, followed by Method BQ
77b	362.1	1H NMR (400 MHz, DMSO-d6): δ 8.50 (d, J = 5.2 Hz, 2H), 7.89 (t, J = 7.6 Hz, 1H), 7.56 - 7.47 (m, 1H), 7.36 (dd, J = 1.2, 8.0 Hz, 1H), 7.26 (d, J = 6.0 Hz, 2H), 3.44 - 3.38 (m, 2H), 3.27 - 3.16 (m, 1H), 2.50 - 2.44 (m, 2H), 2.43 (s, 6H), 2.07 - 1.88 (m, 2H).	peak 2, Rt = 2.713 min, Method AG
78a	350.1	1H NMR (DMSO-d6, 400 MHz): δ 8.49 (dd, J = 1.6, 4.4 Hz, 2H), 7.98 (s, 1H), 7.80 (s, 1H), 7.26 (dd, J = 1.6, 4.4 Hz, 2H), 3.38 - 3.33 (m, 2H), 3.24 - 3.13 (m, 1H), 2.59 - 2.56 (m, 1H), 2.44 - 2.35 (m, 7H), 2.16 - 2.07 (m, 1H), 1.92 - 1.78 (m, 1H).	peak 1, Rt = 1.582 min, Method BR
78b	350.2	1H NMR (DMSO-d6, 400 MHz): δ 8.49 (dd, J = 1.6, 4.4 Hz, 2H), 7.98 (s, 1H), 7.80 (s, 1H), 7.26 (dd, J = 1.6, 4.4 Hz, 2H), 3.37 - 3.34 (m, 2H), 3.23 - 3.13 (m, 1H), 2.59 - 2.54 (m, 1H), 2.43 - 2.35 (m, 7H), 2.17 - 2.07 (m, 1H), 1.92 - 1.79 (m, 1H).	peak 2, Rt = 2.005 min, Method BR

79a	350.0	1H NMR (CDCl3, 400 MHz): δ 8.60 - 8.50 (m, 2H), 7.52 (d, J = 4.0 Hz, 1H), 7.16 (d, J = 5.6 Hz, 2H), 6.89 (d, J = 4.0 Hz, 1H), 3.54 - 3.33 (m, 3H), 2.88 - 2.78 (m, 1H), 2.59 - 2.53 (m, 1H), 2.51 - 2.47 (m, 6H), 2.35 - 2.27 (m, 1H), 2.06 - 1.95 (m, 1H).	peak 1, Rt = 2.527 min, Method BS
79b	350.1	1H NMR (CDCl3, 400 MHz): δ 8.57 - 8.51 (m, 2H), 7.52 (d, J = 4.0 Hz, 1H), 7.19 - 7.11 (m, 2H), 6.89 (d, J = 3.6 Hz, 1H), 3.51 - 3.34 (m, 3H), 2.88 - 2.78 (m, 1H), 2.59 - 2.53 (m, 1H), 2.52 - 2.46 (m, 6H), 2.35 - 2.26 (m, 1H), 2.07 - 1.94 (m, 1H).	peak 2, Rt = 2.907 min, Method BS
80a	360.1	1H NMR (DMSO-d6, 400 MHz): δ 8.52 - 8.45 (m, 2H), 7.75 (s, 1H), 7.28 - 7.22 (m, 2H), 3.61 - 3.51 (m, 1H), 3.41 - 3.40 (m, 1H), 3.33 - 3.30 (m, 1H), 2.69 - 2.61 (m, 1H), 2.57 - 2.53 (m, 1H), 2.38 (s, 6H), 2.29 - 2.20 (m, 1H), 1.99 - 1.87 (m, 1H).	peak 1, Rt = 4.698 min, Method BT
80b	360.1	1H NMR (DMSO-d6, 400 MHz): δ 8.51 - 8.46 (m, 2H), 7.75 (s, 1H), 7.28 - 7.23 (m, 2H), 3.62 - 3.52 (m, 1H), 3.42 - 3.40 (m, 1H), 3.33 - 3.30 (m, 1H), 2.69 - 2.60 (m, 1H), 2.57 - 2.53 (m, 1H), 2.38 (s, 6H), 2.29 - 2.20 (m, 1H), 1.99 - 1.87 (m, 1H).	peak 2, Rt = 5.449 min, Method BT
81a	371.1	1H NMR (DMSO-d6, 400 MHz): δ 8.55 - 8.46 (m, 2H), 7.43 - 7.32 (m, 2H), 7.27 (d, J = 5.6 Hz, 2H), 7.16 - 7.09 (m, 1H), 5.01 (d, J = 4.0 Hz, 1H), 3.99 - 3.96 (m, 1H), 3.40 - 3.35 (m, 2H), 2.99 - 2.88 (m, 1H), 2.43 (s, 6H), 2.17 - 2.04 (m, 1H), 1.95 - 1.90 (m, 1H).	peak 1, Rt = 1.486 min, Method BU
81b	371.1	1H NMR (DMSO-d6, 400 MHz): δ 8.53 (d, J = 5.6 Hz, 2H), 7.43 - 7.33 (m, 2H), 7.33 - 7.30 (m, 2H), 7.16 - 7.10 (m, 1H), 5.01 (br s, 1H), 3.98 (d, J = 10.8 Hz, 1H), 3.48 - 3.37 (m, 2H), 2.99 - 2.87 (m, 1H), 2.44 (s, 6H), 2.14 - 2.04 (m, 1H), 1.95 - 1.90 (m, 1H).	peak 2, Rt = 1.667 min, Method BU
82a	353.1	1H NMR (DMSO-d6, 400 MHz): δ 8.53 - 8.46 (m, 2H), 7.37 - 7.32 (m, 1H), 7.26 - 7.23 (m, 2H), 7.24 - 7.18 (m, 1H), 7.05 - 6.98 (m, 1H), 3.65 - 3.60 (m, 1H), 3.48 - 3.44 (m, 1H), 2.36 - 2.30 (m, 6H), 2.28 - 2.24 (m, 1H), 2.20 - 2.14 (m, 2H).	peak 1, Rt = 1.601 min, Method BH

82b	353.1	1H NMR (DMSO-d6, 400 MHz): δ 8.52 - 8.47 (m, 2H), 7.37 - 7.30 (m, 1H), 7.26 - 7.23 (m, 2H), 7.24 - 7.18 (m, 1H), 7.04 - 6.98 (m, 1H), 3.65 - 3.60 (m, 1H), 3.48 - 3.44 (m, 1H), 2.36 - 2.30 (m, 6H), 2.28 - 2.24 (m, 1H), 2.21 - 2.14 (m, 2H).	peak 2, Rt =1.736 min, Method BH
83a	348.1	1H NMR (DMSO-d6, 400 MHz,): δ 8.75 (d, J = 2.40 Hz, 1H), 8.70 (dd, J = 1.6, 4.8 Hz, 2H), 8.18 (d, J = 8.4 Hz, 1H), 8.06 (dd, J = 1.6, 4.8 Hz, 2 H), 7.96 (dd, J = 2.4, 8.4 Hz, 1H), 7.45 - 7.36 (m, 2H), 7.19 (t, J = 8.4 Hz, 2H), 3.99 - 3.89 (m, 1H), 3.74 - 3.67 (m, 1H), 3.38 - 3.33 (m, 1H), 2.72 - 2.63 (m, 2H), 2.19 - 2.09 (m, 2 H).	peak 1, Rt = 3.810 min, Method BV
83b	348.0	1H NMR (DMSO-d6, 400 MHz,): δ 8.75 (d, J = 2.40 Hz, 1H), 8.70 (dd, J = 2.0, 4.4 Hz, 2H), 8.18 (d, J = 8.4 Hz, 1H), 8.06 (dd, J = 1.6, 4.4 Hz, 2 H), 7.96 (dd, J = 2.4, 8.0 Hz, 1H), 7.45 - 7.36 (m, 2H), 7.19 (t, J = 8.8 Hz, 2H), 3.99 - 3.89 (m, 1H), 3.74 - 3.67 (m, 1H), 3.38 - 3.33 (m, 1H), 2.71 - 2.64 (m, 2H), 2.20 - 2.10 (m, 2 H).	peak 2, Rt = 4.102 min, Method BV
84a	366.1	1H NMR (DMSO-d6, 400 MHz): δ 8.75 (d, J = 2.4 Hz, 1H), 8.71 (d, J = 4.8 Hz, 2H), 8.18 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 4.8 Hz, 2H), 7.99 - 7.91 (m, 1H), 7.51 - 7.38 (m, 2H), 7.22 - 7.17 (m, 1H), 4.00 - 3.88 (m, 1H), 3.79 - 3.67 (m, 1H), 3.40 - 3.36 (m, 1H), 2.74 - 2.65 (m, 2H), 2.20 - 2.10 (m, 2H).	peak 1, Rt = 3.622 min, Method AH
84b	366.1	1H NMR (DMSO-d6, 400 MHz): δ 8.75 (d, J = 2.4 Hz, 1H), 8.70 (d, J = 5.6 Hz, 2H), 8.18 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 6.0 Hz, 2H), 7.99 - 7.91 (m, 1H), 7.51 - 7.36 (m, 2H), 7.22 - 7.17 (m, 1H), 4.00 - 3.88 (m, 1H), 3.79 - 3.67 (m, 1H), 3.40 - 3.36 (m, 1H), 2.74 - 2.65 (m, 2H), 2.20 - 2.10 (m, 2H).	peak 2, Rt = 4.371 min, Method AH
85	371.0	1H NMR (DMSO-d6, 400 MHz): δ 8.89 (s, 1H), 8.64 (d, J = 6.0 Hz, 2H), 8.28 (s, 1H), 7.91 - 7.84 (m, 2H), 7.62 - 7.52 (m, 1H), 7.48 - 7.35 (m, 2H), 5.83 (s, 1H), 3.97 - 3.85 (m, 1H), 3.80 - 3.71 (m, 1H), 3.03 (d, J = 17.2 Hz, 1H), 2.55 - 2.50 (m, 1H), 2.48 - 2.43 (m, 1H), 2.05 - 1.95 (m, 1H).	Method AS
86a	370.1	1H NMR (DMSO-d6, 400 MHz): δ 8.48 (d, J = 5.6 Hz, 2H), 8.26 (d, J = 1.6 Hz, 1H), 7.52 - 7.39 (m, 2H), 7.25 (d, J = 6.0	peak 1, Rt = 1.709 min,

