(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 August 2023 (10.08.2023)

WIPO | PCT

(10) International Publication Number
WO 2023/150547 A2

(51) International Patent Classification:
C07D 403/10 (2006.01) *C07D 209/16* (2006.01)

(21) International Application Number:
PCT/US2023/061744

(22) International Filing Date:
01 February 2023 (01.02.2023)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

63/305,309	01 February 2022 (01.02.2022)	US
63/305,312	01 February 2022 (01.02.2022)	US
63/305,314	01 February 2022 (01.02.2022)	US
63/305,315	01 February 2022 (01.02.2022)	US
63/375,459	13 September 2022 (13.09.2022)	US

(71) Applicant: **CAAMTECH, INC.** [US/US]; 58 East Sunset Way, Suite 208, Issaquah, WA 98027 (US).

(72) Inventor: **DISCORDIA, Robert**; 3475 Governors Island Drive, Denver, NC 28037 (US).

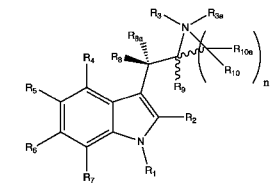
(74) Agent: **WECKESSER, Kayla, N.**; Raphael Bellum, PLLC, 3190 Fairview Park Drive, Suite 1070, Falls Church, VA 22042 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

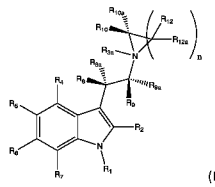
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: PSYCHEDELIC COMPOUNDS AND THEIR THERAPEUTIC USES



(I);



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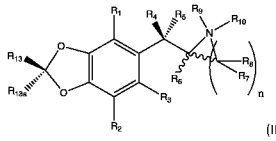
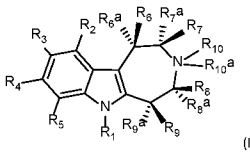


(III); and



(IV).

(57) Abstract: The disclosure relates to compounds of formulae (I), (II), (III), and (IV): The disclosure relates to compositions comprising, consisting essentially of, or consisting of a compound of formulae (I), (II), (III), or (IV) and an excipient. The disclosure also relates to pharmaceutical compositions comprising a therapeutically effective amount of a compound of formulae (I), (II), (III), or (IV) where the excipient is a pharmaceutically acceptable carrier. The disclosure further relates to therapeutic uses of compounds of formulae (I), (II), (III), or (IV).

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PSYCHEDELIC COMPOUNDS AND THEIR THERAPEUTIC USES

Cross Reference to Related Applications

[001] This application claims priority to U.S. Provisional Application No. 63/305,309, filed on February 1, 2022; U.S. Provisional Application No. 63/305,312, filed on February 1, 2022; U.S. Provisional Application No. 63/305,314, filed on February 1, 2022; U.S. Provisional Application No. 63/305,315, filed on February 1, 2022; and U.S. Provisional Application No. 63/375,459, filed on September 13, 2022; the disclosures of which are incorporated by reference.

Technical Field

[002] This disclosure relates to tryptamine compounds, compositions, and pharmaceutical compositions containing them as well as their use in treating various diseases.

[003] This disclosure further relates to phenethylamine compounds, compositions, and pharmaceutical compositions containing them as well as their use in treating various diseases.

Background

[004] Ibogaine (CAS 83-74-9) is a psychedelic tryptamine alkaloid first isolated in 1901 from the root bark of the *Tabernanthe* iboga shrub (also called iboga) of Central Africa and the root bark of a shrub in the genus *Tabernaemontana* found in the Congo (Dybowski, 1901; Haller, 1901). Since that time, ibogaine has been isolated from several plant species particularly those in the family *Apocynaceae* to which T. iboga belongs. Plants containing ibogaine as well as extracts and preparations made from them include many other active and inactive molecules including several different ibogaine derivatives. Ibogaine exhibits relatively low potency at target sites. Studies in rats suggest high doses may cause adverse effects. In 1988, Dzoljic et al. were the first to publish on the ability of ibogaine to relieve withdrawal from narcotics addiction (Dzolkic, 1988). Maisonneuve et al. elucidated the pharmacological interactions between ibogaine and morphine in 1991 (Maisonneuve, 1991). After this, several other researchers showed ibogaine's ability to reduce or interrupt the self-administration of opiates in rats and mice and alter their behaviors (Glick, 1991; Cappendijk, 1993; Broderick, 1985; Broderick, 1994; Sershen, 1994). Additional study results showed ibogaine was more effective in multiple administrations over time than from a single dose (Glick, 1991; Cappendijk, 1993). Recent review papers and meta-analyses have concluded that ibogaine is effective for treating substance addiction and warrants further investigation (Schenberg, 2014; Winkelman, 2014; Belgers, 2016). Several current studies have found ibogaine effective for treating opioid addiction (Noller, 2018, Mash, 2018; Brown, 2018; Davis, 2017).

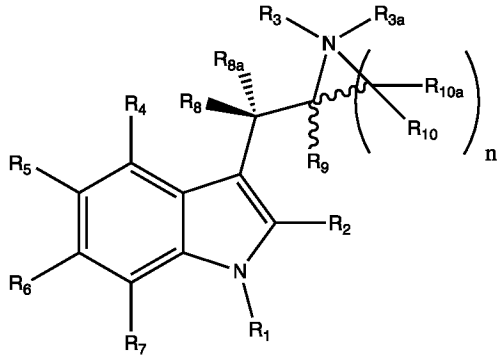
[005] Psilocybin is a breakthrough drug that has received FDA approval for therapeutic applications. Psilocybin is one of several naturally occurring psychoactive tryptamines found in "magic" mushrooms.

When consumed by humans, psilocybin serves as a prodrug of psilocin. Psilocin is a potent serotonin 2a-agonist, which is responsible for its psychoactive properties (Dinis-Oliveira, 2017; Nichols, 2012). Upon digestion, intestinal alkaline phosphate dephosphorylates psilocybin to generate psilocin (Horita and Weber, 1961). Psychoactive tryptamines like psilocin have garnered significant interest recently because of their potential for treating mood disorders, including depression, anxiety, addiction, and post-traumatic stress disorder (PTSD) (Johnson & Griffiths, 2017; Carhart-Harris & Goodwin, 2017). Altering the chemical structure within this class of compounds can dramatically influence the potency and action of the drugs. Psilocybin is converted to psilocin by an enzyme-catalyzed hydrolysis reaction. In humans it was found that after oral administration, psilocin is detectable in significant amounts in the plasma within 20-40 minutes (Passie, 2002). Psilocybin is more soluble in water than psilocin (Ballesteros, 2006). Therefore, psilocin is more easily absorbed from the rat jejunum and colon gastrointestinal track, which suggests greater central nervous system bioavailability (Eivindvik, 1989). Therefore, there is a need for rationally designed analogs of already psychoactive naturally occurring substances to enhance or throttle back activity, reduce side-effects, increase bioavailability and/or other pharmacokinetic and therapeutic properties for treating human conditions.

[006] The compound 3,4-methylenedioxymethamphetamine (MDMA) is a serotonergic drug that enhances serotonergic neurotransmission via release of 5-HT through the serotonin transporter (SERT). MDMA is also known to trigger oxytocin release which may contribute to its effects to increase trust, prosociality, and enhanced empathy. Although psychedelics, such as MDMA, have significant potential for treating many mood disorders, such treatment options often have side-effects which can be generally categorized as “dysphoria.” This dysphoric or unpleasant subjective effects include negative thoughts, rumination, anxiety, panic, paranoia, loss of trust towards other people and perceived loss of control, depending on the dose of the psychedelic drug used, the personality traits of the person consuming it (i.e., 'set'), the environment in which it is consumed (i.e., 'setting'), and other factors yet to be determined. Acute negative psychological effects are considered the main risk of psychedelic substance use in humans. There is an unmet need for mitigating these acute negative psychological effects when administering psychedelic drugs to human subjects. There is an unmet need for methods which are capable of reducing bad drug effects while enhancing good drug effects to optimize a psychedelic experience. Altering the chemical structure within this class of compounds can dramatically influence the potency and action of the drugs.

Summary of the Disclosure

[007] The disclosure relates to a compound of formula (I):



(I)

wherein:

R_1 is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, $-OR_{11}$, $-C(O)R_{11}$, $-C(O)OR_{11}$, $-SO_2R_{11}$, and $-C(O)NR_{11}R_{12}$;

R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{10}, and R_{10a} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6-heteroalkyl, optionally substituted heteroaryl, optionally substituted aryl, halogen, hydroxy, CN, $-OR_{11}$, $-OC(O)R_{11}$, $-OC(O)OR_{11}$, $-OSO_2R_{11}$, $-OC(O)NR_{11}R_{12}$, $-OP(O)(OH)_2$, and $-OP(O)(OH)OP(O)(OH)_2$;

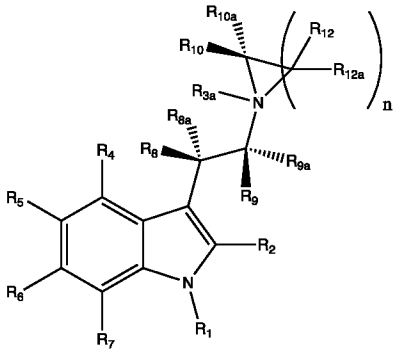
R_3 is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, and $-SO_2R_{11}$;

R_{3a} is selected from an electron pair, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl, wherein when R_{3a} is not an electron pair the compound of formula (I) is a quaternary amine cation with a pharmaceutically acceptable anion, X^-;

R_{11} and R_{12} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl; and

n is an integer defining the variable number of ring carbons carrying R_{10} and R_{10a} and is selected from 1 to 4.

[008] The disclosure further relates to a compound of formula (II):



(II)

wherein:

R_1 is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, -OR_{11}, -$C(O)R_{11}$, -$C(O)OR_{11}$, -SO_2R_{11}, and -$C(O)NR_{11}R_{13}$;

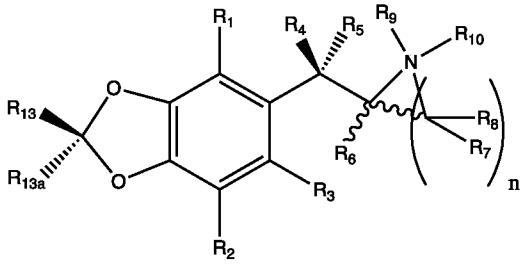
R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{9a}, R_{10}, R_{10a}, R_{12}, and R_{12a} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6-heteroalkyl, optionally substituted heteroaryl, optionally substituted aryl, halogen, hydroxy, CN, -OR_{11}, -$OC(O)R_{11}$, -$OC(O)OR_{11}$, -OSO_2R_{11}, -$OC(O)NR_{11}R_{13}$, -$OP(O)(OH)_2$, and -$OP(O)(OH)OP(O)(OH)_2$;

R_{3a} is selected from an electron pair, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl, wherein when R_{3a} is not an electron pair the compound of formula (II) is a quaternary amine cation with a pharmaceutically acceptable anion, X^-;

R_{11} and R_{13} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl; and

n is an integer defining the variable number of ring carbons carrying R_{12} and R_{12a} and is selected from 1 to 4.

[009] The disclosure further relates to a compound of formula (III):



(III)

wherein:

R_1, R_2, and R_3 are independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, halogen, -OR_{11}, -$C(O)R_{11}$, -$C(O)OR_{11}$, -$OC(O)R_{11}$, $C(O)NR_{11}R_{12}$, CN, $C(NR_{12})R_{11}$, $C(NOR_{12})OR_{11}$, -SO_2R_{11}, and -$C(O)NR_{11}R_{12}$;

R_4, R_5, R_6, R_7, and R_8 are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted heteroaryl, optionally substituted aryl, halogen, hydroxy, -OR_{11}, -$OC(O)R_{11}$, -$OC(O)OR_{11}$, -OSO_2R_{11}, and -$OC(O)NR_{11}R_{12}$;

R_9 is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, and -SO_2R_{11};

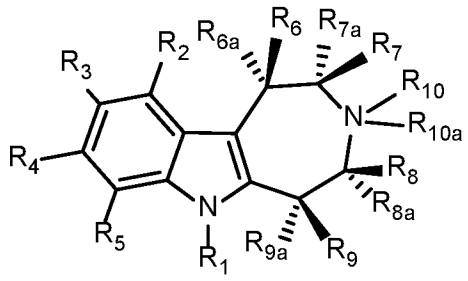
R_{10} is selected from an electron pair, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl, wherein when R_{10} is not an electron pair the compound of formula (III) is a quaternary amine cation with a pharmaceutically acceptable anion, X^-;

R_{11} and R_{12} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl;

R_{13} and R_{13a} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl, or R_{13} and R_{13a} are taken together with the carbon to which they are bound to form a 3- to 6-membered cycloalkyl; and

n is an integer defining the variable number of ring carbons carrying R_7 and R_8 and is selected from 1 to 4.

[010] The disclosure further relates to a compound of formula (IV):



(IV)

wherein:

R_1 is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, $-OR_{11}$, $-C(O)R_{11}$, $-C(O)OR_{11}$, $-SO_2R_{11}$, and $-C(O)NR_{11}R_{12}$;

R_2, R_3, R_4, R_5, R_6, R_{6a}, R_7, R_{7a}, R_8, R_{8a}, R_9, and R_{9a} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6-heteroalkyl, optionally substituted heteroaryl, optionally substituted aryl, halogen, hydroxy, $-OR_{11}$, $-OC(O)R_{11}$, $-OC(O)OR_{11}$, $-OSO_2R_{11}$, and $-OC(O)NR_{11}R_{12}$;

R_{10} is selected from an electron pair, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl, wherein when R_{10} is not an electron pair the compound of formula (IV) is a quaternary amine cation with a pharmaceutically acceptable anion, X^-;

R_{10a} is taken together with one of R_8, R_{8a}, R_9, or R_{9a} to form optionally substituted 3- to 6-membered heterocyclic ring; and

R_{11} and R_{12} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl.

[011] The disclosure relates to compositions comprising, consisting essentially of, or consisting of a compound of formulae (I), (II), (III), or (IV) and an excipient. The disclosure also relates pharmaceutical compositions comprising a therapeutically effective amount of a compound of formulae (I), (II), (III), or (IV), wherein the excipient is a pharmaceutically acceptable carrier. The disclosure further relates to a method of preventing or treating a psychological disorder comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of formulae (I), (II), (III), or (IV), or a pharmaceutical composition according to this disclosure.

[012] The disclosure also relates to a composition comprising, consisting essentially of, or consisting of as a first active component: a compound of formulae (I), (II), (III), or (IV); and as a second active component selected from (a) a serotonergic drug, (b) a purified psilocybin derivative, (c) a purified cannabinoid, (d) a purified terpene, (e) an adrenergic drug, (f) a dopaminergic drug, (g) a monoamine oxidase inhibitor, (h) a purified erinacine, and (i) a purified hericenone; and a pharmaceutically acceptable excipient.

[013] The disclosure further relates to methods of preventing or treating a physical and/or psychological disorders comprising the step of administering to a subject in need thereof an effective amount of a compound of formulae (I), (II), (III), or (IV), or a composition (e.g., a pharmaceutically-acceptable composition) comprising a compound of formulae (I), (II), (III), or (IV), according to this disclosure.

[014] The disclosure further relates to methods of treating and/or preventing a substance use disorder comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of formulae (I), (II), (III), or (IV), or a composition (e.g., a pharmaceutically-acceptable composition) comprising a compound of formulae (I), (II), (III), or (IV), according to the disclosure.

[015] The disclosure also relates to methods of preventing or treating inflammation and/or pain comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of formulae (I), (II), (III), or (IV), and to administering a pharmaceutical composition or a composition according to the disclosure.

[016] The disclosure also relates to methods of preventing or treating inflammation and/or pain, preventing or treating a neurological disorder, modulating activity of a mitogen-activated protein kinase (MAPK), modulating neurogenesis, or modulating neurite outgrowth comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of

formulae (I), (II), (III), or (IV), and to administering a pharmaceutical composition or a composition according to the disclosure.

[017] The disclosure also relates to methods of preventing or treating sexual health disorders including, but not limited to, hypoactive sexual desire disorder, hyperactive sexual desire disorder, orgasmic disorder, arousal disorder, vaginismus, and dyspareunia, comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of formulae (I), (II), (III), or (IV), and to administering a pharmaceutical composition or a composition according to the disclosure. In some embodiments, the disorder is a male sexual dysfunction disorder. In some embodiments, the disorder is a female sexual dysfunction disorder.

[018] The disclosure also relates to methods of preventing or treating women's health disorders including, but not limited to, menstrual cramping, dysmenorrhea, post-hysterectomy pain, vaginal or vulvar vestibule mucosa disorder, vaginal atrophy, or vulvar vestibulitis, comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of formulae (I), (II), (III), or (IV), and to administering a pharmaceutical composition or a composition according to the disclosure.

[019] As used herein, the term "a subject in need thereof" refers to a person requiring a composition to treat a particular disease or condition (e.g., inflammation, pain, a psychological disorder, modulating activity at a receptor, etc.). In one embodiment, the "subject in need thereof" may be identified by analyzing, diagnosing, and/or determining whether the person (or subject) requires the composition for treatment of a particular disease or condition. In one embodiment, identifying a person in need of treatment comprises diagnosing a person with a medical condition, e.g., a neurological disorder, a chemical imbalance, a hereditary condition, etc. In one embodiment, identifying a person in need of treatment comprises performing a psychiatric evaluation. In one embodiment, identifying a person in need of treatment comprises performing a blood test. In one embodiment, identifying a person in need of treatment comprises determining whether a person has a compulsive disorder. In one embodiment, identifying a person in need of treatment comprises self-identifying as having a compulsive disorder.

Description of the Figures

[020] FIG. 1 shows the ^{1}H NMR spectrum of (S)-3-((1-methylaziridin-2-yl)methyl)-1H-indol-4-ol.

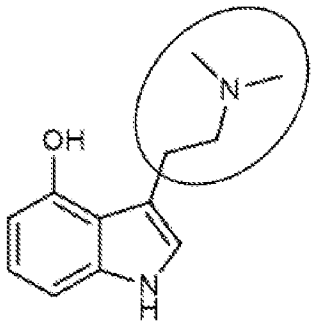
[021] FIG. 2 shows the ^{1}H NMR spectrum of Azacyclopropyl-MDMA analog.

Detailed Description

[022] Compounds of the Disclosure

[023] The disclosure specifically relates to the purposeful design of novel molecular structures, so designed to impart rotational and conformational restrictions at the loci of putative binding of the subject molecules with CNS receptors. These modifications involve the "tying up" of otherwise freely rotational moieties into conformations that cause bond angles and bond lengths to be changed to afford useful improvements in biological profile over the naturally derived substances. The effects are enhancements to the pharmacological profile of the naturally derived parent molecules to be useful in psychiatric therapy for presently unmet medical needs. There is a wealth of information on the utility of certain hallucinogenic substances to possess the ability to treat heretofore hard to treat or untreatable psychological ailments such as depression, anxiety, post-traumatic stress disorder (PTSD), traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), etc.

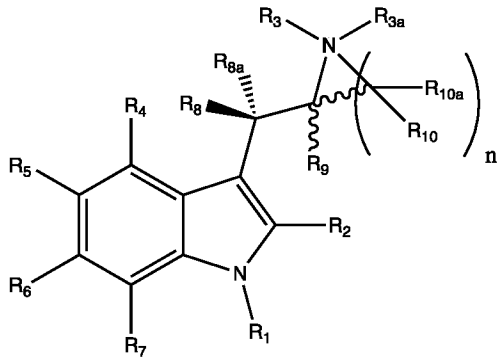
[024] The derivatization of psilocin, such as from a structure-activity relationship, indicates a significant diminution of affinity and efficacy at $5HT_{2A}R$ and other receptors in proportion to increasing steric bulk about the terminal N,N-dialkylaminoethyl side chain functionality (Klein) circled in the following chemical structure:



[025] It is reasoned that the binding affinity to and fidelity for critical receptors may be modulated by conformational and/or rotational restriction about the moieties that bind the receptor sites. In addition, changes in C-N-C atomic bond lengths and nitrogen hybridization and barrier to pyramidal inversion can also be levers to adjust pharmacological properties (Padwa; Katritzky). To that end, tryptamine and serotonin analogs have been designed and the following Markush structure depicting the scope of such derivatives is shown in formula (I) below. A key feature of formula (I) is the appearance of small 3- to 6-membered ring heterocycles which change bond lengths and angles in the N,N-dimethylamino-ethyl moiety of Psilocybin/Psilocin. Formula (I) also introduces chirality at one or more of the ring carbons,

which also modulates activity. Additional modulation of activity can be brought about through changes in the electronics of the indole ring through substitution with different elements.

