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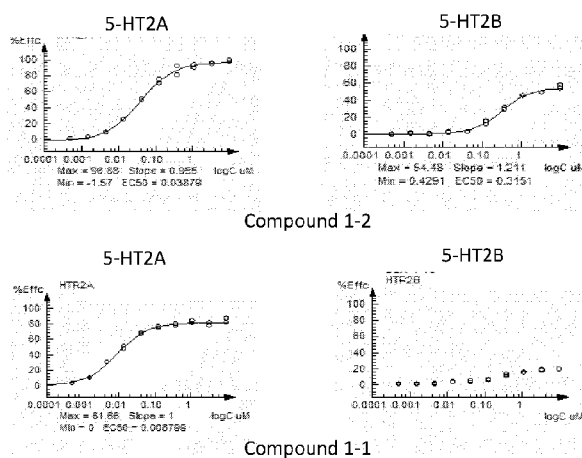
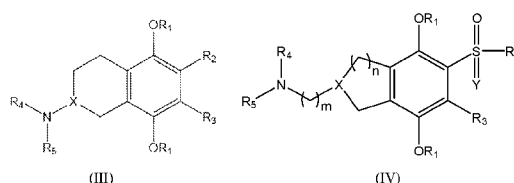


FIG. 1A



(57) **Abstract:** Provided herein are compounds of Formula (I), (I-A), (I-B), (II), (II-A), (II-B), (III), (III-A), (IV), and (IV-A), or pharmaceutically acceptable salt thereof described herein. Also provided herein are pharmaceutical compositions comprising a compound Formula (I), (I-A), (I-B), (II), (II-A), (II-B), (III), (III-A), (IV), and (IV-A), or pharmaceutically acceptable salt thereof, and methods of using a compound of Formula (I), (I-A), (I-B), (II), (II-A), (II-B), (III), (III-A), (IV), and (IV-A), or pharmaceutically acceptable salt thereof, e.g., in the treatment of a mental health disease or disorder.

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- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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AMINOTETRALINE ACTIVATORS OF SEROTONIN RECEPTORS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] The present application claims the benefit of priority to U.S. Provisional Application No. 63/294,030, filed December 27, 2021, the contents of which are hereby incorporated by reference in its entirety.

BACKGROUND

[0002] Psychedelics can be classified into three main classes: indoleamines, phenylalkylamines, and ergolines. The first class, indolamines include N,N-dimethyltryptamine (DMT), 5-methoxy-DMT (5-MeO-DMT), psilocybin and 4-hydroxy-DMT. The second class, phenylalkylamines, include mescaline, as well as synthetic mescaline analogs such as 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-bromoamphetamine (DOB). The third class are ergolines, such as LSD. The phenylalkylamines are selective agonists of 5-HT₂ receptors, including 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors. The indoleamines and ergolines act as partial agonists of 5-HT₁, 5-HT₂, 5-HT₆ and 5-HT₇ receptors. LSD and other ergolines also act upon D₁ and D₂ dopamine receptors and adrenergic receptors.

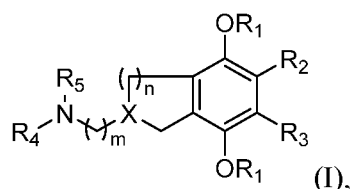
[0003] Activation of 5-HT_{2A} receptors located in cortical and subcortical structures of the brain are thought to mediate the subjective, behavioral, and psychological effects of psychedelics in both animals and humans. Serotonergic psychedelics have demonstrated potential for treating a range of mental health diseases or disorders.

[0004] There remains a need for compounds that act as agonists of serotonin receptors, such as the 5-HT_{2A} receptor as well as compositions and methods of use thereof.

SUMMARY

[0005] In one aspect, the present disclosure provides compounds which act as agonists of serotonin receptors e.g., the 5-HT_{2A} receptor, as well as compositions and methods of use thereof e.g., for the treatment of a mental health disease or disorder.

[0006] In embodiments, the present disclosure provides a compound of Formula (I):



or a pharmaceutically acceptable salt thereof; wherein,

R₁ is independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl;

R₂ and R₃ are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, CN, OR₁

S(O)NHR₁R₂, or SR₁;

R₄ and R₅ are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl;

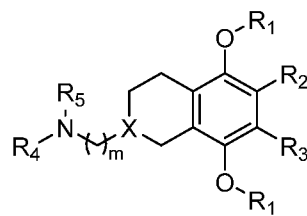
X is C or N;

m is 0, 1, 2 or 3; and

n is 0, 1, 2 or 3;

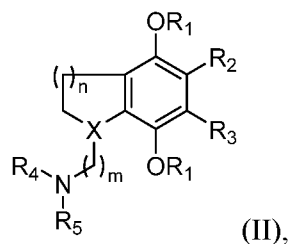
wherein the compound is not 5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; 5,8-dimethoxy-N-methyl-1,2,3,4-tetrahydronaphthalen-2-amine; or (5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-yl)methanamine.

[0007] In embodiments, the compound of Formula (I) is a compound of Formula (I-A):



wherein R₁, R₂, R₃, R₄, R₅, X and m have the definitions provided herein.

[0008] In embodiments, the present disclosure provides a compound of Formula (II):



or a pharmaceutically acceptable salt thereof; wherein,

R₁ is independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl;

R₂ and R₃ are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, CN, OR₁

S(O)NHR₁R₂, or SR₁;

R₄ and R₅ are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl;

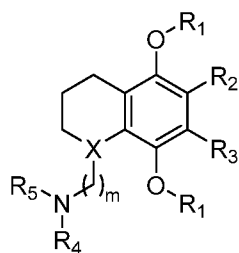
X is C or N;

m is 0, 1, 2 or 3; and

n is 0, 1, 2 or 3;

wherein the compound is not (5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methanamine.

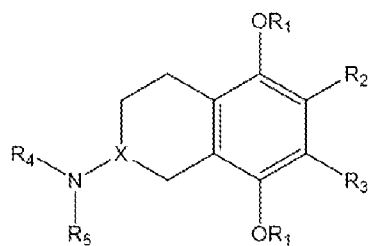
[0009] In embodiments, the compound of Formula (II) is a compound of Formula (II-A):



(II-A), wherein R₁, R₂, R₃, R₄, R₅, X and m have the definitions provided

herein.

[0010] In embodiments, the present disclosure provides a compound of Formula (III):



(III),

or a pharmaceutically acceptable salt thereof; wherein,

R₁ is independently methyl or C₂-C₆ fluoroalkyl;

R₂ and R₃ are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, CN, OR₇ or -S(O)(Y)R₆;

Y is =O or =NH;

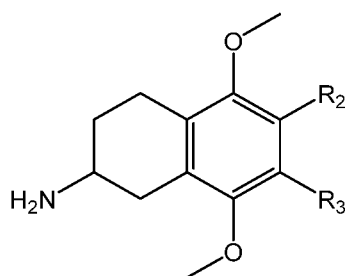
R₄ and R₅ are independently H or C₁-C₆ fluoroalkyl;

R₆ and R₇ are independently H, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl; and

X is CH or N;

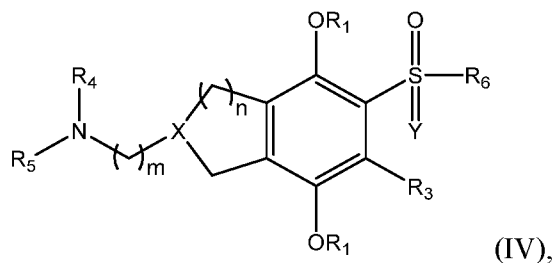
wherein the compound is not 5,8-dimethoxy-6-methyl-1,2,3,4-tetrahydronaphthalen-2-amine; 5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; 6-bromo-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; 7-bromo-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; 5,7,8-trimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; or 5,6,8-trimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine.

[0011] In embodiments, the present disclosure provides a compound of Formula (III-A):



(III-A), wherein R₂ and R₃ have definitions as provided herein.

[0012] In embodiments, the present disclosure provides a compound of Formula (IV):



or a pharmaceutically acceptable salt thereof; wherein,

R₁ is independently H, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl;

R₃ is H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, CN, OR₇ or SR₁;

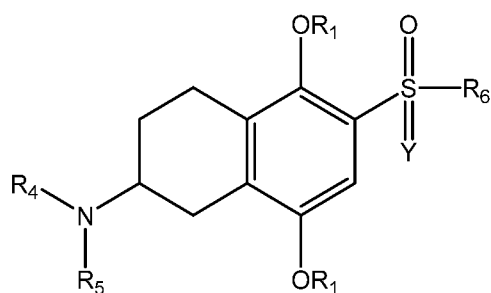
R₄ and R₅ are independently H, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl;

[0013] R₆ and R₇ are independently H, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl;

X is CH or N;

m is 0, 1, 2 or 3; and

n is 0, 1, 2 or 3. In embodiments, the present disclosure provides a compound of Formula (IV-A):



(IV-A), wherein R₁, R₄, R₅, R₆, and Y have the

definitions provided herein.

BRIEF DESCRIPTION OF THE FIGURES

[0014] FIG. 1A shows EC₅₀ profiles of Compounds 1-2 and 1-1, comparing 5-HT_{2A} and 5-HT_{2B} activity.

[0015] **FIG. 1B** shows EC₅₀ profiles of Compounds **1-2** and **1-1**, for comparing Gq and β -arrestin biased signaling pathways.

DETAILED DESCRIPTION

[0016] Throughout this disclosure, various patents, patent applications and publications are referenced. The disclosures of these patents, patent applications and publications in their entireties are incorporated into this disclosure by reference for all purposes in order to more fully describe the state of the art as known to those skilled therein as of the date of this disclosure. This disclosure will govern in the instance that there is any inconsistency between the patents, patent applications and publications cited and this disclosure.

Definitions

[0017] For convenience, certain terms employed in the specification, examples and claims are collected here. Unless defined otherwise, all technical and scientific terms used in this disclosure have the same meanings as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0018] The terms “administer,” “administering” or “administration” as used herein refer to administering a compound or pharmaceutically acceptable salt of the compound or a composition or formulation comprising the compound or pharmaceutically acceptable salt of the compound to a patient.

[0019] The term “treating” as used herein with regard to a patient or subject, refers to improving at least one symptom of the patient’s or subject’s disorder. In embodiments, treating can be improving, or at least partially ameliorating a disorder or one or more symptoms of a disorder.

[0020] The term “therapeutically effective” applied to dose or amount refers to that quantity of a compound or pharmaceutical formulation that is sufficient to result in a desired clinical benefit after administration to a patient or subject in need thereof.

[0021] The term “pharmaceutically acceptable salts” includes both acid and base addition salts. Pharmaceutically acceptable salts include those obtained by reacting the active compound functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methanesulfonic acid, camphorsulfonic acid, oxalic acid, maleic acid, succinic acid, citric acid, formic acid, hydrobromic acid, benzoic acid, tartaric acid, fumaric acid, salicylic acid, mandelic acid, carbonic acid, etc. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds

are those that form non-toxic acid addition salts, i.e., salts containing pharmaceutically acceptable anions, including but not limited to malate, oxalate, chloride, bromide, iodide, nitrate, acetate, tartrate, oleate, fumarate, formate, benzoate, glutamate, methanesulfonate, benzenesulfonate, and p-toluenesulfonate salts. Base addition salts include but are not limited to, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chlorprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris-(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, triethylamine, dibenzylamine, ephenamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, ethylamine, basic amino acids, e. g., lysine and arginine dicyclohexylamine and the like. Examples of metal salts include lithium, sodium, potassium, magnesium, calcium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methylammonium, dimethylammonium, trimethylammonium, ethylammonium, hydroxyethylammonium, diethylammonium, butylammonium, tetramethylammonium salts and the like. Examples of organic bases include lysine, arginine, guanidine, diethanolamine, choline and the like. Those skilled in the art will further recognize that acid addition salts may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods.

[0022] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, "C₁-C₆ alkyl" is intended to encompass C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅, and C₅₋₆ alkyl.

[0023] "Alkyl" or "alkyl group" refers to a fully saturated, straight or branched hydrocarbon chain having from one to twelve carbon atoms, and which is attached to the rest of the molecule by a single bond. Alkyls comprising any number of carbon atoms from 1 to 12 are included. An alkyl comprising up to 12 carbon atoms is a C₁-C₁₂ alkyl, an alkyl comprising up to 10 carbon atoms is a C₁-C₁₀ alkyl, an alkyl comprising up to 6 carbon atoms is a C₁-C₆ alkyl and an alkyl comprising up to 5 carbon atoms is a C₁-C₅ alkyl. A C₁-C₅ alkyl includes C₅ alkyls, C₄ alkyls, C₃ alkyls, C₂ alkyls and C₁ alkyl (*i.e.*, methyl). A C₁-C₆ alkyl includes all moieties described above for C₁-C₅ alkyls but also includes C₆ alkyls. A C₁-C₁₀ alkyl includes all moieties described above for C₁-C₅ alkyls and C₁-C₆ alkyls, but also includes C₇, C₈, C₉ and C₁₀ alkyls. Similarly, a C₁-C₁₂ alkyl includes all the foregoing moieties, but also includes C₁₁ and C₁₂ alkyls. Non-limiting examples of C₁-C₁₂ alkyl include methyl, ethyl, *n*-propyl, *i*-propyl, *sec*-propyl, *n*-butyl, *i*-butyl, *sec*-butyl, *t*-butyl, *n*-pentyl, *t*-amyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-

nonyl, *n*-decyl, *n*-undecyl, and *n*-dodecyl. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[0024] “Alkoxy” refers to a group of the formula -OR_a where R_a is an alkyl, alkenyl or alkynyl as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkoxy group can be optionally substituted.

[0025] “Haloalkyl” refers to an alkyl, as defined above, that is substituted by one or more halo radicals, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. Unless stated otherwise specifically in the specification, a haloalkyl group can be optionally substituted.

[0026] The term “substituted” used herein means any of the groups described herein (*e.g.*, alkyl, alkenyl, alkynyl, alkoxy, aryl, cycloalkyl, cycloalkenyl, cycloalkynyl, haloalkyl, heterocyclyl, and/or heteroaryl) wherein at least one hydrogen atom is replaced by a bond to a non-hydrogen atoms such as, but not limited to: a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, and ester groups; a sulfur atom in groups such as thiol groups, thioalkyl groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as trialkylsilyl groups, dialkylarylsilyl groups, alkylarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. “Substituted” also means any of the above groups in which one or more hydrogen atoms are replaced by a higher-order bond (*e.g.*, a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; and nitrogen in groups such as imines, oximes, hydrazones, and nitriles. For example, “substituted” includes any of the above groups in which one or more hydrogen atoms are replaced

with -NR_gR_h, -NR_gC(=O)R_h, -NR_gC(=O)NR_gR_h, -NR_gC(=O)OR_h, -NR_gSO₂R_h, -OC(=O)NR_gR_h, -OR_g, -SR_g, -SOR_g, -SO₂R_g, -OSO₂R_g, -SO₂OR_g, =NSO₂R_g, and -SO₂NR_gR_h. “Substituted” also means any of the above groups in which one or more hydrogen atoms are replaced with -C(=O)R_g, -C(=O)OR_g, -C(=O)NR_gR_h, -CH₂SO₂R_g, -CH₂SO₂NR_gR_h. In the foregoing, R_g and R_h are the same or different and independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl. “Substituted” further means any of the above groups in which one or more hydrogen atoms are replaced by a bond to an amino, cyano,

hydroxyl, imino, nitro, oxo, thioxo, halo, alkyl, alkenyl, alkynyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl group. In addition, each of the foregoing substituents can also be optionally substituted with one or more of the above substituents.

Compounds

[0027] In one aspect, the present disclosure provides compounds that are agonists of the 5-HT_{2A} receptor. In embodiments, the compounds are full agonists of the 5-HT_{2A} receptor. In embodiments, the compounds are partial agonists of the 5-HT_{2A} receptor. In embodiments, the compounds selectively bind to the 5-HT_{2A} receptor. In embodiments, the compounds of the present disclosure are compounds of Formula (I), (I-A), (I-B), (II), (II-A), (II-B), (III), (III-A), (IV) and (IV-A).

[0028] Activation of 5-HT_{2A} receptors located in cortical and subcortical structures of the brain are thought to mediate the subjective, behavioral and psychological effects of psychedelics in both animals and humans. In rodents, psychedelics have been shown to elicit a ‘head twitch response’ which has been demonstrated to be a direct and selective consequence of 5-HT_{2A} activation over other similar serotonin receptors including both 5-HT_{2C} and 5-HT_{2B} (Halberstadt, A. L., *Behav. Brain Res.* 277, 99–120 (2015); Winter et al., *Pharmacol. Biochem. Behav.* 87, 472–480 (2007); Benneyworth et al., *Psychopharmacology* 179, 854–862 (2005); Titeler et al., *Psychopharmacology*, 94, 213–216 (1988)). Similar observations have been made in humans where the administration of ketanserin, a 5-HT_{2A} receptor antagonist, blocked the majority of subjective effects induced by DMT, psilocylin and LSD (Preller, *Curr. Biol.* 27, 451–457 (2017).; Preller, *J. Neurosci.* 38, 3603–3611 (2018).; Kraehenmann, *Front. Pharmacol.* 8, 814 (2017).; Kraehenmann, *Psychopharmacology* 234, 2031–2046 (2017).; Vollenweider, *Neuroreport* 9, 3897–3902 (1998); Preller, *Acad. Sci. USA* 113, 5119–5124 (2016).; Valle, *Eur. Neuropsychopharm* 26, 1161–1175 (2016).). In addition, psychedelic effects elicited by psilocybin have correlated with 5-HT_{2A} receptor occupancy as measured by positron emission tomography in the prefrontal cortex (PFC) and other cortical regions in humans (Madsen, *Neuropsychopharmacology* 44, 1328–1334 (2019).). While 5-HT_{2A} is the predominant driver of psychedelic effects in humans, other serotonin receptors, like 5-HT_{1A}, are likely contributing to the overall psychedelic experience including both visual and attention-disrupting effects in humans (Pokorny et al., *Eur. Neuropsychopharmacol.* 26, 756–766 (2016).; Carter et al., *Neuropsychopharmacology* 30, 1154–1162 (2005).).

