



(51) International Patent Classification:

C07D 487/04 (2006.01)

(21) International Application Number:

PCT/US2020/047791

(22) International Filing Date:

25 August 2020 (25.08.2020)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/891,388	25 August 2019 (25.08.2019)	US
63/007,653	09 April 2020 (09.04.2020)	US
63/053,976	20 July 2020 (20.07.2020)	US

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

(72) Inventor: CHADEAYNE, Andrew, R.; 13200 Squak Mt. Road S.E., Issaquah, WA 98027 (US).

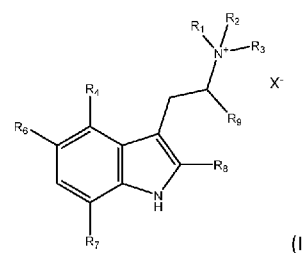
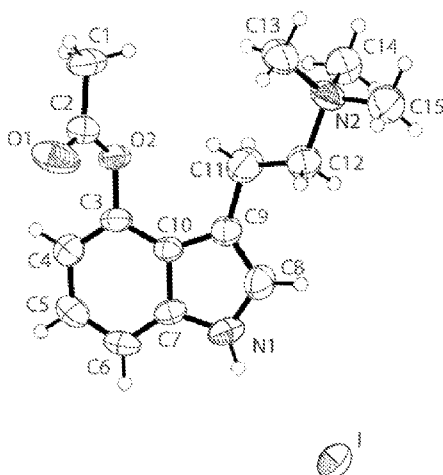
(74) Agent: RAPHAEL, Aaron, M.; J.A. Lindeman & Co., PLLC, 3190 Fairview Park Drive, Suite 1070, Falls Church, VA 22042 (US).

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

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

(54) Title: ALKYL QUARTERNARY AMMONIUM TRYPTAMINES AND THEIR THERAPEUTIC USES

FIG. 1



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

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

ALKYL QUARTERNARY AMMONIUM TRYPTAMINES AND THEIR THERAPEUTIC USES

Related Applications

[001] This application claims priority to US application 62/891,388, filed August 25, 2019; to US application 63/007,653, filed April 9, 2020; and to US application 63/053,976, filed July 20, 2020; each of which are incorporated herein by reference.

Technical Field

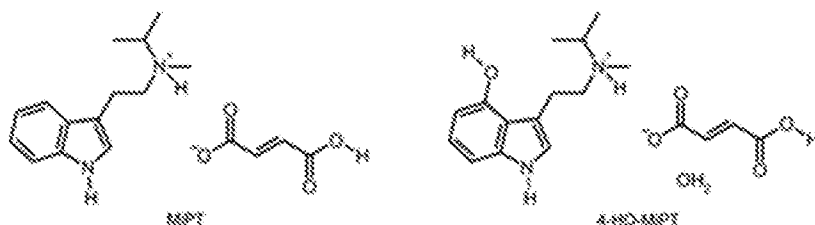
[002] This disclosure relates to alkyl quaternary ammonium tryptamines, compositions and pharmaceutical compositions containing them as well as their use in treating various diseases.

Background

[003] *N,N*-dimethyltryptamine (DMT) and its derivatives have been used by humans for centuries because of their psychoactive, entheogenic, or hallucinogenic effects, or combinations thereof (Cameron & Olson, 2018). Psilocybin, the 4-phosphate variant of DMT, is arguably its most studied derivative. Psilocybin is one of several naturally occurring psychoactive tryptamines found in “magic” mushrooms. When consumed by humans, psilocybin serves as a prodrug of psilocin. Upon digestion, psilocybin hydrolyses to generate psilocin, the 4-hydroxy derivative of DMT. Psilocin is a potent serotonin 2a-agonist, which is responsible for its psychoactive properties (Dinis-Oliveira, 2017; Nichols, 2012).

[004] Psychoactive tryptamines like DMT and psilocin have garnered significant interest recently because of their potential for treating mood disorders, including depression, anxiety, addiction, and post-traumatic stress disorder (PTSD) (Johnson & Griffiths, 2017; Carhart-Harris & Goodwin, 2017). Altering the chemical structure within this class of compounds can dramatically influence the potency and action of the drugs. For example, merely changing the *N,N*-dialkyl groups on DMT can modify its psychoactive properties: increasing the chain length of the two alkyl groups of the tryptamine to larger than *n*-butyl dramatically reduces or eliminates the psychoactive effects (Bradley & Johnston, 1970).

[005] The synthesis of *N*-methyl-*N*-isopropyltryptamine (MiPT) was reported in 1981 (Repke *et al.*, 1981). In 1985, Repke and co-workers reported that of the compounds in the series of *N,N*-dialkyl-4-hydroxytryptamines, the *N*-methyl-*N*-isopropyl derivative (4-HO-MiPT) is the most potent based upon qualitative effects on humans (Repke *et al.*, 1985). Later quantitative studies showed the *N*-methyl-*N*-isopropyl derivatives of DMT and psilocin to be more potent as serotonin-1A, -2A and -2B receptors compared to the analogous dimethyl compounds (McKenna *et al.*, 1990).

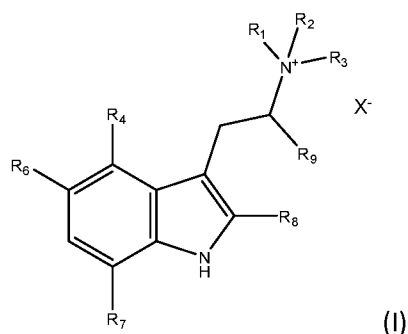


[006] New psychoactive tryptamines have been identified in “magic mushrooms” as recently as 2017. (Lentz, et al., 2017.) Until this year, there was no general synthetic method for producing useful amounts of the minor psychoactive tryptamines. (Sherwood, Halberstadt, et al.) One of these minor components is aeruginascin, (Jensen, et al., 2006) the *N*-trimethyl analogue of psilocybin. The limited exposure of humans to *Inocybe aeruginascens* mushrooms, the only known species in which aeruginascin has been found, has resulted in hallucinations that exhibited only euphoric experiences. (Gartz, 1989). This is in contrast to psilocybin and psilocin mushrooms, which often lead to dysphoric moods during the psychedelic experience. Despite these observations, the pharmacological activity of aeruginascin has remained unexplored.

[007] Even with this previous work, there is a need to develop new psilocybin derivatives with improved properties for treatment of psychological disorders.

Summary of the Invention

[008] The invention relates to a compound of formula (I):



wherein

R_1 , R_2 and R_3 are each independently a straight chain or branched C_1 - C_6 alkyl or C_2 - C_6 alkenyl,

R_4 is hydrogen, hydroxyl, C_1 - C_6 alkoxy, $-OC(O)R_5$, or $-OC(O)OR_5$,

R_5 is a straight chain or branched C_1 - C_6 alkyl,

R_6 is R_4 or a straight chain or branched C_1 - C_6 alkyl with the proviso that R_6 is not hydroxyl when R_1 , R_2 and R_3 are all methyl,

R₇, R₈ and R₉ are each independently hydrogen or a straight chain or branched C₁-C₆ alkyl, and X⁻ is a pharmaceutically acceptable anion. The invention also provides a method of making compounds of formula (I).

[009] The invention relates to compositions comprising, consisting essentially of, or consisting of a compound of formula (I) and an excipient. The invention also relates pharmaceutical compositions comprising a therapeutically effective amount of a compound of formula (I) where the excipient is a pharmaceutically acceptable carrier. The invention further relates to a method of preventing or treating a psychological disorder comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I) or of a pharmaceutical composition containing the compound.

[010] The invention also relates to a composition comprising, consisting essentially of, or consisting of as a first active component: a compound of formula (I) of the disclosure; and as a second active component selected from (a) a serotonergic drug, (b) a purified psilocybin derivative, (c) one or two purified cannabinoids and (d) a purified terpene; and a pharmaceutically acceptable excipient.

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

Brief Description of the Figures

[012] FIG. 1 is the fully labelled displacement ellipsoid representation (50%) of the asymmetric unit of crystalline 4-AcO-TMT iodide.

[013] FIG. 2 is the simulated X-ray Powder Diffraction Pattern (XRPD) for 4-AcO-TMT iodide from its single crystal structure.

[014] FIG. 3 is the fully labelled displacement ellipsoid representation (50%) of the asymmetric unit of crystalline 4-HO-TMT iodide.

[015] FIG. 4 is the simulated X-ray Powder Diffraction Pattern (XRPD) for 4-AcO-TMT iodide from its single crystal structure.

[016] FIG. 5 shows the molecular structure of crystalline DMPT iodide.

[017] FIG. 6 shows the packing of crystalline DMPT iodide.

[018] FIG. 7 is a simulated x-ray powder diffraction (XRPD) pattern of crystalline DMPT iodide from its single crystal data.

[019] FIG. 8 shows the molecular structure of crystalline DMALT iodide.

[020] FIG. 9 shows the packing of crystalline DMALT iodide.

[021] FIG. 10 is a simulated x-ray powder diffraction (XRPD) pattern of crystalline DMALT iodide from its single crystal data.

[022] FIG. 11 shows the molecular structure of crystalline 4-AcO-DMET iodide hemihydrate showing the atomic labelling.

[023] FIG. 12 is a simulated x-ray powder diffraction (XRPD) pattern of crystalline 4-AcO-DMET iodide hemihydrate from its single crystal data.

[024] FIG. 13 shows the molecular structure of crystalline 4-AcO-DMPT iodide showing the atomic labelling.

[025] FIG. 14 is a simulated x-ray powder diffraction (XRPD) pattern of crystalline 4-AcO-DMPT iodide from its single crystal data.

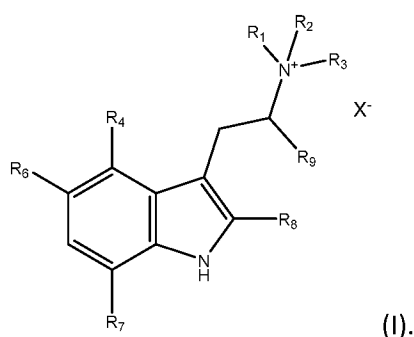
[026] FIG. 15 shows the molecular structure of 4-HO-DMPT iodide showing the atomic labelling.

[027] FIG. 16 is a simulated x-ray powder diffraction (XRPD) pattern of crystalline 4-HO-DMPT iodide from its single crystal data.

Detailed Description

[028] Compounds of the Invention

[029] This invention relates to alkyl quaternary ammonium tryptamine compounds of formula (I):

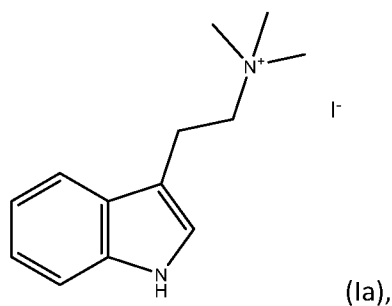


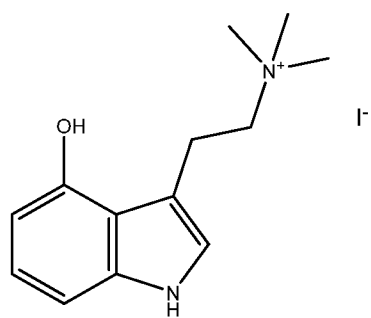
In formula (I), R_1 , R_2 and R_3 are each independently a straight chain or branched C_1 - C_6 alkyl, for example a straight chain C_1 - C_6 alkyl, or a C_2 - C_6 alkenyl, for example allyl. In some embodiments, R_1 , R_2 and R_3 are each independently a straight chain or branched C_1 - C_4 alkyl, for example a straight chain C_1 - C_4 alkyl, or a C_2 - C_4 alkenyl. R_1 , R_2 and R_3 may each independently be selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and tert-butyl. In other embodiments, R_1 , R_2 and R_3 are each methyl, are each ethyl, or a mixture of methyl and ethyl groups. R_4 is hydrogen, hydroxyl, C_1 - C_6 alkoxy, $-OC(O)R_5$ or $-OC(O)OR_5$.

When R_4 is a C_1 - C_6 alkoxy group, or in some embodiments a C_1 - C_4 alkoxy group, it may be a straight chain or branched C_1 - C_6 alkoxy group or C_1 - C_4 alkoxy group, for example a straight chain, and may be methoxy or ethoxy. R_5 is a straight chain or branched C_1 - C_6 alkyl or C_1 - C_4 alkyl, for example a straight chain C_1 - C_4 alkyl. In some embodiments, R_5 is selected from methyl, ethyl, n-propyl or n-butyl, and for example is methyl or ethyl. R_6 is R_4 or a straight chain or branched C_1 - C_4 alkyl, with the exemplary embodiments just discussed and with the proviso that R_6 is not hydroxyl when R_1 , R_2 and R_3 are all methyl. R_7 , R_8 and R_9 are each independently hydrogen or a straight chain or branched C_1 - C_4 alkyl, for example a straight chain C_1 - C_4 alkyl. In some embodiments, R_6 , R_7 , R_8 and R_9 are each independently selected hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl and isobutyl. In other embodiments, R_6 , R_7 , R_8 and R_9 are each independently hydrogen, methyl, ethyl. The anion, X^- , may be any pharmaceutically acceptable anion, for example, Cl^- , I^- , Br^- , ascorbate, hydrofumarate, fumarate, maleate, and the like. A preferred anion, X^- , is iodide, I^- . When the pharmaceutically acceptable anion is a di-anion it balances two of the ammonium cations.

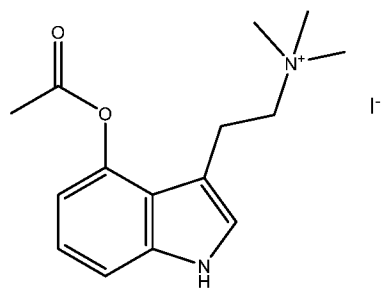
[030] Preferred compounds of formula (I) are those where R_1 , R_2 and R_3 are each independently a C_1 - C_4 alkyl or a C_2 - C_4 alkenyl; R_4 is hydrogen, hydroxyl, C_1 - C_4 alkoxy, $-OC(O)R_5$ or $-OC(O)OR_5$; R_5 is selected from methyl, ethyl, n-propyl and n-butyl; R_6 , R_7 , R_8 and R_9 are each independently hydrogen, methyl, or ethyl; and X^- is Cl^- , I^- , Br^- , ascorbate, hydrofumarate, fumarate, or maleate. Other preferred compounds are those where R_1 , R_2 and R_3 are each independently methyl, ethyl, propyl or allyl; R_4 is hydrogen, hydroxyl, or $-OC(O)R_5$; R_5 is methyl or ethyl; R_6 , R_7 , and R_9 are each independently hydrogen; R_8 is hydrogen or methyl; and X^- is I^- .