[026] The disclosure relates to a compound of formula (I):



(I)

wherein:

R_1 is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, -OR_{11}, -$C(O)R_{11}$, -$C(O)OR_{11}$, -SO_2R_{11}, and -$C(O)NR_{11}R_{12}$;

R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{10}, and R_{10a} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6-heteroalkyl, optionally substituted heteroaryl, optionally substituted aryl, halogen, hydroxy, CN, -OR_{11}, -$OC(O)R_{11}$, -$OC(O)OR_{11}$, -OSO_2R_{11}, -$OC(O)NR_{11}R_{12}$, -$OP(O)(OH)_2$, and -$OP(O)(OH)OP(O)(OH)_2$;

R_3 is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, and -SO_2R_{11};

R_{3a} is selected from an electron pair, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl, wherein when R_{3a} is not an electron pair the compound of formula (I) is a quaternary amine cation with a pharmaceutically acceptable anion, X^-;

R_{11} and R_{12} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl; and

n is an integer defining the variable number of ring carbons carrying R_{10} and R_{10a} and is selected from 1 to 4.

[027] In formula (I), R_1 is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, -OR_{11}, -$C(O)R_{11}$, -$C(O)OR_{11}$, -SO_2R_{11}, and -$C(O)NR_{11}R_{12}$. R_1 may be hydrogen. R_1 may be an optionally substituted straight chain or branched C_1-C_6 alkyl, for example a straight chain C_1-C_6 alkyl, or an optionally substituted straight chain or branched C_2-C_6 alkenyl, for example allyl, 2-butenyl, etc. In some embodiments R_1 may be a straight chain or branched C_1-C_4 alkyl, for example a straight chain C_1-C_4 alkyl, or a C_2-C_4 alkenyl. R_1 may be an optionally

substituted aryl. An aryl is a 6- to 14-membered aromatic ring, preferably a 6- to 10-membered aromatic ring and includes polycyclic ring systems in which two or more carbon atoms are common to adjoining rings where at least one ring is aromatic. Examples of aryl groups include, but are not limited to phenyl, naphthyl, anthracenyl, and phenantherenyl. An aryl group may be substituted with one or more C_1-C_4 alkyl or perfluoralkyl groups, C_1-C_4 hydroxyalkyl groups, hydroxyl groups, nitro groups or halo groups (e.g., F, Cl, I, or Br). An aryl group may be ortho-, meta-, and/or para-substituted, preferably para-substituted. R_1 may be $-OR_{11}$, $-C(O)R_{11}$, $-C(O)OR_{11}$, $-SO_2R_{11}$, or $-C(O)NR_{11}R_{12}$, wherein R_{11} and R_{12} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl.

[028] In formula (I), R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{10}, and R_{10a} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6-heteroalkyl, optionally substituted heteroaryl, optionally substituted aryl, halogen, hydroxy, CN, $-OR_{11}$, $-OC(O)R_{11}$, $-OC(O)OR_{11}$, $-OSO_2R_{11}$, $-OC(O)NR_{11}R_{12}$, $-OP(O)(OH)_2$, and $-OP(O)(OH)OP(O)(OH)_2$. R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{10}, and R_{10a} may each independently be hydrogen. R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{10}, and R_{10a} may each independently be an optionally substituted straight chain or branched C_1-C_6 alkyl, for example, a straight chain C_1-C_6 alkyl, or an optionally substituted straight chain or branched C_2-C_6 alkenyl, for example allyl, 2-butenyl, etc. In some embodiments R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{10}, and R_{10a} may each independently be a straight chain or branched C_1-C_4 alkyl, for example a straight chain C_1-C_4 alkyl, or a C_2-C_4 alkenyl. R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{10}, and R_{10a} may each independently be an optionally substituted C_1-C_6-heteroalkyl, including but not limited to alkoxy, alkylthio, and alkylamino. R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{10}, and R_{10a} may each independently be an optionally substituted heteroaryl, including, but not limited to, furano, pyridinyl, pyrimidinyl, etc. R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{10}, and R_{10a} may each independently be an optionally substituted aryl. An aryl is a 6- to 14-membered aromatic ring, preferably a 6- to 10-membered aromatic ring and includes polycyclic ring systems in which two or more carbon atoms are common to adjoining rings where at least one ring is aromatic. Examples of aryl groups include, but are not limited to phenyl, naphthyl, anthracenyl, and phenantherenyl. An aryl group may be substituted with one or more C_1-C_4 alkyl or perfluoralkyl groups, C_1-C_4 hydroxyalkyl groups, hydroxyl groups, nitro groups or halo groups (e.g., F, Cl, I, or Br). An aryl group may be ortho-, meta-, and/or para-substituted, preferably para-substituted. R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{10}, and R_{10a} may each independently be a halogen. Exemplary halogens include fluorine (F), chlorine (Cl), bromine (Br), and iodine (I). R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{10}, and R_{10a} may each independently be hydroxy. R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{10}, and R_{10a} may each independently be CN. R_2, R_4, R_5, R_6, R_7, R_8, R_{8a},

R_9, R_{10}, and R_{10a} may each independently be $-OR_{11}$, $-OC(O)R_{11}$, $-OC(O)OR_{11}$, $-OSO_2R_{11}$, $-OC(O)NR_{11}R_{12}$, $-OP(O)(OH)_2$, or $-OP(O)(OH)OP(O)(OH)_2$, wherein R_{11} and R_{12} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl.

[029] In formula (I), R_3 is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, and $-SO_2R_{11}$. R_3 may be hydrogen. R_3 may be an optionally substituted straight chain or branched C_1-C_6 alkyl, for example a straight chain C_1-C_6 alkyl, or an optionally substituted straight chain or branched C_2-C_6 alkenyl, for example allyl, 2-butenyl, etc. In some embodiments R_3 may be a straight chain or branched C_1-C_4 alkyl, for example a straight chain C_1-C_4 alkyl, or a C_2-C_4 alkenyl. R_3 may be an optionally substituted aryl. An aryl is a 6- to 14-membered aromatic ring, preferably a 6- to 10-membered aromatic ring and includes polycyclic ring systems in which two or more carbon atoms are common to adjoining rings where at least one ring is aromatic. Examples of aryl groups include, but are not limited to phenyl, naphthyl, anthracenyl, and phenantherenyl. An aryl group may be substituted with one or more C_1-C_4 alkyl or perfluoralkyl groups, C_1-C_4 hydroxyalkyl groups, hydroxyl groups, nitro groups or halo groups (e.g., F, Cl, I, or Br). An aryl group may be ortho-, meta-, and/or para-substituted, preferably para-substituted. R_3 may be $-SO_2R_{11}$, wherein R_{11} is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl.

[030] In formula (I), R_{3a} is selected from an electron pair, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl, wherein when R_{3a} is not an electron pair the compound of formula (I) is a quaternary amine cation with a pharmaceutically acceptable anion, X^-. R_{3a} may be an electron pair. R_{3a} may be hydrogen. R_{3a} may be an optionally substituted straight chain or branched C_1-C_6 alkyl, for example a straight chain C_1-C_6 alkyl, or an optionally substituted straight chain or branched C_2-C_6 alkenyl, for example allyl, 2-butenyl, etc. In some embodiments R_{3a} may be a straight chain or branched C_1-C_4 alkyl, for example a straight chain C_1-C_4 alkyl, or a C_2-C_4 alkenyl. R_{3a} may be an optionally substituted aryl. An aryl is a 6- to 14-membered aromatic ring, preferably a 6- to 10-membered aromatic ring and includes polycyclic ring systems in which two or more carbon atoms are common to adjoining rings where at least one ring is aromatic. Examples of aryl groups include, but are not limited to phenyl, naphthyl, anthracenyl, and phenantherenyl. An aryl group may be substituted with one or more C_1-C_4 alkyl or perfluoralkyl groups, C_1-C_4 hydroxyalkyl groups, hydroxyl groups, nitro groups or halo groups (e.g., F, Cl, I, or Br). An aryl group may be ortho-, meta-, and/or para-substituted, preferably para-substituted.

[031] The anion of formula (I), X^-, may be any pharmaceutically acceptable anion, for example, Cl^-, I^-, Br^-, ascorbate, hydrofumarate, fumarate, maleate, and the like.

[032] In formula (I), R_{11} and R_{12} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl. R_{11} and R_{12} may each independently be hydrogen. R_{11} and R_{12} may each independently be an optionally substituted straight chain or branched C_1-C_6 alkyl, for example a straight chain C_1-C_6 alkyl, or an optionally substituted straight chain or branched C_2-C_6 alkenyl, for example allyl, 2-butenyl, etc. In some embodiments R_{11} and R_{12} may each independently be a straight chain or branched C_1-C_4 alkyl, for example a straight chain C_1-C_4 alkyl, or a C_2-C_4 alkenyl. R_{11} and R_{12} may each independently be an optionally substituted aryl. An aryl is a 6- to 14-membered aromatic ring, preferably a 6- to 10-membered aromatic ring and includes polycyclic ring systems in which two or more carbon atoms are common to adjoining rings where at least one ring is aromatic. Examples of aryl groups include, but are not limited to phenyl, naphthyl, anthracenyl, and phenantherenyl. An aryl group may be substituted with one or more C_1-C_4 alkyl or perfluoralkyl groups, C_1-C_4 hydroxyalkyl groups, hydroxyl groups, nitro groups or halo groups (e.g., F, Cl, I, or Br). An aryl group may be ortho-, meta-, and/or para-substituted, preferably para-substituted.

[033] In formula (I), n is an integer defining the variable number of ring carbons carrying R_{10} and R_{10a} and is selected from 1 to 4. In one embodiment, n is 1. In one embodiment, n is 2. In one embodiment, n is 3. In one embodiment, n is 4.

[034] Exemplary compounds of formula (I) are those wherein at least one of R_4 or R_5 is selected from hydroxy, $-OR_{11}$, $-OC(O)R_{11}$, $-OC(O)OR_{11}$, $-OSO_2R_{11}$, $-OC(O)NR_{11}R_{12}$, $-OP(O)(OH)_2$, and $-OP(O)(OH)OP(O)(OH)_2$.

[035] Other exemplary compounds of formula (I) are those wherein at least one of R_4 or R_5 is selected from hydroxy and $-OC(O)R_{11}$.

[036] Other exemplary compounds of formula (I) are those wherein R_{11} is an optionally substituted C_1-C_6 alkyl.

[037] Other exemplary compounds of formula (I) are those wherein R_{11} is an unsubstituted C_1-C_6 alkyl.

[038] Other exemplary compounds of formula (I) are those wherein R_{11} is methyl.

[039] Other exemplary compounds of formula (I) are those wherein R_3 is selected from optionally substituted C_1-C_6 alkyl and optionally substituted C_2-C_6 alkenyl.

[040] Other exemplary compounds of formula (I) are those wherein R_3 is an unsubstituted C_1-C_6 alkyl.

[041] Other exemplary compounds of formula (I) are those wherein R_3 is methyl.

[042] Other exemplary compounds of formula (I) are those wherein R_{3a} is an electron pair.

[043] Other exemplary compounds of formula (I) are those wherein R_6 is hydrogen.

[044] Other exemplary compounds of formula (I) are those wherein R_7 is hydrogen.

[045] Other exemplary compounds of formula (I) are those wherein R_9 is hydrogen.

[046] Other exemplary compounds of formula (I) are those wherein R_1 is selected from hydrogen and optionally substituted C_1-C_6 alkyl.

[047] Other exemplary compounds of formula (I) are those wherein R_1 is a 2-(S)-methyl-2-N,N-dimethylamino-ethyl or 2-(R)-methyl-2-N,N-dimethylamino-ethyl.

[048] Other exemplary compounds of formula (I) are those wherein R_{10} is hydrogen.

[049] Other exemplary compounds of formula (I) are those wherein R_{10a} is hydrogen.

[050] Other exemplary compounds of formula (I) are those wherein R_8 is hydrogen.

[051] Other exemplary compounds of formula (I) are those wherein R_{8a} is hydrogen.

[052] Other exemplary compounds of formula (I) are those wherein n = 1.

[053] Other exemplary compounds of formula (I) are those wherein n = 2.

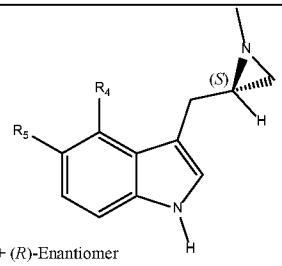
[054] Other exemplary compounds of formula (I) are those wherein n = 3.

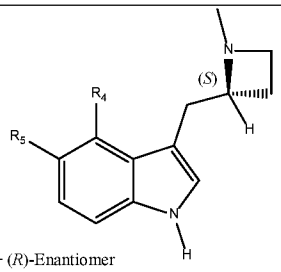
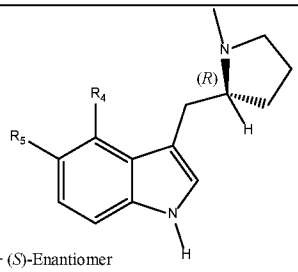
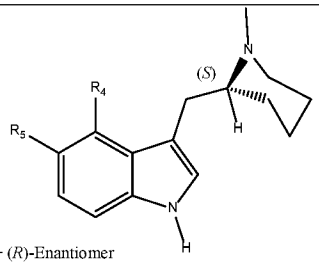
[055] Other exemplary compounds of formula (I) are those wherein n = 4.

[056] Other exemplary compounds of formula (I) are those wherein R_2 is hydrogen.

[057] Exemplary lead compounds of formula (I) can be found in Table 1.

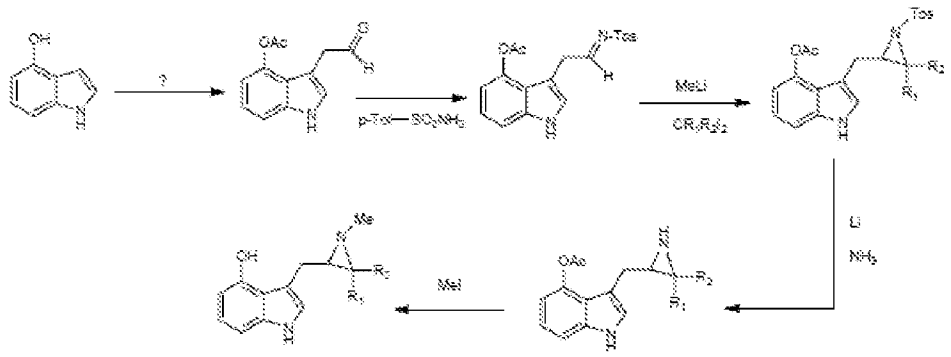
Table 1

Compound	**Structural Formula**
N-Methyl Aziridinyltryptamine Series	 + (*R*)-Enantiomer R_4 = OH; R_5 = H R_4 = H; R_5 = OH R_4 = OAc; R_5 = H R_4 = H; R_5 = OAc

N-Methyl Azacyclobutyltryptamine Series	 + (*R*)-Enantiomer R_4 = OH; R_5 = H R_4 = H; R_5 = OH R_4 = OAc; R_5 = H R_4 = H; R_5 = OAc
N-Methyl Azacyclopentyltryptamine Series	 + (*S*)-Enantiomer R_4 = OH; R_5 = H R_4 = H; R_5 = OH R_4 = OAc; R_5 = H R_4 = H; R_5 = OAc
N-Methyl Azacyclohexyltryptamine Series	 + (*R*)-Enantiomer R_4 = OH; R_5 = H R_4 = H; R_5 = OH R_4 = OAc; R_5 = H R_4 = H; R_5 = OAc

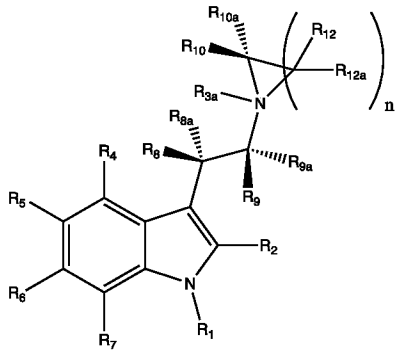
[058] Tryptamine analogs with endocyclic amines such as those represented in formula (I), can be prepared by synthesis of tryptamine analogs. The following reaction mechanism shows the synthesis of both 3-((1-methylaziridin-2-yl)methyl)-1H-indol-4-ol as well as the acetate prodrug 3-((1-methylaziridin-2-yl)methyl)-1H-indol-4-yl acetate. 4-Acetoxyindole can be alkylated at the 3-position to provide the intermediate aldehyde which is converted to the p-toluenesulfonimine by addition of the corresponding sulfonamide. The aziridine moiety is created by the action of in situ generated iodomethyllithium (in this case where R_1 and R_2 = H). (Concellón) The N-tosyl bond is cleaved through direct reduction to produce the secondary aziridine which can be alkylated with methyl iodide to produce the target compound (the

4-acetoxy derivative) which can be converted to the 4-hydroxy compound through saponification of the following reaction mechanism.



[059] Formula (II) below depicts derivatives that provide for further optionality for the modulation of effect.

[060] The disclosure further relates to a compound of formula (II):



(II)

wherein:

R_1 is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, $-OR_{11}$, $-C(O)R_{11}$, $-C(O)OR_{11}$, $-SO_2R_{11}$, and $-C(O)NR_{11}R_{13}$;

R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{9a}, R_{10}, R_{10a}, R_{12}, and R_{12a} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6-heteroalkyl, optionally substituted heteroaryl, optionally substituted aryl, halogen, hydroxy, CN, $-OR_{11}$, $-OC(O)R_{11}$, $-OC(O)OR_{11}$, OSO_2R_{11}, $-OC(O)N\ R_{11}R_{13}$, $-OP(O)(OH)_2$, and $-OP(O)(OH)OP(O)(OH)_2$;

R_{3a} is selected from an electron pair, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl, wherein when R_{3a} is not an electron pair the compound of formula (II) is a quaternary amine cation with a pharmaceutically acceptable anion, X^-;

R_{11} and R_{13} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl; and

n is an integer defining the variable number of ring carbons carrying R_{12} and R_{12a} and is selected from 1 to 4.

[061] In formula (II), R_1 is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, $-OR_{11}$, $-C(O)R_{11}$, $-C(O)OR_{11}$, $-SO_2R_{11}$, and $-C(O)NR_{11}R_{13}$. R_1 may be hydrogen. R_1 may be an optionally substituted straight chain or branched C_1-C_6 alkyl, for example a straight chain C_1-C_6 alkyl, or an optionally substituted straight chain or branched C_2-C_6 alkenyl, for example allyl, 2-butenyl, etc. In some embodiments R_1 may be a straight chain or branched C_1-C_4 alkyl, for example a straight chain C_1-C_4 alkyl, or a C_2-C_4 alkenyl. R_1 may be an optionally substituted aryl. An aryl is a 6- to 14-membered aromatic ring, preferably a 6- to 10-membered aromatic ring and includes polycyclic ring systems in which two or more carbon atoms are common to adjoining rings where at least one ring is aromatic. Examples of aryl groups include, but are not limited to phenyl, naphthyl, anthracenyl, and phenantherenyl. An aryl group may be substituted with one or more C_1-C_4 alkyl or perfluoralkyl groups, C_1-C_4 hydroxyalkyl groups, hydroxyl groups, nitro groups or halo groups (e.g., F, Cl, I, or Br). An aryl group may be ortho-, meta-, and/or para-substituted, preferably para-substituted. R_1 may be $-OR_{11}$, $-C(O)R_{11}$, $-C(O)OR_{11}$, $-SO_2R_{11}$, or $-C(O)N\ R_{11}R_{13}$, wherein R_{11} and R_{13} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl.