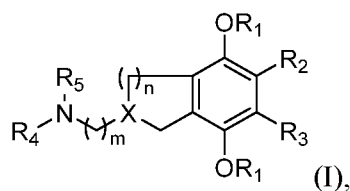
[0029] Biased signaling consequences of 5-HT_{2A} activation by various agonists strongly impact whether or not a compound will be hallucinogenic or non-hallucinogenic. For example, LSD and lisuride both activate the 5-HT_{2A} receptor but in slightly different ways which result in the activation of different intracellular signaling cascades. LSD and lisuride have been shown to activate canonical Gq-based signaling downstream of 5-HT_{2A}, but only LSD stimulated the expression of early growth response proteins (EGR1 and EGR2) by activating Gi/o subunits and the SRC protein kinase (Gonzalez-Maeso et al, Neuron 53, 439–452 (2007)). Differential functional selectivity has been shown for several phenalkylamine psychedelics which were found to be biased 5-HT_{2A} agonists (Pottie et al, Biochemical pharmacology, 182, 114251, 2020). The compounds, including 25H-NBF, 25H-NBMD, 25H-NBOH and 25H-NBOMe showed a statistically significant preference towards the recruitment of β -arrestin 2 over miniG α q, as compared to the reference psychedelic substance LSD.

[0030] Differential biased agonism elicited across multiple classes of psychedelics warrants further investigation to identify whether this functional selectivity may provide compounds with greater selectivity, fewer side effects, greater neuroplastic effects and improved therapeutic benefit.

[0031] Studies of aminotetralines such as lysergic acid congeners demonstrated that while 2-amino-5,8-dimethoxy-6-methyl-1,2,3,4-tetrahydronaphthalene has activity at 5-HT receptors, the compound failed to elicit common psychedelic side effects in rats in comparison to mescaline or 2,5-dimethoxy-4-methylphenylisopropylamine at similar doses (Nichols et al, 1974). Additional drug discrimination studies in LSD-trained rats and MDMA-trained rats found that stimulus generalization did not occur with any of the 2-aminotetralins studied suggesting that consistent with previous studies the tetralin congeners are most likely not hallucinogenic (Nichols et al, 1990).

Formula (I):

[0032] In embodiments, the present disclosure provides a compound of Formula (I):



or a pharmaceutically acceptable salt thereof; wherein,

R₁ is independently H, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl;

R₂ and R₃ are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, CN, OR₁, S(O)NHR₁R₂, or SR₁;

R₄ and R₅ are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl;

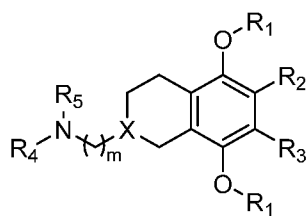
X is CH or N;

m is 0, 1, 2 or 3; and

n is 0, 1, 2 or 3;

wherein the compound is not 5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; 5,8-dimethoxy-N-methyl-1,2,3,4-tetrahydronaphthalen-2-amine; or (5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-yl)methanamine.

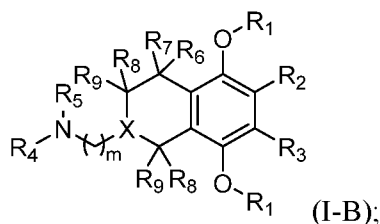
[0033] In embodiments, the present disclosure provides a compound of Formula (I-A):



(I-A), wherein R₁, R₂, R₃, R₄, R₅, X and m have the definitions

provided herein.

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



(I-B);

wherein,

R₆, R₇, R₈, and R₉ are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, CN, or R₆ and R₇ taken together with the atoms to which they are attached form a C₃-C₇ carbocycle, or R₈, and R₉, taken together with the atoms to which they are attached form a C₃-C₇ carbocycle; and wherein when X is N, R₈ and R₉ are not halogen or CN.

[0035] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₁ is independently C₁-C₆ alkyl.

[0036] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₁ is methyl.

[0037] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₂ and R₃ are independently H or C₁-C₆ alkyl.

[0038] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₂ and R₃ are independently H, methyl or ethyl.

[0039] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₂ and R₃ are independently H or C₁-C₆ fluoroalkyl.

[0040] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₂ and R₃ are independently H or trifluoromethyl.

[0041] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₂ and R₃ are independently H, F, Cl, Br, I or CN.

[0042] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₂ and R₃ are independently H or halogen.

[0043] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₂ and R₃ are independently H or I.

[0044] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₂ and R₃ are independently H or OR₁.

[0045] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₂ and R₃ are independently H or SR₁.

[0046] In embodiments of the compounds of Formula (I), (I-A) or (I-B), at least one of R₂ and R₃ is H.

[0047] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₂ and R₃ are independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, halogen, cyano, OR₁ or SR₁, wherein at least one of R₂ and R₃ is H.

[0048] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₂ and R₃ are independently H, C₁-C₆ alkyl, halogen, cyano, OR₁ or SR₁, wherein at least one of R₂ and R₃ is H.

[0049] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₂ and R₃ are independently H, halogen, C₁-C₆ alkyl, or C₁-C₆ haloalkyl, wherein at least one of R₂ and R₃ is H.

[0050] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₂ and R₃ are independently H, halogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl, wherein at least one of R₂ and R₃ is H.

[0051] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₂ and R₃ are independently H, C₁-C₆ alkyl, or C₁-C₆ haloalkyl, wherein at least one of R₂ and R₃ is H.

[0052] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₂ and R₃ are independently H, C₁-C₃ alkyl, or C₁-C₃ haloalkyl, wherein at least one of R₂ and R₃ is H.

[0053] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₂ and R₃ are independently H, or C₁-C₆ alkyl, wherein at least one of R₂ and R₃ is H.

[0054] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₂ and R₃ are independently H, or C₁-C₃ alkyl, wherein at least one of R₂ and R₃ is H.

[0055] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₂ and R₃ are independently H, -CF₃, methyl or ethyl, wherein at least one of R₂ and R₃ is H.

[0056] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₂ and R₃ are independently H, methyl or ethyl, wherein at least one of R₂ and R₃ is H.

[0057] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₂ and R₃ are independently H or methyl, wherein at least one of R₂ and R₃ is H.

[0058] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₄ and R₅ are independently H, methyl, ethyl or propyl.

[0059] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₄ and R₅ are independently H or methyl.

[0060] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₄ and R₅ are independently H or methyl.

[0061] In embodiments of the compounds of Formula (I), (I-A) or (I-B), at least one of R₄ and R₅ is H.

[0062] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₄ is H.

[0063] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₄ is methyl.

[0064] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₄ is ethyl.

[0065] In embodiments of the compounds of Formula (I), (I-A) or (I-B), R₅ is H.

[0066] In embodiments of the compounds of Formula (I), (I-A) or (I-B), X is CH.

[0067] In embodiments of the compounds of Formula (I), (I-A) or (I-B), X is N.

[0068] In embodiments of the compounds of Formula (I), (I-A) or (I-B), m is 0.

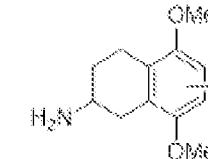
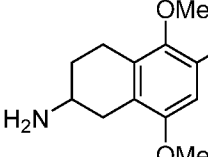
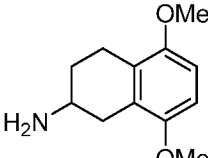
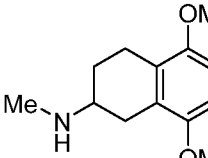
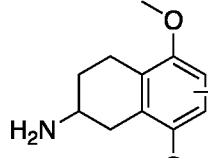
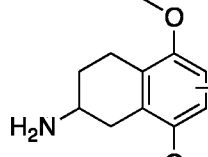
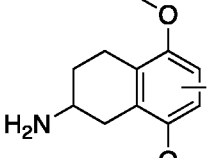
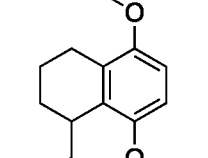
[0069] In embodiments of the compounds of Formula (I), (I-A) or (I-B), m is 1.

[0070] In embodiments of the compounds of Formula (I), n is 2.

[0071] In embodiments, the present disclosure provides a compound selected from Table 1.

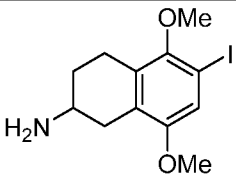
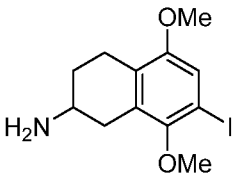
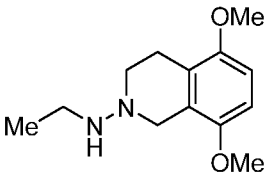
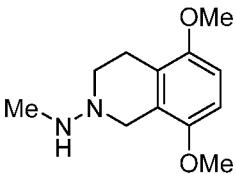
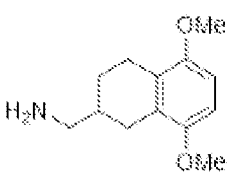
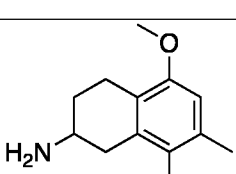
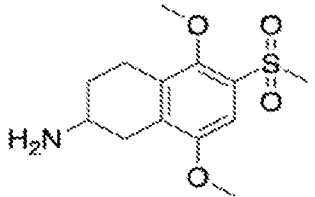
[0072] In embodiments, the present disclosure provides a compound selected from Table 1 or a pharmaceutically acceptable salt thereof.

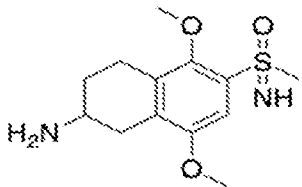
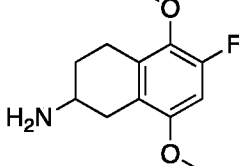
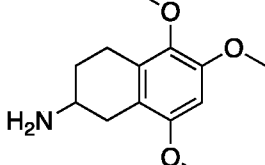
Table 1. Compounds

No.	Structure	5HT2A activation (%) max @ 30 and 03 μ M
1-1		72.2/55.4
1-2		81.9/60.9
1-3		67.1/12.1
1-4		20.3/8.5
1-5		82.7/73.8
1-6		66.6/64
1-7		-
3-1		53/1.5

[0073] In embodiments, the present disclosure provides a compound selected from Table 2 or a pharmaceutically acceptable salt thereof.

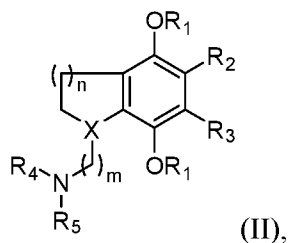
Table 2. Compounds

No.	Structure
2-1	
2-2	
2-3	
2-4	
2-5	
2-6	
2-7	

No.	Structure
2-8	
2-9	
2-10	

Formula (II):

[0074] In embodiments, the present disclosure provides a compound of Formula (II):



or a pharmaceutically acceptable salt thereof; wherein,

R₁ is independently H, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl;

R₂ and R₃ are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, CN, S(O)NHR₁R₂, OR₁ or SR₁;

R₄ and R₅ are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl;

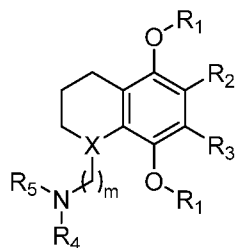
X is CH or N;

m is 0, 1, 2 or 3; and

n is 0, 1, 2 or 3;

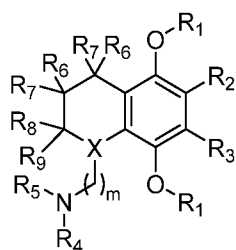
wherein the compound is not (5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methanamine.

[0075] In embodiments, the present disclosure provides a compound of Formula (II-A):



(II-A), wherein R₁, R₂, R₃, R₄, R₅, X and m have the definitions provided herein.

[0076] In embodiments, the present disclosure provides a compound of Formula (II-B):



(II-B);

wherein,

R₆, R₇, R₈, and R₉ are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, CN, or R₆ and R₇ taken together with the atoms to which they are attached form a C₃-C₇ carbocycle, or R₈, and R₉ taken together with the atoms to which they are attached form a C₃-C₇ carbocycle; and

wherein X is N, R₈ and R₉ are not halogen or CN.

[0077] R₂ and R₃ are S(O)NHR₁R₂,

[0078] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₁ is independently C₁-C₆ alkyl.

[0079] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₁ is methyl.

[0080] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₂ and R₃ are independently H or C₁-C₆ alkyl.

[0081] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₂ and R₃ are independently H, methyl or ethyl.

[0082] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₂ and R₃ are independently H or C₁-C₆ fluoroalkyl.

[0083] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₂ and R₃ are independently H or trifluoromethyl.

[0084] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₂ and R₃ are independently H, F, Cl, Br, I or CN.

[0085] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₂ and R₃ are independently H or halogen.

[0086] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₂ and R₃ are independently H or I.

[0087] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₂ and R₃ are independently H or OR₁.

[0088] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₂ and R₃ are independently H or SR₁.

[0089] In embodiments of the compounds of Formula (II), (II-A) or (II-B), at least one of R₂ and R₃ is H.

[0090] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₂ and R₃ are independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, halogen, cyano, OR₁ or SR₁, wherein at least one of R₂ and R₃ is H.

[0091] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₂ and R₃ are independently H, C₁-C₆ alkyl, halogen, cyano, OR₁ or SR₁, wherein at least one of R₂ and R₃ is H.

[0092] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₂ and R₃ are independently H, halogen, C₁-C₆ alkyl, or C₁-C₆ haloalkyl, wherein at least one of R₂ and R₃ is H.

[0093] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₂ and R₃ are independently H, halogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl, wherein at least one of R₂ and R₃ is H.

[0094] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₂ and R₃ are independently H, C₁-C₆ alkyl, or C₁-C₆ haloalkyl, wherein at least one of R₂ and R₃ is H.

[0095] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₂ and R₃ are independently H, C₁-C₃ alkyl, or C₁-C₃ haloalkyl, wherein at least one of R₂ and R₃ is H.

[0096] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₂ and R₃ are independently H, or C₁-C₆ alkyl, wherein at least one of R₂ and R₃ is H.

[0097] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₂ and R₃ are independently H, or C₁-C₃ alkyl, wherein at least one of R₂ and R₃ is H.

[0098] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₂ and R₃ are independently H, -CF₃, methyl or ethyl, wherein at least one of R₂ and R₃ is H.

[0099] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₂ and R₃ are independently H, methyl or ethyl, wherein at least one of R₂ and R₃ is H.

[0100] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₂ and R₃ are independently H or methyl, wherein at least one of R₂ and R₃ is H.

[0101] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₄ and R₅ are independently H, methyl, ethyl or propyl.

[0102] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₄ and R₅ are independently H or methyl.

[0103] In embodiments of the compounds of Formula (II), (II-A) or (II-B), at least one of R₄ and R₅ is H.

[0104] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₄ is H.

[0105] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₄ is methyl.

[0106] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₄ is ethyl.

[0107] In embodiments of the compounds of Formula (II), (II-A) or (II-B), R₅ is H.

[0108] In embodiments of the compounds of Formula (II), (II-A) or (II-B), X is CH.

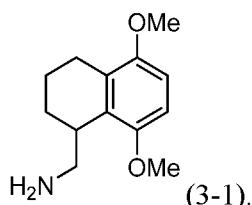
[0109] In embodiments of the compounds of Formula (II), (II-A) or (II-B), X is N.

[0110] In embodiments of the compounds of Formula (II), (II-A) or (II-B), m is 0.

[0111] In embodiments of the compounds of Formula (II), (II-A) or (II-B), m is 1.

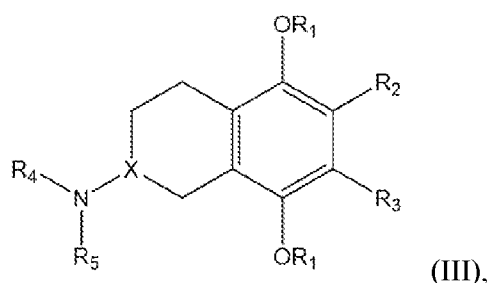
[0112] In embodiments of the compounds of Formula (II), n is 2.

[0113] In embodiments, the present disclosure provides compound (3-1) or a pharmaceutically acceptable salt thereof:



Formula (III):

[0114] In embodiments, the present disclosure provides a compound of Formula (III):



or a pharmaceutically acceptable salt thereof; wherein,

R₁ is independently methyl or C₂-C₆ fluoroalkyl;

R₂ and R₃ are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, CN, OR₇ or -S(O)(Y)R₆;

Y is =O or =NH;

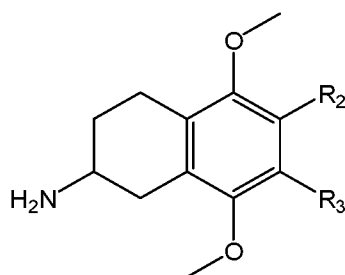
R₄ and R₅ are independently H or C₁-C₆ fluoroalkyl;

R₆ and R₇ are independently H, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl; and

X is CH or N;

wherein the compound is not 5,8-dimethoxy-6-methyl-1,2,3,4-tetrahydronaphthalen-2-amine; 5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; 6-bromo-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; 7-bromo-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; 5,7,8-trimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; or 5,6,8-trimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine.

[0115] In embodiments, the present disclosure provides a compound of Formula (III-A):



[0116] In embodiments of the compounds of Formula (III), R₁ is methyl.