[031] Exemplary compounds of formula (I) are:

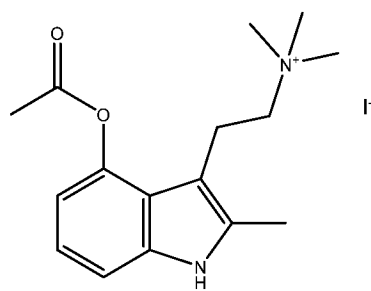




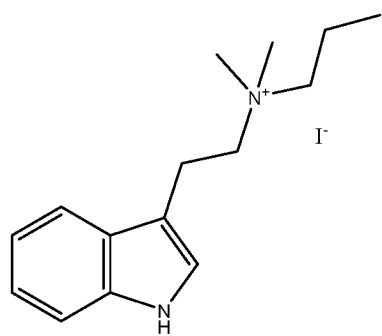
(Ib)



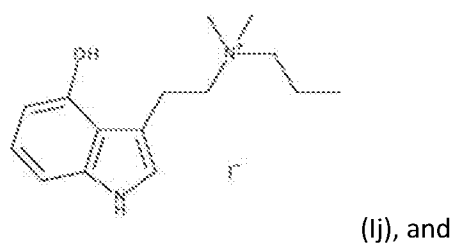
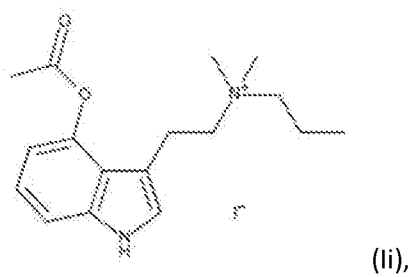
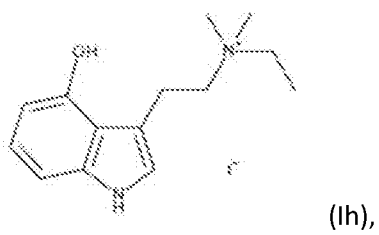
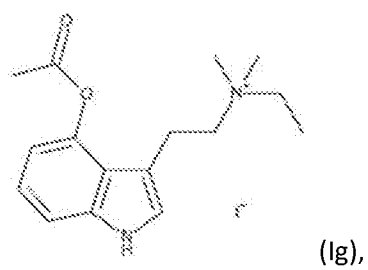
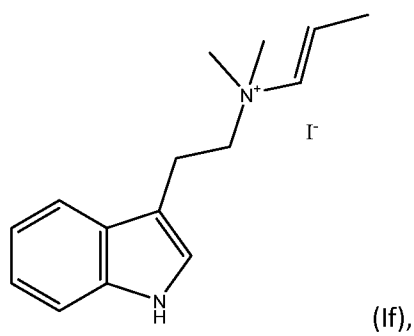
(Ic),

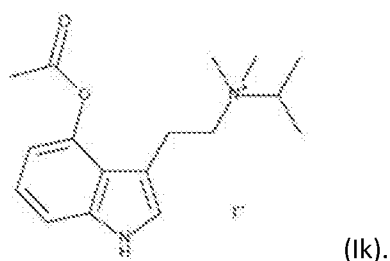


(Id),

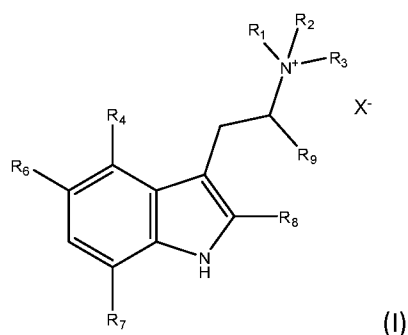


(Ie),

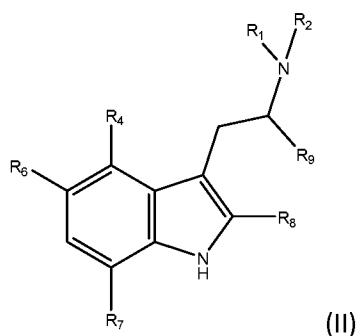




[032] A compound of formula (I)



may be prepared formula (II) (below) with XR_3 , where X is I, by refluxing in an appropriate organic solvent, such as methanol or THF, under an inert atmosphere.



In a preferred embodiment, XR_3 is ICH_3 or ICH_2CH_3 . When R_4 or R_6 are hydroxyl they can be converted to esters, $-\text{OC}(\text{O})\text{R}_5$, or carbonate esters, $-\text{OC}(\text{O})\text{OR}_5$, as is known in the art. Hydroxyl groups may be introduced by hydrolysis of a corresponding ester. Other pharmaceutically acceptable salts may be prepared by anion exchange techniques known in the art to exchange the iodide anion for a desired pharmaceutically acceptable anion. For example, the iodide anion may be exchanged using an anion exchange resin.

[033] Methods of Treatment and Therapeutic Uses

[034] In one embodiment, the compounds of formula (I), the methods, and the pharmaceutical compositions of the invention are used to regulate the activity of a neurotransmitter receptor by

administering a therapeutically effective dose of a compound formula (I). Methods of the invention administer a therapeutically effective amount of a compound of formula (I) to prevent or treat a psychological disorder such as those discussed below. Compounds of formula (I) may be administered neat or as a pharmaceutical composition comprising a compound of formula (I) as discussed below.

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

[036] Compounds of formula (I) may be used to prevent and/or treat a brain disorder. The invention provides a method for preventing and/or treating a brain disorder by administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I), including the preferred embodiments discussed above. The brain disorder may be chosen from Huntington's disease, Alzheimer's disease, dementia, and Parkinson's disease.

[037] Compounds of formula (I) may be used to prevent and/or treat developmental disorders, delirium, dementia, amnesic disorders and other cognitive disorders, psychiatric disorders due to a somatic condition, drug-related disorders, schizophrenia and other psychotic disorders, mood disorders, anxiety disorders, somatoform disorders, factitious disorders, dissociative disorders, eating disorders, sleep disorders, impulse control disorders, adjustment disorders, or personality disorders. The invention provides a method for preventing and/or treating these disorders by administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I), including the preferred embodiments discussed above.

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

[039] Compositions

[040] The invention relates to compositions comprising, consisting essentially of, or consisting of an effective amount of a compound of formula (I), including its preferred embodiments discussed above, and an excipient. In another embodiment of the invention, the invention also relates to pharmaceutical compositions comprising, consisting essentially of, or consisting of a therapeutically effective amount of a compound of formula (I) according to the invention, including its preferred embodiments discussed above, and a pharmaceutically acceptable excipient (also known as a pharmaceutically acceptable carrier). As discussed above, a compound of formula (I) according to the invention may be, for example, therapeutically useful to prevent and/or treat the psychological disorders, brain disorders, pain and inflammation as well as the other disorders discussed above.

[041] A composition or a pharmaceutical composition of the invention may be in any form which contains a compound of formula (I) according to the invention. The composition may be, for example, a tablet, capsule, liquid suspension, injectable, topical, or transdermal. The compositions generally

contain, for example, about 1% to about 99% by weight of a compound of formula (I) and, for example, 99% to 1% by weight of at least one suitable pharmaceutically acceptable excipient. In one embodiment, the composition may be between about 5% and about 75% by weight of a compound of formula (I) with the rest being at least one suitable pharmaceutically acceptable excipient or at least one other adjuvant, as discussed below.

[042] Published US applications US 2018/0221396 A1 and US 2019/0142851 A1 disclose compositions comprising a combination of a first purified psilocybin derivative with a serotonergic drug, a second purified psilocybin derivative, with one or two purified cannabinoids or with a purified terpene. Various ratios of these components in the composition are also disclosed. The disclosures of US 2018/0221396 A1 and US 2019/0142851 A1 are incorporated herein by reference. According to this invention, a compound of formula (I) of the invention, and the preferred embodiments described herein, may be used as the “first purified psilocybin derivative” in the compositions described in US 2018/0221396 A1 and US 2019/0142851 A1. Accordingly, this invention provides a composition comprising as a first component: a compound of formula (I) of the disclosure; and as a second component selected from (a) a serotonergic drug, (b) a purified psilocybin derivative, (c) one or two purified cannabinoids and (d) a purified terpene; with the rest being at least one suitable pharmaceutical excipient or at least one other adjuvant, as discussed below. Such a composition may be a pharmaceutical composition wherein the components are present individually in therapeutic effective amounts or by combination in a therapeutically effective amount to treat a disease, disorder or condition as described herein.

[043] A serotonergic drug refers to a compound that binds to, blocks, or otherwise influences (e.g., via an allosteric reaction) activity at a serotonin receptor as described in paragraphs [0245]-[0253] of US 2018/0221396 A1 and [0305]-[0311] US 2019/0142851 A1 as well as the disclosed preferred embodiments, incorporated here by reference. Some exemplary serotonergic drugs include the following molecules: 6-Allyl-N,N-diethyl-NL, N,N-Dibutyl-T, N,N-Diethyl-T, N,N-Diisopropyl-T, 5-Methoxy-alpha-methyl-T, N,N-Dimethyl-T, 2, alpha-Dimethyl-T, alpha, N-Dimethyl-T, N,N-Dipropyl-T, N-Ethyl-N-isopropyl-T, alpha-Ethyl-T, 6, N,N-Triethyl-NL, 3,4-Dihydro-7-methoxy-1-methyl-C, 7-Methoxy-1-methyl-C, N,N-Dibutyl-4-hydroxy-T, N,N-Diethyl-4-hydroxy-T, N,N-Diisopropyl-4-hydroxy-T, N,N-Dimethyl-4-hydroxy-T, N,N-Dimethyl-5-hydroxy-T, N, N-Dipropyl-4-hydroxy-T, N-Ethyl-4-hydroxy-N-methyl-T, 4-Hydroxy-N-isopropyl-N-methyl-T, 4-Hydroxy-N-methyl-N-propyl-T, 4-Hydroxy-N-tetramethylene-T Ibogaine, N,N-Diethyl-L, N-Butyl-N-methyl-T, N,N-Diisopropyl-4,5-methylenedioxy-T, N,N-Diisopropyl-5,6-methylenedioxy-T, N,N-Dimethyl-4,5-methylenedioxy-T, N,N-Dimethyl-5,6-methylenedioxy-T, N-Isopropyl-N-methyl-5,6-methylenedioxy-T, N,N-Diethyl-2-methyl-T, 2, N,N-

Trimethyl-T, N-Acetyl-5-methoxy-T, N,N-Diethyl-5-methoxy-T, N,N-Diisopropyl-5-methoxy-T, 5-Methoxy-N,N-dimethyl-T, N-Isopropyl-4-methoxy-N-methyl-T, N-Isopropyl-5-methoxy-N-methyl-T, 5,6-Dimethoxy-N-isopropyl-N-methyl-T, 5-Methoxy-N-methyl-T, 5-Methoxy-N,N-tetramethylene-T, 6-Methoxy-1-methyl-1,2,3,4-tetrahydro-C, 5-Methoxy-2,N,N-trimethyl-T, N,N-Dimethyl-5-methylthio-T, N-Isopropyl-N-methyl-T, alpha-Methyl-T, N-Ethyl-T, N-Methyl-T, 6-Propyl-N L, N,N-Tetramethylene-T, Tryptamine, and 7-Methoxy-1-methyl-1,2,3,4-tetrahydro-C, alpha,N-Dimethyl-5-methoxy-T. For additional information regarding these compounds See Shulgin, A. T., & Shulgin, A. (2016). Tihkal: The Continuation. Berkeley, Calif.: Transform Press. In one embodiment, a serotonergic drug is chosen from alprazolam, amphetamine, aripiprazole, azapirone, a barbiturate, bromazepam, bupropion, buspirone, a cannabinoid, chlordiazepoxide, citalopram, clonazepam, clorazepate, dextromethorphan, diazepam, duloxetine, escitalopram, fluoxetine, flurazepam, fluvoxamine, lorazepam, lysergic acid diethylamide, lysergamide, 3,4-methylenedioxymethamphetamine, milnacipran, mirtazapine, naratriptan, paroxetine, pethidine, phenethylamine, psilocaine, oxazepam, reboxetine, serenic, serotonin, sertraline, temazepam, tramadol, triazolam, a tryptamine, venlafaxine, vortioxetine, and/or derivatives thereof.

[044] Exemplary psilocybin derivatives include but are not limited to psilocybin itself and the psilocybin derivatives described in paragraphs [0081]-[0109] of US 2018/0221396 A1 and [082]-[0110] US 2019/0142851 A1 as well as the disclosed preferred embodiments, incorporated here by reference. In one embodiment, the compositions disclosed herein comprise one or more purified psilocybin derivatives chosen from: [3-(2-Dimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate, 4-hydroxytryptamine, 4-hydroxy-N,N-dimethyltryptamine, [3-(2-methylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate, 4-hydroxy-N-methyltryptamine, [3-(aminoethyl)-1H-indol-4-yl] dihydrogen phosphate, [3-(2-trimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate, and 4-hydroxy-N,N-trimethyltryptamine.

[045] Exemplary cannabinoids include but are not limited to the cannabinoids described in paragraphs [0111]-[0159] of US 2018/0221396 A1 and [0112]-[0160] US 2019/0142851 A1 as well as the disclosed preferred embodiments, incorporated here by reference. Examples of cannabinoids within the context of this disclosure include the following molecules: Cannabichromene (CBC), Cannabichromenic acid (CBCA), Cannabichromevarin (CBCV), Cannabichromevarinic acid (CBCVA), Cannabicyclol (CBL), Cannabicyclic acid (CBLA), Cannabicyclovarin (CBLV), Cannabidiol (CBD), Cannabidiol monomethylether (CBDM), Cannabidiolic acid (CBDA), Cannabidiolcol (CBD-C1), Cannabidivarin (CBDV), Cannabidivarinic acid (CBDVA), Cannabielsoic acid B (CBEA-B), Cannabielsoin (CBE), Cannabielsoin acid A (CBEA-A), Cannabigerol (CBG), Cannabigerol monomethylether (CBGM), Cannabigerolic acid (CBGA),

Cannabigerolic acid monomethylether (CBGAM), Cannabigerovarin (CBGV), Cannabigerovarinic acid (CBGVA), Cannabinodiol (CBND), Cannabinodivarin (CBDV), Cannabinol (CBN), Cannabinol methylether (CBNM), Cannabinol-C2 (CBN-C2), Cannabinol-C4 (CBN-C4), Cannabinolic acid (CBNA), Cannabiorcool (CBN-C1), Cannabivarin (CBV), Cannabitriol (CBT), Cannabitriolvarin (CBTV), 10-Ethoxy-9-hydroxy-delta-6a-tetrahydrocannabinol, Cannbicitran (CBT), Cannabiripsol (CBR), 8,9-Dihydroxy-delta-6a-tetrahydrocannabinol, Delta-8-tetrahydrocannabinol (.DELTA.8-THC), Delta-8-tetrahydrocannabinolic acid (.DELTA.8-THCA), Delta-9-tetrahydrocannabinol (THC), Delta-9-tetrahydrocannabinol-C4 (THC-C4), Delta-9-tetrahydrocannabinolic acid A (THCA-A), Delta-9-tetrahydrocannabinolic acid B (THCA-B), Delta-9-tetrahydrocannabinolic acid-C4 (THCA-C4), Delta-9-tetrahydrocannabiorcol (THC-C1), Delta-9-tetrahydrocannabiorcolic acid (THCA-C1), Delta-9-tetrahydrocannabivarin (THCV), Delta-9-tetrahydrocannabivarinic acid (THCVA), 10-Oxo-delta-6a-tetrahydrocannabinol (OTHC), Cannabichromanon (CBCF), Cannabifuran (CBF), Cannabiglendol, Delta-9-cis-tetrahydrocannabinol (cis-THC), Tryhydroxy-delta-9-tetrahydrocannabinol (triOH-THC), Dehydrocannabifuran (DCBF), and 3,4,5,6-Tetrahydro-7-hydroxy-alpha-alpha-2-trimethyl-9-n-propyl-2,6-metha- no-2H-1-benzoxocin-5-methanol. In one embodiment, the purified cannabinoid is chosen from THC, THCA, THCV, THCVA, CBC, CBCA, CBCV, CBCVA, CBD, CBDA, CBDV, CBDVA, CBG, CBGA, CBGV, or CBGVA.