[062] In formula (II), R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{9a}, R_{10}, R_{10a}, R_{12}, and R_{12a} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6-heteroalkyl, optionally substituted heteroaryl, optionally substituted aryl, halogen, hydroxy, CN, $-OR_{11}$, $-OC(O)R_{11}$, $-OC(O)OR_{11}$, $-OSO_2R_{11}$, $-OC(O)NR_{11}R_{13}$, $-OP(O)(OH)_2$, and $-OP(O)(OH)OP(O)(OH)_2$. R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{9a}, R_{10}, R_{10a}, R_{12}, and R_{12a} may each independently be hydrogen. R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{9a}, R_{10}, R_{10a}, R_{12}, and R_{12a} may each independently be an optionally substituted straight chain or branched C_1-C_6 alkyl, for example a straight chain C_1-C_6 alkyl, or an optionally substituted straight chain or branched C_2-C_6 alkenyl, for example allyl, 2-butenyl, etc. In some embodiments R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{9a}, R_{10}, R_{10a}, R_{12}, and R_{12a} may each independently be a straight chain or branched C_1-C_4 alkyl, for example a straight chain C_1-C_4 alkyl, or a C_2-C_4 alkenyl. R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{9a}, R_{10}, R_{10a}, R_{12}, and R_{12a} may each independently be an optionally substituted C_1-C_6-heteroalkyl, including but not limited to alkoxy, alkylthio, and alkylamino. R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{9a}, R_{10}, R_{10a}, R_{12}, and R_{12a} may each independently be an optionally substituted

heteroaryl, including, but not limited to, furano, pyridinyl, pyrimidinyl, etc. R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{9a}, R_{10}, R_{10a}, R_{12}, and R_{12a} may each independently be an optionally substituted aryl. An aryl is a 6- to 14-membered aromatic ring, preferably a 6- to 10-membered aromatic ring and includes polycyclic ring systems in which two or more carbon atoms are common to adjoining rings where at least one ring is aromatic. Examples of aryl groups include, but are not limited to phenyl, naphthyl, anthracenyl, and phenantherenyl. An aryl group may be substituted with one or more C_1-C_4 alkyl or perfluoralkyl groups, C_1-C_4 hydroxyalkyl groups, hydroxyl groups, nitro groups or halo groups (e.g., F, Cl, I, or Br). An aryl group may be ortho-, meta-, and/or para-substituted, preferably para-substituted. R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{9a}, R_{10}, R_{10a}, R_{12}, and R_{12a} may each independently be a halogen. Exemplary halogens include fluorine (F), chlorine (Cl), bromine (Br), and iodine (I). R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{9a}, R_{10}, R_{10a}, R_{12}, and R_{12a} may each independently by hydroxy. R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{9a}, R_{10}, R_{10a}, R_{12}, and R_{12a} may each independently be CN. R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{9a}, R_{10}, R_{10a}, R_{12}, and R_{12a} may each independently be -OR_{11}, -$OC(O)R_{11}$, -$OC(O)OR_{11}$, -OSO_2R_{11}, -$OC(O)NR_{11}R_{13}$, -$OP(O)(OH)_2$, or -$OP(O)(OH)OP(O)(OH)_2$, wherein R_{11} and R_{13} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl.

[063] In formula (II), R_{3a} is selected from an electron pair, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl, wherein when R_{3a} is not an electron pair the compound of formula (II) is a quaternary amine cation with a pharmaceutically acceptable anion, X^-. R_{3a} may be an electron pair. R_{3a} may be hydrogen. R_{3a} may be an optionally substituted straight chain or branched C_1-C_6 alkyl, for example a straight chain C_1-C_6 alkyl, or an optionally substituted straight chain or branched C_2-C_6 alkenyl, for example allyl, 2-butenyl, etc. In some embodiments R_{3a} may be a straight chain or branched C_1-C_4 alkyl, for example a straight chain C_1-C_4 alkyl, or a C_2-C_4 alkenyl. R_{3a} may be an optionally substituted aryl. An aryl is a 6- to 14-membered aromatic ring, preferably a 6- to 10-membered aromatic ring and includes polycyclic ring systems in which two or more carbon atoms are common to adjoining rings where at least one ring is aromatic. Examples of aryl groups include, but are not limited to phenyl, naphthyl, anthracenyl, and phenantherenyl. An aryl group may be substituted with one or more C_1-C_4 alkyl or perfluoralkyl groups, C_1-C_4 hydroxyalkyl groups, hydroxyl groups, nitro groups or halo groups (e.g., F, Cl, I, or Br). An aryl group may be ortho-, meta-, and/or para-substituted, preferably para-substituted.

[064] The anion of formula (II), X^-, may be any pharmaceutically acceptable anion, for example, Cl^-, I^-, Br^-, ascorbate, hydrofumarate, fumarate, maleate, and the like.

[065] In formula (II), R_{11} and R_{13} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl. R_{11} and R_{13} may each independently be hydrogen. R_{11} and R_{13} may each independently be an optionally substituted straight chain or branched C_1-C_6 alkyl, for example a straight chain C_1-C_6 alkyl, or an optionally substituted straight chain or branched C_2-C_6 alkenyl, for example allyl, 2-butenyl, etc. In some embodiments R_{11} and R_{13} may each independently be a straight chain or branched C_1-C_4 alkyl, for example a straight chain C_1-C_4 alkyl, or a C_2-C_4 alkenyl. R_{11} and R_{13} may each independently be an optionally substituted aryl. An aryl is a 6- to 14-membered aromatic ring, preferably a 6- to 10-membered aromatic ring and includes polycyclic ring systems in which two or more carbon atoms are common to adjoining rings where at least one ring is aromatic. Examples of aryl groups include, but are not limited to phenyl, naphthyl, anthracenyl, and phenantherenyl. An aryl group may be substituted with one or more C_1-C_4 alkyl or perfluoralkyl groups, C_1-C_4 hydroxyalkyl groups, hydroxyl groups, nitro groups or halo groups (e.g., F, Cl, I, or Br). An aryl group may be ortho-, meta-, and/or para-substituted, preferably para-substituted.

[066] In formula (II), n is an integer defining the variable number of ring carbons carrying R_{12} and R_{12a} and is selected from 1 to 4. In one embodiment, n is 1. In one embodiment, n is 2. In one embodiment, n is 3. In one embodiment, n is 4.

[067] Exemplary compounds of formula (II) are those with the proviso that when n=2, R_{3a} is not an electron pair and/or at least one of R_8, R_{8a}, R_9, or R_{9a} is not hydrogen.

[068] Other exemplary compounds of formula (II) are those wherein at least one of R_4 or R_5 is selected from hydroxy, $-OR_{11}$, $-OC(O)R_{11}$, $-OC(O)OR_{11}$, $-OSO_2R_{11}$, $-OC(O)NR_{11}R_{12}$, $-OP(O)(OH)_2$, and $-OP(O)(OH)OP(O)(OH)_2$.

[069] Other exemplary compounds of formula (II) are those wherein at least one of R_4 or R_5 is selected from hydroxy and $-OC(O)R_{11}$.

[070] Other exemplary compounds of formula (II) are those wherein R_{11} is an optionally substituted C_1-C_6 alkyl.

[071] Other exemplary compounds of formula (II) are those wherein R_{11} is an unsubstituted C_1-C_6 alkyl.

[072] Other exemplary compounds of formula (II) are those wherein R_{11} is methyl.

[073] Other exemplary compounds of formula (II) are those wherein R_{3a} is an electron pair.

[074] Other exemplary compounds of formula (II) are those wherein R_6 is hydrogen.

[075] Other exemplary compounds of formula (II) are those wherein R_7 is hydrogen.

[076] Other exemplary compounds of formula (II) are those wherein R_9 is hydrogen.

[077] Other exemplary compounds of formula (II) are those wherein R_{9a} is hydrogen.

[078] Other exemplary compounds of formula (II) are those wherein R_8 is hydrogen.

[079] Other exemplary compounds of formula (II) are those wherein R_{8a} is hydrogen.

[080] Other exemplary compounds of formula (II) are those wherein R_1 is selected from hydrogen and optionally substituted C_1-C_6 alkyl.

[081] Other exemplary compounds of formula (II) are those wherein R_1 is selected from 2-(S)-methyl-2-N,N-dimethylamino-ethyl or 2-(R)-methyl-2-N,N-dimethylamino-ethyl.

[082] Other exemplary compounds of formula (II) are those wherein R_{10} is hydrogen.

[083] Other exemplary compounds of formula (II) are those wherein R_{10a} is hydrogen.

[084] Other exemplary compounds of formula (II) are those wherein R_{12} is hydrogen.

[085] Other exemplary compounds of formula (II) are those wherein R_{12a} is hydrogen.

[086] Other exemplary compounds of formula (II) are those wherein n = 1.

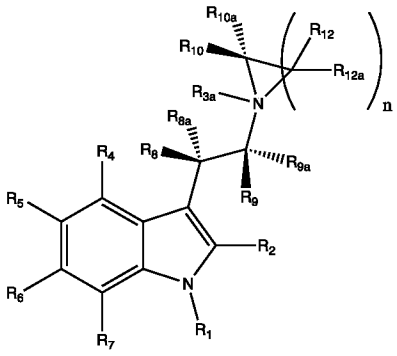
[087] Other exemplary compounds of formula (II) are those wherein n = 2.

[088] Other exemplary compounds of formula (II) are those wherein n=2, with the proviso that R_{3a} is not an electron pair and/or at least one of R_8, R_{8a}, R_9, or R_{9a} is not hydrogen.

[089] Other exemplary compounds of formula (II) are those wherein n = 3.

[090] Other exemplary compounds of formula (II) are those wherein n = 4.

[091] An exemplary compound of formula (II):



(II)

wherein:

R_1 is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, $-OR_{11}$, $-C(O)R_{11}$, $-C(O)OR_{11}$, $-SO_2R_{11}$, and $-C(O)NR_{11}R_{13}$;

R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{9a}, R_{10}, R_{10a}, R_{12}, and R_{12a} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6-heteroalkyl, optionally substituted heteroaryl, optionally substituted aryl,

halogen, hydroxy, CN, -OR_{11}, -$OC(O)R_{11}$, -$OC(O)OR_{11}$, OSO_2R_{11}, -$OC(O)N\ R_{11}R_{13}$, -$OP(O)(OH)_2$, and -$OP(O)(OH)OP(O)(OH)_2$;

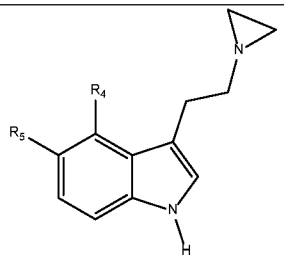
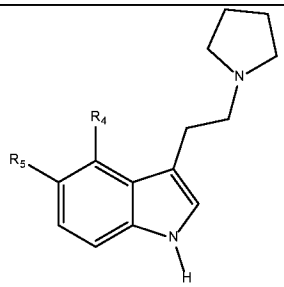
R_{3a} is selected from an electron pair, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl, wherein when R_{3a} is not an electron pair the compound of formula (II) is a quaternary amine cation with a pharmaceutically acceptable anion, X^-;

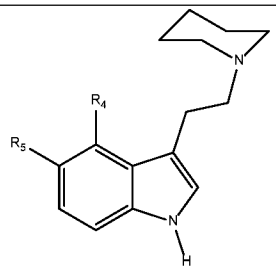
R_{11} and R_{13} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl; and

n is an integer defining the variable number of ring carbons carrying R_{12} and R_{12a} and is selected from 1 to 4, with the proviso that when n=2, R_{3a} is not an electron pair and/or at least one of R_8, R_{8a}, R_9, or R_{9a} is not hydrogen.

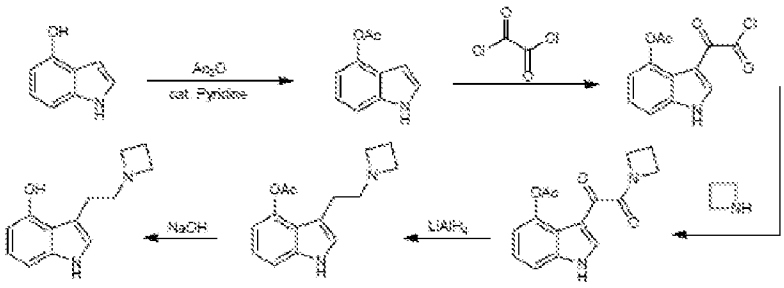
[092] Exemplary lead compounds of formula (II) can be found in Table 2.

Table 2

Compound	**Structural Formula**
Aziridinyltryptamine Series	 R_4 = OH; R_5 = H R_4 = H; R_5 = OH R_4 = OAc; R_5 = H R_4 = H; R_5 = OAc
Azacyclopentyltryptamine Series	 R_4 = OH; R_5 = H R_4 = H; R_5 = OH R_4 = OAc; R_5 = H R_4 = H; R_5 = OAc

Azacyclohexyltryptamine Series	 R_4 = OH; R_5 = H R_4 = H; R_5 = OH R_4 = OAc; R_5 = H R_4 = H; R_5 = OAc

[093] Tryptamine analogs with exocyclic amines, such as those represented in formula (II), are easily prepared by the venerable Speeter-Anthony synthesis of tryptamine analogs. (Speeter) The following reaction mechanism shows the synthesis of both 3-(2-(azetidin-1-yl)ethyl)-1H-indol-4-yl acetate as well as 3-(2-(azetidin-1-yl)ethyl)-1H-indol-4-ol. Widely available 4-hydroxyindole is acetylated to provide 4-acetoxyindole. Alternatively, 4-acetoxy-indole, since it is also widely available, may be purchased as the starting material. 4-Acetoxyindole is acylated at the 3-position with oxalyl chloride to provide the intermediate acyl chloride which is converted to the terminal amide by addition of the cyclic amine, in this case, azacyclobutane. The carbonyls are readily reduced by the action of lithium aluminum hydride to provide the acetoxy tryptamine derivative. This compound can be saponified to provide the 4-hydroxytryptamine derivative as shown in the following reaction mechanism.



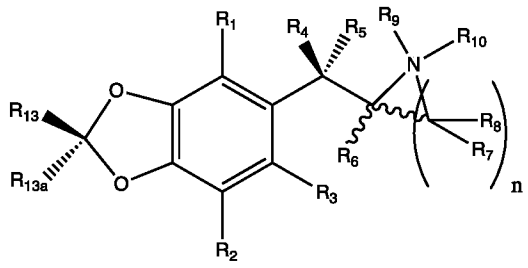
Other compounds of formula (II) can be formed in a similar manner.

[094] It is reasoned that for MDMA, the binding affinity to and fidelity for critical receptors may be modulated by conformational and/or rotational restriction about the moieties that bind the receptor sites. In addition, changes in C-N-C atomic bond lengths and nitrogen hybridization and barrier to pyramidal inversion can also be levers to adjust pharmacological properties. (Padwa; Katritzky) To that

end, derivatives of MDMA have been designed and the following Markush structure depicting the scope of such derivatives is shown in formula (III) below.

[095] A key feature of this molecular genus is the appearance of small ring heterocycles which change bond lengths and angles in the α-methyl-N-methylethylamine moiety of MDMA. Additional modulation of activity can be brought about through substitutions on the aryl ring and other portions of the molecule with different elements.

[096] The disclosure further relates to a compound of formula (III):



(III)

wherein:

R_1, R_2, and R_3 are independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, halogen, -OR_{11}, -$C(O)R_{11}$, -$C(O)OR_{11}$, -$OC(O)R_{11}$, $C(O)NR_{11}R_{12}$, CN, $C(NR_{12})R_{11}$, $C(NOR_{12})OR_{11}$, -SO_2R_{11}, and -C(O)N $R_{11}R_{12}$;

R_4, R_5, R_6, R_7, and R_8 are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted heteroaryl, optionally substituted aryl, halogen, hydroxy, -OR_{11}, -$OC(O)R_{11}$, -$OC(O)OR_{11}$, -OSO_2R_{11}, and -$OC(O)NR_{11}R_{12}$;

R_9 is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, and -SO_2R_{11};

R_{10} is selected from an electron pair, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl, wherein when R_{10} is not an electron pair the compound of formula (III) is a quaternary amine cation with a pharmaceutically acceptable anion, X^-;

R_{11} and R_{12} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl;

R_{13} and R_{13a} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl, or R_{13} and R_{13a} are taken together with the carbon to which they are bound to form a 3- to 6-membered cycloalkyl; and

n is an integer defining the variable number of ring carbons carrying R_7 and R_8 and is selected from 1 to 4.

[097] In formula (III), R_1, R_2, and R_3 are independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, halogen, -OR_{11}, -$C(O)R_{11}$, -$C(O)OR_{11}$, -$OC(O)R_{11}$, $C(O)NR_{11}R_{12}$, CN, $C(NR_{12})R_{11}$, $C(NOR_{12})OR_{11}$, -SO_2R_{11}, and -C(O)N $R_{11}R_{12}$. R_1, R_2, and R_3 may each independently be hydrogen. R_1, R_2, and R_3 may each independently be an optionally substituted straight chain or branched C_1-C_6 alkyl, for example a straight chain C_1-C_6 alkyl, or an optionally substituted straight chain or branched C_2-C_6 alkenyl, for example allyl, 2-butenyl, etc. In some embodiments R_1, R_2, and R_3 may each independently be a straight chain or branched C_1-C_4 alkyl, for example a straight chain C_1-C_4 alkyl, or a C_2-C_4 alkenyl. R_1, R_2, and R_3 may each independently be an optionally substituted aryl. An aryl is a 6- to 14-membered aromatic ring, preferably a 6- to 10-membered aromatic ring and includes polycyclic ring systems in which two or more carbon atoms are common to adjoining rings where at least one ring is aromatic. Examples of aryl groups include, but are not limited to phenyl, naphthyl, anthracenyl, and phenantherenyl. An aryl group may be substituted with one or more C_1-C_4 alkyl or perfluoralkyl groups, C_1-C_4 hydroxyalkyl groups, hydroxyl groups, nitro groups or halo groups (e.g., F, Cl, I, or Br). An aryl group may be ortho-, meta-, and/or para-substituted, preferably para-substituted. R_1, R_2, and R_3 may each independently be a halogen. Exemplary halogens include fluorine (F), chlorine (Cl), bromine (Br), and iodine (I). R_1, R_2, and R_3 may each independently be -OR_{11}, -$C(O)R_{11}$, -$C(O)OR_{11}$, -$OC(O)R_{11}$, $C(O)NR_{11}R_{12}$, CN, $C(NR_{12})R_{11}$, $C(NOR_{12})OR_{11}$, -SO_2R_{11}, and -C(O)N $R_{11}R_{12}$, wherein R_{11} and R_{12} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl.

[098] In formula (III), R_4, R_5, R_6, R_7, and R_8 are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted heteroaryl, optionally substituted aryl, halogen, hydroxy, -OR_{11}, -$OC(O)R_{11}$, -$OC(O)OR_{11}$, -OSO_2R_{11}, and -OC(O)N $R_{11}R_{12}$. R_4, R_5, R_6, R_7, and R_8 may each independently be hydrogen. R_4, R_5, R_6, R_7, and R_8 may each independently be an optionally substituted straight chain or branched C_1-C_6 alkyl, for example a straight chain C_1-C_6 alkyl, or an optionally substituted straight chain or branched C_2-C_6 alkenyl, for example allyl, 2-butenyl, etc. In some embodiments R_4, R_5, R_6, R_7, and R_8 may each independently be a straight chain or branched C_1-C_4 alkyl, for example a straight chain C_1-C_4 alkyl, or a C_2-C_4 alkenyl. R_4, R_5, R_6, R_7, and R_8 may each independently be an optionally substituted C_1-C_6-heteroalkyl, including but not limited to alkoxy, alkylthio, and alkylamino. R_4, R_5, R_6, R_7, and R_8 may each independently be an optionally substituted heteroaryl, including, but not limited to, furano, pyridinyl,

pyrimidinyl, etc. R_4, R_5, R_6, R_7, and R_8 may each independently be an optionally substituted aryl. An aryl is a 6- to 14-membered aromatic ring, preferably a 6- to 10-membered aromatic ring and includes polycyclic ring systems in which two or more carbon atoms are common to adjoining rings where at least one ring is aromatic. Examples of aryl groups include, but are not limited to phenyl, naphthyl, anthracenyl, and phenantherenyl. An aryl group may be substituted with one or more C_1-C_4 alkyl or perfluoralkyl groups, C_1-C_4 hydroxyalkyl groups, hydroxyl groups, nitro groups or halo groups (e.g., F, Cl, I, or Br). An aryl group may be ortho-, meta-, and/or para-substituted, preferably para-substituted. R_4, R_5, R_6, R_7, and R_8 may each independently be a halogen. Exemplary halogens include fluorine (F), chlorine (Cl), bromine (Br), and iodine (I). R_4, R_5, R_6, R_7, and R_8 may each independently be hydroxy. R_4, R_5, R_6, R_7, and R_8 may each independently be $-OR_{11}$, $-OC(O)R_{11}$, $-OC(O)OR_{11}$, $-OSO_2R_{11}$, or $-OC(O)N\ R_{11}R_{12}$, wherein R_{11} and R_{12} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl.