[0117] In embodiments of the compounds of Formula (III), R₁ is C₂-C₆ fluoroalkyl.

[0118] In embodiments of the compounds of Formula (III) or (III-A), R₂ is H.

[0119] In embodiments of the compounds of Formula (III) or (III-A), R₂ is halogen.

[0120] In embodiments of the compounds of Formula (III) or (III-A), R₂ is F, Cl, or I.

[0121] In embodiments of the compounds of Formula (III) or (III-A), R₂ is CN.

[0122] In embodiments of the compounds of Formula (III) or (III-A), R₂ is -S(O)(Y)R₆.

- [0123] In embodiments of the compounds of Formula (III) or (III-A), R₂ is -S(O)₂R₆.
- [0124] In embodiments of the compounds of Formula (III) or (III-A), R₂ is -S(O)₂R₆, wherein R₆ is H or C₁-C₆ alkyl.
- [0125] In embodiments of the compounds of Formula (III) or (III-A), R₂ is -S(O)₂R₆, wherein R₆ is H or C₁-C₃ alkyl.
- [0126] In embodiments of the compounds of Formula (III) or (III-A), R₂ is -S(O)₂R₆, wherein R₆ is H or C₁-C₆ fluoroalkyl.
- [0127] In embodiments of the compounds of Formula (III) or (III-A), R₂ is -S(O)₂R₆, wherein R₆ is H or C₁-C₃ fluoroalkyl.
- [0128] In embodiments of the compounds of Formula (III) or (III-A), R₂ is -S(O)₂R₆, wherein R₆ is C₁-C₆ alkyl or C₁-C₆ fluoroalkyl.
- [0129] In embodiments of the compounds of Formula (III) or (III-A), R₂ is -S(O)(NH)R₆.
- [0130] In embodiments of the compounds of Formula (III) or (III-A), R₂ is -S(O)(NH)R₆, wherein R₆ is H or C₁-C₆ alkyl.
- [0131] In embodiments of the compounds of Formula (III) or (III-A), R₂ is -S(O)(NH)R₆, wherein R₆ is H or C₁-C₃ alkyl.
- [0132] In embodiments of the compounds of Formula (III) or (III-A), R₂ is -S(O)(NH)R₆, wherein R₆ is H or C₁-C₆ fluoroalkyl.
- [0133] In embodiments of the compounds of Formula (III) or (III-A), R₂ is -S(O)(NH)R₆, wherein R₆ is H or C₁-C₃ fluoroalkyl.
- [0134] In embodiments of the compounds of Formula (III) or (III-A), R₂ is -S(O)(NH)R₆, wherein R₆ is C₁-C₆ alkyl or C₁-C₆ fluoroalkyl.
- [0135] In embodiments of the compounds of Formula (III) or (III-A), R₂ is -S(O)₂H.
- [0136] In embodiments of the compounds of Formula (III) or (III-A), R₂ is -S(O)(NH)H.
- [0137] In embodiments of the compounds of Formula (III) or (III-A), R₂ is -S(O)₂CH₃.
- [0138] In embodiments of the compounds of Formula (III) or (III-A), R₂ is -S(O)(NH)CH₃.
- [0139] In embodiments of the compounds of Formula (III) or (III-A), R₃ is H.
- [0140] In embodiments of the compounds of Formula (III) or (III-A), R₃ is halogen.
- [0141] In embodiments of the compounds of Formula (III) or (III-A), R₃ is F, Cl, or I.
- [0142] In embodiments of the compounds of Formula (III) or (III-A), R₃ is CN.
- [0143] In embodiments of the compounds of Formula (III) or (III-A), R₃ is -S(O)(Y)R₆.
- [0144] In embodiments of the compounds of Formula (III) or (III-A), R₃ is -S(O)₂R₆.

[0145] In embodiments of the compounds of Formula (III) or (III-A), R₃ is -S(O)₂R₆, wherein R₆ is H or C₁-C₆ alkyl.

[0146] In embodiments of the compounds of Formula (III) or (III-A), R₃ is -S(O)₂R₆, wherein R₆ is H or C₁-C₃ alkyl.

[0147] In embodiments of the compounds of Formula (III) or (III-A), R₃ is -S(O)₂R₆, wherein R₆ is H or C₁-C₆ fluoroalkyl.

[0148] In embodiments of the compounds of Formula (III) or (III-A), R₃ is -S(O)₂R₆, wherein R₆ is H or C₁-C₃ fluoroalkyl.

[0149] In embodiments of the compounds of Formula (III), R₃ is -S(O)₂R₆, wherein R₆ is C₁-C₆ alkyl or C₁-C₆ fluoroalkyl.

[0150] In embodiments of the compounds of Formula (III) or (III-A), R₃ is -S(O)(NH)R₆.

[0151] In embodiments of the compounds of Formula (III) or (III-A), R₃ is -S(O)(NH)R₆, wherein R₆ is H or C₁-C₆ alkyl.

[0152] In embodiments of the compounds of Formula (III) or (III-A), R₃ is -S(O)(NH)R₆, wherein R₆ is H or C₁-C₃ alkyl.

[0153] In embodiments of the compounds of Formula (III) or (III-A), R₃ is -S(O)(NH)R₆, wherein R₆ is H or C₁-C₆ fluoroalkyl.

[0154] In embodiments of the compounds of Formula (III) or (III-A), R₃ is -S(O)(NH)R₆, wherein R₆ is H or C₁-C₃ fluoroalkyl.

[0155] In embodiments of the compounds of Formula (III) or (III-A), R₃ is -S(O)(NH)R₆, wherein R₆ is C₁-C₆ alkyl or C₁-C₆ fluoroalkyl.

[0156] In embodiments of the compounds of Formula (III) or (III-A), R₃ is -S(O)₂H.

[0157] In embodiments of the compounds of Formula (III) or (III-A), R₃ is -S(O)(NH)H.

[0158] In embodiments of the compounds of Formula (III) or (III-A), R₃ is -S(O)₂CH₃.

[0159] In embodiments of the compounds of Formula (III) or (III-A), R₃ is -S(O)(NH)CH₃.

[0160] In embodiments of the compounds of Formula (III) or (III-A), R₂ and R₃ are H.

[0161] In embodiments of the compounds of Formula (III) or (III-A), R₂ and R₃ are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, CN, OR₇ or -S(O)(Y)R₆, wherein at least one of R₂ and R₃ is H.

[0162] In embodiments of the compounds of Formula (III) or (III-A), R₂ and R₃ are independently H, C₁-C₆ fluoroalkyl, halogen, CN, OR₇ or -S(O)(Y)R₆, wherein at least one of R₂ and R₃ is H.

[0163] In embodiments of the compounds of Formula (III) or (III-A), R₂ and R₃ are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, CN, OR₇ or -S(O)(Y)R₆, wherein at least one of R₂ and R₃ is H.

[0164] In embodiments of the compounds of Formula (III) or (III-A), R₂ and R₃ are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, OR₇ or -S(O)(Y)R₆, wherein at least one of R₂ and R₃ is H.

[0165] In embodiments of the compounds of Formula (III) or (III-A), R₂ and R₃ are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, CN, or -S(O)(Y)R₆, wherein at least one of R₂ and R₃ is H.

[0166] In embodiments of the compounds of Formula (III) or (III-A), R₂ and R₃ are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, CN, or OR₇, wherein at least one of R₂ and R₃ is H.

[0167] In embodiments of the compounds of Formula (III) or (III-A), R₂ and R₃ are independently H, halogen, CN, OR₇ or -S(O)(Y)R₆, wherein at least one of R₂ and R₃ is H.

[0168] In embodiments of the compounds of Formula (III) or (III-A), R₂ and R₃ are independently H, CN, OR₇ or -S(O)(Y)R₆, wherein at least one of R₂ and R₃ is H.

[0169] In embodiments of the compounds of Formula (III) or (III-A), R₂ and R₃ are independently H, OR₇ or -S(O)(Y)R₆, wherein at least one of R₂ and R₃ is H.

[0170] In embodiments of the compounds of Formula (III) or (III-A), R₂ and R₃ are independently H or -S(O)(Y)R₆, wherein at least one of R₂ and R₃ is H.

[0171] In embodiments of the compounds of Formula (III) or (III-A), R₂ and R₃ are independently H, C₁-C₆ alkyl, halogen, CN, or -S(O)(Y)R₆, wherein at least one of R₂ and R₃ is H.

[0172] In embodiments of the compounds of Formula (III) or (III-A), R₂ and R₃ are independently H, halogen, CN, or -S(O)(Y)R₆, wherein at least one of R₂ and R₃ is H.

[0173] In embodiments of the compounds of Formula (III), X is CH.

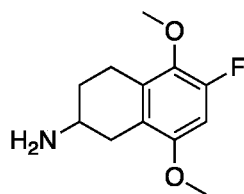
[0174] In embodiments of the compounds of Formula (III), X is N.

[0175] In embodiments of the compounds of Formula (III), R₄ is H.

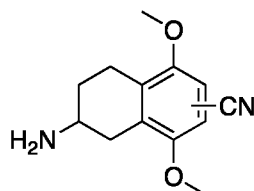
[0176] In embodiments of the compounds of Formula (III), R₅ is H.

[0177] In embodiments of the compounds of Formula (III), R₄ and R₅ are each independently H.

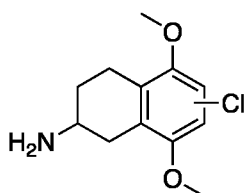
[0178] In embodiments of the compounds of Formula (III) or (III-A), the compound has the following chemical formula:



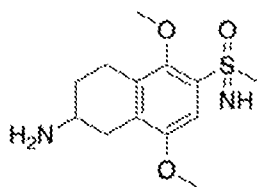
Compound (2-9);



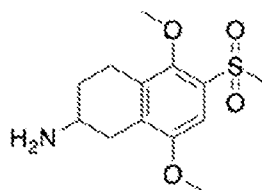
Compound (1-7);



Compound (1-6);



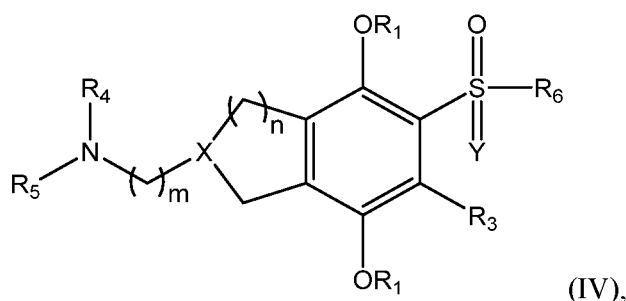
Compound (2-7); or



Compound (2-8).

Formula (IV):

[0179] In embodiments, the present disclosure provides compounds of Formula (IV):



or a pharmaceutically acceptable salt thereof; wherein,

R₁ is independently H, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl;

R₃ is H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, CN, OR₇ or SR₁;

R₄ and R₅ are independently H, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl;

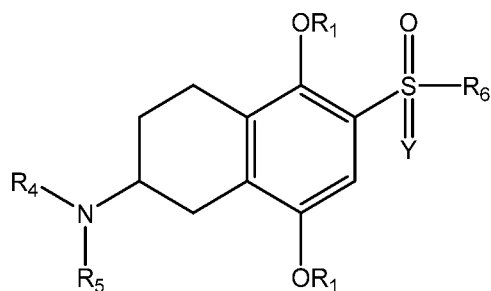
R₆ and R₇ are independently H, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl;

X is CH or N;

m is 0, 1, 2 or 3; and

n is 0, 1, 2 or 3.

[0180] In embodiments, the present disclosure provides a compound of Formula (IV-A):



(IV-A), wherein R₁, R₄, R₅, R₆, and Y have the

definitions provided herein.

[0181] In embodiments of the compounds of Formula (IV) or (IV-A), Y is =O.

[0182] In embodiments of the compounds of Formula (IV) or (IV-A), Y is =NH.

[0183] In embodiments of the compounds of Formula (IV) or (IV-A), R₁ is C₁-C₆ alkyl.

[0184] In embodiments of the compounds of Formula (IV) or (IV-A), R₁ is C₁-C₃ alkyl.

[0185] In embodiments of the compounds of Formula (IV) or (IV-A), R₁ is methyl.

[0186] In embodiments of the compounds of Formula (IV) or (IV-A), R₁ is H.

[0187] In embodiments of the compounds of Formula (IV) or (IV-A), R₁ is C₁-C₆ fluoroalkyl.

[0188] In embodiments of the compounds of Formula (IV) or (IV-A), R₁ is independently C₁-C₆ alkyl or C₁-C₆ fluoroalkyl.

[0189] In embodiments of the compounds of Formula (IV) or (IV-A), R₁ is independently H or C₁-C₆ fluoroalkyl.

[0190] In embodiments of the compounds of Formula (IV) or (IV-A), R₁ is independently H or C₁-C₆ alkyl.

[0191] In embodiments of the compounds of Formula (IV) or (IV-A), R₁ is independently C₁-C₃ alkyl or C₁-C₃ fluoroalkyl.

[0192] In embodiments of the compounds of Formula (IV) or (IV-A), R₁ is independently H or C₁-C₃ fluoroalkyl.

[0193] In embodiments of the compounds of Formula (IV) or (IV-A), R₁ is independently H or C₁-C₃ alkyl.

[0194] In embodiments of the compounds of Formula (IV) or (IV-A), R₁ is independently H or methyl.

[0195] In embodiments of the compounds of Formula (IV), R₃ is H.

[0196] In embodiments of the compounds of Formula (IV), R₃ is halogen.

[0197] In embodiments of the compounds of Formula (IV), R₃ is I, Br, Cl, or F.

[0198] In embodiments of the compounds of Formula (IV), R₃ is C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, CN, OR₇ or SR₁.

[0199] In embodiments of the compounds of Formula (IV), R₃ is H, C₁-C₆ fluoroalkyl, halogen, CN, OR₇ or SR₁.

[0200] In embodiments of the compounds of Formula (IV), R₃ is H, C₁-C₆ alkyl, halogen, CN, OR₇ or SR₁.

[0201] In embodiments of the compounds of Formula (IV), R₃ is H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, CN, OR₇ or SR₁.

[0202] In embodiments of the compounds of Formula (IV), R₃ is H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, OR₇ or SR₁.

[0203] In embodiments of the compounds of Formula (IV), R₃ is H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, CN or SR₁.

[0204] In embodiments of the compounds of Formula (IV), R₃ is H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, or CN.

[0205] In embodiments of the compounds of Formula (IV), R₃ is H, methyl, halogen, or CN.

[0206] In embodiments of the compounds of Formula (IV), R₃ is H, halogen, or CN.

[0207] In embodiments of the compounds of Formula (IV), R₃ is H, methyl, or halogen.

[0208] In embodiments of the compounds of Formula (IV), R₃ is H or methyl.

[0209] In embodiments of the compounds of Formula (IV), R₃ is H or halogen.

[0210] In embodiments of the compounds of Formula (IV) or (IV-A), R₄ and R₅ are independently H, methyl, ethyl or propyl.

[0211] In embodiments of the compounds of Formula (IV) or (IV-A), R₄ and R₅ are independently H or methyl.

[0212] In embodiments of the compounds of Formula (IV) or (IV-A), R₄ and R₅ are independently H or methyl.

[0213] In embodiments of the compounds of Formula (IV) or (IV-A), R₆ is C₁-C₆ alkyl or C₁-C₆ fluoroalkyl.

[0214] In embodiments of the compounds of Formula (IV) or (IV-A), R₆ is C₁-C₃ alkyl or C₁-C₃ fluoroalkyl.

[0215] In embodiments of the compounds of Formula (IV) or (IV-A), R₆ is H or C₁-C₆ alkyl.

[0216] In embodiments of the compounds of Formula (IV) or (IV-A), R₆ is H or C₁-C₆ fluoroalkyl.

[0217] In embodiments of the compounds of Formula (IV) or (IV-A), R₆ is H or C₁-C₃ alkyl.

[0218] In embodiments of the compounds of Formula (IV) or (IV-A), R₆ is H or C₁-C₃ fluoroalkyl.

[0219] In embodiments of the compounds of Formula (IV) or (IV-A), R₆ is C₁-C₆ alkyl.

[0220] In embodiments of the compounds of Formula (IV) or (IV-A), R₆ is C₁-C₆ fluoroalkyl.

[0221] In embodiments of the compounds of Formula (IV) or (IV-A), R₆ is C₁-C₃ alkyl.

[0222] In embodiments of the compounds of Formula (IV) or (IV-A), R₆ is C₁-C₃ fluoroalkyl.

[0223] In embodiments of the compounds of Formula (IV) or (IV-A), R₆ is H.

[0224] In embodiments of the compounds of Formula (IV), X is CH.

[0225] In embodiments of the compounds of Formula (IV), X is N.

[0226] In embodiments of the compounds of Formula (IV), m is 0.

[0227] In embodiments of the compounds of Formula (IV), m is 1.

[0228] In embodiments of the compounds of Formula (IV), m is 2.

[0229] In embodiments of the compounds of Formula (IV), m is 3.

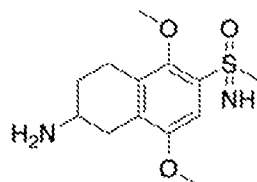
[0230] In embodiments of the compounds of Formula (IV), n is 0.

[0231] In embodiments of the compounds of Formula (IV), n is 1.

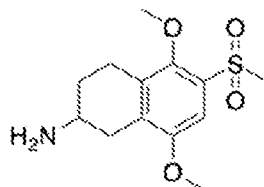
[0232] In embodiments of the compounds of Formula (IV), n is 2.

[0233] In embodiments of the compounds of Formula (IV), n is 3.