		Hz, 2H), 7.21 - 7.15 (m, 1H), 4.75 - 4.56 (m, 1H), 2.97 - 2.88 (m, 1H), 2.87 - 2.78 (m, 1H), 2.54 (s, 6H).	Method BJ
86b	370.1	1H NMR (DMSO-d6, 400 MHz): δ 8.48 (d, J = 5.6 Hz, 2H), 8.27 (d, J = 1.6 Hz, 1H), 7.50 - 7.37 (m, 2H), 7.25 (d, J = 6.0 Hz, 2H), 7.22 - 7.15 (m, 1H), 4.76 - 4.56 (m, 1H), 2.97 - 2.88 (m, 1H), 2.87 - 2.78 (m, 1H), 2.54 (s, 6H).	peak 2, Rt = 2.105 min, Method BJ
87	391.0	1H NMR (DMSO-d6, 400 MHz): δ 8.52 (d, J = 5.2 Hz, 2H), 7.58 - 7.47 (m, 1H), 7.46 - 7.34 (m, 1H), 7.28 (d, J = 5.2 Hz, 2H), 7.25 - 7.18 (m, 1H), 3.52 - 3.38 (m, 4H), 3.31 - 3.21 (m, 1H), 2.48 - 2.35 (m, 6H), 1.85 - 1.71 (m, 2H).	Method BW

Preparation of recombinant human SARM1 protein.

pRK5 plasmid containing human SARM1 (E26-T274, EC 3.2.2.6) with N-terminal His and C-terminal Avi and Flag tags was transfected into Expi293F™ cells (ThermoFisher Scientific #A14527) were cultured in Expi293 expression medium at 37 °C, 8% CO2. Cells were seeded at 2.5–3 × 10^6 viable cells per ml and transfected with 0.8 mg/ml DNA construct using 1:3 PEI Max transfection reagent (PolySciences #24765). Post transfection, cells were fed and 4mM valproic acid was added. The cells were harvested after 48 h, by centrifuging at 500 × *g*, 15 min, 4 °C. For purification, cell paste was resuspended in (100 mL per liter of cell paste) ice-cold lysis buffer (50 mM Tris-HCl pH 8.0, 200mM NaCl, 5 % Glycerol, 1.0 mM TCEP (*Tris-HCl*(2-carboxyethyl)phosphine), 10 Roche Complete EDTA-Free Protease Inhibitor Cocktail Tablets (Millipore Sigma #4693132001) and cells were homogenized then disrupted by double passage using Microfluidizer â Processor (Microfluidics Model M-110Y). Insoluble matter was separated by ultracentrifugation at 40,000 RPM for 1 hour. The soluble supernatant was decanted and passed through a monoclonal ANTI-FLAG® M2 antibody (Millipore Sigma #F1804). The resin column was equilibrated with Lysis Buffer and the bound protein was eluted by 100 ug/mL of 3X FLAG® Peptide (Sigma-Aldrich #F4799). The eluent protein was injected on a Superdex 200 16/60 (Amersham Biosciences # GE28-9893-35) column equilibrated in 25 mM Tris pH 8.0, 1 mM TCEP, 150 mM NaCl, 5% Glycerol.

LCMS Assay Protocol

The enzymatic assay was performed in 384-well polypropylene plate in assay buffer (50 mM

Tris pH 7.5, 0.5 mM dithiothreitol, 0.05 %w/v bovine gamma globulin) in a final assay volume of 15 µL. Recombinant full-length SARM1(E26-T274) with a final concentration of 7.5 nM was pre-incubated with the respective compound at 1% DMSO final assay concentration for 15 min at room temperature. The reaction was initiated by addition of 20 µM NAD and 20 µM NMN, final concentrations. After a 45 min room temperature incubation, the reaction was terminated by addition of 60 µL methanol. Samples were diluted in water (4 µL samples + 80 µL water) and nicotinamide concentrations were analyzed by liquid chromatography mass spectrometry using a Waters Acquity UPLC coupled to a AB Sciex 4500 triple quadropole mass spectrometer. Percent inhibition was calculated as (sample – low control)/(high control – low control) x 100. IC50 values were calculated from an 11-point dose response curve using a four-parameter logistic model.

Cellular Viability Assay

The ability of compounds to rescue cells from SARM1-induced death were tested in HEK cells stably transfected with a doxycycline inducible construct encoding constitutively active form of SARM1 that is missing ARM domain (SAM-TIR). Cell viability was determined 24 hours after addition of doxycycline by measuring ATP levels using a commercially available kit (CellTiter-Glo, Promega). The results of dose-response experiments were normalized to a neutral control (doxycycline plus DMSO) and a blank control (no doxycycline plus DMSO) and fitted to a four-parameter logistic model to calculate EC50 values. References: CellTiter-Glo assay. CellTiter-Glo® 2.0 Assay Technical Manual TM403 (promega.com).

Potency Data Table

Example	LCMS IC50 (uM)	HEK IC50 (uM)
1a	0.57	1.4
1b	0.14	0.34
2	54	>20
3	2.1	18
4a	0.06	2.3
4b	0.17	1.6
5a	0.0029	0.059
5b	0.005	0.057
6a	0.14	1.2
6b	0.12	1.3
7a	0.039	0.4
7b	0.032	0.44

8a	0.042	0.36
8b	0.03	0.46
9a	0.9	8.7
9b	0.43	3.1
10	0.11	0.51
11a	0.026	0.26
11b	0.015	0.086
12a	0.021	0.45
12b	0.024	0.41
13a	0.019	0.13
13b	0.0068	0.16
14a	0.0073	0.027
14b	0.0061	0.054
15a	1.2	14
15b	1.6	16
16a	8	>20
16b	5.8	>20
17a	0.25	4
17b	0.32	2.1
18a	0.028	0.69
18b	0.024	0.64
19	3	19
20a	2.3	>20
20b	1.2	>20
21a	16	>20
21b	14	>20
22a	3.3	>20
22b	1.6	>20
23	0.78	2.3
24a	42	>20
24b	1.6	8.8
25a	1.3	7.7
25b	1.4	6.6
26a	2.5	15

26b	0.25	1.6
27a	1.5	7
27b	1.5	8.2
28a	0.16	0.61
28b	0.14	0.71
29a	0.031	0.45
29b	0.053	1.1
30a	4.7	>20
30b	0.8	9.4
31	4.4	>20
32	2.3	>20
33a	0.022	0.15
33b	0.037	0.12
34a	0.014	0.084
34b	0.0093	0.074
35a	0.3	0.73
35b	0.31	0.58
36a	0.18	1.3
36b	0.11	0.49
37a	6.6	>20
37b	39	>20
38a	3	>20
38b	2.6	14
39a	0.035	1.4
39b	0.054	1.3
40	40	>20
41a	0.89	1.6
41b	0.9	1.5
42a	0.028	1.5
42b	0.0022	0.045
42c	0.0017	0.039
42d	0.0033	0.11
43a	0.01	0.26
43b	0.019	0.38

44a	0.05	0.84
44b	0.016	0.28
45	0.16	6.3
46	0.77	3.8
47a	0.0067	0.043
47b	0.0048	0.033
48a	0.0053	0.089
48b	0.0033	0.061
49a	0.23	2
49b	0.07	0.34
50a	0.012	0.13
50b	0.023	0.11
51	0.2	1
52	0.032	0.21
53a	0.25	0.23
53b	0.28	0.19
53c	2.7	5.8
53d	28	>20
54	0.44	>20
55	0.022	0.24
56	0.059	0.24
57	2.3	>20
58	0.091	0.2
59a	1.2	6
59b	1.1	5.5
60a	27	>20
60b	12	>20
61	0.052	0.27
62	0.02	0.082
63a	11	>20
63b	74	>20
64a	2.2	2.8
64b	2.8	3.2
65a	0.21	0.26

65b	0.22	0.39
66a	4.7	16
66b	2.7	5.9
67a	1.5	2.3
67b	1.8	4
68a	1.2	1.6
68b	0.87	0.76
69a	1.3	1.8
69b	1.6	1.7
70	0.019	0.083
71a	0.85	2
71b	0.27	0.55
71c	0.18	0.76
71d	0.85	2.3
72a	21	>20
72b	2.6	8.4
73a	0.21	0.28
73b	0.1	0.17
74a	0.12	0.12
74b	0.19	0.13
75a	2.7	8.2
75b	0.73	1.5
76a	0.89	2.4
76b	0.57	1.1
77a	0.22	0.46
77b	0.19	0.37
78a	0.42	0.9
78b	0.53	1.8
79a	1.1	1.8
79b	0.47	1.3
80a	4.7	7.3
80b	3.6	9.5
81a	0.18	0.37
81b	0.54	0.95

82a	1.3	12.7
82b	1	2.37
83a	0.076	0.14
83b	0.15	0.55
84a	0.036	0.1
84b	0.04	0.071
85	2.1	2.7
86a	0.25	0.29
86b	2.1	4
87	0.87	2.3

Automated Hepatocyte Stability Assay

Parent compound depletion is measured by comparing the amount of drug at time points 60, 120, 180 and 240 min to a reference amount at the initial starting time 0 min. Metabolic stability studies in hepatocytes are performed using cryopreserved primary human, rat, and mouse hepatocytes. Incubations are performed at 1 μM drug concentration and 0.5 million cells mL^{-1} at 37°C with 5% CO_2. Hepatocytes are prepared manually by thawing in INVITROGRO HT media and diluted to 1 million cells mL^{-1} with DMEM buffer. Compound dilution, incubation, and various liquid handling procedures are carried out using a Tecan Fluent liquid handling system.

