

Complement Factor B Inhibitors and Uses Thereof**Field**

The disclosure relates to the inhibition of the complement alternative pathway, and particularly to inhibition of factor B. It also relates to treatment of patients suffering from conditions and diseases associated with complement alternative pathway activation.

Background

The complement system is a crucial component of the innate immunity system and comprises a group of proteins that are normally present in an inactive state. These proteins are organized in three activation pathways: the classical, the lectin, and the alternative pathways (V. M. Holers, In Clinical Immunology: Principles and Practice, ed. R.R. Rich, Mosby Press; 1996, 363-391). Molecules from microorganisms, antibodies or cellular components can activate these pathways resulting in the formation of protease complexes known as the C3-convertase and the C5-convertase. The classical pathway is a calcium/magnesium-dependent cascade, which is normally activated by the formation of antigen-antibody complexes. It can also be activated in an antibody-independent manner by the binding of C-reactive protein complexed to ligand and by many pathogens including gram-negative bacteria. The alternative pathway is a magnesium-dependent cascade that is activated by deposition and activation of C3 on certain susceptible surfaces (e.g., cell wall polysaccharides of yeast and bacteria, and certain biopolymer materials).

Factor B is a suitable target for the inhibition of this amplification of the complement pathways because its plasma concentration in humans is typically about 200 µg/mL (or about 2 µM), and it has been shown to be a critical enzyme for activation of the alternative complement pathway (P.H. Lesavre and H.J. Müller-Eberhard. J. Exp. Med., 1978; 148: 1498-1510; J.E. Volanakis et al., New Eng. J. Med., 1985; 312:395-401).

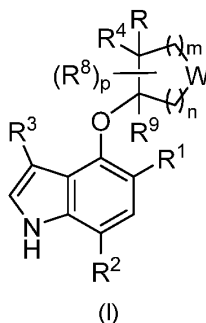
Summary

The present disclosure provides compounds that modulate, and/or inhibit, activation of the alternative complement pathway. In certain embodiments, the present disclosure provides compounds that modulate, and/or inhibit, factor B activity and/or factor B mediated complement pathway activation. Such factor B modulators are preferably high affinity factor B inhibitors that inhibit the catalytic activity of complement factor B, such as primate factor B and particularly human factor B.

The compounds of the present disclosure inhibit or suppress the amplification of the complement system caused by C3 activation irrespective of the initial mechanism of activation (including for example activation of the classical, lectin or alternative pathways).

The disclosure also relates to compounds effective as factor B modulators, pharmaceutically acceptable salts thereof, compositions thereof, and their use in therapies for the conditions and purposes detailed herein.

The disclosure provides, in a first aspect, a compound of Formula (I)



or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein the variables are defined herein.

In a second aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, and a pharmaceutically acceptable carrier or excipient.

In a third aspect, there is provided a method of treating or preventing a disease or disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

In a further aspect, there is provided a method of modulating the complement alternative pathway activity in a subject, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

In a further aspect, there is provided a method of treating a disease or disorder mediated by complement activation, in particular mediated by activation of the complement alternative pathway, in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

In a further aspect, there is provided a method of treating a disease or disorder that is affected by the modulation of complement alternative pathway comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

In a further aspect, there is provided a method of treating a disease or disorder associated with dysregulation of the complement alternative pathway comprising administering to the subject

a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

In a further aspect, there is provided a method of inhibiting the expression or activity of complement factor B, the method comprising administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

In a further aspect, there is provided a method of treating age-related macular degeneration comprising administering to a subject in need thereof an effective amount of a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

In a further aspect, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, for use as a medicament.

In a further aspect, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, for use in inhibiting the expression or activity of complement factor B, in a subject in need thereof.

In a further aspect, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, for use in treating a disease or disorder associated with dysregulation of the complement alternative pathway.

In a further aspect, there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, in the manufacture of a medicament for the treatment of a disease or disorder mediated by complement activation or activation of the complement alternative pathway.

In a further aspect, there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, for the treatment of a disease or disorder mediated by complement activation or activation of the complement alternative pathway.

In a further aspect, there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, for the treatment of a disease or disorder that is affected by the modulation of complement alternative pathway.

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Detailed Description

Macular degeneration is a clinical term that is used to describe a family of diseases that are characterized by a progressive loss of central vision associated with abnormalities of Bruch's membrane, the choroid, the neural retina and/or the retinal pigment epithelium. In the center of the retina is the macula lutea, which is about $\frac{1}{3}$ to $\frac{1}{2}$ cm in diameter. The macula provides detailed vision, particularly in the center (the fovea), because the cones are higher in density and because

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of the high ratio of ganglion cells to photoreceptor cells. Blood vessels, ganglion cells, inner nuclear layer and cells, and the plexiform layers are all displaced to the side (rather than resting above the photoreceptor cells), thereby allowing light a more direct path to the cones. Under the retina is the choroid, a part of the uveal tract, and the retinal pigmented epithelium (RPE), which is between the neural retina and the choroid. The choroidal blood vessels provide nutrition to the retina and its visual cells.

Age-related macular degeneration (AMD), the most prevalent form of macular degeneration, is associated with progressive loss of visual acuity in the central portion of the visual field, changes in color vision, and abnormal dark adaptation and sensitivity. Two principal clinical manifestations of AMD have been described as the dry, or atrophic, form and the neovascular, or exudative, form. The dry form is associated with atrophic cell death of the central retina or macula, which is required for fine vision used for activities such as reading, driving or recognizing faces. About 10-20% of these AMD patients progress to the second form of AMD, known as neovascular AMD (also referred to as wet AMD).

Neovascular AMD is characterized by the abnormal growth of blood vessels under the macula and vascular leakage, resulting in displacement of the retina, hemorrhage and scarring. This results in a deterioration of sight over a period of weeks to years. Neovascular AMD cases originate from Intermediate or advanced dry AMD. The neovascular form accounts for 85% of legal blindness due to AMD. In neovascular AMD, as the abnormal blood vessels leak fluid and blood, scar tissue is formed that destroys the central retina.

The new blood vessels in neovascular AMD are usually derived from the choroid and are referred to as choroidal neovascularization (CNV). The pathogenesis of new choroidal vessels is poorly understood, but such factors as inflammation, ischemia, and local production of angiogenic factors are thought to be important. A published study suggests that CNV is caused by complement activation in a mouse laser model (Bora P.S., J. Immunol. 2005;174: 491-497).

As noted above, the present disclosure provides compounds that modulate factor B activation and/or factor B-mediated signal transduction of the complement system. Such compounds may be used *in vitro* or *in vivo* to modulate factor B activity in a variety of contexts. The compounds disclosed herein are effective as factor B modulators and/or inhibitors. The compounds provided herein are useful for the treatment of disorders associated with factor B.

Definitions

Unless specified otherwise, the terms "compounds of the present disclosure," "compounds of the disclosure," "compound of the disclosure," "or compounds provided herein" refer to compounds of the formulae disclosed herein, exemplified compounds, salts thereof, particularly pharmaceutically acceptable salts thereof, hydrates, solvates, as well as all stereoisomers (including diastereoisomers and enantiomers), rotamers, tautomers, and isotopically labeled compounds (including deuterium substitutions), as well as inherently formed moieties.

In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, C₁-C₁₀alkyl means an alkyl group or radical having 1 to 10 carbon atoms.

Furthermore, the use of a term designating a monovalent radical where a divalent radical is appropriate shall be construed to designate the respective divalent radical and vice versa. Unless otherwise specified, conventional definitions of terms control and conventional stable atom valences are presumed and achieved in all formulas and groups. The articles "a" and "an" refer to one or more than one (e.g., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

10 The term "and/or" means either "and" or "or" unless indicated otherwise.

The term "substituted" means that the specified group or moiety bears one or more suitable substituents wherein the substituents may connect to the specified group or moiety at one or more positions. For example, an aryl substituted with a cycloalkyl may indicate that the cycloalkyl connects to one atom of the aryl with a bond or by fusing with the aryl and sharing two or more common atoms.

As used herein the term "C₁-C₆alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to six carbon atoms, and which is attached to the rest of the molecule by a single bond. The terms C₁-C₃alkyl and C₁-C₄alkyl are to be construed accordingly. Examples of C₁-C₆alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, 1-methylpropyl (*sec*-butyl), 2-methylpropyl (*iso*-butyl), 1,1-dimethylethyl (*tert*-butyl), *n*-pentyl and *n*-hexyl.

The term "alkenyl" employed alone or in combination with other terms, refers to a straight-chain or branched hydrocarbon group corresponding to an alkyl group having one or more double carbon-carbon bonds. An alkenyl group formally corresponds to an alkene with one C H bond replaced by the point of attachment of the alkenyl group to the remainder of the compound. The term "C_{n-m} alkenyl" refers to an alkenyl group having *n* to *m* carbons. In some embodiments, the alkenyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms. Example alkenyl groups include, but are not limited to, ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, *sec*-butenyl and the like.

As used herein, the term "C₁-C₆alkoxy" refers to a radical of the formula -OR_a where R_a is a C₁-C₆alkyl radical as generally defined above. Examples of C₁-C₆alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, *tert*-butoxy, *sec*-butoxy, pentoxy, and hexoxy.

The term "amino," employed alone or in combination with other terms, refers to a group of formula -NH₂, wherein the hydrogen atoms may be substituted with a substituent described herein. For example, "alkylamino" can refer to -NH(alkyl) and -N(alkyl)₂.

The term "cyano" or "nitrile" refers to a group of formula -C≡N, which also may be written as -CN.

The term "halogen" or "halo" means fluorine, chlorine, bromine or iodine.

The term 'hydroxy' refers to an alcohol group of formula -OH.

As used herein, the term "cycloalkyl" or "carbocycle" means a monocyclic or polycyclic saturated or partially unsaturated carbon ring containing 3-18 carbon atoms wherein there are no delocalized pi electrons (aromaticity) shared among the ring carbons. The term "C₃-C₅cycloalkyl" is to be construed accordingly. The term polycyclic encompasses bridged (e.g., norbornane), fused (e.g., decalin) and spirocyclic cycloalkyl. Preferably, cycloalkyl, e.g., C₃-C₅cycloalkyl, is a monocyclic hydrocarbon group of 3 to 5 carbon atoms.

Examples of cycloalkyl groups include, without limitations, cyclopropenyl, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, bicyclo[1.1.1]pentanyl and derivatives thereof.

Examples of C₃-C₅cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, and cyclopentyl.

"Heterocyclyl" means a saturated or partially saturated monocyclic or polycyclic ring containing carbon and at least one heteroatom selected from oxygen, nitrogen, and sulfur (O, N, and S) and wherein there are no delocalized pi electrons (aromaticity) shared among the ring carbons or heteroatoms. The term "4- to 6-membered heterocyclyl" is to be construed accordingly. The heterocyclyl ring structure may be substituted by one or more substituents. The substituents can themselves be optionally substituted. The heterocyclyl may be bonded via a carbon atom or heteroatom. The term polycyclic encompasses bridged, fused and spirocyclic heterocyclyl.

Examples of heterocyclyl rings include, but are not limited to, oxetanyl, azetidiny, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidiny, oxazoliny, isoxazoliny, oxazolidiny, thiazolidiny, pyranly, thiopyranly, tetrahydropyranyl, dioxaliny, piperidiny, morpholiny, thiomorpholiny, thiomorpholiny S-oxide, thiomorpholiny S-dioxide, piperaziny, azepiny, oxepiny, diazepiny, tropany, oxazolidinony, 1,4-dioxany, dihydrofurany, 1,3-dioxolany, imidazolidiny, dihydroisoxazoliny, pyrroliny, pyrazoliny, oxazepiny, dithiolany, homotropany, dihydropyranyl (e.g., 3,6-dihydro-2H-pyranyl), oxaspiroheptany (e.g., 2-oxaspiro[3.3]heptan-6-yl) and the like.

Examples of 4- to 6-membered heterocyclyl include, without limitations, azetidiny, pyrrolidiny, tetrahydrofurany, tetrahydrothieny, piperidiny, piperaziny, dihydroisoxazoliny, tetrahydropyrany, morpholiny, dihydropyrany (e.g., 3,6-dihydro-2H-pyrany) and oxaspiroheptany (e.g., 2-oxaspiro[3.3]heptan-6-yl).

As used herein, the term "heteroaryl" is intended to include monocyclic heterocyclic aromatic rings containing one or more heteroatoms selected from oxygen, nitrogen, and sulfur (O, N, and S). Representative examples are pyrroly, furany, thieny, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isothiazolyl, isooxazolyl, triazolyl, (e.g., 1,2,4-triazolyl), oxadiazolyl, (e.g., 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl), tetrazolyl, pyranly, pyridiny, pyridaziny, pyrimidiny, pyraziny, 1,2,3-triaziny, 1,2,4-triaziny, 1,3,5-triaziny, thiadiaziny, azepiny, azeciny, and the like.

Heteroaryl is also intended to include bicyclic heterocyclic aromatic rings containing one or more heteroatoms selected from oxygen, nitrogen, and sulfur (O, N, and S). Representative examples are indolyl, isoindolyl, benzofuranyl, benzothiophenyl, indazolyl, benzopyranyl, benzimidazolyl, benzothiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, benzoxazinyl, 5 benzotriazolyl, naphthyridinyl, phthalazinyl, pteridinyl, purinyl, quinazolinyl, cinnolinyl, quinolinyl, isoquinolinyl, quinoxalinyl, oxazolopyridinyl, isooxazolopyridinyl, pyrrolopyridinyl, furopyridinyl, thienopyridinyl, imidazopyridinyl, imidazopyrimidinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrazolotriazinyl, thiazolopyridinyl, thiazolopyrimidinyl, imdazothiazolyl, triazolopyridinyl, triazolopyrimidinyl, and the like.

10 Heteroaryl is also intended to include polycyclic heterocyclic aromatic rings containing one or more heteroatoms selected from oxygen, nitrogen, and sulfur (O, N, and S). Representative examples are carbazolyl, phenoxazinyl, phenazinyl, acridinyl, phenothiazinyl, carbolinyl, phenanthrolinyl, and the like.

The heteroaryl ring structure may be substituted by one or more substituents. The 15 substituents can themselves be optionally substituted. The heteroaryl ring may be bonded via a carbon atom or heteroatom.

The term "5 or 6 membered heteroaryl" is to be construed accordingly.

Examples of 5 or 6 membered heteroaryl include, but are not limited to, furan, indolyl, pyridinyl, pyrimidinyl, pyridinonyl, pyridazinyl, triazolyl, (e.g., 1,2,4-triazolyl), pyrazolyl, thiazolyl, 20 oxazolyl, isooxazolyl, pyrrolyl, oxadiazolyl, (e.g., 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl), imidazolyl, thiophenyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl), pyrazinyl, isooxazolopyridinyl, dihydropyridooxazinyl and tetrazolyl. The term "5 or 6 membered heteroaryl ring having 1-2 heteroatoms independently selected from N, O, and S" is to be construed accordingly.

25 As used herein "modulator," means, for example, a compound of the disclosure that modulates, decreases, or reduces the levels of a specific protein (e.g., complement factor B). The amount of a specific protein (e.g., complement factor B) modulated can be measured by comparing the amount of the specific protein (e.g., complement factor B) remaining after treatment with a compound of the disclosure as compared to the initial amount or level of the 30 specific protein (e.g., complement factor B) present as measured prior to treatment with a compound of the disclosure.

As used herein, "inhibitor" means, for example, a compound of the disclosure, that inhibits or reduces the activity of at least one component of the complement pathway, e.g., the compound inhibits binding of one component to another component of the pathway. For example, the 35 complement pathway is the alternative complement pathway. For example, the component of the complement pathway is complement factor B.

As used herein, the term “inhibit,” “inhibition,” or “inhibiting” refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

5 The term “effective amount” of the compounds described herein, refers to that amount of a therapeutic compound necessary or sufficient to perform its intended function within a mammal. An effective amount of the therapeutic compound can vary according to factors such as the amount of the causative agent already present in the mammal, the age, sex, and weight of the mammal, and the ability of the therapeutic compounds of the present disclosure to treat the conditions wherein complement factor B plays a role.

10 Thus, the term “a therapeutically effective amount” of a compound of the disclosure refers to an amount of the compound of the disclosure that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. In one embodiment, the term “a therapeutically effective amount” refers to the amount of the
15 compound of the disclosure that, when administered to a subject, is effective to (1) at least partially alleviate, prevent and/or ameliorate a condition, or a disorder or a disease (i) mediated by complement factor B, or (ii) associated with complement factor B activity, or (iii) characterized by activity (normal or abnormal) of complement factor B: (2) reduce or inhibit the activity of complement factor B; or (3) reduce or inhibit the expression of complement factor B. In another
20 embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the disclosure that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially reducing or inhibiting the activity of complement factor B; or at least partially reducing or inhibiting the expression of complement factor B.

As used herein, the term “subject” or “patient” refers to human and non-human mammals,
25 including but, not limited to, primates, rabbits, pigs, horses, dogs, cats, sheep, and cows. In particular embodiments, a subject or patient is a human. In some embodiments, the term “patient” or “subject” refers to a human being who is diseased with the condition (*i.e.*, disease or disorder) described herein and who would benefit from the treatment. As used herein, a subject is “in need of” a treatment if such subject (patient) would benefit biologically, medically or in quality of life
30 from such treatment. In particular embodiments, the subject is an adult human at least about 18 years of age. In particular embodiments, the subject is an adult human from about 18 to about 75 years of age. In some embodiments, the subject is a human child up to about 18 years of age.

As used herein, the term “treating” or “treatment” refers to inhibiting a disease; for example, inhibiting a disease, condition, or disorder in an individual who is experiencing or
35 displaying the pathology or symptomology of the disease, condition, or disorder (*i.e.*, arresting further development of the pathology and/or symptomology) or ameliorating the disease; for example, ameliorating a disease, condition, or disorder in an individual who is experiencing or

displaying the pathology or symptomology of the disease, condition, or disorder (i.e., reversing the pathology and/or symptomology) such as decreasing the severity of the disease.

The term "prevent," "preventing," or "prevention" as used herein, comprises the prevention of at least one symptom associated with or caused by the state, disease or disorder being prevented. As used herein, a subject is "in need of" a treatment if such subject would benefit
5 biologically, medically or in quality of life from such treatment.

As used herein, the term "about" refers to a range of values +/- 10% of a specified value.

As used herein, the term "a," "an," "the" and similar terms used in the context of the disclosure (especially in the context of the claims) are to be construed to cover both the singular
10 and plural unless otherwise indicated herein or clearly contradicted by the context.

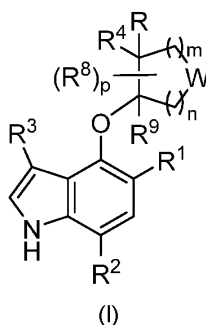
As used herein, the term "pharmaceutically acceptable carrier" refers to a substance useful in the preparation or use of a pharmaceutical composition and includes, for example, suitable diluents, solvents, dispersion media, surfactants, antioxidants, preservatives, isotonic agents, buffering agents, emulsifiers, absorption delaying agents, salts, drug stabilizers, binders,
15 excipients, disintegration agents, lubricants, wetting agents, sweetening agents, flavoring agents, dyes, and combinations thereof, as would be known to those skilled in the art (see, for example, Remington The Science and Practice of Pharmacy, 22nd Ed. Pharmaceutical Press, 2013, pp. 1049-1070).

The term "pharmaceutically acceptable salts" refers to derivatives of the disclosed
20 compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the non-toxic salts of the parent compound formed, e.g., from non-toxic
25 inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl
30 acetate, alcohols (e.g., methanol, ethanol, iso-propanol or butanol) or acetonitrile (MeCN) are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th Ed., (Mack Publishing Company, Easton, 1985), p. 1418, Berge et al., J. Pharm. Sci., 1977, 66(1), 1-19 and in Stahl et al., Handbook of Pharmaceutical Salts: Properties, Selection, and Use, (Wiley, 2002). In some embodiments, the compounds described herein include the N-oxide forms.

35 Various enumerated embodiments of the disclosure are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments of the disclosure.

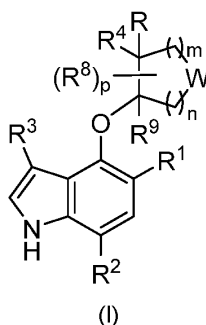
Compounds

The invention provides a compound of Formula (I), or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein the variables are defined herein.



Various enumerated embodiments of the invention are described herein, it will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments of the present invention.

Embodiment 1 provides a compound of Formula (I)



or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein:

W is O, C(R⁶)₂, or NR⁷;

R is hydrogen, halogen, C₁-C₄alkyl, haloC₁-C₄alkyl, or hydroxyC₁-C₄alkyl;

R¹ is hydrogen, halogen, hydroxy, C₁-C₆alkyl, C₂-C₆alkenyl, C₃-C₆cycloalkyl, C₁-C₆alkoxy, haloC₁-C₆alkyl, haloC₃-C₆cycloalkyl, haloC₁-C₆alkoxy, hydroxyC₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, aminoC₁-C₆alkyl, C₁-C₆alkoxyC₁-C₆alkyl, C₁-C₆alkoxyC₁-C₆alkoxy, or C₃-C₆cycloalkylC₁-C₆alkoxy;

R² is C₁-C₃alkyl, C₃cycloalkyl, C₁-C₃alkoxy, hydroxyC₁-C₆alkyl, or halogen, wherein the C₁-C₃alkyl, C₃cycloalkyl, or C₁-C₃alkoxy are unsubstituted or substituted with 1, 2, or 3 halogen substituents;

R³ is hydrogen, halogen, or cyano;

R⁴ is phenyl, naphthyl or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N, O, and S, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵;

R⁵ is selected from hydrogen, -CO₂R^{5b}, C₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, C₁-C₆alkoxyC₁-C₆alkyl, -CH₂CO₂R^{5b}, -C(O)NHSO₂C₁-C₄alkyl, -SO₂NHC(O)C₁-C₄alkyl, -SO₂C₁-C₄alkyl, cyano, hydroxy, halogen, -C(O)N(R^{5b})₂ and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein alkyl and heteroaryl are unsubstituted or substituted with 1, 2, or 3 R^{5a};

each R^{5a} is independently selected from fluoro, hydroxyl, and C₁-C₆alkyl that is unsubstituted or substituted with -CO₂H;

each R^{5b} is independently selected from hydrogen and C₁-C₅alkyl;

each R⁶ is independently selected from hydrogen, halogen, hydroxy, amino, mono- and di- C₁-C₄alkylamino, C₃-C₆cycloalkylC₁-C₄alkylamino, haloC₃-C₆cycloalkylC₁-C₄alkylamino, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₁-C₆alkyl, cyanoC₁-C₆alkyl, C₁-C₆alkoxy, haloC₁-C₆alkoxy, C₃-C₆cycloalkoxy, haloC₃-C₆cycloalkoxy, and 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, and wherein the C₁-C₆alkyl is unsubstituted or substituted with 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, wherein each 4- to 6-membered heterocyclyl is independently unsubstituted or substituted with 1, 2, or 3 halogen ;

or two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic carbocycle having 3 to 6 ring atoms, wherein the spirocyclic carbocycle is unsubstituted or substituted with 1 or 2 substituents selected from halogen, C₁-C₆alkyl, and C₁-C₆alkoxy;

or two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 or 2 ring heteroatoms independently selected from N, O, and S(O)_q, wherein the spirocyclic heterocycle is unsubstituted or substituted with 1 or 2 halogen, C₁-C₆alkyl, haloC₁-C₆alkyl, C₃-C₆cycloalkyl, or haloC₃-C₆cycloalkyl;

q is 0, 1, or 2;

R⁷ is hydrogen, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₂-C₆alkyl, C₃-C₆cycloalkyl, C₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkyl, C₁-C₆alkoxyC₁-C₆alkyl, haloC₁-C₆alkoxyC₁-C₆alkyl, -COR^{7a}, aryl, 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N, O, and S(O)_q, or 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein C₁-C₆alkyl is unsubstituted or substituted with 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N, O, and S(O)_q, wherein the 4- to 6-membered heterocyclyl is unsubstituted or substituted with 1, 2, or 3 halogen, further wherein the aryl or heteroaryl is unsubstituted or substituted with halo, C₁-C₆alkyl, haloC₁-C₆alkyl, C₃-C₅cycloalkyl, haloC₃-C₅cycloalkyl;

10 R^{7a} is hydrogen or C₁-C₆alkyl;

each R^8 is independently selected from hydrogen, halogen, hydroxy, amino, mono- and di- C_1 - C_4 alkylamino, C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, hydroxy C_1 - C_6 alkyl, cyano C_1 - C_6 alkyl, C_1 - C_6 alkoxy, and halo C_1 - C_6 alkoxy;

R^9 is H, D, or T;

m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3;

provided that both m and n are not 0; and

p is 0, 1, 2, or 3.

Embodiment 2 provides the compound of Formula (I) of embodiment 1, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein:

W is $C(R^6)_2$, or NR^7 ;

R is hydrogen;

R^1 is hydrogen, halogen, hydroxy, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_6 cycloalkyl, C_1 - C_6 alkoxy, halo C_1 - C_6 alkyl, hydroxy C_1 - C_6 alkyl, or amino C_1 - C_6 alkyl;

R^2 is C_1 - C_3 alkyl, C_3 cycloalkyl, C_1 - C_3 alkoxy, hydroxy C_1 - C_6 alkyl, or halogen, wherein the C_1 - C_3 alkyl, C_3 cycloalkyl, or C_1 - C_3 alkoxy are unsubstituted or substituted with 1, 2, or 3 halogen substituents;

R^3 is hydrogen, halogen, or cyano;

R^4 is phenyl, naphthyl or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N, O, and S, wherein phenyl or heteroaryl is unsubstituted or substituted with R^5 ;

R^5 is selected from hydrogen, $-CO_2R^{5b}$, C_1 - C_6 alkyl, hydroxy C_3 - C_6 cycloalkyl, C_1 - C_6 alkoxy C_1 - C_6 alkyl, $-CH_2CO_2R^{5b}$, cyano, hydroxy, halogen, $-C(O)N(R^{5b})_2$ and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein alkyl and heteroaryl are unsubstituted or substituted with 1, 2, or 3 R^{5a} ;

each R^{5a} is independently selected from fluoro, hydroxyl, and C_1 - C_6 alkyl that is unsubstituted or substituted with $-CO_2H$;

R^{5b} is selected from hydrogen and C_1 - C_5 alkyl;

each R^6 is independently selected from hydrogen, halogen, hydroxy, C_3 - C_6 cycloalkyl C_1 - C_4 alkylamino, halo C_3 - C_6 cycloalkyl C_1 - C_4 alkylamino, C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, hydroxy C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo C_1 - C_6 alkoxy, C_3 - C_6 cycloalkoxy, halo C_3 - C_6 cycloalkoxy, and 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, and wherein the C_1 - C_6 alkyl is unsubstituted or substituted with 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, wherein each 4- to 6-membered heterocyclyl is independently unsubstituted or substituted with 1, 2, or 3 halogen;

or two R⁸ in combination with the carbon atom to which they are attached form a spirocyclic carbocycle having 3 to 6 ring atoms, wherein the spirocyclic carbocycle is unsubstituted or substituted with 1 or 2 substituents selected from halogen, C₁-C₆alkyl, and C₁-C₆alkoxy;

or two R⁸ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 or 2 ring heteroatoms independently selected from N and O, wherein the spirocyclic heterocycle is unsubstituted;

R⁷ is hydrogen, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₂-C₆alkyl, haloC₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkyl, haloC₁-C₆alkoxyC₁-C₆alkyl, -COR^{7a}, C₃-C₆cycloalkyl, 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N or O, or 5- to 6-membered heteroaryl having 1 heteroatom selected from O, wherein the 4- to 6-membered
5 heterocyclyl and the 5- to 6-membered heteroaryl are unsubstituted;

R^{7a} is C₁-C₆alkyl;

each R⁸ is independently selected from hydrogen, halogen, hydroxy, amino, mono- and di- C₁-C₄alkylamino, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₁-C₆alkyl, cyanoC₁-C₆alkyl, C₁-C₆alkoxy, and haloC₁-C₆alkoxy;

R⁹ is H, D, or T;

m is 1, 2, or 3;

n is 1, 2, or 3; and

p is 0, 1, or 2.

Embodiment 3 provides the compound of Formula (I) of embodiment 1 or 2, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein:

W is C(R⁶)₂, or NR⁷;

R is hydrogen;

R¹ is hydrogen, halogen, hydroxy, C₁-C₆alkyl, C₃-C₆cycloalkyl, C₁-C₆alkoxy, or haloC₁-C₆alkyl;

R² is C₁-C₃alkyl, C₃cycloalkyl, C₁-C₃alkoxy, hydroxyC₁-C₆alkyl, or halogen;

R³ is hydrogen;

R⁴ is phenyl, naphthyl or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N, and O, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵;

R⁵ is selected from hydrogen, -CO₂R^{5b}, C₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, -CH₂CO₂R^{5b}, cyano, hydroxy, halogen, -C(O)N(R^{5b})₂ and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, and O, wherein alkyl and heteroaryl are unsubstituted or substituted with 1, 2, or 3 R^{5a};

each R^{5a} is independently selected from fluoro, hydroxyl, and C₁-C₆alkyl that is unsubstituted or substituted with -CO₂H;

each R^{5b} is selected from hydrogen and C₁-C₅alkyl;

each R^6 is independently selected from hydrogen, halogen, hydroxy, C_3 - C_6 cycloalkyl C_1 - C_4 alkylamino, halo C_3 - C_6 cycloalkyl C_1 - C_4 alkylamino, C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, hydroxy C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo C_1 - C_6 alkoxy, C_3 - C_6 cycloalkoxy, halo C_3 - C_6 cycloalkoxy, and 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, and wherein the C_1 - C_6 alkyl is unsubstituted or substituted with 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, wherein each 4- to 6-membered heterocyclyl is independently unsubstituted or substituted with 1, 2, or 3 halogen;

or two R^6 in combination with the carbon atom to which they are attached form a spirocyclic carbocycle having 3 to 6 ring atoms, wherein the spirocyclic carbocycle is unsubstituted or substituted with 1 or 2 substituents selected from halogen, C_1 - C_6 alkyl, and C_1 - C_6 alkoxy;

or two R^6 in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 or 2 ring heteroatoms independently selected from N and O, wherein the spirocyclic heterocycle is unsubstituted;

R^7 is hydrogen, C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, hydroxy C_2 - C_6 alkyl, halo C_3 - C_6 cycloalkyl C_1 - C_3 alkyl, halo C_3 - C_6 cycloalkyl, halo C_1 - C_6 alkoxy C_1 - C_6 alkyl, $-COR^{7a}$, C_3 - C_6 cycloalkyl, 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N or O, or 5- to 6-membered heteroaryl having 1 heteroatom selected from O, wherein the 4- to 6-membered heterocyclyl and the 5- to 6-membered heteroaryl are unsubstituted;

R^{7a} is C_1 - C_6 alkyl;

each R^8 is independently selected from hydrogen, halogen, hydroxy, amino, mono- and di- C_1 - C_4 alkylamino, C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, hydroxy C_1 - C_6 alkyl, cyano C_1 - C_6 alkyl, C_1 - C_6 alkoxy, and halo C_1 - C_6 alkoxy;

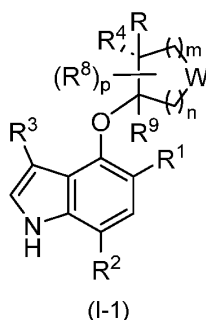
R^9 is H;

m is 1, or 2;

n is 1, 2, or 3; and

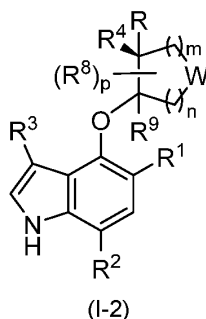
p is 0.

Embodiment 4 provides the compound of Formula (I) of any of embodiments 1 to 3, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the compound of Formula (I) is a compound of Formula (I-1):



or a pharmaceutically acceptable salt thereof.

Embodiment 5 provides the compound of Formula (I) of any of embodiments 1 to 3, wherein the compound of Formula (I) is a compound of Formula (I-2):



or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

Embodiment 6 provides the compound of Formula (I) in any of embodiments 1 to 5, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein:

W is $C(R^6)_2$;

R is hydrogen;

R^1 is hydrogen, halogen, hydroxy, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_6 cycloalkyl, C_1 - C_6 alkoxy, halo C_1 - C_6 alkyl, hydroxy C_1 - C_6 alkyl, or amino C_1 - C_6 alkyl;

R^2 is C_1 - C_3 alkyl, C_3 cycloalkyl, C_1 - C_3 alkoxy, hydroxy C_1 - C_6 alkyl, or halogen, wherein the C_1 - C_3 alkyl, C_3 cycloalkyl, or C_1 - C_3 alkoxy are unsubstituted or substituted with 1, 2, or 3 halogen substituents;

R^3 is hydrogen, halogen, or cyano;

R^4 is phenyl, naphthyl or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N, O, and S, wherein phenyl or heteroaryl is unsubstituted or substituted with R^5 ;

R^5 is selected from hydrogen, $-CO_2R^{5b}$, C_1 - C_6 alkyl, hydroxy C_3 - C_6 cycloalkyl, C_1 - C_6 alkoxy C_1 - C_6 alkyl, $-CH_2CO_2R^{5b}$, cyano, hydroxy, halogen, $-C(O)N(R^{5b})_2$ and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein alkyl and heteroaryl are unsubstituted or substituted with 1, 2, or 3 R^{5a} ;

each R^{5a} is independently selected from fluoro, hydroxyl, and C_1 - C_6 alkyl that is unsubstituted or substituted with $-CO_2H$;

each R^{5b} is selected from hydrogen and C_1 - C_5 alkyl;

each R^6 is independently selected from hydrogen, halogen, hydroxy, C_3 - C_6 cycloalkyl C_1 - C_4 alkylamino, halo C_3 - C_6 cycloalkyl C_1 - C_4 alkylamino, C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, hydroxy C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo C_1 - C_6 alkoxy, C_3 - C_6 cycloalkoxy, halo C_3 - C_6 cycloalkoxy, and 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, and wherein the C_1 - C_6 alkyl is unsubstituted or substituted with 4- to 6-membered heterocyclyl having

1-2 heteroatoms independently selected from N and O, wherein each 4- to 6-membered heterocyclyl is independently unsubstituted or substituted with 1, 2, or 3 halogen;

or two R⁸ in combination with the carbon atom to which they are attached form a spirocyclic carbocycle having 3 to 6 ring atoms, wherein the spirocyclic carbocycle is unsubstituted or substituted with 1 or 2 substituents selected from halogen, C₁-C₆alkyl, and C₁-C₆alkoxy;

or two R⁸ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 or 2 ring heteroatoms independently selected from N and O, wherein the spirocyclic heterocycle is unsubstituted;

each R⁸ is independently selected from hydrogen, halogen, hydroxy, amino, mono- and di- C₁-C₄alkylamino, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₁-C₆alkyl, cyanoC₁-C₆alkyl, C₁-C₆alkoxy, and haloC₁-C₆alkoxy;

R⁹ is H, D, or T;

m is 1, 2, or 3;

n is 1, 2, or 3; and

p is 0, 1, or 2.

Embodiment 7 provides the compound of Formula (I) of any of embodiments 1 to 5, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein

W is NR⁷;

R is hydrogen;

R¹ is hydrogen, halogen, hydroxy, C₁-C₆alkyl, C₂-C₆alkenyl, C₃-C₆cycloalkyl, C₁-C₆alkoxy, haloC₁-C₆alkyl, hydroxyC₁-C₆alkyl, or aminoC₁-C₆alkyl;

R² is C₁-C₃alkyl, C₃cycloalkyl, C₁-C₃alkoxy, hydroxyC₁-C₆alkyl, or halogen, wherein the C₁-C₃alkyl, C₃cycloalkyl, or C₁-C₃alkoxy are unsubstituted or substituted with 1, 2, or 3 halogen substituents;

R³ is hydrogen, halogen, or cyano;

R⁴ is phenyl, naphthyl or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N, O, and S, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵;

R⁵ is selected from hydrogen, -CO₂R^{5b}, C₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, C₁-C₆alkoxyC₁-C₆alkyl, -CH₂CO₂R^{5b}, cyano, hydroxy, halogen, -C(O)N(R^{5b})₂ and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein alkyl and heteroaryl are unsubstituted or substituted with 1, 2, or 3 R^{5a};

each R^{5a} is independently selected from fluoro, hydroxyl, and C₁-C₆alkyl that is unsubstituted or substituted with -CO₂H;

each R^{5b} is selected from hydrogen and C₁-C₅alkyl;

R⁷ is hydrogen, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₂-C₆alkyl, haloC₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkyl, haloC₁-C₆alkoxyC₁-C₆alkyl, -COR^{7a}, C₃-C₆cycloalkyl, 4- to 6-

membered heterocyclyl having 1-2 heteroatoms independently selected from N or O, or 5- to 6-membered heteroaryl having 1 heteroatom selected from O, wherein the 4- to 6-membered heterocyclyl and the 5- to 6-membered heteroaryl are unsubstituted;

R^{7a} is C_1 - C_6 alkyl;

each R^8 is independently selected from hydrogen, halogen, hydroxy, amino, mono- and di- C_1 - C_4 alkylamino, C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, hydroxy C_1 - C_6 alkyl, cyano C_1 - C_6 alkyl, C_1 - C_6 alkoxy, and halo C_1 - C_6 alkoxy;

5 R^9 is H, D, or T;

m is 1, 2, or 3;

n is 1, 2, or 3; and

p is 0, 1, or 2.

Embodiment 8 provides the compound of Formula (I) of any of embodiments 1-6, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein

W is $C(R^6)_2$;

R is hydrogen;

R^1 is hydrogen, halogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, or halo C_1 - C_6 alkyl;

R^2 is C_1 - C_3 alkyl, or halogen, wherein the C_1 - C_3 alkyl is unsubstituted or substituted with 1, 2, or 3 halogen substituents;

R^3 is hydrogen;

R^4 is phenyl or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N, O, and S, wherein phenyl or heteroaryl is unsubstituted or substituted with R^5 ;

R^5 is selected from hydrogen, $-CO_2R^{5b}$, C_1 - C_6 alkyl, hydroxy C_3 - C_6 cycloalkyl, $-CH_2CO_2R^{5b}$, cyano, $-C(O)N(R^{5b})_2$ and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein alkyl and heteroaryl are unsubstituted or substituted with 1 R^{5a} ;

each R^{5a} is independently selected from hydroxy and C_1 - C_6 alkyl;

each R^{5b} is independently selected from hydrogen and C_1 - C_3 alkyl;

each R^6 is independently selected from hydrogen, halogen, hydroxy, C_3 - C_6 cycloalkyl C_1 - C_4 alkylamino, halo C_3 - C_6 cycloalkyl C_1 - C_4 alkylamino, C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo C_1 - C_6 alkoxy, C_3 - C_6 cycloalkoxy, halo C_3 - C_6 cycloalkoxy, and 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, and wherein the C_1 - C_6 alkyl is unsubstituted or substituted with 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, wherein the 4- to 6-membered heterocyclyl is unsubstituted or substituted with 1, 2, or 3 halogen;

or two R⁸ in combination with the carbon atom to which they are attached form a spirocyclic carbocycle having 3 to 6 ring atoms, wherein the spirocyclic carbocycle is unsubstituted or substituted with 1 or 2 substituents selected from halogen, C₁-C₆alkyl, and C₁-C₆alkoxy;

or two R⁸ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 or 2 ring heteroatoms independently selected from N and O;

each R⁸ is independently selected from hydrogen and C₁-C₆alkyl;

R⁹ is H;

m is 1 or 2;

n is 1, 2, or 3; and

p is 0, 1, or 2.

Embodiment 9 provides the compound of Formula (I) of any of embodiments 1-5 and 7, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein

W is NR⁷;

R is hydrogen;

R¹ is hydrogen, halogen, C₁-C₆alkyl, C₃-C₆cycloalkyl, or haloC₁-C₆alkyl;

R² is C₁-C₃alkyl, or halogen, wherein the C₁-C₃alkyl is unsubstituted or substituted with 1, 2, or 3 halogen substituents;

R³ is hydrogen;

R⁴ is phenyl or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N, O, and S, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵;

R⁵ is selected from hydrogen, -CO₂R^{5b}, C₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, -CH₂CO₂R^{5b}, cyano, -C(O)N(R^{5b})₂ and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein alkyl and heteroaryl are unsubstituted or substituted with 1 R^{5a};

each R^{5a} is independently selected from hydroxy and C₁-C₆alkyl;

each R^{5b} is independently selected from hydrogen and C₁-C₃alkyl;

R⁷ is C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₂-C₆alkyl, haloC₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkyl, haloC₁-C₆alkoxyC₁-C₆alkyl, -COR^{7a}, 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N or O, or 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, ;

R^{7a} is C₁-C₆alkyl;

each R⁸ is independently selected from hydrogen and C₁-C₆alkyl;

R⁹ is H;

m is 1 or 2;

n is 1, 2, or 3; and

p is 0, 1, or 2.

Embodiment 10 provides the compound of Formula (I) of any of embodiments 1-6 and 8, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein

W is C(R⁶)₂;

R is hydrogen;

R¹ is hydrogen, halogen, C₁-C₆alkyl, C₃-C₆cycloalkyl, haloC₁-C₆alkyl;

R² is C₁-C₃alkyl, or halogen, wherein the C₁-C₃alkyl is unsubstituted or substituted with 1, 2, or 3 halogen substituents;

R³ is hydrogen;

R⁴ is phenyl, or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N and O, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵;

R⁵ is selected from hydrogen, -CO₂R^{5b}, C₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, -CH₂CO₂R^{5b}, cyano, hydroxy, halogen, -C(O)N(R^{5b})₂ and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein alkyl and heteroaryl are unsubstituted or substituted with 1, 2, or 3 R^{5a};

each R^{5a} is independently selected from hydroxyl, and C₁-C₆alkyl;

each R^{5b} is independently selected from hydrogen;

each R⁶ is independently selected from hydrogen, halogen, hydroxy, C₃-C₆cycloalkylC₁-C₄alkylamino, haloC₃-C₆cycloalkylC₁-C₄alkylamino, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkoxy, haloC₁-C₆alkoxy, C₃-C₆cycloalkoxy, haloC₃-C₆cycloalkoxy, and 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, and wherein the C₁-C₆alkyl is unsubstituted or substituted with 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, wherein each 4- to 6-membered heterocyclyl is independently unsubstituted or substituted with 1, 2, or 3 halogen;

or two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic carbocycle having 3 to 6 ring atoms, wherein the spirocyclic carbocycle is unsubstituted or substituted with 1 or 2 substituents selected from halogen;

or two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 or 2 ring heteroatoms independently selected from N and O;

each R⁸ is independently selected from hydrogen, halogen;

R⁹ is H or D;

m is 1 or 2;

n is 1, 2, or 3; and

p is 0.

Embodiment 11 provides the compound of Formula (I) of any of embodiments 1-5, 7 and 9, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein

W is NR⁷;

R is hydrogen;

R¹ is hydrogen, halogen, C₁-C₆alkyl, C₃-C₆cycloalkyl, haloC₁-C₆alkyl;

R² is C₁-C₃alkyl, or halogen, wherein the C₁-C₃alkyl is unsubstituted or substituted with 1, 2, or 3 halogen substituents;

R³ is hydrogen;

R⁴ is phenyl, or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N and O, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵;

R⁵ is selected from hydrogen, -CO₂R^{5b}, C₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, -CH₂CO₂R^{5b}, cyano, hydroxy, halogen, -C(O)N(R^{5b})₂ and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein alkyl and heteroaryl are unsubstituted or substituted with 1, 2, or 3 R^{5a};

each R^{5a} is independently selected from hydroxyl, and C₁-C₆alkyl;

each R^{5b} is independently selected from hydrogen;

R⁷ is C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₂-C₆alkyl, haloC₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkyl, haloC₁-C₆alkoxyC₁-C₆alkyl, -COR^{7a}, 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N or O, or 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S;

each R⁸ is independently selected from hydrogen, halogen;

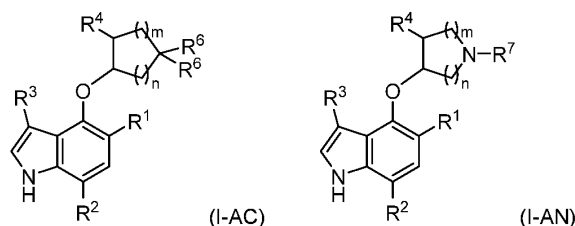
5 R⁹ is H or D;

m is 1 or 2;

n is 1, 2, or 3; and

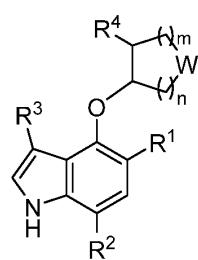
p is 0.

Embodiment 12 provides the compound of Formula (I) of any of applicable embodiments 1 to 11, wherein the compound of Formula (I) is a compound of Formula (I-AC), or (I-AN):

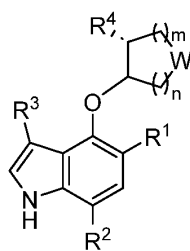


or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

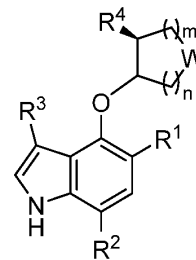
Embodiment 13 provides the compound of Formula (I) of any of embodiments 1 to 12, wherein the compound of Formula (I) is a compound of Formula (I-A0), (I-A1) or (I-A2):



(I-A0),



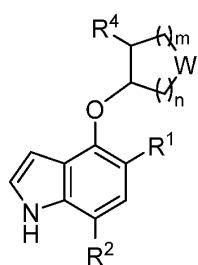
(I-A1)



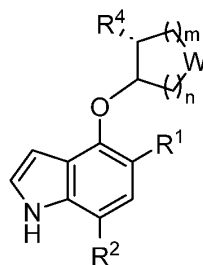
(I-A2)

or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

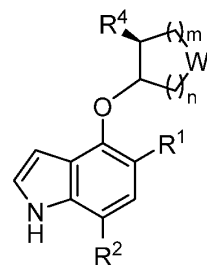
Embodiment 14 provides the compound of Formula (I) of embodiment 13, wherein the compound of Formula (I) is a compound of Formula (I-A), Formula (I-A11) or Formula (I-A12):



(I-A)



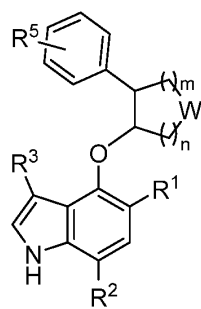
(I-A11)



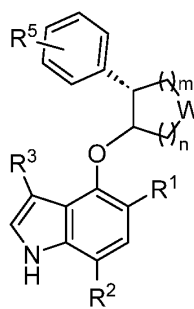
(I-A12)

or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

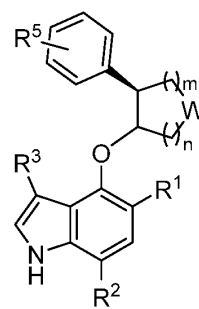
Embodiment 15 provides the compound of Formula (I) of any of embodiments 1 to 13, wherein the compound of Formula (I) is a compound of Formula (I-D), (I-D1) or (I-D2):



(I-D)



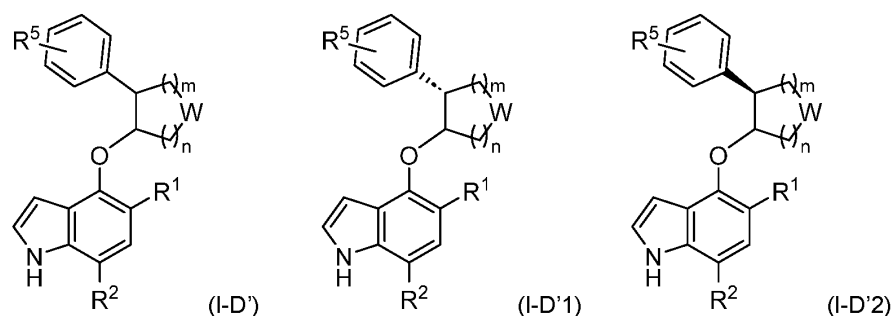
(I-D1)



(I-D2)

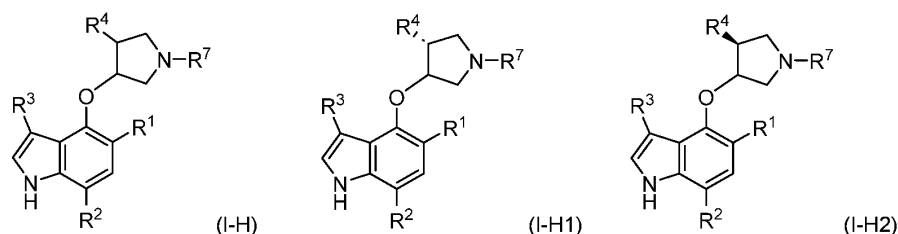
or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

Embodiment 16 provides the compound of Formula (I) of embodiment 15, wherein the compound of Formula (I) is a compound of Formulas (I-D'), (I-D'1) or (I-D'2):



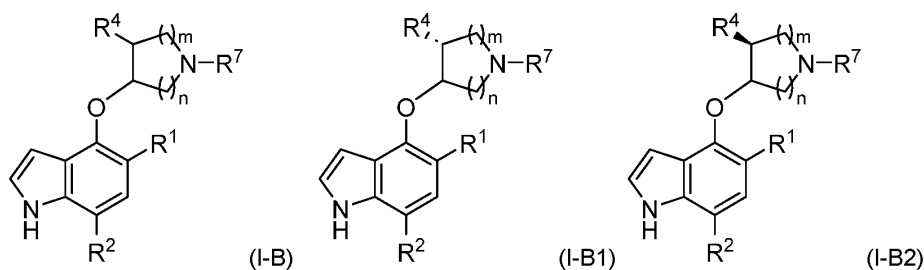
or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

Embodiment 17 provides the compound of Formula (I) of embodiment 13, wherein the compound of Formula (I) is a compound of Formula (I-H), (I-H1), or (I-H2):



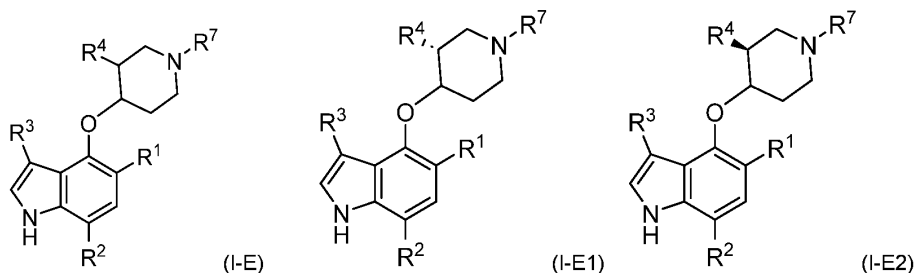
or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

Embodiment 18 provides the compound of Formula (I) of embodiment 17, wherein the compound of Formula (I) is a compound of Formula (I-B), (I-B1) or (I-B2):



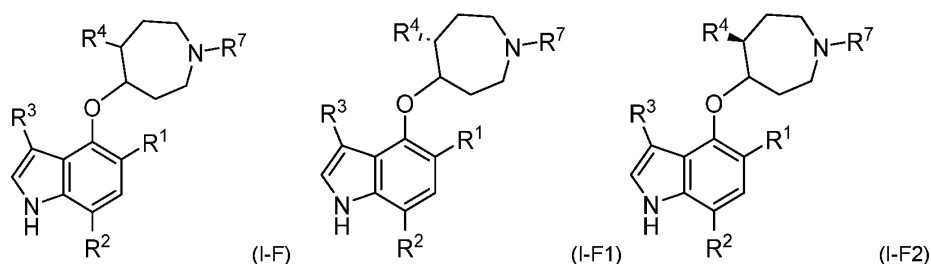
or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

Embodiment 19 provides the compound of Formula (I) of embodiment 13, wherein the compound of Formula (I) is a compound of Formula (I-E), (I-E1), or (I-E2):



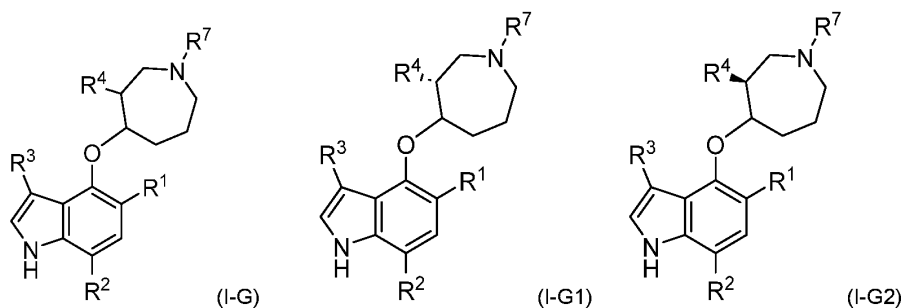
or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

Embodiment 20 provides the compound of Formula (I) of embodiment 13, wherein the compound of Formula (I) is a compound of Formula (I-F), (I-F1), or (I-F2):



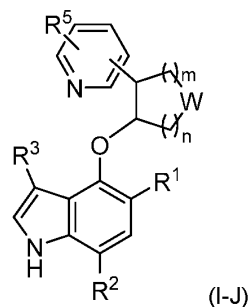
or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

Embodiment 21 provides the compound of Formula (I) of embodiment 13, wherein the compound of Formula (I) is a compound of Formula (I-G), (I-G1), or (I-G2):

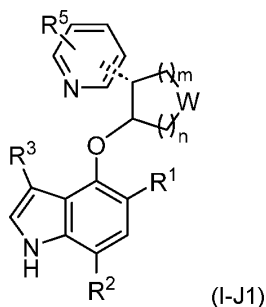


or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

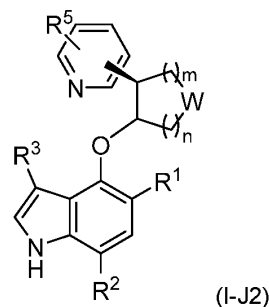
Embodiment 22 provides the compound of Formula (I) of embodiment 13, wherein the compound of Formula (I) is a compound of Formula (I-J), (I-J1) or (I-J2):



(I-J)



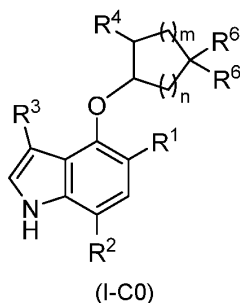
(I-J1)



(I-J2)

or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

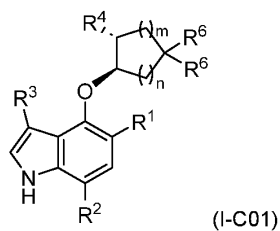
Embodiment 23 provides the compound of Formula (I) of embodiment 13, wherein the compound of Formula (I) is a compound of Formula (I-C0):



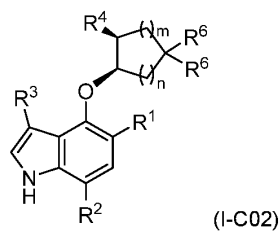
(I-C0)

or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

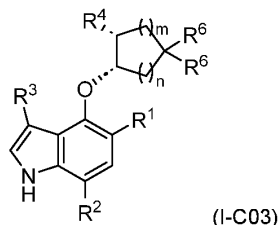
Embodiment 24 provides the compound of Formula (I) of embodiment 23, wherein the compound of Formula (I) is a compound of Formula (I-C01), (I-C02), (I-C03) or (I-C04):



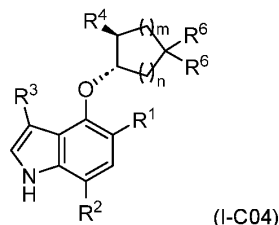
(I-C01)



(I-C02)



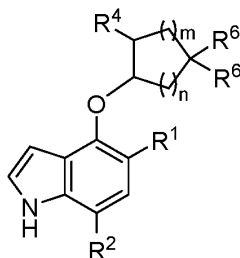
(I-C03)



(I-C04)

or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

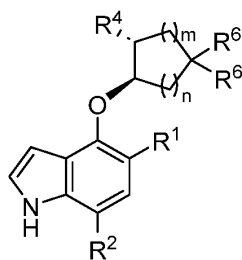
Embodiment 25 provides the compound of Formula (I) of embodiment 24, wherein the compound of Formula (I) is a compound of Formula (I-C):



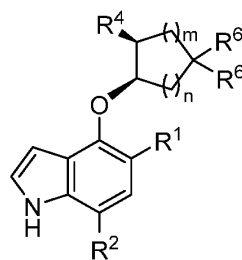
(I-C)

or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

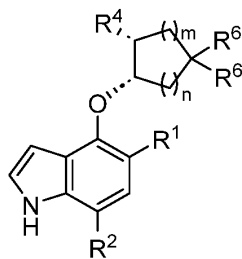
Embodiment 26 provides the compound of Formula (I) of embodiment 25, wherein the compound of Formula (I) is a compound of Formula (I-C1), (I-C2), (I-C3) or (I-C4):



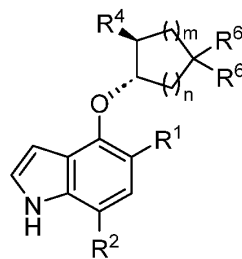
(I-C1)



(I-C2)



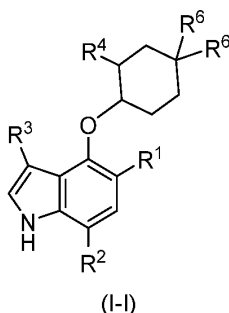
(I-C3)



(I-C4)

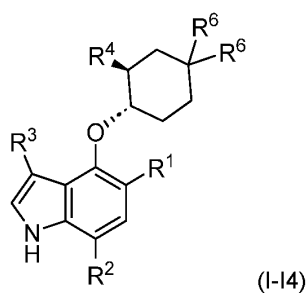
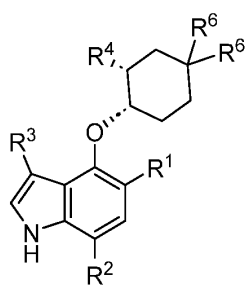
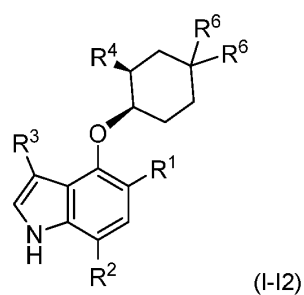
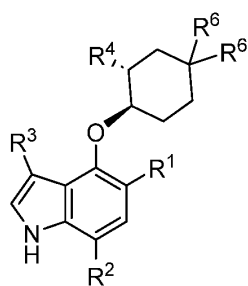
or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

Embodiment 27 provides the compound of Formula (I) of embodiment 23, wherein the compound of Formula (I) is a compound of Formula (I-I):



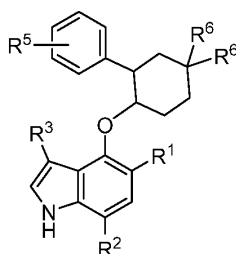
or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

Embodiment 28 provides the compound of Formula (I) of embodiment 27, wherein the compound of Formula (I) is a compound of Formula (I-I1), (I-I2), (I-I3) or (I-I4):



or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

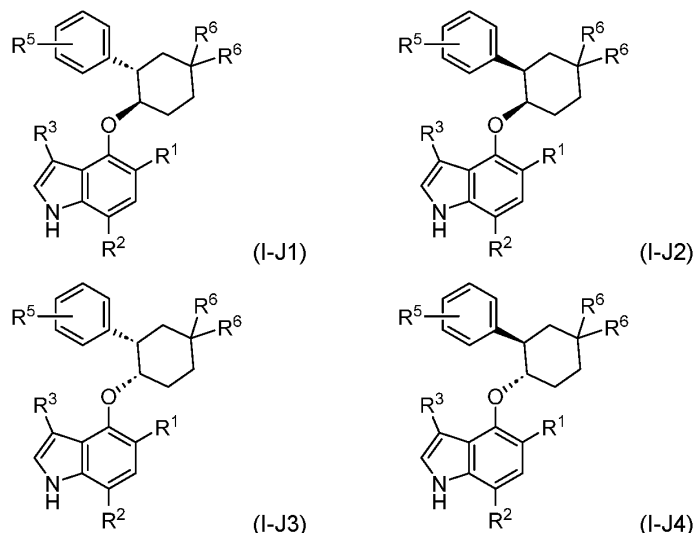
Embodiment 29 provides the compound of Formula (I) of embodiment 28, wherein the compound of Formula (I) is a compound of Formula (I-J):



(I-J)

or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

Embodiment 30 provides the compound of Formula (I) of embodiment 29, wherein the compound of Formula (I) is a compound of Formula (I-J1), (I-J2), (I-J3) or (I-J4):



or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

Embodiment 31 provides the compound of Formula (I) of any of embodiments 1 to 30, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R¹ is hydrogen, halogen, hydroxy, C₁-C₆alkyl, C₂-C₆alkenyl, C₃-C₆cycloalkyl, C₁-C₆alkoxy, haloC₁-C₆alkyl, haloC₃-C₆cycloalkyl, haloC₁-C₆alkoxy, hydroxyC₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, aminoC₁-C₆alkyl, C₁-C₆alkoxyC₁-C₆alkyl, C₁-C₆alkoxyC₁-C₆alkoxy, or C₃-C₆cycloalkylC₁-C₆alkoxy.

Embodiment 32 provides the compound of Formula (I) of any of embodiments 1 to 31, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R¹ is hydrogen, halogen, C₁-C₆alkyl, C₃-C₆cycloalkyl, haloC₁-C₆alkyl, haloC₃-C₆cycloalkyl, haloC₁-C₆alkoxy, hydroxyC₁-C₆alkyl, or hydroxyC₃-C₆cycloalkyl.

Embodiment 33 provides the compound of Formula (I) of any of embodiments 1 to 32, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R¹ is hydrogen, halogen, hydroxy, C₁-C₆alkyl, C₃-C₆cycloalkyl, or haloC₁-C₆alkyl.

Embodiment 34 provides the compound of Formula (I) of any of embodiments 1 to 33, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R¹ is hydrogen, halogen, C₁-C₆alkyl, C₃-C₆cycloalkyl, or haloC₁-C₆alkyl.

Embodiment 35 provides the compound of Formula (I) of any of embodiments 1 to 34, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof,

wherein R^2 is C_1 - C_3 alkyl, C_3 cycloalkyl, C_1 - C_3 alkoxy, hydroxy C_1 - C_6 alkyl, or halogen, wherein the C_1 - C_3 alkyl, C_3 cycloalkyl, or C_1 - C_3 alkoxy are unsubstituted or substituted with 1, 2, or 3 halogen substituents.

Embodiment 36 provides the compound of Formula (I) of any of embodiments 1 to 35, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R^2 is C_1 - C_3 alkyl, C_3 cycloalkyl, C_1 - C_3 alkoxy, hydroxy C_1 - C_6 alkyl, or halogen, wherein the C_1 - C_3 alkyl, C_3 cycloalkyl, or C_1 - C_3 alkoxy are unsubstituted or substituted with 1, 2, or 3 halogen substituents.

Embodiment 37 provides the compound of Formula (I) of any of embodiments 1 to 36, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R^2 is C_1 - C_3 alkyl, or halogen, wherein the C_1 - C_3 alkyl is unsubstituted or substituted with 1, 2, or 3 halogen substituents.

Embodiment 38 provides the compound of Formula (I) of any of embodiments 1 to 37, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R^2 is C_1 - C_3 alkyl, or halogen.

Embodiment 39 provides the compound of Formula (I) of any of applicable embodiments 1 to 38, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein where applicable R^3 is hydrogen, halogen, or cyano.

Embodiment 40 provides the compound of Formula (I) of any of applicable embodiments 1 to 39, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein where applicable R^3 is hydrogen.

Embodiment 41 provides the compound of Formula (I) of any of applicable embodiments 1 to 40, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R^4 is phenyl, naphthyl or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N, O, and S, wherein phenyl or heteroaryl is unsubstituted or substituted with R^5 .

Embodiment 42 provides the compound of Formula (I) of any of applicable embodiments 1 to 41, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R^4 is phenyl, or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N, and O, wherein phenyl or heteroaryl is unsubstituted or substituted with R^5 .

Embodiment 43 provides the compound of Formula (I) of any of applicable embodiments 1 to 42, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R^4 is phenyl, or 5- to 6-membered heteroaryl having 1 or 2 ring heteroatoms independently selected from N, and O, wherein phenyl or heteroaryl is unsubstituted or substituted with R^5 .

Embodiment 44 provides the compound of Formula (I) of any of applicable embodiments 1 to 43, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled

compound thereof, wherein R^4 is 5- to 6-membered heteroaryl having 1 or 2 ring heteroatoms selected from N, wherein phenyl or heteroaryl is unsubstituted or substituted with R^5 .

Embodiment 45 provides the compound of Formula (I) of any of applicable embodiments 1 to 44, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R^4 is phenyl, wherein the phenyl is unsubstituted or substituted with R^5 .

Embodiment 46 provides the compound of Formula (I) of any of applicable embodiments 1 to 45, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R^4 is pyridinyl, or pyrazolyl, wherein the pyridinyl, or pyrazolyl is unsubstituted or substituted with R^5 .

Embodiment 47 provides the compound of Formula (I) of any of applicable embodiments 1 to 46, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R^5 is selected from hydrogen, $-\text{CO}_2R^{5b}$, $\text{C}_1\text{-C}_6\text{alkyl}$, hydroxy $\text{C}_3\text{-C}_6\text{cycloalkyl}$, $\text{C}_1\text{-C}_6\text{alkoxyC}_1\text{-C}_6\text{alkyl}$, $-\text{CH}_2\text{CO}_2R^{5b}$, $-\text{C}(\text{O})\text{NHSO}_2\text{C}_1\text{-C}_4\text{alkyl}$, $-\text{SO}_2\text{NHC}(\text{O})\text{C}_1\text{-C}_4\text{alkyl}$, $-\text{SO}_2\text{C}_1\text{-C}_4\text{alkyl}$, cyano, hydroxy, halogen, $-\text{C}(\text{O})\text{N}(\text{R}^{5b})_2$ and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein alkyl and heteroaryl are unsubstituted or substituted with 1, 2, or 3 R^{5a} .

Embodiment 48 provides the compound of Formula (I) of any of applicable embodiments 1 to 47, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R^5 is selected from hydrogen, $-\text{CO}_2R^{5b}$, $\text{C}_1\text{-C}_6\text{alkyl}$, hydroxy $\text{C}_3\text{-C}_6\text{cycloalkyl}$, $-\text{CH}_2\text{CO}_2R^{5b}$, cyano, $-\text{C}(\text{O})\text{N}(\text{R}^{5b})_2$ and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein alkyl and heteroaryl are unsubstituted or substituted with 1, 2, or 3 R^{5a} .

Embodiment 49 provides the compound of Formula (I) of any of applicable embodiments 1 to 48, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R^5 is selected from hydrogen, $-\text{CO}_2R^{5b}$, $\text{C}_1\text{-C}_6\text{alkyl}$, hydroxy $\text{C}_3\text{-C}_6\text{cycloalkyl}$, $-\text{CH}_2\text{CO}_2R^{5b}$, cyano, $-\text{C}(\text{O})\text{N}(\text{R}^{5b})_2$ and 5-membered heteroaryl having 1-4 heteroatoms independently selected from N, wherein alkyl and heteroaryl are unsubstituted or substituted with 1 R^{5a} .