[0234] In embodiments of the compounds of Formula (IV) or (IV-A), the compound has the following chemical formula:

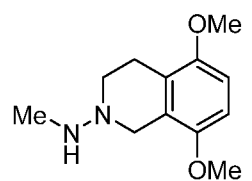
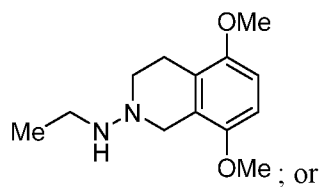
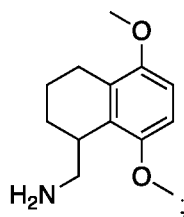


Compound (2-7); or



Compound (2-8).

[0235] In embodiments, the present disclosure provides compounds of the following chemical formulas:



Compositions

[0236] In embodiments, the present disclosure provides a pharmaceutical composition comprising a therapeutically effective amounts of one or more compounds of the present disclosure (e.g., a compound of Formula (I), (I-A), (I-B), (II), (II-A), (II-B), (III), (III-A), (IV),

(IV-A) (3-1), Table 1 or Table 2) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient is provided.

[0237] The pharmaceutically acceptable excipients and adjuvants are added to the composition or formulation for a variety of purposes. In embodiments, a pharmaceutical composition comprising one or more compounds disclosed herein, or a pharmaceutically acceptable salt thereof, further comprise a pharmaceutically acceptable carrier. In embodiments, a pharmaceutically acceptable carrier includes a pharmaceutically acceptable excipient, binder, and/or diluent. In embodiments, suitable pharmaceutically acceptable carriers include, but are not limited to, inert solid fillers or diluents and sterile aqueous or organic solutions. In embodiments, suitable pharmaceutically acceptable excipients include, but are not limited to, water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylase, magnesium stearate, talc, silicic acid, viscous paraffin, and the like.

[0238] For the purposes of this disclosure, the compounds of the present disclosure can be formulated for administration by a variety of means including orally, parenterally, by inhalation spray, topically, or rectally in formulations containing pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used here includes subcutaneous, intravenous, intramuscular, and intraarterial injections with a variety of infusion techniques. Intraarterial and intravenous injection as used herein includes administration through catheters.

Methods of Treatment

[0239] In one aspect, the compounds of the present disclosure are administered to a patient in need thereof to modulate a serotonin receptor, e.g., 5-HT_{2A} receptor. In embodiments, the present disclosure provides methods of modulating serotonin receptor activity comprising administering a therapeutically effect amount of a compound of the present disclosure (e.g., a compound of Formula (I), (I-A), (I-B), (II), (II-A), (II-B), (III), (III-A), (IV), (IV-A) (3-1), Table 1 or Table 2) or a pharmaceutically acceptable salt thereof. In embodiments, modulating is activating or agonizing a serotonin receptor, e.g., 5-HT_{2A} receptor. In embodiments, the subject is a human.

[0240] In embodiments, the present disclosure provides methods of treating a disease or disorder that is treatable by administration of a serotonin receptor agonist, e.g., 5-HT_{2A} receptor agonist. In embodiments, the agonist is a partial agonist of the 5-HT_{2A} receptor. In embodiments, the agonist is a full agonist of the 5-HT_{2A} receptor.

[0241] In embodiments, the present disclosure provides methods of treating a mental health disease or disorder, the method comprising administering a therapeutically effective amount of

a compound of the present disclosure (e.g., Formula (I), (I-A), (I-B), (II), (II-A), (II-B), (III), (III-A), (IV), (IV-A) (3-1), Table 1 or Table 2 or a pharmaceutically acceptable salt thereof).

[0242] In embodiments, the present disclosure provides methods of treating a mental health disease or disorder, the method comprising administering a pharmaceutical composition comprising a compound of the present disclosure (e.g., Formula (I), (I-A), (I-B), (II), (II-A), (II-B), (III), (III-A), (IV), (IV-A), (3-1), Table 1 or Table 2 or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable excipient.

[0243] In embodiments, the mental health disease or disorder is selected from the group consisting of major depressive disorder, treatment resistant depression, substance use disorders and eating disorders. In embodiments, eating disorders include illnesses such as anorexia nervosa, bulimia nervosa, and other disorders related to eating (e.g., binge eating).

[0244] In embodiments, the mental health disease or disorder is an eating disorder.

[0245] In embodiments, the mental health disease or disorder is selected from the group consisting of compulsive disorders, anxiety disorders, stress disorders, and rumination.

[0246] In embodiments, the mental health disease or disorder is a mood disorder. In embodiments, mood disorders include e.g., depressive disorders, such as major depressive disorder or treatment resistant depression.

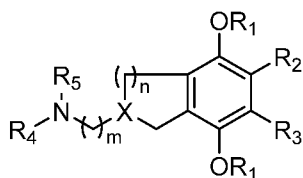
[0247] In embodiments, the mental health disorder is a substance abuse disorder. In embodiments, substance use related disorders are disorders of maladaptive patterns of substance use, and include criteria, such as recurrent substance use related problems, tolerance to a substance, withdrawal upon discontinuing use, an inability to cut down or control use of the substance, and giving up important social, occupational, or recreational activities because of using the substance. See e.g., the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). In embodiments, the substance use related disorder is a disorder resulting from the use of: alcohol; caffeine; cannabis; hallucinogens (such as phencyclidine or similarly acting arylcyclohexylamines, and other hallucinogens, such as LSD); inhalants; opioids; sedatives, hypnotics, or anxiolytics; stimulants (including amphetamine-type substances, cocaine, and other stimulants); tobacco; and other substances.

NUMBERED EMBODIMENTS OF THE DISCLOSURE

[0248] In addition to the disclosure above, the Examples below, and the appended claims, the disclosure sets for the following numbered embodiments.

[0249] Provided below are embodiments related to compounds of Formula (I) and (II).

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof; wherein,

R₁, is independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl;

R₂, and R₃, are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, CN, OR₁ or SR₁;

R₄ and R₅ are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl;

X is C or N;

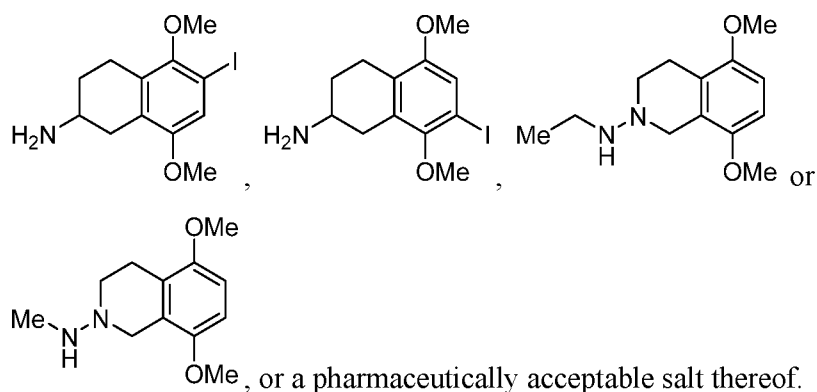
m is 0, 1, 2 or 3;

n is 0, 1, 2 or 3;

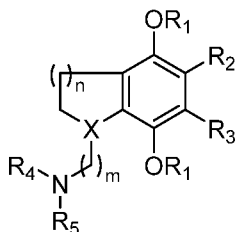
wherein the compound is not 5,8-dimethoxy-6-methyl-1,2,3,4-tetrahydronaphthalen-2-amine; 5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; 5,8-dimethoxy-N-methyl-1,2,3,4-tetrahydronaphthalen-2-amine; or (5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-yl)methanamine.

2. The compound of embodiment 1, wherein R₁ is independently C₁-C₆ alkyl.
3. The compound of any one of embodiments 1-2, wherein R₁ is methyl.
4. The compound of any one of embodiments 1-3, wherein R₂ and R₃ are independently H or C₁-C₆ alkyl.
5. The compound of any one of embodiments 1-3, wherein R₂ and R₃ are independently H, methyl or ethyl.
6. The compound of any one of embodiments 1-3, wherein R₂ and R₃ are independently H or C₁-C₆ fluoroalkyl.
7. The compound of any one of embodiments 1-3, wherein R₂ and R₃ are independently H or trifluoromethyl.
8. The compound of any one of embodiments 1-3, wherein R₂ and R₃ are independently H, F, Cl, Br, I or CN.

9. The compound of any one of embodiments 1-3, wherein R_2 and R_3 are independently H or halogen.
10. The compound of any one of embodiments 1-3, wherein R_2 and R_3 are independently H or I.
11. The compound of any one of embodiments 1-10, wherein R_4 and R_5 are independently H, methyl, ethyl or propyl.
12. The compound of any one of embodiments 1-10, wherein R_4 and R_5 are independently H or methyl.
13. The compound of any one of embodiments 1-10, wherein R_4 is H.
14. The compound of any one of embodiments 1-10, wherein R_4 is methyl.
15. The compound of any one of embodiments 1-10, wherein R_4 is ethyl.
16. The compound of any one of embodiments 1-15, wherein R_5 is H.
17. The compound of any one of embodiments 1-16, wherein X is CH.
18. The compound of any one of embodiments 1-16, wherein X is N.
19. The compound of any one of embodiments 1-18, wherein m is 0.
20. The compound of any one of embodiments 1-18, wherein m is 1.
21. The compound of any one of embodiments 1-20, wherein n is 2.
22. The compound of embodiment 1, having the following chemical formula:



23. A compound of Formula (II):



or a pharmaceutically acceptable salt thereof; wherein,

R_1 is independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl;

R_2 , and R_3 , are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, CN, OR_1 , $S(O)NHR_1$, or SR_1 ;

R_4 and R_5 are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl;

X is C or N;

m is 0, 1, 2 or 3;

n is 0, 1, 2 or 3;

wherein the compound is not (5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl) methanamine.

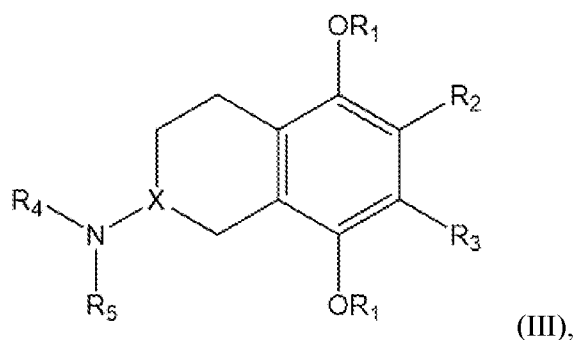
24. The compound of embodiment 23, wherein R_1 is independently C₁-C₆ alkyl.
25. The compound of embodiment 23, wherein R_1 is methyl.
26. The compound of any one of embodiments 23-25, wherein R_2 and R_3 are independently H or C₁-C₆ alkyl.
27. The compound of any one of embodiments 23-25, wherein R_2 and R_3 are independently H, methyl or ethyl.
28. The compound of any one of embodiments 23-25, wherein R_2 and R_3 are independently H or C₁-C₆ fluoroalkyl.
29. The compound of any one of embodiments 23-25, wherein R_2 and R_3 are independently H or trifluoromethyl.
30. The compound of any one of embodiments 23-25, wherein R_2 and R_3 are independently H, F, Cl, Br, I or CN.

31. The compound of any one of embodiments 23-25, wherein R_2 and R_3 are independently H or halogen.
32. The compound of any one of embodiments 23-25, wherein R_2 and R_3 are independently H or I.
33. The compound of any one of embodiments 23-32, wherein R_4 and R_5 are independently H, methyl, ethyl or propyl.
34. The compound of any one of embodiments 23-32, wherein R_4 and R_5 are independently H or methyl.
35. The compound of any one of embodiments 23-32, wherein R_4 is H.
36. The compound of any one of embodiments 23-32, wherein R_4 is methyl.
37. The compound of any one of embodiments 23-32, wherein R_4 is ethyl.
38. The compound of any one of embodiments 23-32, wherein R_5 is H.
39. The compound of any one of embodiments 23-38, wherein X is CH.
40. The compound of any one of embodiments 23-38, wherein X is N.
41. The compound of any one of embodiments 23-38, wherein m is 0.
42. The compound of any one of embodiments 23-38, wherein m is 1.
43. The compound of any one of embodiments 23-42, wherein n is 2.
44. A pharmaceutical composition, comprising a compound of any one of embodiments 1-43 and a pharmaceutically acceptable excipient.
45. A method of treating a mental health disease or disorder, the method comprising administering a therapeutically effective amount of a compound of any one of embodiments 1-43 or the pharmaceutical composition of embodiment 44.
46. The method of embodiment 45, wherein the mental health disease or disorder is selected from the group consisting of major depressive disorder, treatment resistant depression, substance use disorders and eating disorders.

47. The method of embodiment 45, wherein the mental health disease or disorder is selected from the group consisting of compulsive disorders, anxiety disorders, stress disorders, and rumination.

[0250] Provided below are embodiments related to compounds of Formula (III) and (IV).

1. A compound of Formula (III):



or a pharmaceutically acceptable salt thereof; wherein,

R₁ is independently methyl or C₂-C₆ fluoroalkyl;

R₂ and R₃ are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, CN, OR₇ or -S(O)(Y)R₆;

Y is =O or =NH;

R₄ and R₅ are independently H or C₁-C₆ fluoroalkyl;

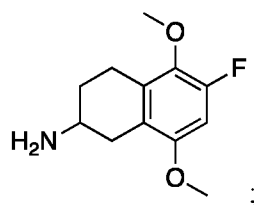
R₆ and R₇ are independently H, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl; and

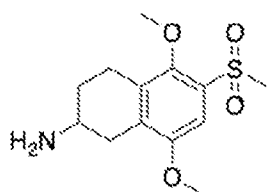
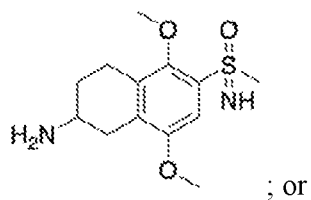
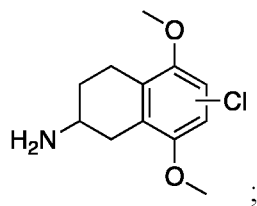
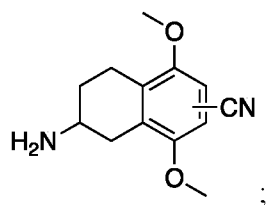
X is CH or N;

wherein the compound is not 5,8-dimethoxy-6-methyl-1,2,3,4-tetrahydronaphthalen-2-amine; 5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; 6-bromo-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; 7-bromo-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; 5,7,8-trimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; or 5,6,8-trimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine.

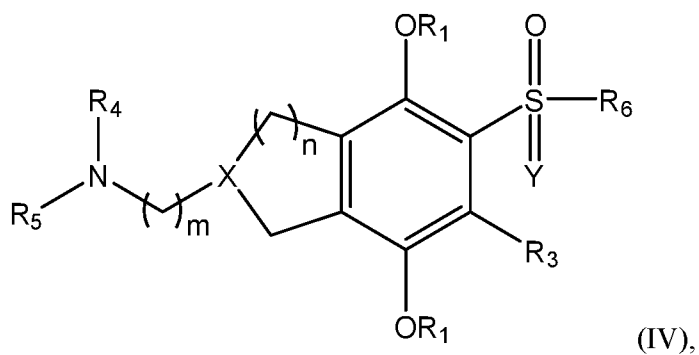
2. The compound of embodiment 1, wherein R₁ is methyl.
3. The compound of embodiment 1, wherein R₁ is C₂-C₆ fluoroalkyl.
4. The compound of any one of embodiments 1-3, wherein R₂ is H.
5. The compound of any one of embodiments 1-3, wherein R₂ is a halogen.
6. The compound of any one of embodiments 1-3, wherein R₂ is F, Cl, or I.

7. The compound of any one of embodiments 1-3, wherein R_2 is CN.
8. The compound of any one of embodiments 1-3, wherein R_2 is $-S(O)_2R_6$.
9. The compound of any one of embodiments 1-3, wherein R_2 is $-S(O)(NH)R_6$.
10. The compound of any one of embodiments 1-9, wherein R_3 is H.
11. The compound of any one of embodiments 1-9, wherein R_3 is a halogen.
12. The compound of any one of embodiments 1-9, wherein R_3 is F, Cl, or I.
13. The compound of any one of embodiments 1-9, wherein R_3 is CN.
14. The compound of any one of embodiments 1-9, wherein R_3 is $-S(O)_2R_6$.
15. The compound of any one of embodiments 1-9, wherein R_3 is $-S(O)(NH)R_6$.
16. The compound of any one of embodiments 1-9, wherein R_2 and R_3 are H.
17. The compound of any one of embodiments 1-16, wherein X is CH.
18. The compound of any one of embodiments 1-16, wherein X is N.
19. The compound of any one of embodiments 1-18, wherein R_4 is H.
20. The compound of any one of embodiments 1-19, wherein R_5 is H.
21. The compound of any one of embodiments 1-20, wherein R_4 and R_5 are each independently H.
22. The compound of any one of embodiments 1-21, having the following chemical formula:





23. A compound of Formula (IV):



or a pharmaceutically acceptable salt thereof; wherein,

R₁ is independently H, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl;

R₃ is H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, CN, OR₇ or SR₁;

R₄ and R₅ are independently H, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl;

R₆ and R₇ are independently H, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl;

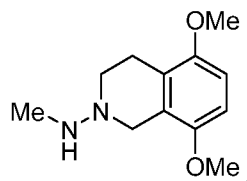
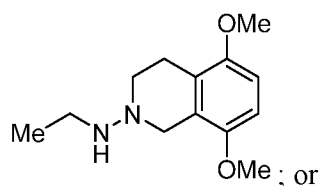
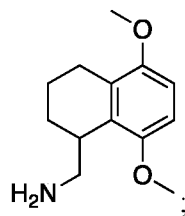
X is CH or N;

m is 0, 1, 2 or 3; and

n is 0, 1, 2 or 3.