The automated assay is composed of two separately coded protocols. The first protocol is the compound dilution protocol where test compounds are diluted from stock vials and aliquoted to the incubation plates. The second protocol is the incubation protocol, which adds the hepatocytes, incubates the plates, and quenches the plates at their respective timepoints.

In the dilution protocol, compounds at 1 mM in DMSO are diluted 500-fold to 2 μM in a two-step serial dilution using DMEM. Compounds are first diluted to 10 μM by adding 5 μL of test compound to 495 μL DMEM and mixing via aspiration. Subsequently, 200 μL of the 10 μM compound is added to 800 μL DMEM and mixed to reach the target concentration of 2 μM. 50 μL of 2 μM drug is added in triplicate columns to 5 separate round bottom 96-well plates using the Fluent FCA multi-dispense. One plate is allocated for each timepoint (i.e. 0 min, 60 min, 120 min, 180 min, 240 min) being taken during the time course.

In the incubation protocol, 50 µL of 1 million cells mL^{-1} is added to each well of each plate using wide-bore tips (Tecan Pure, Männedorf, Switzerland). The hepatocytes are placed on an INHECO Thermoshake RM on-deck shaking incubator set at 37°C and 650 rpm to keep the cells in suspension until they are added to each plate. After addition of the cells, the plates are immediately lidded and placed in the attached Thermo Cytomat 2 incubator set at 37°C with 5% CO_2 to be quenched with 200 µL of ACN containing internal standard (IS) at their respective times. The T0 min plate is immediately quenched after hepatocytes are added. The ACN quench solution is kept on an identical on-deck incubator set at 4°C to mitigate evaporation over the course of the experiment. Upon quenching, samples are centrifuged at 3700 rpm for 10 minutes utilizing a below-deck Agilent vSpin centrifuge, and the supernatant is added to a separate plate for LC-MS analysis. Standard 200 µL Tecan MCA tips are assigned per set to aliquot the ACN quench and supernatant and are rinsed in methanol (MeOH) in between each use to prevent cross-timepoint contamination.

Permeability Assay Protocols

Madin-Darby Kidney cells (MDCKI) were obtained from the ATCC, (Manassas, VA). CRISPR Cas9 was used to knock-out the endogenous canine Mdr1 gene to generate the gMDCK cell line. The human MDR1 and ABCG2 (BCRP) genes were stably overexpressed in the gMDCKI cells. Cells were maintained in Dulbecco's Modified Eagle Medium supplemented with 10% fetal bovine serum, pen-strep, puromycin and plasmocin before seeding on Millipore Millicell-24 well plates at 2.5 x 10^5 cells/mL and allowed to grow for 5 days. Prior to the permeability experiment cell monolayers were equilibrated in transport buffer (Hank's Balanced Salt Solution with 10 mM HEPES, pH 7.4) for 60 minutes at 37°C with 5% CO2 and 95% relative humidity. Test compound dose solutions were prepared at 1 µM in transport buffer containing the monolayer integrity marker lucifer yellow (100 µM). The dose solutions were added to the donor chambers and transport buffer was added to all receiver chambers. The permeability was examined in the apical to basolateral (A:B) and basolateral to apical (B:A) directions. The receiver chambers were sampled at 60, 120, and 180 min and were replenished with fresh transport buffer. Lucifer yellow was measured using a fluorescence plate reader (ex: 425 nm; em: 530 nm) and compound concentrations in the donor and receiving compartments were determined by LC-MS/MS analysis. The apparent permeability (P_{app}) in the A:B and B:A directions, was calculated as follows:

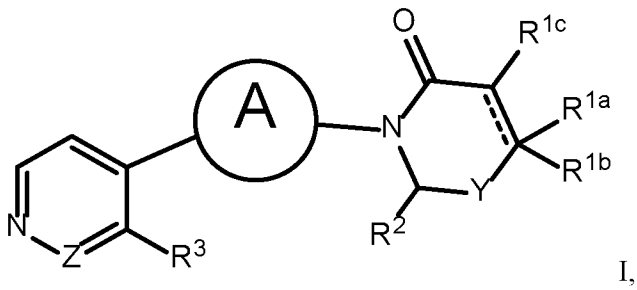
$$P_{app} = (dQ/dt)\bullet(1/AC_0),$$

Where: dQ/dt = rate of compound appearance in the receiver compartment; A = surface area of the insert; and C_0 = initial substrate concentration at time 0 min.

This written description uses examples to disclose the invention, including the best mode, and also to enable any person skilled in the art to practice the invention, including making and using any devices or systems and performing any incorporated methods. The patentable scope of the invention is defined by the claims, and may include other examples that occur to those skilled in the art. Such other examples are intended to be within the scope of the claims if they have structural elements that do not differ from the literal language of the claims, or if they include equivalent structural elements with insubstantial differences from the literal languages of the claims.

WHAT IS CLAIMED IS:

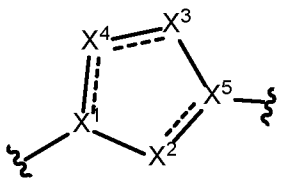
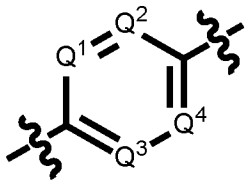
1. A compound of Formula I:



I,

or a pharmaceutically acceptable salt thereof;

wherein:

Ring A is  ; or 

X^1 is CR^7 or N;

X^2 is CR^4, CHR^4, or N;

X^3 is absent, CH, CH_2, NH, or S;

X^4 is N, CH_2, CH, NH, O, or S;

X^5 is CR^8;

Y is absent, CR^5R^6, or CH_2CH_2, wherein R^5 and R^6 are independently H, OH, CN, halo, C_{1-6} alkyl, or C_{1-6} cycloalkyl, or R^5 and R^6, taken together with the carbon to which they are bonded, form a C_{3-6} cycloalkyl;

Z is CH or N;

one of Q^1 and Q^2 is N and the other is CR^4;

one of Q^3 and Q^4 is N and the other is CR^4; or Q^3 and Q^4 are CR^4;

R^{1a} is H or C_{1-6} alkyl;

R^{1b} is selected from C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, bicyclo[1.1.1]pentan-1-yl, and C_{1-6} alkyl substituted with C_{6-10} aryl or C_{1-6} haloalkoxy; wherein each aryl, heteroaryl, cycloalkyl, and bicyclo[1.1.1]pentan-1-yl is optionally substituted with one to four substituents, wherein each substituent is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{3-6} cycloalkyl; or

R^{1a} and R^{1b} taken together with the carbon to which they are bonded, form a C_{3-6} cycloalkyl;

R^{1c} is H, F, or C_{1-6} alkyl;

R^2 is H, OH, CN, oxo or C_{1-6} alkyl;

R^3 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, and 5- to 10-membered heteroaryl;

R^4 is H, halo, cyano, C_{1-6} haloalkyl, or C_{1-6} hydroxyalkyl;

R^7 and R^8 are either absent, or form a -CH_2- bridge between the carbon atoms to which they are attached;

〰 represents the point of attachment to the rest of the compound; and

⁼⁼⁼ represents a single or double bond.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

X^1 is CR^7;

X^2 is CHR^4;

X^3 is absent or CH_2;

X^4 is CH_2 or O;

X^5 is CR^8; and

R^7 and R^8 form a -CH_2- bridge between the carbon atoms to which they are attached.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein

X^1 is CR^7;

X^2 is CHR^4;

X^3 is absent;

X^4 is CH_2;

X^5 is CR^8; and

R^7 and R^8 form a -CH_2- bridge between the carbon atoms to which they are attached.

4. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein

X^1 is CR^7;

X^2 is CHR^4;

X^3 is CH_2;

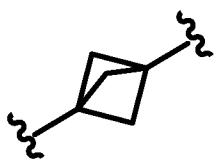
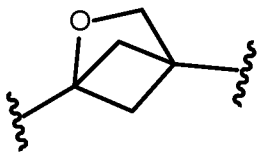
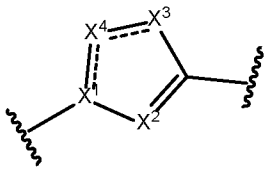
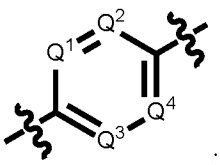
X^4 is O;

X^5 is CR^8; and

R^7 and R^8 form a -CH_2- bridge between the carbon atoms to which they are attached.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^4 is H.