Embodiment 50 provides the compound of Formula (I) of any of applicable embodiments 1 to 49, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R^5 is selected from hydrogen, $-\text{CO}_2R^{5b}$, $\text{C}_1\text{-C}_6\text{alkyl}$, hydroxy $\text{C}_3\text{-C}_6\text{cycloalkyl}$, $-\text{CH}_2\text{CO}_2R^{5b}$, cyano, $-\text{C}(\text{O})\text{N}(\text{R}^{5b})_2$ and 5-membered heteroaryl having 1-3 heteroatoms independently selected from N, wherein alkyl and heteroaryl are unsubstituted or substituted with 1 R^{5a} .

Embodiment 51 provides the compound of Formula (I) of any of applicable embodiments 1 to 50, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled

compound thereof, wherein where applicable each R^{5a} is independently selected from fluoro, hydroxyl, and C₁-C₆alkyl that is unsubstituted or substituted with -CO₂H.

Embodiment 52 provides the compound of Formula (I) of any of applicable embodiments 1 to 51, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein where applicable each R^{5a} is hydroxyl.

Embodiment 53 provides the compound of Formula (I) of any of applicable embodiments 1 to 52, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein where applicable each R^{5b} is independently selected from hydrogen and C₁-C₅alkyl.

Embodiment 54 provides the compound of Formula (I) of any of applicable embodiments 1 to 53, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein where applicable each R^{5b} is independently selected from hydrogen.

Embodiment 55 provides the compound of Formula (I) of any of applicable embodiments 1 to 54, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R⁵ is selected from hydrogen, -CO₂H, C₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, hydroxyC₃-C₆alkyl, cyano, -CONH₂, pyrazolyl, triazolyl, and tetrazolyl, wherein the pyrazolyl, triazolyl, and tetrazolyl are unsubstituted or substituted with 1 C₁-C₆alkyl.

Embodiment 56 provides the compound of Formula (I) of any of applicable embodiments 1 to 55, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein each R⁶ is independently selected from hydrogen, halogen, hydroxy, C₃-C₆cycloalkylC₁-C₄alkylamino, haloC₃-C₆cycloalkylC₁-C₄alkylamino, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkoxy, haloC₁-C₆alkoxy, C₃-C₆cycloalkoxy, haloC₃-C₆cycloalkoxy, and 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, wherein the C₁-C₆alkyl is unsubstituted or substituted with 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, wherein the 4- to 6-membered heterocyclyl is unsubstituted or substituted with 1, 2, or 3 halogen.

Embodiment 57 provides the compound of Formula (I) of any of applicable embodiments 1 to 56, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein each R⁶ is independently selected from C₁-C₆alkyl, C₃-C₆cycloalkylC₁-C₄alkylamino, haloC₃-C₆cycloalkylC₁-C₄alkylamino, haloC₁-C₆alkyl, C₃-C₆cycloalkoxy, haloC₃-C₆cycloalkoxy, and 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, wherein the C₁-C₆alkyl is unsubstituted or substituted with 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, wherein the 4- to 6-membered heterocyclyl is unsubstituted or substituted with 1, 2, or 3 halogen.

Embodiment 58 the compound of Formula (I) of any of applicable embodiments 1 to 57, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein each R⁶ is independently selected from hydrogen, halogen, hydroxy, C₃-C₆cycloalkylC₁-C₄alkylamino, haloC₃-C₆cycloalkylC₁-C₄alkylamino, C₁-C₆alkyl, haloC₁-C₆alkyl,

hydroxyC₁-C₆alkyl, C₁-C₆alkoxy, haloC₁-C₆alkoxy, C₃-C₆cycloalkoxy, haloC₃-C₆cycloalkoxy, and 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, and wherein the C₁-C₆alkyl is unsubstituted or substituted with 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, wherein the 4- to 6-membered heterocyclyl is unsubstituted or substituted with 1, 2, or 3 halogen.

Embodiment 59 provides the compound of Formula (I) of any of applicable embodiments 1 to 58, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein each R⁶ is independently selected from hydrogen, halogen, hydroxy, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkoxy, and haloC₁-C₆alkoxy.

Embodiment 60 provides the compound of Formula (I) of any of applicable embodiments 1 to 59, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic carbocycle having 3 to 6 ring atoms, wherein the spirocyclic carbocycle is unsubstituted or substituted with 1 or 2 substituents selected from halogen, C₁-C₆alkyl, and C₁-C₆alkoxy.

Embodiment 61 provides the compound of Formula (I) of any of applicable embodiments 1 to 60, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic carbocycle having 3 to 4 ring atoms, wherein the spirocyclic carbocycle is unsubstituted or substituted with 1 or 2 substituents selected from halogen.

Embodiment 62 provides the compound of Formula (I) of any of applicable embodiments 1 to 61, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 or 2 ring heteroatoms independently selected from N, O, and S(O)_q, wherein the spirocyclic heterocycle is unsubstituted or substituted with 1 or 2 halogen, C₁-C₆alkyl, haloC₁-C₆alkyl, C₃-C₆cycloalkyl, or haloC₃-C₆cycloalkyl; wherein q is 0, 1, or 2.

Embodiment 63 provides the compound of Formula (I) of any of applicable embodiments 1 to 62, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 or 2 ring heteroatoms independently selected from N and O.

Embodiment 64 provides the compound of Formula (I) of any of applicable embodiments 1 to 63, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 or 2 ring heteroatoms independently selected from N and O, wherein the spirocyclic heterocycle has 3 to 6 ring atoms.

Embodiment 65 provides the compound of Formula (I) of any of applicable embodiments 1 to 64, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled

compound thereof, wherein two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 ring heteroatom selected from O.

Embodiment 66 provides the compound of Formula (I) of any of applicable embodiments 1 to 65, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 ring heteroatom selected from O, wherein the spirocyclic heterocycle has 5 ring atoms.

Embodiment 67 provides the compound of Formula (I) of any of applicable applicable embodiments 1 to 66, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R⁷ is C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₂-C₆alkyl, C₃-C₆cycloalkyl, C₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkyl, C₁-C₆alkoxyC₁-C₆alkyl, haloC₁-C₆alkoxyC₁-C₆alkyl, -COR^{7a}, aryl, 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N, O, and S(O)_q, or 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein C₁-C₆alkyl is unsubstituted or substituted with 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N, O, and S(O)_q, wherein the 4- to 6-membered heterocyclyl is unsubstituted or substituted with 1, 2, or 3 halogen, further wherein the aryl or heteroaryl is unsubstituted or substituted with halo, C₁-C₆alkyl, haloC₁-C₆alkyl, C₃-C₅cycloalkyl, haloC₃-C₅cycloalkyl.

Embodiment 68 provides the compound of Formula (I) of any of applicable applicable embodiments 1 to 67, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R⁷ is C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₂-C₆alkyl, C₃-C₆cycloalkyl, C₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkyl, haloC₁-C₆alkoxyC₁-C₆alkyl, -COR^{7a}, 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, or 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein the 4- to 6-membered heterocyclyl is unsubstituted or substituted with 1, 2, or 3 halogen, further wherein the heteroaryl is unsubstituted or substituted with halo, C₁-C₆alkyl, haloC₁-C₆alkyl, C₃-C₅cycloalkyl, haloC₃-C₅cycloalkyl.

Embodiment 69 provides the compound of Formula (I) of any of applicable embodiments 1 to 68, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R⁷ is C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₂-C₆alkyl, haloC₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkyl, haloC₁-C₆alkoxyC₁-C₆alkyl, -COR^{7a}, 4- to 6-membered heterocyclyl having 1 heteroatoms selected from O, or 5- to 6-membered heteroaryl having 1 heteroatoms independently selected from O, wherein the 4- to 6-membered heterocyclyl is unsubstituted or substituted with 1, 2, or 3 halogen, further wherein the heteroaryl is unsubstituted or substituted with halo, C₁-C₆alkyl, haloC₁-C₆alkyl, C₃-C₅cycloalkyl, haloC₃-C₅cycloalkyl.

Embodiment 70 provides the compound of Formula (I) of any of applicable embodiments 1 to 69, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R^7 is C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, hydroxy C_2 - C_6 alkyl, halo C_3 - C_6 cycloalkyl C_1 - C_3 alkyl, halo C_3 - C_6 cycloalkyl, halo C_1 - C_6 alkoxy C_1 - C_6 alkyl, $-COR^{7a}$, 4- to 6-membered heterocyclyl having 1 heteroatoms selected from O, or 5-membered heteroaryl having 1 heteroatom selected from O.

Embodiment 71 provides the compound of Formula (I) of any of applicable embodiments 1 to 70, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R^{7a} is C_1 - C_6 alkyl.

Embodiment 72 provides the compound of Formula (I) of any of applicable embodiments 1 to 71, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein p is 0.

Embodiment 73 provides the compound of Formula (I) of any of applicable embodiments 1 to 72, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R^9 is H.

Embodiment 74 provides the compound of Formula (I) of any of applicable embodiments 1 to 73, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein m is 1, or 2.

Embodiment 75 provides the compound of Formula (I) of any of applicable embodiments 1 to 74, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein n is 1, 2, or 3.

Embodiment 76 provides the compound of Formula (I) of any of applicable embodiments 1 to 75, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein:

W is $C(R^6)_2$, or NR^7 ;

R is hydrogen;

R^1 is hydrogen, halogen, hydroxy, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_6 cycloalkyl, C_1 - C_6 alkoxy, halo C_1 - C_6 alkyl, halo C_3 - C_6 cycloalkyl, halo C_1 - C_6 alkoxy, hydroxy C_1 - C_6 alkyl, hydroxy C_3 - C_6 cycloalkyl, amino C_1 - C_6 alkyl, C_1 - C_6 alkoxy C_1 - C_6 alkyl, C_1 - C_6 alkoxy C_1 - C_6 alkoxy, or C_3 - C_6 cycloalkyl C_1 - C_6 alkoxy;

R^2 is C_1 - C_3 alkyl, C_3 cycloalkyl, C_1 - C_3 alkoxy, hydroxy C_1 - C_6 alkyl, or halogen, wherein the C_1 - C_3 alkyl, C_3 cycloalkyl, or C_1 - C_3 alkoxy are unsubstituted or substituted with 1, 2, or 3 halogen substituents;

R^3 is hydrogen, halogen, or cyano;

R^4 is phenyl, naphthyl or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N, O, and S, wherein phenyl or heteroaryl is unsubstituted or substituted with R^5 ;

R^5 is selected from hydrogen, $-\text{CO}_2R^{5b}$, $\text{C}_1\text{-C}_6\text{alkyl}$, hydroxy $\text{C}_3\text{-C}_6\text{cycloalkyl}$, $\text{C}_1\text{-C}_6\text{alkoxyC}_1\text{-C}_6\text{alkyl}$, $-\text{CH}_2\text{CO}_2R^{5b}$, $-\text{C}(\text{O})\text{NHSO}_2\text{C}_1\text{-C}_4\text{alkyl}$, $-\text{SO}_2\text{NHC}(\text{O})\text{C}_1\text{-C}_4\text{alkyl}$, $-\text{SO}_2\text{C}_1\text{-C}_4\text{alkyl}$, cyano, hydroxy, halogen, $-\text{C}(\text{O})\text{N}(\text{R}^{5b})_2$ and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein alkyl and heteroaryl are unsubstituted or substituted with 1, 2, or 3 R^{5a} ;

each R^{5a} is independently selected from fluoro, hydroxyl, and $\text{C}_1\text{-C}_6\text{alkyl}$ that is unsubstituted or substituted with $-\text{CO}_2\text{H}$;

each R^{5b} is independently selected from hydrogen and $\text{C}_1\text{-C}_5\text{alkyl}$;

each R^6 is independently selected from hydrogen, halogen, hydroxy, amino, mono- and di- $\text{C}_1\text{-C}_4\text{alkylamino}$, $\text{C}_3\text{-C}_6\text{cycloalkylC}_1\text{-C}_4\text{alkylamino}$, halo $\text{C}_3\text{-C}_6\text{cycloalkylC}_1\text{-C}_4\text{alkylamino}$, $\text{C}_1\text{-C}_6\text{alkyl}$, halo $\text{C}_1\text{-C}_6\text{alkyl}$, hydroxy $\text{C}_1\text{-C}_6\text{alkyl}$, cyano $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_1\text{-C}_6\text{alkoxy}$, halo $\text{C}_1\text{-C}_6\text{alkoxy}$, $\text{C}_3\text{-C}_6\text{cycloalkoxy}$, halo $\text{C}_3\text{-C}_6\text{cycloalkoxy}$, and 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, wherein the 4- to 6-membered heterocyclyl is unsubstituted or substituted with 1, 2, or 3 halogen, and wherein the $\text{C}_1\text{-C}_6\text{alkyl}$ is unsubstituted or substituted with 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, wherein each 4- to 6-membered heterocyclyl is independently unsubstituted or substituted with 1, 2, or 3 halogen;

or two R^6 in combination with the carbon atom to which they are attached form a spirocyclic carbocycle having 3 to 6 ring atoms, wherein the spirocyclic carbocycle is unsubstituted or substituted with 1 or 2 substituents selected from halogen, $\text{C}_1\text{-C}_6\text{alkyl}$, and $\text{C}_1\text{-C}_6\text{alkoxy}$;

or two R^6 in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 or 2 ring heteroatoms independently selected from N, O, and $\text{S}(\text{O})_q$, wherein the spirocyclic heterocycle is unsubstituted or substituted with 1 or 2 halogen, $\text{C}_1\text{-C}_6\text{alkyl}$, halo $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_3\text{-C}_6\text{cycloalkyl}$, or halo $\text{C}_3\text{-C}_6\text{cycloalkyl}$;

q is 0, 1, or 2;

R^7 is hydrogen, $\text{C}_1\text{-C}_6\text{alkyl}$, halo $\text{C}_1\text{-C}_6\text{alkyl}$, hydroxy $\text{C}_2\text{-C}_6\text{alkyl}$, $\text{C}_3\text{-C}_6\text{cycloalkyl}$, $\text{C}_3\text{-C}_6\text{cycloalkylC}_1\text{-C}_3\text{alkyl}$, halo $\text{C}_3\text{-C}_6\text{cycloalkylC}_1\text{-C}_3\text{alkyl}$, halo $\text{C}_3\text{-C}_6\text{cycloalkyl}$, $\text{C}_1\text{-C}_6\text{alkoxyC}_1\text{-C}_6\text{alkyl}$, halo $\text{C}_1\text{-C}_6\text{alkoxyC}_1\text{-C}_6\text{alkyl}$, $-\text{COR}^{7a}$, aryl, 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N, O, and $\text{S}(\text{O})_q$, or 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein $\text{C}_1\text{-C}_6\text{alkyl}$ is unsubstituted or substituted with 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N, O, and $\text{S}(\text{O})_q$, wherein the 4- to 6-membered heterocyclyl is unsubstituted or substituted with 1, 2, or 3 halogen, further wherein the aryl or heteroaryl is unsubstituted or substituted with halo, $\text{C}_1\text{-C}_6\text{alkyl}$, halo $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_3\text{-C}_5\text{cycloalkyl}$, halo $\text{C}_3\text{-C}_5\text{cycloalkyl}$;

10 R^{7a} is hydrogen or $\text{C}_1\text{-C}_6\text{alkyl}$;

R^8 is H;

m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3;

p is 0.

Embodiment 77 provides the compound of Formula (I) of any of applicable embodiments 1 to 76, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein:

W is NR⁷;

R is hydrogen; or hydroxyC₃-C₆cycloalkyl;

R¹ is hydrogen, halogen, hydroxy, C₁-C₆alkyl, C₃-C₆cycloalkyl, haloC₁-C₆alkyl, haloC₃-C₆cycloalkyl, haloC₁-C₆alkoxy, hydroxyC₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl;

preferably hydrogen, halogen, hydroxy, C₁-C₆alkyl, C₃-C₆cycloalkyl, haloC₁-C₆alkyl;

more preferably hydrogen, halogen, hydroxy, C₁-C₆alkyl, C₃-C₆cycloalkyl, or haloC₁-C₆alkyl;

more preferably hydrogen, halogen, C₁-C₆alkyl, C₃-C₆cycloalkyl, or haloC₁-C₆alkyl;

R² is C₁-C₃alkyl, C₃cycloalkyl, C₁-C₃alkoxy, hydroxyC₁-C₆alkyl, or halogen, wherein the C₁-C₃alkyl, C₃cycloalkyl, or C₁-C₃alkoxy are unsubstituted or substituted with 1, 2, or 3 halogen substituents;

preferably C₁-C₃alkyl, C₃cycloalkyl, C₁-C₃alkoxy, hydroxyC₁-C₆alkyl, or halogen;

more preferably C₁-C₃alkyl, or halogen;

R³ is hydrogen;

R⁴ is phenyl, or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N, and O, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵;

preferably phenyl, or 5- to 6-membered heteroaryl having 1 or 2 ring heteroatoms independently selected from N, and O, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵;

more preferably phenyl, or 5- to 6-membered heteroaryl having 1 or 2 ring heteroatoms independently selected from N, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵;

R⁵ is selected from hydrogen, -CO₂R^{5b}, C₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, -CH₂CO₂R^{5b}, cyano, -C(O)N(R^{5b})₂ and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein alkyl and heteroaryl are unsubstituted or substituted with 1, 2, or 3 R^{5a};

preferably hydrogen, -CO₂R^{5b}, C₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, -CH₂CO₂R^{5b}, cyano, -C(O)N(R^{5b})₂ and 5-membered heteroaryl having 1-4 heteroatoms independently selected from N, wherein alkyl and heteroaryl are unsubstituted or substituted with 1 R^{5a};

more preferably hydrogen, -CO₂R^{5b}, C₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, -CH₂CO₂R^{5b}, cyano, -C(O)N(R^{5b})₂ and 5-membered heteroaryl having 1-3 heteroatoms independently selected from N, wherein alkyl and heteroaryl are unsubstituted or substituted with 1 R^{5a};

each R^{5a} is independently selected from fluoro, hydroxyl, and C₁-C₆alkyl; preferably hydroxyl;

each R^{5b} is independently selected from hydrogen;

R⁵ is preferably selected from hydrogen, -CO₂H, C₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, hydroxyC₃-C₆alkyl, cyano, -CONH₂, pyrazolyl, triazolyl, and tetrazolyl, wherein the pyrazolyl, triazolyl, and tetrazolyl are unsubstituted or substituted with 1 C₁-C₆alkyl;

R⁷ is hydrogen, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₂-C₆alkyl, C₃-C₆cycloalkyl, C₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkyl, C₁-C₆alkoxyC₁-C₆alkyl, haloC₁-C₆alkoxyC₁-C₆alkyl, -COR^{7a}, aryl, 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N, O, and S(O)_q, or 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein C₁-C₆alkyl is unsubstituted or substituted with 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N, O, and S(O)_q, wherein the 4- to 6-membered heterocyclyl is unsubstituted or substituted with 1, 2, or 3 halogen, further wherein the aryl or heteroaryl is unsubstituted or substituted with halo, C₁-C₆alkyl, haloC₁-C₆alkyl, C₃-C₅cycloalkyl, haloC₃-C₅cycloalkyl;

preferably C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₂-C₆alkyl, C₃-C₆cycloalkyl, C₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkyl, haloC₁-C₆alkoxyC₁-C₆alkyl, -COR^{7a}, 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, or 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein the 4- to 6-membered heterocyclyl is unsubstituted or substituted with 1, 2, or 3 halogen, further wherein the heteroaryl is unsubstituted or substituted with halo, C₁-C₆alkyl, haloC₁-C₆alkyl, C₃-C₅cycloalkyl, haloC₃-C₅cycloalkyl;

more preferably C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₂-C₆alkyl, haloC₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkyl, haloC₁-C₆alkoxyC₁-C₆alkyl, -COR^{7a}, 4- to 6-membered heterocyclyl having 1 heteroatoms independently selected from O, or 5- to 6-membered heteroaryl having 1 heteroatoms independently selected from O;

R^{7a} is C₁-C₆alkyl;

each R⁸ is independently selected from hydrogen and halogen;

R⁹ is H, or D; preferably H;

m is 1, 2, or 3; preferably 1 or 2;

n is 1, 2, or 3; and

p is 0, 1, 2, or 3; preferably 0.

Embodiment 78 provides the compound of Formula (I) of any of applicable embodiments 1 to 77, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein:

W is C(R⁶)₂;

R is hydrogen;

R¹ is hydrogen, halogen, hydroxy, C₁-C₆alkyl, C₃-C₆cycloalkyl, haloC₁-C₆alkyl, haloC₃-C₆cycloalkyl, haloC₁-C₆alkoxy, hydroxyC₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl;

preferably hydrogen, halogen, hydroxy, C₁-C₆alkyl, C₃-C₆cycloalkyl, haloC₁-C₆alkyl;

more preferably hydrogen, halogen, hydroxy, C₁-C₆alkyl, C₃-C₆cycloalkyl, and haloC₁-C₆alkyl;

more preferably hydrogen, halogen, C₁-C₆alkyl, C₃-C₆cycloalkyl;

R² is C₁-C₃alkyl, C₃cycloalkyl, C₁-C₃alkoxy, hydroxyC₁-C₆alkyl, or halogen, wherein the C₁-C₃alkyl, C₃cycloalkyl, or C₁-C₃alkoxy are unsubstituted or substituted with 1, 2, or 3 halogen substituents;

preferably C₁-C₃alkyl, C₃cycloalkyl, C₁-C₃alkoxy, hydroxyC₁-C₆alkyl, or halogen;

more preferably C₁-C₃alkyl, or halogen;

R³ is hydrogen;

R⁴ is phenyl, or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N, and O, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵;

preferably phenyl, or 5- to 6-membered heteroaryl having 1 or 2 ring heteroatoms independently selected from N, and O, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵;

more preferably phenyl, or 5- to 6-membered heteroaryl having 1 or 2 ring heteroatoms independently selected from N, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵;

R⁵ is selected from hydrogen, -CO₂R^{5b}, C₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, -CH₂CO₂R^{5b}, cyano, -C(O)N(R^{5b})₂ and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein alkyl and heteroaryl are unsubstituted or substituted with 1, 2, or 3 R^{5a};

preferably hydrogen, -CO₂R^{5b}, C₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, -CH₂CO₂R^{5b}, cyano, -C(O)N(R^{5b})₂ and 5-membered heteroaryl having 1-4 heteroatoms independently selected from N, wherein alkyl and heteroaryl are unsubstituted or substituted with 1 R^{5a};

more preferably hydrogen, -CO₂R^{5b}, C₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, -CH₂CO₂R^{5b}, cyano, -C(O)N(R^{5b})₂ and 5-membered heteroaryl having 1-3 heteroatoms independently selected from N, wherein alkyl and heteroaryl are unsubstituted or substituted with 1 R^{5a};

each R^{5a} is independently selected from fluoro, hydroxyl, and C₁-C₆alkyl; preferably hydroxyl;

each R^{5b} is independently selected from hydrogen;

R⁵ is preferably selected from hydrogen, -CO₂H, C₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, hydroxyC₃-C₆alkyl, cyano, -CONH₂, pyrazolyl, triazolyl, and tetrazolyl, wherein the pyrazolyl, triazolyl, and tetrazolyl are unsubstituted or substituted with 1 C₁-C₆alkyl;

each R⁶ is independently selected from hydrogen, halogen, hydroxy, C₃-C₆cycloalkylC₁-C₄alkylamino, haloC₃-C₆cycloalkylC₁-C₄alkylamino, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkoxy, haloC₁-C₆alkoxy, C₃-C₆cycloalkoxy, haloC₃-C₆cycloalkoxy, and 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, and wherein the C₁-C₆alkyl is unsubstituted or substituted with 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, wherein each 4- to 6-membered heterocyclyl is independently unsubstituted or substituted with 1, 2, or 3 halogen;

preferably from hydrogen, halogen, hydroxy, C₁-C₆alkyl, haloC₁-C₆alkyl C₁-C₆alkoxy, and haloC₁-C₆alkoxy;

preferably from C₁-C₆alkyl, C₃-C₆cycloalkylC₁-C₄alkylamino, haloC₃-C₆cycloalkylC₁-C₄alkylamino, haloC₁-C₆alkyl, C₃-C₆cycloalkoxy, haloC₃-C₆cycloalkoxy, and 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, wherein the C₁-C₆alkyl is unsubstituted or substituted with 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, wherein each 4- to 6-membered heterocyclyl is independently unsubstituted or substituted with 1, 2, or 3 halogen;

or two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic carbocycle having 3 to 6 ring atoms, preferably 3 to 4 ring atoms, wherein the spirocyclic carbocycle is unsubstituted or substituted with 1 or 2 substituents selected from halogen;

or two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 or 2 ring heteroatoms independently selected from N and O;

preferably two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 or 2 ring heteroatoms independently selected from N and O, wherein the spirocyclic heterocycle has 3 to 6 ring atoms;

preferably two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 ring heteroatom selected from O;

preferably two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 ring heteroatom selected from O, wherein the spirocyclic heterocycle has 5 ring atoms;

each R⁸ is independently selected from hydrogen and halogen;

R⁹ is H, or D; preferably H;

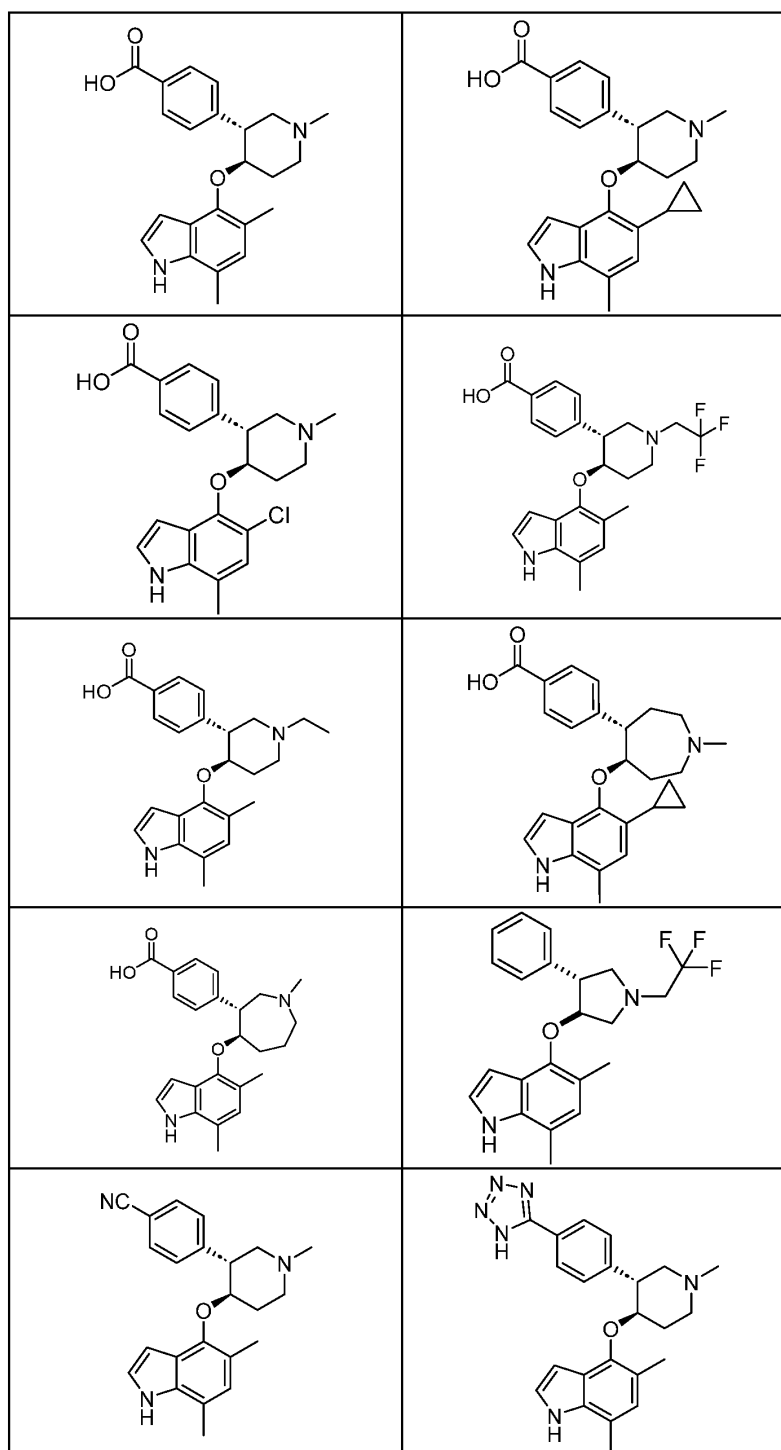
m is 1, 2, or 3; preferably 1 or 2;

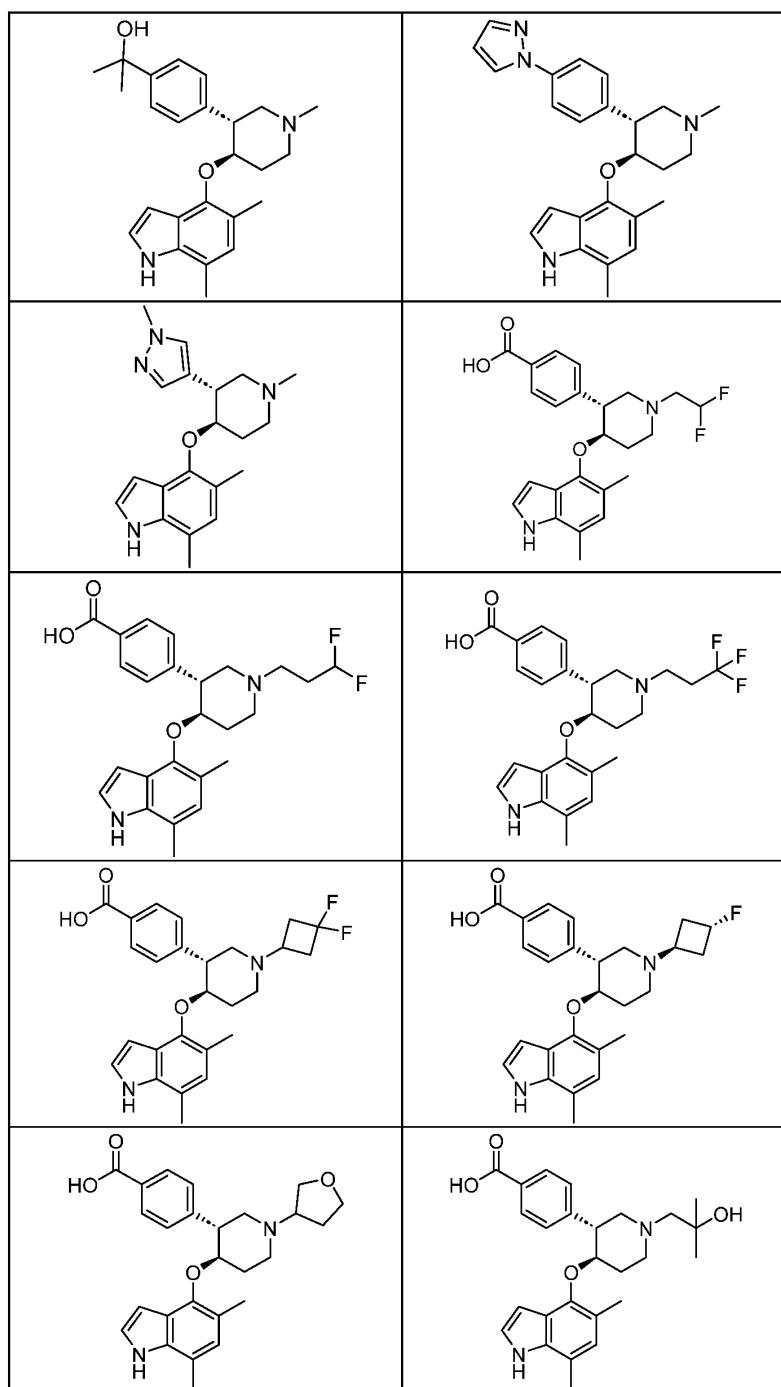
n is 1, 2, or 3; and

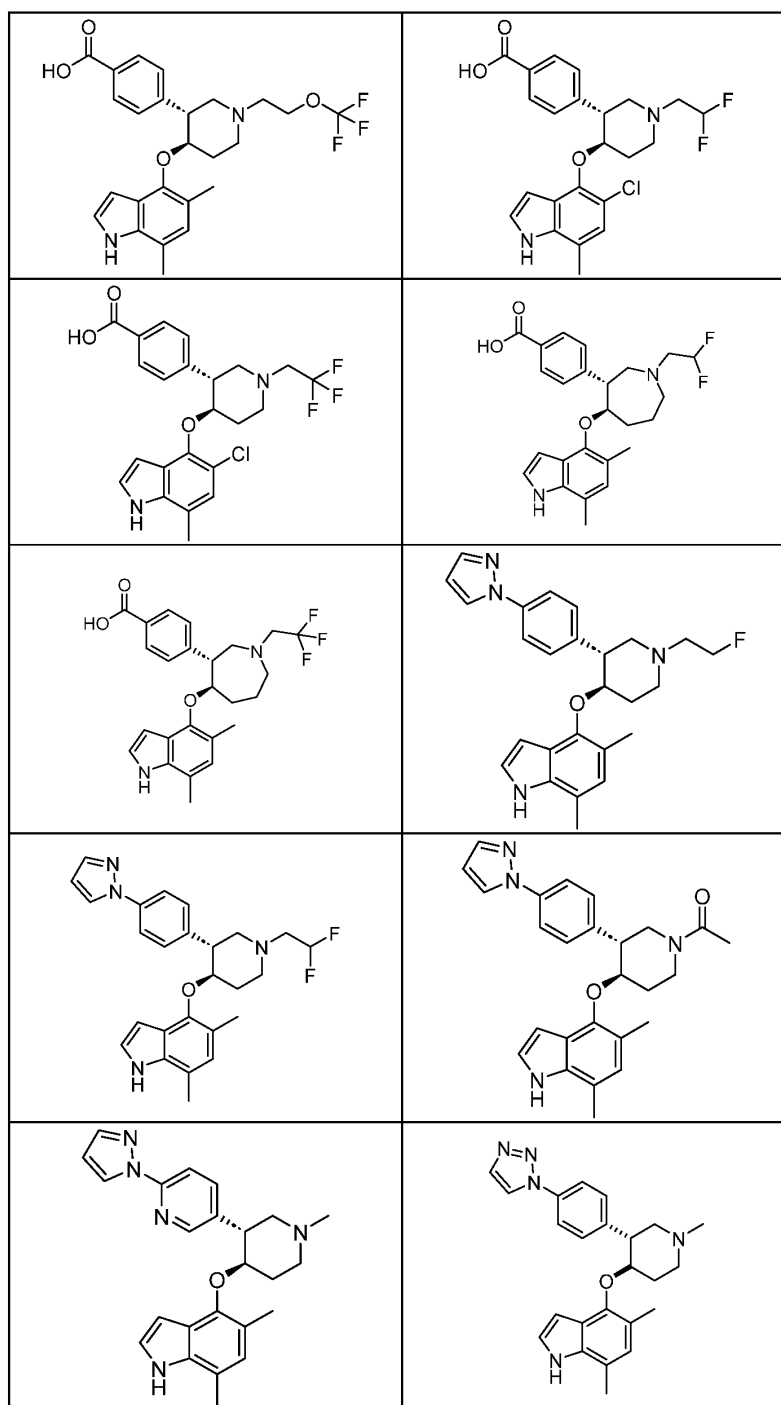
p is 0, 1, 2, or 3; preferably 0.

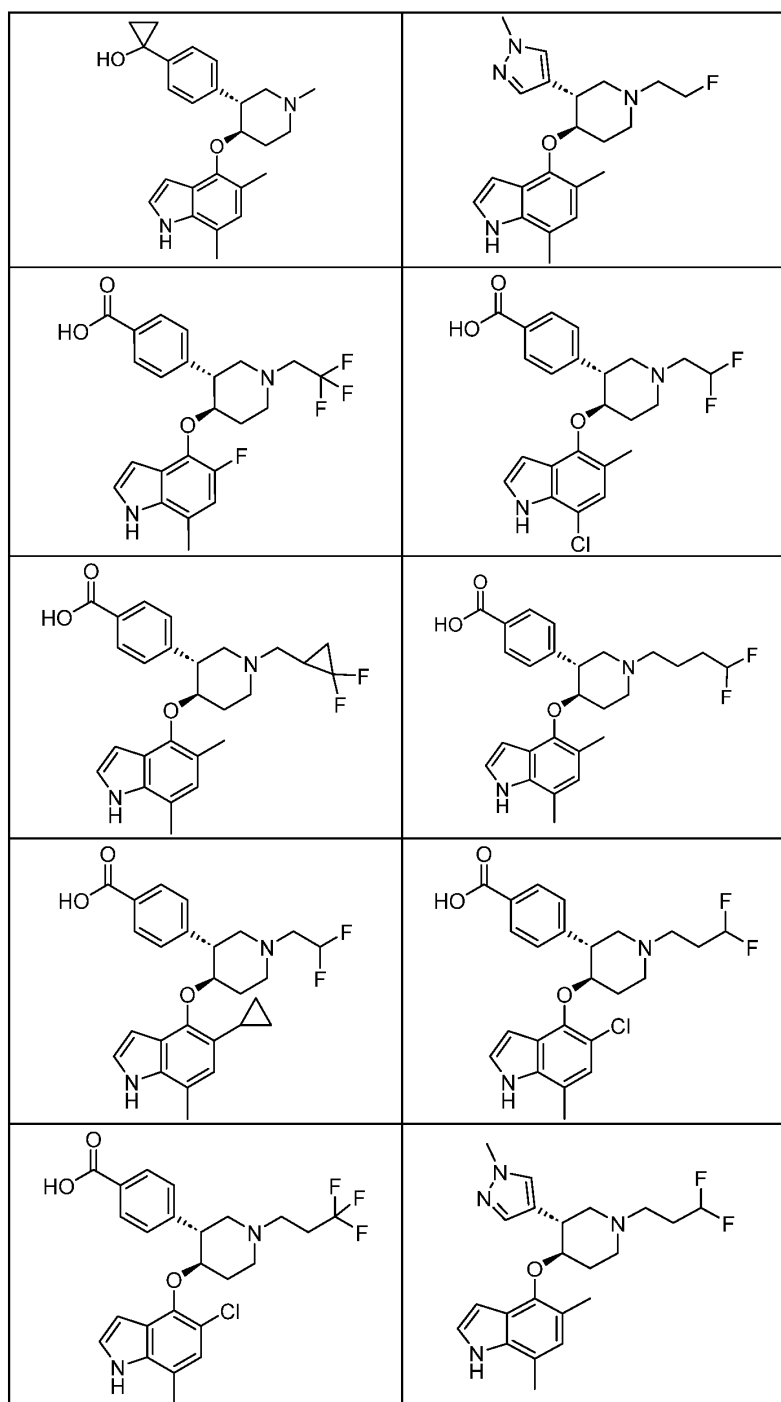
In an embodiment, the invention provides the compound of Formula (I) selected from the compounds in **Table 1**.

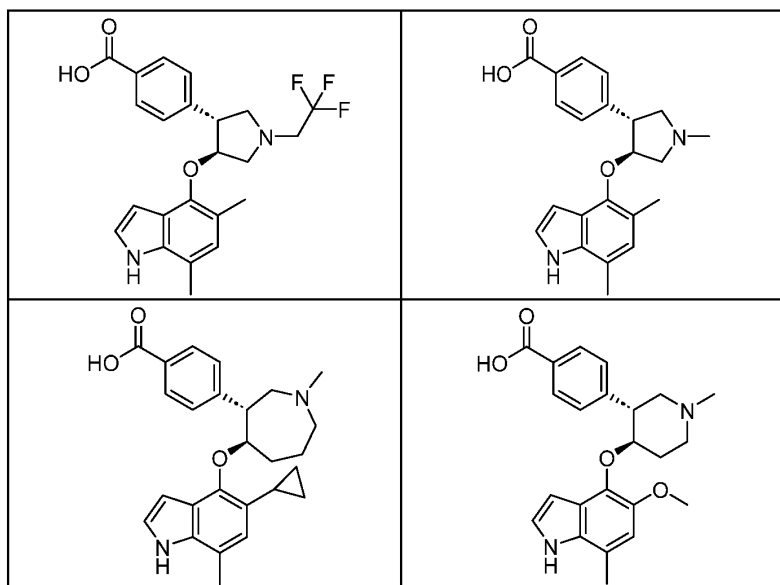
Table 1







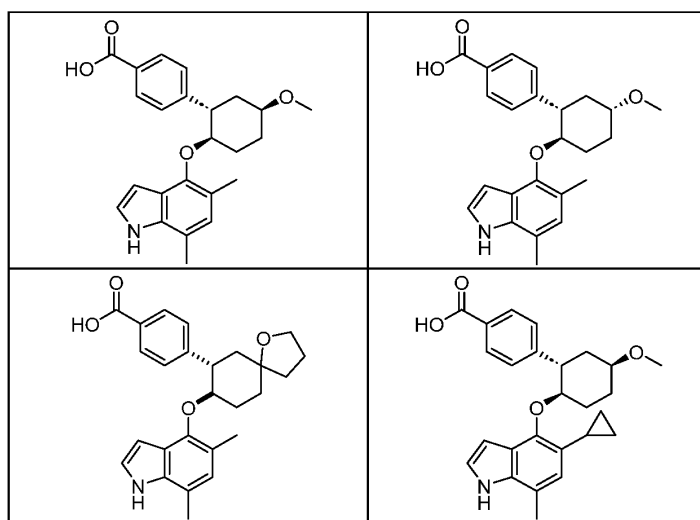


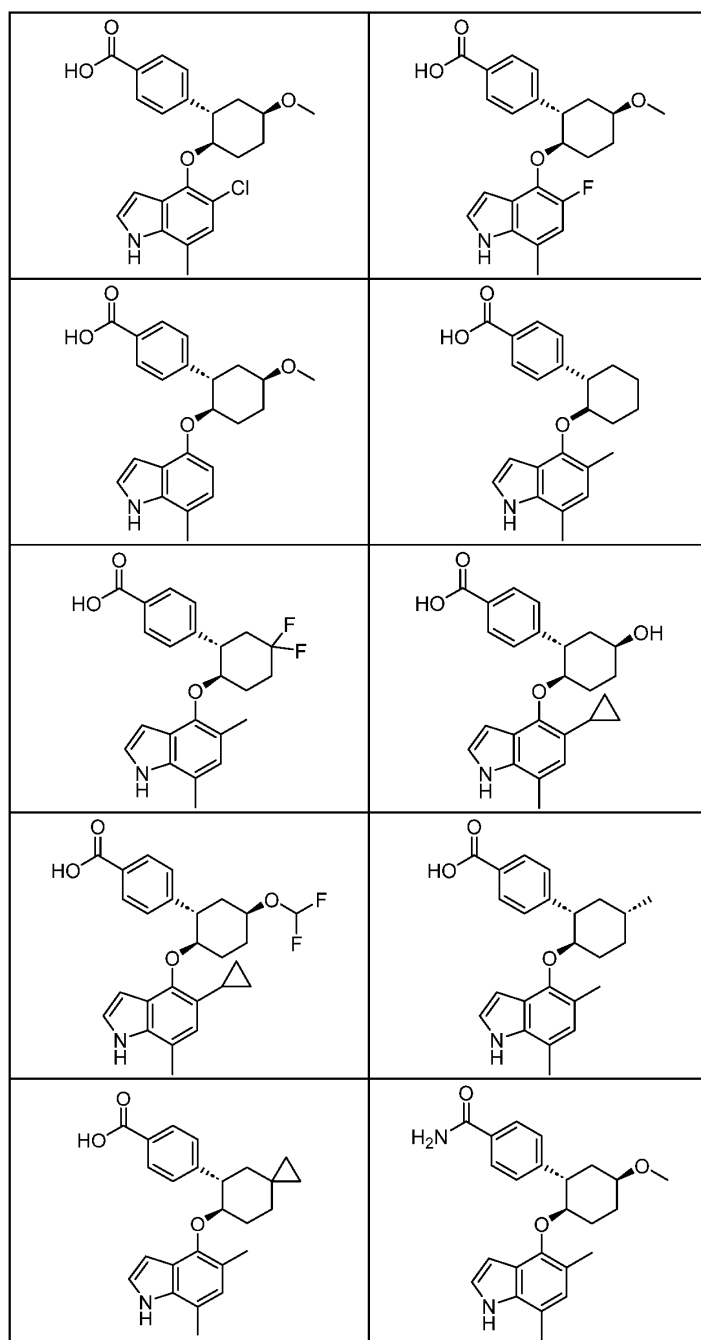


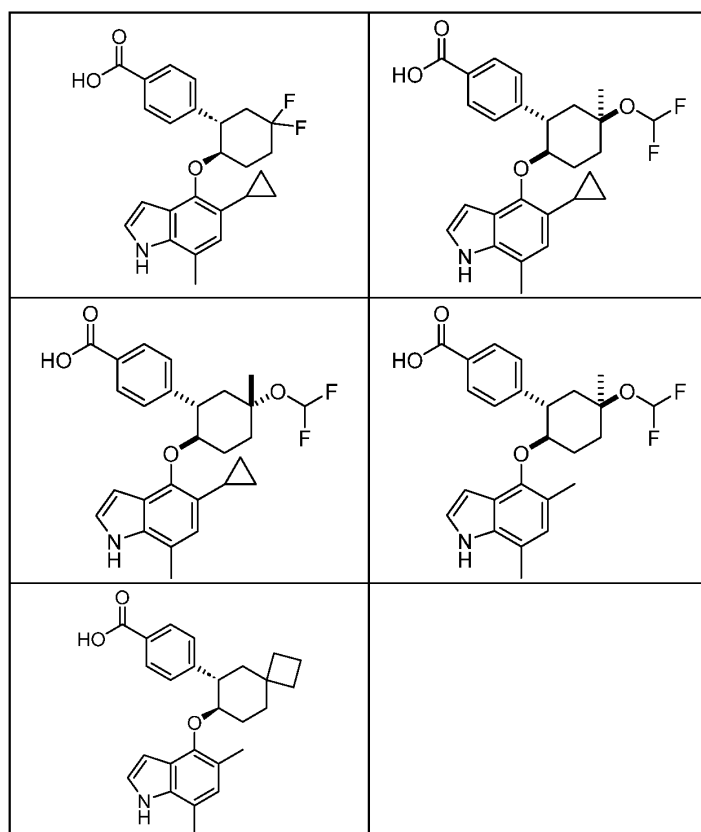
or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

In an embodiment, the invention provides the compound of Formula (I) selected from the compounds in **Table 2**.

Table 2







or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

In an embodiment, the compound of Formula (I) is selected from the group consisting of:

- 4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid;
- 4-(4-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid;
- 4-(4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid;
- 4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)piperidin-3-yl)benzoic acid;
- 4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-ethylpiperidin-3-yl)benzoic acid;
- 5
- 4-(5-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-1-methylazepan-4-yl)benzoic acid;
- 4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylazepan-3-yl)benzoic acid;
- 5,7-dimethyl-4-((4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)oxy)-1*H*-indole;
- 4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzonitrile;
- 4-((3-(4-(1*H*-tetrazol-5-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
- 10
- 2-(4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)phenyl)propan-2-ol;
- 4-((3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
- 5,7-dimethyl-4-((1-methyl-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-1*H*-indole;
- 4-(1-(2,2-difluoroethyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid;

- 4-(1-(3,3-difluoropropyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid;
4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(3,3,3-trifluoropropyl)piperidin-3-yl)benzoic acid;
4-(1-(3,3-difluorocyclobutyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic
acid;
5 4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(3-fluorocyclobutyl)piperidin-3-yl)benzoic acid;
4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(tetrahydrofuran-3-yl)piperidin-3-yl)benzoic acid;
4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2-hydroxy-2-methylpropyl)piperidin-3-yl)benzoic
acid;
4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2-(trifluoromethoxy)ethyl)piperidin-3-yl)benzoic
10 acid;
4-(4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-(2,2-difluoroethyl)piperidin-3-yl)benzoic
acid;
4-(4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)piperidin-3-yl)benzoic
acid;
15 4-(1-(2,2-difluoroethyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)azepan-3-yl)benzoic acid;
4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)azepan-3-yl)benzoic acid;
4-((3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-(2-fluoroethyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-
indole;
4-((3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-(2,2-difluoroethyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-
20 indole;
1-(3-(4-(1*H*-pyrazol-1-yl)phenyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-1-yl)ethan-
1-one;
4-((3-(6-(1*H*-pyrazol-1-yl)pyridin-3-yl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
4-((3-(4-(1*H*-1,2,3-triazol-1-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
25 1-(4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)phenyl)cyclopropan-1-ol;
4-((1-(2-fluoroethyl)-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-
indole;
4-(4-((5-fluoro-7-methyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)piperidin-3-yl)benzoic
acid;
30 4-(4-((7-chloro-5-methyl-1*H*-indol-4-yl)oxy)-1-(2,2-difluoroethyl)piperidin-3-yl)benzoic
acid;
4-(1-((2,2-difluorocyclopropyl)methyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-
yl)benzoic acid;
4-(1-(4,4-difluorobutyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid;
35 4-(4-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-1-(2,2-difluoroethyl)piperidin-3-
yl)benzoic acid;
4-(4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-(3,3-difluoropropyl)piperidin-3-yl)benzoic
acid;

4-(4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-(3,3,3-trifluoropropyl)piperidin-3-yl)benzoic acid;

4-((1-(3,3-difluoropropyl)-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;

5 4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)benzoic acid;

4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpyrrolidin-3-yl)benzoic acid;

4-(4-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-1-methylazepan-3-yl)benzoic acid;

4-(4-((5-methoxy-7-methyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid,

or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

In an embodiment, the compound of Formula (I) is selected from the group consisting of:

4-(2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;

4-(8-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-oxaspiro[4.5]decan-7-yl)benzoic acid;

10 4-(2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;

4-(2-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;

4-(2-((5-fluoro-7-methyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;

4-(5-methoxy-2-((7-methyl-1*H*-indol-4-yl)oxy)cyclohexyl)benzoic acid;

4-(2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)cyclohexyl)benzoic acid;

15 4-(2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5,5-difluorocyclohexyl)benzoic acid;

4-(2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-hydroxycyclohexyl)benzoic acid;

4-(2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-(difluoromethoxy)cyclohexyl)benzoic

acid;

4-(2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methylcyclohexyl)benzoic acid;

20 4-(6-((5,7-dimethyl-1*H*-indol-4-yl)oxy)spiro[2.5]octan-5-yl)benzoic acid;

4-(2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzamide;

4-(2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5,5-difluorocyclohexyl)benzoic acid;

4-(2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-(difluoromethoxy)-5-

methylcyclohexyl)benzoic acid;

25 4-(5-(difluoromethoxy)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methylcyclohexyl)benzoic

acid; and

4-(7-((5,7-dimethyl-1*H*-indol-4-yl)oxy)spiro[3.5]nonan-6-yl)benzoic acid,

or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

In another embodiment, the compound of Formula (I) is selected from the group consisting of:

4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid;

30 4-((3*S*,4*S*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid;

4-((3*R*,4*S*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid;

- 4-((3*S*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid;
4-((3*R*,4*R*)-4-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic
acid;4-((3*R*,4*R*)-4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid;
4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)piperidin-3-
5 yl)benzoic acid;
4-((3*S*,4*S*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)piperidin-3-
yl)benzoic acid ;
4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-ethylpiperidin-3-yl)benzoic acid;
4-((4*S*,5*R*)-5-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-1-methylazepan-4-yl)benzoic
10 acid;
4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylazepan-3-yl)benzoic acid;
racemic 5,7-dimethyl-4-(((3*S**,4*R**)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)oxy)-
1*H*-indole;
5,7-dimethyl-4-(((3*S*,4*R*)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)oxy)-1*H*-indole;
15 5,7-dimethyl-4-(((3*R*,4*S*)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)oxy)-1*H*-indole;
4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzonitrile;
4-(((3*R*,4*R*)-3-(4-(1*H*-tetrazol-5-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-
indole;
2-(4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)phenyl)propan-
20 2-ol;
4-(((3*R*,4*R*)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-
indole;
5,7-dimethyl-4-(((3*R*,4*R*)-1-methyl-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-1*H*-
indole;
25 4-((3*R*,4*R*)-1-(2,2-difluoroethyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic
acid;
4-((3*R*,4*R*)-1-(3,3-difluoropropyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-
yl)benzoic acid;
4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(3,3,3-trifluoropropyl)piperidin-3-
30 yl)benzoic acid;
4-((3*R*,4*R*)-1-(3,3-difluorocyclobutyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-
yl)benzoic acid;
4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-((1*r*,3*R*)-3-fluorocyclobutyl)piperidin-3-
yl)benzoic acid;
35 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(tetrahydrofuran-3-yl)piperidin-3-
yl)benzoic acid;
4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2-hydroxy-2-methylpropyl)piperidin-3-
yl)benzoic acid;

- 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2-(trifluoromethoxy)ethyl)piperidin-3-yl)benzoic acid;
- 4-((3*R*,4*R*)-4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-(2,2-difluoroethyl)piperidin-3-yl)benzoic acid;
- 5 4-((3*R*,4*R*)-4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)piperidin-3-yl)benzoic acid;
- 4-((3*R*,4*R*)-1-(2,2-difluoroethyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)azepan-3-yl)benzoic acid;
- 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)azepan-3-yl)benzoic
- 10 acid;
- 4-(((3*R*,4*R*)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-(2-fluoroethyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
- 4-(((3*R*,4*R*)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-(2,2-difluoroethyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
- 15 *racemic* 1-((3*R**,4*R**)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-1-yl)ethan-1-one;
- 1-((3*R*,4*R*)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-1-yl)ethan-1-one;
- 1-((3*S*,4*S*)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-1-
- 20 yl)ethan-1-one;
- racemic* 4-(((3*R**,4*R**)-3-(6-(1*H*-pyrazol-1-yl)pyridin-3-yl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
- 4-(((3*R*,4*R*)-3-(6-(1*H*-pyrazol-1-yl)pyridin-3-yl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
- 25 4-(((3*S*,4*S*)-3-(6-(1*H*-pyrazol-1-yl)pyridin-3-yl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
- racemic* 4-(((3*R**,4*R**)-3-(4-(1*H*-1,2,3-triazol-1-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
- 4-(((3*R*,4*R*)-3-(4-(1*H*-1,2,3-triazol-1-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-
- 30 1*H*-indole;
- 4-(((3*S*,4*S*)-3-(4-(1*H*-1,2,3-triazol-1-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
- 1-(4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)phenyl)cyclopropan-1-ol;
- 35 4-(((3*R*,4*R*)-1-(2-fluoroethyl)-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
- 4-((3*R*,4*R*)-4-((5-fluoro-7-methyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)piperidin-3-yl)benzoic acid;

- 4-((3*R*,4*R*)-4-((7-chloro-5-methyl-1*H*-indol-4-yl)oxy)-1-(2,2-difluoroethyl)piperidin-3-yl)benzoic acid;
- 4-((3*R*,4*R*)-1-((2,2-difluorocyclopropyl)methyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid;
- 5 4-((3*R*,4*R*)-1-(4,4-difluorobutyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid;
- 4-((3*R*,4*R*)-4-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-1-(2,2-difluoroethyl)piperidin-3-yl)benzoic acid;
- 4-((3*R*,4*R*)-4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-(3,3-difluoropropyl)piperidin-3-yl)benzoic acid;
- 10 4-((3*R*,4*R*)-4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-(3,3,3-trifluoropropyl)piperidin-3-yl)benzoic acid;
- 4-((3*R*,4*R*)-1-(3,3-difluoropropyl)-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
- 15 4-((3*R*,4*S*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)benzoic acid;
- 4-((3*R*,4*S*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpyrrolidin-3-yl)benzoic acid;
- 4-((3*R*,4*R*)-4-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-1-methylazepan-3-yl)benzoic acid;
- 20 4-((3*R*,4*R*)-4-((5-methoxy-7-methyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid;
- or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.
- In another embodiment, the compound of Formula (I) is selected from the group
- 25 consisting of:
- 4-((1*S*,2*R*,5*S*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 4-((1*R*,2*S*,5*R*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid ;
- racemic* 4-((1*S**,2*R**,5*R**)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 30 4-((1*S*,2*R*,5*R*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 4-((1*R*,2*S*,5*S*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- racemic* 4-((1*S**,2*S**,5*S**)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 4-((1*S*,2*S*,5*S*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 35 4-((1*R*,2*R*,5*R*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- racemic* 4-((1*S**,2*S**,5*R**)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 4-((1*S*,2*S*,5*R*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;

- 4-((1*R*,2*R*,5*S*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
racemic 4-((7*S**,8*R**)-8-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-oxaspiro[4.5]decan-7-yl)benzoic acid;
- 5 4-((5*R*,7*S*,8*R*)-8-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-oxaspiro[4.5]decan-7-yl)benzoic acid;
- 4-((5*S*,7*S*,8*R*)-8-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-oxaspiro[4.5]decan-7-yl)benzoic acid;
- 4-((1*S*,2*R*,5*S*)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 10 4-((1*S*,2*R*,5*S*)-2-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 4-((1*S*,2*R*,5*S*)-2-((5-fluoro-7-methyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 4-((1*S*,2*R*,5*S*)-5-methoxy-2-((7-methyl-1*H*-indol-4-yl)oxy)cyclohexyl)benzoic acid;
- 15 *racemic* 4-((1*S**,2*R**)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)cyclohexyl)benzoic acid;
- 4-((1*S*,2*R*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)cyclohexyl)benzoic acid;
- 4-((1*R*,2*S*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)cyclohexyl)benzoic acid;
- 4-((1*S*,2*R*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5,5-difluorocyclohexyl)benzoic acid;
- 4-((1*S*,2*R*,5*S*)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-
- 20 hydroxycyclohexyl)benzoic acid;
- 4-((1*S*,2*R*,5*S*)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-(difluoromethoxy)cyclohexyl)benzoic acid;
- 4-((1*S*,2*R*,5*R*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methylcyclohexyl)benzoic acid;
- 4-((1*S*,2*R*,5*S*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methylcyclohexyl)benzoic acid;
- 25 4-((5*S*,6*R*)-6-((5,7-dimethyl-1*H*-indol-4-yl)oxy)spiro[2.5]octan-5-yl)benzoic acid;
- 4-((1*S*,2*R*,5*S*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzamide;
- 4-((1*S*,2*R*)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5,5-difluorocyclohexyl)benzoic acid;
- racemic* 4-((1*S**,2*R**,5*S**)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-
- 30 (difluoromethoxy)-5-methylcyclohexyl)benzoic acid;
- 4-((1*S*,2*R*,5*S*)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-(difluoromethoxy)-5-methylcyclohexyl)benzoic acid;
- 4-((1*S*,2*R*,5*R*)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-(difluoromethoxy)-5-methylcyclohexyl)benzoic acid;
- 35 *racemic* 4-((1*S**,2*R**,5*S**)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-(difluoromethoxy)-5-methylcyclohexyl)benzoic acid;
- 4-((1*S*,2*R*,5*S*)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-(difluoromethoxy)-5-methylcyclohexyl)benzoic acid;

4-((1*S*,2*R*,5*S*)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-(difluoromethoxy)-5-methylcyclohexyl)benzoic acid;

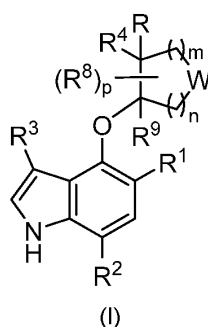
4-((6*S*,7*R*)-7-((5,7-dimethyl-1*H*-indol-4-yl)oxy)spiro[3.5]nonan-6-yl)benzoic acid,

or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled

5 compound thereof.

In an embodiment, the invention provides a tautomer, a diastereomer, or an enantiomer of the compound of Formula (I) of any of the embodiments herein described.

In an aspect, provided herein is a compound of Formula (I)



or a pharmaceutically acceptable salt thereof;

wherein:

W is O, C(R⁶)₂, or NR⁷;

R is hydrogen, halogen, C₁-C₄alkyl, haloC₁-C₄alkyl, or hydroxyC₁-C₄alkyl;

R¹ is hydrogen, halogen, hydroxy, C₁-C₆alkyl, C₂-C₆alkenyl, C₃-C₆cycloalkyl, C₁-C₆alkoxy, haloC₁-C₆alkyl, haloC₃-C₆cycloalkyl, haloC₁-C₆alkoxy, hydroxyC₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, aminoC₁-C₆alkyl, C₁-C₆alkoxyC₁-C₆alkyl, C₁-C₆alkoxyC₁-C₆alkoxy, or C₃-C₆cycloalkylC₁-C₆alkoxy;

R² is C₁-C₃alkyl, C₃cycloalkyl, C₁-C₃alkoxy, hydroxyC₁-C₆alkyl, or halogen, wherein the C₁-C₃alkyl, C₃cycloalkyl, or C₁-C₃alkoxy are unsubstituted or substituted with 1, 2, or 3 halogen substituents;

R³ is hydrogen, halogen, or cyano;

R⁴ is phenyl, naphthyl or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N, O, and S, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵;

R⁵ is selected from -CO₂R^{5b}, C₁-C₆alkyl, C₁-C₆alkoxyC₁-C₆alkyl, -CH₂CO₂R^{5b}, -C(O)NHSO₂C₁-C₄alkyl, -SO₂NHC(O)C₁-C₄alkyl, -SO₂C₁-C₄alkyl, cyano, hydroxy, halogen, and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein alkyl and heteroaryl are unsubstituted or substituted with 1, 2, or 3 R^{5a};

each R^{5a} is independently selected from fluoro, hydroxyl, and C₁-C₆alkyl that is unsubstituted or substituted with -CO₂H;

each R^{5b} is independently selected from hydrogen and C₁-C₅alkyl;

each R⁶ is independently selected from hydrogen, halogen, hydroxy, amino, mono- and di- C₁-C₄alkylamino, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₁-C₆alkyl, cyanoC₁-C₆alkyl, C₁-C₆alkoxy, and haloC₁-C₆alkoxy;

or two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic carbocycle having 3 to 6 ring atoms, wherein the spirocyclic carbocycle is unsubstituted or substituted with 1 or 2 substituents selected from halogen, C₁-C₆alkyl, and C₁-C₆alkoxy;

or two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 or 2 ring heteroatoms independently selected from N, O, and S(O)_q, wherein the spirocyclic heterocycle is unsubstituted or substituted with 1 or 2 halogen, C₁-C₆alkyl, haloC₁-C₆alkyl, C₃-C₆cycloalkyl, or haloC₃-C₆cycloalkyl;

q is 0, 1, or 2;

R⁷ is hydrogen, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₂-C₆alkyl, C₃-C₆cycloalkyl, C₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkyl, C₁-C₆alkoxyC₁-C₆alkyl, haloC₁-C₆alkoxyC₁-C₆alkyl, -COR^{7a}, aryl, 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N, O, and S(O)_q, or 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein C₁-C₆alkyl is unsubstituted or substituted with 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N, O, and S(O)_q, wherein the 4- to 6-membered heterocyclyl is unsubstituted or substituted with 1, 2, or 3 halogen, further wherein the aryl or heteroaryl is unsubstituted or substituted with halo, C₁-C₆alkyl, haloC₁-C₆alkyl, C₃-C₅cycloalkyl, haloC₃-C₅cycloalkyl;

10 R^{7a} is hydrogen or C₁-C₆alkyl;

each R⁸ is independently selected from hydrogen, halogen, hydroxy, amino, mono- and di- C₁-C₄alkylamino, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₁-C₆alkyl, cyanoC₁-C₆alkyl, C₁-C₆alkoxy, and haloC₁-C₆alkoxy;

R⁹ is H, D, or T;

m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3;

provided that both m and n are not 0; and

p is 0, 1, 2, or 3.

In an embodiment,

W is C(R⁶)₂ or NR⁷;

R is hydrogen;

R¹ is halogen, hydroxy, C₁-C₆alkyl, C₂-C₆alkenyl, C₃-C₆cycloalkyl, C₁-C₆alkoxy, haloC₁-C₆alkyl, hydroxyC₁-C₆alkyl, or aminoC₁-C₆alkyl;

R² is C₁-C₃alkyl, C₃cycloalkyl, C₁-C₃alkoxy, hydroxyC₁-C₆alkyl, or halogen;

R³ is hydrogen, halogen, or cyano;

R⁴ is phenyl, naphthyl or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N, O, and S, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵;

R⁵ is selected from -CO₂R^{5b}, C₁-C₆alkyl, C₁-C₆alkoxyC₁-C₆alkyl, - cyano, hydroxy, halogen, and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein alkyl and heteroaryl are unsubstituted or substituted with 1, 2, or 3 R^{5a};

each R^{5a} is independently selected from fluoro, hydroxyl, and C₁-C₆alkyl that is unsubstituted or substituted with -CO₂H;

R^{5b} is selected from hydrogen and C₁-C₅alkyl;

each R⁶ is independently selected from hydrogen, halogen, hydroxy, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₁-C₆alkyl, C₁-C₆alkoxy, and haloC₁-C₆alkoxy; or two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic carbocycle having 3 to 6 ring atoms, wherein the spirocyclic carbocycle is unsubstituted or substituted with 1 or 2 substituents selected from halogen, C₁-C₆alkyl, and C₁-C₆alkoxy; or two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 or 2 ring heteroatoms independently selected from N and O;

R⁷ is hydrogen, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₂-C₆alkyl, -COR^{7a}, or C₃-C₆cycloalkyl;

R^{7a} is C₁-C₆alkyl;

each R⁸ is independently selected from hydrogen, halogen, hydroxy, amino, mono- and di- C₁-C₄alkylamino, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₁-C₆alkyl, cyanoC₁-C₆alkyl, C₁-C₆alkoxy, and haloC₁-C₆alkoxy;

R⁹ is H, D, or T;

m is 1, 2, or 3;

n is 1, 2, or 3; and

p is 0, 1, or 2.

In another embodiment,

W is C(R⁶)₂ or NR⁷;

R is hydrogen;

R¹ is halogen, C₁-C₆alkyl, or C₃-C₆cycloalkyl;

R² is C₁-C₃alkyl;

R³ is hydrogen;

R⁴ is phenyl or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N, O, and S, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵;

R⁵ is selected from -CO₂R^{5b}, C₁-C₆alkyl, cyano, and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein alkyl and heteroaryl are unsubstituted or substituted with R^{5a};

R^{5a} is hydroxy or C₁-C₆alkyl;

R^{5b} is hydrogen or C₁-C₃alkyl;

each R⁶ is independently selected at each occurrence from hydrogen and C₁-C₆alkoxy; or two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 or 2 ring heteroatoms independently selected from N and O;

R⁷ is C₁-C₆alkyl -COR^{7a}, or haloC₁-C₆alkyl;

R^{7a} is C₁-C₆alkyl;

each R⁸ is independently selected from hydrogen and C₁-C₆alkyl;

R⁹ is H;

m is 1 or 2;

n is 1, 2, or 3; and

p is 0, 1, or 2.