24. The compound of embodiment 23, wherein Y is =O.
25. The compound of embodiment 23, wherein Y is =NH.
26. The compound of any one of embodiments 23-25, wherein R₁ is C₁-C₆ alkyl.
27. The compound of any one of embodiments 23-25, wherein R₁ is C₁-C₃ alkyl.
28. The compound of any one of embodiments 23-25, wherein R₁ is methyl.
29. The compound of any one of embodiments 23-25, wherein R₁ is H.
30. The compound of any one of embodiments 23-25, wherein R₁ is C₁-C₆ fluoroalkyl.
31. The compound of any one of embodiments 23-30, wherein R₃ is H.
32. The compound of any one of embodiments 23-30, wherein R₃ is halogen.
33. The compound of any one of embodiments 23-32, wherein R₄ is H.
34. The compound of any one of embodiments 23-32, wherein R₄ is C₁-C₆ alkyl.
35. The compound of any one of embodiments 23-34, wherein R₅ is H.
36. The compound of any one of embodiments 23-34, wherein R₅ is C₁-C₆ alkyl.
37. The compound of any one of embodiments 23-34, wherein R₄ and R₅ are H.
38. The compound of any one of embodiments 23-37, wherein X is CH.
39. The compound of any one of embodiments 23-37, wherein X is N.
40. The compound of any one of embodiments 23-40, wherein m is 0.
41. The compound of any one of embodiments 23-40, wherein m is 1.
42. The compound of any one of embodiments 23-41, wherein n is 1.
43. The compound of any one of embodiments 23-41, wherein n is 2.

44. The compound of any one of embodiments 23-43, wherein R_6 is H.
45. The compound of any one of embodiments 23-43, wherein R_6 is C_1 - C_6 alkyl.
46. The compound of any one of embodiments 23-43, wherein R_6 is C_1 - C_3 alkyl.
47. A compound selected from:



48. A pharmaceutical composition, comprising a compound of any one of embodiments 1-47 and a pharmaceutically acceptable excipient.
49. A method of treating a mental health disease or disorder, the method comprising administering a therapeutically effective amount of a compound of any one of embodiments 1-47 or the pharmaceutical composition of embodiment 48.
50. The method of embodiment 49, wherein the mental health disease or disorder is selected from the group consisting of major depressive disorder, treatment resistant depression, substance use disorders and eating disorders.
51. The method of embodiment 49 wherein the mental health disease or disorder is selected from the group consisting of compulsive disorders, anxiety disorders, stress disorders, and rumination.

EXAMPLES

Abbreviations

[0251] dppf : 1,1'-bis(diphenylphosphino)ferrocene

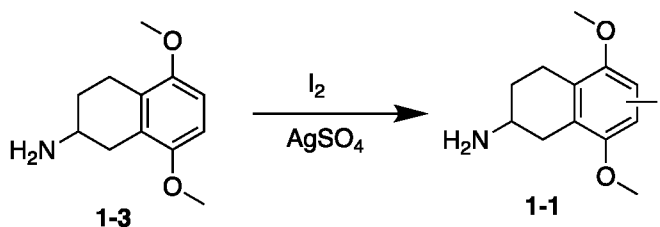
[0252] dba: dibenzylideneacetone or dibenzalacetone

General Methods of preparing the compounds of the present disclosure

[0253] The following schemes provide methods for preparing the compounds of the present disclosure.

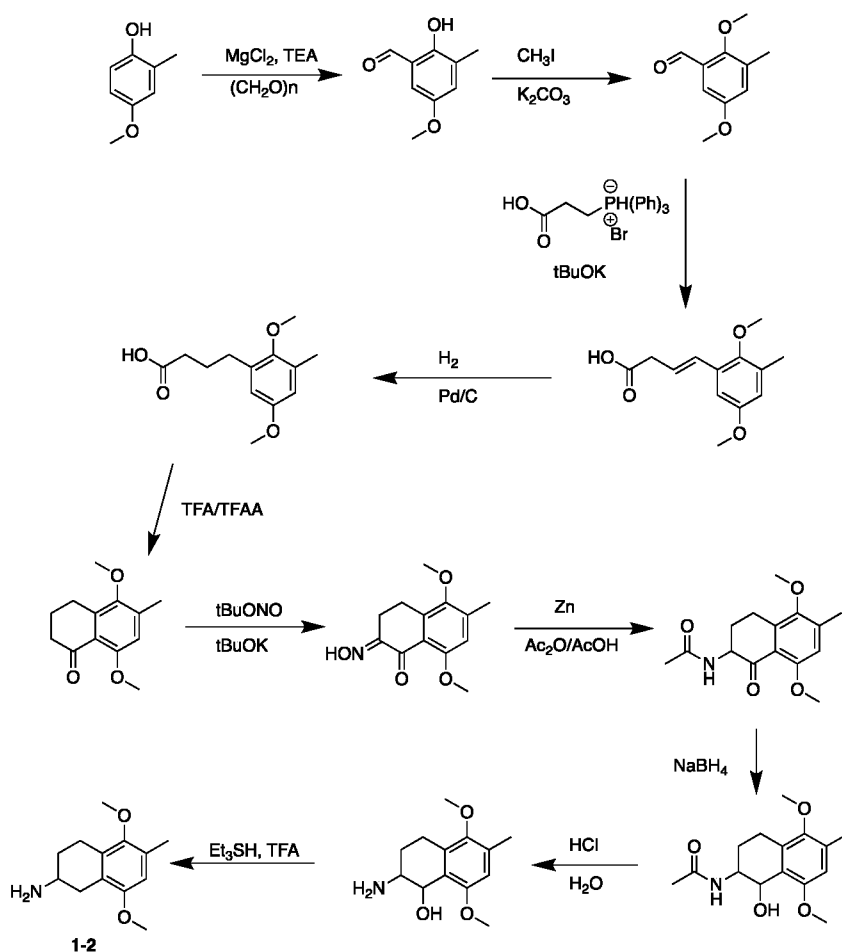
[0254] Unless otherwise noted, all materials/reagents were obtained from commercial suppliers and used without further purification. Reactions were monitored by LC-MS and/or thin layer chromatography (TLC) on silica gel 60 F254 (0.2mm) pre-coated aluminum foil or glass-backed and visualized using UV light. ¹HNMR (400 MHz) spectra was recorded on Bruker spectrometers at RT with TMS or the residual solvent peak as the internal standard. Chemical shifts are given in (δ) and the coupling constants (J) are given as absolute values in Hertz (Hz). The multiplicities in ¹HNMR spectra are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br or broad (broadened). Preparative HPLC purifications were performed on Shimadzu LC-6AD. All purification work was completed using a Shim-pack PREP-DDS(H)KIT Column. The mobile phases were water (with 0.1% HCO₂H) and acetonitrile; all reagents used were of HPLC grade. The flow rate was 10ml/min. LC-MS analyses were performed on Shimadzu LCMS-2020 equipped with LC-20AD or 30AD pumps, SPD-M20A PDA and Alltech 3300 ELSD; Mobile Phase: A: Water (0.1% Formic acid), B: ACN; 5 minute run; Column: Sepax BR-C18 4.6*50mm,3um; Flow Rate:1.0ml/min; Oven Temperature: 40°C; Gradient: 20% B for 0.2 min, increase to 70% B within 1.8 min, 70% B for 2.8 min, back to 20% B within 0.2 min, 20% B for 2 min). Preparative TLC was performed on Whatman LK6F Silica Gel 60A size 20x20 cm plates with a thickness of 1000 μm or equivalent.

Example 1: Preparation of 6-iodo-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine/7-iodo-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine



[0255] To a stirred solution of 5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine (100 mg, 0.41 mmol, 1.0 eq), Ag_2SO_4 (192 mg, 0.615 mmol, 1.5 eq) in MeOH (8 mL) was added I_2 (157 mg, 0.615 mmol, 1.5 eq). The resulting mixture was stirred at RT overnight. The reaction mixture was quenched with aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product which was purified by preparative-HPLC to afford the title compound which was converted to its TFA salt (40 mg, 25%) as a brown solid. LCMS: (ES^+): m/z 334.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.08 (s, 3H), 7.16 (s, 1H), 3.76 (dd, $J = 4.4$ Hz, 3H), 3.63 (dd, $J = 2$ Hz 2H), 3.18 (m, 1H), 2.95 (m, 1H), 2.75 (m, 1H), 2.65 (m, 1H), 2.05 (m, 1H), 1.65 (m, 1H).

Example 2: Preparation of 5,8-dimethoxy-6-methyl-1,2,3,4-tetrahydronaphthalen-2-amine (1-2)



Step 1: Preparation of 2-hydroxy-5-methoxy-3-methylbenzaldehyde

[0256] A solution of 4-methoxy-2-methylphenol (4.6 g, 33.3 mmol, 1.0 eq), MgCl_2 (5.0 g, 50.0 mmol, 1.5 eq), $(\text{CH}_2\text{O})_n$ (3.3 g, 110.0 mmol, 3.2 eq) and TEA (5.0 g, 50.0 mmol, 1.5 eq) in ACN (25 mL) was stirred at 85°C for 2~3 hours. The reaction mixture was cooled to RT and poured into ice-water (200mL), the resulting mixture was adjusted to pH = 3 with hydrochloric acid (4 N) and extracted with EA. The organic layer was washed with water and brine, dried over Na_2SO_4 , filtered and concentrated to give a crude product which was purified through silica gel column chromatography (petroleum ether:EA=95:5) to afford the title compound (5.0 g, 80%) as a yellow solid. ^1H NMR (400 MHz, Solvent: CDCl_3) ppm 10.94 (s, 1H), 9.84 (s, 1H), 7.02–7.03 (d, $J = 3.2\text{Hz}$, 1H), 6.83–6.84 (d, $J = 3.2$, 1H), 3.80 (s, 3H), 2.26 (s, 3H).

Step 2: Preparation of 2,5-dimethoxy-3-methylbenzaldehyde

[0257] A solution of 2-hydroxy-5-methoxy-3-methylbenzaldehyde (5.0 g, 30.0 mmol, 1.0 eq), CH_3I (8.5 g, 60.0 mmol, 2.0 eq) and K_2CO_3 (10.0 g) in DMF (20 mL) was stirred at RT overnight. The TLC was monitored until the starting material was consumed. The reaction mixture was poured into water (30mL) and extracted with MTBE (50 mL $\times$ 3). The combined organic extracts were washed with water (25 mL), brine (25 mL), dried over Na_2SO_4 and concentrated to give a crude product which was purified by silica gel column chromatography (petroleum ether:EA=95: 5) to afford the title product EGX-9-1-2 (5.2 g, 90%) as a yellow solid. ^1H NMR (400 MHz, Solvent: CDCl_3) ppm 10.35 (s, 1H), 7.14–7.15 (d, $J = 3.2\text{ Hz}$, 1H), 7.01–7.02 (d, $J = 3.2$, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 2.31 (s, 3H).

Step 3: Preparation of (E)-4-(2,5-dimethoxy-3-methylphenyl)but-3-enoic acid

[0258] To a solution of 2,5-dimethoxy-3-methylbenzaldehyde (2.4 g, 13.3 mmol) in THF (40 mL) was added (2-carboxyethyl)triphenylphosphonium (8.3 g, 20 mmol, 1.5 eq) and t-BuOK solution in THF (40 mL, 40 mmol, 3 eq) at 0°C. The reaction mixture was stirred at RT overnight. The solvent was removed, the residue was diluted with water, basified with sodium hydroxide and extracted with EtOAc (50 mL). The aqueous phase was adjusted to pH = 2 with aqueous hydrochloric acid and extracted with DCM (30 mL $\times$ 3). The combined organic extracts were washed with water (25 mL), brine (25 mL), dried over Na_2SO_4 , filtered and concentrated to give the crude product (4.48 g) which was used in the next step without further purification.

Step 4: Preparation of 4-(2,5-dimethoxy-3-methylphenyl)butanoic acid

[0259] To a solution of (E)-4-(2,5-dimethoxy-3-methylphenyl)but-3-enoic acid (4.48 mg, 13.2 mmol) in MeOH (20 mL) was added Pd/C (250 mg) at RT and the reaction mixture was stirred

overnight. The suspension was filtered and the filtrate was concentrated to afford the crude product which was used in next step without further purification (3.88 g, 100 %).

Step 5: Preparation of 5,8-dimethoxy-6-methyl-3,4-dihydronaphthalen-1(2H)-one

[0260] To a solution of 4-(2,5-dimethoxy-3-methylphenyl)butanoic acid (3.88 g, 13.3 mmol) in TFA (10 mL) was added TFAA (8.5 mL, 66.6 mmol, 5 eq) at RT and the reaction mixture was stirred overnight. The reaction was diluted with EtOAc and washed with water (25 mL), brine (25 mL), dried over Na₂SO₄, filtered and concentrated to give a crude product which was purified by silica gel chromatography (petroleum ether: EtOAc=5:1) to afford the title compound as a colorless oil (1.2 g, 56%).

Step 6: Preparation of (E)-2-(hydroxyimino)-5,8-dimethoxy-6-methyl-3,4-dihydronaphthalen-1(2H)-one

[0261] To a solution of 5,8-dimethoxy-6-methyl-3,4-dihydronaphthalen-1(2H)-one (1.2 g, 5.45 mmol) in t-BuOH/Et₂O (10 mL/10 mL) was added t-BuOK (911 mg, 8.12 mmol, 1.5 eq) and tert-butyl nitrite (843 mg, 8.12 mmol, 1.5 eq) at RT and the reaction mixture was stirred overnight. The reaction was quenched with water (25 mL), adjusted to pH = 2 with aqueous hydrochloric acid and extracted with DCM (30 mL x 3). The combined organic extracts were washed with water (25 mL), brine (25 mL), dried over Na₂SO₄, filtered and concentrated to give a crude product which was purified by silica gel chromatography (DCM: MeOH = 100:1) to afford the title compound as a yellow solid (700 mg, 51%).

Step 7: Preparation of N-(5,8-dimethoxy-6-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide

[0262] To a solution of (E)-2-(hydroxyimino)-5,8-dimethoxy-6-methyl-3,4-dihydronaphthalen-1(2H)-one (500 mg, 2.27 mmol, 1.3 eq) in AcOH (6 mL) was added Zn (445 mg, 6.81 mmol, 3 eq) and Ac₂O (4 mL) at RT under N₂ and the reaction mixture was stirred overnight. The suspension was filtered, the filtrate diluted with water, adjusted to pH = 8 with sodium hydroxide (4 M in water) and extracted with EtOAc. The extract was washed with water (25 mL), brine (25 mL), dried over Na₂SO₄, filtered, and concentrated to give a crude product which was purified by silica gel chromatography (DCM: MeOH=100:1) to afford the title compound as a colorless oil (180 mg, 40%).

Step 8: Preparation of N-(1-hydroxy-5,8-dimethoxy-6-methyl-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide

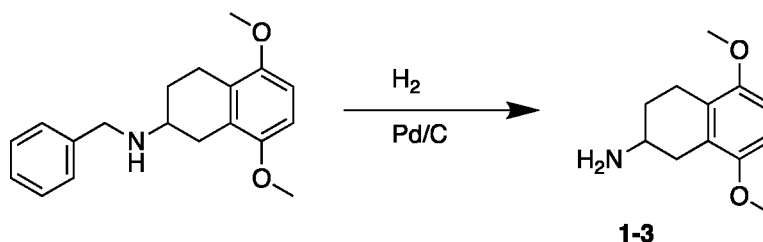
[0263] To a solution of N-(5,8-dimethoxy-6-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide (184 mg, 0.664 mmol) in MeOH (10 mL) was added NaBH₄ (76 g, 2.0 mmol, 3 eq) at 0°C. The reaction mixture was stirred at RT overnight. The reaction was diluted with EtOAc, washed with water (25 mL), brine (25 mL), dried over Na₂SO₄, filtered and concentrated to give the crude product which was used in next step without further purification (203 mg, 100%).

Step 9: Preparation of 2-amino-5,8-dimethoxy-6-methyl-1,2,3,4-tetrahydronaphthalen-1-ol

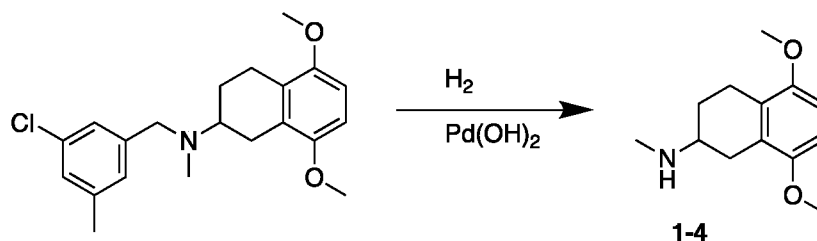
[0264] To a solution of N-(1-hydroxy-5,8-dimethoxy-6-methyl-1,2,3,4-tetrahydronaphthalen-2-yl)-acetamide (158 mg, 0.565 mmol) in H₂O (5 mL) was added concentrated hydrochloric acid (12 M in water, 0.8 mL) at RT. The reaction mixture was stirred at reflux for 2h, cooled to room temperature and adjusted to pH = 8 with sodium hydroxide (4 M in water). The reaction mixture was extracted with EtOAc. The organic layer was washed with water (25 mL), brine (25 mL), dried over Na₂SO₄, filtered and concentrated to give the crude product which was used in next step without further purification (143 mg, 56%). ¹H NMR (400 MHz, methanol-d₄) δ 6.74 (s, 1H), 5.03 (dd, *J* = 3.7, 1.3 Hz, 1H), 3.85 (s, 3H), 3.69 (s, 3H), 3.38-3.34 (m, 1 H), 3.16-3.10 (m, 1H), 2.76-2.67 (m, 1H), 2.30 (s, 3H), 2.14-2.04 (m, 1H), 1.99-1.92 (m, 1H).