[046] Exemplary terpenes include but are not limited to the terpenes described in paragraphs [0160]-[0238] of US 2018/0221396 A1 and [0161]-[0300] US 2019/0142851 A1 as well as the disclosed preferred embodiments, incorporated here by reference. In one embodiment, a purified terpene is chosen from acetanisole, acetyl cedrene, anethole, anisole, benzaldehyde, bornyl acetate, borneol, cadinene, cafestol, caffeic acid, camphene, camphor, capsaicin, carene, carotene, carvacrol, carvone, alpha-caryophyllene, beta-caryophyllene, caryophyllene oxide, cedrene, cedrene epoxide, cecanal, cedrol, cembrene, cinnamaldehyde, cinnamic acid, citronellal, citronellol, cymene, eicosane, elemene, estragole, ethyl acetate, ethyl cinnamate, ethyl maltol, eucalyptol/1,8-cineole, eudesmol, eugenol, euphol, farnesene, farnesol, fenchone, geraniol, geranyl acetate, guaia-1(10),11-diene, guaiacol, guaiol, guaiane, gurjunene, herniarin, hexanaldehyde, hexanoic acid, humulene, ionone, ipsdienol, isoamyl acetate, isoamyl alcohol, isoamyl formate, isoborneol, isomyrcenol, isoprene, isopulegol, isovaleric acid, lavandulol, limonene, gamma-linolenic acid, linalool, longifolene, lycopene, menthol, methyl butyrate, 3-mercapto-2-methylpentanal, beta-mercaptoethanol, mercaptoacetic acid, methyl salicylate, methylbutenol, methyl-2-methylvalerate, methyl thiobutyrate, beta-myrcene, gamma-murolene, nepetalactone, nerol, nerolidol, neryl acetate, nonanaldehyde, nonanoic acid, ocimene, octanal, octanoic acid, pentyl butyrate, phellandrene, phenylacetaldehyde, phenylacetic acid, phenylethanethiol,

phytol, pinene, propanethiol, pristimerin, pulegone, retinol, rutin, sabinene, squalene, taxadiene, terpineol, terpine-4-ol, terpinolene, thujone, thymol, umbelliferone, undecanal, verdoxan, or vanillin. In one embodiment, a purified terpene is chosen from bornyl acetate, alpha-bisabolol, borneol, camphene, camphor, carene, beta-caryophyllene, cedrene, cymene, elemene, eucalyptol, eudesmol, farnesene, fenchol, geraniol, guaiacol, humulene, isoborneol, limonene, linalool, menthol, beta-myrcene, nerolidol, ocimene, phellandrene, phytol, pinene, pulegone, sabinene, terpineol, terpinolene, or valencene.

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

[048] Depending on the type of pharmaceutical composition, the pharmaceutically acceptable carrier may be chosen from any one or a combination of carriers known in the art. The choice of the pharmaceutically acceptable carrier depends upon the pharmaceutical form and the desired method of administration to be used. Preferred carriers include those that do not substantially alter the salt of ritonavir or produce undesirable biological effects or otherwise interact in a deleterious manner with any other component(s) of the pharmaceutical composition.

[049] The pharmaceutical compositions of the invention may be prepared by methods known in the pharmaceutical formulation art, for example, see Remington’s Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990), which is incorporated herein by reference. In a solid dosage form, a compound of formula (I) may be admixed with at least one pharmaceutically acceptable

excipient such as, for example, sodium citrate or dicalcium phosphate or (a) fillers or extenders, such as, for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, such as, for example, cellulose derivatives, starch, alginates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, such as, for example, glycerol, (d) disintegrating agents, such as, for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, such as, for example, paraffin, (f) absorption accelerators, such as, for example, quaternary ammonium compounds, (g) wetting agents, such as, for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like, (h) adsorbents, such as, for example, kaolin and bentonite, and (i) lubricants, such as, for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

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

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

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

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

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

[055] Examples

[056] Example 1: 4-Acetoxy-*N,N,N*-trimethyltryptammonium Iodide (4-AcO-TMT iodide)

[057] 4-acetoxy-*N,N*-dimethyltryptamine (4-AcO-DMT) fumarate was stirred in a 1:1 solution of methanol and iodomethane and heated to reflux for four hours. Solvent is removed *in vacuo*, and a white powder is obtained after triturating and washing the resulting residue with tetrahydrofuran. ¹H NMR (400 MHz, D₂O): δ 7.46 (d, *J* = 8.1 Hz, 1H, ArH), 7.33 (s, 1H, ArH), 7.27 (t, *J* = 8.0 Hz, 1H, ArH), 6.90 (d, *J* = 7.8 Hz, 1H, ArH), 3.63 (t, *J* = 7.5 Hz, 2H, CH₂), 3.27 (t, *J* = 8.6 Hz, 2H, CH₂), 3.21 (s, 9H, NCH₃), 2.47 (s, 3H, C(O)CH₃). Unit Cell: *a* = 7.8459(9) Å, *b* = 9.8098(12) Å, *c* = 11.0823(12) Å, α = 90°, β = 101.069(3)°, γ = 90°, *V* = 837.10(17) Å³.

[058] Second Preparation of 4-AcO-TMT iodide: 250 mg of 4-acetoxy-*N,N*-dimethyltryptammonium (4-AcO-DMT) fumarate was dissolved in 10 mL of methanol in a 50 mL round bottom flask, and 10 mL of iodomethane was then added. The mixture was stirred for 24 hours under an atmosphere of dinitrogen. The solvent was removed *in vacuo*. The resulting powder was washed with diethyl ether and filtered to yield 313 mg of yellow powder. This powder was dissolved in 75 mL of acetone. The solution was heated with stirring and reduced in volume to 40 mL. The mixture was cooled in an ice bath, yielding a white precipitate. The powder was filtered to yield 142 mg of white powder (53.01% yield). ¹H NMR (400 MHz, D₂O): δ 7.46 (d, *J* = 8.6 Hz, 1 H, ArH), 7.34 (s, 1 H, ArH), 7.22 (t, *J* = 7.8 Hz, 1 H, ArH), 6.95 (d, *J* = 8.3 Hz, 1H, ArH) 3.63 (t, *J* = 7.9 Hz, 2 H, CH₂), 3.28 (t, *J* = 8.0 Hz, 2 H, CH₂), 3.21 (s, 9 H, CH₃), 2.47 (s, 3 H, C(O)CH₃); ¹³C NMR (100 MHz, D₂O): δ 174.32 (C=O), 143.59 (ArC), 139.28 (ArC), 125.82 (ArC), 123.01

(ArC), 119.11 (ArC), 112.92 (ArC), 111.13 (ArC), 107.32 (ArC), 67.64 (NCH₂), 53.73 (NCH₃), 21.25 (CH₂), 20.48 (C(O)CH₃). Elemental analysis calcd. for C₁₅H₂₁N₂O₂I: C 46.40, H 5.45, N 7.22; Found: C 46.17, H 5.35, N 7.11.

[059] X-Ray data collection and refinement details for 4-AcO-TMT iodide: Crystals suitable for X-ray diffraction studies were grown from the slow evaporation of an aqueous solution. All operations were performed on a Bruker D8 Venture CMOS diffractometer, using Mo K α radiation with a TRIUMPH monochromator at a temperature of 298 K. Data collection was carried out using the Bruker APEX3 software. Cell refinement and data reduction were performed with the SAINT program. The structure solution was done with SHELXS and structure refinement was performed with SHELXL. Further refinement and molecular graphics were generated using the OLEX2 and Mercury CSD software.

[060] All non-hydrogen atoms were refined anisotropically (XL) by full matrix least squares on F^2 . Hydrogen atom H1 was found from a Fourier difference map, and refined with a fixed distance of 0.87 Å. Isotropic displacement parameters were set to 1.20 times U_{eq} of the parent N atoms. The remaining hydrogen atoms were placed in calculated positions and then refined with a riding model with C–H lengths of 0.93 Å (sp^2), 0.96 Å (CH_3) and 0.97 Å (CH_2) with isotropic displacement parameters set to 1.20 (sp^2 and CH_2) and 1.50 (CH_3) times U_{eq} of the parent C atom. Further details are in Table 1. FIG. 1 is the fully labelled displacement ellipsoid representation (50%) of the asymmetric unit of 4-AcO-TMT iodide.

Table 1. Crystal data and structure refinement for 4-AcO-TMT iodide.

Empirical formula	C ₁₅ H ₂₁ IN ₂ O ₂
Formula weight	388.24
Temperature/K	299.05
Crystal system	Monoclinic
Space group	$P2_1$
a/Å	7.8459(9)
b/Å	9.8098(12)
c/Å	11.0823(12)
$\alpha/^\circ$	90
$\beta/^\circ$	101.069(3)
$\gamma/^\circ$	90
Volume/Å ³	837.10(17)
Z	2
ρ_{calc}/cm^3	1.540
μ/mm^{-1}	1.916
F(000)	388.0
Crystal size/mm ³	0.2 × 0.1 × 0.05
Radiation	MoK α (λ = 0.71073)

2 θ range for data collection/°	5.866 to 50.852
Index ranges	$-9 \leq h \leq 9$, $-11 \leq k \leq 11$, $-13 \leq l \leq 13$
Reflections collected	18328
Independent reflections	3076 [$R_{\text{int}} = 0.0424$, $R_{\text{sigma}} = 0.0298$]
Data/restraints/parameters	3076/2/189
Goodness-of-fit on F^2	1.064
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0300$, $wR_2 = 0.0548$
Final R indexes [all data]	$R_1 = 0.0396$, $wR_2 = 0.0583$
Largest diff. peak/hole / e $\text{\AA}^{-3}$	0.51/−0.40
Flack parameter	−0.001(11)

[061] FIG. 2 is a simulated x-ray powder diffraction (XRPD) pattern of crystalline 4-Acetoxy-*N,N,N*-trimethyltryptammonium iodide (4-AcO-TMT iodide) from its single crystal data. Crystalline 4-Acetoxy-*N,N,N*-trimethyltryptammonium iodide (4-AcO-TMT iodide) may be characterized by the XRPD peaks at 8.1, 14.6 and 19.8 $^{\circ}2\theta \pm 0.2^{\circ}2\theta$ as well as by an XRPD pattern substantially similar to FIG. 2.

[062] Example 2: 4-Hydroxy-*N,N,N*-trimethyltryptammonium (4-HO-TMT) iodide

[063] 4-acetoxy-*N,N,N*-trimethyltryptammonium (4-AcO-TMT) iodide was stirred in a 1:1 solution of water and acetic acid in air for 12 hours. Solvent is removed *in vacuo*, and a white powder is obtained after triturating and washing the resulting residue with tetrahydrofuran. ^1H NMR (400 MHz, D_2O): δ 7.18 (s, 1H, ArH), 7.12–7.06 (m, 2H, ArH), 6.57 (dd, $J = 6.0, 2.4$ Hz, 1H, ArH), 3.62 (t, $J = 7.8$ Hz, 2H, CH_2), 3.37 (t, $J = 8.1$ Hz 2H, CH_2), 3.19 (s, 9H, NCH_3). Unit Cell: $a = 11.3057(9)$ Å, $b = 11.2370(10)$ Å, $c = 12.7785(10)$ Å, $\alpha = 90^{\circ}$, $\beta = 113.087(2)^{\circ}$, $\gamma = 90^{\circ}$, $V = 1493.4(2)$ Å ^{3} .

[064] Second preparation of 4-HO-TMT iodide: 95 mg of 4-AcO TMT iodide was dissolved in 4 mL of deionized (DI) water in a 50 mL round bottom flask. 20 mL of acetic acid was added to the mixture, and it was refluxed under an atmosphere of dinitrogen for 2 days. Solvent was removed *in vacuo* to obtain a green/blue oil. 3 mL of methanol and 20 mL of ethyl acetate were added to the green/blue oil, leaving a green/blue powder that was removed via filtration. Solvent was removed *in vacuo*. The resulting oil was dissolved in 5 mL of ethanol, and 30 mL of pentane was added to generate a precipitate. The resulting powder was isolated via filtration to give 53.1 g (60% yield) to give an off-white powder. ^1H NMR (400 MHz, D_2O): δ 7.19 (s, 1 H, ArH), 7.12–7.07 (m, 2 H, ArH), 6.56 (dd, $J = 5.9, 2.5$ Hz, 1 H, ArH), 3.66–3.62 (m, 2 H, CH_2), 3.40–3.36 (m, 2 H, CH_2), 3.20 (s, 9 H, CH_3); ^{13}C NMR (100 MHz, D_2O): δ 150.62 (ArC), 139.37 (ArC), 123.89 (ArC), 123.86 (ArC), 116.56 (ArC), 108.72 (ArC), 105.23 (ArC), 104.43 (ArC), 68.20 (NCH_2), 53.59 (NCH_3), 21.20 (CH_2). Elemental analysis calcd. For $\text{C}_{13}\text{H}_{19}\text{N}_2\text{OI}$: C 45.10, H 5.53, N 8.09; Found: C 44.84, H 5.23, N 7.98.

[065] X-Ray data collection and refinement details for 4-HO-TMT iodide: Crystals suitable for X-ray diffraction studies were grown from the slow evaporation of an aqueous solution. All operations were performed on a Bruker D8 Venture CMOS diffractometer, using Mo K α radiation with a TRIUMPH monochromator at a temperature of 200 K. Data collection was carried out using the Bruker APEX3 software. Cell refinement and data reduction were performed with the SAINT program. The structure solution was done with SHELXS and structure refinement was performed with SHELXL. Further refinement and molecular graphics were generated using the OLEX2 and Mercury CSD software.

[066] All non-hydrogen atoms were refined anisotropically (XL) by full matrix least squares on F^2 . Hydrogen atom H1 and H1A were found from a Fourier difference map, and refined with a fixed distance of 0.86 Å and 0.85 Å respectively. Isotropic displacement parameters were set to 1.20 times U_{eq} of the parent N atom, and 1.50 times U_{eq} of the parent O atom. The remaining hydrogen atoms were placed in calculated positions and then refined with a riding model with C–H lengths of 0.95 Å (sp^2), 0.98 Å (CH_2) and 0.99 Å (CH_3) with isotropic displacement parameters set to 1.20 (sp^2 and CH_2) and 1.50 (CH_3) times U_{eq} of the parent C atom. Further details are in Table 2. FIG. 3 is the fully labelled displacement ellipsoid representation (50%) of the asymmetric unit of 4-HO-TMTI.

Table 2. Crystal data and structure refinement for 4-HO-TMT iodide.

Empirical formula	C ₁₃ H ₁₉ IN ₂ O
Formula weight	346.20
Temperature/K	200.0
Crystal system	Monoclinic
Space group	$P2_1/n$
a/Å	11.3057(9)
b/Å	11.2370(10)
c/Å	12.7785(10)
$\alpha/^\circ$	90
$\beta/^\circ$	113.087(2)
$\gamma/^\circ$	90
Volume/Å ³	1493.4(2)
Z	4
ρ_{calc}/cm^3	1.540
μ/mm^{-1}	2.133
F(000)	688.0
Crystal size/mm ³	0.4 × 0.2 × 0.1
Radiation	MoK α (λ = 0.71073)
2 θ range for data collection/ $^\circ$	6.164 to 52.884
Index ranges	−13 ≤ h ≤ 14, −14 ≤ k ≤ 14, −15 ≤ l ≤ 15
Reflections collected	29269
Independent reflections	3063 [R_{int} = 0.0564, R_{sigma} = 0.0277]

Data/restraints/parameters	3063/2/161
Goodness-of-fit on F^2	1.073
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0368$, $wR_2 = 0.0797$
Final R indexes [all data]	$R_1 = 0.0574$, $wR_2 = 0.0885$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$	1.05/−0.93

[067] FIG. 4 is a simulated x-ray powder diffraction (XRPD) pattern of crystalline 4-Hydroxy-*N,N,N*-trimethyltryptammonium Iodide (4-HO-TMT iodide) from its single crystal data. Crystalline 4-Hydroxy-*N,N,N*-trimethyltryptammonium Iodide (4-HO-TMT iodide) may be characterized by the XRPD peaks at 17.0 , 18.1 and $19.5^\circ 2\theta \pm 0.2^\circ 2\theta$ as well as by an XRPD pattern substantially similar to FIG. 4.

