Harvey Bartle IV
MORGAN, LEWIS & BOCKIUS LLP
502 Carnegie Center
Princeton, NJ 08540-6241
Phone: (609) 919-6600

OF COUNSEL
Michael J. Abernathy
Margaret A. McGreal
Karon N. Fowler
MORGAN, LEWIS & BOCKIUS LLP
110 North Wacker Drive
Chicago, IL 60606-1511
Phone: (312) 324-1000

Attorneys for Plaintiffs

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

REUNION NEUROSCIENCE INC. AND REUNION NEUROSCIENCE CANADA INC., a Canadian company	)	
Plaintiffs,	)	Case No. _____
v.	)	
MINDSET PHARMA INC., a Canadian company,	)	Jury trial requested
Defendant.	)	

COMPLAINT

Plaintiffs Reunion Neuroscience Inc. and Reunion Neuroscience Canada Inc. (collectively "Reunion"), by their attorneys, allege as follows for their Complaint against Mindset Pharma Inc. ("Mindset").

INTRODUCTION

1. Reunion is a pioneering biotech company that has developed a novel serotonergic psychedelic compound—RE-104—for patients suffering from mental health conditions, including an initial indication for postpartum depression. Recognizing the novelty of Reunion's RE-104, the United States Patent and Trademark Office ("PTO") issued United States Patent No. 11,292,765 ("'765 Patent") on April 5, 2022, providing Reunion with exclusive rights to that composition.

2. Reunion brings this action because Mindset—which also develops serotonergic psychedelic drugs—knowingly copied Reunion's RE-104 compound and presented that *exact* composition to the PTO as *its* invention.

3. In doing so, Mindset committed inequitable conduct in the PTO in two ways: first, by misrepresenting to the Examiner that its employees invented RE-104; and second, by fraudulently omitting RE-104's actual inventor—Dr. Nathan Bryson, Reunion's Chief Scientific Officer.

4. The law has long instructed that conception is the touchstone of inventorship, and Dr. Bryson solely conceived Reunion's RE-104 in mid-2020.

5. To protect his proprietary intellectual property, Dr. Bryson filed provisional patent applications disclosing RE-104 on November 3, 2020 and June 30, 2021.

6. On December 30, 2021, the PTO published Reunion's related non-provisional patent application, thereby publicly disclosing the structure of RE-104 and how to make it.

7. And on April 5, 2022, the PTO issued the '765 Patent, which claims and publicly discloses Reunion's RE-104.

8. Around this time, Mindset also was experimenting with psychedelic drug candidates for the treatment of psychiatric disorders and was actively monitoring Reunion's PTO filings.

9. From February 2020 through July 2021—*before* the PTO published Reunion's RE-104 compound—Mindset filed three related patent applications for serotonergic psychedelic agents. Tellingly, *none* disclosed RE-104 or contained any data relating to that compound.

10. But on June 6, 2022, for the first time, Mindset added Reunion's RE-104 as claim 13 of its application for United States Patent No. 11,591,353 ("'353 Patent). Mindset only included that compound *after* RE-104's chemical structure became public following the publications of Reunion's patent application and subsequently issued patent.

11. The '353 Patent names Mindset employees Dr. Abdelmalik Slassi and Joseph Araujo as co-inventors. Yet neither conceived nor developed RE-104—they had nothing to do with its invention.

12. Mindset and the named inventors violated their duty of candor to the PTO by failing to inform the Examiner that Dr. Bryson had invented RE-104. This misrepresentation was material, as the Examiner could not have allowed claim 13 had it known that the named inventors did not actually invent it.

13. But not only did it patent Reunion's RE-104 compound, Mindset asserted that *Reunion* needed a license from Mindset to use that compound—even though Dr. Bryson had invented it.

14. In late January 2023, Mindset brazenly informed Reunion that Mindset's patent rights cover RE-104 and proposed "to enter into negotiations with Reunion for a commercial resolution including licensing rights to Mindset's claims covering compound RE-104 . . . rather

than becoming involved in legal proceedings." Mindset made clear that it "fully intends" to publicly announce "its patent rights around RE-104 and to enforce its patent rights."

15. Reunion strongly disagreed, explaining in a February 2023 letter that Dr. Bryson had independently conceived of Reunion's RE-104 compound and was erroneously omitted as the only true inventor on Mindset's patent application. Although Reunion detailed its "serious concerns" about the validity, inventorship, enforceability and ultimate ownership of the Mindset then-pending application, Reunion agreed to meet with Mindset to explore a business resolution "rather than becoming involved in legal proceedings."

16. On February 15, 2023, Reunion and Mindset's CEOs—Greg Mayes and James Lanthier, respectively—met to discuss a licensing arrangement.

17. During that meeting, the parties disclosed their general financial conditions, and Reunion made clear that its potential funding would be contingent on resolving Mindset's public allegations.

18. The discussions were successful. After meeting privately, Messrs. Mayes and Lanthier announced they had reached an agreement, shaking hands in confirmation.

19. But shortly after its counsel circulated a draft settlement license reflecting the "terms discussed during the meeting," Mindset attempted to renege on this agreement, opting instead to pursue "strategic alternatives."

20. Accordingly, Reunion brings this action to protect its intellectual property and hold Mindset liable for the consequences of its illicit conduct. Since Dr. Bryson conceived of the compound recited in claim 13, he is the only true inventor of at least one claim of Mindset's '353 Patent. Thus, under settled law, Reunion co-owns the '353 Patent in its entirety. Mindset also should be held to its promises at the parties' settlement meeting. And for its employees'

inequitable conduct before the PTO, Mindset should be barred from enforcing the ’353 Patent against Reunion.

THE PARTIES

21. Reunion Neuroscience Inc. and Reunion Neuroscience Canada Inc. (collectively “Reunion”) are Canadian companies with their principal place of business at 30 Duncan Street, Lower North Suite, Toronto, Ontario M5V 2C3, Canada.

22. As part of a corporate reorganization in August 2022, Field Trip Health Ltd. was renamed Reunion Neuroscience Inc. Earlier, Field Trip Ventures Inc., a subsidiary of Field Trip Health Ltd., became Field Trip Psychedelics Inc., which is now part of Reunion, and was subsequently renamed Reunion Neuroscience Canada Inc.[1]

23. On information and belief, Mindset also is a Canadian corporation with its principal place of business at 217 Queen Street West, 401, Toronto, Ontario M5V 0R2, Canada.

JURISDICTION AND VENUE

24. This is a civil action brought under Federal and state laws against Mindset for (i) correction of inventorship of the ’353 Patent under 35 U.S.C. § 256; (ii) a declaratory judgment to correct ownership of the ’353 Patent under 28 U.S.C. §§ 2201 and 2202; (iii) a declaratory judgment of inequitable conduct; (iv) breach of an oral settlement agreement; (v) promissory estoppel; and (vi) tortious interference with prospective business.

25. This Court has subject matter jurisdiction under 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

[1] References to “Reunion” include its predecessors, Field Trip Ventures Inc. and Field Trip Psychedelics Inc.

26. This Court has supplemental jurisdiction over the state law claims under 28 U.S.C. § 1367 because those claims are so related to the federal claims that they form part of the same case or controversy.

27. This Court has personal jurisdiction over Mindset under Federal Rule of Civil Procedure 4(k)(2) at least because (i) certain of Reunion's claims arise under federal law; (ii) Mindset is a foreign entity; (iii) Mindset is not subject to jurisdiction in any state's courts of general jurisdiction; and (iv) exercising jurisdiction over Mindset comports with due process and would not offend traditional notions of fair play and substantial justice.

28. Venue is proper in this District under 28 U.S.C. § 1391(c)(3) at least because Mindset is not a resident in the United States.

29. An actual and justiciable controversy exists between Reunion and Mindset as alleged herein.

FACTUAL BACKGROUND

30. Mental health is a worldwide crisis affecting approximately 900 million people globally, with approximately 322 million persons suffering depression. Unfortunately, only one in three patients adequately responds to first-line therapy.

31. Serotonin is a neurotransmitter that is known to regulate mood, appetite, sleep, learning, memory and many other biological and physiological functions.

32. The most frequently prescribed drugs to treat depression—selective serotonin reuptake inhibitors ("SSRIs")—work by modulating serotonin receptor concentrations in the brain. But they have many problems.

33. For many patients, SSRIs have delayed response rates, up to three to four weeks. And for some, the response is poor. In addition, SSRIs have many side effects, including anxiety,

nausea, indigestion, diarrhea, constipation, loss of appetite, weight loss, dizziness, blurred vision and dry mouth. For long-term SSRI therapy, adverse effects include sexual dysfunction, weight gain and sleep disturbance. They also require continuous dosing.

34. Postpartum depression ("PPD") affects about 10-15% of mothers of newborns. Women suffering from PPD can experience changes in mood, appetite and sleep. PPD patients often feel hopeless, lacking concentration, energy and self-esteem and maternal disinterest.

35. The only approved pharmaceutical treatment in the United States specifically for PPD is brenaxolone (Zulresso®), which requires a 60-hour inpatient infusion, resulting in three days away from the patient's baby and family.

36. SSRIs are frequently prescribed off-label for PPD, but they can take three to four weeks to take effect, have significant side effects and are not effective for many patients.

37. Psychedelics are one of the oldest forms of psychopharmaceutical treatments and have been used to alter perception and mood and affect cognition for thousands of years. Recently, the use of psychedelics to treat anxiety and depressive disorders has been on the rise due to the limited efficacy of existing pharmacological treatments for these disorders. Unlike the existing treatments, recent innovative psychedelics have exhibited rapid and sustained clinical benefits, potentially from just one dose.

38. Although sometimes perceived as dangerous, psychedelics are among the safest classes of drugs. They are considered physiologically safe, do not cause addiction and have not been associated with overdose deaths.

Reunion's RE-104 Compound

39. A leader in novel psychedelic drug development, Reunion focuses on developing proprietary drug candidates designed to engage serotonergic receptors in the brain to treat a variety

of psychiatric conditions, including depression. Reunion is pioneering the advancement of innovative synthetic molecules targeting serotonin receptors.

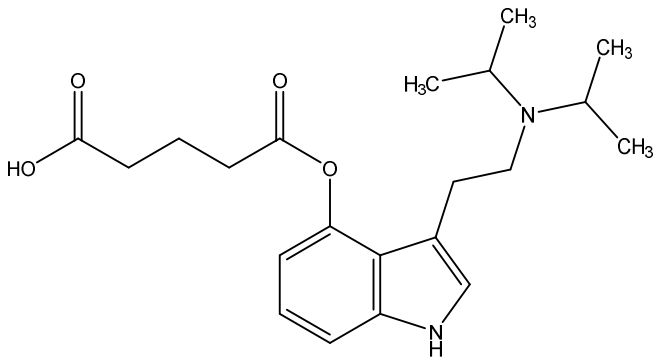
40. Reunion set out to develop a potentially fast-acting, short duration treatment with durable efficacy that provides lasting benefits to underserved patients suffering from depression.

41. To that end, Reunion developed RE-104, a serotonergic psychedelic therapy that directly agonizes the serotonin receptor. RE-104 rapidly produces a psychedelic experience, has few metabolites, and is quickly eliminated. Its prodrug design also improves solubility, stability, and bioavailability.

42. In a recent Phase 1 trial, RE-104 was shown to be safe and well tolerated, with no serious or severe adverse events. The interim analysis included 32 healthy volunteers across four ascending dose cohorts, with two of the eight subjects in each cohort receiving placebo. RE-104 showed robust and pervasive pharmacodynamic effects with a shorter duration of psychedelic experience compared to published data with psilocybin (approximately three to four hours for RE-104 versus six to eight hours for psilocybin).

43. Reunion plans to start a Phase 2 trial in PPD patients and conduct other population pharmacokinetics ("PK") and lacteal transfer sub-studies this year, with a Phase 3 study to follow. Clinical trials for other mental health conditions are planned.

44. RE-104's chemical structure is depicted as follows:



Reunion's '765 Patent

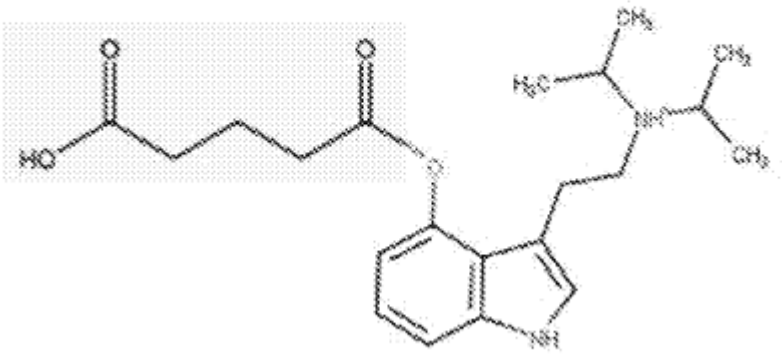
45. Dr. Bryson conceived of RE-104 no later than July 2020.

46. To secure its proprietary RE-104 compound, Reunion filed for patent protection.

47. On November 3, 2020, Reunion filed US Provisional Patent Application No. PR 63/109,095 for Tryptamine Prodrugs, identifying Dr. Nathan Bryson as the Inventor.

48. Claim 2 of the provisional application filed on November 3, 2020, discloses Reunion's RE-104 compound:

Hemiglutarate of 4-hydroxy-diisopropyltryptamine

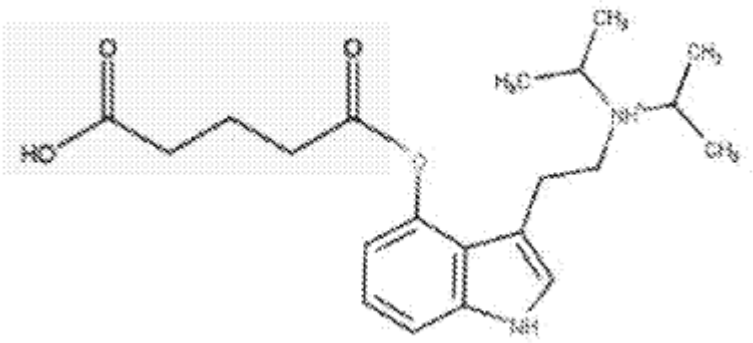


49. The November 3, 2020 patent application further discloses the synthesis of RE-104 (Examples 6 and 9), various properties of RE-104 such as its rate of hydrolysis in animal serums (Example 11), validity of design through demonstrated PK properties in an animal model (Example 12), and possible formulations of RE-104 (Example 18). The patent application also discusses how RE-104 could be used in humans (Examples 13-17).

50. Thereafter, on June 30, 2021, Reunion filed Non-provisional Patent Application No. 17/364,047 ("'047 Application") for Tryptamin Prodrugs, identifying Dr. Bryson as the First

Named Inventor and claiming priority to its earlier Provisional Application No. 63/109,095 filed on November 3, 2020.

51. Both Example 6 and claim 2 of the '047 Application also disclose the proprietary RE-104 compound:



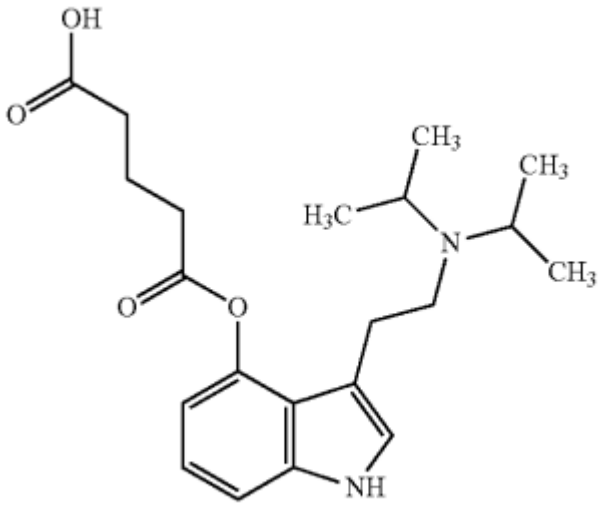
52. On December 30, 2021, the PTO published Reunion's application US 2021-040325, including the structural depictions of RE-104, thereby disclosing it to the public, including Mindset.

53. On January 20, 2022, the PTO communicated a Notice of Allowance and Fees Due, indicating the allowed claims and subject matter, followed on February 9, 2022 by an Issue Notification, setting an issue date of March 1, 2022. Shortly thereafter, Mindset provided Reunion with copies of certain published Mindset patent applications. Even though Reunion had already submitted to the PTO a related Mindset published patent application, Reunion petitioned the PTO to pull its application from issue and submitted the additional references. In response, on February 24, 2022, the PTO communicated a renewed Notice of Allowance and Fees Due, followed on March 16, 2022, by a renewed Issue Notification setting an issue date of April 5, 2022.

54. On April 5, 2022, the PTO issued the '765 Patent, naming Dr. Nathan Bryson as the inventor and Field Trip Psychedelics Inc. (now Reunion) as the Assignee. A copy of the '765 Patent is attached as Exhibit A.

55. Compound 6 and claim 2 of Reunion's '765 Patent publicly disclose the structure of RE-104:[2]

(6)



N,N diisopropyltryptamine-4-glutarate

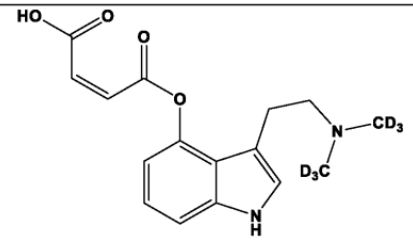
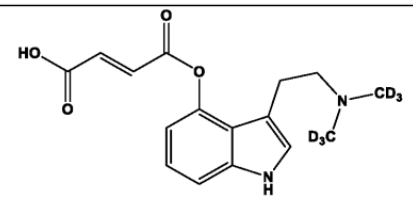
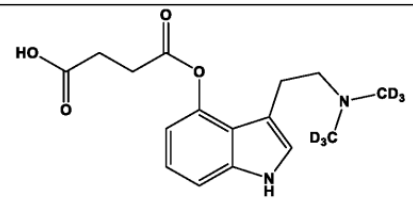
56. In addition, Reunion's '765 Patent describes data relating to the synthesis and utility of RE-104. For instance, Examples 6 and 9 describe the synthesis of RE-104 and its hydrochloric acid salt; Example 12, Table 1, describes the rate of RE-104 hydrolysis in serum; Example 13; Tables 2 and 3; and Figures 1 and 2 describe RE-104's PK parameters in rats, while other Examples describe how RE-104 could be used in humans.

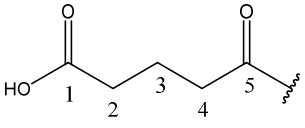
[2] A skilled artisan would understand that this two-dimensional representation—which depicts RE-104's left-hand side chain rotated about a particular carbon-oxygen single bond—discloses the same chemical structure as those previously shown.

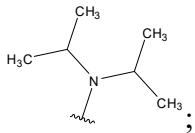
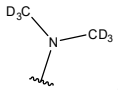
Mindset's '353 Patent

57. On February 4, 2020, Mindset filed US Provisional Patent Application No. PR 62/969,934, which did not include Reunion's RE-104 compound.

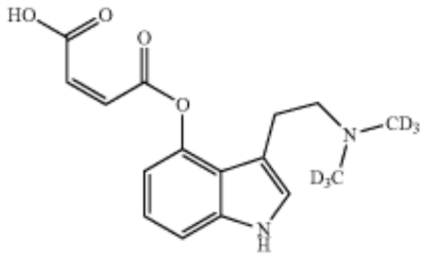
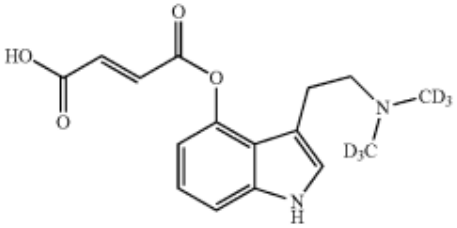
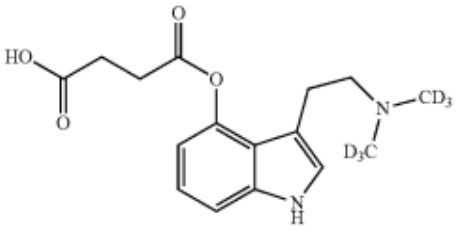
58. One year later, on February 4, 2021, Mindset filed PCT Application No PCT/CA2021/050125, which also did not include Reunion's RE-104 compound. Instead, Mindset disclosed in the PCT Application compounds such as I-18, I-19, and I-20:

I-18	
I-19	
I-20	

59. None of these disclosed compounds has a glutaric acid derived side chain on the left-hand side of the molecule, i.e., a side chain with five carbon atoms:  ; rather, each has a side chain with only four carbon atoms. Furthermore, none of these compounds

discloses a diisopropyl substituted amine moiety, i.e.,  ; rather, each discloses a deuterated dimethyl amine moiety:  .

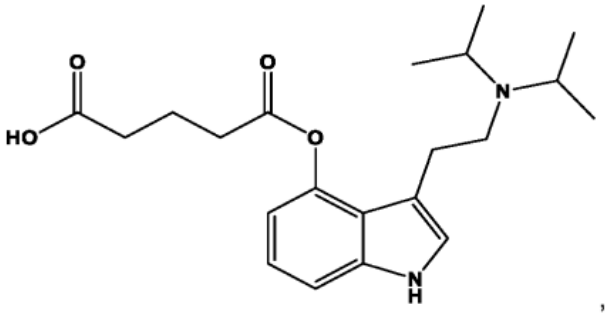
60. On July 28, 2021, Mindset filed US Patent Application No. 17/387,883, which likewise did not include Reunion's RE-104 compound. Mindset similarly disclosed in that application compounds I-18, I-19, and I-20 (pp. 52-53):

Compound ID #	Chemical Structure
I-18	
I-19	
I-20	

61. But, on June 6, 2022, over six months after the PTO first publicly disclosed Reunion's RE-104 compound on December 30, 2021, Mindset filed US Patent Application No. 17/833,341(CON), which included Reunion's RE-104 compound for the first time.

62. Claim 13 of Mindset's application depicts for the first time Reunion's patented RE-104 that Dr. Bryson had independently conceived years earlier:

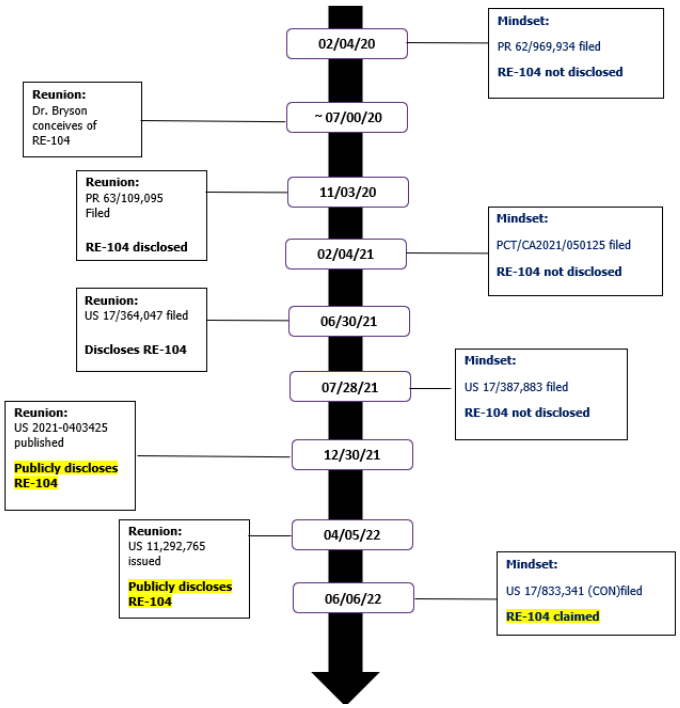
13. The compound of claim 1 that is:



or a pharmaceutically acceptable salt or solvate thereof.

63. The timing of Mindset's inclusion of the RE-104 compound makes clear that the named inventors of US Patent Application No. 17/833,341 did not conceive that compound. Instead, Mindset only included Reunion's RE-104 compound structure in its patent application *after* the publication of Reunion's application and the issuance of its patent, both of which disclose RE-104.

64. The following timeline confirms this conclusion:



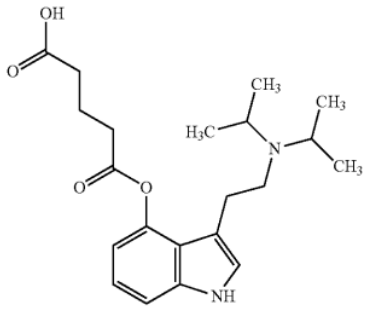
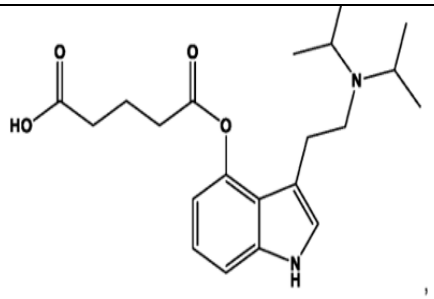
65. Mindset failed to inform the PTO that Dr. Bryson had solely conceived of RE-104 that it included in claim 13 of its patent application.

66. To the contrary, the named inventors of the ’353 Patent, Dr. Abdelmalik Slassi and Joseph Araujo, both signed declarations affirming each was the “original inventor or an original joint inventor of the claimed invention in the application.”

67. As the named inventors on the ’353 Patent, Dr. Slassi and Mr. Araujo owed a duty of candor to the PTO during the prosecution of that patent under 35 C.F.R. § 1.56. On information and belief, both Dr. Slassi and Mr. Araujo made materially misleading statements regarding inventorship with the intent to deceive the PTO to allow claims during prosecution of the ’353 Patent.

68. Mindset’s ’353 Patent issued on February 28, 2023, naming Dr. Slassi and Mr. Araujo as its only inventors and including claim 13 that discloses Reunion’s patented RE-104 compound. The ’ 353 Patent is attached as Exhibit B.

69. A side-by-side comparison shows that the compound in claim 13 of Mindset's '353 Patent is structurally identical to that disclosed in claim 2 of Reunion's '765 Patent:

Claim 2 of the '765 Patent	Claim 13 of the '353 Patent
(6)  N,N diisopropyltryptamine-4-glutarate	

70. As these figures show, both patents disclose a glutaric acid derived side chain on the left-hand side of the molecule, i.e., a side chain with five carbon atoms, and a diisopropyl substituted amine moiety. The two-dimensional graphical representations describe the same chemical structure—Reunion's RE-104 compound.

71. On information and belief, Mindset and the named inventors knowingly and deliberately failed to disclose to the PTO that Dr. Bryson had solely conceived of the invention in claim 13 of Mindset's '353 Patent. On information and belief, the named inventors' failure to disclose Dr. Bryson's inventorship was knowingly false and intended to deceive the PTO so that Mindset could improperly secure the claim.

72. The misrepresentations about inventorship also were material to the Examiner's decision to issue the '353 Patent. But for Mindset's knowing and deliberate misrepresentations regarding conception and inventorship, claim 13 of the '353 Patent would not have issued.

73. Indeed, Mindset allowed the ’353 Patent to issue without correcting inventorship even though, as discussed below, (i) Reunion’s outside counsel had informed Mindset’s counsel in writing about Dr. Bryson’s conception of RE-104, and (ii) the parties’ CEOs discussed this issue during their February 15, 2023 settlement meeting.

Mindset’s Demand Letter

74. On January 20, 2023, outside counsel for Mindset wrote to Joseph Del Moral, Founder and Chairman of Reunion, regarding “Mindset’s patent rights covering Reunion’s RE-104 compound.” Mindset’s counsel stated that Mindset’s patent publications “contain claims that cover Reunion’s RE-104 compound.”

75. Mindset’s counsel also informed Reunion that the PTO had issued a Notice of Allowance for its patent application, including “claims 1-10 and 13-15 that cover the RE-104 compound” and that “we expect the patent to issue shortly.”

76. Mindset’s counsel proposed “to enter into negotiations with Reunion for a commercial resolution including licensing rights to Mindset’s claims covering compound RE-104.” He also requested Reunion to “carefully review this information and agree to discuss a commercial resolution to this matter rather than becoming involved in legal proceedings.”

77. Mindset’s counsel cautioned Reunion that “it would appear that Reunion must divulge that Mindset has patent rights covering RE-104 during due diligence investigations and fund-raising discussions.”

78. Finally, Mindset’s counsel concluded that Mindset “fully intends to take all necessary steps to expand on this morning’s public disclosure to specify its patent rights around RE-104 and to enforce its patent rights.”

79. Tellingly, Mindset's counsel did not assert that the named inventors of the '353 Patent had conceived or independently developed the compound disclosed in claim 13.

80. On February 13, 2023, counsel for Reunion responded to Mindset's demand letter, explaining that although it was amenable to exploring a commercial resolution, it had serious concerns about the validity, inventorship, enforceability and ultimate ownership of the Mindset application. Reunion detailed those concerns in its response.

The Parties' February 15, 2023 Settlement Agreement

81. On February 15, 2023, the parties met in person at counsel for Mindset's offices in Washington, D.C. to attempt to resolve Mindset's allegations. Outside counsel for Mindset participated, along with Mindset's Chief Executive Officer, James Lanthier, and other Mindset executives. Outside counsel for Reunion also participated, along with Reunion's President and Chief Executive Officer, Greg Mayes, and its General Counsel.

82. During that meeting, Reunion made clear that it needed to resolve any intellectual property issues by the end of February 2023 to secure third-party funding that it was negotiating.

83. The parties met for about three hours, exploring potential various commercial arrangements, including Reunion potentially licensing the '353 Patent.

84. Towards the end of the meeting, Mindset's CEO, Mr. Lanthier, and Reunion's CEO, Mr. Mayes, had a private conversation. Afterwards, Messrs. Lanthier and Mayes announced that they had reached an agreement, shaking hands to confirm the deal.

85. The parties reached a meeting of the minds as to all the material terms of a non-exclusive license between Mindset and Reunion for the '353 Patent.

86. In particular, the parties orally agreed on the timing, form and amount of upfront payments, milestone payments, and royalties, and the disposition of claim 13.

87. Within five days of the settlement meeting, outside counsel for Mindset circulated a proposed license agreement between Mindset and Reunion "in accordance with the terms discussed." He also thanked Reunion's counsel for the "productive meeting."

88. On March 2, 2023, Mindset informed Reunion that it intended to walk away from its oral settlement license with Reunion because it wanted to pursue "strategic alternatives."

89. As Mindset predicted in its initial assertion letter, Reunion has had to divulge Mindset's allegations during its fund-raising and related due diligence efforts. Because Mindset has backed out of its oral agreement, Reunion must continue to disclose that its dispute with Mindset remains unresolved.

90. Reunion's opportunity to pursue clinical trials of RE-104 will be impaired due to Mindset's actions.

91. If left unanswered, Mindset's assertion that Reunion must have a license for RE-104 would irreparably harm Reunion in the near and long term.

COUNT I

(Correction of Inventorship of Claim 13 Under 35 U.S.C. § 256)

92. Reunion realleges and incorporates by reference the allegations contained in paragraphs 1-91.

93. The '353 Patent names Dr. Abdelmalik Slassi and Joseph Araujo as the only inventors of the subject matter claimed in the '353 Patent.

94. By conceiving the RE-104 compound disclosed in claim 13 of the '353 Patent, however, Dr. Nathan Bryson is the *sole* inventor of the claim.

95. The named inventors did not conceive of the invention in claim 13 of the '353 Patent. Thus, Dr. Bryson should be completely substituted as the inventor of that claim.

96. Dr. Bryson has assigned his rights, title, and interest in the invention to Reunion. Thus, Reunion has standing to request correction of inventorship.

97. Omitting Dr. Bryson from the ’353 Patent has injured and will continue to injure Reunion by depriving it of an ownership interest, control and financial stake in the ’353 Patent.

98. Dr. Bryson has received notice of and consented to this action to correct inventorship.

99. Under 35 U.S.C. § 256, the ’353 Patent should be corrected to reflect that Dr. Bryson is the sole inventor of the subject matter of claim 13, and he should be completely substituted as the sole inventor of that claim.

100. Reunion is entitled to an order from this Court declaring Dr. Bryson as *the sole* inventor of claim 13 of the ’353 Patent and ordering the Director of the PTO to issue a certificate of correction to that effect.

COUNT II

(Declaratory Judgment of Ownership Interest in the ‘353 Patent)

101. Reunion realleges and incorporates by reference the allegations contained in paragraphs 1-100.

102. Reunion seeks a declaratory judgment that it has an ownership interest in the ’353 Patent.

103. A substantial and continuing justiciable controversy exists between Reunion and Mindset as to Reunion’s ownership interest in the ’353 Patent.

104. A valid case and controversy exist sufficient for this Court to declare the parties’ rights and remedies because the parties dispute ownership of the inventions disclosed and claimed in the ’353 Patent.

105. This controversy is ripe for determination because the parties dispute ownership of the inventions disclosed and claimed in the ’353 Patent.

106. Dr. Bryson conceived of the invention recited in claim 13 of the ’353 Patent.

107. Dr. Bryson has assigned his rights, title, and interest in the invention to Reunion. Thus, Reunion has standing to request this declaration.

108. Reunion has an ownership interest in the ’353 Patent by virtue of Dr. Bryson having assigned his rights, title, and interest in the invention to Reunion.

109. Because Dr. Bryson is an inventor of claim 13 of the ’353 Patent and assigned his rights to Reunion, the named inventors could not assign complete ownership in the ’353 patent to Mindset.

110. To redress this controversy, Reunion requests that the Court declare that Reunion is a co-owner of the ’353 Patent.

COUNT III

(Declaratory Judgement of Inequitable Conduct)

111. Reunion realleges and incorporates by reference the allegations contained in paragraphs 1-110.

112. Mindset purports to be the lawful owner of all right, title and interest in the ’353 Patent.

113. Inventorship is material to patentability. On information and belief, the named inventors knew or should have known that their omission of Dr. Bryson as the inventor of claim 13 was intentional, false and misleading, and they purposefully withheld that material information from the Examiner during the prosecution of the ’353 Patent.

114. The Examiner relied on the named inventors' misrepresentation or omission regarding inventorship in allowing the claims of the '353 Patent. Specifically, under 35 U.S.C. § 101, patents may not be issued to those who are not true inventors. *See, e.g.*, M.P.E.P. § 2104 (II) (instructing examiners to "reject the claims under 35 U.S.C. 101" where inventorship is not correct).

115. The named inventors' deceptive intent in committing inequitable conduct before the PTO during the prosecution of the '353 Patent is the single most reasonable inference draw from the facts alleged herein. For example, but for the named inventors' misrepresentation or omission regarding inventorship, the '353 Patent would not have issued. Mindset has been able to improperly demand a license from Reunion by virtue of the '353 Patent's improper issuance.

116. Given the failure to include Dr. Bryson as the inventor of claim 13 with deceptive intent, the '353 Patent is legally unenforceable against Reunion due to the named inventors' inequitable conduct.

117. Mindset's conduct renders this case exceptional under 35 U.S.C. § 285.

118. An actual and justiciable controversy exists between Reunion and Mindset regarding the '353 Patent—including its unenforceability.

119. Reunion is entitled to a declaratory judgment that the '353 Patent is legally unenforceable.

COUNT IV

(Breach of Oral Settlement Agreement)

120. Reunion realleges and incorporates by reference the allegations contained in paragraphs 1-119.

121. On February 15, 2023, Reunion's President and Chief Executive Officer, Greg Mayes, and Mindset's Chief Executive Officer, James Lanthier, met in Washington, DC at the offices of Mindset's outside counsel "to discuss a commercial resolution to this matter rather than becoming involved in legal proceedings."

122. At that meeting, for valuable consideration including a sum certain to be paid by Reunion, Reunion and Mindset entered into an oral non-exclusive license agreement to settle Mindset's allegations regarding the '353 Patent.

123. Both Reunion's and Mindset's CEOs agreed to the essential terms of the oral license settlement agreement.

124. The parties had a meeting of the minds of all the material terms of the oral license settlement agreement for the '353 Patent, including the timing, form and amount of upfront payments, milestone payments, and royalties, and the disposition of claim 13.

125. On March 2, 2023, Mindset informed Reunion that it was walking away from the oral license settlement agreement to pursue "strategic alternatives," thereby refusing to perform its obligations under the agreement and thus breaching it.

126. As a result of Mindset's breach, Reunion has been damaged.

COUNT V

(Promissory Estoppel)

127. Reunion realleges and incorporates by reference the allegations contained in paragraphs 1-126.

128. On February 15, 2023, Reunion's President and Chief Executive Officer, Greg Mayes, and Mindset's Chief Executive Officer, James Lanthier, met in Washington, DC at the offices of Mindset's outside counsel "to discuss a commercial resolution to this matter rather than becoming involved in legal proceedings."

129. During that meeting, Reunion expressly stated that it needed to resolve any intellectual property issues by the end of February 2023 to secure third-party funding that it was negotiating.

130. Mindset made clear and definite promises to Reunion that Mindset would enter into a non-exclusive licensing agreement with Reunion to resolve the dispute. Mindset made clear and definite promises to Reunion regarding the licensing agreement, timing, form and amount of upfront payments, milestone payments, and royalties, and the disposition of claim 13.

131. Mindset's clear and definite promises to Reunion were made with the expectation that those promises would induce reliance by Reunion and specifically Reunion would report to its potential investors that the parties had resolved their differences.

132. After the February 15, 2023 settlement, Reunion reasonably relied on Mindset's promises in initially deciding to forego litigation to resolve the patent inventorship and ownership issues that it had raised with Mindset before the parties' settlement meeting. Mindset's subsequent conduct alleged above forced Reunion to bring this action to resolve the parties' dispute.

133. Reunion relied on Mindset's promises to its definite and substantial detriment in the form of significant economic damages.

COUNT VI

(Tortious Interference with Prospective Business)

134. Reunion realleges and incorporates by reference the allegations contained in paragraphs 1-133.

135. Reunion has a protectable interest in the reasonable expectation of economic advantage, including opportunities to secure funding for its ongoing clinical development.

136. Mindset knew of this expectancy because Reunion communicated it to Mindset during their settlement negotiations. It also made clear that resolution of Mindset's allegations was critical to Reunion's ability to secure that funding.

137. In its January 20, 2023 Demand Letter, Mindset acknowledged it intended to publicly disclose its allegations against Reunion and asserted that Reunion would have to divulge those allegations during due diligence investigations and fund-raising discussions.

138. After admittedly injecting its allegations into the market publicly, Mindset tortiously interfered with Reunion's prospective economic advantage by refusing to license the '353 Patent to Reunion despite its promise to do so.

139. Mindset did so with malice and without justification or excuse. For example, on information and belief, Mindset knew or should have known that refusing to license the '353 Patent after expressly promising to do so would affect Reunion's opportunity to obtain funding. Thus, on information and belief, Mindset committed these acts knowing they would impair Reunion's opportunity to obtain funding.

140. As a result of Mindset's conduct as alleged herein, there is a reasonable likelihood that Reunion's opportunity to prospectively obtain funding will be impaired. In addition, there is a reasonable probability that Reunion would have obtained the anticipated economic benefit in the absence of Mindset's interference at least because resolution of Mindset's allegations was critical to Reunion's ability to secure funding.

141. Mindset's tortious interference has damaged Reunion.

142. Based on information and belief, Mindset's conduct as alleged herein was willful and wanton because Mindset deliberately interfered with Reunion's prospective economic advantage knowing that it would likely harm Reunion.

PRAYER FOR RELIEF

WHEREFORE, Reunion respectfully requests that this Court enter judgment in favor of Reunion granting the following relief:

A. A judgment in favor of Reunion and against Mindset correcting inventorship of the '353 Patent and ordering the Director of the PTO to issue a certificate of correction to that effect.

B. A declaratory judgment in favor of Reunion and against Mindset that Reunion co-owns the '353 Patent and the inventions disclosed and claimed in it.

C. A declaratory judgment in favor of Reunion and against Mindset that the '353 Patent is legally unenforceable due to Mindset's inequitable conduct.

D. A judgment that this is an exceptional case under 35. U.S.C. § 285 and an award of Reunion's reasonable attorneys' fees.

E. A judgment that Mindset breached its February 15, 2023 oral license settlement agreement with Reunion and an award of damages to compensate Reunion for that breach.

F. In the alternative, a judgment that Mindset is estopped from refusing to license the '353 Patent to Reunion as promised during the February 15, 2023 settlement meeting.

G. A judgment that Mindset tortiously interfered with Reunion's prospective economic advantage and an award of damages of more than $25 million for that conduct.

H. An award of punitive damages resulting from Mindset's willful and wanton actions.

I. Such other and further relief as this Court may deem just and proper, in law or equity.

Date: March 13, 2023

Respectfully submitted,

By: */s/ Harvey Bartle IV*
Harvey Bartle IV

MORGAN, LEWIS & BOCKIUS LLP
502 Carnegie Center
Princeton, NJ 08540-6241
Phone: (609) 919-6600

Michael J. Abernathy (*pro hac vice* forthcoming)
mike.abernathy@morganlewis.com
Margaret A. McGreal (*pro hac vice* forthcoming)
margaret.mcgreal@morganlewis.com
Karon N. Fowler (*pro hac vice* forthcoming)
karon.fowler@morganlewis.com
MORGAN, LEWIS & BOCKIUS LLP
110 N. Wacker Drive
Chicago, IL 60606
+1.312.324.1000

Attorneys for Plaintiffs

Exhibit A

US011292765B2

(12) **United States Patent**
Bryson

(10) **Patent No.: US 11,292,765 B2**
(45) **Date of Patent: Apr. 5, 2022**

(54) **TRYPTAMINE PRODRUGS**

(71) Applicant: **Field Trip Psychedelics Inc.**, Toronto (CA)

(72) Inventor: **Nathan Bryson**, Toronto (CA)

(73) Assignee: **Field Trip Psychedelics Inc.**, Toronto (CA)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **17/364,047**

(22) Filed: **Jun. 30, 2021**

(65) **Prior Publication Data**

US 2021/0403425 A1 Dec. 30, 2021

Related U.S. Application Data

(60) Provisional application No. 63/045,901, filed on Jun. 30, 2020, provisional application No. 63/109,095, filed on Nov. 3, 2020.

(51) **Int. Cl.**

C07D 209/16	(2006.01)
C07D 209/08	(2006.01)
A61K 9/08	(2006.01)
A61K 9/00	(2006.01)
A61K 9/20	(2006.01)

(52) **U.S. Cl.**

CPC ***C07D 209/16*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 9/0053*** (2013.01); ***A61K 9/08*** (2013.01); ***C07D 209/08*** (2013.01); *A61K 9/20* (2013.01)

(58) **Field of Classification Search**

CPC C07D 209/16

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,075,992	A	1/1963	Hofmann et al.
2022/0017549	A1	1/2022	Slassi et al.
2022/0024956	A1	1/2022	Slassi et al.

FOREIGN PATENT DOCUMENTS

WO	9506638	A1	9/1995
WO	2006047032	A2	4/2006
WO	2020181194	A1	10/2020
WO	2021155470	A1	12/2021

OTHER PUBLICATIONS

Il'ina et al. CAS: 83: 201816, 1975.*

Makhaeva et al. CAS: 83: 113322, 1975.*

International Search Report, dated Oct. 20, 2021, in International application No. PCT/CA2021/050907, filed on Jun. 30, 2021 (4 pages).

Makhaeva et al., "Synthesis and kinetics of the hydrolysis of serotonin terephthalates and succinates." Zhurnal Organicheskoi Khimii, 1975, vol. 11(7) 1489-1498, * compounds la and lb, Scheme 1, p. 1489 *.

Database CAS Chemcats [Online], "1,4-Benzenedicarboxylic acid, 1-[3-(2-aminoethyl)-1H-indol-4-yl] ester," Chemical Abstracts Service, Columbus, OH, USA. STN entry date Aug. 17, 2006 (Aug. 17, 2006), Retrieved from STN, CAS RN: 902412-24-2.

Database CAS Registry [Online], "Hexanedioic acid, 1-[3-2-aminoethyl)-1H-indol-5-yl] ester," Chemical Abstracts Service, Columbus, OH USA. STN entry date Nov. 16, 1984 (Nov. 16, 1984), Retrieved from STN, CAS RN: 33598-45-7.

Database CAS Chemcats [Online], "2-Butenedioic acid, 1-[3-(2-aminoethyl)-1H-indol-5-yl] ester," Chemical Abstracts Service, Columbus, OH, USA. STN entry date Nov. 19, 2020 (Nov. 19, 2020), Retrieved from STN, CAS RN: 2519519-21-0, Retrieved from STN, CAS RN: 2519519-21-0.

Glennon et al., "Butofenine Esters," Journal of Medicinal Chemistry, 1979, vol. 22(11), pp. 1414-1416.

Glennon et al., "Synthesis and Evaluation of a Novel Series of N,N-Dimethylisotryptamines." Journal of Medicinal Chemistry, 1984, vol. 27(1), pp. 41-45.

Troxler et al., "Synthetic indole compounds. II. Psilocybin and psilocin modifications." Helvetica Chimica Acta, 1959, vol. 42, pp. 2073-2103.

Certified priority document for U.S. Appl. No. 62/969,934, filed Feb. 4, 2020.

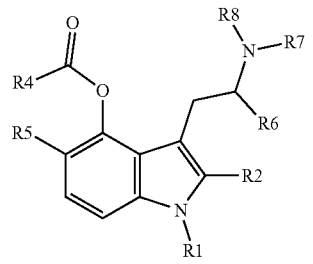
* cited by examiner

Primary Examiner — Rei Tsang Shiao

(74) *Attorney, Agent, or Firm* — Michael Stanley Tomsa; McAndrews, Held & Malloy, Ltd.

(57) **ABSTRACT**

The present invention provides a tryptamine prodrug compound. A compound represented by the formula (I)



where each symbol is as described in the specification, or a salt or zwitterion thereof, is converted to an active which has 5HT2A receptor agonist activity, and is useful as an agent for the treatment of depression.

23 Claims, 1 Drawing Sheet

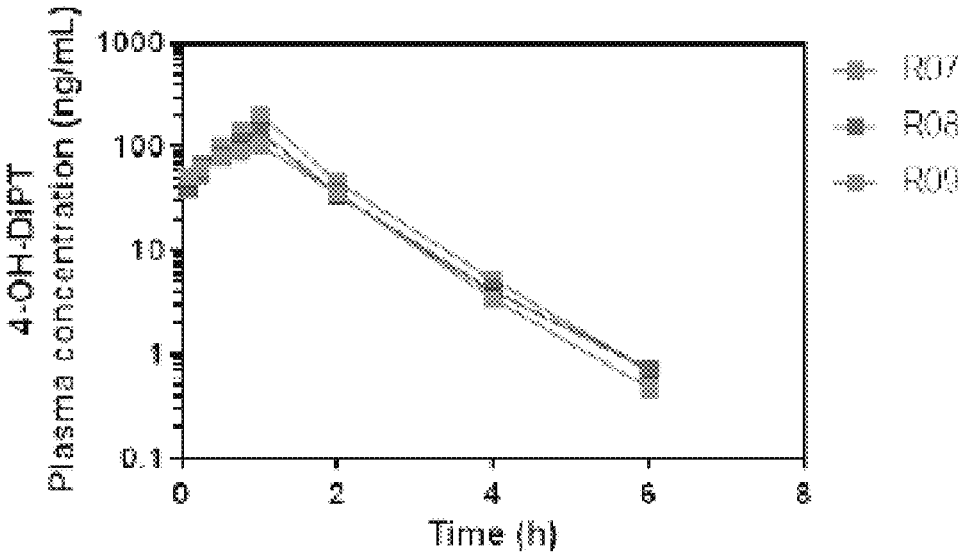


Figure 1

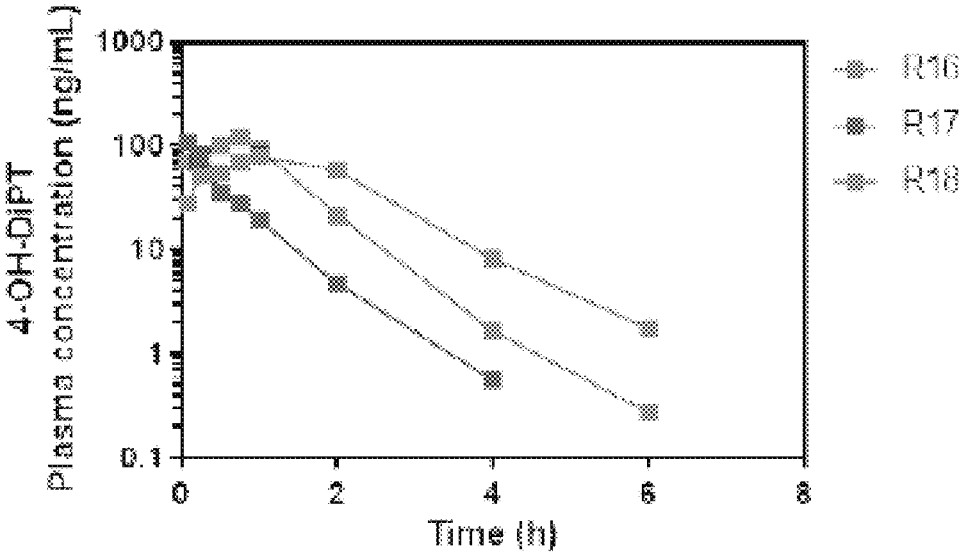


Figure 2

TRYPTAMINE PRODRUGS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application Ser. No. 63/045,901 filed on Jun. 30, 2020, entitled "TRYPTAMINE PRODRUGS", and to U.S. Provisional Application Ser. No. 63/109,095 filed on Nov. 3, 2020, entitled "TRYPTAMINE PRODRUGS". The entire contents of U.S. Provisional Application Ser. No. 63/045,901 and U.S. Provisional Application Ser. No. 63/109,095 are hereby incorporated by reference in this application.

FIELD OF THE INVENTION

The present invention relates to novel tryptamine compounds, methods of making and using such compounds, compositions comprising such compounds, and their uses.

BACKGROUND

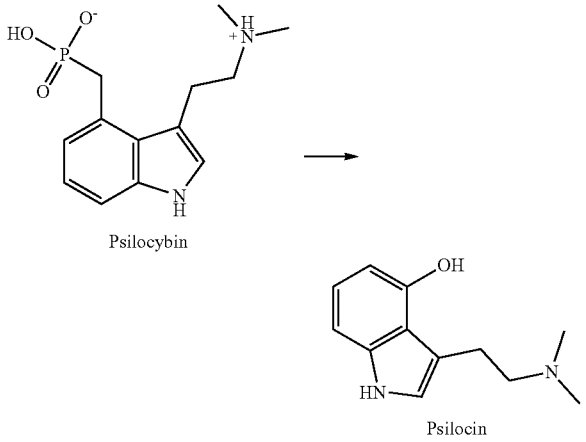
Tryptamines are a class of 3-aminoethyl-indoles that bind and activate the serotonin receptor, also called the 5HT receptor. A psychedelic state may be achieved by activation of the 2A form of the serotonin receptor by 5HT2A receptor agonist compounds. The endogenous substance for this receptor is 5-hydroxy-tryptamine (serotonin). The tryptamine 3-(2-aminoethyl)-indole is also an endogenous neurotransmitter.

The serotonin receptor system is implicated in depression and depressive states which are commonly treated with 5HT1A antagonists (Affective Disorders: Depression in Neuropsychopharmacology and Therapeutics, Chapter 6, First Edition. Ivor S. Ebenezer, 2015). More recently, 5HT2A agonists have shown potential as medicines for depression (Carhart-Harris 2018 Psychopharmacology).

Tryptamine molecules which produce a psychedelic state and which have been used in traditional medicine, may have therapeutic potential for the treatment of mood disorders, distress, depression and others. For example, ayahuasca is a natural form of dimethyltryptamine (DMT) which when combined with a monoamine oxidase inhibitor can be ingested and produces a variable, but prolonged psychedelic state that can last for 6 to 15 hours. DMT is also naturally found to occur in small amounts in the brain and may act as a neurotransmitter.