Step 10: Preparation of 5,8-dimethoxy-6-methyl-1,2,3,4-tetrahydronaphthalen-2-amine

[0265] To a solution of 2-amino-5,8-dimethoxy-6-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (80 mg, 0.33 mmol) in TFA (6 mL) was added Et₃SiH (206 mg, 1.65 mmol, 5 eq) at RT and the reaction mixture was stirred. The reaction was diluted with water (25 mL), adjust to pH = 10 with sodium hydroxide (4 M in water). The reaction mixture was extracted with EtOAc. The organic layer was washed with water, brine (25 mL each), dried over Na₂SO₄, filtered and concentrated to give a crude product which was purified by silica gel chromatography (DCM:MeOH=100:1) to afford the title compound as a colorless oil (64 mg, 86%). ¹H NMR (400 MHz, methanol-d₄) δ 6.65 (s, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 3.50 (m, 1H), 3.19 (dd, *J* = 17.2 Hz, 6.0 Hz, 1H), 3.06 (dt, *J* = 17.5, 4.8 Hz, 1H), 2.81 (m, 1H), 2.53 (dd, *J* = 16.8, 9.8 Hz, 1H), 2.28 (s, 3H), 2.25 – 2.14 (m, 1H), 1.90 – 1.65 (m, 1H).

Example 3: Preparation of 5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine hydrochloride (1-3)

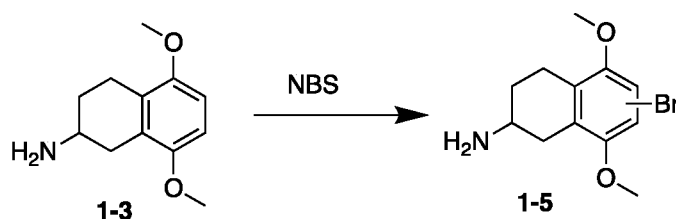
[0266] To a solution of N-benzyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine (3.92 mg, 13.2 mmol) in MeOH (20 mL) was added Pd(OH)₂/C (400 mg) at RT and the resulting mixture was stirred overnight. The suspension was filtered and the filtrate was concentrated to afford a crude product which was dissolved in MTBE (5 mL) and treated with 4M HCl in dioxane (5 mL, 19.8 mmol, 1.5 eq) at RT. The resulting mixture was stirred at room temperature for 2 h. The suspension was filtered to afford the title compound as a white solid (2.25 g, 78%). LCMS: (ES⁻): m/z 208.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.31 (s, 2H), 6.75 (s, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 3.14 – 3.01 (m, 1H), 2.90-2.80 (m, 1H), 2.55-2.44 (m, 1H), 2.18 – 2.04 (m, 1H), 1.66 (qd, *J* = 11.7, 5.5 Hz, 1H).

Example 4: Preparation of 5,8-dimethoxy-N-methyl-1,2,3,4-tetrahydronaphthalen-2-amine hydrochloride (1-4)

[0267] A suspension of N-(3-chloro-5-methylbenzyl)-5,8-dimethoxy-N-methyl-1,2,3,4-tetrahydro-naphthalen-2-amine (100 mg, 0.322 mmol, 1.0 eq) and Pd(OH)₂ (10 mg, 10%) in MeOH (5 mL) was stirred at RT under H₂ overnight. The reaction was monitored by TLC until the reaction was complete. The Pd(OH)₂ was filtered, and the filtered cake was washed with MeOH twice. The combined organic layers were concentrated under reduced pressure to give a crude residue which was purified by silica gel flash column chromatography (eluted with DCM/MeOH = 15:1 gradient) to afford the title compound as the free base (30 mg, 42%) which was converted to the HCl salt (35 mg, 42%) as a white solid after treatment with HCl in dioxane. LCMS: m/z 222.35 [M+H]⁺. ¹H NMR (400 MHz, DMSO) δ 9.03 (s, 2H), 6.76 (s,

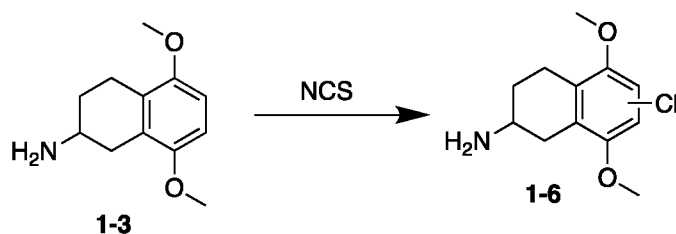
2H), 3.74 (s, 3H), 3.72 (s, 3H), 3.12 (dd, $J = 17.3, 5.1$ Hz, 1H), 2.92 – 2.81 (m, 1H), 2.61 (s, 3H), 2.55 (d, $J = 10.8$ Hz, 1H), 2.52 (d, $J = 1.9$ Hz, 1H), 2.44 (s, 1H), 2.26 – 2.16 (m, 1H), 1.65 (qd, $J = 11.6, 5.5$ Hz, 1H).

Example 5: Preparation of 6-bromo-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine / 7-bromo-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine



[0268] To a solution of 5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine hydrobromide (200 mg, 1.735 mmol, 1 eq) in DCM (5 mL) was added NBS (386 mg, 2.17 mmol, 1.25 eq) at RT and the resulting mixture was stirred overnight. The reaction was quenched with water and extracted with EA (50 ml x 3). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated to give a crude product which was purified by silica gel chromatography (DCM: MeOH = 100: 1) to afford the title compound (46 mg, 23%) as a colorless oil. LCMS: 1.867 min, m/z 287.90 $[M+H]^+$ ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.00 (s, 1H), 3.82 – 3.72 (m, 6H), 3.55 – 3.45 (m, 1H), 3.29 – 3.02 (m, 1H), 2.96 – 2.76 (m, 1H), 2.76 – 2.44 (m, 2H), 2.25 – 2.15 (m, 1H), 1.85 – 1.71 (m, 1H).

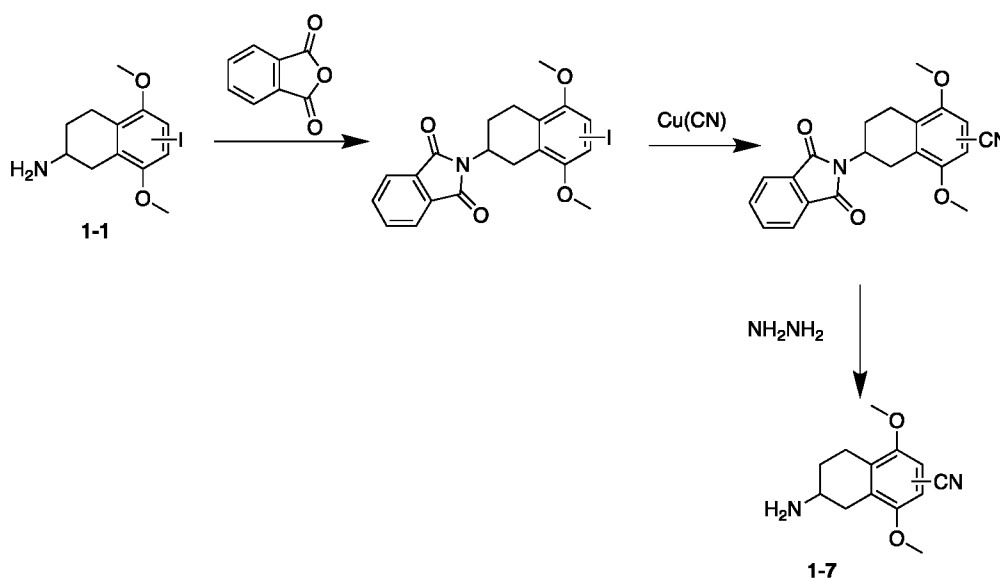
Example 6: Preparation of 6-chloro-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine / 7-chloro-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine



[0269] To a solution of 5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine hydrochloride (200 mg, 0.82 mmol, 1 eq) in DCM (5 mL) was added NCS (132 mg, 0.985 mmol, 1.2 eq) at RT and the resulting mixture was stirred overnight. The reaction was quenched with water, and extracted with EA (50 mL x 3). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated to give a crude product which was purified by silica gel chromatography (DCM: MeOH = 100: 1) to afford the title compound (41 mg, 20%) as a

colorless oil. LCMS: 1.952 min, m/z 241.50 $[M+H]^+$ 1H NMR (400 MHz, Methanol- d_4) δ 6.85 (s, 1H), 3.85 – 3.69 (m, 6H), 3.59 – 3.44 (m, 1H), 3.28 – 3.02 (m, 1H), 2.99 – 2.75 (m, 1H), 2.76 – 2.46 (m, 2H), 2.26 – 2.15 (m, 1H), 1.86 – 1.70 (m, 1H).

Example 7: Preparation of 6-amino-1,4-dimethoxy-5,6,7,8-tetrahydronaphthalene-2-carbonitrile/6-amino-1,4-dimethoxy-5,6,7,8-tetrahydronaphthalene-3-carbonitrile (2-6)



Step 1: Preparation of 2-(6-iodo-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-yl)isoindoline-1,3-dione/2-(7-iodo-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-yl)isoindoline-1,3-dione

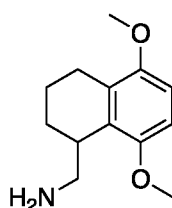
[0270] A solution of 6-iodo-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine/7-iodo-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine (400 mg, 1.20 mmol, 1 eq), isobenzofuran-1,3-dione (220 mg, 1.44 mmol, 1.2 eq) and Et_3N (266 mg, 2.6 mmol, 2.2 eq) in 20 mL toluene was heated to $110^\circ C$ under N_2 for 16 h. The reaction mixture was washed with water and extracted with EA. The organic phase was collected and concentrated under reduced pressure to afford the crude product which was purified by flash chromatography (eluting with petroleum ether:EA = 3:1) to afford the title compound (380 mg, 68%). 1H NMR (400 MHz, Solvent: $CDCl_3$) ppm 7.90 – 7.80 (m, 2H), 7.77 – 7.69 (m, 2H), 7.04 (d, $J = 4.7$ Hz, 1H), 4.55 – 4.42 (m, 1H), 3.75 (dd, $J = 18.1, 15.6$ Hz, 6H), 3.44 (dd, $J = 16.3, 11.7$ Hz, 1H), 3.25 – 3.16 (m, 1H), 3.12 – 2.91 (m, 2H), 2.79 (dd, $J = 20.6, 8.7$ Hz, 1H), 2.62 (dd, $J = 13.4, 5.5$ Hz, 2H), 2.01 (d, $J = 5.5$ Hz, 1H).

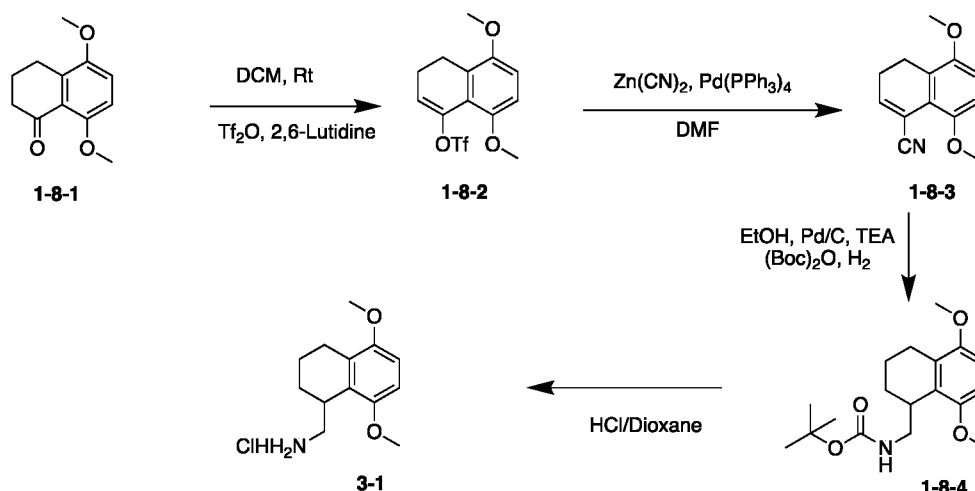
Step 2: Preparation of 6-amino-1,4-dimethoxy-5,6,7,8-tetrahydronaphthalene-2-carbonitrile/6-amino-1,4-dimethoxy-5,6,7,8-tetrahydronaphthalene-3-carbonitrile

[0271] A solution of 2-(6-iodo-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-yl)isoindoline-1,3-dione/2-(7-iodo-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-yl)isoindoline-1,3-dione (380 mg, 0.82 mmol, 1 eq) in DMF was added CuCN (90 mg, 1 mmol, 1.2 eq) and the reaction was heated to 150 °C under N₂ for 16 h. The reaction mixture was washed with water and extracted with DCM. The organic phase was collected and concentrated under reduced pressure to afford the crude product which was purified by flash chromatography (eluting with petroleum ether:EA =1:1) to afford the title compound (200 mg, 67%).

Step 3: 6-amino-1,4-dimethoxy-5,6,7,8-tetrahydronaphthalene-2-carbonitrile/6-amino-1,4-dimethoxy-5,6,7,8-tetrahydronaphthalene-3-carbonitrile

[0272] A solution of 6-(1,3-dioxoisindolin-2-yl)-1,4-dimethoxy-5,6,7,8-tetrahydronaphthalene-2/3-carbonitrile (200 mg, 0.8 mmol, 1 eq) and hydrazine (200 mg, 2 mmol, 2.5 eq) in EtOH (2 mL) was heated to 80°C under N₂ for 15 min. The reaction mixture was washed with water and extracted by DCM. The organic phase was collected and concentrated under reduced pressure to afford the crude product which was purified by flash chromatography (eluting with DCM:MeOH =10:1) to afford the title compound (100 mg, 50%).

Example 8: Synthesis of (5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methanamine (3-1)



Step 1: Synthesis of intermediate 1-8-2: 5,8-dimethoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate

[0273] A suspension of 5,8-dimethoxy-3,4-dihydronaphthalen-1(2H)-one (1.0 g, 4.8 mmol, 1.0 eq) and 2,6-dimethylpyridine (778 g, 7.2 mmol, 1.5 eq) in DCM (20 mL) was stirred at 0°C for 30 min. Tf_2O (1.1 g, 7.2 mmol, 1.5 eq) was slowly added to the mixture. The resulting mixture was stirred at RT overnight. The organic phase was concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluted with petroleum ether/EA = 10:1 gradient) to afford the title compound EGX-19-3-1 as an oil (1.0 g, 61%).

Step 2: Synthesis of intermediate 1-8-3: 5,8-dimethoxy-3,4-dihydronaphthalene-1-carbonitrile

[0274] A suspension of 5,8-dimethoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (500 mg, 1.47 mmol, 1.0 eq), $\text{Zn}(\text{CN})_2$ (190 mg, 1.62 mmol, 1.1 eq) and $\text{Pd}(\text{PPh}_3)_4$ (84 mg, 0.07 mmol, 0.05 eq) in DMF (8 mL) was heated to 75°C overnight. The organic phase was concentrated under reduced pressure to give a crude residue which was purified by silica gel flash column chromatography (eluted with petroleum ether/EA = 15:1 gradient) to afford the title compound EGX-19-3-2 (100 mg, 32%).

Step 3: Synthesis of intermediate 1-8-4: tert-butyl ((5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)carbamate

[0275] A suspension of 5,8-dimethoxy-3,4-dihydronaphthalene-1-carbonitrile (70 mg, 0.32 mmol, 1.0 eq), TEA (98.5 mg, 0.97 mmol, 3 eq), $(\text{Boc})_2\text{O}$ (212 mg, 0.97 mmol, 3 eq) and Pd/C (10 mg) in EtOH (10 mL) was stirred under H_2 at RT overnight. The reaction mixture was

filtered. The organic phase was concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (eluted with petroleum ether/EA = 50:1 gradient) to afford the title compound as a white solid, EGX-19-3-3 (90 mg, 87 %).

Step 4: Synthesis of final product 3-1: (5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methanamine hydrochloride

[0276] A suspension of tert-butyl ((5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)carbamate (90 mg, 0.28 mmol, 1.0 eq) in EA (10 mL) was stirred at RT and HCl/Dioxane (0.5 mL) was added to the solution. The reaction was monitored by TLC until the reaction was complete. The solvent was concentrated under reduced pressure to afford the title compound EGX-19-6 (60 mg, 83 %) as a white solid.

[0277] LCMS: 0.941 min, m/z 222.30 [M+H]⁺, ¹H NMR (400 MHz, MeOD) δ 6.77 (s, 2H), 3.82 (s, 3H), 3.75 (s, 3H), 3.33-3.31 (m, 1H), 3.19-3.15 (m, 1H), 2.98-2.92 (m, 1H), 2.91 (m, 1H), 2.48 – 2.38 (m, 1H), 1.99 (m, 1H), 1.88-1.85 (m, 2H).

Example 9: GPCR Arrestin Assay

Arrestin Pathway (Performed by DiscoverX Eurofins)

[0278] The PathHunter[®] β -Arrestin assay monitors the activation of a GPCR in a homogenous, non-imaging assay format using a technology developed by DiscoverX called Enzyme Fragment Complementation (EFC) with β -galactosidase (β -Gal) as the functional reporter. The enzyme is split into two inactive complementary portions (EA for Enzyme Acceptor and PK for ProLink) expressed as fusion proteins in the cell. EA is fused to β -Arrestin and PK is fused to the GPCR of interest. When the GPCR is activated and β -Arrestin is recruited to the receptor, ED and EA complementation occurs, restoring β -Gal activity which is measured using chemiluminescent PathHunter[®] Detection Reagents.

[0279] PathHunter cell lines (DiscoverX Eurofins) were expanded from freezer stocks according to standard procedures. Human 5-HT_{2A} receptor-mediated GPCR β -arrestin activity was evaluated in stably transfected human-derived U2OS cells. Cells were seeded in a total volume of 20 μ L into white walled, 384-well microplates and incubated at 37 °C overnight prior to testing.