[068] Example 3: Cellular Assays

[069] Cellular assays were performed by Eurofins CEREP SA, Celle-Lévescault, France. All receptors were separately expressed in HEK-293 cells. Cell membrane homogenates (30 μg protein) are incubated for 60 min (5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}) or 120 min (5-HT₃) at 22°C with radiolabeled ligand in the absence or presence of the test compound in a buffer containing 50 mM Tris-HCl (pH 7.4), 5 mM MgCl₂, 10 μM pargyline and 0.1% ascorbic acid. For 5-HT₃, the buffer contained 50 mM Tris-HCl (pH 7.4), 5 mM MgCl₂, and 1mM EDTA. Binding was reported as the K_i for the inhibition of binding of well-characterized orthosteric ligands. The ligands used for each receptor were:

5-HT_{1A}: [^3H] 8-OH-DPAT

5-HT_{2A}: [^{125}I] ($\pm$)DOI

5-HT_{2B}: [^{125}I] ($\pm$)DOI

5-HT₃: [^3H] BRL 43694

[070] Nonspecific binding was determined in the presence of 1 μM unlabeled ligand listed above. Following incubation, the samples were filtered rapidly under vacuum through glass fiber filters (GF/B, Packard) presoaked with 0.3% PEI and rinsed several times with ice-cold 50 mM Tris-HCl using a 96-sample cell harvester (Unifilter, Packard). The filters were dried then counted for radioactivity in a scintillation counter (Topcount, Packard) using a scintillation cocktail (Microscint O, Packard). The results are expressed as a percent inhibition of the control radioligand specific binding.

[071] The IC_{50} values and Hill coefficients (n_H) were determined by non-linear regression analysis of the competition curves generated with mean replicate values using Hill equation curve fitting $Y = D + (A - D) / (1 + (C/C_{50})^{n_H})$ where Y = specific binding, A = left asymptote of the curve, D = right asymptote of the curve, C = compound concentration, $C_{50} = \text{IC}_{50}$, and n_H = slope factor.

[072] Analysis was performed using software developed at Cerep (Hill software) and validated by comparison with data generated by the commercial software SigmaPlot® 4.0 for Windows® (© 1997 by SPSS Inc.). The inhibition constants (K_i) were calculated using the Cheng Prusoff equation: $K_i = IC_{50} / (1 + L/K_D)$, where L = concentration of radioligand in the assay, and K_D = affinity of the radioligand for the receptor. A scatchard plot was used to determine the K_D .

[073] The results in terms of inhibition constants (K_i) are shown in Table 3. The aeruginascin active metabolite, 4-HO-TMTI, shows activity at 5-HT_{1A}, 5-HT_{2A} and 5-HT_{2B}. Counter to the prevailing theory that aeruginascin should function as a powerful 5-HT₃ agonist, there is no activity observed at this receptor. The aeruginascin functional analogue, 4-AcO-TMTI shows no activity at any of the receptors. For comparison, psilocybin, the pro-drug of psilocin, shows no activity at 5-HT_{1A}, 5-HT_{2A}, nor 5-HT₃, but does show itself to be a potent 5-HT_{2B} agonist. Psilocin, its active metabolite, shows activity at 5-HT_{1A} and 5-HT_{2A} that is more active though comparable to 4-HO-TMTI. (Roth et al.) It is significantly more potent than 4-HO-TMTI at the 5-HT_{2B} receptor, and in fact, psilocybin is more active at this receptor as well.

Table 3. Inhibition constants (K_i) in nM units.

Compound	5-HT _{1A}	5-HT _{2A}	5-HT _{2B}	5-HT ₃
4-HO-TMTI	4,400	670	120	>10,000
4-AcO-TMTI	>10,000	>10,000	>10,000	>10,000
Psilocin [†]	567.4	107.2	4.6	>10,000
Psilocybin [†]	>10,000	>10,000	98.7	>10,000

[074] Example 4: *N,N*-di-methyl-*N*-propyl-tryptammonium (DMPT) iodide

[075] *N,N*-di-methyl-*N*-propyl-tryptammonium (DMPT) iodide was prepared by mixing 101 mg of a commercial sample of *N*-methyl-*N*-propyl-tryptamine (The Indole Shop) and 4 mL of methyl iodide in 4 mL of methanol. The mixture was refluxed for twelve hours under an atmosphere of nitro-gen. The solvent was removed in vacuo, and the remaining residue was recrystallized from ethanol to yield colorless single crystals suitable for X-ray diffraction studies. The product was also characterized by nuclear magnetic resonance. ¹H NMR (400 MHz, D₂O): d 7.69 (d, J = 8.0 Hz, 1 H, ArH), 7.55 (d, J = 8.2 Hz, 1 H, ArH), 7.33-7.28 (m, 2 H, ArH), 7.22 (t, J = 7.0 Hz, 1 H, ArH), 3.60 (m, 2 H, CH₂), 3.36 (m, 4 H, CH₂), 3.17 (s, 6 H, CH₃), 1.82 (m, 2 H, CH₂), 0.97 (t, J = 7.0 Hz, 3 H, CH₃).

[076] The molecular structure of crystalline DMPT iodide is shown in FIG. 5. Crystal data, data collection and structure refinement details are summarized in Table 4. The asymmetric unit contains one *N,N*-di-methyl-*N*-*n*-propyl tryptammonium (C₁₅H₂₃N₂⁺) cation and one iodide anion. The indole ring

of the cation is near, planar with a mean deviation from planarity of 0.011 Å. The ethyl-ammonium arm is turned away from the plane with a C7—C8—C9—C10 torsion angle of 89.1 (4)°. The DMPT cation and the iodide anion are held together in the asymmetric unit via N(1)—H(1)···I(1) hydrogen bonds, between the indole nitrogen and the iodide. The packing of crystalline DMPT iodide is shown in FIG. 6.

[077] Crystal data, data collection and structure refinement details are summarized in Table 4.

Table 4: Crystalline DMPT Iodide	
Chemical formula	I·C ₁₅ H ₂₃ N ₂
<i>M_r</i>	358.25
Crystal system, space group	Monoclinic, <i>P</i> 2 ₁ / <i>c</i>
Temperature (K)	303
<i>a</i> , <i>b</i> , <i>c</i> (Å)	7.4471 (6), 9.9016 (9), 22.052 (2)
β (°)	94.184 (3)
<i>V</i> (Å ³)	1621.8 (2)
<i>Z</i>	4
Radiation type	Mo Kα
<i>m</i> (mm ⁻¹)	1.96
Crystal size (mm)	0.40 × 0.14 × 0.12
Diffractometer	Bruker D8 Venture CMOS
Absorption correction	Multi-scan SADABS2016/2 (Bruker,2016/2) was used for absorption correction. <i>w</i> R ₂ (int) was 0.0600 before and 0.0507 after correction. The Ratio of minimum to maximum transmission is 0.8362. The <i>I</i> /2 correction factor is Not present.
<i>T_{min}</i> , <i>T_{max}</i>	0.470, 0.562
No. of measured, independent and observed [<i>I</i> > 2 <i>s</i> (<i>I</i>)] reflections	44530, 3071, 2362
<i>R_{int}</i>	0.036
(sin <i>q</i> / <i>I</i>) _{max} (Å ⁻¹)	0.611
<i>R</i> [<i>F</i> ² > 2 <i>s</i> (<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.028, 0.054, 1.13
No. of reflections	3071
No. of parameters	170
No. of restraints	1
H-atom treatment	H atoms treated by a mixture of independent and constrained

	refinement
$D\rho_{\max}, D\rho_{\min}$ (e Å ⁻³)	0.53, -0.47
Absolute structure	—
Absolute structure parameter	—

Computer programs: *APEX3* (Bruker, 2018), *SAINT* (Bruker, 2018), *SHELXT2014* (Sheldrick, 2015a), *SHELXL2018* (Sheldrick, 2015b), *Olex2* (Dolomanov *et al.*, 2009), *publCIF* (Westrip, 2010).

Table 5 Hydrogen-bond geometry (Å, °) for Crystalline DMPT iodide

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
N1—H1...I1	0.86 (1)	2.91 (2)	3.733 (3)	162 (3)

[078] FIG. 7 is a simulated x-ray powder diffraction (XRPD) pattern of crystalline *N,N*-dimethyl-*N*-propyl (DMPT) iodide from its single crystal data. Crystalline *N,N*-dimethyl-*N*-propyl (DMPT) iodide may be characterized by the XRPD peaks at 8.0, 17.9 and 23.3 °2θ ± 0.2°2θ as well as by an XRPD pattern substantially similar to FIG. 7.

[079] Example 5: *N,N*-di-methyl-*N*-allyl-tryptammonium (DMALT) iodide

[080] *N,N*-di-methyl-*N*-allyl-tryptammonium (DMALT) iodide was prepared by mixing 101 mg of a commercial sample of *N*-allyl-*N*-methyl-tryptamine (The Indole Shop) with 4 mL of methyl iodide in 4 mL of methanol. The mixture was refluxed for twelve hours under an atmosphere of nitrogen. The solvent was removed in vacuo, and the remaining residue was recrystallized from acetone to yield colorless crystals suitable for X-ray diffraction studies. The product was also characterized by nuclear magnetic resonance. ¹H NMR (400 MHz, D₂O): d 7.69 (d, *J* = 7.8 Hz, 1 H, *ArH*), 7.55 (d, *J* = 8.2 Hz, 1 H, *ArH*), 7.32-7.28 (m, 1 H, *ArH*), 7.22 (t, *J* = 7.2 Hz, 1 H, *ArH*), 6.13-6.03 (m, 1 H, *CH*), 5.77-5.71 (m, 2 H, *CH*₂), 4.04 (d, *J* = 7.3 Hz, 1 H, *CH*₂), 3.61-3.56 (m, 2 H, *CH*₂), 3.37-3.32 (m, 2 H, *CH*₂), 3.17 (s, 6 H, *CH*₃).

[081] The molecular structure of crystalline DMALT iodide is shown in FIG. 8. The asymmetric unit contains one *N*-allyl-*N,N*-di-methyl-tryptammonium (C₁₅H₂₁N₂⁺) cation and one iodide anion. The indole ring of the cation is near planar, with a mean deviation from planarity of 0.013 Å. The ethyl-ammonium arm is turned away from the plane with a C7—C8—C9—C10 torsion angle of 101.9 (9)°. The allyl group is disordered over two orientations with a 0.30 (4) to 0.70 (4) occupancy ratio for C14, C15 and C14A, C15A, respectively. The DMALT structure is very similar to that of DMPT, with the ions held together in the asymmetric unit through N(1)—H(1)···I(1) hydrogen bonds. The packing of crystalline DMALT iodide is shown in FIG. 9.

[082] Crystal data, data collection and structure refinement details are summarized in Table 6.

Table 6: Crystalline DMALT Iodide	
Chemical formula	0.5(I)·0.5(C ₁₅ H ₂₁ N ₂)
M_r	178.12
Crystal system, space group	Monoclinic, $P2_1$
Temperature (K)	303
a, b, c (Å)	7.3471 (8), 9.9672 (9), 10.9499 (11)
β (°)	94.671 (3)
V (Å ³)	799.20 (14)
Z	4
Radiation type	Mo Ka
μ (mm ⁻¹)	1.99
Crystal size (mm)	0.39 × 0.22 × 0.15
Diffractometer	Bruker D8 Venture CMOS
Absorption correction	Multi-scan <i>SADABS2016/2</i> (Bruker, 2016/2) was used for absorption correction. $wR2(int)$ was 0.0671 before and 0.0484 after correction. The Ratio of minimum to maximum transmission is 0.8154. The $l/2$ correction factor is Not present.
T_{min}, T_{max}	0.608, 0.745
No. of measured, independent and observed [$I > 2s(I)$] reflections	26314, 3038, 2868
R_{int}	0.031
$(\sin \theta/\lambda)_{max}$ (Å ⁻¹)	0.611
$R[F^2 > 2s(F^2)], wR(F^2), S$	0.027, 0.071, 1.13
No. of reflections	3038
No. of parameters	174
No. of restraints	5
H-atom treatment	H-atom parameters constrained
$D\rho_{max}, D\rho_{min}$ (e Å ⁻³)	0.46, -0.48
Absolute structure	Refined as an inversion twin.
Absolute structure parameter	0.29 (5)

Computer programs: *APEX3* (Bruker, 2018), *SAINT* (Bruker, 2018), *SHELXT2014* (Sheldrick, 2015a), *SHELXL2018* (Sheldrick, 2015b), *Olex2* (Dolomanov *et al.*, 2009), *publCIF* (Westrip, 2010).

Table 7 Hydrogen-bond geometry (Å, °) for Crystalline DMALT Iodide

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
---------------	-------	-------------	-------------	---------------

N1—H1...I1	0.86	2.95	3.727 (6)	152
------------	------	------	-----------	-----

[083] FIG. 10 is a simulated x-ray powder diffraction (XRPD) pattern of crystalline N,N-dimethyl-N-allyl (DMALT) iodide from its single crystal data. Crystalline N,N-dimethyl-N-allyl (DMALT) iodide may be characterized by the XRPD peaks at 12.0, 18.5 and 23.4 °2θ ± 0.2°2θ as well as by an XRPD pattern substantially similar to FIG.10.

[084] Example 6: 4-acetoxy-N,N-dimethyl-N-ethyltryptammonium (4-AcO-DMET) iodide

[085] *Synthesis:* 300 mg of 4-acetoxy-N,N-dimethyl- tryptammonium (4-AcO-DMT) fumarate was dissolved in 30 mL of tetrahydrofuran, and 6 mL of iodoethane was added. The mixture was refluxed overnight under an atmosphere of nitrogen. This resulted in the precipitation of a white powder from the yellow solution. The precipitate was isolated via vacuum filtration to give white powder, which was washed with diethyl ether to yield 303 mg of pure product (91% yield). ¹H NMR (400 MHz, D₂O): δ 7.46 (dd, *J* = 8.2, 0.7 Hz, 1 H, ArH), 7.33 (s, 1 H, ArH), 7.25 (t, *J* = 7.9 Hz, 1 H, ArH), 6.90 (dd, *J* = 7.7, 0.7 Hz, 1 H, ArH), 3.58-3.54 (m, 2 H, CH₂), 3.46 (q, *J* = 7.3 Hz, 2 H, CH₂), 3.25-3.20 (m, 2 H, CH₂), 3.12 (s, 6 H, CH₃), 2.47 (s, 3 H, (CO)CH₃), 1.38-1.35 (m, 3 H, CH₃); ¹³C NMR (100 MHz, D₂O): δ 174.3(CO), 143.6 (ArC), 139.2(ArC), 125.7 (ArC), 123.0 (ArC), 119.1 (ArC), 112.9 (ArC), 111.1 (ArC), 107.4 (ArC), 64.6 (AkC), 60.6 (AkC), 50.7 (AkC), 21.3 (AkC), 19.9 (AkC), 8.1 (AkC).

[086] 4-AcO-DMET iodide was recrystallized by slow evaporation of an ethanol solution to yield crystals suitable for X-ray diffraction studies. Crystal data, data collection and structure refinement details are summarized in Table 8. FIG. 11 shows the molecular structure of crystalline 4-AcO-DMET iodide hemihydrate showing the atomic labelling. Displacement ellipsoids are drawn at the 50% probability level. There are two distinct tryptammonium cations and two iodides in the asymmetric unit. The solvate water molecule is modeled at 50% occupancy.