In another embodiment,

W is O, C(R⁶)₂, or NR⁷;

R is hydrogen, halogen, C₁-C₄alkyl, haloC₁-C₄alkyl, or hydroxyC₁-C₄alkyl;

R¹ is hydrogen, halogen, hydroxy, C₁-C₆alkyl, C₂-C₆alkenyl, C₃-C₆cycloalkyl, C₁-C₆alkoxy, haloC₁-C₆alkyl, haloC₃-C₆cycloalkyl, haloC₁-C₆alkoxy, hydroxyC₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, aminoC₁-C₆alkyl, C₁-C₆alkoxyC₁-C₆alkyl, C₁-C₆alkoxyC₁-C₆alkoxy, or C₃-C₆cycloalkylC₁-C₆alkoxy;

R² is C₁-C₃alkyl, C₃cycloalkyl, C₁-C₃alkoxy, hydroxyC₁-C₆alkyl, or halogen, wherein the C₁-C₃alkyl, C₃cycloalkyl, or C₁-C₃alkoxy are unsubstituted or substituted with 1, 2, or 3 halogen substituents;

R³ is hydrogen, halogen, or cyano;

R⁴ is phenyl, naphthyl or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N, O, and S, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵;

R⁵ is selected from -CO₂R^{5b}, C₁-C₆alkyl, C₁-C₆alkoxyC₁-C₆alkyl, -CH₂CO₂R^{5b}, -C(O)NHSO₂C₁-C₄alkyl, -SO₂NHC(O)C₁-C₄alkyl, -SO₂C₁-C₄alkyl, cyano, hydroxy, halogen, and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein alkyl and heteroaryl are unsubstituted or substituted with 1, 2, or 3 R^{5a};

each R^{5a} is independently selected from fluoro, hydroxyl, and C₁-C₆alkyl that is unsubstituted or substituted with -CO₂H;

each R^{5b} is independently selected from hydrogen and C₁-C₅alkyl;

each R⁶ is independently selected from hydrogen, halogen, hydroxy, amino, mono- and di- C₁-C₄alkylamino, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₁-C₆alkyl, cyanoC₁-C₆alkyl, C₁-C₆alkoxy, and haloC₁-C₆alkoxy; or two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic carbocycle having 3 to 6 ring atoms, wherein the spirocyclic carbocycle is unsubstituted or substituted with 1 or 2 substituents selected from halogen, C₁-C₆alkyl, and C₁-C₆alkoxy; or two R⁶ in combination with the carbon atom to which they are

attached form a spirocyclic heterocycle having 1 or 2 ring heteroatoms independently selected from N, O, and S(O)_q, wherein the spirocyclic heterocycle is unsubstituted or substituted with 1 or 2 halogen, C₁-C₆alkyl, haloC₁-C₆alkyl, C₃-C₆cycloalkyl, or haloC₃-C₆cycloalkyl;

q is 0, 1, or 2;

- R⁷ is hydrogen, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₂-C₆alkyl, C₃-C₆cycloalkyl, C₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkyl, C₁-C₆alkoxyC₁-C₆alkyl, haloC₁-C₆alkoxyC₁-C₆alkyl, aryl, 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N, O, and S(O)_q, or 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein C₁-C₆alkyl is unsubstituted or substituted with 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N, O, and S(O)_q, wherein the 4- to 6-membered heterocyclyl is unsubstituted or substituted with 1, 2, or 3 halogen, further wherein the aryl or heteroaryl is unsubstituted or substituted with halo, C₁-C₆alkyl, haloC₁-C₆alkyl, C₃-C₅cycloalkyl, haloC₃-C₅cycloalkyl;

each R⁸ is independently selected from hydrogen, halogen, hydroxy, amino, mono- and di-C₁-C₄alkylamino, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₁-C₆alkyl, cyanoC₁-C₆alkyl, C₁-C₆alkoxy, and haloC₁-C₆alkoxy;

- 10 R⁹ is H, D, or T;
m is 0, 1, 2, or 3;
n is 0, 1, 2, or 3;
provided that both m and n are not 0; and
p is 0, 1, 2, or 3.

In another embodiment,

W is C(R⁶)₂ or NR⁷;

R is hydrogen;

R¹ is halogen, hydroxy, C₁-C₆alkyl, C₂-C₆alkenyl, C₃-C₆cycloalkyl, C₁-C₆alkoxy, haloC₁-C₆alkyl, hydroxyC₁-C₆alkyl, or aminoC₁-C₆alkyl;

R² is C₁-C₃alkyl, C₃cycloalkyl, C₁-C₃alkoxy, hydroxyC₁-C₆alkyl, or halogen;

R³ is hydrogen, halogen, or cyano;

R⁴ is phenyl, naphthyl or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N, O, and S, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵;

R⁵ is selected from -CO₂R^{5b}, C₁-C₆alkyl, C₁-C₆alkoxyC₁-C₆alkyl, - cyano, hydroxy, halogen, and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein alkyl and heteroaryl are unsubstituted or substituted with 1, 2, or 3 R^{5a};

each R^{5a} is independently selected from fluoro, hydroxyl, and C₁-C₆alkyl that is unsubstituted or substituted with -CO₂H;

R^{5b} is selected from hydrogen and C₁-C₅alkyl;

each R⁶ is independently selected from hydrogen, halogen, hydroxy, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₁-C₆alkyl, C₁-C₆alkoxy, and haloC₁-C₆alkoxy; or two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic carbocycle having 3 to 6 ring atoms, wherein the spirocyclic carbocycle is unsubstituted or substituted with 1 or 2 substituents selected from halogen, C₁-C₆alkyl, and C₁-C₆alkoxy; or two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 or 2 ring heteroatoms independently selected from N and O;

R⁷ is hydrogen, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₂-C₆alkyl, or C₃-C₆cycloalkyl;

each R⁸ is independently selected from hydrogen, halogen, hydroxy, amino, mono- and di- C₁-C₄alkylamino, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₁-C₆alkyl, cyanoC₁-C₆alkyl, C₁-C₆alkoxy, and haloC₁-C₆alkoxy;

R⁹ is H;

m is 1, 2, or 3;

n is 1, 2, or 3; and

p is 0, 1, or 2.

In another embodiment,

W is C(R⁶)₂ or NR⁷;

R is hydrogen;

R¹ is halogen, C₁-C₆alkyl, or C₃-C₆cycloalkyl;

R² is C₁-C₃alkyl;

R³ is hydrogen;

R⁴ is phenyl or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N, O, and S, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵;

R⁵ is selected from -CO₂R^{5b}, C₁-C₆alkyl, cyano, and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein alkyl and heteroaryl are unsubstituted or substituted with R^{5a};

R^{5a} is hydroxy or C₁-C₆alkyl;

R^{5b} is hydrogen or C₁-C₃alkyl;

each R⁶ is independently selected at each occurrence from hydrogen and C₁-C₆alkoxy; or two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 or 2 ring heteroatoms independently selected from N and O;

R⁷ is C₁-C₆alkyl or haloC₁-C₆alkyl;

each R⁸ is independently selected from hydrogen and C₁-C₆alkyl;

R⁹ is H;

m is 1 or 2;

n is 1, 2, or 3; and

p is 0, 1, or 2.

In another embodiment, W is NR⁷. In another embodiment, W is C(R⁶)₂.

In another embodiment, R is hydrogen.

In another embodiment, R¹ is halogen, C₁-C₃alkyl, or C₃cycloalkyl. In still another embodiment, R¹ is halogen. In another embodiment, R¹ is C₁-C₃alkyl. In another embodiment, R¹ is C₃cycloalkyl.

In another embodiment, R² is methyl.

In another embodiment, R³ is hydrogen.

In another embodiment, R⁴ is phenyl or 5-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N, O, and S, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵. In another embodiment, R⁴ is phenyl, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵. In yet another embodiment, R⁴ is 5-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N, O, and S, wherein heteroaryl is unsubstituted or substituted with R⁵. In still another embodiment, R⁴ is phenyl or pyrazolyl, wherein phenyl or pyrazolyl is unsubstituted or substituted with R⁵.

In another embodiment, R⁵ is selected from -CO₂H, C₁-C₆alkyl, cyano, and 5-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein alkyl is unsubstituted or substituted with hydroxy. In another embodiment, R⁵ is -CO₂H. In yet another embodiment, R⁵ is cyano. In still another embodiment, R⁵ is 5-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S. In an embodiment, R⁵ is C₁-C₆alkyl, wherein alkyl is unsubstituted or substituted with hydroxy.

In another embodiment, each R⁶ is independently selected from hydrogen and C₁-C₃alkoxy. In yet another embodiment, each R⁶ is hydrogen. In still another embodiment, each R⁶ is independently selected from C₁-C₃alkoxy.

In an embodiment, two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 or 2 ring heteroatoms independently selected from N and O. In another embodiment, two R⁶ in combination with the carbon atom to which they are attached form a 4-6 membered spirocyclic heterocycle having 1 or 2 ring heteroatoms independently
5 selected from N and O. In yet another embodiment, two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic carbocycle having 3 to 6 ring atoms.

In another embodiment, R⁷ is methyl, -COR^{7a}, or haloC₁-C₃alkyl. In an embodiment, R⁷ is methyl or haloC₁-C₃alkyl. In another embodiment, R⁷ is methyl. In yet another embodiment, R⁷ is haloC₁-C₃alkyl. In still another embodiment, R⁷ is -C(O)C₁-C₃alkyl.

In another embodiment, each R⁸ is independently selected from hydrogen and C₁-C₆alkyl. In another embodiment, each R⁸ is hydrogen.

In another embodiment, R⁹ is H.

In another aspect, provided herein is a pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of the preceding

embodiments, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

Methods of Treatment

In an aspect, provided herein is a method of treating or preventing a disease or disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

In another aspect, provided herein is a method of modulating the complement alternative pathway activity in a subject, the method comprising administering to the subject a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

5 In yet another aspect, provided herein is a method of treating a disease or disorder mediated by complement activation, in particular mediated by activation of the complement alternative pathway, in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

10 In still another aspect, provided herein is a method of treating a disease or disorder that is affected by the modulation of complement alternative pathway comprising administering to the subject a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

15 In an aspect, provided herein is a method of treating a disease or disorder associated with dysregulation of the complement alternative pathway comprising administering to the subject a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

20 In another aspect, provided herein is a method of inhibiting the expression or activity of complement factor B, the method comprising administering to the subject a compound provided herein, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

In an embodiment of the invention, the diseases or disorders is selected from age-related macular degeneration, geographic atrophy, diabetic retinopathy, uveitis, retinitis pigmentosa, macular edema, Behcet's uveitis, multifocal choroiditis, Vogt-Koyangi-Harada syndrome, intermediate uveitis, birdshot retino-choroiditis, sympathetic ophthalmia, ocular cicatricial pemphigoid, ocular pemphigus, nonarteritic ischemic optic neuropathy, post-operative inflammation, retinal vein occlusion, glaucoma, Doyne honeycomb retinal dystrophy/Malattia leventinese, Sorsby fundus dystrophy, Late onset retinal macular dystrophy, North carolina macular dystrophy, Stargardt disease, corneal inflammation, neurological disorders such as multiple sclerosis including primary progressive multiple sclerosis (PPMS), secondary

progressive multiple sclerosis (SPMS) and relapsing remitting multiple sclerosis (RRMS), stroke, Guillain Barré Syndrome, spinal cord injury, traumatic brain injury, Parkinson's disease, Alzheimer's disease, schizophrenia, amyotrophic lateral sclerosis (ALS), Huntington's disease, multifocal motor neuropathy, autism spectrum disorders, schizophrenia, drug-induced neurotoxicity, Aquaporin-4 IgG seropositive neuromyelitis optica spectrum disorder (NMOSD), cerebral amyloid angiopathy, cerebral malaria, Charcot-Marie-Tooth disease, chemotherapy-induced peripheral neuropathy, chronic inflammatory demyelinating polyneuropathy, frontotemporal dementia, genetic demyelinating neuropathy due to CD59 p.Cys89Tyr mutation, Lewy bodies dementia, multiple system atrophy (MSA), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), opsoclonus myoclonus syndrome (OMS), progressive supranuclear palsy; disorders of inappropriate or undesirable complement activation such as hemodialysis complications, hyperacute allograft rejection, xenograft rejection, interleukin-2 induced toxicity during IL-2 therapy, inflammatory disorders, paroxysmal nocturnal hemoglobinuria, C3 glomerulonephritis (including dense deposit disease and C3 glomerulonephritis), immune complex membranoproliferative glomerulonephritis (IC-MPGN), IgA nephropathy, membranous nephropathy including idiopathic membranous nephropathy, diabetic nephropathy, atypical hemolytic uremic syndrome (aHUS), Hemolytic uremic syndrome, STEC-HUS (Shiga toxin-producing Escherichia coli hemolytic uremic syndrome), peridontitis, CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, protein-losing enteropathy (CHAPLE syndrome), inflammation or autoimmune diseases such as Crohn's disease, neuromyelitis optica (NMO), IgA vasculitis (formerly known as Henoch-Schönlein purpura or HSP), CHAPLE syndrome, hematopoietic stem cell transplantation-associated thrombotic microangiopathy (HSCT-TMA), adult respiratory distress syndrome (ARDS), myocarditis, post-ischemic reperfusion conditions, myocardial infarction, balloon angioplasty, post-pump syndrome in cardiopulmonary bypass or renal bypass, atherosclerosis, hemodialysis, renal ischemia, acute kidney injury mesenteric artery reperfusion after aortic reconstruction, infectious disease or sepsis; COVID-19, immune complex disorders and autoimmune diseases, rheumatoid arthritis, osteoarthritis, Spondyloarthropathies, psoriatic arthritis, systemic lupus erythematosus (SLE), lupus nephritis, SLE nephritis, proliferative nephritis, myasthenia gravis, liver fibrosis, hemolytic anemia, tissue regeneration, neural regeneration, dyspnea, hemoptysis, acute respiratory distress syndrome (ARDS), asthma, chronic obstructive pulmonary disease (COPD), emphysema, pulmonary embolisms and infarcts, pneumonia, fibrogenic dust diseases, pulmonary fibrosis, asthma, allergy, bronchoconstriction, hypersensitivity pneumonitis, parasitic diseases, Goodpasture's Syndrome, pulmonary vasculitis, Pauci-immune vasculitis, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV), Buerger's vasculitis, cryoglobulinemia, Kawasaki disease, Takayasu arteritis, cryoglobulinemia, immune complex-associated inflammation, antiphospholipid syndrome, glomerulonephritis and obesity; immune

thrombocytopenia, Cold agglutinin disease, Warm autoimmune hemolytic anemia (wAIHA), thrombotic thrombocytopenic purpura (TTP), abdominal aortic aneurisms, and Grave's disease.

In yet another aspect, provided herein is a method of treating age-related macular degeneration comprising administering to a subject in need thereof an effective amount of a composition comprising a compound provided herein, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

In still another aspect, provided herein is a compound provided herein, or a pharmaceutically acceptable salt or a stereoisomer thereof, for use as a medicament.

In an aspect, provided herein is a compound provided herein, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, for use in inhibiting
5 the expression or activity of complement factor B, in a subject in need thereof.

In another aspect, provided herein is a compound provided herein, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, for use in treating a disease or disorder associated with dysregulation of the complement alternative pathway.

In an aspect, provided herein is the use of a compound a provided herein, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, in the manufacture of a medicament for the treatment of a disease or disorder mediated by complement activation or activation of the complement alternative pathway.

10 In another aspect, provided herein is the use of a compound provided herein, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, in the manufacture of a medicament for the treatment of a disease or disorder.

In yet another aspect, provided herein is the use of a compound provided herein, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, for the treatment of a disease or disorder mediated by complement activation or activation of the complement alternative pathway.

In still another embodiment, provided herein is the use of a compound provided herein, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, for the treatment of a disease or disorder that is affected by the modulation of complement alternative pathway.

In an aspect, provided herein is the use of a compound provided herein, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, for the treatment of a disease or disorder.

In yet another aspect, provided herein is the use of a provided herein, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, for the treatment of age-related macular degeneration.

In still another aspect, provided herein is a pharmaceutical combination comprising a compound provided herein, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, and one or more additional therapeutic agent(s).

Depending on the choice of the starting materials and procedures, the compounds can be present in the form of one of the possible isomers or as mixtures thereof, for example as pure optical isomers, or as isomer mixtures, such as racemates and diastereomeric mixtures, depending on the number of asymmetric centres. The disclosure is meant to include all such possible isomers, including racemic mixtures, enantiomerically enriched mixtures, diastereomeric mixtures and optically pure forms. Optically active (*R*)- and (*S*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a disubstituted or trisubstituted cycloalkyl, the cycloalkyl substituent(s) may have a *cis*- or *trans*-configuration. The disclosure includes *cis* and *trans* configurations of substituted cycloalkyl groups, e.g., cyclobutyl group, as well as mixtures thereof. All tautomeric forms are also intended to be included. In particular, where a heteroaryl ring containing N as a ring atom is 2-pyridone, for example, tautomers where the carbonyl is depicted as a hydroxy (e.g., 2-hydroxypyridine) are included.

Separation of *cis* and *trans* isomers can be achieved according to methods known to a person of skill in the art, such as chromatographic methods, with tools such as HPLC (High Performance Liquid Chromatography), Thin Layer Chromatography, SFC (Supercritical Fluid Chromatography), GC (Gas Chromatography), or recrystallization techniques.

Isotopically Labelled Compounds

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, sulfur, fluorine, chlorine and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{18}O , ^{15}N , ^{18}F , ^{17}O , ^{18}O , ^{35}S , ^{36}Cl , ^{123}I , ^{124}I , ^{125}I respectively. The disclosure includes various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as ^3H and ^{14}C , or those into which non-radioactive isotopes, such as ^2H and ^{13}C are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F compound may be particularly desirable for PET or SPECT studies. Isotopically-labeled compounds of formula (I), or sub-formulae thereof, can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and General Schemes using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Further, substitution with heavier isotopes, particularly deuterium (*i.e.*, ^2H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of the formula (I), or any of the sub-formulae thereof. The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this disclosure is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

Pharmaceutically acceptable solvates in accordance with the disclosure include those wherein the solvent of crystallization may be isotopically substituted, *e.g.*, D_2O , d_6 -acetone, d_6 -DMSO.

Compounds of the disclosure that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of formula (I), or sub-formulae thereof, by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds provided herein, with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163.

All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (*e.g.*, "such as") provided herein is intended merely to better illuminate the disclosure and does not pose a limitation on the scope of the disclosure otherwise claimed.

Any asymmetric center (*e.g.*, carbon or the like) of the compound(s) of the disclosure can be present in racemic or enantiomerically enriched, for example the (R)-, (S)- or (R,S)-configuration. In certain embodiments, for example, as a mixture of enantiomers, each asymmetric center is present in at least 10% enantiomeric excess, at least 20% enantiomeric excess, at least 30% enantiomeric excess, at least 40% enantiomeric excess, at least 50% enantiomeric excess, at least 60% enantiomeric excess, at least 70% enantiomeric excess, at least 80% enantiomeric excess, at least 90% enantiomeric excess, at least 95% enantiomeric excess, or at least 99% enantiomeric excess. In certain embodiments, for example, in enantiomerically enriched form, each asymmetric center is present in at least 50% enantiomeric

excess, at least 60% enantiomeric excess, at least 70% enantiomeric excess, at least 80% enantiomeric excess, at least 90% enantiomeric excess, at least 95% enantiomeric excess, or at least 99% enantiomeric excess. Thus, compounds of the disclosure can be present in a racemic mixture or in enantiomerically enriched form or in an enantiopure form or as a mixture of diastereoisomers.

In an embodiment, there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, present in at least 90% enantiomeric excess, at least 95% enantiomeric excess, or at least 99% enantiomeric excess.

In an embodiment, there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, present in at least 90% diastereomeric excess, at least 95% diastereomeric excess, or at least 99% diastereomeric excess.

In the formulae of the present application the term "" on a C-sp³ indicates the absolute stereochemistry, either (*R*) or (*S*). In the formulae of the present application the term "" on a C-sp³ indicates the absolute stereochemistry, either (*R*) or (*S*). In the formulae of the present application the term "" on a C-sp³ represents a covalent bond wherein the stereochemistry of the bond is not defined. This means that the term "" on a C-sp³ comprises an (*S*) configuration or an (*R*) configuration of the respective chiral centre. Furthermore, mixtures may also be present. Therefore, mixtures of stereoisomers, e.g., mixtures of enantiomers, such as racemates, and/or mixtures of diastereoisomers are encompassed by the present disclosure.

For the avoidance of doubt, where compound structures are drawn with undefined stereochemistry with respect to any R group, as represented by a bond () , this means the asymmetric center has either a (*R*)- or (*S*)- configuration, or exists as a mixture thereof and stated as such.

For the avoidance of doubt, in any of formulae of the present application when the R⁵ group is shown with attachment to ring A, this means that the R⁵ group(s) can be bonded via a carbon atom or heteroatom, e.g., nitrogen.

For the avoidance of doubt, the compounds structures shown herein, when appropriate, may exist in their zwitterionic form.

Accordingly, as used herein a compound of the disclosure can be in the form of one of the possible stereoisomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (*cis* or *trans*) stereoisomers, diastereomers, optical isomers, racemates or mixtures thereof.

Any resulting mixtures of stereoisomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of compounds of the disclosure or of intermediates can be resolved into the optical isomers (enantiomers) by known methods, e.g., by separation of the

diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the disclosure into their optical antipodes, *e.g.*, by fractional crystallization of a salt formed with an optically active acid, *e.g.*, tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O,O'*-*p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic compounds of the disclosure or racemic intermediates can also be resolved by chiral chromatography, *e.g.*, high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Furthermore, the compounds of the disclosure, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization. The compounds of the disclosure may inherently or by design form solvates with pharmaceutically acceptable solvents (including water); therefore, it is intended that the disclosure embrace both solvated and unsolvated forms. The term "solvate" refers to a molecular complex of a compound of the disclosure (including pharmaceutically acceptable salts thereof) with one or more solvent molecules. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to the recipient, *e.g.*, water, ethanol, and the like. The term "hydrate" refers to the complex where the solvent molecule is water. The presence of solvates can be identified by a person of skill in the art with tools such as NMR.

The compounds of the disclosure, including salts, hydrates and solvates thereof, may inherently or by design form polymorphs.

Pharmaceutical Compositions

In another aspect, the disclosure provides a pharmaceutical composition comprising one or more compounds of described herein or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.

In a further embodiment, the composition comprises at least one or two pharmaceutically acceptable carriers, such as those described herein. For purposes of the disclosure, unless designated otherwise, solvates and hydrates are generally considered compositions.

The compounds of Formula (I), and subformulae thereof, described herein may be administered alone or as an active ingredient of a pharmaceutical composition. Accordingly, provided herein are pharmaceutical compositions comprising a compounds of Formula (I), or subformulae thereof, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, and one or more pharmaceutically acceptable carriers.

Methods of preparing various pharmaceutical compositions are known to those of skill in the art and may be described in, for example, in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (current edition); Pharmaceutical Dosage Forms Tablets (Lieberman, Lachman and Schwartz, editors) current edition, published by Marcel Dekker, Inc.,

as well as Remington's Pharmaceutical Sciences (Arthur Osol, editor), 1553-1593 (current edition).

The pharmaceutical composition can be formulated for particular routes of administration such as oral administration, topical administration, parenteral administration, and rectal administration, etc. In addition, the pharmaceutical compositions of the disclosure can be made up in a solid form (including without limitation capsules, tablets, pills, granules, powders or suppositories), or in a liquid form (including without limitation solutions, gels, suspensions or emulsions). The pharmaceutical compositions can be subjected to conventional pharmaceutical operations such as sterilization and/or can contain conventional inert diluents, lubricating agents, or buffering agents, as well as adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers and buffers, etc.

Typically, the pharmaceutical compositions are tablets or gelatin capsules comprising the active ingredient together with one or more of:

- a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;
- b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol;
- c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone;
- d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and
- e) absorbents, colorants, flavors and sweeteners.

In an embodiment, the pharmaceutical compositions are capsules comprising the active ingredient only.

Tablets may be either film coated or enteric coated according to methods known in the art.

The mode of administration and pharmaceutical composition are closely related to the therapeutic amounts of the compounds or compositions which are desirable and efficacious for the given treatment application. Pharmaceutical compositions provided herein can be formulated for ophthalmic, ocular, topical, and transdermal administration. In particular embodiments, the pharmaceutical compositions provided herein are suitable for ocular administration. To prepare pharmaceutical compositions, the active ingredient may be mixed with one or more pharmaceutically acceptable carrier(s) according to conventional pharmaceutical compounding techniques. The carrier(s) may take a wide variety of forms depending on the form of preparation desired for administration.

Suitable compositions for oral administration include an effective amount of a compound of the disclosure in the form of tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs, solutions or solid dispersion. Compositions intended for oral use are prepared according to any method known in

the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with nontoxic
5 pharmaceutically acceptable excipients, which are suitable for the manufacture of tablets. These excipients are, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets are uncoated or coated
10 by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules
15 wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

Certain injectable compositions are aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting
20 or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1-75%, or contain about 1-50%, of the active ingredient.

Suitable compositions for transdermal application include an effective amount of a
25 compound of the disclosure with a suitable carrier. Carriers suitable for transdermal delivery include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over
30 a prolonged period of time, and means to secure the device to the skin.

Suitable compositions for topical application, *e.g.*, to the skin and eyes, include aqueous solutions, suspensions, ointments, creams, gels or sprayable formulations, *e.g.*, for delivery by aerosol or the like. Such topical delivery systems will in particular be appropriate for dermal application, *e.g.*, for the treatment of skin cancer, *e.g.*, for prophylactic use in sun creams, lotions,
35 sprays and the like. They are thus particularly suited for use in topical, including cosmetic, formulations well-known in the art. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

As used herein a topical application may also pertain to an inhalation or to an intranasal application. They may be conveniently delivered in the form of a dry powder (either alone, as a mixture, for example a dry blend with lactose, or a mixed component particle, for example with phospholipids) from a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomizer or nebuliser, with or without the use of a suitable propellant.

In certain embodiments, the pharmaceutical compositions provided herein are formulated as solutions, suspensions, gels, creams, ointments, liposomes, ocular inserts or other pharmaceutical compositions suitable, in particular embodiments, for topical administration to the ocular surface, the cornea, the eyelid, margins of the eye, eyelashes and/or eye lid margin in order to deliver the composition to the eye. In some embodiments, liquid (aqueous or non-aqueous) solutions may be used. In certain embodiments the pharmaceutical compositions are formulated as eye drops for topical administration to the ocular surface, the cornea, the eyelid, eye lid margins, eyelashes and/or margins of the eye in order to deliver the composition to the eye. Application of the pharmaceutical composition may be performed with an applicator, such as the subject's finger, a Weck-Cel®, Q-tip®, or other device capable of delivering a formulation to the eyelid, eyelashes and/or eyelid margin in order to deliver the formulation to the eye. The pharmaceutical compositions provided herein may be viscous or semi-viscous; liquid, solid, or semi-solid; aqueous or non-aqueous, depending on the site of application, dose, solubility of drug, and a variety of other factors that are considered by those of skill in the art.

Any of a variety of carriers may be used in a pharmaceutical composition provided herein. In one embodiment, the pharmaceutically acceptable carrier is a non-aqueous carrier (e.g., oil, or oil mixture) having a viscosity in a range from about 50 cps to about 1000 cps, about 50 cps to about 500 cps, about 50 cps to about 200 cps, or about 60 cps to about 120 cps. In certain embodiments, the non-aqueous carrier comprises an oil, e.g., vegetable oils, silicone oils, mineral oil or any combination thereof. In some embodiments, the carrier may be liquid paraffin, white petrolatum, purified lanolin, gelation hydrocarbon, polyethylene glycol, hydrophilic ointment base, white ointment base, absorptive ointment base, Macrogol ointment base, simple ointment base, and the like. In certain embodiments, the pharmaceutical composition may include a monomeric polyol such as, glycerol, propylene glycol, and ethylene glycol, polymeric polyols such as polyethylene glycol, cellulose esters such hydroxypropylmethyl cellulose, carboxy methylcellulose sodium and hydroxy propylcellulose; dextrans such as dextran 70; water soluble proteins such as gelatin, polymers such as polyvinyl alcohol, polyvinylpyrrolidone, and povidone; carbomers, such as carbomer 934P, carbomer 941, carbomer 940 and carbomer 974P; and gums such as HP-guar.

Additional excipients may optionally be included in the pharmaceutical compositions provided herein. Examples of additional excipients include, for example, tonicity enhancers, preservatives, solubilizers, non-toxic excipients, demulcents, sequestering agents, pH adjusting agents, co-solvents, viscosity building agents, and combinations thereof.

The pharmaceutical composition of the disclosure may be in the form of an aqueous suspension or an aqueous solution. In one embodiment, the aqueous pharmaceutical composition of the disclosure is in the form of an aqueous suspension. Aqueous pharmaceutical compositions according to the disclosure can be prepared using standard procedures that are familiar to the person skilled in the art, e.g., by admixture of the various components, suitably at ambient temperature and atmospheric pressure. In one embodiment, the aqueous pharmaceutical compositions of the disclosure are suitable for ocular administration.

In a further embodiment, the pharmaceutical composition of the disclosure is in the form of eye ointment, eye gel, eye cream, or eye drops.

In a further embodiment, the pharmaceutical composition of the disclosure is administered to the subject topically in the eyes.

The compounds of formula (I), in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, e.g., complement factor B modulating properties e.g., as indicated in the *in vitro* tests as provided in the examples, and are therefore indicated for therapy or for use as research chemicals, e.g., as tool compounds.

Additional properties of the disclosed compounds include having good potency in the biological assays described herein, favorable safety profile, and possess favorable pharmacokinetic properties.

Diseases and Disorders and Methods of Use

In a further aspect, the disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, for use in therapy.

In a further aspect, the disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, for use in the treatment of a disease or disorder for which complement factor B is indicated. In one embodiment, the disease or disorder is affected by the inhibition of complement factor B activity.

Compounds of formula (I) and their pharmaceutically acceptable salts or stereoisomers or diastereomers have complement factor B modulating and/or inhibitory activity and are believed to be of potential use for the treatment or prophylaxis of certain diseases or disorders.

The diseases or disorders is selected from age-related macular degeneration, geographic atrophy, diabetic retinopathy, uveitis, retinitis pigmentosa, macular edema, Behcet's uveitis, multifocal choroiditis, Vogt-Koyangi-Harada syndrome, intermediate uveitis, birdshot retino-choroiditis, sympathetic ophthalmia, ocular cicatricial pemphigoid, ocular pemphigus, nonarteritic ischemic optic neuropathy, post-operative inflammation, retinal vein occlusion, glaucoma, Doyne honeycomb retinal dystrophy/Malattia leventinese, Sorsby fundus dystrophy, Late onset retinal macular dystrophy, North carolina macular dystrophy, Stargardt disease, corneal inflammation,

neurological disorders such as multiple sclerosis including primary progressive multiple sclerosis (PPMS), secondary progressive multiple sclerosis (SPMS) and relapsing remitting multiple sclerosis (RRMS), stroke, Guillain Barré Syndrome, spinal cord injury, traumatic brain injury, Parkinson's disease, Alzheimer's disease, schizophrenia, amyotrophic lateral sclerosis (ALS), Huntington's disease, multifocal motor neuropathy, autism spectrum disorders, schizophrenia, drug-induced neurotoxicity, Aquaporin-4 IgG seropositive neuromyelitis optica spectrum disorder (NMOSD), cerebral amyloid angiopathy, cerebral malaria, Charcot-Marie-Tooth disease, chemotherapy-induced peripheral neuropathy, chronic inflammatory demyelinating polyneuropathy, frontotemporal dementia, genetic demyelinating neuropathy due to CD59 p.Cys89Tyr mutation, Lewy bodies dementia, multiple system atrophy (MSA), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), opsoclonus myoclonus syndrome (OMS), progressive supranuclear palsy; disorders of inappropriate or undesirable complement activation such as hemodialysis complications, hyperacute allograft rejection, xenograft rejection, interleukin-2 induced toxicity during IL-2 therapy, inflammatory disorders, paroxysmal nocturnal hemoglobinuria, C3 glomerulonephritis (including dense deposit disease and C3 glomerulonephritis), immune complex membranoproliferative glomerulonephritis (IC-MPGN), IgA nephropathy, membranous nephropathy including idiopathic membranous nephropathy, diabetic nephropathy, atypical hemolytic uremic syndrome (aHUS), Hemolytic uremic syndrome, STEC-HUS (Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome), peridontitis, CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, protein-losing enteropathy (CHAPLE syndrome), inflammation or autoimmune diseases such as Crohn's disease, neuromyelitis optica (NMO), IgA vasculitis (formerly known as Henoch-Schönlein purpura or HSP), CHAPLE syndrome, hematopoietic stem cell transplantation-associated thrombotic microangiopathy (HSCT-TMA), adult respiratory distress syndrome (ARDS), myocarditis, post-ischemic reperfusion conditions, myocardial infarction, balloon angioplasty, post-pump syndrome in cardiopulmonary bypass or renal bypass, atherosclerosis, hemodialysis, renal ischemia, acute kidney injury mesenteric artery reperfusion after aortic reconstruction, infectious disease or sepsis; COVID-19, immune complex disorders and autoimmune diseases, rheumatoid arthritis, osteoarthritis, Spondyloarthropathies, psoriatic arthritis, systemic lupus erythematosus (SLE), lupus nephritis, SLE nephritis, proliferative nephritis, myasthenia gravis, liver fibrosis, hemolytic anemia, tissue regeneration, neural regeneration, dyspnea, hemoptysis, acute respiratory distress syndrome (ARDS), asthma, chronic obstructive pulmonary disease (COPD), emphysema, pulmonary embolisms and infarcts, pneumonia, fibrogenic dust diseases, pulmonary fibrosis, asthma, allergy, bronchoconstriction, hypersensitivity pneumonitis, parasitic diseases, Goodpasture's Syndrome, pulmonary vasculitis, Pauci-immune vasculitis, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV), Buerger's vasculitis, cryoglobulinemia, Kawasaki disease, Takayasu arteritis, cryoglobulinemia, immune complex-associated inflammation, antiphospholipid syndrome,

glomerulonephritis and obesity; immune thrombocytopenia, Cold agglutinin disease, Warm autoimmune hemolytic anemia (wAIHA), thrombotic thrombocytopenic purpura (TTP), abdominal aortic aneurisms, and Grave's disease.

Having regard to their activity as complement factor B modulator or inhibitors, compounds of formula (I) and sub-formulae thereof, in free or pharmaceutically acceptable salt form, are useful in the treatment of conditions which may be treated by inhibition of complement factor B activity. In one aspect, the disclosure provides a method of treating or preventing a disease or disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of formula (I) or sub-formula thereof, or a pharmaceutically acceptable salt or a diastereomer thereof.

In another aspect, the disclosure provides a method of modulating the complement alternative pathway activity in a subject, the method comprising administering to the subject a therapeutically effective amount of a compound of formula (I) or sub-formula thereof, or a pharmaceutically acceptable salt or a diastereomer thereof.

In another aspect, the disclosure provides a method of treating a disease or disorder mediated by complement activation, in particular mediated by activation of the complement alternative pathway, in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of formula (I) or sub-formula thereof, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

In another aspect, the disclosure provides a method of treating a disease or disorder that is affected by the modulation of complement alternative pathway comprising administering to the subject a therapeutically effective amount of a compound of formula (I) or sub-formula thereof, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

In another aspect, the disclosure provides a method of treating a disease or disorder associated with dysregulation of the complement alternative pathway comprising administering to the subject a therapeutically effective amount of a compound of formula (I) or sub-formula thereof, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

In another aspect, the disclosure provides a method of inhibiting the expression or activity of complement factor B, the method comprising administering to the subject a compound of formula (I) or sub-formula thereof, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

In another aspect, the disclosure provides a method of treating disease or disorder.

In certain aspects, methods are provided for the treatment of diseases associated with increased activity of the C3 amplification loop of the complement pathway. In certain embodiments, methods of treating or preventing complement mediated diseases are provided in which the complement activation is induced by antibody-antigen interactions, by a component of an autoimmune disease, or by ischemic damage.

In a specific embodiment, the present disclosure provides a method of treating or preventing age-related macular degeneration (AMD) by administering to a subject in need thereof an effective amount of the compound of Formula (I) of the disclosure. In certain embodiments, patients who are currently asymptomatic but are at risk of developing a symptomatic macular degeneration related disorder are suitable for administration with a compound of the disclosure. The methods of treating or preventing AMD include, but are not limited to, methods of treating or preventing one or more symptoms or aspects of AMD selected from formation of ocular drusen, inflammation of the eye or eye tissue, loss of photoreceptor cells, loss of vision (including loss of visual acuity or visual field), neovascularization (including CNV), retinal detachment, photoreceptor degeneration, RPE degeneration, retinal degeneration, chorioretinal degeneration, cone degeneration, retinal dysfunction, retinal damage in response to light exposure, damage of the Bruch's membrane, and/ or loss of RPE function.

The compound of Formula (I) of the disclosure can be used, *inter alia*, to prevent the onset of AMD, to prevent the progression of early AMD to advanced forms of AMD including neovascular AMD or geographic atrophy, to slow and/or prevent progression of geographic atrophy, to treat or prevent macular edema from AMD or other conditions (such as diabetic retinopathy, uveitis, or post surgical or non-surgical trauma), to prevent or reduce the loss of vision from AMD, and to improve vision lost due to pre-existing early or advanced AMD. It can also be used in combination with anti-VEGF therapies for the treatment of neovascular AMD patients or for the prevention of neovascular AMD.

All the aforementioned embodiments relating to the methods of treatment of the aforementioned diseases are equally applicable to:

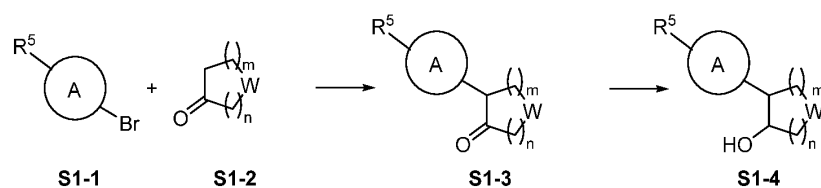
- a compound of formula (I) or sub-formula thereof or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, for use in the treatment of the
- 5 aforementioned diseases according to the present disclosure;
- use of a compound of formula (I) or sub-formula thereof, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, in the manufacture of a medicament for the treatment of the aforementioned diseases according to the present disclosure;
- use of a compound of formula (I) or sub-formula thereof, or a pharmaceutically acceptable
- 10 salt or a stereoisomer or an isotopically labeled compound thereof, for the treatment of the aforementioned diseases according to the present disclosure; and
- a pharmaceutical composition comprising a compound of formula (I) or sub-formula thereof, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, and one or more pharmaceutically acceptable carriers, for use in the treatment
- 15 of the aforementioned diseases according to the present disclosure.

Methods of Making

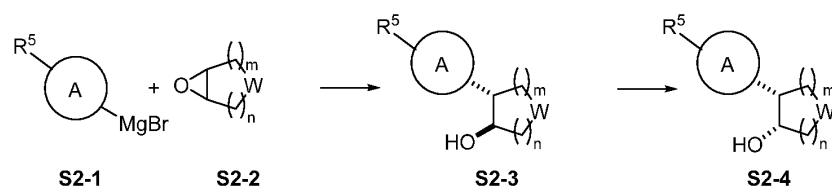
The compounds of the disclosure can be prepared in a number of ways well known to those skilled in the art of organic synthesis. By way of example, compounds of the present disclosure can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art.

Generally, the compounds of formula (I) can be prepared according to the Schemes provided *infra*.

Compounds provided herein can be prepared according to the following Examples. In the following Schemes, R, R¹, R², R³, R⁵, R⁶, R⁸, W, m, n, and p are defined according to enumerated Embodiment 1. In an embodiment, R, R¹, R², R³, R⁵, R⁶, R⁸, W, m, n, and p are defined according to any one of enumerated Embodiments 1 to 23. PG refers to protecting groups. Suitable protecting groups are known to one skilled in the art and the same or different protecting groups may be used in any Scheme. Additional definitions are provided as applicable in the General Schemes below.

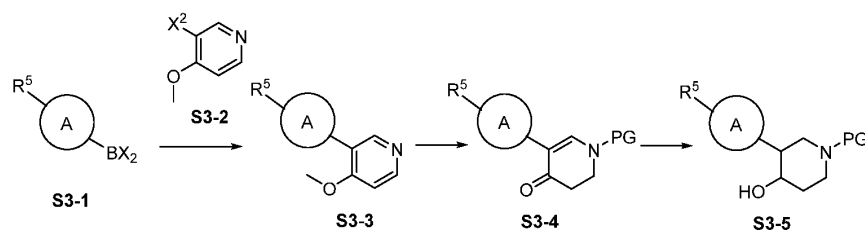
General Scheme 1

Alcohol intermediates **S1-4** can be prepared as outlined in General Scheme 1. Arylation of ketone **S1-2** with aryl bromide **S1-1** can be performed utilizing Buchwald coupling conditions. Ketone reduction of **S1-3** can be accomplished with a hydride reducing agent such as sodium borohydride or lithium tri-*sec*-butylborohydride.

General Scheme 2

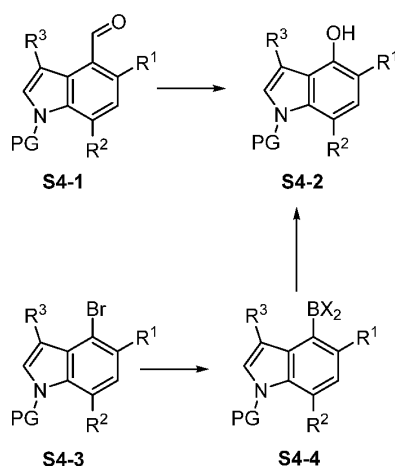
Alternatively, alcohol intermediates **S2-4** can be prepared as outlined in General Scheme 2. Reaction of aryl magnesium bromide **S2-1** with epoxide **S2-2** provides alcohol **S2-3** with *trans* relative configuration at the vicinal stereocenters. Inversion to *cis*-configured **S2-4** is achieved through Mitsunobu reaction with a carboxylic acid such as 4-nitro benzoic acid followed by base-promoted hydrolysis.

General Scheme 3



Piperidinol intermediates **S3-5** can be prepared as outlined in General Scheme 3. Boronic acid or ester **S3-1** and pyridyl halide **S3-2** are coupled to provide biaryl **S3-3** using Suzuki cross-coupling conditions. Nitrogen protection with a reagent like CbzCl followed by treatment with a reducing agent such as sodium borohydride provides enone **S3-4**. Further reduction to the alcohol **S3-5** is achieved through metal-catalyzed hydrogenation with a catalyst such as platinum oxide.

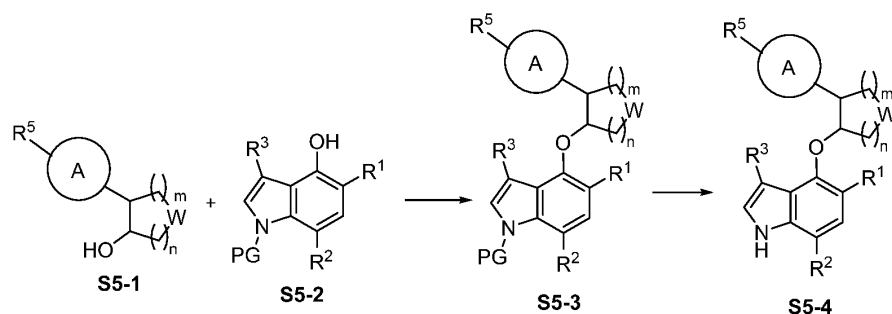
General Scheme 4



10

Synthesis of hydroxy indoles **S4-2** is outlined in General Scheme 4. Baeyer-Villiger oxidation of aldehyde **S4-1** followed by hydrolysis under basic aqueous conditions can provide **S4-2**. Alternatively, 4-bromo indole **S4-3** can be borylated using Miyura conditions. Boronic ester **S4-4** can be oxidized to **S4-2** using a suitable oxidizing agent such as sodium perborate.

15 General Scheme 5



Synthesis of examples **S5-4** is outlined in General Scheme 5. Alcohol intermediates **S5-1** react with hydroxy indole **S5-2** in a Mitsunobu reaction with inversion at the reacting stereocenter to provide **S5-3**. Deprotection can provide final Examples **S5-4**. If W is N-PG, **S5-3** can be selectively deprotected to give the secondary amine where W is N-H. This intermediate can be reacted with a suitable electrophile, e. g. an alkyl halogenide or triflate, in the presence of base such as di-isopropyl ethyl amine. Alternatively, the N-H intermediate can be reacted with a suitable aldehyde or ketone in the presence of a reducing agent such as sodium triacetoxyborohydride. Deprotection provides the final Examples **S5-4**.

In a further aspect, the disclosure provides a process for the preparation of a compound of formula (I), in free form or in pharmaceutically acceptable salt form, comprising the step as described above.

It is understood that in the following description, combinations of substituents and/or variables of the depicted formulae are permissible only if such combinations result in stable compounds.

It will also be appreciated by those skilled in the art that in the processes described below, the functional groups of intermediate compounds may need to be protected by suitable protecting groups. Such functional groups include hydroxy, phenol, amino and carboxylic acid. Suitable protecting groups for hydroxy or phenol include trialkylsilyl or diarylalkylsilyl (e.g., *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, substituted benzyl, methyl, and the like. Suitable protecting groups for amino, amidino and guanidino include *t*-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for carboxylic acid include alkyl, aryl or arylalkyl esters.

Protecting groups may be added or removed in accordance with standard techniques, which are well-known to those skilled in the art and as described herein. The use of protecting groups is described in detail in J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973; T. W. Greene and P. G. M. Wuts, "Greene's Protective Groups in Organic Synthesis", Fourth Edition, Wiley, New York 2007; P. J. Kocienski, "Protecting Groups", Third Edition, Georg Thieme Verlag, Stuttgart and New York 2005; and in

"Methoden der organischen Chemie" (Methods of Organic Chemistry), Houben Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974.

The protecting group may also be a polymer resin, such as a Wang resin or a 2-chlorotriptyl-chloride resin.

- 5 The following reaction Examples illustrate methods to make compounds of this disclosure. It is understood that one skilled in the art would be able to make these compounds by similar methods or by methods known to one skilled in the art. In general, starting components and reagents may be obtained from sources such as Sigma Aldrich, Lancaster Synthesis, Inc., Maybridge, Matrix Scientific, TCI, and Fluorochem USA, Strem, other commercial vendors, or
10 synthesized according to sources known to those skilled in the art, or prepared as described in this disclosure.

Examples

15 Analytical Methods, Materials, and Instrumentation

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Proton nuclear magnetic resonance (NMR) spectra were obtained on either Bruker Avance, Avance III or Avance Neo spectrometer 400 MHz, Varian Oxford 400 MHz, or Varian Mercury 300 MHz spectrometer unless otherwise noted. Spectra are given in ppm (δ) and
20 coupling constants, J , are reported in Hertz. Tetramethylsilane (TMS) was used as an internal standard. Chemical shifts are reported in ppm relative to dimethyl sulfoxide (δ 2.50), methanol (δ 3.31), chloroform (δ 7.26) or other solvent as indicated in NMR spectral data. A small amount of the dry sample (typically 2-5 mg) is dissolved in an appropriate deuterated solvent (1 mL). The chemical names were generated using ChemBioDraw Ultra v19 from CambridgeSoft.

25 Mass spectra (ESI-MS) were collected using a Waters System (Acquity UPLC and a Micromass ZQ mass spectrometer) or Agilent-1260 Infinity (6120 Quadrupole); all masses reported are the m/z of the protonated parent ions unless recorded otherwise. The sample was dissolved in a suitable solvent such as MeCN, DMSO, or MeOH and was injected directly into the column using an automated sample handler.

30 Abbreviations

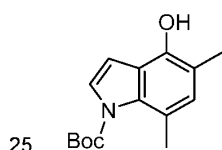
	ACN	acetonitrile
	AcOH	acetic acid
	aq	aqueous
	Boc	<i>tert</i> -butyl carboxy
35	br	broad
	BTMG	<i>tert</i> -butyl tetramethy guanidine
	Cbz	benzyloxycarbonyl
	CD ₃ OD	methanol- <i>d</i> ₄
	CDCl ₃	chloroform- <i>d</i>
40	CO ₂	carbon dioxide
	d	doublet

	DAD	diode-array detection
	DCM	dichloromethane
	DEAD	diethyl azodicarboxylate
	DIAD	diisopropyl azodicarboxylate
5	DMAP	<i>N,N</i> -dimethylaminopyridine
	DMF	<i>N,N</i> -dimethylformamide
	DMSO	dimethylsulfoxide
	<i>ee</i>	enantiomeric excess
	EtOAc	ethyl acetate
10	EtOH	ethanol
	FA	formic acid
	h	hour(s)
	H ₂	hydrogen
	HATU	hexafluorophosphate azabenzotriazole
15		tetramethyl uronium
	HCl	hydrochloric acid
	HPLC	high performance liquid chromatography
	IPA	<i>iso</i> -propanol
	K ₂ CO ₃	potassium carbonate
20	KOAc	potassium acetate
	K ₃ PO ₄	potassium phosphate, tribasic
	LC-MS	liquid chromatography and mass spectrometry
	LED	light emitting diode
	<i>m</i>	multiplet
25	<i>m/z</i>	mass to charge ratio
	<i>m</i> CPBA	<i>meta</i> -chloro perbenzoic acid
	MeOH	methanol
	Me-THF	2-methyltetrahydrofuran
	MgSO ₄	magnesium sulfate
30	min	minutes
	MS	mass spectrometry
	N ₂	nitrogen
	Na(OAc) ₃ BH	sodium triacetoxo borohydride
	NaBH ₄	sodium borohydride
35	NaHCO ₃	sodium bicarbonate
	Na ₂ SO ₄	sodium sulfate
	NaOH	sodium hydroxide
	NH ₄ Cl	ammonium chloride
	NH ₄ OH	ammonium hydroxide
40	NMR	nuclear magnetic resonance
	NP	normal phase
	org	organic
	Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)
	PdCl ₂ (dppf)	1,1'-bis(diphenylphosphino)ferrocene-palladium(II)
45		dichloride
	PE	petroleum ether
	PPh ₃	triphenylphosphine
	ppm	parts per million
	PtO ₂	platinum oxide

	<i>rac</i>	racemic
	RM	reaction mixture
	RP	reversed phase
	Rt	retention time
5	RT	room temperature
	s	singlet
	sat.	saturated
	scCO ₂	super critical carbon dioxide
	<i>sec</i>	secondary
10	SFC	supercritical fluid chromatography
	soln	solution
	SPhos	dicyclohexyl(2',6'-dimethoxy[1,1'-biphenyl]-yl)phosphane
	t	triplet
15	<i>t</i> Bu	tertiary butyl
	<i>tert</i>	tertiary
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	Ts	tosyl
20	Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
	wt%	weight percent

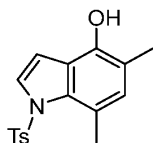
Intermediates

Intermediate I-1: *tert*-butyl 4-hydroxy-5,7-dimethyl-1*H*-indole-1-carboxylate



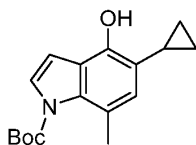
tert-Butyl 4-formyl-5,7-dimethyl-1*H*-indole-1-carboxylate (CAS# 1644667-04-8, 2.7 g, 10 mmol) was dissolved in DCM (25 mL), and the mixture was cooled to 0 °C. TFA (0.77 mL, 10 mmol) and *m*CPBA (77 wt%, 2.69 g, 12 mmol) were added sequentially. The RM was stirred for 1 h, during which time it was allowed to warm to RT. The mixture was partitioned between sat. aq NaHCO₃ soln and DCM. The org phase was dried through an Isolute® phase separator and concentrated under reduced pressure. The resulting oil was dissolved in THF (21 mL), and aq NaOH soln (1M, 21 mL, 21 mmol) was added. The RM was stirred at RT for 15 min. The mixture was neutralized with sat. aq NH₄Cl soln and extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The resulting oil was purified over silica gel (eluent: 0 to 35% EtOAc in heptane) to provide *tert*-butyl 4-hydroxy-5,7-dimethyl-1*H*-indole-1-carboxylate as a brown oil (2.02 g). LC-MS Method C-1: Rt = 1.18 min; MS *m/z* [M+H]⁺ = 262.2.

Intermediate I-2: 5,7-dimethyl-1-tosyl-1*H*-indol-4-ol



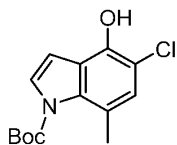
5,7-Dimethyl-1-tosyl-1*H*-indole-4-carbaldehyde (CAS# 1481633-44-6, 376 mg, 1.15 mmol) was dissolved in DCM (5 mL), and the soln was cooled to 0 °C. TFA (88 µL, 1.15 mmol) and *m*CPBA (77 wt%, 238 mg, 1.38 mmol) were added sequentially. The mixture was stirred for 1 h, during which time it was allowed to warm to RT. The RM was diluted with DCM and washed with sat. aq NaHCO₃ soln (2x). The separated org phase was dried through an Isolute® phase separator and concentrated under reduced pressure. The resulting residue was dissolved in THF (1 mL) and MeOH (1 mL), and aq NaOH soln (4M, 1.4 mL, 5.6 mmol) was added. The RM was stirred at RT for 15 min. The RM was partially concentrated under reduced pressure, and the pH was adjusted to 7 with 6M aq HCl. The mixture was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The resulting residue was purified over silica gel (eluent: 0 to 50% EtOAc in heptane) to provide 5,7-dimethyl-1-tosyl-1*H*-indol-4-ol as a grey solid (296 mg). ¹H NMR (400 MHz, CDCl₃) δ [ppm] 7.70 (d, *J* = 3.8 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.26 – 7.17 (m, 2H), 6.81 – 6.70 (m, 2H), 2.45 (s, 3H), 2.38 (s, 3H), 2.25 (s, 3H). 16 of 17H reported (OH not observed)

Intermediate I-3: *tert*-butyl 5-cyclopropyl-4-hydroxy-7-methyl-1*H*-indole-1-carboxylate

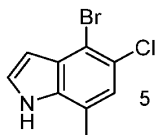


tert-Butyl 5-cyclopropyl-4-formyl-7-methyl-1*H*-indole-1-carboxylate (CAS# 1628640-27-6, 830 mg, 2.77 mmol) was dissolved in DCM (10 mL), and the soln was cooled to 0 °C. TFA (0.21 mL, 2.77 mmol) and *m*CPBA (77 wt%, 574 mg, 3.33 mmol) were added sequentially. The mixture was stirred for 1 h, during which time it was allowed to warm to RT. The RM was partitioned between sat. aq NaHCO₃ soln and DCM. The separated org phase was dried through an Isolute® phase separator and concentrated under reduced pressure. The resulting residue was dissolved in THF (3 mL) and MeOH (3 mL), and aq NaOH soln (4M, 3.46 mL, 13.85 mmol) was added. The RM was stirred at RT for 15 min. The mixture was partially concentrated, and the pH was adjusted to 4 with 6M aq HCl. The mixture was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The resulting oil was purified over silica gel (eluent: 0 to 50% EtOAc in heptane) to provide *tert*-butyl 5-cyclopropyl-4-hydroxy-7-methyl-1*H*-indole-1-carboxylate as a grey oil (585 mg). LC-MS Method C-1: Rt = 1.26 min; MS *m/z* [M-Boc+2H]⁺ = 188.2.

Intermediate I-4: *tert*-butyl 5-chloro-4-hydroxy-7-methyl-1*H*-indole-1-carboxylate

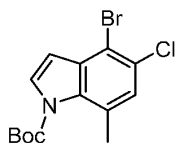


Step 1: **4-bromo-5-chloro-7-methyl-1H-indole (Intermediate I-4-1)**



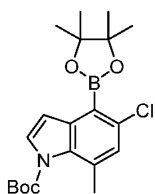
1-Bromo-2-chloro-4-methyl-5-nitrobenzene (2.5 g, 10 mmol) was dissolved in THF (20 mL), and cooled to -40 °C. A vinyl magnesium bromide soln (1M in THF, 40 mL, 40 mmol) was added slowly, and the mixture was stirred at approximately -40 °C for 3.5 h. The RM was quenched with sat. aq NH₄Cl soln and extracted with EtOAc (2x). The combined org phases were washed with brine, dried through an Isolute® phase separator, and concentrated under reduced pressure. The resulting residue was purified over silica gel (eluent: 0 to 50% EtOAc in heptane) to provide 4-bromo-5-chloro-7-methyl-1H-indole as an orange solid (960 mg). ¹H NMR (400 MHz, CDCl₃) δ [ppm] 8.25 (s, 1H), 7.31 – 7.29 (m, 1H), 7.11 – 7.09 (m, 1H), 6.62 (dd, *J* = 3.3, 2.2 Hz, 1H), 2.46 (s, 3H).

Step 2: ***tert*-butyl 4-bromo-5-chloro-7-methyl-1H-indole-1-carboxylate (Intermediate I-4-2)**



4-Bromo-5-chloro-7-methyl-1H-indole (Intermediate I-4-1, 960 mg, 3.93 mmol) and DMAP (24 mg, 0.19 mmol) were combined in DCM (20 mL). Di-*tert*-butyl dicarbonate 1.08 mL, 4.7 mmol) was added, and the RM was stirred at RT for 30 min. The RM was concentrated under reduced pressure, and the resulting oil was purified over silica gel (eluent: 0 to 25% EtOAc in heptane) to provide *tert*-butyl 4-bromo-5-chloro-7-methyl-1H-indole-1-carboxylate as an orange solid (850 mg). ¹H NMR (400 MHz, CDCl₃) δ 7.49 (d, *J* = 3.6 Hz, 1H), 7.14 – 7.05 (m, 1H), 6.55 (d, *J* = 3.8 Hz, 1H), 2.50 (s, 3H), 1.56 (s, 9H).

Step 3: ***tert*-butyl 5-chloro-7-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-1-carboxylate (Intermediate I-4-3)**

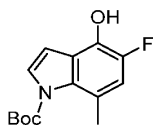


tert-Butyl 4-bromo-5-chloro-7-methyl-1*H*-indole-1-carboxylate (**Intermediate I-4-2**, 300 mg, 0.87 mmol), bis(pinacolato)diboron (332 mg, 1.3 mmol), KOAc (256 mg, 2.6 mmol), and PdCl₂(dppf) (71 mg, 0.09 mmol) were combined in a vial. The vial was purged and filled with N₂. Dioxane (5 mL) was added, and the RM was stirred at 90 °C for 16 h. The RM was filtered through Celite®, and the solids were washed with DCM. The combined filtrates were concentrated under reduced pressure and the resulting residue was enriched over silica gel (eluent: 0 to 30% EtOAc in heptane) to provide *tert*-butyl 5-chloro-7-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole-1-carboxylate as a colorless oil containing *tert*-butyl 5-chloro-7-methyl-1*H*-indole-1-carboxylate (140 mg). LC-MS Method C-1: Rt = 1.52 min; MS m/z [M-Boc+2H]⁺ = 292.3.

10 Step 4: ***tert*-butyl 5-chloro-4-hydroxy-7-methyl-1*H*-indole-1-carboxylate (Intermediate I-4)**

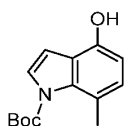
Enriched *tert*-butyl 5-chloro-7-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole-1-carboxylate (**Intermediate I-4-3**, 140 mg) was dissolved in THF (0.5 mL) and H₂O (0.5 mL) and cooled to 0 °C. Sodium perborate 1-hydrate (39.8 mg, 0.4 mmol) was added, and the RM was stirred at 0 °C for 1 h. Additional THF (0.5 mL) and H₂O (0.5 mL) were added, and stirring was continued for 3 h, during which time the mixture was allowed to warm to RT. The mixture was diluted with H₂O and extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The resulting residue was purified over silica gel (eluent: 0 to 30% EtOAc in heptane) to provide *tert*-butyl 5-chloro-4-hydroxy-7-methyl-1*H*-indole-1-carboxylate as a brown oil (30 mg). LC-MS Method C-1 Rt = 1.52 min; MS m/z [M-Boc+2H]⁺ = 182.1.

Intermediate I-5: *tert*-butyl 5-fluoro-4-hydroxy-7-methyl-1*H*-indole-1-carboxylate



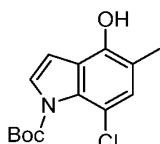
To a soln of *tert*-butyl 4-bromo-5-fluoro-7-methyl-1*H*-indole-1-carboxylate (460 mg, 1.4 mmol) and bis(pinacolato)diboron (533.9 mg, 2.1 mmol) in dioxane (2 mL) were added PdCl₂(dppf) (102.5 mg, 0.14 mmol) and KOAc (412.7 mg, 4.2 mmol). The RM was stirred at 90 °C for 18 h. Additional PdCl₂(dppf) (102.4 mg, 0.14 mmol) was added, and the RM was stirred at 90 °C for 6 h. The RM was allowed to cool to RT, and H₂O₂ (30 wt% in H₂O, 0.72 mL, 7.0 mmol) was added slowly. The RM was stirred at RT for 18 h. The RM was diluted with EtOAc and H₂O and filtered through a pad of Celite®. The phases were separated, and the aq phase was extracted with EtOAc (2x). The combined org phases were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The resulting residue was purified over silica gel (50 g; eluent: 0 to 13% EtOAc in heptane) to provide *tert*-butyl 5-fluoro-4-hydroxy-7-methyl-1*H*-indole-1-carboxylate as a pink solid (220 mg). LC-MS Method B-1: Rt = 1.20 min; MS m/z [M-H]⁻ = 263.9.

35 **Intermediate I-6: *tert*-butyl 4-hydroxy-7-methyl-1*H*-indole-1-carboxylate**



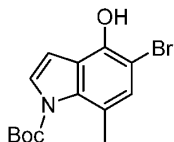
7-Methyl-1*H*-indol-4-ol (75 mg, 0.51 mmol) and DMAP (3.1 mg, 25 μ mol) were combined in ACN (1 mL). Di-*tert*-butyl dicarbonate (0.35 mL, 1.5 mmol) was added, and the RM was stirred at RT for 1 h. The RM was concentrated under reduced pressure. The resulting residue was combined with K_2CO_3 (281 mg, 2.0 mmol) and MeOH (2 mL). The RM was stirred at RT for 2 h. Additional K_2CO_3 (70 mg, 0.5 mmol) was added, and the RM was stirred at RT overnight. The RM was partitioned between H_2O and DCM. The org phase was concentrated under reduced pressure. The resulting residue was purified over silica gel (eluent: 0 to 50% EtOAc in heptane) to provide *tert*-butyl 4-hydroxy-7-methyl-1*H*-indole-1-carboxylate as a colorless oil (87 mg). LC-MS Method C-1: Rt = 1.09 min; MS m/z $[M+H]^+$ = 248.2.

Intermediate I-7: *tert*-butyl 7-chloro-4-hydroxy-5-methyl-1*H*-indole-1-carboxylate



tert-Butyl 4-bromo-7-chloro-5-methyl-1*H*-indole-1-carboxylate (5.8 g, 16.4 mmol), bis(pinacolato)diboron (8.5 g, 33.7 mmol), KOAc (4.9 g, 50.5 mmol), and $PdCl_2(dppf) \cdot DCM$ (1.37 g, 1.68 mmol) were combined in a vial. Dioxane (5 mL) was added, and the RM was stirred at 90 $^{\circ}C$ for 16 h. The RM was filtered through Celite®, and the solids were washed with EtOAc. The combined filtrates were concentrated under reduced pressure. The resulting residue was dissolved in THF (20 mL) and H_2O (10 mL). Sodium perborate 1-hydrate (3.48 g, 34.8 mmol) was added, and the RM was stirred at RT overnight. The RM was diluted with EtOAc, and the separated aq phase was extracted with EtOAc. The combined org phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified over silica gel (24 g; 10 to 20% EtOAc in hexane) to provide *tert*-butyl 7-chloro-4-hydroxy-5-methyl-1*H*-indole-1-carboxylate as a light brown solid (1.4 g). 1H NMR (400 MHz, $DMSO-d_6$) δ [ppm] 9.45 (s, 1H), 7.50 (d, J = 3.6 Hz, 1H), 7.07 (s, 1H), 6.88 (d, J = 3.6 Hz, 1H), 2.20 (s, 3H), 1.58 (s, 9H).

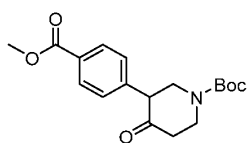
Intermediate I-8: *tert*-butyl 5-bromo-4-hydroxy-7-methyl-1*H*-indole-1-carboxylate



tert-Butyl 5-bromo-4-formyl-7-methyl-1*H*-indole-1-carboxylate (2.37 g, 7.0 mmol) was dissolved in DCM (35 mL), and the soln was cooled to 0 $^{\circ}C$. TFA (0.54 mL, 7.0 mmol) and *m*CPBA (77 wt%, 1.45 g, 8.41 mmol) were added sequentially. The mixture was stirred for 2.5 h, during which time it was allowed to warm to RT. The RM was partitioned between sat. aq $NaHCO_3$ soln and DCM.

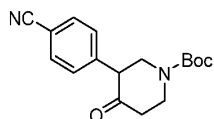
The separated org phase was dried through an Isolute® phase separator and concentrated under reduced pressure. The resulting residue was dissolved in THF (8 mL) and MeOH (8 mL), and aq NaOH soln (4M, 8.7 mL, 35.0 mmol) was added. The RM was stirred at RT for 20 min. The RM was partially concentrated, and the pH was adjusted to 4 with aq HCl (6M). The mixture was
 5 extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The resulting oil was purified over silica gel (eluent: 0 to 50% EtOAc in heptane) to provide *tert*-butyl 5-bromo-4-hydroxy-7-methyl-1*H*-indole-1-carboxylate as an orange solid (1.74 g). LC-MS Method C-1: Rt = 1.15 min; MS m/z [M-H]⁻ = 324.0.

10 **Intermediate K-1: *tert*-butyl 3-(4-(methoxycarbonyl)phenyl)-4-oxopiperidine-1-carboxylate**



To a soln of methyl 4-bromobenzoate (200 g, 930 mmol) in toluene (2 L) was added *tert*-butyl 4-oxopiperidine-1-carboxylate (333.56 g, 1.67 mol), K₃PO₄ (454.05 g, 2.10 mol), Xantphos (21.53 g, 37.20 mmol), and Pd₂(dba)₃ (17.03 g, 18.60 mmol) at 25 °C under N₂. The RM was stirred at
 15 80 °C under N₂ for 16 h. The mixture was filtered, and the solids were washed with DCM (4 L). The filtrate was concentrated under reduced pressure. Column chromatography over silica gel (eluent: 3:1 PE/EtOAc) provided enriched material which was purified by RP chromatography (eluent: 0 to 100% ACN in H₂O with 0.1 NH₄OH) to provide *tert*-butyl 3-(4-(methoxycarbonyl)phenyl)-4-oxopiperidine-1-carboxylate as a white solid (99.2 g). ¹H NMR (400
 20 MHz, DMSO-*d*₆) δ [ppm] 7.92 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 4.15 – 4.02 (m, 2H), 3.96 (dd, *J* = 5.9, 10.8 Hz, 1H), 3.83 (s, 3H), 3.67 – 3.42 (m, 2H), 2.66 – 2.55 (m, 1H), 2.41 (dt, *J* = 4.0, 14.9 Hz, 1H), 1.43 (br s, 9H).