6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Ring A is selected from

 ,  ,  , and  :

wherein:

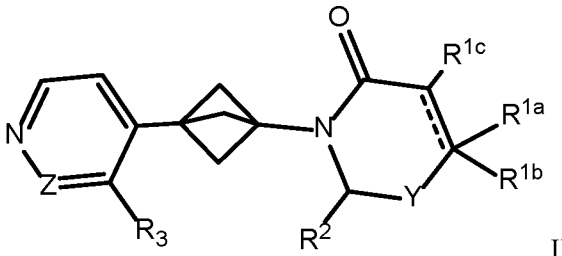
X^1 is C or N;

X^2 is CR^4 or N;

X^3 is CH, NH, or S; and

X^4 is N, CH, NH, or S.

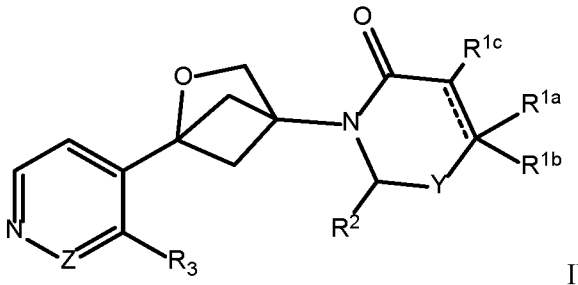
7. The compound of claim 6, having Formula III:



III,

or a pharmaceutically acceptable salt thereof.

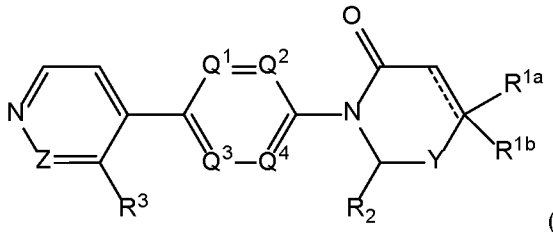
8. The compound of claim 6, having Formula IV:



IV,

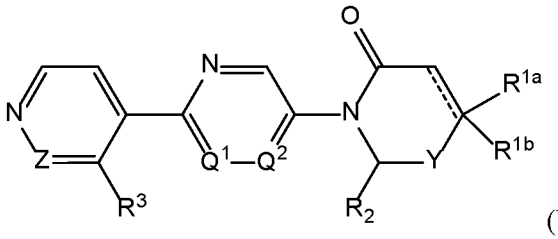
or a pharmaceutically acceptable salt thereof.

9. The compound of claim 6, having Formula V



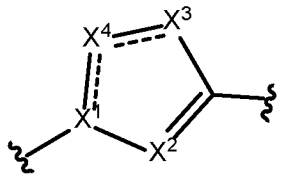
(V)

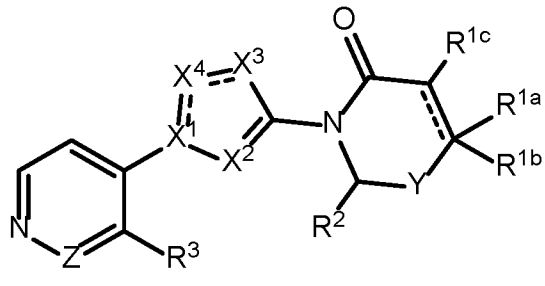
10. The compound of claim 6, having Formula (Va):



(Va)

or a pharmaceutically acceptable salt thereof.

11. The compound of claim 6, wherein Ring A is  , and the compound has Formula II:



II,

or a pharmaceutically acceptable salt thereof.

12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein X^1 is C; X^2 is N; X^3 is NH; and X^4 is N.

13. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein X^1 is C; X^2 is CR^4; X^3 is NH; and X^4 is N.

14. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein X^1 is N; X^2 is CR^4; X^3 is CH; and X^4 is N.

15. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein X^1 is C; X^2 is CR^4; X^3 is S; and X^4 is N.

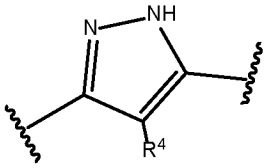
16. The compound of any one of claims 13-15, or a pharmaceutically acceptable salt thereof, wherein R^4 is H.

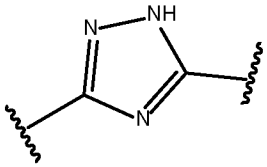
17. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein X^1 is N; X^2 is N; X^3 is CH; and X^4 is N.

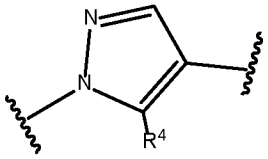
18. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein X^1 is N; X^2 is N; X^3 is CH; and X^4 is CH.

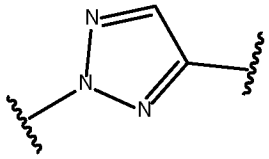
19. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein X^1 is C; X^2 is N; X^3 is NH; and X^4 is CH.

20. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein Ring A is selected from



,


,


,


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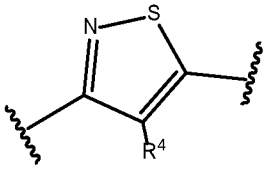
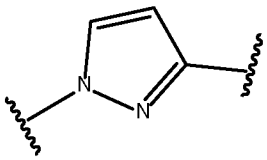
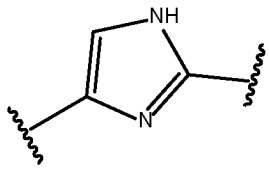


,


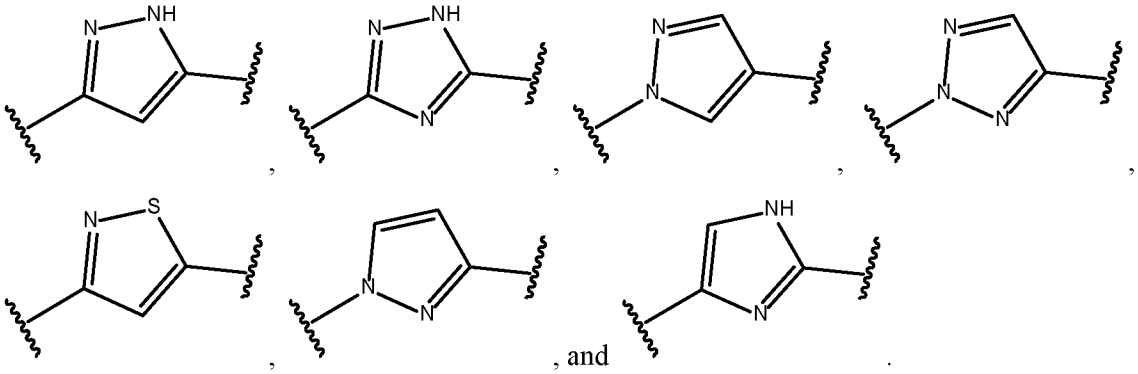
, and


.

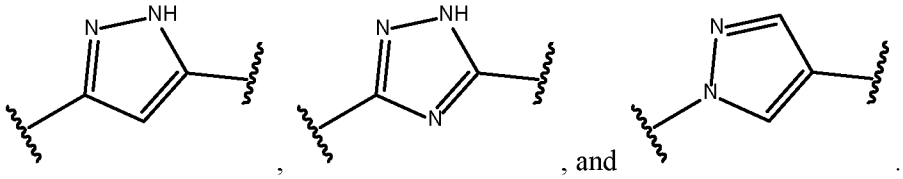
21. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein R^4 is H, halo, or C_{1-6} hydroxyalkyl.

22. The compound of claim 21, or a pharmaceutically acceptable salt thereof, wherein R^4 is H.

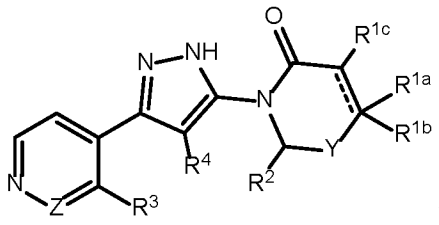
23. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein Ring A is selected from



24. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein Ring A is selected from



25. The compound of claim 11, having Formula IIa:

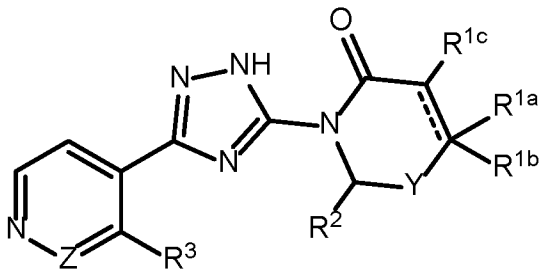


IIa,

or a pharmaceutically acceptable salt thereof.

26. The compound of claim 25, or a pharmaceutically acceptable salt thereof, wherein R^4 is H.

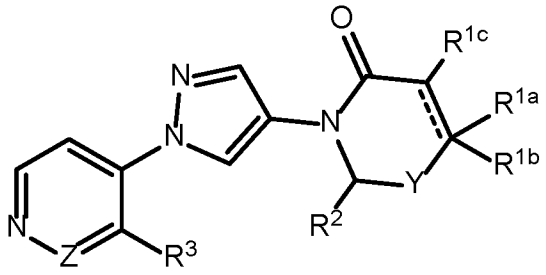
27. The compound of claim 11, having Formula IIb:



IIb,

or a pharmaceutically acceptable salt thereof.

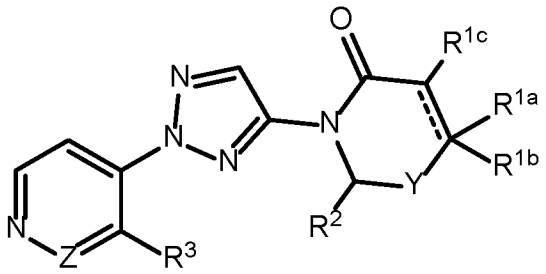
28. The compound of claim 11, having Formula IIc:



IIc,

or a pharmaceutically acceptable salt thereof.

