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(54) Title: FUSED PYRROLIDINE PSYCHOPLASTOGENS AND USES THEREOF

(57) Abstract: Disclosed herein are compounds, compositions, and methods for promoting neuronal growth and/or improving neuronal structure with the compounds and compositions disclosed herein. Also described are methods of treating diseases or disorders that are mediated by the loss of synaptic connectivity and/or plasticity, such as neurological diseases and disorders, with fused pyrrolidine psychoplastogens.

FUSED PYRROLIDINE PSYCHOPLASTOGENS AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Serial No. 63/387,225, filed on December 13, 2022, and U.S. Provisional Application Serial No. 63/290,037, filed on December 15, 2021, each of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

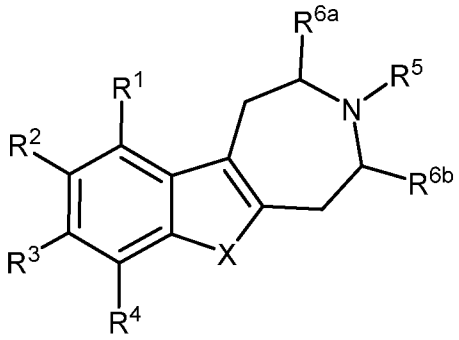
[0002] Described herein are compounds, methods of making such compounds, pharmaceutical compositions and medicaments comprising such compounds, and methods of using such compounds for the treatment of conditions, diseases, or disorders that would benefit from promoting neuronal growth and/or improving neuronal structure.

BACKGROUND OF THE INVENTION

[0003] Altered synaptic connectivity and plasticity has been observed in the brains of individuals with neurological diseases and disorders. Psychoplastogens promote neuronal growth and improve neuronal architecture through mechanisms involving the activation of AMPA receptors, the tropomyosin receptor kinase B (TrkB), and the mammalian target of rapamycin (mTOR). Modulators of these biological targets, such as, for example, ketamine, scopolamine, N,N-dimethyltryptamine (DMT), and rapastinel have demonstrated psychoplastogenic properties. For example, ketamine is capable of rectifying deleterious changes in neuronal structure that are associated with neurological diseases and disorders. Such structural alterations include, for example, the loss of dendritic spines and synapses in the prefrontal cortex (PFC) as well as reductions in dendritic arbor complexity. Furthermore, pyramidal neurons in the PFC exhibit top-down control over areas of the brain controlling motivation, fear, and reward. Psychedelic psychoplastogens have demonstrated antidepressant, anxiolytic, and anti-addictive effects of in the clinic.

SUMMARY OF THE INVENTION

[0004] In some embodiments, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I)

wherein:

- X is NR^7, O or $S(=O)_x$;
- x is 0, 1, or 2;
- each of R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, $-OR^a$, cyano, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

  or any of R^1 and R^2, R^2 and R^3, or R^3 and R^4 are taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring;
- R^5 is hydrogen, halogen, $-OR^a$, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- each R^{6a} and R^{6b} is independently hydrogen, halogen, $-OR^a$, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

  or R^5 is taken together with R^{6a} or R^{6b} and the atoms to which they are attached to form an optionally substituted heterocyclic ring;

  or R^{6a} and R^{6b} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring;
- R^7 is hydrogen, alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted; and
- R^a is hydrogen, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

wherein

(i) R^5 and R^{6a} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring;

(ii) R^5 and R^{6b} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring; or

(iii) R^{6a} and R^{6b} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring; and

provided that when X is NH, R^{6a} is hydrogen, and each of R^1, R^2, R^3 and R^4 is hydrogen, then R^5 and R^{6b} are not taken together with the atoms to which they are attached to form a 6-membered heterocyclic ring substituted by ethyl or ethylidene.

[0005] In one embodiment, provided herein is a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0006] In some embodiments, the compounds disclosed herein, or a pharmaceutically acceptable salt thereof, are formulated for administration to a mammal by intravenous administration, subcutaneous administration, oral administration, inhalation, nasal administration, dermal administration, or ophthalmic administration. In some embodiments, the compound disclosed herein, or a pharmaceutically acceptable salt thereof, is in the form of a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion.

[0007] In one embodiment, described herein is a method of promoting neuronal growth in a mammal comprising administering to the mammal a compound described herein, or any pharmaceutically acceptable salt or solvate thereof.

[0008] In another embodiment, described herein is a method of improving neuronal structure comprising administering to the mammal a compound provided herein, or a pharmaceutically acceptable salt or solvate thereof.

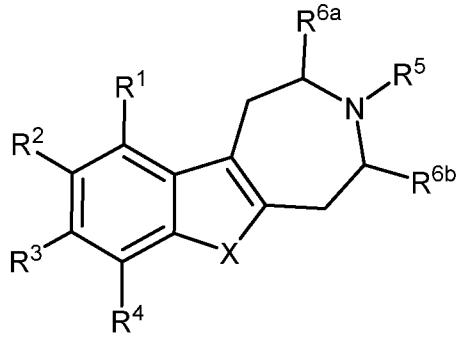
[0009] In another embodiment, described herein is a method of method of modulating the activity of 5-hydroxytryptamine receptor 2A (5-HT_{2A}) receptor in a mammal comprising administering to the mammal a compound provided herein, or any pharmaceutically acceptable salt or solvate thereof.

[0010] In another embodiment, described herein is a method of treating a disease or disorder in a mammal that is mediated by the action of 5-hydroxytryptamine (5-HT) at 5-hydroxytryptamine receptor 2A (5-HT_{2A}) comprising administering to the mammal a compound provided herein, or any pharmaceutically acceptable salt or solvate thereof.

[0011] In another embodiment, described herein is a method of treating a disease or disorder in a mammal that is mediated by the loss of synaptic connectivity, plasticity, or a combination thereof

comprising administering to the mammal a compound provided herein, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the disease or disorder is neurological disease or disorder.

[0012] In another embodiment, described herein is a method for treating neurological disease or disorder in a mammal, the method comprising administering to the mammal a compound represented by the structure of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I)

wherein:

- X is NR^7, O or $S(=O)_x$;
- x is 0, 1, or 2;
- each of R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, $-OR^a$, cyano, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

  or any of R^1 and R^2, R^2 and R^3, or R^3 and R^4 are taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring;
- R^5 is hydrogen, halogen, $-OR^a$, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- each R^{6a} and R^{6b} is independently hydrogen, halogen, $-OR^a$, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

  or R^5 is taken together with R^{6a} or R^{6b} and the atoms to which they are attached to form an optionally substituted heterocyclic ring;

  or R^{6a} and R^{6b} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring;

- R^7 is hydrogen, alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted; and
- R^a is hydrogen, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

wherein

(i) R^5 and R^{6a} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring;

(ii) R^5 and R^{6b} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring; or

(iii) R^{6a} and R^{6b} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring; and

[0013] provided that when X is NH, R^{6a} is hydrogen, and each of R^1, R^2, R^3 and R^4 is hydrogen, then R^5 and R^{6b} are not taken together with the atoms to which they are attached to form a 6-membered heterocyclic ring substituted by ethyl or ethylidene.In some embodiments, the neurological disease or disorder is a neurodegenerative, a neuropsychiatric, or a substance use disease or disorder.

[0014] In some embodiments, the neurological disease or disorder is an injury.

[0015] In some embodiments, the neurological disease or disorder is selected from the group consisting of an anxiety disorder, a mood disorder, a psychotic disorder, a personality disorder, an eating disorder, a sleep disorder, a sexuality disorder, an impulse control disorder, a substance use disorder, a dissociative disorder, a cognitive disorder, a developmental disorder, and a factitious disorder.

[0016] In some embodiments, the mammal is a human.

[0017] In any of the aforementioned aspects are further embodiments in which an effective amount of the compound described herein, or a pharmaceutically acceptable salt thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by injection to the mammal.

[0018] In any of the aforementioned aspects are further embodiments comprising single administrations of an effective amount of the compound, including further embodiments in which the compound is administered once a day to the mammal or the compound is administered to the mammal multiple times over the span of one day. In some embodiments, the compound is administered on a continuous dosing schedule. In some embodiments, the compound is administered on a continuous daily dosing schedule.

[0019] Articles of manufacture, which include packaging material, a formulation within the packaging material (e.g. a formulation suitable for topical administration), and a label that indicates that the compound or composition, or pharmaceutically acceptable salt, or solvate thereof, is used for promoting neuronal growth and/or improving neuronal structure, or for the treatment, prevention or amelioration of one or more symptoms of a disease or disorder that is associated with promoting neuronal growth and/or improving neuronal structure, are provided.

[0020] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

[0021] The present disclosure provides non-hallucinogenic compounds useful for the treatment of a variety of neurological diseases and disorders as well as increasing neuronal plasticity.

[0022] Psychedelic compounds promote structural and functional neural plasticity in key circuits, elicit therapeutic responses in multiple neuropsychiatric disorders, and produce beneficial neurological effects that can last for months following a single administration. Compounds capable of modifying neural circuits that control motivation, anxiety, and drug-seeking behavior have potential for treating neurological diseases and disorders that are mediated by the loss of synaptic connectivity and/or plasticity. Moreover, such compounds are likely to produce sustained therapeutic effects because, for example, of the potential to treat the underlying pathological changes in circuitry.

[0023] In some embodiments, 5-HT_{2A} antagonists abrogate the neuritogenesis and spinogenesis effects of hallucinogenic compounds with 5-HT_{2A} agonist activity, e.g., DMT, LSD, and DOI, demonstrating the correlation of 5-HT_{2A} agonism and the promotion of neural plasticity (Ly et al., 2018; Dunlap et al., 2020). However, the hallucinogenic and dissociative potential of such compounds has limited the use of these compounds in the clinic for neurological diseases, such as, for example, neuropsychiatric diseases. (Ly et al., 2018)

[0024] In addition, non-hallucinogenic analogs of psychedelic compounds, such as, for example, lisuride and sumatriptan, have been examined as treatments for various neurological diseases and disorders, such as, but not limited to, neurodegenerative diseases (e.g., Alzheimer's disease and Parkinson's disease) and headaches (e.g., migraines).

Certain Terminology

[0025] Unless otherwise stated, the following terms used in this application have the definitions given below. It must be noted that, as used in the specification and the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. In this application, the use of "or" means "and/or" unless stated otherwise. The use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0026] As used herein, C_1-C_x includes C_1-C_2, C_1-C_3 . . . C_1-C_x. By way of example only, a group designated as "C_1-C_4" indicates that there are one to four carbon atoms in the moiety, i.e. groups containing 1 carbon atom, 2 carbon atoms, 3 carbon atoms or 4 carbon atoms. Thus, by way of example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl group, *i.e.*, the alkyl group is selected from among methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, and *t*-butyl.

[0027] "Alkyl" generally refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, such as having from one to fifteen carbon atoms (*e.g.*, C_1-C_{15} alkyl). Unless otherwise state, alkyl is saturated or unsaturated (e.g., an alkenyl, which comprises at least one carbon-carbon double bond). Disclosures provided herein of an "alkyl" are intended to include independent recitations of a saturated "alkyl," unless otherwise stated. Alkyl groups described herein are generally monovalent, but may also be divalent (which may also be described herein as "alkylene" or "alkylenyl" groups). In certain embodiments, an alkyl comprises one to thirteen carbon atoms (*e.g.*, C_1-C_{13} alkyl). In certain embodiments, an alkyl comprises one to eight carbon atoms (*e.g.*, C_1-C_8 alkyl). In other embodiments, an alkyl comprises one to five carbon atoms (*e.g.*, C_1-C_5 alkyl). In other embodiments, an alkyl comprises one to four carbon atoms (*e.g.*, C_1-C_4 alkyl). In other embodiments, an alkyl comprises one to three carbon atoms (*e.g.*, C_1-C_3 alkyl). In other embodiments, an alkyl comprises one to two carbon atoms (*e.g.*, C_1-C_2 alkyl). In other embodiments, an alkyl comprises one carbon atom (*e.g.*, C_1 alkyl). In other embodiments, an alkyl comprises five to fifteen carbon atoms (*e.g.*, C_5-C_{15} alkyl). In other embodiments, an alkyl comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkyl). In other embodiments, an alkyl comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkyl). In other embodiments, an alkyl comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkyl). In other embodiments, the alkyl group is selected from methyl, ethyl, 1-propyl (*n*-propyl), 1-methylethyl (*iso*-propyl), 1-butyl (*n*-butyl), 1-methylpropyl (*sec*-butyl), 2-methylpropyl (*iso*-butyl), 1,1-dimethylethyl (*tert*-butyl), 1-pentyl (*n*-pentyl). The alkyl is attached to the rest of the molecule by a single bond. In general, alkyl groups are each independently substituted or unsubstituted. Each recitation of "alkyl" provided herein, unless

otherwise stated, includes a specific and explicit recitation of an unsaturated "alkyl" group. Similarly, unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^x$, $-SR^x$, $-OC(O)-R^x$, $-N(R^x)_2$, $-C(O)R^x$, $-C(O)OR^x$, $-C(O)N(R^x)_2$, $-N(R^x)C(O)OR^x$, $-OC(O)-N(R^x)_2$, $-N(R^x)C(O)R^x$, $-N(R^x)S(O)_tR^x$ (where t is 1 or 2), $-S(O)_tOR^x$ (where t is 1 or 2), $-S(O)_tR^x$ (where t is 1 or 2) and $-S(O)_tN(R^x)_2$ (where t is 1 or 2) where each R^x is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, carbocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), carbocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl). In some embodiments, an alkyl group is substituted with one or more fluorine.

[0028] An "alkylene" group refers to a divalent alkyl radical. Any of the above mentioned monovalent alkyl groups may be an alkylene by abstraction of a second hydrogen atom from the alkyl. In some embodiments, an alkelene is a C_1-C_6alkylene. In other embodiments, an alkylene is a C_1-C_4alkylene. Typical alkylene groups include, but are not limited to, $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH_2CH_2-$, $-CH_2CH(CH_3)-$, $-CH_2C(CH_3)_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, and the like. Unless stated otherwise specifically in the specification, an alkylene chain is optionally substituted as described for alkyl groups herein.

[0029] The term "alkenyl" refers to a type of alkyl group in which at least one carbon-carbon double bond is present. In one embodiment, an alkenyl group has the formula $-C(R)=CR_2$, wherein R refers to the remaining portions of the alkenyl group, which may be the same or different. In some embodiments, R is H or an alkyl. Non-limiting examples of an alkenyl group include $-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CHCH_3$, $-C(CH_3)=CHCH_3$, and $-CH_2CH=CH_2$.

[0030] The term "alkynyl" refers to a type of alkyl group in which at least one carbon-carbon triple bond is present. In one embodiment, an alkenyl group has the formula $-C\equiv C-R$, wherein R refers to the remaining portions of the alkynyl group. In some embodiments, R is H or an alkyl. Non-limiting examples of an alkynyl group include $-C\equiv CH$, $-C\equiv CCH_3$ $-C\equiv CCH_2CH_3$, $-CH_2C\equiv CH$.

[0031] An "alkoxy" group refers to a (alkyl)O- group, where alkyl is as defined herein.

[0032] The term "alkylamine" refers to -NH(alkyl), or -N(alkyl)$_2$.

[0033] The term "aromatic" refers to a planar ring having a delocalized π-electron system containing 4n+2 π electrons, where n is an integer. The term "aromatic" includes both carbocyclic aryl ("aryl", *e.g.*, phenyl) and heterocyclic aryl (or "heteroaryl" or "heteroaromatic") groups (*e.g.*, pyridine). The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of carbon atoms) groups.

[0034] The term "carbocyclic" or "carbocycle" refers to a ring or ring system where the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from "heterocyclic" rings or "heterocycles" in which the ring backbone contains at least one atom which is different from carbon. In some embodiments, at least one of the two rings of a bicyclic carbocycle is aromatic. In some embodiments, both rings of a bicyclic carbocycle are aromatic. In certain embodiments, a carbocyclyl comprises three to ten carbon atoms. In other embodiments, a carbocyclyl comprises five to seven carbon atoms. The carbocyclyl is attached to the rest of the molecule by a single bond. Carbocyclyl or cycloalkyl is saturated (*i.e.*, containing single C-C bonds only) or unsaturated (*i.e.*, containing one or more double bonds or triple bonds). Examples of saturated cycloalkyls include, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. An unsaturated carbocyclyl is also referred to as "cycloalkenyl." Examples of monocyclic cycloalkenyls include, *e.g.*, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Polycyclic carbocyclyl radicals include, for example, adamantyl, norbornyl (*i.e.*, bicyclo[2.2.1]heptanyl), norbornenyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, the term "carbocyclyl" is meant to include carbocyclyl radicals that are optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, -R^y-OR^x, -R^y-OC(O)-R^x, -R^y-OC(O)-OR^x, -R^y-OC(O)-N(R^x)$_2$, -R^y-N(R^x)$_2$, -R^y-C(O)R^x, -R^y-C(O)OR^x, -R^y-C(O)N(R^x)$_2$, -R^y-O-R^z-C(O)N(R^x)$_2$, -R^y-N(R^x)C(O)OR^x, -R^y-N(R^x)C(O)R^x, -R^y-N(R^x)S(O)$_t$$R^x$ (where t is 1 or 2), -R^y-S(O)$_t$$R^x$ (where t is 1 or 2), -R^y-S(O)$_t$$OR^x$ (where t is 1 or 2) and -R^y-S(O)$_t$N(R^x)$_2$ (where t is 1 or 2), where each R^x is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, cycloalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), cycloalkylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl),

aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), each R^y is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^z is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0035] As used herein, the term "aryl" refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. The aromatic monocyclic or multicyclic hydrocarbon ring system contains only hydrogen and carbon from five to eighteen carbon atoms, where at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. The ring system from which aryl groups are derived include, but are not limited to, groups such as benzene, fluorene, indane, indene, tetralin and naphthalene. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^y-OR^x$, $-R^y-OC(O)-R^x$, $-R^y-OC(O)-OR^x$, $-R^y-OC(O)-N(R^x)_2$, $-R^y-N(R^x)_2$, $-R^y-C(O)R^x$, $-R^y-C(O)OR^x$, $-R^y-C(O)N(R^x)_2$, $-R^y-O-R^z-C(O)N(R^x)_2$, $-R^y-N(R^x)C(O)OR^x$, $-R^y-N(R^x)C(O)R^x$, $-R^y-N(R^x)S(O)_tR^x$ (where t is 1 or 2), $-R^y-S(O)_tR^x$ (where t is 1 or 2), $-R^y-S(O)_tOR^x$ (where t is 1 or 2) and $-R^y-S(O)_tN(R^x)_2$ (where t is 1 or 2), where each R^x is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, cycloalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), cycloalkylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), each R^y is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^z is a straight or branched alkylene

or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0036] "Aralkyl," "aryl-alkyl," or "arylalkyl" refers to a radical of the formula -R^z-aryl where R^z is an alkylene chain as defined above, for example, methylene, ethylene, and the like. The alkylene chain part of the aralkyl radical is optionally substituted as described above for an alkylene chain. The aryl part of the aralkyl radical is optionally substituted as described above for an aryl group.

[0037] The term "cycloalkyl" refers to a monocyclic or polycyclic aliphatic, non-aromatic radical, wherein each of the atoms forming the ring (i.e., skeletal atoms) is a carbon atom. In some embodiments, cycloalkyls are spirocyclic or bridged compounds. In some embodiments, cycloalkyls are optionally fused with an aromatic ring, and the point of attachment is at a carbon that is not an aromatic ring carbon atom. Cycloalkyl groups include groups having from 3 to 10 ring atoms. In some embodiments, cycloalkyl groups are selected from among cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, spiro[2.2]pentyl, norbornyl and bicycle[1.1.1]pentyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, cis-decalin, trans-decalin, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, and bicyclo[3.3.2]decane, adamantyl, norbornyl, and decalinyl. In some embodiments, a cycloalkyl is a C_3-C_6cycloalkyl.

[0038] The term "halo" or, alternatively, "halogen" or "halide" means fluoro, chloro, bromo or iodo. In some embodiments, halo is fluoro, chloro, or bromo. In some embodiments, halo is fluoro or chloro.

[0039] The term "fluoroalkyl" refers to an alkyl in which one or more hydrogen atoms are replaced by a fluorine atom, such as, for example, trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. In some embodiments, the alkyl part of the fluoroalkyl radical is optionally substituted as defined above for an alkyl group. In one embodiment, a fluoralkyl is a C_1-C_6fluoroalkyl.

[0040] The term "heteroalkyl" refers to an alkyl group as defined above in which one or more skeletal carbon atoms of the alkyl are substituted with a heteroatom (with the appropriate number of substituents or valencies – for example, -CH_2- may be replaced with -NH-, -S-, or -O-). For example, each substituted carbon atom is independently substituted with a heteroatom, such as wherein the carbon is substituted with a nitrogen, oxygen, selenium, or other suitable heteroatom. In some embodiments, each substituted carbon atom is independently substituted for an oxygen, nitrogen (e.g. -NH-, -N(alkyl)-, or -N(aryl)- or having another substituent contemplated herein), or sulfur (e.g. -S-, -S(=O)-, or -S(=O)$_2$-). In some embodiments, a heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In some embodiments, a heteroalkyl is attached to

the rest of the molecule at a heteroatom of the heteroalkyl. In some embodiments, a heteroalkyl is a C_1-C_{18} heteroalkyl. In some embodiments, a heteroalkyl is a C_1-C_{12} heteroalkyl. In some embodiments, a heteroalkyl is a C_1-C_6 heteroalkyl. In some embodiments, a heteroalkyl is a C_1-C_4 heteroalkyl. In some embodiments, a heteralkyl is or includes one or more cyclic group(s). In some embodiments, heteroalkyl includes alkylamino, alkylaminoalkyl, aminoalkyl, heterocyclyl, heterocycloalkyl, heterocycloalkyl, and heterocycloalkylalkyl, as defined herein. Unless stated otherwise specifically in the specification, a heteroalkyl group is optionally substituted as defined above for an alkyl group. In one embodiment, a heteroalkyl is a C_1-C_6heteroalkyl.

[0041] "Heteroalkylene" refers to a divalent heteroalkyl group defined above which links one part of the molecule to another part of the molecule. Unless stated specifically otherwise, a heteroalkylene is optionally substituted, as defined above for an alkyl group.

[0042] The terms "heterocyclyl," "heterocycle," or "heterocyclic" generally refer to heteroaromatic rings (also known as heteroaryls) and heterocycloalkyl rings (also known as heteroalicyclic groups) containing one to four heteroatoms in the ring(s), where each heteroatom in the ring(s) is selected from O, S and N, wherein each heterocyclic group has from 3 to 10 atoms in its ring system, and with the proviso that any ring does not contain two adjacent O or S atoms. Unless stated otherwise specifically in the specification, the heterocyclyl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which optionally includes fused or bridged ring systems. The heteroatoms in the heterocyclyl radical are optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heterocyclyl radical is partially or fully saturated. The heterocyclyl radical is saturated (*i.e.*, containing single C-C bonds only) or unsaturated (e.g., containing one or more double bonds or triple bonds in the ring system). In some embodiments, the heterocyclyl radical is saturated. In some embodiments, the heterocyclyl radical is saturated and substituted. In some embodiments, the heterocyclyl radical is unsaturated. The heterocyclyl is attached to the rest of the molecule through any atom of the ring(s). Non-aromatic heterocyclic groups (also known as heterocycloalkyls) include rings having 3 to 10 atoms in its ring system and aromatic heterocyclic groups include rings having 5 to 10 atoms in its ring system. The heterocyclic groups include benzo-fused ring systems. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, pyrrolin-2-yl, pyrrolin-3-yl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl,

imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl, indolin-2-onyl, isoindolin-1-onyl, isoindoline-1,3-dionyl, 3,4-dihydroisoquinolin-1(2H)-onyl, 3,4-dihydroquinolin-2(1H)-onyl, isoindoline-1,3-dithionyl, benzo[d]oxazol-2(3H)-onyl, 1H-benzo[d]imidazol-2(3H)-onyl, benzo[d]thiazol-2(3H)-onyl, and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups are either C-attached (or C-linked) or *N*-attached where such is possible. For embodiment, a group derived from pyrrole includes both pyrrol-1-yl (*N*-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole includes imidazol-1-yl or imidazol-3-yl (both *N*-attached) or imidazol-2-yl, imidazol-4-yl or imidazol-5-yl (all C-attached). The heterocyclic groups include benzo-fused ring systems. Non-aromatic heterocycles are optionally substituted with one or two oxo (=O) moieties, such as pyrrolidin-2-one. In some embodiments, at least one of the two rings of a bicyclic heterocycle is aromatic. In some embodiments, both rings of a bicyclic heterocycle are aromatic. Unless stated otherwise specifically in the specification, the term "heterocyclyl" is meant to include heterocyclyl radicals as defined above that are optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^y-OR^x$, $-R^y-OC(O)-R^x$, $-R^y-OC(O)-OR^x$, $-R^y-OC(O)-N(R^x)_2$, $-R^y-N(R^x)_2$, $-R^y-C(O)R^x$, $-R^y-C(O)OR^x$, $-R^y-C(O)N(R^x)_2$, $-R^y-O-R^z-C(O)N(R^x)_2$, $-R^y-N(R^x)C(O)OR^x$, $-R^y-N(R^x)C(O)R^x$, $-R^y-N(R^x)S(O)_tR^x$ (where t is 1 or 2), $-R^y-S(O)_tR^x$ (where t is 1 or 2), $-R^y-S(O)_tOR^x$ (where t is 1 or 2) and $-R^y-S(O)_tN(R^x)_2$ (where t is 1 or 2), where each R^x is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, cycloalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), cycloalkylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally

substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), each R^y is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^z is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0043] "Heterocyclylalkyl" refers to a radical of the formula $-R^z$-heterocyclyl where R^z is an alkylene chain as defined above. If the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocyclylalkyl radical is optionally substituted as defined above for an alkylene chain. The heterocyclyl part of the heterocyclylalkyl radical is optionally substituted as defined above for a heterocyclyl group.

[0044] "Heterocyclylalkoxy" refers to a radical bonded through an oxygen atom of the formula $-O-R^z$-heterocyclyl where R^z is an alkylene chain as defined above. If the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocyclylalkoxy radical is optionally substituted as defined above for an alkylene chain. The heterocyclyl part of the heterocyclylalkoxy radical is optionally substituted as defined above for a heterocyclyl group.