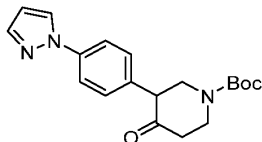
Intermediate K-2: *tert*-butyl 3-(4-cyanophenyl)-4-oxopiperidine-1-carboxylate



25 To a stirred soln of 4-bromobenzonitrile (10.0 g, 54.93 mmol) in toluene (100 mL) was added *tert*-butyl 4-oxopiperidine-1-carboxylate (21.9 g, 109.8 mmol), followed by K₃PO₄ (23.3 g, 109.8 mmol) and the RM was degassed with argon for 15 min at RT. Xantphos (1.58 g, 2.74 mmol) and Pd₂(dba)₃ (1 g, 1.09 mmol) were added, and the RM was stirred at 100 °C for 12 h. The RM was allowed to cool to RT, filtered through Celite®, and the solids were washed with THF (200 mL).
 30 The filtrate was concentrated under reduced pressure, and the resulting residue was diluted with H₂O and extracted with EtOAc (2x 100 mL). The combined org layers were washed with brine (50 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified over silica gel (80 g; eluent: 0 to 100% EtOAc in hexane) to provide *tert*-butyl 3-(4-cyanophenyl)-4-

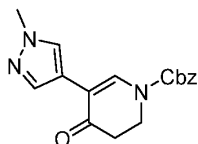
oxopiperidine-1-carboxylate as a brown oil (5 g). LC-MS Method A-1: R_t = 1.75 min; MS m/z $[M-H]^-$ = 299.1.

Intermediate K-3: *tert*-butyl 3-(4-(1*H*-pyrazol-1-yl)phenyl)-4-oxopiperidine-1-carboxylate

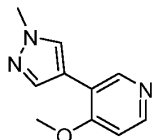


- 5 1-(4-Bromophenyl)-1*H*-pyrazole (339 mg, 1.52 mmol), *tert*-butyl 4-oxopiperidine-1-carboxylate (363 mg, 1.82 mmol), K_3PO_4 (742 mg, 3.50 mmol), and XantPhos-Pd-G2 (CAS#: 1375325-77-1, 95 mg, 0.11 mmol) were combined in a vial. The vial was purged with N_2 , and toluene (3 mL) was added. The mixture was purged with N_2 and stirred at 90 °C for 24 h. The RM was allowed to cool to RT and filtered through Celite®. The solids were washed with DCM, and the combined filtrates
- 10 were concentrated under reduced pressure. The residue was purified over silica gel (40 g; eluent: 15 to 40% EtOAc in heptane) to provide *tert*-butyl 3-(4-(1*H*-pyrazol-1-yl)phenyl)-4-oxopiperidine-1-carboxylate as a pale yellow solid (180 mg). LC-MS Method C-1: R_t = 1.00 min; MS m/z $[M+H]^+$ = 342.2.

Intermediate K-4: benzyl 5-(1-methyl-1*H*-pyrazol-4-yl)-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate



Step 1: 4-methoxy-3-(1-methyl-1*H*-pyrazol-4-yl)pyridine (Intermediate K-4-1)

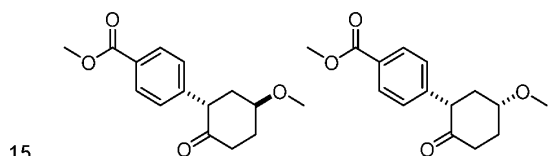


- To a stirred soln of 3-bromo-4-methoxypyridine (10.0 g, 53 mmol) in dioxane/ H_2O (4:1, 100 mL) was added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (13.2 g, 63.82 mmol), followed by K_2CO_3 (14.6 g, 106.4 mmol). The RM was degassed with argon for 15 min at RT. $Pd(dppf)Cl_2 \cdot DCM$ (2.16 g, 2.65 mmol) was added to the mixture, and the RM was stirred at 95 °C for 12 h. The RM was filtered through Celite®, and the solids were washed with THF (100 mL). The filtrate was concentrated under reduced pressure. The residue was diluted with H_2O
- 20 and extracted with EtOAc (2x 100 mL). The combined org layers were washed with brine (50 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. The residue was purified over silica gel (40 g; eluent: 0 to 100% EtOAc in hexane) to provide 4-methoxy-3-(1-methyl-1*H*-pyrazol-4-yl)pyridine as a yellow semi-solid (11 g). LC-MS Method A-1: R_t = 0.21 min; MS m/z $[M+H]^+$ = 190.1.
- 25

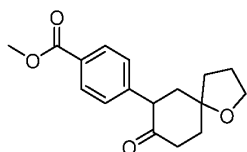
Step 2: **benzyl 5-(1-methyl-1*H*-pyrazol-4-yl)-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (Intermediate K-4)**

To a stirred soln of 4-methoxy-3-(1-methyl-1*H*-pyrazol-4-yl)pyridine (**Intermediate K-4-1**, 8.0 g, 42.78 mmol) in MeOH (80 mL) was added benzyl chloroformate (9.37 g, 54.96 mmol) at 0 °C. The RM was stirred for 10 min, and then NaBH₄ (2.08 g, 54.96 mmol) was added in portions at 0 °C. The RM was allowed to warm to RT and stirred for 2.5 h. The mixture was quenched with H₂O (50 mL) and extracted with EtOAc (3x 50 mL). The combined extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified over silica gel (40 g; eluent: 0 to 100% EtOAc in hexane) to provide benzyl 5-(1-methyl-1*H*-pyrazol-4-yl)-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate as a yellow oil (6.5 g). LC-MS Method A-1: Rt = 1.49 min; MS m/z [M+H]⁺ = 312.1.

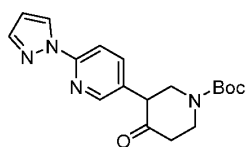
Intermediate *rac*-K-5 and Intermediate *rac*-K-6: *racemic* methyl 4-((1*S,5*S**)-5-methoxy-2-oxocyclohexyl)benzoate and *racemic* methyl 4-((1*S**,5*R**)-5-methoxy-2-oxocyclohexyl)benzoate**



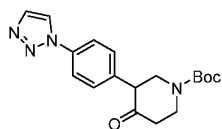
Methyl 4-bromobenzoate (1.050 g, 4.88 mmol), 4-methoxycyclohexan-1-one (1.24 g, 9.68 mmol), K₃PO₄ (2.38 g, 11.2 mmol), Xantphos (113 mg, 0.195 mmol), and Pd₂dba₃ (67 mg, 73 μmol) were combined in a vial. The vial was purged with N₂, and toluene (5 mL) was added. The mixture was purged with N₂ and was stirred at 80 °C overnight. The RM was allowed to cool to RT, filtered to remove solids, and the filtrate was partitioned between EtOAc and H₂O. The separated aq layer was extracted with EtOAc (3x). The combined org phases were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was enriched over silica gel (120 g; eluent: 0 to 40 % EtOAc in heptane) to provide *racemic* methyl 4-((1*S**,5*S**)-5-methoxy-2-oxocyclohexyl)benzoate (**Intermediate *rac*-K-5**, first peak eluting) and *racemic* methyl 4-((1*S**,5*R**)-5-methoxy-2-oxocyclohexyl)benzoate (**Intermediate *rac*-K-6**, second peak eluting). Enriched **Intermediate *rac*-K-5** was purified by RP chromatography (50 g C18 column; eluent: 25 to 50 % ACN in H₂O, each with 0.1% FA) to provide *racemic* methyl 4-((1*S**,5*S**)-5-methoxy-2-oxocyclohexyl)benzoate as a white solid (816 mg). ¹H NMR (400 MHz, CDCl₃) δ [ppm] 8.06 – 7.97 (m, 2H), 7.24 – 7.18 (m, 2H), 4.13 – 4.02 (m, 1H), 3.91 (s, 3H), 3.80 – 3.73 (m, 1H), 3.47 (s, 3H), 2.90 – 2.73 (m, 1H), 2.55 – 2.32 (m, 3H), 2.18 – 2.03 (m, 1H), 2.00 – 1.83 (m, 1H). Enriched **Intermediate *rac*-K-6** was purified by RP chromatography (50 g C18 column; eluent: 25 to 50% ACN in H₂O, each with 0.1 % FA) to provide *racemic* methyl 4-((1*S**,5*R**)-5-methoxy-2-oxocyclohexyl)benzoate as a white solid (217 mg). ¹H NMR (400 MHz, CDCl₃) δ [ppm] 8.05 – 7.99 (m, 2H), 7.22 – 7.17 (m, 2H), 3.91 (s, 3H), 3.86 – 3.75 (m, 1H), 3.74 – 3.61 (m, 1H), 3.43 (s, 3H), 2.65 – 2.49 (m, 3H), 2.49 – 2.36 (m, 1H), 2.06 – 1.93 (m, 1H), 1.89 – 1.75 (m, 1H).

Intermediate K-7: methyl 4-(8-oxo-1-oxaspiro[4.5]decan-7-yl)benzoate

Methyl 4-bromobenzoate (433 mg, 2.01 mmol), Cs₂CO₃ (1.51 g, 4.63 mmol), Pd₂dba₃ (22 mg, 24 μmol), and SPhos (CAS# 657408-07-6, 41 mg, 0.099 mmol) were combined in a vial. The vial was purged with N₂, then toluene (2.5 mL) and 1-oxaspiro[4.5]decan-8-one (379 mg, 2.46 mmol) were added. The RM was purged with N₂ and then stirred at 95 °C for 24 h. The RM was allowed to cool to RT and filtered to remove solids. The solids were washed with DCM, and the combined filtrates were concentrated under reduced pressure. The residue was enriched over silica gel (40 g; eluent: 0 to 40% EtOAc in heptane). The enriched residue from the first diastereomer eluting was purified by RP chromatography (15.5 g C18 column; eluent: 25 to 60 % ACN in H₂O, each with 0.1% FA) to provide methyl 4-(8-oxo-1-oxaspiro[4.5]decan-7-yl)benzoate (105 mg). LC-MS Method C-1: Rt = 0.96 min; MS m/z [M+H]⁺ = 289.0.

Intermediate K-8: *tert*-butyl 3-(6-(1*H*-pyrazol-1-yl)pyridin-3-yl)-4-oxopiperidine-1-carboxylate

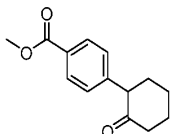
5-Bromo-2-(1*H*-pyrazol-1-yl)pyridine (318 mg, 1.4 mmol), *tert*-butyl 4-oxopiperidine-1-carboxylate (339 mg, 1.7 mmol), K₃PO₄ (692 mg, 3.26 mmol), Xantphos (32.9 mg, 56.8 μmol), and Pd₂dba₃ (26 mg, 28 μmol) were combined in a vial. The vial was purged with N₂, and toluene (3.5 mL) was added. The mixture was purged with N₂ and stirred at 80 °C overnight. The RM was allowed to cool to RT and filtered through Celite®. The solids were washed with DCM, and the combined filtrates were concentrated under reduced pressure. The residue was purified over silica gel (24 g; eluent: 0 to 45% EtOAc in heptane) to provide *tert*-butyl 3-(6-(1*H*-pyrazol-1-yl)pyridin-3-yl)-4-oxopiperidine-1-carboxylate as a colorless oil (100 mg). LC-MS Method C-1: Rt = 0.98 min; MS m/z [M+H]⁺ = 343.2.

Intermediate K-9: *tert*-butyl 3-(4-(1*H*-1,2,3-triazol-1-yl)phenyl)-4-oxopiperidine-1-carboxylate

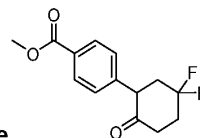
1-(4-Bromophenyl)-1*H*-1,2,3-triazole (679 mg, 3.03 mmol), *tert*-butyl 4-oxopiperidine-1-carboxylate (845 mg, 4.24 mmol), K₃PO₄ (1.48 g, 6.97 mmol), Xantphos (157.8 mg, 0.27 mmol) and Pd₂dba₃ (111 mg, 0.12 mmol) were combined in a vial. The vial was purged with N₂, and

toluene (6 mL) was added. The mixture was purged with N₂ and stirred at 100 °C overnight. The RM was allowed to cool to RT and filtered through Celite®. The solids were washed with DCM, and the combined filtrates were concentrated under reduced pressure. The residue was purified over silica gel (40 g; eluent: 35 to 80% EtOAc in heptane) to provide *tert*-butyl 3-(4-(1*H*-1,2,3-triazol-1-yl)phenyl)-4-oxopiperidine-1-carboxylate (500 mg). LC-MS Method C-1: Rt = 0.91 min; MS m/z [M+H]⁺ = 343.2.

Intermediate K-15: methyl 4-(2-oxocyclohexyl)benzoate



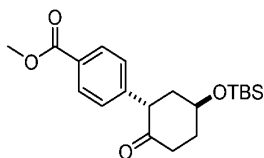
To a soln of methyl 4-bromobenzoate (1.0 g, 4.7 mmol), cyclohexanone (0.82 g, 8.4 mmol), and Xantphos (0.12 g, 0.2 mmol) in toluene (9 mL) was added K₃PO₄ (2.3 g, 11 mmol), and the vial was purged with N₂. Pd₂(dba)₃ (85 mg, 93 μmol) was added, and the RM was stirred at 80 °C for 16 h. The RM was allowed to cool to RT and diluted with H₂O and EtOAc. The org phase was washed with sat. aq NaHCO₃ soln and brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified over silica gel (25 g; eluent: 0 to 50% EtOAc in hexane) to provide methyl 4-(2-oxocyclohexyl)benzoate as a pink solid (705 mg). LC-MS Method B-1: Rt = 0.87 min; MS m/z [M+H]⁺ = 233.2.



Intermediate K-16: methyl 4-(5,5-difluoro-2-oxocyclohexyl)benzoate

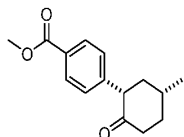
Methyl 4-bromobenzoate (400 mg, 1.86 mmol), 4,4-difluorocyclohexan-1-one (349 mg, 2.6 mmol), K₃PO₄ (908 mg, 4.28 mmol), Xantphos (47.4 mg, 81 μmol), Pd₂dba₃ (34.1 mg, 37.1 μmol), and toluene (5 mL) were combined in a vial. The mixture was purged with N₂ and stirred at 90 °C for 18 h. The RM was allowed to cool to RT and diluted with DCM and H₂O. The separated org phase was concentrated under reduced pressure. The residue was purified over silica gel (24 g; eluent: 0 to 30% EtOAc in cyclohexane) to provide methyl 4-(5,5-difluoro-2-oxocyclohexyl)benzoate as a light brown oil (190 mg). LC-MS Method B-1: Rt = 0.84 min; MS m/z [M+H]⁺ = 269.2.

Intermediate *rac*-K-17: *racemic* methyl 4-((1*S5*S**)-5-((*tert*-butyldimethylsilyl)oxy)-2-oxocyclohexyl)benzoate**



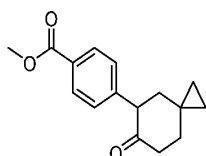
Intermediate *rac*-K-17 was prepared as described for **Intermediate K-16** using 4-((*tert*-butyldimethylsilyl)oxy)cyclohexan-1-one (743.5 mg, 3.26 mmol) to provide *racemic* methyl 4-((1*S**5*S**)-5-((*tert*-butyldimethylsilyl)oxy)-2-oxocyclohexyl)benzoate as a light brown oil (190 mg). LC-MS Method B-1: Rt = 1.55 min; MS m/z [M+H₂O]⁺ = 380.3

5 **Intermediate *rac*-K-18: *racemic* methyl 4-((1*S**,5*R**)-5-methyl-2-oxocyclohexyl)benzoate**



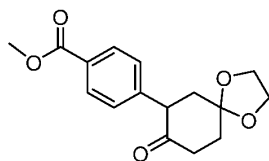
To a stirred soln of methyl 4-bromobenzoate (20.1 g, 93.6 mmol) in toluene (100 mL) was added methyl 4-methylcyclohexan-1-one (21.0 g, 187.2 mmol). The mixture was purged with argon for 10 min. K₃PO₄ (55.6 g, 262.1 mmol), Xantphos (1.08 g, 1.87 mmol), and Pd₂(dba)₃ (1.71 g, 1.87 mmol) were added, and the RM was purged with argon for 10 min. The RM was stirred at 100 °C for 16 h. The RM was allowed to cool to RT and filtered through Celite®. The solids were washed with EtOAc, and the combined filtrates were washed with water. The org phase was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was divided into four portions and each was purified over silica gel (80 g; eluent: 0 to 20% EtOAc in hexane) to provide *racemic* methyl 4-((1*S**,5*R**)-5-methyl-2-oxocyclohexyl)benzoate as an off-white solid (9.0 g total). LC-MS Method A-1: Rt = 3.05 min; MS m/z [M+H]⁺ = 247.1.

Intermediate K-19: methyl 4-(6-oxospiro[2.5]octan-5-yl)benzoate



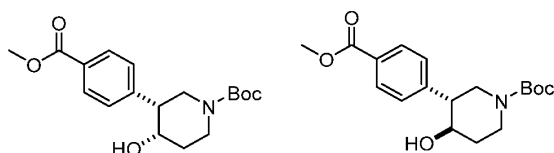
To a stirred soln of methyl 4-bromobenzoate (3.1 g, 14.2 mmol), spiro[2.5]octan-6-one (2.5 g, 20.2 mmol), and Xantphos (367 mg, 0.63 mmol) in toluene (35 mL) was added K₃PO₄ (7.04 g, 33.2 mmol). The mixture was purged with N₂. Pd₂(dba)₃ (264 mg, 0.29 mmol) was added, and the mixture was purged with N₂. The RM was heated at 90 °C for 5 h. The RM was allowed to cool to RT and diluted with toluene and water. The mixture was filtered through Celite®. The org phase of the filtrate was washed with NaHCO₃ and brine, dried over MgSO₄, and concentrated under reduced pressure. Column chromatography over silica gel (220 g; eluent: 5 to 34% EtOAc in hexane) provided enriched material which was then further purified by RP chromatography (86 g C18; eluent: 15 to 75% ACN in H₂O with 0.1% NH₄OH) to provide methyl 4-(6-oxospiro[2.5]octan-5-yl)benzoate as a white solid (1.6 g). LC-MS Method B-1: Rt = 1.05 min; MS m/z [M+H]⁺ = 259.2.

30 **Intermediate K-23: methyl 4-(8-oxo-1,4-dioxaspiro[4.5]decan-7-yl)benzoate**



Methyl 4-bromobenzoate (2.0 g, 9.3 mmol), 1,4-dioxaspiro[4.5]decan-8-one (2.03 g, 13.0 mmol), K_3PO_4 (4.5 g, 21.4 mmol), Xantphos (236.8 mg, 0.41 mmol), Pd_2dba_3 (170.3 mg, 0.19 mol), and toluene (24 mL) were split between two vials. The mixtures were purged with N_2 and stirred at 90 °C for 18 h. The mixtures were allowed to cool to RT, combined, and diluted with DCM and H_2O . The separated org phase was concentrated under reduced pressure. The residue was purified over silica gel (120 g; eluent: 0 to 30% EtOAc in cyclohexane) to provide methyl 4-(8-oxo-1,4-dioxaspiro[4.5]decan-7-yl)benzoate as a light brown solid (1.25 g). LC-MS Method B-1: R_t = 0.73 min; MS m/z $[M+H]^+$ = 291.3.

10 **Intermediate *rac*-A-1 and Intermediate *rac*-A-2: *racemic tert*-butyl (3*R**,4*S**)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate and *racemic tert*-butyl (3*R**,4*R**)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate**

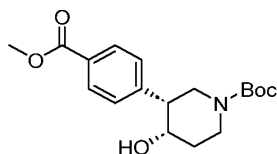


tert-Butyl 3-(4-(methoxycarbonyl)phenyl)-4-oxopiperidine-1-carboxylate (**Intermediate K-1**, 1.09 g, 3.27 mmol) was dissolved in MeOH (25 mL) and cooled to 0 °C. $NaBH_4$ (124 mg, 3.27 mmol) was added, and the RM was stirred for 30 min, during which time it was allowed to warm to RT. The RM was partially concentrated under reduced pressure and then partitioned between EtOAc and sat. aq NH_4Cl soln. The separated org phase was dried over Na_2SO_4 , concentrated under reduced pressure, and purified over silica gel (24 g; eluent: 0 to 100% EtOAc in heptane) to provide *racemic tert*-butyl (3*R**,4*S**)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate (**Intermediate *rac*-A-1**, first peak eluting) as a white solid (299 mg) and *racemic tert*-butyl (3*R**,4*R**)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate (**Intermediate *rac*-A-2**, second peak eluting) as a white solid (558 mg).

Intermediate *rac*-A-1 1H NMR (400 MHz, $CDCl_3$) δ [ppm] 8.09 – 8.00 (m, 2H), 7.39 – 7.33 (m, 2H), 4.18 – 4.16 (m, 1H), 4.07 (dd, J = 13.0, 4.2 Hz, 1H), 4.01 – 3.95 (m, 1H), 3.94 (s, 3H), 3.57 – 3.50 (m, 1H), 3.30 – 3.17 (m, 1H), 2.97 (ddd, J = 11.9, 4.3, 2.4 Hz, 1H), 1.94 – 1.82 (m, 2H), 1.49 (s, 9H). 24 of 25H reported (OH not observed)

Intermediate *rac*-A-2 1H NMR (400 MHz, $CDCl_3$) δ [ppm] 8.10 – 7.98 (m, 2H), 7.43 – 7.31 (m, 2H), 4.34 – 4.09 (m, 2H), 3.94 – 3.87 (m, 4H), 2.94 – 2.75 (m, 2H), 2.68 (ddd, J = 11.5, 9.9, 4.2 Hz, 1H), 2.10 – 2.04 (m, 1H), 1.65 – 1.55 (m, 1H), 1.48 (s, 9H). 24 of 25H reported (OH not observed)

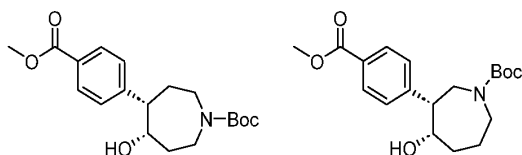
Intermediate A-3: *tert*-butyl (3*R*,4*S*)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate



Step 1a: *tert*-Butyl 3-(4-(methoxycarbonyl)phenyl)-4-oxopiperidine-1-carboxylate (**Intermediate K-1**, 4.19 g, 12.6 mmol) was dissolved in THF (45 mL) and cooled to 0 °C. Potassium tri-*sec*-butylborohydride soln (1M in THF, 20 mL, 20 mmol) was added in a dropwise manner, and the RM was stirred at 0 °C for 1 h. Additional potassium tri-*sec*-butylborohydride soln (1M in THF, 5 mL, 5 mmol) was added in a dropwise manner. The RM was stirred at 0 °C for 30 min. The RM was allowed to warm to RT and then stirred for an additional 20 min. The RM was cooled to 0 °C and quenched with sat. aq NH₄Cl soln. The mixture was extracted with DCM (3x), and the combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified over silica gel (80 g; eluent: 0 to 70% EtOAc in heptane) to provide *racemic tert*-butyl (3*R*,4*S*)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate as a white solid (2.63 g). LC-MS Method C-1: Rt = 0.97 min; MS m/z [M-*t*Bu+2H]⁺ = 280.1.

Step 1b: Chiral separation and analytics according to Method SFC-1: 2.3 g provided **Intermediate A-3** (peak 1): 1.22 g, white solid. LC-MS Method C-1: Rt = 0.99 min; MS m/z [M-*t*Bu+2H]⁺ = 280.1. Analytical chiral HPLC: Rt = 1.67 min; 100% ee.

Intermediate A-4 and Intermediate A-5: *tert*-butyl (4*S*,5*S*)-4-hydroxy-5-(4-(methoxycarbonyl)phenyl)azepane-1-carboxylate and *tert*-butyl (3*R*,4*S*)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)azepane-1-carboxylate



Step 1a: To a soln of methyl 4-bromobenzoate (8.0 g, 37.2 mmol) in toluene (80 mL) was added *tert*-butyl 4-oxoazepane-1-carboxylate (9.52 g, 44.6 mmol), followed by K₃PO₄ (15.7 g, 74.4 mmol). The RM was degassed with argon for 15 min at RT, and then Xantphos (1.07 g, 1.86 mmol) and Pd₂(dba)₃ (681.2 mg, 0.74 mmol) were added. The RM was stirred at 100 °C for 12 h. The RM was allowed to cool to RT, filtered through Celite®, and the solids were washed with THF (200 mL). The combined filtrates were concentrated under reduced pressure, and the resulting residue was diluted with H₂O and extracted with EtOAc (2x 100 mL). The combined org layers were washed with brine (50 mL), dried over Na₂SO₄, and concentrated under reduced pressure. Column chromatography over silica gel (48 g; eluent: 0 to 100% EtOAc in hexane) provided enriched material which was purified using RP chromatography (24 g C18 column; eluent: 0 to

100% ACN in H₂O with 0.05% NH₄OH) to provide a mixture of *tert*-butyl 4-(4-(methoxycarbonyl)phenyl)-5-oxoazepane-1-carboxylate and *tert*-butyl 3-(4-(methoxycarbonyl)phenyl)-4-oxoazepane-1-carboxylate as a yellow solid (4.0 g).

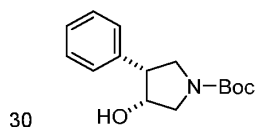
Step 1a: To a stirred soln of *tert*-butyl 4-(4-(methoxycarbonyl)phenyl)-5-oxoazepane-1-carboxylate and *tert*-butyl 3-(4-(methoxycarbonyl)phenyl)-4-oxoazepane-1-carboxylate (4.0 g, 11.5 mmol) in THF (80 mL) was added lithium tri-*sec*-butylborohydride soln (1M in THF, 13.8 mL, 13.8 mmol) at -20 °C. The RM was stirred at -20 °C for 10 min. The mixture was diluted with EtOAc (50 mL), quenched with sat. aq NH₄Cl soln (50 mL), and allowed to warm to RT. The aq was phase was extracted with EtOAc (2x 50 mL). The combined org phases were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was enriched over silica gel (24 g; eluent: 0 to 100% EtOAc in hexane) to provide a mixture of *racemic tert*-butyl (4*S**,5*S**)-4-hydroxy-5-(4-(methoxycarbonyl)phenyl)azepane-1-carboxylate and *racemic tert*-butyl (3*R**,4*S**)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)azepane-1-carboxylate as an off-white solid (2.7 g).

Step 1c: Chiral separation according to Method SFC-2: 2.7 g provided a mixture of *tert*-butyl (4*S*,5*S*)-4-hydroxy-5-(4-(methoxycarbonyl)phenyl)azepane-1-carboxylate and *racemic tert*-butyl (3*R**,4*S**)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)azepane-1-carboxylate (peak 1, 1.6 g).

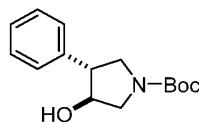
Step 1d: Chiral separation and analytics according to Method SFC-3: 1.6 g peak 1 from Step 1c above provided **Intermediate A-4** (peak 1): 375 mg, off-white solid. Analytical chiral HPLC: Rt = 4.85 min; 98.6% ee. ¹H NMR (400 MHz, CD₃OD) δ [ppm] 7.97 – 7.88 (m, 2H), 7.43 (d, *J* = 7.04 Hz, 2H), 4.07 – 4.02 (m, 1H), 3.88 (s, 3H), 3.76 – 3.59 (m, 2H), 3.49 – 3.35 (m, 2H), 2.87 – 2.79 (m, 1H), 2.52 – 2.33 (m, 1H), 1.94 – 1.79 (m, 3H), 1.50 (d, *J* = 3.37 Hz, 9H). 26 of 27H reported (OH not observed).

Intermediate A-5 (peak 3): 470 mg, off-white solid. Analytical chiral HPLC: Rt = 10.04 min, 98.9% ee. NMR (400 MHz, CD₃OD) δ [ppm] 8.00 – 7.91 (m, 2H), 7.45 – 7.40 (m, 2H), 4.10 – 4.05 (m, 1H), 3.89 (s, 3H) 3.81 – 3.63 (m, 2H), 3.65 – 3.53 (m, 2H), 3.27 – 3.21 (m, 1H), 3.07 – 2.97 (m, 1H), 2.19 - 2.03 (m, 2H), 1.85 – 1.74 (m, 1H), 1.73 – 1.62 (m, 1H), 1.49 – 1.40 (m, 9 H).

Intermediate rac-A-6: *racemic tert*-butyl (3*R**,4*R**)-3-hydroxy-4-phenylpyrrolidine-1-carboxylate

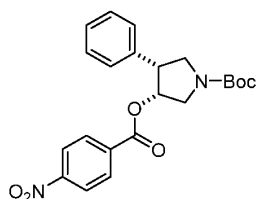


Step 1: *racemic tert*-butyl (3*S**,4*R**)-3-hydroxy-4-phenylpyrrolidine-1-carboxylate (**Intermediate rac-A-6-1**)



tert-Butyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (881 mg, 4.76 mmol) and copper(I) iodide (90 mg, 0.47 mmol) were combined in a dry flask, and THF (9 mL) was added. The mixture was cooled to 0 °C, and a phenylmagnesium chloride soln (2M in THF, 5.0 mL, 10 mmol) was added in a dropwise manner. The RM was allowed to warm to RT and stirred overnight. The RM was quenched with sat. aq NH₄Cl soln, and the separated aq layer was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified over silica gel (40 g; eluent: 0 to 50% EtOAc in heptane) to provide *racemic tert*-butyl (3*S**,4*R**)-3-hydroxy-4-phenylpyrrolidine-1-carboxylate as a colorless oil (1.07 g). LC-MS Method C-1: Rt = 0.95 min; MS m/z [M-Boc+2H]⁺ = 164.2.

- 10 Step 2: ***racemic tert*-butyl (3*R**,4*R**)-3-((4-nitrobenzoyl)oxy)-4-phenylpyrrolidine-1-carboxylate (Intermediate *rac*-A-6-2)**

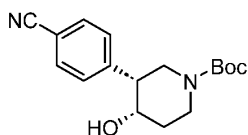


- Racemic tert*-butyl (3*S**,4*R**)-3-hydroxy-4-phenylpyrrolidine-1-carboxylate (**Intermediate *rac*-A-6-1**, 530 mg, 2.01 mmol), 4-nitrobenzoic acid (673 mg, 4.03 mmol), and PPh₃ (1.06 g, 4.03 mmol) were dissolved in toluene (6 mL) and cooled to 0 °C. DIAD (0.78 mL, 4.03 mmol) was added, the RM was stirred at 0 °C for 15 min, and then the RM was allowed to warm to RT. The RM was stirred at RT for 4 h. Sat. aq NaHCO₃ soln was added, and the aq phase was extracted with DCM. The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified over silica gel (40 g; eluent: 0 to 40% EtOAc in heptane) to provide *racemic tert*-butyl (3*R**,4*R**)-3-((4-nitrobenzoyl)oxy)-4-phenylpyrrolidine-1-carboxylate as a colorless oil (1.03 g). LC-MS Method C-1 Rt = 0.95 min; MS m/z [M-*t*Bu+2H]⁺ = 357.2.

Step 3: ***racemic tert*-butyl (3*R**,4*R**)-3-hydroxy-4-phenylpyrrolidine-1-carboxylate (Intermediate *rac*-A-5)**

- 25 *Racemic tert*-butyl (3*R**,4*R**)-3-((4-nitrobenzoyl)oxy)-4-phenylpyrrolidine-1-carboxylate (**Intermediate *rac*-A-6-2**, 1.03 g, 2.50 mmol) was dissolved in MeOH (10 mL), and K₂CO₃ (1.39 g, 10 mmol) was added. The RM was stirred at RT for 90 min, and then concentrated under reduced pressure. The residue was partitioned between DCM and sat. aq NH₄Cl soln. The aq layer was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified over silica gel (24 g; eluent: 0 to 45% EtOAc in heptane) to provide *racemic tert*-butyl (3*R**,4*R**)-3-hydroxy-4-phenylpyrrolidine-1-carboxylate as a colorless oil (548 mg). LC-MS Method C-1: Rt = 0.93 min; MS m/z [M-*t*Bu+2H]⁺ = 208.1.

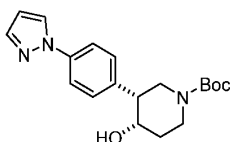
Intermediate A-7: *tert*-butyl (3*R*,4*S*)-3-(4-cyanophenyl)-4-hydroxypiperidine-1-carboxylate



Step 1a: Prepared as described for **Intermediate A-4** using *tert*-butyl 3-(4-cyanophenyl)-4-oxopiperidine-1-carboxylate (**Intermediate K-2**, 1.0 g, 3.32 mmol) at 0 °C to provide *racemic tert*-butyl (3*R**,4*S**)-3-(4-cyanophenyl)-4-hydroxypiperidine-1-carboxylate as an off-white solid (300 mg).

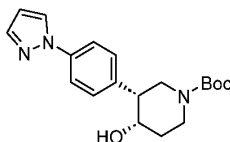
Step 1b: Chiral separation and analytics according to Method SFC-4: 1.5 g from multiple batches of *racemic tert*-butyl (3*R**,4*S**)-3-(4-cyanophenyl)-4-hydroxypiperidine-1-carboxylate provided **Intermediate A-7**: 700 mg, off-white solid. Analytical chiral HPLC: Rt = 6.34 min; 96% ee. ¹H NMR (400 MHz, CD₃OD) δ [ppm] 7.71 – 7.64, (m, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 4.13 – 4.08 (m, 1H), 3.98 – 3.83 (m, 1H), 3.86 – 3.81 (m, 1H), 3.83 – 3.76 (m, 1H), 3.63 – 3.44 (m, 1H), 3.12 – 2.98 (m, 1H), 2.95 – 2.87 (m, 1H), 1.85 – 1.76 (m, 2H), 1.51 (s, 9 H).

Intermediate rac-A-8: *racemic tert*-butyl (3*R,4*S**)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-4-hydroxypiperidine-1-carboxylate**



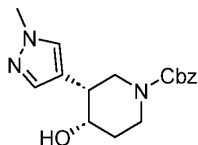
tert-Butyl 3-(4-(1*H*-pyrazol-1-yl)phenyl)-4-oxopiperidine-1-carboxylate (**Intermediate K-3**, 500 mg, 1.47 mmol) was dissolved in MeOH (3 mL) and NaBH₄ (100 mg, 2.64 mmol) was added. The RM was stirred at RT for 2 h. The RM was quenched with H₂O, and the mixture was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. Column chromatography over silica gel (24 g; eluent: 10 to 80 % EtOAc in heptane) provided enriched material from the first peak to elute. The material was purified by RP chromatography (50 g C18 column; eluent: 25 to 50% ACN in H₂O, each with 0.1% FA) to provide *racemic tert*-butyl (3*R**,4*S**)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-4-hydroxypiperidine-1-carboxylate as a colorless oil (82 mg). ¹H NMR (400 MHz, CDCl₃) δ [ppm] 7.91 (d, *J* = 2.4 Hz, 1H), 7.71 (d, *J* = 1.8 Hz, 1H), 7.68 – 7.61 (m, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 6.49 – 6.40 (m, 1H), 4.15 – 4.08 (m, 1H), 3.98 – 3.82 (m, 1H), 3.57 – 3.41 (m, 1H), 3.30 – 3.16 (m, 1H), 2.97 – 2.85 (m, 1H), 1.88 – 1.79 (m, 2H), 1.68 – 1.60 (m, 1H), 1.47 (s, 9H). 24 of 25 reported (OH not observed).

Intermediate A-8-1: *tert*-butyl (3*R*,4*S*)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-4-hydroxypiperidine-1-carboxylate



Chiral separation of **Intermediate rac-A-8** and analytics according to Method SFC-11: 271 mg provided **Intermediate A-8-1** (peak 1): 99 mg, white solid. LC-MS Method C-4: Rt = 2.11 min; MS m/z [M-fBu+2H]⁺ = 288.6. Analytical chiral HPLC: Rt = 2.38 min; 96% ee.

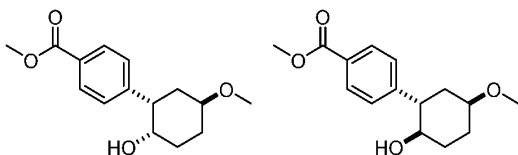
Intermediate A-9: benzyl (3R,4S)-4-hydroxy-3-(1-methyl-1H-pyrazol-4-yl)piperidine-1-carboxylate



Step 1a: To a stirred soln of benzyl 5-(1-methyl-1H-pyrazol-4-yl)-4-oxo-3,4-dihydropyridine-1(2H)-carboxylate (**Intermediate K-4**, 4.9 g, 15.7 mmol) in EtOH (50 mL) was added PtO₂ (4.9 g) at room temperature. The RM was stirred at RT for 16 h under H₂ atmosphere (balloon). The RM was filtered through Celite®, and the solids were washed with DCM. The combined filtrates were concentrated under reduced pressure. The crude material was purified by preparatory HPLC (Waters XBridge C18 19 x 250 mm; 5 µm; eluent: 0 to 60% ACN in H₂O with 0.02% NH₄OH) to provide *racemic* benzyl (3R*,4S*)-4-hydroxy-3-(1-methyl-1H-pyrazol-4-yl)piperidine-1-carboxylate and *racemic* benzyl (3R*,4R*)-4-hydroxy-3-(1-methyl-1H-pyrazol-4-yl)piperidine-1-carboxylate as a mixture of diastereomers (1.6 g).

Step 1b: Separation and analytics according to Method SFC-5: 1.6 g provided **Intermediate A-9** (peak 2): 367 mg. Analytical chiral HPLC: Rt = 4.77 min; 98.8% ee. ¹H NMR (400 MHz, CD₃OD) δ [ppm] 7.49 – 7.42 (m, 1H), 7.41 – 7.27 (m, 6H), 5.19 – 5.06 (m, 2H), 4.03 – 3.99 (m, 1H), 3.82 (s, 3H), 3.76 (dd, J = 13.20, 4.11 Hz, 1H), 3.75 – 3.63 (m, 1H), 3.58 – 3.46 (m, 2H), 2.89 (dt, J = 9.28, 3.58 Hz, 1H), 1.69 – 1.79 (m, 2H). 20 of 21H reported (OH not observed)

Intermediate rac-A-10 and Intermediate rac-A-11: *racemic* methyl 4-((1S*,2S*,5S*)-2-hydroxy-5-methoxycyclohexyl)benzoate and *racemic* methyl 4-((1S*,2R*,5S*)-2-hydroxy-5-methoxycyclohexyl)benzoate

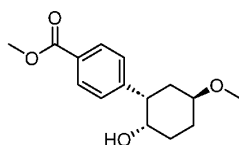


Racemic methyl 4-((1R*,5R*)-5-methoxy-2-oxocyclohexyl)benzoate (**Intermediate rac-K-5**, 817 mg, 3.12 mmol) was combined with MeOH (3 mL) and THF (3 mL). The soln was cooled to 0 °C, and NaBH₄ (118 mg, 3.12 mmol) was added. The RM was allowed to warm to RT and stirred for 1 h. The RM was quenched with H₂O and partially concentrated under reduced pressure. The mixture was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified over silica gel (40 g; eluent: 0 to 50% EtOAc in heptane) to provide *racemic* methyl 4-((1S*,2S*,5S*)-2-hydroxy-5-methoxycyclohexyl)benzoate (**Intermediate rac-A-10**, first peak eluting, 160 mg) and

racemic methyl 4-((1*S**,2*R**,5*S**)-2-hydroxy-5-methoxycyclohexyl)benzoate (**Intermediate rac-A-11**, second peak eluting, 587 mg). **Intermediate rac-A-10**: ¹H NMR (400 MHz, CDCl₃) δ [ppm] 8.04 – 7.91 (m, 2H), 7.37 – 7.29 (m, 2H), 4.06 – 3.99 (m, 1H), 3.90 (s, 3H), 3.73 – 3.64 (m, 1H), 3.34 (s, 3H), 3.24 – 3.15 (m, 1H), 2.29 – 2.14 (m, 1H), 2.09 – 1.95 (m, 1H), 1.95 – 1.86 (m, 1H), 1.86 – 1.69 (m, 3H), 1.43 – 1.25 (m, 1H).

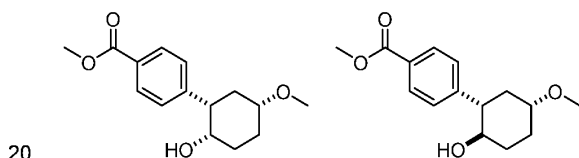
Intermediate rac-A-11: ¹H NMR (400 MHz, CDCl₃) δ [ppm] 8.04 – 7.97 (m, 2H), 7.45 – 7.30 (m, 2H), 3.91 (s, 3H), 3.82 – 3.68 (m, 1H), 3.57 – 3.51 (m, 1H), 3.35 (s, 3H), 3.00 – 2.87 (m, 1H), 2.20 – 2.02 (m, 2H), 1.96 – 1.85 (m, 1H), 1.85 – 1.70 (m, 1H), 1.68 – 1.48 (m, 2H), 1.48 – 1.41 (m, 1H).

Intermediate A-10-1: methyl 4-((1*S*,2*S*,5*S*)-2-hydroxy-5-methoxycyclohexyl)benzoate



Chiral separation of **Intermediate rac-A-10** and analytics according to Method SFC-12: 20 g provided **Intermediate A-10-1** (peak 1): 9.0 g, gray solid. ¹H NMR (400 MHz, CDCl₃) δ [ppm] 8.02 – 7.92 (m, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 4.00 – 3.95 (m, 1H), 3.85 (s, 3H), 3.70 (s, 1H), 3.35 – 3.29 (m, 3H), 3.22 – 3.13 (m, 1H), 2.24 – 2.15 (m, 1H), 2.03 – 1.94 (m, 1H), 1.89 – 1.86 (m, 1H), 1.84 – 1.67 (m, 3H), 1.50 (s, 1H). Analytical chiral HPLC: *R*_t = 1.63 min; 99% *ee*.

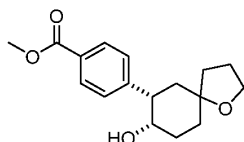
Intermediate rac-A-12 and **Intermediate rac-A-13**: *racemic* methyl 4-((1*S**,2*S**,5*R**)-2-hydroxy-5-methoxycyclohexyl)benzoate and *racemic* methyl 4-((1*S**,2*R**,5*R**)-2-hydroxy-5-methoxycyclohexyl)benzoate



Intermediate rac-A-12 and **Intermediate rac-A-13** were prepared as described for **Intermediate rac-A-10** and **Intermediate rac-A-11** using *racemic* methyl 4-((1*S**,5*R**)-5-methoxy-2-oxocyclohexyl)benzoate (**Intermediate rac-K-6**, 217 mg, 0.83 mmol) to provide *racemic* methyl 4-((1*S**,2*S**,5*R**)-2-hydroxy-5-methoxycyclohexyl)benzoate (**Intermediate rac-A-12**, first peak eluting, 45 mg) and *racemic* methyl 4-((1*S**,2*R**,5*R**)-2-hydroxy-5-methoxycyclohexyl)benzoate (**Intermediate rac-A-13**, second peak eluting, 137 mg). **Intermediate rac-A-12**: ¹H NMR (400 MHz, CDCl₃) δ [ppm] 8.05 – 7.98 (m, 2H), 7.38 – 7.31 (m, 2H), 4.01 – 3.96 (m, 1H), 3.91 (s, 3H), 3.41 (s, 3H), 3.39 – 3.25 (m, 1H), 2.90 – 2.75 (m, 1H), 2.14 – 2.00 (m, 3H), 1.99 – 1.87 (m, 1H), 1.73 – 1.61 (m, 2H), 1.59 – 1.44 (m, 1H).

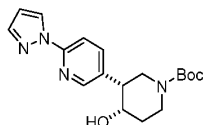
Intermediate rac-A-13: ¹H NMR (400 MHz, CDCl₃) δ [ppm] 8.01 (d, *J* = 7.6 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 3.90 (s, 3H), 3.77 – 3.64 (m, 1H), 3.35 (s, 3H), 3.33 – 3.25 (m, 1H), 2.66 – 2.49 (m, 1H), 2.23 – 2.07 (m, 3H), 1.62 – 1.34 (m, 4H).

Intermediate rac-A-14: *racemic* methyl 4-((7*S**,8*S**)-8-hydroxy-1-oxaspiro[4.5]decan-7-yl)benzoate



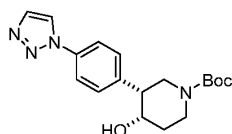
Racemic methyl 4-((5*S**,7*S**)-8-oxo-1-oxaspiro[4.5]decan-7-yl)benzoate (**Intermediate rac-K-7**, 128 mg, 0.44 mmol) was combined with MeOH (2 mL) and THF (0.5 mL). NaBH₄ (50 mg, 1.3 mmol) was added, and the RM was stirred at RT for 1 h. The RM was quenched with H₂O and partially concentrated under reduced pressure. The mixture was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified over silica gel (12 g; eluent: 10 to 50% EtOAc in heptane) to provide *racemic* methyl 4-((7*S**,8*S**)-8-hydroxy-1-oxaspiro[4.5]decan-7-yl)benzoate (first diastereomer to elute, 20.9 mg). ¹H NMR (400 MHz, CDCl₃) δ [ppm] 8.04 – 7.95 (m, 2H), 7.38 – 7.30 (m, 2H), 4.05 – 3.97 (m, 1H), 3.91 (s, 3H), 3.88 – 3.78 (m, 2H), 3.31 – 3.20 (m, 1H), 2.21 (t, *J* = 13.2 Hz, 1H), 2.14 – 1.71 (m, 7H), 1.70 – 1.51 (m, 2H). 21 of 22H reported (OH not observed).

Intermediate rac-A-15: *racemic tert*-butyl (3*R**,4*S**)-3-(6-(1*H*-pyrazol-1-yl)pyridin-3-yl)-4-hydroxypiperidine-1-carboxylate



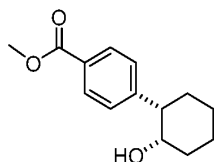
tert-Butyl 3-(6-(1*H*-pyrazol-1-yl)pyridin-3-yl)-4-oxopiperidine-1-carboxylate (**Intermediate K-8**, 96 mg, 0.28 mmol) was dissolved in MeOH (3 mL), and NaBH₄ (25 mg, 0.66 mmol) was added. The RM was stirred at RT for 1 h. The RM was quenched with H₂O, and the mixture was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified over silica gel (24 g; eluent: 15 to 50 % EtOAc in heptane) to provide *racemic tert*-butyl (3*R**,4*S**)-3-(6-(1*H*-pyrazol-1-yl)pyridin-3-yl)-4-hydroxypiperidine-1-carboxylate as a colorless oil (82 mg). ¹H NMR (400 MHz, CDCl₃) δ [ppm] 8.53 (d, *J* = 2.6 Hz, 1H), 8.30 (d, *J* = 2.3 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.74 (dd, *J* = 15.6, 2.1 Hz, 2H), 6.50 – 6.47 (m, 1H), 4.18 – 4.14 (m, 1H), 3.98 – 3.89 (m, 1H), 3.60 – 3.50 (m, 1H), 3.37 – 3.19 (m, 1H), 2.97 – 2.90 (m, 1H), 1.91 – 1.81 (m, 2H), 1.77 – 1.68 (m, 1H), 1.47 (s, 9H). 23 of 24H reported (OH not observed).

Intermediate rac-A-16: *racemic tert*-butyl (3*R**,4*S**)-3-(4-(1*H*-1,2,3-triazol-1-yl)phenyl)-4-hydroxypiperidine-1-carboxylate



Intermediate *rac*-A-16 was prepared as described for **Intermediate *rac*-A-15** using *tert*-butyl 3-(4-(1*H*-1,2,3-triazol-1-yl)phenyl)-4-oxopiperidine-1-carboxylate (**Intermediate K-9**, 500 mg, 1.46 mmol) to provide *racemic tert*-butyl (3*R**,4*S**)-3-(4-(1*H*-1,2,3-triazol-1-yl)phenyl)-4-hydroxypiperidine-1-carboxylate as white solid (72 mg). ¹H NMR (400 MHz, CDCl₃) δ [ppm] 7.99 (d, *J* = 1.3 Hz, 1H), 7.86 (d, *J* = 1.2 Hz, 1H), 7.76 – 7.70 (m, 2H), 7.47 – 7.41 (m, 2H), 4.20 – 4.15 (m, 1H), 4.10 – 4.04 (m, 1H), 4.00 – 3.92 (m, 1H), 3.58 – 3.48 (m, 1H), 3.28 – 3.24 (m, 1H), 3.00 – 2.94 (m, 1H), 1.92 – 1.81 (m, 2H), 1.48 (s, 9H). 23 of 24H reported (OH not observed).

Intermediate *rac*-A-22: *racemic* methyl 4-((1*S,2*S**)-2-hydroxycyclohexyl)benzoate**

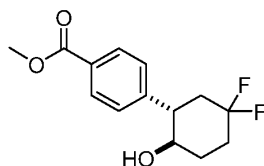


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Methyl 4-(2-oxocyclohexyl)benzoate (**Intermediate K-15**, 705 mg, 3.03 mmol) was combined with MeOH (4 mL). The soln was cooled to 0 °C, and NaBH₄ (264 mg, 6.98 mmol) was added. The RM was allowed to warm to RT and stirred for 1 h. The RM was quenched with H₂O and extracted with DCM (2x). The combined org phases were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified over silica gel (25 g; eluent: 0 to 30% EtOAc in heptane) to provide *racemic* methyl 4-((1*S**,2*S**)-2-hydroxycyclohexyl)benzoate as a white solid (first peak eluting, 264 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ [ppm] 7.87 – 7.84 (m, 2H), 7.41 – 7.38 (m, 2H), 4.30 – 4.28 (m, 1H), 3.89 – 3.85 (m, 1H), 3.83 (s, 3H), 2.74 – 2.66 (m, 1H), 2.05 – 1.96 (m, 1H), 1.79 – 1.73 (m, 2H), 1.69 – 1.63 (m, 1H), 1.59 – 1.53 (m, 1H), 1.50 – 1.45 (m, 1H), 1.44 – 1.39 (m, 1H), 1.39 – 1.29 (m, 1H).

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Intermediate *rac*-A-23: *racemic* methyl 4-((1*S,2*R**)-5,5-difluoro-2-hydroxycyclohexyl)benzoate**

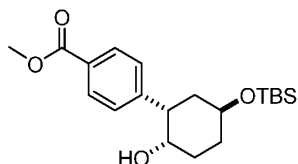


Methyl 4-(5,5-difluoro-2-oxocyclohexyl)benzoate (**Intermediate K-16**, 100 mg, 0.37 mmol) was dissolved in MeOH (2.5 mL). The soln was cooled to 0 °C, and NaBH₄ (32.4 mg, 0.86 mmol) was added. The RM was stirred for 1 h. The RM was quenched with sat NH₄Cl soln and EtOAc and allowed to warm to RT. The aq phase was extracted with EtOAc (2x). The combined org phases were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified over silica gel (12 g; eluent: 0 to 30% EtOAc in cyclohexane) to

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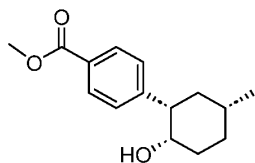
provide *racemic* methyl 4-((1*S**,2*R**)-5,5-difluoro-2-hydroxycyclohexyl)benzoate as a white solid (82.5 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ [ppm] 7.95 – 7.81 (m, 2H), 7.52 – 7.35 (m, 2H), 4.66 (d, *J* = 6.1 Hz, 1H), 3.84 (s, 3H), 3.80 – 3.69 (m, 1H), 2.81 – 2.69 (m, 1H), 2.32 – 2.14 (m, 1H), 2.12 – 1.93 (m, 4H), 1.61 – 1.48 (m, 1H).

- 5 **Intermediate *rac*-A-24: *racemic* methyl 4-((1*S**,2*S**,5*S**)-5-((*tert*-butyldimethylsilyl)oxy)-2-hydroxycyclohexyl)benzoate**



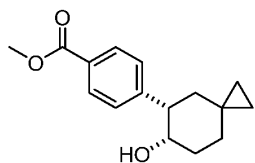
- Intermediate *rac*-A-24** was prepared as described for **Intermediate *rac*-A-23** using *racemic* methyl 4-((1*S**5*S**)-5-((*tert*-butyldimethylsilyl)oxy)-2-oxocyclohexyl)benzoate (**Intermediate *rac*-K-17**, 235 mg, 0.64 mmol) and lithium tri-*sec*-butylborohydride soln (1M in THF, 0.84 mL, 0.84 mmol) to provide *racemic* methyl 4-((1*S**,2*S**,5*S**)-5-((*tert*-butyldimethylsilyl)oxy)-2-hydroxycyclohexyl)benzoate as colorless semi-solid (73 mg). LC-MS Method B-1: *R*_t = 1.6 min; MS *m/z* [*M*+*H*]⁺ = 365.4.

Intermediate A-25: methyl 4-((1*S*,2*S*,5*R*)-2-hydroxy-5-methylcyclohexyl)benzoate



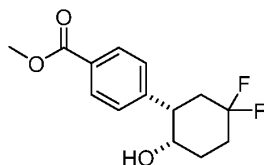
- 15 Step 1a: *Racemic* methyl 4-((1*S**,5*R**)-5-methyl-2-oxocyclohexyl)benzoate (**Intermediate K-18**, 6.5 g, 26.4 mmol) was dissolved in MeOH (65 mL) and cooled to 0 °C. NaBH₄ (2.0 mg, 52.8 mmol) was added, and the RM was stirred for 30 min. The RM was diluted with H₂O and EtOAc and allowed to warm to RT. The separated org phase was dried over Na₂SO₄, concentrated under reduced pressure, and purified over silica gel (80 g; eluent: 0 to 30% EtOAc in heptane) to provide *racemic* methyl 4-((1*S**,2*S**,5*R**)-2-hydroxy-5-methylcyclohexyl)benzoate (first peak eluting) as an off-white solid (1.0 g).
- 20 Step 1b: Chiral separation and analytics according to Method SFC-18: 2.67 g provided **Intermediate A-25** (peak 1): 1.17 g, white solid. LC-MS Method A-1: *R*_t = 3.27 min; MS *m/z* [*M*+*H*]⁺ = 249.1. Analytical chiral HPLC: *R*_t = 2.87 min; 99.7% ee.

Intermediate *rac*-A-26: *racemic* methyl 4-((5*S,6*S**)-6-hydroxyspiro[2.5]octan-5-yl)benzoate**



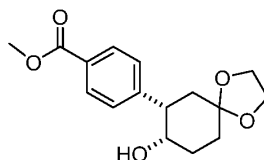
Methyl 4-(6-oxospiro[2.5]octan-5-yl)benzoate (**Intermediate K-19**, 1.05 g, 4.07 mmol) was combined with THF (10.5 mL). The soln was cooled to -78 °C, and lithium tri-*sec*-butylborohydride soln (1M in THF, 8.1 mL, 8.1 mmol) was added in a dropwise manner. The RM was stirred for 1 h. The RM was quenched with MeOH and aq HCl (2M) and allowed to warm to RT. EtOAc and H₂O were added. The separated aq phase was extracted with EtOAc. The combined org phases were washed with brine, dried over MgSO₄, and concentrated under reduced pressure. Column chromatography over silica gel (40 g; eluent: 5 to 30% EtOAc in heptane) followed by recrystallization from hexane provided *racemic* methyl 4-((5*S**,6*S**)-6-hydroxyspiro[2.5]octan-5-yl)benzoate as a white solid (399 mg). LC-MS Method B-1: Rt = 1.15 min; MS m/z [M+H]⁺ = 261.2.

Intermediate *rac*-A-28: *racemic* methyl 4-((1*S**,2*S**)-5,5-difluoro-2-hydroxycyclohexyl)benzoate



Methyl 4-(5,5-difluoro-2-oxocyclohexyl)benzoate (**Intermediate K-16**, 97 mg, 0.36 mmol) was combined with THF (2 mL). The soln was cooled to -78 °C, and lithium tri-*sec*-butylborohydride soln (1M in THF, 0.58 mL, 0.58 mmol) was added. The RM was stirred for 1 h. The RM was quenched with sat. aq NH₄Cl soln, allowed to warm to RT, and diluted with EtOAc. The aq phase was extracted with EtOAc (2x). The combined org phases were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified over silica gel (12 g; eluent: 0 to 25% EtOAc in cyclohexane) to provide *racemic* methyl 4-((1*S**,2*S**)-5,5-difluoro-2-hydroxycyclohexyl)benzoate as a white solid (82.5 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ [ppm] 7.93 – 7.83 (m, 2H), 7.52 – 7.34 (m, 2H), 4.74 (d, *J* = 4.4 Hz, 1H), 3.92 – 3.87 (m, 1H), 3.84 (s, 3H), 3.09 – 2.98 (m, 1H), 2.58 – 2.40 (m, 1H), 2.24 – 2.02 (m, 1H), 2.01 – 1.73 (m, 4H).

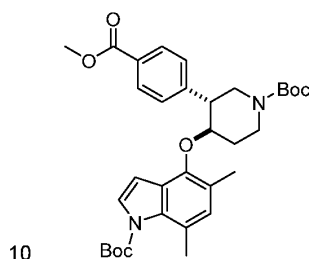
Intermediate *rac*-A-31: *racemic* methyl 4-((7*S**,8*S**)-8-hydroxy-1,4-dioxaspiro[4.5]decan-7-yl)benzoate



Methyl 4-(8-oxo-1,4-dioxaspiro[4.5]decan-7-yl)benzoate (**Intermediate K-23**, 1.50 g, 5.17 mmol) was combined with THF (50 mL). The soln was cooled to -78 °C, and a lithium tri-*sec*-butylborohydride soln (1M in THF, 8.7 mL, 8.7 mmol) was added in a dropwise manner. The RM was stirred for 1 h. Additional lithium tri-*sec*-butylborohydride soln (1M in THF, 3.1 mL, 3.1 mmol)

was added in a dropwise manner, and the RM was stirred for 1 h. The RM was diluted with MeOH, sat. aq NH₄Cl soln, and MeOH, and allowed to warm to RT. The separated aq phase was extracted with EtOAc. The combined org phases were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. Column chromatography over silica gel (120 g; eluent: 0 to 30% EtOAc in cyclohexane) provided *racemic* methyl 4-((7*S**,8*S**)-8-hydroxy-1,4-dioxaspiro[4.5]decan-7-yl)benzoate as a white solid (960 mg). LC-MS Method B-1: Rt = 0.71 min; MS m/z [M+H]⁺ = 293.1.

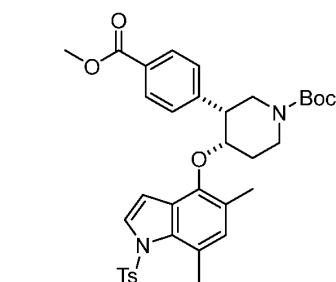
Intermediate *rac*-M-1: *racemic tert*-butyl 4-(((3*R**,4*R**)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate



Racemic tert-butyl (3*R**,4*S**)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate (**Intermediate *rac*-A-1**, 150 mg, 0.45 mmol), PPh₃ (160 mg, 0.61 mmol), and *tert*-butyl 4-hydroxy-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate I-1**, 93 mg, 0.36 mmol) were dissolved in THF (1.25 mL). DIAD (115 μ L, 0.59 mmol) was added, and the RM was stirred at RT overnight.

15 The RM was concentrated under reduced pressure and purified over silica gel (12 g; eluent: 0 to 30% EtOAc in heptane) to provide *racemic tert*-butyl 4-(((3*R*,4*R**)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate as a colorless foam (48 mg). LC-MS Method C-1: Rt = 1.57 min; MS m/z [M+H]⁺ = 579.3.

Intermediate *rac*-M-2: *racemic tert*-butyl (3*R**,4*S**)-4-((5,7-dimethyl-1-tosyl-1*H*-indol-4-yl)oxy)-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate

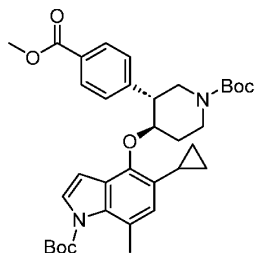


5,7-Dimethyl-1-tosyl-1*H*-indol-4-ol (**Intermediate I-2**, 60 mg, 0.19 mmol), *racemic tert*-butyl (3*R**,4*R**)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate (**Intermediate *rac*-A-2**, 64 mg, 0.19 mmol), and PPh₃ (54.7 mg, 0.28 mmol) were dissolved in THF (0.7 mL). DIAD (55 μ L, 0.26 mmol) was added in a dropwise manner, and the RM was stirred at RT overnight.

25 The RM was concentrated under reduced pressure and purified over silica gel (eluent: 0 to 100%

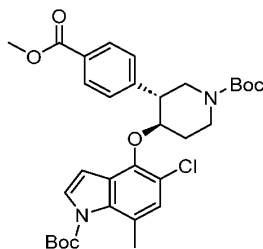
EtOAc in heptane) to provide *racemic* *tert*-butyl (3*R**,4*S**)-4-((5,7-dimethyl-1-*H*-indol-4-yl)oxy)-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate as a light yellow oil (87.3 mg). LC-MS Method C-1: Rt = 1.49 min; MS m/z [M-Boc+2H]⁺ = 533.1.

Intermediate M-3: *tert*-butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5-cyclopropyl-7-methyl-1*H*-indole-1-carboxylate



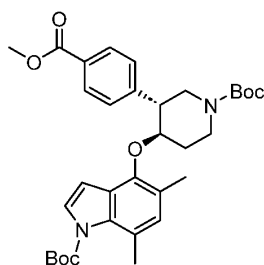
tert-Butyl 5-cyclopropyl-4-hydroxy-7-methyl-1*H*-indole-1-carboxylate (**Intermediate I-3**, 50 mg, 0.17 mmol), *tert*-butyl (3*R*,4*S*)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate (**Intermediate A-3**, 61 mg, 0.18 mmol), and PPh₃ (54.7 mg, 0.21 mmol) were dissolved in toluene (0.4 mL). A DIAD (55 μ L, 0.26 mmol) soln in toluene (0.15 mL) was added in a dropwise manner over 10 min. The RM was stirred at RT overnight. The RM was concentrated under reduced pressure and purified over silica gel (eluent: 0 to 40% EtOAc in heptane) to provide *tert*-butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5-cyclopropyl-7-methyl-1*H*-indole-1-carboxylate as a colorless oil (26.2 mg). LC-MS Method C-1: Rt = 1.55 min; MS m/z [M+H]⁺ = 605.2.

Intermediate M-4: *tert*-butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5-chloro-7-methyl-1*H*-indole-1-carboxylate



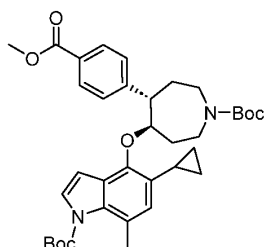
Intermediate M-4 was prepared as described for **Intermediate M-3** using *tert*-butyl 5-chloro-4-hydroxy-7-methyl-1*H*-indole-1-carboxylate (**Intermediate I-4**, 30 mg, 0.11 mmol) and *tert*-butyl (3*R*,4*S*)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate (**Intermediate A-3**, 64.3 mg, 0.19 mmol) to provide *tert*-butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5-chloro-7-methyl-1*H*-indole-1-carboxylate as a colorless oil (39 mg). LC-MS Method C-1: Rt = 1.57 min; MS m/z [M-Boc+2H]⁺ = 499.2.

Intermediate M-5: *tert*-butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate



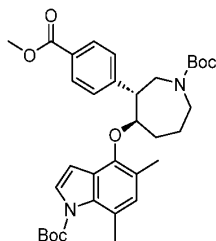
tert-Butyl (3*R*,4*S*)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate (Intermediate A-3, 152 mg, 0.45 mmol) was dissolved in toluene (4 mL) and THF (0.5 mL). PPh₃ (178 mg, 0.68 mmol) and *tert*-butyl 4-hydroxy-5,7-dimethyl-1*H*-indole-1-carboxylate (Intermediate I-1, 118 mg, 0.45 mmol) were added, and the soln was cooled to 0 °C. A DEAD soln (40 wt% in toluene, 0.31 mL 0.68 mmol) was diluted with toluene (0.25 mL), and the DEAD soln was added to the cooled soln in a dropwise manner over 30 min. The RM was stirred at 0 °C for 15 min, and then it was gradually allowed to warm RT and stirred overnight. Column chromatography over silica gel (12 g; eluent: 0 to 25% EtOAc in heptane) provided enriched *tert*-butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate as a colorless oil (112 mg). LC-MS Method C-1: Rt = 1.55 min; MS *m/z* [M-Boc+2H]⁺ = 479.3.

Intermediate M-6: *tert*-butyl 4-(((4*R*,5*S*)-1-(*tert*-butoxycarbonyl)-5-(4-(methoxycarbonyl)phenyl)azepan-4-yl)oxy)-5-cyclopropyl-7-methyl-1*H*-indole-1-carboxylate



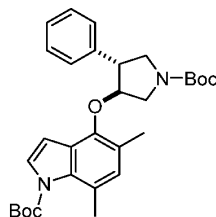
tert-Butyl (4*S*,5*S*)-4-hydroxy-5-(4-(methoxycarbonyl)phenyl)azepane-1-carboxylate (Intermediate A-4, 80 mg, 0.23 mmol), *tert*-butyl 5-cyclopropyl-4-hydroxy-7-methyl-1*H*-indole-1-carboxylate (Intermediate I-3, 67 mg, 0.23 mmol), and PPh₃ (90 mg, 0.34 mmol) were dissolved in toluene (0.4 mL). The mixture was cooled to 0 °C, and a soln of DIAD (67 μL, 0.34 mmol) in toluene (0.4 mL) was added in a dropwise manner. The RM was allowed to warm to RT and stirred for 18 h. The mixture was purified over silica gel (12 g; eluent: 0 to 45% EtOAc in heptane) to provide *tert*-butyl 4-(((4*R*,5*S*)-1-(*tert*-butoxycarbonyl)-5-(4-(methoxycarbonyl)phenyl)azepan-4-yl)oxy)-5-cyclopropyl-7-methyl-1*H*-indole-1-carboxylate as a colorless oil (15 mg). LC-MS Method C-1: Rt = 1.55 min; MS *m/z* [M-*t*Bu+2H]⁺ = 563.2.

Intermediate M-7: *tert*-butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)azepan-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate



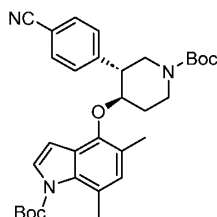
tert-Butyl (3*R*,4*S*)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)azepane-1-carboxylate (**Intermediate A-5**, 100 mg, 0.378 mmol), *tert*-butyl 4-hydroxy-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate I-1**, 99 mg, 0.38 mmol), and PPh₃ (149 mg, 0.57 mmol) were dissolved in a mixture of toluene (0.6 mL) and THF (0.1 mL). The soln was cooled to 0 °C. A DEAD soln (40 wt% in toluene, 0.26 mL, 0.57 mmol) was further diluted with toluene (0.3 mL), and the DEAD soln was added to the cooled soln in a dropwise manner over 1 h. The RM was stirred at RT for 18 h. The RM was concentrated under reduced pressure and purified over silica gel (12 g; eluent: 0 to 20% EtOAc in heptane) to provide *tert*-butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)azepan-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate as a colorless oil (45.7 mg). LC-MS Method C-1: Rt = 1.57 min; MS m/z [M-Boc+2H]⁺ = 493.3.