[099] In formula (III), R_9 is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, and $-SO_2R_{11}$. R_9 may be hydrogen. R_9 may be an optionally substituted straight chain or branched C_1-C_6 alkyl, for example a straight chain C_1-C_6 alkyl, or an optionally substituted straight chain or branched C_2-C_6 alkenyl, for example allyl, 2-butenyl, etc. In some embodiments R_9 may be a straight chain or branched C_1-C_4 alkyl, for example a straight chain C_1-C_4 alkyl, or a C_2-C_4 alkenyl. R_9 may be an optionally substituted aryl. An aryl is a 6- to 14-membered aromatic ring, preferably a 6- to 10-membered aromatic ring and includes polycyclic ring systems in which two or more carbon atoms are common to adjoining rings where at least one ring is aromatic. Examples of aryl groups include, but are not limited to phenyl, naphthyl, anthracenyl, and phenantherenyl. An aryl group may be substituted with one or more C_1-C_4 alkyl or perfluoralkyl groups, C_1-C_4 hydroxyalkyl groups, hydroxyl groups, nitro groups or halo groups (e.g., F, Cl, I, or Br). An aryl group may be ortho-, meta-, and/or para-substituted, preferably para-substituted. R_9 may be $-SO_2R_{11}$, wherein R_{11} may be selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl.

[100] In formula (III), R_{10} is selected from an electron pair, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl, wherein when R_{10} is not an electron pair the compound of formula (III) is a quaternary amine cation with a pharmaceutically acceptable anion, X^-. R_{10} may be an electron pair. R_{10} may be hydrogen. R_{10} may be an optionally substituted straight chain or branched C_1-C_6 alkyl, for example a straight chain C_1-C_6 alkyl, or an optionally substituted straight chain or branched C_2-C_6 alkenyl, for example allyl, 2-butenyl, etc. In some embodiments R_{10} may

be a straight chain or branched C_1-C_4 alkyl, for example a straight chain C_1-C_4 alkyl, or a C_2-C_4 alkenyl. R_{10} may be an optionally substituted aryl. An aryl is a 6- to 14-membered aromatic ring, preferably a 6- to 10-membered aromatic ring and includes polycyclic ring systems in which two or more carbon atoms are common to adjoining rings where at least one ring is aromatic. Examples of aryl groups include, but are not limited to phenyl, naphthyl, anthracenyl, and phenantherenyl. An aryl group may be substituted with one or more C_1-C_4 alkyl or perfluoralkyl groups, C_1-C_4 hydroxyalkyl groups, hydroxyl groups, nitro groups or halo groups (e.g., F, Cl, I, or Br). An aryl group may be ortho-, meta-, and/or para-substituted, preferably para-substituted.

[101] The anion of formula (III), X^-, may be any pharmaceutically acceptable anion, for example, Cl^-, I^-, Br^-, ascorbate, hydrofumarate, fumarate, maleate, and the like.

[102] In formula (III), R_{11} and R_{12} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl. R_{11} and R_{12} may each independently be hydrogen. R_{11} and R_{12} may each independently be an optionally substituted straight chain or branched C_1-C_6 alkyl, for example a straight chain C_1-C_6 alkyl, or an optionally substituted straight chain or branched C_2-C_6 alkenyl, for example allyl, 2-butenyl, etc. In some embodiments R_{11} and R_{12} may each independently be a straight chain or branched C_1-C_4 alkyl, for example a straight chain C_1-C_4 alkyl, or a C_2-C_4 alkenyl. R_{11} and R_{12} may each independently be an optionally substituted aryl. An aryl is a 6- to 14-membered aromatic ring, preferably a 6- to 10-membered aromatic ring and includes polycyclic ring systems in which two or more carbon atoms are common to adjoining rings where at least one ring is aromatic. Examples of aryl groups include, but are not limited to phenyl, naphthyl, anthracenyl, and phenantherenyl. An aryl group may be substituted with one or more C_1-C_4 alkyl or perfluoralkyl groups, C_1-C_4 hydroxyalkyl groups, hydroxyl groups, nitro groups or halo groups (e.g., F, Cl, I, or Br). An aryl group may be ortho-, meta-, and/or para-substituted, preferably para-substituted.

[103] In formula (III), R_{13} and R_{13a} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl, or R_{13} and R_{13a} are taken together with the carbon to which they are bound to form a 3- to 6-membered cycloalkyl. R_{13} and R_{13a} may each independently be hydrogen. R_{13} and R_{13a} may each independently be an optionally substituted straight chain or branched C_1-C_6 alkyl, for example a straight chain C_1-C_6 alkyl, or an optionally substituted straight chain or branched C_2-C_6 alkenyl, for example allyl, 2-butenyl, etc. In some embodiments R_{13} and R_{13a} may each independently be a straight chain or branched C_1-C_4 alkyl, for example a straight chain C_1-C_4 alkyl, or a C_2-C_4 alkenyl. R_{13} and R_{13a} may each independently be an

optionally substituted aryl. An aryl is a 6- to 14-membered aromatic ring, preferably a 6- to 10-membered aromatic ring and includes polycyclic ring systems in which two or more carbon atoms are common to adjoining rings where at least one ring is aromatic. Examples of aryl groups include, but are not limited to phenyl, naphthyl, anthracenyl, and phenantherenyl. An aryl group may be substituted with one or more C_1-C_4 alkyl or perfluoralkyl groups, C_1-C_4 hydroxyalkyl groups, hydroxyl groups, nitro groups or halo groups (e.g., F, Cl, I, or Br). An aryl group may be ortho-, meta-, and/or para-substituted, preferably para-substituted. R_{13} and R_{13a} may be taken together with the carbon to which they are bound to form a 3- to 6-membered cycloalkyl. In some embodiments, R_{13} and R_{13a} may be taken together with the carbon to which they are bound to form cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[104] In formula (III), n is an integer defining the variable number of ring carbons carrying R_7 and R_8 and is selected from 1 to 4. In one embodiment, n is 1. In one embodiment, n is 2. In one embodiment, n is 3. In one embodiment, n is 4.

[105] Exemplary compounds of formula (III) are those wherein R_1 is hydrogen.

[106] Other exemplary compounds of formula (III) are those wherein R_2 is hydrogen.

[107] Other exemplary compounds of formula (III) are those wherein R_3 is hydrogen.

[108] Other exemplary compounds of formula (III) are those wherein R_4 is hydrogen.

[109] Other exemplary compounds of formula (III) are those wherein R_5 is hydrogen.

[110] Other exemplary compounds of formula (III) are those wherein R_6 is hydrogen.

[111] Other exemplary compounds of formula (III) are those wherein R_9 is an optionally substituted C_1-C_6 alkyl.

[112] Other exemplary compounds of formula (III) are those wherein R_9 is an unsubstituted C_1-C_6 alkyl.

[113] Other exemplary compounds of formula (III) are those wherein R_9 is methyl.

[114] Other exemplary compounds of formula (III) are those wherein R_{10} is an electron pair.

[115] Other exemplary compounds of formula (III) are those wherein R_7 is hydrogen.

[116] Other exemplary compounds of formula (III) are those wherein R_8 is hydrogen.

[117] Other exemplary compounds of formula (III) are those wherein R_{13} is hydrogen.

[118] Other exemplary compounds of formula (III) are those wherein R_{13a} is hydrogen.

[119] Other exemplary compounds of formula (III) are those wherein R_{13} and R_{13a} are taken together with the carbon to which they are bound to form a cyclopropyl group.

[120] Other exemplary compounds of formula (III) are those wherein R_{13} and R_{13a} are taken together with the carbon to which they are bound to form a cyclobutyl group.

[121] Other exemplary compounds of formula (III) are those wherein R_{13} and R_{13a} are taken together with the carbon to which they are bound to form a cyclopentyl group.

[122] Other exemplary compounds of formula (III) are those wherein R_{13} and R_{13a} are taken together with the carbon to which they are bound to form a cyclohexyl group.

[123] Other exemplary compounds of formula (III) are those wherein n = 1.

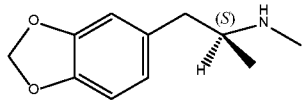
[124] Other exemplary compounds of formula (III) are those wherein n = 2.

[125] Other exemplary compounds of formula (III) are those wherein n = 3.

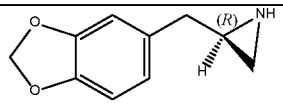
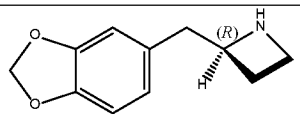
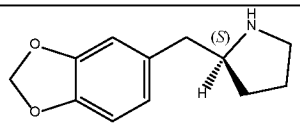
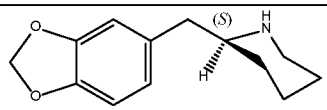
[126] Other exemplary compounds of formula (III) are those wherein n = 4.

[127] Exemplary lead compounds of formula (III) can be found in Table 3.

Table 3

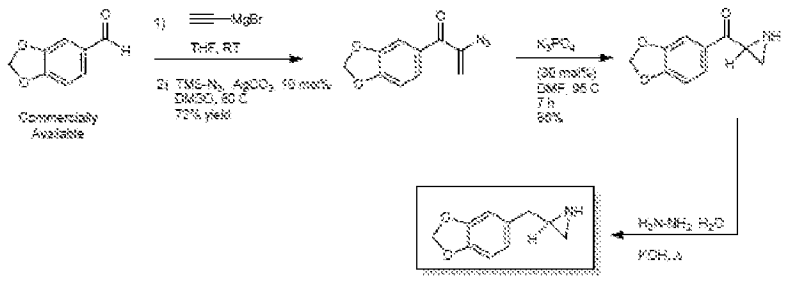
(*S*)-MDMA 

(*S*)-MDMA Derivatives
+
(*R*)-Enantiomer

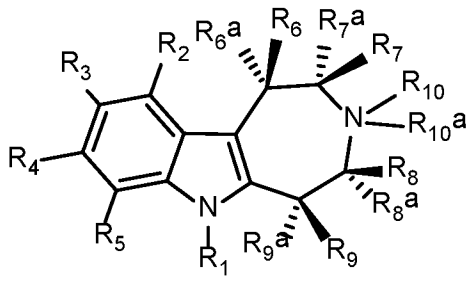
Compound	**Structural Formula**
Azacyclopropane Series	
Azcyclobutane Series	
Azacyclopentane Series	
Azacyclohexane Series	

[128] Commercially available piperonal (shown in the following reaction mechanism) can be converted to the vinyl azide in 72 % yield in a single pot with first, reaction with ethynyl magnesium bromide to produce the in situ carbinol. A silver-(I) catalyzed hydroazidation yields the α,β-unsaturated-α-vinyl azide. The a-keto-aziridine is formed by treatment with potassium phosphate (K_3PO_4) in DMF at 95°C in 86% yield. (Liu). Reduction of the aryl ketone to produce the target compound can be

accomplished through a Wolff-Kishner reduction shown below or by any number of transformations known to those skilled in the art.



[129] The disclosure further relates to a compound of formula (IV):



(IV)

wherein:

R_1 is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, -OR_{11}, -$C(O)R_{11}$, -$C(O)OR_{11}$, -SO_2R_{11}, and -$C(O)NR_{11}R_{12}$;

R_2, R_3, R_4, R_5, R_6, R_{6a}, R_7, R_{7a}, R_8, R_{8a}, R_9, and R_{9a} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6-heteroalkyl, optionally substituted heteroaryl, optionally substituted aryl, halogen, hydroxy, -OR_{11}, -$OC(O)R_{11}$, -$OC(O)OR_{11}$, -OSO_2R_{11}, and -$OC(O)N$ $R_{11}R_{12}$;

R_{10} is selected from an electron pair, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl, wherein when R_{10} is not an electron pair the compound of formula (IV) is a quaternary amine cation with a pharmaceutically acceptable anion, X^-;

R_{10a} is taken together with one of R_8, R_{8a}, R_9, or R_{9a} to form optionally substituted 3- to 6-membered heterocyclic ring; and

R_{11} and R_{12} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl.

[130] In formula (IV), R_1 is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, -OR_{11}, -$C(O)R_{11}$, -$C(O)OR_{11}$, -SO_2R_{11}, and -$C(O)N$

$R_{11}R_{12}$. R_1 may be hydrogen. R_1 may be an optionally substituted straight chain or branched C_1-C_6 alkyl, for example a straight chain C_1-C_6 alkyl, or an optionally substituted straight chain or branched C_2-C_6 alkenyl, for example allyl, 2-butenyl, etc. In some embodiments R_1 may be a straight chain or branched C_1-C_4 alkyl, for example a straight chain C_1-C_4 alkyl, or a C_2-C_4 alkenyl. R_1 may be an optionally substituted aryl. An aryl is a 6- to 14-membered aromatic ring, preferably a 6- to 10-membered aromatic ring and includes polycyclic ring systems in which two or more carbon atoms are common to adjoining rings where at least one ring is aromatic. Examples of aryl groups include, but are not limited to phenyl, naphthyl, anthracenyl, and phenantherenyl. An aryl group may be substituted with one or more C_1-C_4 alkyl or perfluoralkyl groups, C_1-C_4 hydroxyalkyl groups, hydroxyl groups, nitro groups or halo groups (e.g., F, Cl, I, or Br). An aryl group may be ortho-, meta-, and/or para-substituted, preferably para-substituted. R_1 may be -OR_{11}, -$C(O)R_{11}$, -$C(O)OR_{11}$, -SO_2R_{11}, or -$C(O)N\ R_{11}R_{12}$, wherein R_{11} and R_{12} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl.

[131] In formula (IV), R_2, R_3, R_4, R_5, R_6, R_{6a}, R_7, R_{7a}, R_8, R_{8a}, R_9, and R_{9a} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6-heteroalkyl, optionally substituted heteroaryl, optionally substituted aryl, halogen, hydroxy, -OR_{11}, -$OC(O)R_{11}$, -$OC(O)OR_{11}$, -OSO_2R_{11}, and -$OC(O)N\ R_{11}R_{12}$. R_2, R_3, R_4, R_5, R_6, R_{6a}, R_7, R_{7a}, R_8, R_{8a}, R_9, and R_{9a} may each independently be hydrogen. R_2, R_3, R_4, R_5, R_6, R_{6a}, R_7, R_{7a}, R_8, R_{8a}, R_9, and R_{9a} may each independently be an optionally substituted straight chain or branched C_1-C_6 alkyl, for example a straight chain C_1-C_6 alkyl, or an optionally substituted straight chain or branched C_2-C_6 alkenyl, for example allyl, 2-butenyl, etc. In some embodiments R_2, R_3, R_4, R_5, R_6, R_{6a}, R_7, R_{7a}, R_8, R_{8a}, R_9, and R_{9a} may each independently be a straight chain or branched C_1-C_4 alkyl, for example a straight chain C_1-C_4 alkyl, or a C_2-C_4 alkenyl. R_2, R_3, R_4, R_5, R_6, R_{6a}, R_7, R_{7a}, R_8, R_{8a}, R_9, and R_{9a} may each independently be an optionally substituted C_1-C_6-heteroalkyl, including but not limited to alkoxy, alkylthio, and alkylamino. R_2, R_3, R_4, R_5, R_6, R_{6a}, R_7, R_{7a}, R_8, R_{8a}, R_9, and R_{9a} may each independently be an optionally substituted heteroaryl, including, but not limited to, furano, pyridinyl, pyrimidinyl, etc. R_2, R_3, R_4, R_5, R_6, R_{6a}, R_7, R_{7a}, R_8, R_{8a}, R_9, and R_{9a} may each independently be an optionally substituted aryl. An aryl is a 6- to 14-membered aromatic ring, preferably a 6- to 10-membered aromatic ring and includes polycyclic ring systems in which two or more carbon atoms are common to adjoining rings where at least one ring is aromatic. Examples of aryl groups include, but are not limited to phenyl, naphthyl, anthracenyl, and phenantherenyl. An aryl group may be substituted with one or more C_1-C_4 alkyl or perfluoralkyl groups, C_1-C_4 hydroxyalkyl groups, hydroxyl groups, nitro groups or halo groups (e.g., F, Cl,

I, or Br). An aryl group may be ortho-, meta-, and/or para-substituted, preferably para-substituted. R_2, R_3, R_4, R_5, R_6, R_{6a}, R_7, R_{7a}, R_8, R_{8a}, R_9, and R_{9a} may each independently be a halogen. Exemplary halogens include fluorine (F), chlorine (Cl), bromine (Br), and iodine (I). R_2, R_3, R_4, R_5, R_6, R_{6a}, R_7, R_{7a}, R_8, R_{8a}, R_9, and R_{9a} may each independently be hydroxy. R_2, R_3, R_4, R_5, R_6, R_{6a}, R_7, R_{7a}, R_8, R_{8a}, R_9, and R_{9a} may each independently be $-OR_{11}$, $-OC(O)R_{11}$, $-OC(O)OR_{11}$, $-OSO_2R_{11}$, or $-OC(O)N\ R_{11}R_{12}$, wherein R_{11} and R_{12} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl.

[132] In formula (IV), R_{10} is selected from an electron pair, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl, wherein when R_{10} is not an electron pair the compound of formula (IV) is a quaternary amine cation with a pharmaceutically acceptable anion, X^-. R_{10} may be an electron pair. R_{10} may be hydrogen. R_{10} may be an optionally substituted straight chain or branched C_1-C_6 alkyl, for example a straight chain C_1-C_6 alkyl, or an optionally substituted straight chain or branched C_2-C_6 alkenyl, for example allyl, 2-butenyl, etc. In some embodiments R_{10} may be a straight chain or branched C_1-C_4 alkyl, for example a straight chain C_1-C_4 alkyl, or a C_2-C_4 alkenyl. R_{10} may be an optionally substituted aryl. An aryl is a 6- to 14-membered aromatic ring, preferably a 6- to 10-membered aromatic ring and includes polycyclic ring systems in which two or more carbon atoms are common to adjoining rings where at least one ring is aromatic. Examples of aryl groups include, but are not limited to phenyl, naphthyl, anthracenyl, and phenantherenyl. An aryl group may be substituted with one or more C_1-C_4 alkyl or perfluoralkyl groups, C_1-C_4 hydroxyalkyl groups, hydroxyl groups, nitro groups or halo groups (e.g., F, Cl, I, or Br). An aryl group may be ortho-, meta-, and/or para-substituted, preferably para-substituted.

[133] The anion of formula (IV), X^-, may be any pharmaceutically acceptable anion, for example, Cl^-, I^-, Br^-, ascorbate, hydrofumarate, fumarate, maleate, and the like.

[134] In formula (IV), R_{10a} is taken together with one of R_8, R_{8a}, R_9, or R_{9a} to form optionally substituted 3- to 6-membered heterocyclic ring. In some embodiments, R_{10a} may be taken together with one of R_8, R_{8a}, R_9, or R_{9a} to form cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[135] In formula (IV), R_{11} and R_{12} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl. R_{11} and R_{12} may each independently be hydrogen. R_{11} and R_{12} may each independently be an optionally substituted straight chain or branched C_1-C_6 alkyl, for example a straight chain C_1-C_6 alkyl, or an optionally substituted straight chain or branched C_2-C_6 alkenyl, for example allyl, 2-butenyl, etc. In some embodiments R_{11} and R_{12} may each independently be a straight chain or branched C_1-C_4 alkyl, for

example a straight chain C_1-C_4 alkyl, or a C_2-C_4 alkenyl. R_{11} and R_{12} may each independently be an optionally substituted aryl. An aryl is a 6- to 14-membered aromatic ring, preferably a 6- to 10-membered aromatic ring and includes polycyclic ring systems in which two or more carbon atoms are common to adjoining rings where at least one ring is aromatic. Examples of aryl groups include, but are not limited to phenyl, naphthyl, anthracenyl, and phenantherenyl. An aryl group may be substituted with one or more C_1-C_4 alkyl or perfluoralkyl groups, C_1-C_4 hydroxyalkyl groups, hydroxyl groups, nitro groups or halo groups (e.g., F, Cl, I, or Br). An aryl group may be ortho-, meta-, and/or para-substituted, preferably para-substituted.