Lysergic acid diethylamide (LSD), is a diethylamide derivative of a naturally occurring substance from fungus found in rye grain, which also produces a prolonged psychedelic state up to 8 to 12 hours long.

Psilocybin is a naturally occurring plant-based tryptamine found in Psilocybe mushrooms, and produces a prolonged psychedelic state of about 6 to 8 hours. Psilocybin was first synthesized in 1958 and is currently being investigated as a treatment for depression. Psilocybin is a prodrug, with psilocin being the active species in vivo. Psilocybin contains a phosphate bound to the 4-hydroxy group of psilocin, which is cleaved in the gut when Psilcybe mushrooms or the drug substance is taken orally:



Simple mono-functional organic esters of psilocin have been reported. Lower alkoxy radical modified psilocins have also been described. Sulfate-bound psilocin has been produced and other mono- and di-basic mineral acid modified psilocins have been described. Psilocin acetate is known and has been used in underground psychedelic subculture.

Psychedelic substances have been shown to be effective for treating depression, and even more effective for treating depression when associated with psychotherapy (Watts 2020 J Contextual Behavioral Science).

A limited number of synthetic tryptamine substances have been prepared since perhaps the earliest recorded work of Albert Hoffman. Structure-activity relationships have been described for a variety of tryptamine substances (Claire 1988).

Succinate and other diacid functions have been explored as components of a prodrug delivery system toward water-soluble, injectable forms of hydrophobic or poorly water soluble drug substances, such as testosterone, haloperidol, chloramphenicol or estradiol (Silverman and Holladay, Chapter 9.2: Prodrugs and Drug Delivery Systems in The Organic Chemistry of Drug Design and Drug Action (3rd Ed), 2014). Tetrahydrocannabinol ester of succinic acid has been patented to treat glaucoma. However, ester cleavage is not consistently rapid, is not predictable and can depend on the structure of the moiety attached to the drug and therefore must be investigated (Anderson 1984 JPharmaSci). Esterase enzymes are responsible for active cleavage of the prodrug ester group in vivo and species differences in esterase quantities and specificity in various tissues complicate investigations and optimizations (Bahar 2012 JPharmSci).

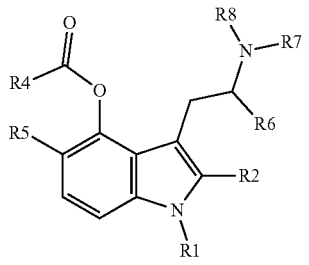
This background information is believed to be relevant to a basic understanding of the present invention. It is not an admission that any of the foregoing is prior art against any aspect of the claimed invention.

SUMMARY OF THE INVENTION

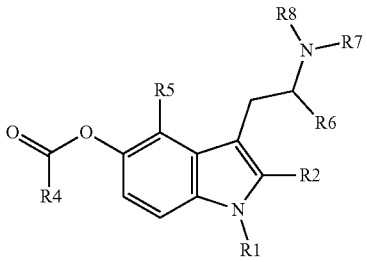
The present invention relates to novel tryptamine compounds, which when administered, convert to an active form in vivo, and act as a 5HT2A agonist. The compounds described herein may be useful to treat mental disorders, such as a depressive condition, including unipolar and bipolar depressive conditions, such as but not limited to depression, depression from generalized anxiety, major depression, treatment resistant depression and postpartum depression.

In one aspect, the present invention relates to a tryptamine or isotryptamine compound of Formula (I) (II), (III) or (IV) or a pharmaceutically acceptable salt or zwitterion thereof:

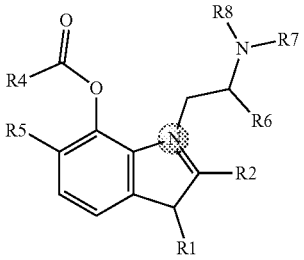
(I)



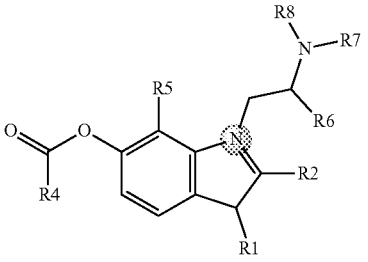
(II)



(III)



(IV)



wherein:

(1) R1, R2, and R6 are each independently selected from hydrogen, linear or branched alkyl, preferably C_{1-5} alkyl, or arylalkyl;

(2) R4 is

a. —X—CO2H, where X is a linear, cyclic or branched, saturated or unsaturated carbon chain (preferably C_{1-5} alkyl), optionally substituted with —OH or —CO2H, or an aromatic ring, optionally substituted with alkyl or CO2H; or

b. (R9)(R10)N—, wherein R9 is X—CO2H, where X is defined as above, and R10 is hydrogen, linear or branched alkyl (preferably C_{1-5} alkyl) or arylalkyl, optionally substituted by —OH or —CO2H;

(3) R5 is hydrogen, linear or branched alkyl (preferably C_{1-5} alkyl), arylalkyl, or O—R5', where R5' is hydrogen, linear or branched alkyl (preferably C_{1-5} alkyl); and

(4) R7 and R8:

a. are each independently selected from hydrogen, linear or branched alkyl (preferably C_{1-5} alkyl), or arylalkyl, or

b. together form a non-aromatic N-containing heterocycle, optionally substituted with alkyl, preferably where the entire heterocyclic structure does not contain more than 12 atoms.

In another aspect, the invention comprises diacid esters of a hydroxytryptamine, such as 4-hydroxy and 5-hydroxytryptamines and 6-hydroxy and 7-hydroxy isotryptamines, and other structural or functional analogs of psychedelic tryptamines.

In some embodiments, R7 and R8 are the same or different, and are linear or branched C_{1-4} alkyl; or are the same or different, and are methyl or isopropyl; such as R7 and R8 are both methyl, or R7 and R8 are both isopropyl, or where one of R7 and R8 is methyl and the other is isopropyl.

In some embodiments, X is a linear C1-C3 chain, optionally substituted with OH or —CO2H, such as X is an unsubstituted linear C3 chain.

In another aspect, the invention relates to a composition comprising a compound described herein, and a pharmaceutically acceptable excipient. In some embodiments, the composition comprises an oral dosage formulation or an injectable formulation.

In another aspect, the invention comprises a method of treating a mental disorder, comprising the step of administering an effective amount of a compound described herein. In some embodiments, the mental disorder is a depressive condition, including unipolar and bipolar depressive conditions, such as but not limited to depression, depression from generalized anxiety, major depression, treatment resistant depression and postpartum depression.

In another aspect, the invention relates to the use of a compound described herein to treat a mental disorder, or in the manufacture of a medicament for treating a mental disorder, such as depression.

In another aspect, the invention relates to a method of making a compound described herein, comprising reacting a tryptamine comprising a hydroxytryptamine or hydroxyisotryptamine with a cyclic anhydride in a suitable anhydrous solvent. In some embodiments, the solvent contains a base with pKa greater than 4 but less than 9, and the resulting compound is isolated as a zwitterion. In some embodiments, the tryptamine comprises 4-hydroxy or 5-hydroxy tryptamine or a 6-hydroxy or 7-hydroxy isotryptamine. In some embodiments, the solvent is pyridine.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a graph showing plasma concentration of 4-HO-DiPT (ng/ml) time after subcutaneous administration of N,N diisopropyltryptamine-4-glutarate at a rate of 2 mg/kg.

FIG. **2** is a graph showing plasma concentration of 4-HO-DiPT (ng/ml) after subcutaneous administration of N,N diisopropyltryptamine-4-glutarate at a rate of 1.4 mg/kg

DETAILED DESCRIPTION

Embodiments of the present invention comprise novel synthetic tryptamine prodrugs. The prodrugs may be useful for treatment of mental disorders such as depression, including without limitation, major depression, treatment resistant depression and postpartum depression. As used herein, the term "mental disorder" includes those disorders which may

be diagnosed by a mental health professional as a psychological or psychiatric disorder, including those which may be diagnosed by reference to Diagnostic and Statistical Manual of Mental Disorders (DSM-5).

The term "treating", "treat" or "treatment" as used herein embraces both preventative, i.e., prophylactic, and palliative treatment, i.e., relieve, alleviate, or slow the progression of the patient's disease, disorder or condition.

As used herein, "psychedelic state" is an altered state of consciousness experienced by a person, which may include intensified sensory perception, perceptual distortion or hallucinations, and/or feelings of euphoria or despair. Psychedelic states have been described as resulting from psychedelic drugs such as DMT (dimethyltryptamine), LSD, mescaline or psilocybin. Other known psychedelic drugs include the 4-hydroxy analogs of N-Methyl-N-isopropyltryptamine (MiPT) and N,N-diisopropyltryptamine (DiPT).

The present invention comprises prodrugs of hydroxyindole 5HT2A agonists which induce a psychedelic state or which still provide a beneficial therapeutic effect without being associated with a psychedelic state. The prodrugs may be used in combination with other treatments known to be effective for treating mental disorders, such as psychotherapy, electroconvulsive therapy and/or other pharmaceutical compounds, for example, with concomitant use of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MOAIs) or other anti-depressants. In preferred embodiments, the treatment may produce lasting effects, for example longer than 1 month after a single treatment, preferably longer than 3 months, and more preferably longer than 6 months. In some embodiments, additional therapy may not be required.

Compounds

"Compounds" when used herein includes any pharmaceutically acceptable derivative or variation, including conformational isomers (e.g., cis and trans isomers) and all optical isomers (e.g., enantiomers and diastereomers), racemic, diastereomeric and other mixtures of such isomers, as well as solvates, hydrates, isomorphs, polymorphs, tautomers, esters, salt forms, and prodrugs. The expression "prodrug" refers to compounds that are drug precursors which following administration, release the drug (or "active") in vivo via some chemical or physiological process (e.g., hydrolysis, enzymatic cleavage or hydrolysis, or metabolism is converted to the desired drug form). The invention includes within its scope the pharmaceutically acceptable salts of the compounds of the invention. Accordingly, the phrase "or a pharmaceutically acceptable salt thereof" is implicit in the description of all compounds described herein unless explicitly indicated to the contrary.

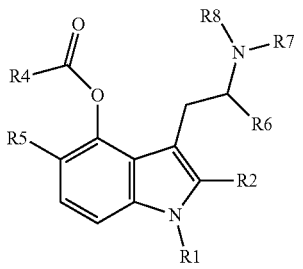
In some embodiments, the compounds of the present invention comprise prodrug compounds that are readily purified, formulated and stable, and preferably may be used to provide highly soluble drug substances, with fast onset and elimination for convenient use in a clinical setting. In some embodiments, the compounds may be produced as a zwitterion, which may be converted to a pharmaceutically acceptable salt.

In some embodiments, the compounds of the present invention preferably allow for fast cleavage in vivo of the prodrug moiety to give the active pharmacophore, for example, 90% conversion may occur in under 4 hours, preferably in less than 2 hours, and more preferably in less than 1 hour. Prodrugs may have lesser, little or no pharmacological activity themselves, however when administered to a patient, may be converted into an active compound, for example, by hydrolytic cleavage.

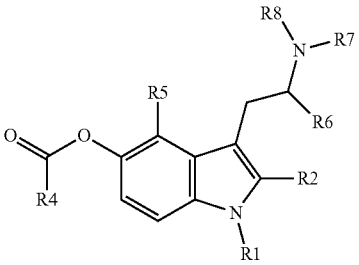
Diacid hemiesters of tryptamines, such as psilocin or other hydroxytryptamines or isotryptamines, have not previously been described. A prodrug strategy implemented by combining a diacid and a 4-hydroxy-tryptamine or 5-hydroxy-tryptamine has likely not been proposed, as a prodrug strategy is typically not necessary when the drug is already soluble. Therefore, aspects of this diacid hemiester prodrug strategy, as described herein, are believed to be novel and inventive.

In one aspect, the present invention comprises a tryptamine or isotryptamine compound of Formula (I) (II), (III) or (IV), or a pharmaceutically acceptable salt or zwitterion thereof:

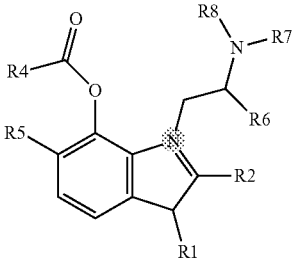
(I)



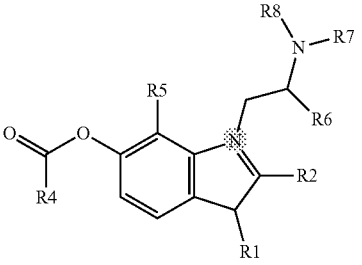
(II)



(III)



(IV)



wherein:

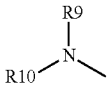
(1) R1, R2, and R6 are each independently selected from hydrogen, linear or branched alkyl, preferably C_{1-5} alkyl, or arylalkyl;

(2) R4 is

a. —X—CO2H, where X is a linear, cyclic or branched, saturated or unsaturated carbon chain (preferably

C_{1-5} alkyl), optionally substituted with —OH or —CO2H, or an aromatic ring, optionally substituted with alkyl or CO2H; or

b.



wherein R9 is X—CO2H, where X is as defined (2)(a) above and R10 is hydrogen, linear or branched alkyl (preferably C_{1-5} alkyl) or arylalkyl, optionally substituted by —OH or —CO2H;

(3) R5 is hydrogen, linear or branched alkyl (preferably C_{1-5} alkyl), arylalkyl, or O—R5', where R5' is hydrogen, linear or branched alkyl (preferably C_{1-5} alkyl); and

(4) R7 and R8:

a. are each independently selected from hydrogen, linear or branched alkyl (preferably C_{1-5} alkyl), or arylalkyl, or

b. together form a non-aromatic N-containing heterocycle, optionally substituted with alkyl, preferably where the entire heterocyclic structure does not contain more than 12 atoms, for example, pyrrolidine (NC4 ring) piperidine (NC5 ring), or morpholine (NC4O ring).

"Alkyl," by itself or as part of another substituent, refers to a saturated branched, straight-chain or cyclic monovalent hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. The term "alkyl" includes cycloalkyl. Typical alkyl groups include, but are not limited to, methyl; ethyl; propyls such as propan-1-yl, propan-2-yl (isopropyl), cyclopropan-1-yl, etc.; butanyls such as butan-1-yl, butan-2-yl (sec-butyl), 2-methyl-propan-1-yl (isobutyl), 2-methyl-propan-2-yl (t-butyl), cyclobutan-1-yl, etc.; and the like. In some embodiments, an alkyl group comprises from 1 to 20 carbon atoms (C_1-C_{20} alkyl). In other embodiments, an alkyl group comprises from 1 to 10 carbon atoms (C_1-C_{10} alkyl). In still other embodiments, an alkyl group comprises from 1 to 6 carbon atoms (C_1-C_6 alkyl) or 1 to 4 carbon atoms (C_1-C_4). C_1-C_6 alkyl is also known as "lower alkyl".

The term "arylalkyl" is a term of the art and as used herein refers to an alkyl group, for example a C_{1-6} alkyl group, substituted with an aryl group, where the residue is linked to the main molecule through the alkyl group. An example of arylalkyl is the benzyl group, that is, the phenyl-methyl group.

"Substituted," when used to modify a specified group or radical, means that one or more hydrogen atoms of the specified group or radical are each, independently of one another, replaced with the same or different substituent(s). The term "substituted" specifically envisions and allows for one or more substitutions that are common in the art. However, it is generally understood by those skilled in the art that the substituents should be selected so as to not adversely affect the useful characteristics of the compound or adversely interfere with its function.

The term "optionally substituted" denotes the presence or absence of the substituent group(s). That is, it means "substituted or unsubstituted". For example, optionally substituted alkyl includes both unsubstituted alkyl and substituted alkyl. The substituents used to substitute a specified group can be further substituted, typically with one or more of the same or different groups selected from the various groups specified above.

These prodrug structures are converted to an active hydroxy-indole 5HT2A agonist after hydrolysis or metabolization of the ester function R4-CO—.

In some non-limiting examples, the compounds comprise diacid esters of tryptamine structures such as 4-hydroxy-N,N-dimethyltryptamine (psilocin or 4-HO-DMT), 4-hydroxy-N,N-diethyltryptamine (4-HO-DET), 4-hydroxy-N,N-diisopropyltryptamine (4-OH-DiPT), 4-hydroxy-N-methyl-N-isopropyltryptamine (4-OH-MIPT), 5-hydroxy-N,N-dimethyltryptamine, 4-methyl-5-hydroxy-N,N-dimethyl) tryptamine and 4-hydroxy-5-methyl-N,N-dialkyltryptamine. In some embodiments, the compounds include the 4- and 5-substituted hemisuccinates, hemiglutarates and citrates of 4-hydroxy derivatives of N,N-dimethyltryptamine (psilocin), N,N-diisopropyltryptamine (4-HO-DiPT), or N-methyl-N-isopropyl-tryptamine (4-HO-MiPT).

In some embodiments, the compound comprises a compound of Formula I, II, III or IV, wherein R1, R2, R5, R6, are each hydrogen; X is a linear C1-4 alkyl; and R7 and R8 are each methyl. In a preferred embodiment, the compound is a compound of Formula I or II and X is C2 alkyl, thus forming a 4- or 5-hemisuccinate of psilocin.

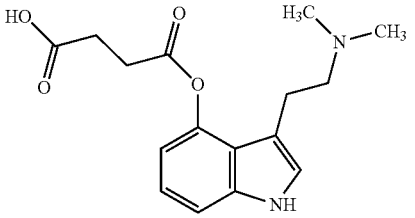
In some embodiments, the compound comprises a compound of Formula I, II, III or IV, wherein R1, R2, R5, R6, are each hydrogen; X is a linear C1-C4 alkyl chain; and R7 and R8 are each isopropyl. In some embodiments, the compound is a compound of Formula I or II, X is C2 alkyl, thus forming a hemisuccinate of 4- or 5-hydroxy-diisopropyltryptamine. In some embodiments, the compound is a compound of Formula I or II, X is a C2 alkene, thus forming a hemifumarate of 4- or 5-hydroxy-diisopropyltryptamine. In some embodiments, the compound is a compound of Formula I or II and X is a C3 alkyl chain, thus forming a hemiglutarate of 4- or 5-hydroxy-diisopropyltryptamine.

In some embodiments, R7 and R8 are each chosen on the basis of retaining or enhancing the compound's ability to induce a psychedelic state. It is known that psychedelic activity of a tryptamine is reduced if R7 or R8 become larger than C4. However, such compounds are still within the scope of the present invention if they are still 5HT2A agonists which can produce beneficial therapeutic effect without a psychedelic state.

In some embodiments, compounds of the present invention are diacid zwitterions. Thus, where X is a linear saturated alkyl, the diacid may comprise a common linear alkyl α,ω-diacid, including without limitation oxalic, malonic, succinic, glutaric (pentanedioic), adipic (hexanedioic), pimelic (heptanedioic) and suberic acid (octanedioic). In some embodiments, where X is a linear alkene, the diacid may comprise an acid such as maleic, fumaric, or glutaconic acid. In other embodiments, the diacid may comprise a branched acid such as citraconic, mesaconic, 2,2-dimethylsuccinic acid; a substituted acid such as tartronic, 2-(2-hydroxyethyl)-malonic acid, a-hydroxyglutaric; citric acid; or an aryl dioic acid such as phthalic acid, isophthalic and p-phthalic, optionally with organic substituents on the aromatic ring.

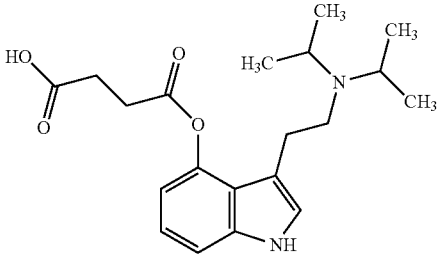
In some embodiments, the compound may be one of the following:

(1)



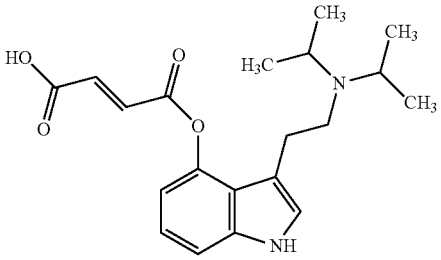
psilocin-4-succinate

(2)



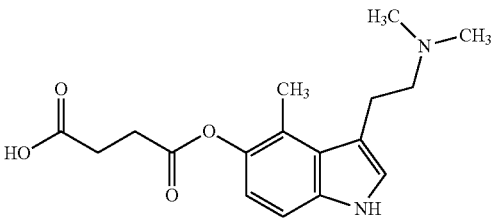
N,N diisopropyltryptamine-4-succinate

(3)



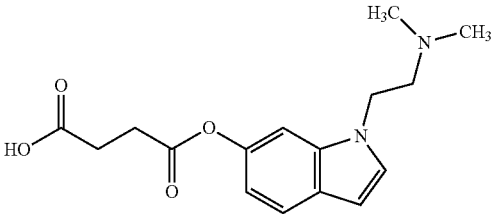
N,N diisopropyltryptamine-4-Fumarate

(4)



Psilocin-4-Methyl-5-succinate

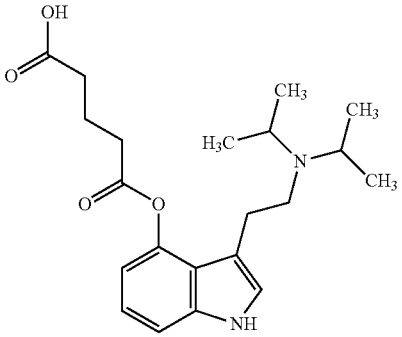
(5)



Iso-N,N dimethyltryptamine-6-succinate

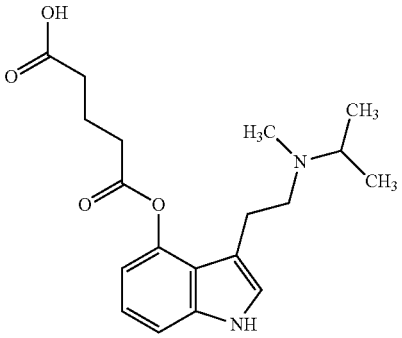
-continued

(6)



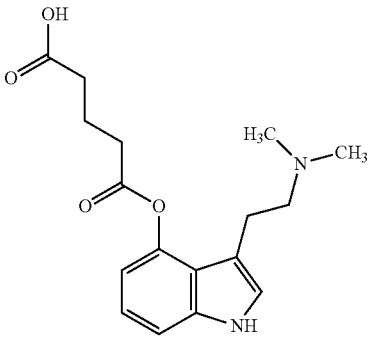
N,N diisopropyltryptamine-4-glutarate

(7)



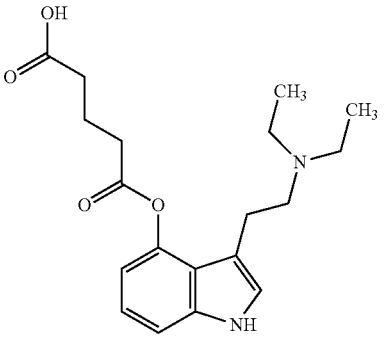
N-methyl N-isopropyltryptamine-4-glutarate

(8)



Psilocin-4-glutarate

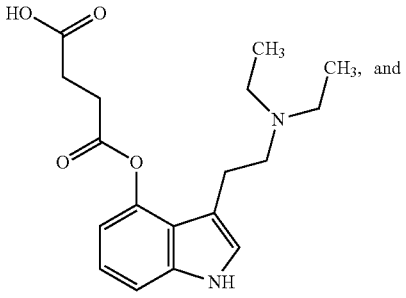
(9)



N,N diethyltryptamine-4-glutarate

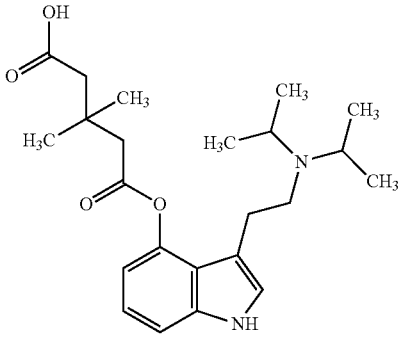
-continued

(10)



N,N diethyltryptamine-4-succinate

(11)



N,N diisopropyltryptamine-4-(3,3-dimethylglutarate)

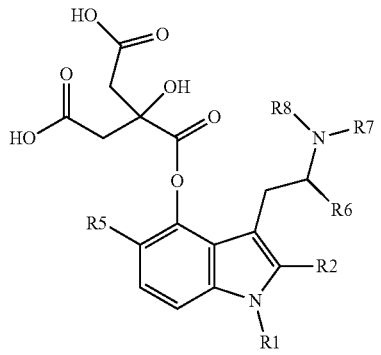
In some embodiments, the diacid-modified tryptamines or isotryptamines exhibit product stability (oxidation and hydrolysis) and can be readily synthesized and purified. The diacid-modified tryptamines or isotryptamines preferably exhibit solubility in biological matrices in excess of the drug absent the diacid modification, making them superior drug candidates. As well, the diacid-modified tryptamines preferably exhibit relatively quick rates of hydrolysis in vivo, so as to convert the prodrug rapidly to the active form of the drug. This can result in improved and desirable pharmacokinetic properties with the prodrug, including more reproducible pharmacokinetic profiles. These properties can depend on the nature of the indole, the various substituents attached to the indole and the nature of the diacid ester. Stability and hydrolysis rates can be determined experimentally.

In some embodiments, the compound may comprise a carbamate ester of tryptamine, where R4 is (R9)(R10)N— where R9 and R10 define a carbamate residue and are defined as above. In some embodiments, the carbamate function comprises a zwitterionic amino-functional mono or dicarboxylic acid which is linked via the carbamate, including without limitation, zwitterionic compounds such as:

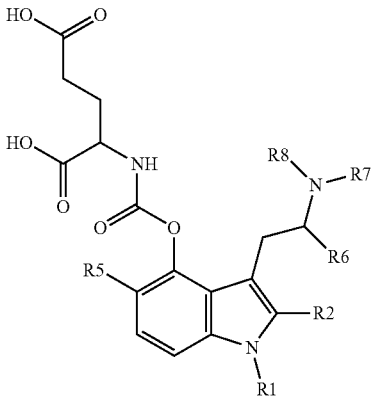
- natural and unnatural neutral or anionic amino acids, such as glycine, alanine, leucine, isoleucine, serine, theonine, glutamic acid, aspartic acid;
- linear alkyl α,ω-amino acids, such as 3-aminoproprionic acid, 4-amino-butyric acid;
- other branched amino acids and aromatic amino acids, such as 4-amino-benzoic acid.

In some embodiments, the invention may comprise zwitterionic compounds where R4 comprises more than one non-ester carboxy function, such as the citrate derivative of a 4-hydroxytryptamine (V) or a glutamic acid carbamate of a 4-hydroxytryptamine (VI):

(V)



(VI)



In some embodiments, the zwitterionic compound is preferably stable at neutral or slightly acidic pH. Acylation of the hydroxy functions of an indole can prevent oxidative reactions typical of substituted phenolic compounds and indoles specifically (Manevski 2010 Drug Metabolism and Disposition and Napolitano 1989 Tetrahedron), while also allowing for solubility. In some embodiments, the zwitterion has sufficient solubility (>30 mg/ml) in the range of neutral and pharmaceutically-acceptable pH values (3-8) to achieve the required potency/efficacy. Conventionally, non-prodrug pharmacophore tryptamines must be placed and held in acidic medium to achieve good solubility and stability. Acidic medium can preclude use as an injectable formulation and can cause irritation.

Embodiments of the zwitterion may also provide for convenient purification and isolation by recrystallization from common pharmaceutical solvents, such as water, methanol, ethanol, propanol or isopropanol or acetone, or mixtures thereof.

The diacid moiety is cleaved metabolically in vivo providing the active ingredient in doses and with kinetics sufficient to achieve the psychedelic state believed to be necessary for use in the treatment of depressive conditions, such as psychedelic-assisted psychotherapy. This is particularly advantageous in designing convenient medications that produce a psychedelic experience with a duration of less than 8 hours, preferably less than 6 hours, and more preferably less than 4 hours. In this sense, the requirement of hydrolysis is an additional step and therefore can reduce the speed of onset of psychoactive properties when compared to injection of the free drug (with no acylation of the hydroxy function). A slightly slower speed of onset may be preferred in some cases, so as to avoid a sudden onset which can cause anxiety, particularly in the psychedelic-naïve patient. Thus, in preferred embodiments, the speed of onset may be con-

trolled by the rate of metabolism which can be a function of the ester and the target enzyme required for hydrolysis.

In some embodiments, certain prodrug diacid moieties, for example a succinate, may reduce the potential for abuse by inhalation or snorting. As a zwitterion, it is not likely to be absorbed rapidly through tissue devoid of esterase activity. Furthermore, the zwitterion is likely not absorbed directly by a passive mechanism into the brain. The rate of cleavage in the gut may be slower and absorption slower versus the non-acylated version and thus delay peak rates and the "rush" feeling that may be sought by persons with the intent to abuse.

Methods of Preparation

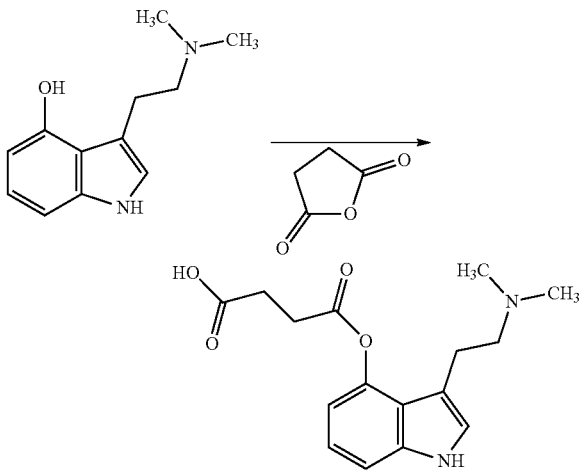
The compounds described herein can be synthesized using the methods described below, or similar methods, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods may include, but are not limited to, those described below. The reactions are performed in a solvent or solvent mixture appropriate to the reagents and materials employed and suitable for the transformations being affected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment, well within the skill of a skilled artisan, to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

Protection and de-protection in the processes below may be carried out by procedures generally known in the art (see, for example, Greene, T. W. et al, *Protecting Groups in Organic Synthesis,* 3rd Edition, Wiley (1999)). General methods of organic synthesis and functional group transformations are found in: Trost, B. M. et al, eds., *Comprehensive Organic Synthesis: Selectivity, Strategy & Efficiency in Modern Organic Chemistry,* 1' Edition, Pergamon Press, New York, N.Y. (1991); March, J., Advanced Organic Chemistry.

4- and 5-hydroxy-tryptamines can be made by adapting methods described in the art by Baumann et al. (Beilstein 2011, 7, 442) Shulgin (The Vaults of Erowid: TiHKAL: The Chemical Story, by Alexander and Ann Shulgin) and Fricke (Eur Chem J 2019, 25, 897), as well as in U.S. Pat. No. 3,075,992 and Chen (JOC 1994, 3738).

For example, succinate prodrug compounds described herein may be prepared using the synthetic scheme as outlined in Scheme 1 starting from the corresponding hydroxy-indole and the diacid anhydride. The reaction conditions such as temperature, time, choice of solvent and workup procedures are selected which may be suitable for experimental conditions recognized by one skilled in the art. Restrictions to the substituents that are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate or analogous methods must then be used.

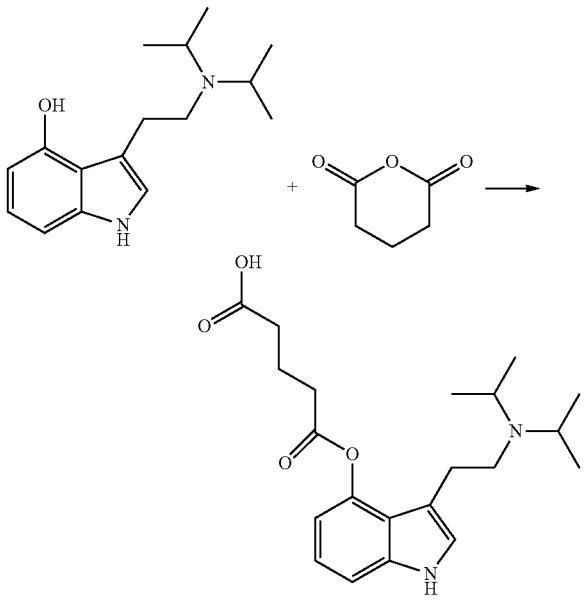
Scheme 1



Other diacid prodrugs may be prepared using other diacid anhydrides, as may be readily visualized by those skilled in the art.

A glutarate prodrug compound may be made using glutaric anhydride, using Scheme 2 below:

Scheme 2



One skilled in the art may readily select suitable conditions and solvents. The reaction with the diacid anhydride may take place in dichloromethane and triethylamine, or pyridine. In some embodiments, the solvent contains a base with pKa greater than 4 but less than 9. If pyridine is used, the product precipitates directly from the reaction mixture in pure form as the zwitterion.

The solid zwitterion may be converted to a suitable salt, for example, a hydrochloride salt, by addition of anhydrous HCl (gas) in a suitable solvent or by triturating in anhydrous ether HCl or dioxane HCl.

Synthesis of the diacid hemiester prodrugs may also be produced using a variety of other methods and techniques

well known to those skilled in the art (Rautio, Nature Rev in Drug Discovery 2018, 17, 559), for example, using anhydride or doubly-activated forms of the diacids, such as dichloride, di-N-hydroxysuccinimide (using dicyclohexylcarbodiimide (DCC) or 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC), N-hydroxysuccinimide and DMAP), di-imizadolide (using carbonyldimidizole), or other activated form of the diacid with the hydroxy form of the active heterocyclic species. When using the diactivated forms, it is preferable to use a 2-25-fold excess of the doubly activated diacid to avoid covalently binding 2 tryptamines to the diacid.

Similarly, one skilled in the art can apply these methods to 6- or 7-hydroxy isotryptamines.

Formulations and Compositions

The invention also provides pharmaceutically acceptable compositions which comprise a therapeutically effective amount of one or more of the compounds described herein, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents, and optionally, one or more additional therapeutic agents. While it is possible for a compound described herein to be administered alone, it is preferable to administer the compound as a pharmaceutical composition.

The term "pharmaceutical composition" means a composition comprising a compound of the invention in combination with at least one additional pharmaceutically acceptable carrier. A "pharmaceutically acceptable carrier" refers to media generally accepted in the art for the delivery of biologically active agents to animals, in particular, mammals, including, i.e., adjuvant, excipient or vehicle, such as diluents, osmotic complement, preserving agents, fillers, flow regulating agents, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents, polymers, solubilizing agents, stabilizers, antioxidants and dispensing agents, depending on the nature of the mode of administration and dosage forms. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient.

As used herein, "oral" administration includes swallowing for ingestion in the stomach or gut, and further includes lingual, sublingual, buccal and oropharyngeal administration. The compounds of this invention can be administered for any of the uses or methods described herein by any suitable means, for example, orally, such as tablets, capsules (each of which may include sustained release or timed release formulations), pills, powders, granules, elixirs, suspensions (including nano suspensions, micro suspensions, spray-dried dispersions), syrups, and emulsions; sublingually (e.g. as thin films, effervescent tablets or tablets that dissolve spontaneously under the tongue); parenterally, such as by subcutaneous, intravenous, intramuscular injection, or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally, including administration to the nasal membranes, such as by inhalation spray; or rectally such as in the form of suppositories.

The dosage regimen for the compounds described herein will, of course, vary depending upon known factors, such as the pharmacokinetic and pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient; and, the effect desired. The selected dosage level may also depend on the additional factors including the activity of the particular compounds and pharmaceutical compositions described herein, whether an ester, salt or amide substituent is of the compound is used, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the rate and extent of absorption, the duration of the treatment, other drugs that may be administered to the patient, compounds and/or materials used in combination with the particular compound employed and like factors well known in the medical arts.

Generally, the dosage of the prodrug for a therapy session, when used for the indicated effects, will range between about 0.001 to about 500 mg per dose, preferably between about 0.01 to about 200 mg per dose, and most preferably between about 0.1 to about 50 mg per dose, such as 10, 20, 30, 40, 50, 100 or 200 mg. Intravenously, the most preferred doses will range from about 0.01 to about 10 mg/kg/minute during a constant rate infusion.

Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in multiple divided doses, such as two, three, or four times daily. Alternatively, the doses may be provided on a weekly, biweekly, or monthly basis. In a preferred embodiment, only one or two doses are required for an antidepressant effect than may extend for 1, 2, 3 or 6 months, or more.

For tablet dosage forms, depending on dose, the drug may make up from 1 wt % to 80 wt % of the dosage form, more typically from 5 wt % to 60 wt % of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl substituted hydroxypropyl cellulose, starch, pregelatinized starch and sodium alginate. Generally, the disintegrant will comprise from 1 wt % to 25 wt %, preferably from 5 wt % to 20 wt % of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinized starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally include surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents are typically in amounts of from 0.2 wt % to 5 wt % of the tablet, and glidants typically from 0.2 wt % to 1 wt % of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally are present in amounts from 0.25 wt % to 10 wt %, preferably from 0.5 wt % to 3 wt % of the tablet.

Other conventional ingredients include anti-oxidants, colorants, flavoring agents, preservatives and taste masking agents.

Exemplary tablets contain up to about 80 wt % drug, from about 10 wt % to about 90 wt % binder, from about 0 wt %

to about 85 wt % diluent, from about 2 wt % to about 10 wt % disintegrant, and from about 0.25 wt % to about 10 wt % lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet, dry, or melt granulated, melt congealed, or extruded before tableting. The final formulation may include one or more layers and may be coated or uncoated; or encapsulated.

The formulation of tablets is discussed in detail in "Pharmaceutical Dosage Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0 8247 6918 X), the disclosure of which is incorporated herein by reference in its entirety.

A typical capsule for oral administration contains at least one of the compounds of the present invention (e.g. 25 mg), lactose (e.g. 75 mg), and magnesium stearate (e.g. 15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be used as fillers in soft or hard capsules and typically include a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including micro needle) injectors, needle free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and pH adjusting or buffering agents (preferably to a pH of from 3.0 and 7.0, preferably 4.0 to 6.0, and more preferably 4.5 to 5.5), but, for some applications, they may be more suitably formulated as a sterile non aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen free water or pre-fabricated, ready-to-mix aqueous buffer. Osmotic agents may be included to control tonicity.

The preparation of parenteral kits for reconstitution at point-of-care under sterile conditions, for example, by lyophilization, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

A typical injectable preparation is produced by aseptically placing at least one of the compounds of the present invention (e.g. 25 mg) into a vial as a sterile filtered solution, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with e.g. 2 mL of physiological saline for injection, optionally with an appropriate amount of osmotic complements and pH adjusters to achieve a slightly acidic to neutral pH (e.g. pH 4-7), to produce an injectable preparation with low irritation but retain solubility and/or stability of the prodrug.

Compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol containing polymers, in order to improve their solubility, dissolution rate, taste masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, i.e. as a carrier, diluent, or solubilizer. Most commonly used for these purposes are alpha, beta and gamma cyclodextrins, examples of which may be found in PCT Publication Nos. WO 91/11172, WO 94/02518 and WO 98/55148, the disclosures of which are incorporated herein by reference in their entireties.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art. Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above.

As used herein, a "therapeutically effective amount" refers to that amount of a compound being administered which will relieve to some extent one or more of the symptoms of the disorder being treated. In reference to the treatment of depression, a therapeutically effective amount refers to that amount which has the effect of reducing the severity of depression. Depression severity may be assessed using well-known structured assessment tools such as Structured Clinical Interview for DSM-5 (SCID-5) and the GRID-Hamilton Depression Rating Scale (GRID-HAMD). A therapeutically effective amount may be less than that required for a psychedelic state.

An effective dosage can be administered in one or more administrations. For the purposes of this invention, an effective dosage of drug, compound, or pharmaceutical composition is an amount sufficient to accomplish prophylactic or therapeutic treatment either directly or indirectly. As is understood in the clinical context, an effective dosage of drug, compound or pharmaceutical composition may or may not be achieved in conjunction with another therapy, drug, compound or pharmaceutical composition.

Therapeutic Methods and Uses

Treatment with the novel prodrugs of the present invention may substantially alleviate clinical or subclinical depression and may avoid relapse, particularly if used in combination with psychotherapy for the treatment of depression. It is known that administration of an effective dose of psilocybin produced rapid and large reductions in depressive symptoms, and many subjects achieve remission through a four-week follow up (Davis et. al.) Without restriction to a theory, it is believed that the psychedelic state is associated with the beneficial effects, however, some compounds which

are 5HT2A agonists may provide the desired therapeutic effect without the psychedelic state. One aspect of the invention comprises prodrugs of those 5HT2A agonists which do provide a beneficial therapeutic state.

In general, the present invention includes the use of a compound of the present invention herein, to treat any disease or disorder which may be alleviated by a 5HT2A agonist, or the use of a compound of the present invention herein to manufacture a medicament to treat any disease or disorder which may be alleviated by a 5HT2A agonist, or a method of treating any disease or disorder which may be alleviated by a 5HT2A agonist.

In some embodiments, the invention may comprise the use of the compounds of the present invention to treat mental disorders. In some embodiments, the invention may comprise the use of the compounds of the present invention to treat depression, and particularly drug resistant depression. Other conditions that may be treated include: anxiety disorders, including anxiety in advanced stage illness e.g. cancer as well as generalized anxiety disorder, depression including major depressive disorder, postpartum depression, cluster headaches, obsessive compulsive disorder, personality disorders including conduct disorder, drug disorders including: alcohol dependence, nicotine dependence, opioid dependence, cocaine dependence and other addictions including gambling disorder, eating disorder and body dysmorphic disorder, chronic pain, or chronic fatigue.

In some embodiments, the invention may comprise a method of treating mental disorders comprising administering to a subject in need thereof a therapeutically effective amount of a compound of the present invention. In one embodiment, there is provided a method of treating depression comprising administering to a subject in need thereof therapeutically effective amount of a compound of the present invention. The depression may be drug-resistant depression or major depressive disorder.

For example, a patient diagnosed with depression may be screened prior to treatment, and then prepared for a dosing session by a trained psychotherapist. Within a dosing session, a compound of the present invention may be administered by injection of a sterile solution at a rate of 0.01-0.3 mg/kg to the patient. The patient is preferably seated for the duration of the session while being blindfolded. For safety, a trained health care professional may monitor the patient throughout the dosing session, which may last up to 12 hours. In some cases, music may be played for the patient. When the health care professional can determine that the drug substance has cleared, the psychotherapist may assist the patient with any questions relating to the psychedelic experience, and then the patient may be discharged.

To further alleviate any anxiety that may occur relative to therapy, the physician may prefer to divide the therapeutic dose and thereby reduce the initial onset of psychoactivity before applying the full complement of the dosage to achieve the full effect.

In some embodiments, treatment with a compound of the present invention may be combined with concomitant treatment with another anti-depressant drugs, either concurrently or consecutively. In preferred embodiments, treatment with a compound of the present invention is combined with psychotherapy, which may be applied prior to or after treatment. If prior to, the session may focus the patient on the intent of treatment. If after, psychotherapy is preferably performed within 48 hours of the dosing session to help the patient integrate any feelings, emotions, visions or thoughts that may have occurred during the session, as well as to allow the psychotherapist may offer advice on how best to change thinking or behavior patterns so as to improve anti-depression outcomes. Psychotherapy may continue as needed after the dosing session, for example, up to an additional 3 months, to help the patient integrate any experiences or learnings that occurred to the patient during the dosing session.

EXAMPLES

The present invention may be described with reference to the following Examples. These Examples are provided for the purpose of illustration only. All terms, names, abbreviations or acronyms are those commonly understood by those skilled in the art. Compounds shown in their zwitterionic form may readily be visualized in their neutral form by one skilled in the art, and vice versa.

Where a compound is referred to as a glutaroyl or succinoyl, or hemiglutarate or hemisuccinate, it is understood to be same as the succinate or glutarate. For example, the 4-hemiglutarate of psilocin is the same as psilocin-4-glutarate or N,N dimethyltryptamine-4-glutarate. Similarly, the 4-hemiglutarate of 4-OH-DiPT is the same as N,N diisopropyltryptamine-4-glutarate.

Example 1. 4-Hemisuccinate of Psilocin

4-Hydroxyindoles were prepared using methods or modestly adapted from methods described in the literature, such as in Kargbo 2020 ACS Omega): Accordingly, 4-acetoxyindole was reacted with oxalyl chloride in methyl-t-butyl ether (MTBE) and the resulting intermediate was quenched with dimethylamine. The indole-oxalyl-dimethylamide was reduced with Lithium Aluminum Hydride (LAH) in tetrahydrofuran (THF) to give the 4-acetoxy-3-(N,N-dimethylaminoethyl)indole, which was deprotected using aqueous base to give 4-hydroxy-dimethyltryptamine (psilocin).

The 4-hydroxytryptamine was reacted with an excess of succinic anhydride in dichloromethane (DCM) containing triethylamine, and catalyzed by N,N-dimethylaminopyridine, to give psilocin-4-succinate. A precipitate was formed which was recovered after decantation and trituration with DCM. The solid was acidified in aqueous HCl, purified by chromatography and recovered after evaporation of solvents. The structure was confirmed by NMR. Purity was determined by HPLC.

Example 2. 4-hemisuccinate of 4-hydroxy-diisopropyltryptamine (4-OH-DiPT)

4-Acetoxyindole was reacted with oxalyl chloride in MTBE and the resulting intermediate was quenched with diisopropylamine. The resulting oxalyl-amide was reduced with Lithium Aluminum Hydride (LAH) in THF to give the 4-acetoxy-3-(N,N-diisopropylaminoethyl)indole, which was in turn deprotected with aqueous base to give 4-hydroxy-3-(N,N-diisopropylaminoethyl)indole. In a 250 mL round-bottom flask containing a stir bar was added 4-OH-DiPT (5.8 g, 22.3 mmol, 1 eq.), dissolved in dichloromethane (28 mL, 5×V) and stirred at room temperature. Then succinic anhydride (1.3 eq.) was added slowly to the stirring solution, and the resulting suspension was stirred overnight at room temperature. The precipitate formed in the reaction was recovered by decantation and trituration with DCM. The solid was acidified in aqueous HCl, purified by chromatography and recovered after evaporation of solvents. The structure was confirmed by NMR. Purity was determined by HPLC.

Example 3. 4-hemifumarate of 4-OH-DiPT

4-Benzyloxyindole is reacted with oxalyl chloride in diethylether in the presence of a Friedel-Kraft catalyst and the resulting intermediate is quenched with di-isopropylamine. The resulting oxalyl-amide is reduced with Lithium

Aluminum Hydride (LAH) in THF to give the 4-benzyloxy-3-(N,N-diisopropylaminoethyl)indole, which is in turn deprotected using a H2 and Pd/C to give 4-hydroxy-3-(N,N-diisopropylaminoethyl)indole. This substance is reacted with an excess of a diactivated fumaric acid (N-hydroxysuccinimide) in dichloromethane, followed by quenching any unreacted N-hydroxysuccinimide ester with aqueous acid, leaving 4-fumaroyl-3-(N,N-diisopropylaminoethyl)indole.

Example 4. 5-hemi succinate of 5-hydroxy-4-methyl-dimethyltryptamine

4-methyl-5-hydroxyindole (1) is reacted with benzyl chloride in the presence of K_2CO_3 in ACN to give 5-benzyloxy-4-methyl-indole, which is then reacted with oxalyl chloride in diethylether in the presence of a Friedel-Kraft catalyst and the resulting intermediate is quenched with di-methylamine. The resulting oxalyl-amide is reduced with Lithium Aluminum Hydride (LAH) in THF to give the 4-methyl-5-benzyloxy-3-(N,N-dimethylaminoethyl)indole, which is in turn deprotected using a H2 and Pd/C to give 4-methyl-5-hydroxy-3-(N,N-dimethylaminoethyl)indole. This substance is reacted with succinic anhydride in dichloromethane, catalyzed by N,N-dimethylamino-pyridine to give 4-methyl-5-succinoyl-3-(N,N-dimethylaminoethyl)indole.

Example 5. N,N dimethylisotryptamine-6-succinate

Following methods outlined in Glennon (JMedChem 1984), 6-O-Benzyl-dimethylisotryptamine is prepared by N-alkylation of 5-BzO-indole using NaH. The benzyl group is removed by catalytic hydrogenation using Pd/C/H2 to give the HO— function which is succinylated in a subsequent step using succinic anhydride, resulting in the named species.

Example 6. N,N diisopropyltryptamine-4-glutarate

In an oven-dried 50 mL round bottom flask containing 1.2 mL of anhydrous DCM was added glutaric anhydride (0.205 g, 1.8 mmol, 1.8 eq.) and the suspension was stirred under Ar. A solution of 4-OH-DiPT (0.26 g, 1 mmol, 1 eq.) in 1.5 mL anhydrous DCM was added, followed by addition of 4-dimethylaminopyridine (DMAP) (37 mg, 0.3 mmol, 0.3 eq.) and trimethylamine (0.18 mL, 1.3 eq.) and the resulting suspension was stirred overnight at r.t. under Ar.

The mixture was decanted, and the solid was triturated with anhydrous DCM (3 mL) with a few drops of anhydrous MeCN. The suspension was acidified with 1M HCl (~1.1 eq.) and concentrated to dryness. The crude product was purified by C18 reverse-phase column chromatography (40 g, A: 0.05% HCl in H_2O, B: 0.05% HCl in MeCN).

The structure was confirmed by NMR. Purity was determined by HPLC (>97%). The solid was resuspended in 1M HCl-dioxane to form the HCl salt which was filtered, washed with ether and dried. Yield (>95%, purity >95%; DSC endotherm 174C). The solid could be dissolved in water up to 50 mg/ml and lyophilized to form a white "cake".

Example 7. Hemiester of 3,3-dimethylglutaric acid and 4-hydroxydiisopropyltryptamine

4-Hydroxy-3-(N,N-diisopropylaminoethyl)indole was reacted with 3,3-dimethyl glutaric anhydride in pyridine to give 4-succinoyl-3-(N,N-diisopropylaminoethyl)indole with stoichiometries and parameters mentioned in example 6. A precipitate formed in the reaction was recovered by decantation and trituration in THF. The solid was washed with DCM and dried. The structure was confirmed by NMR.

Example 8. Psilocin-4-glutarate

4-Hydroxydimethyltryptamine (psilocin) was reacted with an excess of glutaric anhydride in dichloromethane (DCM) containing triethylamine to give psilocin-4-glutarate. In another example, the reaction occurred in pyridine. In either case, a precipitate was formed which was recovered after decantation and trituration with THF. The solid was washed with DCM and then dried. The structure was confirmed by NMR.

The reaction product was suspended in 1M HCl-ether to yield the corresponding HCl salt form of the product which was recovered by filtration in high yield and purity.

Example 9. HCl salt of N,N diisopropyltryptamine-4-glutarate

In a 3-neck 1 L round bottom flask under argon was added 4-OH-DiPT (31.8 g, 0.122 mol, 1 eq.), dissolved in 160 mL of anhydrous pyridine (160 mL). After stirring for 15 mins, glutaric anhydride (18.1 g, 0.158 mol, 1.3 eq.) was added in portions. The resulting suspension was stirred at r.t. overnight.

Anhydrous DCM (160 mL) was added to the suspension and it was cooled to 0° C. with for 2 h. The solid was filtered and washed with 60 mL of cold anhydrous DCM and dried overnight.

The dried solid was triturated with 160 mL of anhydrous DCM, followed by 160 mL of anhydrous THF, and then 160 mL of anhydrous DCM at 0° C. After drying, 33.0 g was obtained with 72% yield and 98.1% purity by HPLC. The structure of the zwitterion was confirmed by 1H-NMR (DMSO-d6) and MS $[M+H]^+$=375.2.

