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(54) Benævnelse: **SPECIFIKKE TRYPTAMINER TIL BRUG I BEHANDLINGEN AF HUMØRSVINGNINGER**

(56) Fremdragne publikationer:

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US-A1- 2018 221 396
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BRANDT SIMON D. ET AL: "Analytical chemistry of synthetic routes to psychoactive tryptamines : Part II. Characterisation of the Speeter and Anthony synthetic route to N,N-dialkylated tryptamines using GC-EI-ITMS, ESI-TQ-MS-MS and NMR", ANALYST, vol. 130, no. 3, 1 January 2005 (2005-01-01), UK, pages 330, XP055805886, ISSN: 0003-2654, DOI: 10.1039/b413014f
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DESCRIPTION

Description

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of, and priority to, U.S. Provisional Application No. 62/978,075, filed on February 18, 2020.

BACKGROUND

[0002] Depression is a common psychological problem and refers to a mental state of low mood and aversion to activity. Various symptoms associated with depression include persistent anxious or sad feelings, feelings of helplessness, hopelessness, pessimism, and/or worthlessness, low energy, restlessness, irritability, fatigue, loss of interest in pleasurable activities or hobbies, excessive sleeping, overeating, appetite loss, Insomnia, thoughts of suicide, and suicide attempts. The presence, severity, frequency, and duration of the above-mentioned symptoms vary on a case-by-case basis.

[0003] Approximately one third of patients with major depressive disorder (MDD) fail to achieve remission of their symptoms, even after multiple rounds of treatment with several known classes of antidepressants, including selective serotonin reuptake inhibitors (SSRIs) (Rush *et al.* 2006). This high prevalence of treatment-resistant depression (TRD) makes clear the need for new, more efficacious pharmacotherapies for depression that will target new mechanisms and/or patient populations.

[0004] Tryptamines are monoamine alkaloids that contain an indole ring and are structurally similar to the amino acid tryptophan, from which the name derives.

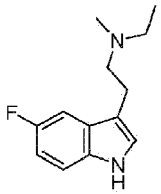
[0005] There are a significant number of tryptamine compounds that include naturally occurring compounds and chemical derivatives with similar structure that may be ring unsubstituted or ring substituted. Many tryptamines are $5HT_{2A}$ receptor agonists and/or modulators of other serotonin receptors and are known to be psychoactive and, in many cases, cause prolonged hallucinations. The most well-known tryptamines are psychedelic compounds, including compounds derived from entheogenic fungi (psilocybin and psilocin), *N,N*-dimethyltryptamine (DMT), lysergic acid diethylamide (LSD), 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), bufotenin, and ibogaine. These compounds are known to have significant effects on thought, perception, and behavior. However, these compounds are currently classified as Schedule I drugs under the Controlled Substances Act due to their high abuse potential, no accepted medical use, and lack of established safety. Moreover, tryptamines are metabolized by a number of pathways, in some cases including monoamine oxidase, limiting the oral bioavailability of some compounds and resulting in very short durations of action. Conversely, other tryptamines have very long durations of action, which makes them challenging to use in a guided therapy setting, where supervised sessions of many hours in duration are costly for patients and inconvenient for healthcare providers.

[0006] Accordingly, there remains a need for safe and effective tryptamine compounds that can reliably be used for the treatment of mood disorders.

[0007] WO 2018064465 describes a method of using non-hallucinogenic analogs of psychedelic compounds for increasing neural plasticity of the neuronal cell, and a method of using thereof for treating a brain disorder, wherein the non-hallucinogenic analog of a psychedelic is compound 6-methoxy-N,N-dimethyltryptamine, and 6-fluoro-N,N-dimethyltryptamine. US 2018021326 describes N,N-dimethyltryptamine as candidate for neurogenesis. BRANDT SIMON D. ET AL, "Analytical chemistry of synthetic routes to psychoactive tryptamines : Part II. Characterisation of the Speeter and Anthony synthetic route to N,N-dialkylated tryptamines using GC-EI-ITMS, ESI-TQ-MS-MS and NMR", ANALYST, UK, (20050101), vol. 130, no. 3, page 330,describes N,methyl-N,ethyl-tryptamine as a psychoactive tryptamine. ADAMOWICZ PIOTR ET AL, "Simple and rapid screening procedure for 143 new psychoactive substances by liquid chromatography-tandem mass spectrometry : Simple and rapid screening procedure for 143 new psychoactive substances", DRUG TESTING AND ANALYSIS, GB, (20160701), vol. 8, no. 7, pages 652 - 667, describes =N-methyl-N-ethyltryptamine as a psycoactive substance.

SUMMARY

[0008] The present invention is defined in the appended claims. The present invention provides the compound 2:

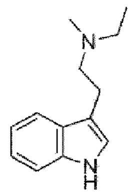


Compound 2

or a pharmaceutically acceptable salt thereof.

[0009] Additionally, the present invention provides pharmaceutical compositions of compound 2 and methods of using the same.

[0010] The present disclosure includes methods of treating mood disorders in a patient in need thereof, comprising administering an effective amount of Compound 2 or compound 4:



Compound 4.

or a pharmaceutically acceptable salt thereof.

[0011] For example, disclosed herein are methods and compositions directed to treating a mood disorder by administering to a patient in need thereof a pharmaceutical composition comprising an effective amount of compound 2 or compound 4, or a pharmaceutically acceptable salt thereof. In certain cases, the methods and compositions may treat mood disorders that include depressive disorders, bipolar and related disorders, substance-related disorders, and/or anxiety disorders.

[0012] In certain cases, the methods and compositions may treat mood disorders that include obsessive-compulsive and related disorders. In certain cases, the methods and compositions may treat mood disorders that include trauma- and stressor-related disorders. In certain cases, the methods and compositions may treat mood disorders that include feeding and eating disorders. In certain cases, the methods and compositions may treat mood disorders that include neurocognitive disorders. In certain cases, the methods and compositions may treat mood disorders that include neurodevelopmental disorders. In certain cases, the methods and compositions may treat mood disorders that include personality disorders. In certain cases, the methods and compositions may treat mood disorders that include sexual dysfunctions. In certain cases, the methods and compositions may treat mood disorders that include gender dysphoria.

BRIEF DESCRIPTION OF THE DRAWINGS

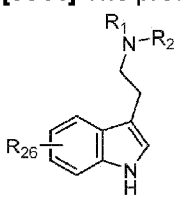
[0013]

FIG. 1 depicts immobility time in the FST. A one-way ANOVA revealed a significant main effect of treatment ($F(9,99) = 12.42$, $P < 0.0001$) on the total time spent immobile in the FST. Dunnett's multiple comparisons test was used to test if a group was significantly different from vehicle. All treatments except for Compound 2 at 0.1 mg/kg were significantly different from vehicle. * $P < .05$, ** $P < .01$, *** $P < .001$, **** $P < .0001$ vs. vehicle.

FIG. 2 depicts swimming time in the FST. A one-way ANOVA revealed a significant main effect of treatment ($F(9,99) = 2.653$, $P = 0.0090$) on the total time spent swimming in the FST. Dunnett's multiple comparisons test was used to test if a group was significantly different from vehicle. * $P < .05$, ** $P < .01$, *** $P < .001$, **** $P < .0001$ vs. vehicle.

DETAILED DESCRIPTION

[0014] The present disclosure includes a compound according to Formula I:



I,

or a pharmaceutically acceptable salt thereof,
wherein

R_1 is optionally substituted C_1-C_4 aliphatic;

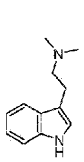
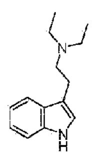
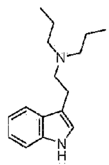
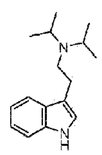
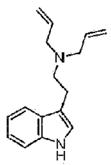
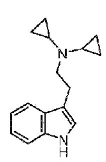
R_2 is optionally substituted C_1-C_4 aliphatic;

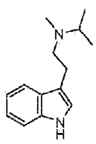
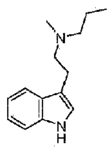
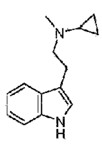
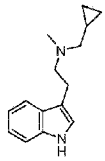
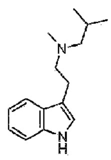
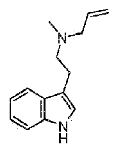
R_{26} is selected from the group consisting of hydrogen, halogen, -CN, -OH, C_1-C_3 alkoxy, C_1-C_3 haloalkyl, OAc, $-OPO(OH)_2$ and NH_2.

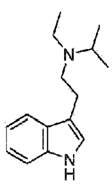
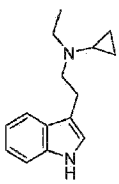
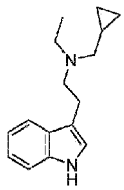
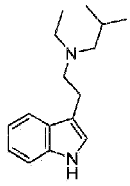
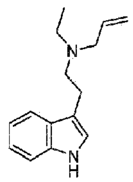
[0015] In some cases, R_1 is selected from the group consisting of Me, Et, nPr, iPr, cyclopropyl, allyl, isobutyl, cyclopropylmethyl. In some cases, R_2 is selected from the group consisting of Me, Et, nPr, iPr, cyclopropyl, allyl, isobutyl, cyclopropylmethyl.

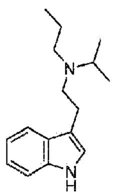
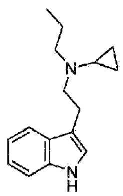
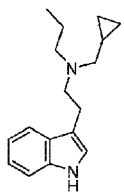
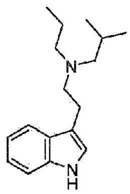
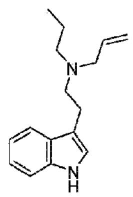
[0016] In some cases, R_{26} is selected from the group consisting of hydrogen, F, Cl, Br, I, CF_3, Me, CN, OMe, OH, OAc, and NH_2. In some cases, R_{26} is selected from the group consisting of F, Cl, Br, I, CF_3, Me, CN, OMe, OH, OAc, and NH_2. In some cases, R_{26} is halogen. In some cases, R_{26} is fluoro. In some cases, R_{26} is chloro. In some cases, R_{26} is bromo. In some cases, R_{26} is iodo.

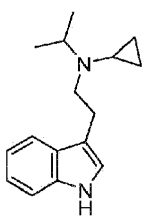
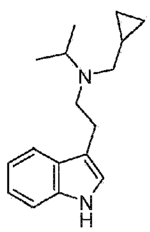
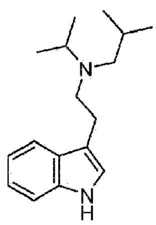
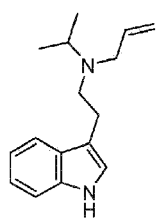
[0017] In certain cases, the present disclosure includes a compound selected from the group consisting of:

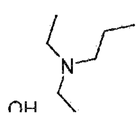
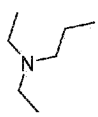
    

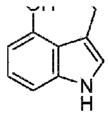
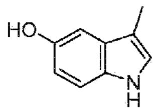
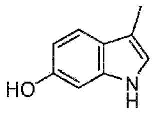
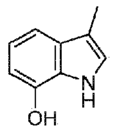
    

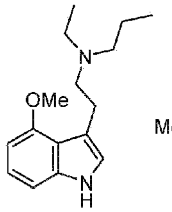
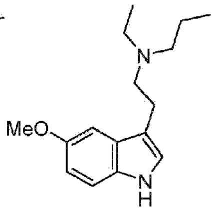
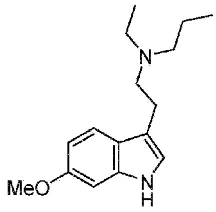
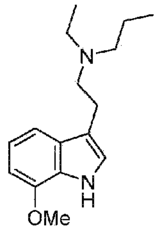
   

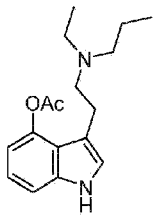
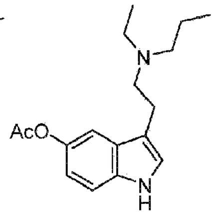
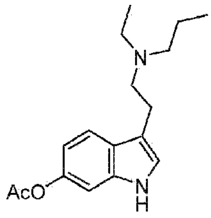
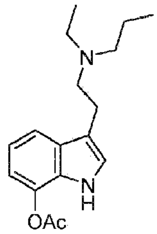
or a pharmaceutically acceptable salt thereof.

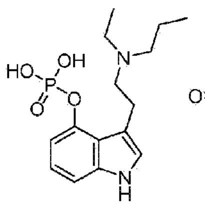
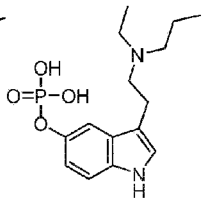
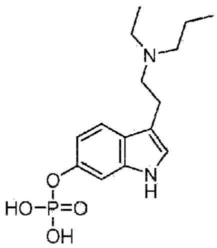
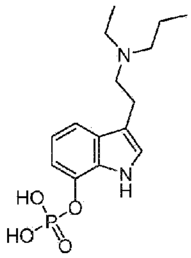
[0018] In certain cases, the present disclosure includes a compound selected from the group consisting of:

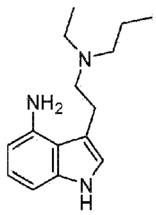
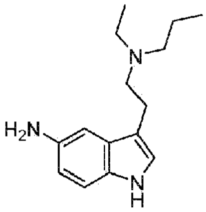
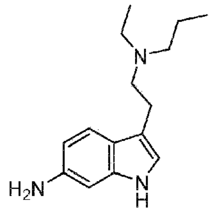
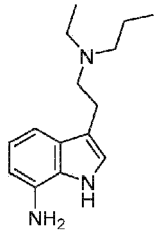
   

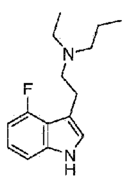
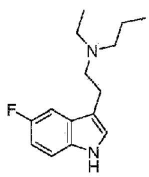
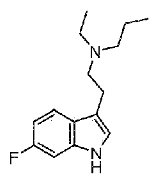
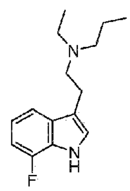
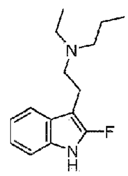





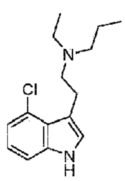
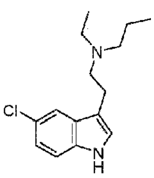
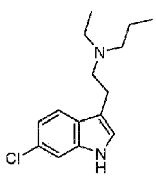
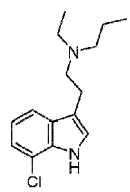
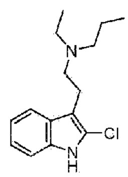





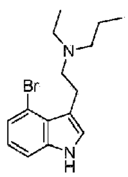
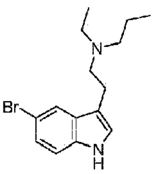
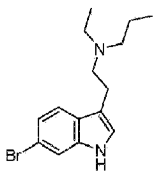
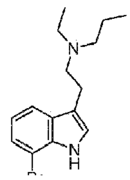
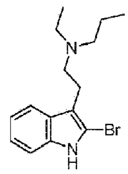





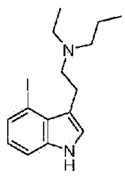
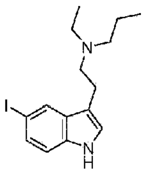
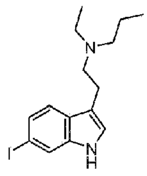
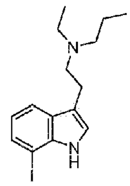
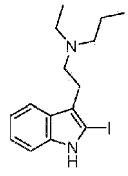





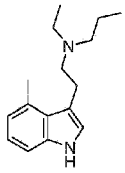
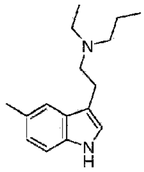
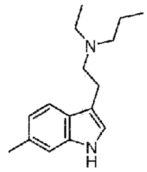
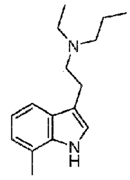
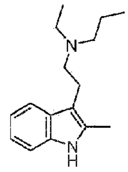