[136] Exemplary compounds of formula (IV) are those wherein at least one of R_2, R_3, R_4, or R_5 is selected from hydroxy, $-OR_{11}$, $-OC(O)R_{11}$, $-OC(O)OR_{11}$, $-OSO_2R_{11}$, and $-OC(O)NR_{11}R_{12}$.

[137] Other exemplary compounds of formula (IV) are those wherein at least one of R_2, R_3, R_4, or R_5 is selected from hydroxy and $-OR_{11}$.

[138] Other exemplary compounds of formula (IV) are those wherein at least one of R_2, R_3, R_4, or R_5 is $-OR_{11}$.

[139] Other exemplary compounds of formula (IV) are those wherein R_{11} is unsubstituted C_1-C_6 alkyl.

[140] Other exemplary compounds of formula (IV) are those wherein R_{11} is methyl.

[141] Other exemplary compounds of formula (IV) are those wherein R_3 is methoxy.

[142] Other exemplary compounds of formula (IV) are those wherein R_{10a} is taken together with R_8 to form an optionally substituted 3-membered heterocyclic ring.

[143] Other exemplary compounds of formula (IV) are those wherein R_{10a} is taken together with R_8 to form an optionally substituted 4-membered heterocyclic ring.

[144] Other exemplary compounds of formula (IV) are those wherein R_{10a} is taken together with R_8 to form an optionally substituted 5-membered heterocyclic ring.

[145] Other exemplary compounds of formula (IV) are those wherein R_{10a} is taken together with R_8 to form an optionally substituted 6-membered heterocyclic ring.

[146] Other exemplary compounds of formula (IV) are those wherein R_{10a} is taken together with R_9 to form an optionally substituted 4-membered heterocyclic ring.

[147] Other exemplary compounds of formula (IV) are those wherein R_{10a} is taken together with R_9 to form an optionally substituted 5-membered heterocyclic ring.

[148] Other exemplary compounds of formula (IV) are those wherein R_{10a} is taken together with R_9 to form an optionally substituted 6-membered heterocyclic ring.

[149] Other exemplary compounds of formula (IV) are those wherein the heterocyclic ring is unsubstituted.

[150] Other exemplary compounds of formula (IV) are those wherein R_{10} is a lone pair.

[151] Other exemplary compounds of formula (IV) are those wherein R_6 is hydrogen.

[152] Other exemplary compounds of formula (IV) are those wherein R_{6a} is hydrogen.

[153] Other exemplary compounds of formula (IV) are those wherein R_7 is hydrogen.

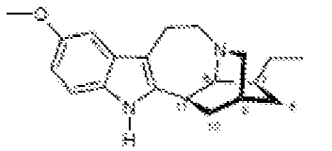
[154] Other exemplary compounds of formula (IV) are those wherein R_{7a} is hydrogen.

[155] Other exemplary compounds of formula (IV) are those wherein R_1 is hydrogen.

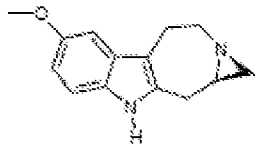
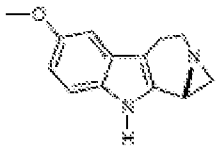
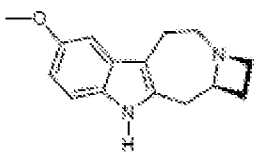
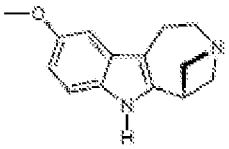
[156] Exemplary Ibogaine analogs of formula (IV) are shown in Table 4.

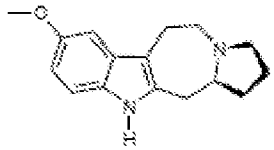
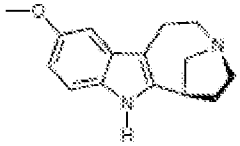
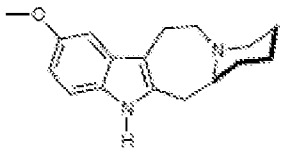
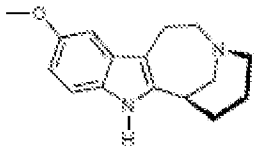
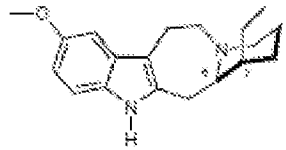
Table 4

Ibogaine



(6*R*,7*S*,9*S*,11*S*)-7-ethyl-2-methoxy-6,8a,7,8,9,10,12,13-octahydro-5*H*-6,9-methanopyrido[1',2':1,2]azepino[4,5-*b*]indole

Exocyclic Series	Endocyclic Series
 (*R*)-6-methoxy-1,3,4,9,10,10a-hexahydroazirino[1',2':1,2]azepino[4,5-*b*]indole	 (*R*)-6-methoxy-3,4,9,9b-tetrahydro-1*H*-azirino[1',2':1,2]pyrido[3,4-*b*]indole
 (*S*)-7-methoxy-1,4,5,10,11,11a-hexahydro-3*H*-azeto[1',2':1,2]azepino[4,5-*b*]indole	 (2*a*,5*r*)-9-methoxy-1,4,5,6-tetrahydro-2*H*-3,5-methanoazepino[4,5-*b*]indole

 (S)-8-methoxy-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole	 (3R,6R)-10-methoxy-1,2,4,5,6,7-hexahydro-3,6-methanoazocino[5,4-b]indole
 (S)-2-methoxy-6,6a,7,8,9,10,12,13-octahydro-5H-pyrido[1',2':1,2]azepino[4,5-b]indole	 (3R,7R)-11-methoxy-1,4,5,6,7,8-hexahydro-2H-3,7-methanoazonino[5,4-b]indole
 (6aR,7R)-7-ethyl-2-methoxy-6,6a,7,8,9,10,12,13-octahydro-5H-pyrido[1',2':1,2]azepino[4,5-b]indole	

[157] Methods of Treatment and Therapeutic Uses

[158] Compounds of formulae (I), (II), (III), or (IV) according to the disclosure, crystalline forms thereof, and the methods and the compositions (e.g., pharmaceutical compositions) are used to regulate the activity of a neurotransmitter receptor by administering a therapeutically effective dose of a compound of formulae (I), (II), (III), or (IV) according to the disclosure, and the methods and the compositions (e.g., pharmaceutical compositions) are used to treat inflammation and/or pain by administering a therapeutically effective dose of a compound of formulae (I), (II), (III), or (IV) according to the disclosure.

[159] Methods of the disclosure also related to the administration of a therapeutically effective amount of a compound of formulae (I), (II), (III), or (IV) according to the disclosure to prevent or treat a disease or condition, such as those discussed below for a subject in need of treatment. Compounds of formulae (I), (II), (III), or (IV) according to the disclosure may be administered neat or as a composition comprising a compound of formulae (I), (II), (III), or (IV) according to the disclosure as discussed below.

[160] Compounds of formulae (I), (II), (III), or (IV) according to the disclosure may be used to prevent and/or treat a psychological disorder. The disclosure provides a method for preventing and/or treating a psychological disorder by administering to a subject in need thereof a therapeutically effective amount of a compound of formulae (I), (II), (III), or (IV) according to the disclosure, including the exemplary embodiments discussed herein. The psychological disorder may be chosen from depression; psychotic disorder; schizophrenia; schizophreniform disorder (acute schizophrenic episode); schizoaffective disorder; bipolar I disorder (mania, manic disorder, manic-depressive psychosis); bipolar II disorder; major depressive disorder; major depressive disorder with psychotic feature (psychotic depression); delusional disorders (paranoia); Shared Psychotic Disorder (Shared paranoia disorder); Brief Psychotic disorder (Other and Unspecified Reactive Psychosis); Psychotic disorder not otherwise specified (Unspecified Psychosis); paranoid personality disorder; schizoid personality disorder; schizotypal personality disorder; anxiety disorder; social anxiety disorder; substance-induced anxiety disorder; selective mutism; panic disorder; panic attacks; agoraphobia; attention deficit syndrome; post-traumatic stress disorder (PTSD); premenstrual dysphoric disorder (PMDD); and premenstrual syndrome (PMS).

[161] Compounds of formulae (I), (II), (III), or (IV) according to the disclosure may be used to treat and/or prevent a substance use disorder. The disclosure provides a method for treating and/or preventing a substance use disorder by administering to a subject in need thereof a therapeutically effective amount of a compound of formulae (I), (II), (III), or (IV) according to the disclosure, including the exemplary embodiments discussed herein. The substance use disorder may be chosen from opioid use disorder; cannabis or marijuana use disorder; nicotine use disorder; stimulant use disorder; sedative use disorder; hypnotic use disorder; anxiolytic use disorder; hallucinogen use disorder; phencyclidine use disorder; inhalant use disorder; caffeine use disorder; and alcohol use disorder.

[162] Compounds of formulae (I), (II), (III), or (IV) according to the disclosure may be used to prevent and/or treat a brain disorder. The disclosure provides a method for preventing and/or treating a brain disorder (e.g., Huntington's disease, Alzheimer's disease, dementia, and Parkinson's disease) by administering to a subject in need thereof a therapeutically effective amount of a compound of formulae (I), (II), (III), or (IV) according to the disclosure, including the exemplary embodiments discussed above.

[163] Compounds of formulae (I), (II), (III), or (IV) according to the disclosure may be used to prevent and/or treat developmental disorders, delirium, dementia, amnestic disorders and other cognitive disorders, psychiatric disorders due to a somatic condition, drug-related disorders, schizophrenia and other psychotic disorders, mood disorders, anxiety disorders, somatoform disorders, factitious

disorders, dissociative disorders, eating disorders, sleep disorders, impulse control disorders, adjustment disorders, or personality disorders. The disclosure provides a method for preventing and/or treating these disorders by administering to a subject in need thereof a therapeutically effective amount of a compound of formulae (I), (II), (III), or (IV) according to the disclosure, including the exemplary embodiments discussed above.

[164] Compounds of formulae (I), (II), (III), or (IV) according to the disclosure may be used to prevent and/or treat inflammation and/or pain, such as for example inflammation and/or pain associated with inflammatory skeletal or muscular diseases or conditions. The disclosure provides a method for preventing and/or treating an inflammation and/or pain by administering to a subject in need thereof a therapeutically effective amount of a compound of formulae (I), (II), (III), or (IV) according to the disclosure, including the exemplary embodiments discussed herein. Generally speaking, treatable "pain" includes nociceptive, neuropathic, and mix-type. A method of the disclosure may reduce or alleviate the symptoms associated with inflammation, including but not limited to treating localized manifestation of inflammation characterized by acute or chronic swelling, pain, redness, increased temperature, or loss of function in some cases. A method of the disclosure may reduce or alleviate the symptoms of pain regardless of the cause of the pain, including but not limited to reducing pain of varying severity, i.e., mild, moderate and severe pain, acute pain and chronic pain. A method of the disclosure is effective in treating joint pain, muscle pain, tendon pain, burn pain, and pain caused by inflammation such as rheumatoid arthritis. Skeletal or muscular diseases or conditions which may be treated include but are not limited to musculoskeletal sprains, musculoskeletal strains, tendinopathy, peripheral radiculopathy, osteoarthritis, joint degenerative disease, polymyalgia rheumatica, juvenile arthritis, gout, ankylosing spondylitis, psoriatic arthritis, systemic lupus erythematosus, costochondritis, tendonitis, bursitis, such as the common lateral epicondylitis (tennis elbow), medial epicondylitis (pitchers elbow) and trochanteric bursitis, temporomandibular joint syndrome, and fibromyalgia.

[165] Compounds of formulae (I), (II), (III), or (IV) according to the disclosure may be used to modulate activity of a mitogen-activated protein kinase (MAPK), comprising administering a composition of the disclosure. MAPKs provide a wide-ranging signaling cascade that allow cells to quickly respond to biotic and abiotic stimuli. Exemplary MAPKs include, but are not limited to, Tropomyosin Receptor Kinase A (TrkA), P38-alpha, and c-Jun N-Terminal Kinase 3 (JNK3). TrkA is a high affinity catalytic receptor of nerve growth factor (NGF) protein. TrkA regulates NGF response, influencing neuronal differentiation and outgrowth as well as programmed cell death. p38-alpha is involved with the regulation of pro-inflammatory cytokines, including TNF-a. In the central nervous system, p38-alpha regulates neuronal

death and neurite degeneration, and it is a common target of Alzheimer's disease therapies. JNK3 is neuronal specific protein isoform of the JNKs. It is involved with the regulation of apoptosis. JNK3 also plays a role in modulating the response of cytokines, growth factors, and oxidative stress.

[166] As used herein, the term "modulating activity of a mitogen-activated protein kinase" refers to changing, manipulating, and/or adjusting the activity of a mitogen-activated protein kinase. In one embodiment, modulating the activity of a MAPK can influence neural health, neurogenesis, neural growth and differentiation, and neurodegenerative diseases.

[167] Compounds of formulae (I), (II), (III), or (IV) according to the disclosure may be used to modulate neurogenesis, comprising administering a composition of the disclosure. As used herein, the term "modulating neurogenesis" refers to changing, manipulating, and/or adjusting the growth and development of neural tissue. In one embodiment, neurogenesis comprises adult neurogenesis, in which new neural stem cells are generated from neural stem cells in an adult animal. In one embodiment, modulating neurogenesis comprises increasing and/or enhancing the rate at which new neural tissue is developed.

[168] Compounds of formulae (I), (II), (III), or (IV) according to the disclosure may be used to modulate neurite outgrowth, comprising administering a composition of the disclosure. As used herein, the term "modulating neurite outgrowth" refers to changing, manipulating, and/or adjusting the growth and development of neural projections, or "neurites." In one embodiment, neurogenesis comprises modulating the growth of new neurites, the number of neurites per neuron, and/or neurite length. In one embodiment, modulating neurite outgrowth comprises increasing and/or enhancing the rate and/or length at which neurites develop.

[169] Compounds of formulae (I), (II), (III), or (IV) according to the disclosure may be used to prevent and/or treat sexual health disorders including, but not limited to, hypoactive sexual desire disorder, hyperactive sexual desire disorder, orgasmic disorder, arousal disorder, vaginismus, and dyspareunia. In some embodiments, the disorder is a male sexual dysfunction disorder. In some embodiments, the disorder is a female sexual dysfunction disorder.

[170] Compounds of formulae (I), (II), (III), or (IV) according to the disclosure may be used to prevent and/or treat women's health disorders including, but not limited to, menstrual cramping, dysmenorrhea, post-hysterectomy pain, vaginal or vulvar vestibule mucosa disorder, menopausal-related disorders, vaginal atrophy, or vulvar vestibulitis.

[171] Compositions

[172] The disclosure also relates to compositions comprising an effective amount of compounds of formulae (I), (II), (III), or (IV) according to the disclosure, including its exemplary embodiments discussed above, and an excipient (e.g., a pharmaceutically-acceptable excipient). In another embodiment, the disclosure also relates to pharmaceutical compositions comprising a therapeutically effective amount of a compound of formulae (I), (II), (III), or (IV) according to the disclosure, including their exemplary embodiments discussed above, and a pharmaceutically acceptable excipient (also known as a pharmaceutically acceptable carrier). As discussed above, a compound of formulae (I), (II), (III), or (IV) according to the disclosure may be, for example, therapeutically useful to prevent and/or treat the psychological disorders, brain disorders, pain, and inflammation as well as the other disorders described herein.

[173] A composition or a pharmaceutical composition of the disclosure may be in any form which contains a compound of formulae (I), (II), (III), or (IV) according to the disclosure. The composition may be, for example, a tablet, capsule, liquid suspension, injectable, topical, or transdermal. The compositions generally contain, for example, about 1% to about 99% by weight of a compound of formulae (I), (II), (III), or (IV) according to the disclosure and, for example, 99% to 1% by weight of at least one suitable pharmaceutically acceptable excipient. In one embodiment, the composition may be between about 5% and about 75% by weight of a compound of formulae (I), (II), (III), or (IV) according to the disclosure, with the rest being at least one suitable pharmaceutically acceptable excipient or at least one other adjuvant, as discussed below.

[174] Published US applications US 2018/0221396 A1 and US 2019/0142851 A1 disclose compositions comprising a combination of a first purified psilocybin derivative with a second purified psilocybin derivative, with one or two purified cannabinoids or with a purified terpene. Various ratios of these components in the composition are also disclosed. The disclosures of US 2018/0221396 A1 and US 2019/0142851 A1 are incorporated herein by reference. According to this disclosure, a compound of formulae (I), (II), (III), or (IV) according to the disclosure may be used as the “first purified psilocybin derivative” in the compositions described in US 2018/0221396 A1 and US 2019/0142851 A1. Accordingly, this disclosure provides a composition comprising: a first component comprising at least one compound of formulae (I), (II), (III), or (IV) according to the disclosure; at least one second component selected from at least one of (a) a serotonergic drug, (b) a purified psilocybin derivative, (c) a purified cannabinoid or (d) a purified terpene; and at least one pharmaceutically-acceptable excipient or at least one other adjuvant. Such a composition may be a pharmaceutical composition wherein the

components are present individually in therapeutically effective amounts or by combination in a therapeutically effective amount to treat a disease, disorder, or condition as described herein.

[175] When used in such compositions as a first component comprising at least one compound of formulae (I), (II), (III), or (IV) according to the disclosure with a second component selected from at least one of (a) a serotonergic drug, (b) a purified psilocybin derivative, (c) a purified cannabinoid, or (d) a purified terpene, the compositions represent particular embodiments of the disclosure. Compositions having as a first component at least one compound of formulae (I), (II), (III), or (IV) according to the disclosure with a second component selected from at least one of (e) an adrenergic drug, (f) a dopaminergic drug, (g) a monoamine oxidase inhibitor, (h) a purified erinacine, or (i) a purified hericenone, also represent additional particular embodiments of the disclosure represented by the compositions having the compound of formulae (I), (II), (III), or (IV) according to the disclosure. In some embodiments, the first and second components can be administered at the same time (e.g., together in the same composition), or at separate times over the course of treating a patient in need thereof. Such a composition may be a pharmaceutical composition wherein the components are present individually in therapeutically effective amounts or by combination in a therapeutically effective amount to treat a disease, disorder, or condition as described herein.

[176] Within the context of this disclosure, the term “purified” means separated from other materials, such as plant or fungal material, e.g., protein, chitin, cellulose, or water. In one embodiment, the term “purified” refers to a compound substantially free of other materials. In one embodiment, the term “purified” refers to a compound that is substantially free from a second tryptamine compound. In one embodiment, the term “purified” refers to a compound substantially free from histidine. In one embodiment, the term “purified” refers to a compound substantially free from a biological material, such as mold, fungus, plant matter, or bacteria. In one embodiment, the term “purified” refers to a compound substantially free from a paralytic.

[177] In one embodiment, the term “purified” refers to a compound which has been separated from other compounds that are typically co-extracted when the purified compound is extracted from a naturally occurring organism. In one embodiment, a “purified” psilocybin derivative is partially or completely isolated from other psilocybin derivatives present in a source material, such as a psilocybin-containing mushroom. In one example, “purified” baeocystin is substantially free from psilocybin and/or psilocin. By contrast, traditional psilocybin mushroom extracts (aka crude extracts or fruit body extracts) would be expected to contain an unpredictable and varying amount of psilocybin, psilocin, baeocystin, norbaeocystin, salts thereof, or combinations thereof. Other examples of unpurified psilocybin

derivatives would include mycelium containing psilocybin derivatives and/or naturally occurring fungal material such as biological material and/or structural material such as chitin. Similarly, the term "cannabis extracts'' or "cannabinoid extracts" traditionally refers to whole plants (aka crude or full spectrum extracts) which have not been subjected to further purification to eliminate unwanted molecules that naturally occur in the cannabis plant. For example, a "cannabis extract comprising cannabidiol" could be expected to include cannabidiol (aka "CBD") and also varying amounts of other compounds, including cannabinoids, terpenes, and other biological material.

[178] In one embodiment, the term "purified" refers to a compound or composition that has been crystallized.

[179] In one embodiment, the term "purified" refers to a compound or composition that has been chromatographed, for example by gas chromatography, liquid chromatography (e.g., LC, HPLC, etc.), etc.

[180] In one embodiment, the term "purified" refers to a compound or composition that has been distilled.

[181] In one embodiment, the term "purified" refers to a compound or composition that has been sublimed.

[182] In one embodiment, the term "purified" refers to a compound or composition that has been subject to two or more steps chosen from crystallization, chromatography, distillation, or sublimation.