Table 8

Crystal data

2(I)·2(C ₁₆ H ₂₃ N ₂ O ₂)·0.5(H ₂ O)	<i>F</i> (000) = 818
<i>M_r</i> = 813.53	<i>D_x</i> = 1.471 Mg m ⁻³
Monoclinic, <i>P</i> 2 ₁	Mo <i>K</i> α radiation, <i>l</i> = 0.71073 Å
<i>a</i> = 11.8538 (8) Å	Cell parameters from 9080 reflections
<i>b</i> = 10.3179 (7) Å	<i>q</i> = 3.0–25.7°
<i>c</i> = 15.0132 (10) Å	<i>m</i> = 1.75 mm ⁻¹

$\beta = 90.611 (2)^\circ$	$T = 297 \text{ K}$
$V = 1836.1 (2) \text{ \AA}^3$	BLOCK, colourless
$Z = 2$	$0.23 \times 0.22 \times 0.21 \text{ mm}$

Data collection

Bruker D8 Venture CMOS diffractometer	6527 reflections with $I > 2s(I)$
θ and ω scans	$R_{\text{int}} = 0.029$
Absorption correction: multi-scan SADABS2016/2 (Bruker,2016/2) was used for absorption correction. $wR2(\text{int})$ was 0.0602 before and 0.0524 after correction. The Ratio of minimum to maximum transmission is 0.9438. The $I/2$ correction factor is Not present.	$q_{\text{max}} = 25.7^\circ$, $q_{\text{min}} = 2.7^\circ$
$T_{\text{min}} = 0.531$, $T_{\text{max}} = 0.562$	$h = -14^{\circ}14$
47080 measured reflections	$k = -12^{\circ}12$
6821 independent reflections	$l = -18^{\circ}18$

Refinement

Refinement on F^2	Hydrogen site location: mixed
Least-squares matrix: full	H atoms treated by a mixture of independent and constrained refinement
$R[F^2 > 2s(F^2)] = 0.029$	$w = 1/[s^2(F_o^2) + (0.0298P)^2 + 1.2326P]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.072$	$(D/s)_{\text{max}} = 0.001$
$S = 1.05$	$Dn_{\text{max}} = 0.66 \text{ e \AA}^{-3}$
6821 reflections	$Dn_{\text{min}} = -0.46 \text{ e \AA}^{-3}$
410 parameters	Absolute structure: Flack x determined using 2968 quotients $[(I^+)-(I^-)]/[(I^+)+(I^-)]$ (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
6 restraints	Absolute structure parameter: -0.009 (5)

[087] FIG. 12 is a simulated x-ray powder diffraction (XRPD) pattern of crystalline 4-acetoxy-*N,N*-dimethyl-*N*-ethyltryptammonium (4-AcO-DMET) iodide hemihydrate from its single crystal data.

Crystalline 4-acetoxy-*N,N*-dimethyl-*N*-ethyltryptammonium (4-AcO-DMET) iodide hemihydrate may be characterized by the XRPD peaks at 11.4, 14.6 and 19.2 °2 θ $\pm$ 0.2°2 θ as well as by an XRPD pattern substantially similar to FIG. 12.

[088] Example 7: 4-hydroxy-*N,N*-dimethyl-*N*-ethyltryptammonium (4-HO-DMET) iodide

[089] Synthesis: 150 mg of 4-AcO-DMET iodide was dissolved in 2 mL of DI water, and 10 mL of acetic acid was added. The mixture was refluxed overnight under an atmosphere of nitrogen. The solvent was removed via distillation, yielding an orange sticky oil. The oil was dissolved in a small volume of tetrahydrofuran and acetone. Hexanes was added to the solution, producing a white precipitate. The powder was isolated via vacuum filtration to give 90 mg (67% yield) of pure product. ¹H NMR (400 MHz, D₂O): δ 7.19 (s, 1 H, ArH), 7.12-7.07 (m, 2 H, ArH), 6.59-6.54 (m, 1 H, ArH), 3.60-3.56 (m, 2 H, CH₂), 3.46 (q, J = 7.3 Hz, 2 H, CH₂), 3.35-3.31 (m, 2 H, CH₂), 3.12 (s, 6 H, CH₃), 1.39 (t, J = 7.3 Hz, 3 H, CH₃); ¹³C NMR (100 MHz, D₂O): δ 150.6 (ArC), 139.3(ArC), 123.9 (ArC), 116.6 (ArC), 108.8 (ArC), 105.2 (ArC), 104.4 (ArC), 65.0 (AkC), 60.3 (AkC), 50.7 (AkC), 20.7 (AkC), 8.0 (AkC).

[090] Example 8: 4-acetoxy-*N,N*-dimethyl-*N*-*n*-propyltryptammonium (4-AcO-DMPT) iodide

[091] Synthesis: 323 mg of 4-AcO-DMT fumarate was dissolved in 30 mL of tetrahydrofuran, and 6 mL of 1-iodopropane was added. The mixture was refluxed overnight under an atmosphere of nitrogen. This resulted in the precipitation of a white powder from the yellow solution. The precipitate was isolated via vacuum filtration to give a white powder, which was washed with diethyl ether to yield 314 mg of pure product (85% yield). ¹H NMR (400 MHz, D₂O): δ 7.46 (dd, J = 8.2, 0.5 Hz, 1 H, ArH), 7.33 (s, 1 H, ArH), 7.26 (t, J = 7.9 Hz, 1 H, ArH), 6.90 (d, J = 7.7 Hz, 1 H, ArH), 3.61-3.57 (m, 2 H, CH₂), 3.35-3.29 (m, 2 H, CH₂), 3.27-3.21 (m, 2 H, CH₂), 3.14 (s, 6 H, CH₃), 2.47 (s, 3 H, (CO)CH₃), 1.81-1.72 (m, 2 H, CH₂), 0.91 (t, J = 7.3 Hz, 3 H, CH₃); ¹³C NMR (100 MHz, D₂O): δ 174.3(CO), 143.6 (ArC), 139.3(ArC), 125.8 (ArC), 123.0 (ArC), 119.1 (ArC), 112.9 (ArC), 111.1 (ArC), 107.5 (ArC), 66.4 (AkC), 65.1 (AkC), 51.3 (AkC), 21.3 (AkC), 20.1 (AkC), 16.3 (AkC), 10.4 (AkC).

[092] 4-AcO-DMPT iodide was recrystallized by slow evaporation of an ethanol solution to yield crystals suitable for X-ray diffraction studies. Crystal data, data collection and structure refinement details are summarized in Table 9. FIG. 13 shows the molecular structure of crystalline 4-AcO-DMPT iodide showing the atomic labelling. Displacement ellipsoids are drawn at the 50% probability level. Dashed bonds indicate a disordered component in the structure.

Table 9

Crystal data

$I \cdot C_{17}H_{25}N_2O_2$	$F(000) = 420$
$M_r = 416.29$	$D_x = 1.495 \text{ Mg m}^{-3}$
Monoclinic, $P2_1$	Mo K α radiation, $\lambda = 0.71073 \text{ \AA}$
$a = 7.7067 (4) \text{ \AA}$	Cell parameters from 9480 reflections
$b = 10.3424 (4) \text{ \AA}$	$q = 2.7\text{--}25.7^\circ$
$c = 11.6302 (6) \text{ \AA}$	$m = 1.74 \text{ mm}^{-1}$
$\beta = 94.222 (2)^\circ$	$T = 273 \text{ K}$
$V = 924.48 (8) \text{ \AA}^3$	BLOCK, colourless
$Z = 2$	$0.23 \times 0.2 \times 0.07 \text{ mm}$

Data collection

Bruker D8 Venture CMOS diffractometer	3251 reflections with $I > 2s(I)$
θ and ω scans	$R_{\text{int}} = 0.030$
Absorption correction: multi-scan SADABS2016/2 (Bruker,2016/2) was used for absorption correction. $wR2(\text{int})$ was 0.0659 before and 0.0527 after correction. The Ratio of minimum to maximum transmission is 0.8900. The $I/2$ correction factor is Not present.	$q_{\text{max}} = 25.8^\circ$, $q_{\text{min}} = 2.7^\circ$
$T_{\text{min}} = 0.663$, $T_{\text{max}} = 0.745$	$h = -9^{\circ}9$
32264 measured reflections	$k = -12^{\circ}12$
3428 independent reflections	$l = -14^{\circ}14$

Refinement

Refinement on F^2	Hydrogen site location: mixed
Least-squares matrix: full	H atoms treated by a mixture of independent and constrained refinement
$R[F^2 > 2s(F^2)] = 0.035$	$w = 1/[s^2(F_o^2) + (0.0233P)^2 + 1.3282P]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.081$	$(D/s)_{\text{max}} < 0.001$
$S = 1.04$	$D\tilde{n}_{\text{max}} = 1.09 \text{ e \AA}^{-3}$
3428 reflections	$D\tilde{n}_{\text{min}} = -0.78 \text{ e \AA}^{-3}$
243 parameters	Absolute structure: Flack x determined

	using 1473 quotients $[(I^+)-(I^-)]/[(I^+)+(I^-)]$ (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
35 restraints	Absolute structure parameter: 0.009 (7)

[093] FIG. 14 is a simulated x-ray powder diffraction (XRPD) pattern of crystalline 4-acetoxy-*N,N*-dimethyl-*N-n*-propyltryptammonium (4-AcO-DMPT) iodide from its single crystal data. Crystalline 4-acetoxy-*N,N*-dimethyl-*N-n*-propyltryptammonium (4-AcO-DMPT) iodide may be characterized by the XRPD peaks at 11.5, 16.7 and 19.8 $^{\circ}2\theta \pm 0.2^{\circ}2\theta$ as well as by an XRPD pattern substantially similar to FIG. 14.

[094] Example 9: 4-hydroxy-*N,N*-dimethyl-*N-n*-propyltryptammonium (4-HO-DMPT) iodide

[095] Synthesis: 200 mg of 4-AcO-DMPT iodide was dissolved in 3 mL of deionized (DI) water, and 10 mL of acetic acid was added. The mixture was refluxed overnight under an atmosphere of nitrogen. The solvent was removed via distillation, yielding an orange sticky oil. The oil was dissolved in a small volume of tetrahydrofuran and acetone. Hexanes was then added to the solution, producing a light green precipitate. This powder was isolated via vacuum filtration and washed with diethyl ether to give 157 mg (87% yield) of pure product. ^1H NMR (400 MHz, D_2O): δ 7.17 (s, 1 H, ArH), 7.12-7.07 (m, 2 H, ArH), 6.57-6.55 (m, 1 H, ArH), 3.57-3.53 (m, 2 H, CH_2), 3.32-3.26 (m, 4 H, CH_2), 3.11 (s, 6 H, CH_3), 1.85-1.75 (m, 2 H, CH_2), 0.95 (t, $J = 7.3$ Hz, 3 H, CH_3); ^{13}C NMR (100 MHz, D_2O): δ 150.6 (ArC), 139.3 (ArC), 123.9 (ArC), 116.7 (ArC), 108.9 (ArC), 105.2 (ArC), 104.4 (ArC), 66.1 (AkC), 65.4 (AkC), 51.3 (AkC), 20.8 (AkC), 16.2 (AkC), 10.4 (AkC).

[096] 4-HO-DMPT iodide was recrystallized by slow evaporation of an ethanol solution to yield crystals suitable for X-ray diffraction studies. Crystal data, data collection and structure refinement details are summarized in Table 10. FIG. 15 shows the molecular structure of 4-HO-DMPT iodide showing the atomic labelling. Displacement ellipsoids are drawn at the 50% probability level.

Table 10

Crystal data

$\text{I} \cdot \text{C}_{15}\text{H}_{23}\text{N}_2\text{O}$	$F(000) = 752$
$M_r = 374.25$	$D_x = 1.487 \text{ Mg m}^{-3}$
Monoclinic, $P2_1/c$	Mo K α radiation, $\lambda = 0.71073 \text{ \AA}$
$a = 9.4296 (8) \text{ \AA}$	Cell parameters from 9954 reflections
$b = 14.1816 (11) \text{ \AA}$	$q = 2.7\text{--}25.7^{\circ}$

$c = 13.2586 (10) \text{ \AA}$	$m = 1.91 \text{ mm}^{-1}$
$\beta = 109.423 (3)^\circ$	$T = 297 \text{ K}$
$V = 1672.1 (2) \text{ \AA}^3$	BLOCK, colourless
$Z = 4$	$0.25 \times 0.2 \times 0.19 \text{ mm}$

Data collection

Bruker D8 Venture CMOS diffractometer	2808 reflections with $I > 2s(I)$
θ and ω scans	$R_{\text{int}} = 0.025$
Absorption correction: multi-scan SADABS2016/2 (Bruker,2016/2) was used for absorption correction. $wR2(\text{int})$ was 0.0578 before and 0.0440 after correction. The Ratio of minimum to maximum transmission is 0.9109. The $I/2$ correction factor is Not present.	$q_{\text{max}} = 25.7^\circ$, $q_{\text{min}} = 2.7^\circ$
$T_{\text{min}} = 0.679$, $T_{\text{max}} = 0.745$	$h = -11^{\circ}11$
38248 measured reflections	$k = -17^{\circ}17$
3102 independent reflections	$l = -16^{\circ}16$

Refinement

Refinement on F^2	Hydrogen site location: mixed
Least-squares matrix: full	H atoms treated by a mixture of independent and constrained refinement
$R[F^2 > 2s(F^2)] = 0.027$	$w = 1/[s^2(F_o^2) + (0.0259P)^2 + 1.4322P]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.069$	$(D/s)_{\text{max}} = 0.001$
$S = 1.05$	$D\tilde{n}_{\text{max}} = 0.85 \text{ e \AA}^{-3}$
3102 reflections	$D\tilde{n}_{\text{min}} = -0.64 \text{ e \AA}^{-3}$
182 parameters	Extinction correction: SHELXL2018/3 (Sheldrick 2018), $F_c^* = kF_c[1 + 0.001x F_c^2 I^3 / \sin(2q)]^{-1/4}$
16 restraints	Extinction coefficient: 0.0082 (16)
Primary atom site location: structure-invariant direct methods	

[097] FIG. 16 is a simulated x-ray powder diffraction (XRPD) pattern of crystalline 4-hydroxy-*N,N*-dimethyl-*N-n*-propyltryptammonium (4-HO-DMPT) iodide from its single crystal data. Crystalline 4-hydroxy-*N,N*-dimethyl-*N-n*-propyltryptammonium (4-HO-DMPT) iodide may be characterized by the XRPD peaks at 12.5, 18.9 and 19.9 °2θ ± 0.2°2θ as well as by an XRPD pattern substantially similar to FIG. 16.

[098] Example 10: 4-acetoxy-*N,N*-dimethyl-*N*-isopropyltryptammonium (4-AcO-DMiPT) iodide

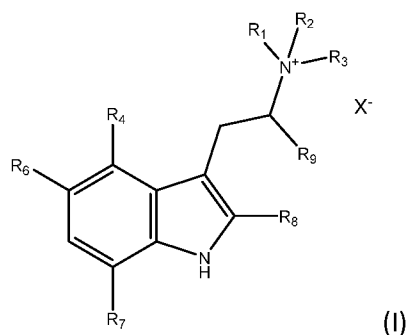
[099] Synthesis: 320 mg of 4-AcO-DMT fumarate was dissolved in 30 mL of tetrahydrofuran, and 12 mL of 2-iodopropane was added. The mixture was refluxed overnight under an atmosphere of nitrogen. A mixture of orange/yellow solid and yellow liquid was obtained. The liquid was decanted and the remaining solid was triturated with ethyl acetate to yield a white powder. The powder was isolated via vacuum filtration to give 151 mg of pure product (41% yield). ¹H NMR (400 MHz, D₂O): δ 7.46 (dd, *J* = 8.2, 0.7 Hz, 1 H, ArH), 7.33 (s, 1 H, ArH), 7.26 (t, *J* = 7.9 Hz, 1 H, ArH), 6.89 (dd, *J* = 7.7, 0.6 Hz, 1 H, ArH), 3.86-3.76 (sep, *J* = 6.6 Hz, 1 H, CH), 3.57-3.53 (m, 2 H, CH₂), 3.26-3.22 (m, 2 H, CH₂), 3.07 (s, 6 H, CH₃), 2.47 (s, 3 H, (CO)CH₃), 1.41 (d, *J* = 6.6 Hz, 6 H, CH₃); ¹³C NMR (100 MHz, D₂O): δ 174.2(CO), 143.6 (ArC), 139.2 (ArC), 125.7 (ArC), 123.0 (ArC), 119.1 (ArC), 113.0 (ArC), 111.1 (ArC), 107.5 (ArC), 66.0 (AkC), 63.5 (AkC), 48.1 (AkC), 21.3 (AkC), 19.7 (AkC), 16.2 (AkC).