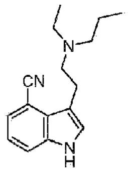
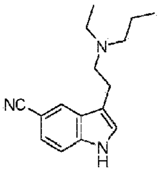
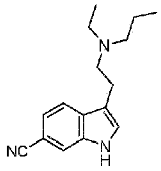
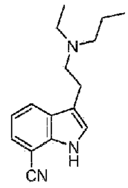
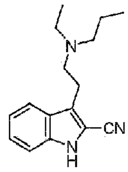






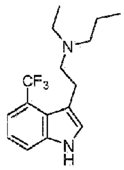
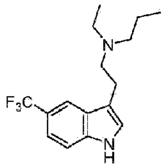
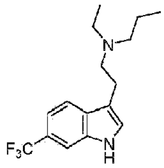
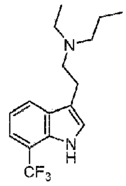
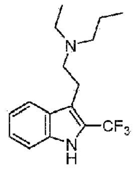






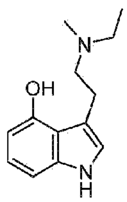
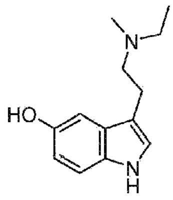
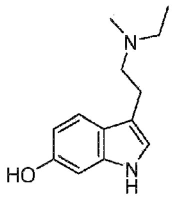
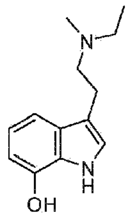
    

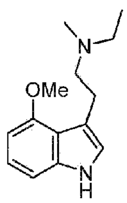
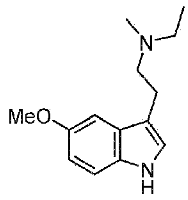
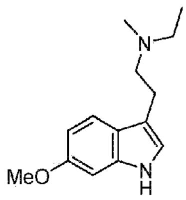
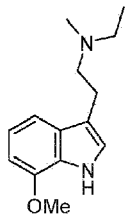
    

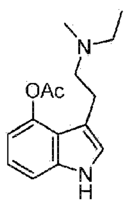
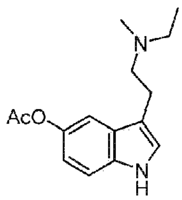
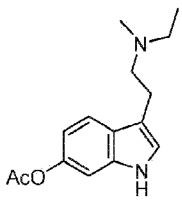
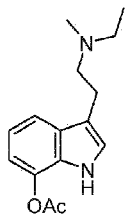
    

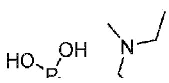
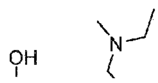
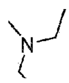
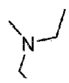
or a pharmaceutically acceptable salt thereof.

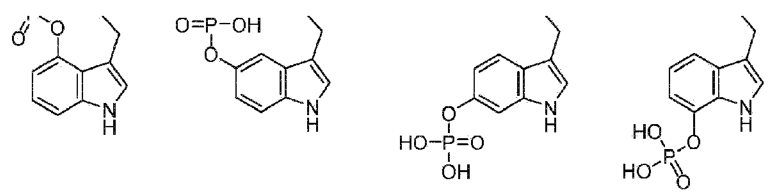
[0019] In certain cases, the present disclosure includes a compound selected from the group consisting of:

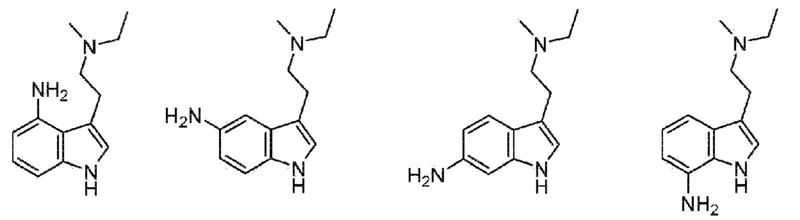
   

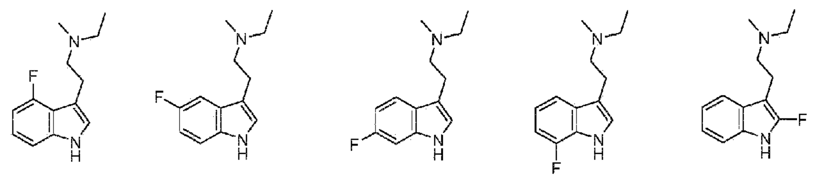
   

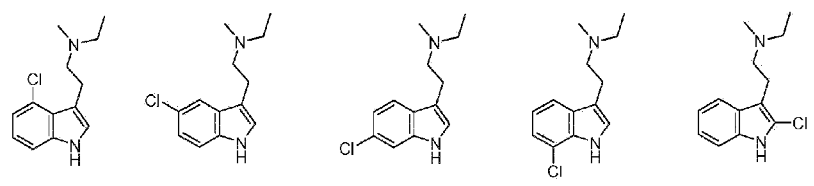
   

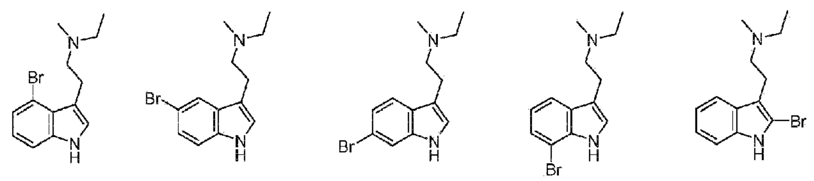
   

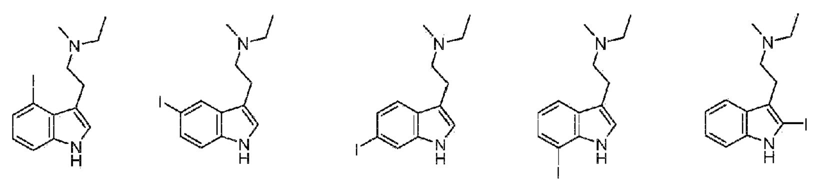


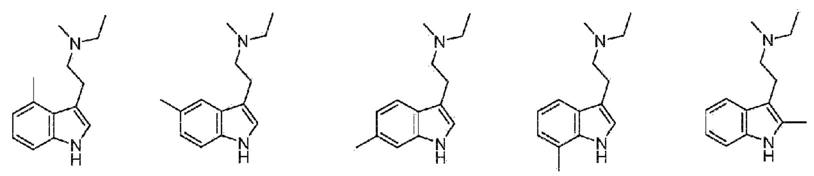


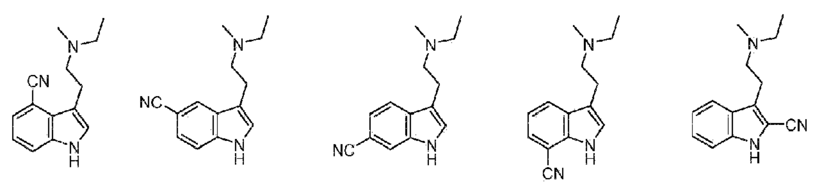


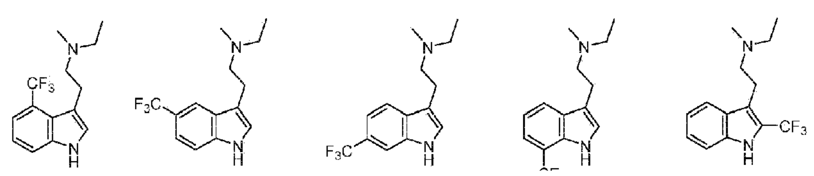












or a pharmaceutically acceptable salt thereof.

[0020] Described herein are methods and compositions for treating a mood disorder by administering to a patient in need thereof a compound disclosed herein. Also provided are pharmaceutical compositions that include a compound disclosed herein.

[0021] In certain cases, the methods and compositions may be used to treat a mood disorder including depressive disorders, e.g., major depressive disorder, persistent depressive disorder, postpartum depression, premenstrual dysphoric disorder, seasonal affective disorder, psychotic depression, disruptive mood dysregulation disorder, substance/medication-induced depressive disorder, and depressive disorder due to another medical condition.

[0022] In some cases, depression conditions include major depressive disorder and dysthymic disorder. In some cases, depression conditions develop under unique circumstances, including, but are not limited to, psychotic depression, postpartum depression, seasonal affective disorder (SAD), mood disorder, depressions caused by chronic medical conditions such as cancer or chronic pain, chemotherapy, chronic stress, post traumatic stress disorders, and bipolar disorder (or manic depressive disorder). In some cases, depression conditions that are expected to be treated according to this aspect of the present disclosure include, but are not limited to, major depressive disorder, dysthymic disorder, psychotic depression, postpartum depression, premenstrual syndrome, premenstrual dysphoric disorder, seasonal affective disorder (SAD), anxiety, mood disorder, depressions caused by chronic medical conditions such as cancer or chronic pain, chemotherapy, chronic stress, post traumatic stress disorders, and bipolar disorder (or manic depressive disorder).

[0023] Also disclosed herein are methods of treating refractory depression, *e.g.*, patients suffering from a depressive disorder that does not, and/or has not, responded to adequate courses of at least one, or at least two, other antidepressant compounds or therapeutics. For example, provided herein is a method of treating depression in a treatment resistant patient, comprising a) optionally identifying the patient as treatment resistant and b) administering an effective dose of a disclosed compound. As used herein "depressive disorder" encompasses refractory depression. In some cases, refractory depression occurs in patients suffering from depression who are resistant to standard pharmacological treatments, including tricyclic antidepressants, MAOIs, SSRIs, and double and triple uptake inhibitors and/or anxiolytic drugs, as well non-pharmacological treatments such as psychotherapy, electroconvulsive therapy, vagus nerve stimulation and/or transcranial magnetic stimulation. In some cases, a treatment resistant-patient may be identified as one who fails to experience alleviation of one or more symptoms of depression (e.g., persistent anxious or sad feelings, feelings of helplessness, hopelessness, pessimism) despite undergoing one or more standard pharmacological or non-pharmacological treatment. In certain cases, a treatment-resistant patient is one who fails to experience alleviation of one or more symptoms of depression despite undergoing treatment with two different antidepressant drugs. In other cases, a treatment-resistant patient is one who fails to experience alleviation of one or more symptoms of depression despite undergoing treatment with four different antidepressant drugs. In some cases, a treatment-resistant patient may also be identified as one who is unwilling or unable to tolerate the side effects of one or more standard pharmacological or non-pharmacological treatment.

[0024] In some cases, symptoms associated with depression include, but are not limited to, persistent anxious or sad feelings, feelings of helplessness, hopelessness, pessimism, and/or worthlessness, low energy, restlessness, irritability, fatigue, loss of interest in pleasurable activities or hobbies, excessive sleeping, overeating, appetite loss, insomnia, thoughts of suicide, or suicide attempts. In some case, various symptoms associated with anxiety include fear, panic, heart palpitations, shortness of breath, fatigue, nausea, and headaches among others. In addition, patients suffering from any form of depression often experience anxiety. It is expected that the methods of the present condition can be used to treat anxiety or any of the symptoms thereof. In some embodiments, presence, severity, frequency, and duration of symptoms of depression vary on a case to case basis.

[0025] In certain cases, the methods and compositions may be used to treat a mood disorder including bipolar and related disorders, *e.g.*, bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance/medication-induced bipolar and related disorder, and bipolar and related disorder due to another medical condition.

[0026] In certain cases s, the methods and compositions may be used to treat a mood disorder including substance-related disorders, *e.g.*, preventing a substance use craving, diminishing a substance use craving, and/or facilitating substance use cessation or withdrawal. Substance use disorders involve abuse of psychoactive compounds such as alcohol, caffeine, cannabis, inhalants, opioids, sedatives, hypnotics, anxiolytics, stimulants, nicotine and tobacco. As used herein "substance" or "substances" are psychoactive compounds which can be addictive such as alcohol, caffeine, cannabis, hallucinogens, inhalants, opioids, sedatives, hypnotics, anxiolytics, stimulants, nicotine and tobacco. For example, the methods and compositions may be used to facilitate smoking cessation or cessation of opioid use.

[0027] In certain cases, the methods and compositions may be used to treat a mood disorder including anxiety disorders, *e.g.*, separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder (social phobia), panic disorder, panic attack, agoraphobia, generalized anxiety disorder, substance/medication-induced anxiety disorder, and anxiety disorder due to another medical condition.

[0028] In certain cases, the methods and compositions may be used to treat a mood disorder including obsessive-compulsive and related disorders, e.g., obsessive-compulsive disorder, body dysmorphic disorder, hoarding disorder, trichotillomania (hair-pulling disorder), excoriation (skinpicking) disorder, substance/medication-induced obsessive-compulsive and related disorder, and obsessive-compulsive and related disorder due to another medical condition.

[0029] In certain cases, the methods and compositions may be used to treat a mood disorder including trauma- and stressor-related disorders, *e.g.,* reactive attachment disorder, disinhibited social engagement disorder, posttraumatic stress disorder, acute stress disorder, and adjustment disorders.

[0030] In certain cases, the methods and compositions may be used to treat a mood disorder including feeding and eating disorders, *e.g.,* anorexia nervosa, bulimia nervosa, binge-eating disorder, pica, rumination disorder, and avoidant/restrictive food intake disorder.

[0031] In certain cases, the methods and compositions may be used to treat a mood disorder including neurocognitive disorders, *e.g.,* delirium, major neurocognitive disorder, mild neurocognitive disorder, major or mild neurocognitive disorder due to Alzheimer's disease, major or mild frontotemporal neurocognitive disorder, major or mild neurocognitive disorder with Lewy bodies, major or mild vascular neurocognitive disorder, major or mild neurocognitive disorder due to traumatic brain injury, substance/medication-induced major or mild neurocognitive disorder, major or mild neurocognitive disorder due to HIV infection, major or mild neurocognitive disorder due to prion disease, major or mild neurocognitive disorder due to Parkinson's disease, major or mild neurocognitive disorder due to Huntington's disease, major or mild neurocognitive disorder due to another medical condition, and major or mild neurocognitive disorder due to multiple etiologies.

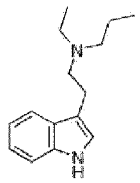
[0032] In certain cases, the methods and compositions may be used to treat a mood disorder including neurodevelopmental disorders, *e.g.,* autism spectrum disorder, attention-deficit/hyperactivity disorder, stereotypic movement disorder, tic disorders, Tourette's disorder, persistent (chronic) motor or vocal tic disorder, and provisional tic disorder. In some certain cases, a variety of other neurological conditions are expected to be treated according to the methods of the present disclosure. In some cases, neurological conditions include, but are not limited to, a learning disorder, autistic disorder, attention-deficit hyperactivity disorder, Tourette's syndrome, phobia, post-traumatic stress disorder, dementia, AIDS dementia, Alzheimer's disease, Parkinson's disease, spasticity, myoclonus, muscle spasm, bipolar disorder, a substance abuse disorder, urinary incontinence, and schizophrenia.

[0033] In certain cases, the methods and compositions may be used to treat a mood disorder including personality disorders, *e.g.*, borderline personality disorder.

[0034] In certain cases, the methods and compositions may be used to treat a mood disorder including sexual dysfunctions, *e.g.*, delayed ejaculation, erectile disorder, female orgasmic disorder, female sexual interest/arousal disorder, genito-pelvic pain/penetration disorder, male hypoactive sexual desire disorder, premature (early) ejaculation, and substance/medication-induced sexual dysfunction.

[0035] In certain cases, the methods and compositions may be used to treat a mood disorder including gender dysphoria.

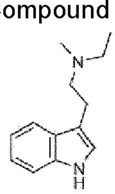
[0036] In certain cases disclosed are methods and compositions for treating a mood disorder by administering to a subject in need thereof an effective amount of ethylpropyltryptamine (EPT; Compound 1) or a pharmaceutically acceptable salt thereof.