Intermediate rac-M-8: racemic *tert*-butyl 4-(((3*S,4*R**)-1-(*tert*-butoxycarbonyl)-4-phenylpyrrolidin-3-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate**



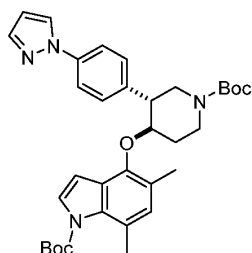
Racemic *tert*-butyl (3*R**,4*R**)-3-hydroxy-4-phenylpyrrolidine-1-carboxylate (**Intermediate rac-A-6**, 100 mg, 0.38 mmol), *tert*-butyl 4-hydroxy-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate I-1**, 89 mg, 0.34 mmol), and PPh₃ (149 mg, 0.57 mmol) were dissolved in toluene (0.4 mL) and the soln was cooled to 0 °C. A DEAD soln (40 wt% in toluene, 0.26 mL, 0.57 mmol) was added in a dropwise manner over approximately 20 min. The RM was stirred at 0 °C for 30 min, and then it was allowed to gradually warm to RT. The RM was stirred at RT for 3 days. Column chromatography over silica gel (12 g; eluent: 0 to 15% EtOAc in heptane) provided enriched *racemic tert*-butyl 4-(((3*S**,4*R**)-1-(*tert*-butoxycarbonyl)-4-phenylpyrrolidin-3-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (124 mg). LC-MS Method C-1: Rt = 1.56 min; MS m/z [M-*t*Bu-Boc+2H]⁺ = 350.9.

Intermediate M-9: *tert*-butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-cyanophenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate



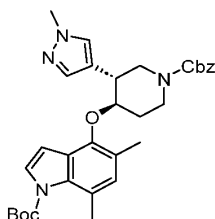
tert-Butyl (3*R*,4*S*)-3-(4-cyanophenyl)-4-hydroxypiperidine-1-carboxylate (**Intermediate A-7**, 106 mg, 0.35 mmol), *tert*-butyl 4-hydroxy-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate I-1**, 96 mg, 0.37 mmol) and PPh₃ (138 mg, 0.53 mmol) were dissolved in toluene (0.5 mL), and the soln was cooled to 0 °C. A DEAD soln (40 wt% in toluene, 0.24 mL, 0.53 mmol) was further diluted with toluene (0.25 mL), and the DEAD soln was added to the cooled soln in a dropwise manner over 45 min. The RM was allowed to gradually warm to RT, and the RM was stirred at RT overnight. The mixture was purified over silica gel (12 g; eluent: 0 to 20% EtOAc in heptane) to provide *tert*-butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-cyanophenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate as a colorless oil (77 mg). LC-MS Method C-1: Rt = 1.53 min; MS m/z [M-Boc+2H]⁺ = 446.3.

Intermediate rac-M-10: racemic *tert*-butyl 4-(((3*R,4*R**)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-(*tert*-butoxycarbonyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate**



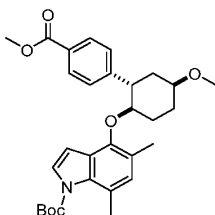
Racemic tert-butyl (3*R**,4*S**)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-4-hydroxypiperidine-1-carboxylate (**Intermediate rac-A-8**, 81 mg, 0.24 mmol) was dissolved in toluene (0.4 mL), and PPh₃ (92 mg, 0.35 mmol) was added followed by *tert*-butyl 4-hydroxy-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate I-1**, 61 mg, 0.24 mmol). The mixture was sonicated and then cooled to 0 °C. A DEAD soln (40 wt% in toluene, 0.16 mL, 0.35 mmol) was further diluted with toluene (0.25 mL), and the DEAD soln was added to the cooled soln in a dropwise manner over 30 min. The RM was stirred at 0 °C for approximately 30 min and then allowed to gradually warm to RT. The RM was stirred overnight at RT and then column chromatography over silica gel (12 g; eluent: 0 to 40% EtOAc in heptane) provided enriched *racemic tert*-butyl 4-(((3*R**,4*R**)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-(*tert*-butoxycarbonyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate as a colorless oil (99 mg). LC-MS Method C-1: Rt = 1.53 min; MS m/z [M+H]⁺ = 587.2.

Intermediate M-11: *tert*-butyl 4-(((3*R*,4*R*)-1-((benzyloxy)carbonyl)-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate



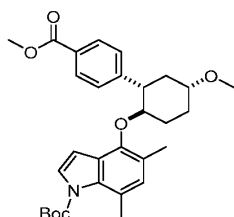
Benzyl (3*R*,4*S*)-4-hydroxy-3-(1-methyl-1*H*-pyrazol-4-yl)piperidine-1-carboxylate (**Intermediate A-9**, 41 mg, 0.13 mmol) was dissolved in THF (0.25 mL), and PPh₃ (51 mg, 0.20 mmol) was added followed by *tert*-butyl 4-hydroxy-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate I-1**, 34 mg, 0.13 mmol). The RM was cooled to 0 °C. A DEAD soln (40 wt% in toluene, 89 µL, 0.20 mmol) was further diluted with toluene (0.25 mL), and the DEAD soln was added to the cooled soln in a dropwise manner over 45 min. The RM was allowed to warm to RT and stirred overnight. Column chromatography over silica gel (12 g; eluent: 0 to 100 % EtOAc in heptane) provided enriched *tert*-butyl 4-(((3*R*,4*R*)-1-((benzyloxy)carbonyl)-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (86 mg). LC-MS Method C-1: Rt = 1.39 min; MS m/z [M+H]⁺ = 559.3.

Intermediate rac-M-12: *racemic tert*-butyl 4-(((1*R**,2*S**,4*S**)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate



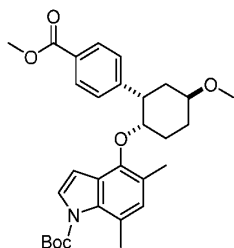
Racemic methyl 4-(((1*S**,2*S**,5*S**)-2-hydroxy-5-methoxycyclohexyl)benzoate (**Intermediate rac-A-10**, 56 mg, 0.21 mmol), *tert*-butyl 4-hydroxy-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate I-1**, 55 mg, 0.21 mmol), and PPh₃ (83 mg, 0.32 mmol) were dissolved in toluene (0.3 mL). The mixture was sonicated 1 min and then cooled to 0 °C. A DEAD soln (40 wt% in toluene, 0.15 mL, 0.32 mmol) was further diluted with toluene (0.3 mL), and the DEAD soln was added to the cooled soln in a dropwise manner over 20 to 30 min. The RM was stirred at 0 °C for 20 min and then allowed gradually warm to RT. The RM was stirred for 2 days at RT. The RM was concentrated under reduced pressure and purified over silica gel (12 g; eluent: 0 to 20% EtOAc in heptane) to provide *racemic tert*-butyl 4-(((1*R**,2*S**,4*S**)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (84 mg). LC-MS Method C-1: Rt = 1.53 min; MS m/z [M-Boc+2H]⁺ = 408.3.

Intermediate rac-M-13: *racemic tert*-butyl 4-(((1*R**,2*S**,4*R**)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate



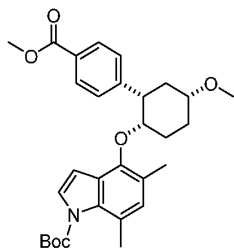
Racemic methyl 4-((1*S**,2*S**,5*R**)-2-hydroxy-5-methoxycyclohexyl)benzoate (**Intermediate rac-A-12**, 45 mg, 0.17 mmol), *tert*-butyl 4-hydroxy-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate I-1**, 44 mg, 0.17 mmol), and PPh₃ (66 mg, 0.25 mmol) were dissolved in toluene (0.4 mL). The mixture was sonicated for 1 min and then was cooled to 0 °C. A DEAD soln (40 wt% in toluene, 0.12 mL, 0.25 mmol) was further diluted with toluene (0.3 mL), and the DEAD soln was added to the cooled soln in a dropwise manner over approximately 25 min. The RM was stirred at 0 °C for 20 min and then allowed to gradually warm to RT. The RM was stirred for 2 days at RT. The RM was concentrated under reduced pressure and purified over silica gel (12 g; eluent: 0 to 20% EtOAc in heptane) to provide *racemic tert*-butyl 4-(((1*R**,2*S**,4*R**)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (8.7 mg). LC-MS Method C-1: Rt = 1.52 min; MS m/z [M-Boc+2H]⁺ = 408.2.

Intermediate rac-M-14: *racemic tert*-butyl 4-(((1*S**,2*S**,4*S**)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate



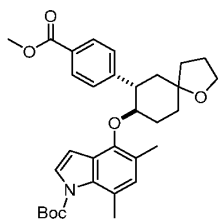
Racemic methyl 4-((1*S**,2*S**,5*R**)-2-hydroxy-5-methoxycyclohexyl)benzoate (**Intermediate rac-A-11**, 60.7 mg, 0.23 mmol), *tert*-butyl 4-hydroxy-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate I-1**, 60.0 mg, 0.23 mmol), and PPh₃ (90.3 mg, 0.34 mmol) were dissolved in toluene (0.5 mL), and the mixture was cooled to 0 °C. A DEAD soln (40 wt% in toluene, 0.16 mL, 0.34 mmol) was further diluted with toluene (0.3 mL), and the DEAD soln was added to the cooled soln in a dropwise manner over 20 min. The RM was stirred at 0 °C for 20 min and then allowed to gradually warm to RT. The RM was stirred for 3 days at RT. The RM was concentrated under reduced pressure and purified over silica gel (12 g; eluent: 0 to 20% EtOAc in heptane) to provide *racemic tert*-butyl 4-(((1*S**,2*S**,4*S**)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (36 mg). LC-MS Method C-1 Rt = 1.53 min; MS m/z [M+H]⁺ = 508.0.

Intermediate rac-M-15: *racemic tert*-butyl 4-(((1*S**,2*S**,4*R**)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate



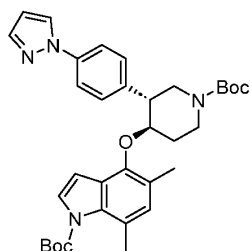
Racemic methyl 4-((1*S**,2*R**,5*R**)-2-hydroxy-5-methoxycyclohexyl)benzoate (**Intermediate rac-A-13**, 60 mg, 0.23 mmol), *tert*-butyl 4-hydroxy-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate I-1**, 59.3 mg, 0.23 mmol), and PPh₃ (90.3 mg, 0.34 mmol) were dissolved in toluene (0.3 mL), and the mixture was cooled to 0 °C. A DEAD soln (40 wt% in toluene, 0.16 mL, 0.34 mmol) was further diluted with toluene (0.3 mL), and the DEAD soln was added to the cooled soln in a dropwise manner over 20 min. The RM was stirred at 0 °C for 20 min and then allowed to gradually warm to RT. The RM was stirred overnight at RT. The RM was concentrated under reduced pressure and purified over silica gel (12 g; eluent: 0 to 20% EtOAc in heptane) to provide *racemic tert*-butyl 4-(((1*S**,2*S**,4*R**)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate as a colorless oil (36 mg). LC-MS Method C-1: Rt = 1.53 min; MS m/z [M+H]⁺ = 508.2.

Intermediate rac-M-16: *Racemic tert*-butyl 4-(((7*S,8*R**)-7-(4-(methoxycarbonyl)phenyl)-1-oxaspiro[4.5]decan-8-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate**



Racemic methyl 4-((5*S**,7*S**,8*S**)-8-hydroxy-1-oxaspiro[4.5]decan-7-yl)benzoate (**Intermediate rac-A-12**, 20 mg, 70 μmol), *tert*-butyl 4-hydroxy-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate I-1**, 18 mg, 70 μmol), and PPh₃ (27 mg, 0.11 mmol) were dissolved in toluene (0.3 mL). The mixture was sonicated for 1 min and then cooled to 0 °C. A DEAD soln (40 wt% in toluene, 48 μL, 0.11 mmol) was further diluted with toluene (0.3 mL), and the DEAD soln was added to the cooled soln in a dropwise manner over 30 min. The RM was stirred at 0 °C for 15 min and then allowed to gradually warm to RT. The RM was stirred overnight at RT and then purified over silica gel (12 g; eluent: 0 to 25% EtOAc in heptane) to provide *racemic tert*-butyl 4-(((7*S**,8*R**)-7-(4-(methoxycarbonyl)phenyl)-1-oxaspiro[4.5]decan-8-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate as a colorless oil (37 mg). LC-MS Method C-1: Rt = 1.56 min; MS m/z [M-Boc+2H]⁺ = 434.3.

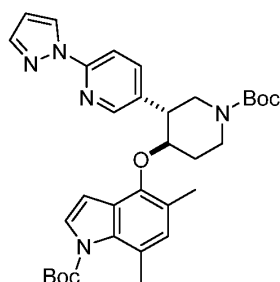
Intermediate M-17: *tert*-butyl 4-(((3*R*,4*R*)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-(*tert*-butoxycarbonyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate



tert-Butyl (3*R*,4*S*)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-4-hydroxypiperidine-1-carboxylate

(**Intermediate A-8-1**, 101.2 mg, 0.29 mmol), PPh₃ (105.4 mg, 0.40 mmol), and *tert*-butyl 4-hydroxy-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate I-1**, 70 mg, 0.27 mmol) were
 5 combined in THF (3 mL). The mixture was cooled to 0 °C. A soln of DBAD (92.5 mg, 0.4 mmol) in toluene (0.5 mL) was added to the cooled soln in a dropwise manner over 10 min. The RM was allowed to gradually warm to RT and stirred overnight. The RM was diluted with H₂O, and the mixture was extracted with EtOAc (3x). The combined org phases were dried over MgSO₄ and concentrated under reduced pressure. Column chromatography over silica gel (eluent: 0 to 50%
 10 EtOAc in heptane) provided enriched *tert*-butyl 4-(((3*R*,4*R*)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-(*tert*-butoxycarbonyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate as a white solid (128 mg. LC-MS Method C-1: Rt = 1.54 min; MS *m/z* [M+H]⁺ = 587.4.

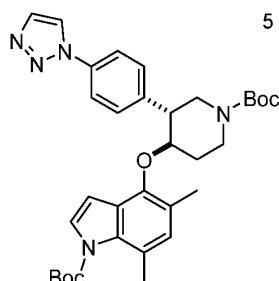
Intermediate rac-M-18: racemic *tert*-butyl 4-(((3*R*^{*},4*R*^{*})-3-(6-(1*H*-pyrazol-1-yl)pyridin-3-yl)-1-(*tert*-butoxycarbonyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate



Racemic tert-butyl (3*R*^{*},4*S*^{*})-3-(6-(1*H*-pyrazol-1-yl)pyridin-3-yl)-4-hydroxypiperidine-1-carboxylate (**Intermediate rac-A-15**, 59 mg, 0.17 mmol), *tert*-butyl 4-hydroxy-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate I-1**, 44.7 mg, 0.17 mmol), and PPh₃ (67 mg, 0.26 mmol) were
 15 dissolved in toluene (0.5 mL). The mixture was cooled to 0 °C. A DEAD soln (40 wt% in toluene, 0.12 mL, 0.26 mmol) was further diluted with toluene (0.25 mL), and the DEAD soln was added to the cooled soln in a dropwise manner over 30 min. The RM was stirred at 0 °C for 15 min and then allowed to warm to RT. The RM was stirred overnight at RT. Column chromatography over silica gel (12 g; eluent: 0 to 25% EtOAc in heptane) provided enriched material which was purified by RP chromatography (15.5 g C18; eluent: 60% to 100% ACN in H₂O, each with 0.1% FA) to
 20 provide *racemic tert*-butyl 4-(((3*R*^{*},4*R*^{*})-3-(6-(1*H*-pyrazol-1-yl)pyridin-3-yl)-1-(*tert*-

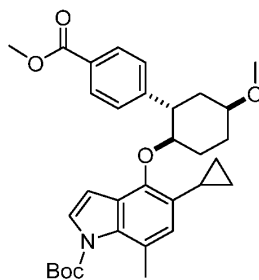
butoxycarbonyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate as a colorless oil (37.8 mg). LC-MS Method C-1: Rt = 1.53 min; MS m/z [M+H]⁺ = 588.3.

Intermediate *rac*-M-19: *racemic tert*-butyl 4-(((3*R**,4*R**)-3-(4-(1*H*-1,2,3-triazol-1-yl)phenyl)-1-(*tert*-butoxycarbonyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate



Racemic tert-butyl (3*R**,4*S**)-3-(4-(1*H*-1,2,3-triazol-1-yl)phenyl)-4-hydroxypiperidine-1-carboxylate (**Intermediate *rac*-A-16**, 72 mg, 0.21 mmol), *tert*-butyl 4-hydroxy-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate I-1**, 54.6 mg, 0.21 mmol), and PPh₃ (82.3 mg, 0.31 mmol) were dissolved in toluene (0.2 mL) and THF (1 mL). The mixture was cooled to 0 °C. A DEAD soln (40 wt% in toluene, 0.14 mL, 0.31 mmol) was further diluted with toluene (0.5 mL), and the DEAD soln was added to the cooled soln in a dropwise manner over 30 min. The RM was stirred at 0 °C for 15 min and then allowed to warm to RT. The RM was stirred overnight at RT. Column chromatography over silica gel (12 g; eluent: 0 to 25% EtOAc in heptane) provided enriched material which was purified by RP chromatography (15.5 g C18; eluent: 55% to 100% ACN in H₂O, each with 0.1% FA) to provide *racemic tert*-butyl 4-(((3*R**,4*R**)-3-(4-(1*H*-1,2,3-triazol-1-yl)phenyl)-1-(*tert*-butoxycarbonyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate as a white solid (30.5 mg). LC-MS Method C-1: Rt = 1.42 min; MS m/z [M+H]⁺ = 588.5.

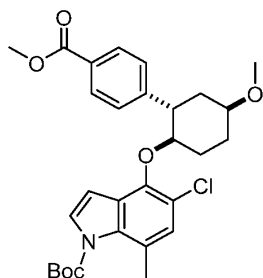
Intermediate *rac*-M-28: *racemic tert*-butyl 5-cyclopropyl-4-(((1*R**,2*S**,4*S**)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate



Racemic methyl 4-(((1*S**,2*S**,5*S**)-2-hydroxy-5-methoxycyclohexyl)benzoate (**Intermediate *rac*-A-10**, 100 mg, 0.38 mmol), *tert*-butyl 4-hydroxy-5-cyclopropyl-7-methyl-1*H*-indole-1-carboxylate (**Intermediate I-3**, 108.7 mg, 0.38 mmol), and PPh₃ (148.8 mg, 0.57 mmol) were dissolved in toluene (0.4 mL). The mixture was cooled to 0 °C. A DEAD soln (40 wt% in toluene, 0.26 mL, 0.57 mmol) was further diluted with toluene (0.5 mL), and the DEAD soln was added to the cooled

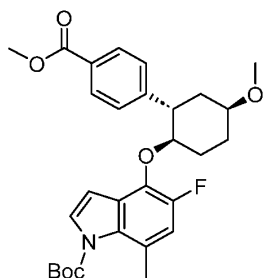
soln in a dropwise manner. The RM was stirred at 0 °C for 20 min and then allowed to warm to RT. The RM was stirred overnight at RT and then purified over silica gel (12 g; eluent: 0 to 15% EtOAc in heptane) to provide *racemic tert*-butyl 5-cyclopropyl-4-(((1*R**,2*S**,4*S**)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate as a colorless oil
 5 (130 mg). LC-MS Method C-1: Rt = 1.52 min; MS m/z [M-Boc+2H]⁺ = 434.3.

Intermediate *rac*-M-29: *racemic tert*-butyl 5-chloro-4-(((1*R**,2*S**,4*S**)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate



tert-Butyl 5-chloro-4-hydroxy-7-methyl-1*H*-indole-1-carboxylate (**Intermediate I-4**, 131 mg, 0.46
 10 mmol), *racemic* methyl 4-((1*S**,2*S**,5*S**)-2-hydroxy-5-methoxycyclohexyl)benzoate (**Intermediate *rac*-A-10**, 135.2 mg, 0.51 mmol), and PPh₃ (146.3 mg, 0.56 mmol) were dissolved in toluene (0.4 mL). A DIAD (0.14 mL, 0.70 mmol) soln in toluene (0.1 mL) was added in a dropwise manner over 10 min. The RM was stirred at RT overnight. The RM was concentrated under reduced pressure and purified over silica gel (eluent: 0 to 25% EtOAc in heptane) to provide
 15 *racemic tert*-butyl 5-cyclopropyl-4-(((1*R**,2*S**,4*S**)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate as a colorless oil (163 mg). LC-MS Method C-2: Rt = 1.57 min; MS m/z [M-Boc] = 426.3.

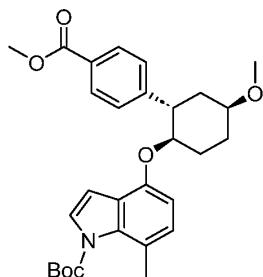
Intermediate M-30: *tert*-butyl 5-fluoro-4-(((1*R*,2*S*,4*S*)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate



tert-Butyl 5-fluoro-4-hydroxy-7-methyl-1*H*-indole-1-carboxylate (**Intermediate I-5**, 15 mg, 56
 μmol), methyl 4-((1*S*,2*S*,5*S*)-2-hydroxy-5-methoxycyclohexyl)benzoate (**Intermediate A-10-1**,
 22.4 mg, 85 μmol), and PPh₃ (37.1 mg, 0.14 mmol) were dissolved in THF (0.5 mL). DIAD (27
 μL, 0.14 mmol) was added in a dropwise manner. The RM was stirred at RT for 4 h. The RM was
 25 quenched with H₂O and extracted with EtOAc (2x). The combined org phases were washed with
 brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified

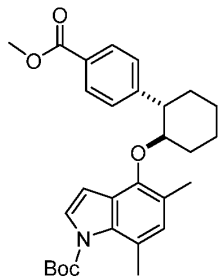
over silica gel (10 g; eluent: 0 to 15% EtOAc in heptane) to provide *tert*-butyl 5-fluoro-4-(((1*R*,2*S*,4*S*)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate as a yellow solid (163 mg). LC-MS Method B-1: *R*_t = 1.67 min; MS *m/z* [M+H₂O]⁺ = 529.5.

5 **Intermediate M-31:** *tert*-butyl 4-(((1*R*,2*S*,4*S*)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate



tert-Butyl 4-hydroxy-7-methyl-1*H*-indole-1-carboxylate (**Intermediate I-6**, 45.0 mg, 0.18 mmol), methyl 4-((1*S*,2*S*,5*S*)-2-hydroxy-5-methoxycyclohexyl)benzoate (**Intermediate A-10-1**, 64.1 mg, 0.19 mmol), and PPh₃ (57.3 mg, 0.21 mmol) were dissolved in toluene (0.3 mL). A DIAD (53 μL, 0.70 mmol) soln in toluene (0.1 mL) was added in a dropwise manner over 10 min. The RM was stirred at RT overnight. The RM was concentrated under reduced pressure and purified over silica gel (12 g; eluent: 0 to 50% EtOAc in heptane) to provide *tert*-butyl 4-(((1*R*,2*S*,4*S*)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate as a colorless oil (14 mg). LC-MS Method C-2: *R*_t = 1.52 min; MS *m/z* [M-Boc+2H]⁺ = 394.4.

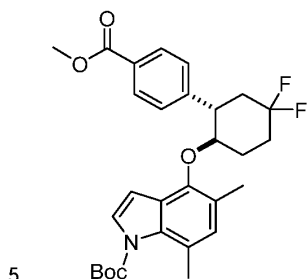
15 **Intermediate rac-M-32:** *racemic tert*-butyl 4-(((1*R*^{*},2*S*^{*})-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate



Racemic methyl 4-((1*S*^{*},2*S*^{*})-2-hydroxycyclohexyl)benzoate (**Intermediate rac-A-22**, 264 mg, 1.13 mmol), *tert*-butyl 4-hydroxy-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate I-1**, 323.9 mg, 1.24 mmol), and PPh₃ (591.1 mg, 2.25 mmol) were dissolved in toluene (6 mL). The mixture was cooled to 0 °C. A DEAD soln (40 wt% in toluene, 0.88 mL, 2.25 mmol) was added to the cooled soln. The RM was stirred at 0 °C for 30 min and then allowed to warm to RT. The RM was stirred overnight at RT and concentrated under reduced pressure. Column chromatography over silica gel (25 g; eluent: 0 to 30% EtOAc in heptane) provided enriched *racemic tert*-butyl 4-

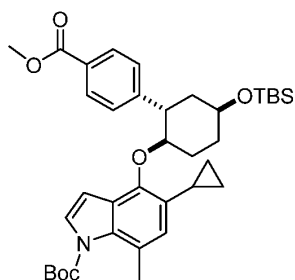
((1*R**,2*S**)-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate as a white solid (317.8 mg). LC-MS Method B-1: *R*_t = 1.73 min; MS *m/z* [M+H]⁺ = 478.3.

Intermediate rac-M-33: *racemic tert*-butyl 4-(((1*R**,2*S**)-4,4-difluoro-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate



In a glovebox *racemic* methyl 4-((1*R**,2*S**)-5,5-difluoro-2-hydroxycyclohexyl)benzoate (**Intermediate rac-A-23**, 73.5 mg, 0.27 mmol), *tert*-butyl 4-bromo-5,7-dimethyl-1*H*-indole-1-carboxylate (70.0 mg, 0.22 mmol), phthalimide (47.7 mg, 0.32 mmol), Ir[p-F(Me)ppy]₂(dtbbpy)PF₆ (CAS# 1335047-34-1, 4.2 mg, 3.4 μmol), and (4,4'-dtbbpy)NiCl₂ (CAS# 1034901-50-2, 8.6 mg, 21.6 μmol) were combined in ACN (1 mL). BTMG (66 μL, 0.32 mmol) was added, and the sealed vial was removed from the glovebox. The vial was placed in a Penn photoreactor and irradiated at 450 nm, 100% LED, 6800 rpm, and cooling fan at full intensity for 80 h. The RM was diluted with DCM and H₂O and filtered through an Isolute® phase separator. The filtrate was concentrated under reduced pressure and purified by preparatory HPLC (Waters XBridge C18 50 x 100 mm, 5 μm; eluent: 40 to 100% ACN in H₂O with 0.2% FA) to provide *racemic tert*-butyl 4-(((1*R**,2*S**)-4,4-difluoro-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate as a white powder (18.3 mg). LC-MS Method B-1: *R*_t = 1.71 min; MS *m/z* [M+H]⁺ = 514.4.

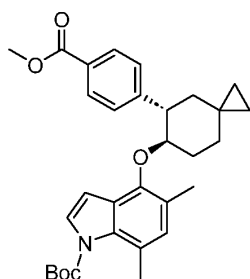
Intermediate rac-M-34: *racemic tert*-butyl 4-(((1*R**,2*S**,4*S**)-4-((*tert*-butyldimethylsilyl)oxy)-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-5-cyclopropyl-7-methyl-1*H*-indole-1-carboxylate



Racemic methyl 4-((1*S**,2*S**,5*S**)-5-((*tert*-butyldimethylsilyl)oxy)-2-hydroxycyclohexyl)benzoate (**Intermediate rac-A-24**, 105 mg, 0.29 mmol) and *tert*-butyl 4-hydroxy-5-cyclopropyl-7-methyl-1*H*-indole-1-carboxylate (**Intermediate I-3**, 91.0 mg, 0.32 mmol) were dissolved in toluene (2 mL). PPh₃ (90.7 mg, 0.35 mmol) was added, and then DIAD (84 L, 0.43 mmol) was added in a dropwise

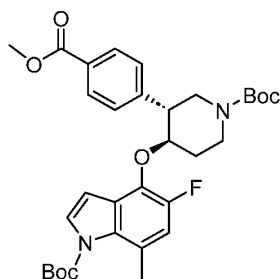
manner. The RM was stirred overnight at RT. The RM was diluted with DCM and H₂O and filtered through an Isolute® phase separator. The filtrate was concentrated under reduced pressure. Column chromatography over silica gel (24 g; eluent: 0 to 20% EtOAc in cyclohexane) provided enriched material which was purified by preparatory HPLC (Waters XBridge C18 50 x 100 mm, 5 μ m; eluent: 35 to 100% ACN in H₂O with 0.2% FA) to provide *racemic tert*-butyl 4-(((1*R**,2*S**,4*S**)-4-((*tert*-butyldimethylsilyl)oxy)-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-5-cyclopropyl-7-methyl-1*H*-indole-1-carboxylate (30.5 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.91 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 3.7 Hz, 1H), 6.36 (s, 1H), 6.24 (d, *J* = 3.8 Hz, 1H), 4.44 – 4.32 (m, 1H), 4.15 – 4.03 (m, 1H), 3.83 (s, 3H), 3.47 – 3.24 (m, 1H), 2.36 (s, 3H), 2.01 – 1.81 (m, 3H), 1.79 – 1.70 (m, 1H), 1.68 – 1.58 (m, 1H), 1.55 (s, 9H), 1.54 – 1.43 (m, 2H), 0.93 (s, 9H), 0.91 – 0.84 (m, 1H), 0.72 – 0.47 (m, 3H), 0.06 (d, *J* = 2.7 Hz, 6H).

Intermediate M-35: *racemic tert*-butyl 4-(((5*S**,6*R**)-5-(4-(methoxycarbonyl)phenyl)spiro[2.5]octan-6-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate



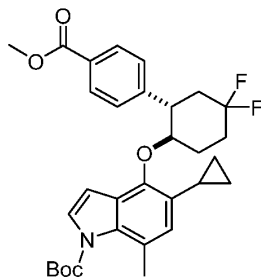
Racemic methyl 4-((5*S**,6*S**)-6-hydroxyspiro[2.5]octan-5-yl)benzoate (**Intermediate rac-A-26**, 344.0 mg, 1.24 mmol), *tert*-butyl 4-hydroxy-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate I-1**, 324.6 mg, 1.24 mmol), and PPh₃ (488.7 mg, 1.86 mmol) were dissolved in toluene (1 mL). The mixture was cooled to 0 °C. DIAD (0.39 mL, 1.86 mmol) was added in a dropwise manner. The RM allowed to gradually warm to RT and stirred overnight. The RM was concentrated under reduced pressure and purified over silica gel (40 g; eluent: 0 to 9% EtOAc in heptane) to provide *racemic tert*-butyl 4-(((5*S**,6*R**)-5-(4-(methoxycarbonyl)phenyl)spiro[2.5]octan-6-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate as a white foam (195 mg). LC-MS Method B-2: Rt = 9.29 min; MS *m/z* [M-H]⁺ = 502.2.

Intermediate M-38: *tert*-butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5-fluoro-7-methyl-1*H*-indole-1-carboxylate



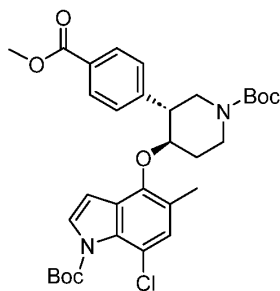
tert-Butyl (3*R*,4*S*)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate (**Intermediate A-3**, 103.7 mg, 0.29 mmol), *tert*-butyl 4-hydroxy-5-fluoro-7-methyl-1*H*-indole-1-carboxylate (**Intermediate I-5**, 77.9 mg, 0.26 mmol), and PPh₃ (173.3 mg, 0.66 mmol) were dissolved in THF (2 mL). DIAD (0.13 mL, 0.66 mmol) was added in a dropwise manner, and the RM was stirred overnight at RT. Additional *tert*-butyl (3*R*,4*S*)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate (**Intermediate A-3**, 44.3 mg, 0.13 mmol), PPh₃ (69.3 mg, 0.26 mmol), and DIAD (51 μL, 0.26 mmol) were added sequentially, and the RM was stirred at RT for 3 h. The mixture was diluted with EtOAc and washed with H₂O. The aq phase was extracted with EtOAc (2x). The combined org phases were washed with brine, dried through an Isolute® phase separator, and concentrated under reduced pressure. Column chromatography over silica gel (eluent: 0 to 40% EtOAc in cyclohexane) provided enriched *tert*-butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5-fluoro-7-methyl-1*H*-indole-1-carboxylate as an orange oil (145 mg). LC-MS Method B-1: Rt = 1.68 min; MS m/z [M+Na]⁺ = 605.2.

Intermediate rac-M-39: racemic tert-butyl 5-cyclopropyl-4-(((1*R,2*S**)-4,4-difluoro-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate**



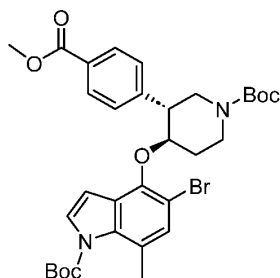
Intermediate rac-M-39 was prepared as described in Step 1a for **Intermediate M-34** using *racemic* methyl 4-(((1*S**,2*S**)-5,5-difluoro-2-hydroxycyclohexyl)benzoate (**Intermediate rac-A-28**, 87 mg, 0.32 mmol) and *tert*-butyl 4-hydroxy-5-cyclopropyl-7-methyl-1*H*-indole-1-carboxylate (**Intermediate I-3**, 101.7 mg, 0.35 mmol) to provide *racemic tert*-butyl 5-cyclopropyl-4-(((1*R**,2*S**)-4,4-difluoro-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate as a light yellow powder (35.4 mg). LC-MS Method B-1: Rt = 1.71 min; MS m/z [M+H]⁺ = 540.5.

Intermediate M-42: tert-butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-7-chloro-5-methyl-1*H*-indole-1-carboxylate



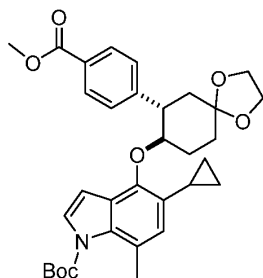
5 *tert*-Butyl (3*R*,4*S*)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate (Intermediate A-3, 261.9 mg, 0.78 mmol), PPh₃ (279.3 mg, 1.07 mmol), and *tert*-butyl 7-chloro-4-hydroxy-5-methyl-1*H*-indole-1-carboxylate (Intermediate I-7, 200 mg, 0.91 mmol) were combined in toluene (5 mL). The mixture was cooled to 0 °C. A soln of DBAD (245.2 mg, 1.07 mmol) in toluene (1 mL) was added to the cooled soln in a dropwise manner over 10 min. The RM was allowed to gradually warm to RT and stirred overnight. The RM was diluted with H₂O, and the mixture was extracted with EtOAc (3x). The combined org phases were dried over MgSO₄ and concentrated under reduced pressure. Column chromatography over silica gel (eluent: 0 to 10 50% EtOAc in heptane) provided *tert*-butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-7-chloro-5-methyl-1*H*-indole-1-carboxylate as a white solid (129.3 mg). LC-MS Method C-2: Rt = 1.52 min; MS *m/z* [M+H]⁺ = 599.2.

Intermediate M-43: *tert*-butyl 5-bromo-4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-7-methyl-1*H*-indole-1-carboxylate



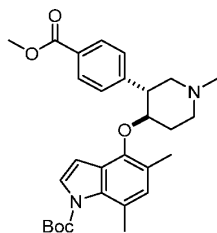
15 *tert*-Butyl (3*R*,4*S*)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate (Intermediate A-3, 501.1 mg, 1.49 mmol), PPh₃ (534.3 mg, 2.03 mmol), and *tert*-butyl 5-bromo-4-hydroxy-7-methyl-1*H*-indole-1-carboxylate (Intermediate I-8, 443.0 mg, 1.36 mmol) were combined in THF (5 mL). The mixture was cooled to 0 °C. A soln of DBAD (469.1 mg, 2.04 mmol) in toluene (5 mL) was added to the cooled soln in a dropwise manner over 10 min. The RM was allowed to gradually warm to RT and stirred overnight. The RM was concentrated, and column chromatography over silica gel (eluent: 0 to 50% EtOAc in heptane) provided enriched *tert*-butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-7-chloro-5-methyl-1*H*-indole-1-carboxylate as a white solid (813 mg). LC-MS Method C-1: Rt = 1.57 min; MS 20 *m/z* [M+H]⁺ = 645.8.

Intermediate rac-M-44: *racemic tert-butyl 5-cyclopropyl-4-(((7S*,8R*)-7-(4-(methoxycarbonyl)phenyl)-1,4-dioxaspiro[4.5]decan-8-yl)oxy)-7-methyl-1H-indole-1-carboxylate*



- 5 *Racemic methyl 4-((7S*,8S*)-8-hydroxy-1,4-dioxaspiro[4.5]decan-7-yl)benzoate (Intermediate rac-A-31, 960 mg, 3.28 mmol) and tert-butyl 4-hydroxy-5-cyclopropyl-7-methyl-1H-indole-1-carboxylate (Intermediate I-3, 1.04 g, 4.93 mmol) were dissolved in toluene (8 mL). PPh₃ (1.03 g, 3.94 mmol) was added, and then DIAD (0.96 mL, 4.93 mmol) was added in a dropwise manner. The RM was stirred overnight at RT. The RM was diluted with DCM and H₂O and filtered through*
- 10 *an Isolute® phase separator. The filtrate was concentrated under reduced pressure. Column chromatography over silica gel (120 g; eluent: 0 to 30% EtOAc in cyclohexane) provided enriched material which was purified by preparatory HPLC (Waters XBridge C18 50 x 100 mm, 5 µm; eluent: 30 to 100% ACN in H₂O with 0.2% FA) to provide racemic tert-butyl 5-cyclopropyl-4-(((7S*,8R*)-7-(4-(methoxycarbonyl)phenyl)-1,4-dioxaspiro[4.5]decan-8-yl)oxy)-7-methyl-1H-*
- 15 *indole-1-carboxylate as a light orange powder (570 mg). LC-MS Method B-1: Rt = 1.65 min; MS m/z [M+H]⁺ = 562.3.*

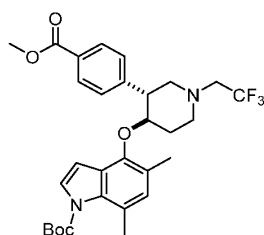
Intermediate rac-B-1: *tert-butyl 4-(((3R*,4R*)-3-(4-(methoxycarbonyl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1H-indole-1-carboxylate*



- 20 **Step 1a:** *Racemic tert-butyl 4-(((3R*,4R*)-1-(tert-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1H-indole-1-carboxylate (Intermediate M-1, 72 mg, 0.12 mmol) was dissolved in MeOH (1.5 mL), and HCl soln (4M in dioxane, 1 mL, 4.0 mmol) was added. The RM was stirred at RT for 20 min and concentrated under reduced pressure. The residue was diluted with sat. aq NaHCO₃ soln and extracted with*
- 25 *DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure.*

Step 1b: The residue was dissolved in MeOH (1 mL). Aq formaldehyde soln (37 wt%, 1 mL, 13.4 mmol) and Na(OAc)₃BH (79.7 mg, 0.37 mmol) were added. The RM was stirred at RT for 20 min. The RM was partitioned between DCM and sat. aq NaHCO₃ soln. The aq phase was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified over silica gel (12 g; eluent: 0 to 100% 3:1 EtOAc/EtOH with 2% NH₄OH in heptane) to provide *racemic tert*-butyl 5,7-dimethyl-4-(((3*R**,4*R**)-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-1*H*-indole-1-carboxylate as a colorless oil (42 mg). LC-MS Method C-2: Rt = 1.42 min; MS m/z [M+H]⁺ = 493.3.

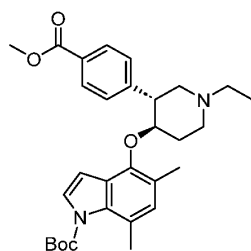
Intermediate *rac*-B-2: *racemic tert*-butyl 4-(((3*R**,4*R**)-3-(4-(methoxycarbonyl)phenyl)-1-(2,2,2-trifluoroethyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate



Step 1a: *Racemic tert*-butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate *rac*-M-1**, 42 mg, 73 μmol) was dissolved in MeOH (1.5 mL), and HCl soln (4M in dioxane, 1 mL, 4.0 mmol) was added. The RM was stirred at RT for 50 min and concentrated under reduced pressure. The residue was partitioned between DCM and sat. aq NaHCO₃ soln. The aq phase was extracted with DCM (2x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure.

Step 1b: The residue was dissolved in ACN (1.5 mL). NEt₃ (30 μL, 0.22 mmol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (15.68 μL, 0.11 mmol) were added sequentially, and the RM was stirred at RT overnight. Sat. aq NaHCO₃ soln was added, and the mixture was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified over silica gel (4 g; eluent: 0 to 100% 3:1 EtOAc/EtOH in heptane) to provide *racemic tert*-butyl 4-(((3*R**,4*R**)-3-(4-(methoxycarbonyl)phenyl)-1-(2,2,2-trifluoroethyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate as a colorless oil (31 mg). LC-MS Method C-1: Rt = 1.49 min; MS m/z [M+H]⁺ = 561.1

Intermediate B-3: *tert*-butyl 4-(((3*R*,4*R*)-1-ethyl-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate

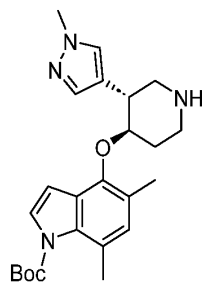


Step 1a: Enriched *tert*-butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate

(**Intermediate M-5**, 54 mg) was dissolved in MeOH (1.5 mL), and HCl soln (4M in dioxane, 0.5 mL, 2.0 mmol) was added. The RM was stirred at RT for 2 h and then concentrated under reduced pressure. The residue was partitioned between DCM and sat. aq NaHCO₃ soln. The aq phase was extracted with DCM (2x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure.

Step 1b: The residue was dissolved in DCM (1 mL), and acetaldehyde (10 µL, 0.19 mmol) was added followed by Na(OAc)₃BH (30 mg, 0.14 mmol). The RM was stirred at RT overnight. The RM was neutralized with sat. aq NaHCO₃ soln, and the mixture was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified over silica gel (4 g; eluent: 0 to 100% 3:1 EtOAc:EtOH mixture in heptane with 2% NH₄OH) to provide *tert*-butyl 4-(((3*R*,4*R*)-1-ethyl-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (47 mg). LC-MS Method C-1: Rt = 1.08 min; MS m/z [M+H]⁺ = 507.2.

Intermediate B-4: *tert*-butyl 5,7-dimethyl-4-(((3*R*,4*R*)-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-1*H*-indole-1-carboxylate



Enriched *tert*-Butyl 5,7-dimethyl-4-(((3*R*,4*R*)-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-1*H*-indole-1-carboxylate (**Intermediate M-11**, 86 mg) was dissolved in MeOH (2 mL) and Pd/C (10 wt% Pd, 41 mg, 39 µmol) was added. The flask was purged with H₂ (3x) and then stirred at RT under H₂ atmosphere (balloon) for 1 h. The RM was filtered to remove solids. The solids were washed with MeOH, and the combined filtrates were concentrated under reduced pressure to provide *tert*-butyl 5,7-dimethyl-4-(((3*R*,4*R*)-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-1*H*-

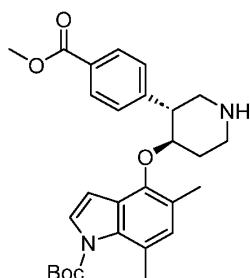
indole-1-carboxylate (65 mg) which was directly used without further purification. LC-MS Method C-1: Rt = 0.87 min; MS m/z $[M+H]^+$ = 425.1.

The following examples were synthesized from the appropriate starting materials by applying similar methods described in the examples above.

	Chemical Structure	Name	LC-MS MS m/z
Intermediate rac-B-5		<i>racemic</i> methyl 4-(((3 <i>R</i> *,4 <i>S</i> *)-4-((5,7-dimethyl-1-tosyl-1 <i>H</i> -indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoate	Method C-2: Rt = 1.38 min; $[M+H]^+$ = 547.3
Intermediate B-6		<i>tert</i> -butyl 5-cyclopropyl-4-(((3 <i>R</i> ,4 <i>R</i>)-3-(4-(methoxycarbonyl)phenyl)-1-methylpiperidin-4-yl)oxy)-7-methyl-1 <i>H</i> -indole-1-carboxylate	Method C-2: Rt = 1.45 min; $[M+H]^+$ = 519.1
Intermediate B-7		<i>tert</i> -butyl 5-chloro-4-(((3 <i>R</i> ,4 <i>R</i>)-3-(4-(methoxycarbonyl)phenyl)-1-methylpiperidin-4-yl)oxy)-7-methyl-1 <i>H</i> -indole-1-carboxylate	Method C-2: Rt = 1.47 min; $[M+H]^+$ = 513.2
Intermediate rac-B-8		<i>racemic tert</i> -butyl 5,7-dimethyl-4-(((3 <i>S</i> *,4 <i>R</i> *)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)oxy)-1 <i>H</i> -indole-1-carboxylate	Method C-1: Rt = 1.58 min; $[M+H]^+$ = 489.2
Intermediate B-9		<i>tert</i> -butyl 4-(((3 <i>R</i> ,4 <i>R</i>)-3-(4-cyanophenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1 <i>H</i> -indole-1-carboxylate	Method C-1: Rt = 1.14 min; $[M+H]^+$ = 460.3

Intermediate B-10		<i>tert</i> -butyl 4-(((3 <i>R</i> ,4 <i>R</i>)-3-(4-(methoxycarbonyl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1 <i>H</i> -indole-1-carboxylate	Method C-1: Rt = 1.42 min; [M+H] ⁺ = 493.3
Intermediate rac-B-11		<i>racemic tert</i> -butyl 4-(((3 <i>R</i> [*] ,4 <i>R</i> [*])-3-(4-(1 <i>H</i> -pyrazol-1-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1 <i>H</i> -indole-1-carboxylate	Method C-1: Rt = 1.40 min; [M+H] ⁺ = 501.3

Intermediate B-12: *tert*-butyl 4-(((3*R*,4*R*)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate



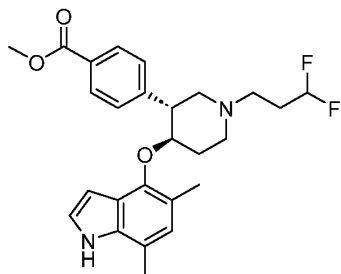
- 5 Step 1a: *tert*-Butyl (3*R*,4*S*)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate (**Intermediate A-3**, 353.0 mg, 1.05 mmol), *tert*-butyl 4-hydroxy-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate I-1**, 250.0 mg, 0.96 mmol), and PPh₃ (376.4 mg, 1.43 mmol) were dissolved in THF (3 mL). The mixture was cooled to 0 °C. A DBAD (330.4 mg, 0.51 mmol) soln in toluene (0.5 mL) was added to the cooled soln in a dropwise manner over 10 min. The RM was
- 10 allowed to gradually warm to RT and stirred overnight. The mixture was diluted with H₂O and extracted with EtOAc (3x). The combined org phases were washed with water, dried over Mg₂SO₄, and concentrated under reduced pressure. Column chromatography over silica gel (eluent: 0 to 50% EtOAc in heptane) provided enriched *tert*-butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-
- 15 carboxylate (306 mg).

Step 1b: The material was dissolved in MeOH (2 mL). HCl soln (4M in dioxane, 0.59 mL, 2.35 mmol) was added, and the RM was stirred for 3.5 h. The pH was adjusted to 6 with NaOH, and the mixture was partitioned between EtOAc and H₂O. The aq phase was extracted with EtOAc (2x). The combined org phases were dried over Mg₂SO₄ and concentrated under reduced

20 pressure. The residue was purified over silica gel (eluent: 0 to 30% MeOH in DCM) to provide

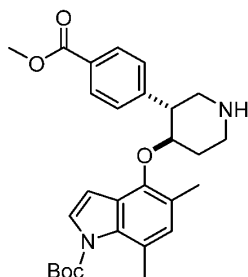
tert-butyl 4-(((3*R*,4*R*)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (108.3 mg). LC-MS Method C-2: *R*_t = 1.31 min; MS *m/z* [*M*+*H*]⁺ = 479.4.

Intermediate B-13: methyl 4-(((3*R*,4*R*)-1-(3,3-difluoropropyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoate



5

Step 1: **racemic** *tert*-butyl 4-(((3*R**,4*R**)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate rac-B-13-1**)



Racemic tert-butyl (3*R**,4*S**)-4-hydroxy-3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate (**Intermediate rac-A-1**, 983.1 mg, 1.84 mmol), PPh₃ (722.7 mg, 2.76 mmol) and *tert*-butyl 4-hydroxy-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate I-1**, 500 mg, 1.84 mmol) were dissolved in THF (15 mL), and the mixture was cooled to 0 °C. DIAD (0.55 mL, 2.76 mmol) was added in a dropwise manner. The RM was allowed to warm to RT and stirred overnight. Additional PPh₃ (481.2 mg, 1.84 mmol) and DIAD (0.55 mL, 2.76 mmol) were added, and the RM was stirred at RT for 5h. The RM was diluted with EtOAc, and the mixture was washed with H₂O and brine. The org phase was dried through an Isolute® phase separator and concentrated under reduced pressure. Column chromatography over silica gel (80 g; eluent: 0 to 30% EtOAc in cyclohexane) provided enriched *racemic tert*-butyl 4-(((3*R**,4*R**)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate. The material (1.24 g) was dissolved in MeOH (3 mL), and the soln was cooled to 0 °C. HCl soln (4M in dioxane, 3.12 mL, 12.5 mmol) was added, and RM was stirred for 1.5 h. The RM was quenched with sat. aq NaHCO₃ soln, and the mixture was extracted with DCM (2x). The combined org phases were dried through and Isolute® phase separator and concentrated under reduced pressure. The residue was purified over silica gel (40 g; eluent: 0 to 20% MeOH in DCM) to provide *racemic tert*-butyl 4-(((3*R**,4*R**)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-

carboxylate as a brown foam (236.6 mg). LC-MS Method B-1: Rt = 1.26 min; MS m/z [M+H]⁺ = 479.4.

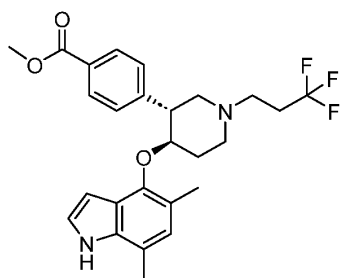
Step 2: methyl 4-((3*R*,4*R*)-1-(3,3-difluoropropyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoate (**Intermediate B-13**)

- 5 Step 2a: *Racemic tert*-butyl 4-(((3*R**,4*R**)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate rac-B-13-1**, 130 mg, 0.24 mmol) and 3-bromo-1,1-difluoropropane (42.8 mg, 0.27 mmol) were combined in ACN (2 mL), and DIPEA (0.15 mL, 0.86 mmol) was added. The RM was stirred at 50 °C for 5 h. The RM was allowed to cool to RT, diluted with EtOAc, and the mixture was washed with H₂O. The aq phase was extracted with
- 10 EtOAc (2x). The combined org phases were washed with brine, dried through an Isolute® phase separator, and concentrated under reduced pressure.

- Step 2b: The residue was dissolved in MeOH (2 mL), and HCl soln (4M in dioxane, 1.22 mL, 4.89 mmol) was added. The RM was stirred at RT overnight. The RM was diluted with DCM and neutralized with sat. aq NaHCO₃ soln. The phases were separated and the aq phase was
- 15 extracted with DCM (2x). The combined org phases were washed with brine, dried through an Isolute® phase separator, and concentrated under reduced pressure. The residue was purified over silica gel (12 g; eluent: 0 to 100% EtOAc in cyclohexane) to provide *racemic* methyl 4-((3*R**,4*R**)-1-(3,3-difluoropropyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoate as a colorless oil (59.1 mg). LC-MS Method B-1: Rt = 0.77 min; MS m/z [M+H]⁺ = 457.4.

- 20 Step 2c: Chiral separation and analytics according to Method SFC-21: 59.1 mg provided **Intermediate B-13** (peak 2): 19.8 mg, white solid. LC-MS Method B-1: Rt = 0.75 min; MS m/z [M+H]⁺ = 457.3. Analytical chiral HPLC: Rt = 1.92 min; 99.9% ee.

Intermediate B-14: methyl 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(3,3,3-trifluoropropyl)piperidin-3-yl)benzoate



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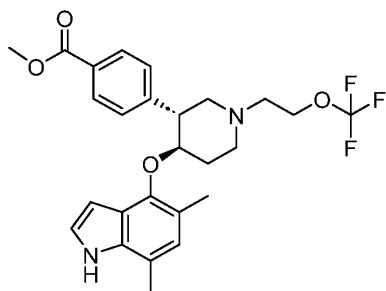
- Step 1a: *Racemic tert*-butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate rac-B-13-1**, 130 mg, 0.24 mmol) and 1,1,1-trifluoro-3-iodopropane (60.2 mg, 0.27 mmol) were combined in ACN (2 mL), and DIPEA (0.15 mL, 0.86 mmol) was added. The RM
- 30 was stirred at 50 °C overnight. An additional portion of 1,1,1-trifluoro-3-iodopropane (60.2 mg, 0.27 mmol) was added, and the RM was stirred at 50 °C for 2 h. The RM was allowed to cool to RT, diluted with EtOAc, and the mixture was washed with H₂O. The aq phase was extracted with

EtOAc (2x). The combined org phases were washed with brine, dried through an Isolute® phase separator, and concentrated under reduced pressure.

Step 1b: The residue was dissolved in MeOH (2 mL), and HCl soln (4M in dioxane, 1.22 mL, 4.89 mmol) was added. The RM was stirred at RT overnight. The RM was diluted with DCM and
 5 neutralized with sat. aq NaHCO₃ soln. The phases were separated and the aq phase was extracted with DCM (2x). The combined org phases were washed with brine, dried through an Isolute® phase separator, and concentrated under reduced pressure. The residue was purified over silica gel (12 g; eluent: 0 to 60% EtOAc in cyclohexane) to provide *racemic* methyl 4-((3*R**,4*R**)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(3,3,3-trifluoropropyl)piperidin-3-yl)benzoate as
 10 a colorless oil (35.2 mg). LC-MS Method B-1: Rt = 1.10 min; MS m/z [M+H]⁺ = 475.2.

Step 1c: Chiral separation and analytics according to Method SFC-22: 235.2 mg provided **Intermediate B-14** (peak 2): 14.3 mg, white solid. LC-MS Method B-1: Rt = 1.09 min; MS m/z [M+H]⁺ = 475.3. Analytical chiral HPLC: Rt = 1.30 min; 99.9% ee.

Intermediate B-15: methyl 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2-(trifluoromethoxy)ethyl)piperidin-3-yl)benzoate
 15

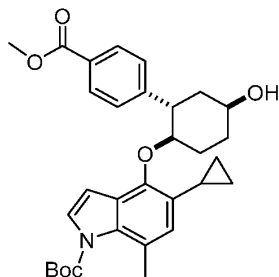


Racemic tert-butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate rac-B-13-1**, 92.7 mg, 0.15 mmol) and 2-bromoethyl trifluoromethyl ether (31 µL, 0.27 mmol) were combined in ACN (1.5 mL), and
 20 NEt₃ (62 µL, 0.86 mmol) was added. The RM was stirred at 50 °C for 3 days. The RM was allowed to cool to RT and concentrated under reduced pressure.

Step 1b: The residue was dissolved in MeOH (1.5 mL), and HCl soln (4M in dioxane, 0.45 mL, 1.80 mmol) was added. The RM was stirred at RT overnight. The RM was diluted with DCM and neutralized with sat. aq NaHCO₃ soln. The phases were separated and the aq phase was
 25 extracted with DCM (2x). The combined org phases were washed with brine, dried through an Isolute® phase separator, and concentrated under reduced pressure. The residue was purified over silica gel (24 g; eluent: 0 to 100% EtOAc in cyclohexane) to provide *racemic* methyl 4-((3*R**,4*R**)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2-(trifluoromethoxy)ethyl)piperidin-3-yl)benzoate as an orange oil (26.6 mg). LC-MS Method B-1: Rt = 1.11 min; MS m/z [M+H]⁺ =
 30 491.3.

Step 1c: Chiral separation and analytics according to Method SFC-23: 26.6 mg provided **Intermediate B-15** (peak 2): 9.9 mg, colorless oil. LC-MS Method B-1: Rt = 1.12 min; MS m/z [M+H]⁺ = 491.3. Analytical chiral HPLC: Rt = 1.24 min; 99.5% ee.

Intermediate rac-B-16: racemic tert-butyl 5-cyclopropyl-4-(((1*R,2*S**,4*S**)-4-hydroxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate**

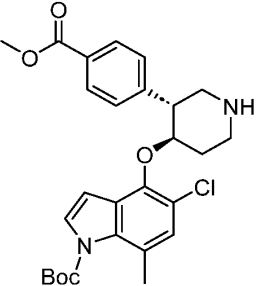
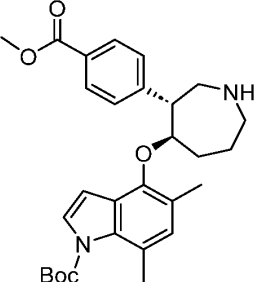
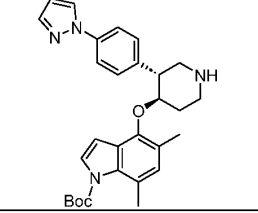
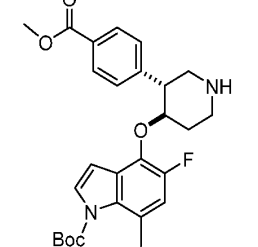
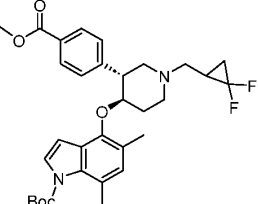
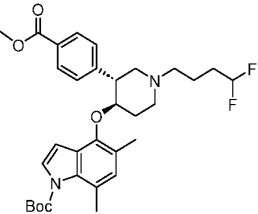


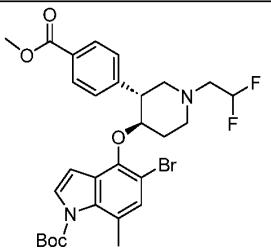
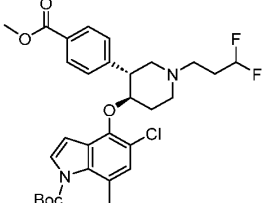
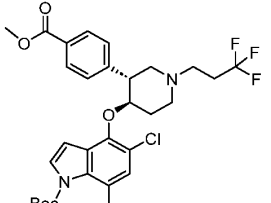
Racemic *tert*-butyl 4-(((1*R**,2*S**,4*S**)-4-((*tert*-butyldimethylsilyl)oxy)-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-5-cyclopropyl-7-methyl-1*H*-indole-1-carboxylate

(Intermediate rac-M-34, 910 mg, 1.44 mmol) was dissolved in MeOH (15 mL), and HCl soln (4M in dioxane, 3.59 mL, 14.36 mmol) was added. The RM was stirred at RT for 1 h. The RM was quenched with sat. aq NaHCO₃ soln, and the mixture was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified over silica gel (120 g; eluent: 0 to 30% EtOAc in cyclohexane) to provide *racemic tert*-butyl 5-cyclopropyl-4-(((1*R**,2*S**,4*S**)-4-hydroxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate as a white foam (641 mg). LC-MS Method B-1: Rt = 1.51 min; MS m/z [M-Boc+2H]⁺ = 420.3.

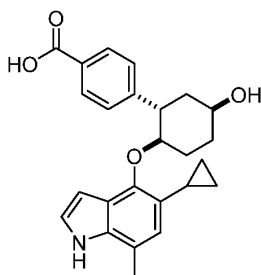
The following examples were synthesized from the appropriate starting materials by applying similar methods described in the examples above.

	Chemical Structure	Name	LC-MS MS m/z
Intermediate B-18		<i>tert</i> -butyl 4-(((3 <i>R</i> ,4 <i>R</i>)-3-(4-(methoxycarbonyl)phenyl)-1-(tetrahydrofuran-3-yl)piperidin-4-yl)oxy)-5,7-dimethyl-1 <i>H</i> -indole-1-carboxylate	Method C-2: Rt = 1.39 min; [M+H] ⁺ = 549.4

Intermediate B-19		<i>tert</i> -butyl 5-chloro-4-(((3 <i>R</i> ,4 <i>R</i>)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-7-methyl-1 <i>H</i> -indole-1-carboxylate	Method C-2: Rt = 1.39 min; [M+H] ⁺ = 499.2
Intermediate B-20		<i>tert</i> -butyl 4-(((3 <i>R</i> ,4 <i>R</i>)-3-(4-(methoxycarbonyl)phenyl)azepan-4-yl)oxy)-5,7-dimethyl-1 <i>H</i> -indole-1-carboxylate	Method C-2: Rt = 1.39 min; [M+H] ⁺ = 493.2
Intermediate B-21		<i>tert</i> -butyl 4-(((3 <i>R</i> ,4 <i>R</i>)-3-(4-(1 <i>H</i> -pyrazol-1-yl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1 <i>H</i> -indole-1-carboxylate	Method C-2: Rt = 1.31 min; [M+H] ⁺ = 487.4
Intermediate rac-B-31		<i>tert</i> -butyl 5-fluoro-4-(((3 <i>R</i> *,4 <i>R</i> *)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-7-methyl-1 <i>H</i> -indole-1-carboxylate	Method B-1: Rt = 1.01 min; [M+H] ⁺ = 483.4
Intermediate B-34		<i>tert</i> -butyl 4-(((3 <i>R</i> ,4 <i>R</i>)-1-((2,2-difluorocyclopropyl)methyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1 <i>H</i> -indole-1-carboxylate	Method C-2: Rt = 1.49 min; [M+H] ⁺ = 569.5
Intermediate B-35		<i>tert</i> -butyl 4-(((3 <i>R</i> ,4 <i>R</i>)-1-(4,4-difluorobutyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1 <i>H</i> -indole-1-carboxylate	Method C-2: Rt = 1.49 min; [M+H] ⁺ = 571.4

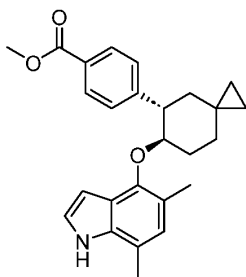
Intermediate B-36		<i>tert</i> -butyl 5-bromo-4-(((3 <i>R</i> ,4 <i>R</i>)-1-(2,2-difluoroethyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-7-methyl-1 <i>H</i> -indole-1-carboxylate	Method C-1: Rt = 1.42 min; [M+H] ⁺ = 607.4
Intermediate B-38		<i>tert</i> -butyl 5-chloro-4-(((3 <i>R</i> ,4 <i>R</i>)-1-(3,3-difluoropropyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-7-methyl-1 <i>H</i> -indole-1-carboxylate	Method C-2: Rt = 1.49 min; [M+H] ⁺ = 577.6
Intermediate B-39		<i>tert</i> -butyl 5-chloro-4-(((3 <i>R</i> ,4 <i>R</i>)-3-(4-(methoxycarbonyl)phenyl)-1-(3,3,3-trifluoropropyl)piperidin-4-yl)oxy)-7-methyl-1 <i>H</i> -indole-1-carboxylate	Method C-2: Rt = 1.54 min; [M+H] ⁺ = 595.4

Intermediate *rac*-B-32: *racemic* 4-((1*S**,2*R**,5*S**)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-hydroxycyclohexyl)benzoic acid



5 *Racemic* *tert*-butyl 5-cyclopropyl-4-(((1*R**,2*S**,4*S**)-4-hydroxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate (**Intermediate *rac*-B-16**, 43 mg, 83 μ mol) was dissolved in THF (1 mL) and MeOH (0.5 mL). Aq NaOH soln (1M, 0.41 mL, 0.41 mmol) was added, and the RM was stirred at 50 °C for 18 h. The RM allowed to cool to RT, quenched with FA (31 μ L, 0.82 mmol), and diluted with ACN. The mixture was purified by preparatory HPLC (Waters XBridge C18 30 x 100 mm, 5 μ m; eluent: 15 to 100% ACN in H₂O with 0.2% FA) to provide *racemic* 4-((1*S**,2*R**,5*S**)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-hydroxycyclohexyl)benzoic acid as a white solid (25.7 mg). LC-MS Method B-1: Rt = 0.93 min; MS *m/z* [M+H]⁺ = 406.2.

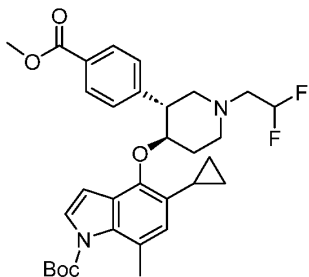
15 **Intermediate B-33:** methyl 4-((5*S*,6*R*)-6-((5,7-dimethyl-1*H*-indol-4-yl)oxy)spiro[2.5]octan-5-yl)benzoate



Step 1a: *racemic tert*-butyl 4-(((5*S**,6*R**)-5-(4-(methoxycarbonyl)phenyl)spiro[2.5]octan-6-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate rac-M-35**, 221 mg, 0.44 mmol) was dissolved in DCM (6 mL), and TFA (2 mL) was added. The RM was stirred at RT for 40 min. The RM was poured into a mixture of 10 wt% aq Na₂CO₃ and MBTE. The phases were separated, and the aq phase was extracted with MBTE. The org phase was washed with brine. The combined org phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified using preparatory HPLC (Waters XBridge C18 50 x 100 mm; 5 μm; eluent: 40 to 90% ACN in H₂O with 0.1% NH₄OH) to provide *racemic* methyl 4-(((5*S**,6*R**)-6-((5,7-dimethyl-1*H*-indol-4-yl)oxy)spiro[2.5]octan-5-yl)benzoate as a white foam (65.5 mg).

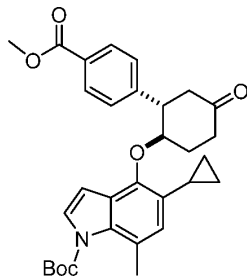
Step 1b: Chiral separation and analytics according to Method SFC-25: 65 mg provided **Intermediate B-33** (peak 2): 30.3 mg, white solid. LC-MS Method B-1: Rt = 1.54 min; MS m/z [M+H]⁺ = 404.3. Analytical chiral HPLC: Rt = 1.44 min; 99.5% ee.

Intermediate B-37: *tert*-butyl 5-cyclopropyl-4-(((3*R*,4*R*)-1-(2,2-difluoroethyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-7-methyl-1*H*-indole-1-carboxylate



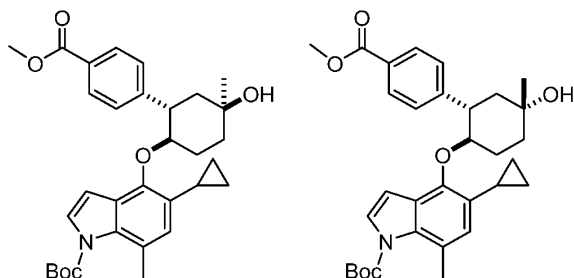
tert-Butyl 5-bromo-4-(((3*R*,4*R*)-1-(2,2-difluoroethyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-7-methyl-1*H*-indole-1-carboxylate (**Intermediate B-36**, 23.2 mg, 38 μmol) was combined with cyclopropyl boronic acid (3.9 mg, 46 μmol), tricyclohexylphosphine (1.1 mg, 4 μmol), and Pd₂dba₃ (2.1 mg, 2 μmol). The vial was purged with N₂, and toluene (0.3 mL) and H₂O (10 μL) were added. The RM was stirred at 100 °C overnight. The RM was concentrated under reduced pressure, and column chromatography over silica gel (12 g; eluent 0 to 100% EtOAc in heptane) provided enriched *tert*-butyl 5-cyclopropyl-4-(((3*R*,4*R*)-1-(2,2-difluoroethyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-7-methyl-1*H*-indole-1-carboxylate (16 mg). LC-MS Method C-1: Rt = 1.37 min; MS m/z [M+H]⁺ = 569.5.