[0045] The terms “heteroaryl” or, alternatively, “heteroaromatic” refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. Illustrative examples of heteroaryl groups include monocyclic heteroaryls and bicyclcic heteroaryls. Monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. Bicyclic heteroaryls include indolizine, indole, benzofuran, benzothiophene, indazole, benzimidazole, purine, quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, and pteridine. In some embodiments, a heteroaryl contains 0-4 N atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms in the ring. In some embodiments, a heteroaryl contains 0-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, heteroaryl is a C_1-C_9heteroaryl. In some embodiments, monocyclic heteroaryl is a C_1-C_5heteroaryl. In some embodiments, monocyclic heteroaryl is a 5-membered or 6-membered heteroaryl. In some embodiments, bicyclic heteroaryl is a C_6-C_9heteroaryl. Unless stated otherwise specifically in the specification, the term "heteroaryl" is meant to include heteroaryl radicals as defined above which are optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, haloalkenyl, haloalkynyl,

oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^y-OR^x$, $-R^y-OC(O)-R^x$, $-R^y-OC(O)-OR^x$, $-R^y-OC(O)-N(R^x)_2$, $-R^y-N(R^x)_2$, $-R^y-C(O)R^x$, $-R^y-C(O)OR^x$, $-R^y-C(O)N(R^x)_2$, $-R^y-O-R^z-C(O)N(R^x)_2$, $-R^y-N(R^x)C(O)OR^x$, $-R^y-N(R^x)C(O)R^x$, $-R^y-N(R^x)S(O)_tR^x$ (where t is 1 or 2), $-R^y-S(O)_tR^x$ (where t is 1 or 2), $-R^y-S(O)_tOR^x$ (where t is 1 or 2) and $-R^y-S(O)_tN(R^x)_2$ (where t is 1 or 2), where each R^x is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, cycloalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), cycloalkylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), each R^y is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^z is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0046] "Heteroarylalkyl" refers to a radical of the formula $-R^z$-heteroaryl, where R^z is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkyl radical is optionally substituted as defined above for an alkylene chain. The heteroaryl part of the heteroarylalkyl radical is optionally substituted as defined above for a heteroaryl group.

[0047] "Heteroarylalkoxy" refers to a radical bonded through an oxygen atom of the formula $-O-R^z$-heteroaryl, where R^z is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkoxy radical is optionally substituted as defined above for an alkylene chain. The heteroaryl part of the heteroarylalkoxy radical is optionally substituted as defined above for a heteroaryl group.

[0048] A "heterocycloalkyl" or "heteroalicyclic" group refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen and sulfur. In some embodiments, a heterocycloalkyl is fused with an aryl or heteroaryl. In some embodiments, the heterocycloalkyl is oxazolidinonyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl,

tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidin-2-onyl, pyrrolidine-2,5-dithionyl, pyrrolidine-2,5-dionyl, pyrrolidinonyl, imidazolidinyl, imidazolidin-2-onyl, or thiazolidin-2-onyl. The term heteroalicyclic also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. In one embodiment, a heterocycloalkyl is a C_2-C_{10}heterocycloalkyl. In another embodiment, a heterocycloalkyl is a C_4-C_{10}heterocycloalkyl. In some embodiments, a heterocycloalkyl contains 0-2 N atoms in the ring. In some embodiments, a heterocycloalkyl contains 0-2 N atoms, 0-2 O atoms and 0-1 S atoms in the ring.

[0049] The term "bond" or "single bond" refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. In one embodiment, when a group described herein is a bond, the referenced group is absent thereby allowing a bond to be formed between the remaining identified groups.

[0050] The term "moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[0051] In general, optionally substituted groups are each independently substituted or unsubstituted. Each recitation of an optionally substituted group provided herein, unless otherwise stated, includes an independent and explicit recitation of both an unsubstituted group and a substituted group (e.g., substituted in certain embodiments, and unsubstituted in certain other embodiments). Unless otherwise stated, a substituted group provided herein (e.g., substituted alkyl) is substituted by one or more substituent, each substituent being independently selected from the group consisting of: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^x$, $-SR^x$, $-OC(O)-R^x$, $-N(R^x)_2$, $-C(O)R^x$, $-C(O)OR^x$, $-C(O)N(R^x)_2$, $-N(R^x)C(O)OR^x$, $-OC(O)-N(R^x)_2$, $-N(R^x)C(O)R^x$, $-N(R^x)S(O)_tR^x$ (where t is 1 or 2), $-S(O)_tOR^x$ (where t is 1 or 2), $-S(O)_tR^x$ (where t is 1 or 2) and $-S(O)_tN(R^x)_2$ (where t is 1 or 2) where each R^x is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, carbocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), carbocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl). In some other embodiments, optional substituents are independently selected from halogen, -CN, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, -OH, $-CO_2H$, $-CO_2(C_1$-

C_4alkyl), -C(=O)NH_2, -C(=O)NH(C_1-C_4alkyl), -C(=O)N(C_1-C_4alkyl)$_2$, -S(=O)$_2NH_2$, -S(=O)$_2$NH(C_1-C_4alkyl), -S(=O)$_2$N(C_1-C_4alkyl)$_2$, C_1-C_4alkyl, C_3-C_6cycloalkyl, C_1-C_4fluoroalkyl, C_1-C_4heteroalkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkoxy, -SC_1-C_4alkyl, -S(=O)C_1-C_4alkyl, and -S(=O)$_2C_1$-C_4alkyl. In some embodiments, optional substituents are independently selected from halogen, -CN, -NH_2, -OH, -NH(CH_3), -N(CH_3)$_2$, -CH_3, -CH_2CH_3, -CF_3, -OCH_3, and -OCF_3. In some embodiments, substituted groups are substituted with one or two of the preceding groups. In some embodiments, an optional substituent on an aliphatic carbon atom (acyclic or cyclic) includes oxo (=O).

[0052] The term "acceptable" with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[0053] The term "modulate" as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target. In some embodiments, "modulate" means to interact with a target either directly or indirectly so as to decrease or inhibit receptor activity. In some embodiments. modulation is an increase or decrease in the amount, quality, or effect of a particular activity, function or molecule. By way of illustration and not limitation, agonists, partial agonists, antagonists, and allosteric modulators (e.g., a positive allosteric modulator) of a G protein-coupled receptor (e.g., $5HT_{2A}$) are modulators of the receptor.

[0054] The term "modulator" as used herein, refers to a molecule that interacts with a target either directly or indirectly. The interactions include, but are not limited to, the interactions of an agonist, partial agonist, an inverse agonist, antagonist, or combinations thereof. In some embodiments, a modulator is an antagonist. Receptor antagonists are inhibitors of receptor activity. Antagonists mimic ligands that bind to a receptor and prevent receptor activation by a natural ligand. Preventing activation may have many effects. If a natural agonist binding to a receptor leads to an increase in cellular function, an antagonist that binds and blocks this receptor decreases the function of the receptor.

[0055] The term "agonism," as used herein, generally refers to the activation of a receptor or enzyme by a modulator, or agonist, to produce a biological response.

[0056] The term "agonist," as used herein, generally refers to a modulator that binds to a receptor or enzyme and activates the receptor to produce a biological response. By way of example only, a "$5HT_{2A}$ agonist" can be used to refer to a compound that exhibits an EC_{50} with respect to $5HT_{2A}$ activity of no more than about 100 μM. In some embodiments, the term "agonist" includes

full agonists or partial agonists. "Full agonist" refers to a modulator that binds to and activates a receptor with the maximum response that an agonist can elicit at the receptor. "Partial agonist" refers to a modulator that binds to and activates a given receptor, but has partial efficacy, that is, less than the maximal response, at the receptor relative to a full agonist.

[0057] The term "positive allosteric modulator," as used herein, generally refers to a modulator that binds to a site distinct from the orthosteric binding site and enhances or amplifies the effect of an agonist.

[0058] The term "antagonism," as used herein, generally refers to the inactivation of a receptor or enzyme by a modulator, or antagonist. Antagonism of a receptor, for example, is when a molecule binds to the receptor and blocks function of the receptor.

[0059] The term "antagonist" or "neutral antagonist," as used herein, generally refers to a modulator that binds to a receptor or enzyme and blocks a biological response. An antagonist may have no activity in the absence of an agonist or inverse agonist but can block the activity of either, causing no change in the biological response.

[0060] The terms "administer," "administering", "administration," and the like, as used herein, refer to the methods that may be used to enable delivery of compounds or compositions to the desired site of biological action. These methods include, but are not limited to oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular or infusion), topical and rectal administration. Those of skill in the art are familiar with administration techniques that can be employed with the compounds and methods described herein. In some embodiments, the compounds and compositions described herein are administered orally.

[0061] The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of an agent or a compound being administered, which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case is optionally determined using techniques, such as a dose escalation study.

[0062] The terms "enhance" or "enhancing," as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the

effect of other therapeutic agents on a system. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[0063] The terms "kit" and "article of manufacture" are used as synonyms.

[0064] The term "subject" or "patient" encompasses mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one embodiment, the mammal is a human.

[0065] The terms "treat," "treating" or "treatment," as used herein, include alleviating, abating or ameliorating at least one symptom of a disease or condition, preventing additional symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

[0066] The term "pharmaceutically acceptable," as used herein, generally refers a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, i.e., the material is administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[0067] The term "pharmaceutically acceptable salt," as used herein, generally refers to a form of a therapeutically active agent that consists of a cationic form of the therapeutically active agent in combination with a suitable anion, or in alternative embodiments, an anionic form of the therapeutically active agent in combination with a suitable cation. Handbook of Pharmaceutical Salts: Properties, Selection and Use. International Union of Pure and Applied Chemistry, Wiley-VCH 2002. S.M. Berge, L.D. Bighley, D.C. Monkhouse, J. Pharm. Sci. 1977, 66, 1-19. P. H. Stahl and C. G. Wermuth, editors, *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, Weinheim/Zürich:Wiley-VCH/VHCA, 2002. Pharmaceutical salts typically are more soluble and more rapidly soluble in stomach and intestinal juices than non-ionic species and so are useful in solid dosage forms. Furthermore, because their solubility often is a function of pH, selective dissolution in one or another part of the digestive tract is possible and this capability can be manipulated as one aspect of delayed and sustained release behaviours. Also, because the salt-forming molecule can be in equilibrium with a neutral form, passage through biological membranes can be adjusted.Provided herein are non-hallucinogenic compounds that promote neuronal growth and/or improve neuronal structure.

[0068] The term "significant" or "significantly" as used herein regarding 5-HT_{2A} agonism refers to a compound capable of providing 5-HT_{2A} receptor agonism with an EC_{50} of less than 10 μM.

[0069] In some embodiments, compounds provided herein possess comparable affinity for serotonin receptors (e.g., $5HT_{2A}$) as compared to their hallucinogenic counterparts. In some embodiments, the compounds provided herein have improved physiochemical properties as a result of the loss of a hydrogen bond donor, decreasing total polar surface area and improving central nervous system multiparameter optimization (MPO) scores. Described herein in some embodiments are non-hallucinogenic compounds that demonstrate similar therapeutic potential as hallucinogenic 5-HT_{2A} agonists. In some embodiments, the non-hallucinogenic compounds described herein provide better therapeutic potential than hallucinogenic 5-HT_{2A} agonists for neurological diseases.

Neurological Disorders

[0070] Neuronal plasticity, and changes thereof, have been attributed to many neurological diseases and disorders. For example, during development and in adulthood, changes in dendritic spine number and morphology (e.g., lengths, crossings, density) accompany synapse formation, maintenance and elimination; these changes are thought to establish and remodel connectivity within neuronal circuits. Furthermore, dendritic spine structural plasticity is coordinated with synaptic function and plasticity. For example, spine enlargement is coordinated with long-term potentiation in neuronal circuits, whereas long-term depression is associated with spine shrinkage.

[0071] In addition, dendritic spines undergo experience-dependent morphological changes in live animals, and even subtle changes in dendritic spines can affect synaptic function, synaptic plasticity, and patterns of connectivity in neuronal circuits. For example, disease-specific disruptions in dendritic spine shape, size, and/or number accompany neurological diseases and disorders, such as, for example, neurodegenerative (e.g., Alzheimer's disease or Parkinson's disease) and neuropsychiatric (e.g., depression or schizophrenia) diseases and disorders, suggesting that dendritic spines may serve as a common substrate in diseases that involve deficits in information processing.

[0072] In some embodiments, disclosed herein are methods of treating neurological diseases and disorders with a compound of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), or any compound covered by such formulae, for example any compound described in Table 1, or a pharmaceutically acceptable salt or solvate thereof.

[0073] In some embodiments, a neurological disease or disorder is a disease or disorder of the central nervous system (CNS) (e.g., brain, spine, and/or nerves) of an individual.

[0074] Types of neurological diseases and disorders include, but are not limited to, neurodegenerative diseases (such as Alzheimer's disease, Parkinson's disease, and dementia), headaches (e.g., migraines), brain injury (e.g., stroke or traumatic brain injury), brain cancer, an anxiety disorder (e.g., post-traumatic stress disorder (PTSD) or obsessive-compulsive disorder (OCD)), a mood disorder (e.g., suicidal ideation, depression, or bipolar disorder), a psychotic disorder (e.g., schizophrenia or substance-induced psychotic disorder), a personality disorder, an eating disorder (e.g., binge eating disorder), a sleep disorder, a sexuality disorder, an impulse control disorder (e.g., gambling, compulsive sexuality, or kleptomania), a substance use disorder (e.g., alcohol dependence, opioid addiction, or cocaine addiction), a dissociative disorder (e.g., epilepsy, amnesia, or dissociative identity disorder), a cognitive disorder (e.g., substance-induced cognitive impairment), a developmental disorder (e.g., Attention-Deficit/Hyperactivity Disorder (ADHD)), an autoimmune disease (e.g., multiple sclerosis (MS)), pain (e.g., chronic pain), and a factitious disorder. In some embodiments, a mammal treated with a compound described herein has a disease or disorder that is or is associated with a disease or disorder of the CNS.

[0075] Neurodegenerative diseases or disorders include, but are not limited to, Alzheimer's disease (AD), Parkinson's disease (PD), prion disease, frontotemporal dementia, motor neuron disease (MND), Huntington's disease (HD), Lewy Body dementia (LBD), and the like.

[0076] Substance use disorders include, but are not limited to, substance abuse, addiction and dependence, such as addiction or dependence to alcohol, opioids (e.g., heroin, oxycodone, and hydrocodone), cocaine, amphetamines (e.g., methamphetamine), nicotine, cannabinoids (e.g., tetrahydrocannabinol (THC)), caffeine, phencyclidine, paint thinner, glue, steroids (e.g., anabolic steroids), barbiturates (e.g., phenobarbital), methadone, benzodiazepines (e.g., diazepam), and the like.

[0077] Impulse control disorders include, but are not limited to, gambling, kleptomania, trichotillomania, intermittent explosive disorder, pyromania, skin picking, compulsive buying, Tourette syndrome, compulsive sexual behavior, and the like.

[0078] Neuropsychiatric disorders include, but are not limited to, seizures (e.g., epilepsy), attention deficit disorders (e.g., ADHD and Autism), eating disorders (e.g., bulimia, anorexia, binge eating disorder, and pica), depression (e.g., clinical depression, persistent depressive disorder, bipolar disorder, postpartum depression, suicidal ideation, major depressive disorder, seasonal depression, and the like), anxiety (e.g., panic attacks, social anxiety disorder, panic disorder, and the like), schizophrenia, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), substance-induced psychotic disorder, substance-induced cognitive impairment, and the like.

[0079] Brain injury includes, but is not limited to, stroke, traumatic brain injury, dementia pugiliistica, chronic traumatic encephalopathy (CTE), or the like.

[0080] In some embodiments, a compound provided herein (e.g., a compound represented by the structure of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), or any compound covered by such formulae, for example any compound described in Table 1), or a pharmaceutically acceptable salt or solvate thereof, improves dendritic spine number and dendritic spine morphology that is lost in neurological diseases and disorders.

5-HT_{2A}

[0081] 5-HT_{2A} agonism has been correlated with the promotion of neural plasticity (Ly et al., 2018). In some embodiments, 5-HT_{2A} antagonists abrogate the neuritogenesis and spinogenesis effects of hallucinogenic compounds with 5-HT_{2A} agonist activity, e.g., DMT, LSD, and DOI. Furthermore, DMT and other psychedelic compounds promote increased dendritic arbor complexity, dendritic spine density, and synaptogenesis through a 5-HT_{2A}-dependent process. In some embodiments, pretreating cortical cultures with a 5-HT_{2A} antagonist blocked the ability of 5-MeO-DMT to increase dendritic growth. Importantly, the psychoplastogenic effects of compounds provided herein are also blocked under these conditions, implicating the 5-HT_{2A} receptor in their mechanism of action.

[0082] Furthermore, in some embodiments, non-hallucinogenic compounds (e.g., lisuride and 6-MeO-DMT) compete off 5-HT when an $5HT_{2A}$ sensor assay is run in antagonist mode. Additionally, compounds, such as, for example, 6-F-DET, Ketanserin, BOL148, which are non-hallucinogenic in animals (e.g., humans), can compete with 5HT binding to $5HT_{2A}$ in an antagonist mode sensor assay. In some embodiments, a compound provided herein prevents binding of 5-HT to $5HT_{2A}$. In some embodiments, the $5HT_{2A}$ sensor assay is in an antagonist mode. In some embodiments, a compound provided herein prevents binding of 5-HT to $5HT_{2A}$ and has non-hallucinogenic potential. In some embodiments, a compound provided herein prevents binding of 5-HT to $5HT_{2A}$ and is non-hallucinogenic. In some embodiments, a compound provided herein prevents binding of 5-HT to $5HT_{2A}$ in antagonist mode has non-hallucinogenic potential. In some embodiments, a compound provided herein prevents binding of 5-HT in antagonist mode is a non-hallucinogenic compound. In some embodiments, a compound provided herein inhibits the response of a sensor assay in antagonist mode has non-hallucinogenic potential. In some embodiments, a compound provided herein inhibits the response of a sensor assay in antagonist mode is a non-hallucinogenic compound.

[0083] In some embodiments, the effect of a compound provided herein on an agonist mode sensor assay suggests the compound is a non-hallucinogenic ligand of the 5-HT_{2A} receptor. In some

embodiments, the effect of a compound provided herein on an antagonist mode sensor assay suggests the compound is a non-hallucinogenic ligand of the 5-HT_{2A} receptor. In some embodiments, effect of a compound provided herein on an agonist mode and an antagonist mode sensor assay together suggest the compound is a non-hallucinogenic ligand of the 5-HT_{2A} receptor.

[0084] Described in some embodiments are non-hallucinogenic compounds that demonstrate similar therapeutic potential as hallucinogenic 5-HT_{2A} agonists. In some embodiments, the non-hallucinogenic compounds described herein provide better therapeutic potential than hallucinogenic 5-HT_{2A} agonists for neurological diseases. In some embodiments, the compounds of the present disclosure are 5-HT_{2A} modulators and promote neural plasticity (e.g., cortical structural plasticity).

[0085] Provided herein are compounds (e.g., a compound represented by the structure of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), or any compound covered by such formulae, for example any compound described in Table 1) useful for the treatment of a brain disorder and other conditions described herein. In some embodiments, a compound provided herein is a 5-HT_{2A} modulator and promote neural plasticity (e.g., cortical structural plasticity). In some embodiments, 5-HT_{2A} modulators (e.g., 5-HT_{2A} agonists) are used to treat a brain disorder. In some embodiments, the brain disorder or other conditions described herein comprise decreased neural plasticity, decreased cortical structural plasticity, decreased 5-HT_{2A} receptor content, decreased dendritic arbor complexity, loss of dendritic spines, decreased dendritic branch content, decreased spinogenesis, decreased neuritogenesis, retraction of neurites, or any combination thereof.

[0086] In some embodiments, a compound provided herein (e.g., a compound represented by the structure of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), or any compound covered by such formulae, for example any compound described in Table 1) is neuroplastic (e.g., promotes neural plasticity (e.g., cortical structural plasticity), such as increases neurite outgrowth).

[0087] In some embodiments, the compounds provided herein (e.g., a compound represented by the structure of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), or any compound covered by such formulae, for example any compound described in Table 1)have activity as 5-HT_{2A} modulators. In some embodiments, the compounds provided herein elicit a biological response by activating the 5-HT_{2A} receptor (e.g., allosteric modulation or modulation of a biological target that activates the 5-HT_{2A} receptor). In some embodiments, the compounds provided herein are selective 5-HT_{2A} modulators and promote neural plasticity (e.g., cortical structural plasticity). In some embodiments, promotion of neural plasticity includes, for example, increased dendritic spine growth, increased synthesis of synaptic proteins, strengthened synaptic responses, increased dendritic arbor complexity, increased dendritic branch content, increased spinogenesis, increased neuritogenesis, or any combination thereof. In some embodiments,

increased neural plasticity includes, for example, increased cortical structural plasticity in the anterior parts of the brain.

[0088] In some embodiments, a compound provided herein (e.g., a compound represented by the structure of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), or any compound covered by such formulae, for example any compound described in Table 1) is a 5-HT modulator (e.g., a 5-HT_{2A} agonist or a 5-HT_{2A} antagonist). In some embodiments, a compound provided herein is a 5-HT_{2A} modulator (e.g., a 5-HT_{2A} agonist or a 5-HT_{2A} antagonist). In some embodiments, a compound provided herein is a 5-HT modulator and promotes neural plasticity (e.g., cortical structural plasticity), such as increases neurite outgrowth. In some embodiments, a compound provided herein is a 5-HT modulator, promotes neural plasticity (e.g., cortical structural plasticity), and is non-hallucinogenic.

[0089] In some embodiments, a compound provided herein (e.g., a compound represented by the structure of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), or any compound covered by such formulae, for example any compound described in Table 1) is a 5-HT_{2A} antagonist. In some embodiments, a compound provided herein is a 5-HT_{2A} antagonist and promotes neural plasticity (e.g., cortical structural plasticity), such as increases neurite outgrowth. In some embodiments, the compound provided herein is unable to (significantly) provide 5-HT_{2A} agonism and promotes neural plasticity (e.g., cortical structural plasticity), such as increases neurite outgrowth. In some embodiments, the compound provided herein is unable to (significantly) provide 5-HT_{2A} agonism, promotes neural plasticity (e.g., cortical structural plasticity), and has a low potential for hallucinogenic activity (e.g., is non-hallucinogenic).

[0090] In some embodiments, a compound provided herein (e.g., a compound represented by the structure of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), or any compound covered by such formulae, for example any compound described in Table 1) is a 5-HT_{2A} agonist. In some embodiments, a compound provided herein is a 5-HT_{2A} agonist and promotes neural plasticity (e.g., cortical structural plasticity), such as increases neurite outgrowth. In some embodiments, the compound provided herein provides (significant) 5-HT_{2A} agonism and promotes neural plasticity (e.g., cortical structural plasticity), such as increases neurite outgrowth. In some embodiments, the compound provided herein provides (significant) 5-HT_{2A} agonism, promotes neural plasticity (e.g., cortical structural plasticity), and has a low potential for hallucinogenic activity (e.g., is non-hallucinogenic).

[0091] In some embodiments, the 5-HT_{2A} modulators (e.g., 5-HT_{2A} agonists) are non-hallucinogenic. In some embodiments, non-hallucinogenic 5-HT_{2A} modulators (e.g., 5-HT_{2A} agonists) are used to treat neurological diseases, which modulators do not elicit dissociative side-

effects. In some embodiments, the hallucinogenic potential of the compounds described herein is assessed in vitro. In some embodiments, the hallucinogenic potential assessed in vitro of the compounds described herein is compared to the hallucinogenic potential assessed in vitro of hallucinogenic homologs. In some embodiments, the compounds of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), or (IB-3) provided herein elicit less hallucinogenic potential in vitro than the hallucinogenic homologs.

[0092] In some embodiments, non-hallucinogenic 5-HT_{2A} modulators (e.g., 5-HT_{2A} agonists) are used to treat neurological diseases. In some embodiments, the neurological diseases comprise decreased neural plasticity, decreased cortical structural plasticity, decreased 5-HT_{2A} receptor content, decreased dendritic arbor complexity, loss of dendritic spines, decreased dendritic branch content, decreased spinogenesis, decreased neuritogenesis, retraction of neurites, or any combination thereof.

[0093] In some embodiments, non-hallucinogenic 5-HT_{2A} modulators (e.g., 5-HT_{2A} agonists) are used for increasing neuronal plasticity. In some embodiments, non-hallucinogenic 5-HT_{2A} modulators (e.g., 5-HT_{2A} agonists) are used for treating a brain disorder. In some embodiments, non-hallucinogenic 5-HT_{2A} modulators (e.g., 5-HT_{2A} agonists) are used for increasing at least one of translation, transcription, or secretion of neurotrophic factors.

[0094] In some embodiments, the experiment or assay to determine increased neuronal plasticity of any compound of the present disclosure is a phenotypic assay, a dendritogenesis assay, a spinogenesis assay, a synaptogenesis assay, a Sholl analysis, a concentration-response experiment, a 5-HT_{2A} agonist assay, a 5-HT_{2A} antagonist assay, a 5-HT_{2A} binding assay, or a 5-HT_{2A} blocking experiment (e.g., ketanserin blocking experiments). In some embodiments, the experiment or assay to determine the hallucinogenic potential of a compound of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), or (IB-3) provided herein is a mouse head-twitch response (HTR) assay.

Compounds

[0095] In some embodiments, a compound described herein, including pharmaceutically acceptable salts, prodrugs, active metabolites and solvates thereof, is a pyrrolidine psychoplastogen. In some embodiments, a compound described herein, including pharmaceutically acceptable salts, prodrugs, active metabolites and solvates thereof, is a fused pyrrolidine psychoplastogen. In some embodiments, a compound described herein, including pharmaceutically acceptable salts, prodrugs, active metabolites and solvates thereof, is a psychoplastogen comprising an indole moiety. In some embodiments, a compound described herein, including pharmaceutically acceptable salts, prodrugs, active metabolites and solvates thereof, is a psychoplastogen comprising a 1,2,3,4,5,6-hexahydroazepino[4,5-b]indole moiety. In some embodiments, a compound described

herein, including pharmaceutically acceptable salts, prodrugs, active metabolites and solvates thereof, is a psychoplastogen comprising a 1,2,3,4,5,6-hexahydroazepino[4,5-b]indole moiety fused to a pyrrolidine moiety. In some embodiments, a compound described herein, including pharmaceutically acceptable salts, prodrugs, active metabolites and solvates thereof, is a psychoplastogen comprising a 1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole moiety. In some embodiments, a compound described herein, including pharmaceutically acceptable salts, prodrugs, active metabolites and solvates thereof, is a psychoplastogen comprising a 1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole moiety.