EPT

(Compound 1)

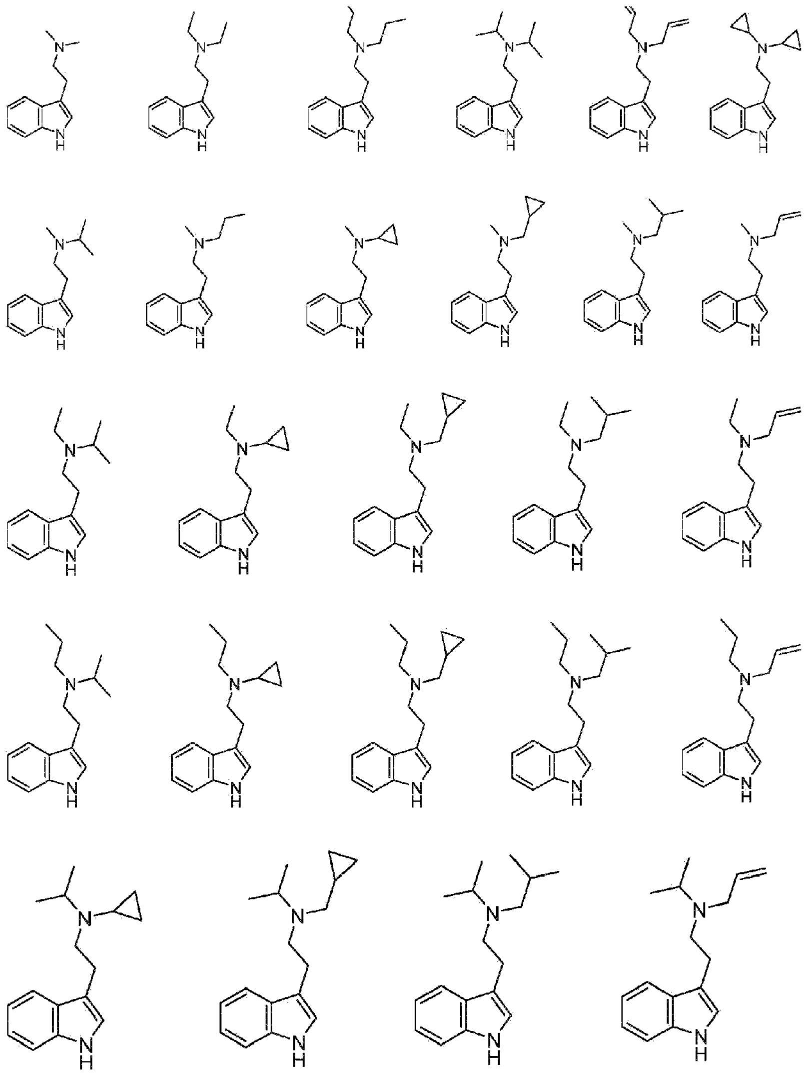
[0037] In other cases disclosed are methods and compositions for treating a mood disorder by administering to a subject in need thereof an effective amount of methylethyltryptamine (MET; Compound 2) or a pharmaceutically acceptable salt thereof.



MET

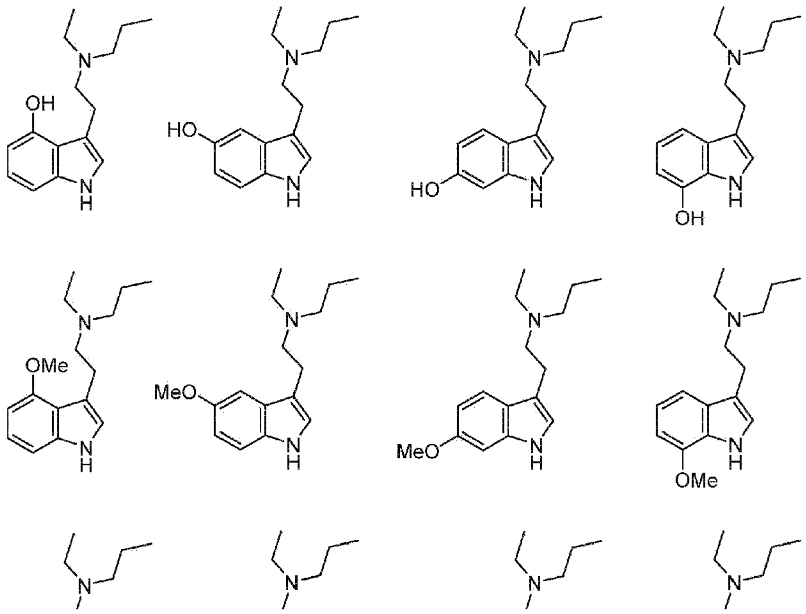
(Compound 2)

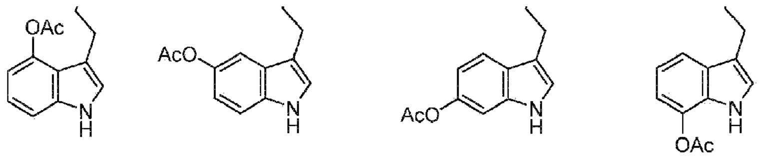
[0038] In other cases disclosed are methods and compositions for treating a mood disorder by administering to a subject in need thereof an effective amount of a compound disclosed herein selected from the following structures:

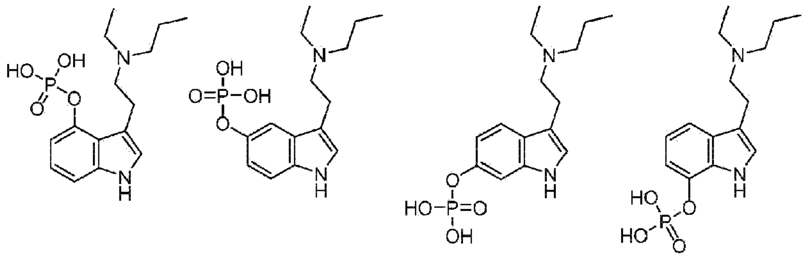


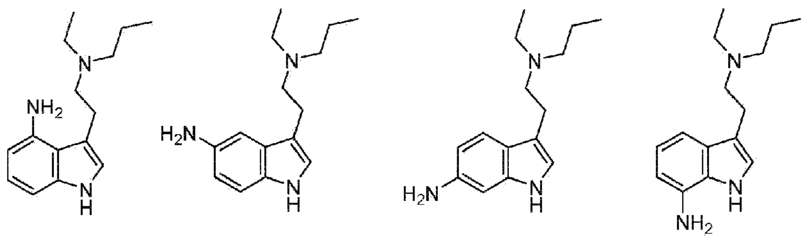
or a pharmaceutically acceptable salt thereof.

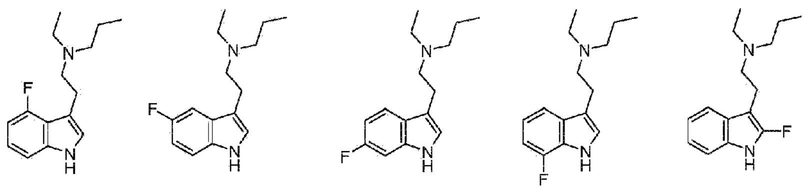
[0039] In other cases disclosed are methods and compositions for treating a mood disorder by administering to a subject in need thereof an effective amount of a compound disclosed herein selected from the following structures:

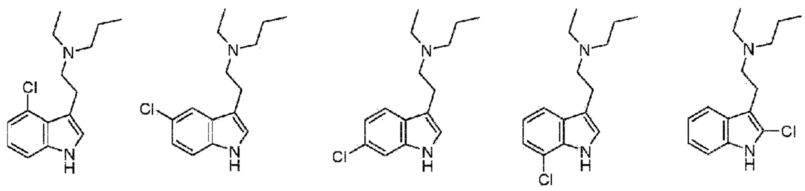


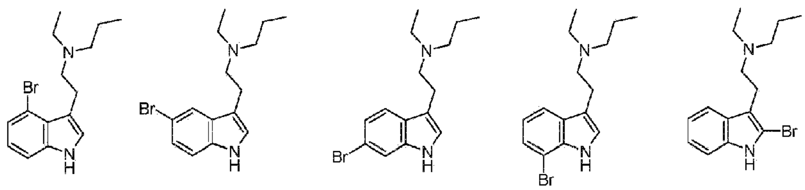


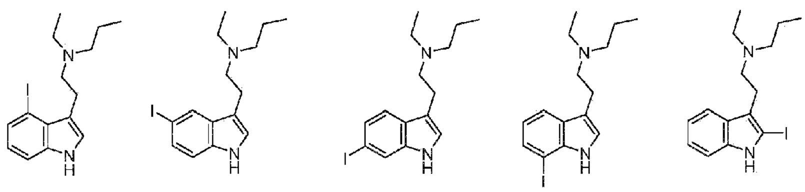


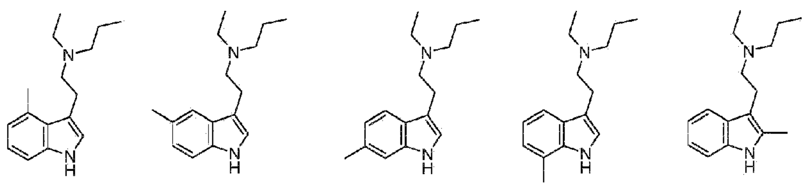


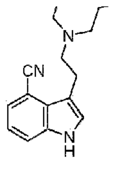
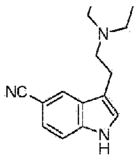
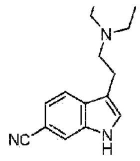
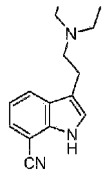
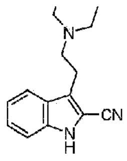


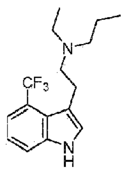
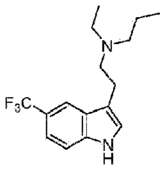
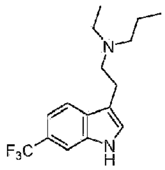
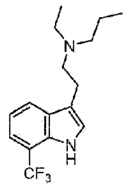
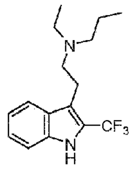






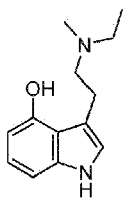
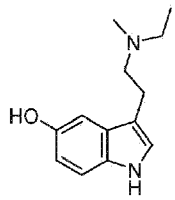
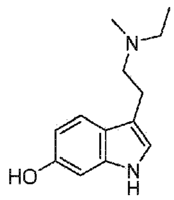
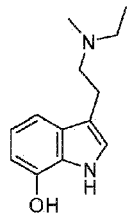


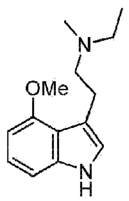
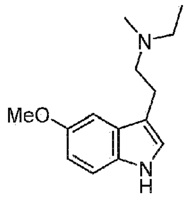
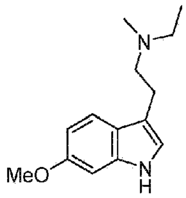
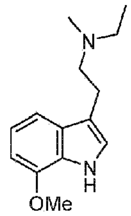
    

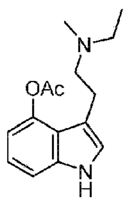
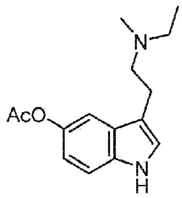
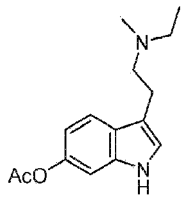
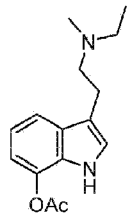
    

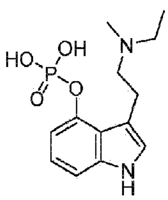
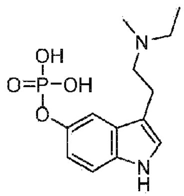
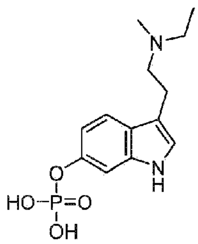
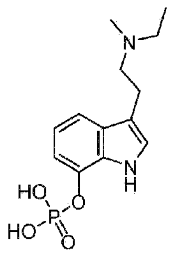
or a pharmaceutically acceptable salt thereof.

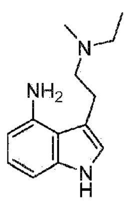
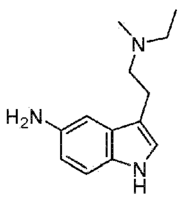
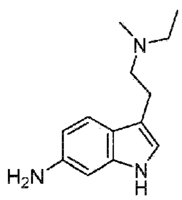
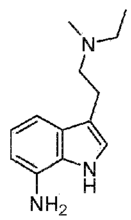
[0040] In other cases disclosed are methods and compositions for treating a mood disorder by administering to a subject in need thereof an effective amount of a compound disclosed herein selected from the following structures:

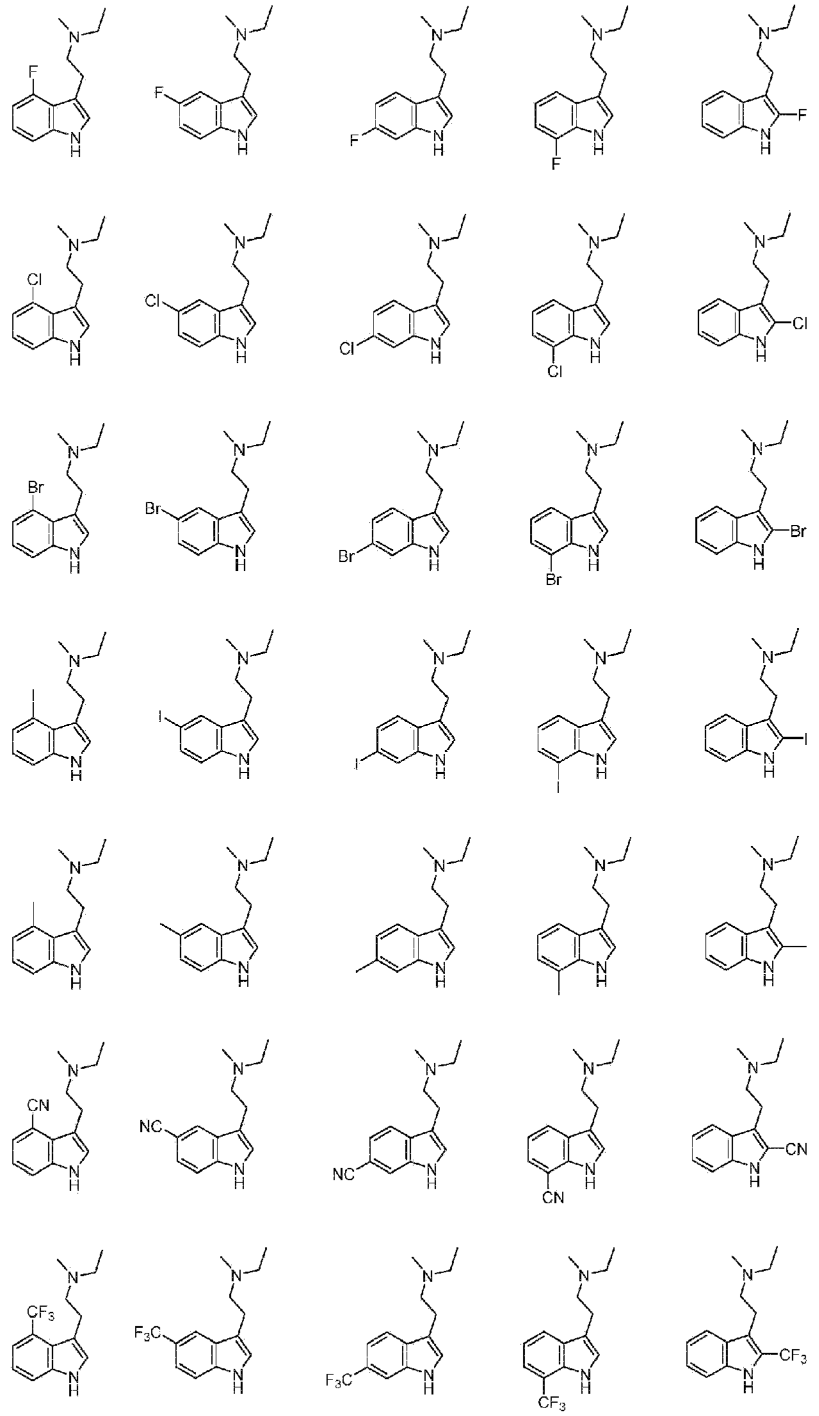
   



or a pharmaceutically acceptable salt thereof. In other cases, disclosed herein are methods and compositions for treating migraine or cluster headache by administering to a patient in need thereof a compound of the present disclosure.