[183] In one embodiment, the term "purified" refers to a compound that is between 80-100% pure.

[184] In one embodiment, the term "purified" refers to a compound that is between 90-100% pure.

[185] In one embodiment, the term "purified" refers to a compound that is between 95-100% pure.

[186] In one embodiment, the term "purified" refers to a compound that is between 99-100% pure.

[187] In one embodiment, the term "purified" refers to a compound that is between 99.9-100% pure.

[188] A serotonergic drug refers to a compound that binds to, blocks, or otherwise influences (e.g., via an allosteric reaction) activity at a serotonin receptor as described in paragraphs [0245]-[0253] of US 2018/0221396 A1 and [0305]-[0311] US 2019/0142851 A1 as well as the disclosed exemplary embodiments, incorporated here by reference. Exemplary psilocybin derivatives include but are not limited to psilocybin itself and the psilocybin derivates described in paragraphs [0081]-[0109] of US 2018/0221396 A1 and [0082]-[0110] US 2019/0142851 A1 as well as the disclosed exemplary embodiments. Exemplary cannabinoids include but are not limited to the cannabinoids described in paragraphs [0111]-[0145] of US 2018/0221396 A1 and [0112]-[0146] US 2019/0142851 A1 as well as the disclosed exemplary embodiments. Exemplary terpenes include but are not limited to the terpenes

described in paragraphs [0160]-[0238] of US 2018/0221396 A1 and [0161]-[0300] US 2019/0142851 A1 as well as the disclosed exemplary embodiments.

[189] A pharmaceutical formulation of the disclosure may comprise, consist essentially of, or consist of (a) at least one compound of formulae (I), (II), (III), or (IV) according to the disclosure and (b) at least one second active compound selected from a serotonergic drug, a purified psilocybin derivative, a purified cannabinoid, a purified terpene, an adrenergic drug, a dopaminergic drug, a monoamine oxidase inhibitor, a purified erinacine, or a purified hericenone and (c) a pharmaceutically acceptable excipient. In some embodiments, the compound(s) of formulae (I), (II), (III), or (IV) according to the disclosure and the second active compound(s) are each present in a therapeutically effective amount using a purposefully engineered and unnaturally occurring molar ratios. Exemplary molar ratios of the compounds of formulae (I), (II), (III), or (IV) according to the disclosure to the second active compound in a composition of the disclosure include but are not limited to from about 0.1:100 to about 100:0.1, from about 1:100 to about 100:1, from about 1:50 to about 50:1, from about 1:25 to about 25:1, from about 1:20 to about 20:1, from about 1:10 to about 10:1, from about 1:5 to about 5:1, from about 1:2 to about 2:1 or may be about 1:1.

[190] A pharmaceutical formulation of the disclosure may comprise a composition containing a compound of formulae (I), (II), (III), or (IV) according to the disclosure and a serotonergic drug, a purified psilocybin derivative, a purified cannabinoid, or a purified terpene, each present in a therapeutically effective amount using a purposefully engineered and unnaturally occurring molar ratios. Published US applications US 2018/0221396 A1 and US 2019/0142851 A1 disclose compositions comprising a combination of a purified psilocybin derivative with a second purified psilocybin derivative, with one or two purified cannabinoids or with a purified terpene. According to this disclosure composition containing a compound of formulae (I), (II), (III), or (IV) according to the disclosure may be used in place of a “purified psilocybin derivative” in the compositions described in US 2018/0221396 A1 and US 2019/0142851 A1. Accordingly, the disclosure provides a pharmaceutical formulation comprising as (a) at least one compound of formulae (I), (II), (III), or (IV) according to the disclosure and at least one second component selected from (b) a purified psilocybin derivative, (c) a purified cannabinoid or (d) a purified terpene; and at least one pharmaceutically-acceptable excipient or at least one other adjuvant, as described herein. Such a composition may be a pharmaceutical composition wherein the components are present individually in therapeutically effective amounts or by combination in a therapeutically effective amount to treat a disease, disorder, or condition as described herein.

[191] A serotonergic drug refers to a compound that binds to, blocks, or otherwise influences (e.g., via an allosteric reaction) activity at a serotonin receptor as described in paragraphs [0245]-[0253] of US 2018/0221396 A1 and [0305]-[0311] US 2019/0142851 A1 as well as the disclosed exemplary embodiments. Some exemplary serotonergic drugs include SSRIs and SNRIs. Some examples of specific serotonergic drugs include the following molecules, including any salts, solvates, or polymorphs thereof: 6-allyl-N,N-diethyl-NL; N,N-dibutyl-T; N,N-diethyl-T; N,N-diisopropyl-T; 5-methyoxy-alpha-methyl-T; N,N-dimethyl-T; 2,alpha-dimethyl-T; alpha,N-dimethyl-T; N,N-dipropyl-T; N-ethyl-N-isopropyl-T; alpha-ethyl-T; 6-N,N-triethyl-NL; 3,4-dihydro-7-methoxy-1-methyl-C; 7-methyoxy-1-methyl-C; N,N-dibutyl-4-hydroxy-T; N,N-diethyl-4-hydroxy-T; N,N-diisopropyl-4-hydroxy-T; N,N-dimethyl-4-hydroxy-T; N,N-dimethyl-5-hydroxy-T; N,N-dipropyl-4-hydroxy-T; N-ethyl-4-hydroxy-N-methyl-T; 4-hydroxy-N-isopropyl-N-methyl-T; 4-hydroxy-N-methyl-N-propyl-T; 4-hydroxy-N,N-tetramethylene-T; ibogaine; N,N-diethyl-L; N-butyl-N-methyl-T; N,N-diisopropyl-4,5-methylenedioxy-T; N,N-diisopropyl-5,6-methylenedioxy-T; N,N-dimethyl-4,5-methylenedioxy-T; N,N-dimethyl-5,6-methylenedioxy-T; N-isopropyl-N-methyl-5,6-methylenedioxy-T; N,N-diethyl-2-methyl-T; 2-N,N-trimethyl-T; N-acetyl-5-methoxy-T; N,N-diethyl-5-methoxy-T; N,N-diisopropyl-5-methoxy-T; 5-methoxy-N,N-dimethyl-T; N-isopropyl-4-methoxy-N-methyl-T; N-isopropyl-5-methoxy-N-methyl-T; 5,6-dimethoxy-N-isopropyl-N-methyl-T; 5-methoxy-N-methyl-T; 5-methoxy-N,N-tetramethylene-T; 6-methoxy-1-methyl-1,2,3,4-tetrahydro-C; 5-methoxy-2-N,N-trimethyl-T; N,N-dimethyl-5-methylthio-T; N-isopropyl-N-methyl-T; alpha-methyl-T; N-ethyl-T; N-methyl-T; 6-propyl-NL; N,N-tetramethylene-T; tryptamine; 7-methoxy-1-methyl-1,2,3,4-tetrahydro-C; and alpha,N-dimethyl-5-methoxy-T. For additional information regarding these compounds see Shulgin, A. T., & Shulgin, A. (2016). Tihkal: The Continuation. Berkeley, Calif.: Transform Press. In one embodiment, a serotonergic drug is chosen from alprazolam, amphetamine, aripiprazole, azapirone, a barbiturate, bromazepam, bupropion, buspirone, a cannabinoid, chlordiazepoxide, citalopram, clonazepam, clorazepate, dextromethorphan, diazepam, duloxetine, escitalopram, fluoxetine, flurazepam, fluvoxamine, lorazepam, lysergic acid diethylamide, lysergamide, 3,4-methylenedioxymethamphetamine, milnacipran, mirtazapine, naratriptan, paroxetine, pethidine, phenethylamine, psicaine, oxazepam, reboxetine, serenic, serotonin, sertraline, temazepam, tramadol, triazolam, a tryptamine, venlafaxine, vortioxetine, and/or derivatives thereof. In an exemplary embodiment, the serotonergic drug is 3,4-methylenedioxymethamphetamine.

[192] Exemplary psilocybin derivatives include but are not limited to psilocybin itself and the psilocybin derivates described in paragraphs [0081]-[0109] of US 2018/0221396 A1 and [0082]-[0110] US 2019/0142851 A1 as well as the disclosed exemplary embodiments. In one embodiment, the

compositions disclosed herein comprise one or more purified psilocybin derivatives chosen from: [3-(2-dimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate; 4-hydroxytryptamine; 4-hydroxy-N,N-dimethyltryptamine; [3-(2-methylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate; 4-hydroxy-N-methyltryptamine; [3-(aminoethyl)-1H-indol-4-yl] dihydrogen phosphate; [3-(2-trimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate; and 4-hydroxy-N,N,N-trimethyltryptamine.

[193] Exemplary cannabinoids include but are not limited to the cannabinoids described in paragraphs [0111]-[0145] of US 2018/0221396 A1 and [0112]-[0146] US 2019/0142851 A1 as well as the disclosed exemplary embodiments, incorporated here by reference. Examples of cannabinoids within the context of this disclosure include the following molecules: cannabichromene (CBC); cannabichromenic acid (CBCA); cannabichromevarin (CBCV); cannabichromevarinic acid (CBCVA); cannabicyclol (CBL); cannabicyclolic acid (CBLA); cannabicyclovarin (CBLV); cannabidiol (CBD); cannabidiol monomethylether (CBDM); cannabidiolic acid (CBDA); cannabidiorcol (CBD-C1); cannabidivarin (CBDV); cannabidivarinic acid (CBDVA); cannabielsoic acid B (CBEA-B); cannabielsoin (CBE); cannabielsoin acid A (CBEA-A); cannabigerol (CBG); cannabigerol monomethylether (CBGM); cannabigerolic acid (CBGA); cannabigerolic acid monomethylether (CBGAM); cannabigerovarin (CBGV); cannabigerovarinic acid (CBGVA); cannabinodiol (CBND); cannabinodivarin (CBVD); cannabinol (CBN); cannabinol methylether (CBNM); cannabinol-C2 (CBN-C2); cannabinol-C4 (CBN-C4); cannabinolic acid (CBNA); cannabiorcol (CBN-C1); cannabivarin (CBV); cannabitriol (CBT); cannabitriolvarin (CBTV); 10-ethoxy-9-hydroxy-delta-6a-tetrahydrocannabinol; cannabicitran (CBTC); cannabiripsol (CBR); 8,9-dihydroxy-delta-6a-tetrahydrocannabinol; delta-8-tetrahydrocannabinol (Δ8-THC); delta-8-tetrahydrocannabinolic acid (Δ8-THCA); delta-9-tetrahydrocannabinol (THC); delta-9-tetrahydrocannabinol-C4 (THC-C4); delta-9-tetrahydrocannabinolic acid A (THCA-A); delta-9-tetrahydrocannabinolic acid B (THCA-B); delta-9-tetrahydrocannabinolic acid-C4 (THCA-C4); delta-9-tetrahydrocannabiorcol (THC-C1); delta-9-tetrahydrocannabiorcolic acid (THCA-C1); delta-9-tetrahydrocannabivarin (THCV); delta-9-tetrahydrocannabivarinic acid (THCVA); 10-oxo-delta-6a-tetrahydrocannabinol (OTHC); cannabichromanon (CBCF); cannabifuran (CBF); cannabiglendol; delta-9-cis-tetrahydrocannabinol (cis-THC); trihydroxy-delta-9-tetrahydrocannabinol (triOH-THC); dehydrocannabifuran (DCBF); and 3,4,5,6-tetrahydro-7-hydroxy-alpha-alpha-2-trimethyl-9-n-propyl-2,6-methano-2H-1-benzoxocin-5-methanol. In one embodiment, the purified cannabinoid is chosen from THC, THCA, THCV, THCVA, CBC, CBCA, CBCV, CBCVA, CBD, CBDA, CBDV, CBDVA, CBG, CBGA, CBGV, or CBGVA.

[194] Exemplary terpenes include but are not limited to the terpenes described in paragraphs [0160]-[0238] of US 2018/0221396 A1 and [0161]-[0300] US 2019/0142851 A1 as well as the disclosed

exemplary embodiments. In one embodiment, a purified terpene is chosen from acetanisole, acetyl cedrene, anethole, anisole, benzaldehyde, bornyl acetate, borneol, cadinene, cafestol, caffeic acid, camphene, camphor, capsaicin, carene, carotene, carvacrol, carvone, caryophyllene, caryophyllene, caryophyllene oxide, cedrene, cedrene epoxide, cecanal, cedrol, cembrene, cinnamaldehyde, cinnamic acid, citronellal, citronellol, cymene, eicosane, elemene, estragole, ethyl acetate, ethyl cinnamate, ethyl maltol, eucalyptol/1,8-cineole, eudesmol, eugenol, euphol, farnesene, farnesol, fenchone, geraniol, geranyl acetate, guaia-1(10),11-diene, guaiacol, guaiol, guaiene, gurjunene, herniarin, hexanaldehyde, hexanoic acid, humulene, ionone, ipsdienol, isoamyl acetate, isoamyl alcohol, isoamyl formate, isoborneol, isomyrcenol, isoprene, isopulegol, isovaleric acid, lavandulol, limonene, gamma-linolenic acid, linalool, longifolene, lycopene, menthol, methyl butyrate, 3-mercapto-2-methylpentanal, beta-mercaptoethanol, mercaptoacetic acid, methyl salicylate, methylbutenol, methyl-2-methylvalerate, methyl thiobutyrate, myrcene, gamma-muurolene, nepetalactone, nerol, nerolidol, neryl acetate, nonanaldehyde, nonanoic acid, ocimene, octanal, octanoic acid, pentyl butyrate, phellandrene, phenylacetaldehyde, phenylacetic acid, phenylethanethiol, phytol, pinene, propanethiol, pristimerin, pulegone, retinol, rutin, sabinene, squalene, taxadiene, terpineol, terpine-4-ol, terpinolene, thujone, thymol, umbelliferone, undecanal, verdoxan, or vanillin. In one embodiment, a purified terpene is chosen from bornyl acetate, alpha-bisabolol, borneol, camphene, camphor, carene, caryophyllene, cedrene, cymene, elemene, eucalyptol, eudesmol, farnesene, fenchol, geraniol, guaiacol, humulene, isoborneol, limonene, linalool, menthol, myrcene, nerolidol, ocimene, phellandrene, phytol, pinene, pulegone, sabinene, terpineol, terpinolene, or valencene.

[195] As used herein, the term “adrenergic drug” refers to a compound that binds, blocks, or otherwise influences (e.g., via an allosteric reaction) activity at an adrenergic receptor. In one embodiment, an adrenergic drug binds to an adrenergic receptor. In one embodiment, an adrenergic drug indirectly affects an adrenergic receptor, e.g., via interactions affecting the reactivity of other molecules at the adrenergic receptor. In one embodiment, an adrenergic drug is an agonist, e.g., a compound activating an adrenergic receptor. In one embodiment, an adrenergic drug is an antagonist, e.g., a compound binding but not activating an adrenergic receptor, e.g., blocking a receptor. In one embodiment, an adrenergic drug is an effector molecule, e.g., a compound binding to an enzyme for allosteric regulation. In one embodiment, an adrenergic drug acts (either directly or indirectly) at more than one type of receptor (e.g., 5HT, dopamine, adrenergic, acetylcholine, etc.).

[196] In one embodiment, an adrenergic drug is an antidepressant. In one embodiment, an adrenergic drug is a norepinephrine transporter inhibitor. In one embodiment, an adrenergic drug is a vesicular

monoamine transporter inhibitor. In one embodiment, an adrenergic drug is chosen from adrenaline, agmatine, amoxapine, aptazapine, atomoxetine, bupropion, clonidine, doxepin, duloxetine, esmirtazpine, mianserin, ketanserin, mirabegron, mirtazapine, norepinephrine, phentolamine, phenylephrine, piperoxan, reserpine, ritodrine, setiptiline, tesofensine, timolol, trazodone, trimipramine, or xylazine.

[197] As used herein, the term "dopaminergic drug" refers to a compound that binds, blocks, or otherwise influences (e.g., via an allosteric reaction) activity at a dopamine receptor. In one embodiment, a dopaminergic drug binds to a dopamine receptor. In one embodiment, a dopaminergic drug indirectly affects a dopamine receptor, e.g., via interactions affecting the reactivity of other molecules at the dopamine receptor. In one embodiment, a dopaminergic drug is an agonist, e.g., a compound activating a dopamine receptor. In one embodiment, a dopaminergic drug is an antagonist, e.g., a compound binding but not activating a dopamine receptor, e.g., blocking a receptor. In one embodiment, a dopaminergic drug is an effector molecule, e.g., a compound binding to an enzyme for allosteric regulation. In one embodiment, a dopaminergic drug acts (either directly or indirectly) at more than one type of receptor (e.g., 5HT, dopamine, adrenergic, acetylcholine, etc.).

[198] In one embodiment, a dopaminergic drug is a dopamine transporter inhibitor. In one embodiment, a dopaminergic drug is a vesicular monoamine transporter inhibitor. In one embodiment, a dopaminergic drug is chosen from amineptine, apomorphine, benzylpiperazine, bromocriptine, cabergoline, chlorpromazine, clozapine, dihydrexidine, domperidone, dopamine, fluphenazine, haloperidol, ketamine, loxapine, methamphetamine, olanzapine, pemoline, perphenazine, pergolide, phencyclidine, phenethylamine, phenmetrazine, pimozide, piribedil, a psychostimulant, reserpine, risperidone, ropinirole, tetrabenazine, or thioridazine.

[199] As used herein, the term "monoamine oxidase inhibitor" (MAOI) refers to a compound that blocks the actions of monoamine oxidase enzymes. In one embodiment, a MAOI inhibits the activity of one or both monoamine oxidase A and monoamine oxidase B. In one embodiment a MAOI is a reversible inhibitors of monoamine oxidase A. In one embodiment a MAOI is a drug chosen from isocarboxazid, phenelzine, or tranylcypromine. In one embodiment, a MAOI is β-carboline, pinoline, harmane, harmine, harmaline, harmalol, tetrahydroharmine, 9-methyl-β-carboline, or 3-carboxy-tetrahydrononharman.

[200] In one embodiment, the compositions and methods disclosed herein include one or more purified erinacine molecules. In one embodiment, the compositions and methods disclosed herein comprise purified erinacine A. In one embodiment, the compositions and methods disclosed herein

comprise erinacine B. In one embodiment, the compositions and methods disclosed herein comprise erinacine C. In one embodiment, the compositions and methods disclosed herein comprise erinacine D. In one embodiment, the compositions and methods disclosed herein comprise erinacine E. In one embodiment, the compositions and methods disclosed herein comprise erinacine F. In one embodiment, the compositions and methods disclosed herein comprise erinacine G. In one embodiment, the compositions and methods disclosed herein comprise erinacine H. In one embodiment, the compositions and methods disclosed herein comprise erinacine I. In one embodiment, the compositions and methods disclosed herein comprise erinacine J. In one embodiment, the compositions and methods disclosed herein comprise erinacine K In one embodiment, the compositions and methods disclosed herein comprise erinacine P. In one embodiment, the compositions and methods disclosed herein comprise erinacine Q. In one embodiment, the compositions and methods disclosed herein comprise erinacine R. In one embodiment, the compositions and methods disclosed herein comprise erinacine S.

[201] In one embodiment, the compositions and methods disclosed herein include one or more purified hericenone molecules. In one embodiment, the compositions and methods disclosed herein comprise purified hericenone A. In one embodiment, the compositions and methods disclosed herein comprise purified hericenone B. In one embodiment, the compositions and methods disclosed herein comprise purified hericenone C. In one embodiment, the compositions and methods disclosed herein comprise purified hericenone D. In one embodiment, the compositions and methods disclosed herein comprise purified hericenone E. In one embodiment, the compositions and methods disclosed herein comprise purified hericenone F. In one embodiment, the compositions and methods disclosed herein comprise purified hericenone G. In one embodiment, the compositions and methods disclosed herein comprise purified hericenone H.

[202] Exemplary compositions of a compound of formulae (I), (II), (III), or (IV) according to the disclosure and a second compound selected from a serotonergic drug, a purified psilocybin derivative, a purified cannabinoid, a purified terpene, an adrenergic drug, a dopaminergic drug, a monoamine oxidase inhibitor, a purified erinacine, or a purified hericenone in exemplary molar ratios are shown in Table 5. A compound of formulae (I), (II), (III), or (IV) according to the disclosure may be any one of the exemplary embodiments described above including their crystalline forms as disclosed herein.