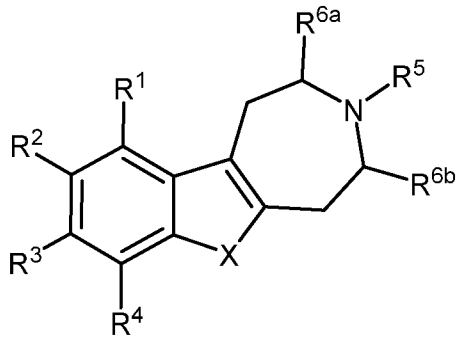
[0096] In some embodiments, a compound described herein, including pharmaceutically acceptable salts, prodrugs, active metabolites and solvates thereof, is a psychoplastogen comprising a benzofuran moiety. In some embodiments, a compound described herein, including pharmaceutically acceptable salts, prodrugs, active metabolites and solvates thereof, is a psychoplastogen comprising a 2,3,4,5-tetrahydro-1H-benzofuro[2,3-d]azepine moiety. In some embodiments, a compound described herein, including pharmaceutically acceptable salts, prodrugs, active metabolites and solvates thereof, is a psychoplastogen comprising a 2,3,4,5-tetrahydro-1H-benzofuro[2,3-d]azepine moiety fused to a pyrrolidine moiety. In some embodiments, a compound described herein, including pharmaceutically acceptable salts, prodrugs, active metabolites and solvates thereof, is a psychoplastogen comprising a 2,3,5,6,12,12a-hexahydro-1H-benzofuro[2,3-d]pyrrolo[1,2-a]azepine moiety. In some embodiments, a compound described herein, including pharmaceutically acceptable salts, prodrugs, active metabolites and solvates thereof, is a psychoplastogen comprising a 2,3,5,6,12,12a-hexahydro-1H-benzofuro[3,2-d]pyrrolo[1,2-a]azepine moiety.

[0097] In some embodiments, a compound described herein, including pharmaceutically acceptable salts, prodrugs, active metabolites and solvates thereof, is a psychoplastogen comprising a benzothiophene moiety or an oxidized (e.g., sulfoxide, sulfone) derivative thereof. In some embodiments, a compound described herein, including pharmaceutically acceptable salts, prodrugs, active metabolites and solvates thereof, is a psychoplastogen comprising a 2 2,3,4,5-tetrahydro-1H-benzo[4,5]thieno[2,3-d]azepine moiety or an oxidized (e.g., sulfoxide, sulfone) derivative thereof. In some embodiments, a compound described herein, including pharmaceutically acceptable salts, prodrugs, active metabolites and solvates thereof, is a psychoplastogen comprising a 2,3,4,5-tetrahydro-1H-benzo[4,5]thieno[2,3-d]azepine or an oxidized (e.g., sulfoxide, sulfone) derivative thereof, fused to a pyrrolidine moiety. In some embodiments, a compound described herein, including pharmaceutically acceptable salts, prodrugs, active metabolites and solvates thereof, is a psychoplastogen comprising a 2,3,5,6,12,12a-hexahydro-1H-benzo[4,5]thieno[2,3-d]pyrrolo[1,2-

a]azepine moiety, or an oxidized (e.g., sulfoxide, sulfone) derivative thereof. In some embodiments, a compound described herein, including pharmaceutically acceptable salts, prodrugs, active metabolites and solvates thereof, is a psychoplastogen comprising a 2,3,5,6,12,12a-hexahydro-1H-benzo[4,5]thieno[3,2-d]pyrrolo[1,2-a]azepine moiety, or an oxidized (e.g., sulfoxide, sulfone) derivative thereof.

[0098] In some embodiments, the fused pyrrolidine psychoplastogen is a non-hallucinogenic fused pyrrolidine psychoplastogen. In some embodiments, a fused pyrrolidine psychoplastogen (e.g., described herein) promotes neuronal growth, improve neuronal structure, or a combination thereof.

[0099] In some embodiments, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I)

wherein:

- X is NR^7, O or $S(=O)_x$;
- x is 0, 1, or 2;
- each of R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, $-OR^a$, cyano, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

  or any of R^1 and R^2, R^2 and R^3, or R^3 and R^4 are taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring;
- R^5 is hydrogen, halogen, $-OR^a$, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- each R^{6a} and R^{6b} is independently hydrogen, halogen, $-OR^a$, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl,

heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

or R^5 is taken together with R^{6a} or R^{6b} and the atoms to which they are attached to form an optionally substituted heterocyclic ring;

or R^{6a} and R^{6b} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring;

- R^7 is hydrogen, alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted; and
- R^a is hydrogen, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

wherein

(i) R^5 and R^{6a} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring;

(ii) R^5 and R^{6b} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring; or

(iii) R^{6a} and R^{6b} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring; and

provided that when X is NH, R^{6a} is hydrogen, and each of R^1, R^2, R^3 and R^4 is hydrogen, then R^5 and R^{6b} are not taken together with the atoms to which they are attached to form a 6-membered heterocyclic ring substituted by ethyl or ethylidene.

[00100] For any and all of the embodiments, substituents are selected from among a subset of the listed alternatives. For example, in some embodiments of Formula (I) , X is O. In some embodiments of Formula (I), X is S. In some embodiments of Formula (I), X is S(=O). In some embodiments of Formula (I), X is $S(=O)_2$. In some embodiments of Formula (I), X is NR^7. In some embodiments of Formula (I), R^7 is an unsubstituted or substituted alkyl, e.g., methyl. In some embodiments of Formula (I), R^7 is hydrogen.

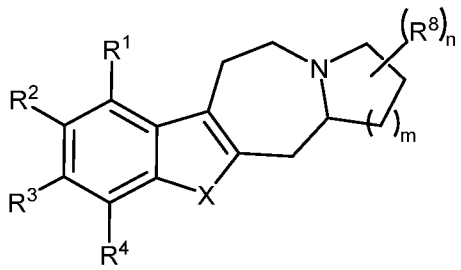
[00101] In some embodiments of Formula (I), R^5 is hydrogen. In some embodiments, R^{6a} is hydrogen. In some embodiments, R^{6b} is hydrogen.

[00102] In some embodiments of Formula (I), R^5 and R^{6a} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring. In some embodiments, R^{6b} is hydrogen.

[00103] In some embodiments of Formula (I), R^5 and R^{6b} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring. In some embodiments, R^{6a} is hydrogen.

[00104] In some embodiments of Formula (I), R^{6a} and R^{6b} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring. In some embodiments, R^5 is hydrogen.

[00105] In some embodiments, provided herein is a compound of Formula (I), wherein R^{6a} is hydrogen and R^{6b} is taken together with R^5 and the atoms to which R^5 and R^{6b} are attached to form an optionally substituted heterocyclic ring, and wherein the compound of Formula (I) has the structure of Formula (IA):



Formula (IA)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

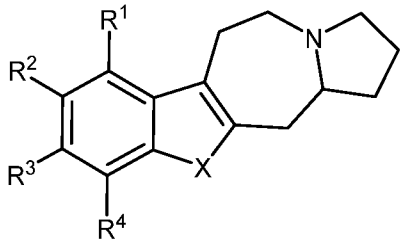
- X is NR^7, O or $S(=O)_x$;
- x is 0, 1, or 2;
- each of R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, $-OR^a$, cyano alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

  or any of R^1 and R^2, R^2 and R^3, or R^3 and R^4 are taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring;
- R^7 is hydrogen, alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- each R^8 is independently halogen, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

- R^a is hydrogen, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- m is 0, 1, 2 or 3; and
- n is 0, 1, 2, 3, 4, 5, 6, or 7; and

provided that when X is NH, m is 2, and R^1-R^4 are hydrogen, then R^8 is not ethyl.

[00106] In some embodiments of formula (IA), n is 0, m is 1, and the compound has the structure of Formula (IA-1):



Formula (IA-1)

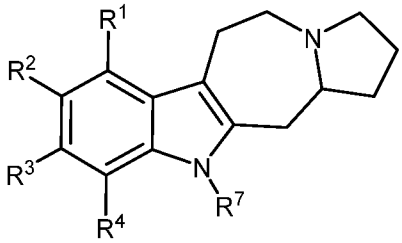
or a pharmaceutically acceptable salt or solvate thereof;

wherein

- X is NR^7, O or $S(=O)_x$;
- x is 0, 1, or 2;
- each of R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, -OR^a, cyano, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

  or any of R^1 and R^2, R^2 and R^3, or R^3 and R^4 are taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring;
- R^7 is hydrogen, alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted; and
- R^a is hydrogen, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted.

[00107] In some embodiments of Formula (IA) or (IA-1), X is NR^7, and the compound has the structure of Formula (IA-2):



Formula (IA-2)

or a pharmaceutically acceptable salt or solvate thereof;

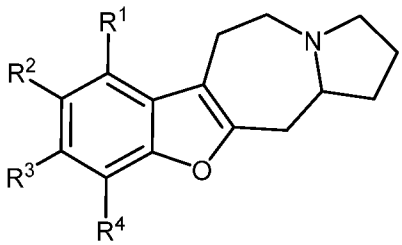
wherein

- each of R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, -OR^a, cyano, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

  or any of R^1 and R^2, R^2 and R^3, or R^3 and R^4 are taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring;
- R^7 is hydrogen, alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted; and
- R^a is hydrogen, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted.

[00108] In some embodiments of Formula (IA), (IA-1) or (IA-2), R^7 is hydrogen. In some embodiments of Formula (IA), (IA-1), or (IA-2) , R^7 is methyl.

[00109] In some embodiments of Formula (IA) or (IA-1), X is O, and the compound has the structure of Formula (IA-3):



Formula (IA-3)

or a pharmaceutically acceptable salt or solvate thereof;

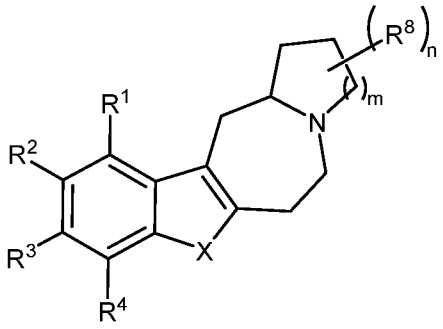
wherein

- each of R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, -OR^a, cyano, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

or any of R^1 and R^2, R^2 and R^3, or R^3 and R^4 are taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring; and

- R^a is hydrogen, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted.

[00110] In some embodiments, provided herein is a compound of Formula (I), R^{6b} is hydrogen and R^{6a} is taken together with R^5 and the atoms to which R^5 and R^{6a} are attached to form an optionally substituted heterocyclic ring, and wherein the compound of Formula (I) has the structure of Formula (IB):



Formula (IB)

or a pharmaceutically acceptable salt or solvate thereof,

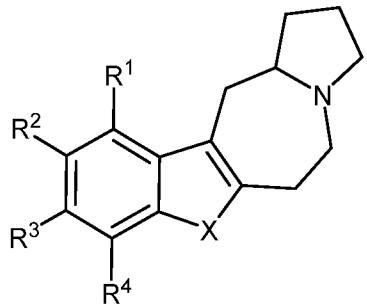
wherein

- X is NR^7, O or $S(=O)_x$;
- x is 0, 1, or 2;
- each of R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, $-OR^a$, cyano, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

  or any of R^1 and R^2, R^2 and R^3, or R^3 and R^4 are taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring;
- R^7 is hydrogen, alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- each R^8 is independently halogen, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

- R^a is hydrogen, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- m is 0, 1, 2 or 3; and
- n is 0, 1, 2, 3, 4, 5, 6, or 7.

[00111] In some embodiments of Formula (IB), n is 0, m is 1, and the compound has the structure of Formula (IB-1):



Formula (IB-1)

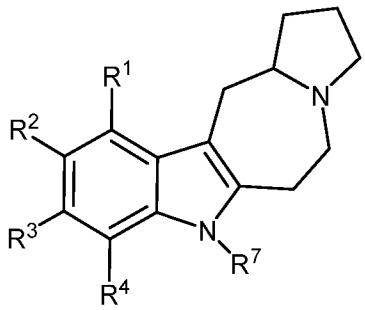
or a pharmaceutically acceptable salt or solvate thereof;

wherein

- X is NR^7, O or $S(=O)_x$;
- x is 0, 1, or 2;
- each of R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, $-OR^a$, cyano, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

  or any of R^1 and R^2, R^2 and R^3, or R^3 and R^4 are taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring;
- R^7 is hydrogen, alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted; and
- R^a is hydrogen, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted.

[00112] In some embodiments of formula (IB) or (IB-1), X is NR^7, and the compound has the structure of Formula (IB-2):



Formula (IB-2)

or a pharmaceutically acceptable salt or solvate thereof;

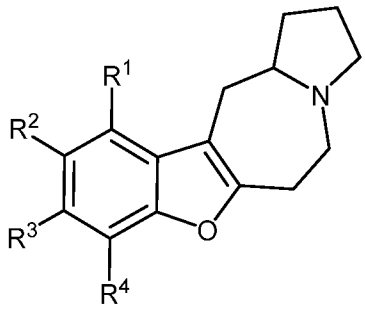
wherein

- each of R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, -OR^a, cyano, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

  or any of R^1 and R^2, R^2 and R^3, or R^3 and R^4 are taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring;
- R^7 is hydrogen, alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted; and
- R^a is hydrogen, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted.

[00113] In some embodiments of Formula (IB), (IB-1), or (IB-2), R^7 is hydrogen. In some embodiments of Formula (IB), (IB-1), or (IB-2),, R^7 is methyl.

[00114] In some embodiments of Formula (IB) or (IB-1), X is O, and the compound has the structure of Formula (IB-3)



Formula (IB-3)

or a pharmaceutically acceptable salt or solvate thereof;

wherein

- each of R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, -OR^a, cyano, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

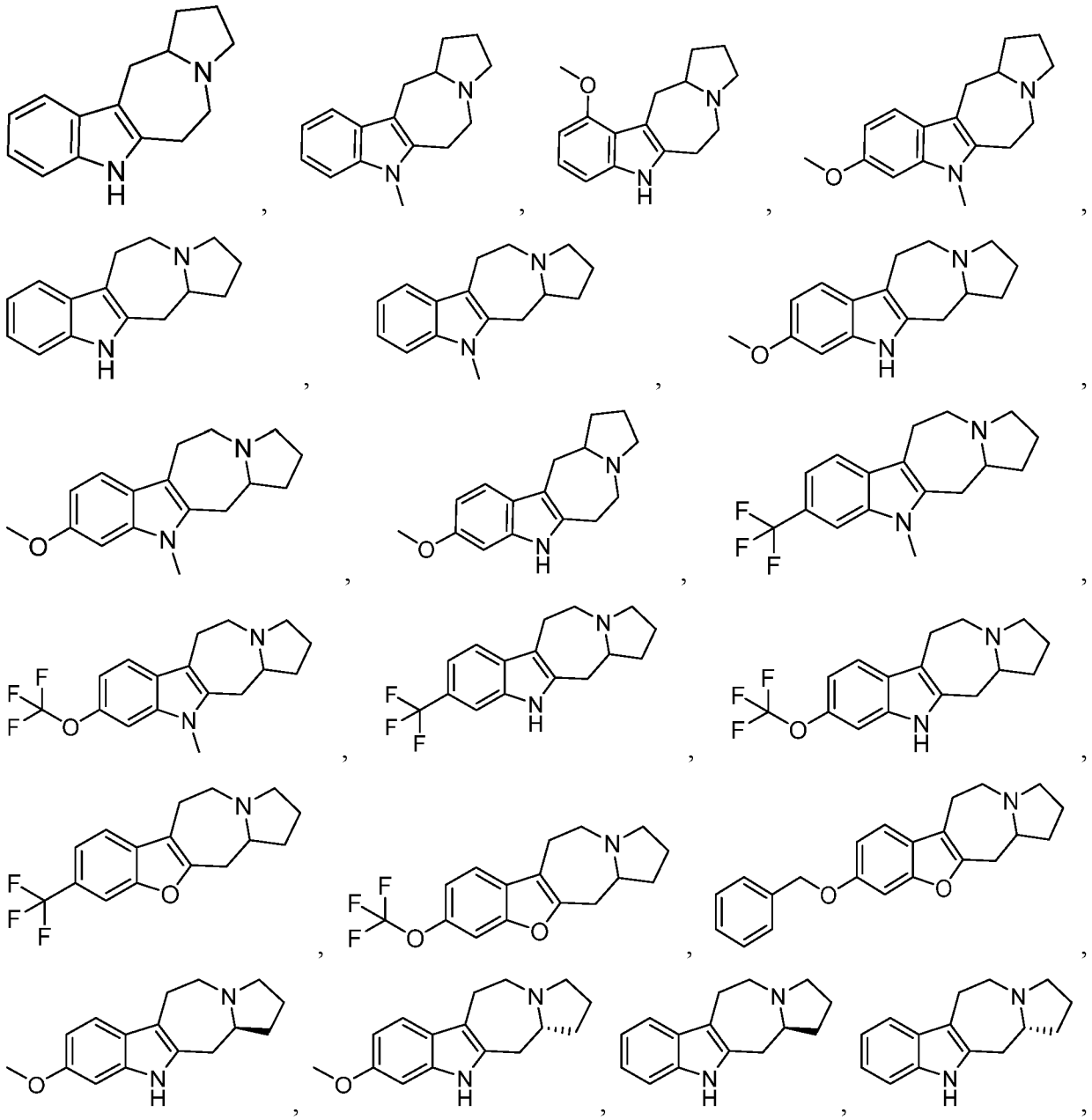
  or any of R^1 and R^2, R^2 and R^3, or R^3 and R^4 are taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring; and
- R^a is hydrogen, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted.

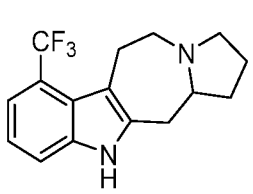
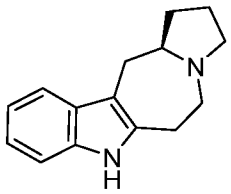
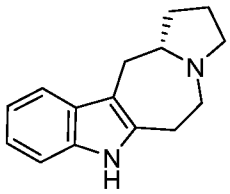
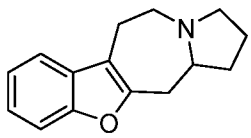
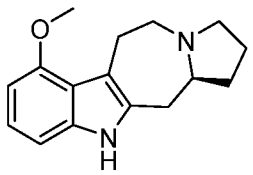
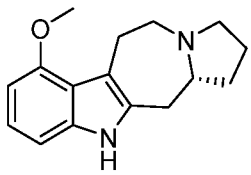
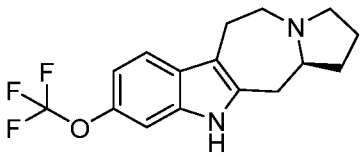
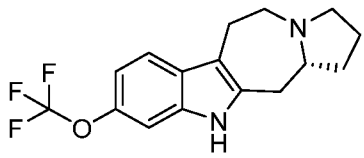
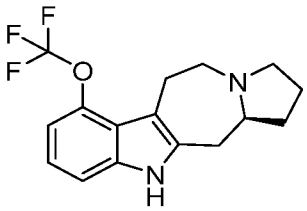
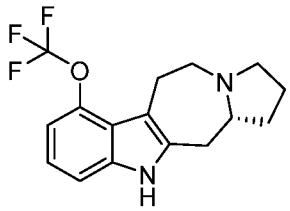
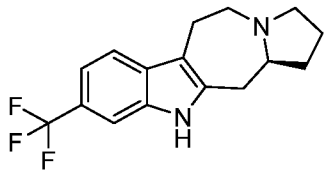
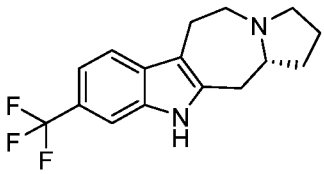
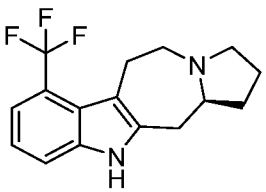
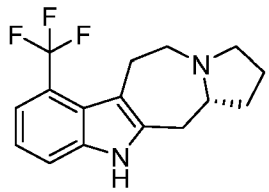
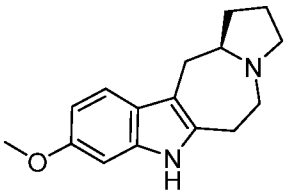
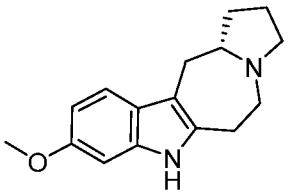
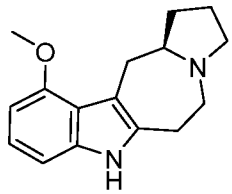
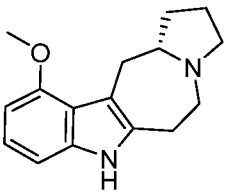
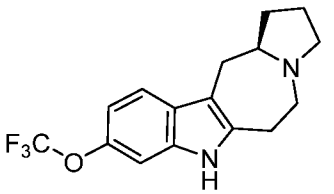
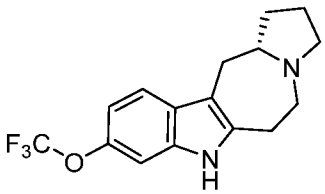
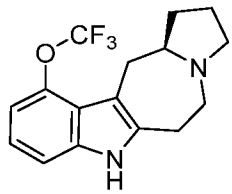
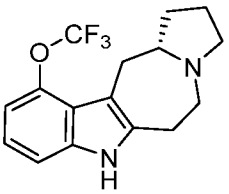
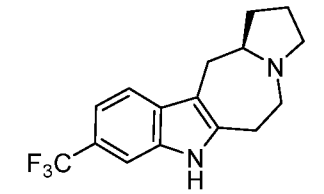
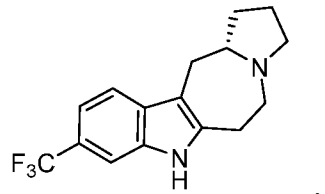
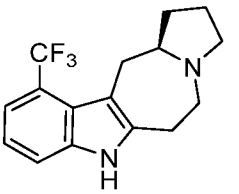
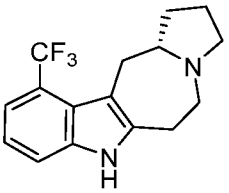
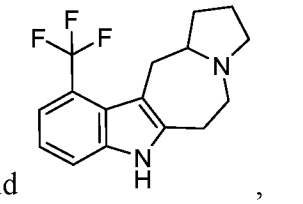
[00115] In some embodiments of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), or (IB-3), each of R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, -OR^a, or haloalkyl. In some embodiments, each of R^1, R^2, R^3 and R^4 is hydrogen. In some embodiments, at least one of R^1, R^2, R^3 and R^4 is halogen (e.g., Fl, Cl, Br, I). In some embodiments, one of R^1, R^2, R^3 and R^4 is halogen (e.g., Fl, Cl, Br, I). In some embodiments, one of R^1, R^2, R^3 and R^4 is halogen (eg., F, Cl, Br, I). In some embodiments, at least one of R^1, R^2, R^3 and R^4 is haloalkyl (e.g., fluoromethyl, fluoroethyl). In some embodiments, one of R^1, R^2, R^3 and R^4 is haloalkyl (e.g., fluoromethyl, fluoroethyl). In some embodiments, at least one of R^1, R^2, R^3 and R^4 is OR^a, wherein R^a is haloalkyl (e.g., at least one of R^1, R^2, R^3 and R^4 is haloalkyloxy, for example trifluoromethoxy or trifluoroethoxy). In some embodiments, one of R^1, R^2, R^3 and R^4 is OR^a, wherein R^a is haloalkyl (e.g., one of R^1, R^2, R^3 and R^4 is haloalkyloxy, for example trifluoromethoxy or trifluoroethoxy). In some embodiments, at least one of R^1, R^2, R^3 and R^4 is OR^a, wherein R^a is arylalkyl (e.g., at least one of R^1, R^2, R^3 and R^4 is arylalkyloxy, for eample benzyloxy). In some embodiments, one of R^1, R^2, R^3 and R^4 is OR^a, wherein R^a is arylalkyl (e.g., at least one of R^1, R^2, R^3 and R^4 is arylalkyloxy, for eample benzyloxy). In some embodiments, at least one of R^1, R^2, R^3 and R^4 is OR^a, wherein R^a is alkyl (e.g., at least one of R^1, R^2, R^3 and R^4 is alkoxy, for example methoxy). In some embodiments, one of R^1, R^2, R^3 and R^4 is OR^a, wherein R^a is alkyl (e.g., one of R^1, R^2, R^3 and R^4 is alkoxy, for example methoxy).

[00116] In some embodiments of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), or (IB-3), at least one of R^1, R^2, R^3 and R^4 is hydrogen, benzyloxy, methoxy, fluoro, trifluoromethyl, or trifluoromethoxy. In some embodiments, R^1 is hydrogen. In some embodiments, R^2 is hydrogen. In some embodiments, R^3 is hydrogen. In some embodiments, R^4 is hydrogen. In some embodiments, R^1 is benzyloxy. In some embodiments, R^2 is benzyloxy. In some embodiments, R^3 is benzyloxy In some embodiments, R^4 is benzyloxy. In some embodiments, R^1 is methoxy. In some embodiments, R^2 is methoxy. In some embodiments, R^3 is methoxy. In some embodiments,

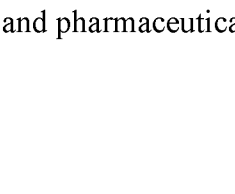
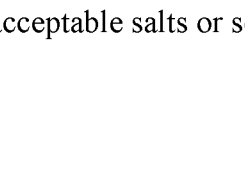
R^4 is methoxy. In some embodiments, R^1 is fluoro. In some embodiments, R^2 is fluoro. In some embodiments, R^3 is fluoro. In some embodiments, R^4 is fluoro. In some embodiments, R^1 is trifluoromethyl. In some embodiments, R^2 is trifluoromethyl. In some embodiments, R^3 is trifluoromethyl. In some embodiments, R^4 is trifluoromethyl. In some embodiments, R^1 is trifluoromethoxy. In some embodiments, R^2 is trifluoromethoxy. In some embodiments, R^3 is trifluoromethoxy. In some embodiments, R^4 is trifluoromethoxy.