[0041] In other cases, disclosed herein are methods and compositions for treating inflammation by administering to a patient in need thereof a compound of the present disclosure.

[0042] In certain cases, methods include treating a mood disorder, *e.g.*, a depressive disorder, by administering to a patient in need thereof a pharmaceutical composition including about 0.01 mg to about 400 mg of a compound disclosed herein. In cases, doses may be, *e.g.,* in the range of about 0.01 to 400 mg, 0.01 to 300 mg, 0.01 to 250 mg, 0.01 to 200 mg, 0.01 to 150 mg, 0.01 to 100 mg, 0.01 to 75 mg, 0.01 to 50 mg, 0.01 to 25 mg, 0.01 to 20 mg, 0.01 to 15 mg, 0.01 to 10 mg, 0.01 to 5 mg, 0.01 to 1 mg, 0.01 to 0.5 mg, 0.01 to 0.1 mg, 0.1 to 300 mg, 0.1 to 250 mg, 0.1 to 200 mg, 0.1 to 150 mg, 0.1 to 100 mg, 0.1 to 75 mg, 0.1 to 50 mg, 0.1 to 25 mg, 0.1 to 20 mg, 0.1 to 15 mg, 0.1 to 10 mg, 0.1 to 5 mg, 0.1 to 1 mg, 10 to 300 mg, 10 to 250 mg, 10 to 200 mg, 10 to 150 mg, 10 to 100 mg, 10 to 50 mg, 10 to 25 mg, 10 to 15 mg, , 20 to 300 mg, 20 to 250 mg, 20 to 200 mg, 20 to 150 mg, 20 to 100 mg, 20 to 50 mg, 50 to 300 mg, 50 to 250 mg, 50 to 200 mg, 50 to 150 mg, 50 to 100 mg, 100 to 300 mg, 100 to 250 mg, 100 to 200 mg, with doses of, *e.g.,* about 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.25 mg, 1.5 mg, 1.75 mg, 2.0 mg, 2.5 mg, 3.0 mg, 3.5 mg, 4.0 mg, 4.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30, mg, 35 mg, 40 mg, 45 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, and 400 mg being examples.

[0043] In specific cases, dosages may include amounts of a compound disclosed herein in the range of about, *e.g.,* 1 mg to 200 mg, 1 mg to 100 mg, 1 mg to 50 mg, 1 mg to 40 mg, 1 mg to 30 mg, 1 mg to 20 mg, 1 mg to 15 mg, 0.01 mg to 10 mg, 0.1 mg to 15 mg, 0.15 mg to 12.5 mg, or 0.2 mg to 10 mg, with doses of 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg, 0.9 mg, 1.0 mg, 1.5 mg, 1.75 mg, 2 mg, 2.5 mg, 2.75 mg, 3 mg, 3.5 mg, 3.75 mg, 4 mg, 4.5 mg, 4.75 mg, 5 mg, 5.5 mg, 6 mg, 6.5 mg, 7 mg, 7.5 mg, 8 mg, 8.5 mg, 9 mg, 9.5 mg, 10 mg, 11 mg, 12 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 60 mg, 75 mg, 80 mg, 90 mg, 100 mg, 125 mg, 150 mg, and 200 mg being specific examples of doses.

[0044] Typically, dosages of a compound disclosed herein are administered once, twice, three or four times daily, every other day, every three days, once weekly, twice monthly, once monthly, or 3-4 times yearly to a patient in need thereof. In cases, the dosage is about, *e.g.,* 1-400 mg/day, or 1-300 mg/day, or 1-250 mg/day, or 1-200 mg/day, for example 300 mg/day, 250 mg/day, 200 mg/day, 150 mg/day, 100 mg/day, 75 mg/day, 50 mg/day, 40 mg/day, 30 mg/day, 25 mg/day, 20 mg/day, 15 mg/day, 10 mg/day, 5 mg/day, or 1 mg/day.

[0045] In certain cases, pharmaceutical compositions for parenteral administration or inhalation, *e.g.,* a spray or mist, of a compound disclosed herein include a concentration of about 0.005 mg/ml to about 500 mg/mL. In cases, the compositions include a compound disclosed herein at a concentration of, *e.g.,* about 0.05 mg/mL to about 50 mg/mL, about 0.05 mg/mL to about 100 mg/mL, about 0.005 mg/mL to about 500 mg/mL, about 0.1 mg/mL to about 50 mg/mL, about 0.1 mg/mL to about 10 mg/mL, about 0.05 mg/mL to about 25 mg/mL, about 0.05 mg/mL to about 10 mg/mL, about 0.05 mg/mL to about 5 mg/mL, or about 0.05 mg/mL to about 1 mg/mL.

[0046] In certain cases, the composition includes a compound disclosed herein at a concentration of, *e.g.,* about 0.05 mg/mL to about 15 mg/mL, about 0.5 mg/mL to about 10 mg/mL, about 0.25 mg/mL to about 5 mg/mL, about 0.5 mg/mL to about 7 mg/mL, about 1 mg/mL to about 10 mg/mL, about 5 mg/mL to about 10 mg/mL, about 5 mg/mL to about 15 mg/mL, about 5 mg/mL to 25 mg/mL, about 5 mg/mL to 50 mg/mL, or about 10 mg/mL to 100 mg/mL. In embodiments, the pharmaceutical compositions are formulated as a total volume of about, *e.g.,* 10 mL, 20 mL, 25 mL, 50 mL, 100 mL, 200 mL, 250 mL, or 500 mL.

[0047] Typically, dosages may be administered to a subject once, twice, three or four times daily, every other day, every three days, once weekly, twice monthly, once monthly, or 3-4 times yearly. In certain cases, a compound disclosed herein is administered to a subject once in the morning, or once in the evening. In certain cases, a compound disclosed herein is administered to a subject once in the morning, and once in the evening. In certain cases, a compound disclosed herein is administered to a subject three times a day (*e.g.,* at breakfast, lunch, and dinner), at a dose, *e.g.,* of 50 mg/administration (*e.g.*, 150 mg/day).

[0048] In certain cases, a compound disclosed herein is administered to a subject 12.5 mg/day in one or more doses. In certain cases, a compound disclosed herein is administered to a subject 25 mg/day in one or more doses. In certain cases, a compound disclosed herein is administered to a subject 35 mg/day in one or more doses. In certain cases s, a compound disclosed herein is administered to a subject 50 mg/day in one or more doses. In certain cases, a compound disclosed herein is administered to a subject 75 mg/day in one or more doses. In certain cases, a compound disclosed herein is administered to a subject 100 mg/day in one or more doses. In certain cases, a compound disclosed herein is administered to a subject 150 mg/day in one or more doses. In certain cases, a compound disclosed herein is administered to a subject 200 mg/day in one or more doses. In certain cases, a compound disclosed herein is administered to a subject 250 mg/day in one or more doses.

[0049] In certain cases, the dosage of a compound disclosed herein is 0.0005-5 mg/kg, 0.001-1 mg/kg, 0.01-1 mg/kg or 0.1-5 mg/kg once, twice, three times or four times daily. For example, in certain cases s, the dosage is 0.0005 mg/kg, 0.001 mg/kg, 0.005 mg/kg, 0.01 mg/kg, 0.025 mg/kg, 0.05 mg/kg, 0.1 mg/kg, 0.15 mg/kg, 0.2 mg/kg, 0.25 mg/kg, 0.3 mg/kg, 0.4 mg/kg, 0.5 mg/kg, 0.75 mg/kg, 1 mg/kg, 2.5 mg/kg, or 5 mg/kg, once, twice, three times or four times daily. In certain cases, a subject is administered a total daily dose of 0.01 mg to 500 mg of a compound disclosed herein once, twice, three times, or four times daily. In certain cases, the total amount administered to a subject in a 24-hour period is, *e.g.,* 0.01 mg, 0.025 mg, 0.05 mg, 0.075 mg, 0.1 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.2 mg, 0.25 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 60 mg, 75 mg, 80 mg, 90 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 250 mg, 300 mg, 400 mg, or 500 mg. In certain cases, the subject may be started at a low dose and the dosage is escalated. In embodiments, the subject may be started at a high dose and the dosage is decreased.

[0050] In certain cases, a compound disclosed herein may be administered, *e.g.,* via inhalation or orally, at specified intervals. For example, during treatment a patient may be administered a compound disclosed herein at intervals of every, *e.g.,* 1 year, 6 months, 90 days, 60 days, 30 days, 14 days, 7 days, 3 days, 24 hours, 12 hours, 8 hours, 6 hours, 5 hours, 4 hours, 3 hours, 2.5 hours, 2.25 hours, 2 hours, 1.75 hours, 1.5 hours, 1.25 hours, 1 hour, 0.75 hour, 0.5 hour, or 0.25 hour.

[0051] In certain cases, a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered to a patient under the supervision of a healthcare provider.

[0052] In certain cases, a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered to a patient under the supervision of a healthcare provider at a clinic specializing in the delivery of psychoactive treatments.

[0053] In certain cases, a compound of the present disclosure is administered to a patient under the supervision of a healthcare provider at a high dose intended to induce a psychedelic experience in the subject, *e.g.,* 12.5 mg, 15 mg, 17.5 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 125 mg, or 150 mg.

[0054] In some certain cases, the administration to a patient of a high dose under the supervision of a healthcare provider occurs periodically in order to maintain a therapeutic effect in the patient, *e.g.*, every three days, twice weekly, once weekly, twice monthly, once monthly, thrice yearly, twice yearly, or once yearly.

[0055] In some certain cases, a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered by a patient on their own at home or otherwise away from the supervision of a healthcare provider.

[0056] In some certain cases, a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered by a patient on their own at home or otherwise away from the supervision of a healthcare provider at a low dose intended to be sub-perceptual or to induce threshold psychoactive effects, *e.g.,* 0.1 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 7.5 mg, or 10 mg.

[0057] In some certain cases, the administration by a patient of a low dose on their own occurs periodically in order to maintain a therapeutic effect in the patient, *e.g.,* daily, every other day, every three days, twice weekly, once weekly, twice monthly, or once monthly.

[0058] Suitable dosage forms for a compound disclosed herein include, but are not limited to, oral forms, such as tablets, hard or soft gelatin capsules, powders, granules and oral solutions, syrups or suspensions, troches, as well as sublingual, buccal, intratracheal, intraocular, or intranasal forms, forms adapted to inhalation, topical forms, transdermal forms, or parenteral forms, for example, forms adapted for intravenous, intra-arterial, intraperitoneal, intrathecal, intraventricular, intramuscular or subcutaneous administration. In certain cases, for such parenteral administration, it may be in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

[0059] Pharmaceutical compositions herein may be provided with immediate release, delayed release, extended release, or modified release profiles. In embodiments, pharmaceutical compositions with different drug release profiles may be combined to create a two-phase or three-phase release profile. For example, pharmaceutical compositions may be provided with an immediate release and an extended release profile. In embodiments, pharmaceutical compositions may be provided with an extended release and delayed release profile. Such composition may be provided as pulsatile formulations, multilayer tablets, or capsules containing tablets, beads, granules, etc. Compositions may be prepared using a pharmaceutically acceptable "carrier" composed of materials that are considered safe and effective. The "carrier" includes all components present in the pharmaceutical formulation other than the active ingredient or ingredients. The term "carrier" includes, but is not limited to, diluents, binders, lubricants, glidants, disintegrants, fillers, and coating compositions.

[0060] Pharmaceutical compositions include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration or administration via an implant. The compositions may be prepared by any method well known in the art of pharmacy.

[0061] Such methods include the step of bringing in association compounds used in the disclosure or combinations thereof with any auxiliary agent. The auxiliary agent(s), also named accessory ingredient(s), include those conventional in the art, such as carriers, fillers, binders, diluents, disintegrants, lubricants, colorants, flavoring agents, anti-oxidants, and wetting agents. Such auxiliary agents are suitably selected with respect to the intended form and route of administration and as consistent with conventional pharmaceutical practices.

[0062] Pharmaceutical compositions suitable for oral administration may be presented as discrete dosage units such as pills, tablets, dragées or capsules, or as a powder or granules, or as a solution or suspension. The active ingredient may also be presented as a bolus or paste. The compositions can further be processed into a suppository or enema for rectal administration.

[0063] Tablets may contain the active ingredient compounds and suitable binders, lubricants, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Gelatin capsules may contain the active ingredient compounds and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract. For instance, for oral administration in the dosage unit form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, gelatin, agar, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

[0064] For oral administration in liquid dosage form, the oral drug components are combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Examples of suitable liquid dosage forms include, but are not limited to, solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents. Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

[0065] For parenteral administration, suitable compositions include aqueous and nonaqueous sterile solutions. In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a watersoluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol. The compositions may be presented in unit-dose or multi-dose containers, for example sealed vials and ampoules, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of sterile liquid carrier, for example water, prior to use. For transdermal administration, e.g. gels, patches or sprays can be contemplated. Compositions or formulations suitable for pulmonary administration e.g. by nasal inhalation, include fine dusts or mists which may be generated by means of metered dose pressurized aerosols, nebulizers or insufflators. Parenteral and intravenous forms may also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

[0066] The compounds used in the method of the present disclosure may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines. The compounds may be administered as components of tissue-targeted emulsions.

[0067] The compounds used in the method of the present disclosure may also be coupled to soluble polymers as targetable drug carriers or as prodrugs. Such polymers include polyvinylpyrrolidone, pyran copolymer, polyhydroxylpropylmethacrylamide-phenol, polyhydroxyethylasparta-midephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

[0068] Pharmaceutical compositions herein may be provided with immediate release, delayed release, extended release, or modified release profiles. In some embodiments, pharmaceutical compositions with different drug release profiles may be combined to create a two-phase or three-phase release profile. For example, pharmaceutical compositions may be provided with an immediate release and an extended-release profile. In some embodiments, pharmaceutical compositions may be provided with an extended release and delayed release profile. Such composition may be provided as pulsatile formulations, multilayer tablets, or capsules containing tablets, beads, granules, etc.

[0069] Pharmaceutical compositions herein may be provided with abuse deterrent features by techniques know in the art, for example, by making a tablet that is difficult to crush or to dissolve in water.

[0070] The disclosure further includes a pharmaceutical composition, as hereinbefore described, in combination with packaging material, including instructions for the use of the composition for a use as hereinbefore described.

[0071] The exact dose and regimen of administration of the composition will necessarily be dependent upon the type and magnitude of the therapeutic or nutritional effect to be achieved and may vary depending on factors such as the particular compound, formula, route of administration, or age and condition of the individual subject to whom the composition is to be administered.

[0072] The compounds used in the method of the present disclosure may be administered in various forms, including those detailed herein. The treatment with the compound may be a component of a combination therapy or an adjunct therapy, i.e. the subject or patient in need of the drug is treated or given another drug for the disease in conjunction with one or more of the instant compounds. This combination therapy can be sequential therapy where the patient is treated first with one drug and then the other or the two drugs are given simultaneously. These can be administered independently by the same route or by two or more different routes of administration depending on the dosage forms employed.

[0073] In some embodiments, compounds disclosed herein may be administered in combination with one or more other antidepressant treatments, such as, tricyclic antidepressants, MAOIs, SSRIs, and double and triple uptake inhibitors and/or anxiolytic drugs for manufacturing a medicament for treating depression, anxiety, and/or other related diseases, including to provide relief from depression or anxiety and preventing recurrence of depression or anxiety. In some embodiments, therapeutics that may be used in combination with a compound of the present disclosure include, but are not limited to, Anafranil, Adapin, Aventyl, Elavil, Norpramin, Pamelor, Pertofrane, Sinequan, Surmontil, Tofranil, Vivactil, Parnate, Nardil, Marplan, Celexa, Lexapro, Luvox, Paxil, Prozac, Zoloft, Wellbutrin, Effexor, Remeron, Cymbalta, Desyrel (trazodone), and Ludiomill.