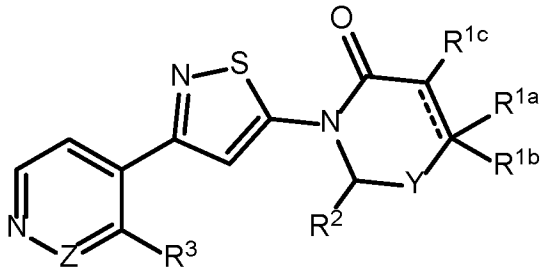
29. The compound of claim 11, having Formula IId:



IId,

or a pharmaceutically acceptable salt thereof.

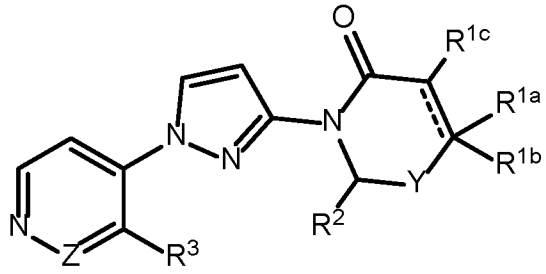
30. The compound of claim 11, having Formula IIe:



IIe,

or a pharmaceutically acceptable salt thereof.

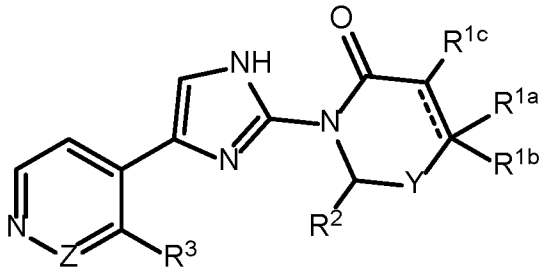
31. The compound of claim 11, having Formula IIf:



IIf,

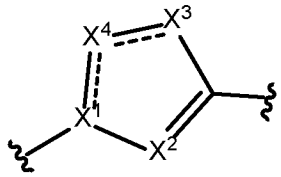
or a pharmaceutically acceptable salt thereof.

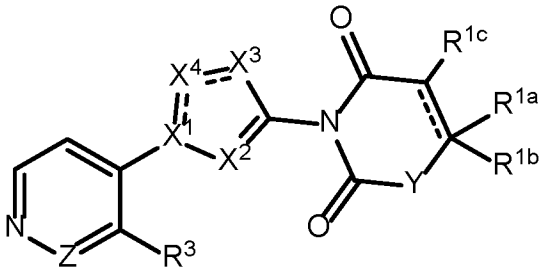
32. The compound of claim 11, having Formula IIg:



(IIg),

or a pharmaceutically acceptable salt thereof.

33. The compound of claim 6, wherein Ring A is  , and the compound has Formula II:



IIh,

or a pharmaceutically acceptable salt thereof.

34. The compound of any one of claims 1-33, or a pharmaceutically acceptable salt thereof, wherein Z is N.

35. The compound of any one of claims 1-33, or a pharmaceutically acceptable salt thereof, wherein Z is CH.

36. The compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof, wherein R^3 is H.

37. The compound of any one of claims 1-36, or a pharmaceutically acceptable salt thereof, wherein Y is absent.

38. The compound of any one of claims 1-36, or a pharmaceutically acceptable salt thereof, wherein Y is CH_2CH_2.

39. The compound of any one of claims 1-36, or a pharmaceutically acceptable salt thereof, wherein Y is CR^5R^6.

40. The compound of claim 39, or a pharmaceutically acceptable salt thereof, wherein R^5 and R^6 are independently H, OH, CN, or halo.

41. The compound of claim 40, or a pharmaceutically acceptable salt thereof, wherein R^5 and R^6 are H.

42. The compound of claim 40, or a pharmaceutically acceptable salt thereof, wherein R^5 is H and R^6 is OH or CN.

43. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof, wherein R^2 is H, OH, CN, oxo or methyl.

44. The compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof, wherein R^2 is H.

45. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is H or methyl.

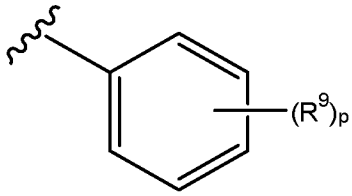
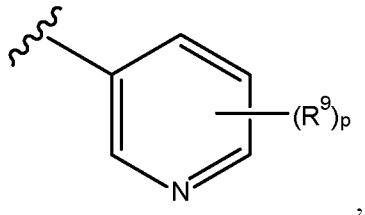
46. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is H.

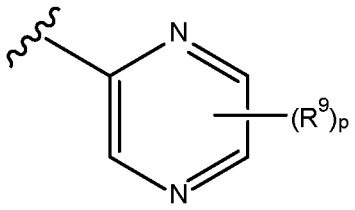
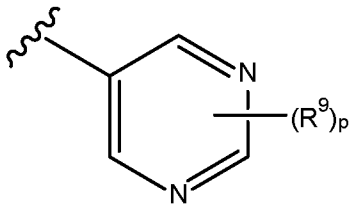
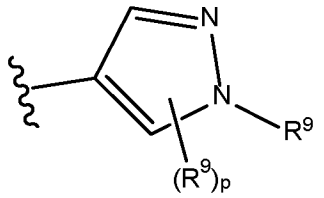
47. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof, wherein R^{1a} and R^{1b} taken together with the carbon to which they are bonded, form a C_{3-6} cycloalkyl.

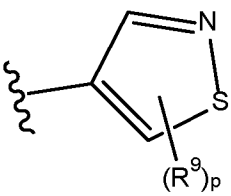
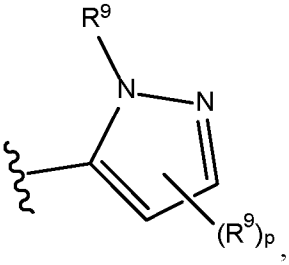
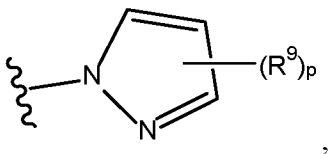
48. The compound of any one of claims 1-36, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is selected from C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, and C_{1-6} alkyl substituted with C_{6-10} aryl or C_{1-6} haloalkoxy; wherein each aryl or heteroaryl is optionally substituted with one to four substituents, wherein each substituent is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{3-6} cycloalkyl.

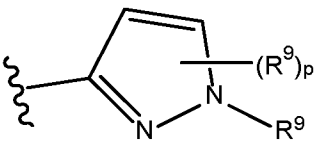
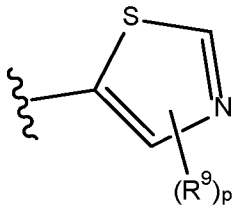
49. The compound of claim 48, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is selected from C_{6-10} aryl and 5- to 10-membered heteroaryl, wherein each aryl or heteroaryl is optionally substituted with one to four substituents, wherein each substituent is independently selected from C_{1-6} alkyl, halo, C_{1-6} alkoxy, and C_{1-6} haloalkyl.

50. The compound of any one of claims 1-36, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is selected from

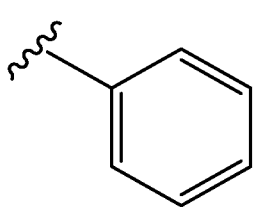
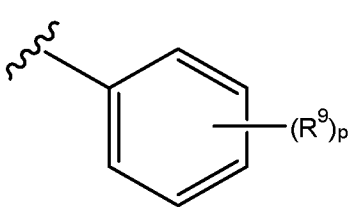
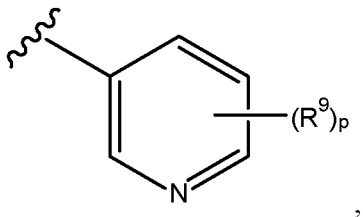
 ,  ,

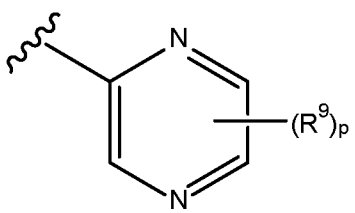
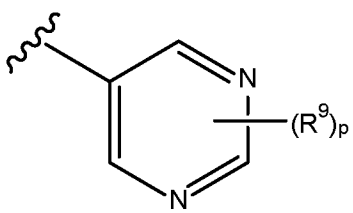
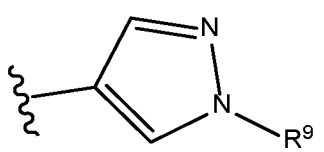
 ,  ,  ,

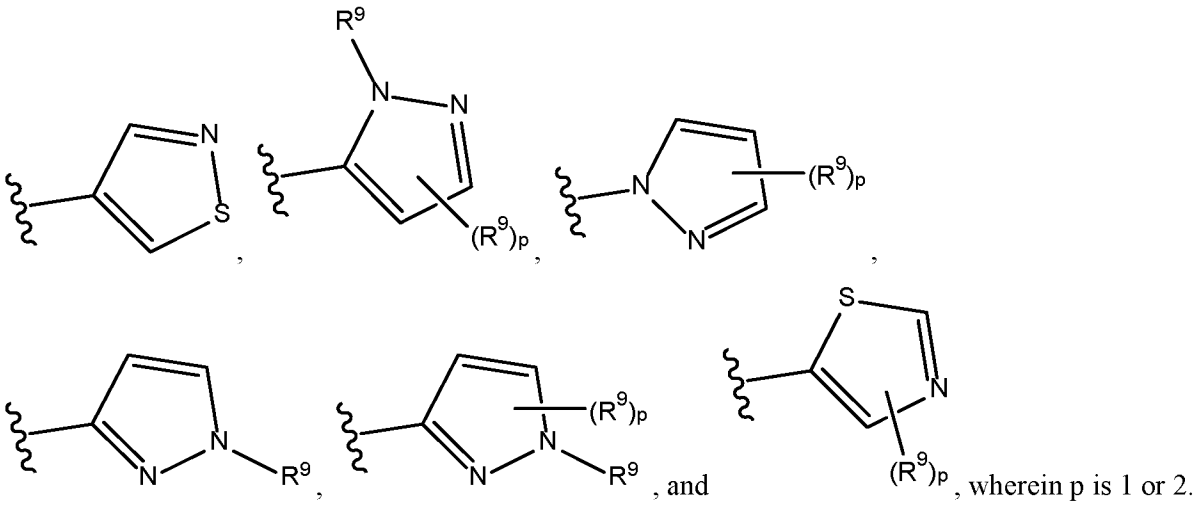
 ,  ,  ,

 , and  , wherein each R^9 is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{3-6} cycloalkyl; and p is 0, 1, 2, 3, or 4.