In a 100 mL round bottom flask was charged 18 mL of anhydrous diethyl ether HCl solution (4M in dioxane, 2.4 mL, 9.6 mmol, 1.2 eq.) was added slowly and stirred at r.t. for 10 mins. The zwitterion from above (3.0 g, 8.0 mmol) was added in portions and the resulting suspension was stirred for 2 h. The solid was filtered off and washed with 6 mL of Et_2O. The solid was dried yielding 3.16 g of the corresponding hemiester tryptamine HCl salt (96% yield, 99.0% purity by HPLC, $[M+H]^+$=375.1).

Example 10. Hemiglutarate of psilocin

Psilocin is reacted with 1.2 equivalents glutaric anhydride in warm THF to give psilocin-4-glutarate which precipitates from the reaction mixture according to methods above. The precipitate is recovered by filtration, is washed with cold 1:1 DCM/THF and dried.

Example 11. 4-Hemimalonate of 4-OH-DiPT

4-OH-DiPT was dissolved in pyridine and coupled with an excess of malonic acid and 1.2 equivalents of DCC at room temperature for 18 h. The reaction mixture was passed through a flash column (5 parts diatomaceous earth), and the first fractions containing the prodrug compound were isolated by precipitation and washing. Yield approx. 50%. Purity >95% by HPLC.

Example 12. Comparative Rates of Prodrug Hydrolysis in Serum

Pooled mixed gender human plasma (2 ml), mouse plasma, rat plasma and dog plasma were equilibrated at 37° C. The compound of example 9 was added so as to achieve

a concentration of 1.0 ug/mL. Aliquots (50 uL) of the mixture were withdrawn at timed intervals (0, 0.004, 0.5, 1, 2 and 4 hours) and quenched with 200 uL of methanol/acetonitrile (1:1). The samples were vortexed and stored at −80° C. until analysis. Assays were done in triplicate. Control samples were done in phosphate buffered saline (PBS, pH 7.4) and simulated gastric fluid (SGF, pH 2). Analysis of samples as performed by HPLC-MS to determine the amounts of prodrug and drug in each sample tested. Table 1 provides the mean concentrations of prodrug remaining at different time points of the experiment. The experiment demonstrates the rapid enzymatic cleavage of the prodrug in plasma versus slow non-enzymatic hydrolysis in relevant biological media.

TABLE 1

Percentage of remaining prodrug, N,N diisopropyltryptamine-4-glutarate

Time (h)	Mouse	Rat	Dog	Human	SGF (pH2)	PBS (pH7)
0	100	100	100	100	100	100
0.004	0	0	100	100	100	—
0.5	0	0	87	3.0	100	—
1	0	0	79	0.23	100	—
2	0	0	64	0	—	—
4	0	0	39	0	101	93

Example 13. Pharmacokinetics in Rats

The compound from example 9 was administered to rats by injection (intravenous and subcutaneous) with a sterile solution (2 mg/ml) at a rate of 1.4-2 mg/kg. Blood samples were taken at 15, 30, 45, 60, 120, 240 min and 360 min and analyzed by LCMS for drug and prodrug. PK profile for the prodrug and active species were obtained and relative bioavailability was determined for each of the routes of administration.

PK-PD type curves were generated to demonstrate the activity of the drug (FIGS. **1** and **2**). In rodent, prodrug was not observed, as it was rapidly converted to the active form. Relevant PK parameters for i.v. and s.c administrations 4-HO-DiPT were determined and are shown in Table 2:

TABLE 2

PK parameters (% coefficient of variation in parentheses) for 4-HO-DiPT after subcutaneous administration of N,N diisopropyltryptamine-4-glutarate (2 mg/kg).

Route admin	Cmax (ng/ml)	Tmax (h)	t½ (h)	AUC h*ng/ml	Bioavailability (%)
i.v.	305 (9.8)	n/a	0.601 (3.3)	146 (3.1)	97 (3.1)*
s.c.	150 (30)	1.0 (0)	0.67 (0.1)	203 (21)	n/a

Based on PK parameters from the i v. administration of 4-HO-DIPT

In some cases, Head Twitch Response (HTR) or Wet Dog Shakes (WDS) were recorded by visual observation and counting of the relevant muscle twitches. In general, the intensity of the HTR was proportional to the plasma concentration of 4-HO-DIPT with the highest intensity of head twitch occurring at the Tmax of the PK profile.

FIG. **1** show plasma concentration of 4-HO-DiPT (ng/ml) and versus time after subcutaneous administration of N,N diisopropyltryptamine-4-glutarate at a rate of 2 mg/kg.

Pharmacokinetics of 1.34 mg/ml 4-HO-DiPT HCl administered by intravenous or subcutaneous injection were performed in parallel under identical conditions as above. FIG. **2** shows show plasma concentration of 4-HO-DiPT (ng/ml) versus time for the different administrations. Immediately obvious is the increased variability with the active species when administered s.c. and intravenous administrations. PK parameters are shown in Table 3.

TABLE 3

PK parameters (% coefficient variation in parentheses) for 4-HO-DiPT after subcutaneous administration of N,N diisopropyltryptamine-4-glutarate (2 mg/kg).

Route admin	Cmax, ng/ml	Tmax, h	t½, h	AUC, h*ng/ml	Bioavailability, %
i.v.	458 (12)	n/a	0.74 (22)	152 (22)	100%
s.c.	103 (21)	0.61 (77)	0.67 (15)	134 (48)	89%

Example 17. Pharmacokinetics in Human Volunteers

The compound from example 6 (N,N diisopropyltryptamine-4-glutarate) is administered to human volunteers by subcutaneous injection of a sterile solution (1 mg/ml) at a dosage of 0.1-0.6 mg/kg. Blood samples are taken at 5, 15, 30, 45, 60, 120, 240 and 480 min and 24 h. Samples are analyzed by LCMS for drug and prodrug. Subjective effects are measured using standardized questionnaires. The PK analysis shows a maximal plasma concentration (CMax) at approx. 45 min after the injection. Subjective effects show an intensity of psychoactivity that correlates with blood levels.

The compound from example 2 (4-hemisuccinate of 4-OH-DiPT) is administered to human volunteers by oral ingestion of a tablet containing 50 mg of the prodrug. Blood samples are taken at 5, 15, 30, 45, 60, 120, 240 and 480 min and 24 h. Samples are analyzed by LCMS for drug and prodrug. Subjective effects are measured using standardized questionnaires. The PK analysis shows a CMax at approx. 90 min for the injection. Subjective effects show an intensity of psychoactivity that correlates with blood levels.

Example 18. Use in Treatment

The compound of example 6 (N,N diisopropyltryptamine-4-glutarate) is administered by i.m. or s.c. injection (ca. 25

mg; 0.4-0.5 mg/kg) to a human patient suffering depression, or by oral administration (ca. 50-200 mg; 0.8-3.2 mg/kg) with tablets. In another example of use, the compound of example 6 (4-hemiglutarate of 4-OH-DiPT) is similarly administered. Prior to the dosing session, the patient is qualified for the experience by measurement of depression scores, screened for exclusions (e.g. history of psychoses, unfavorable heart condition, pregnancy) and finally, the patient is encouraged to formulate an intent for the dosing session. Dosing is performed in a quiet clinic setting with the patient resting comfortably in an inclined, but unrestrained, position to avoid falls. The patients' eyes are covered, and music is applied. The drug is administered. After 4 h, the patient reports no longer feeling the effects of the drug and is asked to sit up while under supervision. Feeling normal, the patient is allowed to stand (supervised) and feeling in control, is allowed to move around. One hour later, the patient is discharged. Later by 24 h, the patient returns to the clinic to meet with a psychotherapist to recount the session. The patient records a depression score via questionnaire and is again discharged. At regular intervals the patient is consulted for recurrence of depressive symptoms.

Example 19. Injectable Formulation Kit

A vial is prepared with 25 mg of compound in Example 6 as a hydrochloride salt (sterilized powder or lyophilizate). In a separate vial is placed 1 ml of a sterile filtered solution containing 70 mM Na_2HPO_4. The final pH of the solution is 4.0-5.0. These 2 components constitute a kit for reconstitution of a drug product for subcutaneous injection at point of care.

REFERENCES

All publications, patents, patent applications, etc. mentioned in the above specification are incorporated herein by reference in their entireties, including the following:

1. American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th Ed.). https://doi.org/10.1176/appi.books.9780890425596
2. Anderson, W. K., & Mulumba, B. (1984). Synthesis of Methyl 2,3-bis(hydroxymethyl)-5-phenyl-7-oxabicyclo [2.2.1]hepta-2,5-diene-6-carboxylatebis(N-methylcarbamate) derivatives as potential antitumor agents. *Journal of pharmaceutical sciences,* 73(8), 1182-1183. https://doi.org/10.1002/jps.2600730844
3. Anderson, B. D., Conradi, R. A., & Lambert, W. J. (1984). Carboxyl group catalysis of acyl transfer reactions in corticosteroid 17- and 21-monoesters. *Journal of pharmaceutical sciences,* 73(5), 604-611. https://doi.org/10.1002/jps.2600730507
4. Bahar, F. G., Ohura, K., Ogihara, T., & Imai, T. (2012). Species Difference of Esterase Expression and Hydrolase Activity in Plasma. *Journal of Pharmaceutical Sciences,* 101(10), 3979-3988. https://doi.org/10.1002/jps.23258
5. Baumann, M., Baxendale, I. R., Ley, S. V., & Nikbin, N. (2011). An overview of the key routes to the best selling 5-membered ring heterocyclic pharmaceuticals. *Beilstein Journal of Organic Chemistry,* 7, 442-495. https://doi.org/10.3762/bjoc.7.57
6. Carhart-Harris, R. L., Roseman, L., Haijen, E., Erritzoe, D., Watts, R., Branchi, I., & Kaelen, M. (2018). Psychedelics and the essential importance of context. *Journal of Psychopharmacology,* 32(7), 725-731. https://doi.org/10.1177/0269881118754710
7. Chen, C.-yi, Senanayake, C. H., Bill, T. J., Larsen, R. D., Verhoeven, T. R., & Reider, P. J. (1994). Improved Fischer Indole Reaction for the Preparation of N,N-Dimethyltryptamines: Synthesis of L-695,894, a Potent 5-HT1D Receptor Agonist. *The Journal of Organic Chemistry,* 59(13), 3738-3741. https://doi.org/10.1021/jo00092a046
8. Davis A K, Barrett F S, May D G, et al. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2021; 78(5):481-489. doi:10.1001/jamapsychiatry.2020.3285
9. Ebenezer, I. S. (2015). Affective Disorders: Depression in Neuropsychopharmacology and Therapeutics, Chapter 6 *Neuropsychopharmacology and therapeutics*. John Wiley & Sons Inc.
10. First, M. B., W., W. J. B., Karg, R. S., & Spitzer, R. L. (2016). *Scid-5-Cv: structured clinical interview for Dsm-5 disorders, clinician version*. American Psychiatric Association Publishing.
11. Fricke, J., Lenz, C., Wick, J., Blei, F., & Hoffmeister, D. (2018). Production Options for Psilocybin: Making of the Magic. *Chemistry—A European Journal,* 25(4), 897-903. https://doi.org/10.1002/chem.201802758
12. Glennon, R. A., Jacyno, J. M., Young, R., Mckenney, J. D., & Nelson, D. (1984). Synthesis and Evaluation of a Novel Series of N,N-Dimethylisotryptamines. *Chemischer Informationsdienst,* 15(24). https://doi.org/10.1002/chin.198424187
13. Hofmann A, Troxler F. Esters of indoles. U.S. Pat. No. 3,075,992 and Process for the production of new esters of the indole series Swiss Patent No. 386422.
14. International Society for CNS Drug Development. (2003). GRID-HAMD-17 *Structured Interview Guide*. ISCDD.
15. Kargbo, R. B., Sherwood, A., Walker, A., Cozzi, N. V., Dagger, R. E., Sable, J., O'Hern, K., Kaylo, K., Patterson, T., Tarpley, G., & Meisenheimer, P. (2020). Direct Phosphorylation of Psilocin Enables Optimized cGMP Kilogram-Scale Manufacture of Psilocybin. ACS Omega, 5(27), 16959-16966. https://doi.org/10.1021/acsomega.0c02387
16. Lieberman, H. A., & Lachman, L. (1980). *Pharmaceutical dosage forms—tablets*, vol. 1. Marcel Dekker.
17. Luethi, D., & Liechti, M. E. (2018). Monoamine Transporter and Receptor Interaction Profiles in Vitro Predict Reported Human Doses of Novel Psychoactive Stimulants and Psychedelics. *International Journal of Neuropsychopharmacology,* 21(10), 926-931. https://doi.org/10.1093/ij np/pyy047
18. Manevski, N., Kurkela, M., Hoglund, C., Mauriala, T., Court, M. H., Yli-Kauhaluoma, J., & Finel, M. (2010). Glucuronidation of psilocin and 4-hydroxyindole by the human UDP-glucuronosyltransferases. *Drug metabolism and disposition: the biological fate of chemicals,* 38(3), 386-395. https://doi.org/10.1124/dmd.109.031138
19. Napolitano, A., d'Ischia, M., Prota, G., Schultz, T., & Wolfram, L. (1989). Oxidation of 4,6- and 7-hydroxyindoles. *Tetrahedron,* 45, 6749-6760.
20. Rautio, J., Meanwell, N. A., Di, L., & Hageman, M. J. (2018). The expanding role of prodrugs in contemporary drug design and development. Nature reviews. *Drug discovery,* 17(8), 559-587. https://doi.org/10.1038/nrd.2018.46
21. Shulgin, A. T., & Shulgin, A. (2017). *Tihkal: the continuation*. Transform Press.

22. Silverman, R. B., & Holladay, M. W. (2014). Prodrugs and Drug Delivery Systems. *The organic chemistry of drug design and drug action*. Elsevier Academic Press.

23. Watts, R., & Luoma, J. B. (2020). The use of the psychological flexibility model to support psychedelic assisted therapy. *Journal of Contextual Behavioral Science,* 15, 92-102.

24. Patent Nos. GB942548, GB912714 and U.S. Pat. No. 9,630,941

Definitions and Interpretation

The description of the present invention has been presented for purposes of illustration and description, but it is not intended to be exhaustive or limited to the invention in the form disclosed. Many modifications and variations will be apparent to those of ordinary skill in the art without departing from the scope and spirit of the invention. Embodiments were chosen and described in order to best explain the principles of the invention and the practical application, and to enable others of ordinary skill in the art to understand the invention for various embodiments with various modifications as are suited to the particular use contemplated. To the extent that the following description is of a specific embodiment or a particular use of the invention, it is intended to be illustrative only, and not limiting of the claimed invention.

The corresponding structures, materials, acts, and equivalents of all means or steps plus function elements in the claims appended to this specification are intended to include any structure, material, or act for performing the function in combination with other claimed elements as specifically claimed.

References in the specification to "one embodiment", "an embodiment", etc., indicate that the embodiment described may include a particular aspect, feature, structure, or characteristic, but not every embodiment necessarily includes that aspect, feature, structure, or characteristic. Moreover, such phrases may, but do not necessarily, refer to the same embodiment referred to in other portions of the specification. Further, when a particular aspect, feature, structure, or characteristic is described in connection with an embodiment, it is within the knowledge of one skilled in the art to combine, affect or connect such aspect, feature, structure, or characteristic with other embodiments, whether or not such connection or combination is explicitly described. In other words, any element or feature may be combined with any other element or feature in different embodiments, unless there is an obvious or inherent incompatibility between the two, or it is specifically excluded.

It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for the use of exclusive terminology, such as "solely," "only," and the like, in connection with the recitation of claim elements or use of a "negative" limitation. The terms "preferably," "preferred," "prefer," "optionally," "may," and similar terms are used to indicate that an element, item, condition or step being referred to is an optional (not required) feature of the invention.

The singular forms "a," "an," and "the" include the plural reference unless the context clearly dictates otherwise. The term "and/or" means any one of the items, any combination of the items, or all of the items with which this term is associated.

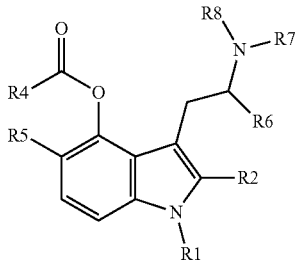
As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges recited herein also encompass any and all possible sub-ranges and combinations of sub-ranges thereof, as well as the individual values making up the range, particularly integer values. A recited range (e.g., weight percents or carbon groups) includes each specific value, integer, decimal, or identity within the range. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, or tenths. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, etc.

As will also be understood by one skilled in the art, all ranges described herein, and all language such as "between", "up to", "at least", "greater than", "less than", "more than", "or more", and the like, include the number(s) recited and such terms refer to ranges that can be subsequently broken down into sub-ranges as discussed above.

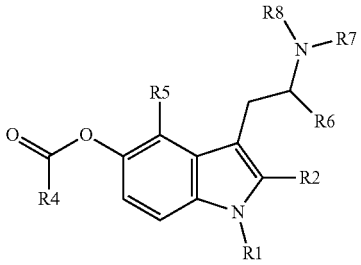
What is claimed is:

1. A compound of Formula (I) (II), (III) or (IV) or a pharmaceutically acceptable salt or zwitterion thereof:

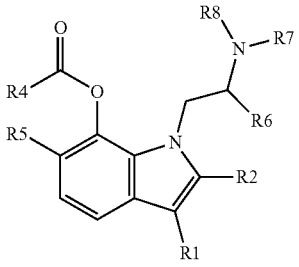
(I)



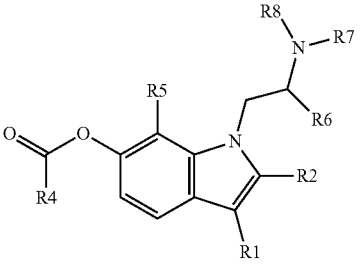
(II)



(III)



(IV)



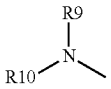
wherein:

(1) R1, R2, and R6 are each independently selected from hydrogen, linear or branched alkyl, or arylalkyl;

(2) R4 is

a. —X—CO2H, where X is a linear, cyclic or branched, saturated or unsaturated carbon chain, optionally substituted with —OH or —CO2H; or an aromatic ring, optionally substituted with alkyl or CO2H; or

b.



wherein R9 is X—CO2H, where X is as defined in (2)(a) above and R10 is linear or branched alkyl or arylalkyl, optionally substituted by —OH or —CO2H;

(3) R5 is hydrogen, linear or branched alkyl, arylalkyl, or O—R5', where R5' is hydrogen, linear or branched alkyl; and

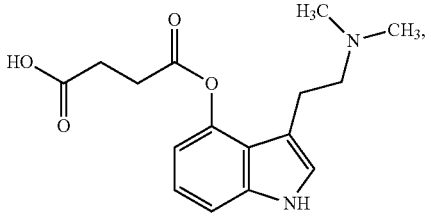
(4) R7 and R8:

c. are each independently selected from hydrogen, linear or branched alkyl, or arylalkyl, with the proviso that each of R7 and R8 is not hydrogen, or

d. together form a non-aromatic N-containing heterocycle, optionally substituted with alkyl.

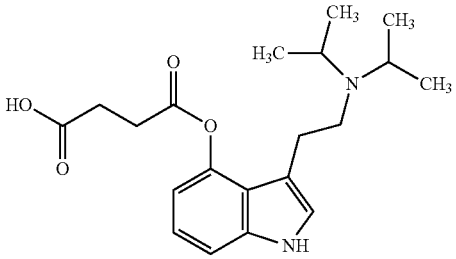
2. The compound of claim **1**, selected from the group consisting of:

(1)



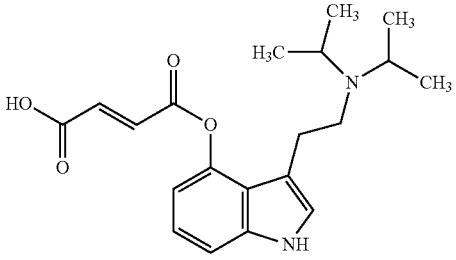
psilocin-4-succinate

(2)



N,N diisopropyltryptamine-4-succinate

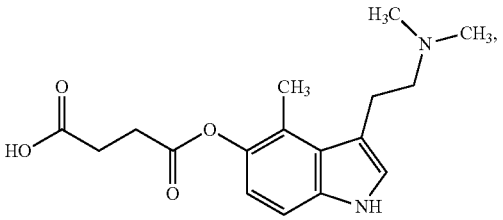
(3)



N,N diisopropyltryptamine-4-Fumarate

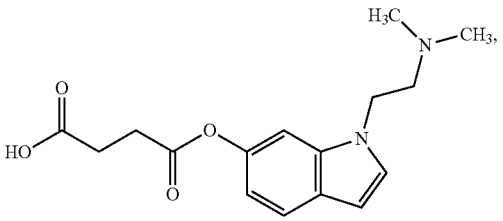
-continued

(4)



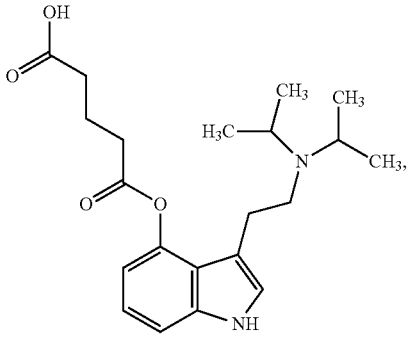
Psilocin-4-Methyl-5-succinate

(5)



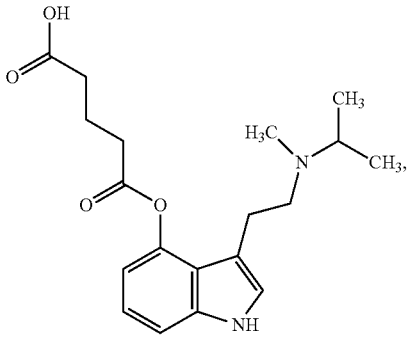
Iso-N,N dimethyltryptamine-6-succinate

(6)



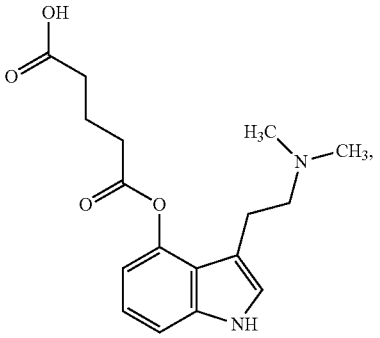
N,N diisopropyltryptamine-4-glutarate

(7)



N-methyl N-isopropyltryptamine-4-glutarate

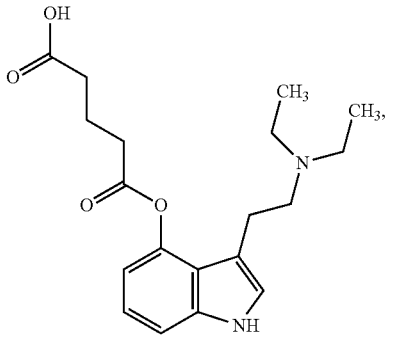
(8)



Psilocin-4-glutarate

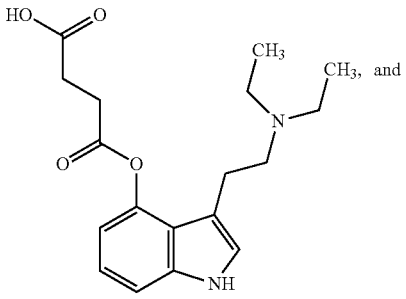
-continued

(9)



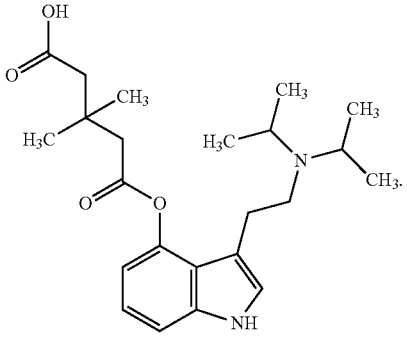
N,N diethyltryptamine-4-glutarate

(10)



N,N diethyltryptamine-4-succinate

(11)



N,N diisopropyltryptamine-4-(3,3-dimethylglutarate)

3. The compound of claim 1 wherein:

(1) R1, R2, and R6 are each independently selected from H or linear C_{1-5} alkyl;

(2) R4 is —X—CO2H, where X is a linear or branched C_{1-5} carbon chain, optionally substituted with OH or CO2H;

(3) R5 is hydrogen, linear or branched C_{1-5} alkyl, arylalkyl, or O-R5', where R5' is hydrogen, linear or branched C_{1-5} alkyl; and/or

(4) R7 and R8 are each independently selected from H or linear or branched C_{1-5} alkyl, with the proviso that each of R7 and R8 is not hydrogen.

4. The compound of claim 3 wherein R7 and R8 are the same or different, and are linear or branched C_{1-4} alkyl.

5. The compound of claim 4 wherein R7 and R8 are each methyl or isopropyl.

6. The compound of claim 3 wherein X is a linear C1-C3 chain, optionally substituted with OH or CO2H.

7. The compound of claim 5 wherein X is a linear C3 chain.

8. The compound of claim 7 wherein R7 and R8 are both methyl, or R7 and R8 are both isopropyl, or one of R7 and R8 is methyl and the other is isopropyl.

9. A composition comprising a compound of claim 1, and a pharmaceutically acceptable excipient.

10. The composition of claim 9 comprising an oral dosage formulation or an injectable formulation.

11. The composition of claim 10 which is a solution for injection.

12. The composition of claim 11 wherein the solution has a pH of between about 3.0 and 7.0, preferably 4.0 to 6.0, and more preferably 4.5 to 5.5.

13. A method of treating a mental disorder, comprising the step of administering an effective amount of a compound of claim 1.

14. The method of claim 13 wherein the mental disorder is depression.

15. A method of making a compound of formula (I), (II), (III) or (IV) in claim 1 comprising reacting a tryptamine with a cyclic anhydride in a suitable anhydrous solvent, wherein the tryptamine is hydroxytryptamine or hydroxyisotryptamine.

16. The method of claim 15, wherein the solvent contains a base with pKa greater than 4 and less than about 9, and the resulting compound is isolated as a zwitterion.

17. The method of claim 16 wherein the solvent is pyridine.

18. The method of claim 17 wherein the compound is a compound of claim 2.

19. The method of claim 15 wherein the tryptamine is 4-OH diisopropyltryptamine or psilocin and the cyclic anhydride is succinic anhydride or glutaric anhydride.

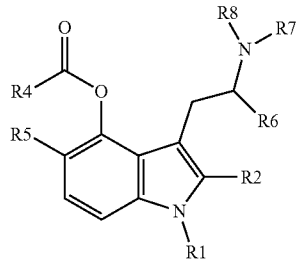
20. N,N diisopropyltryptamine-4-glutarate or a pharmaceutically acceptable salt or zwitterion thereof.

21. A method of treating a mental disorder, comprising the step of administering an effective amount of a compound of claim 20.

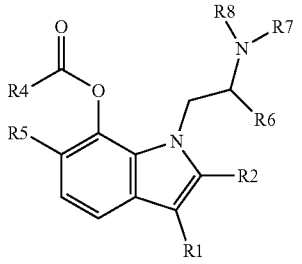
22. The method of claim 21 wherein the mental disorder is depression.

23. A compound of Formula (I) or (III) or a pharmaceutically acceptable salt or zwitterion thereof:

(I)



(III)



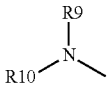
wherein:

(1) R1, R2, and R6 are each independently selected from hydrogen, linear or branched alkyl, or arylalkyl;

(2) R4 is

a. (—X—CO2H, where X is a linear, cyclic or branched, saturated or unsaturated carbon chain, optionally substituted with —OH or —CO2H; or an aromatic ring, optionally substituted with alkyl or CO2H; or

b.



wherein R9 is X**13** CO2H, where X is as defined in (2)(a) above and R10 is linear or branched alkyl or arylalkyl, optionally substituted by —OH or —CO2H;

(3) R5 is hydrogen, linear or branched alkyl, arylalkyl, or O—R5', where R5'- is hydrogen, linear or branched alkyl; and

(4) R7 and R8:

c. are each independently selected from hydrogen, linear or branched alkyl, or arylalkyl, or

d. together form a non-aromatic N-containing heterocycle, optionally substituted with alkyl.

* * * * *

Exhibit B

US011591353B2

(12) **United States Patent**
Slassi et al.

(10) **Patent No.: US 11,591,353 B2**
(45) **Date of Patent: *Feb. 28, 2023**

(54) **PSILOCIN DERIVATIVES AS SEROTONERGIC PSYCHEDELIC AGENTS FOR THE TREATMENT OF CNS DISORDERS**

(71) Applicant: **Mindset Pharma Inc.**, Toronto (CA)

(72) Inventors: **Abdelmalik Slassi**, Mississauga (CA); **Joseph Araujo**, Grimsby (CA)

(73) Assignee: **Mindset Pharma Inc.**, Toronto (CA)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **17/833,341**

(22) Filed: **Jun. 6, 2022**

(65) **Prior Publication Data**

US 2022/0324889 A1 Oct. 13, 2022

Related U.S. Application Data

(63) Continuation of application No. 17/387,883, filed on Jul. 28, 2021, which is a continuation of application No. PCT/CA2021/050125, filed on Feb. 4, 2021.

(60) Provisional application No. 62/969,934, filed on Feb. 4, 2020.

(51) **Int. Cl.**

C07D 209/12	(2006.01)
C07D 403/06	(2006.01)
C07F 9/572	(2006.01)
C07D 209/16	(2006.01)
C07D 401/14	(2006.01)

(52) **U.S. Cl.**

CPC ***C07F 9/5728*** (2013.01); ***C07D 209/16*** (2013.01); ***C07D 401/14*** (2013.01); ***C07D 403/06*** (2013.01); *C07B 2200/05* (2013.01)

(58) **Field of Classification Search**

CPC C07D 209/12; C07D 403/06

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,075,992	A	1/1963	Hofmann et al.
3,078,214	A	2/1963	Hofmann et al.
3,202,675	A	8/1965	Albertson
7,429,575	B2	9/2008	Yu et al.
7,572,776	B2	8/2009	Yu et al.
7,776,844	B2	8/2010	Yu et al.
11,000,534	B1	5/2021	Sippy
11,242,318	B2	2/2022	Nivorozhkin et al.
11,292,765	B2	4/2022	Bryson
11,324,762	B2	5/2022	Sippy
2018/0021326	A1	1/2018	Stamets
2021/0363104	A1	11/2021	Nivorozhkin et al.
2021/0403425	A1	12/2021	Bryson
2022/0110955	A1	4/2022	Sippy
2022/0110956	A1	4/2022	Sippy
2022/0119346	A1	4/2022	Nivorozhkin et al.
2022/0177427	A1	6/2022	Bryson

FOREIGN PATENT DOCUMENTS

BE	615495		9/1962
CA	2934061	A1	6/2015
CA	3078765	A1	4/2019
CH	386422	A	1/1965
CZ	307719	B6	7/2017
GB	942548	A	11/1963
GB	990092	A	4/1965
GB	981192	A	10/1965
WO	2006047032	A2	5/2006
WO	2009007421	A1	1/2009
WO	2010012396	A1	2/2010
WO	2010012397	A1	2/2010
WO	2011019738	A1	2/2011
WO	2016161138	A1	10/2016
WO	2016205304	A1	12/2016
WO	2019073379	A1	4/2019
WO	2019081764	A1	5/2019
WO	2020041329	A1	2/2020
WO	2020157569	A1	8/2020
WO	2020181194	A1	9/2020
WO	2021089873	A1	5/2021

(Continued)

OTHER PUBLICATIONS

International Search Report and Written Opinion of WO2021155470 dated Apr. 8, 2021.

(Continued)

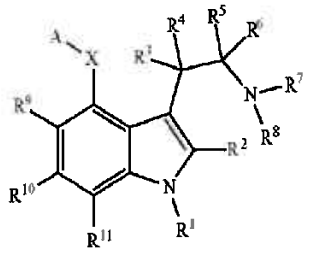
Primary Examiner — Brian E McDowell

(74) *Attorney, Agent, or Firm* — Bereskin & Parr LLP/S.E.N.C.R.L., s.r.l.; Patricia Folkins

(57) **ABSTRACT**

The present application relates to psilocin derivatives of Formula (I), to processes for their preparation, to compositions comprising them and to their use in activation of a serotonin receptor in a cell, as well as to treating diseases, disorders or conditions by activation of a serotonin receptor in a cell.

(I)



15 Claims, 2 Drawing Sheets

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

WO	2020245133	A2	6/2021
WO	2021108911	A1	6/2021
WO	2021116503	A2	6/2021
WO	2021158888	A1	8/2021
WO	2021234608	A1	11/2021
WO	20210226092	A1	11/2021
WO	2022000091	A1	1/2022
WO	2022038170	A1	2/2022
WO	2022038171	A1	2/2022
WO	2022076642	A1	4/2022
WO	2022120181	A1	6/2022

OTHER PUBLICATIONS

Cerletti, A et al, "Pharmacologic studies on the structure-activity relationship of hydroxyindole alkylamines". Advances in Pharmacology, 1968, vol. 6, pp. 233-246.

Bartolucci, S et al, "Observations concerning the synthesis of tryptamine homologues and branched tryptamine derivatives via the borrowing hydrogen process: synthesis of psilocin, bufotenin, and serotonin", Tetrahedron, 2016, vol. 72, pp. 2233-2238.

Grandberg, I I et al, "Indoles. I. A new Method for the Synthesis of 2-Substituted Tryptamines". Chemistry of Heterocyclic Compounds, 1971, vol. 4, pp. 632-633.

Palangsuntikul, R et al, "Holographic quantitative structure-activity relationships of tryptamine derivatives at NMDA, 5HT1A and 5HT2A receptors". Molecules, 2013, vol. 18, pp. 8799-8811.

International Search Report and Written Opinion of WO2021155468 dated Apr. 27, 2021.

Sard et al.,"SAR of philocybin analogs:Discovery of a selective 5-HTC2 agonist", Bioorganic & Medicinal Chemistry letters 15, 2005, pp. 4555-4559.

F. Hasler et al. "Determination of psilocin and 4-hydroxyindole 3 acetic acid in plasma by HPLC-ECD and pharmacokinetic profiles of oral and intravenous psilocybin in man", Pharmaceutica Acta Helvetiae, 1997 vol. 72, pp. 175-184.

Kristen C. Buteau "Deuterated Drugs: Unexpectedly Nonobvious?", 10 J. High Tech. Law 22. 2009, pp. 22-74.

CAS RN 1794789-72-2, Dec. 18, 2017 https://pubchem.ncbi.nlm.nih.gov/substance/348845401#section=2D-Structure.

CAS RN 1794759-76-4, Mar. 27, 2018 https://pubchem.ncbi.nlm.nih.gov/substance/355123594.

CAS-RN 1435934-64-7 https://www.cerilliant.com/shopOnline/Item_Details.aspx?itemno=4973ed15-d59e-4a94-8cd4-ed45a8b6f249&item=P-099, dated June 7, 2013.

CAS RN 1397192-09-4, dated Sep. 27, 2012.

CAS RN 1286546-49-3, dated Apr. 27, 2011.

CAS RN 1246819-43-1, dated Oct. 22, 2010.

CAS RN 1246817-39-9, Mar. 27, 2018 https://pubchem.ncbi.nlm.nih.gov/substance/355191611.

CAS RN 1246816-52-3, Mar. 27, 2018 https://pubchem.ncbi.nlm.nih.gov/substance/355191609.

CAS RN 1216523-27-1, Mar. 27, 2018 https://pubchem.ncbi.nlm.nih.gov/substance/355123592.

Klein et al.,"Investigation of the Structure—Activity Relationships of Psilocybin Analogues", ACS Pharmacology & Translational Science 4(2) 533-542, 2020.

Sherwood et al., "Synthesis and Biological Evaulation of Tryptamines Found in Hallucinogenic Mushrooms: Norbaeocystin, Baeocystin, Norpsilocin, and Aeruginascin", Journal of Natural Products, 83(2), 461-467, 2020.

Raisanen, Martti, et al., "Deuterium Labelling of Tyrptamine, Serotonin and their N-Methylated Metabolites Using Solvent Exchange Reactions", Acta Chemica Scandinavica B 33, 1979, pp. 11-14.

Registry No. 1215365-11-9; entered STN Apr. 1, 2010.

Registry No. 1331669-80-7; entered STN Sep. 12, 2011.

Registry No. 1331669-79-4; entered STN Sep. 12, 2011.

Chadeayne, Andrew R. et al., "Active Metabolite of Aeruginascin (4-Hydroxy-N,N,N-trimethyltryptamine): Synthesis, Structure, and Serotonergic Binding Affinity", ACS Omega (2020), 5(27), pp. 16940-16943.

Yoon, Kyung Sik et al., "Cardiotoxic effects of [3-[2-(diethylamino)ethyl]-1H-indol-4-yl] acetate and 3-[2-[ethyl(methyl)amino]ethyl]-1H-indol-4-ol", Toxicology Letters (2020), 319, pp. 40-48.

Lehmann, Sabrina et al., "Determination of 74 new psychoactive substances in serum using automated in-line solid-phase extraction-liquid chromatography-tandem mass spectrometry", Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences (2017), 1064, pp. 124-138, (Abstract).

Stephanson, N. N. et al., "Use of LC-HRMS in full scan-XIC mode for multi-analyte urine drug testing—a step towards a 'black-box' solution?", Journal of Mass Spectrometry (2017), 52(8), pp. 497-506, (Abstract).

Wille, S. M. R. et al., "Prevalence of new psychoactive substances and prescription drugs in the Belgian driving under the influence of drugs population", Drug Testing and Analysis (2018), 10(3), 539-547, (Abstract).

Andres-Costa et al., "Analysis of psychoactive substances in water by information dependent acquisition on a hybrid quadrupole time-of-flight mass spectrometer", Journal of Chromatography A (2016), 1461, pp. 98-106, (Abstract).

Adamowicz, Piotr et al., "Simple and rapid screening procedure for 143 new psychoactive substances by liquid chromatography-tandem mass spectrometry", Drug Testing and Analysis (2016), 8(7), pp. 652-667.

Armenta, Sergio et al., "Detection and characterization of emerging psychoactive substances by ion mobility spectrometry", Drug Testing and Analysis (2015), 7(4), pp. 280-289.

Meyer, Markus R. et al., "A qualitative/quantitative approach for the detection of 37 tryptamine-derived designer drugs, 5 β-carbolines, ibogaine, and yohimbine in human urine and plasma using standard urine screening and multi-analyte approaches", Analytical and Bioanalytical Chemistry (2014), 406(1), pp. 225-237.

Kurihara, Masaaki, Computational study on prediction of bioactivity for regulation of new designer drugs, Yakugaku Zasshi (2013), 133(1), pp. 13-16.

Karimi, Hamzeh et al., "A QSRR modeling of hazardous psychoactive designer drugs using GA-PIS and L-M ANN", ISRN Chromatography (2012) 838432, 9 pages.

Noorizadeh, Hadi et al., "Application of GA-KPLS and L-M ANN calculations for the prediction of the capacity factor of hazardous psychoactive designer drugs", Medicinal Chemistry Research (2012), 21(9), pp. 2680-2688.

Min, Jun Zhe et al., "Simultaneous and group determination methods for designated substances by HPLC with multi-channel electrochemical detection and their application to real samples", Biomedical Chromatography (2010), 24(12), pp. 1287-1299.

Takahashi, Misako et al., "Creation and application of psychoactive designer drugs data library using liquid chromatography with photodiode array spectrophotometry detector and gas chromatography-mass spectrometry", Talanta (2009), 77(4), pp. 1245-1272.

Kikura-Hanajiri et al., "Analytical data of designated substances (Shitei-Yakubutsu) controlled by the pharmaceutical affairs law in Japan, part I: GC-MS and LC-MS", Yakugaku Zasshi (2008), 128(6), pp. 971-979.

Pichini, Simona et al., "Liquid chromatography-atmospheric pressure ionization electrospray mass spectrometry determination of "hallucinogenic designer drugs" in urine of consumers", Journal of Pharmaceutical and Biomedical Analysis (2008), 47(2), pp. 335-342.

Rodriguez-Cruz, Sandra E., "Analysis and characterization of designer tryptamines using electrospray ionization mass spectrometry (ESI-MS)", Microgram Journal (2005), 3(3-4), pp. 107-129.

Nakamoto, Akihiro et al., "A systematic toxicological analysis for hallucinogenic tryptamines in seized and biological materials", Hiroshima Daigaku Igaku Zasshi (2007), 55(1-3), pp. 1-14 (Abstract).

(56) **References Cited**

OTHER PUBLICATIONS

Kato, Noriyuki et al., "Rapid and sensitive determination of tryptophan, serotonin and psychoactive tryptamines by thin-layer chromatography/fluorescence detection", Journal of Chromatography A (2007), 1145(1-2), pp. 229-233.

Yamada, Fumio et al., "The chemistry of indoles. Part 109. Synthetic studies of psilocin analogs having either a formyl group or bromine atom at the 5- or 7-position", Chemical & Pharmaceutical Bulletin (2002), 50(1), pp. 92-99.

Nichols, David E. et al., "Improvements to the synthesis of psilocybin and a facile method for preparing the O-acetyl prodrug of psilocin", Synthesis (1999), (6), pp. 935-938.

Troxler, F. et al., "Synthetic indole compounds. II. Psilocybin and psilocin modifications", Helvetica Chimica Acta (1959), 42, pp. 2073-2103 (Abstract).

Corey, E. J. et al., "A study of the formation of halo amines and cyclic amines by the free radical chain decomposition of N-haloammonium ions (Hofmann-Loffler reaction)", Journal of the American Chemical Society (1960), 82, pp. 1657-1668 (Abstract).

Repke, David B. et al. "Psilocin analogs. II. Synthesis of 3-[2-(dialkylamino)ethyl]-, 3-[2-(N-methyl-N-alkylamino)ethyl]-, and 3-[2-(cycloalkylamino)ethyl]indol-4-ols", Journal of Heterocyclic Chemistry (1981), 18, pp. 175-179.

Registry No. 1445751-71-2; Entered STN: Jul. 13, 2013.

Reexam certificate for U.S. Pat. No. 11,000,534 issued Jun. 16, 2022 Lennham Pharmaceuticals.

Fig. 1

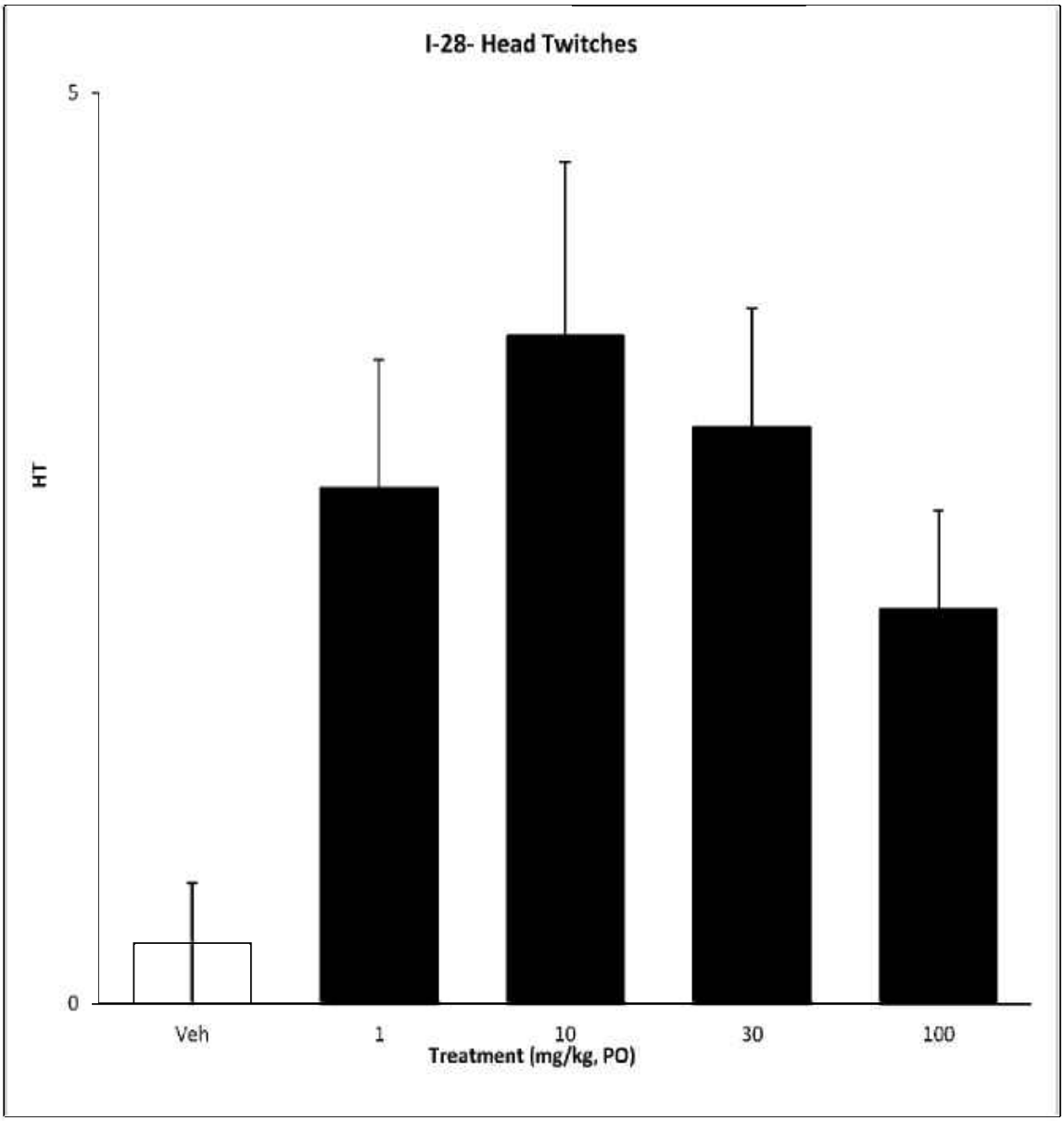
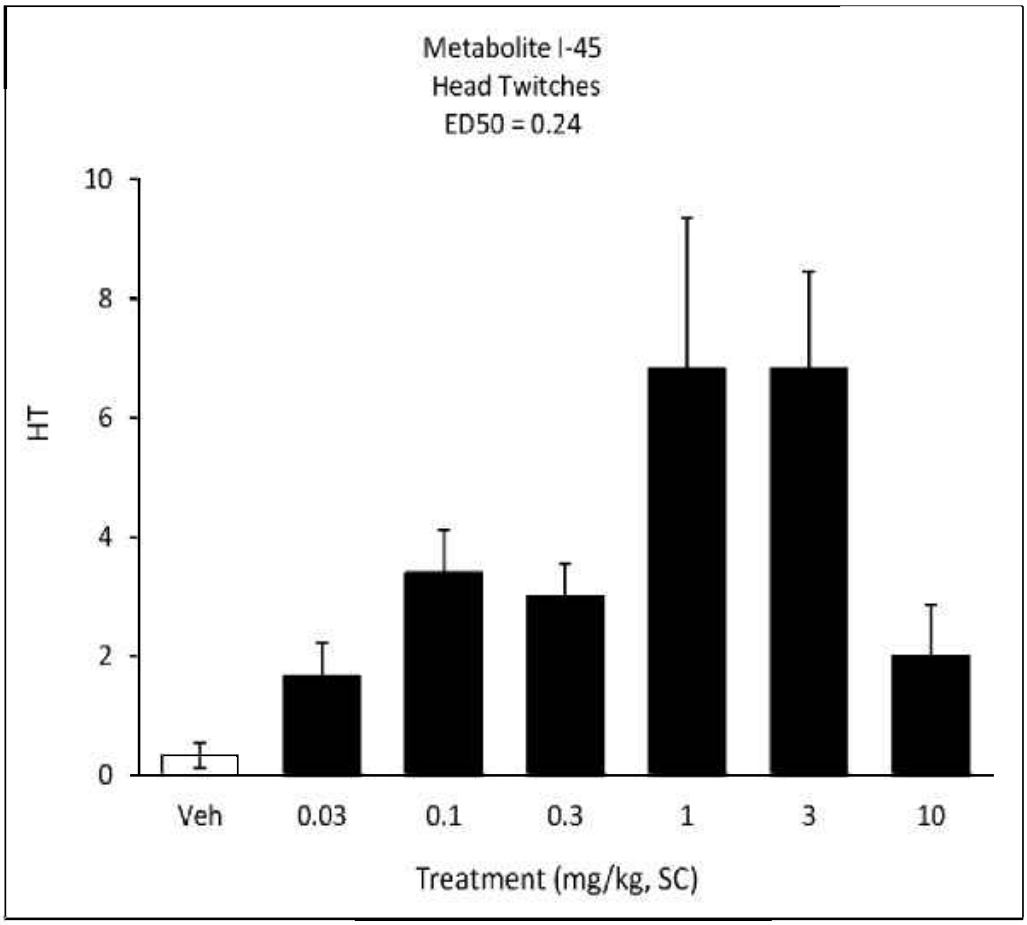


Fig. 2


Metabolite I-45
Head Twitches
ED50 = 0.24
HT
10
8
6
4
2
0
Veh
0.03
0.1
0.3
1
3
10
Treatment (mg/kg, SC)

PSILOCIN DERIVATIVES AS SEROTONERGIC PSYCHEDELIC AGENTS FOR THE TREATMENT OF CNS DISORDERS

RELATED APPLICATIONS

The present application is a continuation of U.S. patent application Ser. No. 17/387,883 filed on Jul. 28, 2021, which is a continuation of International patent application no. PCT/CA2021/050125 filed Feb. 4, 2021 which claims the benefit of priority of U.S. provisional patent application No. 62/969,934 filed on Feb. 4, 2020 the contents of each of which are incorporated herein by reference in their entirety.

FIELD

The application relates to novel psilocin derivatives of Formula (I) for the treatment of different conditions that are treated by activation of serotonin receptor, for example, mental illnesses and other neurological diseases, disorders and conditions, in the fields of psychiatry, neurobiology and pharmacotherapy. The present application further comprises methods for making the compounds of Formula (I) and corresponding intermediates.

BACKGROUND OF THE APPLICATION

Mental health disorders, or mental illness, refer to a wide range of disorders that include, but are not limited to, depressive disorders, anxiety and panic disorders, schizophrenia, eating disorders, substance misuse disorders, post-traumatic stress disorder, attention deficit/hyperactivity disorder and obsessive compulsive disorder. The severity of symptoms varies such that some individuals experience debilitating disease that precludes normal social function, while others suffer with intermittent repeated episodes across their lifespan. Although the presentation and diagnostic criteria among mental illness conditions are distinct in part, there are common endophenotypes of note across the diseases, and often comorbidities exist. Specifically, there exist phenotypic endophenotypes associated with alterations in mood, cognition and behavior. Interestingly, many of these endophenotypes extend to neurological conditions as well. For example, attentional deficits are reported in patients with attention deficit disorder, attention deficit hyperactivity disorder, eating disorders, substance use disorders, schizophrenia, depression, obsessive compulsive disorder, traumatic brain injury, Fragile X, Alzheimer's disease, Parkinson's disease and frontotemporal dementia.