[00117] In some embodiments, representative compounds of Formula (I) include, but are not limited to:




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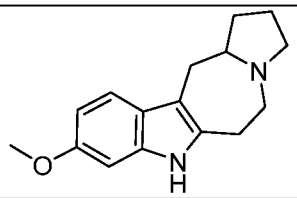
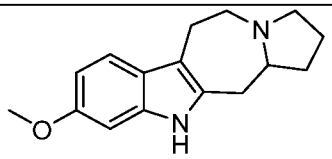
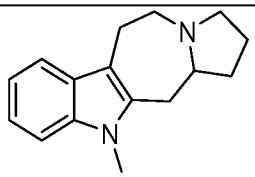
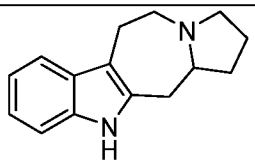
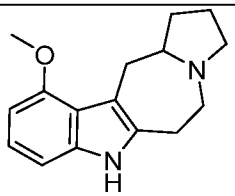
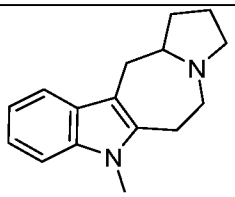
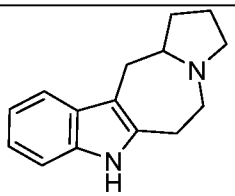
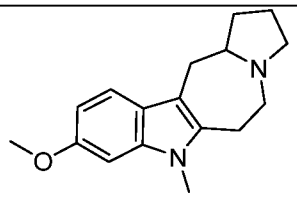
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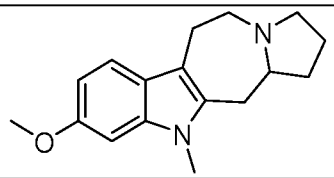
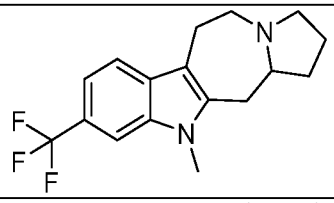
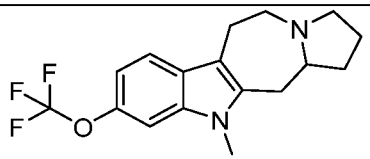
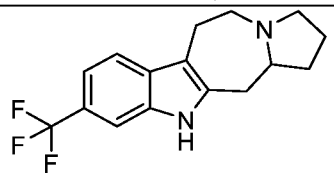
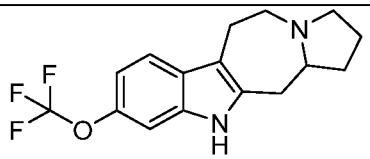
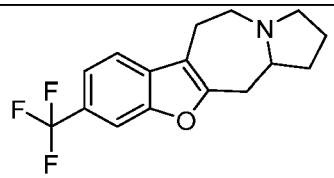
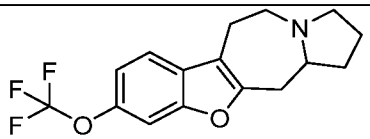
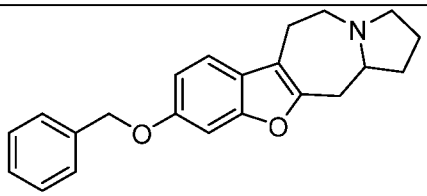
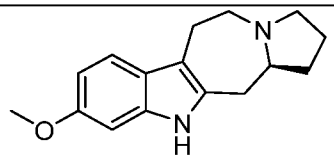
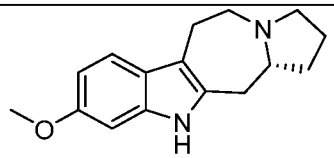
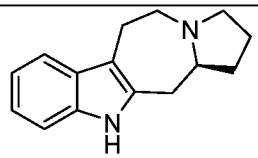
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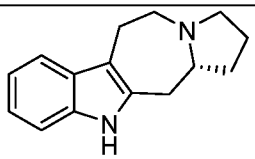
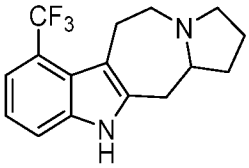
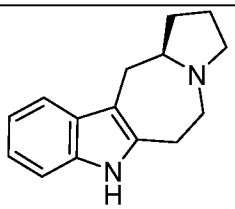
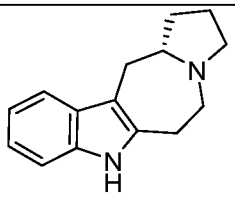
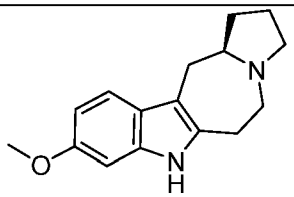
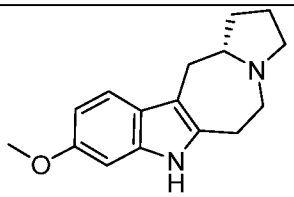
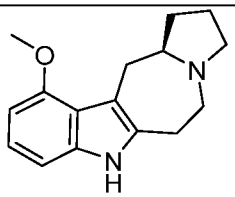
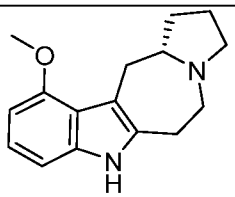
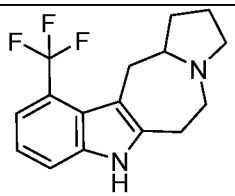
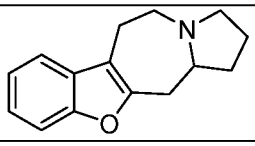
and pharmaceutically acceptable salts or solvates thereof.

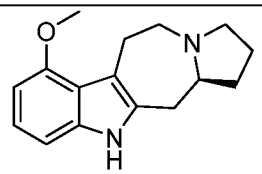
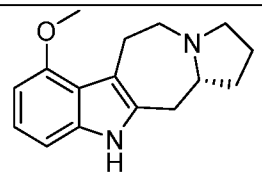
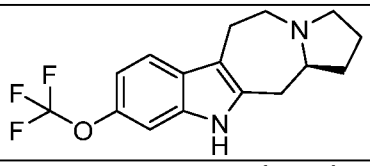
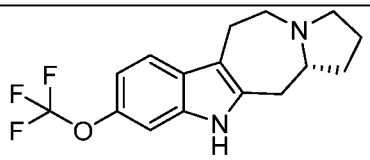
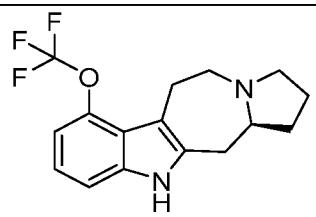
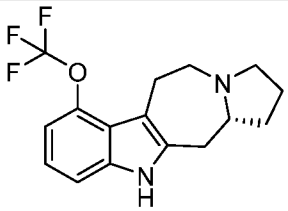
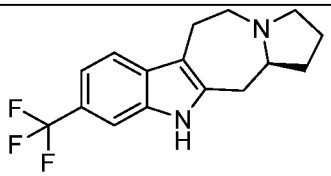
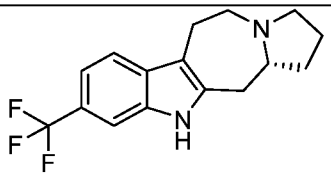
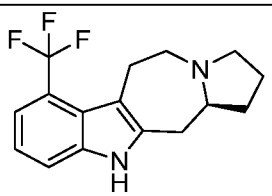
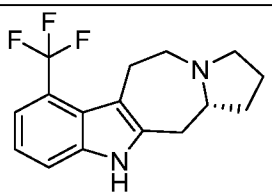
[00118] Provided in some embodiments herein is a compound, a stereoisomer thereof, or a pharmaceutically acceptable salt of the compound or the stereoisomer, having a structure provided in Table 1.

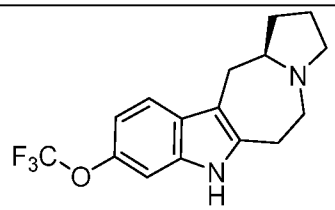
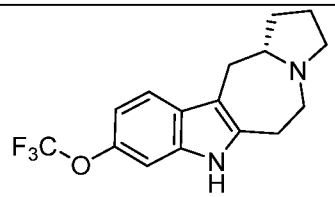
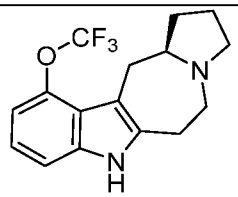
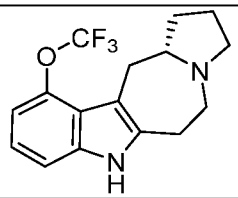
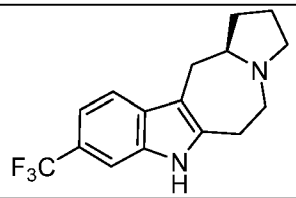
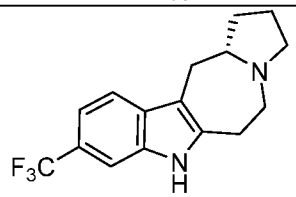
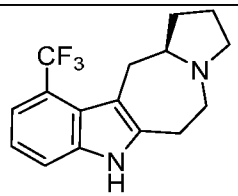
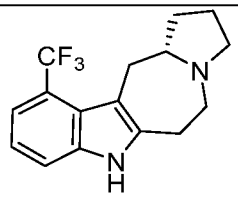
Table 1

Compound	Structure	Chemical Name
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2		9-methoxy-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole
3		11-methyl-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole
4		1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole
5		11-methoxy-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole
6		7-methyl-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole
7		1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole
8		9-methoxy-7-methyl-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole

9		9-methoxy-11-methyl-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole
10		11-methyl-9-(trifluoromethyl)-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole
11		11-methyl-9-(trifluoromethoxy)-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole
12		9-(trifluoromethyl)-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole
13		9-(trifluoromethoxy)-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole
14		9-(trifluoromethyl)-2,3,5,6,12,12a-hexahydro-1H-benzofuro[2,3-d]pyrrolo[1,2-a]azepine
15		9-(trifluoromethoxy)-2,3,5,6,12,12a-hexahydro-1H-benzofuro[2,3-d]pyrrolo[1,2-a]azepine
16		9-(benzyloxy)-2,3,5,6,12,12a-hexahydro-1H-benzofuro[2,3-d]pyrrolo[1,2-a]azepine
17		(S)-9-methoxy-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole
18		(R)-9-methoxy-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole
19		(S)-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole

20		(R)-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole
21		7-(trifluoromethyl)-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole
22		(R)-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole
23		(S)-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole
24		(R)-9-methoxy-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole
25		(S)-9-methoxy-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole
26		(R)-11-methoxy-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole
27		(S)-11-methoxy-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole
28		11-(trifluoromethyl)-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole
29		2,3,5,6,12,12a-hexahydro-1H-benzofuro[2,3-d]pyrrolo[1,2-a]azepine

30		(S)-7-methoxy-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole
31		(R)-7-methoxy-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole
32		(S)-9-(trifluoromethoxy)-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole
33		(R)-9-(trifluoromethoxy)-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole
34		(S)-7-(trifluoromethoxy)-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole
35		(R)-7-(trifluoromethoxy)-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole
36		(S)-9-(trifluoromethyl)-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole
37		(R)-9-(trifluoromethyl)-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole
38		(S)-7-(trifluoromethyl)-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole
39		(R)-7-(trifluoromethyl)-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole

40		(R)-9-(trifluoromethoxy)-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole
41		(S)-9-(trifluoromethoxy)-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole
42		(R)-11-(trifluoromethoxy)-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole
43		(S)-11-(trifluoromethoxy)-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole
44		(R)-9-(trifluoromethyl)-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole
45		(S)-9-(trifluoromethyl)-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole
46		(R)-11-(trifluoromethyl)-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole
47		(S)-11-(trifluoromethyl)-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole

[00119] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

Further Forms of Compounds

[00120] In one embodiment, compounds described herein are in the form of pharmaceutically acceptable salts. In some embodiments, any compound provided herein is a pharmaceutically acceptable salt, such as, for example, any salt described herein (such as, e.g., a fumarate salt of the compound provided herein or maleate salt of the compound provided herein). In some embodiments, any compound provided herein is a fumarate salt of the compound provided herein. In some embodiments, any compound provided herein is a maleate salt of the compound provided herein.

[00121] As well, active metabolites of these compounds having the same type of activity are included in the scope of the present disclosure. In addition, the compounds described herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00122] In some embodiments, pharmaceutically acceptable salts are obtained by reacting a compound of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), for example any compound described in Table 1, with an acid. In some embodiments, the compound of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), for example any compound described in Table 1, (i.e. free base form) is basic and is reacted with an organic acid or an inorganic acid. Inorganic acids include, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and metaphosphoric acid. Organic acids include, but are not limited to, 1-hydroxy-2-naphthoic acid; 2,2-dichloroacetic acid; 2-hydroxyethanesulfonic acid; 2-oxoglutaric acid; 4-acetamidobenzoic acid; 4-aminosalicylic acid; acetic acid; adipic acid; ascorbic acid (L); aspartic acid (L); benzenesulfonic acid; benzoic acid; camphoric acid (+); camphor-10-sulfonic acid (+); capric acid (decanoic acid); caproic acid (hexanoic acid); caprylic acid (octanoic acid); carbonic acid; cinnamic acid; citric acid; cyclamic acid; dodecylsulfuric acid; ethane-1,2-disulfonic acid; ethanesulfonic acid; formic acid; fumaric acid; galactaric acid; gentisic acid; glucoheptonic acid (D); gluconic acid (D); glucuronic acid (D); glutamic acid; glutaric acid; glycerophosphoric acid; glycolic acid; hippuric acid; isobutyric acid; lactic acid (DL); lactobionic acid; lauric acid; maleic acid; malic acid (- L); malonic acid; mandelic acid (DL); methanesulfonic acid; naphthalene-1,5-disulfonic acid; naphthalene-2-sulfonic acid; nicotinic acid; oleic acid; oxalic acid; palmitic acid; pamoic acid; phosphoric acid; proprionic acid; pyroglutamic acid (- L); salicylic acid; sebacic acid; stearic acid; succinic acid; sulfuric acid; tartaric acid (+ L); thiocyanic acid; toluenesulfonic acid (*p*); and undecylenic acid.

[00123] In some embodiments, the compound represented by the structure of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), for example any compound described in Table 1 (i.e. free base form) is basic and is reacted with maleic acid.

[00124] In some embodiments, the compound represented by the structure of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), for example any compound described in Table 1 (i.e. free base form) is basic and is reacted with fumaric acid.

[00125] In some embodiments, pharmaceutically acceptable salts are obtained by reacting a compound represented by the structure of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), for example any compound described in Table 1,with a base. In some embodiments, the compound of represented by the structure of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), for example any compound described in Table 1is acidic and is reacted with a base. In such situations, an acidic proton of the compound represented by the structure of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), for example any compound described in Table 1, is replaced by a metal ion, e.g., lithium, sodium, potassium, magnesium, calcium, or an aluminum ion. In some cases, compounds described herein coordinate with an organic base, such as, but not limited to, ethanolamine, diethanolamine, triethanolamine, tromethamine, meglumine, N-methylglucamine, dicyclohexylamine, tris(hydroxymethyl)methylamine. In other cases, compounds described herein form salts with amino acids such as, but not limited to, arginine, lysine, and the like. Acceptable inorganic bases used to form salts with compounds that include an acidic proton, include, but are not limited to, aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydroxide, lithium hydroxide, and the like. In some embodiments, the compounds provided herein are prepared as a sodium salt, calcium salt, potassium salt, magnesium salt, meglumine salt, N-methylglucamine salt or ammonium salt.

[00126] It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms. In some embodiments, solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of compounds described herein are conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein optionally exist in unsolvated as well as solvated forms.

[00127] The methods and formulations described herein include the use of *N*-oxides (if appropriate), or pharmaceutically acceptable salts of compounds having the structure of Formula

(I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), as well as active metabolites of these compounds having the same type of activity.

[00128] In some embodiments, sites on the organic radicals (e.g. alkyl groups, aromatic rings) of compounds of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), are susceptible to various metabolic reactions. Incorporation of appropriate substituents on the organic radicals will reduce, minimize or eliminate this metabolic pathway. In specific embodiments, the appropriate substituent to decrease or eliminate the susceptibility of the aromatic ring to metabolic reactions is, by way of example only, a halogen, deuterium, an alkyl group, a haloalkyl group, or a deuteroalkyl group.

[00129] In another embodiment, the compounds described herein are labeled isotopically (e.g. with a radioisotope) or by another other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

[00130] Compounds described herein include isotopically-labeled compounds, which are identical to those recited in the various formulae and structures presented herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the present compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, sulfur, fluorine chlorine, iodine, phosphorus, such as, for example, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{32}P and ^{33}P. In one embodiment, isotopically-labeled compounds described herein, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. In one embodiment, substitution with isotopes such as deuterium affords certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements. In some embodiments, one or more hydrogens of the compounds of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), are replaced with deuterium.

[00131] In some embodiments, a compound represented by the structure of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), for example any compound described in Table 1, possesses one or more stereocenters and each stereocenter exists independently in either the R or S configuration. In some embodiments, a compound represented by the structure of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), for example any compound described in Table 1, exists in the R configuration. In some embodiments, a compound represented by the structure of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), for example any compound described in Table 1, exists in the S configuration. The compounds presented herein include all diastereomeric, individual enantiomers, atropisomers, and epimeric forms as well as the appropriate

mixtures thereof. The compounds and methods provided herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof.

[00132] In some embodiments, a composition provided herein comprises a racemic mixture of a compound represented by a structure of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), for example any compound described in Table 1. In some embodiments, a compound provided herein is a racemate of a compound represented by a structure of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), for example any compound described in Table 1.

[00133] Individual stereoisomers are obtained, if desired, by methods such as, stereoselective synthesis and/or the separation of stereoisomers by chiral chromatographic columns or the separation of diastereomers by either non-chiral or chiral chromatographic columns or crystallization and recrystallization in a proper solvent or a mixture of solvents. In certain embodiments, a compound represented by the structure of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), for example any compound described in Table 1, is prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds/salts, separating the diastereomers and recovering the optically pure individual enantiomers. In some embodiments, resolution of individual enantiomers is carried out using covalent diastereomeric derivatives of the compounds described herein. In another embodiment, diastereomers are separated by separation/resolution techniques based upon differences in solubility. In other embodiments, separation of stereoisomers is performed by chromatography or by the forming diastereomeric salts and separation by recrystallization, or chromatography, or any combination thereof. Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981. In some embodiments, stereoisomers are obtained by stereoselective synthesis.

[00134] In some embodiments, compounds described herein are prepared as prodrugs. In some embodiments, a prodrug is an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they are easier to administer than the parent drug. They are, for embodiment, bioavailable by oral administration whereas the parent is not. Further or alternatively, the prodrug also has improved solubility in pharmaceutical compositions over the parent drug. In some embodiments, the design of a prodrug increases the effective water solubility. An example, without limitation, of a prodrug is a compound described herein, which is administered as an ester (the "prodrug") but then is metabolically hydrolyzed to provide the active entity. A further example of a prodrug is a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety. In certain embodiments, upon *in vivo* administration, a prodrug is chemically converted to the biologically, pharmaceutically or

therapeutically active form of the compound. In certain embodiments, a prodrug is enzymatically metabolized by one or more steps or processes to the biologically, pharmaceutically or therapeutically active form of the compound.

[00135] Prodrugs of the compounds described herein include, but are not limited to, esters, ethers, carbonates, thiocarbonates, N-acyl derivatives, N-acyloxyalkyl derivatives, N-alkyloxyacyl derivatives, quaternary derivatives of tertiary amines, N-Mannich bases, Schiff bases, amino acid conjugates, phosphate esters, and sulfonate esters. See for example Design of Prodrugs, Bundgaard, A. Ed., Elseview, 1985 and Method in Enzymology, Widder, K. *et al.*, Ed.; Academic, 1985, vol. 42, p. 309-396; Bundgaard, H. "Design and Application of Prodrugs" in A Textbook of Drug Design and Development, Krosgaard-Larsen and H. Bundgaard, Ed., 1991, Chapter 5, p. 113-191; and Bundgaard, H., Advanced Drug Delivery Review, 1992, 8, 1-38, each of which is incorporated herein by reference. In some embodiments, a hydroxyl group in the compounds disclosed herein is used to form a prodrug, wherein the hydroxyl group is incorporated into an acyloxyalkyl ester, alkoxycarbonyloxyalkyl ester, alkyl ester, aryl ester, phosphate ester, sugar ester, ether, and the like. In some embodiments, a hydroxyl group in the compounds disclosed herein is a prodrug wherein the hydroxyl is then metabolized in vivo to provide a carboxylic acid group. In some embodiments, a carboxyl group is used to provide an ester or amide (i.e. the prodrug), which is then metabolized in vivo to provide a carboxylic acid group. In some embodiments, compounds described herein are prepared as alkyl ester prodrugs.

[00136] Prodrug forms of the herein described compounds, wherein the prodrug is metabolized *in vivo* to produce a compound of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), as set forth herein are included within the scope of the claims.

[00137] In some embodiments, any one of the hydroxyl group(s), amino group(s) and/or carboxylic acid group(s) are functionalized in a suitable manner to provide a prodrug moiety. In some embodiments, the prodrug moiety is as described above.

[00138] In additional or further embodiments, the compounds described herein are metabolized upon administration to an organism in need to produce a metabolite that is then used to produce a desired effect, including a desired therapeutic effect.

[00139] In some embodiments, a metabolite of a compound disclosed herein is a derivative of that compound that is formed when the compound is metabolized. In some embodiments. an "active metabolite" of a compound provided herein is a biologically active derivative of the compound provided herein that is formed when the compound is metabolized. In some embodiments, metabolism is the sum of the processes (including, but not limited to, hydrolysis reactions and reactions catalyzed by enzymes) by which a particular substance is changed by an organism. In

some embodiments, enzymes may produce specific structural alterations to a compound. For example, cytochrome P450 catalyzes a variety of oxidative and reductive reactions while uridine diphosphate glucuronyltransferases catalyze the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulphydryl groups. In some embodiments, a metabolite of a compound disclosed herein is optionally identified either by administration of compounds to a host and analysis of tissue samples from the host, or by incubation of compounds with hepatic cells in vitro and analysis of the resulting compounds.

Synthesis of Compounds

[00140] Compounds of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), described herein are synthesized using standard synthetic techniques or using methods known in the art in combination with methods described herein.

[00141] Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology are employed.

[00142] Compounds are prepared using standard organic chemistry techniques such as those described in, for example, March's Advanced Organic Chemistry, 6th Edition, John Wiley and Sons, Inc. Alternative reaction conditions for the synthetic transformations described herein may be employed such as variation of solvent, reaction temperature, reaction time, as well as different chemical reagents and other reaction conditions.

[00143] In some embodiments, compounds described herein are synthesized as outlined in the Examples.

Pharmaceutical compositions

[00144] In some embodiments, provided herein is a pharmaceutical composition comprising a compound provided herein (e.g., a compound having a structure represented by Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), for example any compound described in Table 1, and a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition further comprises at least one pharmaceutically acceptable excipient.

[00145] In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable inactive ingredients that facilitate processing of the active compounds into preparations that are used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein is found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975;

Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), herein incorporated by reference for such disclosure.

[00146] In some embodiments, the compounds described herein are administered either alone or in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition. Administration of the compounds and compositions described herein can be affected by any method that enables delivery of the compounds to the site of action. These methods include, though are not limited to delivery via enteral routes (including oral, gastric or duodenal feeding tube, rectal suppository and rectal enema), parenteral routes (injection or infusion, including intraarterial, intracardiac, intradermal, intraduodenal, intramedullary, intramuscular, intraosseous, intraperitoneal, intrathecal, intravascular, intravenous, intravitreal, epidural and subcutaneous), inhalational, transdermal, transmucosal, sublingual, buccal and topical (including epicutaneous, dermal, enema, eye drops, ear drops, intranasal, vaginal) administration, although the most suitable route may depend upon for example the condition and disorder of the recipient. By way of example only, compounds described herein can be administered locally to the area in need of treatment, by for example, local infusion during surgery, topical application such as creams or ointments, injection, catheter, or implant. The administration can also be by direct injection at the site of a diseased tissue or organ.

[00147] In some embodiments, pharmaceutical compositions suitable for oral administration are presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. In some embodiments, the active ingredient is presented as a bolus, electuary or paste.

[00148] Pharmaceutical compositions which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. In some embodiments, the tablets are coated or scored and are formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can

contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In some embodiments, stabilizers are added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or Dragee coatings for identification or to characterize different combinations of active compound doses.

[00149] In some embodiments, pharmaceutical compositions are formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[00150] Pharmaceutical compositions for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[00151] It should be understood that in addition to the ingredients particularly mentioned above, the compounds and compositions described herein may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Methods of Treatment, Dosing and Treatment Regimens

[00152] The compounds disclosed herein, or pharmaceutically acceptable salts, solvates, or stereoisomers thereof, are useful for promoting neuronal growth and/or improving neuronal structure.

[00153] Provided herein are non-hallucinogenic psychoplastogens that useful for treating one or more diseases or disorders associated with loss of synaptic connectivity and/or plasticity.

[00154] In some embodiments, provided herein is a method of promoting neural plasticity (e.g., cortical structural plasticity) in an individual by administering a compound described herein (e.g., a compound represented by the structure of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), for example any compound described in Table 1, to the individual. In some embodiments, provided herein are methods of modulating 5-HT_{2A} in an individual by administering a compound described herein (e.g., a compound represented by the structure of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), for example any compound described in Table 1, to the individual. In some embodiments, provided herein are methods of agonizing 5-HT_{2A} in an individual by administering a compound described herein (e.g., a compound represented by the structure of Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), for example any compound described in Table 1, to the individual. In some embodiments, the individual has or is diagnosed with a brain disorder or other conditions described herein.