51. The compound of claim 50, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is selected from

 ,  ,  ,

 ,  ,  ,



, wherein p is 1 or 2.

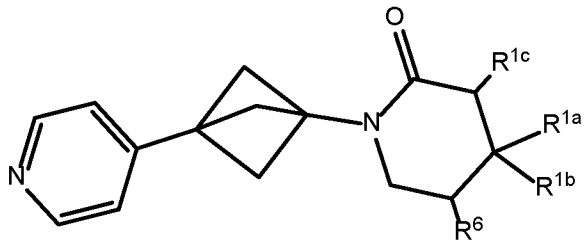
52. The compound of claim 50 or 51, or a pharmaceutically acceptable salt thereof, wherein each R^9 is independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, and C_{1-6} alkoxy.

53. The compound of claim 50 or 51, or a pharmaceutically acceptable salt thereof, wherein each R^9 is independently selected from methyl, halo, C_1 haloalkyl, and methoxy.

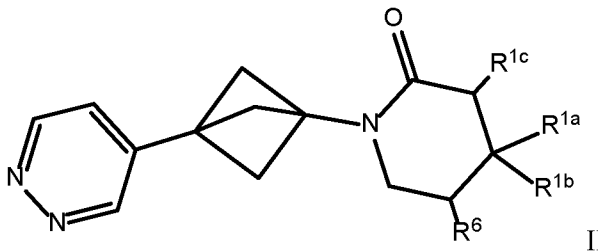
54. The compound of any one of claims 1-53, or a pharmaceutically acceptable salt thereof, wherein R^{1c} is H.

55. The compound of any one of claims 1-53, or a pharmaceutically acceptable salt thereof, wherein R^{1c} is F.

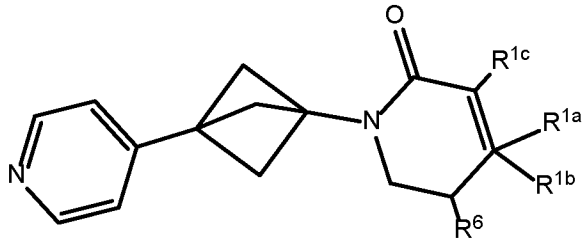
56. The compound of claim 1, having Formula IIIa, IIIb, or IIIc:



IIIa



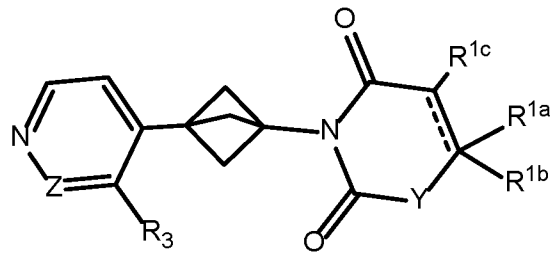
IIIb



IIIc

or a pharmaceutically acceptable salt thereof, wherein R^6 is H, OH, or CN.

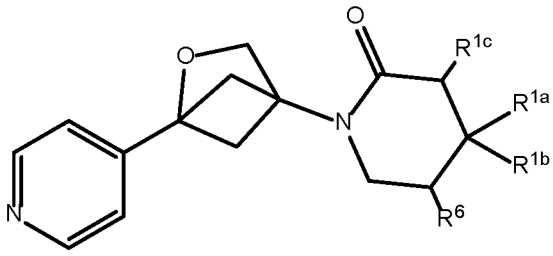
57. The compound of claim 1, having Formula (IIId):



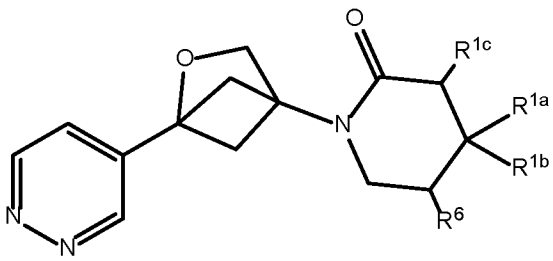
(IIId),

or a pharmaceutically acceptable salt thereof.

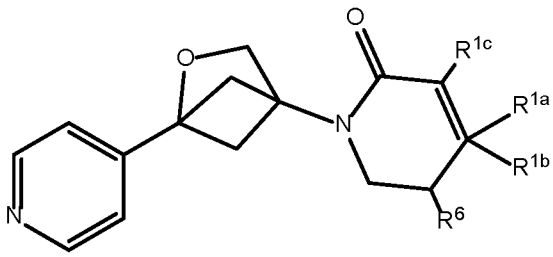
58. The compound of claim 1, having Formula IVa, IVb, or IVc:



IVa



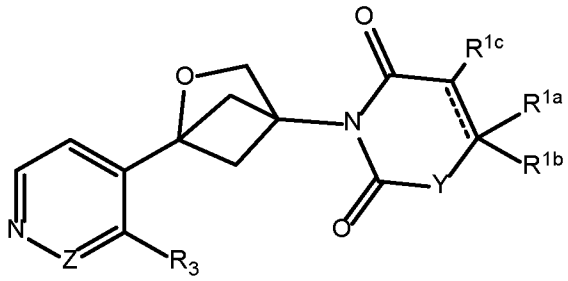
IVb



IVc

or a pharmaceutically acceptable salt thereof, wherein R^6 is H, OH, or CN.

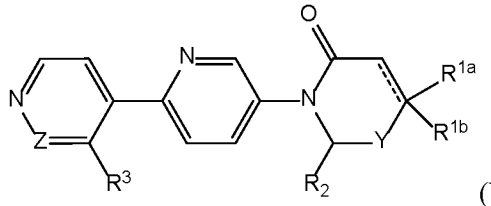
59. The compound of claim 1, having Formula (IVd):



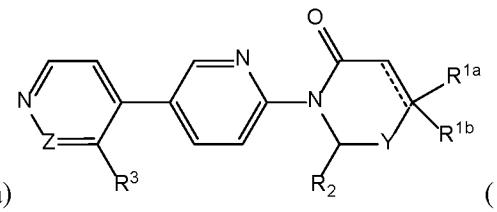
(IVd),

or a pharmaceutically acceptable salt thereof.

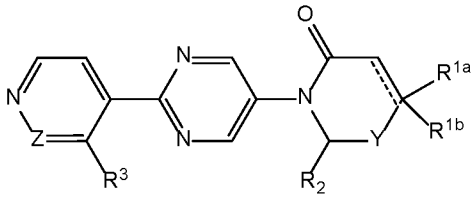
60. The compound of claim 1, having Formula (Va), (Vb), (Vc), (Vd), (Ve) or (Vf)



(Va)

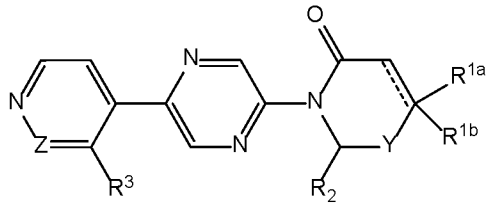


(

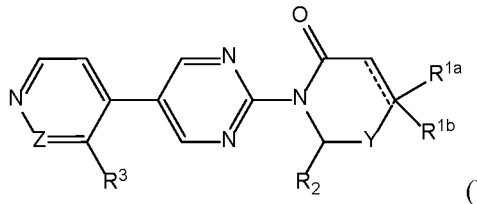


Vb)

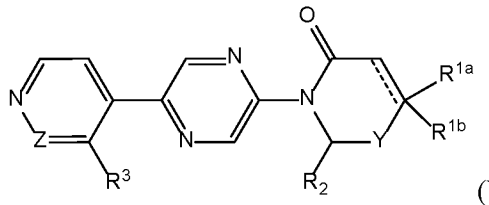
(Vc)



(Vd)



(Ve)



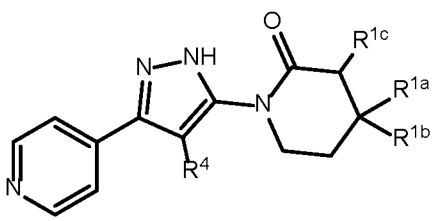
(Vf).

or a pharmaceutically acceptable salt thereof.