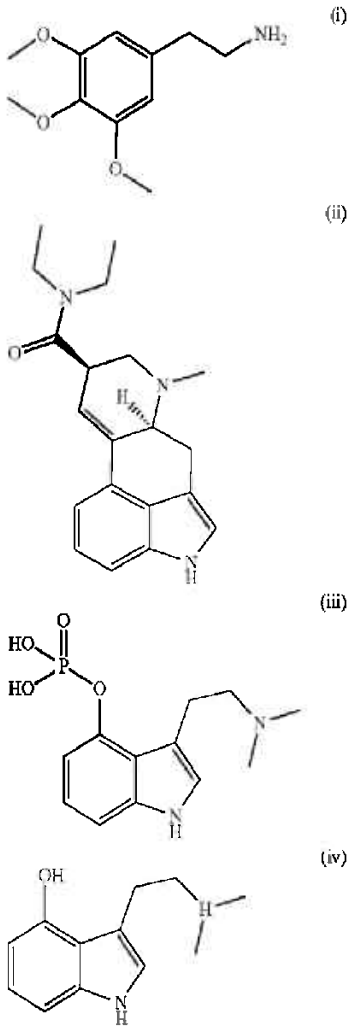
Many mental health disorders, as well as neurological disorders, are impacted by alterations, dysfunction, degeneration, and/or damage to the brain's serotonergic system, which may explain, in part, common endophenotypes and comorbidities among neuropsychiatric and neurological diseases. Many therapeutic agents that modulate serotonergic function are commercially available, including serotonin reuptake inhibitors, selective serotonin reuptake inhibitors, antidepressants, monoamine oxidase inhibitors, and, while primarily developed for depressive disorders, many of these therapeutics are used across multiple medical indications including, but not limited to, depression in Alzheimer's disease and other neurodegenerative disease, chronic pain, existential pain, bipolar disorder, obsessive compulsive disorder, anxiety disorders and smoking cessation. However, in many cases, the marketed drugs show limited benefit compared to placebo, can take six weeks to work and for some patients, and are associated with several side effects including trouble sleeping, drowsiness, fatigue, weakness, changes in blood pressure, memory problems, digestive problems, weight gain and sexual problems.

The field of psychedelic neuroscience has witnessed a recent renaissance following decades of restricted research due to their legal status. Psychedelics are one of the oldest classes of psychopharmacological agents known to man and cannot be fully understood without reference to various fields of research, including anthropology, ethnopharmacology, psychiatry, psychology, sociology, and others. Psychedelics (serotonergic hallucinogens) are powerful psychoactive substances that alter perception and mood and affect numerous cognitive processes. They are generally considered physiologically safe and do not lead to dependence or addiction. Their origin predates written history, and they were employed by early cultures in many sociocultural and ritual contexts. After the virtually contemporaneous discovery of (5R,8R)-(+)-lysergic acid-N,N-diethylamide (LSD) and the identification of serotonin in the brain, early research focused intensively on the possibility that LSD and other psychedelics had a serotonergic basis for their action. Today there is a consensus that psychedelics are agonists or partial agonists at brain serotonin 5-hydroxytryptamine 2 A (5-HT2A) receptors, with particular importance on those expressed on apical dendrites of neocortical pyramidal cells in layer V, but also may bind with lower affinity to other receptors such as the sigma-1 receptor. Several useful rodent models have been developed over the years to help unravel the neurochemical correlates of serotonin 5-HT2A receptor activation in the brain, and a variety of imaging techniques have been employed to identify key brain areas that are directly affected by psychedelics.

Psychedelics have both rapid onset and persisting effects long after their acute effects, which includes changes in mood and brain function. Long lasting effects may result from their unique receptor affinities, which affect neurotransmission via neuromodulatory systems that serve to modulate brain activity, i.e., neuroplasticity, and promote cell survival, are neuroprotective, and modulate brain neuroimmune systems. The mechanisms which lead to these long-term neuromodulatory changes are linked to epigenetic modifications, gene expression changes and modulation of pre- and post-synaptic receptor densities. These, previously under-researched, psychedelic drugs may potentially provide the next-generation of neurotherapeutics, where treatment resistant psychiatric and neurological diseases, e.g., depression, post-traumatic stress disorder, dementia and addiction, may become treatable with attenuated pharmacological risk profiles.

Although there is a general perception that psychedelic drugs are dangerous, from a physiologic safety standpoint, they are one of the safest known classes of CNS drugs. They do not cause addiction, and no overdose deaths have occurred after ingestion of typical doses of classical psychotic agents, such as LSD, psilocybin, or mescaline (Scheme 1). Preliminary data show that psychedelic administration in humans results in a unique profile of effects and potential adverse reactions that need to be appropriately addressed to maximize safety. The primary safety concerns are largely psychologic, rather than physiologic, in nature. Somatic effects vary but are relatively insignificant, even at doses that elicit powerful psychologic effects. Psilocybin, when administered in a controlled setting, has frequently been reported to cause transient, delayed headache, with incidence, duration, and severity increased in a dose-related manner [Johnson et al., Drug Alcohol Depend, 2012, 123

(1-3):132-140]. It has been found that repeated administration of psychedelics leads to a very rapid development of tolerance known as tachyphylaxis, a phenomenon believed to be mediated, in part, by 5-HT2A receptors. In fact, several studies have shown that rapid tolerance to psychedelics correlates with downregulation of 5-HT2A receptors. For example, daily LSD administration selectively decreased 5-HT2 receptor density in the rat brain [Buckholtz et al., Eur. J. Pharmacol., 1990, 109:421-425. 1985; Buckholtz et al., Life Sci. 1985, 42:2439-2445].



Scheme 1: Chemical Structures of or Mescaline (i), LSD (ii), Psilocybin (iii) and Psilocin (iv)

Classic psychedelics and dissociative psychedelics are known to have rapid onset antidepressant and anti-addictive effects, unlike any currently available treatment. Randomized clinical control studies have confirmed antidepressant and anxiolytic effects of classic psychedelics in humans. Ketamine also has well established antidepressant and anti-addictive effects in humans mainly through its action as an NMDA antagonist. Ibogaine has demonstrated potent anti-addictive potential in pre-clinical studies and is in the early stages of clinical trials to determine efficacy in robust human studies [Barsuglia et al., Prog Brain Res, 2018, 242:121-158; Corkery, Prog Brain Res, 2018, 242:217-257].

Psilocybin (4-phosphoryloxy-N,N-dimethyltrypatmine (iii, Scheme 1) has the chemical formula $C_{12}H_{17}N_2O_4P$. It is a tryptamine and is one of the major psychoactive constituents in mushrooms of the psilocybe species. It was first isolated from psilocybe mushrooms by Hofmann in 1957, and later synthesized by him in 1958 [Passie et al. Addict Biol., 2002, 7 (4):357-364], and was used in psychiatric and psychological research and in psychotherapy during the early to mid-1960 s up until its controlled drug scheduling in 1970 in the US, and up until the 1980 s in Germany [Passie 2005; Passie et al., Addict Biol., 2002, 7 (4):357-364]. Research into the effects of psilocybin resumed in the mid-1990 s, and it is currently the preferred compound for use in studies of the effects of serotonergic hallucinogens [Carter et al. J. Cogn. Neurosci., 2005 17 (10):1497-1508; Gouzoulis-Mayfrank et al. Neuropsychopharmacology 1999, 20 (6):565-581; Hasler et al, Psychopharmacology (Berl) 2004, 172 (2):145-156], likely because it has a shorter duration of action and suffers from less notoriety than LSD. Like other members of this class, psilocybin induces sometimes profound changes in perception, cognition and emotion, including emotional lability.

In humans as well as other mammals, psilocybin is transformed into the active metabolite psilocin, or 4-hydroxy-N,N-dimethyltryptamine (iv, Scheme 1). It is likely that psilocin partially or wholly produces most of the subjective and physiological effects of psilocybin in humans and non-human animals. Recently, human psilocybin research confirms the 5HT2A activity of psilocybin and psilocin, and provides some support for indirect effects on dopamine through 5HT2A activity and possible activity at other serotonin receptors. In fact, the most consistent finding for involvement of other receptors in the actions of psychedelics is the 5-HT1 A receptor. That is particularly true for tryptamines and LSD, which generally have significant affinity and functional potency at this receptor. It is known that 5-HT1 A receptors are colocalized with 5-HT2A receptors on cortical pyramidal cells [Martin-Ruiz et al. J Neurosci. 2001, 21 (24):9856-986], where the two receptor types have opposing functional effects [Araneda et al. Neuroscience, 1991, 40 (2):399-412].

Although the exact role of the 5-HT2A receptor, and other 5-HT2 receptor family members, is not well understood with respect to the amygdala, it is evident that the 5-HT2A receptor plays an important role in emotional responses and is an important target to be considered in the actions of 5-HT2A agonist psychedelics. In fact, a majority of known 5HT2A agonists produce hallucinogenic effects in humans, and rodents generalize from one 5HT2A agonist to others, as between psilocybin and LSD [Aghajanian et al., Eur J Pharmacol., 1999, 367 (2-3):197-206; Nichols at al., J Neurochem., 2004, 90 (3):576-584]. Psilocybin has a stronger affinity for the human 5HT2A receptor than for the rat receptor and it has a lower K(i) for both 5HT2A and 5HT2C receptors than LSD. Moreover, results from a series of drug-discrimination studies in rats found that 5HT2A antagonists, and not 5HT1 A antagonists, prevented rats from recognizing psilocybin [Winter et al., Pharmacol Biochem Behav., 2007, 87 (4):472-480]. Daily doses of LSD and psilocybin reduce 5HT2 receptor density in rat brain.

Clinical studies in the 1960 s and 1970 s showed that psilocybin produces an altered state of consciousness with subjective symptoms such as "marked alterations in perception, mood, and thought, changes in experience of time, space, and self." Psilocybin was used in experimental research for the understanding of etiopathogenesis of selective mental disorders and showed psychotherapeutic potential [Rucker et al., Psychopharmacol., 2016, 30 (12):1220-1229]. Psilocybin became increasingly popular as a hallucinogenic recreational drug and was eventually classed

as a Schedule I controlled drug in 1970. Fear of psychedelic abuse led to a significant reduction in research being done in this area until the 1990 s when human research of psilocybin was revived when conditions for safe administration were established [Johnson et al., Psychopharmacol., 2008, 22 (6):603-620]. Today, psilocybin is one of the most widely used psychedelics in human studies due to its relative safety, moderately long active duration, and good absorption in subjects. There remains strong research and therapeutic potential for psilocybin as recent studies have shown varying degrees of success in neurotic disorders, alcoholism, depression in terminally ill cancer patients, obsessive compulsive disorder, addiction, anxiety, post-traumatic stress disorder and even cluster headaches. It could also be useful as a psychosis model for the development of new treatments for psychotic disorders. [Dubovyk and Monahan-Vaughn, ACS Chem. Neurosci., 2018, 9 (9):2241-2251].

Recent developments in the field have occurred in clinical research, where several double-blind placebo-controlled phase 2 studies of psilocybin-assisted psychotherapy in patients with treatment resistant, major depressive disorder and cancer-related psychosocial distress have demonstrated unprecedented positive relief of anxiety and depression. Two recent small pilot studies of psilocybin assisted psychotherapy also have shown positive benefit in treating both alcohol and nicotine addiction. Recently, blood oxygen level-dependent functional magnetic resonance imaging and magnetoencephalography have been employed for in vivo brain imaging in humans after administration of a psychedelic, and results indicate that intravenously administered psilocybin and LSD produce decreases in oscillatory power in areas of the brain's default mode network [Nichols D E. Pharmacol Rev., 2016 68 (2):264-355].

Preliminary studies using positron emission tomography (PET) showed that psilocybin ingestion (15 or 20 mg orally) increased absolute metabolic rate of glucose in frontal, and to a lesser extent in other, cortical regions as well as in striatal and limbic subcortical structures in healthy participants, suggesting that some of the key behavioral effects of psilocybin involve the frontal cortex [Gouzoulis-Mayfrank et al., Neuropsychopharmacology, 1999, 20 (6):565-581; Vollenweider et al., Brain Res. Bull. 2001, 56 (5):495-507]. Although 5HT2A agonism is widely recognized as the primary action of classic psychedelic agents, psilocybin has lesser affinity for a wide range of other pre- and post-synaptic serotonin and dopamine receptors, as well as the serotonin reuptake transporter [Tyls et al., Eur. Neuropsychopharmacol. 2014, 24 (3):342-356]. Psilocybin activates 5HT1 A receptors, which may contribute to antidepressant/anti-anxiety effects.

Depression and anxiety are two of the most common psychiatric disorders worldwide. Depression is a multifaceted condition characterized by episodes of mood disturbances alongside other symptoms such as anhedonia, psychomotor complaints, feelings of guilt, attentional deficits and suicidal tendencies, all of which can range in severity. According to the World Health Organization, the discovery of mainstream antidepressants has largely revolutionized the management of depression, yet up to 60% of patients remain inadequately treated. This is often due to the drugs' delayed therapeutic effect (generally 6 weeks from treatment onset), side effects leading to non-compliance, or inherent non-responsiveness to them. Similarly, anxiety disorders are a collective of etiologically complex disorders characterized by intense psychosocial distress and other symptoms depending on the subtype. Anxiety associated with life-threatening disease is the only anxiety subtype that has been studied in terms of psychedelic-assisted therapy. This form of anxiety affects up to 40% of individuals diagnosed with life-threatening diseases like cancer. It manifests as apprehension regarding future danger or misfortune accompanied by feelings of dysphoria or somatic symptoms of tension, and often coexists with depression. It is associated with decreased quality of life, reduced treatment adherence, prolonged hospitalization, increased disability, and hopelessness, which overall contribute to decreased survival rates. Pharmacological and psychosocial interventions are commonly used to manage this type of anxiety, but their efficacy is mixed and limited such that they often fail to provide satisfactory emotional relief. Recent interest into the use of psychedelic-assisted therapy may represent a promising alternative for patients with depression and anxiety that are ineffectively managed by conventional methods.

Generally, the psychedelic treatment model consists of administering the orally-active drug to induce a mystical experience lasting 4-9 h depending on the psychedelic [Halberstadt, Behav Brain Res., 2015, 277:99-120; Nichols, Pharmacol Rev., 2016, 68 (2): 264-355]. This enables participants to work through and integrate difficult feelings and situations, leading to enduring anti-depressant and anxiolytic effects. Classical psychedelics like psilocybin and LSD are being studied as potential candidates. In one study with classical psychedelics for the treatment of depression and anxiety associated with life-threatening disease, it was found that, in a supportive setting, psilocybin, and LSD consistently produced significant and sustained anti-depressant and anxiolytic effects.

Psychedelic treatment is generally well-tolerated with no persisting adverse effects. Regarding their mechanisms of action, they mediate their main therapeutic effects biochemically via serotonin receptor agonism, and psychologically by generating meaningful psycho-spiritual experiences that contribute to mental flexibility. Given the limited success rates of current treatments for anxiety and mood disorders, and considering the high morbidity associated with these conditions, there is potential for psychedelics to provide symptom relief in patients inadequately managed by conventional methods.

Further emerging clinical research and evidence suggest psychedelic-assisted therapy, also shows potential as an alternative treatment for refractory substance use disorders and mental health conditions, and thus may be an important tool in a crisis where existing approaches have yielded limited success. A recent systematic review of clinical trials published over the last 25 years summarizes some of the anti-depressive, anxiolytic, and anti-addictive effects of classic psychedelics. Among these, are encouraging findings from a meta-analysis of randomized controlled trials of LSD therapy and a recent pilot study of psilocybin-assisted therapy for treating alcohol use disorder [dos Santos et al., Ther Adv Psychopharmacol., 2016, 6 (3):193-213]. Similarly encouraging, are findings from a recent pilot study of psilocybin-assisted therapy for tobacco use disorder, demonstrating abstinence rates of 80% at six months follow-up and 67% at 12 months follow-up [Johnson et al., J Drug Alcohol Abuse, 2017, 43 (1):55-60; Johnson et al., Psychopharmacol. 2014, 28 (11):983-992], such rates are considerably higher than any documented in the tobacco cessation literature. Notably, mystical-type experiences generated from the psilocybin sessions were significantly correlated with positive treatment outcomes. These results coincide with bourgeoning evidence from recent clinical trials lending support to the effectiveness of psilocybin-assisted therapy for treatment-resistant depression and end-of-life

anxiety [Carhart-Harris et al. Neuropsychopharmacology, 2017, 42 (11):2105-2113]. Research on the potential benefits of psychedelic-assisted therapy for opioid use disorder (OUD) is beginning to emerge, and accumulating evidence supports a need to advance this line of investigation. Available evidence from earlier randomized clinical trials suggests a promising role for treating OUD: higher rates of abstinence were observed among participants receiving high dose LSD and ketamine-assisted therapies for heroin addiction compared to controls at long-term follow-ups. Recently, a large United States population study among 44,000 individuals found that psychedelic use was associated with 40% reduced risk of opioid abuse and 27% reduced risk of opioid dependence in the following year, as defined by DSM-IV criteria [Pisano et al., J Psychopharmacol., 2017, 31 (5): 606-613]. Similarly, a protective moderating effect of psychedelic use was found on the relationship between prescription opioid use and suicide risk among marginalized women [Argento et al., J Psychopharmacol., 2018, 32 (12): 1385-1391]. Despite the promise of these preliminary findings with classical psychedelic agents, further research is warranted to determine what it may contribute to the opioid crisis response given their potential toxicity. Meanwhile, growing evidence on the safety and efficacy of psilocybin for the treatment of mental and substance use disorders should help to motivate further clinical investigation into its use as a novel intervention for OUD.

Regular doses of psychedelics also ameliorate sleep disturbances, which are highly prevalent in depressive patients with more than 80% of them having complaints of poor sleep quality. The sleep symptoms are often unresolved by first-line treatment and are associated with a greater risk of relapse and recurrence. Interestingly, sleep problems often appear before other depression symptoms, and subjective sleep quality worsens before the onset of an episode in recurrent depression. Brain areas showing increased functional connectivity with poor sleep scores and higher depressive symptomatology scores included prefrontal and limbic areas, areas involved in the processing of emotions. Sleep disruption in healthy participants has demonstrated that sleep is indeed involved in mood, emotion evaluation processes and brain reactivity to emotional stimuli. An increase in negative mood and a mood-independent mislabeling of neutral stimuli as negative was for example shown by one study while another demonstrated an amplified reactivity in limbic brain regions in response to both negative and positive stimuli. Two other studies assessing electroencephalographic (EEG) brain activity during sleep showed that psychedelics, such as LSD, positively affect sleep patterns. Moreover, it has been shown that partial or a full night of sleep deprivation can alleviate symptoms of depression suggested by resetting circadian rhythms via modification of clock gene expression. It further was suggested that a single dose of a psychedelic causes a reset of the biological clock underlying sleep/wake cycles and thereby enhances cognitive-emotional processes in depressed people but also improving feelings of well-being and enhances mood in healthy individuals [Kuypers, Medical Hypotheses, 2019, 125:21-24].

In a systematic meta-analysis of clinical trials from 1960-2018 researching the therapeutic use of psychedelic treatment in patients with serious or terminal illnesses and related psychiatric illness, it was found that psychedelic therapy (mostly with LSD) may improve cancer-related depression, anxiety, and fear of death. Four randomized controlled clinical trials were published between 2011 and 2016, mostly with psilocybin treatment, that demonstrated psychedelic-assisted treatment can produce rapid, robust, and sustained improvements in cancer-related psychological and existential distress. [Ross S, Int Rev Psychiatry, 2018, 30 (4):317-330]. Thus, the use of psychedelics in the fields of oncology and palliative care is intriguing for several reasons. First, many patients facing cancer or other life-threatening illnesses experience significant existential distress related to loss of meaning or purpose in life, which can be associated with hopelessness, demoralization, powerlessness, perceived burdensomeness, and a desire for hastened death. Those features are also often at the core of clinically significant anxiety and depression, and they can substantially diminish quality of life in this patient population. The alleviation of those forms of suffering should be among the central aims of palliative care. Accordingly, several manualized psychotherapies for cancer-related existential distress have been developed in recent years, with an emphasis on dignity and meaning-making. However, there are currently no pharmacologic interventions for existential distress per se, and available pharmacologic treatments for depressive symptoms in patients with cancer have not demonstrated superiority over placebo. There remains a need for additional effective treatments for those conditions [Rosenbaum et al., Curr. Oncol., 2019, 26 (4): 225-226].

Recently, there has been growing interest in a new dosing paradigm for psychedelics such as psilocybin and LSD referred to colloquially as microdosing. Under this paradigm, sub-perceptive doses of the serotonergic hallucinogens, approximately 10% or less of the full dose, are taken on a more consistent basis of once each day, every other day, or every three days, and so on. Not only is this dosing paradigm more consistent with current standards in pharmacological care, but may be particularly beneficial for certain conditions, such as Alzheimer's disease and other neurodegenerative diseases, attention deficit disorder, attention deficit hyperactivity disorder, and for certain patient populations such as elderly, juvenile and patients that are fearful of or opposed to psychedelic assisted therapy. Moreover, this approach may be particularly well suited for managing cognitive deficits and preventing neurodegeneration. For example, subpopulations of low attentive and low motivated rats demonstrate improved performance on 5 choice serial reaction time and progressive ratio tasks, respectively, following doses of psilocybin below the threshold for eliciting the classical wet dog shake behavioral response associated with hallucinogenic doses (Blumstock et al., WO 2020/157569 A1). Similarly, treatment of patients with hallucinogenic doses of 5HT2A agonists is associated with increased BDNF and activation of the mTOR pathway, which are thought to promote neuroplasticity and are hypothesized to serve as molecular targets for the treatment of dementias and other neurodegenerative disorders (Ly et al. Cell Rep., 2018, 23 (11):3170-3182). Additionally, several groups have demonstrated that low, non-hallucinogenic and non-psychomimetic, doses of 5HT2A agonists also show similar neuroprotective and increased neuroplasticity effects (neuroplastogens) and reduced neuroinflammation, which could be beneficial in both neurodegenerative and neurodevelopmental diseases and chronic disorders (Manfredi et al., WO 2020/181194, Flanagan et al., Int. Rev. Psychiatry, 2018, 13:1-13; Nichols et al., 2016, Psychedelics as medicines; an emerging new paradigm). This repeated, lower, dose paradigm may extend the utility of these compounds to additional indications and may prove useful for wellness applications.

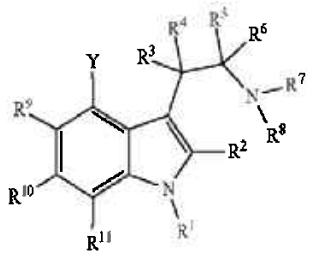
Psychosis is often referred to as an abnormal state of mind that is characterized by hallucinatory experiences, delu-

sional thinking, and disordered thoughts. Moreover, this state is accompanied by impairments in social cognition, inappropriate emotional expressions, and bizarre behavior. Most often, psychosis develops as part of a psychiatric disorder, of which, it represents an integral part of schizophrenia. It corresponds to the most florid phase of the illness. The very first manifestation of psychosis in a patient is referred to as first-episode psychosis. It reflects a critical transitional stage toward the chronic establishment of the disease, that is presumably mediated by progressive structural and functional abnormalities seen in diagnosed patients. [ACS Chem. Neurosci. 2018, 9, 2241-2251]. Anecdotal evidence suggests that low, non-hallucinogenic, doses (microdosing) of psychedelics that are administered regularly can reduce symptoms of schizophrenia and psychosis.

SUMMARY OF THE APPLICATION

The present application includes compounds having the general structural Formula (I) or a pharmaceutically acceptable salt, solvate and/or prodrug thereof:

(I)



wherein R^1 is selected from hydrogen, C_1-C_3 alkyl, C_1-C_6 alkyleneP(O)$(OR^{12})_2$, $C(O)R^{12}$, CO_2R^{12}, $C(O)N(R^{12})_2$, $S(O)R^{12}$ and SO_2R^{12};

R^2 to R^6 are independently selected from hydrogen and C_1-C_6 alkyl;

R^7 and R^8 are independently selected from hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_3-C_7 cycloalkyl, substituted or unsubstituted C_3-C_7 heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl, or R^7 and R^8 are taken together with the nitrogen atom therebetween to form a 3- to 7-membered heterocyclic ring optionally including 1 to 2 additional ring heteromoieties selected from O, S, S(O), SO_2, N and NR^{13},

wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a substituent selected from halogen, CO_2R^{13}, $C(O)N(R^{13})_2$, SO_2R^{13}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_6 cycloalkyl and a 3- to 6-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, N, S(O), SO_2 and NR^{13};

R^9, R^{10} and R^{11} are independently selected from hydrogen, halogen, CN, OR^{13}, $N(R^{13})_2$, SR^{13}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, CO_2R^{13}, $C(O)N(R^{13})_2$, SOR^{13}, SO_2R^{13}, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl and a 3- to 7-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, S(O), SO_2, N and NR^{13}, wherein said C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring groups are optionally substituted by one or more substituents independently selected from CN, OR^{13}, $N(R^{13})_2$ and SR^{13}, and wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a substituent selected from halogen, CO_2R^{13}, $C(O)N(R^{13})_2$, SO_2R^{13}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_6 cycloalkyl and a 3- to 6-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, S(O), SO_2, N and NR^{13};

Y is selected from halogen and X-A;

X is selected from O, NR^{13}, S, S(O) and SO_2;

A is selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_4-C_6 cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, P(O)$(OR^{12})_2$, C_1-C_6 alkyleneP(O)$(OR^{12})_2$, C_1-C_6 alkylene C_3-C_7 cycloalkyl, C_1-C_6 alkylene C_4-C_6 cycloalkenyl, C_1-C_6 alkyleneheterocycloalkyl, C_1-C_3 alkylenearyl, C_1-C_6 alkyleneheteroaryl, C(O)Q', CO_2Q', $C(O)N(Q')_2$, S(O)Q' and SO_2Q',

wherein Q' is selected from C_1-C_{20} alkyl, C_1-C_{20} haloalkyl, C_2-C_{20} alkenyl, C_2-C_{20} haloalkenyl, C_2-C_{20} alkynyl, C_2-C_{20} haloalkynyl, C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and a 3- to 7-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, S(O), SO_2, N and NR^{13}, wherein said C_1-C_{20} alkyl, C_2-C_{20} haloalkyl, C_2-C_{20} alkenyl, C_2-C_{20} haloalkenyl, C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and 3- to 7-membered heterocyclic ring groups are optionally substituted by one or more substituents independently selected from CN, OR^{13}, $N(R^{13})_2$, CO_2R^{13}, SR^{13}, C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and a 3- to 7-membered heterocyclic ring, and/or are disubstituted on the same carbon atom with C_{1-6} alkyl, or with C_{2-6} alkylene to form a C_3-C_7 cycloalkyl ring, and wherein each of said C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl, and 3- to 7-membered heterocyclic ring are each further optionally substituted with a substituent selected from of C_1-C_3 alkyl and C_1-C_3 haloalkyl;

each R^{12} is independently selected from hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_3-C_7 cycloalkyl, substituted or unsubstituted C_3-C_7 heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_6 alkylene C_3-C_7 cycloalkyl, substituted or unsubstituted C_1-C_6 alkylene C_3-C_7 heterocycloalkyl, substituted or unsubstituted C_1-C_6 alkylenearyl, and substituted or unsubstituted C_1-C_6 alkyleneheteroaryl;

each R^{13} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, and a 3- to 7-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, S(O), SO_2, N and NR^{14}, wherein said C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring groups are optionally substituted by one or more substituents independently selected from CN, OR^{14}, $N(R^{14})_2$ and SR^{14}, and wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a substituent selected from halogen, CO_2R^{14}, $C(O)N(R^{14})_2$, SO_2R^{14}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_6 cycloalkyl and a 3- to 6-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, S(O), SO_2, N and NR^{14},

R^{14} is selected from hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_3-C_7 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl; and

wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof,

provided either R^1 is C_1-C_6P(O)$(OR^{12})_2$ and R^2, R^3, R^4, R^5, R^6, R^7R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14}, Q', X, Y and A are as defined above for Formula (I); or

Y is X-A wherein A is selected from C_1-C_6 alkyleneP(O)$(OR^{12})_2$, C_1-C_6 alkylene C_3-C_7 cycloalkyl, C_1-C_6 alkylene C_4-C_6 cycloalkenyl, C_1-C_6 alkyleneheterocycloalkyl, C_1-C_3 alkylenearyl, C_1-C_6 alkyleneheteroaryl, C(O)Q', CO_2Q', $C(O)N(Q')_2$, S(O)Q' and SO_2Q' and R^1, R^2, R^3, R^4, R^5, R^6, R^7R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14}, Q' and X are as defined above for Formula (I).

In some embodiments, the compounds of Formula (I) and pharmaceutically acceptable salts, solvates and/or prodrugs thereof, are isotopically enriched with deuterium. In some embodiments, one or more of A, X, Q', R^1, R^2, R^3, R^4, R^5, R^6, R^7R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} comprises one or more deuterium or one or more of A, X, Q', R^1, R^2, R^3, R^4, R^5, R^6, R^7R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} is deuterium.

In a further embodiment, the compounds of the application are used as medicaments. Accordingly, the application also includes a compound of the application for use as a medicament.

The present application includes a method for activating a serotonin receptor in a cell, either in a biological sample or in a patient, comprising administering an effective amount of one or more compounds of the application to the cell.

The present application also includes a method of treating a mental illness comprising administering a therapeutically effective amount of one or more compounds of the application to a subject in need thereof.

The present application also includes a method of treating a mental illness comprising administering a therapeutically effective amount of one or more compounds of the application to a subject in need thereof.

The present application also includes a method of treating a CNS disease, disorder or condition and/or a neurological disease, disorder or condition comprising administering a therapeutically effective amount of one or more compounds of the application to a subject in need thereof.

The application additionally provides a process for the preparation of compounds of the application. General and specific processes are discussed in more detail below and set forth in the examples below.

Other features and advantages of the present application will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating embodiments of the application, are given by way of illustration only and the scope of the claims should not be limited by these embodiments, but should be given the broadest interpretation consistent with the description as a whole.

DRAWINGS

The embodiments of the application will now be described in greater detail with reference to the attached drawings in which:

FIG. 1 is a graph showing the effect of various doses of exemplary compound of Formula I, I-28, on head-twitch response (HTR) in male C57 BL6 mice. The mice were treated with compound I-28 (I-100 mg/kg) by PO route (N=6 mice/dose), and the total number of head twitches were recorded over a 1 h period. Data is expressed as mean±SEM. The induction of head twitches elicited by 5-HT2A receptor agonists is believed to represent a behavioural proxy of their psychedelic effects.

FIG. 2 is a graph showing the effect of various doses of metabolite (MSP=1007) of exemplary compound of Formula I, I-45, on head-twitch response (HTR) in male C57 BL6 mice. The mice were treated with compound MSP-1007 (0.03-10 mg/kg) by SC route (N=6 mice/dose), and the total number of head twitches were recorded over a 1 h period. Data is expressed as mean±SEM. The induction of head twitches elicited by 5-HT2A receptor agonists is believed to represent a behavioural proxy of their psychedelic effects.

DETAILED DESCRIPTION

I. Definitions

Unless otherwise indicated, the definitions and embodiments described in this and other sections are intended to be applicable to all embodiments and aspects of the present application herein described for which they are suitable as would be understood by a person skilled in the art.

The term "compound(s) of the application" or "compound(s) of the present application" and the like as used herein refers to a compound of Formula (I) and compounds of Formula (I-A) to (I-I) and pharmaceutically acceptable salts, solvates and/or prodrugs thereof.

The term "composition(s) of the application" or "composition(s) of the present application" and the like as used herein refers to a composition, such a pharmaceutical composition, comprising one or more compounds of the application.

The term "and/or" as used herein means that the listed items are present, or used, individually or in combination. In effect, this term means that "at least one of" or "one or more" of the listed items is used or present. The term "and/or" with respect to pharmaceutically acceptable salts, solvates and/or prodrugs thereof means that the compounds of the application exist as individual salts, solvates and prodrugs, as well as a combination of, for example, a salt of a solvate of a compound of the application.

As used in the present application, the singular forms "a", "an" and "the" include plural references unless the content clearly dictates otherwise. For example, an embodiment including "a compound" should be understood to present certain aspects with one compound, or two or more additional compounds.

As used in this application and claim(s), the words "comprising" (and any form of comprising, such as "comprise" and "comprises"), "having" (and any form of having, such as "have" and "has"), "including" (and any form of including, such as "include" and "includes") or "containing" (and any form of containing, such as "contain" and "contains"), are inclusive or open-ended and do not exclude additional, unrecited elements or process steps.

The term "consisting" and its derivatives as used herein are intended to be closed terms that specify the presence of the stated features, elements, components, groups, integers and/or steps and also exclude the presence of other unstated features, elements, components, groups, integers and/or steps.

The term "consisting essentially of", as used herein, is intended to specify the presence of the stated features, elements, components, groups, integers and/or steps as well as those that do not materially affect the basic and novel characteristic(s) of these features, elements, components, groups, integers and/or steps.

In embodiments comprising an "additional" or "second" component, such as an additional or second compound, the second component as used herein is chemically different from the other components or first component. A "third" component is different from the other, first and second components and further enumerated or "additional" components are similarly different.

The term "suitable" as used herein means that the selection of the particular compound or conditions would depend on the specific synthetic manipulation to be performed, the identity of the molecule(s) to be transformed and/or the specific use for the compound, but the selection would be well within the skill of a person trained in the art. All process/method steps described herein are to be conducted under conditions sufficient to provide the product shown. A person skilled in the art would understand that all reaction conditions, including, for example, reaction solvent, reaction time, reaction temperature, reaction pressure, reactant ratio and whether or not the reaction should be performed under an anhydrous or inert atmosphere, can be varied to optimize the yield of the desired product and it is within their skill to do so.

The terms "about", "substantially" and "approximately" as used herein mean a reasonable amount of deviation of the modified term such that the end result is not significantly changed. These terms of degree should be construed as including a deviation of at least ±5% of the modified term if this deviation would not negate the meaning of the word it modifies or unless the context suggests otherwise to a person skilled in the art.

The present description refers to a number of chemical terms and abbreviations used by those skilled in the art. Nevertheless, definitions of selected terms are provided for clarity and consistency.

The term "solvate" as used herein means a compound, or a salt or prodrug of a compound, wherein molecules of a suitable solvent are incorporated in the crystal lattice. A suitable solvent is physiologically tolerable at the dosage administered.

The term "prodrug" as used herein means a compound, or salt of a compound, that, after administration, is converted into an active drug.

The term "alkyl" as used herein, whether it is used alone or as part of another group, means straight or branched chain, saturated alkyl groups. The number of carbon atoms that are possible in the referenced alkyl group are indicated by the prefix "C_{n1-n2}". Thus, for example, the term "C_{1-6} alkyl" (or "C_1-C_6 alkyl") means an alkyl group having 1, 2, 3, 4, 5, or c carbon atoms and includes, for example, any of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and ter-butyl, n- and iso-propyl, ethyl and methyl. As another example, "C_4 alkyl" refers to n-, iso-, sec- and tert-butyl, n- and isopropyl, ethyl and methyl.

The term "alkenyl" whether it is used alone or as part of another group, means a straight or branched chain, saturated alkylene group, that is, a saturated carbon chain that contains substituents on two of its ends. The number of carbon atoms that are possible in the referenced alkylene group are indicated by the prefix "C_{n1-n2}". For example, the term C_{2-6} alkylene means an alkylene group having 2, 3, 4, 5 or 6 carbon atoms.

The term "alkynyl" as used herein, whether it is used alone or as part of another group, means straight or branched chain, unsaturated alkynyl groups containing at least one triple bond. The number of carbon atoms that are possible in the referenced alkyl group are indicated by the prefix "C_{n1-n2}". For example, the term C_{2-6} alkynyl means an alkynyl group having 2, 3, 4, 5 or 6 carbon atoms.

The term "cycloalkyl," as used herein, whether it is used alone or as part of another group, means a saturated carbocyclic group containing from 3 to 20 carbon atoms and one or more rings. The number of carbon atoms that are possible in the referenced cycloalkyl group are indicated by the numerical prefix "C_{n1-n2}". For example, the term C_{3-10} cycloalkyl means a cycloalkyl group having 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms.

The term "aryl" as used herein, whether it is used alone or as part of another group, refers to carbocyclic groups containing at least one aromatic ring and contains either 6 to 20 carbon atoms.

The term "available", as in "available hydrogen atoms" or "available atoms" refers to atoms that would be known to a person skilled in the art to be capable of replacement by a substituent.

The term "heterocycloalkyl" as used herein, whether it is used alone or as part of another group, refers to cyclic groups containing at least one non-aromatic ring containing from 3 to 20 atoms in which one or more of the atoms are a heteromoiety selected from O, S, S(O), SO_2 and N and the remaining atoms are C. Heterocycloalkyl groups are either saturated or unsaturated (i.e. contain one or more double bonds). When a heterocycloalkyl group contains the prefix C_{n1-n2} or "n1 to n2" this prefix indicates the number of carbon atoms in the corresponding carbocyclic group, in which one or more, suitably 1 to 5, of the ring atoms is replaced with a heteromoiety as selected from O, S, S(O), SO_2 and N and the remaining atoms are C. Heterocycloalkyl groups are optionally benzofused.

The term "heteroaryl" as used herein, whether it is used alone or as part of another group, refers to cyclic groups containing at least one heteroaromatic ring containing 5-20 atoms in which one or more of the atoms are a heteroatom selected from O, S and N and the remaining atoms are C. When a heteroaryl group contains the prefix C_{n1-n2} this prefix indicates the number of carbon atoms in the corresponding carbocyclic group, in which one or more, suitably 1 to 5, of the ring atoms is replaced with a heteroatom as defined above. Heteroaryl groups are optionally benzofused.

All cyclic groups, including aryl, heteroaryl, heterocycloalkyl and cycloalkyl groups, contain one or more than one ring (i.e. are polycyclic). When a cyclic group contains more than one ring, the rings may be fused, bridged, spirofused or linked by a bond.

The term "benzofused" as used herein refers to a polycyclic group in which a benzene ring is fused with another ring.

A first ring being "fused" with a second ring means the first ring and the second ring share two adjacent atoms there between.

A first ring being "bridged" with a second ring means the first ring and the second ring share two non-adjacent atoms there between.

A first ring being "spirofused" with a second ring means the first ring and the second ring share one atom there between.

The term "halogen" (or "halo") whether it is used alone or as part of another group, refers to a halogen atom and includes fluoro, chloro, bromo and iodo.

The term "haloalkyl" as used herein refers to an alkyl group as defined above in which one or more of the available hydrogen atoms have been replaced with a halogen. Thus, for example, "C_{1-6} haloalkyl" (or "C_1-C_6 haloalkyl") refers to a C_1 to C_6 linear or branched alkyl group as defined above with one or more halogen substituents.

As used herein, the term "haloalkenyl" refers to an alkenyl group as defined above in which one or more of the available hydrogen atoms have been replaced with a halogen. Thus, for example, "C_{1-6} haloalkenyl" (or "C_1-C_6 haloalkenyl") refers to a C_1 to C_6 linear or branched alkenyl group as defined above with one or more halogen substituents.

As used herein, the term "haloalkynyl" refers to an alkynyl group as defined above in which one or more of the available hydrogen atoms have been replaced with a halogen. Thus, for example, "C_{1-6} haloalkynyl" (or "C_1-C_6 haloalkynyl") refers to a C_1 to C_6 linear or branched alkynyl group as defined above with one or more halogen substituents.

As used herein, the term "alkoxy" as used herein, alone or in combination, includes an alkyl group connected to an oxygen connecting atom.

As used herein, the term "one or more" item includes a single item selected from the list as well as mixtures of two or more items selected from the list.

The term "substituted" as used herein means, unless otherwise indicated, that the referenced group is substituted with one or more substituents independently selected from halogen, CO_2H, CO_2CH_3, $C(O)NH_2$, $C(O)N(CH_3)_2$, $C(O)NHCH_3$, SO_2CH_3, $SOCH_3$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_6 cycloalkyl and a 3- to 6-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, S(O), SO_2, N, NH and NCH_3.

The term "alternate isotope thereof" as used herein refers to an isotope of an element that is other than the isotope that is most abundant in nature.

In the compounds of general Formula (I) and pharmaceutically acceptable salts, solvates and/or prodrug thereof, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present disclosure is meant to include all suitable isotopic variations of the compounds of general Formula (I) and pharmaceutically acceptable salts, solvates and/or prodrug thereof. For example, different isotopic forms of hydrogen (H) include protium (1H), deuterium (2H) and tritium (3H). Protium is the predominant hydrogen isotope found in nature.

The term "all available atoms are optionally substituted with alternate isotope" as used herein means that available atoms are optionally substituted with an isotope of that atom of having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature.

The term "compound" refers to the compound and, in certain embodiments, to the extent they are stable, any hydrate or solvate thereof. A hydrate is the compound complexed with water and a solvate is the compound complexed with a solvent, which may be an organic solvent or an inorganic solvent. A "stable" compound is a compound that can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (e.g., therapeutic administration to a subject). The compounds of the present application are limited to stable compounds embraced by general Formula (I), or pharmaceutically acceptable salts, solvates and/or prodrug thereof.

The term "pharmaceutically acceptable" means compatible with the treatment of subjects.

The term "pharmaceutically acceptable carrier" means a non-toxic solvent, dispersant, excipient, adjuvant or other material which is mixed with the active ingredient in order to permit the formation of a pharmaceutical composition, i.e., a dosage form capable of administration to a subject.

The term "pharmaceutically acceptable salt" means either an acid addition salt or a base addition salt which is suitable for, or compatible with, the treatment of subjects.

An acid addition salt suitable for, or compatible with, the treatment of subjects is any non-toxic organic or inorganic acid addition salt of any basic compound.

A base addition salt suitable for, or compatible with, the treatment of subjects is any non-toxic organic or inorganic base addition salt of any acidic compound The term "protecting group" or "PG" and the like as used herein refers to a chemical moiety which protects or masks a reactive portion of a molecule to prevent side reactions in those reactive portions of the molecule, while manipulating or reacting a different portion of the molecule. After the manipulation or reaction is complete, the protecting group is removed under conditions that do not degrade or decompose the remaining portions of the molecule. The selection of a suitable protecting group can be made by a person skilled in the art. Many conventional protecting groups are known in the art, for example as described in "Protective Groups in Organic Chemistry" McOmie, J. F. W. Ed., Plenum Press, 1973, in Greene, T. W. and Wuts, P. G. M., "Protective Groups in Organic Synthesis", John Wiley & Sons, 3rd Edition, 1999 and in Kocienski, P. Protecting Groups, 3 rd Edition, 2003, Georg Thieme Verlag (The Americas).

The term "subject" as used herein includes all members of the animal kingdom including mammals, and suitably refers to humans. Thus the methods of the present application are applicable to both human therapy and veterinary applications.

The term "treating" or "treatment" as used herein and as is well understood in the art, means an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results include, but are not limited to alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (i.e. not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease and remission (whether partial or total), whether detectable or undetectable. "Treating" and "treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. "Treating" and "treatment" as used herein also include prophylactic treatment. For example, a subject with early cancer can be treated to prevent progression, or alternatively a subject in remission can be treated with a compound or composition of the application to prevent recurrence. Treatment methods comprise administering to a subject a therapeutically effective amount of one or more of the compounds of the application and optionally consist of a single administration, or alliteratively comprise a series of administrations.

As used herein, the term "effective amount" or "therapeutically effective amount" means an amount of one or more compounds of the application that is effective, at dosages and for periods of time necessary to achieve the

desired result. For example, in the context of treating a disease, disorder or condition mediated or treated by agonism or activation of serotonergic receptors and downstream second messengers, an effective amount is an amount that, for example, increases said activation compared to the activation without administration of the one or more compounds.

"Palliating" a disease, disorder or condition means that the extent and/or undesirable clinical manifestations of a disease, disorder or condition are lessened and/or time course of the progression is slowed or lengthened, as compared to not treating the disorder.

The term "administered" as used herein means administration of a therapeutically effective amount of one or more compounds or compositions of the application to a cell, tissue, organ or subject.

The term "prevention" or "prophylaxis", or synonym thereto, as used herein refers to a reduction in the risk or probability of a patient becoming afflicted with a disease, disorder or condition or manifesting a symptom associated with a disease, disorder or condition.

The "disease, disorder or condition" as used herein refers to a disease, disorder or condition treated or treatable by activation a serotonin receptor, for example 5-HT_{2A} and particularly using a serotonin receptor agonist, such as one or more compounds of the application herein described.

The term "treating a disease, disorder or condition by activation of a serotonin receptor" as used herein means that the disease, disorder or condition to be treated is affected by, modulated by and/or has some biological basis, either direct or indirect, that includes serotonergic activity, in particular increases in serotonergic activity. These diseases respond favourably when serotonergic activity associated with the disease, disorder or condition is agonized by one or more of the compounds or compositions of the application.

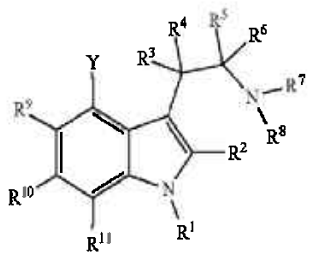
The term "activation" as used herein includes agonism, partial agonist and positive allosteric modulation of a serotonin receptor.

The term "5-HT_{2A}" as used herein mean the 5-HT_{2A} receptor subtype of the 5-HT_2 serotonin receptor.

The term "therapeutic agent" as used herein refers to any drug or active agent that has a pharmacological effect when administered to a subject.

II. Compounds

The present application includes a compound of Formula (I) or a pharmaceutically acceptable salt, solvate and/or prodrug thereof:



(I)

wherein R^1 is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkyleneP(O)$(OR^{12})_2$, C(O)R^{12}, CO_2R^{12}, C(O)N$(R^{12})_2$, S(O)R^{12} and SO_2R^{12};

R^2 to R^6 are independently selected from hydrogen and C_1-C_6 alkyl;

R^7 and R^8 are independently selected from hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_3-C_7 cycloalkyl, substituted or unsubstituted C_3-C_7 heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl, or R^7 and R^8 are taken together with the nitrogen atom therebetween to form a 3- to 7-membered heterocyclic ring optionally including 1 to 2 additional ring heteromoieties selected from O, S, S(O), SO_2, N and NR^{13},

wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a substituent selected from halogen, CO_2R^{13}, C(O)N$(R^{13})_2$, SO_2R^{13}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_6 cycloalkyl and a 3- to 6-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, N, S(O), SO_2 and NR^{13};

R^9, R^{10} and R^{11} are independently selected from hydrogen, halogen, CN, OR^{13}, N$(R^{13})_2$, SR^{13}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, CO_2R^{13}, C(O)N$(R^{13})_2$, SOR^{13}, SO_2R^{13}, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl and a 3- to 7-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, S(O), SO_2, N and NR^{13}, wherein said C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring groups are optionally substituted by one or more substituents independently selected from CN, OR^{13}, N$(R^{13})_2$ and SR^{13}, and wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a substituent selected from halogen, CO_2R^{13}, C(O)N$(R^{13})_2$, SO_2R^3, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_6 cycloalkyl and a 3- to 6-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, S(O), SO_2, N and NR^{13};

Y is selected from halogen and X-A;

X is selected from O, NR^{13}, S, S(O) and SO_2;

A is selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_4-C_6 cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, P(O)$(OR^{12})_2$, C_1-C_6 alkyleneP(O)$(OR^{12})_2$, C_1-C_6 alkylene C_3-C_7 cycloalkyl, C_1-C_6 alkylene C_4-C_6 cycloalkenyl, C_1-C_6 alkyleneheterocycloalkyl, C_1-C_3 alkylenearyl, C_1-C_6 alkyleneheteroaryl, C(O)Q', CO_2Q', C(O)N(Q')$_2$, S(O)Q') and SO_2Q',

wherein Q' is selected from C_1-C_{20} alkyl, C_1-C_{20} haloalkyl, C_2-C_{20} alkenyl, C_2-C_{20} haloalkenyl, C_2-C_{20} alkynyl, C_2-C_{20} haloalkynyl, C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and a 3- to 7-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, S(O), SO_2, N and NR^{13}, wherein said C_1-C_{20} alkyl, C_2-C_{20} haloalkyl, C_2-C_{20} alkenyl, C_2-C_{20} haloalkenyl, C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and 3- to 7-membered heterocyclic ring groups are optionally substituted by one or more substituents independently selected from CN, OR^{13}, N$(R^{13})_2$, CO_2R^{13}, SR^{13}, C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and a 3- to 7-membered heterocyclic ring, and/or are disubstituted on the same carbon atom with C_{1-6} alkyl, or with C_{2-6} alkylene to form a C_3-C_7 cycloalkyl ring, and wherein each of said C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl, and 3- to 7-membered heterocyclic ring are each further optionally substituted with a substituent selected from of C_1-C_6 alkyl and C_1-C_6 haloalkyl;

each R^{12} is independently selected from hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6

alkynyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_3-C_7 cycloalkyl, substituted or unsubstituted C_3-C_7 heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_6 alkylene C_3-C_7 cycloalkyl, substituted or unsubstituted C_1-C_6 alkylene C_3-C_7 heterocycloalkyl, substituted or unsubstituted C_1-C_6 alkylenearyl and substituted or unsubstituted C_1-C_6 alkyleneheteroaryl;

each R^{13} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, and a 3- to 7-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, S(O), SO_2, N and NR^{14}, wherein said C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring groups are optionally substituted by one or more substituents independently selected from CN, OR^{14}, $N(R^{14})_2$ and SR^{14}, and wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a substituent selected from halogen, CO_2R^{14}, $C(O)N(R^{14})_2$, SO_2R^{14}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_6 cycloalkyl and a 3- to 6-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, S(O), SO_2, N and NR^{14}

R^{14} is selected from hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 haloalkyl, substituted or unsubstituted C_3-C_7 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl; and

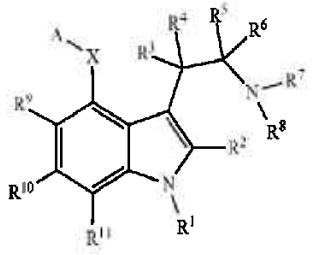
wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof,

provided either R^1 is C_1-C_6P(O)$(OR^{12})_2$ and R^2, R^3, R^4, R^5, R^6, R^7R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14}, Q', X, Y and A are as defined above for Formula (I); or

Y is X-A wherein A is selected from C_1-C_6 alkyleneP(O)$(OR^{12})_2$, C_1-C_6 alkylene C_3-C_7 cycloalkyl, C_1-C_6 alkylene C_4-C_6 cycloalkenyl, C_1-C_6 alkyleneheterocycloalkyl, C_1-C_3 alkylenearyl, C_1-C_6 alkyleneheteroaryl, C(O)Q', CO_2Q', $C(O)N(Q')_2$, S(O)Q' and SO_2Q' and R^1, R^2, R^3, R^4, R^5, R^6, R^7R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14}, Q' and X are as defined above for Formula (I).