Definitions

[0074] In the context of the present disclosure the term "5-HT2a receptor agonist" is intended to mean any compound or substance that activates the 5-HT2a receptor. The agonist may be a partial or full agonist.

[0075] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle" "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some cases, aliphatic groups contain 1-5 aliphatic carbon atoms. In other cases, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other cases, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other cases, aliphatic groups contain 1-2 aliphatic carbon atoms. In some cases, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C_3-C_6 hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0076] The term "alkyl" refers to a straight or branched alkyl group. Exemplary alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and *tert*-butyl.

[0077] The term "haloalkyl" refers to a straight or branched alkyl group that is substituted with one or more halogen atoms.

[0078] The term "halogen" means F, Cl, Br, or I.

[0079] As used herein, the term "pharmaceutically acceptable" refers to molecular entities and compositions that are "generally regarded as safe", *e.g.,* that are physiologically tolerable and do not typically produce an allergic or similar untoward reaction when administered to a human. In embodiments, this term refers to molecular entities and compositions approved by a regulatory agency of the federal or a state government, as the GRAS list under sections 204(s) and 409 of the Federal Food, Drug and Cosmetic Act, that is subject to premarket review and approval by the FDA or similar lists, the U.S. Pharmacopeia or another generally recognized pharmacopeia for use in animals, and more particularly in humans.

[0080] As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted", whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0081] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; $-(CH_2)_{0-4}R°$; $-(CH_2)_{0-4}OR°$; $-O(CH_2)_{0-4}R°$, $-O-(CH_2)_{0-4}C(O)OR°$; $-(CH_2)_{0-4}CH(OR°)_2$; $-(CH_2)_{0-4}SR°$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; -CH=CHPh, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; $-NO_2$; -CN; $-N_3$; $-(CH_2)_{0-4}N(R°)_2$; $-(CH_2)_{0-4}N(R°)C(O)R°$; -N(R°)C(S)R°; $-(CH_2)_{0-4}N(R°)C(O)NR°_2$;$-N(R°)C(S)NR°_2$; $-(CH_2)_{0-4}N(R°)C(O)OR°$; -N(R°)N(R°)C(O)R°; $-N(R°)N(R°)C(O)NR°_2$; - N(R°)N(R°)C(O)OR°; $-(CH_2)_{0-4}C(O)R°$; -C(S)R°; $-(CH_2)_{0-4}C(O)OR°$; $-(CH_2)_{0-4}C(O)SR°$;$-(CH_2)_{0-4}C(O)OSiR°_3$; $-(CH_2)_{0-4}OC(O)R°$; $-OC(O)(CH_2)_{0-4}SR°$, SC(S)SR°; $-(CH_2)_{0-4}SC(O)R°$;$-(CH_2)_{0-4}C(O)NR°_2$; $-C(S)NR°_2$; -C(S)SR°; -SC(S)SR°, $-(CH_2)_{0-4}OC(O)NR°_2$; - C(O)N(OR°)R°; -C(O)C(O)R°; $-C(O)CH_2C(O)R°$; -C(NOR°)R°; $-(CH_2)_{0-4}SSR°$; $-(CH_2)_{0-4}S(O)_2R°$; $-(CH_2)_{0-4}S(O)_2OR°$; $-(CH_2)_{0-4}OS(O)_2R°$; $-S(O)_2NR°_2$; $-(CH_2)_{0-4}S(O)R°$; - $N(R°)S(O)_2NR°_2$; $-N(R°)S(O)_2R°$; -N(OR°)R°; $-C(NH)NR°_2$; $-P(O)_2R°$; $-P(O)R°_2$; - $OP(O)R°_2$; $-OP(O)(OR°)_2$; $SiR°_3$; $-(C_{1-4}$ straight or branched alkylene)$O-N(R°)_2$; or $-(C_1$-a straight or branched alkylene)$C(O)O-N(R°)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$-(5-6 membered heteroaryl ring), or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[0082] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^\bullet$, -(halo$R^\bullet$), $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$; -O(halo$R^\bullet$), —CN, $-N_3$, - $(CH_2)_{0-2}C(O)R^\bullet$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^\bullet$, $-(CH_2)_{0-2}SR^\bullet$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^\bullet$, $-(CH_2)_{0-2}NR^\bullet_2$, $-NO_2$, $-SiR^\bullet_3$, $-OSiR^\bullet_3$, $-C(O)SR^\bullet$, $-(C_{1-4}$ straight or branched alkylene)$C(O)OR^\bullet$, or $-SSR^\bullet$ wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[0083] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O, =S, $=NNR^*_2$, =NNHC(O)R*, =NNHC(O)OR*, $=NNHS(O)_2R^*$, =NR*, =NOR*, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: -O(CR*$_2$)$_{2-3}$O-, wherein each independent occurrence of R* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0084] Suitable substituents on the aliphatic group of R* include halogen, -R$^\bullet$, -(haloR$^\bullet$), -OH, -OR$^\bullet$, -O(haloR$^\bullet$), -CN, -C(O)OH, -C(O)OR$^\bullet$, -NH$_2$, -NHR$^\bullet$, -NR$^\bullet{}_2$, or -NO$_2$, wherein each R$^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, -CH$_2$Ph, -O(CH$_2$)$_{0-1}$Ph, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0085] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include -R†, -NR$^\dagger{}_2$, -C(O)R†, -C(O)OR†, -C(O)C(O)R†, -C(O)CH$_2$C(O)R†, -S(O)$_2$R†, - S(O)$_2$NR$^\dagger{}_2$, -C(S)NR$^\dagger{}_2$, -C(NH)NR$^\dagger{}_2$, or -N(R†)S(O)$_2$R†; wherein each R† is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted -OPh, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R†, taken together with their intervening atom(s) form an unsubstituted 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0086] Suitable substituents on the aliphatic group of R† are independently halogen, -R*, -(haloR*), -OH, -OR$^\bullet$, -O(haloR$^\bullet$), -CN, -C(O)OH, -C(O)OR$^\bullet$, -NH$_2$, -NHR$^\bullet$, -NR$^\bullet{}_2$, or -NO$_2$, wherein each R$^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, -CH$_2$Ph, -O(CH$_2$)$_{0-1}$Ph, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0087] As used herein, the term "pharmaceutically acceptable salts" includes both acid and base addition salts, wherein the compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include but are not limited to mineral or organic acid salts of basic residues such as amines, and alkali or organic salts of acidic residues such as carboxylic acids. Pharmaceutically acceptable salts include conventional non-toxic salts or quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. Such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric acids; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, tolunesulfonic, naphthalenesulfonic, methanesulfonic, ethane disulfonic, and oxalic acids. The pharmaceutically acceptable salts of a compound disclosed herein can be synthesized from the parent compound, which contains a basic or acidic moiety, by conventional chemical methods.

[0088] The terms "about" or "approximately" as used herein mean within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, *i.e.,* the limitations of the measurement system. For example, "about" can mean within 3 or more than 3 standard deviations, per the practice in the art. Alternatively, "about" can mean a range of up to 20%, a range up to 10%, a range up to 5%, and/or a range up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, *e.g.,* within 5-fold, or within 2-fold, of a value. "About" and "approximately" are used interchangeably herein.

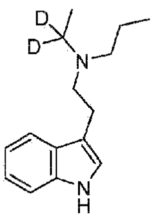
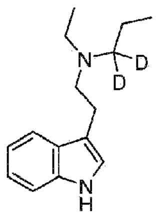
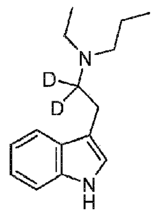
[0089] In embodiments, the terms "effective amount" or "therapeutically effective amount" refer to an amount of a compound, material, composition, medicament, or other material that is effective to achieve a particular pharmacological and/or physiologic effect including but not limited to reducing the frequency or severity of sadness or lethargy, depressed mood, anxious or sad feelings, diminished interest in all or nearly all activities, significant increased or decreased appetite leading to weight gain or weight loss, insomnia, irritability, fatigue, feelings of worthlessness, feelings of helplessness, inability to concentrate, and recurrent thoughts of death or suicide, or to provide a desired pharmacologic and/or physiologic effect, for example, reducing, inhibiting, or reversing one or more of the underlying pathophysiological mechanisms underlying the neurological dysfunction, modulating dopamine levels or signaling, modulating serotonin levels or signaling, modulating norepinephrine levels or signaling, modulating glutamate or GABA levels or signaling, modulating synaptic connectivity or neurogenesis in certain brain regions, or a combination thereof. The precise dosage will vary according to a variety of factors such as subject-dependent variables (*e.g.,* age, immune system health, clinical symptoms etc.), the disease or disorder being treated, as well as the route of administration and the pharmacokinetics of the agent being administered.

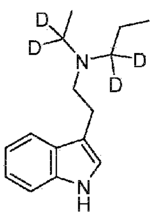
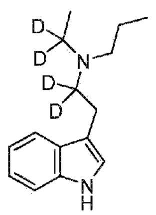
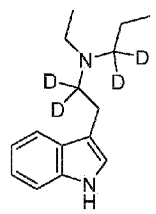
[0090] In certain cases, deuterium-enriched compounds disclosed herein and their use are contemplated and within the scope of the methods and compositions described herein. Deuterium can be incorporated in any position in place of hydrogen (protium) synthetically, according to synthetic procedures known in the art. For example, deuterium may be incorporated to various positions having an exchangeable proton, such as an amine N-H, via proton-deuterium equilibrium exchange. Thus, deuterium may be incorporated selectively or non-selectively through methods known in the art.

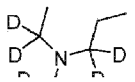
[0091] In some certain cases, the level of deuterium at each deuterium-enriched -H site of the compound is 0.02% to 100%.

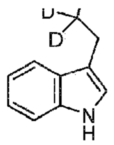
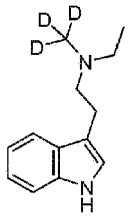
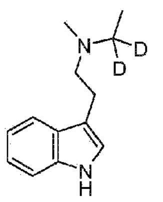
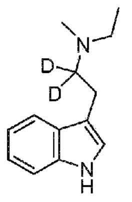
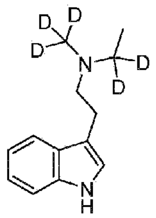
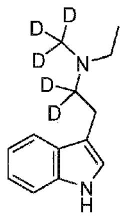
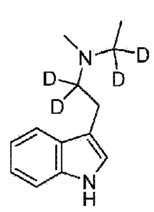
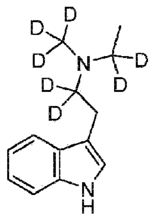
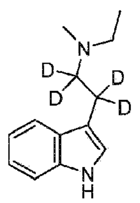
[0092] In some certain in cases, the level of deuterium at each deuterium-enriched -H site of the compound is 50%-100%, 70%-100%, 90%-100%, 95%-100%, 96%-100%, 97%-100%, 98%-100%, or 99%-100%.

[0093] Exemplary deuterium-enriched compounds disclosed herein include:



[0094] The compounds disclosed herein may be racemic and/or optically active isomers thereof. In this regard, some of the compounds can have asymmetric carbon atoms, and therefore, can exist either as racemic mixtures or as individual optical isomers (enantiomers). Compounds described herein that contain a chiral center include all possible stereoisomers of the compound, including compositions including the racemic mixture of the two enantiomers, as well as compositions including each enantiomer individually, substantially free of the other enantiomer. Thus, for example, contemplated herein is a composition including the S enantiomer of a compound substantially free of the R enantiomer, or the R enantiomer substantially free of the S enantiomer. If the named compound includes more than one chiral center, the scope of the present disclosure also includes compositions including mixtures of varying proportions between the diastereomers, as well as compositions including one or more diastereomers substantially free of one or more of the other diastereomers. By "substantially free" it is meant that the composition includes less than 25%, 15%, 10%, 8%, 5%, 3%, or less than 1% of the minor enantiomer or diastereomer(s).Enumerated *Embodiments*

EXEMPLIFICATION

[0095] Methods for synthesizing, isolating, preparing, and administering various stereoisomers are known in the art. Separation of diastereomers or cis and trans isomers may be achieved by conventional techniques, such as, for example, by fractional crystallization, chromatography or High-Performance Liquid Chromatography (HPLC) of a stereoisomeric mixture of the agent or a suitable salt or derivative thereof. An individual enantiomer of a compound disclosed herein may also be prepared from a corresponding optically pure intermediate or by resolution, such as by HPLC of the corresponding racemate using a suitable chiral support or by fractional crystallization of the diastereomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

[0096] The compounds used in the method of the present disclosure may be prepared by techniques well known in organic synthesis and familiar to a practitioner ordinarily skilled in the art. For example, the compounds may be prepared by the synthetic transformations shown below under general procedures and further described in the specific examples that follow.

Abbreviations

[0097]

ACN: Acetonitrile

DCM: Dichloromethane

DIPEA: Diisopropylethylamine

DMAc: Dimethylacetamide

DMSO: Dimethylsulfoxide

DMT: *N,N*-dimethyltryptamine

HLM: human liver microsomes

HPLC: High-performance liquid chromatography

LCMS: Liquid Chromatography-mass spectrometry

MAO: monoamine oxidase

5-MeO-DMT: 5-methoxy-*N,N*-dimethyltryptamine

MLM: mouse liver microsomes

NADPH: Nicotinamide adenine dinucleotide phosphate hydride

NMR: Nuclear magnetic resonance

PBS: phosphate buffered saline

Pd/C: Palladium on carbon

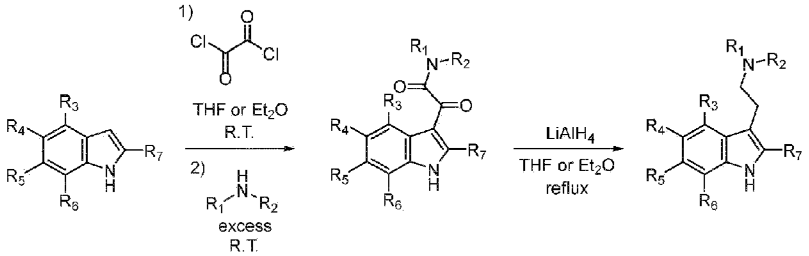
RLM: rat liver microsomes

R.T.: Room temperature/ambient temperature

THF: Tetrahydrofuran

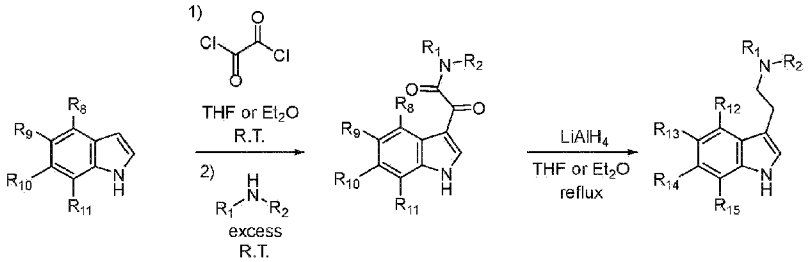
General Procedures

[0098]