[0280] For agonist determination, cells were incubated with sample to induce response. Intermediate dilution of sample stocks was performed to generate 5X sample in assay buffer. 5 μ L of 5X sample was added to cells and incubated at 37 °C or room temperature for 120 minutes. Vehicle concentration was 1%.

[0281] β -Arrestin assay signal was generated through a single addition of 12.5 or 15 μ L (50% v/v) of PathHunter Detection reagent cocktail, followed by a one hour incubation at room temperature. Microplates were read following signal generation with a PerkinElmer EnvisionTM instrument for chemiluminescent signal detection.

[0282] Compound activity was analyzed using CBIS data analysis suite (ChemInnovation, CA). For agonist mode assays, percentage activity was calculated using the following formula:

$$\% \text{ Activity} = 100\% \times (\text{mean RLU of test sample} - \text{mean RLU of vehicle control}) / (\text{mean MAX control ligand} - \text{mean RLU of vehicle control}).$$

[0283] In these studies, the MAX control ligand response was generated using 1 μ M serotonin.

Calcium Mobilization Assay Method (Performed by DiscoverX Eurofins)

[0284] The Calcium No-Wash^{PLUS} assay monitors the activation of a GPCR via Gq secondary messenger signaling in a live cell, non- imaging assay format. Calcium mobilization in PathHunter[®] cell lines or other cell lines stably expressing Gq-coupled GPCRs is monitored using a calcium-sensitive dye that is loaded into cells. GPCR activation by a compound results in the release of calcium from intracellular stores and an increase in dye fluorescence that is measured in real-time.

[0285] Cell lines expressing the GPCR of interest were expanded from freezer stocks according to standard procedures. Human 5-HT_{2A}, 5-HT_{2B} or 5-HT_{2C} receptor-mediated calcium mobilization was evaluated in stably transfected human-derived U2OS (5-HT_{2A} or 5-HT_{2B}) or HEK (5-HT_{2B}) cells. Cells were seeded in a total volume of 20 μ L into black-walled, clear-bottom, Poly-D-lysine coated 384-well microplates and incubated at 37°C overnight prior to testing.

[0286] Assays were performed in 1 x Dye Loading Buffer consisting of 1x Dye, 1x Additive A and 2.5 mM Probenecid in HBSS / 20 mM Hepes. Probenecid was prepared fresh. Cells were loaded with dye prior to testing. Media was aspirated from cells and replaced with 20 μ L Dye Loading Buffer. Cells were incubated for 45 minutes at room temperature.

[0287] For agonist determination, cells were incubated with sample to induce response. After dye loading, cells were removed from the incubator and 10 μ L HBSS / 20 mM Hepes was added. 3x vehicle was included in the buffer when performing agonist dose curves to define the EC₈₀ for subsequent antagonist assays. Cells were incubated for 30 minutes at room temperature in the dark to equilibrate plate temperature.

[0288] Intermediate dilution of sample stocks was performed to generate 4X sample in assay buffer. Compound agonist activity was measured on a FLIPR Tetra (MDS). Calcium mobilization was monitored for 2 minutes and 10 μ L 4X sample in HBSS / 20 mM Hepes was added to the cells 5 seconds into the assay.

[0289] Compound activity data was analyzed using CBIS data analysis suite (ChemInnovation, CA). For agonist mode assays, percentage activity is calculated using the following formula:

$$\% \text{ Activity} = 100\% \times (\text{mean RFU of test sample} - \text{mean RFU of vehicle control}) / (\text{mean MAX RFU control ligand} - \text{mean RFU of vehicle control}).$$

[0290] In these studies, the MAX RFU was generated by using 0.1 μ M serotonin for the calcium mobilization assay.

cAMP Secondary Messenger Pathway Assay Method (Performed by DiscoverX Eurofins)

[0291] DiscoverX has developed a panel of cell lines stably expressing non-tagged GPCRs that signal through cAMP. Hit Hunter® cAMP assays monitor the activation of a GPCR via Gi and Gs secondary messenger signaling in a homogenous, non-imaging assay format using a technology developed by DiscoverX called Enzyme Fragment Complementation (EFC) with β -galactosidase (β -Gal) as the functional reporter. The enzyme is split into two complementary portions: EA for Enzyme Acceptor and ED for Enzyme Donor. ED is fused to cAMP and in the assay competes with cAMP generated by cells for binding to a cAMP-specific antibody. Active β -Gal is formed by complementation of exogenous EA to any unbound ED-cAMP. Active enzyme can then convert a chemiluminescent substrate, generating an output signal detectable on a standard microplate reader.

[0292] cAMP Hunter cell lines were expanded from freezer stocks according to standard procedures. Human 5-HT1A receptor-mediated cAMP signaling was evaluated in stably transfected hamster-derived CHO cells. Cells were seeded in a total volume of 20 μ L into white walled, 384-well microplates and incubated at 37°C overnight. cAMP modulation was determined using the DiscoverX HitHunter cAMP XS+ assay.

[0293] For Gi agonist determination, cells were incubated with sample in the presence of EC80 (15 mM) forskolin to induce response. Media was aspirated from cells and replaced with 10 μ L HBSS/10mM Hepes. Intermediate dilution of sample stocks was performed to generate 4X sample in assay buffer containing 4x EC80 forskolin. 5 μ L of 4x sample was added to cells and incubated at 37°C for 30 minutes. Final assay vehicle concentration was 1%. After compound incubation, assay signal was generated through incubation with 20 μ L cAMP XS+ ED/CL lysis cocktail for one hour followed by incubation with 20 μ L cAMP XS+ EA reagent for three hours

at room temperature. Microplates were read following signal generation with a PerkinElmer Envision™ instrument for chemiluminescent signal detection.

[0294] Compound activity was analyzed using CBIS data analysis suite (ChemInnovation, CA). For Gi agonist mode assays, percentage activity is calculated using the following formula: % Activity = 100% x (1 - (mean RLU of test sample - mean RLU of MAX control) / (mean RLU of vehicle control - mean RLU of MAX control)). In these studies, the MAX RLU was generated by using 1 uM serotonin.

Biological Experiments

[0295] Compounds (2-1), (1-1), (2-2), (2-3), (1-4), (1-5), (2-4) and (3-1) were assessed for biological activity across a panel of 5-HT receptors including 5-HT2A, 5-HT2B, 5-HT2C and 5-HT1A. Biased signaling was assessed by monitoring both intracellular Gq-mediated calcium release, as well as β -arrestin activation and recruitment to the GPCR. The results are shown in Table 3 below.

[0296] All available data for the compounds in this series

Table 3. EC₅₀ values measured for Compounds (1-2) and (1-1) across a panel of 5-HT receptors

5-HT Receptor assessed	EC₅₀ (nM) Compound (1-1)	EC₅₀ (nM) Compound (1-2)
5-HT1A (Gi signaling)	369	438
5-HT2A (Gq signaling)	8.8	38.8
5-HT2B (Gq signaling)	>10,000	315
5-HT2C (Gq signaling)	5.6	4.8
5-HT2A (β -arrestin signaling)	120	386
5-HT1A (β -arrestin signaling)	>10000	Not available

[0297] The 2-aminotetralins studied displayed greater potency for the 5-HT2C receptor compared to the other 5-HT receptors studied (Tables 1 and 2). However, **Compound (1-1)** maintained near equipotency across both 5-HT2A and 5-HT2C. Interestingly, **Compound**

(**1-1**) demonstrated >1136-fold increase in potency at 5-HT_{2A} compared to 5-HT_{2B} (**FIG. 1A**). Substitution of the 6-iodo with 6-methyl, to afford **Compound (1-2)**, yielded a reduced potency of only ~8-fold for 5-HT_{2A} over 5-HT_{2B} (**FIG. 1A**). Modulation of selectivity by such a small molecular change is surprising and unexpected given the structural similarity between the 5-HT_{2A} and 5-HT_{2B} receptors. Moreover, the superior selectivity afforded by **Compound (1-1)** has distinct safety advantages over **Compound (1-2)** and other non-selective psychedelics by potentially decreasing the risk of cardiac valvulopathy associated with prolonged 5-HT_{2B} activation typically encountered upon repeated dosing of known 5-HT_{2B} agonists such as fenphen (combination of fenfluramine/phentermine). The 2-aminotetralins studied afforded sub-micromolar potencies for 5HT_{1A}. In comparison to psilocin, 2-aminotetralins were ~5-fold more potent for 5-HT_{1A}. Given the importance of the 5-HT_{1A} contribution to the psychedelic experience (Pokorny et al., 2016; Carter et al., 2005), 5-HT_{1A} activation afforded by 2-aminotetralins may be therapeutically advantageous.

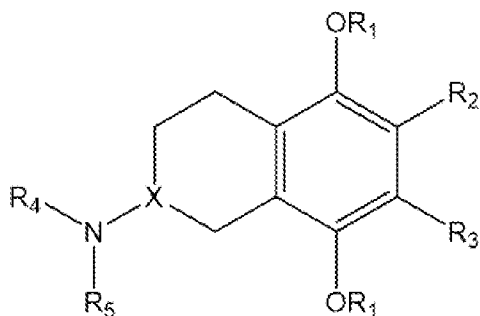
[0298] While the 2-aminotetralins studied were potent activators of 5-HT_{2A} Gq-mediated signaling, these compounds had higher potency values for β -arrestin recruitment at 5-HT_{2A} (**FIG. 1B**). **Compound (1-1)** was observed to maintain a 14-fold potency bias compared to ~10-fold for **Compound (1-2)**. Such a bias may be important to uncoupling the psychedelic experiences of disassociation and hallucination from the therapeutic benefit.

[0299] The EC₅₀ profiles of the compounds demonstrated that all were agonists of 5-HT_{2A} mediated signaling. However, while **Compound (1-2)** displayed full-agonism of 5-HT_{2A} Gq-mediated signaling (97% max activation), **Compound (1-1)** showed reduced efficacy with a max activation of 82% (**FIG. 1A**) when compared to the maximum serotonin response. Both **Compounds (1-2) and (1-1)** exhibited partial agonism with maximum efficacy levels of 66% and 35%, respectively. These results suggest a potential for 5-HT_{2A} Gq-mediated signaling bias for the compounds prepared and studied.

CLAIMS

What is claimed:

1. A compound of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof; wherein,

R₁ is independently methyl or C₂-C₆ fluoroalkyl;

R₂ and R₃ are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, CN, OR₇ or -S(O)(Y)R₆;

Y is =O or =NH;

R₄ and R₅ are independently H or C₁-C₆ fluoroalkyl;

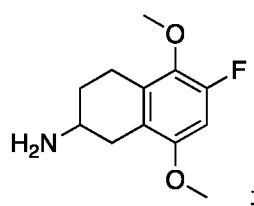
R₆ and R₇ are independently H, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl; and

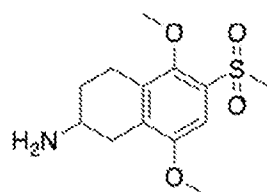
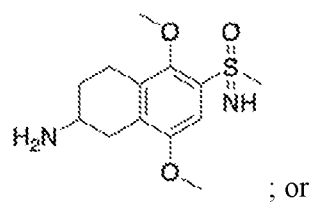
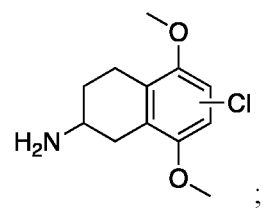
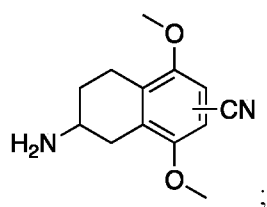
X is CH or N;

wherein the compound is not 5,8-dimethoxy-6-methyl-1,2,3,4-tetrahydronaphthalen-2-amine; 5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; 6-bromo-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; 7-bromo-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; 5,7,8-trimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; or 5,6,8-trimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine.

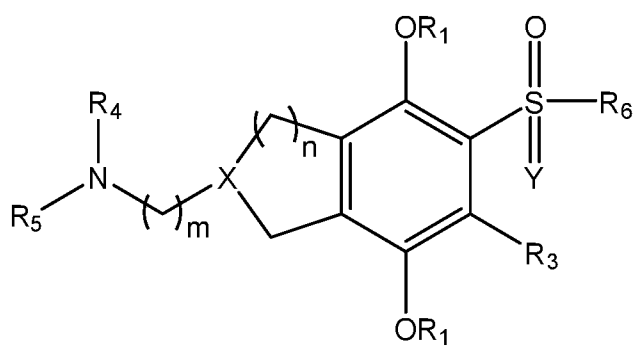
2. The compound of claim 1, wherein R₁ is methyl.
3. The compound of claim 1, wherein R₁ is C₂-C₆ fluoroalkyl.
4. The compound of claim 1, wherein R₂ is H.
5. The compound of claim 1, wherein R₂ is a halogen.
6. The compound of claim 1, wherein R₂ is F, Cl, or I.

7. The compound of claim 1, wherein R_2 is CN.
8. The compound of claim 1, wherein R_2 is $-S(O)_2R_6$.
9. The compound of claim 1, wherein R_2 is $-S(O)(NH)R_6$.
10. The compound of claim 1, wherein R_3 is H.
11. The compound of claim 1, wherein R_3 is a halogen.
12. The compound of claim 1, wherein R_3 is F, Cl, or I.
13. The compound of claim 1, wherein R_3 is CN.
14. The compound of claim 1, wherein R_3 is $-S(O)_2R_6$.
15. The compound of claim 1, wherein R_3 is $-S(O)(NH)R_6$.
16. The compound of claim 1, wherein R_2 and R_3 are H.
17. The compound of claim 1, wherein X is CH.
18. The compound of claim 1, wherein X is N.
19. The compound of claim 1, wherein R_4 is H.
20. The compound of claim 1, wherein R_5 is H.
21. The compound of claim 1, wherein R_4 and R_5 are H.
22. The compound of claim 1, having the following chemical formula:





23. A compound of Formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof; wherein,

R₁ is independently H, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl;

R₃ is H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, CN, OR₇ or SR₁;

R₄ and R₅ are independently H, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl;

R₆ and R₇ are independently H, C₁-C₆ alkyl, or C₁-C₆ fluoroalkyl;

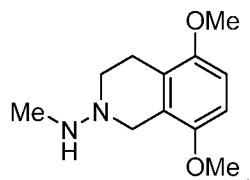
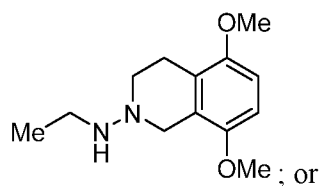
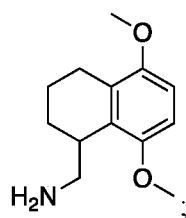
X is CH or N;

m is 0, 1, 2 or 3; and

n is 0, 1, 2 or 3.

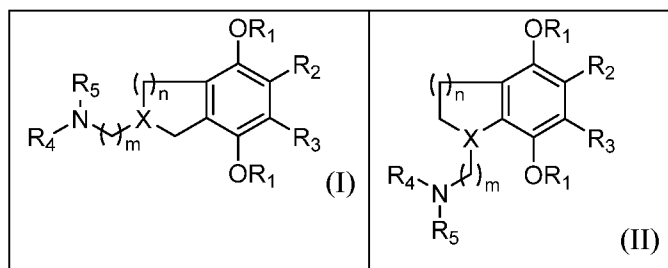
24. The compound of claim 23, wherein Y is =O.
25. The compound of claim 23, wherein Y is =NH.
26. The compound of claim 23, wherein R₁ is C₁-C₆ alkyl.
27. The compound of claim 26, wherein R₁ is C₁-C₃ alkyl.
28. The compound of claim 27, wherein R₁ is methyl.
29. The compound of claim 23, wherein R₁ is H.
30. The compound of claim 23, wherein R₁ is C₁-C₆ fluoroalkyl.
31. The compound of claim 23, wherein R₃ is H.
32. The compound of claim 23, wherein R₃ is halogen.
33. The compound of claim 23, wherein R₄ is H.
34. The compound of claim 23, wherein R₄ is C₁-C₆ alkyl.
35. The compound of claim 23, wherein R₅ is H.
36. The compound of claim 23, wherein R₅ is C₁-C₆ alkyl.
37. The compound of claim 23, wherein R₄ and R₅ are H.
38. The compound of claim 23, wherein X is CH.
39. The compound of claim 23, wherein X is N.
40. The compound of claim 23, wherein m is 0.
41. The compound of claim 23, wherein m is 1.

42. The compound of claim 23, wherein n is 1.
43. The compound of claim 23, wherein n is 2.
44. The compound of claim 23, wherein R₆ is H.
45. The compound of claim 23, wherein R₆ is C₁-C₆ alkyl.
46. The compound of claim 45, wherein R₆ is C₁-C₃ alkyl.
47. A compound selected from:



48. A pharmaceutical composition, comprising a compound of claim 1 and a pharmaceutically acceptable excipient.
49. A method of treating a mental health disease or disorder, the method comprising administering a therapeutically effective amount of the composition of claim 48.
50. The method of claim 49, wherein the mental health disease or disorder is selected from the group consisting of major depressive disorder, treatment resistant depression, substance use disorders and eating disorders.

51. The method of claim 49, wherein the mental health disease or disorder is selected from the group consisting of compulsive disorders, anxiety disorders, stress disorders, and rumination.
52. A pharmaceutical composition, comprising a compound of claim 23 and a pharmaceutically acceptable excipient.
53. A method of treating a mental health disease or disorder, the method comprising administering a therapeutically effective amount of the composition of claim 52.
54. The method of claim 53, wherein the mental health disease or disorder is selected from the group consisting of major depressive disorder, treatment resistant depression, substance use disorders and eating disorders.
55. The method of claim 53, wherein the mental health disease or disorder is selected from the group consisting of compulsive disorders, anxiety disorders, stress disorders, and rumination.
56. A method of treating a mental health disease or disorder, the method comprising administering a therapeutically effective amount of a compound of Formula (I), or a compound of Formula (II):



or a pharmaceutically acceptable salt thereof; wherein,

R₁ is independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl;

R₂, and R₃, are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl, halogen, CN, OR₁, S(O)NHR₁R₂, or SR₁;

R₄ and R₅ are independently H, C₁-C₆ alkyl, C₁-C₆ fluoroalkyl;

X is C or N;

m is 0, 1, 2 or 3;

n is 0, 1, 2 or 3.