The present application includes a compound of Formula (I) or a pharmaceutically acceptable salt, solvate and/or prodrug thereof:

Formula (I)



wherein:

R^1 is selected from the group consisting of hydrogen, C_1-C_3 alkyl, —(CH_2)P(O)(OR^{12}); $CO(R^{12})$, $COO(R^{12})$, $C(O)N(R^{12})_2$, $SO(R^{12})$ and $SO_2(R^{12})$;

R^2 to R^6 are independently selected from the group consisting of hydrogen and lower alkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, R^7 and R^8 are taken together with the atoms to which they are attached form a 3- or 7-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, SO_2, N, and NR^{13} wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a member of the group consisting of C_1-C_3 alkyl and C_1-C_3 haloalkyl, halogen, CN, OR^{13}, $N(R^{13})_2$, $COOR^{13}$, $C(O)N(R^{13})_2$, SR6, SO_2R^{13}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^{13})$, wherein said C_1-C_6 alkyl, C_2-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl;

R^9, R^{10} and, R^{11} are independently selected from the group consisting of hydrogen, halogen, CN, OR^{13}, $N(R^{13})_2$, SR^{13}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^{13}, C_1-C_6 alkyl substituted by SR^{13}, C_1-C_6 alkyl substituted by $N(R^{13})_2$, C_2-C_6 haloalkyl, $COOR^{13}$, $C(O)N(R^{13})_2$, SO_2R^{13}, $COOR^{13}$, $C(O)N(R^{13})_2$, SO_2R^{13}, C_1-C_6 alkyl, C_2-C_6, alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, and a 3- to 67-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^{13})$, wherein said C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, and 3- to 7-membered heterocyclic ring groups are optionally substituted by one or more substituents independently selected from the group consisting of CN, OR^{13}, $N(R^{13})_2$, and SR^{13}, and wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a member of the group consisting of C_1-C_3 alkyl and C_1-C_3 haloalkyl, halogen, CN, OR^{13}, $N(R^{13})_2$, $COOR^{13}$, $C(O)N(R^{13})_2$, SR^{13}, SO_2R^{13}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^{13})$, wherein said C_1-C_6 alkyl, C_2-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl;

X is selected from O, NR^{13}, S, SO and SO_2;

wherein R^{12} is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^{13} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, C_1-C_6 alkyl substituted by OR^{13}, C_1-C_6 alkyl substituted by SR^{13}, C_1-C_6 alkyl substituted by $N(HR^{13})$, $N(R^{13})_2$, C_2-C_6 haloalkyl, $COOR^{13}$, $C(O)N(R^{13})_2$, SO_2R^{13}, $COOR^{13}$, C_1-C_6 alkyl, C_2-C_6, alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, and a 3- to 7-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^{13})$, wherein

said C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, and 3- to 7-membered heterocyclic ring groups are optionally substituted by one or more substituents independently selected from the group consisting of CN, OR^{13}, $N(R^{13})_2$, and SR^{13}, and wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a member of the group consisting of C_1-C_3 alkyl and C_1-C_3 haloalkyl, halogen, CN, OR^{13}, $N(R^{13})_2$, $COOR^{13}$, $C(O)N(R^{13})_2$, SR^{13}, SO_2R^{13}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^{13})$, wherein said C_1-C_6 alkyl, C_2-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl; and

A is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl, heterocycloalkynyl aryl, heteroaryl, C_0-$C_1P(O)(OR^{12})_2$, CO(Q'), COO(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), wherein Q' is selected from hydrogen, C_1-C_{20} alkyl, C_1-C_{20} haloalkyl, C_2-C_{20} alkenyl, C_2-C_{20} haloalkenyl, C_2-C_{20} alkynyl, C_2-C_{20} haloalkynyl, C_3-C_7 cycloalkyl, and a 3- to 7-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^{13})$, wherein said C_1-C_{20} alkyl, C_2-C_{20} haloalkyl, C_2-C_6 alkenyl, C_2-C_{20} haloalkenyl, C_3-C_7 cycloalkyl, and 3- to 7-membered heterocyclic ring groups are optionally substituted by one or more substituents independently selected from the group consisting of CN, OR^{13}, $N(R^{13})_2$, and SR^{13}, and wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a member of the group consisting of C_1-C_3 alkyl and C_1-C_3 haloalkyl; and

wherein R^{12} and R^{13} are independently defined as above.

In some embodiments, when, in the compounds of Formula I, all available hydrogen atoms in a group are optionally replaced with a halogen atom, the halogen atom is F, Cl or Br. In some embodiments, when all available hydrogen atoms in a group are optionally replaced with a halogen atom, the halogen atom is F or Br. In some embodiments, when all available hydrogen atoms in a group are optionally replaced with a halogen atom, the halogen atom is F.

Therefore, in some embodiments, all available hydrogen atoms are optionally substituted with a fluorine, chlorine or bromine atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, all available hydrogen atoms are optionally substituted with a halogen or bromine atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, all available hydrogen atoms are optionally substituted with a halogen or chlorine atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogen atoms are optionally substituted with deuterium. In some embodiments, all available hydrogen atoms are optionally substituted with a fluorine atom and/or all available atoms are optionally substituted with deuterium. In some embodiments, all available atoms are optionally substituted with deuterium.

In some embodiments, all available hydrogen atoms are optionally substituted with an alternate isotope thereof. In some embodiments, the alternate isotope of hydrogen is deuterium. Accordingly, in some embodiments, the compounds of the application are isotopically enriched with deuterium. In some embodiments, one or more of A, X, Q', R^1, R^2, R^3, R^4, R^5, R^6, R^7R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} comprises one or more deuterium or one or more of A, X, Q', R^1, R^2, R^3, R^4, R^5, R^6, R^7R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} is deuterium.

In some embodiments, R^1 is selected from hydrogen, C_1-C_3 alkyl, C_1-C_3 alkylene$P(O)(OR^{12})_2$, $C(O)R^{12}$, CO_2R^{12}, $C(O)N(R^{12})_2$, $S(O)R^{12}$ and SO_2R^{12}; wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^1 is selected from $S(O)R^{12}$ and SO_2R^{12}, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^1 is selected from hydrogen, C_1-C_3 alkyl, $CH_2P(O)(OR^{12})_2$, $CH_2CH_2P(O)(OR^{12})_2$, $CH_2CH(CH_3)P(O)(OR^{12})_2$, $CH(CH_3)CH_2P(O)(OR^{12})_2$, $CH(CH_3)P(O)(OR^{12})_2$, $CH(CH_2CH_3)P(O)(OR^{12})_2$, $C(O)R^{12}$, CO_2R^{12} and $C(O)N(R^9)_2$, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^1 is selected from hydrogen, C_1-C_3 alkyl, $CH_2P(O)(OR^{12})_2$, $CH_2CH_2P(O)(OR^{12})_2$, $CH_2CH(CH_3)P(O)(OR^{12})_2$, $CH(CH_3)CH_2P(O)(OR^{12})_2$, $CH(CH_3)P(O)(OR^{12})_2$, $CH(CH_2CH_3)P(O)(OR^{12})_2$, $C(O)R^{12}$ and CO_2R^{12}, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^1 is selected from hydrogen, CH_3, CH_2CH_3, $CH(CH_3)_2$, $CH_2P(O)(OR^{12})_2$ and $CH(CH_3)P(O)(OR^{12})_2$, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^1 is selected from hydrogen, deuterium, F, CH_3, CF_3, CD_3, CH_2CH_3, CD_2CD_3, CF_2CF_3, $CH(CH_3)_2$, $CD(CD_3)_2$, $CF(CF_3)_2$, $C(CD_3)_3$, $C(CF_3)_3$, and $C(CH_3)_2$. In some embodiments, R^1 is selected from hydrogen, deuterium, CH_3, CF_3 and CD_3. In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is selected from $CH_2P(O)(OR^{12})_2$ and $CH(CH_3)P(O)(OR^{12})_2$, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^1 is $CH(CH_3)P(O)(OR^{12})_2$. In some embodiments, R^1 is $CH_2P(O)(OR^{12})_2$.

In some embodiments, R^2 to R^6 are independently selected from hydrogen and C_1-C_4 alkyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^2 is selected from hydrogen, CH_3, CH_2CH_3, $CH(CH_3)_2$ and $C(CH_3)_3$, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^2 is selected from hydrogen, CH_3, CH_2CH_3, $CH(CH_3)_2$ and $C(CH_3)_3$, wherein all available hydrogen atoms are optionally substituted with a fluorine atom and/or all available hydrogen atoms are optionally substituted with deuterium. In some embodiments, R^2 is selected from hydrogen and deuterium, Br, F, CH_3, CF_3, CH_2CH_3, CD_2CD_3, CF_2CF_3, $CH(CH_3)_2$, $CD(CD_3)_2$, $CF(CF_3)_2$, $C(CD_3)_3$, $C(CF_3)_2$, and $C(CH_3)_3$. In

some embodiments, R^2 is selected from hydrogen and deuterium. In some embodiments, R^2 is hydrogen.

In some embodiments, R^3, R^4, R^5 and R^6 are independently selected from hydrogen, CH_3, CH_2CH_3, $CH(CH_3)_2$ and $C(CH_3)_3$, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^3, R^4, R^5 and R^6 are independently selected from hydrogen, CH_3, CH_2CH_3, $CH(CH_3)_2$ and $C(CH_3)_3$, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogen atoms are optionally substituted with deuterium. In some embodiments, at least one of R^3, R^4, R^5 and R^6 is deuterium or at least one of R^3, R^4, R^5 and R^6 comprises deuterium. In some embodiments, at least one of R^3 and R^4 or R^5 and R^6 is deuterium or at least one of R^3 and R^4 or R^5 and R^6 comprises deuterium. In some embodiments, R^3, R^4, R^5 and R^6 are independently selected from hydrogen, deuterium, Br, F, CH_3, CD_2H, CDH_2, CD_3, CH_2CH_3, CH_2CH_2D, CH_2CD_2H and CD_2CD_3. In some embodiments, R^3, R^4, R^5 and R^6 and R^4 are independently selected from hydrogen, deuterium, F, CH_3, CD_2H, CDH_2 and CD_3. In some embodiments, R^3, R^4, R^5 and R^6 are independently selected from hydrogen, deuterium, F, CH_3 and CD_3. In some embodiments, R^3, R^4, R^5 and R^6 are independently selected from hydrogen, deuterium and F. In some embodiments, at least one of R^3, R^4, R^5 and R^6 is F. In some embodiments, at least one of R^3 and R^4 or R^5 and R^6 is deuterium. In some embodiments, at least one of R^3, R^4, R^5 and R^6 is deuterium. In some embodiments, R^3, R^4, R^5 and R^6 are all hydrogen. In some embodiments, R^3, R^4, R^5 and R^6 are all deuterium.

In some embodiments, R^7 and R^8 are independently selected from hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_4 haloalkyl, substituted or unsubstituted C_3-C_7 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, the C_3-C_7 cycloalkyl in R^7 and R^8 is independently selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, the heterocycloalkyl in R^7 and R^8 is, independently, a saturated or unsaturated heterocycle. In some embodiments heterocycloalkyl in R^7 and R^8 is, independently, a saturated or unsaturated bridged bicyclic heterocycle. In some embodiments, the saturated or unsaturated bridged bicyclic heterocycle is independently selected from azabicyclohexanyl, diazabicycloheptanyl, oxobicyclohexanyl, oxobicycloheptanyl and oxobicycloheptanenyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, the heterocycloalkyl in R^7 and R^8 independently, a saturated or unsaturated heterocycle. In some embodiments, heterocycloalkyl in R^7 and R^8 is, independently, a saturated or unsaturated bridged bicyclic heterocycle. In some embodiments, the saturated or unsaturated bridged bicyclic heterocycle is independently, selected from azabicyclohexanyl, diazabicycloheptanyl, oxobicyclohexanyl, oxobicycloheptanyl and oxobicycloheptanenyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, the heterocycloalkyl in R^7 and R^8 independently selected from aziridinyl, oxiranyl, thiiranyl, oxaxiridinyl, dioxiranyl, azetidinyl, oxetanyl, theitanyl, diazetidinyl, dioxetanyl, dithietanyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, isoxthiolidinyl, thiazolidinyl, isothiazolidinyl, dioxolanyl, dithiolanyl, piperidinyl, triazolyl, furazanyl, oxadiazolyl, thiadiazolyl, dioxazolyl, dithiazolyl, tetrazolyl, oxatetrazolyl, tetrahydropyranyl, diazinanyl (e.g, piperazinyl), morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, azepanyl, oxepanyl, thiepanyl and diazepanyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, the heteroaryl in R^7 and R^8 is independently selected from, azepinyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, 1,3-dioxolanyl, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, triazolyl and thienyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, R^7 and R^8 are independently selected from hydrogen, C_1-C_4 alkyl and C_2-C_6 alkenyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^7 and R^8 are independently selected from hydrogen and C_1-C_4 alkyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^7 and R^8 are independently from hydrogen and C_1-C_4 alkyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogen atoms are optionally substituted with deuterium. In some embodiments, R^7 and R^8 are independently selected from hydrogen, deuterium, Br, F, CH_3, CF_3, CD_2H, CDH_2, CD_3, CH_2CH_3, CF_2CF_3, and CD_2CD_3. In some embodiments, R^7 and R^8 are independently selected from hydrogen, deuterium, CH_3, CD_2H, CDH_2, CD_3, CH_2CH_3 and CD_2CD_3. In some embodiments, R^7 and R^8 are independently selected from hydrogen, deuterium, CH_3, CD_3, CH_2CH_3 and CD_2CD_3. In some embodiments, R^7 and R^8 are independently selected from CH_3, CD_3, CH_2CH_3 and CD_2CD_3. In some embodiments, R^7 and R^3 are both CH_3, CD_3, CH_2CH_3 or CD_2CD_3. In some embodiments, R^7 and R^3 are both CH_3. In some embodiments, R^7 and R^8 are both CD_3. In some embodiments, R^7 and R^8 are both CH_2CH_3. In some embodiments, R^7 and R^3 are both CD_2CD_3.

In some embodiments, R^7 and R^8 are taken together with the nitrogen atom therebetween to form a 3- to 7-membered heterocyclic ring optionally including 1 to 2 additional ring heteromoieties selected from O, S, S(O), SO_2, N and NR^{13}, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^7 and R^8 are taken together with the nitrogen atom therebetween to form a 4- to 7-membered heterocyclic ring optionally including 1 to 2 additional ring heteromoieties selected from O, S, S(O), SO_2, N and NR^{13}, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^7 and R^8 are taken together with the nitrogen atom therebetween to form azetidinyl, diazetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, thiazolidinyl, isothiazolidinyl, piperidinyl, diazinanyl (e.g. piperazinyl), morpholinyl or azepanyl ring, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^7 and R^8 are taken together with the nitrogen atom therebetween to form pyrrolidinyl, piperidinyl or diazinanyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^7 and R^8 are taken together with the nitrogen atom therebetween to form pyrrolidinyl, piperidinyl or diazinanyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogens are optionally substituted with deuterium. In some embodiments, R^7 and R^8 are taken together with the nitrogen atom therebetween to form pyrrolidinyl, piperidinyl or diazinanyl, wherein all available hydrogens are optionally substituted with deuterium.

When R^7 and R^8 are substituted, in some embodiments, the substituents are independently selected from one or more of Br, Cl, F, CO_2H, CO_2CH_3, $C(O)NH_2$, $C(O)N(CH_3)_2$, $C(O)NHCH_3$, SO_2CH_3, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, C_2-C_6 alkenyl, C_2-C_6 fluoroalkenyl, C_2-C_6 alkynyl, C_2-C_6 fluoroalkynyl, C_3-C_6 cycloalkyl and a 3- to 6-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, S(O), SO_2, N, NH and NCH_3. In some embodiments, the substituents on R^7 and R^8 are independently selected from one to three of Br, Cl, F, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, C_2-C_6 alkenyl, C_2-C_6 fluoroalkenyl, C_2-C_6 alkynyl and C_2-C_6 fluoroalkynyl. In some embodiments, the substituents on R^7 and R^8 are independently selected from one or two of Br, Cl, F, CH_3 and CF_3.

In some embodiments, R^9, R^{10} and R^{11} are independently selected from hydrogen, halogen, CN, OR^{13}, $N(R^{13})_2$, SR^{13}, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_6 haloalkenyl, CO_2R^{13}, $C(O)N(R^{13})_2$, $S(O)R^{13}$, SO_2R^{13}, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl and a 3- to 7-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, S(O), SO_2, N and NR^{13}, wherein said C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring groups are optionally substituted by one or more substituents independently selected from CN, OR^{13}, $N(R^{13})_2$ and SR^{13} and wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a substituent selected from halogen, CO_2R^{13}, $C(O)N(R^{13})_2$, SO_2R^{13}, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl and a 3- to 6-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, S(O), SO_2, N and NR^{13}; wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, R^9, R^{10} and R^{11} are independently selected from hydrogen, halogen, CN, OR^{13}, $N(R^{13})_2$, SR^{13}, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_6 haloalkenyl, CO_2R^{13}, $C(O)N(R^{13})_2$, $S(O)R^{13}$, SO_2R^{13}, C_2-C_6 alkenyl, C_2-C_6 alkynyl and C_2-C_6 haloalkynyl, wherein said C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl and C_2-C_6 haloalkynyl groups are optionally substituted by one or more substituents independently selected from CN, OR^{13}, $N(R^{13})_2$ and SR^{13}, and wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^9, R^{10} and R^{11} are independently selected from hydrogen, F, Cl, Br, CN, OR^{13}, $N(R^{13})_2$, SR^{13}, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_6 haloalkenyl, CO_2R^{13}, $C(O)N(R^{13})_2$, $S(O)R^{13}$, SO_2R^{13}, C_2-C_6 alkenyl, C_2-C_6 alkynyl and C_2-C_6 haloalkynyl, wherein said C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl and C_2-C_6 haloalkynyl groups are optionally substituted by one to three substituents independently selected from CN, OR^{13}, $N(R^{13})_2$ and SR^{13}, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^9, R^{10} and R^{11} are independently selected from hydrogen, F, Cl, Br, CN, OR^{13}, $N(R^{13})_2$, SR^{13}, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, C_1-C_4 haloalkyl, C_2-C_6 haloalkenyl, CO_2R^{13}, $S(O)R^{13}$, SO_2R^{13}, $C(O)N(R^{13})_2$, C_2-C_6 alkenyl and C_2-C_6 alkynyl, wherein said C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl and C_2-C_6 alkynyl groups are optionally substituted by one or two substituents independently selected from CN, OR^{13}, $N(R^{13})_2$ and SR^{13}, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^9, R^{10} and R^{11} are independently selected from hydrogen, F, Cl, Br, CN, OR^{13}, $N(R^{13})_2$, SR^{13}, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, C_1-C_4 haloalkyl, C_2-C_6 haloalkenyl, CO_2R^{13}, $S(O)R^{13}$, SO_2R^{13} and C_2-C_6 alkenyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^9, R^{10} and R^{11} are independently selected from hydrogen, F, Cl, Br and CN wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^9, R^{10} and R^{11} are independently selected from hydrogen, deuterium, F, Cl, Br and CN. In some embodiments, R^9, R^{10} and R^{11} are independently selected from hydrogen and deuterium. In some embodiments, R^9, R^{10} and R^{11} are all hydrogen. In some embodiments, R^9, R^{10} and R^{11} are all deuterium. In some embodiments, R^{10} is selected from hydrogen, deuterium, F, Cl, Br and CN and R^9 and R^{10} are selected from hydrogen and deuterium. In some embodiments, R^{10} is selected from hydrogen, deuterium, F and CN and R^9 and R^{11} are selected from hydrogen and deuterium. In some embodiments, R^{10} is selected from hydrogen, F and CN and R^9 and R^{10} are selected from hydrogen and deuterium. In some embodiments, R^{10} is selected from hydrogen, F and CN and R^9 and R^{11} both hydrogen.

In some embodiments, the C_3-C_7 cycloalkyl in R^9, R^{10} and R^{11} is independently selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, the 3- to 7-membered heterocyclic ring in R^9, R^{10} and R^{11} is, independently, a saturated or unsaturated heterocycle. In some embodiments, the 3- to 7-membered heterocyclic ring in R^9, R^{10} and R^{11} is, independently, a saturated or unsaturated bridged bicyclic heterocycle. In some embodiments, the saturated or unsaturated bridged bicyclic heterocycle is independently selected from azabicyclohexanyl, diazabicycloheptanyl, oxobicyclohexanyl, oxobicycloheptanyl and oxobicycloheptanenyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, the 3- to 7-membered heterocyclic ring in R^9, R^{10} and R^{11} is, independently, a saturated or unsaturated heterocycle. In some embodiments, the 3- to 7-membered heterocyclic ring in R^9, R^{10} and R^{11} is, independently, a saturated or unsaturated bridged bicyclic heterocycle. In some embodiments, the saturated or unsaturated bridged bicyclic heterocycle is independently, selected from azabicyclohexanyl, diazabicycloheptanyl, oxobicyclohexanyl, oxobicycloheptanyl and oxobicycloheptanenyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, the 3- to 7-membered heterocyclic ring in R^9, R^{10} and R^{11} is independently selected from aziridinyl, oxiranyl, thiiranyl, oxaxiridinyl, dioxiranyl, azetidinyl, oxetanyl, theitanyl, diazetidinyl, dioxetanyl, dithietanyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, isoxthiolidinyl, thiazolidinyl, isothiazolidinyl, dioxolanyl, dithiolanyl, piperidinyl, triazolyl, furazanyl, oxadiazolyl, thiadiazolyl, dioxazolyl, dithiazolyl, tetrazolyl, oxatetrazolyl, tetrahydropyranyl, diazinanyl (e.g, piperazinyl), morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, azepanyl, oxepanyl, thiepanyl and diazepanyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, each R^{12} is independently selected from hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_4 haloalkyl, substituted or unsubstituted C_3-C_7 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_4 alkylene C_3-C_7 cycloalkyl, substituted or unsubstituted C_1-C_4 alkylene C_3-C_7 heterocycloalkyl, substituted or unsubstituted C_1-C_4 alkylenearyl and substituted or unsubstituted C_1-C_4 alkyleneheteroaryl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, the C_3-C_7 cycloalkyl each R^{12} is independently is selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, the heterocycloalkyl each R^{12} is independently is a saturated or unsaturated heterocycle. In some embodiments heterocycloalkyl in R^{12} is a saturated or unsaturated bridged bicyclic heterocycle. In some embodiments, the saturated or unsaturated bridged bicyclic heterocycle is independently selected from azabicyclohexanyl, diazabicycloheptanyl, oxobicyclohexanyl, oxobicycloheptanyl and oxobicycloheptanenyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, the heterocycloalkyl each R^{12} is independently is selected from aziridinyl, oxiranyl, thiiranyl, oxaxiridinyl, dioxiranyl, azetidinyl, oxetanyl, theitanyl, diazetidinyl, dioxetanyl, dithietanyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, isoxthiolidinyl, thiazolidinyl, isothiazolidinyl, dioxolanyl, dithiolanyl, piperidinyl, triazolyl, furazanyl, oxadiazolyl, thiadiazolyl, dioxazolyl, dithiazolyl, tetrazolyl, oxatetrazolyl, tetrahydropyranyl, diazinanyl (e.g, piperazinyl), morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, azepanyl, oxepanyl, thiepanyl and diazepanyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, the heteroaryl in each R^{12} is independently is selected from, azepinyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, 1,3-dioxolanyl, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, triazolyl and thienyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, each R^{12} is independently selected from hydrogen, C_1-C_4 alkyl and C_2-C_6 alkenyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, each R^{12} is independently selected from hydrogen and C_1-C_4 alkyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, each R^{12} is independently selected from hydrogen and C_1-C_4 alkyl, wherein all available hydrogen atoms are optionally substituted with fluorine atom and/or all available hydrogen atoms are optionally substituted with deuterium. In some embodiments, each R^{12} is independently selected from hydrogen, deuterium, CH_3, CD_2H, CDH_2, CD_3, CH_2CH_3 and CD_2CD_3. In some embodiments, each R^{12} is independently selected from hydrogen, deuterium, CH_3, CD_3, CH_2CH_3 and CD_2CD_3. In some embodiments each R^{12} is independently selected from hydrogen, CH_3, CD_3, CH_2CH_3 and CD_2CD_3. In some embodiments, R^{12} is CH_3. In some embodiments,

R^{12} is CD_3. In some embodiments, each R^{12} is independently CH_2CH_3. In some embodiments, R^{12} is CD_2CD_3.

In some embodiments, each R^{12} is independently selected from substituted or unsubstituted C_1-C_4 alkylene C_3-C_7 cycloalkyl, substituted or unsubstituted C_1-C_4 alkylene C_3-C_7 heterocycloalkyl, substituted or unsubstituted C_1-C_4 alkylenearyl, substituted or unsubstituted C_1-C_4 alkyleneheteroaryl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, each R^{12} is independently selected from substituted or unsubstituted C_1-C_4 alkylenearyl and substituted or unsubstituted C_1-C_4 alkyleneheteroaryl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, each R^{12} is independently substituted or unsubstituted C_1-C_4 alkylenearyl wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, each R^{12} is independently substituted or unsubstituted CH_2 aryl wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, each R^{12} is independently substituted or unsubstituted CH_2 phenyl.

When R^{12} is substituted, in some embodiments, the substituents are independently selected from one or more of Br, Cl, F, CO_2H, CO_2CH_3, $C(O)NH_2$, $C(O)N(CH_3)_2$, $C(O)NHCH_3$, SO_2CH_3, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, C_2-C_6 alkenyl, C_2-C_6 fluoroalkenyl, C_2-C_6 alkynyl, C_2-C_6 fluoroalkynyl, C_3-C_6 cycloalkyl and a 3- to 6-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, S(O), SO_2, N, NH and NCH_3. In some embodiments, the substituents on R^{12} are independently selected from one to three of Br, Cl, F, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, C_2-C_6 alkenyl, C_2-C_6 fluoroalkenyl, C_2-C_6 alkynyl and C_2-C_6 fluoroalkynyl. In some embodiments, the substituents on R^{12} are independently selected from one or two of Br, Cl, F, CH_3 and CF_3.

In some embodiments, Y is halogen. In some embodiments, the halogen in Y is selected from F, Cl and Br. In some embodiments, the halogen in Y is selected from F and Cl. In some embodiments, the halogen in Y is F.

In some embodiments, Y is X-A.

In some embodiments, X is selected from S, S(O) and SO_2. In some embodiments, X is selected from O, NR^{13} and S, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, X is selected from NR^{13} and O. In some embodiments, X is O.

In some embodiments, A is selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, $P(O)(OR^{12})_2$, C_1-C_3 alkylene$P(O)(OR^{12})_2$, C_1-C_3 alkylene C_3-C_7 cycloalkyl, C_1-C_3 alkylene C_4-C_6 cycloalkenyl, C_1-C_3 alkyleneheterocycloalkyl, C_1-C_3 alkylenearyl, C_1-C_3 alkyleneheteroaryl, C(O)Q', CO_2Q', C(O)N(Q')$_2$, S(O)Q' and SO_2Q', wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, A is selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_3 alkylene C_3-C_7 cycloalkyl, C_1-C_3 alkylene C_4-C_6 cycloalkenyl, C_1-C_3 alkyleneheterocycloalkyl, C_1-C_3 alkylenearyl, C_1-C_3 alkyleneheteroaryl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, A is selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and heterocycloalkyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, A is selected from hydrogen, C_1-C_4 alkyl and C_2-C_4 alkenyl, wherein all available hydrogen atoms are optionally substituted with halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, A is selected from hydrogen and C_1-C_4 alkyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, A is selected from hydrogen and C_1-C_4 alkyl, wherein all available hydrogen atoms are optionally substituted with a fluorine atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, A is selected from hydrogen, CH_3, CF_3, CH_2CH_3, CD_2CD_3, CF_2CF_3, $CH(CH_3)_2$, $CD(CD_3)_2$, $CF(CF_3)_2$, $C(CD_3)_3$, $C(CF_3)_3$, and $C(CH_3)_3$. In some embodiments, A is selected from hydrogen, CH_3, CH_2CH_3, CD_2CD_3, $CH(CH_3)_2$, $CD(CD_3)_2$, $C(CD_3)_3$, and $C(CH_3)_3$.

In some embodiments, A is selected from C_1-C_3 alkylene C_3-C_7 cycloalkyl, C_1-C_3 alkylene C_4-C_6 cycloalkenyl, C_1-C_3 alkyleneheterocycloalkyl, C_1-C_3 alkylenearyl and C_1-C_3 alkyleneheteroaryl, wherein all available hydrogen atoms are optionally substituted with halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, A is selected CH_2C_3-C_7 cycloalkyl, CH_2C_4-C_6 cycloalkenyl, CH_2 heterocycloalkyl, CH_2 aryl and CH_2 heteroaryl, wherein all available hydrogen atoms are optionally substituted with halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, A is selected from CH_2C_3-C_7 cycloalkyl, CH_2 aryl and CH_2 heteroaryl, wherein all available hydrogen atoms are optionally substituted with halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, A is CH_2 aryl, wherein all available hydrogen atoms are optionally substituted with halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, A is CH_2 phenyl.

In some embodiments, A is selected from hydrogen, $P(O)(OR^{12})_2$, $CH_2P(O)(OR^{12})_2$, $CH_2CH_2P(O)(OR^{12})_2$, $CH_2CH(CH_3)P(O)(OR^{12})_2$, $CH(CH_3)CH_2P(O)(OR^{12})_2$, $CH(CH_3)P(O)(OR^{12})_2$, $CH(CH_2CH_3)P(O)(OR^{12})_2$, C(O)Q', CO_2Q', C(O)N(Q')$_2$S(O)Q' and SO_2Q', wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, A

is selected from hydrogen, $P(O)(OR^{12})_2$, $CH_2P(O)(OR^{12})_2$, $CH(CH_3)P(O)(OR^{12})_2$, $C(O)N(Q')_2$, $C(O)Q'$, $S(O)Q'$ and SO_2Q', wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, A is selected from $S(O)Q'$ and SO_2Q', wherein all available hydrogen atoms are optionally substituted with halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, A is selected from hydrogen, $P(O)(OR^{12})_2$, $CH_2P(O)(OR^{12})_2$, $CH(CH_3)P(O)(OR^{12})_2$, $C(O)N(Q')_2$ and $C(O)Q'$. In some embodiments, A is selected from hydrogen, $P(O)(OR^{12})_2$ and $C(O)Q'$. In some embodiments, A is hydrogen. In some embodiments, A is $C(O)N(Q')_2$, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, A is $P(O)(OR^{11})_2$, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, A is $C(O)Q'$, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, Q' is selected from C_1-C_{20} alkyl, C_1-C_{20} haloalkyl, C_2-C_{20} alkenyl, C_2-C_{20} haloalkenyl, C_2-C_{20} alkynyl and C_2-C_{20} haloalkynyl wherein said C_1-C_{20} alkyl, C_2-C_{20} haloalkyl, C_2-C_6 alkenyl, C_2-C_{20} haloalkenyl, C_2-C_{20} alkynyl and C_2-C_{20} haloalkynyl groups are optionally substituted by one to three substituents independently selected from CN, OR^{13}, $N(R^{13})_2$, CO_2R^{13}, SR^{13}, C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and a 3- to 7-membered heterocyclic ring, and/or are disubstituted on the same carbon atom with C_{1-6} alkyl, or with C_{2-6} alkylene to form a C_3-C_7 cycloalkyl ring, and wherein each of said C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and 3- to 7-membered heterocyclic ring are further optionally substituted with a substituent selected from C_1-C_3 alkyl and C_1-C_3 haloalkyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, Q' is selected from C_1-C_{20} alkyl, C_2-C_{20} alkenyl and C_2-C_{20} alkynyl wherein said C_1-C_{20} alkyl, C_2-C_6 alkenyl and C_2-C_{20} alkynyl are optionally substituted by one to three substituents independently selected from CN, OR^{13}, $N(R^{13})_2$, CO_2R^{13} and SR^{13}, and/or are disubstituted on the same carbon atom with C_{1-6} alkyl, or with C_{2-6} alkylene to form a C_3-C_7 cycloalkyl ring, and wherein each of said C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and 3- to 7-membered heterocyclic ring are further optionally substituted with a substituent selected from C_1-C_3 alkyl and C_1-C_3 haloalkyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, Q' is selected from C_1-C_{20} alkyl, C_2-C_{20} alkenyl and C_2-C_{20} alkynyl wherein said C_1-C_{20} alkyl, C_2-C_6 alkenyl and C_2-C_{20} alkynyl are optionally substituted by one to three substituents independently selected from $N(R^{13})_2$ and CO_2R^{13}, and/or disubstituted on the same carbon atom with C_{1-6} alkyl, or with C_{2-6} alkylene to form a C_3-C_7 cycloalkyl ring, wherein said C_3-C_7 cycloalkyl is further optionally substituted with a substituent selected from C_1-C_3 alkyl and C_1-C_3 haloalkyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, Q' is selected from C_1-C_{20} alkyl, C_2-C_{20} alkenyl and C_2-C_{20} alkynyl optionally substituted with one or two substituents independently selected from $N(R^{13})_2$ and CO_2R^{13}, and/or disubstituted on the same carbon atom with C_{1-6} alkyl, or with C_{2-6} alkylene to form a C_3-C_7 cycloalkyl ring, wherein said C_3-C_7 cycloalkyl ring is further optionally substituted with a substituent selected from C_1-C_6 alkyl and C_1-C_6 haloalkyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, Q' is C_1-C_{20} alkyl or C_2-C_{20} alkenyl substituted by $N(R^{13})_2$ and/or disubstituted on the same carbon with C_{2-6} alkylene to form a C_3-C_7 cycloalkyl ring, wherein said C_3-C_7 cycloalkyl ring is further optionally substituted with a substituent selected from C_1-C_3 alkyl and C_1-C_3 haloalkyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, Q' is C_1-C_{20} alkyl or C_2-C_{20} alkenyl substituted by $N(R^{13})_2$ wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, Q' is C_1-C_{20} alkyl substituted by $N(R^{13})_2$ wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, Q' is C_1-C_{10} alkyl substituted by $N(R^{13})_2$ wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, Q' is C_1-C_{10} alkyl substituted by $N(R^{13})_2$ wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogen atoms are optionally substituted with deuterium.

In some embodiments, Q' is C_1-C_{20} alkyl or C_2-C_{20} alkenyl substituted by $N(R^{13})_2$ and disubstituted on the same carbon atom with C_{2-6} alkylene to form a C_3-C_7 cycloalkyl ring, wherein said C_3-C_7 cycloalkyl ring is further optionally substituted with a substituent selected from C_1-C_3 alkyl and C_1-C_6 haloalkyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, Q' is C_1-C_{20} alkyl substituted by $N(R^{13})_2$ and disubstituted on the same carbon atom with C_{2-6} alkylene to form a C_3-C_7 cycloalkyl ring, wherein said C_3-C_7 cycloalkyl ring is further optionally substituted with a substituent selected from C_1-C_3 alkyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, Q' is C_1-C_{10} alkyl substituted by $N(R^{13})_2$ and disubstituted on the same carbon atom with C_{2-6} alkylene to form a C_3-C_7 cycloalkyl ring, wherein said C_3-C_7 cycloalkyl ring is further optionally substituted with a substituent selected from C_1-C_3 alkyl and wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogen atoms are optionally substituted with deuterium. In some embodiments, Q' is C_1-C_{10} alkyl substituted by $N(R^{13})_2$ and disubstituted on the same carbon atom with C_{2-6} alkylene to form a C_5-C_6 cycloalkyl ring, wherein said C_3-C_7 cycloalkyl ring is further optionally substituted with a substituent selected from C_1-C_3 alkyl and wherein all available hydrogen atoms

are optionally substituted with a halogen atom and/or all available hydrogen atoms are optionally substituted with deuterium. In some embodiments, Q' is C_1-C_{10} alkyl substituted by $N(R^{13})_2$ and disubstituted on the same carbon atom with C_{2-6} alkylene to form a spirocyclohexanyl ring, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogen atoms are optionally substituted with deuterium.

In some embodiments, Q' is C_1-C_{20} alkyl or C_2-C_{20} alkenyl optionally substituted by CO_2R^{13}, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, Q' is C_1-C_{20} alkyl or C_2-C_{20} alkenyl substituted by CO_2R^{13}, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogens are optionally substituted with a deuterium. In some embodiments, Q' is C_1-C_{10} alkyl or C_2-C_{10} alkenyl substituted by CO_2R^{13}, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogens are optionally substituted with a deuterium. In some embodiments, Q' is C_1-C_6 alkyl or C_2-C_6 alkenyl substituted by CO_2R^{13}, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogens are optionally substituted with a deuterium.

In some embodiments, Q' is C_1-C_{20} alkyl or C_2-C_{20} alkenyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, Q' is C_1-C_{20} alkyl or C_2-C_{20} alkenyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogen atoms are optionally substituted with deuterium. In some embodiments, when Q' is C_1-C_{20} alkyl, Q' is a saturated fatty acid derivative, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogens are optionally substituted with a deuterium. In some embodiments, when Q' is C_2-C_{20} alkenyl, Q' is an unsaturated fatty acid derivative, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogens are optionally substituted with a deuterium.

In some embodiments, Q' is C_1-C_{10} alkyl or C_2-C_{10} alkenyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, Q' is C_1-C_6 alkyl or C_2-C_6 alkenyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, Q' is C_1-C_4 alkyl or C_2-C_4 alkenyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, Q' is C_1-C_4 alkyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiment, Q' is selected from CH_3, CF_3, CD_2H, CDH_2, CD_3, CH_2CH_3, CF_2CF_3, and CD_2CD_3.

In some embodiments, Q' is selected from C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and a 3- to 7-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, S(O), SO_2, N and NR^{13}, wherein said C_3-C_7 cycloalkyl, C_4-C_6 cycloalkenyl and 3- to 7-membered heterocyclic ring groups are optionally substituted by one to three substituents independently selected from CN, OR^{13}, $N(R^{13})_2$, CO_2R^{13}, SR^{13}, C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and a 3- to 7-membered heterocyclic ring and wherein each of said C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and 3- to 7-membered heterocyclic rings are each further optionally substituted with a substituent selected from C_1-C_3 alkyl; wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, Q' is selected from C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and a 3- to 7-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, N, S(O), SO_2 and NR^{13}, wherein said C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and 3- to 7-membered heterocyclic ring groups are optionally substituted by one to three substituents independently selected from $N(R^{13})_2$ and CO_2R^{13}, and wherein said C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a substituent selected from C_1-C_3 alkyl; wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, Q' is selected from C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and a 3- to 7-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from N and NR^{13}, wherein said C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and 3- to 7-membered heterocyclic ring groups are optionally substituted by one to three substituents independently selected from CN, OR^{13}, $N(R^{13})_2$, CO_2R^{13}, SR^{13} and a 3- to 7-membered heterocyclic ring and wherein each of said C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and 3- to 7-membered heterocyclic rings are each further optionally substituted with a substituent selected from C_1-C_3 alkyl and C_1-C_3 haloalkyl; wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, Q' is a 3- to 7-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from N and NR^{13}, wherein said 3- to 7-membered heterocyclic ring group is optionally substituted by one to three substituents independently selected from CN, OR^{13}, $N(R^{13})_2$, CO_2R^{13}, SR^{13} and a 3- to 7-membered heterocyclic ring and wherein each of said 3- to 7-membered heterocyclic rings are each further optionally substituted with a substituent selected from C_1-C_3 alkyl; wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, Q' is a 3- to 7-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from N and NR^{13}, wherein said 3- to 7-membered heterocyclic ring group is optionally substituted by a 3- to 7-membered heterocyclic ring and wherein each of said 3- to 7-membered heterocyclic rings are each further optionally substituted with a substituent selected from C_1-C_3 alkyl; wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, Q' is a 5- to 6-membered heterocyclic ring including 1 ring heteromoiety selected from N and NR^{13}, wherein said 5 to 6-membered heterocyclic ring group is optionally substituted by a 5- to 6-membered heterocyclic ring, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, Q' is a piperidinyl or a pyrrolidinyl substituted by a piperidinyl or a pyrrolidinyl, wherein all available hydrogen atoms are

optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, Q' is a piperidinyl substituted by a piperidinyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, the C_3-C_7 cycloalkyl in Q' is selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

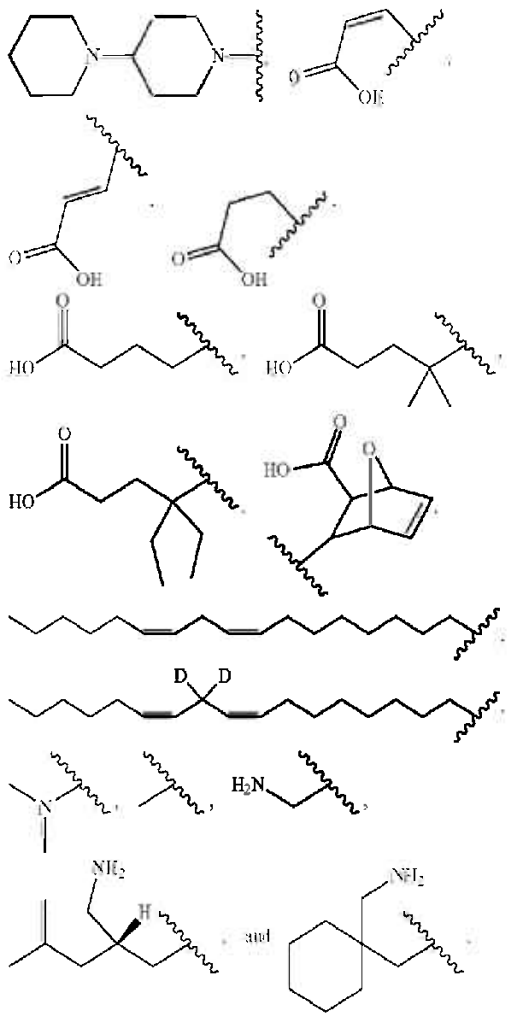
In some embodiments, the C_4-C_7 cycloalkenyl in Q' is selected from cyclobutenyl, cyclopentenyl and cyclohexenyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, the 3- to 7-membered heterocyclic ring in Q' is selected from aziridinyl, oxiranyl, thiiranyl, oxaxiridinyl, dioxiranyl, azetidinyl, oxetanyl, theitanyl, diazetidinyl, dioxetanyl, dithietanyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, isoxthiolidinyl, thiazolidinyl, isothiazolidinyl, dioxolanyl, dithiolanyl, piperidinyl, triazolyl, furazanyl, oxadiazolyl, thiadiazolyl, dioxazolyl, dithiazolyl, tetrazolyl, oxatetrazolyl, tetrahydropyranyl, diazinanyl (e.g, piperazinyl), morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, azepanyl, oxepanyl, thiepanyl and diazepanyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

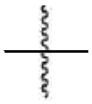
In some embodiments, the 3- to 7-membered heterocyclic ring in Q' is a saturated or unsaturated heterocycle. In some embodiments, the 3- to 7-membered heterocyclic ring in Q' is a saturated or unsaturated bridged bicyclic heterocycle. In some embodiments, the saturated or unsaturated bridged bicyclic heterocycle is selected from azabicyclohexanyl, diazabicycloheptanyl, oxobicyclohexanyl, oxobicycloheptanyl and oxobicycloheptanenyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, the heteroaryl in Q' is selected from, azepinyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, 1,3-dioxolanyl, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, triazolyl and thienyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, Q' is selected from the groups listed below:



wherein:



indicates a point of covalent attachment.

In some embodiments, A is C(O)Q' and Q' is selected from the groups listed above.

In some embodiment, A is $C(O)N(Q')_2$ and each Q' is C_1-C_4 alkyl or C_2-C_4 alkenyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, each Q' is C_1-C_4 alkyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiment, Q' is selected from CH_3, CF_3, CD_2H, CDH_2, CD_3, CH_2CH_3, CF_2CF_3, and CD_2CD_3. In some embodiment, A is $C(O)N(Q')_2$ and each Q' is CH_3 or CD_3.

In some embodiments, each R^{13} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, and a 3- to 7-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, S(O), SO_2,

N and N(R^{14}), wherein said C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring groups are optionally substituted by one or more substituents independently selected from CN, OR^{14}, $N(R^{14})_2$ and SR^{14}, and wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a substituent selected from halogen, CO_2R^{14}, $C(O)N(R^{14})_2$, SO_2R^{14}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, and C_2-C_6 haloalkynyl wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, each R^{13} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, and a 3- to 7-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, S(O), SO_2, N and N(R^{14}), wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, each R^{13} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, and a 3- to 7-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, S(O), SO_2, N and N(R^{14}), wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, each R^{13} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, each R^{13} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogen atoms are optionally substituted with deuterium. In some embodiments, each R^{13} is independently selected from hydrogen and C_1-C_6 alkyl wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogen atoms are optionally substituted with deuterium. In some embodiment, each R^{13} is independently selected from hydrogen, deuterium, F, CH_3, CF_3, CD_2H, CDH_2, CD_3, CH_2CH_3, CF_2CF_3, and CD_2CD_3. In some embodiment, each R^{13} is independently selected from hydrogen, deuterium, CH_3, CD_2H, CDH_2, CD_3, CH_2CH_3, and CD_2CD_3. In some embodiment, each R^{13} is hydrogen. In some embodiment, each R^{13} is independently CH_3 or CD_3.

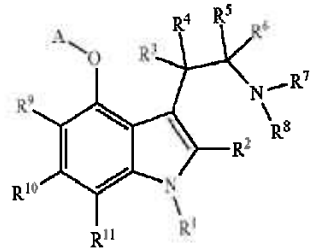
In some embodiments, R^{14} is selected from hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_4 haloalkyl, substituted or unsubstituted C_3-C_7 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, R^{14} is selected from hydrogen, C_1-C_4 alkyl and C_2-C_6 alkenyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^{14} is selected from hydrogen and C_1-C_4 alkyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^{14} is selected from hydrogen and C_1-C_4 alkyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogen atoms are optionally substituted with deuterium. In some embodiments, R^{14} is hydrogen, deuterium, F, CH_3, CF_3, CD_2H, CDH_2, CD_3, CH_2CH_3, CF_2CF_3, and CD_2CD_3. In some embodiments, R^{14} is selected is from hydrogen, deuterium, CH_3, CD_2H, CDH_2, CD_3, CH_2CH_3 and CD_2CD_3. In some embodiments, R^{14} is selected from hydrogen, deuterium, CH_3 and CD_3. In some embodiments, R^{14} is hydrogen.

When R^{14} is substituted, in some embodiments, the substituents are independently selected from one or more of Br, Cl, F, CO_2H, CO_2CH_3, $C(O)NH_2$, $C(O)N(CH_3)_2$, $C(O)NHCH_3$, SO_2CH_3, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, C_2-C_6 alkenyl, C_2-C_6 fluoroalkenyl, C_2-C_6 alkynyl, C_2-C_6 fluoroalkynyl, C_3-C_6 cycloalkyl and a 3- to 6-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, S(O), SO_2, N, NH and NCH_3. In some embodiments, the substituents on R^4 are independently selected from one to three of Br, Cl, F, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, C_2-C_6 alkenyl, C_2-C_6 fluoroalkenyl, C_2-C_6 alkynyl and C_2-C_6 fluoroalkynyl. In some embodiments, the substituents on R^4 are independently selected from one or two of Br, Cl, F, CH_3 and CF_3.

In some embodiments, when Y is X-A and X is O, the compound of Formula (I) is a compound of Formula (I-A). Accordingly, the application includes a compound of Formula (I-A) or a pharmaceutically acceptable salt, solvate and/or prodrug thereof:

(I-A)

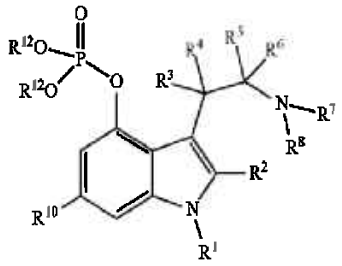


wherein:

A, R^1, R^2, R^3, R^4, R^5, R^8, R^7R^8, R^9, R^{10} and R^{11} are as defined in Formula (I), and wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof, provided either R^1 is C_1-C_6P(O)$(OR^{12})_2$ and R^2, R^3, R^4, R^5, R^8, R^7R^8, Ra, R^{10}, R^{11} and R^{12} and A are as defined in Formula (I); or A is selected from C_1-C_6 alkyleneP(O)$(OR^{12})_2$, C_1-C_6 alkylene C_3-C_7 cycloalkyl, C_1-C_6 alkylene C_4-C_6 cycloalkenyl, C_1-C_6 alkyleneheterocycloalkyl, C_1-C_3 alkylenearyl, C_1-C_6 alkyleneheteroaryl, C(O)Q', CO_2Q', $C(O)N(Q')_2$, S(O)Q' and SO_2Q' and R^1, R^2, R^3, R^4, R^5, R^8, R^7R^8, R^9, R^{10}, R^{11} and R^{12}, and Q' are as defined in Formula (I).

In some embodiments, when Y is X-A, X is O, A is P(O)$(OR^{12})_2$, R^9 and R^{11} are both H, the compound of Formula (I) is a compound of Formula (I-B). Accordingly, the application includes a compound of Formula (I-B) or a pharmaceutically acceptable salt, solvate and/or prodrug thereof:

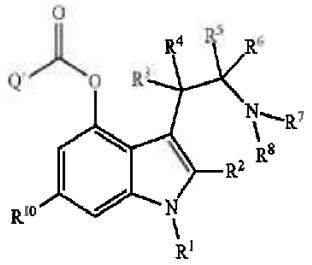
(I-B)



wherein:
R^1, R^2, R^3, R^4, R^5, R^6, R^7R^8, R^{10} and R^{12} are as defined in Formula (I), and wherein all available hydrogen atoms are optionally substituted with a fluorine atom and/or all available atoms are optionally substituted with an alternate isotope thereof provided R^1 is C_1-C_6 alkyleneP(O)$(OR^{12})_2$.

In some embodiments, when Y is X-A, X is O, A is C(O)Q', and R^9 and R^{11} are both H, the compound of Formula (I) is a compound of Formula (I-C). Accordingly, in an embodiment, the application includes a compound of Formula (I-C) or a pharmaceutically acceptable salt, solvate and/or prodrug thereof:

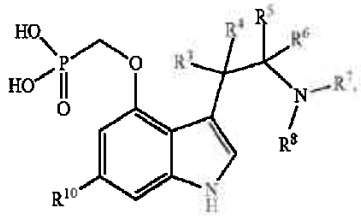
(I-C)



wherein
Q', R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^{10} are as defined in Formula (I), and wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, when Y is X-A, X is O, A is $CH_2P(O)(OR^{12})_2$, R^2 is hydrogen, R^9 and R^{11} are both hydrogen and R^1 is hydrogen, the compound of Formula (I) is a compound of Formula (I-E). Accordingly, the application includes a compound of Formula (I-E) or a pharmaceutically acceptable salt, solvate and/or prodrug thereof:

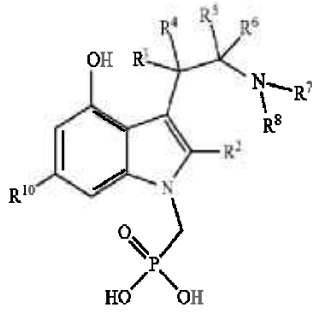
(I-E)



wherein:
R^3, R^4, R^5, R^6, R^7, R^8 and R^{10} are as defined in Formula (I), and wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, when Y is X-A, X is O, A is hydrogen, R^9 and R^{11} are both hydrogen and R^1 is $CH_2P(O)(OH)_2$, the compound of Formula (I) is a compound of Formula (I-F). Accordingly, the application includes a compound of Formula (I-F) or a pharmaceutically acceptable salt, solvate and/or prodrug thereof:

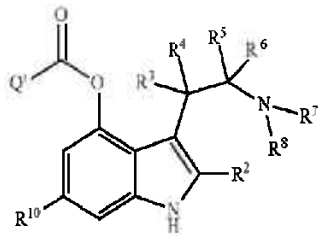
(I-F)



wherein:
R^2, R^3, R^4, R^5, R^6, R^7R^8 and R^{10} are as defined in Formula (I), and wherein all available hydrogen atoms are optionally substituted with a fluorine atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, when Y is X-A, X is O, A is C(O)Q', R^9 and R^{11} are both H and R^1 is H, the compound of Formula (I) is a compound of Formula (I-G). Accordingly, the application includes a compound of Formula (I-G) or a pharmaceutically acceptable salt, solvate and/or prodrug thereof:

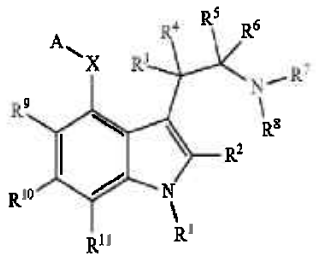
(I-G)



wherein:
R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^{10} are as defined in Formula (I), and
wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, Y is X-A and the compound of Formula (I) is a compound of Formula (I-H). Accordingly, in some embodiments, the application includes a compound of Formula (I-H) or a pharmaceutically acceptable salt, solvate and/or prodrug thereof:

(I-H)



wherein:

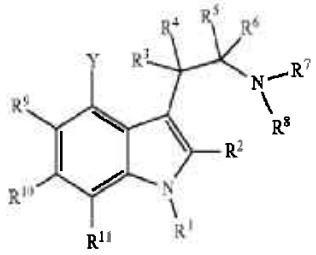
A, X, R^1, R^2, R^3, R^4, R^5, R^6, R^7R^8, R^9, R^{10} and R^{11} are as defined in Formula (I), and wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof,

provided either R^1 is C_1-$C_6P(O)(OR^{12})_2$ and R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and R^{12}, X and A are as defined in Formula (I); or

Y is X-A wherein A is selected from C_1-C_6 alkyleneP(O)$(OR^{12})_2$, C_1-C_6 alkylene C_3-C_7 cycloalkyl, C_1-C_6 alkylene C_4-C_6 cycloalkenyl, C_1-C_6 alkyleneheterocycloalkyl, C_1-C_3 alkylenearyl, C_1-C_6 alkyleneheteroaryl, C(O)Q', CO_2Q', $C(O)N(Q')_2$, S(O)Q' and SO_2Q' and R^1, R^2, R^3, R^4, R^5, R^6, R^7R^8, R^9, R^{10}, R^{11} and R^{12}, Q' and X are as defined in Formula (I).