61. The compound of claim 59 or 60, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is H and R^{1b} is selected from C_{6-10} aryl and 5- to 10-membered heteroaryl, wherein each aryl or heteroaryl is optionally substituted with one to four substituents, wherein each substituent is independently selected from C_{1-6} alkyl, halo, and C_{1-6} haloalkyl.

62. The compound of claim 61, or a pharmaceutically acceptable salt thereof, wherein each aryl or heteroaryl is optionally substituted with one to four substituents, wherein each substituent is independently halo.

63. The compound of claim 1, having a formula selected from:



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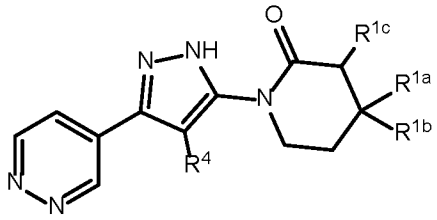
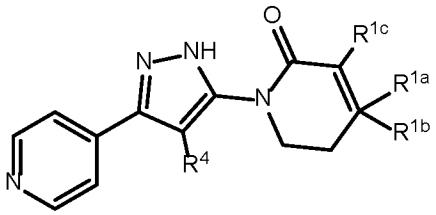
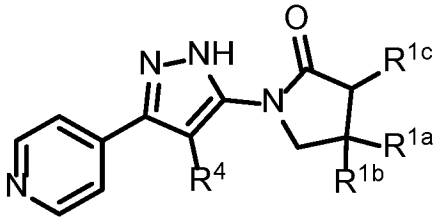


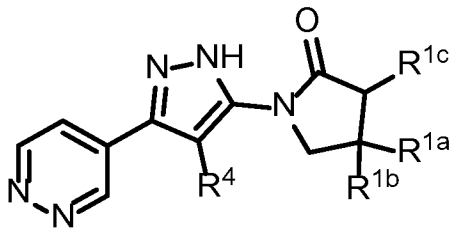
IIa-2,



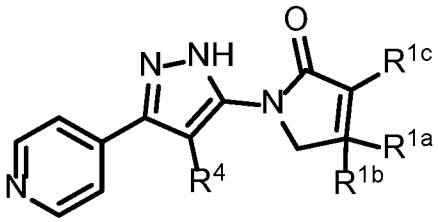
IIa-3,



IIa-4,



IIa-5, and



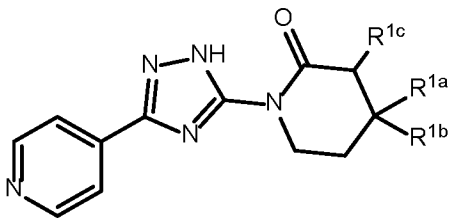
IIa-6,

or a pharmaceutically acceptable salt thereof.

64. The compound of claim 63, or a pharmaceutically acceptable salt thereof, wherein R^4 is H.

65. The compound of claims 63 or 64, or a pharmaceutically acceptable salt thereof, wherein R^{1c} is H or F.

66. The compound of claim 1, having a formula selected from: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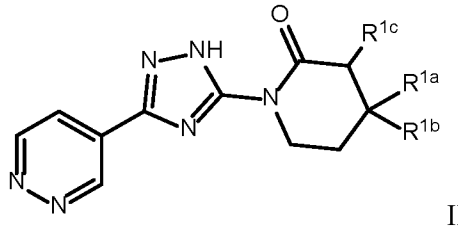
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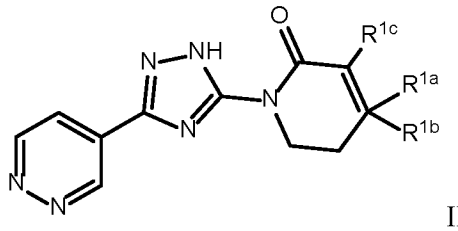
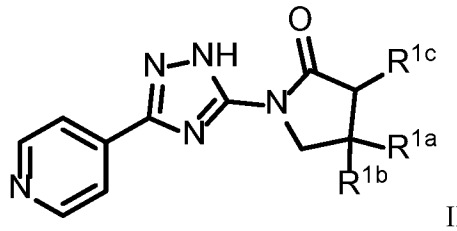

IIb-3,

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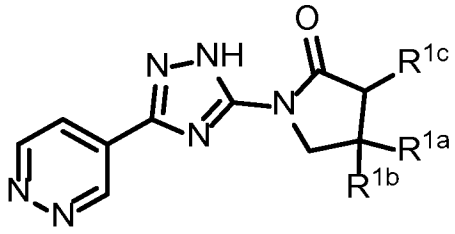
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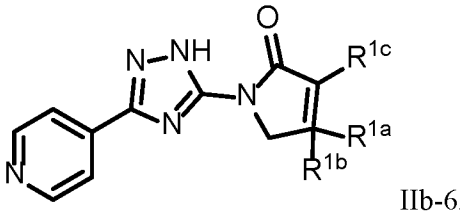
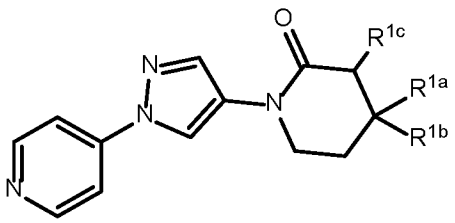

IIb-6,

or a pharmaceutically acceptable salt thereof.

67. The compound of claim 1, having a formula selected from: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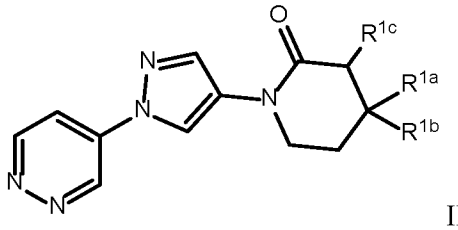
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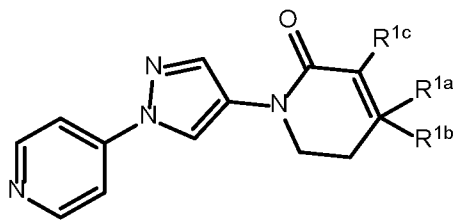
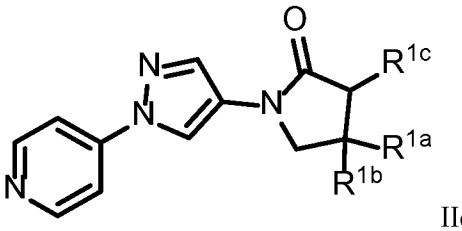

IIc-3,

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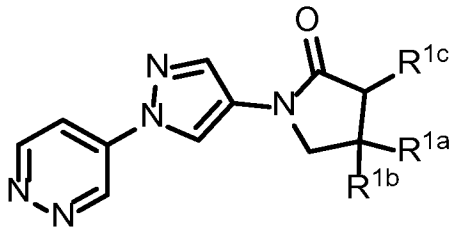
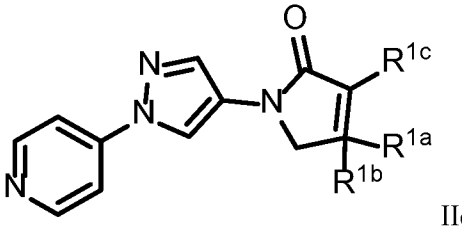
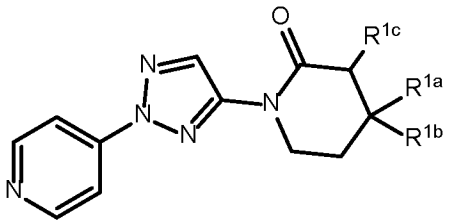
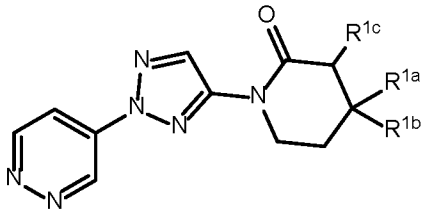

IIc-5, and

IIc-6,

or a pharmaceutically acceptable salt thereof.

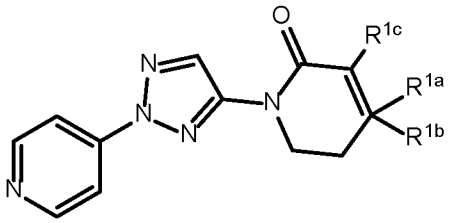
68. The compound of claim 1, having a formula selected from:



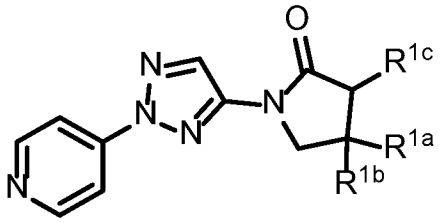
IId-1,



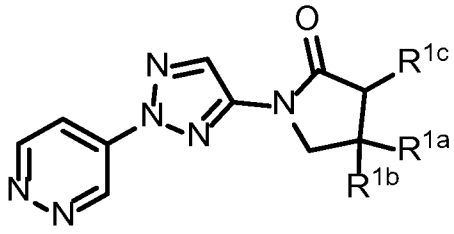
IId-2,



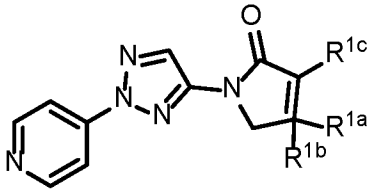
IId-3,



IId-4,



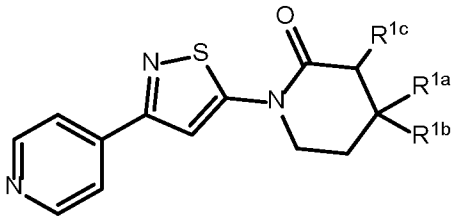
IId-5, and



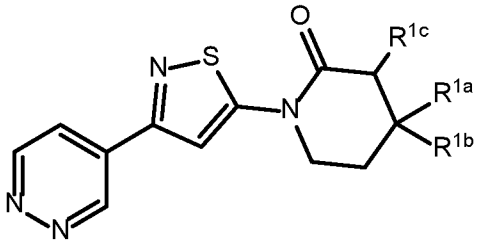
IId-6,

or a pharmaceutically acceptable salt thereof.