References

- Bradley, R. J. & Johnston, V. S. (1970). *Origin and Mechanism of Hallucinations*, edited by W. Keup, pp. 333–344. New York: Plenum Press.
- Cameron, L. P. & Olson, D. E. (2018). *ACS Chem. Neurosci.* **9**, 2344-2357.
- Carhart-Harris, R. L. & Goodwin, G. M. (2017). *Neuropsychopharmacology*, **42**, 2105-2113.
- Dinis-Oliveira, R. J. (2017). *Drug Metab. Rev.* **49**, 84–91.
- Johnson, M. W. & Griffiths, R. R. (2017). *Neurotherapeutics* **14**, 734–740.
- McKenna, D. J., Repke, D. B., Lo, L. & Peroutka, S. J. (1990). *Neuropharmacology*, **29**, 193–198.
- Nichols, D. E. (2012). *WIREs Membr. Transp. Signal.* **1**, 559–579.
- Repke, D. B., Grotjahn, D. B. & Shulgin, A. T. (1985). *J. Med. Chem.* **28**, 892–896.
- C. Lenz, J. Wick and D. Hoffmeister, *J. Nat. Prod.*, 2017, **80**, 2835-2838.
- A. M. Sherwood, A. L. Halberstadt, A. K. Klein, J. D. McCorvy, K. W. Kaylo, R. B. Kargbo and P. Meisenheimer, *J. Nat. Prod.*, Article ASAP, DOI: 10.1021/acs.jnatprod.9b01061.
- N. Jensen, J. Gartz and H. Laatsch, *Planta Med.*, 2006, **72**, 665-666.
- J. Gartz, *Int. J. Crude Drug Res.*, 1989, **27**, 141-144.
- B. L. Roth, W. K. Kroeze, S. Patel and E. Lopez, *The Neuroscientist*, 2000, **6**, 252-262.

The claimed invention is:

1. A compound of formula (I):



wherein

R₁, R₂ and R₃ are each independently a straight chain or branched C₁-C₆ alkyl or C₂-C₆ alkenyl,

R₄ is hydrogen, hydroxyl, C₁-C₆ alkoxy, -OC(O)R₅ or -OC(O)OR₅,

R₅ is a straight chain or branched C₁-C₆ alkyl,

R₆ is R₄ or a straight chain or branched C₁-C₆ alkyl with the proviso that R₆ is not hydroxyl when R₁, R₂ and R₃ are all methyl,

R₇, R₈ and R₉ are each independently hydrogen or a straight chain or branched C₁-C₆ alkyl, and

X⁻ is a pharmaceutically acceptable anion.

2. A compound of formula (I) according to claim 1 wherein:

R₁, R₂ and R₃ are each independently a straight chain or branched C₁-C₄ alkyl or a C₂-C₄ alkenyl;

R₄ is hydrogen, hydroxyl, C₁-C₄ alkoxy, -OC(O)R₅ or -OC(O)OR₅;

R₅ is selected from methyl, ethyl, n-propyl and n-butyl;

R₆, R₇, R₈ and R₉ are each independently hydrogen, methyl, or ethyl; and

X⁻ is Cl⁻, I⁻, Br⁻, ascorbate, hydrofumarate, fumarate, or maleate.

3. A compound of formula (I) according to claim 2 wherein:

R₁, R₂ and R₃ are each independently methyl, ethyl, propyl or allyl;

R₄ is hydrogen, hydroxyl, or -OC(O)R₅;

R₅ is methyl or ethyl;

R₆, R₇, and R₉ are each independently hydrogen;

R₈ is hydrogen or methyl; and

X⁻ is I⁻.

4. A compound of formula (I) according to claim 1 wherein the compound is 4-Acetoxy-*N,N,N*-trimethyltryptammonium iodide.
5. A compound of formula (I) according to claim 4 wherein the compound is crystalline 4-Acetoxy-*N,N,N*-trimethyltryptammonium iodide characterized by:
- a monoclinic, $P2_1$ crystal system space group at a temperature of about 299 K,
 - unit cell dimensions $a = 7.8459(9) \text{ \AA}$, $b = 9.8098(12) \text{ \AA}$, $c = 11.0823(12) \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 101.069(3)^\circ$, and $\gamma = 90^\circ$,
 - an XRPD pattern having peaks at 8.1, 14.6 and $19.8^\circ 2\theta \pm 0.2^\circ 2\theta$, or
 - an XRPD pattern substantially similar to FIG. 2.
6. A compound of formula (I) according to claim 1 wherein the compound is 4-Hydroxy-*N,N,N*-trimethyltryptammonium iodide.
7. A compound of formula (I) according to claim 6 wherein the compound is crystalline 4-Hydroxy-*N,N,N*-trimethyltryptammonium iodide characterized by:
- a monoclinic, $P2_1/n$ crystal system space group at a temperature of about 200 K,
 - unit cell dimensions $a = 11.3057(9) \text{ \AA}$, $b = 11.2370(10) \text{ \AA}$, $c = 12.7785(10) \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 113.087(2)^\circ$, and $\gamma = 90^\circ$,
 - an XRPD pattern having peaks at 17.0, 18.1 and $19.5^\circ 2\theta \pm 0.2^\circ 2\theta$, or
 - an XRPD pattern substantially similar to FIG. 4.
8. A compound of formula (I) according to claim 1 wherein the compound is *N,N*-dimethyl-*N*-propyltryptammonium iodide.
9. A compound of formula (I) according to claim 8 wherein the compound is crystalline *N,N*-dimethyl-*N*-propyltryptammonium iodide characterized by:
- a monoclinic, $P2_1/c$ crystal system space group at a temperature of about 303 K,
 - unit cell dimensions $a = 7.4471(6) \text{ \AA}$, $b = 9.9016(9) \text{ \AA}$, $c = 22.052(2) \text{ \AA}$, and $\beta = 94.184(2)^\circ$,
 - an XRPD having peaks at 8.0, 17.9 and $23.3^\circ 2\theta \pm 0.2^\circ 2\theta$, or
 - an XRPD pattern substantially similar to FIG. 7.

10. A compound of formula (I) according to claim 1 wherein the compound is *N,N*-dimethyl-*N*-allyltryptammonium iodide.
11. A compound of formula (I) according to claim 10 wherein the compound is crystalline *N,N*-dimethyl-*N*-allyltryptammonium iodide characterized by:
- a monoclinic, $P2_1$ crystal system space group at a temperature of about 303 K,
 - unit cell dimensions $a = 7.3471$ (8) Å, $b = 9.9672$ (9) Å, $c = 10.9499$ (11) Å, and $\beta = 94.671$ (2)°,
 - an XRPD pattern having peaks at 12.0, 18.5 and 23.4 °2 θ $\pm$ 0.2°2 θ , or
 - an XRPD pattern substantially similar to FIG. 10.
12. A compound of formula (I) according to claim 1 wherein the compound is 4-acetoxy-*N,N*-dimethyl-*N*-ethyltryptammonium iodide.
13. A compound of formula (I) according to claim 12 wherein the compound is crystalline 4-acetoxy-*N,N*-dimethyl-*N*-ethyltryptammonium iodide as a hemihydrate characterized by:
- a monoclinic, $P2_1$ crystal system space group at a temperature of about 297 K,
 - unit cell dimensions $a = 11.8538$ (8) Å, $b = 10.3179$ (7) Å, $c = 15.0132$ (10) Å, and $\beta = 90.611$ (2)°,
 - an XRPD pattern having peaks at 11.4, 14.6 and 19.2 °2 θ $\pm$ 0.2°2 θ , or
 - an XRPD pattern substantially similar to FIG. 12.
14. A compound of formula (I) according to claim 1 wherein the compound is 4-acetoxy-*N,N*-dimethyl-*N*-*n*-propyltryptammonium iodide.
15. A compound of formula (I) according to claim 14 wherein the compound is crystalline 4-acetoxy-*N,N*-dimethyl-*N*-*n*-propyltryptammonium iodide characterized by:
- a monoclinic, $P2_1$ crystal system space group at a temperature of about 273 K,
 - unit cell dimensions $a = 7.7067$ (4) Å, $b = 10.3424$ (4) Å, $c = 11.6302$ (6) Å, and $\beta = 94.222$ (2)°,
 - an XRPD pattern having peaks at 11.5, 16.7 and 19.8 °2 θ $\pm$ 0.2°2 θ , or
 - an XRPD pattern substantially similar to FIG. 14.

16. A compound of formula (I) according to claim 1 wherein the compound is 4-hydroxy-*N,N*-dimethyl-*N*-*n*-propyltryptammonium iodide.

17. A compound of formula (I) according to claim 16 wherein the compound is crystalline 4-hydroxy-*N,N*-dimethyl-*N*-*n*-propyltryptammonium iodide characterized by:

a monoclinic, $P2_1/c$ crystal system space group at a temperature of about 273 K,
unit cell dimensions $a = 9.4296$ (8) Å, $b = 14.1816$ (11) Å, $c = 13.2586$ (10) Å, and $\beta = 109.423$ (3)°,
an XRPD pattern having peaks at 12.5, 18.9 and 19.9 °2 θ $\pm$ 0.2°2 θ , or
an XRPD pattern substantially similar to FIG. 16.

18. A composition comprising, consisting essentially of, or consisting of a compound according to any one of claims 1-17 and an excipient.

19. A composition of claim 18 wherein the composition is a pharmaceutical composition comprising, consisting essentially of, or consisting of a therapeutically effective amount of a compound according to any one of claims 1-17 and a pharmaceutically acceptable excipient.

20. A composition comprising, consisting essentially of, or consisting of as a first active component: a compound according to any one of claims 1-17; and as a second active component selected from (a) a serotonergic drug, (b) a purified psilocybin derivative, (c) one or two purified cannabinoids and (d) a purified terpene; and a pharmaceutically acceptable excipient.

21. A method of preventing or treating a psychological disorder comprising the step of:
administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1-17 or a composition according to any one of claims 18-20.

22. A method of preventing or treating inflammation and/or pain comprising the step of:
administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1-17 or a composition according to any one of claims 18-20.