In some embodiments, Y is halogen and the compound of Formula (I) is a compound of Formula (I-1). Accordingly, in some embodiments, the application includes a compound of Formula (I-1) or a pharmaceutically acceptable salt, solvate and/or prodrug thereof:

(I-I)



wherein:

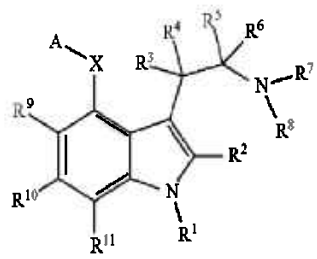
Y is halogen; and

R^1, R^2, R^3, R^4, R^5, R^6, R^7R^8, R^9, R^{10} and R^{11} are as defined in Formula (I), and wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof, provided R^1 is C_1-C_6 alkyleneP(O)$(OR^{12})_2$ and R^{12} is as defined in Formula (I).

In some embodiments, in the compounds of Formula (I-I), Y is selected from F, Cl and Br. In some embodiments, in the compounds of Formula (I-I), Y is selected from F and Br. In some embodiments, in the compounds of Formula (I-I), Y is F

In some embodiments, Y is X-A and A is C_{1-6} alkyl and the compound of Formula (I) is a compound of Formula (I-J). Accordingly, in some embodiments, the application includes a compound of Formula (I-H) or a pharmaceutically acceptable salt, solvate and/or prodrug thereof:

(I-J)



wherein:

A is C_{1-6} alkyl;

R^1 is C_1-C_6 alkyleneP(O)(OR^{12}) and

X, R^1, R^2, R^3, R^4, R^5, R^6, R^7R^8, R^9, R^{10}, R^{11} and R^{12} are as defined in Formula (I), and wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, A in the compound of Formula (I-J) is selected from CH_3, CD_2H, CDH_2, CD_3, CH_2CH_3, CH_2CH_2D, CH_2CD_2H and CD_2CD_3. In some embodiments, A in the compound of Formula (I-J) selected from CH_3, CD_3, CH_2CH_3 and CD_2CD_3. In some embodiments, A in the compound of Formula (I-J) selected from CH_3, and CD_3.

In some embodiments, R^1 in the compounds of Formula (I-A) to (I-C) and (I-H) to (I-J) is selected from hydrogen, C_1-C_3 alkyl, C_1-C_3 alkyleneP(O)$(OR^{12})_2$, C(O)R^{12}, CO_2OR^{12}, $C(O)N(R^{12})_2$, S(O)R^{12} and SO_2R^{12}; wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^1 in the compounds of Formula (I-A) to (I-C) and (I-H) to (I-J) is selected from hydrogen, C_1-C_3 alkyl, $CH_2P(O)(OR^{12})_2$, $CH_2CH_2P(O)(OR^{12})_2$, $CH_2CH(CH_3)P(O)(OR^{12})_2$, $CH(CH_3)CH_2P(O)(OR^{12})_2$, $CH(CH_3)P(O)(OR^{12})_2$, $CH(CH_2CH_3)P(O)(OR^{12})_2$, C(O)$R^{12}$ and CO_2R^{12}, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^1 in the compounds of Formula (I-A) to (I-C) and (I-H) to (I-J) is selected from hydrogen, CH_3, CH_2CH_3, and $CH(CH_3)_2$, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^1 in the compounds of Formula (I-A) to (I-C) and (I-H) to (I-J) is selected from hydrogen, deuterium, Br, F, CH_3, CF_3, CD_3, CH_2CH_3, CD_2CD_3, CF_2CF_3, $CH(CH_3)_2$, $CD(CD_3)_2$, $CF(CF_3)_2$, $C(CD_3)_3$, $C(CF_3)_3$, and $C(CH_3)_2$, In some embodiments, R^1 in the compounds of Formula (I-A) to (I-C) and (I-H) to (I-J) is selected from hydrogen, deuterium, CH_3, CF_3 and CD_3. In some embodiments, R^1 in the compounds of Formula (I-A) to (I-C) and (I-H) to (I-J) is hydrogen. In some embodiments, R^1 in the compounds of Formula (I-A) to (I-C) and (I-H) to (I-J) is selected from $CH_2P(O)(OR^{12})_2$ and $CH(CH_3)P(O)(OR^{12})_2$, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, R^1 in the compounds of Formula (I-A) to (I-C) and (I-H) to (I-J is $CH(CH_3)P(O)(OR^{12})_2$. In some embodiments, R^1 in the compounds of Formula (I-A), (I-C) and (I-H) is $CH_2P(O)(OR^{12})$.

In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), R^2 to R^6 are independently selected from hydrogen and C_1-C_4 alkyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), at least one of R^3, R^4, R^5 and R^6 is deuterium or at least one of R^3, R^4, R^5 and R^6 comprises deuterium. In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), at least one of R^3 and R^4 or R^5 and R^6 is deuterium or at least one of R^3 and R^4 or R^5 and R^6 comprises deuterium. In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), R^3, R^4, R^5 and R^6 are independently selected from hydrogen, deuterium, Br, F, CH_3, CD_2H, CDH_2, CD_3, CH_2CH_3, CH_2CH_2D, CH_2CD_2H and CD_2CD_3. In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), R^3, R^4, R^5 and R^6 and R^4 are independently selected from hydrogen, deuterium, F, CH_3, CD_2H, CDH_2 and CD_3. In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), R^3, R^4, R^5 and R^6 are independently selected from hydrogen, deuterium, F, CH_3 and CD_3. In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), R^3, R^4, R^5 and R^6 are independently selected from hydrogen, deuterium and F. In some embodiments, in the compounds of Formula to (I-C) and (I-E) to (I-J), at least one of R^3, R^4, R^5 and R^6 is F. In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), at least one of R^3 and R^4 or R^5 and R^6 is deuterium. In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), R^3, R^4, R^5 and R^6 are all hydrogen. In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), R^3, R^4, R^5 and R^6 are all deuterium.

In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), R^7 and R^8 are independently selected from hydrogen, deuterium, Br, F, CH_3, CF_3, CD_2H, CDH_2, CD_3, CH_2CH_3, CF_2CF_3, and CD_2CD_3. In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), R^7 and R^8 are independently selected from hydrogen, deuterium, CH_3, CD_3, CH_2CH_3 and CD_2CD_3. In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), R^7 and R^8 are both hydrogen, deuterium, CH_3, CD_3, CH_2CH_3 or CD_2CD_3. In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), R^7 and R^8 are both hydrogen. In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), R^7 and R^8 are both CH_3. In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J) R^7 and R^8 are both CD_3. In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), R^7 and R^8 are both CH_2CH_3. In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), R^7 and R^8 are both CD_2CD_3.

In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), at least one of R^3, R^4, R^5 and R^6 is deuterium or at least one of R^3, R^4, R^5 and R^6 comprises deuterium and R^7 and R^8 are independently selected from hydrogen, deuterium, CH_3, CD_3, CH_2CH_3 and CD_2CD_3. In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), at least one of R^3 and R^4 or R^5 and R^6 is deuterium and R^7 and R^8 are both hydrogen, deuterium, CH_3, CD_3, CH_2CH_3 or CD_2CD_3. In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), R^3, R^4, R^5 and R^6 are all hydrogen or R^3, R^4, R^5 and R^6 are all deuterium and R^7 and R^8 are both hydrogen, deuterium, CH_3, CD_3, CH_2CH_3 or CD_2CD_3.

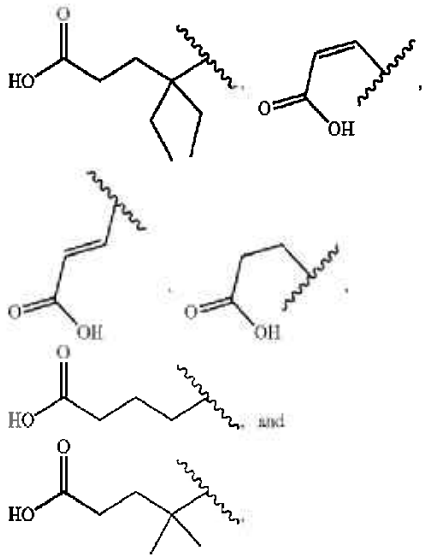
In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), R^7 and R^8 are taken together with the nitrogen atom therebetween to form pyrrolidinyl, piperidinyl or diazinanyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogens are optionally substituted with deuterium. In some embodiments, in the compounds of Formula (I-A) to (I-C) and (I-E) to (I-J), R^3, R^4, R^5 and R^6 are all hydrogen or R^3, R^4, R^5 and R^6 are all deuterium and R^7 and R^8 are taken together with the nitrogen atom therebetween to form pyrrolidinyl, piperidinyl or diazinanyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogens are optionally substituted with deuterium

In some embodiments, in the compound of Formula (I-A), (I-H) to (I-J), R^9, R^{10} and R^{11} are independently selected from hydrogen, F, Cl, Br, CN, OR^{13}, $N(R^{13})_2$, SR^{13}, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, C_1-C_4 haloalkyl, C_2-C_6 haloalkenyl, CO_2R^{13}, $S(O)R^{13}$, SO_2R^{13} and C_2-C_6 alkenyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, in the compound of Formula (I-A), (I-H) to (I-J), R^9, R^{10} and R^{11} are independently selected from hydrogen, F, Cl, Br and CN wherein all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, in the compound of Formula (I-A), (I-H) to (I-J), R^9, R^{10} and R^{11} are independently selected from hydrogen, deuterium, F, Cl, Br and CN. In some embodiments, in the compound of Formula (I-A), (I-H) to (I-J), R^9, R^{10} and R^{11} are independently selected from hydrogen and deuterium. In some embodiments, in the compound of Formula (I-A), (I-H) to (I-J), R^9, R^{10} and R^{11} are all hydrogen. In some embodiments, in the compound of Formula (I-A), (I-H) to (I-J), R^9, R^{10} and R^{11} are all deuterium. In some embodiments, in the compound of Formula (I-A), (I-H) to (I-J), R^{10} is selected from hydrogen, deuterium, F, Cl, Br and CN and R^9 and R^{11} are selected from hydrogen and deuterium. In some embodiments, in the compound of Formula (I-A), (I-H) to (I-J), R^{10} is selected from hydrogen, deuterium, F and CN and R^9 and R^{10} are selected from hydrogen and deuterium. In some embodiments, in the compound of Formula (I-A), (I-H) to (I-J), R^{10} is selected from hydrogen, F and CN and R^9 and R^{10} are selected from hydrogen and deuterium. In some embodiments, in the compound of Formula (I-A), (I-H) to (I-J), R^{10} is selected from hydrogen, F and CN and R^9 and R^{10} both hydrogen. In some embodiments, in the compound of Formula (I-A), (I-H) to (I-J), R^{10} is selected from hydrogen, deuterium, F, Cl, Br and CN.

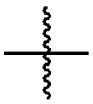
In some embodiments, in the compounds of Formula (I-A) and (I-H) when A is C(O)Q', CO_2(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), and in the compound and in the compounds of Formula (I-C) and (I-G), Q' is selected from hydrogen, C_1-C_{20} alkyl, C_2-C_{20} alkenyl and a 3 to 7-membered heterocyclic group wherein said C_1-C_{20} alkyl and C_2-C_6 alkenyl are optionally substituted by one to three substituents independently selected from $N(R^{13})_2$ and CO_2R^{13} and wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof.

In some embodiments, in the compounds of Formula (I-A) and (I-H) when A is C(O)Q', CO_2(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), and in the compound and in the com-

pounds of Formula (I-C) and (I-G), Q' is C_1-C_{10} alkyl or C_2-C_{10} alkenyl substituted by CO_2R^{10}, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogens are optionally substituted with a deuterium. In some embodiments, in the compounds of Formula (I-A) and (I-H) when A is C(O)Q', CO_2(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), and in the compound and in the compounds of Formula (I-C) and (I-G), Q' is C_1-C_6 alkyl or C_2-C_6 alkenyl substituted by CO_2R^{10}, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogens are optionally substituted with a deuterium. In some embodiments, in the compounds of Formula (I-A) and (I-H) when A is C(O)Q', CO_2(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), and in the compound and in the compounds of Formula (I-C) and (I-G), Q' is selected from

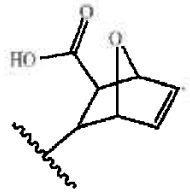


wherein:

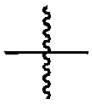


indicates a point of covalent attachment.

In some embodiments, in the compounds of Formula (I-A) and (I-H) when A is C(O)Q', CO_2(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), and in the compound and in the compounds of Formula (I-C) and (I-G), Q' is selected from C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and a 3- to 7-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from O, S, N, S(O), SO_2 and NR^{10}, wherein said C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and 3- to 7-membered heterocyclic ring groups are optionally substituted by one to three substituents independently selected from N(R^{10})$_2$ and CO_2R^{10}, and wherein said C_3-C_7 cycloalkyl, C_4-C_7 cycloalkenyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a substituent selected from C_1-C_3 alkyl; wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, in the compounds of Formula (I-A) and (I-H) when A is C(O)Q', CO_2(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), and in the compound and in the compounds of Formula (I-C) and (I-G), Q' is



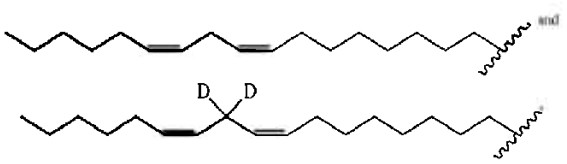
wherein:



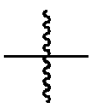
indicates a point of covalent attachment.

In some embodiments, in the compounds of Formula (I-A) and (I-H) when A is C(O)Q', CO_2(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), and in the compound and in the compounds of Formula (I-C) and (I-G), Q' is C_1-C_4 alkyl or C_2-C_4 alkenyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, Q' is C_1-C_4 alkyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, in the compounds of Formula (I-A) and (I-H) when A is C(O)Q', CO_2(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), and in the compound and in the compounds of Formula (I-C) and (I-G), Q' is selected from CH_3, CF_3, CD_2H, CDH_2, CD_3, CH_2CH_3, CF_2CF_3, and CD_2CD_3.

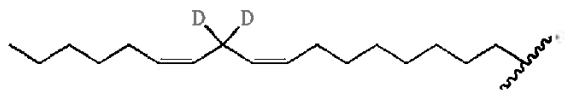
In some embodiments, in the compounds of Formula (I-A) and (I-H) when A is C(O)Q', CO_2(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), and in the compound and in the compounds of Formula (I-C) and (I-G), Q' is C_1-C_{20} alkyl or C_2-C_{20} alkenyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogen atoms are optionally substituted with deuterium. In some embodiments, in the compounds of Formula (I-A) and (I-H) when A is C(O)Q', CO_2(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), and in the compound and in the compounds of Formula (I-C) and (I-G), Q' is selected from



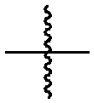
wherein



indicates a point of covalent attachment. In some embodiments, Q' is

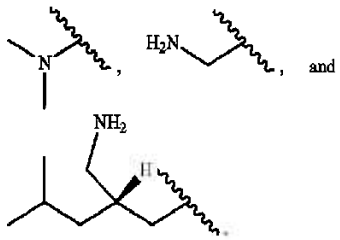


wherein



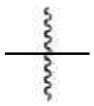
indicates a point of covalent attachment.

In some embodiments, in the compounds of Formula (I-A) and (I-H) when A is C(O)Q', CO_2(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), and in the compound and in the compounds of Formula (I-C) and (I-G), Q' is C_1-C_{20} alkyl substituted by N(R^{10})$_2$ wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, in the compounds of Formula (I-A) and (I-H) when A is C(O)Q', CO_2(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), and in the compound and in the compounds of Formula (I-C) and (I-G), Q' is C_1-C_{10} alkyl substituted by N(R^{10})$_2$ wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogen atoms are optionally substituted with deuterium. In some embodiments, in the compounds of Formula (I-A) and (I-H) when A is C(O)Q', CO_2(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), and in the compound and in the compounds of Formula (I-C) and (I-G), Q' is selected from



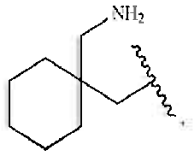
and

wherein

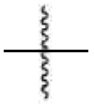


indicates a point of covalent attachment.

In some embodiments, In some embodiments, in the compounds of Formula (I-A) and (I-H) when A is C(O)Q', CO_2(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), and in the compound and in the compounds of Formula (I-C) and (I-G), Q' is C_1-C_{20} alkyl substituted by N(R^{10})$_2$ and disubstituted on the same carbon atom with C_{2-6} alkylene to form a C_3-C_7 cycloalkyl ring, wherein said C_3-C_7 cycloalkyl ring is further optionally substituted with a substituent selected from C_1-C_3 alkyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, In some embodiments, in the compounds of Formula (I-A) and (I-H) when A is C(O)Q', CO_2(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), and in the compound and in the compounds of Formula (I-C) and (I-G), Q' is C_1-C_{10} alkyl substituted by N(R^{10})$_2$ and disubstituted on the same carbon atom with C_{2-6} alkylene to form a spirocyclohexanyl ring, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available hydrogen atoms are optionally substituted with deuterium. In some embodiments, In some embodiments, in the compounds of Formula (I-A) and (I-H) when A is C(O)Q', CO_2(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), and in the compound and in the compounds of Formula (I-C) and (I-G), Q' is



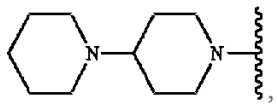
wherein



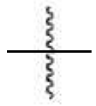
indicates a point of covalent attachment.

In some embodiments, In some embodiments, in the compounds of Formula (I-A) and (I-H) when A is C(O)Q', CO_2(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), and in the compound and in the compounds of Formula (I-C) and (I-G), Q' is a 3- to 7-membered heterocyclic ring including 1 to 2 ring heteromoieties selected from N and NR^{10}, wherein said 3- to 7-membered heterocyclic ring group is optionally substituted by one to three substituents independently selected from CN, OR^{10}, N(R^{10})$_2$, CO_2R^{10}, SR^{10} and a 3- to 7-membered heterocyclic ring and wherein each of said 3- to 7-membered heterocyclic rings are each further optionally substituted with a substituent selected from C_1-C_3 alkyl; wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, In some embodiments, in the compounds of Formula (I-A) and (I-H) when A is C(O)Q', CO_2(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), and in the compound and in the compounds of Formula (I-C) and (I-G), Q' is a 5- to 6-membered heterocyclic ring including 1 ring heteromoiety selected from N and NR^{10}, wherein said 5 to 6-membered heterocyclic ring group is optionally substituted by a 5- to 6-membered heterocyclic ring, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally substituted with an alternate isotope thereof. In some embodiments, In some embodiments, in the compounds of Formula (I-A) and (I-H) when A is C(O)Q', CO_2(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), and in the compound and in the compounds of Formula (I-C) and (I-G), Q' is a piperidinyl substituted by a piperidinyl, wherein all available hydrogen atoms are optionally substituted with a halogen atom and/or all available atoms are optionally

substituted with an alternate isotope thereof. In some embodiments, In some embodiments, in the compounds of Formula (I-A) and (I-H) when A is C(O)Q', CO_2(Q'), C(O)$N(Q')_2$, SO(Q'), SO_2(Q'), and in the compound and in the compounds of Formula (I-C) and (I-G), Q' is



wherein:

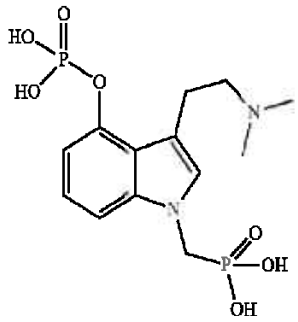


indicates a point of covalent attachment.

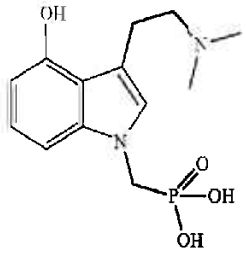
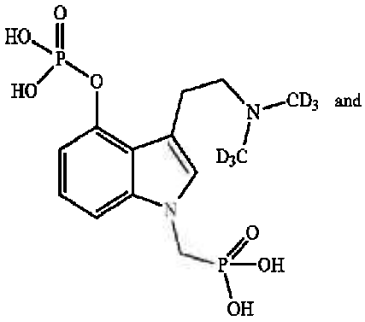
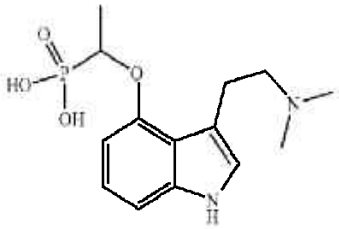
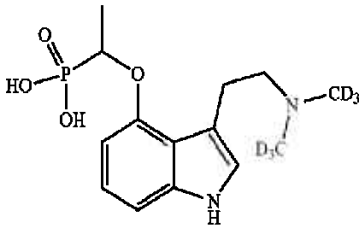
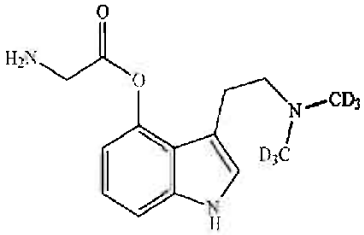
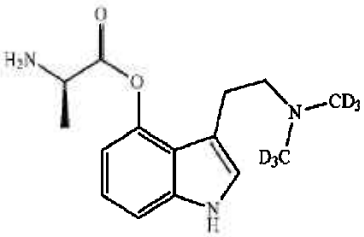
In particular embodiments of the compounds of general formula (I), and pharmaceutically acceptable salts of the foregoing, the compounds are isotopically enriched with deuterium. In aspects of these embodiments, one or more of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} may include deuterium.

In some embodiments, the compounds of Formula (I) are selected from: ((3-(2-(dimethylamino)ethyl)-4-(phosphonooxy)-1H-indol-1-yl)methyl)phosphonic acid; ((3-(2-(dimethylamino)ethyl)-4-hydroxy-1H-indol-1-yl)methyl)phosphonic acid; ((3-(2-(bis(methyl-d3)amino)ethyl)-4-(phosphonooxy)-1H-indol-1-yl)methyl)phosphonic acid; (1-((3-(2-(dimethylamino)ethyl)-1H-indol-4-yl)oxy)ethyl) phosphonic acid; (1-((3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl)oxy)ethyl)phosphonic acid; 3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl glycinate; 3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl D-alaninate; (Z)-4-((3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl)oxy)-4-oxobut-2-enoic acid; (E)-4-((3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl)oxy)-4-oxobut-2-enoic acid; 4-((3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl)oxy)-4-oxobutanoic acid; 3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl acetate; 3 3-(2-(bis(methyl-d3)amino)ethyl-1,1,2,2-d4)-1H-indol-4-yl acetate; ((4-acetoxy-3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-1-yl)methyl)phosphonic acid ((4-acetoxy-3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-1-yl)methyl)phosphonic acid; 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate; 3-(2-(d6-dimethylamino)ethyl)-1H-indol-4-yl(9Z,12Z)-octadeca-9,12-dienoate-11,11-d2; 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate-11,11-d2; 3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate; 3-(2-(bis(methyl-d3)amino)ethyl-1,1,2,2-d4)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate; 3-(2-(bis(methyl-d6)amino)ethyl-1,1,2,2-d4)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate-11,11-d2; 3-(2-(d10-diethylamino)ethyl-d4)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate; 3-(2-(d10-diethylamino)ethyl-d4)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate-11,11-d2; 3-(2-(diethylamino)ethyl-d4)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate; 3-(2-(diethylamino)ethyl-d4)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate-11,11-d2; 3-(2-(pyrrolidin-1-yl)ethyl-1,1,2,2-d4)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate; 3-(2-(pyrrolidin-1-yl)ethyl-1,1,2,2-d4)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate-11,11-d2; 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl (S)-3-(aminomethyl)-5-methylhexanoate; 3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl (S)-3-(aminomethyl)-5-methylhexanoate; 3-(2-(bis(methyl-d3)amino)ethyl-1,1,2,2-d4)-1H-indol-4-yl (S)-3-(aminomethyl)-5-methylhexanoate; 3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 2-(1-(aminomethyl)cyclohexyl)acetate; 3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl 2-(1-(aminomethyl)cyclohexyl)acetate; 3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl [1,4'-bipiperidine]-1'-carboxylate; 3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl dimethylcarbamate; 2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-bis(methyl-d3)ethan-1-amine-1,1,2,2-d4; 2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-bis(methyl-d3)ethan-1-amine; and dibenzyl (((1-((bis(benzyloxy)phosphoryl)methyl)-3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl)oxy)methyl)phosphonate, or a pharmaceutically acceptable salt, solvate and/or prodrug thereof.

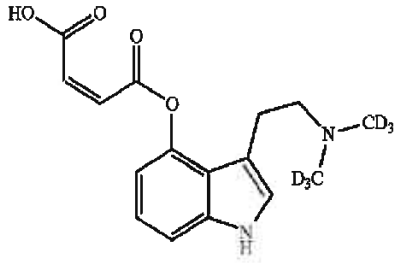
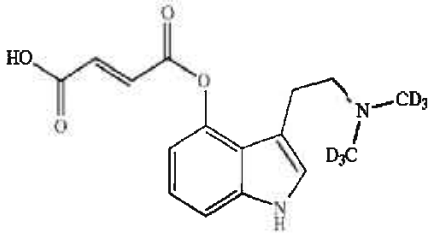
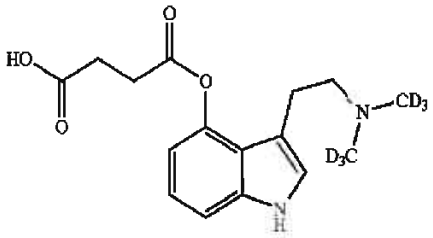
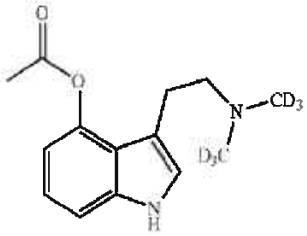
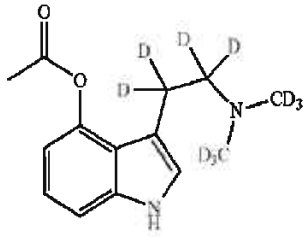
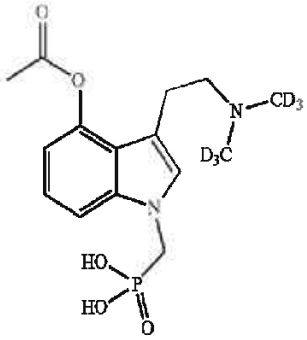
In some embodiments, the compounds of Formula (I) are selected from the compounds listed below:

Compound ID #	IUPAC Name	Chemical Formula/ Molecular Weight	Chemical Structure
I-8	((3-(2-(dimethylamino)ethyl)-4-(phosphonooxy)-1H-indol-1-yl)methyl)phosphonic acid	C13H20N2O7P2 378.26	

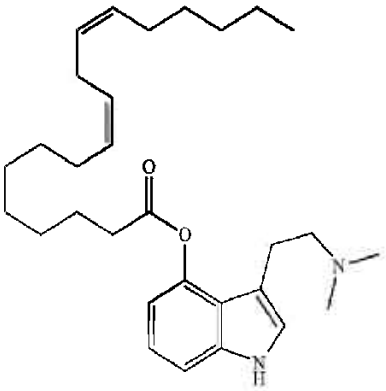
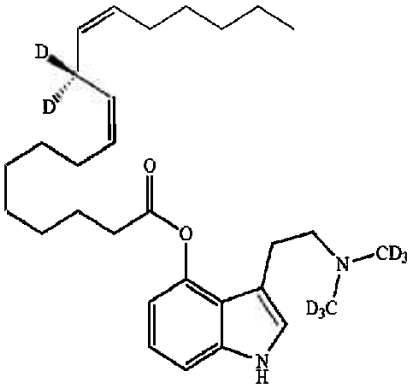
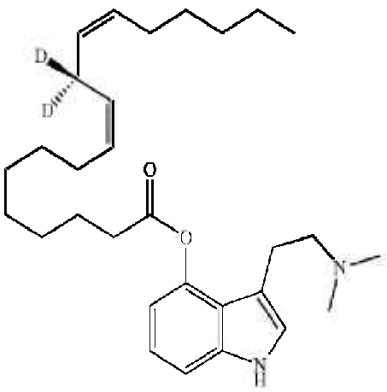
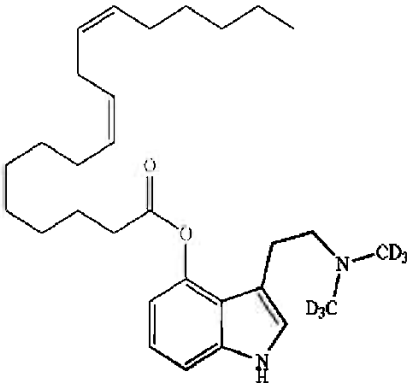
-continued

Compound ID #	IUPAC Name	Chemical Formula/ Molecular Weight	Chemical Structure
I-10	3-(2-(dimethylamino) ethyl)-4-hydroxy-1H-indol-1-yl)methyl) phosphonic acid	C13H19N2O4P: 298.28	
I-13	((3-(2-(bis(methyl-d3)amino) ethyl)-4-(phosphonooxy)-1H-indol-1-yl)methyl) phosphonic acid	C13H14D6N2O7P2 384.29	 and
I-14	(1-((3-(2-(dimethylamino) ethyl)-1H-indol-4-yl)oxy)ethyl) phosphonic acid	C14H21N2O4P 312.31	
I-15	(1-((3-(2-(bis(methyl-d3)amino) ethyl)-1H-indol-4-yl)oxy)ethyl) phosphonic acid	C14H15D6N2O4P 318.34	
I-16	3-(2-(bis(methyl-d3)amino) ethyl)-1H-indol-4-yl glycinate	C14H13D6N3O2 267.36	
I-17	3-(2-(bis(methyl-d3)amino) ethyl)-1H-indol-4-yl D-alaninate	C15H15D6N3O2 281.39	

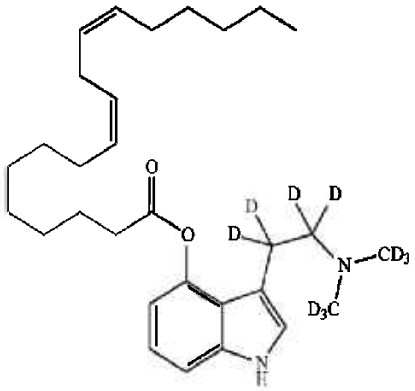
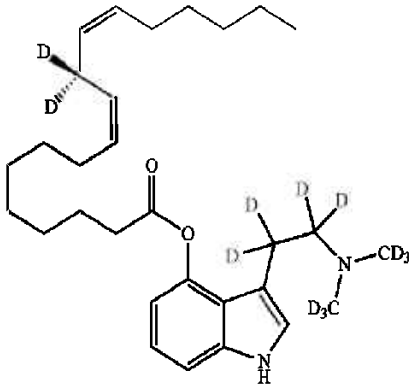
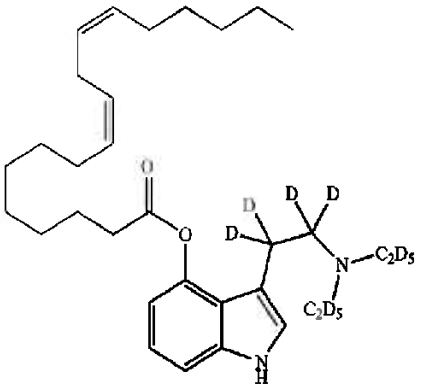
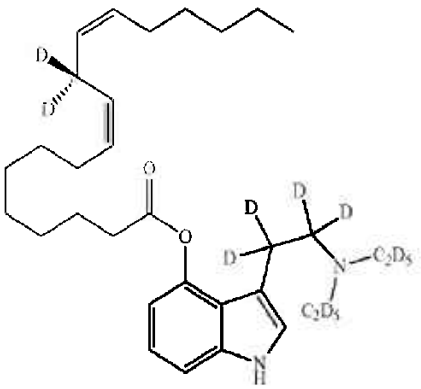
-continued

Compound ID #	IUPAC Name	Chemical Formula/ Molecular Weight	Chemical Structure
I-18	(Z)-4-((3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl)oxy)-4-oxobut-2-enoic acid	C16H12D6N2O4 308.37	
I-19	(E)-4-((3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl)oxy)-4-oxobut-2-enoic acid	C16H12D6N2O4 308.37	
I-20	4-((3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl)oxy)-4-oxobutanoic acid	C16H14D6N2O4 310.38	
I-21	3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl acetate	C14H12D6N2O2 252.35	
I-22	3-(2-(bis(methyl-d3)amino)ethyl-1,1,2,2-d4)-1H-indol-4-yl acetate	C14H8D10N2O2 256.37	
I-23	((4-acetoxy-3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-1-yl)methyl)phosphonic acid	C15H15D6N2O5P 346.35	

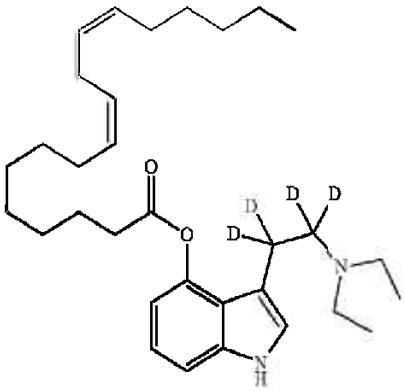
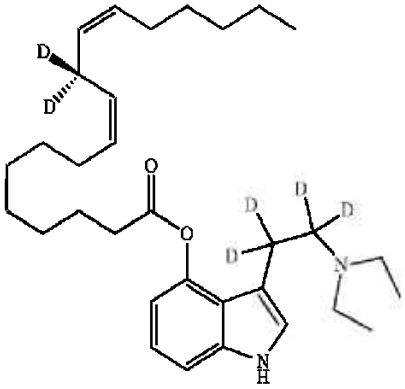
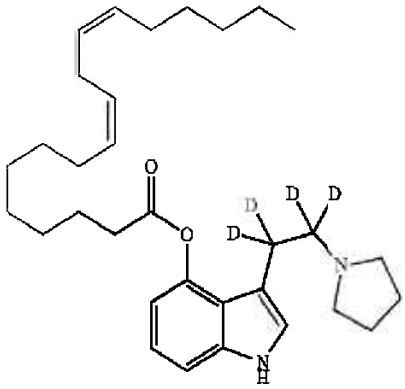
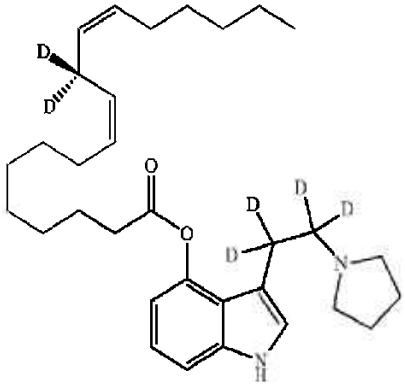
-continued

Compound ID #	IUPAC Name	Chemical Formula/ Molecular Weight	Chemical Structure
1-24	3-(2-(dimethylamino) ethyl)-1H-indol-4-yl(9Z,12Z)-octadeca-9,12-dienoate	C30H46N2O2 466.71	
1-25	3-(2-(d6-dimethylamino) ethyl)-1H-indol-4-yl(9Z,12Z)-octadeca-9,12-dienoate-11,11-d2	C30H38D8N2O2: 474.76	
1-26	3-(2-(dimethylamino) ethyl)-1H-indol-4-yl(9Z,12Z)-octadeca-9,12-dienoate-11,11-d2	C30H44D2N2O2 468.72	
1-27	3-(2-(bis(methyl-d3)amino) ethyl)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate	C30H40D6N2O2 472.75	

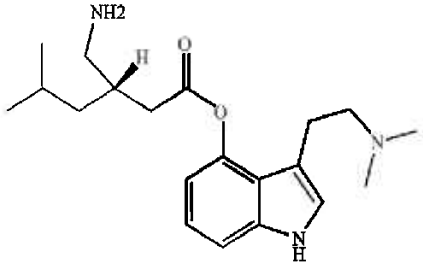
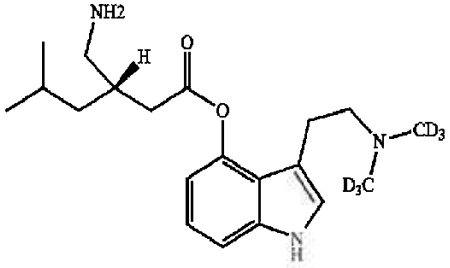
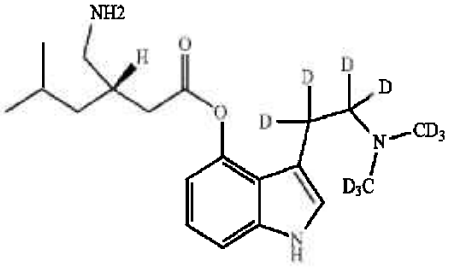
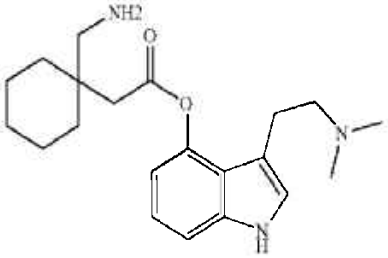
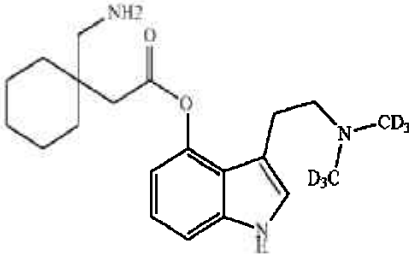
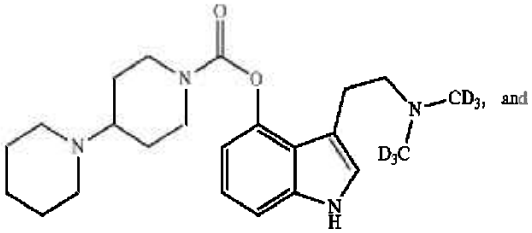
-continued

Compound ID #	IUPAC Name	Chemical Formula/ Molecular Weight	Chemical Structure
I-28	3-(2-(bis(methyl-d3)amino)ethyl-1,1,2,2-d4)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate	C30H36D10N2O2 476.77	
I-29	3-(2-(bis(methyl-d6)amino)ethyl-1,1,2,2-d4)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate-11,11-d2	C30H34D12N2O2: 478.78	
I-30	3-(2-(d10-diethylamino)ethyl-d4)-1H-indol-4-yl(9Z,12Z)-octadeca-9,12-dienoate	C32H36D14N2O2 508.85	
I-31	3-(2-(d10-diethylamino)ethyl-d4)-1H-indol-4-yl(9Z,12Z)-octadeca-9,12-dienoate-11,11-d2	C32H34D16N2O2 510.86	

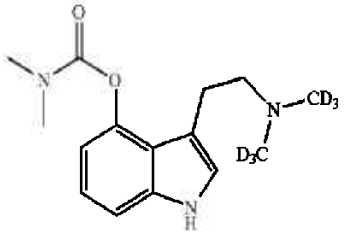
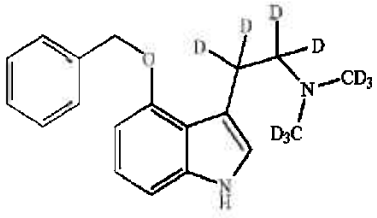
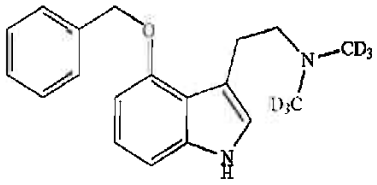
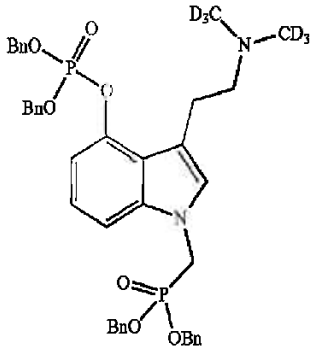
-continued

Compound ID #	IUPAC Name	Chemical Formula/ Molecular Weight	Chemical Structure
1-32	3-(2-(diethylamino)ethyl-d4)-1H-indol-4-yl(9Z,12Z)-octadeca-9,12-dienoate	C32H46D4N2O2 498.79	
1-33	3-(2-(diethylamino)ethyl-d4)-1H-indol-4-yl(9Z,12Z)-octadeca-9,12-dienoate-11,11-d2	C32H44D6N2O2 500.80	
1-34	3-(2-(pyrrolidin-1-yl)ethyl-1,1,2,2-d4)-1H-indol-4-yl(9Z,12Z)-octadeca-9,12-dienoate	C32H44D4N2O2 Exact Mass: 496.40 Molecular Weight: 496.77	
1-35	3-(2-(pyrrolidin-1-yl)ethyl-1,1,2,2-d4)-1H-indol-4-yl(9Z,12Z)-octadeca-9,12-dienoate-11,11-d2	C32H42D6N2O2 498.78	

-continued

Compound ID #	IUPAC Name	Chemical Formula/ Molecular Weight	Chemical Structure
1-36	3-(2-(dimethylamino)ethyl)-1H-indol-4-yl(S)-3-(aminomethyl)-5-methylhexanoate	C20H31N3O2 345.49	
1-37	3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl (S)-3-(aminomethyl)-5-methylhexanoate	C20H25D6N3O2 351.52	
1-38	3-(2-(bis(methyl-d3)amino)ethyl-1,1,2,2-d4)-1H-indol-4-yl (S)-3-(aminomethyl)-5-methylhexanoate	C20H21D10N3O2 355.55	
1-39	3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 2-(1-(aminomethyl)cyclohexyl)acetate	C21H31N3O2 357.50	
1-40	3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl 2-(1-(aminomethyl)cyclohexyacetate	C21H25D6N3O2 363.53	
1-41	3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl [1,4'-bipiperidine]-1'-carboxylate	C23H28D6N4O2 404.59	 and

-continued

Compound ID #	IUPAC Name	Chemical Formula/ Molecular Weight	Chemical Structure
I-42	3-(2-(bis(methyl-d3)amino) ethyl)-1H-indol-4-yl dimethylcarbamate	C15H15D6N3O2 281.39	
I-46	2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-bis(methyl-d3)ethan-1-amine-1,1,2,2-d4	C19H12D10N2O 304.46	
I-47	2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-bis(methyl-d3)ethan-1-amine	C19H16D6N2O 300.43	
I-48	dibenzyl (((1-((bis(benzyloxy) phosphoryl) methyl)-3-(2-(bis(methyl-d3)amino) ethyl)-1H-indol-4-yl)oxy)methyl) phosphonate	C42H40D6N2O7P2 994.12	

or a pharmaceutically acceptable salt, solvate and/or prodrug thereof.

In an embodiment, the compound of the present application is selected from the compounds of Examples 1 to 42 as illustrated below or a pharmaceutically acceptable salt, solvate and/or prodrug thereof

TABLE 1

Representative compounds of compound of Formula (I).

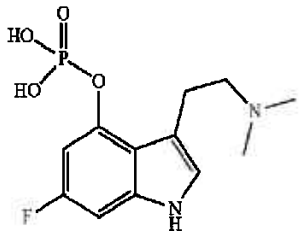
Compound ID #	Chemical Structure	IUPAC Name	Chemical Formula/ Molecular Weight
I-1		3-(2-(dimethyl-amino)ethyl)-6-fluoro-1H-indol-4-yl di-hydrogen phosphate	C12H16FN2O4P 302.24

TABLE 1-continued

Representative compounds of compound of Formula (I).

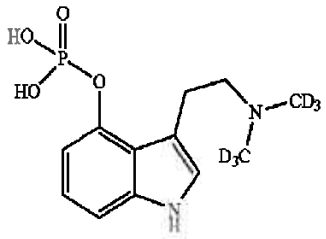
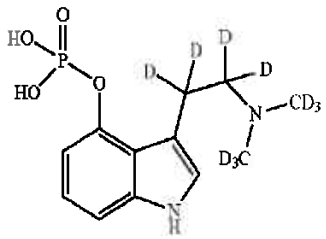
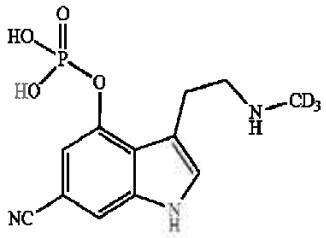
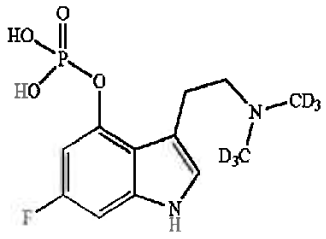
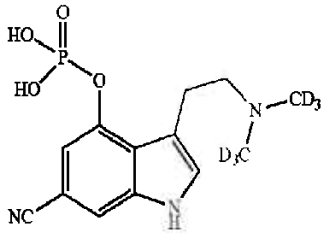
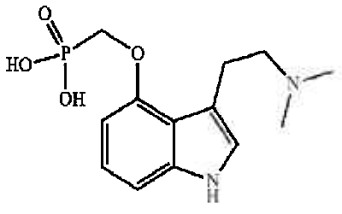
Compound ID #	Chemical Structure	IUPAC Name	Chemical Formula/ Molecular Weight
I-2		3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl dihydrogen phosphate	C12H11D6N2O4P 290.29
I-3		3-(2-(bis(methyl-d3)amino)ethyl-1,1,2,2-d4)-1H-indol-4-yl dihydrogen phosphate	C12H7D10N2O4P 294.31
I-4		6-cyano-3-(2-((methyl-d3)amino)ethyl)-1H-indol-4-yl dihydrogen phosphate	C12H11D3N3O4P 298.25
I-5		3-(2-(bis(methyl-d3)amino)ethyl)-6-fluoro-1H-indol-4-yl dihydrogen phosphate	C12H10D6FN2O4P 308.28
I-6		3-(2-(bis(methyl-d3)amino)ethyl)-6-cyano-1H-indol-4-yl dihydrogen phosphate	C13H10D6N3O4P 315.30
I-7		(((3-(2-(dimethylamino)ethyl)-1H-indol-4-yl)oxy)methyl) phosphonic acid	C13H19N2O4P 298.28

TABLE 1-continued

Representative compounds of compound of Formula (I).

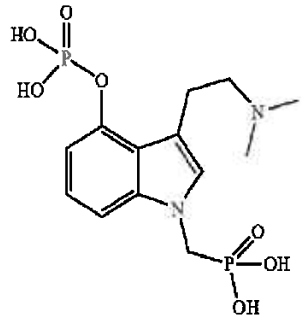
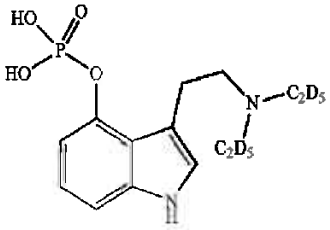
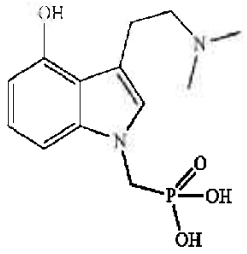
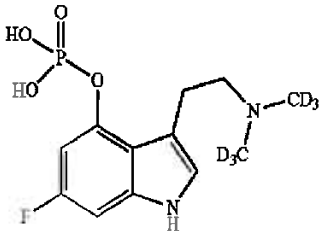
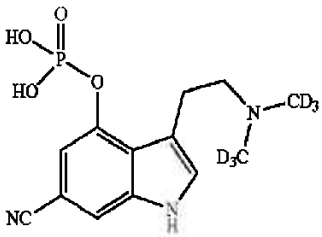
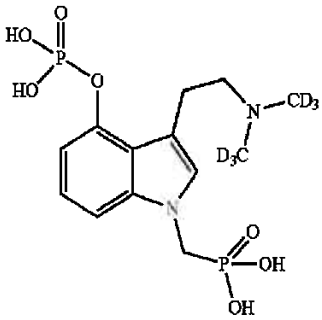
Compound ID #	Chemical Structure	IUPAC Name	Chemical Formula/ Molecular Weight
I-8		((3-(2-(dimethylamino)ethyl)-4-(phosphonooxy)-1H-indol-1-yl)methyl)phosphonic acid	C13H20N2O7P2 378.26
I-9		3-(2-(bis(methyl-d6)amino)ethyl)-1H-indol-4-yl dihydrogen phosphate	C14H11D10N2O4P 322.37
I-10		((3-(2-(dimethylamino)ethyl)-4-hydroxy-1H-indol-1-yl)methyl)phosphonic acid de	C13H19N2O4P: 298.28
I-11		3-(2-(bis(methyl-d6)amino)ethyl)-6-fluoro-1H-indol-4-yl dihydrogen phosphate	C12H10D6FN2O4P 308.28
I-12		3-(2-(bis(methyl-d3)amino)ethyl)-6-cyano-1H-indol-4-yl dihydrogen phosphate	C13H10D6N3O4P 315.30
I-13		((3-(2-(bis(methyl-d3)amino)ethyl)-4-(phosphonooxy)-1H-indol-1-yl)methyl)phosphonic acid	C13H14D6N2O7P2 384.29

TABLE 1-continued

Representative compounds of compound of Formula (I).

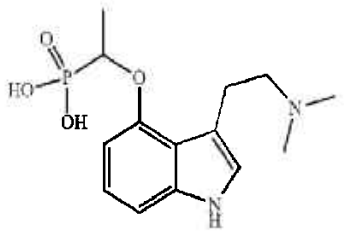
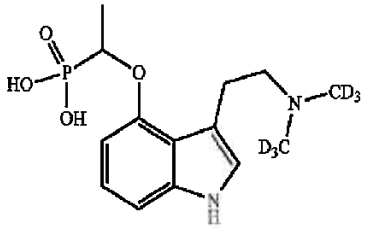
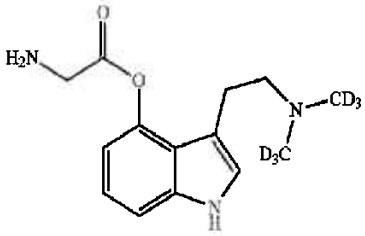
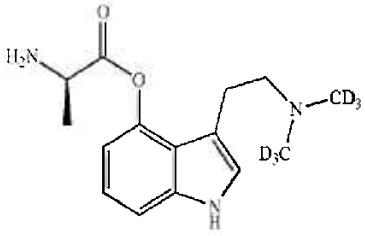
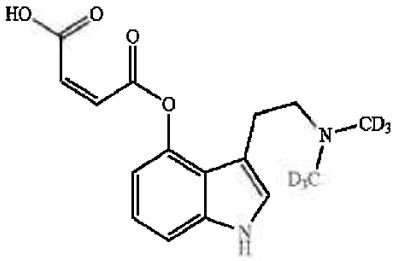
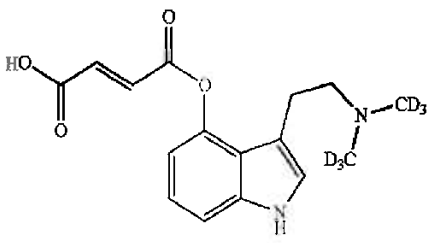
Compound ID #	Chemical Structure	IUPAC Name	Chemical Formula/ Molecular Weight
I-14		(1-((3-(2-(dimethylamino)ethyl)-1H-indol-4-yl)oxy)ethyl)phosphonic acid	C14H21N2O4P 312.31
I-15		(1-((3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl)oxy)ethyl)phosphonic acid	C14H15D6N2O4P 318.34
I-16		3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl glycinate	C14H13D6N3O2 267.36
I-17		3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl D-alaninate	C15H15D6N3O2 281.39
I-18		(Z)-4-((3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl)oxy)-4-oxobut-2-enoic acid	C16H12D6N2O4 308.37
I-19		(E)-4-((3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl)oxy)-4-oxobut-2-enoic acid	C16H12D6N2O4 308.37

TABLE 1-continued

Representative compounds of compound of Formula (I).