[00155] In some embodiments, provided herein is a method of promoting neuronal growth in an individual in need thereof, comprising administering to the individual in need thereof a therapeutically effective amount of a compound or pharmaceutical composition provided herein (e.g., a compound having a structure represented by Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), for example any compound described in Table 1).

[00156] In some embodiments, provided herein is a method of improving neuronal structure in an individual in need thereof, comprising administering to the individual in need thereof a therapeutically effective amount of a compound or pharmaceutical composition provided herein (e.g., a compound having a structure represented by Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), for example any compound described in Table 1).

[00157] In some embodiments, provided herein is a method of modulating the activity of 5-hydroxytryptamine receptor 2A (5-HT_{2A}) receptor in an individual in need thereof, comprising administering to the individual in need thereof a therapeutically effective amount of a compound or pharmaceutical composition provided herein (e.g., a compound having a structure represented by Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), or for example any compound described in Table 1).

[00158] In some embodiments, provided herein is a method of treating a disease or disorder in an individual in need thereof that is mediated by the action of 5-hydroxytryptamine (5-HT) at 5-hydroxytryptamine receptor 2A (5-HT_{2A}), comprising administering to the individual in need thereof a therapeutically effective amount of a compound or pharmaceutical composition provided herein (e.g., a compound having a structure represented by Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), or for example any compound described in Table 1).

[00159] In some embodiments, provided herein is a method of treating a disease or disorder in an individual in need thereof that is mediated by the loss of synaptic connectivity, plasticity, or a combination thereof, comprising administering to the individual in need thereof a therapeutically effective amount of a compound or pharmaceutical composition provided herein (e.g., a compound having a structure represented by Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), or for example any compound described in Table 1).

[00160] In some embodiments, provided herein is a method of treating a neurological disease or disorder in an individual in need thereof, comprising administering to the individual in need thereof a therapeutically effective amount of a compound or pharmaceutical composition provided herein (e.g., a compound having a structure represented by Formula (I), (IA), (IA-1), (IA-2), (IA-3), (IB), (IB-1), (IB-2), (IB-3), or for example any compound described in Table 1).

[00161] In some embodiments, an individual administered a compound provided herein has a hallucinogenic event. In some embodiments, an individual administered a compound provided herein does not have a hallucinogenic event. In some embodiments, an individual administered a compound provided herein has a hallucinogenic event after the compound provided herein reaches a particular maximum concentration (C_{max}) in the individual. In some embodiments, the particular maximum concentration (C_{max}) in the individual is the hallucinogenic threshold of the compound provided herein. In some embodiments, a compound provided herein is administered to an individual in need thereof below the hallucinogenic threshold of the compound provided herein.

[00162] In some embodiments, described herein are methods for treating a disease or disorder, wherein the disease or disorder is a neurological diseases and disorder.

[00163] In some embodiments, a compound of the present disclosure is used to treat neurological diseases. In some embodiments, a compound provided herein has, for example, anti-addictive properties, antidepressant properties, anxiolytic properties, or a combination thereof.

[00164] In some embodiments, the neurological disease is a neuropsychiatric disease. In some embodiments, the neuropsychiatric disease is a mood or anxiety disorder. In some embodiments, the neurological disease is a migraine, headaches (e.g., cluster headache), post-traumatic stress disorder (PTSD), anxiety, depression, neurodegenerative disorder, Alzheimer's disease,

Parkinson's disease, psychological disorder, treatment resistant depression, suicidal ideation, major depressive disorder, bipolar disorder, schizophrenia, stroke, traumatic brain injury, and addiction (e.g., substance use disorder). In some embodiments, the neurological disease is a migraine or cluster headache. In some embodiments, the neurological disease is a neurodegenerative disorder, Alzheimer's disease, or Parkinson's disease. In some embodiments, the neurological disease is a psychological disorder, treatment resistant depression, suicidal ideation, major depressive disorder, bipolar disorder, schizophrenia, post-traumatic stress disorder (PTSD), addiction (e.g., substance use disorder), depression, or anxiety. In some embodiments, the neuropsychiatric disease is a psychological disorder, treatment resistant depression, suicidal ideation, major depressive disorder, bipolar disorder, schizophrenia, post-traumatic stress disorder (PTSD), addiction (e.g., substance use disorder), depression, or anxiety. In some embodiments, the neuropsychiatric disease or neurological disease is post-traumatic stress disorder (PTSD), addiction (e.g., substance use disorder), schizophrenia, depression, or anxiety. In some embodiments, the neuropsychiatric disease or neurological disease is addiction (e.g., substance use disorder). In some embodiments, the neuropsychiatric disease or neurological disease is depression. In some embodiments, the neuropsychiatric disease or neurological disease is anxiety. In some embodiments, the neuropsychiatric disease or neurological disease is post-traumatic stress disorder (PTSD). In some embodiments, the neurological disease is stroke or traumatic brain injury. In some embodiments, the neuropsychiatric disease or neurological disease is schizophrenia.

[00165] In some embodiments, a compound disclosed herein, or pharmaceutically acceptable salts, solvates, or stereoisomers thereof, is useful for the modulation of a 5-hydroxytryptamine (5-HT) receptor. In some embodiments, the 5-HT receptor modulated by the compounds and methods is 5-hydroxytryptamine receptor 2A (5-HT_{2A}).

[00166] Provided in some embodiments herein are modulators of 5-hydroxytryptamine receptor 2A (5-HT_{2A}) that are useful for treating one or more diseases or disorders associated with 5-HT_{2A} activity.

[00167] In some embodiments, a compound described herein, or a pharmaceutically acceptable salt thereof, are used in the preparation of medicaments for the treatment of diseases or conditions in a mammal that would benefit from inhibition or reduction of 5-HT_{2A} activity.

[00168] In some embodiments, a compound described herein, or a pharmaceutically acceptable salt thereof, are used in the preparation of medicaments for the treatment of diseases or conditions in a mammal that would benefit from promoting neuronal growth and/or improving neuronal structure.

[00169] Methods for treating any of the diseases or conditions described herein in a mammal in need of such treatment, involves administration of pharmaceutical compositions that include at least one compound described herein or a pharmaceutically acceptable salt, active metabolite, prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said mammal.

[00170] In certain embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the compositions are administered to a mammal already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the mammal's health status, weight, and response to the drugs, and the judgment of a healthcare practitioner. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation and/or dose ranging clinical trial.

[00171] In prophylactic applications, compositions containing the compounds described herein are administered to a mammal susceptible to or otherwise at risk of a particular disease, disorder or condition. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the mammal's state of health, weight, and the like. When used in mammals, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the mammal's health status and response to the drugs, and the judgment of a healthcare professional. In one embodiment, prophylactic treatments include administering to a mammal, who previously experienced at least one symptom of the disease being treated and is currently in remission, a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt thereof, in order to prevent a return of the symptoms of the disease or condition.

[00172] In certain embodiments wherein the mammal's condition does not improve, upon the discretion of a healthcare professional the administration of the compounds are administered chronically, that is, for an extended period of time, including throughout the duration of the mammal's life in order to ameliorate or otherwise control or limit the symptoms of the mammal's disease or condition.

[00173] In certain embodiments wherein a mammal's status does improve, the dose of drug being administered is temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, or more than 28 days. The dose reduction during a drug holiday is,

by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

[00174] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, in specific embodiments, the dosage or the frequency of administration, or both, is reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In certain embodiments, however, the mammal requires intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00175] The amount of a given agent that corresponds to such an amount varies depending upon factors such as the particular compound, disease condition and its severity, the identity (*e.g.*, weight, sex) of the subject or host in need of treatment, but nevertheless is determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated.

[00176] In general, however, doses employed for adult human treatment are typically in the range of 0.01 mg-5000 mg per day. In one embodiment, doses employed for adult human treatment are from about 1 mg to about 1000 mg per day. In one embodiment, the desired dose is conveniently presented in a single dose or in divided doses administered simultaneously or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00177] In one embodiment, the daily dosages appropriate for the compound described herein, or a pharmaceutically acceptable salt thereof, are from about 0.01 to about 50 mg/kg per body weight. In some embodiments, the daily dosage or the amount of active in the dosage form are lower or higher than the ranges indicated herein, based on a number of variables in regard to an individual treatment regime. In various embodiments, the daily and unit dosages are altered depending on a number of variables including, but not limited to, the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00178] Toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD_{50} and the ED_{50}. The dose ratio between the toxic and therapeutic effects is the therapeutic index and it is expressed as the ratio between LD_{50} and ED_{50}. In certain embodiments, the data obtained from cell culture assays and animal studies are used in formulating the therapeutically effective daily dosage range and/or the therapeutically effective unit dosage amount for use in mammals, including humans. In some embodiments, the daily dosage amount of the compounds described herein lies within a range of circulating concentrations that include the

ED_{50} with minimal toxicity. In certain embodiments, the daily dosage range and/or the unit dosage amount varies within this range depending upon the dosage form employed and the route of administration utilized.

[00179] In any of the aforementioned aspects are further embodiments in which the effective amount of the compound described herein, or a pharmaceutically acceptable salt thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by injection to the mammal; and/or (e) administered topically to the mammal; and/or (f) administered non-systemically or locally to the mammal.

[00180] In any of the aforementioned aspects are further embodiments comprising single administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered once a day; or (ii) the compound is administered to the mammal multiple times over the span of one day.

[00181] In any of the aforementioned aspects are further embodiments comprising multiple administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered continuously or intermittently: as in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the compound is administered to the mammal every 8 hours; (iv) the compound is administered to the mammal every 12 hours; (v) the compound is administered to the mammal every 24 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. In one embodiment, the length of the drug holiday varies from 2 days to 1 year.

[00182] In one embodiment, the therapeutic effectiveness of one of the compounds described herein is enhanced by administration of an adjuvant (*i.e.*, by itself the adjuvant has minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, in some embodiments, the benefit experienced by a patient is increased by administering one of the compounds described herein with another agent (which also includes a therapeutic regimen) that also has therapeutic benefit.

[00183] In certain embodiments, different therapeutically-effective dosages of the compounds disclosed herein will be utilized in formulating pharmaceutical composition and/or in treatment regimens when the compounds disclosed herein are administered in combination with one or more additional agent, such as an additional therapeutically effective drug, an adjuvant or the like. Therapeutically-effective dosages of drugs and other agents for use in combination treatment

regimens is optionally determined by means similar to those set forth hereinabove for the actives themselves. Furthermore, the methods of prevention/treatment described herein encompasses the use of metronomic dosing, i.e., providing more frequent, lower doses in order to minimize toxic side effects. In some embodiments, a combination treatment regimen encompasses treatment regimens in which administration of a compound described herein, or a pharmaceutically acceptable salt thereof, is initiated prior to, during, or after treatment with a second agent described herein, and continues until any time during treatment with the second agent or after termination of treatment with the second agent. It also includes treatments in which a compound described herein, or a pharmaceutically acceptable salt thereof, and the second agent being used in combination are administered simultaneously or at different times and/or at decreasing or increasing intervals during the treatment period. Combination treatment further includes periodic treatments that start and stop at various times to assist with the clinical management of the patient.

[00184] It is understood that the dosage regimen to treat, prevent, or ameliorate the disease(s) for which relief is sought, is modified in accordance with a variety of factors (e.g. the disease or disorder from which the subject suffers; the age, weight, sex, diet, and medical condition of the subject). Thus, in some embodiments, the dosage regimen actually employed varies and, in some embodiments, deviates from the dosage regimens set forth herein.

EXAMPLES

[00185] The following examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

General

[00186] All reagents are obtained commercially and used without purification unless otherwise noted. DMSO is purified by passage under 12 psi N_2 through activated alumina columns. Reactions are performed using glassware that is flame-dried under reduced pressure (~1 Torr). Compounds purified by chromatography are adsorbed to the silica gel before loading. Thin layer chromatography is performed on Millipore silica gel 60 F_{254} Silica Gel plates. Visualization of the developed chromatogram is accomplished by fluorescence quenching or by staining with ninhydrin or aqueous ceric ammonium molybdate (CAM).

[00187] Nuclear magnetic resonance (NMR) spectra are acquired on either a Bruker 400 operating at 400 and 100 MHz, a Varian 400 operating at 400 and 100 MHz, or a Varian 500 operating at 500 and 125 MHz for ^{1}H and ^{13}C, respectively, and are referenced internally according to residual solvent signals. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (Hz), and integration. Data

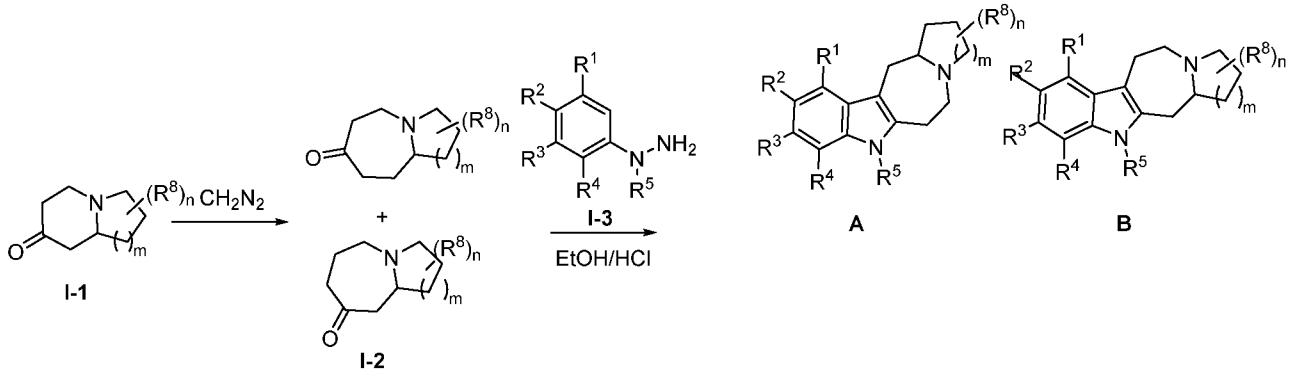
for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Liquid chromatography-mass spectrometry (LC-MS) is performed using a Agilient LC-MS with Ion Trap or ELSD detector, or a Waters LC-MS with an UPLC detector.

Chemistry

General synthetic scheme:

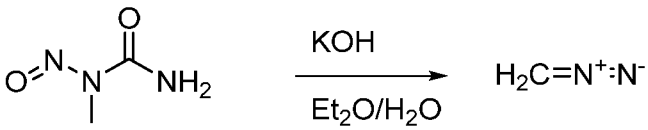
[00188] In some embodiments, compounds provided herein are prepared as outlined in Scheme 1.

Scheme 1



In Scheme 1, R^1-R^5, R^8, m and n are as described herein.

[00189] Preparation of diazomethane:



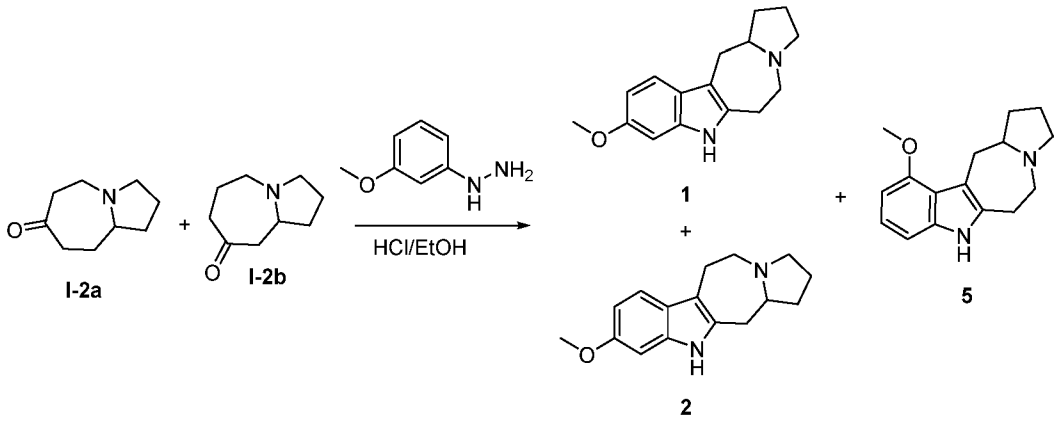
To a biphasic mixture of Et_2O (80.3 mL) and KOH (16.1 g, 287 mmol, 5.28 eq) in water (16.1 mL, 1 vol) was added commercially available N-nitroso-N-methylurea (5.6 g, 54.3 mmol, 1.0 eq) in 7 to 8 portions at 0°C, and the reaction mixture was stirred at at 0°C for additional 20 minutes. The yellow ether layer was decanted and transferred directly to the following reaction without purification or concentration. Additional 15 mL of ether chilled to 0°C was added to the aqueous layer and swirled gently. The ether layer was decanted and transferred to the following reaction. Residual diazomethane in the aqueous layer was neutralized carefully by the careful dropwise addition of concentrated acetic acid at 0 °C until the pale yellow color of diazomethane disappeared.

[00190] Preparation of intermediate I-2: In some embodiments, to a solution of commercially available intermediate **I-1** (1.0 eq) in EtOH (10 vol) was added drop-wise a solution of diazomethane in diethyl ether (2.2 eq) over a period of 10 min at 0°C, the reaction mixture was allowed to slowly warm to room temperature and stirred for an additional 4 hours. The crude

reaction mixture was quenched with acetic acid at 0°C concentrated in *vacuo* to afford intermediate **I-2** as regioisomeric mixture that was used in the next step without further purification.

[00191] Preparation of compounds A and B: In some embodiments, to a stirred solution of intermediate **I-2** (1.0 eq) in EtOH (0.1M) were added commercially available intermediate **I-3** (1.0 eq) followed by HCl (6.0 eq, 37% aqueous solution) and the reaction mixture was stirred under reflux for 24 hours. The crude reaction mixture was concentrated in *vacuo* and the crude residue was diluted with CH_2Cl_2, basified with NaOH (1.0M aqueous solution) and extracted with 10% MeOH in CH_2Cl_2. The combined organic layers were washed with a brine solution, the combined organic layer was dried over anhydrous Na_2SO_4, solids were removed by filtration and the filtrate was concentrated in *vacuo* to provide a crude reaction product. This crude reaction product was purified by silicagel chromatography (5% MeOH in CH_2Cl_2) to afford a regioisomeric mixture that was separated further with reverse-phase HPLC to afford compounds **A and B**. Chemical structure of each analog was assigned by using 2D-NMR spectroscopic techniques.

[00192] Synthesis of 9-methoxy-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole (1), 9-methoxy-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole (2), and 11-methoxy-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole (5) :



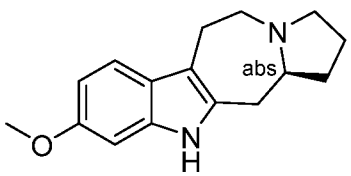
To a stirred solution of a mixture of intermediates **I-2a** and **I-2b** (600 mg, 4.31 mmol, 1.0 eq) in EtOH (43.1 mL) were added (3-methoxyphenyl)hydrazine hydrochloride (751 mg, 4.31 mmol, 1.0 eq) followed by a solution of HCl (930 mg 25.86 mmol, 6.0 eq, 36% w/w in water) and the resulting reaction mixture was sirred at reflux for 24 hours. The reaction mixture was concentrated in *vacuo*, the crude residue was diluted with CH_2Cl_2 and a solution of NaOH was added (1M NaOH in water). The crude reaction mixture was extracted with CH_2Cl_2 (25 mL, 10% MeOH in CH_2Cl_2), the combined organic layers were washed with brine, the combined organic layers were dried over anhydrous Na_2SO_4, solids were removed by filtration and the filtrate was concentrated in *vacuo* to provide a crude product that was purified by silica-gel chromatography (10% MeOH in CH_2Cl_2) to afford a mixture of regiomers (480 mg). LC-MS chromatogram indicated a ratio of 44%, 22% & 21%.

Individual regioisomers were seprataed by reverse phase preparative HPLC to provide compound 1, compound 2 and compound 5.

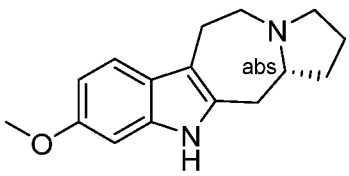
To a solution of Compound 2 (33 mg, 0.13 mmol, 1.0 equiv) in acetone (1.0 ml) was added fumaric acid (12mg, 0.10mmol 0.8 equiv) in acetone (2.0 ml) at 50^0C and the reaction mixture was stirred for 3 hrs at 50^0C. The reaction mixture was concentrated *in vacuo* and the solid residue was washed with diethylether to obtain the fumarate salt of Compound 2.

Compound 1 fumarate salt: prepared as described for Compound 2.

[00193] Chiral resolution of (S)-9-methoxy-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole (17), (R)-9-methoxy-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole (18):



17



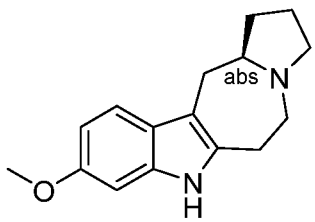
18

Racemic Compound 2 (80 mg) was separated into its enantiomers by using chiral HPLC (Chiralcel OJ-H 250mm (L) x 30mm (ID) 5µ, gradient of 0.1% DEA in Hexane/EtOH (50%/50%, 40.0 mL/min). The first eluting enantiomer had a retention time of 7.60 minutes, and the second eluting enantiomer had a retention time of 9.41 minutes.

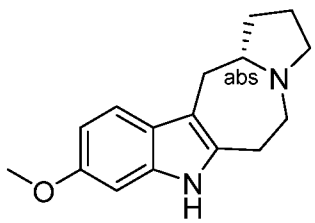
Compound 17 fumarate salt: prepared as described for Compound 2.

Compound 18 fumarate salt: prepared as described for Compound 2.

[00194] Chiral resolution of (R)-9-methoxy-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole (24), (S)-9-methoxy-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole (25),:



24



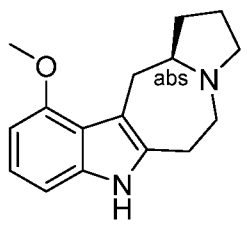
25

Racemic Compound 1 (140 mg) was separated into its enantiomers by using chiral HPLC (Chiralcel OJ-H 250mm (L) x 30mm (ID) 5µ, gradient of 0.1% DEA in Hexane/EtOH (50%/50%, 40.0 mL/min). The first eluting enantiomer had a retention time of 7.560 minutes, and the second eluting enantiomer had a retention time of 9.54 minutes.

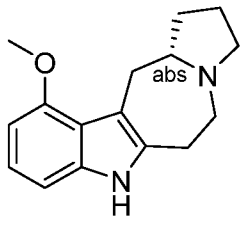
Compound 24 fumarate salt: prepared as described for Compound 2.

Compound 25 fumarate salt: prepared as described for Compound 2.

[00195] Chiral resolution of (R)-11-methoxy-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole (26) & (S)-11-methoxy-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole (27):



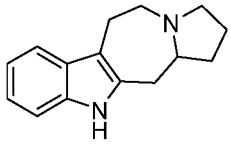
26



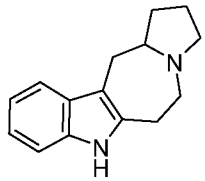
27

Racemic Compound 5 (20 mg) was separated into its enantiomers by using chiral HPLC (Chiral pak-IG (250*30)5um, gradient of 0.1% DEA in Hexane/IPA (90%/10%, 35.0 mL/min). The first eluting enantiomer had a retention time of 7.92 minutes, and the second eluting enantiomer had a retention time of 12.35 minutes.

[00196] Preparation of 1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole (4), and 1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole (7):



4



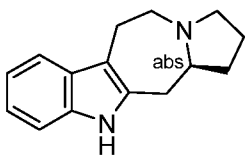
7

The title compounds were prepared as described for Compound 1 & Compound 2 but using phenylhydrazine as the starting material.

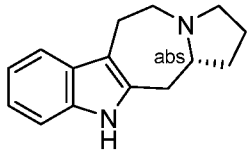
Compound 4 fumarate salt: prepared as described for Compound 2.

Compound 7 fumarate salt: prepared as described for Compound 2.

[00197] Chiral resolution of (S)-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole (19), (R)-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole (20):



19



20

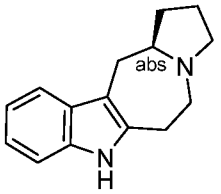
Compound 4 (270 mg) was separated into its enantiomers by using chiral HPLC (Chiral pak-IG (250*20)5um, gradient of 0.1% DEA in Hexane/IPA (80%/20%, 32.0 mL/min). The first eluting

enantiomer had a retention time of 5.45 minutes, and the second eluting enantiomer had a retention time of 6.57 minutes.

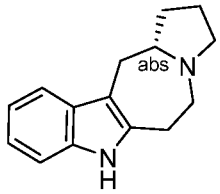
Compound 19 fumarate salt: prepared as described for Compound 2.

Compound 20 fumarate salt: prepared as described for Compound 2.

[00198] Chiral resolution of (R)-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole (22) & (S)-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole (23):



22



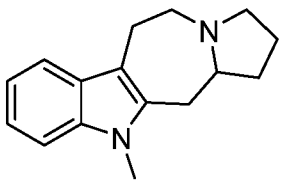
23

Compound 7 (360 mg) was separated into its enantiomers by using chiral HPLC (Chiral pak-IG (250*30)5um, gradient of 0.1% DEA in Hexane/IPA (90%/10%, 33.0 mL/min). The first eluting enantiomer had a retention time of 5.53 minutes, and the second eluting enantiomer had a retention time of 7.41 minutes.

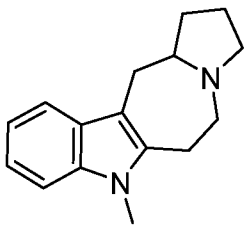
Compound 22 fumarate salt: prepared as described for Compound 2.

Compound 23 fumarate salt: prepared as described for Compound 2.

[00199] Preparation of 11-methyl-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole (3), and 7-methyl-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole (6):



3



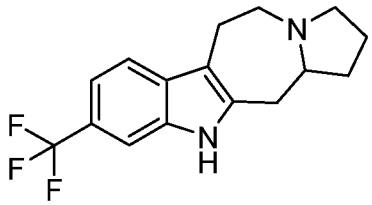
6

The title compounds were prepared as described for Compound 1 & Compound 2 but using 1-methyl-phenylhydrazine as the starting material.