Intermediate rac-B-40: *racemic tert-butyl 5-cyclopropyl-4-(((1*R**,2*S**)-2-(4-(methoxycarbonyl)phenyl)-4-oxocyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate*



*Racemic tert-butyl 5-cyclopropyl-4-(((7*S**,8*R**)-7-(4-(methoxycarbonyl)phenyl)-1,4-dioxaspiro[4.5]decan-8-yl)oxy)-7-methyl-1*H*-indole-1-carboxylate* (492.0 mg, 0.88 mmol) was dissolved in acetone (20 mL), and Amberlyst® 15 (2.75 g, 8.76 mmol) was added. The RM was stirred at RT for 4 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 50 x 100 mm; 5 µm; eluent: 40 to 100% ACN in H₂O with 0.2% FA) to provide *racemic tert-butyl 5-cyclopropyl-4-(((1*R**,2*S**)-2-(4-(methoxycarbonyl)phenyl)-4-oxocyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate* (131 mg). LC-MS Method B-1: Rt = 1.59 min; MS m/z [M-Boc+2H]⁺ = 418.1.

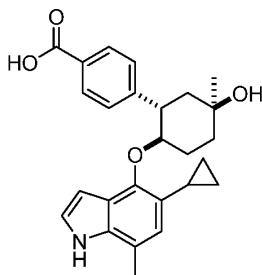
Intermediate rac-B-41 and Intermediate rac-B-42: *racemic tert-butyl 5-cyclopropyl-4-(((1*R**,2*S**,4*S**)-4-hydroxy-2-(4-(methoxycarbonyl)phenyl)-4-methylcyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate and *tert-butyl 5-cyclopropyl-4-(((1*R**,2*S**,4*R**)-4-hydroxy-2-(4-(methoxycarbonyl)phenyl)-4-methylcyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate**



*Racemic tert-butyl 5-cyclopropyl-4-(((1*R**,2*S**)-2-(4-(methoxycarbonyl)phenyl)-4-oxocyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate* (**Intermediate rac-B-40**, 41.3 mg, 80 µmol) was dissolved in THF (1 mL) and cooled to 0 °C. A methyl magnesium bromide soln (3.4M in THF, 28 µL, 96 µmol) was added, and the RM was stirred for 30 min. The RM was quenched with sat aq NH₄Cl soln and allowed to warm to RT. The mixture was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. Column chromatography over silica gel (12 g; eluent: 0 to 20% EtOAc in cyclohexane) provided *racemic tert-butyl 5-cyclopropyl-4-(((1*R**,2*S**,4*S**)-4-hydroxy-2-(4-(methoxycarbonyl)phenyl)-4-methylcyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate* (first peak

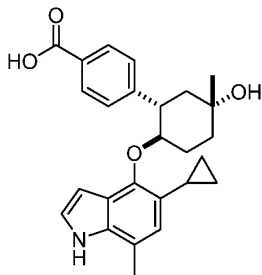
eluting, 24.7 mg) and *racemic tert*-butyl 5-cyclopropyl-4-(((1*R**,2*S**,4*R**)-4-hydroxy-2-(4-(methoxycarbonyl)phenyl)-4-methylcyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate (second peak eluting, 9.1 mg). **Intermediate *rac*-B-41** LC-MS Method B-1: *R*_t = 1.59 min; MS *m/z* [M+H]⁺ = 534.2. **Intermediate *rac*-B-42** LC-MS Method B-1: *R*_t = 1.52 min; MS *m/z* [M+H]⁺ = 534.3.

- 5 **Intermediate *rac*-B-43: *racemic* 4-((1*S**,2*R**,5*S**)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-hydroxy-5-methylcyclohexyl)benzoic acid**



- Racemic tert*-butyl 5-cyclopropyl-4-(((1*R**,2*S**,4*S**)-4-hydroxy-2-(4-(methoxycarbonyl)phenyl)-4-methylcyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate (**Intermediate *rac*-B-41**, 22.4 mg, 42 μmol) was dissolved in MeOH (0.5 mL) and THF (1 mL). Aq NaOH soln (1M, 0.21 mL, 0.21 mmol) was added, and the RM was stirred at 50 °C for 18 h. The RM was quenched with FA (16 μL) and purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 100 mm; 5 μm; eluent: 15 to 100% ACN in H₂O with 0.2% FA) to provide *racemic* 4-((1*S**,2*R**,5*S**)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-hydroxy-5-methylcyclohexyl)benzoic acid as a white solid (12.5 mg). LC-MS Method B-1: *R*_t = 0.99 min; MS *m/z* [M+H]⁺ = 420.4.

Intermediate *rac*-B-44: *racemic* 4-((1*S,2*R**,5*R**)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-hydroxy-5-methylcyclohexyl)benzoic acid**



- Racemic tert*-butyl 5-cyclopropyl-4-(((1*R**,2*S**,4*R**)-4-hydroxy-2-(4-(methoxycarbonyl)phenyl)-4-methylcyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate (**Intermediate *rac*-B-42**, 7.2 mg, 13 μmol) was dissolved in MeOH (0.25 mL) and THF (0.5 mL). Aq NaOH soln (1M, 67 μL, 67 μmol) was added, and the RM was stirred at 50°C for 18 h. The RM was quenched with FA (5 μL) and purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 100 mm; 5 μm; eluent: 15 to 100% ACN in H₂O with 0.2% FA) to provide *racemic* 4-((1*S**,2*R**,5*R**)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-hydroxy-5-methylcyclohexyl)benzoic acid as a white solid (12.5 mg). LC-MS Method B-1: *R*_t = 0.99 min; MS *m/z* [M+H]⁺ = 420.4.

Example Ex-1 and Example Ex-2: 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid and 4-((3*S*,4*S*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid

- 5 Step 1a: *Racemic tert*-butyl 4-(((3*R**,4*R**)-3-(4-(methoxycarbonyl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate rac-B-1**, 42 mg, 85 μmol) was dissolved in MeOH (2 mL), and K₂CO₃ (50 mg, 0.36 mmol) was added. The RM was stirred at 45 °C overnight. Aq NaOH soln (1M, 85 μL, 85 μmol) was added, and the RM was stirred at 60 °C for 90 min. Additional aq NaOH soln (1M, 85 μL, 85 μmol) was added, and the RM was stirred at 10 60 °C for 2 h. The RM was allowed to cool to RT, concentrated under reduced pressure, and purified using preparatory HPLC (15.5 g C18 column; eluent: 15 to 20% ACN in H₂O with 0.1% NH₄OH) to provide *racemic* 4-((3*R**,4*R**)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid as a white solid (28.6 mg).

Step 1b: Chiral separation and analytics according to Method SFC-6: 28.6 mg provided **Example**

- 15 **Ex-1** (peak 2): 10.1 mg, white solid. Analytical chiral HPLC: Rt = 2.64 min; 100% ee. **Example Ex-2** (peak 1): 10.9 mg, white solid. Analytical chiral HPLC: Rt = 2.02 min; 95.9% ee.

Example Ex-3 and Example Ex-4: 4-((3*R*,4*S*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid and 4-((3*S*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid

- 20 Step 1a: A vial was charged with *racemic* methyl 4-((3*R**,4*S**)-4-((5,7-dimethyl-1-*tosyl*-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoate (**Intermediate rac-B-5**, 38 mg, 70 μmol), EtOH (0.50 mL), and aq NaOH soln (4M, 0.52 mL 2.1 mmol). The vial was sealed, and the mixture was stirred at 85 °C overnight. The mixture was purified using RP chromatography (50 g C18 column; eluent: 5% to 60% ACN in H₂O, each with 0.1% NH₄OH) to provide *racemic* 4-((3*R**,4*S**)-4-((5,7- 25 dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid as a white solid (21 mg).

Step 1b: Chiral separation and analytics according to Method SFC-7: 21 mg provided **Example Ex-3** (peak 1): 6.0 mg, white solid. Analytical chiral HPLC: Rt = 1.86 min; 100% ee.

Example Ex-4 (peak 2): 2.2 mg, white solid. Analytical chiral HPLC: Rt = 2.08 min; 100% ee.

- Example Ex-5:** 4-((3*R*,4*R*)-4-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin- 30 3-yl)benzoic acid

- tert*-Butyl 5-cyclopropyl-4-(((3*R*,4*R*)-3-(4-(methoxycarbonyl)phenyl)-1-methylpiperidin-4-yl)oxy)-7-methyl-1*H*-indole-1-carboxylate (**Intermediate B-6**, 50 mg, 96 μmol) was dissolved in EtOH (0.5 mL), and aq NaOH soln (4M, 0.24 mL, 0.96 mmol) was added. The RM was stirred at RT overnight and then stirred at 50 °C for 2 h. The mixture was purified by RP chromatography (50 35 g C18 column; eluent: 5 to 50% ACN in H₂O, each with 0.1% NH₄OH) to provide 4-((3*R*,4*R*)-4-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid as a white solid (22 mg).

Example Ex-6: 4-((3*R*,4*R*)-4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid

tert-Butyl 5-chloro-4-(((3*R*,4*R*)-3-(4-(methoxycarbonyl)phenyl)-1-methylpiperidin-4-yl)oxy)-7-methyl-1*H*-indole-1-carboxylate (**Intermediate B-7**, 22 mg, 43 μ mol) was dissolved in EtOH (0.3 mL), and aq NaOH soln (4M, 0.21 mL, 0.86 mmol) was added. The mixture was gently heated until a clear soln was formed, and the RM was stirred at RT overnight. The mixture was purified by RP chromatography (50 g C18 column; eluent: 5 to 50% ACN in H₂O, each with 0.1% NH₄OH) to provide 4-((3*R*,4*R*)-4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid as a white solid (16.4 mg).

Example Ex-7 and Example Ex-8: 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)piperidin-3-yl)benzoic acid and 4-((3*S*,4*S*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)piperidin-3-yl)benzoic acid

Step 1a: *Racemic tert*-butyl 4-(((3*R**,4*R*)-3-(4-(methoxycarbonyl)phenyl)-1-(2,2,2-trifluoroethyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate rac-B-2**, 31 mg, 55 μ mol) was dissolved in MeOH (2.5 mL), and K₂CO₃ (35 mg, 0.25 mmol) was added. The RM was stirred at 65 °C for 2 h, and then at 75 °C for 75 min. Aq NaOH soln (1M, 0.11 mL, 0.11 mmol) and H₂O (0.3 mL) were added, and the RM was stirred at 60 °C for 2 h. The RM was allowed to cool to RT and stirred overnight. Additional aq NaOH soln (1M, 0.2 mL, 0.2 mmol) was added, and the RM was stirred for 1 h at RT. The RM was concentrated under reduced pressure and purified using preparatory HPLC (15.5 g C18 column; eluent: 15 to 20% ACN in H₂O with 0.1% NH₄OH) to provide *racemic* 4-((3*R**,4*R**)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)piperidin-3-yl)benzoic acid as a white solid (12 mg).

Step 1b: Chiral and analytics according to Method SFC-8: 12 mg provided **Example Ex-7** (peak 1): 5.1 mg, white solid. Analytical chiral HPLC: Rt = 2.36 min; 100% ee. **Example Ex-8** (peak 2): 4.8 mg, white solid. Analytical chiral HPLC: Rt = 2.83 min; 100% ee.

Example Ex-9: 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-ethylpiperidin-3-yl)benzoic acid

tert-Butyl 4-(((3*R*,4*R*)-1-ethyl-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate B-3**, 47 mg, 0.93 mmol) was dissolved in IPA (1.5 mL) and aq NaOH soln (1M, 0.46 mL, 0.46 mmol) was added. The RM was stirred at 60 °C for 2 days. The RM was allowed to cool to RT, concentrated under reduced pressure, and purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm; 5 μ m; eluent: 5 to 20% ACN in H₂O with 0.1% NH₄OH). Pure fractions were combined, and enriched fractions were repurified under the above conditions. Fractions were pooled and lyophilized to provide 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-ethylpiperidin-3-yl)benzoic acid as a white solid (5.3 mg).

Example Ex-10: 4-((4*S*,5*R*)-5-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-1-methylazepan-4-yl)benzoic acid

Step 1a: *tert*-Butyl 4-(((4*R*,5*S*)-1-(*tert*-butoxycarbonyl)-5-(4-(methoxycarbonyl)phenyl)azepan-4-yl)oxy)-5-cyclopropyl-7-methyl-1*H*-indole-1-carboxylate (**Intermediate M-6**, 7 mg, 11 μ mol) was dissolved in MeOH (1 mL), and HCl soln (4M in dioxane, 1 mL, 4.0 mmol) was added. The RM was stirred at RT for 2 h and concentrated under reduced pressure. The residue was partitioned
5 between DCM and sat. aq NaHCO₃ soln. The aq phase was extracted with DCM (2x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure.

Step 1b: The residue was dissolved in MeOH (1 mL). Aq formaldehyde solution (37 wt%, 0.5 mL, 6.7 mmol) and Na(OAc)₃BH (15 mg, 71 mmol) were added. The RM was stirred at RT for 18 h.
10 The RM was partitioned between DCM and sat. aq NaHCO₃ soln. The aq phase was extracted with DCM (2x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure.

Step 1c: The residue was dissolved in MeOH (3 mL), and aq NaOH soln (1M, 150 μ L, 150 μ mol) was added. The RM was stirred at 70 °C for 6 h, allowed to cool to RT, and then stirred at RT for
15 3 days. Additional aq NaOH soln (1M, 0.1 mL, 0.1 mmol) was added, and the RM was stirred at 65 °C for 2 h. The mixture was concentrated under reduced pressure and purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm; 5 μ m; eluent: 10 to 30% ACN in H₂O with 0.1% NH₄OH) to provide 4-(((4*S*,5*R*)-5-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-1-methylazepan-4-yl)benzoic acid as a white solid (2.0 mg).

20 **Example Ex-11: 4-(((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylazepan-3-yl)benzoic acid**

Step 1a: *tert*-Butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)azepan-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate M-7**, 45.7 mg, 77 μ mol) was dissolved in MeOH (1.5 mL), and HCl soln (4M in dioxane, 1 mL, 4.0 mmol) was added. The RM
25 was stirred at RT for 2 h and concentrated under reduced pressure. The residue was partitioned between DCM and sat. aq NaHCO₃ soln. The aq phase was extracted with DCM (2x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure.

Step 1b: The residue was dissolved in MeOH (1.5 mL). Aq formaldehyde (37 wt%, 0.5 mL, 6.7 mmol) and Na(OAc)₃BH (50 mg, 0.23 mmol) were added. The RM was stirred at RT for 30 min.
30 The RM was partitioned between DCM and sat. aq NaHCO₃ soln. The aq phase was extracted with DCM (2x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure.

Step 1c: The residue was dissolved in IPA (1 mL), and aq NaOH soln (1M, 0.5 mL, 0.5 mmol) was added. The RM was stirred at 55 °C for 2 h and then stirred at 50 °C for 18 h. The RM was stirred at 70 °C for 2 h, and then additional aq NaOH soln (1M, 0.15 mL, 0.15 mmol) was added.
35 The RM was stirred at 65 °C for 6 h, allowed to cool to RT, concentrated under reduced pressure, and purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm; 5 μ m; eluent: 10 to

30% ACN in H₂O with 0.1% NH₄OH) to provide 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylazepan-3-yl)benzoic acid as a white solid (5.3 mg).

Example Ex-12: *racemic* **5,7-dimethyl-4-(((3*S**,4*R**)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)oxy)-1*H*-indole**

- 5 *Racemic tert*-butyl 5,7-dimethyl-4-(((3*S**,4*R**)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)oxy)-1*H*-indole-1-carboxylate (**Intermediate rac-B-8**, 71 mg, 0.15 mmol) was dissolved in MeOH (2 mL). THF (0.5 mL) and aq NaOH soln (1M, 0.6 mL, 0.6 mmol) was added. The RM was stirred at 60 °C for 3 h, allowed to cool to RT, and then stirred at RT overnight. The mixture was extracted with DCM (3x). The combined org layers were dried through an Isolute® phase separator and
- 10 concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm; 5 µm; eluent: 10 to 30% ACN in H₂O with 0.1% NH₄OH) to provide *racemic* 5,7-dimethyl-4-(((3*S**,4*R**)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)oxy)-1*H*-indole as a white solid (8.1 mg).

Example Ex-13: **4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzonitrile**

- Step 1a: *tert*-Butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-cyanophenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate M-9**, 77 mg, 0.14 mmol) was dissolved in MeOH (2.5 mL), and HCl soln (4M in dioxane, 0.2 mL, 0.8 mmol) was added. The RM was stirred at RT for 90 min and concentrated under reduced pressure. The residue was partitioned between DCM
- 20 and sat. aq NaHCO₃ soln. The aq phase was extracted with DCM (2x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure.

- Step 1b: The residue was dissolved in MeOH (2.5 mL). Aq formaldehyde soln (37 wt%, 1 mL, 13 mmol) and Na(OAc)₃BH (92 mg, 0.43 mmol) were added. The RM was stirred at RT for 1 h. The RM was partitioned between DCM and sat. aq NaHCO₃ soln. The aq phase was extracted with
- 25 DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified over silica gel (4 g; eluent: 0 to 100% 3:1 EtOAc/EtOH in heptane with 2% NH₄OH).

- Step 1c: The material was dissolved in MeOH (4 mL), and K₂CO₃ (78 mg, 0.56 mmol) was added. The RM was stirred at 60 °C for 1 h, allowed to cool to RT, and then stirred at RT for 3 days. The
- 30 RM was partitioned between sat. aq NaHCO₃ soln and DCM. The aq phase was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm; 5 µm; eluent: 35 to 60% ACN in H₂O with 0.1% FA) to provide 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzonitrile as a white solid
- 35 (18 mg).

Example Ex-14: **4-((3*R*,4*R*)-3-(4-(1*H*-tetrazol-5-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole**

tert-Butyl 4-(((3*R*,4*R*)-3-(4-cyanophenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate B-9**, 27.7 mg, 60.3 μ mol), NH₄Cl (14 mg, 0.26 mmol) and sodium azide (20 mg, 0.31 μ mol) were charged in a vial, and then DMF (0.5 mL) was added. The RM was stirred at 100 °C for 24 h. Additional NH₄Cl (5.1 mg, 95 μ mol) and sodium azide (21 mg, 323 μ mol) were added, and the RM was stirred at 100 °C for 24 h. To the RM was added MeOH (0.5 mL) followed by aq NaOH soln (1M, 0.3 mL, 0.30 mmol). The RM was stirred at 70 °C for 5 h and then at 60 °C for 18 h. The mixture was allowed to cool to RT, concentrated under reduced pressure, and purified by preparatory HPLC (Column: Waters XBridge C18 OBD 30 x 50 mm; 5 μ m; eluent: 5 to 20% ACN in H₂O with 0.1% NH₄OH) to provide the 4-(((3*R*,4*R*)-3-(4-(1*H*-tetrazol-5-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole as an off-white solid (6.0 mg).

Example Ex-15: 2-(4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)phenyl)propan-2-ol

Step 1a: *tert*-Butyl 4-(((3*R*,4*R*)-3-(4-(methoxycarbonyl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate B-10**, 43 mg, 87 μ mol) was dissolved in THF (1.0 mL), and methylmagnesium bromide soln (1.4M in THF/toluene, 0.25 mL, 0.35 mmol) was added. The RM was stirred at RT for 80 min. Additional methylmagnesium bromide soln (0.50 mL, 0.70 mmol) was added, and the RM was stirred at RT for 2 h. A third portion of methylmagnesium bromide soln (0.75 mL, 1.1 mmol) was added, and the RM was stirred at RT for 1 h. A final portion of methylmagnesium bromide soln (0.25 mL, 0.35 mmol) was added, and the RM was stirred at RT for 30 min. The RM was quenched with sat. aq NH₄Cl soln. The separated aq phase was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure.

Step 1b: The residue was dissolved in MeOH (2 mL), and K₂CO₃ (90 mg, 0.65 mmol) was added. The RM was stirred at 65 °C for 90 min, allowed to cool to RT, and then stirred at RT overnight. The RM was diluted with H₂O, and the separated aq phase was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm; 5 μ m; eluent: 35 to 60% ACN in H₂O with 0.1% NH₄OH) to provide 2-(4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)phenyl)propan-2-ol as a white solid (11.2 mg).

Example Ex-16: 4-(((3*R*,4*R*)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole

Step 1a: *Racemic tert*-butyl 4-(((3*R**,4*R**)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate rac-B-11**, 60 mg, 0.12 mmol) was dissolved in MeOH (3 mL), and K₂CO₃ (50 mg, 0.36 mmol) was added. The RM was stirred at 60 °C for 18 h. The mixture was allowed to cool to RT and concentrated under reduced pressure. The residue was diluted with H₂O and extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The

residue was purified by preparatory HPLC (15.5 g C18 column; eluent: 35 to 60% ACN in H₂O with 0.1% NH₄OH to provide *racemic* 4-(((3*R**,4*R**)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole as a white solid (32 mg).

Step 1b: Chiral separation and analytics according to Method SFC-9: 32 mg provided **Example Ex-16** (peak 1): 13.3 mg, white solid. Analytical chiral HPLC: Rt = 2.19 min; 100% ee.

Example Ex-17: 5,7-dimethyl-4-(((3*R*,4*R*)-1-methyl-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-1*H*-indole

Step 1a: *tert*-Butyl 5,7-dimethyl-4-(((3*R*,4*R*)-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-1*H*-indole-1-carboxylate (**Intermediate B-4**, 60 mg, 0.14 mmol) was dissolved in MeOH (1.5 mL). Aq formaldehyde solution (37 wt%, 0.5 mL, 6.7 mmol) and Na(OAc)₃BH (89 mg, 0.42 mmol) were added. The RM was stirred at RT for 1 h. The RM was partitioned between DCM and sat. aq NaHCO₃ soln. The aq phase was extracted with DCM (2x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure.

Step 1b: The residue was dissolved in MeOH (1.5 mL), and K₂CO₃ (89 mg, 0.64 mmol) was added. The RM was stirred at 60 °C for 18 h. The mixture was allowed to cool to RT, diluted with sat. aq NaHCO₃ soln, and extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was enriched by RP chromatography (15.5 g C18 column; eluent: 20 to 60% ACN in H₂O with 0.1 % NH₄OH). Impure fractions were further enriched by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm; 5 µm µm; eluent: 25 to 50% ACN in H₂O with 0.1% NH₄OH). The enriched material was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 100 mm; 5 µm; eluent: 25 to 50 % ACN in H₂O with 0.1% NH₄OH) to provide 5,7-dimethyl-4-(((3*R*,4*R*)-1-methyl-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-1*H*-indole as a white solid (8.2 mg).

Example Ex-18 and Example Ex-19: 4-((1*S*,2*R*,5*S*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid and 4-((1*R*,2*S*,5*R*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid

Step 1a: *Racemic tert*-butyl 4-(((1*R**,2*S**,4*S**)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate rac-M-12**, 84 mg, 0.17 mmol) was dissolved in Me-THF (2 mL). MeOH (1 mL) and aq NaOH soln (1M, 1.5 mL, 1.5 mmol) were added sequentially. The RM was stirred at 60 °C overnight. Additional aq NaOH soln (1M, 1 mL, 1 mmol) was added followed by MeOH (0.5 mL). The RM was stirred at 60 °C for 2 h and then allowed to cool to RT. The mixture was neutralized with 1M aq HCl soln (2.5 mL) and extracted with EtOAc (1x) and DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm; 5 µm; eluent: 35 to 60% ACN in H₂O with 0.1% FA). The aq phase from above was also purified under the same conditions. Fractions from both purifications were combined and lyophilized to provide

racemic 4-((1*S**,2*R**,5*S**)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid as a white solid (25.4 mg).

Step 1b: Chiral separation and analytics according to Method SFC-10: 20 mg provided **Example Ex-18** (peak 1): 6.9 mg, white solid. Analytical chiral HPLC: *R*_t = 2.52 min; 100% ee. **Example Ex-19** (peak 2): 9.2 mg, white solid. Analytical chiral HPLC: *R*_t = 2.79 min; 100% ee.

Example Ex-20: *racemic* 4-((1*S,2*R**,5*R**)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid**

Racemic methyl 4-((1*S**,2*S**,5*R**)-2-hydroxy-5-methoxycyclohexyl)benzoate (**Intermediate rac-M-13**, 8.7 mg, 0.17 mmol) was dissolved in MeOH (2 mL). THF (0.3 mL) was added followed by aq NaOH soln (1M, 0.2 mL, 0.2 mmol). The RM was stirred at 65 °C for 2 h. The mixture was allowed to cool to RT, concentrated under reduced pressure, and purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm; 5 µm; eluent: 35 to 60% ACN in H₂O with 0.1% FA) to provide *racemic* 4-((1*S**,2*R**,5*R**)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid as a white solid (0.9 mg).

Example Ex-21: *racemic* 4-((1*S,2*S**,5*S**)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid**

Racemic tert-butyl 4-(((1*S**,2*S**,4*S**)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate rac-M-14**, 36 mg, 0.23 mmol) was dissolved in MeOH (1 mL) and Me-THF (2 mL). Aq NaOH soln (1M, 1 mL, 1 mmol) was added, and the RM was stirred at 60 °C overnight. Additional MeOH (0.5 mL) and aq NaOH soln (1M, 1 mL, 1 mmol) were added, and the RM was stirred at 60 °C for 2 h. The mixture was allowed to cool to RT and neutralized with aq HCl soln (1M). The mixture was extracted with EtOAc (1x) and DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm; 5 µm; eluent: 45 to 70% ACN in H₂O with 0.1% FA) to provide *racemic* 4-((1*S**,2*S**,5*S**)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid as a white solid (16 mg).

Example Ex-22: *racemic* 4-((1*S,2*S**,5*R**)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid**

Racemic tert-butyl 4-(((1*S**,2*S**,4*R**)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate rac-M-15**, 36 mg, 0.23 mmol) was dissolved in MeOH (1 mL) and THF (1 mL). Aq NaOH soln (1M, 1 mL, 1 mmol) was added, and the RM was stirred at 65 °C for 3 h. The mixture allowed to cool to RT and acidified with aq HCl soln (1M). The mixture was extracted with EtOAc (1x) and DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm; 5 µm; eluent: 35 to 60% ACN in H₂O with 0.1% FA) to provide *racemic* 4-((1*S**,2*S**,5*R**)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid as a white solid (14.7 mg).

Example Ex-23: racemic 4-((7*S,8*R**)-8-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-oxaspiro[4.5]decan-7-yl)benzoic acid**

- Step 1a: *Racemic tert*-butyl 4-(((7*S**,8*R**)-7-(4-(methoxycarbonyl)phenyl)-1-oxaspiro[4.5]decan-8-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate rac-M-16**, 37 mg, 69 μ mol) was dissolved in MeOH (2 mL), and K₂CO₃ (35 mg, 0.25 mmol) was added. The RM was stirred at 65 °C for 3 h, allowed to cool to RT, and then diluted with H₂O. The mixture was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm; 5 μ m; eluent: 55 to 80% ACN in H₂O with 0.1% NH₄OH).
- Step 1b: The material was dissolved in THF (0.4 mL) and MeOH (0.2 mL). Aq NaOH soln (1M, 0.5 mL, 0.5 mmol) was added, and the RM was stirred at 65 °C for 2 h. The mixture was allowed to cool to RT, concentrated under reduced pressure, and purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm, 5 μ m; eluent: 10 to 30% ACN in H₂O with 0.1% NH₄OH) to provide *racemic* 4-((7*S**,8*R**)-8-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-oxaspiro[4.5]decan-7-yl)benzoic acid as a white solid (2.3 mg).

Example Ex-24: 4-((3*R*,4*R*)-1-(2,2-difluoroethyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid

- Step 1a: *tert*-Butyl 4-(((3*R*,4*R*)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate B-12**, 54 mg, 0.11 mmol) was combined with DIPEA (64 μ L, 0.44 mmol) and ACN (1 mL). 2,2-Difluoroethyl trifluoromethanesulfonate (24.7 mg, 0.12 mmol) was added slowly and the RM was stirred at 60 °C for 2 h. The RM was allowed to cool to RT and concentrated under reduced pressure.
- Step 1b: The residue was dissolved in IPA (1 mL). Aq NaOH soln (1M, 0.52 mL, 0.52 mmol) was added, and the RM was stirred at 80 °C for 20 h. The RM was allowed to cool to RT and partially concentrated under reduced pressure. The pH was adjusted to 4 with aq HCl soln (1M), and the mixture was extracted with EtOAc (3x). The combined org phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm, 5 μ m; eluent: 10 to 30% ACN in H₂O with 0.1% NH₄OH) to provide 4-((3*R*,4*R*)-1-(2,2-difluoroethyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid as a white solid (30.1 mg).

Example Ex-25: 4-((3*R*,4*R*)-1-(3,3-difluoropropyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid

- Methyl 4-((3*R*,4*R*)-1-(3,3-difluoropropyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoate (**Intermediate B-13**, 19.8 mg, 43.4 μ mol) was dissolved in MeOH (0.2 mL) and aq NaOH soln (1M, 0.22 mL, 0.22 mmol) was added. The RM was stirred at RT for 3 days. Aq HCl soln (1M, 0.22 mL, 0.22 mmol) was added and the mixture was concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 1000 mm, 5 μ m; eluent: 5 to 100% ACN in H₂O with 0.2% FA) to provide 4-((3*R*,4*R*)-1-(3,3-

difluoropropyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid as a white solid (19.3 mg).

Example Ex-26: 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(3,3,3-trifluoropropyl)piperidin-3-yl)benzoic acid

- 5 **Example Ex-26** was prepared as described for **Example Ex-25** using methyl 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(3,3,3-trifluoropropyl)piperidin-3-yl)benzoate (**Intermediate B-14**, 14.3 mg, 30 μmol) to provide 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(3,3,3-trifluoropropyl)piperidin-3-yl)benzoic acid as a white solid (12.9 mg).

Example Ex-27: 4-((3*R*,4*R*)-1-(3,3-difluorocyclobutyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid

- 10 Step 1a: *tert*-butyl 4-(((3*R*,4*R*)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate B-12**, 49 mg, 95 μmol) was combined with DIPEA (58 μL, 0.33 mmol) in ACN (1 mL). 3,3-Difluorocyclobutyl trifluoromethanesulfonate (24.7 mg, 0.12 mmol) was added slowly and the RM was stirred at 40 °C for 16 h. The RM was allowed to cool to RT and concentrated under reduced pressure.

- 15 Step 1b: The residue was dissolved in IPA (1 mL). Aq NaOH soln (1M, 0.48 mL, 0.48 mmol) was added, and the RM was stirred at 80 °C for 20 h. The RM was allowed to cool to RT and partially concentrated under reduced pressure. The pH was adjusted to 4 with aq HCl soln (1M), and the mixture was extracted with EtOAc (3x). The combined org phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm, 5 μm; eluent: 10 to 30% ACN in H₂O with 0.1% NH₄OH) to provide 4-((3*R*,4*R*)-1-(3,3-difluorocyclobutyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid as a beige solid (14.9 mg).

Example Ex-28: 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-((1*r*,3*R*)-3-fluorocyclobutyl)piperidin-3-yl)benzoic acid

- 25 **Example Ex-28** was prepared as described for **Example Ex-27** using *tert*-butyl 4-(((3*R*,4*R*)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate B-12**, 39 mg, 75 μmol) and enriched (1*s*,3*s*)-3-fluorocyclobutyl trifluoromethanesulfonate (40 wt%, 126 mg, 0.23 mmol) in Step 1a to provide 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-((1*r*,3*R*)-3-fluorocyclobutyl)piperidin-3-yl)benzoic acid as a beige solid (2.0 mg).

Example Ex-29: 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(tetrahydrofuran-3-yl)piperidin-3-yl)benzoic acid

- 35 Enriched *tert*-Butyl 4-(((3*R*,4*R*)-3-(4-(methoxycarbonyl)phenyl)-1-(tetrahydrofuran-3-yl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate B-18**, 27.5 mg) was dissolved in IPA (1 mL). Aq NaOH soln (1M, 0.18 mL, 0.18 mmol) was added, and the RM was stirred at 80 °C for 20 h. The RM was allowed to cool to RT and partially concentrated under reduced pressure. The pH was adjusted to 4 with aq HCl soln (1M), and the mixture was extracted with EtOAc (3x).

The combined org phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm, 5 µm; eluent: 5 to 20% ACN in H₂O with 0.1% NH₄OH) to provide 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(tetrahydrofuran-3-yl)piperidin-3-yl)benzoic acid as a white powder that was a mixture of diastereomers (8.9 mg).

Example Ex-30: 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2-hydroxy-2-methylpropyl)piperidin-3-yl)benzoic acid

Step 1a: *tert*-Butyl 4-(((3*R*,4*R*)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate B-12**, 50.8 mg, 78 µmol) was dissolved in toluene (1 mL). 2,2-Dimethyloxirane (56.2 mg, 0.78 mmol) and AcOH (4 µL, 78 µmol) were added, and the RM was stirred at 70 °C for 3 days. The RM was allowed to cool to RT and concentrated under reduced pressure.

Step 1b: The residue was dissolved in IPA (1 mL). Aq NaOH soln (1M, 0.39 mL, 0.39 mmol) was added, and the RM was stirred at 80 °C for 20 h. The RM was allowed to cool to RT and partially concentrated under reduced pressure. The pH was adjusted to 6 with aq HCl soln (1M), and the mixture was extracted with EtOAc (3x). The combined org phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm, 5 µm; eluent: 10 to 30% ACN in H₂O with 0.1% NH₄OH) to provide 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2-hydroxy-2-methylpropyl)piperidin-3-yl)benzoic acid as a beige solid (26.6 mg).

Example Ex-31: 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2-(trifluoromethoxy)ethyl)piperidin-3-yl)benzoic acid

Example Ex-31 was prepared as described for **Example Ex-25** using methyl 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2-(trifluoromethoxy)ethyl)piperidin-3-yl)benzoate (**Intermediate B-15**, 9.9 mg, 18 µmol) to provide 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2-(trifluoromethoxy)ethyl)piperidin-3-yl)benzoic acid as a white solid (7.6 mg).

Example Ex-32: 4-((3*R*,4*R*)-4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-(2,2-difluoroethyl)piperidin-3-yl)benzoic acid

Step 1a: *tert*-Butyl 5-chloro-4-(((3*R*,4*R*)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-7-methyl-1*H*-indole-1-carboxylate (**Intermediate B-19**, 73.6 mg, 0.11 mmol) was combined with DIPEA (83 µL, 0.48 mmol) in ACN (1 mL). 2,2-Difluoroethyl trifluoromethanesulfonate (32.4 mg, 0.15 mmol) was added slowly and the RM was stirred at 50 °C for 3 h. The RM was allowed to cool to RT and concentrated under reduced pressure.

Step 1b: The residue was dissolved in MeOH (1 mL). Aq NaOH soln (1M, 0.66 mL, 0.66 mmol) was added, and the RM was stirred at 50 °C for 3 days. The RM was allowed to cool to RT and partially concentrated under reduced pressure. The pH was adjusted to 4 with aq HCl soln (1M), and the mixture was extracted with EtOAc (3x). The combined org phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by preparatory HPLC

(Waters XBridge C18 OBD 30 x 50 mm, 5 µm; eluent: 10 to 30% ACN in H₂O with 0.1% NH₄OH) to provide 4-((3*R*,4*R*)-4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-(2,2-difluoroethyl)piperidin-3-yl)benzoic acid as a white solid (51 mg).

Example Ex-33: 4-((3*R*,4*R*)-4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)piperidin-3-yl)benzoic acid

Example Ex-33 was prepared as described for **Example Ex-32** using *tert*-butyl 5-chloro-4-(((3*R*,4*R*)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-7-methyl-1*H*-indole-1-carboxylate (**Intermediate B-19**, 73.6 mg, 0.11 mmol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (35.1 mg, 0.15 mmol) in Step 1a to provide 4-((3*R*,4*R*)-4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)piperidin-3-yl)benzoic acid as a white solid (46.2 mg).

Example Ex-34: 4-((3*R*,4*R*)-1-(2,2-difluoroethyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)azepan-3-yl)benzoic acid

Step 1a: Enriched *tert*-butyl 4-(((3*R*,4*R*)-3-(4-(methoxycarbonyl)phenyl)azepan-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate B-20**, 137 mg) was combined with DIPEA (39 µL, 0.23 mmol) in ACN (1 mL). 2,2-Difluoroethyl trifluoromethanesulfonate (15 mg, 70 µmol) was added slowly and the RM was stirred at 60 °C for 3 h. The RM was allowed to cool to RT and concentrated under reduced pressure.

Step 1b: The residue was dissolved in MeOH (1 mL). Aq NaOH soln (1M, 0.31 mL, 0.31 mmol) was added, and the RM was stirred at 60 °C for 3 days. The RM was allowed to cool to RT and partially concentrated under reduced pressure. The pH was adjusted to 4 with aq HCl soln (1M), and the mixture was extracted with EtOAc (3x). The combined org phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm, 5 µm; eluent: 15 to 40% ACN in H₂O with 0.1% NH₄OH) to provide 4-((3*R*,4*R*)-1-(2,2-difluoroethyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)azepan-3-yl)benzoic acid as a white solid (20.2 mg).

Example Ex-35: 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)azepan-3-yl)benzoic acid

Step 1a: *tert*-Butyl 5-chloro-4-(((3*R*,4*R*)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-7-methyl-1*H*-indole-1-carboxylate (**Intermediate B-20**, 30.8 mg, 58 µmol) was combined with NEt₃ (24 µL, 0.17 mmol) in ACN (1 mL). 2,2,2-Trifluoroethyl trifluoromethanesulfonate (27 mg, 0.12 mol) was added slowly and the RM was stirred at 60 °C for 2 h. The RM was allowed to cool to RT and concentrated under reduced pressure.

Step 1b: The residue was dissolved in IPA (1 mL). Aq NaOH soln (1M, 0.29 mL, 0.29 mmol) was added, and the RM was stirred at 80 °C overnight. The RM was allowed to cool to RT and partially concentrated under reduced pressure. The pH was adjusted to 4 with aq HCl soln (1M), and the mixture was extracted with EtOAc (3x). The combined org phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm, 5 µm; eluent: 15 to 40% ACN in H₂O with 0.1% NH₄OH) to provide

4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)azepan-3-yl)benzoic acid as a white solid (12.4 mg).

Example Ex-36: 4-(((3*R*,4*R*)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-(2-fluoroethyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole

- 5 Step 1a: *Racemic tert*-butyl 4-(((3*R*^{*},4*R*^{*})-3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-(*tert*-butoxycarbonyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate rac-M-10**, 70.5 mg, 0.12 mmol) was dissolved in MeOH (2 mL). HCl soln (4M in dioxane, 1 mL, 4 mmol) was added, and the RM was stirred at RT for 40 min. The RM was concentrated under reduced pressure, and the residue was partitioned between sat. aq NaHCO₃ soln and DCM. The aq phase
10 was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure.

Step 1b: The residue was dissolved in ACN (1 mL), and 1-fluoro-2-iodoethane (50 mg, 0.28 mmol) was added followed by NEt₃ (80 µL, 0.57 mmol). The RM was stirred at 45 °C for 3 days. The RM was allowed to cool to RT, diluted with H₂O, and the mixture was extracted with DCM (3x).

- 15 The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure.

Step 1c: The residue was dissolved in MeOH (2 mL), and K₂CO₃ (60 mg, 0.43 mmol) was added. The RM was stirred at 65 °C for 5 h. The RM was allowed to cool to RT and concentrated under reduced pressure. The residue was purified by RP chromatography (C18, 15.5 g; eluent: 35 to
20 60% ACN in H₂O with 0.1% NH₄OH) to provide *racemic* 4-(((3*R*^{*},4*R*^{*})-3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-(2-fluoroethyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole as an off-white solid (52 mg).

Step 1d: Chiral separation and analytics according to Method SFC-26: 52 mg provided **Example Ex-36** (peak 2): 18.1 mg, white solid. Analytical chiral HPLC: Rt = 2.85 min; 100% ee.

- 25 **Example Ex-37:** 4-(((3*R*,4*R*)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-(2,2-difluoroethyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole

Step 1a: *tert*-butyl 4-(((3*R*,4*R*)-3-(4-(1*H*-pyrazol-1-yl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate B-21**, 35.6 mg, 68 µmol) was combined with NEt₃ (29 µL, 0.20 mmol) in ACN (1 mL). 2,2-Difluoroethyl trifluoromethanesulfonate (16 mg, 75 µmol) was added
30 slowly and the RM was stirred at 60 °C for 2 h. The RM was allowed to cool to RT and concentrated under reduced pressure.

Step 1b: The residue was dissolved in MeOH (1 mL). K₂CO₃ (94.1 mg, 0.68 mmol) was added, and the RM was stirred at 50 °C overnight. The RM was allowed to cool to RT and diluted with H₂O. The mixture was extracted with EtOAc (3x). The combined org phases were dried over
35 Na₂SO₄ and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm, 5 µm; eluent: 45 to 70% ACN in H₂O with 0.1% NH₄OH) to provide 4-(((3*R*,4*R*)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-(2,2-difluoroethyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole as a white solid (21.3 mg).

Example Ex-38: *racemic* 1-((3*R,4*R**)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-1-yl)ethan-1-one**

- Step 1a: *Racemic tert*-butyl 4-(((3*R**,4*R**)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-(*tert*-butoxycarbonyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate *rac*-M-10**, 71.9 mg, 0.12 mmol) was dissolved in MeOH (1.5 mL). HCl soln (4M in dioxane, 0.75 mL, 3 mmol) was added, and the RM was stirred at RT for 2 h. The RM was concentrated under reduced pressure, and the residue was partitioned between sat. aq NaHCO₃ soln and DCM. The aq phase was extracted with DCM (2x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure.
- Step 1b: The residue was dissolved in DCM (2 mL), and NEt₃ (51 µL, 0.37 mmol) and acetyl chloride (20 µL, 0.28 mmol) were added sequentially. The RM was stirred at RT for 90 min. The RM was diluted with H₂O, and the mixture was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure.
- Step 1c: The residue was dissolved in MeOH (1 mL), and K₂CO₃ (100 mg, 0.72 mmol) was added. The RM was stirred at 65 °C for 5 h. The RM was allowed to cool to RT and diluted with H₂O. The mixture was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm, 5 µm; eluent: 25 to 50% ACN in H₂O with 0.1% NH₄OH) to provide *racemic* 1-((3*R**,4*R**)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-1-yl)ethan-1-one as a white solid (19.7 mg).

Example Ex-39: *racemic* 4-((3*R,4*R**)-3-(6-(1*H*-pyrazol-1-yl)pyridin-3-yl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole**

- Step 1a: *Racemic tert*-butyl 4-(((3*R**,4*R**)-3-(6-(1*H*-pyrazol-1-yl)pyridin-3-yl)-1-(*tert*-butoxycarbonyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate *rac*-M-18**, 37.8 mg, 64 µmol) was dissolved in MeOH (2 mL). HCl soln (4M in dioxane, 1 mL, 4 mmol) was added, and the RM was stirred at RT for 1 h. The RM was concentrated under reduced pressure, and the residue was partitioned between sat. aq NaHCO₃ soln and DCM. The aq phase was extracted with DCM (2x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure.
- Step 1b: The residue was dissolved in MeOH (2 mL). Aq formaldehyde soln (37 wt%, 0.5 mL, 6.7 mmol) and Na(OAc)₃BH (28 mg, 0.13 mmol) were added. The RM was stirred at RT for 80 min. The RM was neutralized with sat aq. NaHCO₃ soln and the mixture was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure.
- Step 1c: The residue was dissolved in MeOH (2 mL), and K₂CO₃ (44.4 mg, 0.32 mmol) was added. The RM was stirred at 65 °C for 2 h. The RM was allowed to cool to RT and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30

x 50 mm, 5 µm; eluent: 35 to 60% ACN in H₂O with 0.1% NH₄OH) to provide *racemic* 4-(((3*R**,4*R**)-3-(6-(1*H*-pyrazol-1-yl)pyridin-3-yl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole as a white solid (8 mg).

Example Ex-40: *racemic* 4-(((3*R,4*R**)-3-(4-(1*H*-1,2,3-triazol-1-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole**

Step 1a: *Racemic tert*-butyl 4-(((3*R**,4*R**)-3-(4-(1*H*-1,2,3-triazol-1-yl)phenyl)-1-(*tert*-butoxycarbonyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate rac-M-19**, 30.5 mg, 52 µmol) was dissolved in MeOH (1 mL). HCl soln (4M in dioxane, 1 mL, 4 mmol) was added, and the RM was stirred at RT overnight. The RM was concentrated under reduced pressure.

Step 1b: The residue was dissolved in MeOH (1 mL). Aq formaldehyde soln (37 wt%, 0.5 mL, 6.7 mmol) and Na(OAc)₃BH (33 mg, 0.16 mmol) were added. The RM was stirred at RT for 30 min. The RM was neutralized with sat aq. NaHCO₃ soln and the mixture was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure.

Step 1c: The residue was dissolved in MeOH (3 mL), and K₂CO₃ (35.9 mg, 0.30 mmol) was added. The RM was stirred at 65 °C overnight. The RM was allowed to cool to RT and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm, 5 µm; eluent: 25 to 50% ACN in H₂O with 0.1% NH₄OH) to provide *racemic* 4-(((3*R**,4*R**)-3-(4-(1*H*-1,2,3-triazol-1-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole as a white solid (0.5 mg).

Example Ex-41: 1-(4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)phenyl)cyclopropan-1-ol

tert-Butyl 4-(((3*R*,4*R*)-3-(4-(methoxycarbonyl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate B-10**, 6.5 mg, 17 µmol) was dissolved in THF (1 mL). Titanium(IV) isopropoxide (40 µL, 0.13 mmol) was added, followed by ethylmagnesium bromide soln (40 wt% in Me-THF, 0.3 mL, 1.0 mmol). The RM was stirred at RT overnight. The RM was quenched with sat. aq NH₄Cl soln, and the mixture was extracted with DCM (4x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm, 5 µm; eluent: 25 to 50% ACN in H₂O with 0.1% NH₄OH) to provide 1-(4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)phenyl)cyclopropan-1-ol as a white solid (1.3 mg).

Example Ex-42: 4-(((3*R*,4*R*)-1-(2-fluoroethyl)-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole

Step 1a: *tert*-Butyl 5,7-dimethyl-4-(((3*R*,4*R*)-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-1*H*-indole-1-carboxylate (**Intermediate B-4**, 60 mg, 0.14 mmol) was dissolved in ACN (1.5 mL), and NEt₃ (90 µL, 0.64 mmol) was added followed by 1-fluoro-2-iodoethane (60 mg, 0.34 mmol). The RM was stirred at 60 °C overnight. The RM was allowed to cool to RT, diluted with H₂O, and the

mixture was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure.

Step 1b: The residue was dissolved in MeOH (1.5 mL), and K₂CO₃ (78.1 mg, 0.56 mmol) was added. The RM was stirred at 60 °C for 2 h. The RM was allowed to cool to RT and diluted with H₂O. The mixture was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm, 5 µm; eluent: 25 to 50% ACN in H₂O with 0.1% NH₄OH) to provide 4-(((3*R*,4*R*)-1-(2-fluoroethyl)-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole as a white solid (29.8 mg).

Example Ex-43: 4-((1*S*,2*R*,5*S*)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid

Step 1a: *Racemic* 4-((1*S**,2*R**,5*S**)-2-((1-(*tert*-butoxycarbonyl)-5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid (**Intermediate rac-M-28**, 130 mg, 0.23 mmol) was dissolved in THF (3 mL) and MeOH (3 mL). Aq NaOH soln (1M, 1.5 mL, 1.5 mmol) was added, and the RM was stirred at 60 °C for 6 h. The RM was allowed to cool to RT, acidified with aq HCl soln (1M, 2 mL), and concentrated under reduced pressure. The residue was purified by RP chromatography (C18, 15.5 g; eluent: 35 to 60% ACN in H₂O with 0.1% FA) to provide *racemic* 4-((1*S**,2*R**,5*S**)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid (86.4 mg).

Step 1b: Chiral separation and analytics according to Method SFC-27: 86 mg provided **Example Ex-43** (peak 1): 37.1 mg, white solid. Analytical chiral HPLC: Rt = 2.48 min; 100% ee.

Example Ex-44: 4-((1*S*,2*R*,5*S*)-2-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid

Step 1a: *Racemic tert*-butyl 5-chloro-4-(((1*R**,2*S**,4*S**)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate (**Intermediate rac-M-29**, 160 mg, 0.30 mmol) was dissolved in EtOH (1 mL). Aq NaOH soln (4M, 1.5 mL, 6 mmol) was added, and the RM was stirred at RT for 3 days. The RM was acidified to pH = 2 with aq HCl soln (6M). The resulting mixture was extracted with EtOAc (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure to provide *racemic* 4-((1*S**,2*R**,5*S**)-2-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid (105 mg).

Step 1b: Chiral separation and analytics according to Method SFC-28: 105 mg provided **Example Ex-44** (peak 2): 31.5 mg, white solid. LC-MS Method C-3: Rt = 2.52 min; MS m/z [M+H]⁺ = 414.3. Analytical chiral HPLC: Rt = 2.54 min; 98% ee.

Example Ex-45: 4-((1*S*,2*R*,5*S*)-2-((5-fluoro-7-methyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid

tert-Butyl 5-fluoro-4-(((1*R*,2*S*,4*S*)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate (**Intermediate M-30**, 130 mg, 0.25 mmol) was dissolved in THF

(1 mL) and MeOH (1 mL). Aq NaOH soln (1M, 1.0 mL, 1.0 mmol) was added, and the RM was stirred at 60 °C for for 3 h. The RM was allowed to cool to RT, neutralized with aq HCl soln (1M, 1 mL), and concentrated under reduced pressure. The residue was purified over silica gel (25 g; eluent: 0 to 5% MeOH in DCM) to provide 4-((1S,2R,5S)-2-((5-fluoro-7-methyl-1H-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid as a white solid (44 mg).

Example Ex-46: **4-((1S,2R,5S)-5-methoxy-2-((7-methyl-1H-indol-4-yl)oxy)cyclohexyl)benzoic acid**

tert-Butyl 4-(((1R,2S,4S)-4-methoxy-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-7-methyl-1H-indole-1-carboxylate (**Intermediate M-31**, 34 mg, 61 μmol) was dissolved in EtOH (0.5 mL). Aq NaOH soln (4M, 0.3 mL, 1.2 mmol) was added, and the RM was stirred at RT for 3 days. The RM was partially concentrated under reduced pressure and the remaining mixture was acidified to pH = 2 with aq HCl soln (6M). The resulting mixture was extracted with DCM (3x). The combined org phases were dried through an Isolute® phase separator and concentrated under reduced pressure. The residue was purified by SFC (waters DIOL 5 μm, 19 x 250 mm; eluent: 10 to 60% MeOH in sc CO₂) to provide 4-((1S,2R,5S)-5-methoxy-2-((7-methyl-1H-indol-4-yl)oxy)cyclohexyl)benzoic acid as a white solid (8.9 mg).

Example Ex-47: ***racemic* 4-((1S*,2R*)-2-((5,7-dimethyl-1H-indol-4-yl)oxy)cyclohexyl)benzoic acid**

Example Ex-47 was prepared as described for **Example Ex-45** using enriched *racemic tert*-butyl 4-(((1R*,2S*)-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-5,7-dimethyl-1H-indole-1-carboxylate (**Intermediate rac-M-32**, 317 mg) to provide *racemic* 4-((1S*,2R*)-2-((5,7-dimethyl-1H-indol-4-yl)oxy)cyclohexyl)benzoic acid as a white solid (12.5 mg).

Example Ex-48: **4-((1S,2R)-2-((5,7-dimethyl-1H-indol-4-yl)oxy)-5,5-difluorocyclohexyl)benzoic acid**

Step 1a: *Racemic tert*-butyl 4-(((1R*,2S*)-4,4-difluoro-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-5,7-dimethyl-1H-indole-1-carboxylate (**Intermediate rac-M-33**, 18 mg, 35 μmol) was dissolved in THF (1 mL) and MeOH (0.5 mL). Aq NaOH soln (1M, 0.35 mL, 0.35 mmol) was added, and the RM was stirred at 50 °C for for 18 h. The RM was allowed to cool to RT and purified by preparatory HPLC (Waters XBridge C18 30 x 100 mm, 5 μm; eluent: 20 to 100% ACN in H₂O with 0.2% FA) to provide *racemic* 4-((1S*,2R*)-2-((5,7-dimethyl-1H-indol-4-yl)oxy)-5,5-difluorocyclohexyl)benzoic acid as a white solid (12.5 mg).

Step 1b: Chiral separation and analytics according to Method SFC-29: 12.5 mg provided **Example Ex-48** (peak 2): 5.6 mg, white solid. Analytical chiral HPLC: Rt = 1.33 min; 99.5% ee.

Example Ex-49: **4-((1S,2R,5S)-2-((5-cyclopropyl-7-methyl-1H-indol-4-yl)oxy)-5-hydroxycyclohexyl)benzoic acid**

Chiral separation of **Intermediate rac-B-32** and analytics according to Method SFC-30. 43 mg provided **Example Ex-49** (peak 2): 11.3 mg, white solid. Analytical chiral HPLC: Rt = 1.22 min; 99.6% ee.

Example Ex-50: 4-((1S,2R,5S)-2-((5-cyclopropyl-7-methyl-1H-indol-4-yl)oxy)-5-(difluoromethoxy)cyclohexyl)benzoic acid

Step 1a: *Racemic* 4-((1S*,2R*,5S*)-2-((5-cyclopropyl-7-methyl-1H-indol-4-yl)oxy)-5-hydroxycyclohexyl)benzoic acid (**Intermediate rac-B-32**, 23.6 mg, 58 µmol) was dissolved in DCM (0.25 mL). KOAc (5.7 mg, 58 µmol) and (bromodifluoromethyl)trimethylsilane (47.3 mg, 0.32 mmol) were added, and the RM was stirred at RT for 4 h. Additional bromodifluoromethyl)trimethylsilane (47.3 mg, 0.32 mmol) was added, and the RM was stirred at RT for 16 h. A third portion of (bromodifluoromethyl)trimethylsilane (47.3 mg, 0.32 mmol) was added, and the RM was stirred at RT for 4 h. The RM was diluted with DCM and H₂O, and the org phase was dried through an Isolute® phase separator and concentrated under reduced pressure.

Step 1b: The residue was dissolved in THF (0.8 mL) and MeOH (0.5 mL). Aq NaOH soln (1M, 0.58 mL, 0.58 mmol) was added, and the RM was stirred at RT for 24 h. FA (44 µL) was added, and the mixture was purified by preparatory HPLC (Waters XBridge C18 30 x 100 mm, 5 µm; eluent: 20 to 100% ACN in H₂O with 0.2% FA) to provide *racemic* 4-((1S*,2R*,5S*)-2-((5-cyclopropyl-7-methyl-1H-indol-4-yl)oxy)-5-(difluoromethoxy)cyclohexyl)benzoic acid as a light brown solid (15.8 mg).

Step 1c: Chiral separation and analytics according to Method SFC-31: 11.6 mg provided **Example Ex-50** (peak 1): 4.0 mg, white solid. Analytical chiral HPLC: Rt = 1.17 min; 99.5% ee.

Example Ex-51: 4-((1S,2R,5R)-2-((5,7-dimethyl-1H-indol-4-yl)oxy)-5-methylcyclohexyl)benzoic acid

Step 1a: Methyl 4-((1S,2S,5R)-2-hydroxy-5-methylcyclohexyl)benzoate (**Intermediate A-25**, 52.3 mg, 0.21 mmol), *tert*-butyl 4-hydroxy-5,7-dimethyl-1H-indole-1-carboxylate (**Intermediate I-1**, 50 mg, 0.91 mmol), and PPh₃ (75.3 mg, 0.29 mmol) were dissolved in THF (0.9 mL). A DBAD (66 mg, 0.29 mmol) soln in toluene (0.9 mL) was added to the cooled soln in a dropwise manner over 10 min. The RM was allowed to gradually warm to RT and stirred at RT overnight. Column chromatography over silica gel (eluent: 0 to 80% EtOAc in heptane) provided enriched material. Step 1b: The material was dissolved in IPA (2 mL), and aq NaOH soln (1M, 0.46 mL, 0.46 mmol) was added. The RM was stirred at 80 °C overnight. The RM was allowed to cool to RT, partially concentrated under reduced pressure, and the pH of the remaining mixture was adjusted to 4 with aq HCl soln (1M). The mixture was extracted with EtOAc (3x). The combined org phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm, 5 µm; eluent: 15 to 40% ACN in H₂O with 0.1% NH₄OH) to provide 4-((1S,2R,5R)-2-((5,7-dimethyl-1H-indol-4-yl)oxy)-5-methylcyclohexyl)benzoic acid (2.1 mg).

Example Ex-52: 4-((5S,6R)-6-((5,7-dimethyl-1H-indol-4-yl)oxy)spiro[2.5]octan-5-yl)benzoic acid

Methyl 4-((5S,6R)-6-((5,7-dimethyl-1H-indol-4-yl)oxy)spiro[2.5]octan-5-yl)benzoate (**Intermediate B-33**, 30.3 mg, 75 μ mol) was dissolved in MeOH (1 mL). Aq NaOH soln (4M, 94 μ L, 0.38 mmol) was added, and the RM was stirred at 50 °C for 8 h. The RM was allowed to cool to RT and stirred overnight. The RM was quenched with aq HCl soln (4M, 96 μ L, 0.38 mmol).

- 5 The soln was purified by preparatory HPLC (Waters XBridge C18 30 x 100 mm, 5 μ m; eluent: 10 to 60% ACN in H₂O with 0.1% NH₄OH) to provide 4-((5S,6R)-6-((5,7-dimethyl-1H-indol-4-yl)oxy)spiro[2.5]octan-5-yl)benzoic acid as a white foam (27.8 mg).

Example Ex-53: 4-((1S,2R,5S)-2-((5,7-dimethyl-1H-indol-4-yl)oxy)-5-methoxycyclohexyl)benzamide

- 10 4-((1S,2R,5S)-2-((5,7-Dimethyl-1H-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid (**Example Ex-18**, 50 mg, 0.13 mmol) was dissolved in DMF (0.5 mL), and HATU (60.4 mg, 0.16 mmol) was added. DIPEA (55 μ L, 0.32 mmol) and NH₄Cl (17 mg, 0.32 mmol) were added, and the RM was stirred at RT for 30 min. The RM was quenched with H₂O, and the mixture was extracted with EtOAc (2x). The combined org phases were washed with brine, dried over Na₂SO₄, and
- 15 concentrated under reduced pressure. The residue was purified by RP chromatography (SunFire Prep C18 19x50 mm column, 5 μ m; eluent: 20 to 100% ACN in H₂O with 0.1% TFA) to provide 4-((1S,2R,5S)-2-((5,7-dimethyl-1H-indol-4-yl)oxy)-5-methoxycyclohexyl)benzamide as a light purple solid (6 mg).

Example Ex-54: 4-((3R,4R)-4-((5-fluoro-7-methyl-1H-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)piperidin-3-yl)benzoic acid

- 20 Step 1a: *Racemic tert*-butyl 5-fluoro-4-(((3R*,4R*)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-7-methyl-1H-indole-1-carboxylate (**Intermediate rac-B-31**, 35.9 mg, 74 μ mol) was dissolved in ACN (1 mL). DIPEA (45 μ L, 0.26 mmol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (19 mg, 82 μ mol) were added, and the RM was stirred at 50 °C for 3 h.
- 25 The RM was diluted with EtOAc, and the mixture was washed with H₂O. The aq phase was extracted with EtOAc (2x). The combined org phases were washed with brine, dried through a phase separator, and concentrated under reduced pressure.

- Step 1b: The residue was dissolved in MeOH (0.2 mL) and aq NaOH soln (1M, 0.18 mL, 0.18 mmol) was added. The RM was stirred at 50 °C for 5 h. The RM was allowed to cool to RT and
- 30 stirred overnight. Aq. HCl soln (1M, 0.18 mL) was added, and the mixture was concentrated under reduced pressure. The residue was purified using preparatory HPLC (Waters XBridge C18 30 x 100 mm, 5 μ m; eluent: 5 to 100% ACN in H₂O with 0.2% FA) to provide *racemic* 4-((3R*,4R*)-4-((5-fluoro-7-methyl-1H-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)piperidin-3-yl)benzoic acid as a white solid.

- 35 Step 1c: Chiral separation and analytics according to Method SFC-32: 21 mg provided **Example Ex-54** (peak 2): 8.9 mg, white solid. Analytical chiral HPLC: Rt = 1.35 min; 99.9% ee.

Example Ex-55: 4-((1S,2R)-2-((5-cyclopropyl-7-methyl-1H-indol-4-yl)oxy)-5,5-difluorocyclohexyl)benzoic acid

Step 1a: *Racemic tert*-butyl 5-cyclopropyl-4-(((1*R**,2*S**)-4,4-difluoro-2-(4-(methoxycarbonyl)phenyl)cyclohexyl)oxy)-7-methyl-1*H*-indole-1-carboxylate (**Intermediate rac-M-39**, 36 mg, 65 µmol) was dissolved in THF (1.2 mL) and MeOH (0.6 mL). Aq NaOH soln (1M, 0.66 mL, 0.66 mmol) was added, and the RM was stirred at 50 °C for 18 h. The RM was quenched with FA (62 µL), and the mixture was purified using preparatory HPLC (Waters XBridge C18 30 x 100 mm, 5 µm; eluent: 15 to 100% ACN in H₂O with 0.2% FA) to provide *racemic* 4-((1*S**,2*R**)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5,5-difluorocyclohexyl)benzoic acid as a white solid (64 mg).

Step 1b: Chiral separation and analytics according to Method SFC-33: 64 mg provided **Example Ex-55** (peak 1): 9 mg, white solid. Analytical chiral HPLC: Rt = 1.74 min; 99.5% ee.

Example Ex-56: 4-((3*R*,4*R*)-4-((7-chloro-5-methyl-1*H*-indol-4-yl)oxy)-1-(2,2-difluoroethyl)piperidin-3-yl)benzoic acid

Step 1a: *tert*-Butyl 4-(((3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-7-chloro-5-methyl-1*H*-indole-1-carboxylate (**Intermediate M-42**, 129.3 mg, 0.21 mmol) was dissolved in MeOH (3 mL). HCl soln (4M in dioxane, 0.55 mL, 2.21 mmol) was added, and the RM was stirred at 35 °C for 3 h. The pH of the soln was adjusted to 6 with aq NaOH soln (1M), and the mixture was partitioned between EtOAc and H₂O. The separated aq phase was extracted with EtOAc (2x). The combined org phases were dried over MgSO₄ and concentrated under reduced pressure.

Step 1b: The residue was combined with NEt₃ (0.31 mL, 2.21 mmol) and ACN (1 mL). 2,2-Difluoroethyl trifluoromethanesulfonate (24.7 mg, 0.12 mmol) was added slowly and the RM was stirred at 60 °C for 2 h. The RM was allowed to cool to RT and concentrated under reduced pressure.

Step 1c: The residue was dissolved in THF (1 mL). Aq NaOH soln (1M, 1.42 mL, 1.42 mmol) was added, and the RM was stirred at 70 °C for 20 h. The RM was allowed to cool to RT and partially concentrated under reduced pressure. The pH was adjusted to 4 with aq HCl soln (1M), and the mixture was extracted with EtOAc (3x). The combined org phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm, 5 µm; eluent: 10 to 30% ACN in H₂O with 0.1% NH₄OH) to provide 4-((3*R*,4*R*)-4-((7-chloro-5-methyl-1*H*-indol-4-yl)oxy)-1-(2,2-difluoroethyl)piperidin-3-yl)benzoic acid as a white solid (15.8 mg).

Example Ex-57: 4-((3*R*,4*R*)-1-((2,2-difluorocyclopropyl)methyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid

tert-Butyl 4-(((3*R*,4*R*)-1-((2,2-difluorocyclopropyl)methyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate B-34**, 31.6 mg, 79 µmol) was dissolved in THF (2 mL). Aq NaOH soln (1M, 0.79 mL, 0.79 mmol) was added, and the RM was stirred at 70 °C for 20 h. The RM was allowed to cool to RT and partially concentrated under reduced pressure. The pH was adjusted to 4 with aq

HCl soln (1M), and the mixture was extracted with EtOAc (3x). The combined org phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm, 5 µm; eluent: 10 to 30% ACN in H₂O with 0.1% NH₄OH) to provide 4-((3*R*,4*R*)-1-((2,2-difluorocyclopropyl)methyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid as a white solid (2.2 mg).

Example Ex-58: 4-((3*R*,4*R*)-1-(4,4-difluorobutyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid

tert-Butyl 4-((3*R*,4*R*)-1-(4,4-difluorobutyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole-1-carboxylate (**Intermediate B-35**, 47.4 mg, 83 µmol) was dissolved in THF (2 mL). Aq NaOH soln (1M, 1.66 mL, 1.66 mmol) was added, and the RM was stirred at 70 °C for 20 h. The RM was allowed to cool to RT and partially concentrated under reduced pressure. The pH was adjusted to 4 with aq HCl soln (1M), and the mixture was extracted with EtOAc (3x). The combined org phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm, 5 µm; eluent: 10 to 30% ACN in H₂O with 0.1% NH₄OH) to provide 4-((3*R*,4*R*)-1-(4,4-difluorobutyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid as a white solid (8.2 mg).

Example Ex-59: 4-((3*R*,4*R*)-4-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-1-(2,2-difluoroethyl)piperidin-3-yl)benzoic acid

Enriched *tert*-butyl 5-cyclopropyl-4-((3*R*,4*R*)-1-(2,2-difluoroethyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-7-methyl-1*H*-indole-1-carboxylate (**Intermediate B-37**, 16 mg) was dissolved in THF (1 mL). Aq NaOH soln (1M, 0.28 mL, 0.28 mmol) was added, and the RM was stirred at 70 °C for 20 h. The mixture was allowed to cool to RT and partially concentrated under reduced pressure. The pH was adjusted to 4 with aq HCl soln (1M), and the mixture was extracted with EtOAc (3x). The combined org phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm, 5 µm; eluent: 10 to 30% ACN in H₂O with 0.1% NH₄OH) to provide 4-((3*R*,4*R*)-4-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-1-(2,2-difluoroethyl)piperidin-3-yl)benzoic acid as a white solid (1.6 mg).