R_1, R_2 = Me, Et, nPr, iPr, cyclopropyl, allyl, isobutyl, cyclopropylmethyl

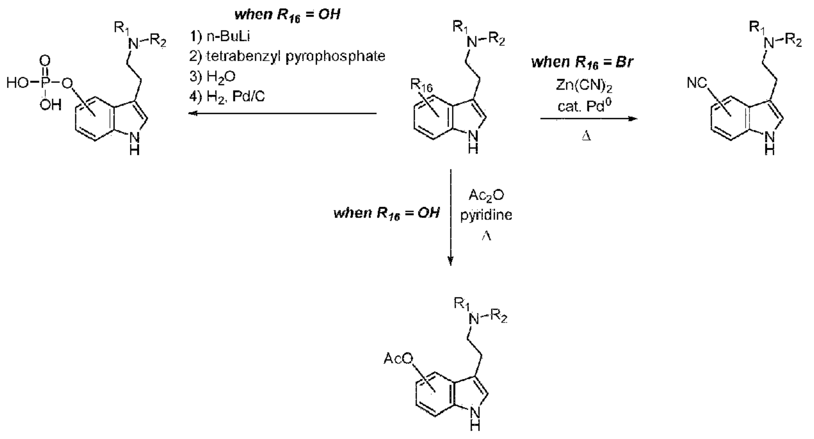
$R_3 - R_7$ = H, F, Cl, Br, I, CF_3, Me



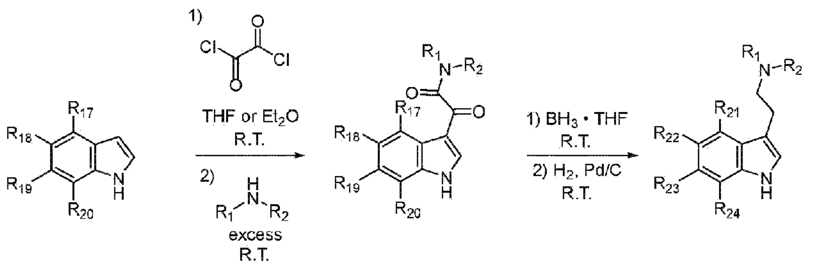
R_1, R_2 = Me, Et, nPr, iPr, cyclopropyl, allyl, isobutyl, cyclopropylmethyl

$R_8 - R_{11}$ = H, OAc, OMe

$R_{12} - R_{15}$ = H, OH, OMe



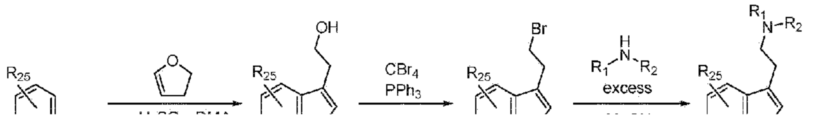
R_1, R_2 = Me, Et, nPr, iPr, cyclopropyl, allyl, isobutyl, cyclopropylmethyl

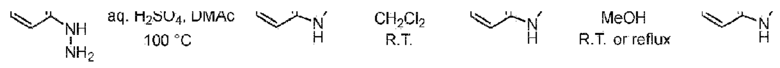


R_1, R_2 = Me, Et, nPr, iPr, cyclopropyl, allyl, isobutyl, cyclopropylmethyl

$R_{17} - R_{20}$ = NO_2

$R_{21} - R_{24}$ = NH_2





R_1, R_2 = Me, Et, nPr, iPr, cyclopropyl, allyl, isobutyl, cyclopropylmethyl

R_{25} = H, F, Cl, Br, I, CF_3, Me, CN, OMe, OH, OAc, NH_2

[0099] However, these may not be the only means by which to synthesize or obtain the desired compounds.

[0100] The present disclosure provides a pharmaceutical composition comprising the compound of the present disclosure and a pharmaceutically acceptable carrier.

[0101] The subject disclosure is also intended to include all isotopes of atoms occurring in the compounds disclosed herein. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include ^{13}C and ^{14}C.

[0102] It will be noted that any notation of a carbon in structures throughout this application, when used without further notation, is intended to represent all isotopes of carbon, such as ^{12}C, ^{13}C, or ^{14}C. Furthermore, any compounds containing ^{13}C or ^{14}C may specifically have the structure of any of the compounds disclosed herein.

[0103] It will also be noted that any notation of a hydrogen in structures throughout this application, when used without further notation, is intended to represent all isotopes of hydrogen, such as ^{1}H, ^{2}H, or ^{3}H. Furthermore, any compounds containing ^{2}H or ^{3}H may specifically have the structure of any of the compounds disclosed herein.

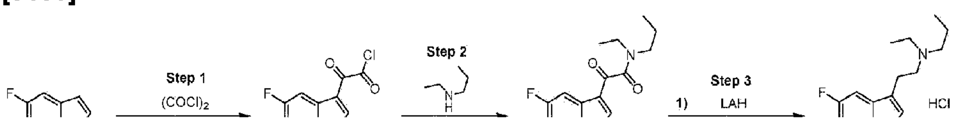
[0104] Isotopically-labeled compounds can generally be prepared by conventional techniques known to those skilled in the art using appropriate isotopically-labeled reagents in place of the nonlabeled reagents employed.

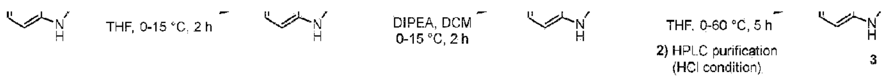
[0105] It should be understood that the examples and embodiments provided herein are exemplary. Those skilled in the art will envision various modifications of the examples and embodiments that are consistent with the scope of the disclosure herein. Such modifications are intended to be encompassed by the claims.
The examples and embodiments not falling within the scope of the appended claims are given for reference.

Examples

Example 1. Preparation of Compound 3·HCl

[0106]





[0107] Step 1: Preparation of 2-(5-fluoro-1*H*-indol-3-yl)-2-oxoacetyl chloride. To a mixture of 5-fluoro-1*H*-indole (3 g, 22.20 mmol, 1 eq) in THF (30 mL) was added oxalyl dichloride (4.23 g, 33.30 mmol, 2.91 mL, 1.5 eq) in one portion at 0 °C under N_2. The mixture was stirred at 15 °C for 2 hours. On completion, the reaction mixture was concentrated to obtain 2-(5-fluoro-1*H*-indol-3-yl)-2-oxo-acetyl chloride as a yellow solid (5.01 g, 22.21 mmol, 100% yield).

[0108] Step 2: Preparation of *N*-ethyl-2-(5-fhioro-1*H*-indol-3-yl)-2-oxo-*N*-propylacetamide. To a solution of *N*-ethylpropan-1-amine (2.90 g, 33.32 mmol, 4.63 mL, 1.5 eq) in DCM (20 mL) was added *N,N*-diisopropylethylamine (5.74 g, 44.42 mmol, 7.74 mL, 2 eq). Then 2-(5-fluoro-1*H*-indol-3-yl)-2-oxoacetyl chloride (5.01 g, 22.21 mmol, 1 eq) in THF (30 mL) was added at 0 °C. Then the mixture was stirred at 15 °C for 2 hours. On completion, aq. NH_4Cl (30 mL) was added and the mixture was stirred for 5 min. The aqueous phase was extracted with DCM (50 mL x 3). The combined organic phase was dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=5/1 to 0/1) to obtain *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-2-oxo-*N*-propylacetamide as a white solid (5.28 g, 19.11 mmol, 86% yield). **^{1}H NMR (400 MHz, $CDCl_3$) (partial integrals due to conformers)** δ 10.80 (br s, 1H), 7.94 (dd, *J* = 2.0, 9.3 Hz, 1H), 7.53 (d, *J* = 3.2 Hz, 1H), 7.17 (ddd, *J* = 1.2, 4.3, 8.9 Hz, 1H), 6.93 (dt, *J* = 2.4, 9.0 Hz, 1H), 3.58 - 3.49 (m, 1H), 3.48 - 3.39 (m, 1H), 3.35 (q, *J* = 7.2 Hz, 1H), 3.29 - 3.20 (m, 1H), 1.76 - 1.53 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 1.5H), 1.17 (t, *J* = 7.2 Hz, 1.5H), 1.00 (t, 7 = 7.6 Hz, 1.5H), 0.80 (t, *J* = 7.2 Hz, 1.5H).

[0109] Step 3: Preparation of *N*-ethyl-*N*-(2-(5-fluoro-1*H*-indol-3-yl)ethyl)propan-1-amine hydrochloride (3·HCl). To a solution of *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-2-oxo-*N*-propylacetamide (2 g, 7.24 mmol, 1 eq) in THF (30 mL) was added lithium aluminum hydride (824.18 mg, 21.72 mmol, 3 eq) at 0 °C. The mixture was then stirred at 60 °C for 5 hours. On completion, the mixture was cooled to 0 °C. Water (0.83 mL) was added and the reaction mixture was stirred for 5 min. Then 0.83 mL 30% aq. NaOH was added. The mixture was filtered and the filtrate was concentrated *in vacuo.* The residue was purified by prep-HPLC column (Phenomenex luna C18 (250*70 mm, 15 µm); mobile phase = water(0.05% HCl)-ACN, B% = 10%-34%; R_T = 22 min) to afford *N*-ethyl-*N*-[2-(5-fluoro-1*H*-indol-3-yl)ethyl]propan-1-amine hydrochloride **(3)** as a white solid (845.6 mg, 2.97 mmol, 41% yield). **^{1}H NMR (400 MHz, DMSO-d6)** δ 11.13 (br s, 1H), 10.53 (br s, 1H), 7.48 - 7.30 (m, 3H), 6.94 (dt, *J* = 2.4, 9.2 Hz, 1H), 3.33 - 2.94 (m, 8H), 1.85 - 1.57 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (101 MHz, DMSO-d6) (extra peaks due to C-F coupling)** δ 158.40, 156.10, 133.35, 127.51, 127.41, 126.00, 113.04, 112.94, 110.07, 110.03, 109.96, 109.70, 103.69, 103.46, 52.87, 52.06, 46.94, 19.87, 17.01, 11.45, 8.86; **LCMS** (R_T = 1.709 min, MS calc.: 248.17, $[M+H]^+$ = 249.1).

[0110] *Example 2. Preparation of Compound 4·HCl*). To a solution of *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methyl-2-oxoacetamide (1.73 g, 6.97 mmol, 1 eq) in THF (30 mL) was added lithium aluminum hydride (795.46 mg, 20.96 mmol, 3 eq) at 0 °C. The mixture was then stirred at 60 °C for 5 hours. On completion, the mixture was cooled to 0 °C. Water (0.8 mL) was added and the mixture was stirred for 5 min. Then 0.8 mL 30% aq. NaOH was added. The mixture was filtered and the filtrate was concentrated *in vacuo.* The residue was purified by prep-HPLC column (Phenomenex luna C18 (250*70mm, 15 um); mobile phase = water(0.04% HCl)-ACN, B% = 10%-30%; R_T = 20 min) to afford *N*-ethyl-2-(5-fluoro-1*H*-indol-3-yl)-*N*-methylethan-1-amine hydrochloride **(4)** as a white solid (670 mg, 2.61 mmol, 37% yield). **^{1}H**

NMR (400 MHz, DMSO-d6) δ 11.11 (br s, 1H), 10.46 (br s, 1H), 7.48 - 7.30 (m, 3H), 6.93 (dt, *J* = 2.4, 9.2 Hz, 1H), 3.36 - 3.00 (m, 6H), 2.79 (d, *J* = 5.2 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (101 MHz, DMSO-d6) (extra peaks due to C-F coupling)** δ 158.39, 156.09, 133.38, 127.49, 127.39, 125.96, 113.04, 112.94, 109.98, 109.94, 109.90, 109.72, 103.74, 103.51, 54.87, 50.38, 38.60, 20.20, 9.32; **LCMS** (R_T = 1.581 min, MS calc.: 220.14, $[M+H]^+$ = 221.1).

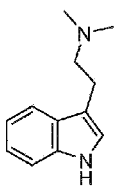
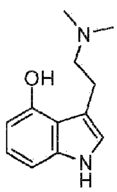
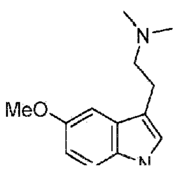
Example 3. Metabolic Stability in Human Liver Microsomes

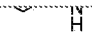
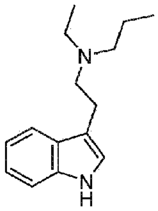
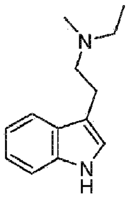
[0111] Disclosed compounds were tested for stability in human liver microsomes (HLM), with the results summarized in **Table 1.** Compound 2 exhibited greater metabolic stability than Compound 1, N,N-dimethyltryptamine (DMT), 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), and psilocin in this model.

[0112] HLM Stability. Pooled HLM from adult male and female donors (Corning 452117) were used. Microsomal incubations were carried out in multi-well plates. Liver microsomal incubation medium consisted of PBS (100 mM, pH 7.4), $MgCl_2$ (1 mM), and NADPH (1 mM), with 0.50 mg of liver microsomal protein per mL. Control incubations were performed by replacing the NADPH-cofactor system with PBS. Test compounds (1 µM, final solvent concentration 1.0%) were incubated with microsomes at 37 °C with constant shaking. Six time points over 60 minutes were analyzed, with 60 µL aliquots of the reaction mixture being drawn at each time point. The reaction aliquots were stopped by adding 180 µL of cold (4°C) acetonitrile containing 200 ng/mL tolbutamide and 200 ng/mL labetalol as internal standards (IS), followed by shaking for 10 minutes, and then protein sedimentation by centrifugation at 4000 rpm for 20 minutes at 4°C. Supernatant samples (80 µL) were diluted with water (240 µL) and analyzed for parent compound remaining using a fit-for-purpose liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

[0113] Data Analysis. The elimination constant (k_{el}), half-life ($t_{1/2}$), and intrinsic clearance (CL_{int}) were determined in a plot of ln(AUC) versus time, using linear regression analysis.

Table 1. Intrinsic clearance (CL_{int}) and half-life ($t_{1/2}$) of compounds in the presence of HLM.

Compound	**Structure**	**Cl_{int} (µL/min/mg)**	**$t_{1/2}$ (min)**
DMT		198.6	7.0
Psilocin		12.6	109.7
5-MeO-DMT		101.9	13.6

Compound	Structure	Cl_{int} (μL/min/mg)	$t_{1/2}$ (min)
			
1*		64.3	21.7
2*		11.2	125.7
*Values are the average of 2 independent experiments.			

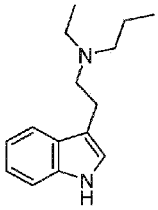
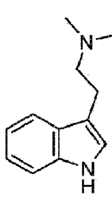
Example 4. Metabolic Stability in Mouse Liver Microsomes

[0114] Disclosed compounds were tested for stability in mouse liver microsomes (MLM), with the results summarized in **Table 2**. Compound 2 exhibited greater metabolic stability than Compound 1 in this model.

[0115] MLM Stability. Pooled MLM from CD-1 mice (BIOIVT M00501) were used. Microsomal incubations were carried out in multi-well plates. Liver microsomal incubation medium consisted of PBS (100 mM, pH 7.4), $MgCl_2$ (1 mM), and NADPH (1 mM), with 0.50 mg of liver microsomal protein per mL. Control incubations were performed by replacing the NADPH-cofactor system with PBS. Test compounds (1 μM, final solvent concentration 1.0%) were incubated with microsomes at 37 °C with constant shaking. Six time points over 60 minutes were analyzed, with 60 μL aliquots of the reaction mixture being drawn at each time point. The reaction aliquots were stopped by adding 180 μL of cold (4°C) acetonitrile containing 200 ng/mL tolbutamide and 200 ng/mL labetalol as internal standards (IS), followed by shaking for 10 minutes, and then protein sedimentation by centrifugation at 4000 rpm for 20 minutes at 4°C. Supernatant samples (80 μL) were diluted with water (240 μL) and analyzed for parent compound remaining using a fit-for-purpose liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

[0116] Data Analysis. The elimination constant (k_{el}), half-life ($t_{1/2}$), and intrinsic clearance (CL_{int}) were determined in a plot of ln(AUC) versus time, using linear regression analysis.

Table 2. Intrinsic clearance (CL_{int}) and half-life ($t_{1/2}$) of compounds in the presence of MLM.

Compound	Structure	Cl_{int} (µL/min/mg)	$t_{1/2}$ (min)
1		231.3	6.0
2		13.6	102.0

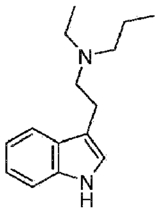
Example 5. Metabolic Stability in Rat Liver Microsomes

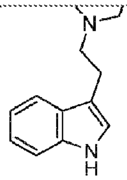
[0117] Disclosed compounds were tested for stability in rat liver microsomes (RLM), with the results summarized in **Table 3.** Both compounds exhibited low stability in this model.