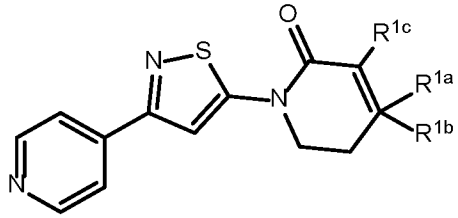
69. The compound of claim 1, having a formula selected from:



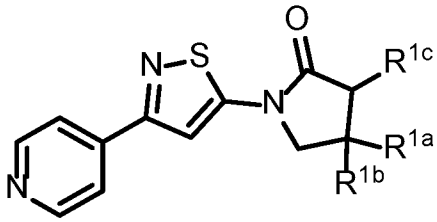
IIe-1,



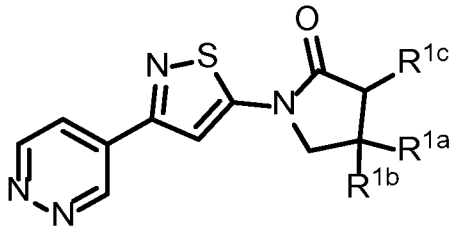
IIe-2,



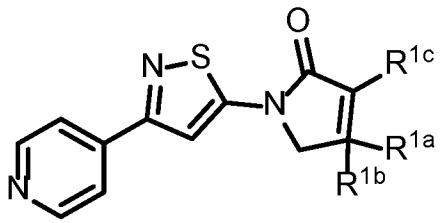
IIe-3,



IIe-4,



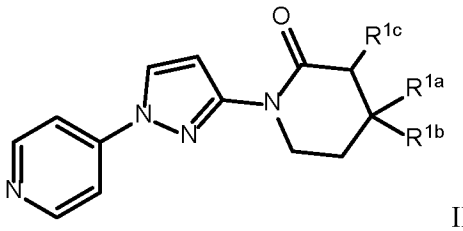
IIe-5, and



IIe-6,

or a pharmaceutically acceptable salt thereof.

70. The compound of claim 1, having a formula selected from:



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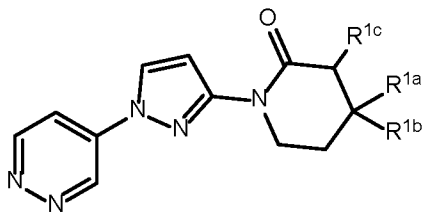

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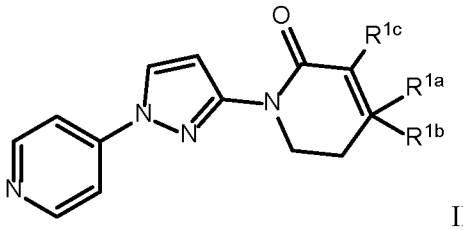

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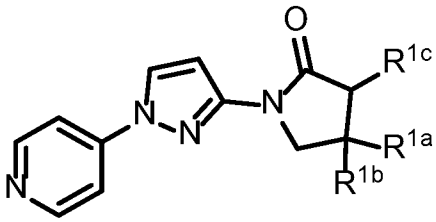

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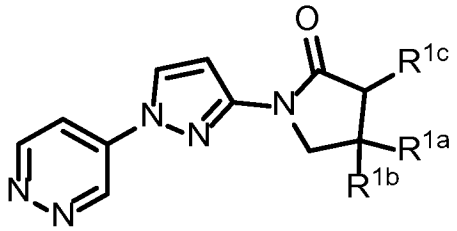
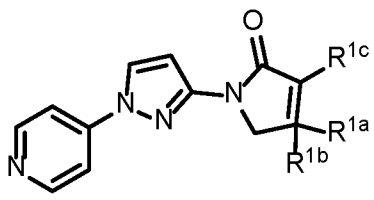


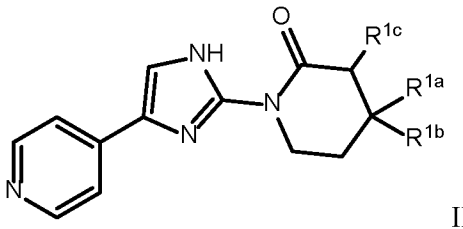
IIf-5, and



IIf-6,

or a pharmaceutically acceptable salt thereof.

71. The compound of claim 1, having a formula selected from:



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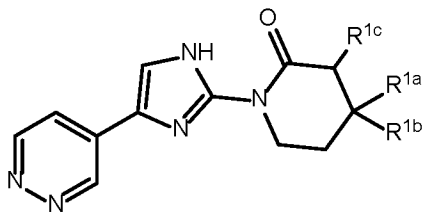
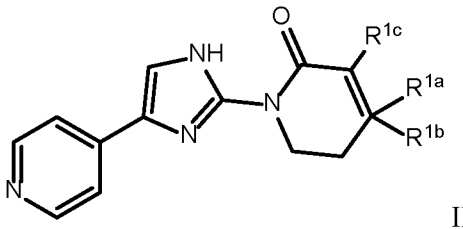
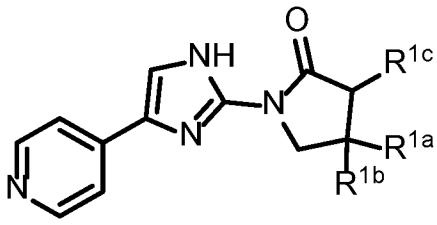


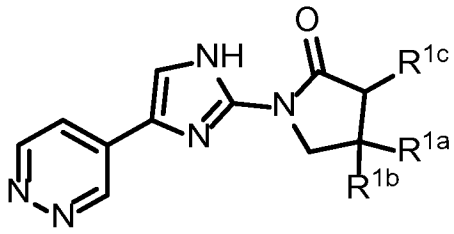
IIg-2,



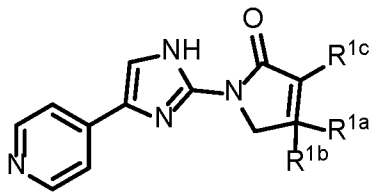
IIg-3,



IIg-4,



IIg-5, and



IIg-6,

or a pharmaceutically acceptable salt thereof.

72. A compound or a pharmaceutically acceptable salt thereof as provided in Table 1.

73. A pharmaceutical composition comprising the compound of any one of claims 1-72, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

74. The pharmaceutical composition of claim 73, wherein the pharmaceutical composition is formulated for oral administration.

75. The pharmaceutical composition of claim 63, wherein the pharmaceutical composition is formulated for injection.

76. A method of treating or preventing axonal degeneration comprising administering to an individual in need thereof a therapeutically effective amount of the compound of any one of claims 1-70, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of any one of claims 73-75.

77. The method of claim 76, wherein the individual is a human.

78. The method of claim 75 or 76, wherein the individual (i) has a condition characterized by axonal degeneration or (ii) is at risk of developing a condition characterized by axonal degeneration.

79. A method of treating a neurodegenerative disease, the method comprising administering to an individual in need thereof a therapeutically effective amount of the compound of any one of claims 1-70, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of any one of claims 73-75.

80. The method of claim 78, wherein the neurodegenerative disease is selected from ALS, CIPN, peripheral neuropathy, and MS.

81. The method of any one of claims 72-80, wherein the administering is via the oral route.

82. The method of any one of claims 72-80, wherein the administering is via injection.

83. A method of inhibiting SARM1 comprising contacting a biological sample with a therapeutically effective amount of the compound of any one of claims 1-60, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of any one of claims 73-75.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/049598

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/08 C07D401/14 C07D409/14 C07D417/08 C07D417/14
A61P25/28 A61K31/444 A61K31/497 A61K31/541
ADD.

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2022/056013 A1 (BOSANAC TODD [US] ET AL) 24 February 2022 (2022-02-24)	34
A	Whole document, particularly claims 1 and 17 and examples	1-33, 35-83

X	WO 2022/031736 A1 (NURA BIO INC [US]) 10 February 2022 (2022-02-10)	1,5,6, 11-14, 16, 19-28, 32,33, 35-46, 48-55, 63-67, 70-83
Y	Whole document, particularly claims 1 and 60 and examples 138, 154-157	34

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

[x] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 December 2024	19/12/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sahagún Krause, H

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/049598

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 2024/123967 A1 (SENYA PHARMACEUTICALS INC [US]) 13 June 2024 (2024-06-13) Whole document, particularly claims 1 and 81 and examples -----	1-83
X	WO 2018/114662 A1 (BAYER CROPSCIENCE AG [DE]; BAYER AG [DE]) 28 June 2018 (2018-06-28) claim 1; formulas (I.25) and (I.27) in page 110 in combination with the definitions of R4: 134 and 137 in page 95 -----	1,5,6, 11, 33-37, 43,45, 46,48

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2024/049598

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		CL 2023000525 A1	15-09-2023
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		US 2020095241 A1	26-03-2020
		WO 2018114662 A1	28-06-2018