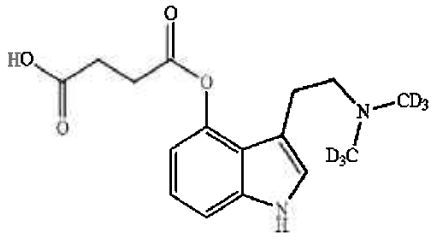
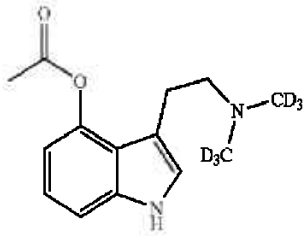
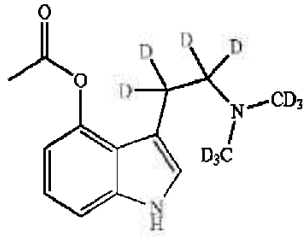
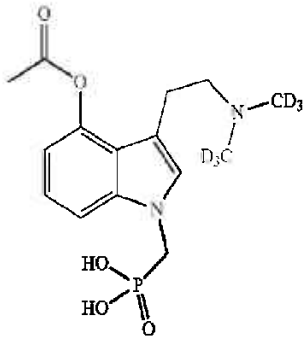
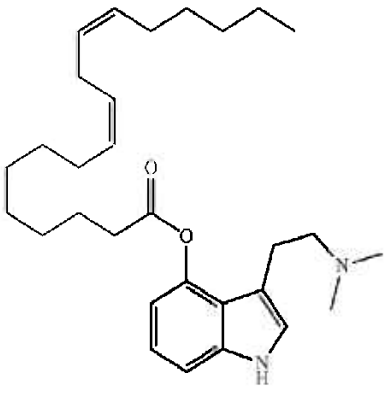
Compound ID #	Chemical Structure	IUPAC Name	Chemical Formula/ Molecular Weight
I-20		4-((3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl)oxy)-4-oxobutanoic acid	C16H14D6N2O4 310.38
I-21		3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl acetate	C14H12D6N2O2 252.35
I-22		3 3-(2-(bis(methyl-d3)amino)ethyl-1,1,2,2-d4)-1H-indol-4-yl acetate	C14H8D10N2O2 256.37
I-23		((4-acetoxy-3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-1-yl)methyl)phosphonic acid	C15H15D6N2O5P 346.35
I-24		3-(2-(dimethylamino)ethyl)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate	C30H46N2O2 466.71

TABLE 1-continued

Representative compounds of compound of Formula (I).

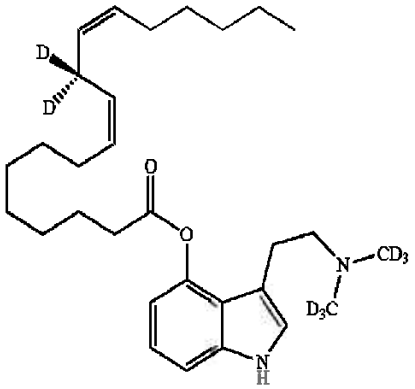
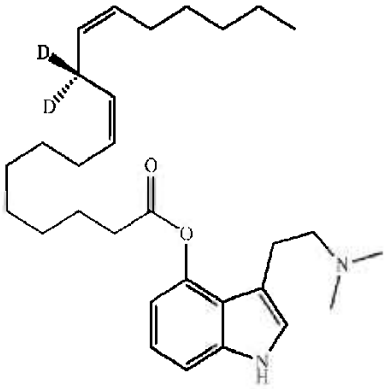
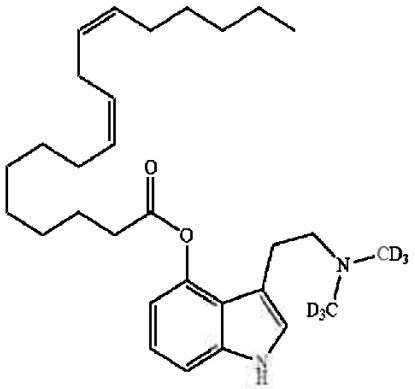
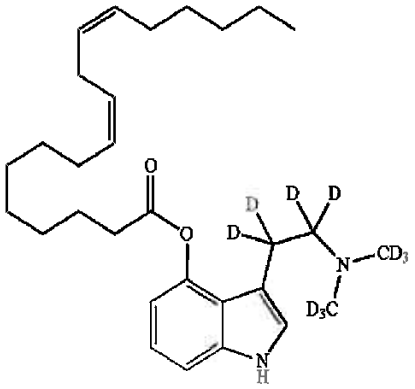
Compound ID #	Chemical Structure	IUPAC Name	Chemical Formula/ Molecular Weight
1-25		3-(2-(d6-dimethylamino)ethyl)-_ 1H-indol-4-yl(9Z,12Z)-octadeca-9,12-dienoate-11,11-d2	C30H38D8N2O2 474.76
1-26		3-(2-(dimethylamino)ethyl)-1H-indol-4-yl(9Z,12Z)-octadeca-9,12-dienoate-11,11-d2	C30H44D2N2O2 468.72
1-27		3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl(9Z,12Z)-octadeca-9,12-dienoate	C30H40D6N2O2 472.75
1-28		3-(2-(bis(methyl-d3)amino)ethyl-1,1,2,2-d4)-1H-indol-4-(9Z,12Z)-octadeca-9,12-dienoate	C30H36D10N2O2 476.77

TABLE 1-continued

Representative compounds of compound of Formula (I).

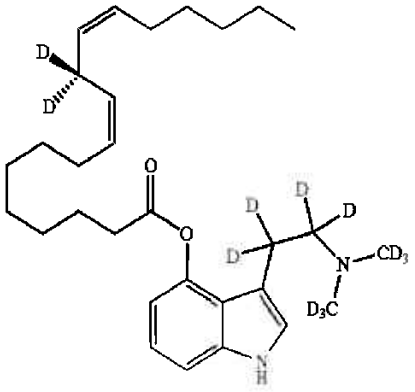
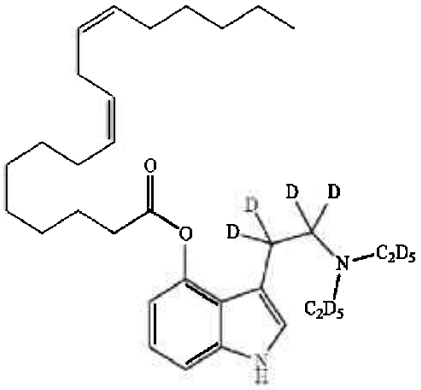
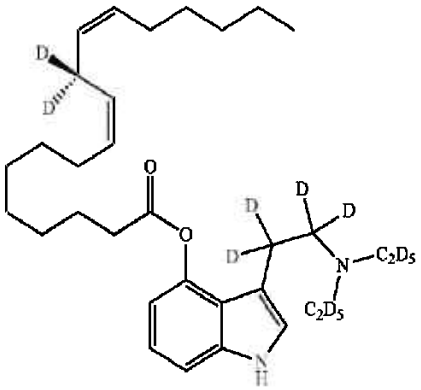
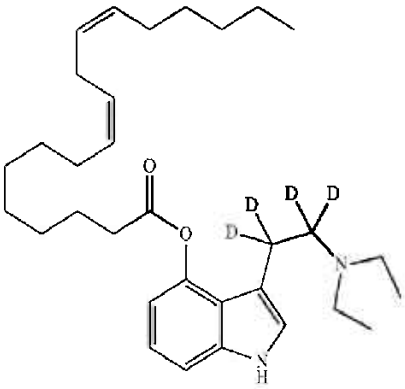
Compound ID #	Chemical Structure	IUPAC Name	Chemical Formula/ Molecular Weight
I-29		3-(2-(bis(methyl-d6)amino)ethyl-1,1,2,2-d4)-1H-indol-4-yl(9Z,12Z)-octadeca-9,12-dienoate-11,11-d2	C30H34D12N2O2: 478.78
I-30		3-(2-(d10-diethylamino)ethyl-d4)-1H-indol-4-yl(9Z,12Z)-octadeca-9,12-dienoate	C32H36D14N2O2 508.85
I-31		3-(2-(d10-diethylamino)ethyl-d4)-1H-indol-4-yl(9Z,12Z)-octadeca-9,12-dienoate-11,11-d2	C32H34D16N2O2 510.86
I-32		3-(2-(diethylamino)ethyl-d4)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate	C32H46D4N2O2 498.79

TABLE 1-continued

Representative compounds of compound of Formula (I).

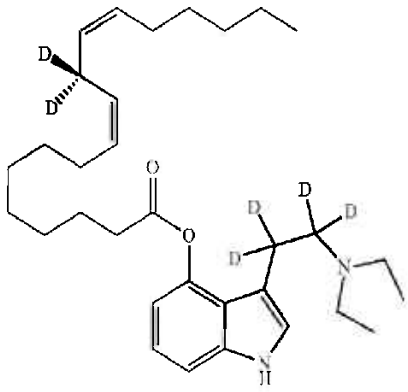
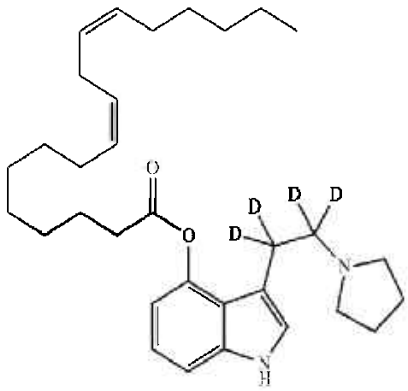
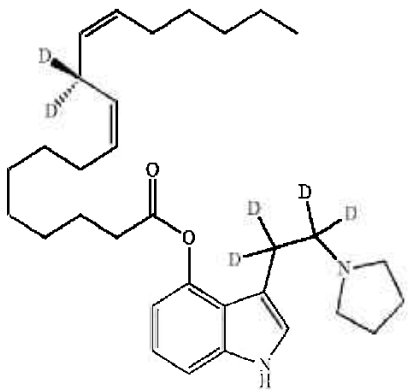
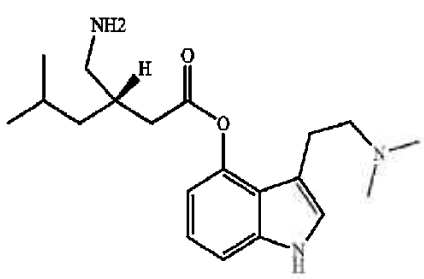
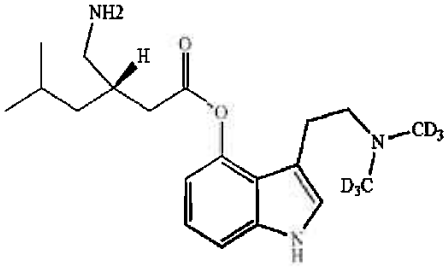
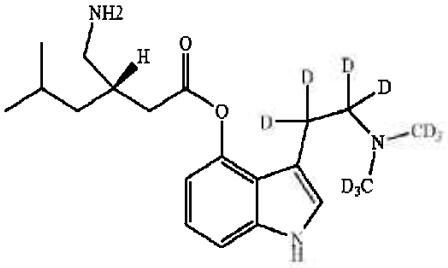
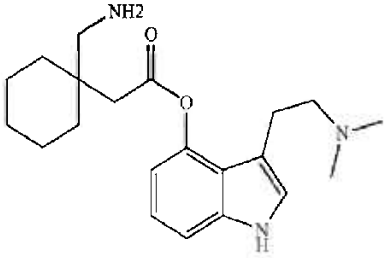
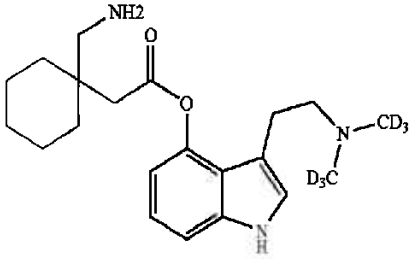
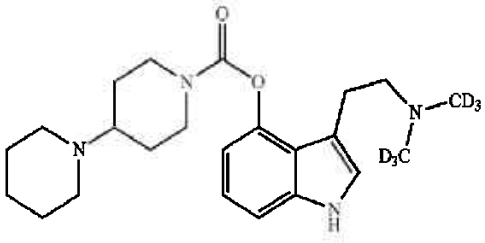
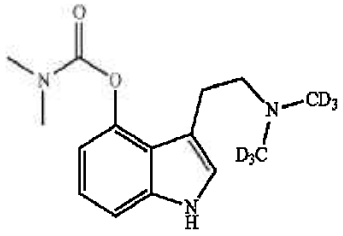
Compound ID #	Chemical Structure	IUPAC Name	Chemical Formula/ Molecular Weight
1-33		3-(2-(diethylamino)ethyl-d4)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate-11,11-d2	C32H44D6N2O2 500.80
1-34		3-(2-(pyrrolidin-1-yl)ethyl-1,1,2,2-d4)-1H-indol-4-yl(9Z,12Z)-octadeca-9,12-dienoate	C32H44D4N2O2 Exact Mass: 496.40 Molecular Weight: 496.77
1-35		3-(2-(pyrrolidin-1-yl)ethyl-1,1,2,2-d4)-1H-indol-4-yl(9Z,12Z)-octadeca-9,12-dienoate-11,11-d2	C32H42D6N2O2 498.78
1-36		3-(2-(dimethylamino)ethyl)-1H-indol-4-yl(S)-3-(aminomethyl)-5-methylhexanoate	C20H31N3O2 345.49

TABLE 1-continued

Representative compounds of compound of Formula (I).

Compound ID #	Chemical Structure	IUPAC Name	Chemical Formula/ Molecular Weight
1-37		3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl(S)-3-(aminomethyl)-5-methylhexanoate	C20H25D6N3O2 351.52
1-38		3-(2-(bis(methyl-d3)amino)ethyl-1,1,2,2-d4)-1H-indol-4-yl(S)-3-(aminomethyl)-5-methylhexanoate	C20H2110N3O2 355.55
1-39		3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 2-(1-(aminomethyl)cyclohexyl) acetate	C21H31N3O2 357.50
1-40		3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl 2-(1-(aminomethyl)cyclohexyl) acetate	C21H25D6N3O2 363.53
1-41		3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl[1,4'-bipiperidine]-1'-carboxylate	C23H28D6N4O2 404.59
1-42		3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl dimethylcarbamate	C15H15D6N3O2 281.39

In some embodiments, the compounds of the present application can also s include tautomeric forms, such as keto-enol tautomers and the like. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. It is intended that any tautomeric forms which the compounds form, as well as mixtures thereof, are included within the scope of the present application.

The compounds of the present application may further exist in varying polymorphic forms and it is contemplated that any polymorphs, or mixtures thereof, which form are included within the scope of the present application.

The compounds of the present application may further be radiolabeled and accordingly all radiolabeled versions of the compounds of the application are included within the scope of the present application. The compounds of the application also include those in which one or more radioactive atoms are incorporated within their structure.

The term "compound" refers to the compound and, in certain embodiments, to the extent they are stable, any hydrate or solvate thereof. A hydrate is the compound complexed with water, and a solvate is the compound complexed with a solvent, which may be an organic solvent or an inorganic solvent. A "stable" compound is a compound that can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (e.g., therapeutic administration to a subject). The compounds of the present invention are limited to stable compounds embraced by general formula (I), or pharmaceutically acceptable salts thereof.

As indicated above, the compounds of the present invention can be employed in the form of pharmaceutically acceptable salts. Those skilled in the art will recognize those instances in which the compounds of the invention may form salts. Examples of such compounds are described herein by reference to possible salts. Such reference is for illustration only. Pharmaceutically acceptable salts can be used with compounds for treating patients. Non pharmaceutical salts may, however, be useful in the preparation of intermediate compounds. The term "pharmaceutically acceptable salt" refers to a salt (including an inner salt such as a zwitterion) that possesses effectiveness similar to the parent compound and that is not biologically or otherwise undesirable (e.g, is neither toxic nor otherwise deleterious to the recipient thereof). Thus, an embodiment of the invention provides pharmaceutically acceptable salts of the compounds of the invention. The term "salt(s)", as employed herein, denotes any of the following: acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. Salts of compounds of the invention may be formed by methods known to those of ordinary skill in the art, for example, by reacting a compound of the invention with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates ("mesylates"), naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates) and the like. Suitable salts include acid addition salts that may, for example, be formed by mixing a solution of a compound with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, or benzoic acid. Additionally, acids that are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl et al, Camille G. (eds.), and Handbook of Pharmaceutical Salts. Properties, Selection and Use. (2002) Zurich: Wiley VCH; S. Berge et al, Journal of Pharmaceutical Sciences 1977 66 (1) 1-19; P. Gould, International J. of Pharmaceutics (1986) 33 201-217; Anderson et al, The Practice of Medicinal Chemistry (1996), Academic Press, New York; and in The Orange Book (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamine, abutyl amine, choline, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen containing groups may be quarternized with agents such as lower alkyl halides (e.g., methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g., decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g., benzyl and phenethyl bromides), and others. Compounds carrying an acidic moiety can be mixed with suitable pharmaceutically acceptable salts to provide, for example, alkali metal salts (e.g., sodium or potassium salts), alkaline earth metal salts (e.g., calcium or magnesium salts), and salts formed with suitable organic ligands such as quaternary ammonium salts. Also, in the case of an acid (—COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed to modify the solubility or hydrolysis characteristics of the compound.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention. In addition, when a compound of the invention contains both a basic moiety, such as, but not limited to an aliphatic primary, secondary, tertiary or cyclic amine, an aromatic or heteroaryl amine, pyridine or imidazole, and an acidic moiety, such as, but not limited to tetrazole or carboxylic acid, zwitterions ("inner salts") may be formed and are included within the terms "salt(s)" as used herein. It is understood that certain compounds of the invention may exist in zwitterionic form, having both anionic and cationic centers within the same compound and a net neutral charge. Such zwitterions are included within the invention.

III. Compositions

The compounds of the present application are suitably formulated in a conventional manner into compositions using one or more carriers. Accordingly, the present application also includes a composition comprising one or more compounds of the application and a carrier. The compounds of the application are suitably formulated into pharmaceutical compositions for administration to subjects in a biologically compatible form suitable for administration in vivo. Accordingly, the present application further includes a pharmaceutical composition comprising one or more compounds of the application and a pharmaceutically acceptable carrier. In embodiments of the application the pharmaceu-

tical compositions are used in the treatment of any of the diseases, disorders or conditions described herein.

The compounds of the application are administered to a subject in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. For example, a compound of the application is administered by oral, inhalation, parenteral, buccal, sublingual, insufflation, epidurally, nasal, rectal, vaginal, patch, pump, minipump, topical or transdermal administration and the pharmaceutical compositions formulated accordingly. In some embodiments, administration is by means of a pump for periodic or continuous delivery. Conventional procedures and ingredients for the selection and preparation of suitable compositions are described, for example, in Remington's Pharmaceutical Sciences (2000-20 th edition) and in The United States Pharmacopeia: The National Formulary (USP 24 NF19) published in 1999.

Parenteral administration includes systemic delivery routes other than the gastrointestinal (GI) tract and includes, for example intravenous, intra-arterial, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary (for example, by use of an aerosol), intrathecal, rectal and topical (including the use of a patch or other transdermal delivery device) modes of administration. Parenteral administration may be by continuous infusion over a selected period of time.

In some embodiments, a compound of the application is orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it is enclosed in hard or soft shell gelatin capsules, or it is compressed into tablets, or it is incorporated directly with the food of the diet. In some embodiments, the compound is incorporated with excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, caplets, pellets, granules, lozenges, chewing gum, powders, syrups, elixirs, wafers, aqueous solutions and suspensions and the like. In the case of tablets, carriers that are used include lactose, corn starch, sodium citrate and salts of phosphoric acid. Pharmaceutically acceptable excipients include binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate), or solvents (e.g. medium chain triglycerides, ethanol, water). In embodiments, the tablets are coated by methods well known in the art. In the case of tablets, capsules, caplets, pellets or granules for oral administration, pH sensitive enteric coatings, such as Eudragits™ designed to control the release of active ingredients are optionally used. Oral dosage forms also include modified release, for example immediate release and timed-release, formulations. Examples of modified-release formulations include, for example, sustained-release (SR), extended-release (ER, XR, or XL), time-release or timed-release, controlled-release (CR), or continuous-release (CR or Contin), employed, for example, in the form of a coated tablet, an osmotic delivery device, a coated capsule, a microencapsulated microsphere, an agglomerated particle, e.g., as of molecular sieving type particles, or, a fine hollow permeable fiber bundle, or chopped hollow permeable fibers, agglomerated or held in a fibrous packet. Timed-release compositions are formulated, for example as liposomes or those wherein the active compound is protected with differentially degradable coatings, such as by microencapsulation, multiple coatings, etc. Liposome delivery systems include, for example, small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. In some embodiments, liposomes are formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines. For oral administration in a capsule form, useful carriers, solvents or diluents include lactose, medium chain triglycerides, ethanol and dried corn starch.

In some embodiments, liquid preparations for oral administration take the form of, for example, solutions, syrups or suspensions, or they are suitably presented as a dry product for constitution with water or other suitable vehicle before use. When aqueous suspensions and/or emulsions are administered orally, the compound of the application is suitably suspended or dissolved in an oily phase that is combined with emulsifying and/or suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents are added. Such liquid preparations for oral administration are prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., medium chain triglycerides, almond oil, oily esters or ethyl alcohol); and preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid). Useful diluents include lactose and high molecular weight polyethylene glycols.

It is also possible to freeze-dry the compounds of the application and use the lyophilizates obtained, for example, for the preparation of products for injection.

In some embodiments, a compound of the application is administered parenterally. For example, solutions of a compound of the application are prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. In some embodiments, dispersions are prepared in glycerol, liquid polyethylene glycols, DMSO and mixtures thereof with or without alcohol and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms. A person skilled in the art would know how to prepare suitable formulations. For parenteral administration, sterile solutions of the compounds of the application are usually prepared and the pH's of the solutions are suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled to render the preparation isotonic. For ocular administration, ointments or droppable liquids are delivered, for example, by ocular delivery systems known to the art such as applicators or eye droppers. In some embodiments, such compositions include mucomimetics such as hyaluronic acid, chondroitin sulfate, hydroxypropyl methylcellulose or polyvinyl alcohol, preservatives such as sorbic acid, EDTA or benzyl chromium chloride and the usual quantities of diluents or carriers. For pulmonary administration, diluents or carriers will be selected to be appropriate to allow the formation of an aerosol.

In some embodiments, a compound of the application is formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection are, for example, presented in unit dosage form, e.g., in ampoules or in multidose containers, with an added preservative. In some embodiments, the compositions take such forms as sterile suspensions, solutions or emulsions in oily or aqueous vehicles and contain formulating agents such as suspending, stabilizing and/or dispersing agents. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. Alternatively, the compounds of the

application are suitably in a sterile powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

In some embodiments, compositions for nasal administration are conveniently formulated as aerosols, drops, gels and powders. For intranasal administration or administration by inhalation, the compounds of the application are conveniently delivered in the form of a solution, dry powder formulation or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which, for example, take the form of a cartridge or refill for use with an atomising device. Alternatively, the sealed container is a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which is, for example, a compressed gas such as compressed air or an organic propellant such as fluorochlorohydrocarbon. Suitable propellants include but are not limited to dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, heptafluoroalkanes, carbon dioxide or another suitable gas. In the case of a pressurized aerosol, the dosage unit is suitably determined by providing a valve to deliver a metered amount. In some embodiments, the pressurized container or nebulizer contains a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator are, for example, formulated containing a powder mix of a compound of the application and a suitable powder base such as lactose or starch. The aerosol dosage forms can also take the form of a pump-atomizer.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein a compound of the application is formulated with a carrier such as sugar, acacia, tragacanth, or gelatin and glycerine. Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Suppository forms of the compounds of the application are useful for vaginal, urethral and rectal administrations. Such suppositories will generally be constructed of a mixture of substances that is solid at room temperature but melts at body temperature. The substances commonly used to create such vehicles include but are not limited to *Theobroma* oil (also known as cocoa butter), glycerinated gelatin, other glycerides, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol. See, for example: Remington's Pharmaceutical Sciences, 16 th Ed., Mack Publishing, Easton, Pa., 1980, pp. 1530-1533 for further discussion of suppository dosage forms.

In some embodiments a compound of the application is coupled with soluble polymers as targetable drug carriers. Such polymers include, for example, polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxy-ethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, in some embodiments, a compound of the application is coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

A compound of the application including pharmaceutically acceptable salts, solvates and/or prodrugs thereof is suitably used on their own but will generally be administered in the form of a pharmaceutical composition in which the one or more compounds of the application (the active ingredient) is in association with a pharmaceutically acceptable carrier. Depending on the mode of administration, the pharmaceutical composition will comprise from about 0.05 wt % to about 99 wt % or about 0.10 wt % to about 70 wt %, of the active ingredient and from about 1 wt % to about 99.95 wt % or about 30 wt % to about 99.90 wt % of a pharmaceutically acceptable carrier, all percentages by weight being based on the total composition.

In some embodiments, the compounds of the application including pharmaceutically acceptable salts, solvates and/or prodrugs thereof are used are administered in a composition comprising an additional therapeutic agent. Therefore the present application also includes a pharmaceutical composition comprising one of more compounds of the application, or pharmaceutically acceptable salts, solvates and/or prodrugs thereof and an additional therapeutic agent, and optionally one or more pharmaceutically acceptable excipients. In some embodiments, the additional therapeutic agent is another known agent useful for treatment of a disease, disorder or condition by activation of a serotonin receptor, for example those listed in the Methods and Uses section below. In some embodiments, the additional therapeutic agent is a psychoactive drug.

In the above, the term "a compound" also includes embodiments wherein one or more compounds are referenced.

IV. Methods and Uses of the Application

The compounds of the application are serotonergic binding agents that act as agonists or partial agonists at a serotonin receptor.

Accordingly, the present application includes a method for activating a serotonin receptor in a cell, either in a biological sample or in a patient, comprising administering an effective amount of one or more compounds of the application to the cell. The application also includes a use of one or more compounds of the application for activating a serotonin receptor in a cell as well as a use of one or more compounds of the application for the preparation of a medicament for activating a serotonin receptor in a cell. The application further includes one or more compounds of the application for use in activating a serotonin receptor in a cell.

As the compounds of the application are capable of activating a serotonin receptor, the compounds of the application are useful for treating diseases, disorders or conditions by activating a serotonin receptor. Therefore, the compounds of the present application are useful as medicaments. Accordingly, the application also includes a compound of the application for use as a medicament.

The present application also includes a method of treating a disease, disorder or condition by activation of a serotonin receptor comprising administering a therapeutically effective amount of one or more compounds of the application to a subject in need thereof.

The present application also includes a use of one or more compounds of the application for treatment of a disease, disorder or condition by activation of a serotonin receptor as well as a use of one or more compounds of the application

for the preparation of a medicament for treatment of a disease, disorder or condition by activation of a serotonin receptor. The application further includes one or more compounds of the application for use in treating a disease, disorder or condition by activation of a serotonin receptor.

In some embodiments, the serotonin receptor is 5-HT_{2A}. Accordingly, the present application includes a method for activating 5-HT_{2A} in a cell, either in a biological sample or in a patient, comprising administering an effective amount of one or more compounds of the application to the cell. The application also includes a use of one or more compounds of the application for activating 5-HT_{2A} in a cell as well as a use of one or more compounds of the application for the preparation of a medicament for activating 5-HT_{2A} in a cell. The application further includes one or more compounds of the application for use in activating 5-HT_{2A} in a cell.

The present application also includes a method of treating a disease, disorder or condition by activation of 5-HT_{2A} comprising administering a therapeutically effective amount of one or more compounds of the application to a subject in need thereof. The present application also includes a use of one or more compounds of the application for treatment of a disease, disorder or condition by activation of 5-HT_{2A} as well as a use of one or more compounds of the application for the preparation of a medicament for treatment of a disease, disorder or condition by activation of 5-HT_{2A}. The application further includes one or more compounds of the application for use in treating a disease, disorder or condition by activation of 5-HT_{2A}.

In some embodiments, the compounds of the application are useful for preventing, treating and/or reducing the severity of a mental illness disorder and/or condition in a subject. Therefore, in some embodiments, the disease, disorder or condition that is treated by activation of a serotonin receptor is a mental illness. Accordingly, the present application also includes a method of treating a mental illness comprising administering a therapeutically effective amount of one or more compounds of the application to a subject in need thereof. The present application also includes a use of one or more compounds of the application for treatment a mental illness, as well as a use of one or more compounds of the application for the preparation of a medicament for treatment of a mental illness. The application further includes one or more compounds of the application for use in treating a mental illness.

In some embodiments, the mental illness is selected from anxiety disorders such as generalized anxiety disorder, panic disorder, social anxiety disorder and specific phobias; depression such as, hopelessness, loss of pleasure, fatigue and suicidal thoughts; mood disorders, such as depression, bipolar disorder, cancer-related depression, anxiety and cyclothymic disorder; psychotic disorders, such as hallucinations, delusions, schizophrenia; impulse control and addiction disorders, such as pyromania (starting fires), kleptomania (stealing) and compulsive gambling; alcohol addiction; drug addiction, such as opioid addiction; personality disorders, such as antisocial personality disorder, obsessive-compulsive personality disorder and paranoid personality disorder; obsessive-compulsive disorder (OCD), such as thoughts or fears that cause a subject to perform certain rituals or routines; post-traumatic stress disorder (PTSD); stress response syndromes (formerly called adjustment disorders); dissociative disorders, formerly called multiple personality disorder, or "split personality," and depersonalization disorder; factitious disorders; sexual and gender disorders, such as sexual dysfunction, gender identity disorder and the paraphilia's; somatic symptom disorders, formerly known as a psychosomatic disorder or somatoform disorder; and combinations thereof.

In some embodiments, the disease, disorder or condition that is treated by activation of a serotonin receptor is neurodegeneration. In some embodiments, the disease, disorder or condition that is treated by activation of a serotonin receptor is reduced brain-derived neurotrophic factor (BDNF), mammalian target of rapamycin (mTOR) activation and/or inflammation.

In some embodiments, the disease, disorder or condition that is treated by activation of a serotonin receptor comprises cognitive impairment; ischemia including stroke; neurodegeneration; refractory substance use disorders; sleep disorders; pain, such as social pain, acute pain, cancer pain, chronic pain, breakthrough pain, bone pain, soft tissue pain, nerve pain, referred pain, phantom pain, neuropathic pain, cluster headaches and migraine; obesity and eating disorders; epilepsies and seizure disorders; neuronal cell death; excitotoxic cell death; or a combination thereof. In some embodiments, the mental illness is selected from hallucinations and delusions and a combination thereof.

In some embodiments, the hallucinations are selected from visual hallucinations, auditory hallucinations, olfactory hallucinations, gustatory hallucinations, tactile hallucinations, proprioceptive hallucinations, equilibrioceptive hallucinations, nociceptive hallucinations, thermoceptive hallucinations and chronoceptive hallucinations, and a combination thereof.

In some embodiments, the disease, disorder or condition that is treated by activation of a serotonin receptor is psychosis or psychotic symptoms. Accordingly, the present application also includes a method of treating psychosis or psychotic symptoms comprising administering a therapeutically effective amount of one or more compounds of the application to a subject in need thereof.

The present application also includes a use of one or more compounds of the application for treatment of psychosis or psychotic symptoms, as well as a use of one or more compounds of the application for the preparation of a medicament for treatment of psychosis or psychotic symptoms. The application further includes one or more compounds of the application for use in treating psychosis or psychotic symptoms.

In some embodiments, administering to said subject in need thereof a therapeutically effective amount of the compounds of the application does not result in a worsening of psychosis or psychotic symptoms such as, but not limited to, hallucinations and delusions. In some embodiments, administering to said subject in need thereof a therapeutically effective amount of the compounds of the application results in an improvement of psychosis or psychotic symptoms such as, but not limited to, hallucinations and delusions. In some embodiments, administering to said subject in need thereof a therapeutically effective amount of the compounds of the application results in an improvement of psychosis or psychotic symptoms.

In some embodiments, the compounds of the application are useful for treating a central nervous system (CNS) disease, disorder or condition and/or a neurological disease, disorder or condition in a subject in need of therapy, comprising administering a therapeutically effective amount of a compound of general formula (I), or a pharmaceutically acceptable salt thereof to the subject.

Therefore, in some embodiments, the disease, disorder or condition that is treated by activation of a serotonin receptor is a central nervous system (CNS) disease, disorder or condition and/or a neurological disease, disorder or condi-

tion. Accordingly, the present application also includes a method of treating a CNS disease, disorder or condition and/or a neurological disease, disorder or condition comprising administering a therapeutically effective amount of one or more compounds of the application to a subject in need thereof. The present application also includes a use of one or more compounds of the application for treatment a CNS disease, disorder or condition and/or a neurological disease, disorder or condition, as well as a use of one or more compounds of the application for the preparation of a medicament for treatment of a CNS disease, disorder or condition and/or a neurological disease, disorder or condition. The application further includes one or more compounds of the application for use in treating a CNS disease, disorder or condition and/or a neurological disease, disorder or condition.

In some embodiments the CNS disease, disorder or condition and/or neurological disease, disorder or condition is selected from neurological diseases including neurodevelopmental diseases and neurodegenerative diseases such as Alzheimer's disease; presenile dementia; senile dementia; vascular dementia; Lewy body dementia; cognitive impairment, Parkinson's disease and Parkinsonian related disorders such as Parkinson dementia, corticobasal degeneration, and supranuclear palsy; epilepsy; CNS trauma; CNS infections; CNS inflammation; stroke; multiple sclerosis; Huntington's disease; mitochondrial disorders; Fragile X syndrome; Angelman syndrome; hereditary ataxias; neuro-ontological and eye movement disorders; neurodegenerative diseases of the retina amyotrophic lateral sclerosis; tardive dyskinesias; hyperkinetic disorders; attention deficit hyperactivity disorder and attention deficit disorders; restless leg syndrome; Tourette's syndrome; schizophrenia; autism spectrum disorders; tuberous sclerosis; Rett syndrome; cerebral palsy; disorders of the reward system including eating disorders such as anorexia nervosa ("AN") and bulimia nervosa ("BN"); and binge eating disorder ("BED"), trichotillomania, dermotillomania, nail biting; migraine; fibromyalgia; and peripheral neuropathy of any etiology, and combinations thereof.

In some embodiments, the subject is a mammal. In another embodiment, the subject is human. In some embodiments, the subject is a non-human animal. In some embodiments, the subject is canine. In some embodiments, the subject is feline. Accordingly, the compounds, methods and uses of the present application are directed to both human and veterinary diseases, disorders and conditions.

In some embodiments, the compounds of the application are useful for treating behavioral problems in subjects that are felines or canines.

Therefore, in some embodiments, the disease, disorder or condition that is treated by activation of a serotonin receptor is behavioral problems in subjects that are felines or canines. Accordingly, the present application also includes a method of treating a behavioral problem comprising administering a therapeutically effective amount of one or more compounds of the application to a non-human subject in need thereof. The present application also includes a use of one or more compounds of the application for treatment a behavioral problem in a non-human subject, as well as a use of one or more compounds of the application for the preparation of a medicament for treatment of a behavioral problem in a non-human subject. The application further includes one or more compounds of the application for use in treating a behavioral problem in a non-human subject.

In some embodiments, the behavioral problems are selected from, but are not limited to, anxiety, fear, stress, sleep disturbances, cognitive dysfunction, aggression, excessive noise making, scratching, biting and a combination thereof.

In some embodiments, the non-human subject is canine. In some embodiments, the non-human subject is feline.

The present application also includes a method of treating a disease, disorder or condition by activation of a serotonin receptor comprising administering a therapeutically effective amount of one or more compounds of the application in combination with another known agent useful for treatment of a disease, disorder or condition by activation of a serotonin receptor to a subject in need thereof. The present application also includes a use of one or more compounds of the application in combination with another known agent useful for treatment of a disease, disorder or condition by activation of a serotonin receptor for treatment of a disease, disorder or condition by activation of a serotonin receptor, as well as a use of one or more compounds of the application in combination with another known agent useful for treatment of a disease, disorder or condition by activation of a serotonin receptor for the preparation of a medicament for treatment of a disease, disorder or condition by activation of a serotonin receptor. The application further includes one or more compounds of the application in combination with another known agent useful for treatment of a disease, disorder or condition by activation of a serotonin receptor for use in treating a disease, disorder or condition by activation of a serotonin receptor.

In some embodiments, the disease, disorder or condition that is treated by activation of a serotonin receptor is a mental illness. In some embodiments, the disease, disorder or condition that is treated by activation of a serotonin receptor is a central nervous system (CNS) disease, disorder or condition and/or a neurological disease, disorder or condition. In some embodiments, the disease, disorder or condition that is treated by activation of a serotonin receptor is psychosis or psychotic symptoms. In some embodiments, the disease, disorder or condition that is treated by activation of a serotonin receptor is behavioral problems in a non-human subject.

In some embodiments, the disease, disorder or condition that is treated by activation of a serotonin receptor is a mental illness and the one or more compounds of the application are administered in combination with one or more additional treatments for a mental illness. In some embodiments, the additional treatments for a mental illness is selected from antipsychotics, including typical antipsychotics and atypical antipsychotics; antidepressants including selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) (e.g. bupropion); anti-anxiety medication including benzodiazepines such as alprazolam; mood stabilizers such as lithium and anticonvulsants such carbamazepine, divalproex (valproic acid), lamotrigine, gabapentin and topiramate.

In some embodiments, the disease, disorder or condition that is treated by activation of a serotonin receptor is selected from attention deficit hyperactivity disorder and attention deficit disorder and a combination thereof. In some embodiments, the disease, disorder or condition that is treated by activation of a serotonin receptor is attention deficit hyperactivity disorder and/or attention deficit disorder and a combination thereof and the one or more compounds of the application are administered in combination with one or more additional treatments for attention deficit hyperactivity disorder and/or attention deficit disorder and a combination

thereof. In some embodiments, the additional treatments for attention deficit hyperactivity disorder and/or attention deficit disorder and a combination thereof are selected from methylphenidate, atomoxetine and amphetamine and a combination thereof.

In some embodiments, the disease, disorder or condition that is treated by activation of a serotonin receptor is dementia or Alzheimer's disease and the one or more compounds of the application are administered in combination with one or more additional treatments for dementia or Alzheimer's disease. In some embodiments, the additional treatments for dementia and Alzheimer's disease are selected acetylcholinesterase inhibitors, NMDA antagonists and nicotinic agonists.

In some embodiments, the acetylcholinesterase inhibitors are selected from donepezil, galantamine, rivastigmine, and phenserine, and combinations thereof.

In some embodiments, the NMDA antagonists are selected from MK-801, ketamine, phencyclidine, and memantine, and combinations thereof.

In some embodiments, the nicotinic agonists is nicotine, nicotinic acid, nicotinic alpha7 agonists, or nicotinic alpha2 beta4 agonists, or combinations thereof.

In some embodiments, the muscarinic agonists is a muscarinic M1 agonist, or a muscarinic M4 agonist, or combinations thereof.

In some embodiments, the muscarinic antagonist is a muscarinic M2 antagonist.

In some embodiments, the disease, disorder or condition that is treated by activation of a serotonin receptor is psychosis or psychotic symptoms and the one or more compounds of the application are administered in combination with one or more additional treatments for psychosis or psychotic symptoms. In some embodiments, the additional treatments for psychosis or psychotic symptom are selected typical antipsychotics and atypical antipsychotics.

In some embodiments, the typical antipsychotics are selected from acepromazine, acetophenazine, benperidol, bromperidol, butaperazine, carfenazine, chlorproethazine, chlorpromazine, chlorprothixene, clopenthixol, cyamemazine, dixyrazine, droperidol, fluanisone, flupentixol, fluphenazine, fluspirilene, haloperidol, levomepromazine, lenperone, loxapine, mesoridazine, metitepine, molindone, moperone, oxypertine, oxyprotepine, penfluridol, perazine, periciazine, perphenazine, pimozide, pipamperone, piperacetazine, pipotiazine, prochlorperazine, promazine, prothipendyl, spiperone, sulforidazine, thiopropazate, thioproperazine, thioridazine, thiothixene, timiperone, trifluoperazine, trifluperidol, triflupromazine and zuclopenthixol and combinations thereof.

In some embodiments, the atypical antipsychotics are selected from amoxapine, amisulpride, aripiprazole, asenapine, blonanserin, brexpiprazole, cariprazine, carpipramine, clocapramine, clorotepine, clotiapine, clozapine, iloperidone, levosulpiride, lurasidone, melperone, mosapramine, nemonapride, olanzapine, paliperidone, perospirone, quetiapine, remoxipride, reserpine, risperidone, sertindole, sulpiride, sultopride, tiapride, veralipride, ziprasidone and zotepine, and combinations thereof.

In some embodiments, effective amounts vary according to factors such as the disease state, age, sex and/or weight of the subject or species. In some embodiments, the amount of a given compound or compounds that will correspond to an effective amount will vary depending upon factors, such as the given drug(s) or compound(s), the pharmaceutical formulation, the route of administration, the type of condition, disease or disorder, the identity of the subject being treated and the like, but can nevertheless be routinely determined by one skilled in the art.

In some embodiment, the compounds of the application are administered one, two, three or four times a year. In some embodiments, the compounds of the application are administered at least once a week. However, in another embodiment, the compounds are administered to the subject from about one time per two weeks, three weeks or one month. In another embodiment, the compounds are administered about one time per week to about once daily. In another embodiment, the compounds are administered 1, 2, 3, 4, 5 or 6 times daily. The length of the treatment period depends on a variety of factors, such as the severity of the disease, disorder or condition, the age of the subject, the concentration and/or the activity of the compounds of the application and/or a combination thereof. It will also be appreciated that the effective dosage of the compound used for the treatment may increase or decrease over the course of a particular treatment regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration is required. For example, the compounds are administered to the subject in an amount and for duration sufficient to treat the subject.

In some embodiments, the compounds of the application are administered at doses that are hallucinogenic or psychotomimetic and taken in conjunction with psychotherapy or therapy and may occur once, twice, three, or four times a year. However, in some embodiments, the compounds are administered to the subject once daily, once every two days, once every 3 days, once a week, once every two weeks, once a month, once every two months, or once every three months at doses that are not hallucinogenic or psychotomimetic.

A compound of the application is either used alone or in combination with other known agents useful for treating diseases, disorders or conditions by activation of a serotonin receptor, such as the compounds of the application. When used in combination with other known agents useful in treating diseases, disorders by activation of a serotonin receptor, it is an embodiment that a compound of the application is administered contemporaneously with those agents. As used herein, "contemporaneous administration" of two substances to a subject means providing each of the two substances so that they are both active in the individual at the same time. The exact details of the administration will depend on the pharmacokinetics of the two substances in the presence of each other and can include administering the two substances within a few hours of each other, or even administering one substance within 24 hours of administration of the other, if the pharmacokinetics are suitable. Design of suitable dosing regimens is routine for one skilled in the art. In particular embodiments, two substances will be administered substantially simultaneously, i.e., within minutes of each other, or in a single composition that contains both substances. It is a further embodiment of the present application that a combination of agents is administered to a subject in a non-contemporaneous fashion. In some embodiments, a compound of the present application is administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present application provides a single unit dosage form comprising one or more compounds of the application, an additional therapeutic agent and a pharmaceutically acceptable carrier.

The dosage of a compound of the application varies depending on many factors such as the pharmacodynamic properties of the compound, the mode of administration, the

age, health and weight of the recipient, the nature and extent of the symptoms, the frequency of the treatment and the type of concurrent treatment, if any and the clearance rate of the compound in the subject to be treated. One of skill in the art can determine the appropriate dosage based on the above factors. In some embodiments, one or more compounds of the application are administered initially in a suitable dosage that is adjusted as required, depending on the clinical response. Dosages will generally be selected to maintain a serum level of the one or more compounds of the application from about 0.01 μg/cc to about 1000 μg/cc, or about 0.1 μg/cc to about 100 μg/cc. As a representative example, oral dosages of one or more compounds of the application will range between about 10 μg per day to about 1000 mg per day for an adult, suitably about 10 μg per day to about 500 mg per day, more suitably about 10 μg per day to about 200 mg per day. For parenteral administration, a representative amount is from about 0.0001 mg/kg to about 10 mg/kg, about 0.0001 mg/kg to about 1 mg/kg, about 0.01 mg/kg to about 0.1 mg/kg or about 0.0001 mg/kg to about 0.01 mg/kg will be administered. For oral administration, a representative amount is from about 0.001 μg/kg to about 10 mg/kg, about 0.1 μg/kg to about 10 mg/kg, about 0.01 μg/kg to about 1 mg/kg or about 0.1 μg/kg to about 1 mg/kg. For administration in suppository form, a representative amount is from about 0.1 mg/kg to about 10 mg/kg or about 0.1 mg/kg to about 1 mg/kg. In some embodiments of the application, compositions are formulated for oral administration and the one or more compounds are suitably in the form of tablets containing 0.1, 0.25, 0.5, 0.75, 1.0, 5.0, 10.0, 20.0, 25.0, 30.0, 40.0, 50.0, 60.0, 70.0, 75.0, 80.0, 90.0, 100.0, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950 or 1000 mg of active ingredient (one or more compounds of the application) per tablet. In some embodiments of the application the one or more compounds of the application are administered in a single daily, weekly or monthly dose or the total daily dose is divided into two, three or four daily doses.

In some embodiments, the compounds of the application are used or administered in an effective amount which comprises administration of doses or dosage regimens that are devoid of clinically meaningful psychedelic/psychotomimetic actions. In some embodiments, the compounds of the application are used or administered in an effective amount which comprises administration of doses or dosage regimens that provide clinical effects similar to those exhibited by a human plasma psilocin Cmax of 4 ng/mL or less and/or human 5-HT_{2A} human CNS receptor occupancy of 40% or less or those exhibited by a human plasma psilocin Cmax of 1 ng/mL or less and/or human 5-HT_{2A} human CNS receptor occupancy of 30% or less. In some embodiments, the compounds of the application are used or administered in an effective amount which comprises administration of doses or dosage regimens that provide clinical effects similar to those exhibited by a human plasma psilocin Tmax in excess of 60 minutes, in excess of 120 minutes or in excess of 180 minutes.

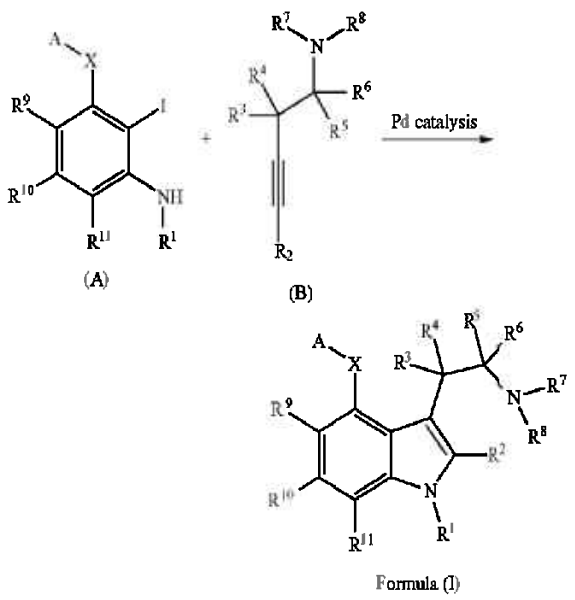
V. Preparation of Compounds

Compounds of the present application can be prepared by various synthetic processes. The choice of particular structural features and/or substituents may influence the selection of one process over another. The selection of a particular process to prepare a given compound of the application is within the purview of the person of skill in the art. Some starting materials for preparing compounds of the present application are available from commercial chemical sources or may be extracted from cells, plants, animals or fungi. Other starting materials, for example as described below, are readily prepared from available precursors using straightforward transformations that are well known in the art. In the Schemes below showing some embodiments of methods of preparation of compounds of the application, all variables are as defined in Formula (I), unless otherwise stated.

In some embodiments of the application, the compounds of the application are generally prepared according to the process illustrated in Schemes II-IV.

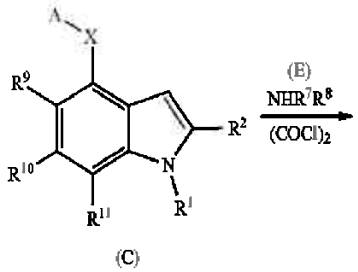
In some embodiments, the compounds of Formula (I) are prepared as shown in Scheme II. Therefore, ortho-iodoanilin compounds of Formula (A) are coupled with suitable unsaturated precursors such as disubstituted alkyne compound of Formula (B) in the presence of a catalyst, such as a Pd catalyst, to provide a compound of Formula (I) through known methods, for example, using the Pd catalysis procedure found in Chem. Eur. J. 2019, 25, 897-903.

Scheme II

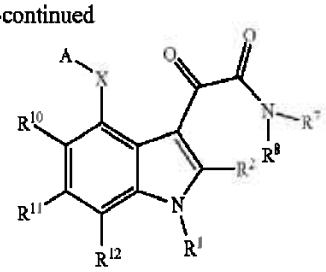


In some embodiments, the compounds of Formula (I) are synthesized according to Scheme III. Therefore, a substituted indole compound of Formula (C) is coupled with a suitable amino compound of Formula (E) in the present of suitable coupling reagents such as oxalyl chloride to provide compounds of Formula (D). The compounds of Formula (D) are reduced with suitable reducing agents such as Al-based reducing agents to provide the compounds of general Formula (I).

Scheme III

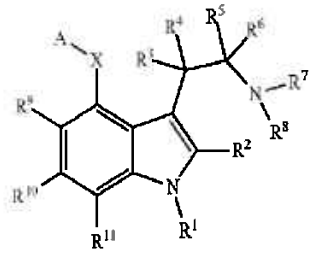


-continued



(D)

Al-reducation



Formula (I)

A person skilled in the art would appreciate that further manipulation of the substituent groups using known chemistry can be performed on the intermediates and final compounds in the Schemes above to provide alternative compounds of the application.

Salts of compounds of the application may be formed by methods known to those of ordinary skill in the art, for example, by reacting a compound of the application with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in aqueous medium followed by lyophilization.

The formation of solvates will vary depending on the compound and the solvate. In general, solvates are formed by dissolving the compound in the appropriate solvent and isolating the solvate by cooling or using an antisolvent. The solvate is typically dried or azeotroped under ambient conditions. The selection of suitable conditions to form a particular solvate can be made by a person skilled in the art. Examples of suitable solvents are ethanol, water and the like. When water is the solvent, the molecule is referred to as a "hydrate". The formation of solvates of the compounds of the application will vary depending on the compound and the solvate. In general, solvates are formed by dissolving the compound in the appropriate solvent and isolating the solvate by cooling or using an antisolvent. The solvate is typically dried or azeotroped under ambient conditions. The selection of suitable conditions to form a particular solvate can be made by a person skilled in the art.

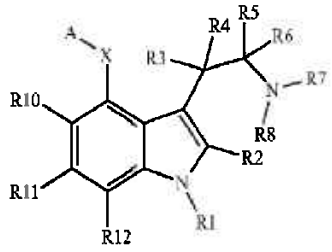
Isotopically-enriched compounds of the application and pharmaceutically acceptable salts, solvates and/or prodrug thereof, can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using suitable isotopically-enriched reagents and/or intermediates.