[0118] RLM Stability. Pooled RLM from adult male and female donors (Xenotech R1000) were used. Microsomal incubations were carried out in multi-well plates. Liver microsomal incubation medium consisted of PBS (100 mM, pH 7.4), $MgCl_2$ (1 mM), and NADPH (1 mM), with 0.50 mg of liver microsomal protein per mL. Control incubations were performed by replacing the NADPH-cofactor system with PBS. Test compounds (1 µM, final solvent concentration 1.0%) were incubated with microsomes at 37 °C with constant shaking. Six time points over 60 minutes were analyzed, with 60 µL aliquots of the reaction mixture being drawn at each time point. The reaction aliquots were stopped by adding 180 µL of cold (4°C) acetonitrile containing 200 ng/mL tolbutamide and 200 ng/mL labetalol as internal standards (IS), followed by shaking for 10 minutes, and then protein sedimentation by centrifugation at 4000 rpm for 20 minutes at 4°C. Supernatant samples (80 µL) were diluted with water (240 µL) and analyzed for parent compound remaining using a fit-for-purpose liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

[0119] Data Analysis. The elimination constant (k_{el}), half-life ($t_{1/2}$), and intrinsic clearance (CL_{int}) were determined in a plot of ln(AUC) versus time, using linear regression analysis.

Table 3. Intrinsic clearance (CL_{int}) and half-life ($t_{1/2}$) of compounds in the presence of RLM.

Compound	Structure	Cl_{int} (µL/min/mg)	$t_{1/2}$ (min)
1		970.3	1.4
2		1561.0	0.9

Compound	Structure	Cl_{int} (µL/min/mg)	$t_{1/2}$ (min)
			

Example 6. Pharmacokinetics in Mice

[0120] The pharmacokinetics of disclosed compounds were studied in the plasma **(Table 4)** and brains **(Table 5)** of mice after intravenous (iv) and oral (po) dosing. Compound 2 demonstrated much improved absolute oral bioavailability (F) compared to Compound 1, consistent with its greater stability in mouse liver microsomes (see Example 4 above). Despite this much improved oral exposure, the half-life of Compound 2 in plasma was similar to Compound 1. Overall, the findings indicate that Compound 2 may serve as an orally active and short-acting therapeutic agent.

[0121] Animals. Male C57BL/6 mice, aged 8-12 weeks, were used in these studies. Four mice were housed in each cage. Temperature and humidity were maintained at 22 ± 3 °C and 30-70%, respectively, and illumination was controlled to give a 12 h light and 12 h dark cycle. Temperature and humidity were recorded by an auto-controlled data logger system. All animals were provided laboratory rodent diet. Reverse osmosis water treated with ultraviolet light was provided *ad libitum.* Animals were randomly assigned to treatment groups.

[0122] Drugs. Test compounds were used as the hydrogen fumarate salts and were dissolved in a vehicle consisting of normal saline. They were then administered intravenously (iv) via the tail vein or orally (po) via gavage at a dose of 10 mg/kg (calculated based on the free base) and at a volume of 5 mL/kg body weight.

[0123] Sample Collection and Bioanalysis. Blood samples (approximately 60 µL) were collected under light isoflurane anesthesia (Surgivet®) from the retro orbital plexus at 0.08, 0.25, 0.5, 1, 2, 4, 8, and 24 h (4 animals per time point). Immediately after blood collection, plasma was harvested by centrifugation at 4000 rpm for 10 min at 4 °C and samples were stored at -70±10 °C until bioanalysis. Following blood collection, animals were immediately sacrificed, the abdominal venacava was cut open, and the whole body was perfused from the heart using 10 mL of normal saline, and brain samples were collected from all animals. After isolation, brain samples were rinsed three times in ice-cold normal saline (for 5-10 seconds/rinse using ~5-10 mL normal saline in disposable petri dish for each rinse) and dried on blotting paper. Brain samples were homogenized using ice-cold phosphate-buffered saline (pH 7.4). Total homogenate volume was three times the tissue weight. All homogenates were stored at -70±10 °C until bioanalysis. For bioanalysis, 25 µL aliquots of plasma/brain study samples or spiked plasma/brain calibration standards were added to individual pre-labeled micro-centrifuge tubes followed by 100 µL of an internal standard solution (glipizide, 500 ng/mL in acetonitrile) except for blanks, where 100 µL of acetonitrile was added. Samples were vortexed for 5 minutes and then centrifuged for 10 minutes at 4000 rpm at 4 °C. Following centrifugation, 100 µL of each clear supernatant was transferred to a 96 well plate and analyzed with a fit-for-purpose LC-MS/MS method, with authentic samples of each analyte used for calibration and identification.

[0124] Data Analysis. Pharmacokinetic parameters were estimated using the non-compartmental analysis tool of Phoenix® WinNonlin software (Ver 8.0).

Table 4. Selected pharmacokinetic parameters of compounds in plasma of C57BL/6 mice.

Compound	C_0 (iv) (ng/mL)*	C_{max} (po) (ng/mL)	$AUC_{0\text{-last}}$ (iv) (h*ng/mL)	$AUC_{0\text{-last}}$ (po) (h*ng/mL)	$t_{1/2}$ (iv) (h)	$t_{1/2}$ (po) (h)	CL (iv) (mL/min/kg)	V_{ss} (iv) (L/kg)	F (%)
1	3,820	20.3	844	22.1	1.90	1.88	197	9.35	2.6
2	963	102	545	238	1.48	1.37	304	14.3	44
*Back-extrapolated concentration at t = 0.									

Table 5. Selected pharmacokinetic parameters of compounds in brains of C57BL/6 mice.

Compound	C_0 (iv) (ng/g)*	C_{max} (po) (ng/g)	$AUC_{0\text{-last}}$ (iv) (h*ng/mL)	$AUC_{0\text{-last}}$ (po) (h*ng/g)	$t_{1/2}$ (iv) (h)	$t_{1/2}$ (po) (h)	F (%)**
1	15,400	101	4,750	68.9	1.73	0.66	1.5
2	6,250	957	3,920	1,990	1.54	7.52	51
*Back-extrapolated concentration at t = 0; **Based on brain $AUC_{0\text{-last}}$.							

Example 7. CYP Inhibition in Human Liver Microsomes

[0125] Inhibition of five major cytochrome P450 (CYP) enzymes (1A2, 2C9, 2C19, 2D6, and 3A4) by the disclosed compounds was determined in human liver microsomes (HLM) by using LC-MS/MS to monitor the metabolic conversion of a cocktail of reference CYP substrates in the presence and absence of the test compounds **(Table 6).** At the test concentration of 10 µM, the test compounds generally exhibited limited inhibition of CYPs. At most of the CYPs tested, Compound 1 exhibited the least inhibition.

[0126] HLM Incubations. Pooled HLM from adult male and female donors (Corning 452117) were used. Microsomal incubations were carried out in multi-well plates. Liver microsomal incubation aliquots contained 1) PBS (100 mM, pH 7.4), $MgCl_2$ (3.3 mM), and NADPH (1 mM); 2) liver microsomal protein (0.2 mg/mL); 3) the reference CYP substrates: phenacetin for CYP1A2 (10 µM), diclofenac for CYP2C9 (5 µM), (S)-mephenytoin for CYP2C19 (30 µM), dextromethorphan for CYP2D6 (5 µM), and midazolam for CYP3A4 (2 µM); and 4) test compounds (10 µM), control inhibitors (3 µM α-naphthoflavone for CYP1A2, 3 µM sulfaphenazole for CYP2C9, 1 µM (+)-N-3-benzylnirvanol for 2C19, 3 µM quinidine for CYP2D6, or 3 µM ketoconazole for CYP3A4), or solvent (for uninhibited condition). Incubations were carried out at 37 °C with constant shaking for 10 minutes. The reaction aliquots were stopped by adding 400 µL of cold (4°C) acetonitrile containing 200 ng/mL tolbutamide and 200 ng/mL labetalol as internal standards (IS), followed by protein sedimentation by centrifugation at 4000 rpm for 20 minutes at 4°C.

[0127] Sample Analysis. Supernatant samples (200 µL) were diluted with water (100 µL) and the reference metabolites of each reference CYP substrate were quantified using a fit-for-purpose liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Percent inhibition by test compounds or control inhibitors was calculated by comparing the metabolite formation in the presence of the inhibitor compared to the metabolite formation in the absence of the inhibitor.

Table 6. Percent inhibition of indicated CYPs by test compounds at 10 µM.

	CYP (% inhibition at 10 µM)				
Compound	3A4	2D6	1A2	2C19	2C9
DMT	5.5	5.8	7.3	0.0	2.7
Psilocin	0.0	13.7	22.5	0.0	0.0
5-MeO-DMT	0.0	4.4	4.0	0.0	1.0
1*	2.0	58.6	37.1	2.3	0.1
2	0.0	11.5	0.5	0.0	0.0
*Values are the average of 2 independent experiments.					

Example 8. Stability in the Presence of Monoamine Oxidases

[0128] Disclosed compounds were tested for stability in the presence of monoamine oxidase A and B (MAO-A and MAO-B) in human liver mitochondria preparations, with the results summarized in **Table 7.** Disclosed compounds exhibited much greater MAO stability than DMT in this model.

[0129] Liver Mitochondria Incubations. Human liver mitochondria (Xenotech H0610.M) were used. Mitochondrial incubations were carried out in multi-well plates. Liver mitochondrial incubation medium consisted of PBS (100 mM, pH 7.4) with 0.30 mg of liver mitochondrial protein per mL. Test compounds (1 µM, final solvent concentration 1.0%) were incubated with liver mitochondrial protein at 37 °C with constant shaking (total reaction volume 100 µL per well). Six time points over 60 minutes were analyzed. At each time point, reactions were stopped by adding 300 µL of cold (4°C) acetonitrile containing 200 ng/mL tolbutamide and 200 ng/mL labetalol as internal standards (IS), followed by shaking for 10 minutes, and then protein sedimentation by centrifugation at 4000 rpm for 20 minutes at 4°C. Supernatant samples (100 µL) were diluted with 5% trichloroacetic acid in water (300 µL) and analyzed for parent compound remaining using a fit-for-purpose liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

[0130] Data Analysis. The elimination constant (k_{el}), half-life ($t_{1/2}$), and intrinsic clearance (CL_{int}) were determined in a plot of ln(AUC) versus time, using linear regression analysis.

Table 7. Intrinsic clearance (CL_{int}), half-life ($t_{1/2}$), and percent remaining of compounds in the presence of monoamine oxidases (human mitochondrial preparation).

Compound	**$t_{1/2}$ (min)**	**CLint(MAO) (µL/min/mg)**	**Remaining (t = 60 min)**
1	>145	< 15.9	95.1%
2	>145	< 15.9	84.5%
DMT	17.1	134.9	8.9%

Example 9. Functional Activity at Serotonin Receptors

[0131] Disclosed compounds were tested for agonist activity at several serotonin receptor subtypes (5-

HT2A, 5-HT2B, 5-HT2C, and 5-HT1A) using Ca^{2+} flux functional assays, with the results summarized in **Table 8.** All compounds exhibited potent agonist activity at 5-HT2A, suggestive of potential hallucinogenic activity as well as possible therapeutic effects. However, the signaling efficacy at 5-HT2A and the selectivity for this target over other serotonin receptors varied dramatically with even small changes to the chemical structure. For example, Compound 1 showed little selectivity for 5-HT2A over 5-HT2B, whereas Compound 2 was highly selective for 5-HT2A relative to 5-HT2B. At the same time, Compound 1 was a highly efficacious agonist at 5-HT2A (E_{max} = 85.2%), whereas Compound 2 was a low efficacy partial agonist (E_{max} = 36.2%). Fluorination at the 5 position of the indole ring also had unpredictable effects. For example, Compounds 3 and 4 were both significantly more potent at the 5-HT1A receptor than their nonfluorinated analogs Compounds 1 and 2, respectively. In the case of Compound 3, fluorination also increased potency at 5-HT2A relative to Compound 1. In the case of Compound 4, fluorination had little effect on potency at 5-HT2A, but dramatically increased the maximal efficacy compared to Compound 2, resulting in a high efficacy rather than partial agonist.

[0132] Functional Assays at 5-HT2A, 5-HT2B, and 5-HT1A. Agonist activity at 5-HT2A, 5-HT2B, and 5-HT1A receptors was determined using a FLIPR Ca^{2+} flux assay at WuXi AppTec (Hong Kong) Limited according to their standard protocols. Briefly, stably transfected cells expressing the receptor of interest (HEK293 for 5-HT2A and 5-HT2B; CHO cells for 5-HT1A) were grown and plated in a 384 well plate and incubated at 37°C and 5% CO_2 overnight. A solution of 250 mM probenecid in 1mL FLIPR assay buffer was prepared fresh. This was combined with a fluorescent dye (Fluo-4 DirectTM) to make a final assay concentration of 2.5 mM. Compounds were diluted 1:3.16 for 10 points and 750 nL was added to a 384 well compound plate using ECHO along with 30 µL assay buffer. The fluorescent dye was then added to the assay plate along with assay buffer to a final volume of 40 µL. The cell plate was incubated for 50 min at 37°C and 5% CO_2 and placed into the FLIPR Tetra along with the compound plate. 10µL of references and compounds were then transferred from the compound plate into the cell plate and the fluorescent signal was read.

[0133] Functional Assays at 5-HT2C. Agonist activity at 5-HT2C was determined using a FLIPR Ca^{2+} flux assay at Eurofins DiscoverX (Fremont, CA) according to their standard protocols. Briefly, stably transfected cells expressing the human 5-HT2C receptor were grown and plated in a 384 well plate and incubated at 37 °C and 5% CO_2 overnight. Assays were performed in 1x 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 and incubated at 37 °C for 30-60 minutes. After dye loading, cells were removed from the incubator and 10 µL HBSS / 20 mM Hepes was added. 3x vehicle was included in the assay buffer. Cells were incubated for 30 mins at room temperature in the dark to equilibrate plate temperature. 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 µL 4X sample in HBSS / 20 mM Hepes was added to the cells 5 seconds into the assay.

Table 8. Agonist activity of compounds at select serotonin receptors in Ca^{2+} flux functional assays.

Compound	5-HT2A EC_{50} (nM)	5-HT2A %Act @ Max Dose	5-HT2B EC_{50} (nM)	5-HT2B % Act @ Max Dose	5-HT2C EC_{50} (nM)	5-HT2C %Act @ Max Dose	5-HT1A EC_{50} (nM)	5-HT1A %Act @ Max Dose
1	30.5	85.2	40.3	80.4	33.4	90.8	88,700	75.5
2	17.1	36.2	> 100,000	22.5	28.3	89.7	59,500	73.6

Compound	5-HT2A EC_{50} (nM)	5-HT2A %Act @ Max Dose	5-HT2B EC_{50} (nM)	5-HT2B % Act @ Max Dose	5-HT2C EC_{50} (nM)	5-HT2C %Act @ Max Dose	5-HT1A EC_{50} (nM)	5-HT1A %Act @ Max Dose
3	5.54	104	NT	NT	NT	NT	19,600	88.3
4	20.6	87.6	NT	NT	NT	NT	16,900	83.0
DMT*	22.2	93.4	>31,600	10.4	31.3	92.0	> 100,000	68.1
psilocin*	6.50	95.6	4,290	1.44	30.3	95.1	>3,160	0.720
5-MeO-DMT*	1.76	106	30.1	20.5	10.1	89.8	280	78.8
*Values are the average of 2 or more independent experiments.								

Example 10. Effects on the Head Twitch Response (HTR) in Mice

[0134] Disclosed compounds were tested for their ability to induce a head twitch response (HTR) in mice, with the results summarized in **Table 9.** Consistent with their agonist activity at the 5-HT2A receptor, both Compound 1 and Compound 2 induced a HTR. However, the maximal effect of the disclosed compounds was less than that of the prototype 5-HT2A agonist 4-iodo-2,5-dimethoxyamphetamine (DOI) (35.6 head twitches/20 min). The maximal effect of Compound 2 in this assay (6.00 head twitches/20 min) was also less than that of Compound 1 (14.7 head twitches/20 min), consistent with the lesser efficacy of Compound 2 as an agonist of 5-HT2A *in vitro* (see **Example 9** above).