FIG. 1

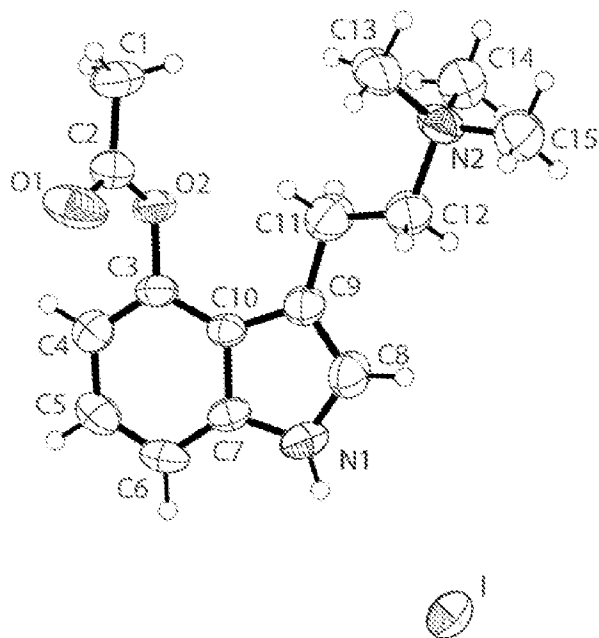


FIG. 2

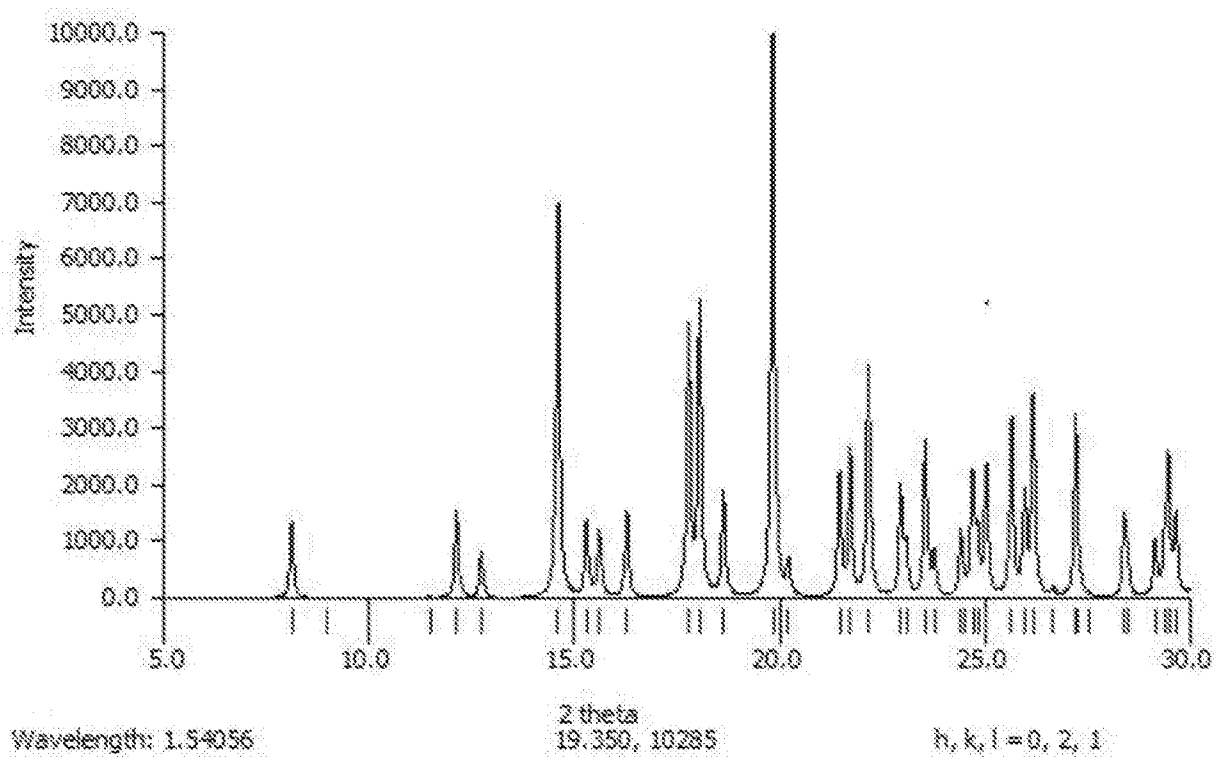


FIG. 3

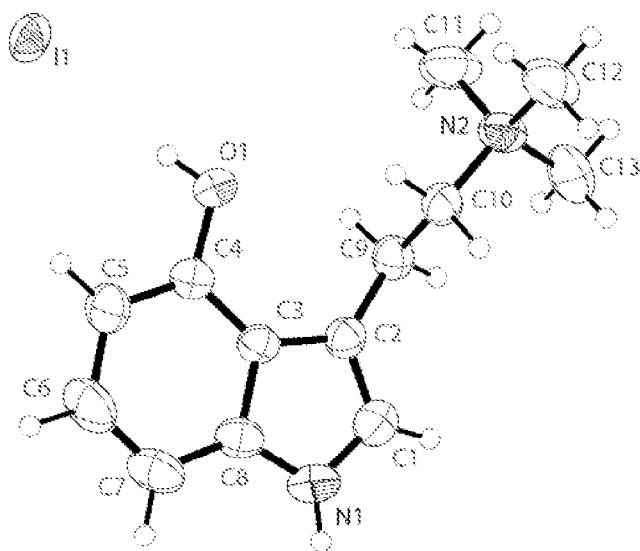


FIG. 4

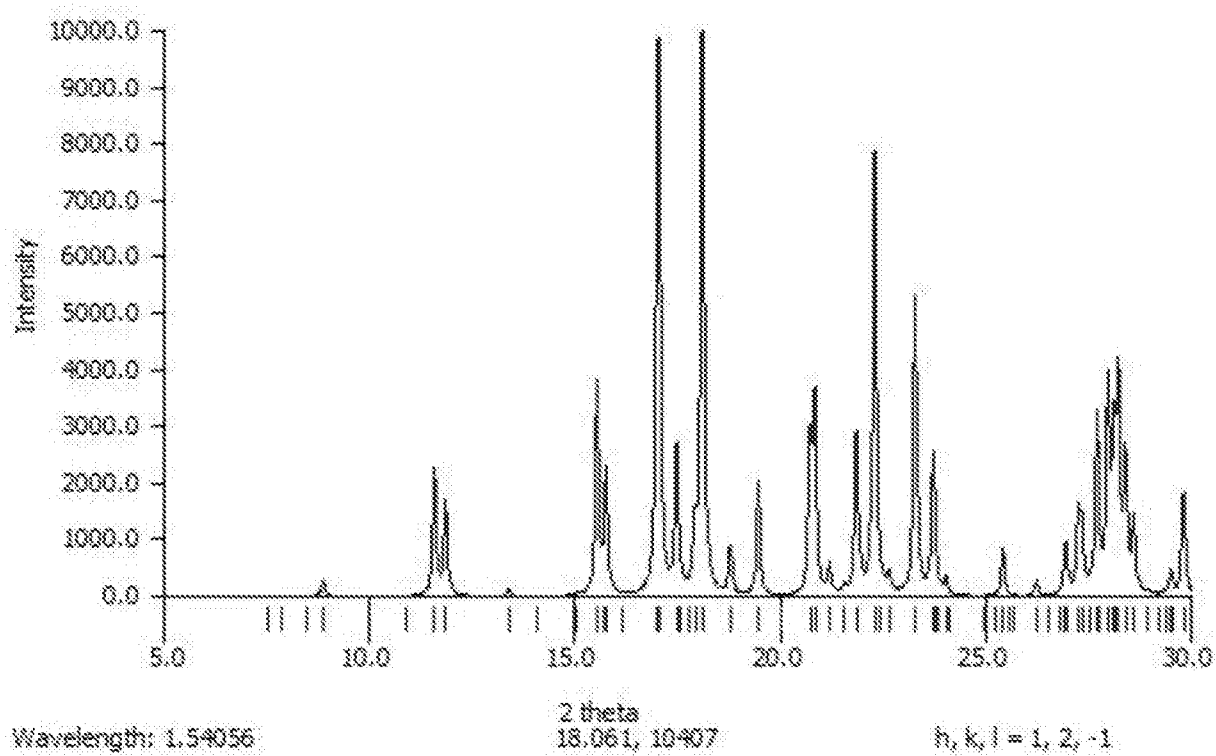


FIG. 5

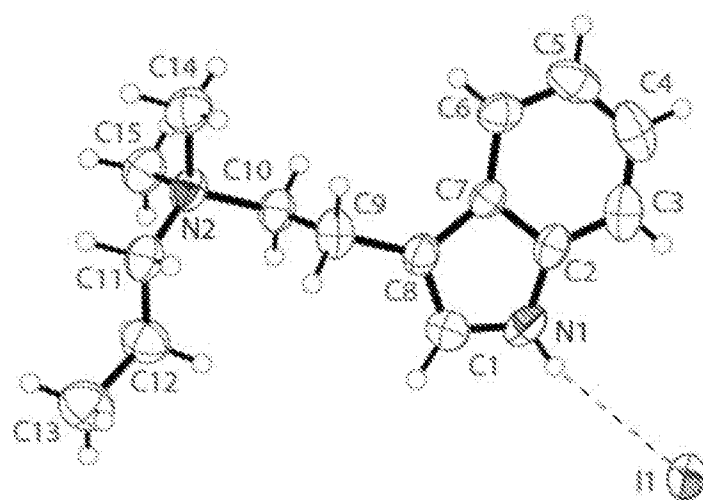


FIG. 6

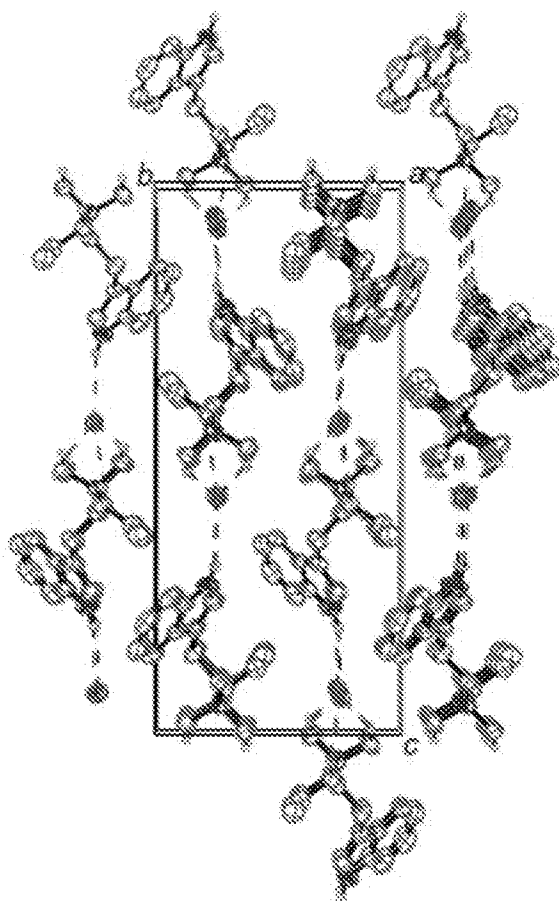


FIG. 7

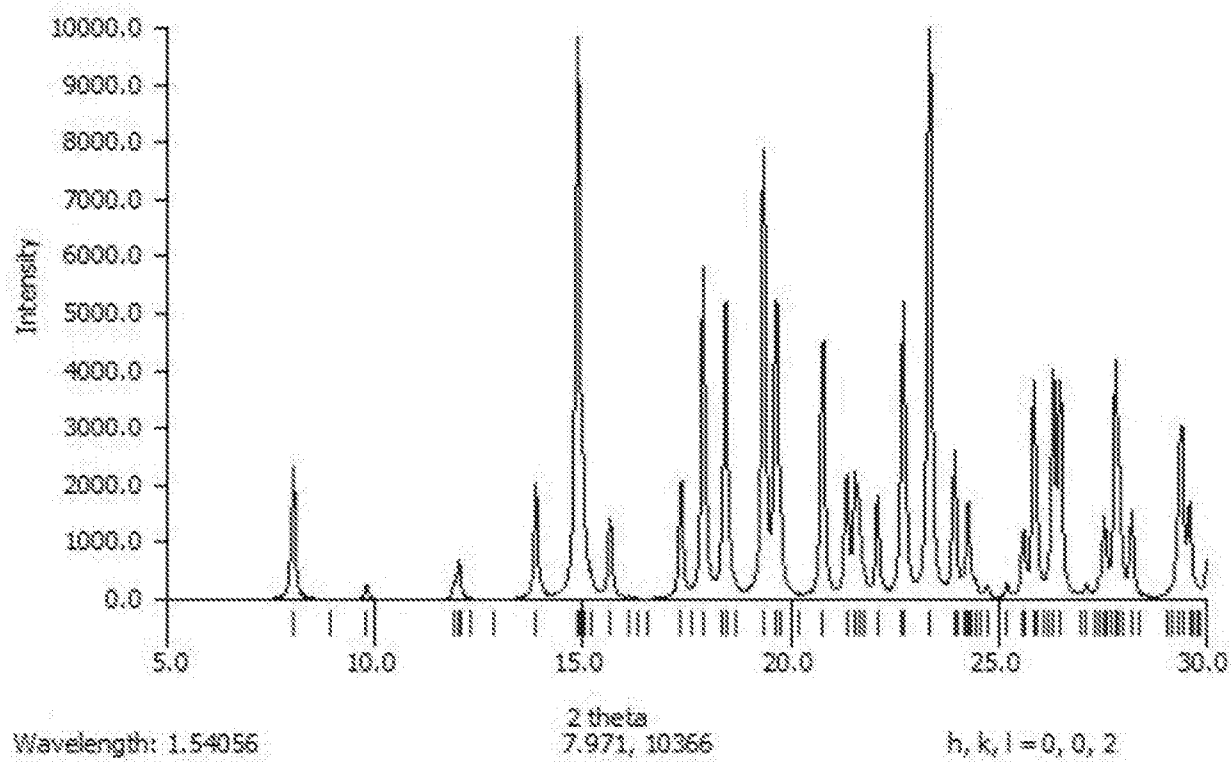


FIG. 8

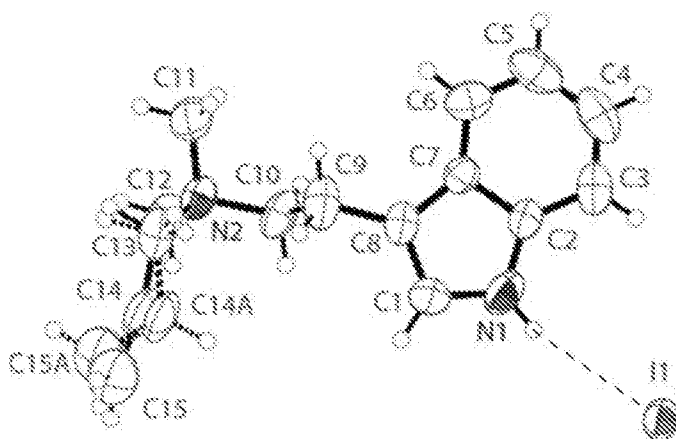


FIG. 9

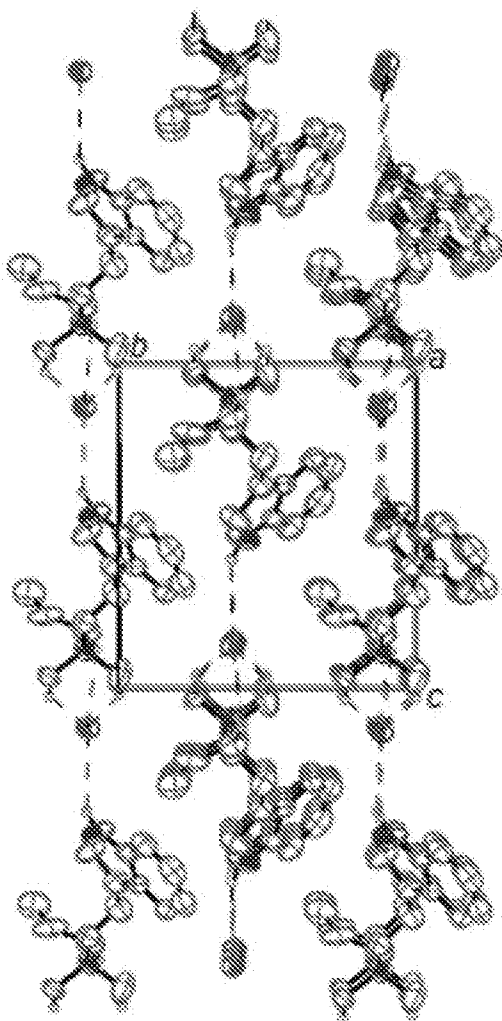


FIG. 10

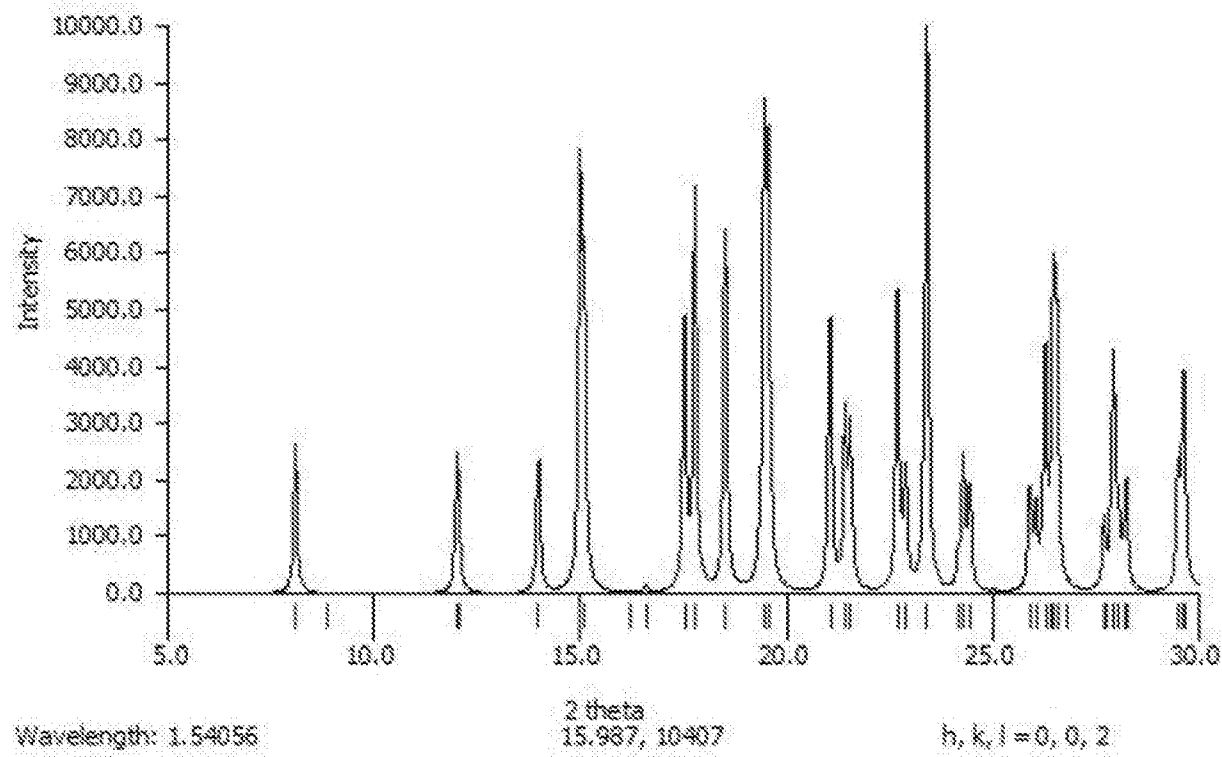


FIG. 11

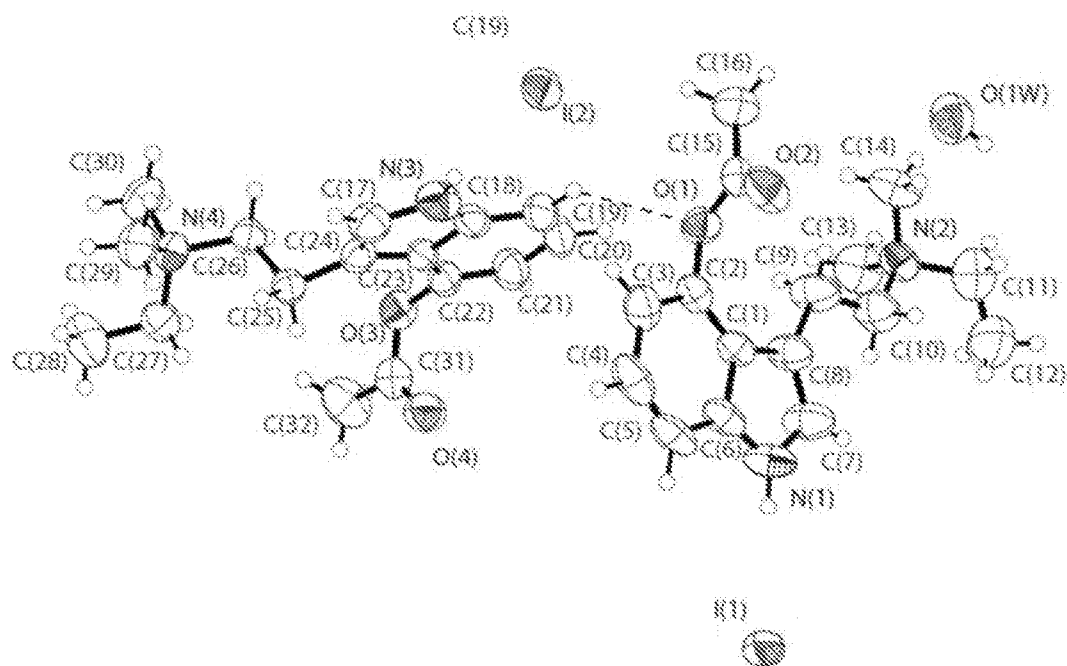


FIG. 12

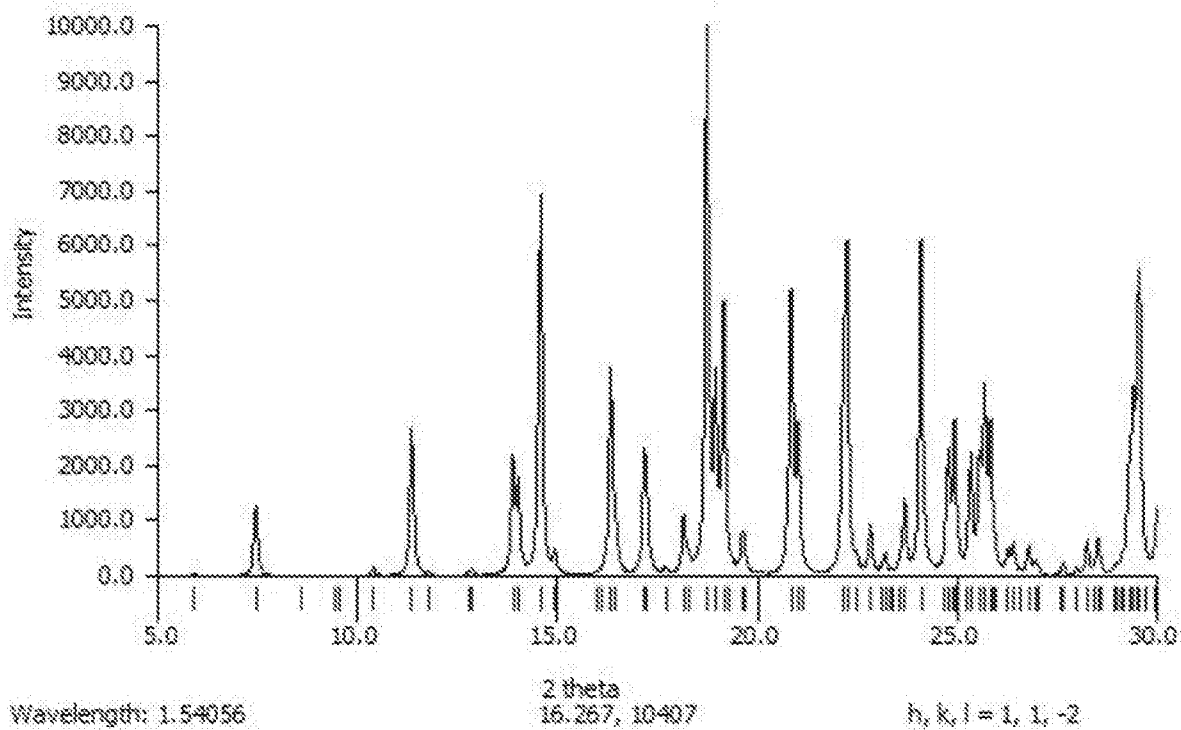


FIG. 13

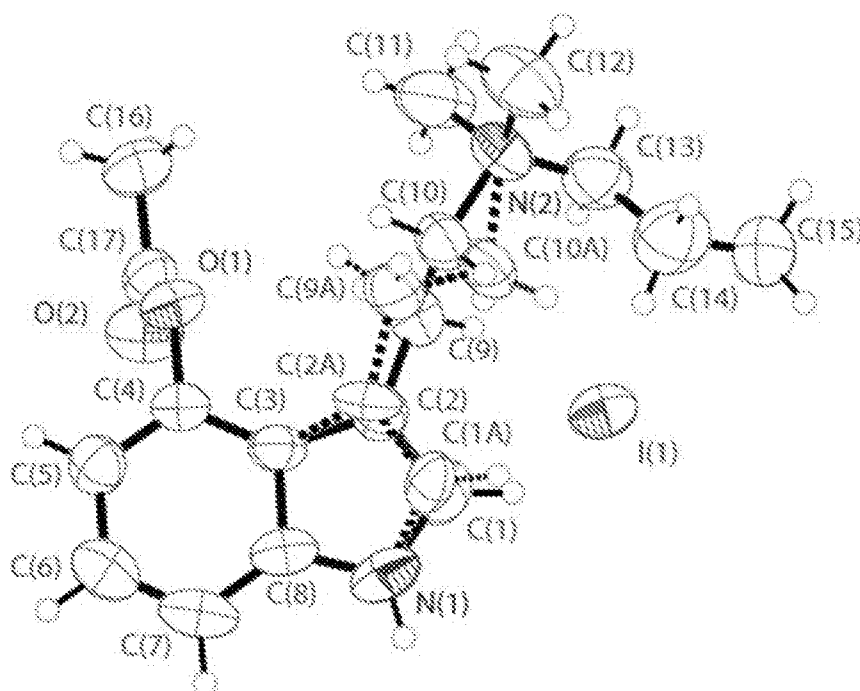


FIG. 14

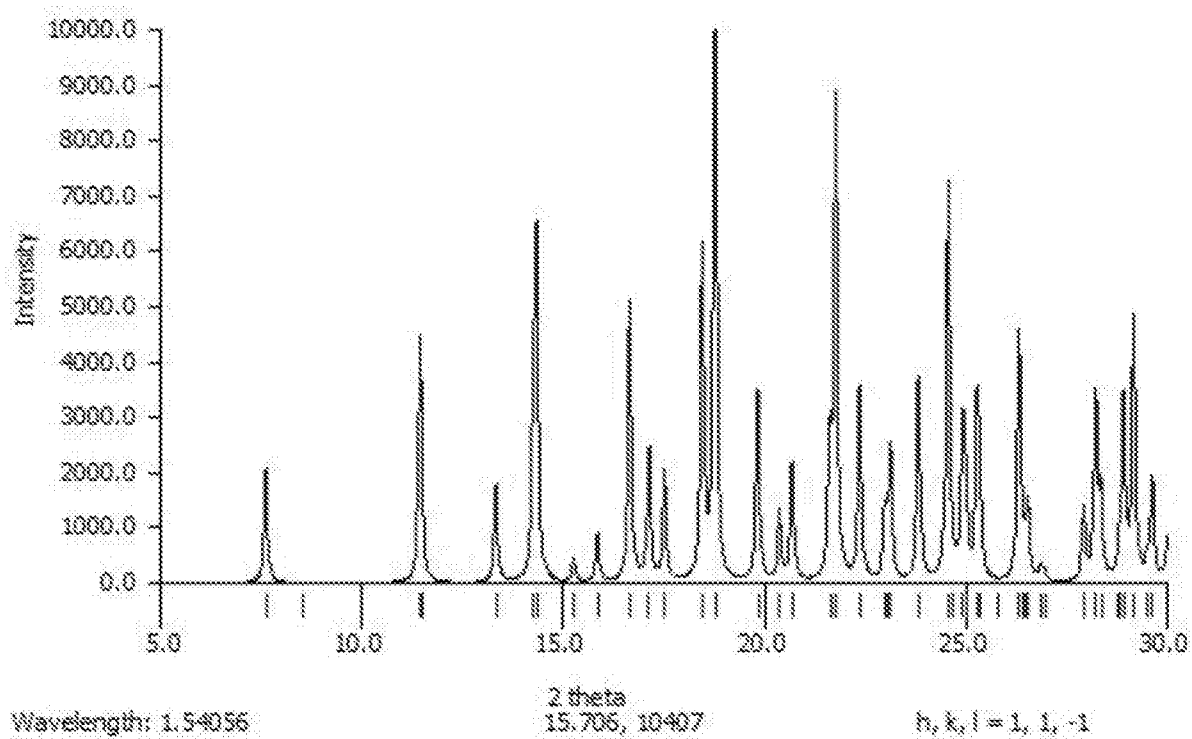


FIG. 15

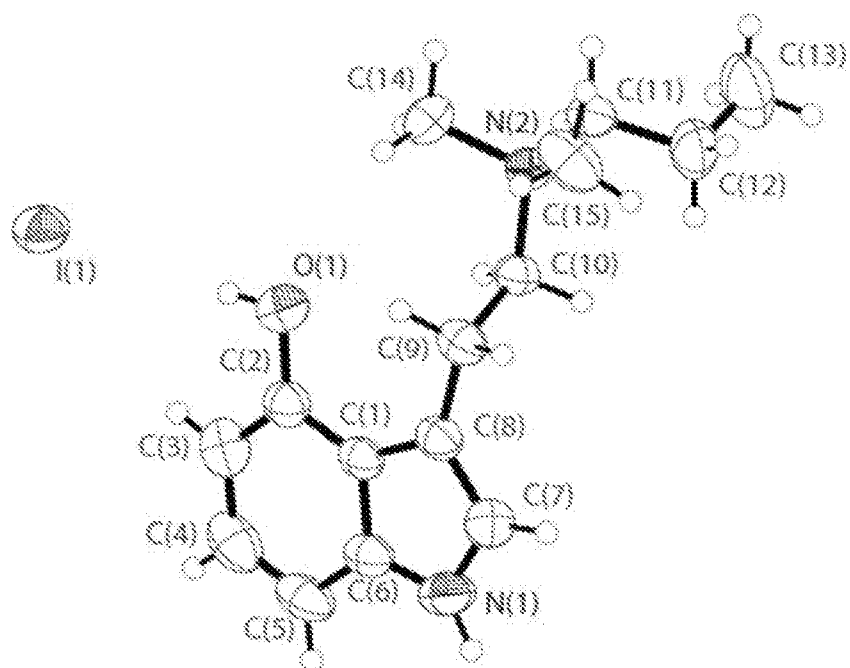
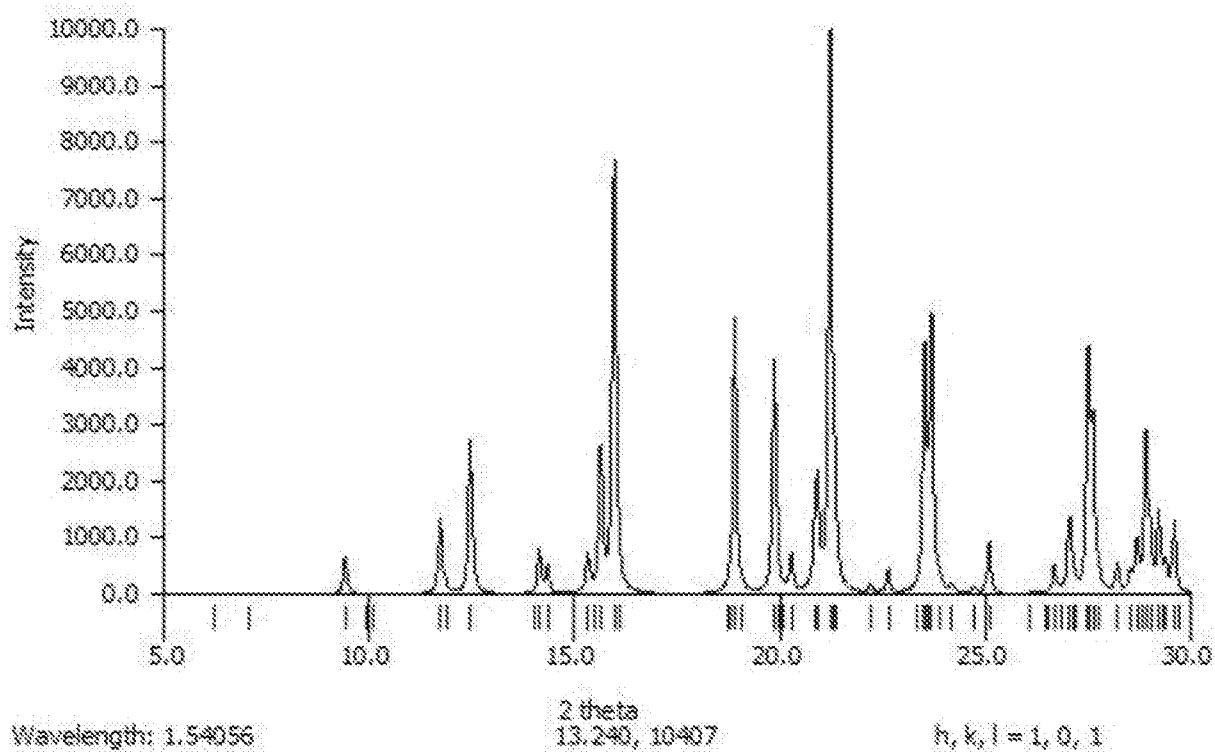


FIG. 16



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 20/47791

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C07D 487/04 (2020.01)

CPC - A61K 31/519; A61K 31/5377; A61P 25/00; A61P 25/22

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

D. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

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

See Search History document

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Pubmed Compound Record for CID 44719452, 'Dimethyltryptamine methiodide', U.S. National Library of Medicine, 14 March 2010 (14.03.2010), pages1-9 (https://pubchem.ncbi.nlm.nih.gov/compound/44719452); p2	1-3
X — Y	Servillo et al. 'N-Methylated Tryptamine Derivatives in Citrus Genus Plants: Identification of N,N,N-Trimethyltryptamine in Bergamot', Journal of Agricultural and Food Chemistry, 07 September 2012 (07.09.2012), Vol.60, pages9512-9518; p9513 p9516 p9517	1, 18-19 ----- 20
Y	US 2018/0221396 A1 (CaaMTech, LLC) 09 August 2018 (09.08.2018); Abstract para[0023]	20
A	US 6,306,181 B1 (Terranova et al.) 23 October 2001 (23.10.2001); col5	1-3, 18-20
A	US 2019/0142851 A1 (CaaMTech, LLC) 16 May 2019 (16.05.2019); entire document	1-3, 18-20



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

28 October 2020

Date of mailing of the international search report

21 JAN 2021

Name and mailing address of the ISA/US

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

Facsimile No. 571-273-8300

Authorized officer

Lee Young

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 20/47791

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 21-22
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

—See Supplemental Box—