Table 5

Second Compound	Molar ratio of a compound of formulae (I), (II), (III), or (IV): second compound	Molar ratio of a compound of formulae (I), (II), (III), or (IV): second compound	Molar ratio of a compound of formulae (I), (II), (III), or (IV): second compound
3,4-methylenedioxymethamphetamine	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Citalopram	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Escitalopram	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Fluoxetine	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Paroxetine	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Sertraline	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Duloxetine	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
[3-(2-dimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
4-hydroxytryptamine	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
4-hydroxy-N,N-dimethyltryptamine	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
[3-(2-methylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
4-hydroxy-N-methyltryptamine	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
[3-(aminoethyl)-1H-indol-4-yl] dihydrogen phosphate	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
[3-(2-trimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
4-hydroxy-N,N,N-trimethyltryptamine	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
THC	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
CBC	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
CBD	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
CBG	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Myrcene	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1

Pinene	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Caryophyllene	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Limonene	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Humulene	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Linalool	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Adrenaline	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Amineptine	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Erinacine A	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Hericenone A	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Phenelzine	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1

[203] Exemplary pharmaceutical compositions of a compound of formulae (I), (II), (III), or (IV) according to the disclosure and a second compound selected from a serotonergic drug, a purified psilocybin derivative, a purified cannabinoid, a purified terpene, an adrenergic drug, a dopaminergic drug, a monoamine oxidase inhibitor, a purified erinacine, and a purified hericenone and an excipient with exemplary molar ratios of a compound of formulae (I), (II), (III), or (IV) according to the disclosure to the second compound are shown in Table 6. A compound of formulae (I), (II), (III), or (IV) according to the disclosure may be any one of the exemplary embodiments described above including their crystalline forms as disclosed herein.

Table 6

Second Compound	**Molar ratio of a compound of formulae (I), (II), (III), or (IV): second compound**	**Molar ratio of a compound of formulae (I), (II), (III), or (IV): second compound**	**Molar ratio of a compound of formulae (I), (II), (III), or (IV): second compound**
3,4-methylenedioxymethamphetamine	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Citalopram	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Escitalopram	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1

Fluoxetine	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Paroxetine	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Sertraline	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Duloxetine	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
[3-(2-dimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
4-hydroxytryptamine	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
4-hydroxy-N,N-dimethyltryptamine	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
[3-(2-methylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
4-hydroxy-N-methyltryptamine	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
[3-(aminoethyl)-1H-indol-4-yl] dihydrogen phosphate	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
[3-(2-trimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
4-hydroxy-N,N,N-trimethyltryptamine	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
THC	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
CBC	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
CBD	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
CBG	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Myrcene	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Pinene	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Caryophyllene	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Limonene	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Humulene	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Linalool	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Adrenaline	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1

Amineptine	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Erinacine A	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Hericenone A	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1
Phenelzine	About 1:100 to about 100:1	About 1:25 to about 25:1	About 1:5 to about 5:1

[204] An “effective amount” or a “therapeutically effective amount” of a compound of formulae (I), (II), (III), or (IV) according to the disclosure is generally in the range of about 0.1 to about 100 mg daily (oral dose), of about 0.1 to about 50 mg daily (oral dose) of about 0.25 to about 25 mg daily (oral dose), of about 0.1 to about 5 mg daily (oral dose) or of about 0.5 to about 2.5 mg daily (oral dose). The actual amount required for treatment of any particular patient may depend upon a variety of factors including, for example, the disease being treated and its severity; the specific pharmaceutical composition employed; the age, body weight, general health, sex, and diet of the patient; the mode of administration; the time of administration; the route of administration; and the rate of excretion; the duration of the treatment; any drugs used in combination or coincidental with the specific compound employed; and other such factors well known in the medical arts. These factors are discussed in Goodman and Gilman’s “The Pharmacological Basis of Therapeutics,” Tenth Edition, A. Gilman, J. Hardman and L. Limbird, eds., McGraw-Hill Press, 155-173 (2001), which is incorporated herein by reference. A compound of formulae (I), (II), (III), or (IV) according to the disclosure and pharmaceutical compositions containing it may be used in combination with other agents that are generally administered to a patient being treated for psychological and other disorders discussed above. They may also be co-formulated with one or more of such agents in a single pharmaceutical composition.

[205] Depending on the type of pharmaceutical composition, the pharmaceutically acceptable carrier may be chosen from any one or a combination of carriers known in the art. The choice of the pharmaceutically acceptable carrier depends upon the pharmaceutical form and the desired method of administration to be used. Exemplary carriers include those that do not substantially alter the structure or activity of a compound of formulae (I), (II), (III), or (IV) according to the disclosure, nor produce undesirable biological effects or otherwise interact in a deleterious manner with any other component(s) of the pharmaceutical composition.

[206] The pharmaceutical compositions of the disclosure may be prepared by methods know in the pharmaceutical formulation art, for example, see Remington’s Pharmaceutical Sciences, 18th Ed., (Mack

Publishing Company, Easton, Pa., 1990), which is incorporated herein by reference. In a solid dosage form, a compound of formulae (I), (II), (III), or (IV) according to the disclosure may be admixed with at least one pharmaceutically acceptable excipient such as, for example, sodium citrate or dicalcium phosphate or (a) fillers or extenders, such as, for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, such as, for example, cellulose derivatives, starch, alginates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, such as, for example, glycerol, (d) disintegrating agents, such as, for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, such as, for example, paraffin, (f) absorption accelerators, such as, for example, quaternary ammonium compounds, (g) wetting agents, such as, for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like, (h) adsorbents, such as, for example, kaolin and bentonite, and (i) lubricants, such as, for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. In some embodiments, the excipient is not water. In some embodiments, the excipient is not a solvent (e.g., EtOH, diethyl ether, ethyl acetate, or hydrocarbon-based solvents (e.g., hexanes). In some embodiments, the dosage form is substantially free of water and/or solvents, for example less than about 5% water by mass, less than 2% water by mass, less than 1% water by mass, less than 0.5% water by mass, or less than 0.1% water by mass.

[207] Excipients or pharmaceutically acceptable adjuvants known in the pharmaceutical formulation art may also be used in the pharmaceutical compositions of the disclosure. These include, but are not limited to, preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms may be ensured by inclusion of various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example, sugars, sodium chloride, and the like. If desired, a pharmaceutical composition of the disclosure may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylated hydroxytoluene, etc.

[208] Solid dosage forms as described above may be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Non-limiting examples of embedded compositions that may be used are polymeric

substances and waxes. The active compounds may also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[209] Suspensions, in addition to the active compounds, may contain suspending agents, such as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

[210] Solid dosage forms for oral administration, which includes capsules, tablets, pills, powders, and granules, may be used. In such solid dosage forms, the active compound may be mixed with at least one inert, pharmaceutically acceptable excipient (also known as a pharmaceutically acceptable carrier).

[211] Administration of compounds of formulae (I), (II), (III), or (IV) according to the disclosure in pure form or in an appropriate pharmaceutical composition may be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration may be, for example, orally, buccally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, or intrasystemically, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as, for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, such as, for example, in unit dosage forms suitable for simple administration of precise dosages. One route of administration may be oral administration, using a convenient daily dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

Examples

[212] Examples

[213] Example 1: Synthesis of Compounds of Formula (I)

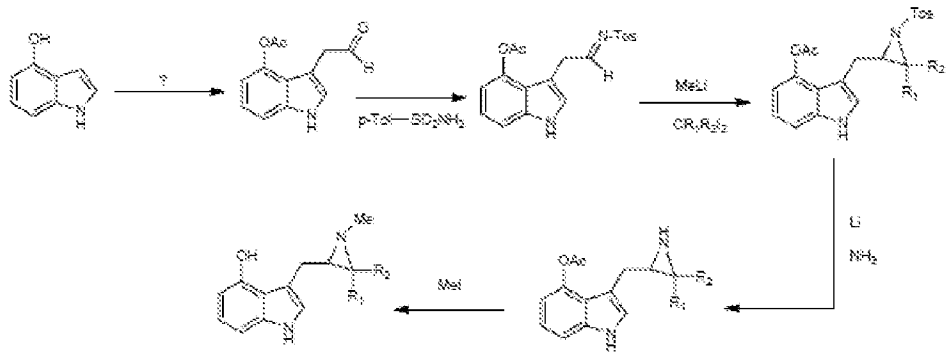
[214] Each of the derivatives exemplified in Table 1 above, where R_4 = OH and R_5 = H, plus psilocin were constructed in silico using ChemDraw® and Chem3D® 20.1.1. Each structure's energy was minimized using MM2 regression and the final C-N-C exterior angle and interior angle was calculated along with the molecule's overall ground state energy. Results are shown in Table 7.

Table 7

COMPOUND	EXT ANGLE (DEG)	INT ANGLE (DEG)	ENERGY (KCAL/MOL)
Psilocin	249.9	110.1	13.36
Azacyclohexyl	249.5	110.5	20.69
Azacyclopentyl	248.4	111.6	23.38

Azacyclobutyl	247.0	113.0	44.83
Azacycpropyl	241.8	118.2	125.0

[215] Tryptamine analogs with endocyclic amines such as those represented in formula (I), were prepared by synthesis of tryptamine analogs. The following reaction mechanism shows the synthesis of both 3-((1-methylaziridin-2-yl)methyl)-1H-indol-4-ol as well as the acetate prodrug 3-((1-methylaziridin-2-yl)methyl)-1H-indol-4-yl acetate. 4-Acetoxyindole was alkylated at the 3-position to provide the intermediate aldehyde which was converted to the p-toluenesulfonimine by addition of the corresponding sulfonamide. The aziridine moiety was created by the action of in situ generated iodomethyllithium (in this case where R_1 and R_2 = H). (Concellón) The N-tosyl bond was cleaved through direct reduction to produce the secondary aziridine which can be alkylated with methyl iodide to produce the target compound (the 4-acetoxy derivative) which was converted to the 4-hydroxy compound through saponification of the following reaction mechanism.



[216] Analytical data for the compounds shown above have been produced via ChemDraw 20.1.1. The spectrum and data for (S)-3-((1-methylaziridin-2-yl)methyl)-1H-indol-4-ol is shown in Table 8.

Table 8

Chemical Formula	**$C_{12}H_{14}N_2O$**
Exact Mass	202.11
Molecular Weight	202.26
M/Z	202.11 (100.0%), 203.11 (13.8%)
Elemental Analysis	C, 71.26; H, 6.98; N, 13.85; O, 7.91
Log P	1.14
tPSA	35.27
CLogP	1.114

pKa	9.005, 12.265

[217] ^{1}H NMR spectrum of (S)-3-((1-methylaziridin-2-yl)methyl)-1H-indol-4-ol is shown in FIG. 1.

[218] Example 2: Synthesis of Compounds of Formula (II)

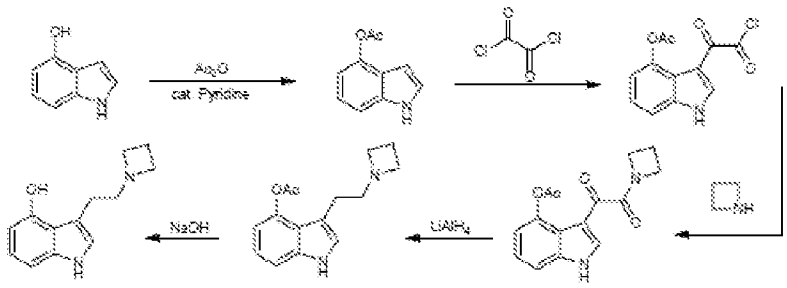
[219] Each of the derivatives exemplified in Table 2 above, where R_4 = OH and R_5 = H, plus psilocin and azacyclobutyl were constructed in silico using ChemDraw® and Chem3D® 20.1.1. Each structure's energy was minimized using MM2 regression and the final C-N-C exterior angle was calculated along with the molecule's overall energy. Results are shown in Table 9.

Table 9

COMPOUND	EXT ANGLE (DEG)	INT ANGLE (DEG)	ENERGY (KCAL/MOL)
Psilocin	249.9	110.1	13.36
Azacyclohexyl	249.2	110.8	18.55
Azacyclopentyl	257.8	102.2	24.33
Azacyclobutyl	268.2	91.8	44.35
Aziridinyl	298.6	61.4	125.3

[220] As exemplified in Table 9, as the ring size decreases (cyclohexyl to aziridinyl), the exterior angle widens and the interior angle closes. These differences may manifest in a different binding affinity for the 5HT receptors.

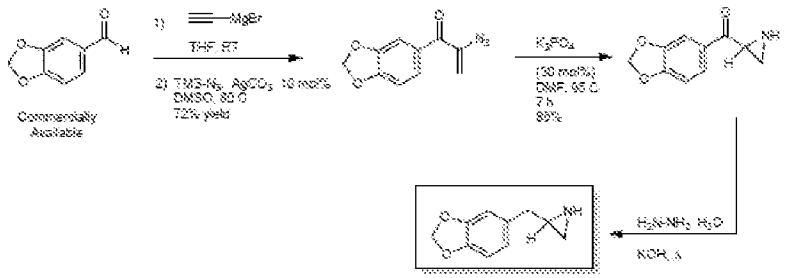
[221] Tryptamine analogs with exocyclic amines, such as those represented in formula (II), are easily prepared by the venerable Speeter-Anthony synthesis of tryptamine analogs. (Speeter) The following reaction mechanism shows the synthesis of both 3-(2-(azetidin-1-yl)ethyl)-1H-indol-4-yl acetate as well as 3-(2-(azetidin-1-yl)ethyl)-1H-indol-4-ol. Widely available 4-hydroxyindole was acetylated to provide 4-acetoxyindole. Alternatively, 4-acetoxy-indole, since it is also widely available, was purchased as the starting material. 4-Acetoxyindole was acylated at the 3-position with oxalyl chloride to provide the intermediate acyl chloride which was converted to the terminal amide by addition of the cyclic amine, in this case, azacyclobutane. The carbonyls were readily reduced by the action of lithium aluminum hydride to provide the acetoxy tryptamine derivative. This compound can be saponified to provide the 4-hydroxytryptamine derivative as shown in the following reaction mechanism.



Other compounds of formula (II) were formed in a similar manner.

[222] Example 3: Synthesis of Compounds of Formula (III)

[223] Commercially available piperonal (shown in the following reaction mechanism) was converted to the vinyl azide in 72 % yield in a single pot with first, reaction with ethynyl magnesium bromide to produce the *in situ* carbinol. A silver-(I) catalyzed hydroazidation yielded the α,β-unsaturated-α-vinyl azide. The a-keto-aziridine was formed by treatment with potassium phosphate (K_3PO_4) in DMF at 95°C in 86% yield. (Liu). Reduction of the aryl ketone to produce the target compound was accomplished through a Wolff-Kishner reduction shown below or by any number of transformations known to those skilled in the art.



[224] Analytical data for the compounds shown above have been produced via ChemDraw 20.1.1. The spectrum and data for Azacyclopropyl-MDMA analog is shown in Table 10.

Table 10

Chemical Formula	**$C_{10}H_{11}NO_2$**
Exact Mass	177.08
Molecular Weight	177.20
M/Z	177.08 (100.0%), 178.08 (11.3%)
Elemental Analysis	C, 67.78; H, 6.26; N, 7.90; O, 18.06

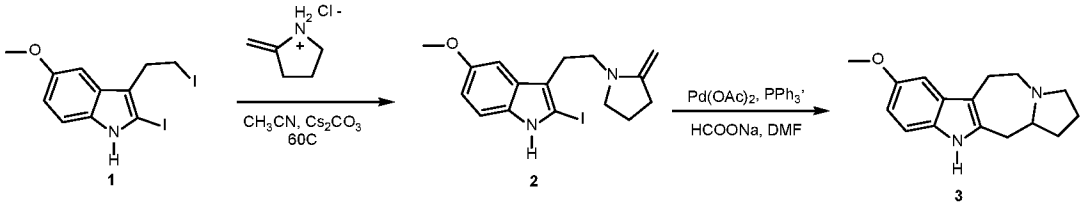
Log P	1.39
tPSA	4.04
CLogP	1.31
pKa	11.573

[225] ^{1}H NMR spectrum of Azacyclopropyl-MDMA analog is shown in FIG. 2.

[226] Example 4: Synthesis of Compounds of Formula (IV)

[227] Synthesis of 8-methoxy-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole (3)

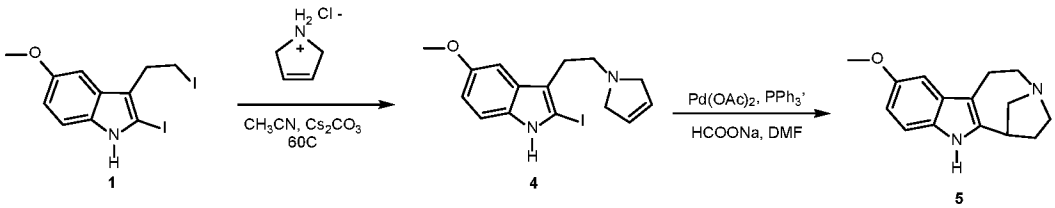
[228] 8-methoxy-1,2,3,5,6,11,12,12a-octahydropyrrolo[1',2':1,2]azepino[4,5-b]indole (3) is synthesized by the following reaction mechanism.



[229] The synthesis of analogue 3 started with 5-Methoxy-2-iodotryptoyl iodide 1 which was prepared by the procedure of Jana and Sinha. Compound 1 was coupled at the alkyl iodide position with 2-methylenepyrrolidine in acetonitrile with cesium carbonate at 60°C followed by intermolecular Heck type coupling using the analogous method of the same authors to generate compound 3.

[230] Synthesis of 10-methoxy-1,2,4,5,6,7-hexahydro-3,6-methanoazocino[5,4-b]indole (5)

[231] 10-methoxy-1,2,4,5,6,7-hexahydro-3,6-methanoazocino[5,4-b]indole (5) is synthesized by the following reaction mechanism.



[232] The synthesis of analogue 5 started with 5-Methoxy-2-iodotryptoyl iodide 1 which was prepared by the procedure of Jana and Sinha. Compound 1 was coupled at the alkyl iodide position with 2,5-dihydro-1h-pyrrole in acetonitrile with cesium carbonate at 60°C followed by intermolecular Heck type coupling using the analogous method of the same authors to generate compound 5.

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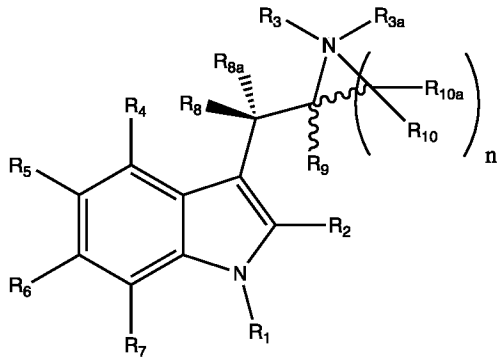
What is claimed is:

1. A compound of formula (I):



(I)

wherein:

R_1 is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, $-OR_{11}$, $-C(O)R_{11}$, $-C(O)OR_{11}$, $-SO_2R_{11}$, and $-C(O)NR_{11}R_{12}$;

R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{10}, and R_{10a} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6-heteroalkyl, optionally substituted heteroaryl, optionally substituted aryl, halogen, hydroxy, CN, $-OR_{11}$, $-OC(O)R_{11}$, $-OC(O)OR_{11}$, $-OSO_2R_{11}$, $-OC(O)NR_{11}R_{12}$, $-OP(O)(OH)_2$, and $-OP(O)(OH)OP(O)(OH)_2$;

R_3 is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, and $-SO_2R_{11}$;

R_{3a} is selected from an electron pair, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl, wherein when R_{3a} is not an electron pair the compound of formula (I) is a quaternary amine cation with a pharmaceutically acceptable anion, X^-;

R_{11} and R_{12} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl; and

n is an integer defining the variable number of ring carbons carrying R_{10} and R_{10a} and is selected from 1 to 4.

2. The compound of claim 1, wherein at least one of R_4 or R_5 is selected from hydroxy, $-OR_{11}$, $-OC(O)R_{11}$, $-OC(O)OR_{11}$, $-OSO_2R_{11}$, $-OC(O)NR_{11}R_{12}$, $-OP(O)(OH)_2$, and $-OP(O)(OH)OP(O)(OH)_2$.