[0135] Animals. Adult male C57BL/6 mice, aged 8 weeks (body weight 20-25g) were used in these experiments. Animals were housed under controlled temperatures and 12-hour light/dark cycles (lights on between 07:00-19:00 h), with *ad libitum* food and water. The protocol was approved by the Eurofins Advinus Institutional Animal Care and Use Committee. This study was carried out in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. All efforts were made to minimize suffering.

[0136] Drugs and Drug administration. Test compounds were used as the hydrogen fumarate salts and DOI was used as the HCl salt. Drugs were dissolved in a vehicle consisting of normal saline and administered subcutaneously (s.c.) in a volume of 10mL/kg. Test compounds were administered at 5 doses per compound (1 to 100 mg/kg, calculated based on the free base) using N = 6 animals/group. The control compound DOI was administered at 1 dose (3.16 mg/kg, calculated based on the HCl salt), using N = 12 animals.

[0137] Procedure. Mice were administered one dose of a test drug (or vehicle) s.c. and immediately placed into a small open field for behavioral observation. Animals were observed continuously for 20 mins and the number of HTRs were counted by an observer blind to the treatment condition.

[0138] Statistical analysis. The data points shown in Table 9 are the mean ± standard error of the mean (SEM). Analysis was performed using GraphPad Prism 9.

Table 9. HTR of compounds in mice.

Compound	Dose (mg/kg)	Average HTR/20 min (SEM)
DOI	3.16	35.583 (3.372)
1	1	14.667 (2.848)
1	3.16	12.167 (1.682)
1	10	8.000 (1.966)
1	31.6	4.750 (1.797)
1	100	4.500 (0.866)
2	1	3.667 (0.615)
2	3.16	6.000 (0.632)
2	10	2.500 (0.563)
2	31.6	1.000 (0.408)
2	100	0.500 (0.500)

Example 11. Forced Swim Test in Rats

[0139] Disclosed compounds induced antidepressant-like effects in the forced swim test (FST) in rats with a 23.5-h pre-treatment time **(FIG. 1).** Specifically, the compounds reduced immobility time relative to vehicle control, indicative of an antidepressant-like effect. These effects on immobility were observed 23.5 hours after a single compound administration, a time point at which most or all of the drug has been cleared from the systemic circulation, suggesting that the compounds have both rapid-acting and long-lasting antidepressant-like effects. Additionally, the compounds induced significant increases in swimming behavior during the test **(FIG. 2).** These effects on swimming were stronger than those induced by the control antidepressant desipramine.

[0140] Animals. Male Sprague Dawley rats, aged 8-10 weeks, were used in the experiments. Animals were housed in groups of 2 under controlled temperature (22 ± 3°C) and relative humidity (30-70%) conditions, with 12-hour light/dark cycles, and with *ad libitum* food and water. These studies were carried out in strict accordance with the requirements of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India. All efforts were made to minimize suffering.

[0141] Drugs and Drug Administration. Test compounds, saline vehicle, and the positive control desipramine were administered subcutaneously (s.c.), with doses calculated based on the free base. Normal saline was used as the vehicle. All compounds were administered at a volume of 5 mL/kg. Test compounds and vehicle were administered 0.5 h after the start of the training swim (Swim 1) and 23.5 h before the test swim (Swim 2). Desipramine was administered 3 times, at 23.5 h, 5 h, and 1 h before the test swim (Swim 2), each time at a dose of 20 mg/kg.

[0142] Forced Swim Test (FST). Animals were randomized based on body weight, and it was ensured that inter-group variations were minimal and did not exceed ± 20% of the mean body weight across the groups. Group size was N = 10 per treatment, except for the vehicle and desipramine groups, which were N = 20. Rats were handled for about 2 min daily for the 5 days prior to the beginning of the experimental procedure. On the first day of the experiment (i.e., Day 0), post randomization, training swim sessions (Swim 1) were conducted between 12:00 and 18:00 h with all animals by placing rats in individual glass cylinders (46 cm tall x 20 cm in diameter) containing 23 - 25 °C water 30 cm deep for 15 minutes. At the conclusion of Swim 1, animals were dried with paper towels, placed in heated drying cages for 15 minutes, and then returned to their home cages. Animals were then administered the appropriate drug or vehicle treatment(s), as described above. For clarity, a compound administration time of 23.5 h before Swim 2 means 0.5 h after the start of Swim 1 and 0.25 h after the completion of Swim 1 (i.e., immediately after return to the home cage). On Day 1 (i.e., 24 h after start of Swim 1), animals performed the test swim (Swim 2) for a period of 5 min but otherwise under the same conditions as Swim 1. During all swim sessions, the water was changed between each animal.

[0143] Behavioral scoring was conducted by observers who were blind to the treatment groups. Animals were continuously observed during Swim 2 and the total time spent engaging in the following behaviors was recorded: immobile, swimming, and climbing. A rat was judged to be immobile when it remained floating in the water without struggling and was making only those movements necessary to keep its head above water. A rat was judged to be swimming when it made active swimming motions, more than necessary to merely maintain its head above water (e.g., moving around in the cylinder). A rat was judged to be climbing when it made active movements with its forepaws in and out of the water, usually directed against the walls.

[0144] Statistical Analysis. The data points shown in **FIG. 1 and FIG. 2** represent the mean ± standard error of the mean (SEM). Analysis was performed using GraphPad Prism 9. Comparisons between groups were performed using the one-way analysis of variance (ANOVA), followed by Dunnett's test for comparisons to vehicle.

Example 12. Stability in Mouse Plasma and Brain Homogenate

[0145] Disclosed compounds were tested for stability in mouse plasma **(Table 10)** and mouse brain homogenate **(Table 11)** by LC-MS/MS. The compounds were stable under the conditions of the experiment, suggesting that they are not subject to substantial plasma or brain metabolism.

[0146] Plasma Stability. Positive controls and test compounds (final concentration in incubation medium = 1 µM, 0.5% DMSO) were incubated in 400 µL of (n = 3) of DBA2 mouse plasma in a CO_2 incubator at 37 °C. An aliquot of 50 µL was withdrawn from each incubation at 0, 5, 15, 30, 60, and 90 min and immediately quenched with 500 µL of ice-cold acetonitrile containing internal standard followed by storage at -80 °C. At the time of bioanalysis, all the samples were thawed to room temperature. Samples were vortexed for 5 min followed by centrifugation at 4,000 RPM for 15 min at 4 °C. Aliquots of 100 µL of each sample were transferred to a 96-well deep plate and analyzed for parent compound remaining with a fit-for-purpose LC-MS/MS method.

[0147] Brain Homogenate Stability. Brain tissue homogenate samples were prepared by diluting one volume of whole brain tissue from C57BL/6 mice with three volumes of dialysis buffer (phosphate buffered saline pH 7.4 - 0.1 M sodium phosphate and 0.15 M sodium chloride) to yield 4 times diluted homogenate. Positive controls and test compounds (final concentration in incubation medium = 1 µM, 0.5% DMSO) were incubated in 400 µL of (n = 3) of the diluted mouse brain homogenate described above in a CO_2 incubator at 37 °C. An aliquot of 50 µL was withdrawn from each incubation at 0, 5, 15, 30, 60, and 90 min and immediately quenched with 500 µL of ice-cold acetonitrile containing internal standard followed by storage at -80 °C. At the time of bioanalysis, all the samples were thawed to room temperature. Samples were vortexed for 5 min followed by centrifugation at 4,000 RPM for 15 min at 4

°C. Aliquots of 100 µL of each sample were transferred to a 96-well deep plate and analyzed for parent compound remaining with a fit-for-purpose LC-MS/MS method.

Table 10. Time versus % of test compound remaining in mouse plasma.

Time (min)	% Parent Compound Remaining	
	Compound 1	Compound 2
0	100	100
5	92	96
15	101	97
30	103	99
60	103	98
90	94	89
$t_{1/2}$ (min)	>90	>90

Table 11. Time versus % of test compound remaining in mouse brain homogenate.

Time (min)	% Parent Compound Remaining	
	Compound 1	Compound 2
0	100	100
5	95	97
15	94	98
30	95	101
60	96	92
90	95	98
$t_{1/2}$ (min)	>90	>90

Example 13. Microsomal Stability of Additional Compounds.

[0148] Additional disclosed compounds, including Compounds 3 and 4, are tested for stability in human, mouse, or rat liver microsomes, as described in **Examples 3-5.** Compound 4 exhibits moderate to high stability in human and mouse microsomes and is more stable than DMT in such preparations.

Example 14. Pharmacokinetics of Additional Compounds in Mice

[0149] Additional disclosed compounds, including Compounds 3 and 4, are tested to determine their pharmacokinetic properties and oral bioavailability in mice, as described in **Example 6.** Compound 4 exhibits moderate to high oral bioavailability.

Example 15. Stability of Additional Compounds in the Presence of Monoamine Oxidases

[0150] Additional disclosed compounds, including Compounds 3 and 4, are tested to determine their stability in the presence of monoamine oxidases using liver mitochondria preparations, as described in

Example 8. Compounds 3 and 4 exhibit moderate to high stability in such preparations.

Example 16. Effects of Additional Compounds in the HTR Assay

[0151] Additional disclosed compounds, including Compounds 3 and 4, are tested to determine their ability to induce a head twitch response (HTR) in mice, as described in **Example 10.** Compounds 3 and 4 induce a head twitch response in mice in a dose-dependent manner, consistent with their agonist activity at the 5-HT2A receptor *in vitro.*

Example 17. Effects of Additional Compounds in the Forced Swim Test in Rats

[0152] Additional disclosed compounds, including Compounds 3 and 4, are tested in the forced swim test (FST) in rats, as described in **Example 11.** Compounds 3 and 4 reduce immobility in this test in a dose-dependent manner, consistent with an antidepressant-like effect.

Example 18. Synthesis of Additional Compounds

[0153] Additional disclosed compounds may be prepared by standard methods known to those skilled in the art of organic synthesis, for example, those presented in **Examples 1-2** and described elsewhere herein.

REFERENCES CITED IN THE DESCRIPTION

Cited references

Patent documents cited in the description

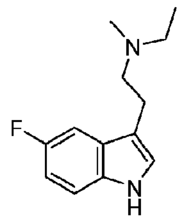
- US62978075 [0001]
- WO2018064465A [0007]
- US2018021326A [0007]

Non-patent literature cited in the description

- **BRANDT SIMON D. et al.**Analytical chemistry of synthetic routes to psychoactive tryptamines : Part II. Characterisation of the Speeter and Anthony synthetic route to N,N-dialkylated tryptamines using GC-EI-ITMS, ESI-TQ-MS-MS and NMRANALYST, UK, 2005, vol. 130, 3330- [0007]
- **ADAMOWICZ PIOTR et al.**Simple and rapid screening procedure for 143 new psychoactive substances by liquid chromatography-tandem mass spectrometry : Simple and rapid screening procedure for 143 new psychoactive substancesDRUG TESTING AND ANALYSIS, GB, 2005, vol. 8, 7652-667 [0007]

P a t e n t k r a v

1. Forbindelse repræsenteret ved:



eller et farmaceutisk acceptabelt salt deraf.

2. Farmaceutisk sammensætning omfattende en forbindelse ifølge krav 1 og en farmaceutisk acceptabel adjuvans eller bærer.

DRAWINGS

Drawing

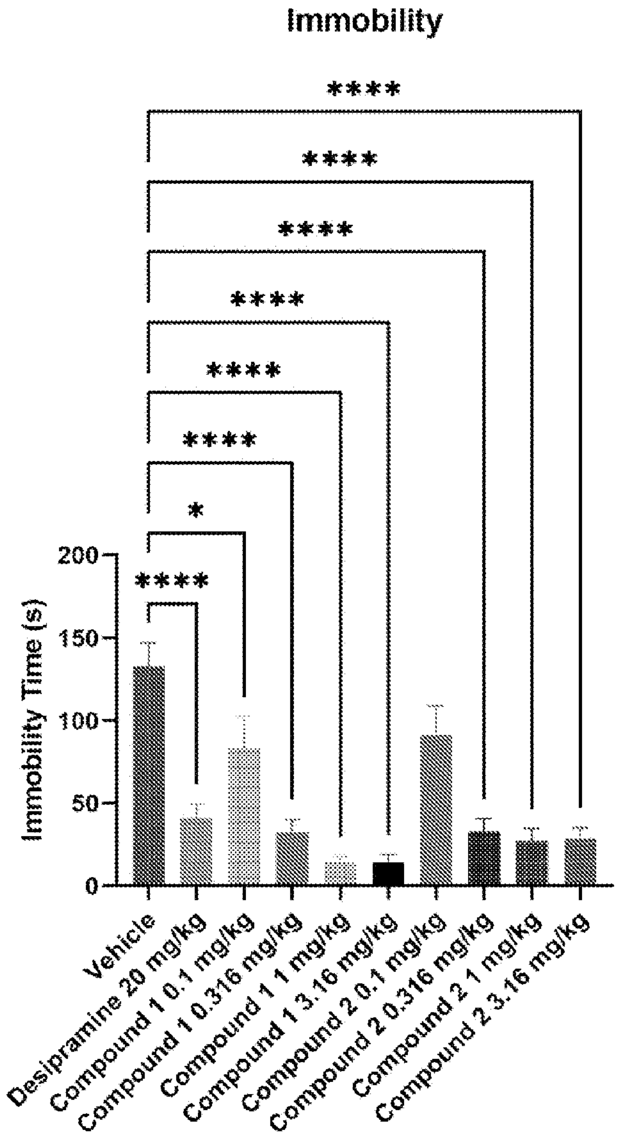
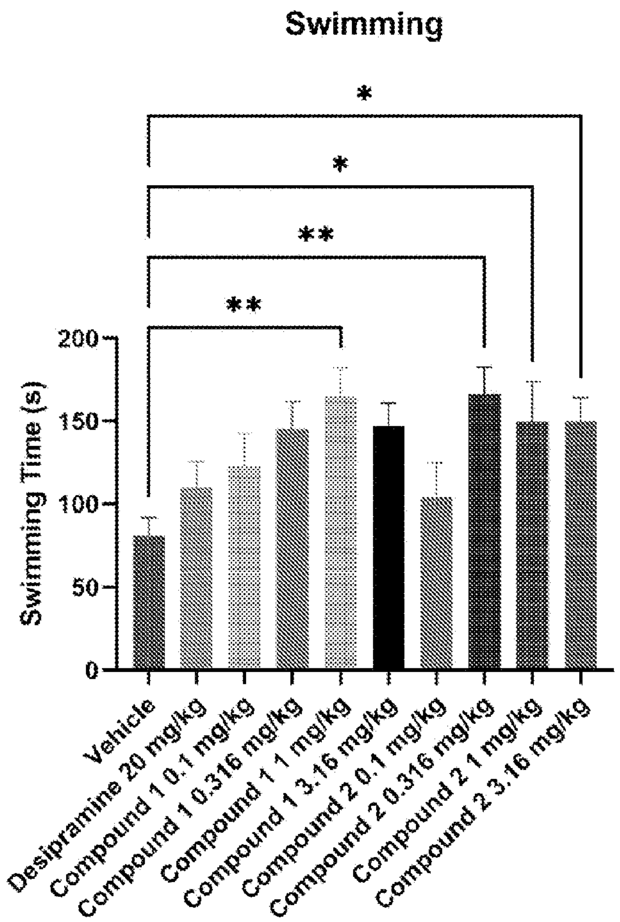


FIG. 1


Swimming
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Swimming Time (s)
200
150
100
50
0
Vehicle
Desipramine 20 mg/kg
Compound 1 0.1 mg/kg
Compound 1 0.316 mg/kg
Compound 1 1 mg/kg
Compound 1 3.16 mg/kg
Compound 2 0.1 mg/kg
Compound 2 0.316 mg/kg
Compound 2 1 mg/kg
Compound 2 3.16 mg/kg

FIG. 2