Example Ex-60: 4-((3*R*,4*R*)-4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-(3,3-difluoropropyl)piperidin-3-yl)benzoic acid

tert-Butyl 5-chloro-4-((3*R*,4*R*)-1-(3,3-difluoropropyl)-3-(4-(methoxycarbonyl)phenyl)piperidin-4-yl)oxy)-7-methyl-1*H*-indole-1-carboxylate (**Intermediate B-38**, 30.2 mg, 52 µmol) was dissolved in THF (1 mL). Aq NaOH soln (1M, 1.04 mL, 1.04 mmol) was added, and the RM was stirred at 70 °C for 20 h. The mixture was allowed to cool to RT and partially concentrated under reduced pressure. The pH was adjusted to 4 with aq HCl soln (1M), and the mixture was extracted with EtOAc (3x). The combined org phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm, 5 µm; eluent: 10 to 30% ACN in H₂O with 0.1% NH₄OH) to provide 4-((3*R*,4*R*)-4-((5-chloro-7-

methyl-1*H*-indol-4-yl)oxy)-1-(3,3-difluoropropyl)piperidin-3-yl)benzoic acid as a white solid (8.2 mg).

Example Ex-61: 4-((3*R*,4*R*)-4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-(3,3,3-trifluoropropyl)piperidin-3-yl)benzoic acid

- 5 *tert*-Butyl 5-chloro-4-(((3*R*,4*R*)-3-(4-(methoxycarbonyl)phenyl)-1-(3,3,3-trifluoropropyl)piperidin-4-yl)oxy)-7-methyl-1*H*-indole-1-carboxylate (**Intermediate B-39**, 48.4 mg, 81 μ mol) was dissolved in THF (1 mL). Aq NaOH soln (1M, 1.63 mL, 1.63 mmol) was added, and the RM was stirred at 70 °C for 20 h. The RM was allowed to cool to RT and partially concentrated under reduced pressure. The pH was adjusted to 4 with aq HCl soln (1M), and the mixture was extracted with EtOAc (3x). The combined org phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 50 mm, 5 μ m; eluent: 15 to 40% ACN in H₂O with 0.1% NH₄OH) to provide 4-((3*R*,4*R*)-4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-(3,3,3-trifluoropropyl)piperidin-3-yl)benzoic acid as a white solid (20.1 mg).

- 15 **Example Ex-62: racemic 4-((1*S**,2*R**,5*S**)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-(difluoromethoxy)-5-methylcyclohexyl)benzoic acid**

- Racemic* 4-((1*S**,2*R**,5*S**)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-hydroxy-5-methylcyclohexyl)benzoic acid (**Intermediate rac-B-43**, 12.5 mg, 30 μ mol) was combined with DCM (0.25 mL) and H₂O (0.25 mL). KOAc (23.4 mg, 0.24 mmol) and bromodifluoromethyltrimethylsilane (19 μ L, 0.12 mmol) was added, and the RM was stirred at RT for 4 h. The mixture was diluted with DCM and H₂O, dried through an Isolute® phase separator, and concentrated under reduced pressure. The residue was dissolved in THF (0.5 mL) and MeOH (0.25 mL). Aq NaOH soln (1M, 0.15 mL, 0.15 mmol) was added, and the RM was stirred overnight at RT. The mixture was quenched with FA (22 μ L) and purified by preparatory HPLC (Waters XBridge C18 OBD 30 x 100 mm; 5 μ m; eluent: 20 to 100% ACN in H₂O with 0.2% FA) to provide *racemic* 4-((1*S**,2*R**,5*S**)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-(difluoromethoxy)-5-methylcyclohexyl)benzoic acid as a light brown solid (2.4 mg).

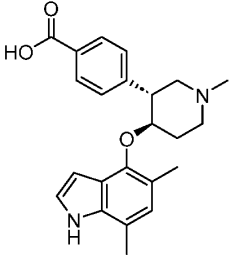
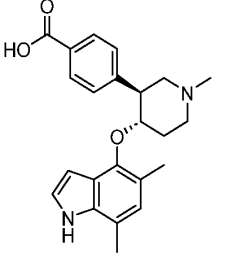
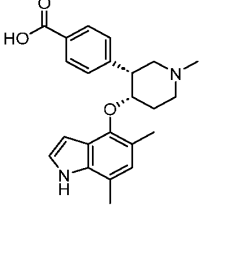
Example Ex-63: racemic 4-((1*S,2*R**,5*R**)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-(difluoromethoxy)-5-methylcyclohexyl)benzoic acid**

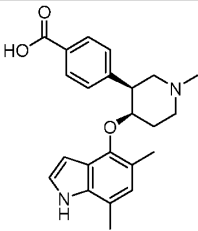
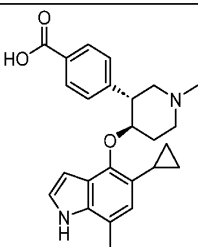
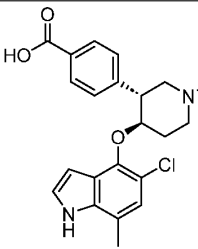
- 30 **Example Ex-63** was prepared as described for **Example Ex-62** using *racemic* 4-((1*S**,2*R**,5*R**)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-hydroxy-5-methylcyclohexyl)benzoic acid (**Intermediate rac-B-44**, 3 mg, 7 μ mol) to provide *racemic* 4-((1*S**,2*R**,5*R**)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-(difluoromethoxy)-5-methylcyclohexyl)benzoic acid as a white solid (1.4 mg).

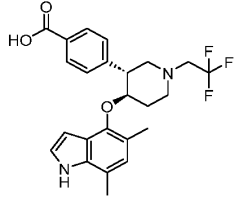
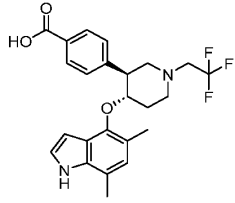
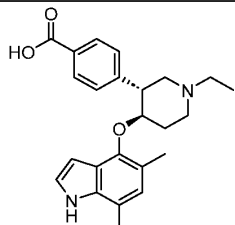
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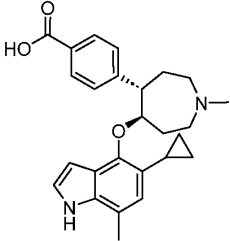
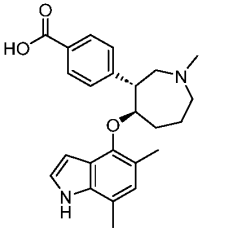
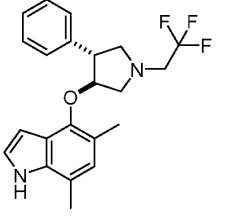
Analytical data from the examples described above are tabulated in the following table.

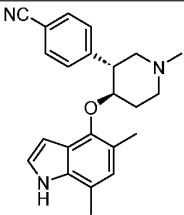
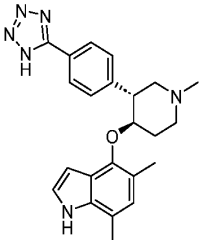
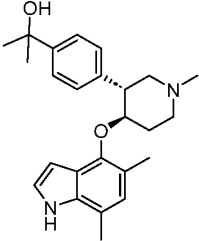
Example	Chemical Structure	¹ H NMR	LC-MS MS m/z
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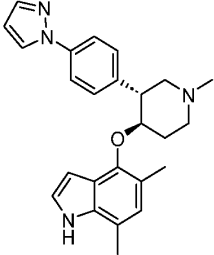
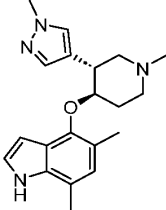
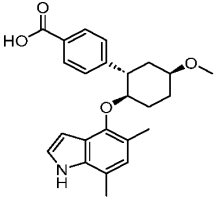
Ex-1		400 MHz, DMSO-<i>d</i>₆ δ [ppm] 10.99 – 10.62 (m, 1H), 7.89 (d, <i>J</i> = 8.2 Hz, 2H), 7.57 (d, <i>J</i> = 8.1 Hz, 2H), 7.19 – 7.04 (m, 1H), 6.68 – 6.42 (m, 1H), 6.21 – 6.06 (m, 1H), 4.50 – 4.29 (m, 1H), 3.20 – 3.10 (m, 1H), 2.87 – 2.70 (m, 2H), 2.35 (s, 3H), 2.32 – 2.24 (m, 1H), 2.20 (s, 3H), 2.04 (s, 3H), 2.02 – 1.92 (m, 1H), 1.76 – 1.64 (m, 2H). 25 of 26H reported (COOH not observed)	Method C-3: Rt = 0.98 min; [M+H]⁺ = 379.4
Ex-2		400 MHz, DMSO-<i>d</i>₆ δ [ppm] 10.99 – 10.76 (m, 1H), 7.89 (d, <i>J</i> = 8.2 Hz, 2H), 7.57 (d, <i>J</i> = 8.2 Hz, 2H), 7.23 – 7.04 (m, 1H), 6.57 (s, 1H), 6.21 – 6.02 (m, 1H), 4.52 – 4.33 (m, 1H), 3.19 – 3.10 (m, 1H), 2.87 – 2.70 (m, 2H), 2.33 (s, 3H), 2.33 – 2.24 (m, 1H), 2.20 (s, 3H), 2.04 (s, 3H), 2.01 – 1.91 (m, 1H), 1.75 – 1.61 (m, 2H). 25 of 26H reported (COOH not observed)	Method C-3: Rt = 0.99 min; [M+H]⁺ = 379.4
Ex-3		400 MHz, DMSO-<i>d</i>₆ [ppm] 10.76 (s, 1H), 7.86 – 7.74 (m, 2H), 7.51 (d, <i>J</i> = 7.9 Hz, 2H), 6.99 – 6.96 (m, 1H), 6.51 (s, 1H), 5.70 (s, 1H), 4.71 – 4.68 (m, 1H), 3.2 (m, 1H, overlap with H₂O peak), 2.82 – 2.78 (m, 1H), 2.65 – 2.58 (m, 1H), 2.50 (m, 2H, overlap with solvent peak), 2.23 (s, 3H), 2.22 (s, 3H), 2.02 (s, 3H), 1.69 – 1.54 (m, 2H). 25 of 26H reported (COOH not observed)	Method C-4: Rt = 1.15 min; [M+H]⁺ = 379.3

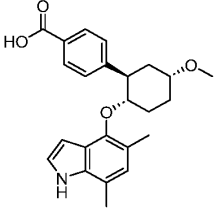
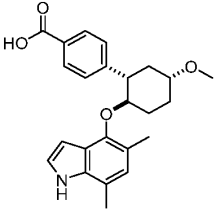
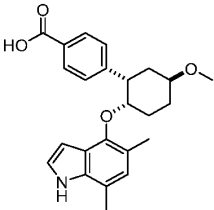
Ex-4		400 MHz, DMSO-<i>d</i>₆ δ [ppm] 10.77 (s, 1H), 7.95 – 7.73 (m, 2H), 7.53 (d, <i>J</i> = 7.9 Hz, 2H), 6.99 – 6.97 (m, 1H), 6.51 (s, 1H), 5.71 (s, 1H), 4.71 – 4.68 (m, 1H), 3.23 (m, 1H, overlap with H₂O peak), 2.82 – 2.78 (m, 1H), 2.66 – 2.57 (m, 1H), 2.50 (m, 2H, overlap with solvent peak), 2.23 (s, 3H), 2.22 (s, 3H), 2.02 (s, 3H), 1.70 – 1.59 (m, 2H). 25 of 26H reported (COOH not observed)	Method C-4: Rt = 1.17 min; [M+H]⁺ = 379.3
Ex-5		400 MHz, DMSO-<i>d</i>₆ δ [ppm] 10.78 (s, 1H), 7.72 (d, <i>J</i> = 7.7 Hz, 2H), 7.24 (d, <i>J</i> = 7.8 Hz, 2H), 7.08 – 7.05 (m, 1H), 6.15 – 6.05 (m, 2H), 4.36 – 4.28 (m, 1H), 3.03 – 2.97 (m, 1H), 2.77 – 2.70 m, 1H), 2.70 – 2.64 m, 1H), 2.29 (s, 3H), 2.28 – 2.15 (m, 1H), 2.11 (s, 3H), 1.99 – 1.92 (m, 1H), 1.89 – 1.80 (m, 1H), 1.73 – 1.60 (m, 2H), 0.79 – 0.70 (m, 1H), 0.69 – 0.58 (m, 1H), 0.50 – 0.32 (m, 2H). 27 of 28H reported (COOH not observed)	Method C-4: Rt = 1.14 min; [M+H]⁺ = 405.3
Ex-6		400 MHz, DMSO-<i>d</i>₆ δ [ppm] 11.23 (s, 1H), 7.90 – 7.69 (m, 2H), 7.37 – 7.29 (m, 2H), 7.28 – 7.26 (m, 1H), 6.81 (s, 1H), 6.22 – 6.20 (m, 1H), 4.57 – 4.51 (m, 1H), 3.10 – 3.05 (m, 1H), 2.86 – 2.77 (m, 1H), 2.76 – 2.70 (m, 1H), 2.36 (s, 3H), 2.25 – 2.19 (m, 1H), 2.18 (s, 3H), 1.98 – 1.91 (m, 1H), 1.85 –	Method C-4: Rt = 0.97 min; [M+H]⁺ = 399.3

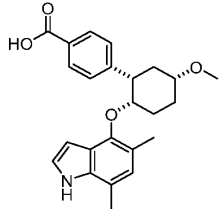
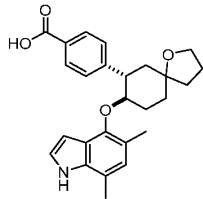
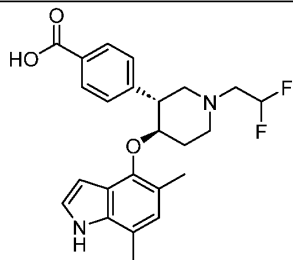
		1.72 (m, 1H), 1.72 – 1.63 (m, 1H). 22 of 23H reported (COOH not observed)	
Ex-7		400 MHz, CD ₃ OD δ [ppm] 7.94 (d, J = 8.2 Hz, 2H), 7.51 (d, J = 8.1 Hz, 2H), 7.13 – 7.05 (m, 1H), 6.57 (s, 1H), 6.28 – 6.20 (m, 1H), 4.64 – 4.49 (m, 1H), 3.25 – 2.96 (m, 5H), 2.81 – 2.71 (m, 1H), 2.57 – 2.46 (m, 1H), 2.34 (s, 3H), 2.09 (s, 3H), 1.98 – 1.82 (m, 2H). 23 of 25H reported (NH and COOH not observed)	Method C-3: Rt = 2.65 min; [M+H] ⁺ = 447.1
Ex-8		400 MHz, CD ₃ OD δ [ppm] 10.39 – 10.08 (m, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.13 – 6.99 (m, 1H), 6.57 (s, 1H), 6.33 – 6.18 (m, 1H), 4.63 – 4.49 (m, 1H), 3.22 – 2.95 (m, 5H), 2.84 – 2.70 (m, 1H), 2.59 – 2.45 (m, 1H), 2.34 (s, 3H), 2.09 (s, 3H), 1.97 – 1.82 (m, 2H). 24 of 25H reported (COOH not observed)	Method C-3: Rt = 2.63 min; [M+H] ⁺ = 447.2
Ex-9		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 11.02 – 10.70 (m, 1H), 7.89 (d, J = 8.1 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 7.20 – 7.02 (m, 1H), 6.57 (s, 1H), 6.21 – 6.04 (m, 1H), 4.52 – 4.36 (m, 1H), 3.19 – 3.05 (m, 1H), 2.96 – 2.82 (m, 2H), 2.42 – 2.33 (m, 2H), 2.31 (s, 3H), 2.31 – 2.22 (m, 1H), 2.04 (s, 3H), 2.00 – 1.88 (m, 1H), 1.80 – 1.58 (m, 2H), 0.99 (t, J = 7.1 Hz, 3H). 27 of 28H reported (COOH not observed)	Method C-4: Rt = 0.58 min; [M+H] ⁺ = 393.2

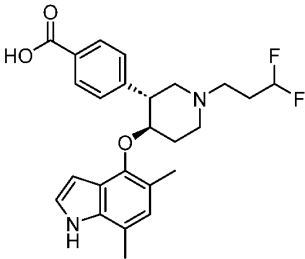
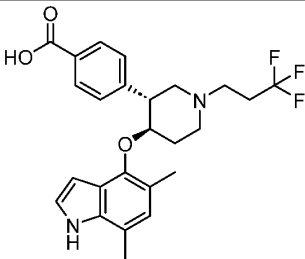
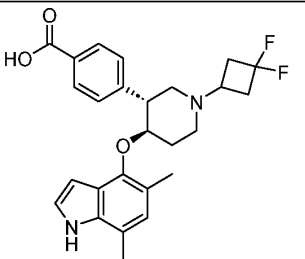
Ex-10		400 MHz, CD ₃ OD δ [ppm] 7.96 – 7.88 (m, 2H), 7.40 – 7.33 (m, 2H), 6.91 (d, J = 3.0 Hz, 1H), 6.17 (s, 1H), 5.61 (d, J = 3.3 Hz, 1H), 4.74 – 4.64 (m, 1H), 3.28 – 3.24 (m, 1H), 3.17 – 3.06 (m, 1H), 3.07 – 2.99 (m, 1H), 2.76 – 2.62 (m, 2H), 2.41 (s, 3H), 2.32 (s, 3H), 2.28 – 2.12 (m, 2H), 2.04 – 1.77 (m, 3H), 0.81 – 0.72 (m, 1H), 0.71 – 0.59 (m, 1H), 0.59 – 0.50 (m, 1H), 0.49 – 0.39 (m, 1H). 28 of 30H reported (NH and COOH not observed)	Method C-3: Rt = 1.22 min; [M+H] ⁺ = 419.4
Ex-11		400 MHz, CD ₃ OD δ [ppm] 8.01 – 7.87 (m, 2H), 7.44 – 7.32 (m, 2H), 6.87 (d, J = 3.0 Hz, 1H), 6.57 (s, 1H), 5.56 (d, J = 3.3 Hz, 1H), 4.77 – 4.61 (m, 1H), 3.45 – 3.38 (m, 1H), 3.06 – 2.94 (m, 2H), 2.81 – 2.72 (m, 1H), 2.44 – 2.35 (m, 1H), 2.42 (s, 3H), 2.32 (s, 3H), 2.26 – 2.13 (m, 1H), 2.11 – 2.02 (m, 1H), 2.10 (s, 3H), 1.86 – 1.73 (m, 1H), 1.70 – 1.56 (m, 1H). 26 of 28H reported (NH and COOH not observed)	Method C-3: Rt = 1.08 min; [M+H] ⁺ = 393.4
Ex-12 (rac)		400 MHz, CD ₃ OD δ [ppm] 7.28 – 7.23 (m, 4H), 7.22 – 7.16 (m, 1H), 7.05 (d, J = 3.0 Hz, 1H), 6.66 (s, 1H), 6.15 (d, J = 3.0 Hz, 1H), 4.95 – 4.90 (m, 1H), 3.66 – 3.58 (m, 1H), 3.49 – 3.42 (m, 1H), 3.28 – 3.16 (m, 3H), 3.03 – 2.96 (m, 1H), 2.92 – 2.84 (m, 1H), 2.38 (s, 3H), 2.22 (s, 3H).	Method C-4: Rt = 3.12 min; [M+H] ⁺ = 389.2

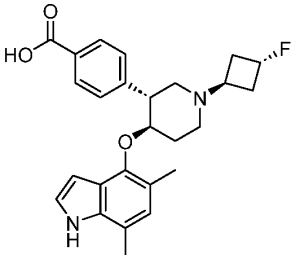
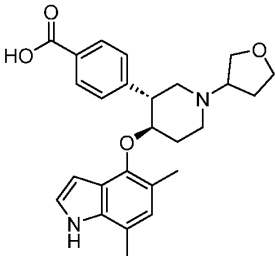
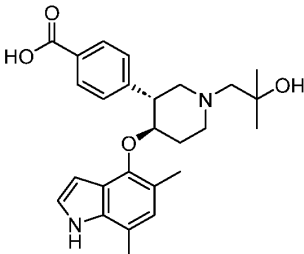
Ex-13		22 of 23H reported (-NH not observed) 400 MHz, CD₃OD δ [ppm] 7.66 – 7.61 (m, 2H), 7.59 – 7.52 (m, 2H), 7.09 (d, J = 3.0 Hz, 1H), 6.55 (s, 1H), 6.18 (d, J = 3.1 Hz, 1H), 4.68 – 4.55 (m, 1H), 3.27 – 3.21 (m, 1H), 3.11 – 3.01 (m, 2H), 2.65 – 2.53 (m, 1H), 2.47 (s, 3H), 2.41 – 2.28 (m, 1H), 2.35 (s, 3H), 2.07 (s, 3H), 2.05 – 2.00 (m, 1H), 1.98 – 1.85 (m, 1H). 24 of 25H reported (NH not observed)	Method C-3: Rt = 1.27 min; [M+H]⁺ = 360.3
Ex-14		400 MHz, DMSO-<i>d</i>₆ δ [ppm] 11.05 – 10.70 (m, 1H), 8.08 – 7.79 (m, 2H), 7.60 – 7.37 (m, 2H), 7.23 – 7.00 (m, 1H), 6.57 (s, 1H), 6.23 – 5.98 (m, 1H), 4.54 – 4.39 (m, 1H), 3.14 – 3.10 (m, 1H), 3.08 – 3.00 (m, 1H), 2.73 – 2.63 (m, 1H), 2.39 – 2.32 (m, 3H), 2.35 – 2.31 (m, 1H), 2.31 (s, 3H), 2.06 (s, 3H), 1.85 – 1.65 (m, 3H). 25 of 26H reported (tetrazole NH not observed)	Method C-3: Rt = 1.13 min; [M+H]⁺ = 403.2
Ex-15		400 MHz, CD₃OD δ [ppm] 7.47 – 7.41 (m, 2H), 7.39 – 7.33 (m, 2H), 7.11 – 6.99 (m, 1H), 6.56 (s, 1H), 6.30 – 6.11 (m, 1H), 4.58 – 4.44 (m, 1H), 3.20 – 3.14 (m, 1H), 3.01 – 2.86 (m, 2H), 2.51 – 2.37 (m, 1H), 2.36 – 2.31 (m, 6H), 2.23 – 2.09 (m, 1H), 2.07 (s, 3H), 1.99 – 1.79 (m, 2H), 1.52 (s, 3H), 1.51 (s, 3H). 30 of 32H reported (NH and OH not observed)	Method C-3: Rt = 1.30 min; [M+H]⁺ = 393.3

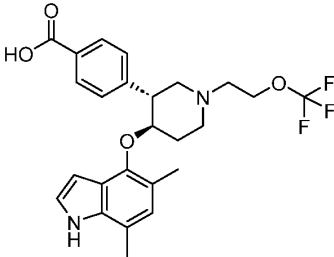
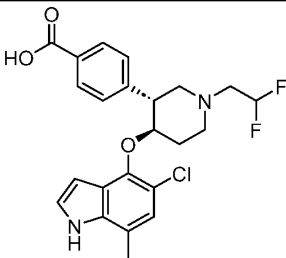
Ex-16		400 MHz, CD₃OD δ [ppm] 8.18 (d, J = 2.5 Hz, 1H), 7.70 (d, J = 1.9 Hz, 1H), 7.69 – 7.63 (m, 2H), 7.57 – 7.50 (m, 2H), 7.07 (d, J = 3.0 Hz, 1H), 6.57 (s, 1H), 6.53 – 6.49 (m, 1H), 6.23 (d, J = 3.3 Hz, 1H), 4.63 – 4.51 (m, 1H), 3.27 – 3.17 (m, 1H), 3.07 – 2.89 (m, 2H), 2.54 – 2.41 (m, 1H), 2.38 (s, 3H), 2.33 (s, 3H), 2.28 – 2.16 (m, 1H), 2.10 (s, 3H), 2.04 – 1.85 (m, 2H). 27 of 28H reported (NH not observed)	Method C-3: Rt = 1.39 min; [M+H]⁺ = 401.3
Ex-17		400 MHz, DMSO-<i>d</i>₆ δ [ppm] 11.06 – 10.60 (m, 1H), 7.63 (s, 1H), 7.41 (s, 1H), 7.18 – 7.06 (m, 1H), 6.61 (s, 1H), 6.15 – 6.00 (m, 1H), 4.20 – 4.07 (m, 1H), 3.77 (s, 3H), 3.02 – 2.93 (m, 1H), 2.91 – 2.84 (m, 1H), 2.71 – 2.65 (m, 1H), 2.33 (s, 3H), 2.24 – 2.15 (m, 1H), 2.19 (s, 3H), 2.12 (s, 3H), 1.98 – 1.86 (m, 1H), 1.73 – 1.57 (m, 2H). 26 of 26H reported	Method C-4: Rt = 1.78 min; [M+H]⁺ = 339.3
Ex-18		400 MHz, CD₃OD δ [ppm] 10.42 – 10.15 (m, 1H), 7.97 – 7.91 (m, 2H), 7.53 – 7.46 (m, 2H), 7.08 – 7.03 (m, 1H), 6.55 (s, 1H), 6.22 – 6.17 (m, 1H), 4.62 – 4.48 (m, 1H), 3.60 – 3.54 (m, 1H), 3.38 (s, 3H), 3.27 – 3.21 (m, 1H), 2.33 (s, 3H), 2.18 – 2.08 (m, 1H), 2.05 (s, 3H), 2.02 – 1.96 (m, 1H), 1.92 – 1.80 (m, 2H), 1.80 – 1.70 (m, 1H), 1.54 – 1.41 (m, 1H). 26 of 27H reported (COOH not observed)	Method C-3: Rt = 2.48 min; [M+H]⁺ = 394.2

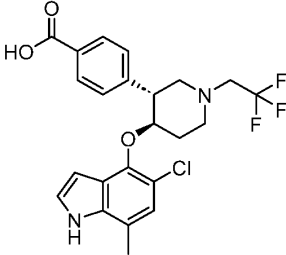
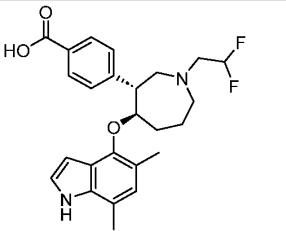
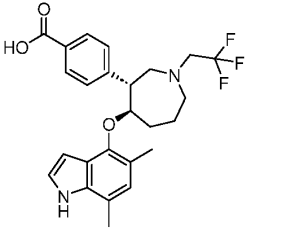
Ex-19		400 MHz, CD ₃ OD δ [ppm] 10.25 (s, 1H), 8.05 – 7.80 (m, 2H), 7.57 – 7.40 (m, 2H), 7.13 – 6.97 (m, 1H), 6.55 (s, 1H), 6.26 – 6.05 (m, 1H), 4.61 – 4.49 (m, 1H), 3.60 – 3.53 (m, 1H), 3.38 (s, 3H), 3.21 – 3.24 (m, 1H, partially under solvent peak), 2.33 (s, 3H), 2.16 – 2.09 (m, 1H), 2.07 – 1.98 (m, 1H), 2.05 (s, 3H), 1.95 – 1.81 (m, 2H), 1.81 – 1.71 (m, 1H), 1.55 – 1.39 (m, 1H). 26 of 27H reported (COOH not observed)	Method C-3: Rt = 2.47 min; [M+H] ⁺ = 394.2
Ex-20 <i>(rac)</i>		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 11.06 – 10.60 (m, 1H), 8.04 – 7.79 (m, 2H), 7.70 – 7.42 (m, 2H), 7.18 – 7.02 (m, 1H), 6.55 (s, 1H), 6.19 – 5.94 (m, 1H), 4.56 – 4.27 (m, 1H), 3.23 (s, 3H), 3.08 – 2.93 (m, 1H), 2.35 – 2.25 (m, 3H), 2.16 – 2.07 (m, 1H), 2.04 – 1.91 (m, 1H), 2.01 (s, 3H), 1.87 – 1.76 (m, 1H), 1.73 – 1.60 (m, 1H), 1.57 – 1.42 (m, 1H), 1.32 – 1.07 (m, 2H). 26 of 27H reported (COOH not observed)	Method C-3: Rt = 2.43 min; [M+H] ⁺ = 394.3
Ex-21 <i>(rac)</i>		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 12.87 – 12.66 (m, 1H), 11.00 – 10.56 (m, 1H), 7.88 (d, <i>J</i> = 8.2 Hz, 2H), 7.58 (d, <i>J</i> = 8.1 Hz, 2H), 7.12 – 6.91 (m, 1H), 6.57 (s, 1H), 5.79 – 5.54 (m, 1H), 4.96 – 4.68 (m, 1H), 3.90 – 3.66 (m, 1H), 3.39 – 3.33 (m, 1H), 3.27 (s, 3H), 2.47 – 2.39 (m, 1H), 2.29 (s, 3H), 2.11 (s, 3H), 1.98 – 1.84 (m, 2H), 1.81 – 1.65 (m, 2H)	Method C-3: Rt = 2.66 min; [M+H] ⁺ = 394.3

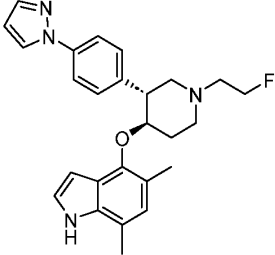
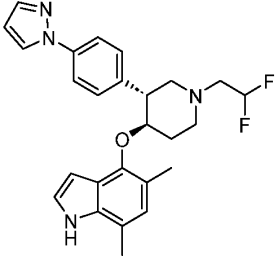
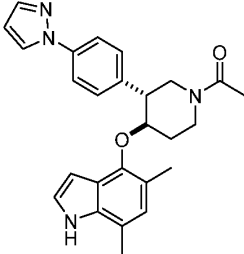
		2H), 1.62 – 1.51 (m, 1H). 27 of 27H reported	
Ex-22 (rac)		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 12.91 – 12.58 (m, 1H), 10.90 – 10.73 (m, 1H), 7.89 (d, <i>J</i> = 8.2 Hz, 2H), 7.57 (d, <i>J</i> = 8.2 Hz, 2H), 7.06 – 6.98 (m, 1H), 6.57 (s, 1H), 5.70 – 5.58 (m, 1H), 4.78 – 4.71 (m, 1H), 3.42 – 3.33 (m, 1H), 3.31 (s, 3H, under solvent peak) 3.14 – 3.05 (m, 1H), 2.29 (s, 3H), 2.20 – 2.14 (m, 1H), 2.12 (s, 3H), 2.08 – 1.98 (m, 1H), 1.94 – 1.75 (m, 2H), 1.73 – 1.58 (m, 1H), 1.58 – 1.44 (m, 1H). 27 of 27H reported	Method C-3: Rt = 2.42 min; [M+H] ⁺ = 394.3
Ex-23 (rac)		400 MHz, CD ₃ OD δ [ppm] 7.98 – 7.87 (m, 2H), 7.50 – 7.43 (m, 2H), 7.04 (d, <i>J</i> = 3.3 Hz, 1H), 6.55 (s, 1H), 6.19 (d, <i>J</i> = 3.0 Hz, 1H), 4.61 – 4.49 (m, 1H), 3.92 – 3.83 (m, 2H), 3.35 – 3.34 (m, 1H, under solvent peak), 2.33 (s, 3H), 2.05 (s, 3H), 2.00 – 1.79 (m, 6H), 1.77 – 1.68 (m, 3H), 1.57 – 1.43 (m, 1H). 27 of 29H reported (COOH and NH not observed)	Method C-4: Rt = 1.38 min; [M+H] ⁺ = 420.1
Ex-24		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 10.89 (d, <i>J</i> = 2.4 Hz, 1H), 7.88 (d, <i>J</i> = 8.1 Hz, 2H), 7.52 (d, <i>J</i> = 8.3 Hz, 2H), 7.18 – 7.13 (m, 1H), 6.58 (s, 1H), 6.28 – 6.00 (m, 1H), 6.19 – 6.15 (m, 1H), 4.51 – 4.41 (m, 1H), 3.15 – 3.09 (m, 1H), 3.01 – 2.87 (m, 2H), 2.85 – 2.72 (m, 2H), 2.64 –	Method C-4: Rt = 1.28 min; [M+H] ⁺ = 429.3

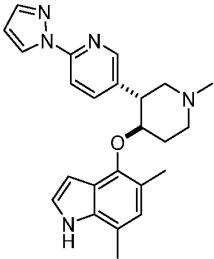
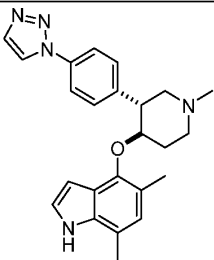
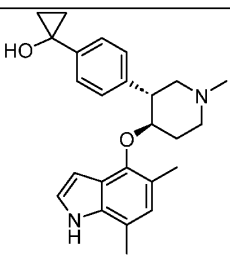
		2.55 (m, 1H), 2.32 (s, 3H), 2.27 (dd, $J = 11.6$, 3.5 Hz, 1H), 2.05 (s, 3H), 1.77 – 1.61 (m, 2H). 25 of 26H reported (COOH not observed)	
Ex-25		400 MHz, DMSO- d_6 δ [ppm] δ 10.88 (s, 1H), 7.89 (d, $J = 8.2$ Hz, 2H), 7.58 (d, $J = 8.1$ Hz, 2H), 7.16 – 7.13 (m, 1H), 6.57 (s, 1H), 6.16 – 6.12 (m, 1H), 6.03 (tt, $J = 56.8$, 4.5 Hz, 1H), 4.51 – 4.39 (m, 1H), 3.17 – 3.08 (m, 1H), 2.95 – 2.89 (m, 1H), 2.89 – 2.84 (m, 1H), 2.47 – 2.44 (m, 1H), 2.39 – 2.32 (m, 2H), 2.31 (s, 3H), 2.04 (s, 3H), 2.03 – 1.92 (m, 3H), 1.77 – 1.62 (m, 2H). 27 of 28H reported (COOH not observed)	Method B-1: $R_t = 0.55$ min; $[M+H]^+ = 443.3$
Ex-26		400 MHz, DMSO- d_6 δ [ppm] 10.88 (s, 1H), 7.90 (d, $J = 8.2$ Hz, 2H), 7.58 (d, $J = 8.1$ Hz, 2H), 7.17 – 7.13 (m, 1H), 6.57 (s, 1H), 6.17 – 6.12 (m, 1H), 4.49 – 4.39 (m, 1H), 3.18 – 3.08 (m, 2H), 2.94 (d, $J = 11.2$ Hz, 1H), 2.87 (d, $J = 11.4$ Hz, 1H), 2.61 – 2.55 (m, 2H), 2.45 – 2.37 (m, 2H), 2.31 (s, 3H), 2.12 – 2.06 (m, 1H), 2.04 (s, 3H), 1.78 – 1.60 (m, 2H). 26 of 27H reported (COOH not observed)	Method B-2: $R_t = 4.07$ min; $[M+H]^+ = 461.1$
Ex-27		400 MHz, DMSO- d_6 δ [ppm] δ 10.81 (s, 1H), 7.83 (d, $J = 8.2$ Hz, 2H), 7.51 (d, $J = 8.0$ Hz, 2H), 7.10 – 7.06 (m, 1H), 6.50 (s, 1H), 6.09 – 6.06 (m, 1H), 4.47 – 4.34 (m, 1H), 3.10 – 2.96 (m, 2H), 2.76 (dd,	Method C-4: $R_t = 1.33$ min; $[M+H]^+ = 455.5$

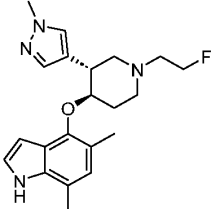
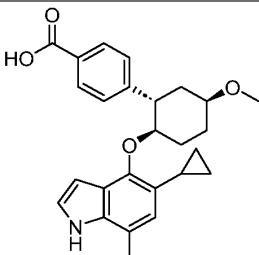
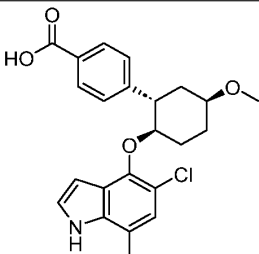
		$J = 18.6, 11.9 \text{ Hz}, 2\text{H}$, 2.62 (dd, $J = 10.6, 5.0$ Hz, 2H), 2.40 – 2.28 (m, 2H), 2.24 (s, 3H), 2.22 – 2.13 (m, 1H), 1.97 (s, 3H), 1.90 – 1.78 (m, 1H), 1.72 – 1.52 (m, 2H). 27 of 28H reported (COOH not observed)	
Ex-28		400 MHz, DMSO- d_6 δ [ppm] δ 10.79 (s, 1H), 7.76 (m, 2H), 7.35 (m, 2H), 7.09 – 7.05 (m, 1H), 6.50 (s, 1H), 6.07 (d, $J = 2.2 \text{ Hz}$, 1H), 4.40 – 4.30 (m, 1H), 3.03 – 2.86 (m, 1H), 2.82 – 2.70 (m, 1H), 2.62 – 2.58 (m, 1H), 2.28 – 2.25 (m, 3H), 2.24 (s, 3H), 1.98 (s, 3H), 1.93 – 1.91 (m, 1H), 1.20 – 1.06 (m, 6H). 28 of 29H reported (COOH not observed)	Method C-4: Rt = 1.36 min; $[M+H]^+ =$ 437.3
Ex-29		400 MHz, DMSO- d_6 δ [ppm] δ 10.80 (s, 1H), 7.81 (d, $J = 7.8 \text{ Hz}$, 2H), 7.47 (dd, $J = 8.3, 3.3$ Hz, 2H), 7.10 – 7.05 (m, 1H), 6.50 (s, 1H), 6.11 – 6.07 (m, 1H), 4.44 – 4.33 (m, 1H), 3.74 – 3.60 (m, 2H), 3.57 – 3.49 (m, 1H), 3.46 – 3.37 (m, 2H), 3.07 – 3.00 (m, 1H), 2.93 – 2.78 (m, 2H), 2.71 – 2.58 (m, 1H), 2.37 – 2.29 (m, 1H), 2.24 (s, 3H), 1.97 (s, 3H), 1.93 – 1.81 (m, 1H), 1.70 – 1.54 (m, 3H). 29 of 30H reported (COOH not observed)	Method C-4: Rt = 1.02 min; $[M+H]^+ =$ 435.5
Ex-30		400 MHz, DMSO- d_6 δ [ppm] δ 10.89 (s, 1H), 7.85 (d, $J = 7.9 \text{ Hz}$, 2H), 7.44 (d, $J = 8.0 \text{ Hz}$, 2H), 7.17 – 7.12 (m, 1H), 6.57 (s, 1H), 6.18 – 6.13 (m, 1H), 4.47 – 4.36 (m, 1H), 4.06 (s, 1H), 3.15 – 3.06 (m,	Method C-4: Rt = 1.18 min; $[M+H]^+ =$ 437.5

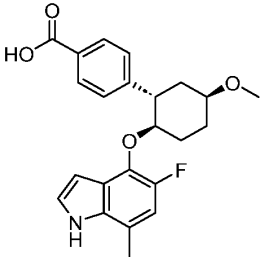
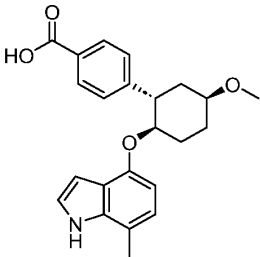
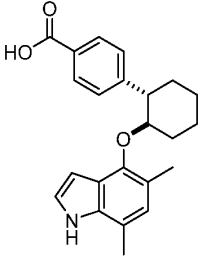
		1H), 3.04 – 3.02 (m, 1H), 2.93 – 2.90 (m, 1H), 2.32 (s, 3H), 2.25 (s, 2H), 2.23 – 2.15 (m, 1H), 2.06 (s, 3H), 1.75 – 1.64 (m, 2H), 1.09 (s, 3H), 1.08 (s, 3H). 30 of 32H reported (COOH not observed, 1H overlap with H ₂ O).	
Ex-31		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 10.88 (s, 1H), 7.89 (d, <i>J</i> = 7.9 Hz, 2H), 7.58 (d, <i>J</i> = 7.9 Hz, 2H), 7.15 (d, <i>J</i> = 3.3 Hz, 1H), 6.57 (s, 1H), 6.16 (s, 1H), 4.51 – 4.40 (m, 1H), 4.18 – 4.08 (m, 2H), 3.15 (d, <i>J</i> = 12.5 Hz, 1H), 2.97 – 2.91 (m, 1H), 2.91 – 2.85 (m, 1H), 2.72 – 2.65 (m, 2H), 2.49 – 2.40 (m, 1H), 2.31 (s, 3H), 2.21 – 2.08 (m, 1H), 2.04 (s, 3H), 1.76 – 1.62 (m, 2H). 26 of 27H reported (COOH not observed)	Method B-2: Rt = 4.13 min; [M+H] ⁺ = 477.4
Ex-32		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 12.7 (s, 1H), 11.16 (s, 1H), 7.82 (d, <i>J</i> = 8.2 Hz, 2H), 7.51 (d, <i>J</i> = 8.2 Hz, 2H), 7.24 – 7.20 (m, 1H), 6.74 (d, <i>J</i> = 1.1 Hz, 1H), 6.21 – 5.93 (m, 1H), 6.18 (dd, <i>J</i> = 3.1, 1.9 Hz, 1H), 4.60 – 4.51 (m, 1H), 3.15 – 3.06 (m, 1H), 2.95 – 2.83 (m, 2H), 2.79 – 2.66 (m, 2H), 2.57 – 2.49 (m, 1H), 2.28 (d, <i>J</i> = 0.9 Hz, 3H), 2.23 (m, 1H), 1.77 – 1.59 (m, 2H). 23 of 23H reported.	Method C-3: Rt = 1.82 min; [M+H] ⁺ = 449.4

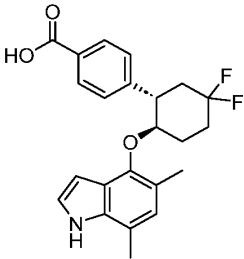
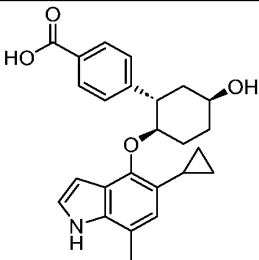
Ex-33		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 11.23 (s, 1H), 7.79 (d, <i>J</i> = 8.0 Hz, 2H), 7.36 (d, <i>J</i> = 7.8 Hz, 2H), 7.29 – 7.26 (m, 1H), 6.82 (d, <i>J</i> = 1.1 Hz, 1H), 6.24 (dd, <i>J</i> = 3.1, 1.9 Hz, 1H), 4.65 – 4.55 (m, 1H), 3.28 – 3.17 (m, 2H), 3.13 – 3.04 (m, 1H), 2.95 (t, <i>J</i> = 14.9 Hz, 2H), 2.78 – 2.69 (m, 1H), 2.51 – 2.41 (m, 1H), 2.36 (s, 3H), 1.84 – 1.64 (m, 2H). 21 of 22H reported (COOH not observed)	Method C-3: Rt = 2.69 min; [M+H] ⁺ = 467.2
Ex-34		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 10.76 (s, 1H), 7.78 (d, <i>J</i> = 8.2 Hz, 2H), 7.34 (d, <i>J</i> = 8.0 Hz, 2H), 6.99 - 6.93 (m, 1H), 6.50 (s, 1H), 6.11 – 5.82 (m, 1H), 5.64 – 5.59 (m, 1H), 4.52 - 4.42 (m, 1H), 3.10 – 3.00 (m, 2H), 2.93 – 2.80 (m, 2H), 2.76 – 2.69 (m, 2H), 2.69 – 2.62 (m, 1H), 2.23 (s, 3H), 1.97 (s, 3H), 1.81 – 1.65 (m, 3H), 1.47 – 1.32 (m, 1H). 27 of 28H reported (COOH not observed)	Method C-4: Rt = 1.15 min; [M+H] ⁺ = 443.3
Ex-35		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 10.84 (s, 1H), 7.90 (d, <i>J</i> = 8.2 Hz, 2H), 7.52 (d, <i>J</i> = 8.1 Hz, 2H), 7.08 – 7.04 (m, 1H), 6.58 (s, 1H), 5.76 – 5.70 (m, 1H), 4.59 – 4.50 (m, 1H), 3.22 – 3.14 (m, 1H), 2.92 – 2.75 (m, 3H), 2.58 – 2.51 (m, 3H), 2.31 (s, 3H), 2.04 (s, 3H), 1.90 – 1.73 (m, 3H), 1.57 – 1.44 (m, 1H). 26 of 27H reported (COOH not observed)	Method C-3: Rt = 2.85 min; [M+H] ⁺ = 461.4

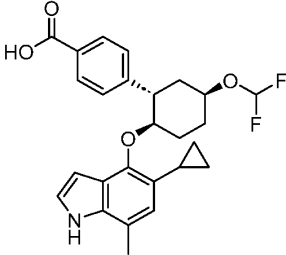
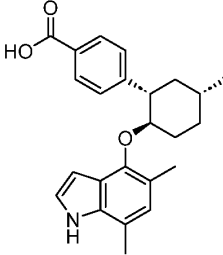
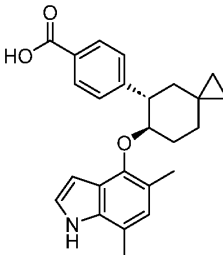
Ex-36		400 MHz, CD ₃ OD δ [ppm] 8.17 (d, J = 2.6 Hz, 1H), 7.70 (d, J = 1.9 Hz, 1H), 7.66 (d, J = 8.6 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 3.0 Hz, 1H), 6.57 (s, 1H), 6.54 – 6.50 (m, 1H), 6.25 (d, J = 3.1 Hz, 1H), 4.66 – 4.63 (m, 1H), 4.60 – 4.49 (m, 2H), 3.27 – 3.20 (m, 1H), 3.11 – 3.02 (m, 2H), 2.83 – 2.79 (m, 1H), 2.76 – 2.71 (m, 1H), 2.56 – 2.44 (m, 1H), 2.33 (s, 3H), 2.31 – 2.21 (m, 1H), 2.11 (s, 3H), 2.00 – 1.88 (m, 2H). 28 of 29H reported (NH not observed)	Method C-4: Rt = 2.52 min; [M+H] ⁺ = 433.3
Ex-37		400 MHz, DMSO- d_6 δ [ppm] 10.82 (s, 1H), 8.40 (d, J = 2.5 Hz, 1H), 7.76 – 7.68 (m, 2H), 7.65 (d, J = 1.8 Hz, 1H), 7.50 (d, J = 8.3 Hz, 2H), 7.08 (d, J = 3.0 Hz, 1H), 6.51 (s, 1H), 6.47 – 6.43 (m, 1H), 6.21 – 5.95 (m, 1H), 6.13 (d, J = 3.1 Hz, 1H), 4.44 – 4.33 (m, 1H), 3.43 – 3.28 (m, 1H), 3.09 – 2.99 (m, 1H), 2.97 – 2.89 (m, 1H), 2.88 – 2.79 (m, 1H), 2.78 – 2.66 (m, 2H), 2.59 – 2.50 (m, 1H), 2.24 (s, 3H), 2.00 (s, 3H), 1.70 – 1.51 (m, 2H). 28 of 28H reported	Method C-4: Rt = 2.76 min; [M+H] ⁺ = 451.4
Ex-38 <i>(rac)</i>		400 MHz, CD ₃ OD δ [ppm] 8.20 – 8.18 (m, 1H), 7.75 – 7.64 (m, 3H), 7.61 – 7.48 (m, 2H), 7.11 – 7.04 (m, 1H), 6.58 (d, J = 3.2 Hz, 1H), 6.54 – 6.50 (m, 1H), 6.25 (dd, J = 13.4, 3.2 Hz, 1H), 4.80 – 4.72 (m, 1H), 4.63 – 4.45 (m, 1H), 4.03 – 3.93 (m, 1H), 3.27 – 2.97 (m,	Method C-4: Rt = 2.22 min; [M+H] ⁺ = 429.3

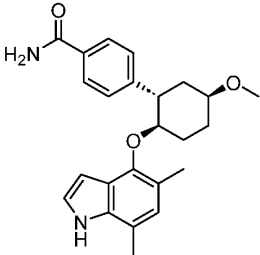
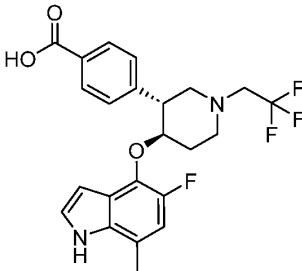
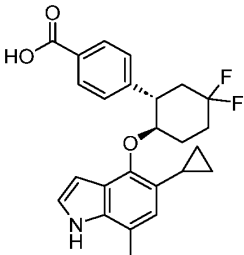
		3H), 2.34 (s, 3H), 2.16 (s, 3H), 2.11 (d, $J = 6.8$ Hz, 3H), 2.08 – 1.98 (m, 1H), 1.84 – 1.61 (m, 1H). 27 of 28H reported (NH not observed)	
Ex-39 (rac)		400 MHz, CD ₃ OD δ [ppm] 8.53 (d, $J = 2.6$ Hz, 1H), 8.40 (d, $J = 2.4$ Hz, 1H), 7.91 (dd, $J = 8.5, 2.4$ Hz, 1H), 7.78 (d, $J = 8.4$ Hz, 1H), 7.73 (d, $J = 1.6$ Hz, 1H), 7.08 (d, $J = 3.3$ Hz, 1H), 6.57 – 6.47 (m, 2H), 6.22 (d, $J = 3.0$ Hz, 1H), 4.62 – 4.53 (m, 1H), 3.25 – 3.09 (m, 1H), 3.03 – 2.93 (m, 2H), 2.48 – 2.40 (m, 1H), 2.36 (s, 3H), 2.26 (s, 3H), 2.25 – 2.14 (m, 1H), 2.10 (s, 3H), 2.08 – 1.91 (m, 2H). 26 of 27H reported (NH not observed)	Method C-3: Rt = 1.34 min; $[M+H]^+ = 402.7$
Ex-40 (rac)		400 MHz, CD ₃ OD δ [ppm] 8.39 (d, $J = 1.4$ Hz, 1H), 7.78 (d, $J = 1.4$ Hz, 1H), 7.68 (d, $J = 8.5$ Hz, 2H), 7.52 (d, $J = 8.7$ Hz, 2H), 6.98 (d, $J = 3.2$ Hz, 1H), 6.46 (s, 1H), 6.14 (d, $J = 3.3$ Hz, 1H), 4.56 – 4.40 (m, 1H), 3.27 – 3.21 (m, 1H), 2.94 – 2.78 (m, 2H), 2.39 – 2.29 (m, 1H), 2.28 (s, 3H), 2.20 (s, 3H), 2.12 – 2.03 (m, 1H), 2.00 (s, 3H), 1.93 – 1.73 (m, 2H). 26 of 27H reported (NH not observed)	Method C-3: Rt = 1.10 min; $[M+H]^+ = 402.5$
Ex-41		400 MHz, CD ₃ OD δ [ppm] 8.55 (s, 1H), 7.41 – 7.32 (m, 2H), 7.30 – 7.19 (m, 2H), 7.05 (d, $J = 3.0$ Hz, 1H), 6.56 (s, 1H), 6.21 (d, $J = 3.3$ Hz, 1H), 4.55 – 4.49 (m, 1H), 3.15 – 3.10 (m, 1H), 2.97 – 2.86 (m, 2H), 2.41 – 2.32 (m,	Method C-3: Rt = 1.24 min; $[M+H]^+ = 391.5$

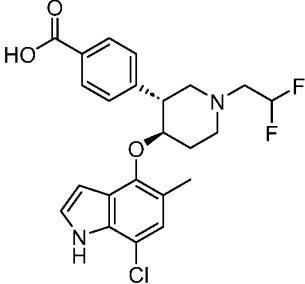
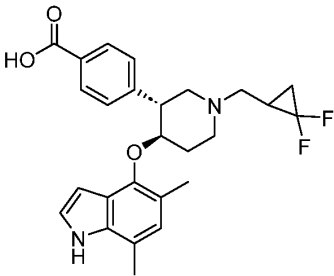
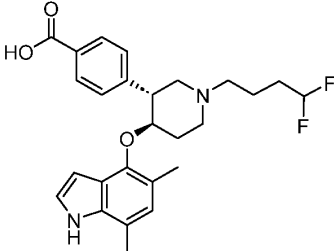
		1H), 2.34 (s, 3H), 2.31 (s, 3H), 2.16 – 2.07 (s, 1H), 2.07 (s, 3H), 1.96 – 1.80 (m, 2H), 1.17 – 1.11 (m, 2H), 1.02 – 0.94 (m, 2H). 29 of 30H reported (OH not observed)	
Ex-42		400 MHz, CD ₃ OD δ [ppm] 7.55 (s, 1H), 7.49 (s, 1H), 7.06 (d, J = 3.3 Hz, 1H), 6.63 (s, 1H), 6.10 (d, J = 3.3 Hz, 1H), 4.70 – 4.67 (m, 1H), 4.59 – 4.55 (m, 1H), 4.33 – 4.18 (m, 1H), 3.82 (s, 3H), 3.20 – 3.09 (m, 2H), 3.03 – 2.97 (m, 1H), 2.84 – 2.77 (m, 1H), 2.75 – 2.70 (m, 1H), 2.50 – 2.40 (m, 1H), 2.37 (s, 3H), 2.25 – 2.26 (m, 1H), 2.16 (s, 3H), 1.96 – 1.77 (m, 2H). 26 of 27H reported (NH not observed)	Method C-3: Rt = 0.94 min; [M+H] ⁺ = 371.4
Ex-43		400 MHz, DMSO- d_6 δ [ppm] 12.77 (s, 1H), 10.83 (s, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 7.12 (s, 1H), 6.14 (s, 1H), 6.06 (s, 1H), 4.49 – 4.41 (m, 1H), 3.43 – 3.36 (m, 1H), 3.26 (s, 3H), 3.20 – 3.13 (m, 1H), 2.28 (s, 3H), 2.05 – 1.83 (m, 4H), 1.81 – 1.67 (m, 1H), 1.65 – 1.58 (m, 1H), 1.44 – 1.32 (m, 1H), 0.83 – 0.77 (m, 1H), 0.71 – 0.65 (m, 1H), 0.48 – 0.42 (m, 2H). 29 of 29H reported	Method C-3: Rt = 2.59 min; [M+H] ⁺ = 420.3
Ex-44		400 MHz, DMSO- d_6 δ [ppm] 12.68 (s, 1H), 11.13 (s, 1H), 7.90 – 7.75 (m, 2H), 7.57 – 7.47 (m, 2H), 7.21 – 7.18 (m, 1H), 6.72 (d, J = 1.1 Hz, 1H), 6.09 (dd, J = 3.1, 1.9 Hz, 1H), 4.59 – 4.51 (m, 1H),	Method C-3: Rt = 2.52 min; [M+H] ⁺ = 414.3

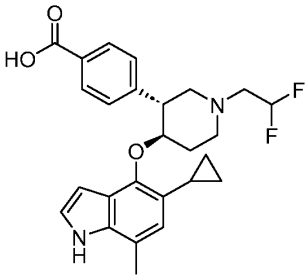
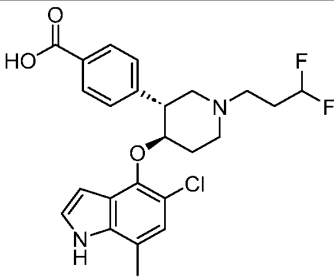
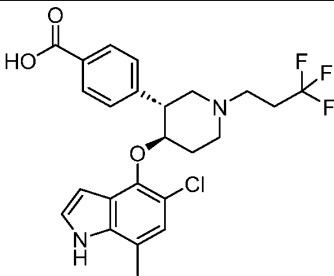
		3.44 – 3.39 (m, 1H), 3.19 (s, 3H), 3.13 (ddd, $J = 13.8, 10.5, 3.9$ Hz, 1H), 2.27 (s, 3H), 1.97 – 1.89 (m, 1H), 1.89 – 1.80 (m, 2H), 1.78 – 1.65 (m, 1H), 1.52 – 1.44 (m, 1H), 1.39 – 1.29 (m, 1H). 24 of 24H reported	
Ex-45		600 MHz, DMSO- d_6 δ [ppm] 12.77 (s, 1H), 11.06 (s, 1H), 7.95 – 7.82 (m, 2H), 7.60 – 7.49 (m, 2H), 7.27 – 7.17 (m, 1H), 6.73 – 6.60 (m, 1H), 6.13 – 6.01 (m, 1H), 4.47 – 4.38 (m, 1H), 3.52 – 3.44 (m, 1H), 3.26 (s, 3H), 3.20 – 3.14 (m, 1H), 2.34 (s, 3H), 2.01 – 1.95 (m, 1H), 1.95 – 1.88 (m, 1H), 1.85 – 1.79 (m, 1H), 1.76 – 1.62 (m, 2H), 1.46 – 1.38 (m, 1H). 24 of 24H reported	Method B-1: Rt = 1.07 min; $[M+H]^+ = 398.3$
Ex-46		400 MHz, CDCl $_3$, δ [ppm] 8.05 – 7.91 (m, 3H), 7.50 – 7.41 (m, 2H), 7.07 – 6.98 (m, 1H), 6.79 (d, $J = 7.8$, 1H), 6.43 – 6.31 (m, 2H), 4.44 – 4.36 (m, 1H), 3.67 – 3.59 (m, 1H), 3.49 – 3.43 (m, 1H), 3.41 (s, 3H), 2.39 (s, 3H), 2.31 – 2.10 (m, 3H), 2.02 – 1.89 (m, 1H), 1.85 – 1.75 (m, 1H), 1.59 (ddd, $J = 14.1, 10.9, 3.2$ Hz, 1H). 24 of 25H reported (COOH not observed)	Method C-3: Rt = 2.60 min; $[M+H]^+ = 380.3$
Ex-47 (rac)		600 MHz, DMSO- d_6 , δ [ppm] 12.71 (s, 1H), 10.90 – 10.77 (m, 1H), 7.93 – 7.85 (m, 2H), 7.59 – 7.52 (m, 2H), 7.15 – 7.08 (m, 1H), 6.58 – 6.53 (m, 1H), 6.15 – 6.07 (m, 1H), 4.46 – 4.38 (m, 1H),	Method B-1: Rt = 1.29 min; $[M+H]^+ = 364.2$

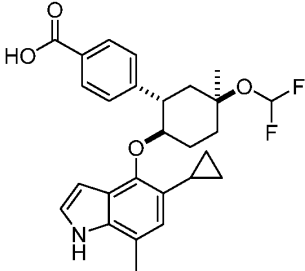
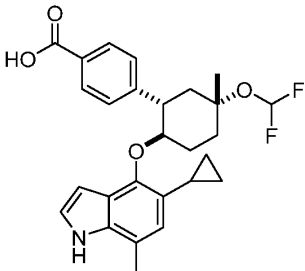
		2.95 – 2.85 (m, 1H), 2.30 (s, 3H), 2.01 (s, 3H), 1.85 – 1.79 (m, 2H), 1.75 – 1.66 (m, 3H), 1.45 – 1.31 (m, 2H), 1.29 – 1.19 (m, 1H). 25 of 25H reported.	
Ex-48		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 10.88 (s, 1H), 7.96 – 7.84 (m, 2H), 7.64 (d, <i>J</i> = 8.1 Hz, 2H), 7.19 – 7.11 (m, 1H), 6.57 (s, 1H), 6.10 (dd, <i>J</i> = 3.1, 1.9 Hz, 1H), 4.69 – 4.54 (m, 1H), 3.24 – 3.14 (m, 1H), 2.63 – 2.44 (m, 1H), 2.32 – 2.28 (m, 3H), 2.24 – 2.12 (m, 1H), 2.08 – 1.91 (m, 5H), 1.91 – 1.81 (m, 1H), 1.75 – 1.59 (m, 1H). 22 of 23H reported (COOH not observed)	Method B-1: Rt = 1.21 min; [M+H] ⁺ = 400.1
Ex-49		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 10.82 (s, 1H), 7.87 (d, <i>J</i> = 8.1 Hz, 2H), 7.51 (d, <i>J</i> = 8.0 Hz, 2H), 7.16 – 7.08 (m, 1H), 6.14 (s, 1H), 6.10 – 6.05 (m, 1H), 4.63 – 4.54 (m, 1H), 4.45 – 4.36 (m, 1H), 3.97 – 3.87 (m, 1H), 3.55 – 3.19 (m, 1H), 2.29 (s, 3H), 2.05 – 1.98 (m, 1H), 1.96 – 1.79 (m, 3H), 1.73 – 1.62 (m, 1H), 1.60 – 1.52 (m, 1H), 1.46 – 1.35 (m, 1H), 0.87 – 0.77 (m, 1H), 0.73 – 0.65 (m, 1H), 0.51 – 0.41 (m, 2H). 26 of 27H reported (COOH not observed)	Method B-1: Rt = 0.91 min; [M+H] ⁺ = 406.3

Ex-50		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 10.85 (s, 1H), 7.90 (d, <i>J</i> = 7.9 Hz, 2H), 7.58 (d, <i>J</i> = 8.0 Hz, 2H), 7.18 – 7.07 (m, 1H), 6.77 (t, <i>J</i> = 76.5 Hz, 1H), 6.15 (s, 1H), 6.09 – 6.00 (m, 1H), 4.57 – 4.36 (m, 2H), 3.28 – 3.14 (m, 1H), 2.29 (s, 3H), 2.17 – 2.10 (m, 1H), 2.05 – 1.93 (m, 2H), 1.91 – 1.75 (m, 2H), 1.74 – 1.67 (m, 1H), 1.66 – 1.54 (m, 1H), 0.89 – 0.77 (m, 1H), 0.73 – 0.63 (m, 1H), 0.54 – 0.39 (m, 2H). 26 of 27H reported (COOH not observed)	Method B-1: Rt = 1.23 min; [M+H] ⁺ = 456.2
Ex-51		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 10.77 (s, 1H), 7.78 (d, <i>J</i> = 8.0 Hz, 2H), 7.39 (d, <i>J</i> = 7.9 Hz, 2H), 7.05 (s, 1H), 6.48 (s, 1H), 6.04 (s, 1H), 4.37 – 4.28 (m, 1H), 2.92 – 2.83 (m, 1H), 2.23 (s, 3H), 1.95 (s, 3H), 1.81 – 1.65 (m, 2H), 1.61 – 1.49 (m, 2H), 1.44 – 1.32 (m, 2H), 0.95 – 0.86 (m, 1H), 0.83 (d, <i>J</i> = 6.1 Hz, 3H). 26 of 27H reported (COOH not observed)	Method C-4: Rt = 1.59 min; [M+H] ⁺ = 378.5
Ex-52		600 MHz, DMSO- <i>d</i> ₆ δ [ppm] 12.77 (br s, 1H), 10.85 (br s, 1H), 7.88 (d, <i>J</i> = 8.1 Hz, 2H), 7.56 (d, <i>J</i> = 8.1 Hz, 2H), 7.14 – 7.13 (m, 1H), 6.56 (s, 1H), 6.13 (dd, <i>J</i> = 3.1, 1.9 Hz, 1H), 4.54 – 4.48 (m, 1H), 3.11 – 3.04 (m, 1H), 2.31 (s, 3H), 2.28 – 2.22 (m, 1H), 2.04 (s, 3H), 1.84 – 1.73 (m, 2H), 1.64 – 1.54 (m, 1H), 1.05 – 0.98 (m, 1H), 0.91 – 0.82 (m, 1H), 0.42 – 0.37 (m, 1H)	Method B-2: Rt = 6.72 min; [M+H] ⁺ = 390.2

		1H), 0.37 – 0.29 (m, 3H). 27 of 27H reported	
Ex-53		600 MHz, DMSO- <i>d</i> ₆ δ [ppm] 10.94 – 10.74 (m, 1H), 7.99 – 7.88 (m, 1H), 7.85 – 7.77 (m, 2H), 7.57 – 7.46 (m, 2H), 7.32 – 7.22 (m, 1H), 7.16 – 7.07 (m, 1H), 6.61 – 6.51 (m, 1H), 6.17 – 6.05 (m, 1H), 4.54 – 4.39 (m, 1H), 3.54 – 3.45 (m, 1H), 3.26 (s, 3H), 3.18 – 3.09 (m, 1H), 2.30 (s, 3H), 2.03 (s, 3H), 2.01 – 1.95 (m, 1H), 1.92 – 1.85 (m, 2H), 1.72 – 1.63 (m, 1H), 1.60 – 1.51 (m, 1H), 1.43 – 1.34 (m, 1H) 28 of 28H reported	Method B-1: Rt = 0.95 min; [M+H] ⁺ = 393.3
Ex-54		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 11.10 (s, 1H), 7.88 (d, <i>J</i> = 8.2 Hz, 2H), 7.55 (d, <i>J</i> = 8.0 Hz, 2H), 7.26 – 7.24 (m, 1H), 6.69 (d, <i>J</i> = 12.2 Hz, 1H), 6.16 (dd, <i>J</i> = 3.1, 1.9 Hz, 1H), 4.49 – 4.37 (m, 1H), 3.27 – 3.22 (m, 2H), 3.18 – 3.11 (m, 1H), 2.99 – 2.96 (m, 1H), 2.96 – 2.92 (m, 1H), 2.75 – 2.70 (m, 1H), 2.57 – 2.53 (m, 1H), 2.35 (s, 3H), 1.81 (d, <i>J</i> = 11.9 Hz, 1H), 1.77 – 1.65 (m, 1H). 21 of 22H reported (COOH not observed)	Method B-2: Rt = 5.87 min; [M+H] ⁺ = 451.1
Ex-55		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 10.87 (s, 1H), 7.91 (d, <i>J</i> = 8.0 Hz, 2H), 7.63 (d, <i>J</i> = 8.0 Hz, 2H), 7.21 – 7.06 (m, 1H), 6.16 (s, 1H), 6.05 (dd, <i>J</i> = 3.1, 1.9 Hz, 1H), 4.65 – 4.51 (m, 1H), 3.25 – 3.17 (m, 1H), 2.65 – 2.54 (m, 1H), 2.29 (s, 3H), 2.25 – 2.13 (m, 1H), 2.06 – 1.99 (m, 1H), 1.98 – 1.84 (m, 1H)	Method B-1: Rt = 1.28 min; [M+H] ⁺ = 426.3

		3H), 1.82 – 1.68 (m, 1H), 0.88 – 0.77 (m, 1H), 0.74 – 0.63 (m, 1H), 0.57 – 0.37 (m, 2H). 24 of 25H reported (COOH not observed)	
Ex-56		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 11.21 (s, 1H), 7.80 (d, <i>J</i> = 8.0 Hz, 2H), 7.48 (d, <i>J</i> = 8.2 Hz, 2H), 7.19 – 7.17 (m, 1H), 6.80 (s, 1H), 6.23 – 6.20 (m, 1H), 6.20 – 5.93 (m, 1H), 4.53 – 4.44 (m, 1H), 3.12 – 3.04 (m, 1H), 2.92 – 2.82 (m, 2H), 2.78 – 2.66 (m, 2H), 2.57 – 2.50 (m, 1H), 2.30 – 2.23 (m, 1H), 1.99 (s, 3H), 1.72 – 1.56 (m, 2H). 22 of 23H reported (COOH not observed)	Method C-4: Rt = 1.47 min; [M+H] ⁺ = 449.2
Ex-57		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 10.89 (s, 1H), 7.90 (d, <i>J</i> = 7.6 Hz, 2H), 7.58 (dd, <i>J</i> = 8.1, 2.8 Hz, 2H), 7.17 – 7.15 (m, 1H), 6.58 (s, 1H), 6.18 (d, <i>J</i> = 2.7 Hz, 1H), 4.51 – 4.44 (m, 1H), 3.19 – 3.09 (m, 1H), 2.90 – 2.82 (m, 2H), 2.66 – 2.58 (m, 1H), 2.44 – 2.34 (m, 2H), 2.32 (s, 3H), 2.20 – 2.09 (m, 1H), 2.05 (s, 3H), 1.90 – 1.79 (m, 1H), 1.79 – 1.66 (m, 2H), 1.61 – 1.52 (m, 1H), 1.26 – 1.03 (m, 1H). 27 of 28H reported (COOH not observed)	Method C-3: Rt = 1.30 min; [M+H] ⁺ = 455.6
Ex-58		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 10.88 (s, 1H), 7.89 (d, <i>J</i> = 8.2 Hz, 2H), 7.55 (d, <i>J</i> = 8.0 Hz, 2H), 7.17 – 7.14 (m, 1H), 6.58 (s, 1H), 6.17 – 6.14 (m, <i>J</i> = 2.5 Hz, 1H), 6.12 – 5.90 (m, 1H), 4.49 – 4.42 (m, 1H), 3.15 – 3.08 (m,	Method C-4: Rt = 1.24 min; [M+H] ⁺ = 457.6

		1H), 2.94 – 2.78 (m, 2H), 2.40 – 2.38 (m, 3H), 2.37 (s, 3H), 2.04 (s, 3H), 2.04 – 1.96 (m, 1H), 1.92 – 1.62 (m, 4H), 1.57 – 1.46 (m, 2H). 29 of 30H reported (COOH not observed)	
Ex-59		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 10.87 (s, 1H), 7.89 (d, <i>J</i> = 8.0 Hz, 2H), 7.55 (d, <i>J</i> = 7.8 Hz, 2H), 7.17 – 7.15 (m, 1H), 6.36 – 5.97 (m, 3H), 4.48 – 4.44 (m, 1H), 3.21 – 3.14 (m, 1H), 3.03 – 2.88 (m, 2H), 2.84 – 2.74 (m, 2H), 2.65 – 2.60 (m, 1H), 2.34 – 2.25 (m, 5H), 2.05 – 1.97 (m, 1H), 1.79 – 1.71 (m, 1H), 0.86 – 0.67 (m, 2H), 0.53 – 0.43 (m, 2H). 27 of 28 H reported (COOH not observed)	Method C-4: Rt = 1.40 min; [M+H] ⁺ = 455.5
Ex-60		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 11.17 (s, 1H), 7.81 (d, <i>J</i> = 8.0 Hz, 2H), 7.49 (d, <i>J</i> = 8.2 Hz, 2H), 7.23 – 7.20 (m, 1H), 6.74 (s, 1H), 6.16 (s, 1H), 6.08 – 5.85 (m, 1H), 4.59 – 4.53 (m, 1H), 3.13 – 3.06 (m, 1H), 2.87 – 2.77 (m, 2H), 2.41 – 2.37 (m, 2H), 2.31 – 2.24 (m, 5H), 2.02 – 1.87 (m, 2H), 1.81 – 1.56 (m, 2H). 24 of 25 H reported (COOH not observed)	Method C-4: Rt = 1.23 min; [M+H] ⁺ = 463.5
Ex-61		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 11.19 (d, <i>J</i> = 2.4 Hz, 1H), 7.80 (d, <i>J</i> = 8.2 Hz, 2H), 7.47 (d, <i>J</i> = 8.3 Hz, 2H), 7.22 – 7.20 (m, 1H), 6.74 (s, 1H), 6.16 – 6.14 (m, 1H), 4.56 – 4.50 (m, 1H), 3.10 – 3.03 (m, 1H), 2.91 – 2.77 (m, 2H), 2.53 – 2.48 (m, 2H), 2.41 –	Method C-2: Rt = 0.78 min; [M+H] ⁺ = 481.3

		2.37 (m, 2H), 2.36 – 2.30 (m, 1H), 2.28 (s, 3H), 2.05 – 2.00 (m, 1H), 1.79 – 1.59 (m, 2H). 23 of 24H reported (COOH not observed)	
Ex-62 (rac)		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 10.84 (s, 1H), 7.89 (d, <i>J</i> = 8.0 Hz, 2H), 7.53 (d, <i>J</i> = 7.9 Hz, 2H), 7.15 – 7.12 (m, 1H), 6.86 (t, <i>J</i> = 75.7 Hz, 1H), 6.15 (s, 1H), 6.10 – 5.96 (m, 1H), 4.54 – 4.40 (m, 1H), 3.56 – 3.17 (m, 1H), 2.29 (s, 3H), 2.13 – 1.75 (m, 5H), 1.64 (d, <i>J</i> = 12.1 Hz, 1H), 1.58 – 1.45 (m, 1H), 1.32 (s, 3H), 0.91 – 0.76 (m, 1H), 0.72 – 0.61 (m, 1H), 0.54 – 0.39 (m, 2H). 28 of 29 H reported (COOH not observed)	Method B-1: Rt = 1.25 min; [M+H] ⁺ = 470.3
Ex-63 (rac)		400 MHz, DMSO- <i>d</i> ₆ δ [ppm] 10.89 – 10.79 (m, 1H), 7.99 (d, <i>J</i> = 8.2 Hz, 2H), 7.91 – 7.45 (m, 3H), 7.17 – 7.08 (m, 1H), 6.14 (s, 1H), 6.11 – 6.06 (m, 1H), 4.50 – 4.42 (m, 1H), 3.22 – 3.12 (m, 1H), 2.28 (s, 3H), 2.01 – 1.85 (m, 2H), 1.77 – 1.51 (m, 4H), 1.50 – 1.38 (m, 1H), 1.31 (s, 3H), 0.84 – 0.75 (m, 1H), 0.73 – 0.64 (m, 1H), 0.50 – 0.43 (m, 2H). 28 of 29 H reported (COOH not observed)	Method B-1: Rt = 1.26 min; [M+H] ⁺ = 470.4

LC-MS Methods**Method A-1:**

Column:	Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7 μm
5 Column temperature:	40 °C
Eluents:	A: H ₂ O + FA (0.1%) B: ACN + FA (0.1%)
Flow rate:	2.0 mL/min
10 Gradient:	Time/% B: 0.1/5; 0.5/5; 1.0/95; 1.5/95; 2.0/5; 3.0/5 (3 min method).