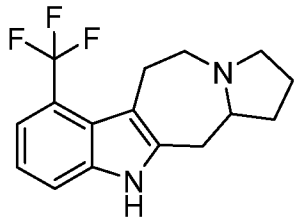
Compound 3 fumarate salt: prepared as described for Compound 2.

Compound 6 fumarate salt: prepared as described for Compound 2.

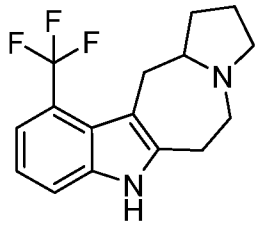
[00200] Preparation of 9-(trifluoromethyl)-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole (12), 7-(trifluoromethyl)-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole (21), and 11-(trifluoromethyl)-1,2,3,5,6,7,12,12a-octahydropyrrolo[1',2':1,7]azepino[4,5-b]indole (28):



12



21



28

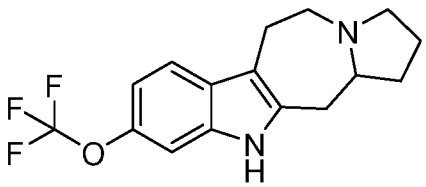
The title compounds were prepared as described for Compound 1 & Compound 2 but using 3-(trifluoromethyl)phenyl)hydrazine as the starting material.

Compound 12 fumarate salt: prepared as described for Compound 2.

Compound 21 fumarate salt: prepared as described for Compound 2.

Compound 28 fumarate salt: prepared as described for Compound 2.

[00201] Preparation of 9-(trifluoromethoxy)-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole (13):



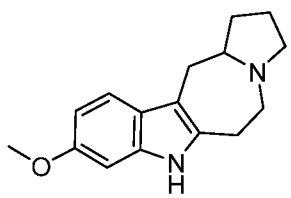
13

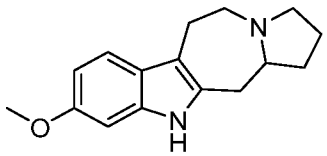
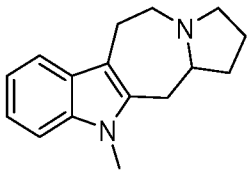
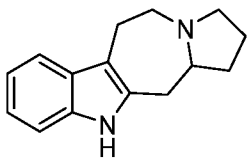
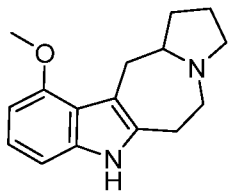
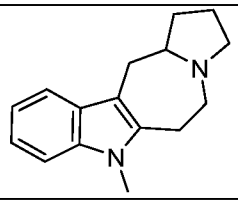
The title compound was prepared as described for Compound 1 & Compound 2 but using 3-(trifluoromethoxy)phenyl)hydrazine.HCl as the starting material.

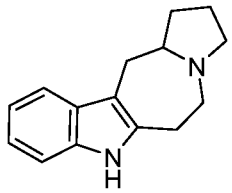
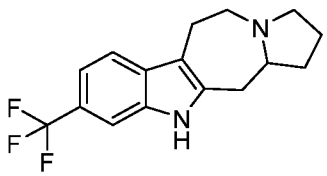
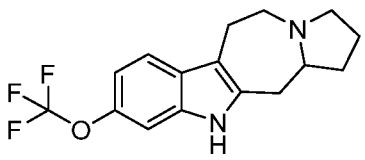
Compound 13 fumarate salt: prepared as described for Compound 2.

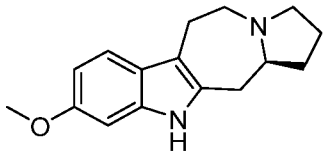
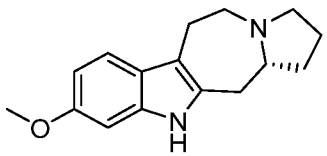
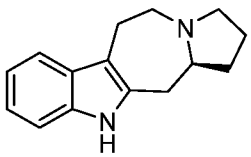
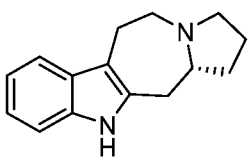
[00202] The compounds in **Table 2** were prepared as described for Compounds A and B using the appropriately substituted starting materials of formula I-2 and I-3.

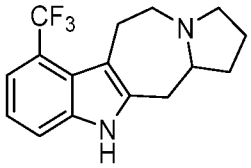
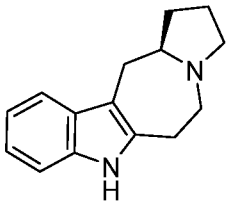
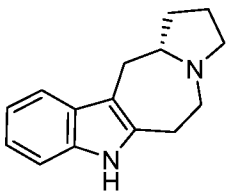
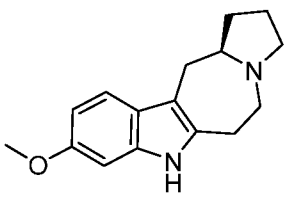
Table 2

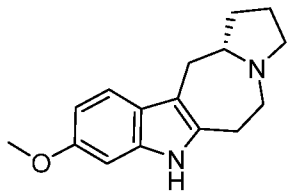
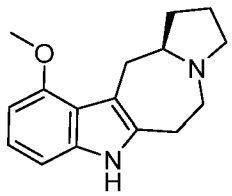
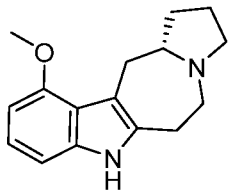
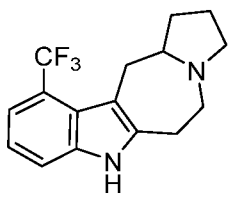
Compound	Structure	NMR and Mass Spectral Data
1		MS: *m/z* = 257.2 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.59 (br s, 1H), 7.33 (d, J = 8.5 Hz, 1H), 6.81 - 6.74 (m, 2H), 3.83 (s, 3H), 3.27 - 3.06 (m, 4H), 2.76 - 2.67 (m, 1H), 2.57 (ddd, J = 15.4, 10.5, 1.3 Hz, 1H), 2.48 - 2.23 (m, 3H), 2.23 - 2.08 (m, 1H), 1.93 - 1.81 (m, 1H), 1.78 - 1.67 (m, 2H) *^{1}H-NMR (400 MHz, DMSO-d6) δ = 13.28 - 12.27 (m, 2H), 10.54 (s, 1H), 7.25 (d, J = 8.5 Hz, 2H), 6.75 (d, J = 2.1 Hz, 2H), 6.58 (s, 4H), 3.76 - 3.69 (m, 3H), 3.21 - 3.11 (m, 3H), 3.08 - 2.93 (m, 3H), 2.86 - 2.78 (m, 1H), 2.67 (br s, 1H), 2.22 - 2.12 (m, 1H), 2.12 - 2.05 (m, 1H), 1.81 - 1.56 (m, 3H)

2		MS: *m/z* =257.1 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.56 (br s, 1H), 7.33 (d, J = 8.6 Hz, 1H), 6.81 - 6.74 (m, 2H), 3.83 (s, 3H), 3.30 (br d, J = 12.5 Hz, 1H), 3.25 - 3.18 (m, 1H), 3.01 - 2.79 (m, 4H), 2.50 - 2.39 (m, 1H), 2.36 - 2.23 (m, 2H), 2.18 - 2.02 (m, 1H), 1.95 - 1.80 (m, 1H), 1.77 - 1.61 (m, 2H) *^{1}H-NMR (400 MHz, DMSO-d6) δ = 10.55 - 10.48 (m, 1H), 7.25 (d, J = 8.7 Hz, 1H), 6.75 (d, J = 2.2 Hz, 1H), 6.57 (s, 3H), 3.73 (s, 4H), 3.32 - 3.29 (m, 2H), 3.24 - 3.21 (m, 1H), 2.96 - 2.67 (m, 5H), 2.41 - 2.31 (m, 1H), 2.19 - 2.09 (m, 1H), 1.81 - 1.53 (m, 3H)
3		MS: m/z=241.1 $[M+H]^+$, ^{1}H-NMR (400 MHz, DMSO-d6) δ = 7.43 - 7.39 (m, 1H), 7.32 (s, 1H), 7.07 - 7.01 (m, 1H), 6.98 - 6.93 (m, 1H), 3.65 (s, 3H), 3.30 - 3.27 (m, 3H), 3.26 - 3.18 (m, 2H), 3.18 - 3.15 (m, 4H), 3.13 - 3.06 (m, 2H), 3.02 - 2.95 (m, 1H), 2.66 (br s, 3H), 2.32 (s, 2H), 2.14 (s, 3H), 1.61 (br s, 3H) *^{1}H-NMR (400 MHz, DMSO-d6) δ = 7.42 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.09 - 7.03 (m, 1H), 7.00 - 6.95 (m, 1H), 6.58 (s, 3H), 3.66 (s, 3H), 3.21 - 3.19 (m, 2H), 3.18 (br d, J = 1.6 Hz, 2H), 3.07 - 2.99 (m, 2H), 2.74 (br s, 2H), 2.39 - 2.31 (m, 1H), 2.23 - 2.13 (m, 1H), 1.79 - 1.61 (m, 3H)
4		MS: m/z=227.1 $[M+H]^+$, ^{1}H-NMR (400 MHz, DMSO-d_6) δ = 10.74 - 10.69 (m, 1H), 8.19 (s, 2H), 7.39 (d, J = 7.7 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.02 - 6.91 (m, 2H), 3.29 (br d, J = 12.2 Hz, 2H), 3.18 (br s, 2H), 3.01 - 2.92 (m, 3H), 2.85 - 2.68 (m, 3H), 2.46 - 2.41 (m, 1H), 2.35 (br d, J = 1.6 Hz, 1H), 2.29 - 2.20 (m, 1H), 2.16 - 2.09 (m, 1H), 1.80 - 1.55 (m, 3H) *^{1}H-NMR (400 MHz, DMSO-d_6) δ = 10.75 (s, 1H), 7.39 (d, J = 7.5 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.00 - 6.91 (m, 2H), 6.57 (s, 2H), 3.38 - 3.32 (m, 2H), 3.28 - 3.22 (m, 2H), 3.03 - 2.95 (m, 2H), 2.90 - 2.83 (m, 1H), 2.77 - 2.68 (m, 1H), 2.38 - 2.32 (m, 1H), 2.20 - 2.10 (m, 1H), 1.82 - 1.59 (m, 3H)
5		MS: *m/z* = 257.1 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d6) δ = 10.68 (s, 1H), 6.83 (s, 2H), 6.39 (dd, J = 7.0, 1.4 Hz, 1H), 4.02 (s, 4H), 3.79 (s, 3H), 3.62 (d, J = 15.0 Hz, 1H), 3.14 - 3.00 (m, 2H), 2.93 - 2.73 (m, 3H), 2.33 (br s, 2H), 2.16 - 1.95 (m, 4H), 1.73 - 1.43 (m, 4H)
6		MS: m/z=241.2 $[M+H]^+$, ^{1}H-NMR (400 MHz, DMSO-d6) δ = 8.18 (s, 3H), 7.42 (d, J = 7.7 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.05 (dt, J = 7.6, 1.1 Hz, 1H), 6.99 - 6.94 (m, 1H), 3.65 (s, 3H), 3.32 - 3.28 (m, 1H), 3.18 - 3.06 (m, 3H), 2.93 - 2.86 (m, 1H),

		2.58 - 2.53 (m, 1H), 2.47 (s, 1H), 2.41 - 2.30 (m, 3H), 2.19 - 2.09 (m, 1H), 1.76 - 1.57 (m, 3H) *^{1}H-NMR (400 MHz, DMSO-d6) δ = 7.42 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.08 - 7.03 (m, 1H), 6.99 - 6.94 (m, 1H), 6.57 (s, 2H), 3.65 (s, 4H), 3.20 - 3.06 (m, 6H), 2.95 - 2.85 (m, 2H), 2.60 - 2.53 (m, 1H), 2.43 - 2.32 (m, 2H), 2.19 - 2.10 (m, 1H), 1.78 - 1.58 (m, 3H)
7		MS: m/z=227.1 $[M+H]^+$, ^{1}H-NMR (400 MHz, DMSO-d_6) δ = 10.74 (s, 1H), 8.18 (s, 2H), 7.38 (d, J = 7.7 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.00 - 6.90 (m, 2H), 3.30 - 3.19 (m, 3H), 3.18 - 3.15 (m, 4H), 3.12 - 3.04 (m, 1H), 3.04 - 2.94 (m, 1H), 2.87 (br d, J = 2.6 Hz, 1H), 2.46 - 2.32 (m, 3H), 2.15 (br s, 1H), 1.78 - 1.59 (m, 3H) *^{1}H-NMR (400 MHz, DMSO-d_6) δ = 13.41 - 12.49 (m, 1H), 10.80 - 10.72 (m, 1H), 7.42 - 7.34 (m, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.02 - 6.85 (m, 2H), 6.57 (s, 2H), 3.21 (br s, 2H), 3.11 - 3.05 (m, 1H), 3.04 - 2.95 (m, 1H), 2.88 (br d, J = 2.5 Hz, 1H), 2.71 - 2.64 (m, 1H), 2.42 - 2.32 (m, 2H), 2.20 - 2.11 (m, 1H), 1.81 - 1.58 (m, 3H)
12		MS: m/z: 295.2 $[M+H]^+$, ^{1}H-NMR (400 MHz, CD3OD) δ = 7.52 (d, J = 9.9 Hz, 2H), 7.21 (dd, J = 8.4, 1.1 Hz, 1H), 3.40 - 3.33 (m, 1H), 3.19 - 3.00 (m, 2H), 2.98 - 2.82 (m, 2H), 2.58 - 2.31 (m, 4H), 2.29 - 2.15 (m, 1H), 1.93 - 1.65 (m, 4H) *^{1}H-NMR (400 MHz, DMSO-d_6) δ = 13.37 - 12.76 (m, 1H), 11.33 - 11.26 (m, 1H), 7.64 - 7.55 (m, 2H), 7.23 (br d, *J* = 7.8 Hz, 1H), 6.60 - 6.59 (m, 4H), 3.10 - 2.95 (m, 3H), 2.85 - 2.57 (m, 2H), 2.23 - 2.11 (m, 1H), 1.85 - 1.58 (m, 3H), 1.33 - 1.08 (m, 1H)
13		MS: m/z: 311.2 $[M+H]^+$, ^{1}H-NMR (400 MHz, DMSO-d_6) δ = 11.08 - 10.92 (m, 1H), 7.45 (br d, *J* = 7.8 Hz, 1H), 7.18 (br s, 1H), 6.90 (br d, *J* = 7.3 Hz, 1H), 3.17 (br s, 2H), 3.07 (br s, 2H), 2.97 - 2.90 (m, 1H), 2.86 - 2.77 (m, 1H), 2.47 - 2.38 (m, 1H), 2.33 (br d, *J* = 7.8 Hz, 1H), 2.23 - 2.04 (m, 3H) *^{1}H-NMR (400 MHz, DMSO-d_6) δ = 11.14 - 10.87 (m, 1H), 7.50 - 7.42 (m, 1H), 7.19 (br s, 1H), 6.96 - 6.82 (m, 1H), 6.55 (s, 1H), 3.25 - 3.21 (m, 1H), 3.17 - 3.06 (m, 2H), 3.00 - 2.92 (m, 1H), 2.88 - 2.81 (m, 1H), 2.45 - 2.38 (m, 1H), 2.34 - 2.19 (m, 2H), 2.08 (s, 1H), 1.80 - 1.50 (m, 3H)

17		MS: *m/z* = 257.0 $[M+H]^+$, ^{1}H-NMR (400 MHz, DMSO-d_6) δ = 10.47 (br s, 1H), 7.23 (br d, *J* = 8.3 Hz, 1H), 6.74 (br s, 1H), 6.58 (br d, *J* = 8.3 Hz, 1H), 5.75 (s, 1H), 3.73 (s, 3H), 3.20 - 3.04 (m, 2H), 2.96 (br s, 2H), 2.80 - 2.68 (m, 1H), 2.44 - 2.27 (m, 2H), 2.10 (br s, 3H), 1.60 (br d, *J* = 14.9 Hz, 3H) *^{1}H-NMR (400 MHz, DMSO-d_6) δ = 13.91 - 12.22 (m, 1H), 10.55 (s, 1H), 7.25 (d, *J* = 8.5 Hz, 1H), 6.75 (d, *J* = 2.1 Hz, 1H), 6.60 - 6.58 (m, 1H), 6.58 - 6.57 (m, 2H), 3.73 (s, 3H), 3.22 - 3.16 (m, 2H), 3.04 (br d, *J* = 14.0 Hz, 2H), 2.85 - 2.78 (m, 1H), 2.57 - 2.53 (m, 1H), 2.47 - 2.37 (m, 2H), 2.20 - 2.11 (m, 1H), 2.08 (s, 1H), 1.78 - 1.59 (m, 3H)
18		MS: *m/z* = 257.0 $[M+H]^+$, ^{1}H-NMR (400 MHz, DMSO-d_6) δ = 10.47 (br s, 1H), 7.22 (br d, *J* = 8.3 Hz, 1H), 6.80 - 6.66 (m, 1H), 6.57 (br d, *J* = 8.3 Hz, 1H), 3.72 (s, 3H), 3.22 - 3.03 (m, 3H), 3.03 - 2.85 (m, 2H), 2.84 - 2.65 (m, 1H), 2.43 - 2.27 (m, 2H), 2.27 - 2.02 (m, 3H), 1.75 - 1.50 (m, 3H) *^{1}H-NMR (400 MHz, DMSO-d_6) δ = 13.14 - 12.37 (m, 1H), 10.69 - 10.35 (m, 1H), 7.24 (d, *J* = 8.5 Hz, 1H), 6.78 - 6.71 (m, 1H), 6.57 (s, 3H), 3.73 (s, 3H), 3.22 - 3.16 (m, 2H), 3.04 - 2.92 (m, 2H), 2.84 - 2.77 (m, 1H), 2.46 - 2.43 (m, 1H), 2.41 - 2.33 (m, 2H), 2.17 - 2.11 (m, 1H), 2.11 - 2.06 (m, 1H), 1.75 - 1.59 (m, 3H)
19		MS: m/z: 226.8 $[M+H]^+$, ^{1}H-NMR (400 MHz, DMSO-d_6) δ = 10.95 - 10.49 (m, 1H), 7.36 (s, 1H), 7.22 (br d, *J* = 7.3 Hz, 1H), 7.00 - 6.86 (m, 2H), 3.27 - 3.18 (m, 1H), 3.14 - 3.05 (m, 1H), 2.98 - 2.85 (m, 2H), 2.79 - 2.61 (m, 2H), 2.40 - 2.30 (m, 1H), 2.07 (br s, 3H), 1.74 - 1.51 (m, 3H) *^{1}H-NMR (400 MHz, DMSO-d_6) δ = 12.97 - 11.82 (m, 1H), 10.80 - 10.67 (m, 1H), 7.38 (br d, *J* = 7.8 Hz, 1H), 7.24 (br d, *J* = 7.8 Hz, 1H), 7.01 - 6.90 (m, 2H), 6.55 (s, 1H), 3.37 - 3.31 (m, 1H), 3.25 - 3.18 (m, 1H), 2.94 (br s, 2H), 2.89 - 2.81 (m, 1H), 2.78 - 2.69 (m, 1H), 2.40 - 2.29 (m, 1H), 2.19 - 2.06 (m, 1H), 1.90 - 1.53 (m, 4H)
20		MS: m/z: 226.8 $[M+H]^+$, ^{1}H-NMR (400 MHz, DMSO-d_6) δ = 11.03 - 10.49 (m, 1H), 7.39 (br d, *J* = 5.4 Hz, 1H), 7.24 (br d, *J* = 7.3 Hz, 1H), 6.96 (br dd, *J* =13.7, 6.8 Hz, 2H), 3.19 - 2.83 (m, 4H), 2.83 - 2.58 (m, 2H), 2.36 - 2.00 (m, 3H), 1.92 - 1.49 (m, 3H) *^{1}H-NMR (400 MHz, DMSO-d_6) δ = 10.89 - 10.73 (m, 1H), 7.40 (br d, *J* = 7.8 Hz, 1H), 7.26 (br d, *J* = 7.8 Hz, 1H), 7.06 - 6.90 (m, 2H), 6.59 (s, 2H), 3.54 - 3.45 (m, 1H), 3.38 (br s, 2H), 3.01 (br s, 3H), 2.86 - 2.69 (m, 3H), 2.65 - 2.56 (m, 1H), 2.26 - 2.16 (m, 1H), 1.80 (br d, *J* = 4.4 Hz, 2H)

21		MS: m/z: 295.2 $[M+H]^+$, ^{1}H-NMR (400 MHz, CD3OD) δ = 7.50 (d, J = 8.1 Hz, 1H), 7.33 (d, J = 7.4 Hz, 1H), 7.08 (t, J = 7.8 Hz, 1H), 3.40 (br d, J = 16.0 Hz, 1H), 3.34 (br d, J = 5.9 Hz, 1H), 3.29 (br d, J = 3.0 Hz, 1H), 3.24 - 3.16 (m, 1H), 3.16 - 3.08 (m, 1H), 3.02 - 2.94 (m, 1H), 2.68 - 2.59 (m, 1H), 2.49 (q, J = 9.2 Hz, 1H), 2.43 - 2.30 (m, 2H), 2.21 - 2.09 (m, 1H), 1.94 - 1.67 (m, 3H) *^{1}H-NMR (400 MHz, CD_3OD) δ = 7.58 (d, *J* = 7.9 Hz, 1H), 7.45 - 7.38 (m, 1H), 7.24 - 7.16 (m, 1H), 6.71 (s, 4H), 3.95 - 3.87 (m, 1H), 3.35 (s, 3H), 2.99 (s, 1H), 2.86 (s, 1H), 2.56 - 2.47 (m, 1H), 2.16 - 2.08 (m, 2H), 2.03 - 1.85 (m, 2H), 1.31 - 1.29 (m, 2H)
22		MS: m/z: 226.9 $[M+H]^+$, ^{1}H-NMR (400 MHz, DMSO-d_6) δ = 10.69 (br s, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 1H), 6.99 - 6.89 (m, 2H), 3.17 (br d, *J* = 12.1 Hz, 1H), 3.12 - 3.00 (m, 2H), 3.00 - 2.89 (m, 1H), 2.89 - 2.73 (m, 1H), 2.43 (br dd, *J* = 14.9, 10.3 Hz, 1H), 2.39 - 2.27 (m, 1H), 2.25 - 2.05 (m, 3H), 1.60 (br s, 3H) *^{1}H-NMR (400 MHz, DMSO-d_6) δ = 10.80 (br s, 1H), 7.39 (br d, *J* = 7.8 Hz, 1H), 7.24 (br d, *J* = 7.8 Hz, 1H), 7.01 - 6.90 (m, 2H), 6.56 (s, 2H), 3.30 (br s, 2H), 3.12 (br d, *J* = 14.2 Hz, 2H), 2.91 (br s, 1H), 2.61 (br d, *J* = 13.7 Hz, 4H), 2.25 - 2.13 (m, 1H), 1.83 - 1.65 (m, 3H)
23		MS: m/z: 227.0 $[M+H]^+$, ^{1}H-NMR (400 MHz, DMSO-d_6) δ = 10.69 (br s, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 1H), 7.01 - 6.86 (m, 2H), 3.20 - 3.14 (m, 1H), 3.12 - 3.01 (m, 2H), 3.01 - 2.91 (m, 1H), 2.87 - 2.75 (m, 1H), 2.44 (br s, 1H), 2.34 (br d, *J* = 8.5 Hz, 1H), 2.25 - 2.03 (m, 3H), 1.77 - 1.53 (m, 3H) *^{1}H-NMR (400 MHz, DMSO-d_6) δ = 10.80 (br s, 1H), 7.39 (br d, *J* = 7.3 Hz, 1H), 7.24 (br d, *J* = 7.8 Hz, 1H), 7.05 - 6.87 (m, 3H), 6.55 (s, 2H), 3.41 - 3.34 (m, 1H), 3.30 (br s, 1H), 3.11 (s, 1H), 3.08 - 3.00 (m, 1H), 2.91 (br s, 1H), 2.68 - 2.55 (m, 3H), 2.25 - 2.13 (m, 1H), 1.74 (br s, 3H)
24		MS: m/z: 257.0 $[M+H]^+$, ^{1}H-NMR (400 MHz, DMSO-d_6) δ = 10.45 (br s, 1H), 7.23 (br d, *J* = 8.3 Hz, 1H), 6.73 (s, 1H), 6.66 - 6.50 (m, 1H), 3.73 (s, 3H), 3.18 (br d, *J* = 12.3 Hz, 1H), 3.14 - 3.02 (m, 1H), 2.86 (br d, *J* = 14.9 Hz, 2H), 2.76 - 2.56 (m, 2H), 2.32 (q, *J* = 8.8 Hz, 1H), 2.25 - 2.01 (m, 3H), 1.78 - 1.45 (m, 3H)

		*^{1}H-NMR (400 MHz, DMSO-d_6) δ = 13.93 - 12.38 (m, 1H), 10.53 (s, 1H), 7.25 (d, *J* = 8.6 Hz, 1H), 6.75 (d, *J* = 2.1 Hz, 1H), 6.57 (s, 4H), 3.73 (s, 3H), 3.36 - 3.32 (m, 2H), 2.98 - 2.89 (m, 2H), 2.86 - 2.78 (m, 1H), 2.76 - 2.66 (m, 1H), 2.56 (br s, 1H), 2.42 - 2.32 (m, 1H), 2.19 - 2.09 (m, 1H), 1.79 - 1.55 (m, 3H)
25		MS: m/z: 257.0 $[M+H]^+$, ^{1}H-NMR (400 MHz, DMSO-d_6) δ = 10.45 (br s, 1H), 7.23 (br d, *J* = 8.3 Hz, 1H), 6.73 (br s, 1H), 6.58 (br d, *J* = 8.3 Hz, 1H), 3.73 (s, 3H), 3.18 (br d, *J* = 12.3 Hz, 1H), 3.12 - 3.03 (m, 1H), 2.84 (br s, 2H), 2.74 - 2.56 (m, 2H), 2.32 (q, *J* = 8.8 Hz, 1H), 2.21 - 2.00 (m, 3H), 1.76 - 1.44 (m, 3H) *^{1}H-NMR (400 MHz, DMSO-d_6) δ = 14.28 - 12.34 (m, 1H), 10.53 (s, 1H), 7.25 (d, *J* = 8.5 Hz, 1H), 6.76 (d, *J* = 2.0 Hz, 1H), 6.58 (s, 3H), 3.74 (s, 3H), 3.22 (br s, 2H), 3.21 - 3.18 (m, 1H), 2.97 - 2.88 (m, 2H), 2.84 - 2.67 (m, 2H), 2.57 - 2.53 (m, 1H), 2.48 - 2.42 (m, 1H), 2.42 - 2.29 (m, 1H), 2.19 - 2.10 (m, 1H), 1.79 - 1.57 (m, 3H)
26		MS: m/z: 257.4 $[M+H]^+$, ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.71 (br s, 2H), 7.03 - 6.95 (m, 1H), 6.89 (dd, *J* = 8.0, 0.6 Hz, 1H), 6.47 (d, *J* = 7.6 Hz, 1H), 3.90 (s, 3H), 3.87 - 3.78 (m, 1H), 3.29 - 3.12 (m, 3H), 2.78 - 2.62 (m, 2H), 2.47 - 2.38 (m, 1H), 2.35 - 2.27 (m, 1H), 2.19 - 2.11 (m, 1H), 1.91 - 1.80 (m, 1H), 1.70 (br s, 2H), 1.30 - 1.21 (m, 1H
27		MS: m/z: 257.4 $[M+H]^+$, ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.78 - 7.68 (m, 1H), 7.00 (s, 1H), 6.91 - 6.86 (m, 1H), 6.52 - 6.43 (m, 1H), 3.90 (s, 3H), 3.87 - 3.80 (m, 1H), 3.32 - 3.13 (m, 3H), 2.81 - 2.65 (m, 2H), 2.52 - 2.26 (m, 3H), 2.22 - 2.10 (m, 1H), 1.94 - 1.83 (m, 1H), 1.77 - 1.70 (m, 2H), 1.26 (s, 3H), 0.90 - 0.81 (m, 1H)
28		MS: m/z:295.2 $[M+H]^+$, ^{1}H-NMR (400 MHz, CD_3OD) δ = 7.50 (d, *J* = 8.1 Hz, 1H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.08 (t, *J* = 7.8 Hz, 1H), 3.45 - 3.37 (m, 1H), 3.31 (td, *J* = 3.2, 1.6 Hz, 2H), 3.24 - 3.20 (m, 1H), 3.19 - 3.09 (m, 1H), 3.08 - 2.88 (m, 1H), 2.71 - 2.56 (m, 1H), 2.49 (br d, *J* = 9.3 Hz, 1H), 2.37 (br d, *J* = 12.3 Hz, 2H), 2.20 - 2.11 (m, 1H), 1.90 - 1.68 (m, 3H) *^{1}H-NMR (400 MHz, CD_3OD) δ = 7.55 (d, *J* = 8.0 Hz, 1H), 7.38 (s, 1H), 7.19 - 7.10 (m, 1H), 6.68 (s, 1H), 3.73 - 3.63 (m, 1H), 3.59 - 3.47 (m, 2H), 3.26 - 3.18 (m, 2H), 3.16 - 2.84 (m, 4H), 2.39 (s, 1H), 2.06 - 1.81 (m, 3H)

* Spectral data for the fumarate salt

PHARMACEUTICAL COMPOSITIONS

Example A-1: Parenteral Pharmaceutical Composition

[00203] To prepare a parenteral pharmaceutical composition suitable for administration by injection (subcutaneous, intravenous), 1-1000 mg of a water-soluble salt of a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, is dissolved in sterile water and then mixed with 10 mL of 0.9% sterile saline. A suitable buffer is optionally added as well as optional acid or base to adjust the pH. The mixture is incorporated into a dosage unit form suitable for administration by injection.