3. The compound of claim 2, wherein at least one of R_4 or R_5 is selected from hydroxy and $-OC(O)R_{11}$.

4. The compound of claim 3, wherein R_{11} is an optionally substituted C_1-C_6 alkyl.

5. The compound of claim 4, wherein R_{11} is an unsubstituted C_1-C_6 alkyl.

6. The compound of claim 5, wherein R_{11} is methyl.

7. The compound of any of claims 1-6, wherein R_3 is selected from optionally substituted C_1-C_6 alkyl and optionally substituted C_2-C_6 alkenyl.

8. The compound of claim 7, wherein R_3 is an unsubstituted C_1-C_6 alkyl.

9. The compound of claim 8, wherein R_3 is methyl.

10. The compound of any of claims 1-9, wherein R_{3a} is an electron pair.

11. The compound of any of claims 1-10, wherein R_6 is hydrogen.

12. The compound of any of claims 1-11, wherein R_7 is hydrogen.

13. The compound of any of claims 1-12, wherein R_9 is hydrogen.

14. The compound of any of claims 1-13, wherein R_1 is selected from hydrogen and optionally substituted C_1-C_6 alkyl.

15. The compound of any of claims 1-14, wherein R_1 is a 2-(S)-methyl-2-N,N-dimethylamino-ethyl or 2-(R)-methyl-2-N,N-dimethylamino-ethyl.

16. The compound of any of claims 1-15, wherein R_{10} is hydrogen.

17. The compound of any of claims 1-16, wherein R_{10a} is hydrogen.

18. The compound of any of claims 1-17, wherein R_8 is hydrogen.

19. The compound of any of claims 1-18, wherein R_{8a} is hydrogen.

20. The compound of any of claims 1-19, wherein n = 1.

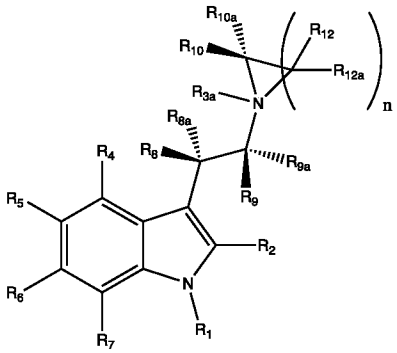
21. The compound of any claims 1-19, wherein n = 2.

22. The compound of any of claims 1-19, wherein n = 3.

23. The compound of any of claims 1-19, wherein n = 4.

24. The compound of any of claims 1-23, wherein R_2 is hydrogen.

25. A compound of formula (II):



(II)

wherein:

R_1 is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, $-OR_{11}$, $-C(O)R_{11}$, $-C(O)OR_{11}$, $-SO_2R_{11}$, and $-C(O)NR_{11}R_{13}$;

R_2, R_4, R_5, R_6, R_7, R_8, R_{8a}, R_9, R_{9a}, R_{10}, R_{10a}, R_{12}, and R_{12a} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6-heteroalkyl, optionally substituted heteroaryl, optionally substituted aryl, halogen, hydroxy, CN, $-OR_{11}$, $-OC(O)R_{11}$, $-OC(O)OR_{11}$, $-OSO_2R_{11}$, $-OC(O)N\ R_{11}R_{13}$, $-OP(O)(OH)_2$, and $-OP(O)(OH)OP(O)(OH)_2$;

R_{3a} is selected from an electron pair, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl, wherein when R_{3a} is not an electron pair the compound of formula (II) is a quaternary amine cation with a pharmaceutically acceptable anion, X^-;

R_{11} and R_{13} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl; and

n is an integer defining the variable number of ring carbons carrying R_{12} and R_{12a} and is selected from 1 to 4.

26. The compound of claim 25, wherein at least one of R_4 or R_5 is selected from hydroxy, $-OR_{11}$, $-OC(O)R_{11}$, $-OC(O)OR_{11}$, $-OSO_2R_{11}$, $-OC(O)NR_{11}R_{12}$, $-OP(O)(OH)_2$, and $-OP(O)(OH)OP(O)(OH)_2$.

27. The compound of claim 26, wherein at least one of R_4 or R_5 is selected from hydroxy and $-OC(O)R_{11}$.

28. The compound of claim 27, wherein R_{11} is an optionally substituted C_1-C_6 alkyl.

29. The compound of claim 28, wherein R_{11} is an unsubstituted C_1-C_6 alkyl.

30. The compound of claim 29, wherein R_{11} is methyl.

31. The compound of any of claims 25-30, wherein R_{3a} is an electron pair.

32. The compound of any of claims 25-31, wherein R_6 is hydrogen.

33. The compound of any of claims 25-32, wherein R_7 is hydrogen.

34. The compound of any of claims 25-33, wherein R_9 is hydrogen.

35. The compound of any of claims 25-34, wherein R_{9a} is hydrogen.

36. The compound of any of claims 25-35, wherein R_8 is hydrogen.

37. The compound of any of claims 25-36, wherein R_{8a} is hydrogen.

38. The compound of any of claims 25-37, wherein R_1 is selected from hydrogen and optionally substituted C_1-C_6 alkyl.

39. The compound of any of claims 25-38, wherein R_1 is selected from 2-(S)-methyl-2-N,N-dimethylamino-ethyl or 2-(R)-methyl-2-N,N-dimethylamino-ethyl.

40. The compound of any of claims 25-39, wherein R_{10} is hydrogen.

41. The compound of any of claims 25-40, wherein R_{10a} is hydrogen.

42. The compound of any of claims 25-41, wherein R_{12} is hydrogen.

43. The compound of any of claims 25-42, wherein R_{12a} is hydrogen.

44. The compound of any of claims 25-43, wherein n = 1.

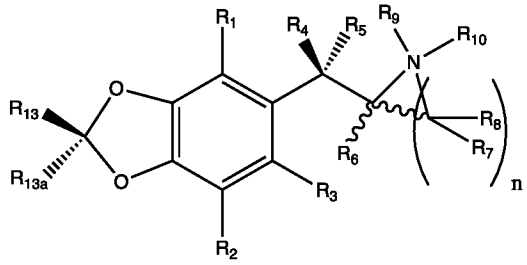
45. The compound of any of claims 25-43, wherein n = 2.

46. The compound of any of claims 25-43, wherein n = 3.

47. The compound of any of claims 25-43, wherein n = 4.

48. The compound of claim 45, wherein when n=2, R_{3a} is not an electron pair and/or at least one of R_8, R_{8a}, R_9, or R_{9a} is not hydrogen.

49. A compound of formula (III):



(III)

wherein:

R_1, R_2, and R_3 are independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, halogen, -OR_{11}, -$C(O)R_{11}$, -$C(O)OR_{11}$, -$OC(O)R_{11}$, $C(O)NR_{11}R_{12}$, CN, $C(NR_{12})R_{11}$, $C(NOR_{12})OR_{11}$, -SO_2R_{11}, and -$C(O)NR_{11}R_{12}$;

R_4, R_5, R_6, R_7, and R_8 are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted heteroaryl, optionally substituted aryl, halogen, hydroxy, -OR_{11}, -$OC(O)R_{11}$, -$OC(O)OR_{11}$, OSO_2R_{11}, and -$OC(O)NR_{11}R_{12}$;

R_9, is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, and -SO_2R_{11};

R_{10} is selected from an electron pair, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl, wherein when R_{10} is not an electron pair the compound of formula (III) is a quaternary amine cation with a pharmaceutically acceptable anion, X^-;

R_{11} and R_{12} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl;

R_{13} and R_{13a} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl, or R_{13} and R_{13a} are taken together with the carbon to which they are bound to form a 3- to 6-membered cycloalkyl; and

n is an integer defining the variable number of ring carbons carrying R_7 and R_8 and is selected from 1 to 4.

50. The compound of claim 49, wherein R_1 is hydrogen.

51. The compound of claim 49 or claim 50, wherein R_2 is hydrogen.

52. The compound of any of claims 49-51, wherein R_3 is hydrogen.

53. The compound of any of claims 49-52, wherein R_4 is hydrogen.

54. The compound of any of claims 49-53, wherein R_5 is hydrogen.

55. The compound of any of claims 49-54, wherein R_6 is hydrogen.

56. The compound of any of claims 49-55, wherein R_9 is an optionally substituted C_1-C_6 alkyl.

57. The compound of claim 56, wherein R_9 is an unsubstituted C_1-C_6 alkyl.

58. The compound of claim 57, wherein R_9 is methyl.

59. The compound of any of claims 49-58, wherein R_{10} is an electron pair.

60. The compound of any of claims 49-59, wherein R_7 is hydrogen.

61. The compound of any of claims 49-60, wherein R_8 is hydrogen.

62. The compound of any of claims 49-61, wherein R_{13} is hydrogen.

63. The compound of any of claims 49-62, wherein R_{13a} is hydrogen.

64. The compound of any of claims 49-61, wherein R_{13} and R_{13a} are taken together with the carbon to which they are bound to form a cyclopropyl group.

65. The compound of any of claims 49-61, wherein R_{13} and R_{13a} are taken together with the carbon to which they are bound to form a cyclobutyl group.

66. The compound of any of claims 49-61, wherein R_{13} and R_{13a} are taken together with the carbon to which they are bound to form a cyclopentyl group.

67. The compound of any of claims 49-61, wherein R_{13} and R_{13a} are taken together with the carbon to which they are bound to form a cyclohexyl group.

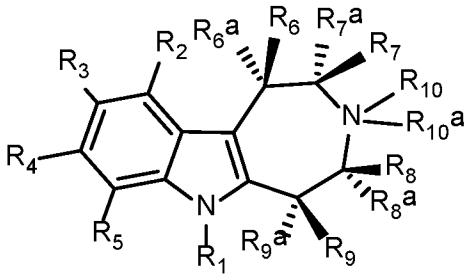
68. The compound of any of claims 49-67, wherein n = 1.

69. The compound of any of claims 49-67, wherein n = 2.

70. The compound of any of claims 49-67, wherein n = 3.

71. The compound of any of claims 49-67, wherein n = 4.

72. A compound of formula (IV):



(IV)

wherein:

R_1 is selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted aryl, $-OR_{11}$, $-C(O)R_{11}$, $-C(O)OR_{11}$, $-SO_2R_{11}$, and $-C(O)N\ R_{11}R_{12}$;

R_2, R_3, R_4, R_5, R_6, R_{6a}, R_7, R_{7a}, R_8, R_{8a}, R_9, and R_{9a} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6-heteroalkyl, optionally substituted heteroaryl, optionally substituted aryl, halogen, hydroxy, $-OR_{11}$, $-OC(O)R_{11}$, $-OC(O)OR_{11}$, $-OSO_2R_{11}$, and $-OC(O)NR_{11}R_{12}$;

R_{10} is selected from an electron pair, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl, wherein when R_{10} is not an electron pair the compound of formula (IV) is a quaternary amine cation with a pharmaceutically acceptable anion, X^-;

R_{10a} is taken together with one of R_8, R_{8a}, R_9, or R_{9a} to form optionally substituted 3- to 6-membered heterocyclic ring; and

R_{11} and R_{12} are for each occurrence independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, and optionally substituted aryl.

73. The compound of claim 72, wherein at least one of R_2, R_3, R_4, or R_5 is selected from hydroxy, -OR_{11}, -$OC(O)R_{11}$, -$OC(O)OR_{11}$, -OSO_2R_{11}, and -$OC(O)NR_{11}R_{12}$.

74. The compound of claim 73, wherein at least one of R_2, R_3, R_4, or R_5 is selected from hydroxy and -OR_{11}.

75. The compound of claim 74, wherein at least one of R_2, R_3, R_4, or R_5 is -OR_{11}.

76. The compound of claim 75, wherein R_{11} is unsubstituted C_1-C_6 alkyl.

77. The compound of claim 76, wherein R_{11} is methyl.

78. The compound of any of claims 72-77, wherein R_3 is methoxy.

79. The compound of any of claims 72-78, wherein R_{10a} is taken together with R_8 to form an optionally substituted 3-membered heterocyclic ring.

80. The compound of any of claims 72-78, wherein R_{10a} is taken together with R_8 to form an optionally substituted 4-membered heterocyclic ring.

81. The compound of any of claims 72-78, wherein R_{10a} is taken together with R_8 to form an optionally substituted 5-membered heterocyclic ring.

82. The compound of any of claims 72-78, wherein R_{10a} is taken together with R_8 to form an optionally substituted 6-membered heterocyclic ring.

83. The compound of any of claims 72-78, wherein R_{10a} is taken together with R_9 to form an optionally substituted 4-membered heterocyclic ring.

84. The compound of any of claims 72-78, wherein R_{10a} is taken together with R_9 to form an optionally substituted 5-membered heterocyclic ring.

85. The compound of any of claims 72-78, wherein R_{10a} is taken together with R_9 to form an optionally substituted 6-membered heterocyclic ring.

86. The compound of any of claims 72-85, wherein the heterocyclic ring is unsubstituted.

87. The compound of any of claims 72-86, wherein R_{10} is a lone pair.

88. The compound of any of claims 72-87, wherein R_6 is hydrogen.

89. The compound of any of claims 72-88, wherein R_{6a} is hydrogen.

90. The compound of any of claims 72-89, wherein R_7 is hydrogen.

91. The compound of any of claims 72-90, wherein R_{7a} is hydrogen.

92. The compound of any of claims 72-91, wherein R_1 is hydrogen.

93. A composition comprising, consisting essentially of, or consisting of a compound according to any one of claims 1-92 and an excipient.

94. A pharmaceutical composition comprising, consisting essentially of, or consisting of a therapeutically effective amount of a compound according to any one of claims 1-92 and a pharmaceutically acceptable excipient.

95. A composition comprising, consisting essentially of, or consisting of as a first active component: a compound according to any one of claims 1-92; and as a second active component selected from (a) a serotonergic drug, (b) a purified psilocybin derivative, (c) one or two purified cannabinoids, and (d) a purified terpene; and a pharmaceutically acceptable excipient.

96. A composition comprising, consisting essentially of, or consisting of as a first active component: a compound according to any one of claims 1-92; and a second active component comprising an adrenergic drug or a dopaminergic drug; and a pharmaceutically acceptable excipient.

97. A composition comprising, consisting essentially of, or consisting of as a first active component: a compound according to any one of claims 1-92; and a second active component comprising a purified monoamine oxidase inhibitor; and a pharmaceutically acceptable excipient.

98. A composition comprising, consisting essentially of, or consisting of as a first active component: a compound according to any one of claims 1-92; and a second active component comprising a purified erinacine or a purified hericenone; and a pharmaceutically acceptable excipient.

99. A method of preventing or treating a psychological disorder comprising the steps of:

identifying a subject in need of treatment or prevention; and

administering to the subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1-92 or a composition according to any one of claims 93-98.

100. A method of preventing or treating inflammation and/or pain comprising the steps of:

identifying a subject in need of treatment or prevention; and

administering to the subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1-92 or a composition according to any one of claims 93-98.

101. A method of preventing or treating sexual health disorders comprising the steps of:

identifying a subject in need of treatment or prevention; and

administering to the subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1-92 or a composition according to any one of claims 93-98.

102. A method of preventing or treating women's health disorders comprising the steps of:

identifying a subject in need of treatment or prevention; and

administering to the subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1-92 or a composition according to any one of claims 93-98.

103. A method of modulating activity of a mitogen-activated protein kinase (MAPK), comprising administering a MAPK activity modulator composition comprising a compound according to any one of claims 1-92 or a composition according to any one of claims 93-98.

104. A method of modulating neurogenesis, comprising administering a neurogenesis modulator composition comprising a compound according to any one of claims 1-92 or a composition according to any one of claims 93-98.

105. A method of modulating neurite outgrowth, comprising administering a MAPK activity modulator composition comprising a compound according to any one of claims 1-92 or a composition according to any one of claims 93-98.

106. A method of treating and/or preventing a substance use disorder comprising the steps of:

identifying a subject in need of treatment or prevention; and

administering to the subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1-92 or a composition according to any one of claims 93-98.

107. The method of claim 106, wherein the substance use disorder is selected from the group consisting of opioid use disorder; cannabis or marijuana use disorder; nicotine use disorder; stimulant use disorder; sedative use disorder; hypnotic use disorder; anxiolytic use disorder; hallucinogen use disorder; phencyclidine use disorder; inhalant use disorder; caffeine use disorder; and alcohol use disorder.

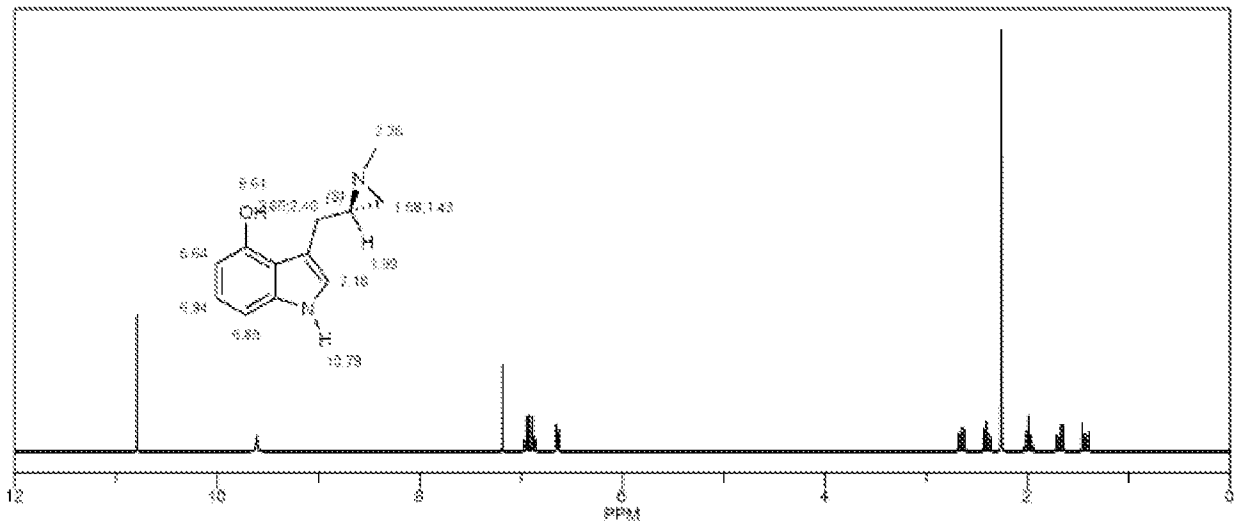


FIG. 1

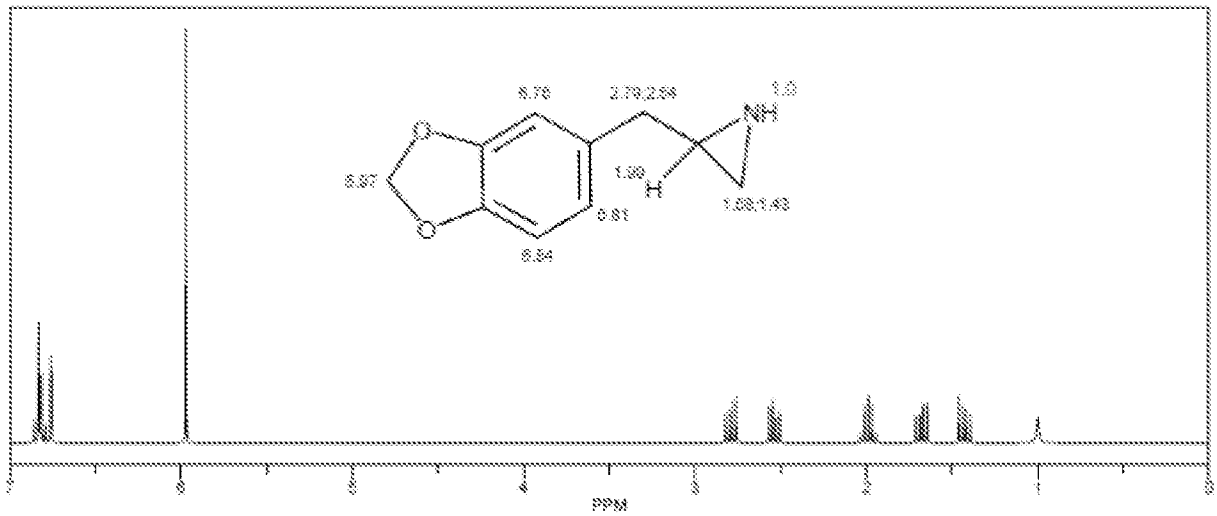


FIG. 2