- Method B-1:**
Column: CORTECS C18+, 2.1 x 50 mm, 2.7 µm
Column temperature: 80 °C
5 Eluents: A: H₂O + 0.05% FA + 3.75 mM ammonium acetate
B: IPA + 0.05% FA
Flow rate: 1.0 mL/min
Gradient: 5% to 50% B in 1.4 min, 50% to 98% B in 0.30 min;
0.10 min 98% B.
- 10 **Method B-2:**
Column: Acquity UPLC BEH C18, 2.1 x 30 mm, 1.7 µm
Column temperature: 80 °C
15 Eluents: A: H₂O + 0.05% FA + 3.75 mM ammonium acetate
B: IPA + 0.05% FA
Flow rate: 0.4 mL/min
Gradient: 5% to 60% B in 8.4 min, 60% to 98% B in 1.00 min;
0.40 min 98% B.
- 20 **Method C-1:**
Column: Acquity UPLC BEH C18, 2.1 x 30 mm, 1.7 µm
Column temperature: 50 °C
Eluents: A: H₂O + 0.1% FA
B: ACN + 0.1% FA
25 Flow rate: 1.0 mL/min
Gradient: 2% B until 0.1 min; 2% to 98% B until 1.5 min, 98% B
until 1.8 min.
- Method C-2:**
30 Column: Acquity UPLC BEH C18, 2.1 x 30 mm, 1.7 µm
Column temperature: 50 °C
Eluents: A: 5 mM NH₄OH in H₂O
B: 5 mM NH₄OH in ACN
Flow rate: 1.0 mL/min
35 Gradient: 2% B until 0.1 min; 2% to 98% B until 1.5 min, 98% B
until 1.8 min.
- Method C-3:**
40 Column: Acquity UPLC BEH C18, 2.1 x 30 mm, 1.7 µm
Column temperature: 50 °C
Eluents: A: 0.1% FA in H₂O
B: 0.1% FA in ACN
Flow rate: 1.0 mL/min
45 Gradient: 2% to 98% B until 4.40 min, 98% B until 5.15 min.
- Method C-4:**
Column: Acquity UPLC BEH C18, 2.1 x 30 mm, 1.7 µm
Column temperature: 50 °C
Eluents: A: 5 mM NH₄OH in H₂O
50 B: 5 mM NH₄OH in ACN
Flow rate: 1.0 mL/min
Gradient: 2% to 98% B until 4.40 min, 98% B until 5.15 min.

Chiral HPLC Methods

- 55 **Method SFC-1:**

Preparative chiral HPLC

	Instrument:	Waters Thar80 System
	Column:	Chiralpak AD-H, 250 mm x 21 mm, 5 µm
	Eluent:	A: 40% 1:1 MeOH/IPA, B: 60% scCO ₂ (isocratic)
5	Flow rate:	80 g/min
	Detection:	UV 237 nm
	Injection volume:	14x 2 mL
	Oven temperature:	25 °C
10	Pressure:	125 bar

Analytical chiral HPLC

	Instrument:	Analytical SFC-MS Waters UPC2
	Injection:	5 µL
15	Mobile phase:	A: 5 to 55% 1:1 MeOH/IPA with 0.1% NH ₃ B: scCO ₂
	Flow rate:	2.5 mL/min
	Column:	Chiralpak AD-3, 3 mm x 100 mm, 3 µm
	Detection UV:	DAD
20	Oven temperature:	40 °C
	Pressure:	1800 psi

Method SFC-2:Preparative chiral HPLC

25	Instrument:	Agilent 1260 Infinity
	Column:	Chiralpak AD, 250 mm x 21 mm, 5 µm
	Eluent:	A: 50% ACN B: 50% 1:1 MeOH/EtOH (isocratic)
	Flow rate:	15 mL/min
30	Detection:	UV 210 nm
	Injection volume:	3x 1.30 mL
	Oven temperature:	23 °C
	Pressure:	80 bar

35

Method SFC-3:Preparative chiral HPLC

	Instrument:	Agilent 1260 Infinity
	Column:	Chiralpak IG, 250 mm x 21 mm, 5 µm
40	Eluent:	A: hexane B: 1:1 MeOH/EtOH (isocratic)
	Flow rate:	15 mL/min
	Detection:	UV 210 nm
	Injection volume:	32x 0.25 mL
45	Oven temperature:	23 °C
	Pressure:	80 bar

Analytical chiral HPLC

	Instrument:	Agilent 1260 Infinity II
50	Injection:	5 µL
	Mobile phase:	A: 70% hexane B: 0.1% FA in 4:1 EtOH/MeOH (isocratic)
	Flow rate:	1 mL/min
	Column:	Chiralpak IG, 4.6 mm x 150 mm 5 µm
55	Detection UV:	DAD
	Oven temperature:	25 °C
	Pressure:	400 bar

Method SFC-4:Preparative chiral HPLC

	Instrument:	Agilent 1260 Infinity
5	Column:	Lux Cellulose-4, 250 mm x 21.2 mm, 5 µm
	Eluent:	A: 80% hexane B: 20% IPA (isocratic)
	Flow rate:	15 mL/min
	Detection:	UV 210 nm
10	Injection volume:	32x 0.5 mL
	Oven temperature:	23 °C
	Pressure:	80 bar

Analytical chiral HPLC

15	Instrument:	Agilent 1260 Infinity II
	Injection:	5 µL
	Mobile phase:	A: 50% hexane B: 50% 1:1 IPA/MeOH (isocratic)
	Flow rate:	1 mL/min
20	Column:	Lux Cellulose-4, 250 mm x 21.2 mm, 5 µm
	Detection UV:	DAD
	Oven temperature:	25 °C
	Pressure:	400 bar

Method SFC-5:Preparative chiral HPLC

	Instrument:	Agilent 1260 Infinity
	Column:	Chiralpak IG, 250 mm x 21 mm, 5 µm
	Eluent:	A: 80% ACN B: 20% 1:1:1 MeOH/EtOH/IPA (isocratic)
30	Flow rate:	15 mL/min
	Detection:	UV 210 nm
	Injection volume:	3x 1.30 mL
	Oven temperature:	23 °C
35	Pressure:	80 bar

Analytical chiral HPLC

	Instrument:	Agilent 1260 Infinity II
	Injection:	5 µL
40	Mobile phase:	A: 85% ACN B: 15% 1:1 MeOH/IPA (isocratic)
	Flow rate:	1 mL/min
	Column:	Chiralpak IG, 4.6 mm x 150 mm, 5 µm
	Detection UV:	DAD
45	Oven temperature:	25 °C
	Pressure:	400 bar

Method SFC-6:Preparative chiral HPLC

50	Instrument:	Waters Thar80 System
	Column:	Chiralpak IG, 250 mm x 21 mm, 5 µm
	Eluent:	A: 40% 10 mM NH ₃ in MeOH B: 60% scCO ₂ (isocratic)
	Flow rate:	80 g/min
55	Detection:	UV 265 nm C
	Injection volume:	2x 4 mL

Oven temperature: 25 °C
Pressure: 125 bar

Analytical chiral HPLC

- 5 Instrument: Analytical SFC-MS Waters UPC2
Injection: 5 µL
Mobile phase: A: 5 to 55% MeOH with 0.1% NH₃
B: scCO₂
Flow rate: 2.5 mL/min
10 Column: Chiralpak IG, 3 mm x 100 mm, 3 µm
Detection UV: DAD
Oven temperature: 25 °C
Pressure: 1800 psi

15 **Method SFC-7:**
Preparative chiral HPLC

- Instrument: Waters Thar80 System
Column: Chiralpak AD-H, 250 mm x 21 mm, 5 µm
Eluent: A: 25% 10 mM NH₃ in MeOH
20 B: 75% scCO₂ (isocratic)
Flow rate: 80 g/min
Detection: UV 220 nm
Injection volume: 3x 2 mL
Oven temperature: 25 °C
25 Pressure: 125 bar

Analytical chiral HPLC

- Instrument: Analytical SFC-MS Waters UPC2
Injection: 5 µL
30 Mobile phase: A: 5 to 55% MeOH with 0.1% NH₃
B: scCO₂
Flow rate: 2.5 mL/min
Column: Chiralpak AD-3, 3 mm x 100 mm, 5 µm
Detection UV: DAD
35 Oven temperature: 40 °C
Pressure: 1800 psi

Method SFC-8:
Preparative chiral HPLC

- 40 Instrument: Waters Thar80 System
Column: Chiralpak AD-H, 250 mm x 21 mm, 5 µm
Eluent: A: 35% 10 mM NH₃ in IPA
B: 65% scCO₂ (isocratic)
Flow rate: 80 g/min
45 Detection: UV 260 nm
Injection volume: 3x 2 mL
Oven temperature: 25 °C
Pressure: 125 bar

50 Analytical chiral HPLC

- Instrument: Analytical SFC-MS Waters UPC2
Injection: 5 µL
Mobile phase: A: 5 to 55% IPA with 0.1% NH₃
55 B: scCO₂
Flow rate: 2.5 mL/min
Column: Chiralpak AD-3, 3 mm x 100 mm, 3 µm

Detection UV: DAD
Oven temperature: 40 °C
Pressure: 1800 psi

5 **Method SFC-9:**

Preparative chiral HPLC

Instrument: Waters Thar80 System
Column: Chiralpak AD-H, 250 mm x 21 mm, 5 µm
Eluent: A: 30% 10 mM NH₃ in MeOH
10 B: 70% scCO₂ (isocratic)
Flow rate: 80 g/min
Detection: UV 257 nm
Injection volume: 3x 2 mL
Oven temperature: 25 °C
15 Pressure: 125 bar

Analytical chiral HPLC

Instrument: Analytical SFC-MS Waters UPC2
Injection: 5 µL
20 Mobile phase: A: 5 to 55% MeOH with 0.1% NH₃
B: scCO₂
Flow rate: 2.5 mL/min
Column: Chiralpak AD-3, 3 mm x 100 mm, 3 µm
Detection UV: DAD
25 Oven temperature: 40 °C
Pressure: 1800 psi

Method SFC-10:

Preparative chiral HPLC

30 Instrument: Waters Thar80 System
Column: Chiralpak AD-H, 250 mm x 21 mm, 5 µm
Eluent: A: 25% 10 mM NH₃ in IPA
B: 75% scCO₂ (isocratic)
Flow rate: 80 g/min
35 Detection: UV 18 nm
Injection volume: 4x 1 mL
Oven temperature: 25 °C
Pressure: 125 bar

40 Analytical chiral HPLC

Instrument: Analytical SFC-MS Waters UPC2
Injection: 5 µL
Mobile phase: A: 5 to 55% IPA with 0.1% NH₃
B: scCO₂
45 Flow rate: 2.5 mL/min
Column: Chiralpak AD-3, 3 mm x 100 mm, 3 µm
Detection UV: DAD
Oven temperature: 40 °C
Pressure: 1800 psi

50

Method SFC-11:

Preparative chiral HPLC

Instrument: Berger Multi-Gram-II Preparative-SFC
Column: ColumnTek EnantioCel C2-5®, 250 x 30 mm
55 Eluent: A: 10% 12 mM NH₃ in MeOH
B: 90% scCO₂ (isocratic)
Flow rate: 90 mL/min

- Detection: UV 220 nM
Oven temperature: 35 °C
Pressure: 100 bar
- 5 Analytical chiral HPLC
Instrument: Agilent 1260 SFC
Injection: 3 µL
Mobile phase: A: 10% 12 mM NH₃ in MeOH
B: 90% scCO₂ (isocratic)
- 10 Flow rate: 2 mL/min
Column: ColumnTek EnantioCel C2-5®, 250 x 4.6 mm
Detection UV: 220 nm
Oven temperature: 20 °C
Pressure: 100 bar
- 15 **Method SFC-12:**
Preparative chiral HPLC
Instrument: Waters 350 Preparative SFC system
Column: Chiralpak AD-3, 250 mm x 50 mm, 10 µm
20 Eluent: A: 40% CO₂
B: 60% 7:3 MeOH/ACN (0.1%NH₄OH) (isocratic)
- Flow rate: 180 g/min
Detection: UV 220 nm
25 Injection volume: 15 mL
Oven temperature: 35 °C
Pressure: 100 bar
- Analytical chiral HPLC
30 Instrument: Shimadzu LC-30ADsf
Injection: 1 µL
Mobile phase: A: 5 to 40% EtOH with 0.05% dimethyl amine
B: scCO₂
- Flow rate: 3 mL/min
35 Column: Chiralpak AD-3, 4.6 mm x 50 mm, 3 µm
Detection UV: 220 nm
Oven temperature: 25 °C
Pressure: 100 bar
- 40 **Method SFC-18:**
Preparative chiral HPLC
Column: Lux Amylose 2 21 x 250 mm, 5 µm
Eluent: A: 15% 1:1 MeOH/IPA with 10 mM NH₃
B: 85% scCO₂ (isocratic)
- 45 Flow rate: 50 mL/min
Detection: 210 nm
Injection volume: 50 x 0.3 mL
Oven temperature: 40 °C
Pressure: 100 bar
- 50 Analytical chiral HPLC
Instrument: SFC-PIC solution
Mobile phase: A: 10% 1:1:1 MeOH/EtOH/IPA with 10 mM NH₃
B: 90% scCO₂ (isocratic)
- 55 Flow rate: 3 mL/min
Column: Lux Amylose 2100 x 4.6 mm, 5 µm
Detection UV: 240 nM

Oven temperature: 40 °C
Pressure: 100 bar

Method SFC-21:

- 5 Preparative chiral HPLC
Instrument: Teledyne ACCQPrep SFC
Column: Chiralpak IC, 250 mm x 30 mm, 5 µm
Eluent: A: 25% MeOH
B: 75% scCO₂ (isocratic)
- 10 Flow rate: 100 mL/min
Detection: UV 214 nm
Injection volume: 1.8 mL
Oven temperature: 40 °C
Pressure: 100 bar
- 15 Analytical chiral HPLC
Instrument: Analytical SFC-MS Waters UPC²
Injection: 5 µL
Mobile phase: A: 25% MeOH with 0.05% NH₃
B: 75% scCO₂ (isocratic)
- 20 Flow rate: 3 mL/min
Column: Chiralpak IC, 4.6 mm x 100 mm, 5 µm
Detection UV: DAD
Oven temperature: 40 °C
- 25 Pressure: 1800 psi

Method SFC-22:

- Preparative chiral HPLC
Instrument: Teledyne ACCQPrep SFC
Column: Chiralpak IC, 250 mm x 30 mm, 5 µm
- 30 Eluent: A: 25% MeOH
B: 75% scCO₂ (isocratic)
- Flow rate: 100 mL/min
Detection: UV 218 nm
Injection volume: 3 mL
- 35 Oven temperature: 40 °C
Pressure: 100 bar
- Analytical chiral HPLC
Instrument: Analytical SFC-MS Waters UPC²
Injection: 5 µL
Mobile phase: A: 25% MeOH with 0.05% NH₃
B: 75% scCO₂ (isocratic)
- Flow rate: 3 mL/min
Column: Chiralpak IC, 4.6 mm x 100 mm, 5 µm
- 45 Detection UV: DAD
Oven temperature: 40 °C
Pressure: 1800 psi

Method SFC-23:

- 50 Preparative chiral HPLC
Instrument: Sepiatec SFC
Column: Chiralpak IC, 250 mm x 30 mm, 5 µm
Eluent: A: 25% MeOH with 0.05% NH₃
B: 75% scCO₂ (isocratic)

- Flow rate: 85 mL/min
 Detection: UV 217 nm
 Injection volume: 3x 1.3 mL
 Oven temperature: 37 °C
 5 Pressure: 110 bar
- Analytical chiral HPLC
 Instrument: Analytical SFC-MS Waters UPC²
 Injection: 5 µL
 10 Mobile phase: A: 25% MeOH with 0.05% NH₃
 B: 75% scCO₂ (isocratic)
 Flow rate: 3 mL/min
 Column: Chiralpak IC, 4.6 mm x 100 mm, 5 µm
 Detection UV: DAD
 15 Oven temperature: 40 °C
 Pressure: 1800 psi
- Method SFC-25:**
Preparative chiral HPLC
 Instrument: Sepiatec Prep SFC 250
 20 Column: Chiralpak IC, 250 mm x 30 mm, 5 µm
 Eluent: A: 35% MeOH with 0.05% NH₃
 B: 65% scCO₂ (isocratic)
 Flow rate: 82 mL/min
 Detection: UV 235 nm
 25 Injection volume: 5x 1.4 mL
 Oven temperature: 37 °C
 Pressure: 120 bar
- Analytical chiral HPLC
 30 Instrument: Analytical SFC-MS Waters UPC²
 Injection: 5 µL
 Mobile phase: A: 35% MeOH with 0.05% NH₃
 B: 65% scCO₂ (isocratic)
 Flow rate: 3 mL/min
 35 Column: Chiralpak IC, 4.6 mm x 100 mm, 5 µm
 Detection UV: DAD
 Oven temperature: 40 °C
 Pressure: 1800 psi
- Method SFC-26:**
Preparative chiral HPLC
 Instrument: Waters SFC 150 MGM
 Column: Chiralpak IC, 250 mm x 21 mm, 5 µm
 Eluent: A: 30% IPA with 10 mM NH₃
 45 B: 70% scCO₂ (isocratic)
 Flow rate: 80 g/min
 Detection: UV 260 nm
 Injection volume: 2x 5 mL
 Oven temperature: 25 °C
 50 Pressure: 125 bar
- Analytical chiral HPLC
 Instrument: Waters UPC²
 Injection: 5 µL
 55 Mobile phase: A: 5 to 55% IPA with 0.1% NH₃

Flow rate: B: scCO₂
2.5 mL/min
Column: Chiralpak IC-3, 3 mm x 100 mm, 3 µm
Detection UV: DAD
5 Oven temperature: 40 °C
Pressure: 1800 psi

Method SFC-27:Preparative chiral HPLC

10 Instrument: Waters Thar80 System
Column: Chiralpak AD-H, 250 mm x 21 mm, 5 µm
Eluent: A: 45% IPA
B: 55% scCO₂ (isocratic)
Flow rate: 80 g/min
15 Detection: UV 222 nm
Injection volume: 3x 3 mL
Oven temperature: 25 °C
Pressure: 125 bar

20 Analytical chiral HPLC

Instrument: SFC-MS Waters UPC2
Injection: 5 µL
Mobile phase: A: 5 to 55% IPA with 0.1% NH₃
B: scCO₂
25 Flow rate: 2.5 mL/min
Column: Chiralpak AD-3, 3 mm x 100 mm, 3 µm
Detection UV: DAD
Oven temperature: 40 °C
Pressure: 1800 psi

30

Method SFC-28:Preparative chiral HPLC

Instrument: Waters SFC Prep 150 MGM
Column: Chiralpak IG, 250 mm x 21 mm, 5 µm
35 Eluent: A: 45% MeOH with 10 mM NH₃
B: 55% scCO₂ (isocratic)
Flow rate: 80 g/min
Detection: UV 270 nm
Injection volume: 5x 2 mL
40 Oven temperature: 25 °C
Pressure: 100 bar

Analytical chiral HPLC

Instrument: Analytical SFC-MS Waters UPC2
45 Injection: 3 µL
Mobile phase: A: 5 to 55% MeOH with 0.1% NH₃
B: scCO₂
Flow rate: 2.5 mL/min
Column: Chiralpak IG-3, 3 mm x 100 mm, 3 µm
50 Detection UV: DAD
Oven temperature: 40 °C
Pressure: 1500 psi

Method SFC-29:Preparative chiral HPLC

	Column:	Chiralpak AD, 250 mm x 30 mm, 5 µm
	Eluent:	A: 30% MeOH B: 70% scCO ₂ (isocratic)
5	Flow rate:	80 mL/min
	Detection:	UV 220 nm
	Injection volume:	1x 3.8 mL
	Oven temperature:	40 °C
10	Pressure:	110 bar

Analytical chiral HPLC

	Instrument:	Analytical SFC-MS Waters UPC ²
	Injection:	5 µL
15	Mobile phase:	A: 30% MeOH with 0.05% NH ₃ B: 70% scCO ₂ (isocratic)
	Flow rate:	3 mL/min
	Column:	Chiralpak AD, 4.6 mm x 100 mm, 5 µm
	Detection UV:	DAD
20	Oven temperature:	40 °C
	Pressure:	1800 psi

Method SFC-30:Preparative chiral HPLC

25	Instrument:	Sepiatec Prep SFC 250
	Column:	Chiralpak AD-H, 250 mm x 30 mm, 5 µm
	Eluent:	A: 27% MeOH with 0.05% NH ₃ B: 73% scCO ₂ (isocratic)
	Flow rate:	88 mL/min
30	Detection:	UV 220 nm
	Injection volume:	5x 1.2 mL
	Oven temperature:	40 °C
	Pressure:	130 bar

35 Analytical chiral HPLC

	Instrument:	Analytical SFC-MS Waters UPC ²
	Injection:	5 µL
	Mobile phase:	A: 30% MeOH with 0.05% NH ₃ B: 70% scCO ₂ (isocratic)
40	Flow rate:	3 mL/min
	Column:	Chiralpak AD, 4.6 mm x 100 mm, 5 µm
	Detection UV:	DAD 220 nm
	Oven temperature:	40 °C
	Pressure:	1800 psi

45

Method SFC-31:Preparative chiral HPLC

	Instrument:	Sepiatec Prep SFC 250
	Column:	Chiralpak AD-H, 250 mm x 30 mm, 5 µm
50	Eluent:	A: 35% IPA with 0.05% NH ₃ B: 65% scCO ₂ (isocratic)
	Flow rate:	88 mL/min
	Detection:	UV 225 nm
	Injection volume:	3x 2.5 mL

	Oven temperature:	37 °C
	Pressure:	125 bar
	<u>Analytical chiral HPLC</u>	
5	Instrument:	Analytical SFC-MS Waters UPC ²
	Injection:	5 µL
	Mobile phase:	A: 35% IPA with 0.05% NH ₃ B: 65% scCO ₂ (isocratic)
	Flow rate:	3 mL/min
10	Column:	Chiralpak AD, 4.6 mm x 100 mm, 5 µm
	Detection UV:	DAD
	Oven temperature:	40 °C
	Pressure:	1800 psi
15	Method SFC-32:	
	<u>Preparative chiral HPLC</u>	
	Instrument:	Sepiatec Prep SFC 250
	Column:	Chiralpak AD-H, 250 mm x 30 mm, 5 µm
	Eluent:	A: 30% MeOH with 0.05% NH ₃ B: 70% scCO ₂ (isocratic)
20	Flow rate:	82 mL/min
	Detection:	UV 235 nm
	Injection volume:	3x 2.3 mL
	Oven temperature:	37 °C
25	Pressure:	120 bar
	<u>Analytical chiral HPLC</u>	
	Instrument:	Analytical SFC-MS Waters UPC ²
	Injection:	5 µL
30	Mobile phase:	A: 30% MeOH with 0.05% NH ₃ B: 70% scCO ₂ (isocratic)
	Flow rate:	3 mL/min
	Column:	Chiralpak IM, 4.6 mm x 100 mm, 5 µm
	Detection UV:	DAD
35	Oven temperature:	40 °C
	Pressure:	1800 psi
	Method SFC-33:	
	<u>Preparative chiral HPLC</u>	
	Instrument:	Sepiatec Prep SFC 250
40	Column:	Chiralpak IM, 250 mm x 30 mm, 5 µm
	Eluent:	A: 35% MeOH with 0.05% NH ₃ B: 65% scCO ₂ (isocratic)
	Flow rate:	86 mL/min
	Detection:	UV 220 nm
45	Injection volume:	6x 1.3 mL
	Oven temperature:	40 °C
	Pressure:	130 bar
	<u>Analytical chiral HPLC</u>	
50	Instrument:	Analytical SFC-MS Waters UPC ²
	Injection:	5 µL
	Mobile phase:	A: 35% MeOH with 0.05% NH ₃ B: 65% scCO ₂ (isocratic)
	Flow rate:	3 mL/min
55	Column:	Chiralpak IM, 4.6 mm x 100 mm, 5 µm

Detection UV: DAD
Oven temperature: 40 °C
Pressure: 1800 psi

5

Biological data

Determination of complement factor B inhibition

Biological Example 1: Human complement factor B ELISA assay

CVF-Bb complex is prepared from purified cobra venom factor (1 μM), recombinant human
10 complement factor B (expressed in drosophila cells and purified using standard methods) and
human complement factor D (expressed in *E. Coli*, refolded and purified using standard methods).
CVF-Bb complex at 3 nM concentration is incubated with test compound at various concentrations
for 1 h at RT in PBS pH 7.4 containing 10 mM MgCl₂ and 0.05% (w/v) CHAPS. Human
complement C3 substrate purified from plasma is added to a final concentration of 1 μM. After 1
15 h incubation at RT, the enzyme reaction is stopped by addition of a cocktail of concentrated pan-
protease inhibitors. The product of the reaction, C3a, is quantified by means of an enzyme-linked-
immunosorbent assay. IC₅₀ values are calculated from percentage of inhibition of CVF-Bb activity
as a function of test compound concentration.

Biological Example 2: Human complement factor B TR-FRET assay

20 Recombinant human factor B (expressed in drosophila cells and purified using standard
methods) labeled with biotin (10 nM), europium-labeled streptavidin (5 nM) and (+) or (-)-2-
((1E,3E,5E)-5-(1-(6-((2-(3-(4-((R)-3-amino-3-phenylpropanoyl)-1-(4-amino-6,7-
dimethoxyquinazolin-2-yl)piperazin-2-yl)phenoxy)ethyl)amino)-6-oxohexyl)-3,3-dimethyl-5-
sulfoindolin-2-ylidene)penta-1,3-dien-1-yl)-1-ethyl-3,3-dimethyl-5-sulfo-3H-indol-1-ium (prepared
25 as described in WO2015/009616, 240 nM activity against factor B when tested using the assay
of Biological Example 1) (75 nM) were incubated with test compound at various concentrations
up to 2 hours at RT in 20 mM Tris/HCl, pH 7.4, 0.005% (v/v) Tween20.

The time-gated decrease in fluorescence intensity related to the competition between
labeled and unlabeled factor B ligands was recorded at both 620 nm and 665 nm, 70 μs after
30 excitation at 337 nm using a microplate spectrofluorimeter. IC₅₀ values were calculated from
percentage of inhibition of complement factor B-(+) or (-)-2-((1E,3E,5E)-5-(1-(6-((2-(3-(4-((R)-3-
amino-3-phenylpropanoyl)-1-(4-amino-6,7-dimethoxyquinazolin-2-yl)piperazin-2-
yl)phenoxy)ethyl)amino)-6-oxohexyl)-3,3-dimethyl-5-sulfoindolin-2-ylidene)penta-1,3-dien-1-yl)-
1-ethyl-3,3-dimethyl-5-sulfo-3H-indol-1-ium (240 nM activity against factor B when tested using the
35 assay of Biological Example 1) displacement as a function of test compound concentration.

Compounds of disclosure are active on factor B inhibition. Data in Table A were collected using
the assay of Biological Example 2.

Table A:

Example	TR-FRET (μM)
Ex-1	0.0054
Ex-2	2.74
Ex-3	11.33
Ex-4	>100
Ex-5	0.0026
Ex-6	0.0053
Ex-7	0.0057
Ex-8	1.63
Ex-9	0.013
Ex-10	0.0035
Ex-11	0.12
Ex-12	3.16
Ex-13	1.58
Ex-14	0.0050
Ex-15	0.34
Ex-16	0.0071
Ex-17	1.97
Ex-18	0.015
Ex-19	10.09
Ex-20	0.32
Ex-21	33.45
Ex-22	28.59
Ex-23	0.012
Ex-24	0.0059
Ex-25	0.0040
Ex-26	0.0090
Ex-27	0.072
Ex-28	0.056
Ex-29	0.72
Ex-30	0.64
Ex-31	0.0092
Ex-32	0.0060
Ex-33	0.0065
Ex-34	0.025
Ex-35	0.048
Ex-36	0.0046
Ex-37	0.012
Ex-38	0.41
Ex-39	0.031
Ex-40	0.17
Ex-41	0.048
Ex-42	0.58
Ex-43	0.0054
Ex-44	0.014
Ex-45	0.075
Ex-46	0.51
Ex-47	0.60
Ex-48	0.26
Ex-49	0.089

Ex-50	0.0080
Ex-51	0.026
Ex-52	0.054
Ex-53	0.089
Ex-54	0.024
Ex-55	0.10
Ex-56	0.039
Ex-57	0.071
Ex-58	0.015
Ex-59	0.0056
Ex-60	0.0015
Ex-61	0.0023
Ex-62	0.0064
Ex-63	0.084

The compounds of the disclosure inhibit complement factor B activity at micromolar IC₅₀ values. As such, the compounds of the disclosure may be useful in treating the diseases and/or disorders described herein, *e.g.*, a disease/disorder mediated by complement factor B.

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All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. The present disclosure and its embodiments have been described in detail. However, the scope of the present disclosure is not intended to be limited to the particular embodiments of any process, manufacture, composition of matter, compounds, means, methods, and/or steps described in the specification. Various modifications, substitutions, and variations can be made to the disclosed material without departing from the spirit and/or essential characteristics of the present disclosure. Accordingly, one of ordinary skill in the art will readily appreciate from the disclosure that later modifications, substitutions, and/or variations performing substantially the same function or achieving substantially the same result as embodiments described herein may be utilized according to such related embodiments of the present disclosure. Thus, the following claims are intended to encompass within their scope modifications, substitutions, and variations to processes, manufactures, compositions of matter, compounds, means, methods, and/or steps disclosed herein. The claims should not be read as limited to the described order or elements unless stated to that effect. It should be understood that various changes in form and detail may be made without departing from the scope of the appended claims.

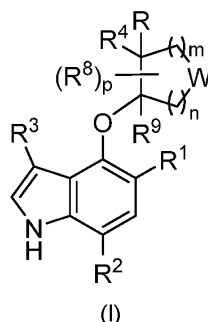
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Claims

1. A compound of Formula (I)



or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof,

wherein:

W is O, C(R⁶)₂, or NR⁷;

R is hydrogen, halogen, C₁-C₄alkyl, haloC₁-C₄alkyl, or hydroxyC₁-C₄alkyl;

R¹ is hydrogen, halogen, hydroxy, C₁-C₆alkyl, C₂-C₆alkenyl, C₃-C₆cycloalkyl, C₁-C₆alkoxy, haloC₁-C₆alkyl, haloC₃-C₆cycloalkyl, haloC₁-C₆alkoxy, hydroxyC₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, aminoC₁-C₆alkyl, C₁-C₆alkoxyC₁-C₆alkyl, C₁-C₆alkoxyC₁-C₆alkoxy, or C₃-C₆cycloalkylC₁-C₆alkoxy;

R² is C₁-C₃alkyl, C₃cycloalkyl, C₁-C₃alkoxy, hydroxyC₁-C₆alkyl, or halogen, wherein the C₁-C₃alkyl, C₃cycloalkyl, or C₁-C₃alkoxy are unsubstituted or substituted with 1, 2, or 3 halogen substituents;

R³ is hydrogen, halogen, or cyano;

R⁴ is phenyl, naphthyl or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N, O, and S, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵;

R⁵ is selected from hydrogen, -CO₂R^{5b}, C₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, C₁-C₆alkoxyC₁-C₆alkyl, -CH₂CO₂R^{5b}, -C(O)NHSO₂C₁-C₄alkyl, -SO₂NHC(O)C₁-C₄alkyl, -SO₂C₁-C₄alkyl, cyano, hydroxy, halogen, -C(O)N(R^{5b})₂ and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein alkyl and heteroaryl are unsubstituted or substituted with 1, 2, or 3 R^{5a};

each R^{5a} is independently selected from fluoro, hydroxyl, and C₁-C₆alkyl that is unsubstituted or substituted with -CO₂H;

each R^{5b} is independently selected from hydrogen and C₁-C₅alkyl;

each R⁶ is independently selected from hydrogen, halogen, hydroxy, amino, mono- and di- C₁-C₄alkylamino, C₃-C₆cycloalkylC₁-C₄alkylamino, haloC₃-C₆cycloalkylC₁-C₄alkylamino, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₁-C₆alkyl, cyanoC₁-C₆alkyl, C₁-C₆alkoxy, haloC₁-C₆alkoxy, C₃-C₆cycloalkoxy, haloC₃-C₆cycloalkoxy, and 4- to 6-membered heterocyclyl having 1-2 heteroatoms

independently selected from N and O, and wherein the C₁-C₆alkyl is unsubstituted or substituted with 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, wherein the 4- to 6-membered heterocyclyl is unsubstituted or substituted with 1, 2, or 3 halogen;

or two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic carbocycle having 3 to 6 ring atoms, wherein the spirocyclic carbocycle is unsubstituted or substituted with 1 or 2 substituents selected from halogen, C₁-C₆alkyl, and C₁-C₆alkoxy;

or two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 or 2 ring heteroatoms independently selected from N, O, and S(O)_q, wherein the spirocyclic heterocycle is unsubstituted or substituted with 1 or 2 halogen, C₁-C₆alkyl, haloC₁-C₆alkyl, C₃-C₆cycloalkyl, or haloC₃-C₆cycloalkyl;

q is 0, 1, or 2;

R⁷ is hydrogen, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₂-C₆alkyl, C₃-C₆cycloalkyl, C₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkyl, C₁-C₆alkoxyC₁-C₆alkyl, haloC₁-C₆alkoxyC₁-C₆alkyl, -COR^{7a}, aryl, 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N, O, and S(O)_q, or 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N, O, and S, wherein C₁-C₆alkyl is unsubstituted or substituted with 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N, O, and S(O)_q, wherein the 4- to 6-membered heterocyclyl is unsubstituted or substituted with 1, 2, or 3 halogen, further wherein the aryl or heteroaryl is unsubstituted or substituted with halo, C₁-C₆alkyl, haloC₁-C₆alkyl, C₃-C₅cycloalkyl, haloC₃-C₅cycloalkyl;

10 R^{7a} is hydrogen or C₁-C₆alkyl;

each R⁸ is independently selected from hydrogen, halogen, hydroxy, amino, mono- and di- C₁-C₄alkylamino, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₁-C₆alkyl, cyanoC₁-C₆alkyl, C₁-C₆alkoxy, and haloC₁-C₆alkoxy;

R⁹ is H, D, or T;

m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3;

provided that both m and n are not 0; and

p is 0, 1, 2, or 3.

2. The compound of claim 1, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein:

W is C(R⁶)₂, or NR⁷;

15 R is hydrogen;

R¹ is hydrogen, halogen, hydroxy, C₁-C₆alkyl, C₃-C₆cycloalkyl, C₁-C₆alkoxy, or haloC₁-C₆alkyl;

R² is C₁-C₃alkyl, C₃cycloalkyl, C₁-C₃alkoxy, hydroxyC₁-C₆alkyl, or halogen;

R³ is hydrogen;

R⁴ is phenyl, naphthyl or 5- to 10-membered heteroaryl having 1, 2 or 3 ring heteroatoms independently selected from N and O, wherein phenyl or heteroaryl is unsubstituted or substituted with R⁵;

R⁵ is selected from hydrogen, -CO₂R^{5b}, C₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, -CH₂CO₂R^{5b}, cyano, hydroxy, halogen, -C(O)N(R^{5b})₂ and 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from N and O, wherein alkyl and heteroaryl are unsubstituted or substituted with 1, 2, or 3 R^{5a};

each R^{5a} is independently selected from fluoro, hydroxyl, and C₁-C₆alkyl that is unsubstituted or substituted with -CO₂H;

R^{5b} is selected from hydrogen and C₁-C₅alkyl;

each R⁶ is independently selected from hydrogen, halogen, hydroxy, C₃-C₆cycloalkylC₁-C₄alkylamino, haloC₃-C₆cycloalkylC₁-C₄alkylamino, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₁-C₆alkyl, C₁-C₆alkoxy, haloC₁-C₆alkoxy, C₃-C₆cycloalkoxy, haloC₃-C₆cycloalkoxy, and 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, and wherein the C₁-C₆alkyl is unsubstituted or substituted with 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, wherein the 4- to 6-membered heterocyclyl is unsubstituted or substituted with 1, 2, or 3 halogen;

or two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic carbocycle having 3 to 6 ring atoms, wherein the spirocyclic carbocycle is unsubstituted or substituted with 1 or 2 substituents selected from halogen, C₁-C₆alkyl, and C₁-C₆alkoxy;

or two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 or 2 ring heteroatoms independently selected from N and O, wherein the spirocyclic heterocycle is unsubstituted;

R⁷ is hydrogen, C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₂-C₆alkyl, haloC₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkyl, haloC₁-C₆alkoxyC₁-C₆alkyl, -COR^{7a}, C₃-C₆cycloalkyl, 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N or O, or 5- to 6-membered heteroaryl having 1 heteroatom selected from O, wherein the 4- to 6-membered heterocyclyl and the 5- to 6-membered heterocyclyl are unsubstituted;

R^{7a} is C₁-C₆alkyl;

each R⁸ is independently selected from hydrogen, and halogen;

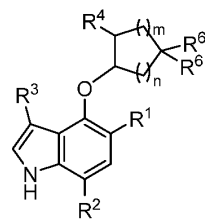
R⁹ is H;

m is 1, or 2;

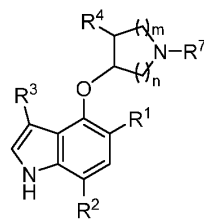
n is 1, 2, or 3; and

p is 0.

3. The compound of claim 1 or 2, wherein the compound of Formula (I) is a compound of Formula (I-AC), or (I-AN):



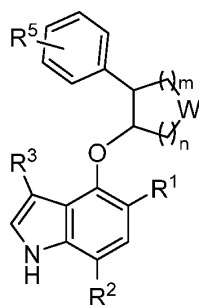
(I-AC)



(I-AN)

or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

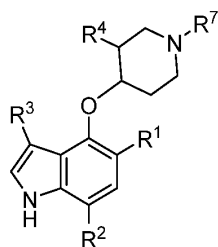
4. The compound of any of claims 1 to 3, wherein the compound of Formula (I) is a compound of Formula (I-D):



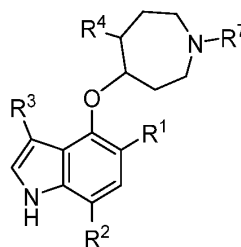
(I-D)

or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein W is $C(R^6)_2$ or NR^7 .

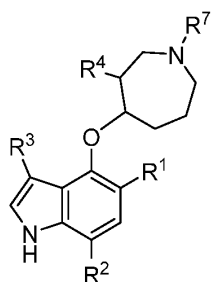
5. The compound of any of claims 1 to 4, wherein the compound of Formula (I) is a compound of Formula (I-E), (I-F), (I-G), or (I-H):



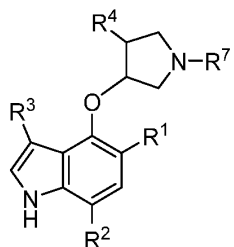
(I-E)



(I-F)



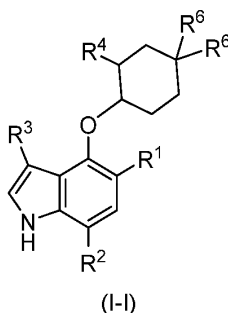
(I-G)



(I-H)

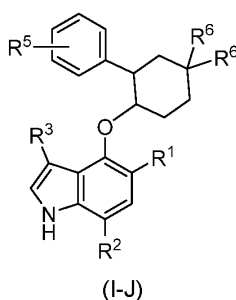
or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

6. The compound of any of claims 1 to 4, wherein the compound of Formula (I) is a compound of Formula (I-I):



or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

7. The compound of any of claims 1 to 4 and 6, wherein the compound of Formula (I) is a compound of Formula (I-J):



or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

- 5 8. The compound of any of claims 1 to 7, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R is hydrogen.
9. The compound of any of claims 1 to 8, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R¹ is hydrogen, halogen, C₁-C₆alkyl, C₃-C₆cycloalkyl, or haloC₁-C₆alkyl.
- 10 10. The compound of any of claims 1 to 9, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R² is C₁-C₃alkyl, or halogen.
11. The compound of any of claims 1 to 10, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R³ is hydrogen.

12. The compound of any of claims 1 to 11, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R⁴ is phenyl, pyridinyl, or pyrazolyl, wherein the phenyl, pyridinyl, or pyrazolyl is unsubstituted or substituted with R⁵.

13. The compound of any of the claims 1 to 12, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R⁵ is selected from hydrogen, -CO₂H, C₁-C₆alkyl, hydroxyC₃-C₆cycloalkyl, hydroxyC₃-C₆alkyl, cyano, -CONH₂, pyrazolyl, triazolyl, and tetrazolyl, wherein the pyrazolyl, triazolyl, and tetrazolyl are unsubstituted or substituted with 1 C₁-C₆alkyl.

14. The compound of any of the claims 1 to 13, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein

each R⁶ is independently selected from hydrogen, halogen, hydroxy, C₃-C₆cycloalkylC₁-C₄alkylamino, haloC₃-C₆cycloalkylC₁-C₄alkylamino, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkoxy, haloC₁-C₆alkoxy, C₃-C₆cycloalkylC₁-C₄alkylamino, haloC₃-C₆cycloalkylC₁-C₄alkylamino, and 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, and wherein the C₁-C₆alkyl is unsubstituted or substituted with 4- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from N and O, wherein each 4- to 6-membered heterocyclyl is independently unsubstituted or substituted with 1, 2, or 3 halogen; or

two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic carbocycle having 3 to 4 ring atoms, wherein the spirocyclic carbocycle is unsubstituted or substituted with 1 or 2 substituents selected from halogen; or

two R⁶ in combination with the carbon atom to which they are attached form a spirocyclic heterocycle having 1 ring heteroatom selected from O, wherein the spirocyclic heterocycle has 5 ring atoms.

15. The compound of any of the claims 1 to 14, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R⁷ is C₁-C₆alkyl, haloC₁-C₆alkyl, hydroxyC₂-C₆alkyl, haloC₃-C₆cycloalkylC₁-C₃alkyl, haloC₃-C₆cycloalkyl, haloC₁-C₆alkoxyC₁-C₆alkyl, -COC₁-C₆alkyl, 4- to 6-membered heterocyclyl having 1 heteroatoms selected from O, or 5-membered heteroaryl having 1 heteroatom selected from O.

16. The compound of any of the claims 1 to 15, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein R⁹ is H.

17. The compound of any of the claims 1 to 16, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, wherein

p is 0;

m is 1, or 2; and

n is 1, 2, or 3.

18. The compound of claim 1, selected from the group consisting of:

- 4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid;
4-(4-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid;
4-(4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid;
5 4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)piperidin-3-yl)benzoic acid;
4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-ethylpiperidin-3-yl)benzoic acid;
4-(5-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-1-methylazepan-4-yl)benzoic acid;
4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylazepan-3-yl)benzoic acid;
5,7-dimethyl-4-((4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)oxy)-1*H*-indole;
10 4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzonitrile;
4-((3-(4-(1*H*-tetrazol-5-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
2-(4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)phenyl)propan-2-ol;
4-((3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
5,7-dimethyl-4-((1-methyl-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-1*H*-indole;
15 4-(1-(2,2-difluoroethyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid;
4-(1-(3,3-difluoropropyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid;
4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(3,3,3-trifluoropropyl)piperidin-3-yl)benzoic acid;
4-(1-(3,3-difluorocyclobutyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic
acid;
20 4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(3-fluorocyclobutyl)piperidin-3-yl)benzoic acid;
4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(tetrahydrofuran-3-yl)piperidin-3-yl)benzoic acid;
4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2-hydroxy-2-methylpropyl)piperidin-3-yl)benzoic
acid;
4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2-(trifluoromethoxy)ethyl)piperidin-3-yl)benzoic
25 acid;
4-(4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-(2,2-difluoroethyl)piperidin-3-yl)benzoic
acid;
4-(4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)piperidin-3-yl)benzoic
acid;
30 4-(1-(2,2-difluoroethyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)azepan-3-yl)benzoic acid;
4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)azepan-3-yl)benzoic acid;
4-((3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-(2-fluoroethyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-
indole;
4-((3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-(2,2-difluoroethyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-
35 indole;

- 1-(3-(4-(1*H*-pyrazol-1-yl)phenyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-1-yl)ethan-1-one;
- 4-((3-(6-(1*H*-pyrazol-1-yl)pyridin-3-yl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
- 4-((3-(4-(1*H*-1,2,3-triazol-1-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
- 5 1-(4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)phenyl)cyclopropan-1-ol;
- 4-((1-(2-fluoroethyl)-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
- 4-(4-((5-fluoro-7-methyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)piperidin-3-yl)benzoic acid;
- 10 4-(4-((7-chloro-5-methyl-1*H*-indol-4-yl)oxy)-1-(2,2-difluoroethyl)piperidin-3-yl)benzoic acid;
- 4-(1-((2,2-difluorocyclopropyl)methyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid;
- 4-(1-(4,4-difluorobutyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid;
- 15 4-(4-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-1-(2,2-difluoroethyl)piperidin-3-yl)benzoic acid;
- 4-((3*R*,4*R*)-4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-(3,3-difluoropropyl)piperidin-3-yl)benzoic acid;
- 4-(4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-(3,3,3-trifluoropropyl)piperidin-3-yl)benzoic acid;
- 20 acid;
- 4-((1-(3,3-difluoropropyl)-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
- 4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)benzoic acid;
- 4-(4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpyrrolidin-3-yl)benzoic acid;
- 25 4-(4-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-1-methylazepan-3-yl)benzoic acid;
- 4-(4-((5-methoxy-7-methyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid;
- 4-(2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 4-(8-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-oxaspiro[4.5]decan-7-yl)benzoic acid;
- 4-(2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 30 4-(2-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 4-(2-((5-fluoro-7-methyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 4-(5-methoxy-2-((7-methyl-1*H*-indol-4-yl)oxy)cyclohexyl)benzoic acid;
- 4-(2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)cyclohexyl)benzoic acid;
- 4-(2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5,5-difluorocyclohexyl)benzoic acid;
- 35 4-(2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-hydroxycyclohexyl)benzoic acid;
- 4-(2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-(difluoromethoxy)cyclohexyl)benzoic acid;
- acid;
- 4-(2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methylcyclohexyl)benzoic acid;

- 4-(6-((5,7-dimethyl-1*H*-indol-4-yl)oxy)spiro[2.5]octan-5-yl)benzoic acid;
 4-(2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzamide;
 4-(2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5,5-difluorocyclohexyl)benzoic acid;
 4-(2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-(difluoromethoxy)-5-methylcyclohexyl)benzoic acid;
 4-(5-(difluoromethoxy)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methylcyclohexyl)benzoic acid; and
 4-(7-((5,7-dimethyl-1*H*-indol-4-yl)oxy)spiro[3.5]nonan-6-yl)benzoic acid,
 or a pharmaceutically acceptable salt or a stereoisomer thereof.
19. The compound of claim 1, selected from the group consisting of:
 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid;
 4-((3*S*,4*S*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid;
 4-((3*R*,4*S*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid;
 4-((3*S*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid;
 4-((3*R*,4*R*)-4-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid;
 4-((3*R*,4*R*)-4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic acid;
 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)piperidin-3-yl)benzoic acid;
 4-((3*S*,4*S*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)piperidin-3-yl)benzoic acid ;
 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-ethylpiperidin-3-yl)benzoic acid;
 4-((4*S*,5*R*)-5-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-1-methylazepan-4-yl)benzoic acid;
 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylazepan-3-yl)benzoic acid;
racemic 5,7-dimethyl-4-(((3*S**,4*R**)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)oxy)-1*H*-indole;
 5,7-dimethyl-4-(((3*S*,4*R*)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)oxy)-1*H*-indole;
 5,7-dimethyl-4-(((3*R*,4*S*)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)oxy)-1*H*-indole;
 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoxazole;
 4-(((3*R*,4*R*)-3-(4-(1*H*-tetrazol-5-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
 2-(4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-methylpiperidin-3-yl)phenyl)propan-2-ol;
 4-(((3*R*,4*R*)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
 5,7-dimethyl-4-(((3*R*,4*R*)-1-methyl-3-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-yl)oxy)-1*H*-indole;

- 4-((3*R*,4*R*)-1-(2,2-difluoroethyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid;
- 4-((3*R*,4*R*)-1-(3,3-difluoropropyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid;
- 5 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(3,3,3-trifluoropropyl)piperidin-3-yl)benzoic acid;
- 4-((3*R*,4*R*)-1-(3,3-difluorocyclobutyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-3-yl)benzoic acid;
- 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-((1*r*,3*R*)-3-fluorocyclobutyl)piperidin-3-yl)benzoic acid;
- 10 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(tetrahydrofuran-3-yl)piperidin-3-yl)benzoic acid;
- 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2-hydroxy-2-methylpropyl)piperidin-3-yl)benzoic acid;
- 15 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2-(trifluoromethoxy)ethyl)piperidin-3-yl)benzoic acid;
- 4-((3*R*,4*R*)-4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-(2,2-difluoroethyl)piperidin-3-yl)benzoic acid;
- 4-((3*R*,4*R*)-4-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)piperidin-3-yl)benzoic acid;
- 20 4-((3*R*,4*R*)-1-(2,2-difluoroethyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)azepan-3-yl)benzoic acid;
- 4-((3*R*,4*R*)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)azepan-3-yl)benzoic acid;
- 25 4-(((3*R*,4*R*)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-(2-fluoroethyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
- 4-(((3*R*,4*R*)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-1-(2,2-difluoroethyl)piperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
- racemic* 1-((3*R**,4*R**)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-1-yl)ethan-1-one;
- 30 1-((3*R*,4*R*)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-1-yl)ethan-1-one;
- 1-((3*S*,4*S*)-3-(4-(1*H*-pyrazol-1-yl)phenyl)-4-((5,7-dimethyl-1*H*-indol-4-yl)oxy)piperidin-1-yl)ethan-1-one;
- 35 *racemic* 4-(((3*R**,4*R**)-3-(6-(1*H*-pyrazol-1-yl)pyridin-3-yl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;
- 4-(((3*R*,4*R*)-3-(6-(1*H*-pyrazol-1-yl)pyridin-3-yl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1*H*-indole;

- 4-(((3S,4S)-3-(6-(1H-pyrazol-1-yl)pyridin-3-yl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1H-indole;
racemic 4-(((3R*,4R*)-3-(4-(1H-1,2,3-triazol-1-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1H-indole;
5 4-(((3R,4R)-3-(4-(1H-1,2,3-triazol-1-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1H-indole;
4-(((3S,4S)-3-(4-(1H-1,2,3-triazol-1-yl)phenyl)-1-methylpiperidin-4-yl)oxy)-5,7-dimethyl-1H-indole;
1-((3R,4R)-4-((5,7-dimethyl-1H-indol-4-yl)oxy)-1-methylpiperidin-3-yl)phenyl)cyclopropan-1-ol;
10 4-(((3R,4R)-1-(2-fluoroethyl)-3-(1-methyl-1H-pyrazol-4-yl)piperidin-4-yl)oxy)-5,7-dimethyl-1H-indole;
4-((3R,4R)-4-((5-fluoro-7-methyl-1H-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)piperidin-3-yl)benzoic acid;
15 4-((3R,4R)-4-((7-chloro-5-methyl-1H-indol-4-yl)oxy)-1-(2,2-difluoroethyl)piperidin-3-yl)benzoic acid;
4-((3R,4R)-1-((2,2-difluorocyclopropyl)methyl)-4-((5,7-dimethyl-1H-indol-4-yl)oxy)piperidin-3-yl)benzoic acid;
4-((3R,4R)-1-(4,4-difluorobutyl)-4-((5,7-dimethyl-1H-indol-4-yl)oxy)piperidin-3-yl)benzoic
20 acid;
4-((3R,4R)-4-((5-cyclopropyl-7-methyl-1H-indol-4-yl)oxy)-1-(2,2-difluoroethyl)piperidin-3-yl)benzoic acid;
4-((3R,4R)-4-((5-chloro-7-methyl-1H-indol-4-yl)oxy)-1-(3,3-difluoropropyl)piperidin-3-yl)benzoic acid;
25 4-((3R,4R)-4-((5-chloro-7-methyl-1H-indol-4-yl)oxy)-1-(3,3,3-trifluoropropyl)piperidin-3-yl)benzoic acid;
4-(((3R,4R)-1-(3,3-difluoropropyl)-3-(1-methyl-1H-pyrazol-4-yl)piperidin-4-yl)oxy)-5,7-dimethyl-1H-indole;
4-((3R,4S)-4-((5,7-dimethyl-1H-indol-4-yl)oxy)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)benzoic acid;
30 4-((3R,4S)-4-((5,7-dimethyl-1H-indol-4-yl)oxy)-1-methylpyrrolidin-3-yl)benzoic acid;
4-((3R,4R)-4-((5-cyclopropyl-7-methyl-1H-indol-4-yl)oxy)-1-methylazepan-3-yl)benzoic acid;
4-((3R,4R)-4-((5-methoxy-7-methyl-1H-indol-4-yl)oxy)-1-methylpiperidin-3-yl)benzoic
35 acid;
4-((1S,2R,5S)-2-((5,7-dimethyl-1H-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
4-((1R,2S,5R)-2-((5,7-dimethyl-1H-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;

- racemic* 4-((1*S**,2*R**,5*R**)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 4-((1*S*,2*R*,5*R*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 4-((1*R*,2*S*,5*S*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 5 *racemic* 4-((1*S**,2*S**,5*S**)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 4-((1*S*,2*S*,5*S*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 4-((1*R*,2*R*,5*R*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- racemic* 4-((1*S**,2*S**,5*R**)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 10 4-((1*S*,2*S*,5*R*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 4-((1*R*,2*R*,5*S*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- racemic* 4-((7*S**,8*R**)-8-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-oxaspiro[4.5]decan-7-yl)benzoic acid;
- 15 4-((5*R*,7*S*,8*R*)-8-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-oxaspiro[4.5]decan-7-yl)benzoic acid;
- 4-((5*S*,7*S*,8*R*)-8-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-1-oxaspiro[4.5]decan-7-yl)benzoic acid;
- 4-((1*S*,2*R*,5*S*)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 20 4-((1*S*,2*R*,5*S*)-2-((5-chloro-7-methyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 4-((1*S*,2*R*,5*S*)-2-((5-fluoro-7-methyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzoic acid;
- 25 4-((1*S*,2*R*,5*S*)-5-methoxy-2-((7-methyl-1*H*-indol-4-yl)oxy)cyclohexyl)benzoic acid;
- racemic* 4-((1*S**,2*R**)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)cyclohexyl)benzoic acid;
- 4-((1*S*,2*R*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)cyclohexyl)benzoic acid;
- 4-((1*R*,2*S*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)cyclohexyl)benzoic acid;
- 4-((1*S*,2*R*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5,5-difluorocyclohexyl)benzoic acid;
- 30 4-((1*S*,2*R*,5*S*)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-hydroxycyclohexyl)benzoic acid;
- 4-((1*S*,2*R*,5*S*)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-(difluoromethoxy)cyclohexyl)benzoic acid;
- 4-((1*S*,2*R*,5*R*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methylcyclohexyl)benzoic acid;
- 35 4-((1*S*,2*R*,5*S*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methylcyclohexyl)benzoic acid;
- 4-((5*S*,6*R*)-6-((5,7-dimethyl-1*H*-indol-4-yl)oxy)spiro[2.5]octan-5-yl)benzoic acid;
- 4-((1*S*,2*R*,5*S*)-2-((5,7-dimethyl-1*H*-indol-4-yl)oxy)-5-methoxycyclohexyl)benzamide;

- 4-((1*S*,2*R*)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5,5-difluorocyclohexyl)benzoic acid;
- racemic* 4-((1*S*^{*},2*R*^{*},5*S*^{*})-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-(difluoromethoxy)-5-methylcyclohexyl)benzoic acid;
- 5 4-((1*S*,2*R*,5*S*)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-(difluoromethoxy)-5-methylcyclohexyl)benzoic acid;
- 4-((1*S*,2*R*,5*R*)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-(difluoromethoxy)-5-methylcyclohexyl)benzoic acid;
- racemic* 4-((1*S*^{*},2*R*^{*},5*S*^{*})-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-(difluoromethoxy)-5-methylcyclohexyl)benzoic acid;
- 10 (difluoromethoxy)-5-methylcyclohexyl)benzoic acid;
- 4-((1*S*,2*R*,5*S*)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-(difluoromethoxy)-5-methylcyclohexyl)benzoic acid;
- 4-((1*S*,2*R*,5*S*)-2-((5-cyclopropyl-7-methyl-1*H*-indol-4-yl)oxy)-5-(difluoromethoxy)-5-methylcyclohexyl)benzoic acid;
- 15 4-((6*S*,7*R*)-7-((5,7-dimethyl-1*H*-indol-4-yl)oxy)spiro[3.5]nonan-6-yl)benzoic acid,
or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof.

20. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 19, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, and a pharmaceutically acceptable carrier or excipient.

21. A method of treating or preventing a disease or disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 19, or a pharmaceutically acceptable salt or a stereoisomer or an isotopically labeled compound thereof, or the pharmaceutical composition of claim 20.

22. The method of claim 21, wherein the diseases or disorders is selected from age-related macular degeneration, geographic atrophy, diabetic retinopathy, uveitis, retinitis pigmentosa, macular edema, Behcet's uveitis, multifocal choroiditis, Vogt-Koyangi-Harada syndrome, intermediate uveitis, birdshot retino-choroiditis, sympathetic ophthalmia, ocular cicatricial pemphigoid, ocular pemphigus, nonarteritic ischemic optic neuropathy, post-operative inflammation, retinal vein occlusion, glaucoma, Doyne honeycomb retinal dystrophy/Malattia leventinese, Sorsby fundus dystrophy, Late onset retinal macular dystrophy, North carolina macular dystrophy, Stargardt disease, corneal inflammation, neurological disorders such as multiple sclerosis including primary progressive multiple sclerosis (PPMS), secondary progressive multiple sclerosis (SPMS) and relapsing remitting multiple sclerosis (RRMS), stroke,

Guillain Barré Syndrome, spinal cord injury, traumatic brain injury, Parkinson's disease, Alzheimer's disease, schizophrenia, amyotrophic lateral sclerosis (ALS), Huntington's disease, multifocal motor neuropathy, autism spectrum disorders, schizophrenia, drug-induced neurotoxicity, Aquaporin-4 IgG seropositive neuromyelitis optica spectrum disorder (NMOSD), cerebral amyloid angiopathy, cerebral malaria, Charcot-Marie-Tooth disease, chemotherapy-induced peripheral neuropathy, chronic inflammatory demyelinating polyneuropathy, frontotemporal dementia, genetic demyelinating neuropathy due to CD59 p.Cys89Tyr mutation, Lewy bodies dementia, multiple system atrophy (MSA), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), opsoclonus myoclonus syndrome (OMS), progressive supranuclear palsy; disorders of inappropriate or undesirable complement activation such as hemodialysis complications, hyperacute allograft rejection, xenograft rejection, interleukin-2 induced toxicity during IL-2 therapy, inflammatory disorders, paroxysmal nocturnal hemoglobinuria, C3 glomerulonephritis (including dense deposit disease and C3 glomerulonephritis), immune complex membranoproliferative glomerulonephritis (IC-MPGN), IgA nephropathy, membranous nephropathy including idiopathic membranous nephropathy, diabetic nephropathy, atypical hemolytic uremic syndrome (aHUS), Hemolytic uremic syndrome, STEC-HUS (Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome), peridontitis, CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, protein-losing enteropathy (CHAPLE syndrome), inflammation or autoimmune diseases such as Crohn's disease, neuromyelitis optica (NMO), IgA vasculitis (formerly known as Henoch-Schönlein purpura or HSP), CHAPLE syndrome, hematopoietic stem cell transplantation-associated thrombotic microangiopathy (HSCT-TMA), adult respiratory distress syndrome (ARDS), myocarditis, post-ischemic reperfusion conditions, myocardial infarction, balloon angioplasty, post-pump syndrome in cardiopulmonary bypass or renal bypass, atherosclerosis, hemodialysis, renal ischemia, acute kidney injury mesenteric artery reperfusion after aortic reconstruction, infectious disease or sepsis; COVID-19, immune complex disorders and autoimmune diseases, rheumatoid arthritis, osteoarthritis, Spondyloarthropathies, psoriatic arthritis, systemic lupus erythematosus (SLE), lupus nephritis, SLE nephritis, proliferative nephritis, myasthenia gravis, liver fibrosis, hemolytic anemia, tissue regeneration, neural regeneration, dyspnea, hemoptysis, acute respiratory distress syndrome (ARDS), asthma, chronic obstructive pulmonary disease (COPD), emphysema, pulmonary embolisms and infarcts, pneumonia, fibrogenic dust diseases, pulmonary fibrosis, asthma, allergy, bronchoconstriction, hypersensitivity pneumonitis, parasitic diseases, Goodpasture's Syndrome, pulmonary vasculitis, Pauci-immune vasculitis, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV), Buerger's vasculitis, cryoglobulinemia, Kawasaki disease, Takayasu arteritis, cryoglobulinemia, immune complex-associated inflammation, antiphospholipid syndrome, glomerulonephritis and obesity; immune thrombocytopenia, Cold agglutinin disease, Warm autoimmune hemolytic anemia (wAIHA), thrombotic thrombocytopenic purpura (TTP), abdominal aortic aneurisms, and Grave's disease.