Example A-2: Oral Solution

[00204] To prepare a pharmaceutical composition for oral delivery, a sufficient amount of a compound described herein, or a pharmaceutically acceptable salt thereof, is added to water (with optional solubilizer(s),optional buffer(s) and taste masking excipients) to provide a 20 mg/mL solution.

Example A-3: Oral Tablet

[00205] A tablet is prepared by mixing 20-50% by weight of a compound described herein, or a pharmaceutically acceptable salt thereof, 20-50% by weight of microcrystalline cellulose, and 1-10% by weight of magnesium stearate or other appropriate excipients. Tablets are prepared by direct compression. The total weight of the compressed tablets is maintained at 100 -500 mg.

Example A-4: Oral Capsule

[00206] To prepare a pharmaceutical composition for oral delivery, 1-1000 mg of a compound described herein, or a pharmaceutically acceptable salt thereof, is mixed with starch or other suitable powder blend. The mixture is incorporated into an oral dosage unit such as a hard gelatin capsule, which is suitable for oral administration.

[00207] In another embodiment, 1-1000 mg of a compound described herein, or a pharmaceutically acceptable salt thereof, is placed into Size 4 capsule, or size 1 capsule (hypromellose or hard gelatin) and the capsule is closed.

BIOLOGICAL EXAMPLES

[00208] Hallucinogenic Potential. Hallucinogenic compound 5-MeO-DMT produces a robust, dose-dependent head-twitch response (HTR) in mice. However, the isosteric compound 6-MeO-DMT is significantly less potent. As expected based on drug-discrimination data, 6-MeO-DMT does not produce a HTR. Finally, potent plasticity-promoting compounds do not produce a HTR, demonstrating that hallucinogenic potential and psychoplastogenicity can be decoupled.

[00209] Hallucinogens (e.g., LSD and 5-MeO-DMT) can activate a $5HT_{2A}$ sensor assay in agonist mode, but their non-hallucinogenic congeners (lisuride (LIS) and 6-MeO-DMT) may not. Moreover, compounds, such as, for example, 5-MeO-DMT, LSD, DMT, DOI, which are hallucinogenic in animals (e.g., humans), activate the $5HT_{2A}$ sensor assay in agonist mode, whereas compounds, such as, for example, 6-MeO-DMT, LIS, 6-F-DET, L-MDMA, R-MDMA, Ketanserin, BOL148, which are non-hallucinogenic in animals (e.g., humans), do not activate the $5HT_{2A}$ sensor assay in agonist mode. In some embodiments, hallucinogenic potential of a compound provided herein is determined in vitro. In some embodiments, hallucinogenic potential of a compound provided herein is determined using a $5HT_{2A}$ sensor assay. In some embodiments, the $5HT_{2A}$ sensor assay is in an agonist mode or an antagonist mode. In some embodiments, the $5HT_{2A}$ sensor assay is in an agonist mode. In some embodiments, a compound provided herein does not activate the sensor in agonist mode and has non-hallucinogenic potential. In some embodiments, a compound provided herein does not activate the sensor in agonist mode and is a non-hallucinogenic compound.

[00210] In some embodiments, the hallucinogenic potential of the compound provided herein are assessed in a $5HT_{2A}$ sensor assay in an agonist mode.

[00211] Furthermore, in some embodiments, non-hallucinogenic compounds (e.g., lisuride and 6-MeO-DMT) compete off 5-HT when the $5HT_{2A}$ sensor assay is run in antagonist mode. Additionally, compounds, such as, for example, 6-F-DET, Ketanserin, BOL148, which are non-hallucinogenic in animals (e.g., humans), can compete with 5HT binding to $5HT_{2A}$ in the antagonist mode sensor assay. In some embodiments, a compound provided herein prevents binding of 5-HT to $5HT_{2A}$. In some embodiments, the $5HT_{2A}$ sensor assay is in an antagonist mode. In some embodiments, a compound provided herein prevents binding of 5-HT to $5HT_{2A}$ and has non-hallucinogenic potential. In some embodiments, a compound provided herein prevents binding of 5-HT to $5HT_{2A}$ and is non-hallucinogenic. In some embodiments, a compound provided herein prevents binding of 5-HT to $5HT_{2A}$ in antagonist mode has non-hallucinogenic potential. In some embodiments, a compound provided herein that prevents binding of 5-HT in antagonist mode is a non-hallucinogenic compound. In some embodiments, a compound provided herein that inhibits the response of the sensor assay in antagonist mode has non-hallucinogenic potential. In some embodiments, a compound provided herein that inhibits the response of the sensor assay in antagonist mode is a non-hallucinogenic compound.

[00212] In some embodiments, the results for the agonist mode sensor assay suggests a compound provided herein is a non-hallucinogenic ligand of the $5\text{-}HT_{2A}$ receptor. In some embodiments, the results for the antagonist mode sensor assay suggests a compound provided herein is a non-

hallucinogenic ligand of the 5-HT_{2A} receptor. In some embodiments, the results for the agonist mode and antagonist mode sensor assay together suggest a compound provided herein is a non-hallucinogenic ligand of the 5-HT_{2A} receptor.

[00213] In some embodiments, the hallucinogenic potential of the compounds are assessed in a $5HT_{2A}$ sensor assay in an antagonist mode.

[00214] **Forced Swim Test.** As increased cortical structural plasticity in the anterior parts of the brain mediates the sustained (>24 h) antidepressant-like effects of ketamine and play a role in the therapeutic effects of 5-HT2A agonists, the impact of compounds on forced swim test (FST) behavior is used evaluate therapeutic potential of compounds provided herein. First, a pretest is used to induce a depressive phenotype. Compounds are administered 24 h after the pre-test, and the FST is performed 24 h and 7 d post drug administration.

[00215] **Neurite outgrowth assay.** Changes in the pattern of neurite outgrowth have been implicated in neurodegenerative disorders as well as traumatic injuries. The discovery of compounds that can positively affect neuritogenesis are important for developing new therapeutics for neurological diseases. In some embodiments, measurement of neurite outgrowth of rat cortical neurons using an automated image-based assay is used to determine the neuroplastic effects of the compounds provided herein. In some embodiments, a compound provided herein increases the pattern of neurite outgrowth. In some embodiments, a compound provided herein increases neurite average length compared to a control. In some embodiments, a compound provided herein increases neurite branch points compared to a control. In some embodiments, a compound provided herein increases neurite average length and neurite branch points compared to a control.

[00216] In some embodiments, the plastogenic potential of compounds provided herein is assessed by measuring the changes in neurite development.

[00217] **Dendritogenesis Assays.** Phenotypic screening has historically proven more successful than target-based approaches for identifying drugs with novel mechanisms of action. Using a phenotypic assay, the compounds provided herein are tested for their ability to increase dendritic arbor complexity in cultures of cortical neurons. Following treatment, neurons are fixed and visualized using an antibody against MAP2—a cytoskeletal protein localized to the somatodendritic compartment of neurons. Sholl analysis is then performed, and the maximum number of crossings (N_{max}) is used as a quantitative metric of dendritic arbor complexity. For statistical comparisons between specific compounds, the raw N_{max} values are compared. Percent efficacies are determined by setting the N_{max} values for the vehicle (DMSO) and positive (ketamine) controls equal to 0% and 100%, respectively.

[00218] Animals. For the dendritogenesis experiments, timed pregnant Sprague Dawley rats are obtained from Charles River Laboratories (Wilmington, MA). In some embodiments, male and female C57BL/6J mice are obtained from Jackson Laboratory (Sacramento, C.A.). In some instnaces, mice are housed in a temperature and humidity-controlled room maintained on a 12-h light/dark cycle in groups of 4–5 (same sex).

[00219] Dendritogenesis – Sholl Analysis. Neurons are plated in 96-well format (200 µL of media per well) at a density of approximately 15,000 cells/well in Neurobasal (Life Technologies) containing 1% penicillin-streptomycin, 10% heat-inactivated fetal bovine serum, and 0.5 mM glutamine. After 24 h, the medium is replaced with Neurobasal containing 1x B27 supplement (Life Technologies), 1% penicillin-streptomycin, 0.5 mM glutamine, and 12.5 µM glutamate. After 3 days in vitro (DIV3), the cells are treated with compounds. Compounds tested in the dendritogenesis assays are treated at 10 µM unless noted otherwise. Stock solutions of the compounds in DMSO are first diluted 100-fold in Neurobasal before an additional 10-fold dilution into each well (total dilution = 1:1000; 0.1% DMSO concentration). Treatments are randomized. After 1 h, the media is removed and replaced with new Neurobasal media containing 1x B27 supplement, 1% penicillin-streptomycin, 0.5 mM glutamine, and 12.5 µM glutamate. The cells grow for an additional 71 h. At that time, neurons are fixed by removing 80% of the media and replacing it with a volume of 4% aqueous paraformaldehyde (Alfa Aesar) equal to 50% of the working volume of the well. Then, the cells are incubated at room temperature for 20 min before the fixative is aspirated and each well washed twice with DPBS. Cells are permeabilized using 0.2% Triton X-100 (ThermoFisher) in DPBS for 20 minutes at room temperature without shaking. Plates are blocked with antibody diluting buffer (ADB) containing 2% bovine serum albumin (BSA) in DPBS for 1 h at room temperature. Then, plates are incubated overnight at 4°C with gentle shaking in ADB containing a chicken anti-MAP2 antibody (1:10,000; EnCor, CPCA-MAP2). The next day, plates are washed three times with DPBS and once with 2% ADB in DPBS. Plates are incubated for 1 h at room temperature in ADB containing an anti-chicken IgG secondary antibody conjugated to Alexa Fluor 488 (Life Technologies, 1:500) and washed five times with DPBS. After the final wash, 100 µL of DPBS is added per well and imaged on an ImageXpress Micro XL High-Content Screening System (Molecular Devices, Sunnyvale,CA) with a 20x objective.

[00220] Images are analyzed using ImageJ Fiji (version 1.51W). First, images corresponding to each treatment are sorted into individual folders that are then blinded for data analysis. Plate controls (both positive and negative) are used to ensure that the assay is working properly as well as to visually determine appropriate numerical values for brightness/contrast and thresholding to be

applied universally to the remainder of the randomized images. Next, the brightness/contrast settings are applied, and approximately 1–2 individual pyramidal-like neurons per image (i.e., no bipolar neurons) are selected using the rectangular selection tool and saved as separate files. Neurons are selected that did not overlap extensively with other cells or extend far beyond the field of view. The threshold settings are then applied to the individual images. The paintbrush tool is used to eliminate artifacts and dendritic processes originating from adjacent neurons (cleanup phaseNext, the point tool is used to select the center of the neuron, and the images are saved and processed using the following Sholl analysis batch macro:

run("Sholl Analysis...", "starting=0 ending=NaN radius_step=2 #_samples=1 integration=Mean enclosing=1 #_primary=4 infer fit linear polynomial=[Best fitting degree] most semi-log normalizer=Area create background=228 save do");

Sholl analysis circle radii = 2 pixel increments = 0.67 μm. All images are taken and analyzed by an experimenter blinded to treatment conditions. The number of crossings for each neuron at each distinct radius is averaged to produce an average Sholl plot for each treatment. The N_{max} values are simply determined by identifying the maximum of each plot. For each treatment, neurons are selected from at least 6 wells spread across 2 plates (9 sites/well x 3 wells/plate x 2 plates). Each plate is prepared using neurons obtained from independent pregnant dams).

[00221] Spinogenesis Experiments. Spinogenesis experiments are performed as previously described with the exception that cells are treated on DIV19 and fixed 24 h after treatment on DIV20. (Ly, C. et al., 2018) The images are taken on a Nikon HCA Confocal microscope a with a 100x/NA 1.45 oil objective. DMSO and ketamine (10 μM) are used as vehicle and positive controls, respectively.

[00222] Serotonin 5-HT2A In Vitro Radioligand Binding Competition Assay. The 5-HT2A radioligand binding competition assay was performed at Epics Therapeutics S.A. (Belgium, FAST-0505B) using conventional methods. Briefly, competition binding is performed in duplicate in the wells of a 96 well plate (Master Block, Greiner, 786201) containing binding buffer (optimized for each receptor), membrane extracts (amount of protein/well optimized for each receptor), radiotracer [^{3}H]-DOI (final concentration optimized for each receptor) and test compound. Nonspecific binding was determined by co-incubation with 200-fold excess of cold competitor. The samples were incubated in a final volume of 0.1 ml at a temperature and for a duration optimized for each receptor and then filtered over filter plates. Filters were washed six times with 0.5 ml of ice-cold washing buffer (optimized for each receptor) and 50 μl of Microscint 20 (Packard) were added in each well. The plates were incubated 15 min on an orbital shaker and then counted with a TopCountTM for 1 min/well.

[00223] Serotonin 5-HT2A In Vitro Cellular IPOne Agonism Assay. The 5-HT2A IPOne HTRF assay was performed at Epics Therapeutics S.A. (Belgium, FAST-0505I) using conventional methods. Briefly, CHO-K1 cells expressing human recombinant 5-HT2A receptor grown to mid-log phase in culture media without antibiotics were detached with PBS-EDTA, centrifuged, and resuspended in medium without antibiotics buffer. 20,000 cells were distributed in a 96 well plate and incubated overnight at 37°C with 5% CO_2.

[00224] For agonist testing, the medium was removed and 20µl of assay buffer plus 20µl of test compound or reference agonist were added in each well. The plate was incubated for 60 min. at 37°C with 5% CO_2.

[00225] After addition of the lysis buffer containing IP1-d2 and anti-IP1 cryptate detection reagents, plates were incubated 1-hour at room temperature, and fluorescence ratios were measured according to the manufacturer specification, with the HTRF kit.

[00226] Serotonin 5-HT2C In Vitro Radioligand Binding Competition Assay. The 5-HT2Cedited (accession number AAF35842.1) radioligand binding competition assay was performed at Epics Therapeutics S.A. (Belgium, FAST-0507B) using conventional methods. Briefly, competition binding was performed in duplicate in the wells of a 96 well plate (Master Block, Greiner, 786201) containing binding buffer (optimized for each receptor), membrane extracts (amount of protein/well optimized for each receptor), radiotracer [^{3}H]-DOI (final concentration optimized for each receptor) and test compound. Nonspecific binding was determined by co-incubation with 200-fold excess of cold competitor. The samples were incubated in a final volume of 0.1 ml at a temperature and for a duration optimized for each receptor and then filtered over filter plates. Filters were washed six times with 0.5 ml of ice-cold washing buffer (optimized for each receptor) and 50 µl of Microscint 20 (Packard) were added in each well. The plates were incubated 15 min on an orbital shaker and then counted with a TopCountTM for 1 min/well.

[00227] Serotonin 5-HT2C In Vitro Cellular IPOne Agonism Assay. The 5-HT2C IPOne HTRF assay was performed at Epics Therapeutics S.A. (Belgium, FAST-0507I) using conventional methods. Briefly, CHO-K1 cells expressing human recombinant 5-HT2Cedited receptor (accession number AAF35842.1) grown to mid-log phase in culture media without antibiotics were detached with PBS-EDTA, centrifuged, and resuspended in medium without antibiotics buffer. 20,000 cells were distributed in a 96 well plate and incubated overnight at 37°C with 5% CO_2.

[00228] For agonist testing, the medium was removed and 20µl of assay buffer plus 20µl of test compound or reference agonist were added in each well. The plate was incubated for 60 min. at 37°C with 5% CO_2.

[00229] After addition of the lysis buffer containing IP1-d2 and anti-IP1 cryptate detection reagents, plates were incubated 1-hour at room temperature, and fluorescence ratios were measured according to the manufacturer specification, with the HTRF kit.

[00230] The compounds provided herein were tested in the Serotonin 5-HT2A and 5-HT2C in vitro radioligand binding and cellular IPOne agonism assays. The binding and agonism functional potencies of the compounds (as indicated by their IC_{50}s or EC_{50}s) are shown in **Table 3.**

Table 3

COMPOUND	5HT2A RADIOLIGAND BINIDNG ACTIVITY	5HT2A IPONE AGONISM ACTIVITY	5HT2C RADIOLIGAND BINIDNG ACTIVITY	5HT2C IPONE AGONISM ACTIVITY
1	D	E	D	E
2	E	E	D	D
3	C	D	C	C
4	C	C	C	C
5	D	D	C	D
6	C	E	C	C
7	C	D	C	C
12	D	E	D	E
13	D	E	D	E
17	E	E	D	E
18	E	E	D	E
19	C	C	C	C
20	C	C	C	B
21	D	E	C	C
22	D	C	C	C
23	C	E	C	C
24	D	E	D	D
25	E	E	D	D
26	C	B	B	B
27	B	B	C	C
28	C	D	B	C

A: IC50 or EC50 is <0.010 μM; **B:** IC50 or EC50 is 0.010 μM - 0.100 μM; **C:** IC50 or EC50 is 0.101 μM - 1 μM; **D:** IC50 or EC50 is 1.001 μM - 10 μM; **E:** IC50 or EC50 is >10 μM

[00231] **Serotonin 5-HT2A In Vitro Cellular IPOne Antagonism Assay**. The 5-HT2A IPOne HTRF assay was performed at Epics Therapeutics S.A. (Belgium, FAST-0505I) in antagonism mode using conventional methods. Briefly, CHO-K1 cells expressing human recombinant 5-HT2A receptor grown to mid-log phase in culture media without antibiotics were detached with PBS-

EDTA, centrifuged, and resuspended in medium without antibiotics buffer. 20,000 cells were distributed in a 96 well plate and incubated overnight at 37°C with 5% CO_2.

[00232] For antagonist testing, a reference agonist a-Me-5HT was added and fluorescence signal monitored for several minutes, followed by addition of 20µl of assay buffer plus 20µl of test compound or reference antagonist ketanserin, in each well. The plate was incubated for 60 min. at 37°C with 5% CO_2.

[00233] After addition of the lysis buffer containing IP1-d2 and anti-IP1 cryptate detection reagents, plates were incubated 1-hour at room temperature, and fluorescence ratios were measured according to the manufacturer specification, with the HTRF kit.

[00234] The compounds provided herein were tested in the Serotonin 5-HT2A antagonism assays. The results are shown in **Table 4**.

Table 4

Compound	5HT2A IPOne Antagonism Activity
3	C
4	C
6	C
7	C
13	C
17	E
18	C
19	C
20	D
21	C
22	C
23	B
24	C
25	C
26	A
27	B
28	B

A: IC50 or EC50 is <0.010 µM; **B:** IC50 or EC50 is 0.010 µM - 0.100 µM; **C:** IC50 or EC50 is 0.101 µM - 1 µM; **D:** IC50 or EC50 is 1.001 µM - 10 µM; **E:** IC50 or EC50 is >10 µM

[00235] **Neurite Outgrowth Assay. Neurite Outgrowth in Primary Neuronal Cultures Assay**. Changes in the pattern of neurite outgrowth have been implicated in psychiatric and

neurodegenerative disorders as well as traumatic injuries. The discovery of new compounds that can positively affect neuritogenesis are important for developing new therapeutics for neurological diseases. Measurement of neurite outgrowth of rat cortical neurons using an automated image-based assay was used to determine the neuroplastic effects of the compounds of the present disclosure. The neurite outgrowth assay was performed at Neurofit SAS (France) as described below.

[00236] Pregnant Wistar rats (Janvier; France) were used for the study. They were delivered 6 days before their use. Upon arrival at Neurofit animal facility, they were housed one per cage and maintained in a room with controlled temperature (21-22°C) and a reversed light-dark cycle (12h/12h; lights on: 17:30 – 05:30; lights off: 05:30 – 17:30) with food and water available ad libitum.

[00237] Female Wistar rats of 17 days gestation were killed by cervical dislocation and the fetuses were removed from the uterus. Their brains were placed in ice-cold medium of Leibovitz (L15, Gibco, Fisher bioblock, France). Cortices were dissected and meninges were carefully removed. The cortical neurons were dissociated by trypsinization for 30 min at 37°C (trypsin-EDTA, Gibco) in presence of 0.1 mg/ml DNAse I (Roche, France). The reaction was stopped by addition of Dulbecco's Modified Eagle Medium (DMEM; Gibco) with 10% of fetal bovine serum (FBS; Gibco). The suspension was triturated with a 10-ml pipette and using a needle syringe 21G and centrifuged at 350 x g for 10 min at room temperature. The pellet of dissociated cells was resuspended in a medium consisting of Neurobasal (Gibco) supplemented with 2% B27 supplement (Gibco), 0.5mM L-Glutamine (Gibco), an antibiotic-antimicotic mixture. Viable cells were counted in a Neubauer cytometer using the trypan blue exclusion test (Sigma). Cells were seeded at a density of 10000 cells per well in 96-well plate (Costar) precoated with poly-L-lysine. Test compound at different concentrations were added to the cultures. Donepezil (positive control) was tested at 250 nM.

[00238] After 72h (3 days) of plating, cultures were fixed with paraformaldehyde in PBS (4%, Sigma) for 30 min at 4°C. Then, cells were successively permeabilized with 0.1% Triton X100 for 30 min, saturated with PBS containing 3% of BSA and were incubated 1h with anti-beta III tubulin antibody (Sigma) at 1/10 000 in PBS containing 0.5% of BSA. Cells were washed three times with PBS containing 0.5% of BSA, and they were incubated 1h with goat anti-mouse antibody coupled with AF488 (Invitrogen A11001) diluted at 1/1000 in PBS containing 0.5% of BSA. Finally, nuclei were staining with DAPI 1 mg/ml at 1/1000 in PBS containing 0.5% of BSA. After rinsing with PBS, the plate was filmed and neurite networks were examined and analyzed using High-Content Screening (CellInsight, Thermo Scientific). The average number of neurites per neuron and the

average total length of neurites per neuron were the main parameters analyzed. Analysis of data was performed using analysis of variance (ANOVA). The Fisher's Protected Least Significant Difference test was used for multiple comparisons. A p value $\leqslant 0.05$ was considered significant. The software used is StatView 5.0 from SAS Institut.

[00239] In some embodiments, a compound of the present disclosure increases the pattern of neurite outgrowth. In some embodiments, a compound of the present disclosure increases neurite average length compared to a control. In some embodiments, a compound of the present disclosure increases neurite branch points compared to a control. In some embodiments, a compound of the present disclosure significantly increases the number of new neurites and/or the average neurite length compared to a control.

[00240] The plastogenic potential of the compounds ((as measured by the Neurite Outgrowth Procedure B) is shown in **Table 5**.