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, 18-20

Remark on Protest

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

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/US 20/47791

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

Group I+: Claims 1-20 directed to a compound of formula (I). The compound of formula (I) will be searched to the extent that it encompasses the compound of formula (I) wherein R1, R2 and R3 are each independently a straight chain C1 alkyl; R4 is hydrogen; R6 is R4, wherein R4 is hydrogen, with the proviso that R6 is not hydroxyl when R1, R2 and R3 are all methyl; R7, R8 and R9 are each independently hydrogen; and X- is a pharmaceutically acceptable anion. It is believed that claims 1-3, and 18-20 read on this first named invention, and thus these claims will be searched without fee. Applicant is invited to elect additional compounds of claim 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be the compound of formula (I), wherein R1, R2 and R3 are each independently a straight chain C1 alkyl; R4 is -OC(O)R5; R5 is a straight chain C1 alkyl; R6 is R4, wherein R4 is hydrogen, with the proviso that R6 is not hydroxyl when R1, R2 and R3 are all methyl; R7, R8 and R9 are each independently hydrogen; and X- is a pharmaceutically acceptable anion (i.e., claims 1-3, 4-5, and 18-20).

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique compound of formula (I), containing the same, which is not required by any other invention of Group I+.

Common technical features:

The inventions of Group I+ share the technical feature of a compound of formula (I) containing the same.

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by US 6,306,181 B1 to Terranova et al. (hereinafter 'Terranova'). Terranova discloses a compound of formula (I), wherein R1, R2 and R3 are each independently a straight chain C1 alkyl; R4 is hydroxyl; R6 is R4, wherein R4 is hydrogen, with the proviso that R6 is not hydroxyl when R1, R2 and R3 are all methyl; R7, R8 and R9 are each independently hydrogen; and X- is a pharmaceutically acceptable anion (col5, ln42-43 "[2-(4-hydroxy-1H-indol-3-yl)ethyl]trimethylammonium methosulphate").

As said compound and compositions were known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+. The inventions of Group I+ thus lack unity under PCT Rule 13.

Note Re: Item 4: claims 21-22 are determined unsearchable because they are not drafted in accordance with the second and third sentences of Rule 6.4(a).