57. The method of claim 56, wherein the mental health disease or disorder is selected from the group consisting of major depressive disorder, treatment resistant depression, substance use disorders and eating disorders.

58. The method of claim 56, wherein the mental health disease or disorder is selected from the group consisting of compulsive disorders, anxiety disorders, stress disorders, and rumination.

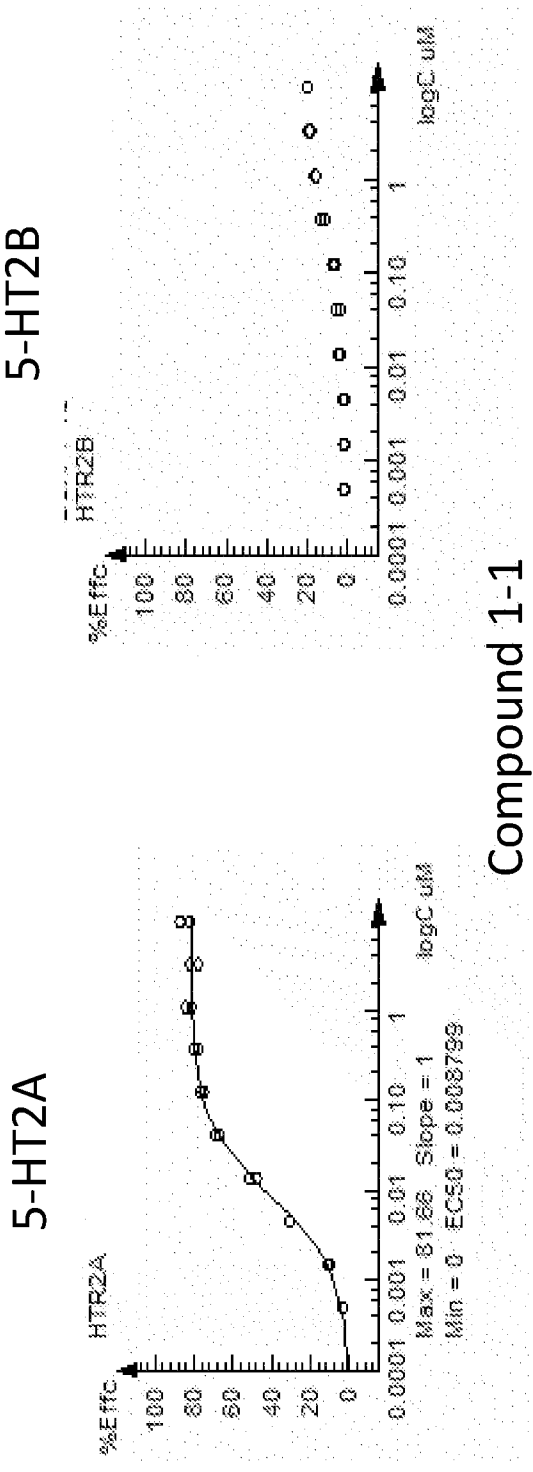
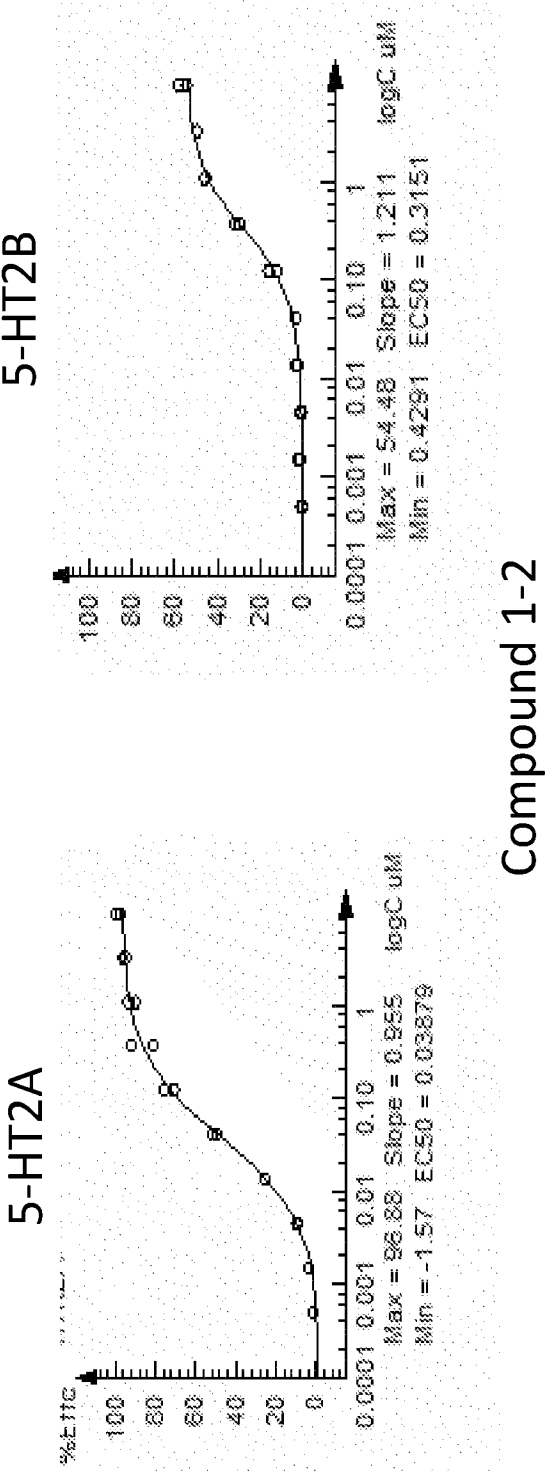
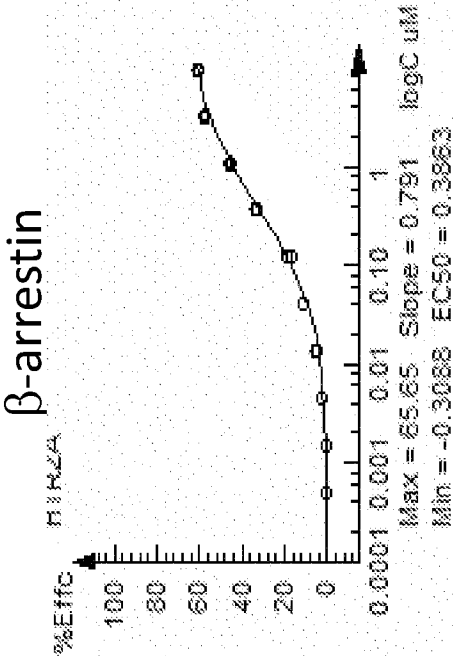
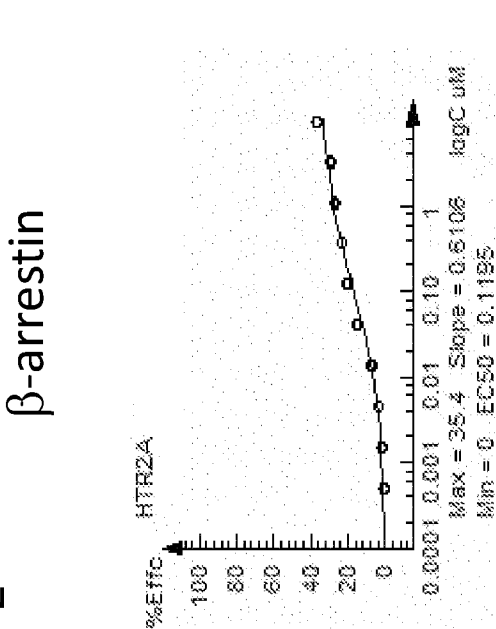


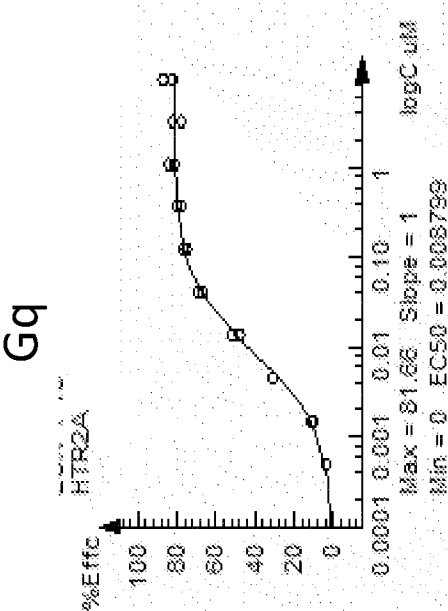
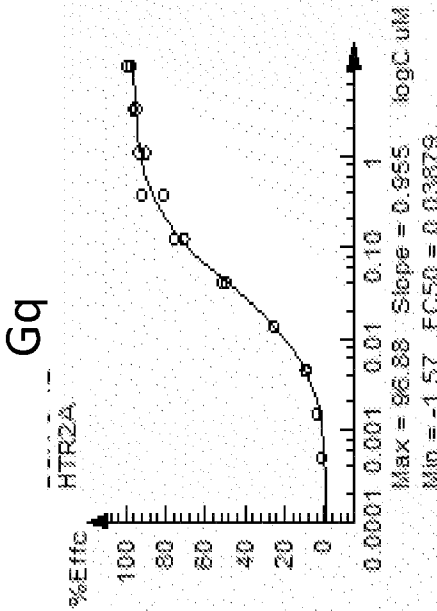
FIG. 1A



Compound 1-2



β -arrestin



Compound 1-1

FIG. 1B

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/082403

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - INV. - C07C 13/48; C07D 217/08 (2023.01)

ADD. - A61P 25/24; A61K 31/015 (2023.01)

CPC - INV. - C07C 13/48; C07D 217/08 (2023.02)

ADD. - A61P 25/24; A61K 31/015 (2023.02)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PUBCHEM, SID 103414083, Modify Date: 17 February 2021 [retrieved on 14 April 2023]. Retrieved from the Internet: <URL: https://pubchem.ncbi.nlm.nih.gov/substance/103414083 > entire document	1, 2, 4, 17, 19-21, 48-51
A	US 2010/0130742 A1 (HARRIS III et al) 27 May 2010 (27.05.2010) entire document	1, 2, 4, 17, 19-21, 48-51
A	PUBCHEM, SID 103936367, Modify Date: 08 October 2015 [retrieved on 22 February 2023]. Retrieved from the Internet: <URL: https://pubchem.ncbi.nlm.nih.gov/substance/103936367 > entire document	1, 2, 4, 17, 19-21, 48-51
A	US 2009/0275563 A1 (BONAVENTURE) 05 November 2009 (05.11.2009) entire document	1, 2, 4, 17, 19-21, 48-51

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

15 April 2023

Date of mailing of the international search report

MAY 17 2023

Name and mailing address of the ISA/

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Taina Matos

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/082403

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet(s).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 2, 4, 17, 19-21, 48-51

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

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International application No.

PCT/US2022/082403

Continued from Box No. III Observations where unity of invention is lacking

Claims 1, 2, 4, 17, 19-21, and 48-51 have been analyzed subject to the restriction that the claims read on a compound of Formula (III), or a pharmaceutically acceptable salt thereof, wherein each R1 is independently methyl; R2 is H; R3 is C1 alkyl, specifically unsubstituted methyl; R4 and R5 are independently H; and X is CH, pharmaceutical compositions thereof, and methods of treating a mental health disease or disorder thereof.

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International application No.

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This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-22 and 47-51 are drawn to compounds of Formula (III), or a pharmaceutically acceptable salt thereof, pharmaceutical compositions thereof, and methods of treating a mental health disease or disorder thereof.

Group II+: claims 23-46 and 52-55 are drawn to compounds of Formula (IV), or a pharmaceutically acceptable salt thereof, pharmaceutical compositions thereof, and methods of treating a mental health disease or disorder thereof.

Group III+: claims 56-58 are drawn to compounds of Formula (I) and Formula (II), or a pharmaceutically acceptable salt thereof, and methods of treating a mental health disease or disorder thereof.

The first invention of Group I+ is based on the proviso that wherein the compound is not 5,8-dimethoxy-6-methyl-1,2,3,4-tetrahydronaphthalen-2-amine; 5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; 6-bromo-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; 7-bromo-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; 5,7,8-trimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine; or 5,6,8-trimethoxy-1,2,3,4-tetrahydronaphthalen-2-amine, and is restricted to a compound of Formula (III), or a pharmaceutically acceptable salt thereof, wherein each R1 is independently methyl; R2 is H; R3 is C1 alkyl, specifically unsubstituted methyl; R4 and R5 are independently H; and X is CH, pharmaceutical compositions thereof, and methods of treating a mental health disease or disorder thereof. It is believed that claims 1, 2, 4, 17, 19-21, and 48-51 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

The first invention of Group II+ is restricted to a compound of Formula (IV), or a pharmaceutically acceptable salt thereof, wherein R1 is H; R3 is H; R4 and R5 are independently H; R6 is H; X is CH; Y is O; m is 0; and n is 0, pharmaceutical compositions thereof, and methods of treating a mental health disease or disorder thereof.

The first invention of Group III+ is restricted to a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R1 is independently H; R2 and R3 are independently H; R4 and R5 are independently H; X is C; m is 0; and n is 0, and methods of treating a mental health disease or disorder thereof.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound of Formula (III), or a pharmaceutically acceptable salt thereof, wherein each R1 is independently methyl; R2 is C1 alkyl, specifically unsubstituted methyl; R3 is C1 alkyl, specifically unsubstituted methyl; R4 and R5 are independently H; and X is CH, pharmaceutical compositions thereof, and methods of treating a mental health disease or disorder thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+, II+, and III+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I+, compounds of Formula (III), or a pharmaceutically acceptable salt thereof, are not present in Groups II+ and III+; the special technical features of Group II+, compounds of Formula (IV), or a pharmaceutically acceptable salt thereof, are not present in Groups I+ and III+; and the special technical features of Group III+, compounds of Formula (I) and Formula (II), or a pharmaceutically acceptable salt thereof, are not present in Groups I+ and II+.

The Groups I+, II+, and III+ formulae do not share a significant structural element requiring the selection of alternatives for the R1, R2, R3, R4, R5, R6, X, Y, m, n, and accordingly these groups lack unity a priori.

Additionally, even if Groups I+, II+, and III+ were considered to share the technical features of a compound having the core structure of Formula (I), or a pharmaceutically acceptable salt thereof; a compound having the core structure of Formula (II), or a pharmaceutically acceptable salt thereof; a compound having the core structure of Formula (III), or a pharmaceutically acceptable salt thereof; and a compound having the core structure of Formula (IV), or a pharmaceutically acceptable salt thereof; a pharmaceutical composition comprising a compound and a pharmaceutically acceptable excipient; a method of treating a mental health disease or disorder, the method comprising administering a therapeutically effective amount of a composition; and a method of treating a mental health disease or disorder, the method comprising administering a therapeutically effective amount of a compound, these shared technical features do not represent a contribution over the prior art as disclosed by the publication entitled "SID 103936367" by PubChem (hereinafter, "PubChem '367'"), US 2010/0130742 A1 to Harris, III et al. (hereinafter, "Harris"), and US 2009/0275563 A1 to Bonaventure (hereinafter, "Bonaventure").

PubChem '367 teaches a compound having the core structure of Formula (I), or a pharmaceutically acceptable salt thereof (Pg. 2, compound as shown); a compound having the core structure of Formula (II), or a pharmaceutically acceptable salt thereof (Pg. 2, compound as shown); and a compound having the core structure of Formula (III), or a pharmaceutically acceptable salt thereof (Pg. 2, compound as shown).

Harris teaches a compound having the core structure of Formula (IV), or a pharmaceutically acceptable salt thereof (Paras. [0004]-[0008], compounds of the formula I wherein m is 2 and each R1 is hydroxy).

Bonaventure teaches a pharmaceutical composition comprising a compound and a pharmaceutically acceptable excipient (Para. [0026], the invention relates to a pharmaceutical composition for treating a serotonin-mediated disease or condition, comprising: (a) (i) an amount of a 5-HT7 receptor antagonist, and (ii) an amount of a selective serotonin reuptake inhibitor, such amounts together providing an effective combined amount; and (b) a pharmaceutically acceptable excipient); a method of treating a mental health disease or disorder, the method comprising administering a therapeutically effective amount of a composition (Para. [0026], a method of treating a subject suffering from or diagnosed with a serotonin-mediated disease or condition, comprising administering to a subject in need of such treatment: an amount of a 5-HT7 receptor antagonist and an amount of an SRI and a 5-HT7 receptor antagonist, the amounts

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together providing an effective combined amount. In another embodiment, the invention relates to a pharmaceutical composition for treating a serotonin-mediated disease or condition, comprising: (a) (i) an amount of a 5-HT7 receptor antagonist, and (ii) an amount of a selective serotonin reuptake inhibitor, such amounts together providing an effective combined amount; and (b) a pharmaceutically acceptable excipient; Para. [0036], the serotonin-mediated disease or disorder is selected from depression, anxiety); and a method of treating a mental health disease or disorder, the method comprising administering a therapeutically effective amount of a compound (Para. [0026], a method of treating a subject suffering from or diagnosed with a serotonin-mediated disease or condition, comprising administering to a subject in need of such treatment: an amount of a 5-HT7 receptor antagonist and an amount of an SRI and a 5-HT7 receptor antagonist, the amounts together providing an effective combined amount; Para. [0036], the serotonin-mediated disease or disorder is selected from depression, anxiety).

The inventions listed in Groups I+, II+, and III+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.