Table 5

COMPOUND	INCREASE IN NEURITE NUMBER	INCREASE IN NEURITE LENGTH	INCREASE IN NEURITE BRANCHING
1	B	B	B
2	B	A	A
3	B	A	B
4	A	A	A
5	B	A	B
6	B	A	B
7	A	A	A
12	B	A	A
13	B	A	B
17	A	A	A
18	A	A	A
19	A	A	A
20	A	A	A
21	B	A	A
22	A	A	A
23	A	A	A
24	A	A	A
25	A	A	A
26	A	A	A
27	A	A	A
28	A	A	A

A: Statistically significant mean increase as a percent of DMSO control at 10 μM or less

B: No statistically significant mean increase as a percent of DMSO control at 10 μM or less

[00241] $5HT_{2A}$ Sensor Assays. HEK293T (ATCC) 5HT2A sensor stable line (sLight1.3s) is generated via lentiviral transduction of HIV-EF1α-sLight1.3 and propagated from a single colony. Lentivirus is produced using 2nd generation lentiviral plasmids pHIV-EF1α -sLight1.3, pHCMV-G, and pCMV-deltaR8.2.

[00242] For the screening, sLight1.3s cells are plated in 96-well plates at a density of 40000 24-hours prior to imaging. On the day of imaging, compounds solubilized in DMSO are diluted from the 100mM stock solution to working concentrations of 1mM, 100μM and 1μM with a DMSO concentration of 1%. Immediately prior to imaging, cells growing in DMEM (Gibco) are washed 2x with HBSS (Gibco) and in agonist mode 180μL of HBSS or in antagonist mode 160μL of HBSS is added to each well after the final wash. For agonist mode, images are taken before and after the addition of the 20μL compound working solution into the wells containing 180μL HBSS. This produces final compound concentrations of 100μM, 10μM and 100nM with a DMSO concentration of 0.1%. For antagonist mode, images are taken before and after addition of 20μL of 900nM 5-HT and again after 20μL of the compound working solutions to produce final concentrations of 100nM for 5HT and 100μM, 10μM and 100nM for the compounds with a DMSO concentration of 0.1%. Compounds are tested in triplicates (3 wells) for each concentration (100μM, 10μM and 100nM). Additionally, within each plate, 100nM 5HT and 0.1% DMSO controls are also imaged.

[00243] Imaging is performed using the Leica DMi8 inverted microscope with a 40x objective using the FITC preset with an excitation of 460nm and emission of 512-542nm. For each well, the cellular membrane where the 5HT2A sensor is targeted is autofocused using the adaptive focus controls and 5 images from different regions within the well are taken with each image processed from a 2x2 binning.

[00244] For data processing, the membranes from each image are segmented and analyzed using a custom algorithm written in MATLAB producing a single raw fluorescence intensity value. For each well the 5 raw fluorescence intensity values generated from the 5 images are averaged and the change in fluorescence intensity (dFF) is calculated as:

$$dFF = (F_{sat} - F_{apo})/ F_{apo}$$

[00245] For both agonist and antagonist modes, the fluorescence intensity values before compound addition in HBSS only are used as the F_{apo} values while the fluorescence intensity values after compound addition are used as the F_{sat} values.

[00246] For agonist mode, data are as percent activation relative to 5HT, where 0 is the average of the DMSO wells and 100 is the average of the 100 uM 5HT wells. For antagonist mode, the inactivation score is calculated as:

$$\text{Inactivation score} = (dFFF(\text{Compound}+5HT) - dFF(5HT))/dFF(5HT)$$

[00247] **Head twitch response (HTR) experiments.** C57BL/6J Mice (9–10 weeks old) are housed following an IACUC approved protocol. The mice are habituated in the test cage for at least 30 min, injected intraperitoneally with compound (injection volume 5 ml/kg), returned to the empty test cage, and filmed for 20 minutes. Each video is scored for the number of head-twitches by a trained observer blinded to treatment condition.

[00248] **Forced Swim Test (FST).** Male Sprague Dawley rats from Envigo (Indianapolis, IN) are obtained and housed 3 rats per cage following an IACUC approved protocol. All experiments are carried out at ambient temperatures (20 and 23°C) under artificial lighting during the light-on part of the light/dark cycle in a Forced Swim chamber constructed of clear acrylic (height = 40 cm; diameter = 20.3 cm). Only one rat is placed in the swim chamber at a time for each swim test. The water is changed and the chamber cleaned between each animal. All rats are exposed to two swim sessions. The water depth is 16 cm in the first swim session and 30 cm in the second swim session, and the water temperature is maintained at 23±1 °C for all swim sessions. During the FST, animals undergo a 15 min swim session (pre-swim), lasting for 15 minutes, dried with paper towels, and returned to the home cage. Rats are injected with either saline, ketamine (positive control), or test compound after the habituation session, returned to home cage, and then tested in a second FST lasting 5 minutes ~24 hours (second swim test) later. The second swim test is video recorded for scoring. Body weights are measured on both days. Scoring of the second swim test is performed by trained technicians using a time sampling technique in which the animal in the video recorded test is viewed every 5 seconds and the behavior seen is noted. The measures noted are immobility, climbing, and swimming behaviors.

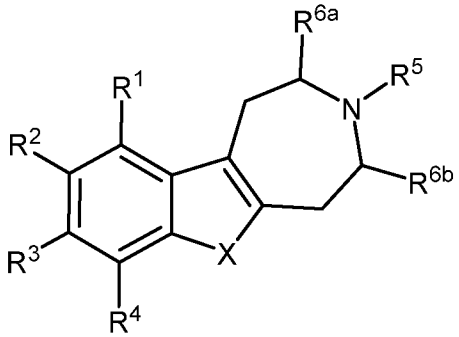
[00249] **Statistical analysis.** Treatments are randomized, and data are analyzed by experimenters blinded to treatment conditions. Statistical analyses are performed using GraphPad Prism (version 8.1.2). Comparisons are planned prior to performing each experiment.

[00250] The examples and embodiments described herein are for illustrative purposes only and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of this application and scope of the appended claims.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I)

wherein:

- X is NR^7, O or $S(=O)_x$;
- x is 0, 1, or 2;
- each of R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, $-OR^a$, cyano, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

  or any of R^1 and R^2, R^2 and R^3, or R^3 and R^4 are taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring;
- R^5 is hydrogen, halogen, $-OR^a$, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- each R^{6a} and R^{6b} is independently hydrogen, halogen, $-OR^a$, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

  or R^5 is taken together with R^{6a} or R^{6b} and the atoms to which they are attached to form an optionally substituted heterocyclic ring;

  or R^{6a} and R^{6b} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring;
- R^7 is hydrogen, alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted; and

- R^a is hydrogen, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

wherein

(i) R^5 and R^{6a} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring;

(ii) R^5 and R^{6b} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring; or

(iii) R^{6a} and R^{6b} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring; and

provided that when X is NH, R^{6a} is hydrogen, and each of R^1, R^2, R^3 and R^4 is hydrogen, then R^5 and R^{6b} are not taken together with the atoms to which they are attached to form a 6-membered heterocyclic ring substituted by ethyl or ethylidene.

2. The compound of claim 1, wherein X is O.

3. The compound of claim 1, wherein X is S.

4. The compound of claim 1, wherein X is S(=O).

5. The compound of claim 1, wherein X is $S(=O)_2$.

6. The compound of claim 1, wherein X is NR^7.

7. The compound of claim 6, wherein R^7 is an unsubstituted or substituted alkyl, or hydrogen.

8. The compound of claim 6 or 7, wherein R^7 is hydrogen.

9. The compound of claim 6 or 7, wherein R^7 is methyl.

10. The compound of any one of claims 1-9, wherein R^5 is hydrogen.

11. The compound of any one of claims 1-10, wherein R^{6a} is hydrogen.

12. The compound of any one of claims 1-11, wherein R^{6b} is hydrogen.

13. The compound of any one of claims 1-9, wherein R^5 and R^{6a} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring.

14. The compound of claim 13, wherein R^{6b} is hydrogen.

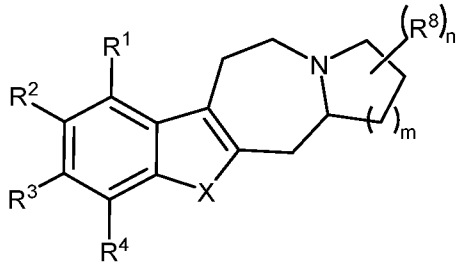
15. The compound of any one of claims 1-9, wherein R^5 and R^{6b} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring.

16. The compound of claim 15, wherein R^{6a} is hydrogen.

17. The compound of any one of claims 1-9, wherein R^{6a} and R^{6b} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring.

18. The compound of claim 17, wherein R^5 is hydrogen.

19. The compound of claim 1, wherein R^{6a} is hydrogen and R^{6b} is taken together with R^5 and the atoms to which R^5 and R^{6b} are attached to form an optionally substituted heterocyclic ring, and wherein the compound of Formula (I) has the structure of Formula (IA):



Formula (IA)

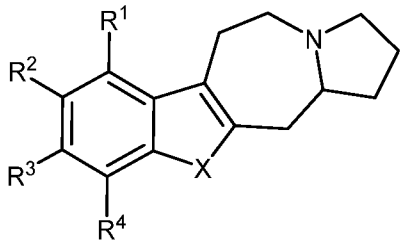
or a pharmaceutically acceptable salt or solvate thereof,

wherein

- each R^8 is independently halogen, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- m is 0, 1, 2 or 3; and
- n is 0, 1, 2, 3, 4, 5, 6, or 7;

provided that when X is NH, m is 2, and R^1-R^4 are hydrogen, then R^8 is not ethyl.

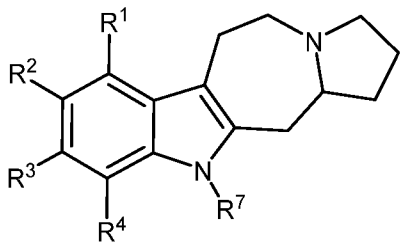
20. The compound of claim 19, wherein n is 0, m is 1, and the compound has the structure of Formula (IA-1):



Formula (IA-1)

or a pharmaceutically acceptable salt or solvate thereof.

21. The compound of claim 19 or 20, wherein X is NR^7, and the compound has the structure of Formula (IA-2):



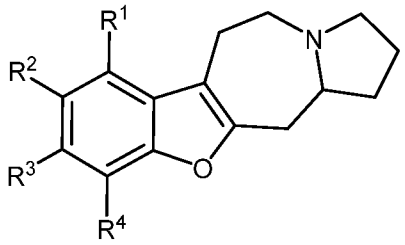
Formula (IA-2)

or a pharmaceutically acceptable salt or solvate thereof.

22. The compound of claim 21, wherein R^7 is hydrogen.

23. The compound of claim 21, wherein R^7 is methyl.

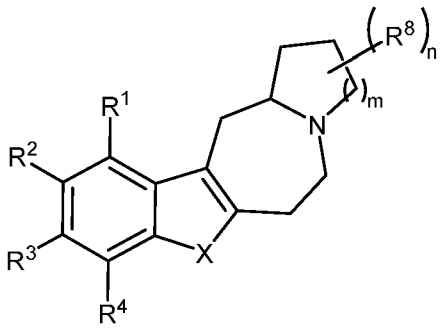
24. The compound of claim 19 or 20, wherein X is O, and the compound has the structure of Formula (IA-3):



Formula (IA-3)

or a pharmaceutically acceptable salt or solvate thereof.

25. The compound of claim 1, wherein R^{6b} is hydrogen and R^{6a} is taken together with R^5 and the atoms to which R^5 and R^{6a} are attached to form an optionally substituted heterocyclic ring, and wherein the compound of Formula (I) has the structure of Formula (IB):



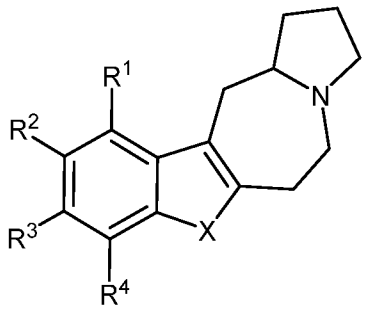
Formula (IB)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

- each R^8 is independently halogen, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- m is 0, 1, 2 or 3; and
- n is 0, 1, 2, 3, 4, 5, 6, or 7.

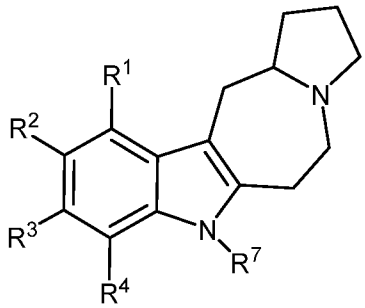
26. The compound of claim 25, wherein n is 0, m is 1, and the compound has the structure of Formula (IB-1):



Formula (IB-1)

or a pharmaceutically acceptable salt or solvate thereof.

27. The compound of claim 25 or 26, wherein X is NR^7, and the compound has the structure of Formula (IB-2):



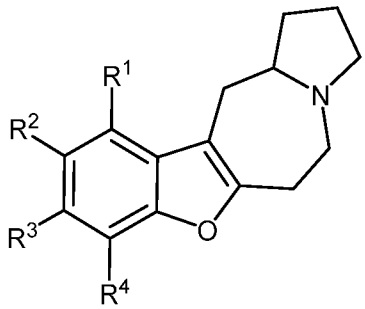
Formula (IB-2)

or a pharmaceutically acceptable salt or solvate thereof.

28. The compound of claim 27, wherein R^7 is hydrogen.

29. The compound of claim 27, wherein R^7 is methyl.

30. The compound of claim 25 or 26, wherein X is O, and the compound has the structure of Formula (IB-3):



Formula (IB-3)

or a pharmaceutically acceptable salt or solvate thereof.

31. The compound of any one of claims 1-30, wherein each of R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, $-OR^a$, cyano, or haloalkyl.

32. The compound of any one of claims 1-31, wherein each of R^1, R^2, R^3 and R^4 is hydrogen.

33. The compound of any one of claims 1-31, wherein at least one of R^1, R^2, R^3 and R^4 is halogen.

34. The compound of any one of claims 1-31, wherein at least one of R^1, R^2, R^3 and R^4 is haloalkyl.

35. The compound of any one of claims 1-31, wherein at least one of R^1, R^2, R^3 and R^4 is OR^a wherein R^a is haloalkyl.

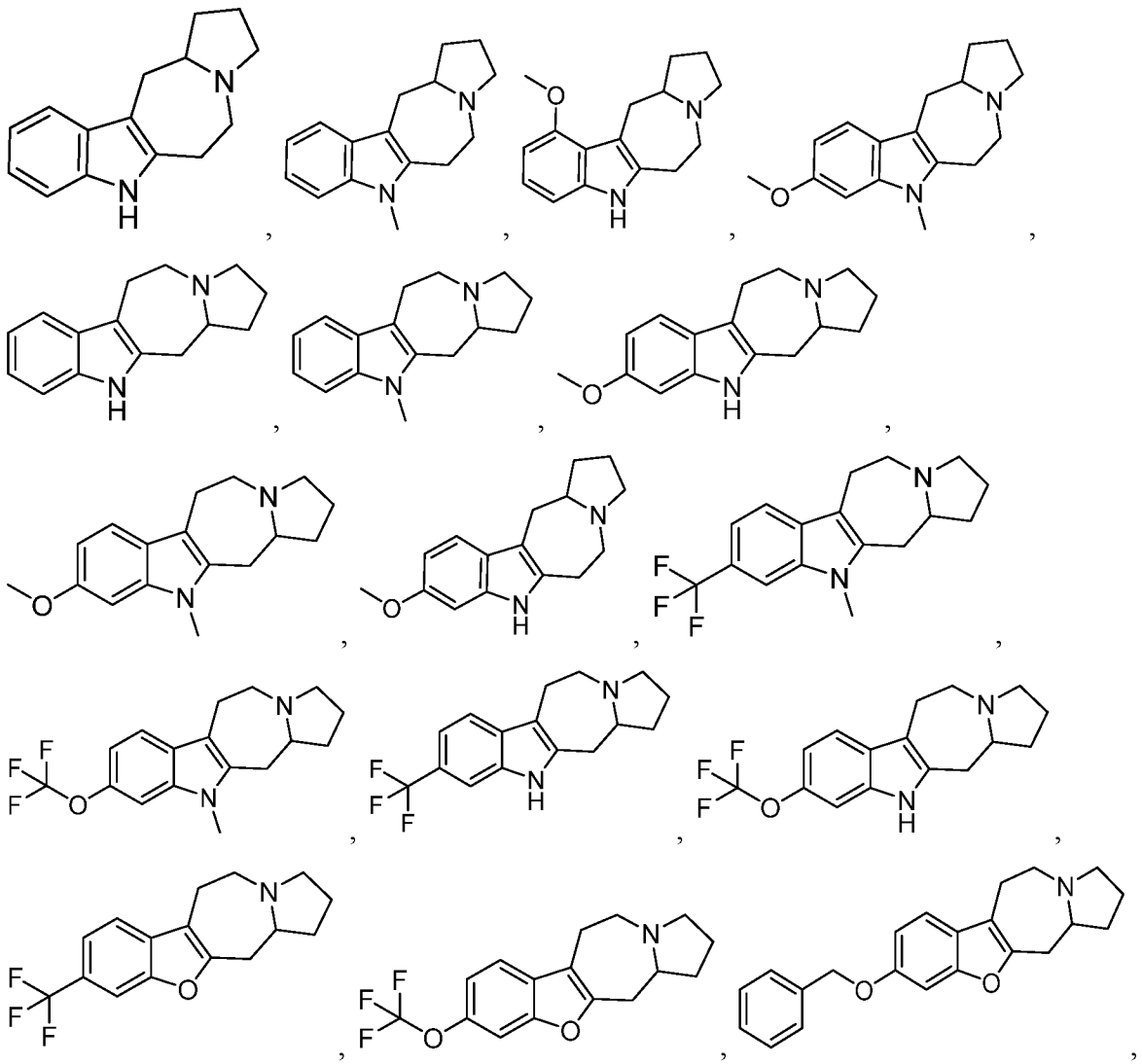
36. The compound of any one of claims 1-31, wherein at least one of R^1, R^2, R^3 and R^4 is OR^a wherein R^a is arylalkyl.

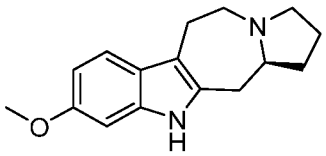
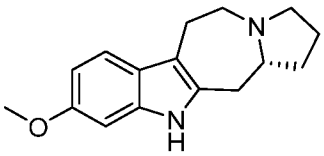
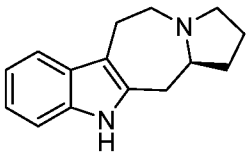
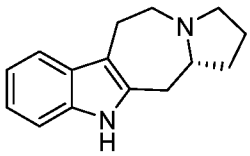
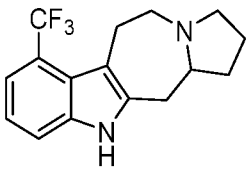
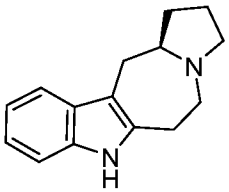
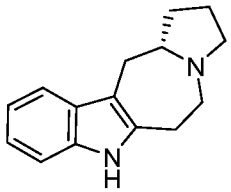
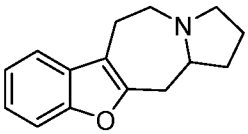
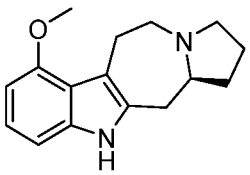
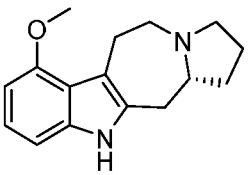
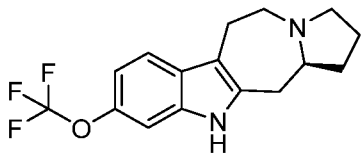
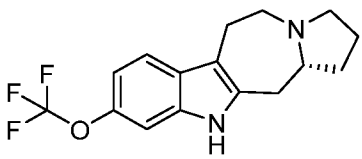
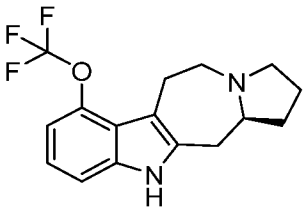
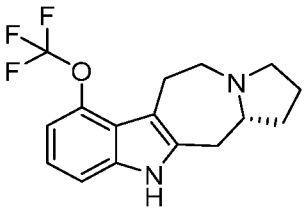
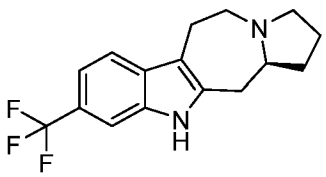
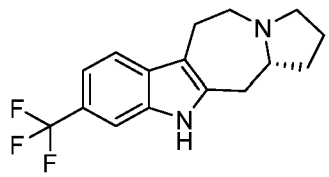
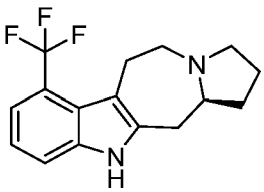
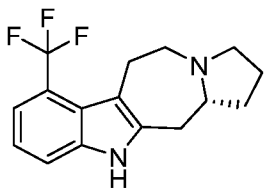
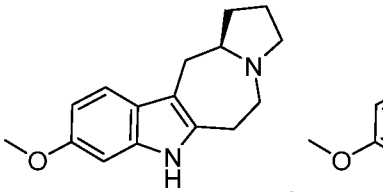
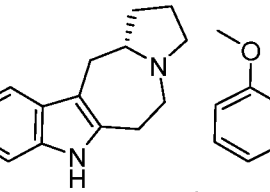
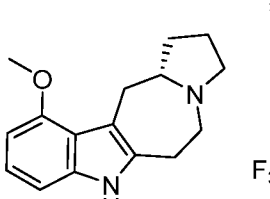
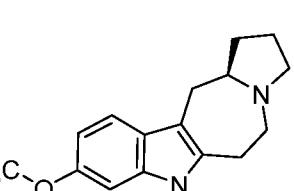
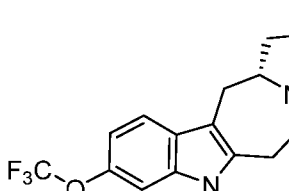
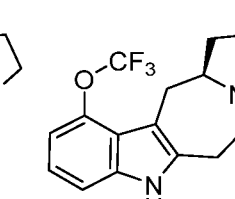
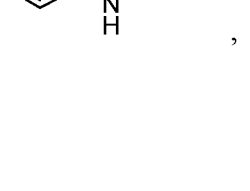
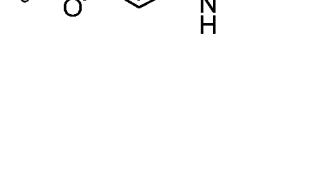
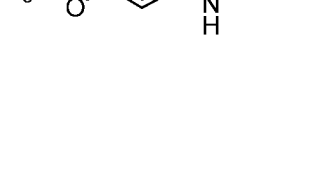
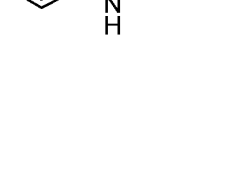
37. The compound of any one of claims 1-31, wherein at least one of R^1, R^2, R^3 and R^4 is OR^a wherein R^a is alkyl.

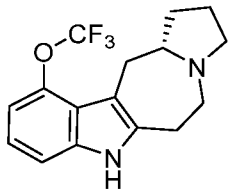
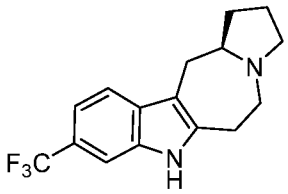
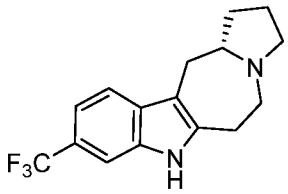
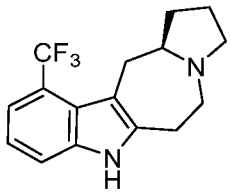
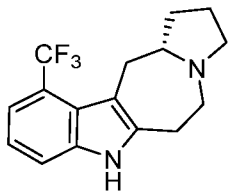
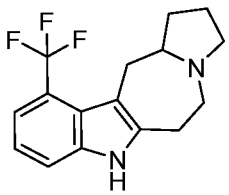
38. The compound of any one of claims 1-31, wherein at least one of R^1, R^2, R^3 and R^4 is hydrogen, benzyloxy, methoxy, fluoro, trifluoromethyl, or trifluoromethoxy.

39. The compound of any one of claims 1-31, wherein R^3 is benzyloxy, methoxy, fluoro, trifluoromethyl, or trifluoromethoxy, and R^1, R^2, and R^4 are each hydrogen.

40. A compound that is:




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or a pharmaceutically acceptable salt or solvate thereof.

41. A pharmaceutical composition comprising a compound of any one of claims 1-40, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

42. A method of promoting neuronal growth in a mammal comprising administering to the mammal a compound of any one of claims 1-40, or any pharmaceutically acceptable salt or solvate thereof.

43. A method of improving neuronal structure in a mammal comprising administering to the mammal a compound of any one of claims 1-40, or any pharmaceutically acceptable salt or solvate thereof.

44. A method of modulating the activity of 5-hydroxytryptamine receptor 2A (5-HT_{2A}) receptor in a mammal comprising administering to the mammal a compound of any one of claims 1-40, or any pharmaceutically acceptable salt or solvate thereof.

45. A method of treating a disease or disorder in a mammal that is mediated by the action of 5-hydroxytryptamine (5-HT) at 5-hydroxytryptamine receptor 2A (5-HT_{2A}) comprising administering to the mammal a compound of any one of claims 1-40, or any pharmaceutically acceptable salt or solvate thereof.

46. A method of treating a disease or disorder in a mammal that is mediated by the loss of synaptic connectivity, plasticity, or a combination thereof, comprising administering to the mammal a compound of any one of claims 1-40, or any pharmaceutically acceptable salt or solvate thereof.

47. A method for treating a neurological disease or disorder in a mammal, the method comprising administering to the mammal a compound of any one of claims 1-40, or any pharmaceutically acceptable salt or solvate thereof.

48. The method of claim 47, wherein the neurological disease or disorder is a neurodegenerative, a neuropsychiatric, or a substance use disease or disorder.

49. The method of claim 47, wherein the neurological disease or disorder is an injury.

50. The method of claim 47, wherein the neurological disease or disorder is selected from the group consisting of an anxiety disorder, a mood disorder, a psychotic disorder, a personality disorder, an eating disorder, a sleep disorder, a sexuality disorder, an impulse control disorder, a substance use disorder, a dissociative disorder, a cognitive disorder, a developmental disorder, and a factitious disorder.

51. The method of any one of claims 42-50, wherein the mammal is a human.