Throughout the processes described herein it is to be understood that, where appropriate, suitable protecting groups will be added to and subsequently removed from, the various reactants and intermediates in a manner that will be readily understood by one skilled in the art. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in "Protective Groups in Organic Synthesis", T. W. Green, P. G. M. Wuts, Wiley-Interscience, New York, (1999). It is also to be understood that a transformation of a group or substituent into another group or substituent by chemical manipulation can be conducted on any intermediate or final product on the synthetic path toward the final product, in which the possible type of transformation is limited only by inherent incompatibility of other functionalities carried by the molecule at that stage to the conditions or reagents employed in the transformation. Such inherent incompatibilities and ways to circumvent them by carrying out appropriate transformations and synthetic steps in a suitable order, will be readily understood to one skilled in the art. Examples of transformations are given herein and it is to be understood that the described transformations are not limited only to the generic groups or substituents for which the transformations are exemplified. References and descriptions of other suitable transformations are given in "Comprehensive Organic Transformations—A Guide to Functional Group Preparations" R. C. Larock, VHC Publishers, Inc. (1989). References and descriptions of other suitable reactions are described in textbooks of organic chemistry, for example, "Advanced Organic Chemistry", March, 4 th ed. McGraw Hill (1992) or, "Organic Synthesis", Smith, McGraw Hill, (1994). Techniques for purification of intermediates and final products include, for example, straight and reversed phase chromatography on column or rotating plate, recrystallisation, distillation and liquid-liquid or solid-liquid extraction, which will be readily understood by one skilled in the art.

NUMBERED EMBODIMENTS OF THE APPLICATION

1. In some embodiments the application includes a compound of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof:

Formula (I)



wherein:

R^1 is selected from the group consisting of hydrogen, C_1-C_3 alkyl, —$(CH_2)P(O)(OR^{12})$; $CO(R^{12})$, $COO(R^{12})$, $C(O)N(R^{12})_2$, $SO(R^{12})$ and $SO_2(R^{12})$;

R^2 to R^6 are independently selected from the group consisting of hydrogen and lower alkyl; R^7 and R^8 are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, R^7 and R^8 may be taken together with the atoms to which they are attached form a 3- or 7-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, SO_2, N, and $N(R^{13})$

wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a member of the group consisting of C_1-C_3 alkyl and C_1-C_3 haloalkyl, halogen, CN, OR^1, $N(R^{13})_2$, $COOR^{13}$, $C(O)N(R^{13})_2$, SR6, SO_2R^{13}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^{13})$, wherein said C_1-C_6 alkyl, C_2-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl;

R^9, R^{10} and, R^{11} are independently selected from the group consisting of hydrogen, halogen, CN, OR^{13}, $N(R^{13})_2$, SR^{13}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^{13}, C_1-C_6 alkyl substituted by SR^{13}, C_1-C_6 alkyl substituted by $N(R^{13})_2$, C_2-C_6 haloalkyl, $COOR^{13}$, $C(O)N(R^{13})_2$, SO_2R^{13}, $COOR^{13}$, $C(O)N(R^{13})_2$, SO_2R^{13}, C_1-C_6 alkyl, C_2-C_6, alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, and a 3- to 67-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^{13})$, wherein said C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, and 3- to 7-membered heterocyclic ring groups are optionally substituted by one or more substituents independently selected from the group consisting of CN, OR^{13}, $N(R^{13})_2$, and SR^{13}, and wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a member of the group consisting of C_1-C_3 alkyl and C_1-C_3 haloalkyl, halogen, CN, OR^{13}, $N(R^{13})_2$, $COOR^{13}$, $C(O)N(R^{13})_2$, SR^{13}, SO_2R^{13}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^{13})$, wherein said C_1-C_6 alkyl, C_2-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl;

X is selected from O, NR^{13}, S, SO and SO_2;

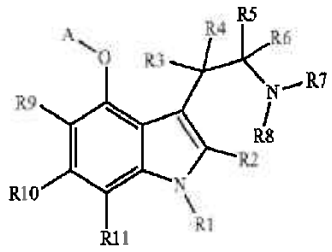
wherein R^{12} is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^{13} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, C_1-C_6 alkyl substituted by OR^{13}, C_1-C_6 alkyl substituted by SR^{13}, C_1-C_6 alkyl substituted by $N(HR^{13})$, $N(R^{13})_2$, C_2-C_6 haloalkyl, $COOR^{13}$, $C(O)N(R^{13})_2$, SO_2R^{13}, $COOR^{13}$, C_1-C_6 alkyl, C_2-C_6, alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, and a 3- to 7-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^{13})$, wherein said C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, and 3- to 7-membered heterocyclic ring groups are optionally substituted by one or more substituents independently selected from the group consisting of CN, OR^{13}, $N(R^{13})_2$, and SR^{13}, and wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a member of the group consisting of C_1-C_3 alkyl and C_1-C_3 haloalkyl, halogen, CN, OR^{13}, $N(R^{13})_2$, $COOR^{13}$, $C(O)N(R^{13})_2$, SR^{13}, SO_2R^{13}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^{13})$, wherein said C_1-C_6 alkyl, C_2-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl; and A is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl, heterocycloalkynyl aryl, heteroaryl, C_0-$C_1P(O)(OR^{12})_2$, CO(Q'), COO(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), where Q' is selected from hydrogen, C_1-C_{20} alkyl, C_1-C_{20} haloalkyl, C_2-C_{20} alkenyl, C_2-C_{20} haloalkenyl, C_2-C_{20} alkynyl, C_2-C_{20} haloalkynyl, C_3-C_7 cycloalkyl, and a 3- to 7-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and $N(R^{13})$, wherein said C_1-C_{20} alkyl, C_2-C_{20} haloalkyl, C_2-C_6 alkenyl, C_2-C_{20} haloalkenyl, C_3-C_7 cycloalkyl, and 3- to 7-membered heterocyclic ring groups are optionally substituted by one or more substituents independently selected from the group consisting of CN, OR^{13}, $N(R^{13})_2$, and SR^{13}, and wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a member of the group consisting of C_1-C_3 alkyl and C_1-C_3 haloalkyl, wherein R^{12} and R^{13} are independently defined as above;

2. In some embodiments compounds of general formula (I) in embodiment 1, and pharmaceutically acceptable salts of the foregoing, are isotopically enriched with deuterium. In aspects of these embodiments, one or more of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} may include deuterium;

3. In some embodiments, the compounds of general formula (I) in embodiment 1 include any compound wherein X═O, and having the structure of Formula (IA) or a pharmaceutically acceptable salt, solvate or prodrug thereof,

(IA)



wherein R^1 is selected from the group consisting of hydrogen, C_1-C_3 alkyl, —$(CH_2)P(O)(OR^{12})$; $CO(R^{12})$, COO (R^{12}), $C(O)N(R^{12})_2$, $SO(R^{12})$ and $SO_2(R^{12})$;

R^2 to R^6 are independently selected from the group consisting of hydrogen and lower alkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, R^7 and R^8 may be taken together with the atoms to which they are attached form a 3- or 7-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, SO_2, N, and $N(R^{13})$ wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a member of the group consisting of C_1-C_3 alkyl and C_1-C_3 haloalkyl, halogen, CN, OR^{13}, $N(R^{13})_2$, $COOR^{13}$, $C(O)N(R^{13})_2$, SR6, SO_2R^{13}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected

from the group consisting of O, S, N, and N(R^{13}), wherein said C_1-C_6 alkyl, C_2-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl;

R^9, R^{10}, and R^{11} are independently selected from the group consisting of hydrogen, halogen, CN, OR^{13}, $N(R^{13})_2$, SR^{13}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl substituted by OR^{13}, C_1-C_6 alkyl substituted by SR^{13}, C_1-C_6 alkyl substituted by $N(R^{13})_2$, C_2-C_6 haloalkyl, $COOR^{13}$, $C(O)N(R^{13})_2$, SO_2R^{13}, $COOR^{13}$, $C(O)N(R^{13})_2$, SO_2R^{13}, C_1-C_6 alkyl, C_2-C_6, alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, and a 3- to 67-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and N(R^{13}), wherein said C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, and 3- to 7-membered heterocyclic ring groups are optionally substituted by one or more substituents independently selected from the group consisting of CN, OR^{13}, $N(R^{13})_2$, and SR^{13}, and wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a member of the group consisting of C_1-C_3 alkyl and C_1-C_3 haloalkyl, halogen, CN, OR^{13}, $N(R^{13})_2$, $COOR^{13}$, $C(O)N(R^{13})_2$, SR^{13}, SO_2R^{13}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and N(R^{13}), wherein said C_1-C_6 alkyl, C_2-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl;

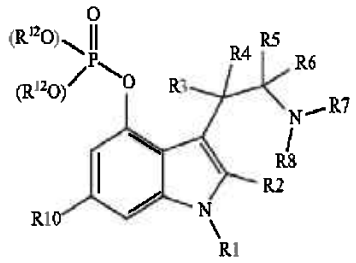
wherein R^{12} is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^{13} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, C_1-C_6 alkyl substituted by OR^{13}, C_1-C_6 alkyl substituted by SR^{13}, C_1-C_6 alkyl substituted by $N(HR^{13})$, $N(R^{13})_2$, C_2-C_6 haloalkyl, $COOR^{13}$, $C(O)N(R^{13})_2$, SO_2R^{13}, $COOR^{13}$, C_1-C_6 alkyl, C_2-C_6, alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, and a 3- to 7-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and N(R^{13}), wherein said C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, and 3- to 7-membered heterocyclic ring groups are optionally substituted by one or more substituents independently selected from the group consisting of CN, OR^{13}, $N(R^{13})_2$, and SR^{13}, and wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a member of the group consisting of C_1-C_3 alkyl and C_1-C_3 haloalkyl, halogen, CN, OR^{13}, $N(R^{13})_2$, $COOR^{13}$, $C(O)N(R^{13})_2$, SR^{13}, SO_2R^{13}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and N(R^{13}), wherein said C_1-C_6 alkyl, C_2-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl; and

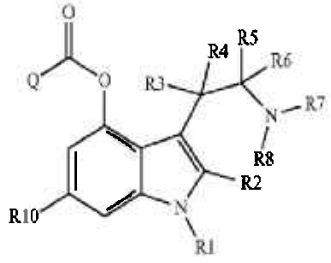
A is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl, heterocycloalkynyl aryl, heteroaryl, C_0-$C_1P(O)(OR^{12})_2$, CO(Q'), COO(Q'), C(O)N(Q')$_2$, SO(Q'), SO_2(Q'), where Q' is selected from hydrogen, C_1-C_{20} alkyl, C_1-C_{20} haloalkyl, C_2-C_{20} alkenyl, C_2-C_{20} haloalkenyl, C_2-C_{20} alkynyl, C_2-C_{20} haloalkynyl, C_3-C_7 cycloalkyl, and a 3- to 7-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and N(R^{13}), wherein said C_1-C_{20} alkyl, C_2-C_{20} haloalkyl, C_2-C_6 alkenyl, C_2-C_{20} haloalkenyl, C_3-C_7 cycloalkyl, and 3- to 7-membered heterocyclic ring groups are optionally substituted by one or more substituents independently selected from the group consisting of CN, OR^{13}, $N(R^{13})_2$, and SR^{13}, and wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a member of the group consisting of C_1-C_3 alkyl and C_1-C_3 haloalkyl, wherein R^{12} and R^{13} are independently defined as above;

4. In some embodiments, the compound of embodiments 1-3, or a pharmaceutically acceptable salt thereof, wherein said compound is selected from the Formula (IB) and Formula (1C):

(IB)



(IC)



wherein R^1 is selected from the group consisting of hydrogen, C_1-C_3 alkyl, —$(CH_2)P(O)(OR^{12})$; $CO(R^{12})$, COO (R^{12}), $C(O)N(R^{12})_2$, $SO(R^{12})$ and $SO_2(R^{12})$;

R^2 to R^6 are independently selected from the group consisting of hydrogen and lower alkyl; R^7 and R^8 are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein R^7 and R^8 may be taken together with the atoms to which they are attached form a 3- or 7-membered cyclic or heterocyclic ring;

R^{10} is selected from the group consisting of hydrogen, halogen, CN, OR^{13}, $N(R^{13})_2$, SR^{13}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, where R^{13} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, wherein R^9 and R^{10} are independently defined as above;

Q is selected from hydrogen, C_1-C_{20} alkyl, C_1-C_{20} haloalkyl, C_2-C_{20} alkenyl, C_2-C_{20} haloalkenyl, C_2-C_{20} alkynyl, C_2-C_{20} haloalkynyl, C_3-C_7 cycloalkyl, and a 3- to 7-membered heterocyclic ring including 1 to 2 ring members selected

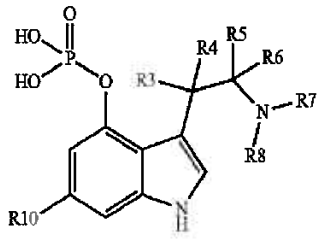
from the group consisting of O, S, N, and N(R^{10}), wherein said C_1-C_{20} alkyl, C_2-C_{20} haloalkyl, C_2-C_6 alkenyl, C_2-C_{20} haloalkenyl, C_3-C_7 cycloalkyl, and 3- to 7-membered heterocyclic ring groups are optionally substituted by one or more substituents independently selected from the group consisting of CN, OR^{10}, $N(R^{10})_2$, and SR^{10}, and wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a member of the group consisting of C_1-C_3 alkyl and C_1-C_3 haloalkyl; wherein R^9 and R^{10} are independently defined as above;

wherein R^{12} is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

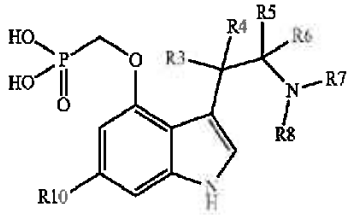
R^{13} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, C_1-C_6 alkyl substituted by OR^{13}, C_1-C_6 alkyl substituted by SR^{13}, C_1-C_6 alkyl substituted by $N(HR^{13})$, $N(R^{13})_2$, C_2-C_6 haloalkyl, $COOR^{13}$, $C(O)N(R^{13})_2$, SO_2R^{13}, $COOR^{13}$, C_1-C_6 alkyl, C_2-C_6, alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, and a 3- to 7-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and N(R^{13}), wherein said C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_7 cycloalkyl, and 3- to 7-membered heterocyclic ring groups are optionally substituted by one or more substituents independently selected from the group consisting of CN, OR^{13}, $N(R^{13})_2$, and SR^{13}, and wherein said C_3-C_7 cycloalkyl and 3- to 7-membered heterocyclic ring are each further optionally substituted with a member of the group consisting of C_1-C_3 alkyl and C_1-C_3 haloalkyl, halogen, CN, OR^{13}, $N(R^{13})_2$, $COOR^{13}$, $C(O)N(R^{13})_2$, SR^{13}, SO_2R^{13}, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkynyl, C_3-C_6 cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring members selected from the group consisting of O, S, N, and N(R^{13}), wherein said C_1-C_6 alkyl, C_2-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 haloalkenyl; and

The compound of any of the proceeding claims, or a pharmaceutically acceptable salt solvate or prodrug thereof, include any compound having the structure of Formula (ID), (1E), (IF) and (IG) thereof:

(ID)

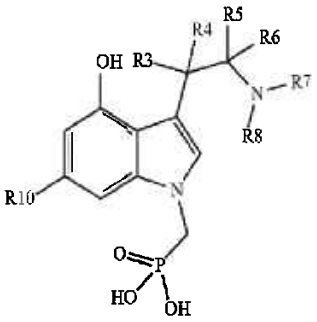


(IE)

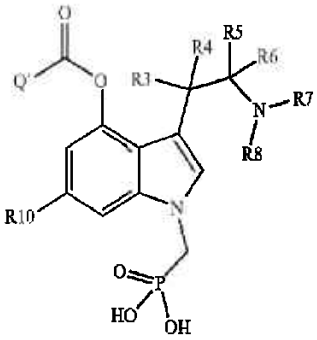


-continued

(IF)



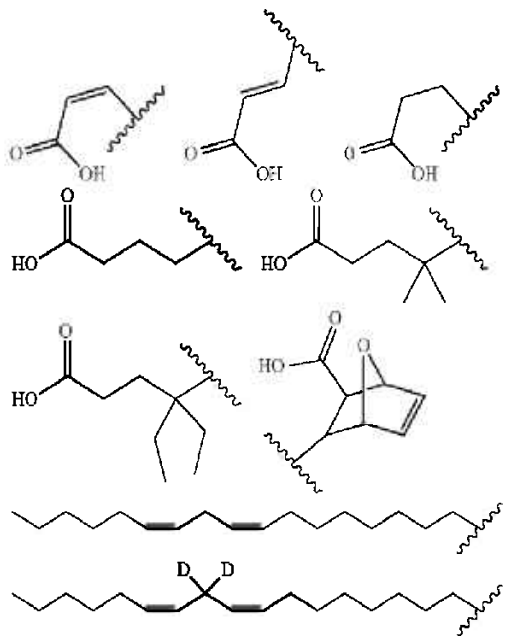
(IG)



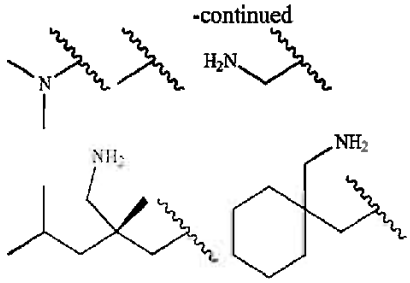
R^3 to R^6 are independently selected from the group consisting of hydrogen and deuterium;

R^7 and R^8 are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein R^7 and R^8 may be taken together with the atoms to which they are attached form a 3- or 7-membered cyclic or heterocyclic ring; R^{10} is selected from the group consisting of hydrogen, halogen, cyano and lower alkyl;

Q' is selected from the group consisting of:



-continued



wherein ~~~ represents the point of attachment of the group to the remaining portion of the compounds of Formula I;

5. In some embodiments, the compound of embodiments 1-4, or a pharmaceutically acceptable salt solvate or prodrug thereof, wherein said compound is selected from Examples 1 to 42 as illustrated below:

3-(2-(dimethyl-amino)ethyl)-6-fluoro-1H-indol-4-yl di-hydrogen phosphate;

3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl dihydrogen phosphate;

3-(2-(bis(methyl-d3)amino)ethyl-1,1,2,2-d4)-1H-indol-4-yl dihydrogen phosphate;

6-cyano-3-(2-((methyl-d3)amino)ethyl)-1H-indol-4-yl dihydrogen phosphate;

3-(2-(bis(methyl-d3)amino)ethyl)-6-fluoro-1H-indol-4-yl dihydrogen phosphate;

3-(2-(bis(methyl-d3)amino)ethyl)-6-fluoro-1H-indol-4-yl dihydrogen phosphate;

3-(2-(bis(methyl-d3)amino)ethyl)-6-cyano-1H-indol-4-yl dihydrogen phosphate;

3-(2-(dimethylamino)ethyl)-1H-indol-4-yl)oxy)methyl) phosphonic acid;

3-(2-(dimethylamino)ethyl)-4-(phosphonooxy)-1H-indol-1-yl)methyl)phosphonic acid;

3-(2-(dimethylamino)ethyl)-4-(phosphonooxy)-1H-indol-1-yl)methyl)phosphonic acid;

3-(2-(bis(methyl-d6)amino)ethyl)-1H-indol-4-yl dihydrogen phosphate;

3-(2-(dimethylamino)ethyl)-4-hydroxy-1H-indol-1-yl) methyl)phosphonic acid;

3-(2-(dimethylamino)ethyl)-4-hydroxy-1H-indol-1-yl) methyl)phosphonic acid;

3-(2-(bis(methyl-d6)amino)ethyl)-6-fluoro-1H-indol-4-yl dihydrogen phosphate;

3-(2-(bis(methyl-d3)amino)ethyl)-6-cyano-1H-indol-4-yl dihydrogen phosphate;

3-(2-(bis(methyl-d3)amino)ethyl)-4-(phosphonooxy)-1H-indol-1-yl)methyl)phosphonic acid;

(1-((3-(2-(dimethylamino)ethyl)-1H-indol-4-yl)oxy)ethyl) phosphonic acid;

(1-((3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl)oxy) ethyl)phosphonic acid;

3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl glycinate;

3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl D-alaninate;

(Z)-4-((3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl) oxy)-4-oxobut-2-enoic acid;

(E)-4-((3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl) oxy)-4-oxobut-2-enoic acid;

4-((3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl)oxy)-4-oxobutanoic acid;

3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl acetate;

3 3-(2-(bis(methyl-d3)amino)ethyl-1,1,2,2-d4)-1H-indol-4-yl acetate;

((4-acetoxy-3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-1-yl)methyl)phosphonic acid;

3-(2-(dimethylamino)ethyl)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate;

3-(2-(d6-dimethylamino)ethyl)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate-11,11-d2;

3-(2-(dimethylamino)ethyl)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate-11,11-d2;

3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate;

3-(2-(bis(methyl-d3)amino)ethyl-1,1,2,2-d4)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate;

3-(2-(bis(methyl-d6)amino)ethyl-1,1,2,2-d4)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate-11,11-d2;

3-(2-(d10-diethylamino)ethyl-d4)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate;

3-(2-(d10-diethylamino)ethyl-d4)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate-11,11-d2;

3-(2-(diethylamino)ethyl-d4)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate;

3-(2-(diethylamino)ethyl-d4)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate-11,11-d2;

3-(2-(pyrrolidin-1-yl)ethyl-1,1,2,2-d4)-1H-indol-4-yl (9Z, 12Z)-octadeca-9,12-dienoate;

3-(2-(pyrrolidin-1-yl)ethyl-1,1,2,2-d4)-1H-indol-4-yl (9Z, 12Z)-octadeca-9,12-dienoate-11,11-d2;

3-(2-(dimethylamino)ethyl)-1H-indol-4-yl (S)-3-(aminomethyl)-5-methylhexanoate;

3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl (S)-3-(aminomethyl)-5-methylhexanoate;

3-(2-(bis(methyl-d3)amino)ethyl-1,1,2,2-d4)-1H-indol-4-yl (S)-3-(aminomethyl)-5-methylhexanoate;

3-(2-(dimethylamino)ethyl)-1H-indol-4-yl 2-(1-(aminomethyl)cyclohexyl)acetate;

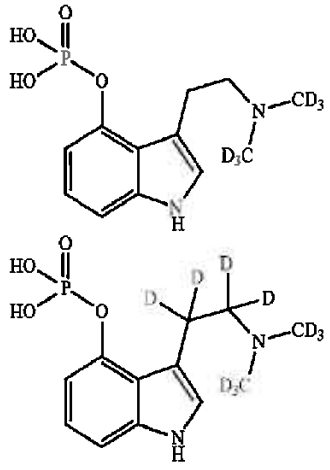
3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl 2-(1-(aminomethyl)cyclohexyl)acetate;

3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl [1,4'-bipiperidine]-1'-carboxylate; and

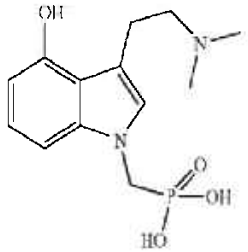
3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl dimethylcarbamate;

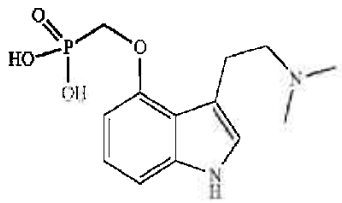
6. In some embodiments, the application includes a pharmaceutical composition comprising a compound of any of the proceeding embodiments, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier;

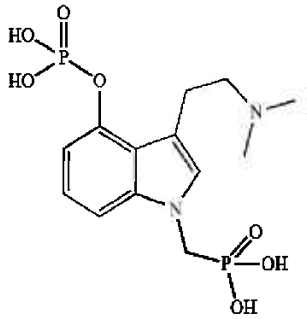
7. In some embodiments, the compounds of embodiments 4-6, or a pharmaceutically acceptable salt thereof, have the structure of:

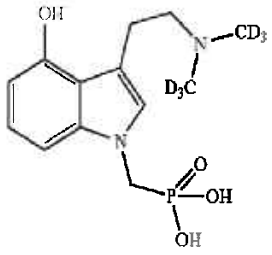


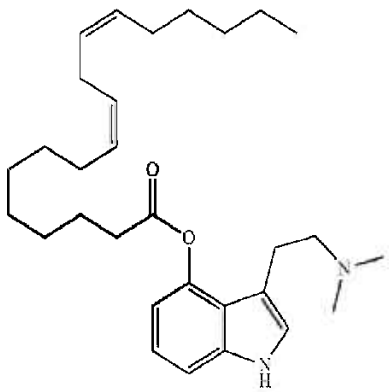
-continued

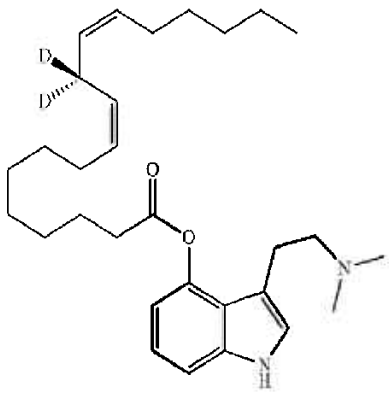




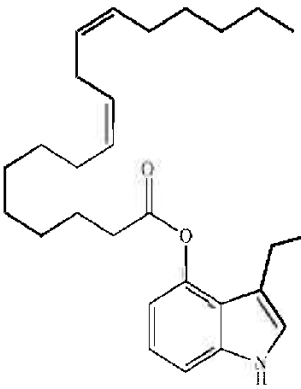


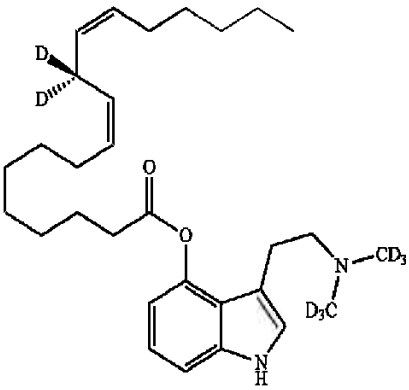


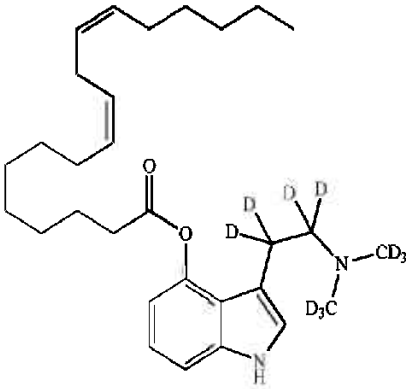


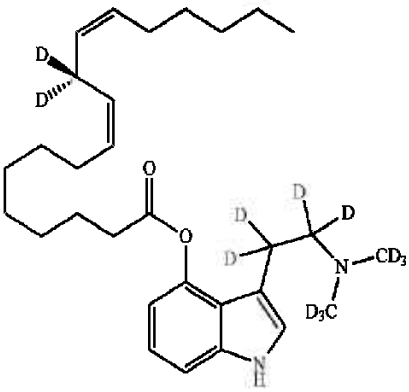


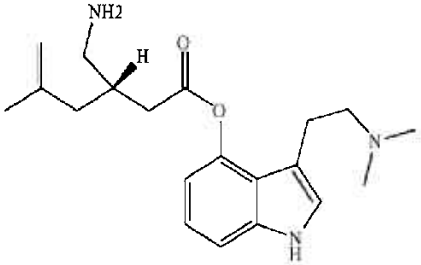
-continued



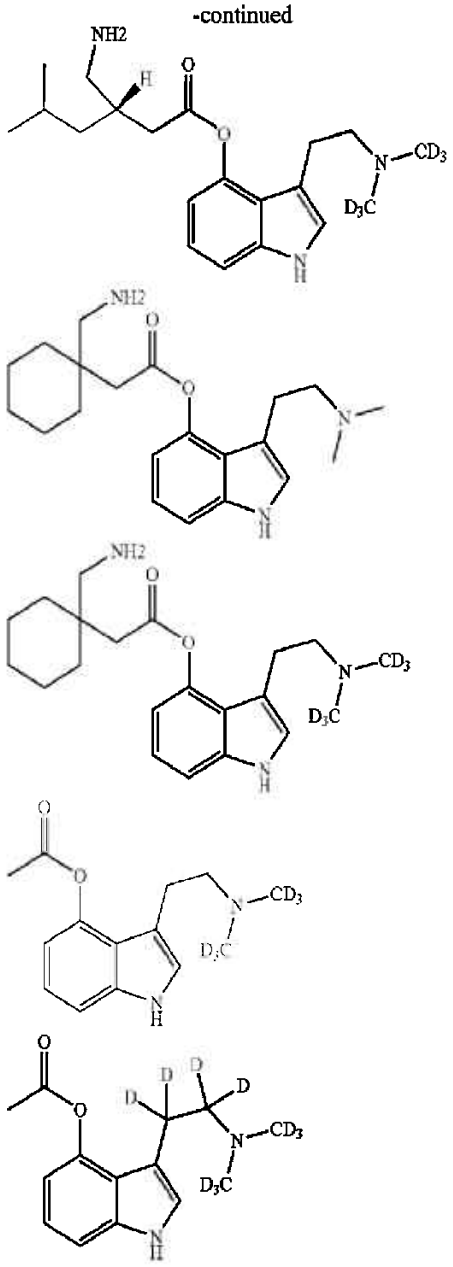








-continued



8. In some embodiments, the application includes a method for the prophylaxis and/or treatment of the psychosis or psychotic symptoms comprising administering to said individual in need thereof a therapeutically effective amount of a 5-HT_{2A} serotonin receptor agonist;

9. In some embodiments, the compounds of general formula (I) are directed towards a method for preventing, treating, and/or reducing the severity of a mental illness disorder and/or condition in a subject. For example, the illness disorder comprises anxiety disorders include generalized anxiety disorder, panic disorder, social anxiety disorder, and specific phobias; depression such as, hopelessness, loss of pleasure, fatigue, and suicidal thoughts; mood disorders, such as depression, bipolar disorder, cancer-related depression, anxiety, and cyclothymic disorder; psychotic disorders, such as hallucinations and delusions, schizophrenia; eating disorders e.g. anorexia nervosa, bulimia nervosa, and binge eating disorder; impulse control and addiction disorders e.g. Pyromania (starting fires), kleptomania (stealing), and compulsive gambling; alcohol addiction; drug addiction including opioid addiction; personality disorders include antisocial personality disorder, obsessive-compulsive personality disorder, and paranoid personality disorder; obsessive-compulsive disorder (OCD) e.g. thoughts or fears that cause them to perform certain rituals or routines; post-traumatic stress disorder (PTSD); stress response syndromes (formerly called adjustment disorders); dissociative disorders, formerly called multiple personality disorder, or "split personality," and depersonalization disorder are examples of dissociative disorders; factitious disorders; sexual and gender disorders e.g. sexual dysfunction, gender identity disorder, and the paraphilia's; somatic symptom disorders, formerly known as a psychosomatic disorder or somatoform disorder; attentional disorders including attentional deficit disorder, attentional deficit hyperactivity disorder and attentional deficits seen in other disorders included here; tic disorders: People with tic disorders such as, Tourette's syndrome; and other diseases or conditions, including various sleep-related problems and many forms of dementia, including Alzheimer's disease, Lewy body dementia, Parkinson's dementia and frontotemporal dementia. In embodiments, the condition comprises cognitive impairment, ischemia including stroke, neurodegeneration, refractory substance use disorders, sleep disorders, pain, e.g. surgical pain, social pain, acute pain, cancer pain, chronic pain, breakthrough pain, bone pain, soft tissue pain, nerve pain, referred pain, phantom pain, neuropathic pain, cluster headaches and migraine, obesity and eating disorders, epilepsies and seizure disorders, neuronal cell death, excitotoxic cell death, or a combination thereof;

10. In some embodiments, the application relates to methods of treating a CNS disorder in a patient in need of therapy, comprising administering a therapeutically effective amount of a compound of general formula (I), or a pharmaceutically acceptable salt thereof to the patient. In aspects of this embodiment, CNS disorder is, but not limited to mental illness disorders above;

11. In some embodiments, the application relates to methods for treating behavioral problems in subjects that are felines or canines comprising administering a therapeutically effective amount of a compound of general formula (I), or a pharmaceutically acceptable salt thereof to the subject. In aspects of this embodiment, behavioral problems include, but are not limited to, anxiety, fear and stress, sleep disturbances, cognitive dysfunction, aggression, or a combination thereof;

12. In some embodiments, the mental illness disorder and/or condition are hallucinations, delusions, or a combination thereof;

13. In some embodiments, the hallucinations are selected from visual hallucinations, auditory hallucinations, olfactory hallucinations, gustatory hallucinations, tactile hallucinations, proprioceptive hallucinations, equilibrioceptive hallucinations, nociceptive hallucinations, thermoceptive hallucinations, chronoceptive hallucinations and any combination thereof; and

14. In some embodiments, the 5-HT2A serotonin receptor agonist is psilocybin derivative, or a pharmaceutically acceptable salt, hydrate, polymorph, or solvate thereof.

EXAMPLES

The following non-limiting examples are illustrative of the present application.

A: Synthesis of Exemplary Compounds of the Application

General Methods

All starting materials used herein were commercially available or earlier described in the literature. The ^1H and

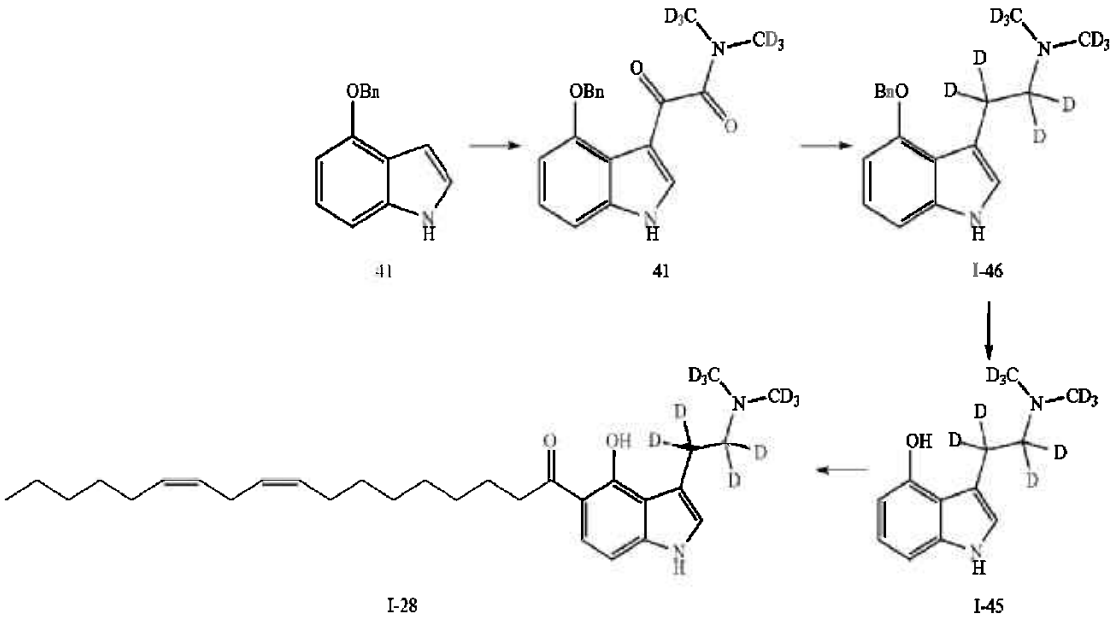
^{13}C NMR spectra were recorded either on Bruker 300, Bruker DPX400 or Varian +400 spectrometers operating at 300, 400 and 400 MHz for ^{1}H NMR respectively, using TMS or the residual solvent signal as an internal reference, in deuterated chloroform as solvent unless otherwise indicated. All reported chemical shifts are in ppm on the delta-scale, and the fine splitting of the signals as appearing in the recordings is generally indicated, for example as s: singlet, br s: broad singlet, d: doublet, t: triplet, q: quartet, m: multiplet. Unless otherwise indicated, in the tables below, ^{1}H NMR data was obtained at 400 MHz, using $CDCl_3$ as the solvent.

Purification of products was carried out using Chem Elut Extraction Columns (Varian, cat #1219-8002), Mega BE-SI (Bond Elut Silica) SPE Columns (Varian, cat #12256018; 12256026; 12256034) or by flash chromatography in silica-filled glass columns.

The following compounds were prepared using one or more of the synthetic methods outlined in Schemes II to IV.A.

A. Synthesis of Exemplary Compounds of the Application

Example 1: 3-(2-(bis(methyl-d_3)amino)ethyl-1,1,2,2-d_4)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate (I-28



Synthesis of 2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-bis(methyl-d_3)-2-oxoacetamide (41)

A solution of 4-(benzyloxy)-1H-indole (2.27 g, 10.16 mmol) in dry ether (50 mL) was treated with oxalyl chloride (0.86 mL, 10.16 mmol) drop-wise at 0° C. The reaction was brought to room temperature and stirred for over night (18 h). The reaction was cooled to 0° C. treated with bis(methyl-d_3)amine hydrochloride (2.22 g, 25.41 mmol, free based with K_2CO_3 in THF) over a period of 5 min. The reaction was brought to room temperature and stirred for 4 h. The reaction was quenched with water (100 mL) and product was extracted into ethyl acetate (2×100 mL). Combined ethyl acetate layer was washed with brine (50 mL) and dried (Na_2SO_4). Solvent was evaporated and crude was purified by flash column chromatography ($MeOH:CH_2Cl_2$, 5:95) on silica gel to obtain the title compound (2.13 g, 63.7%) as a light brown foam. ^{1}H NMR ($CDCl_3$): δ 10.20 (s, 1H), 7.56-7.53 (m, 3H), 7.42-7.30 (m, 3H), 7.05 (t, 1H, J=6.0 Hz), 6.90 (d, 1H, J=6.0 Hz), 6.65 (d, 1H, J=6.0 Hz), 5.26 (s, 2H); ESI-MS (m/z, %): 351 (M+Na, 100), 329 (MH^+).

Synthesis of 2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-bis(methyl-d_3)ethan-1-amine-1,1,2,2-d_4 (I-46

A suspension of lithium aluminum deuteride (1.94 g, 46.28 mmol) in dry THF (20 mL) was treated with 2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-bis(methyl-d_3)-2-oxoacetamide (1.9 g, 5.78 mmol) in dry THF (40 mL) at 0° C. over a period of 10 min. The reaction was brought to room temperature, then refluxed for additional 16 h. The reaction was cooled 0° C., quenched with a sequential addition of water (1.94 mL), 2 N NaOH solution (1.94 mL) and water (1.94 mL). The reaction was brought to room temperature, stirred for 30 min. Solid was filtered and washed with THF (2×50 mL). Combined THF layer was evaporated and crude was purified by column chromatography (2 M NH_3 in $MeOH:CH_2Cl_2$, 5:95) on silica gel to obtain the title compound (0.91 g, 51.7%) as a tan solid. ^{1}H NMR ($CDCl_3$): δ 8.16 (s, 1H), 7.54-7.52 (m, 2H), 7.43-7.33 (m, 2H), 7.08 (t, 1H, J=6.0 Hz), 6.98 (d, 1H, J=6.0 Hz), 6.90 (d, 1H, J=3.0 Hz), 6.57 (d, 1H, J=6.0 Hz), 5.24-5.20 (m, 2H); ESI-MS (m/z, %): 305 (MH^+, 100).

Synthesis of 3-(2-(bis(methyl-d_3)amino)ethyl-1,1,2,2-d_4)-1H-indol-4-ol (I-45

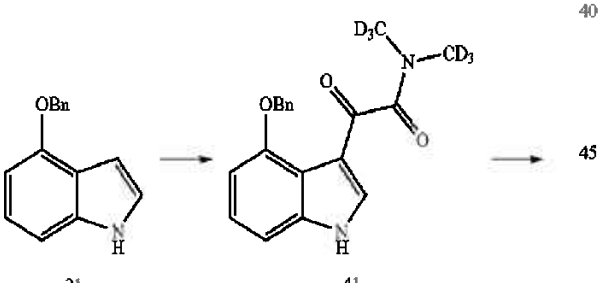
A solution of 2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-bis(methyl-da)ethan-1-amine-1,1,2,2-d_4 (0.88 g, 2.89 mmol) in methanol (25 mL) was treated with Pd—C (0.2 g) and hydrogenated under hydrogen atm. for 2 h. The reaction was filtered through a pad of celite and washed with methanol

(2×25 mL). Combined methanol layer was evaporated and crude was purified by flash column chromatography (2 M NH_3 in MeOH:CH_2Cl_2, 5:95) on silica gel to obtain the title compound (0.53 g, 85.6%) as an off-white solid. ^1H NMR of TFA salt (DMSO-d_6): δ 10.81 (s, 1H), 9.55 (s, 1H), 9.38 (s, 1H), 7.06 (d, 1H, J=1.5 Hz), 6.88-6.80 (m, 2H), 6.38-6.36 (m, 1H); ESI-MS (m/z, %): 215 (MH^+, 100).

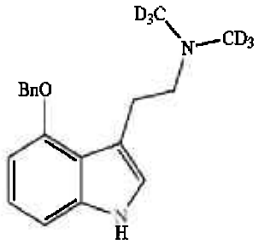
Synthesis of 3-(2-(bis(methyl-d_3)amino)ethyl-1,1,2,2-d_4)-1H-indol-4-yl (9Z,12Z)-octadeca-9,12-dienoate (I-28

A solution of linoleic acid (0.23 g, 0.84 mmol) in dry CH_2Cl_2 (10 mL) was treated with oxalyl chloride (0.1 mL, 1.12 mmol) followed by 1 drop of dry DMF at room temperature and stirred for additional 2 h. Solvent was evaporated and crude product was dried on high vacuum to obtain the corresponding acid chloride. A solution of 3-(2-(bis(methyl-d3)amino)ethyl-1,1,2,2-d_4)-1H-indol-4-ol (0.12 g, 0.55 mmol) in dry CH_2Cl_2 (10 mL) and triethyl amine (0.23 mL, 1.68 mmol) was treated with crude acid chloride in dry CH_2Cl_2 (10 mL) at 0° C. The reaction was brought to room temperature and stirred for additional 2 h. The reaction was quenched with water (50 mL), and product was extracted into CH_2Cl_2 (2×50 mL). Combined CH_2Cl_2 layer was washed with brine (25 mL) and dried (Na_2SO_4). Solvent was evaporated and crude was purified by column chromatography (2 M NH_3 in MeOH:CH_2Cl_2, 5:95) on silica gel to obtain the title compound (0.22 g, 82.7%) as a pale yellow oil. ^1H NMR of TFA salt (DMSO-d_6): δ 11.28 (s, 1H), 9.58 (brs, 1H), 7.30-7.28 (m, 2H), 7.11-7.06 (m, 1H), 6.72 (d, 1H, J=6.0 Hz), 5.41-5.29 (m, 4H), 2.78-2.70 (m, 4H), 2.08-2.01 (m, 4H), 1.73-1.66 (m, 2H), 1.43-1.24 (m, 14H), 0.87 (t, 3H, J=6.0 Hz); ESI-MS (m/z, %): 477 (MH^+, 100).

Example 2: 2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-bis(methyl-d_3)ethan-1-amine (I-47



21 41

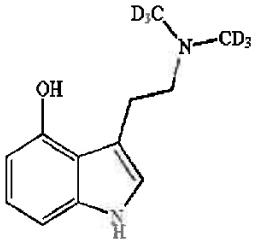


I-47

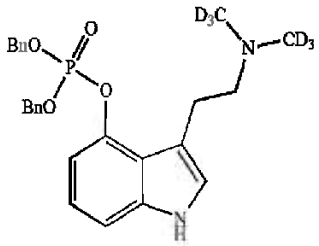
Synthesis of 2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-bis(methyl-d_3)ethan-1-amine (I-47

Prepared from 2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-bis(methyl-d_3)-2-oxoacetamide (0.5 g, 1.52 mmol) as described for compound I-46 using $LiAlH_4$ to obtain the title compound I-47 (0.24 g, 53%) as a pale yellow semi-solid. ^1H NMR ($CDCl_3$): δ 8.10 (s, 1H), 7.54-7.52 (m, 2H), 7.43-7.29 (m, 2H), 7.11-7.03 (m, 1H), 6.91 (s, 1H), 6.57 (d, 1H, J=6.0 Hz), 5.19 (s, 2H), 3.10-3.06 (m, 2H), 2.64-2.60 (m, 2H); ESI-MS (m/z, %): 301 (MH^+, 100).

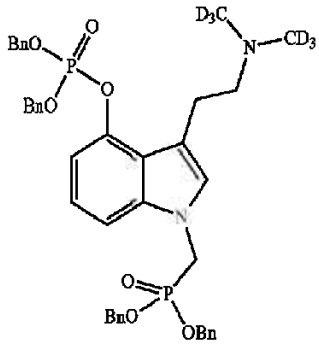
Example 3 and Example 4



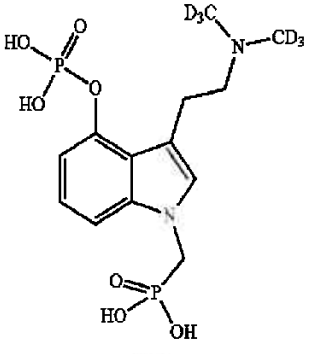
43



54



I-48



I-13

Example 3 (I-48) dibenzyl (((1-((bis(benzyloxy) phosphoryl)methyl)-3-(2-(bis(methyl-d3)amino) ethyl)-1H-indol-4-yl)oxy)methyl)phosphonate

Synthesis of 3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl dihydrogen phosphate (54)

A solution of 3-(2-(bis(methyl-d3)amino)ethyl-1H-indol-4-ol (0.31 g, 1.47 mmol) in dry THF (10 mL) was treated with n-butyl lithium (2.36 mL, 5.90 mmol) at −78° C. The reaction was treated with tetrabenzylpyrophosphate (1.03 g, 1.9 mmol) in dry THF (8 mL) after stirring for 10 min. at same temperature. The reaction was brought to 0° C. over a period of 1 h and stirred for additional 1 h at same temperature. The reaction was treated with aminopropyl silica gel (1.3 g) and diluted with ethyl acetate (50 mL). The reaction was filtered though a pad of celite and washed with ethyl acetate (2×20 mL). Combined organic layer was evaporated and dried under vacuum to obtain crude dibenzyl (3-(2-(bis(methyl-d_3)amino)ethyl-1,1,2,2-d4)-1H-indol-4-yl)phosphate as light brown semi-solid.

Synthesis of dibenzyl (((1-((bis(benzyloxy)phosphoryl)methyl)-3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl)oxy)methyl)phosphonate (I-48

To solution of dibenzyl (3-(2-(bis(methyl-d_3)amino)ethyl-1,1,2,2-d4)-1H-indol-4-yl)phosphate in acetonitrile was added 2 eq. of potassium carbonate and 1.1 eq. of dibenzyl (chloromethyl)phosphonate dropwise. The reaction mixture was heated at 100° C. for 2 hours. After work-up and evaporation of solvent followed by crystallization the targeted compounds I-48 was obtained as light-brown solid.

Example 4 ((3-(2-(bis(methyl-d3)amino)ethyl)-4-(phosphonooxy)-1H-indol-1-yl)methyl)phosphonic acid (I-13

A solution of dibenzyl (((1-((bis(benzyloxy)phosphoryl) methyl)-3-(2-(bis(methyl-d3)amino)ethyl)-1H-indol-4-yl) oxy)methyl)phosphonate in dry methanol is treated with Pd—C and hydrogenated under hydrogen atm. The reaction is filtered through a pad of celite and washed with methanol. Combined methanol layer is evaporated and crude is purified by flash column chromatography on silica gel to obtain the title compound I-13.

B. Biological Testing

Example 5: FLIPR Assay: Human 5-HT2A

I. Assessment of the activated effect of exemplary compounds of Formula I targeting on human 5-HT2A (h5-HT2A) receptor under agonist mode:

Compound Preparation and Assay Controls

I.a. Reagent and Materials:

Regents	Vendor	Cat#
DMEM	Gibco	10569010
FBS	Hyclone	SH30406
Penicillin-Streptomycin	Invitrogen	15140
Hygromycin B	Invivogen	Ant-hg-5
G418	Invitrogen	11811031
Tetracycline hydrochloride	Abcam	ab141223
DPBS	Gibco	14190250
DMSO	Millipore	1029312500

-continued

Regents	Vendor	Cat#
Probenecid	Sigma	P8761
FLIPR Calcium 6 Assay Kit	Molecular Device	R8191
HEPES	Invitrogen	15630
Hank's Buffered Saline Solution	Invitrogen	14025
Serotonin HCl	Selleck	S4244

I.b. Instrumentation and Consumables:

Item	Supplier	Cat#
Fluorometric Imaging Plate Reader (FLIPR)	Molecular Device	Tetra
Countess Automated Cell Counter	Invitrogen	Countess
Cell Counting Chamber Slides	Invitrogen	C10312
STERI-CYCLE CO_2 Incubator	Thermo	371
1300 Series Class II Biological Safety Cabinet	Thermo	1389
Table-type Large Capacity Low Speed Centrifuge	Cence	L550
Centrifuge	Eppendorf	5702
Echo	Labcyte	550
Echo	Labcyte	655
Electro-thermal incubator	Shanghai Yiheng	DHP-9031
plate shaker	IKA	MS3 digital
Water Purification System	ULUPURE	UPH-III-20T
Versatile and Universal pH and Conductivity Meters	Mettler Toledo	S220
384-Well plate	Corning	356663
384-Well LDV Clear microplate	LABCYTE	LP-0200
384-Well Polypropylene microplate	LABCYTE	PP-0200
384-well compound plate	Corning	3657
T25 cell culture flask	Corning	430639
50 mL Polypropylene Centrifuge Tube	JET	CFT011500
15 mL Polypropylene Centrifuge Tube	JET	CFT011150

I.c. Experimental Methods and Procedures:

1. Culture the cells in cell culture medium (DMEM containing 10% FBS 1× penicillin-streptomycin 300 μg/ml G418 and 100 μg/ml hygromycin B) at 37° C., 5% (v/v) CO_2.

2. One day before the assays, detach the cell using TrypLE™ Express and count cells using cell counter. Only cells with >85% viability are used for the assay.

3. Seed 20000 cells/well in 30 μl/well culture medium to a 384-well cell plate and incubate the cells overnight at 37° C., 5% (v/v) CO_2.

4. On the assay day, prepare 2× dye solution following the manual of the FLIPR® Calcium 6 Assay Kit: i. Dilute the dye with assay buffer (20 mM HEPES in 1×HBSS, PH7.4); ii. Add probenecid to the final concentration of 5 mM; iii. Vortex vigorously for 1-2 minutes.

5. Medium from cell plate by flicking the cell plate on towel papers.

6. Add 10 μl of assay buffer and 10 μl of 2× dye solution to each well of the cell plate.

7. Put the cell plate on plate shaker, agitate the plate at 600 rpm for 2 minutes. Incubate the plate at 37° C. for 2 hours followed by additional 15-minute incubation at 25° C.

8. Prepare 3× compound in assay buffer: a. Dilute reference compounds to required concentration with DMSO. Add the compounds to a 384-well compound plate; b. Perform serial dilutions; c. Add 10 mM test compounds to the compound plate, perform 3-fold serial dilutions. d. Transfer 60 nl/well of compounds from source plate to a 384-well compound plate (Corning, 3657) by using an Echo; e. Add 20 μl/well assay buffer to the compound plate; f. Mix the plate on plate shaker for 2 mins;

9. Put the cell plate, compound plate and tips into FLIPR, transfer 10 μl of 3× compound to the cell plate per well with FLIPR.

I.d Data Analysis

i. The normalized fluorescence reading (RFU) is calculated as shown follow, while Fmax and Fmin stand for maximum and minimum of calcium signal during defined time window: RFU=Fmax−Fmin

ii. Calculate the percentage activation by using following equation:

$$\%\,\text{Activation} = \frac{(RFU\text{compound} - RFU\text{ low control})}{(RFU\text{ top concentration of reference agonist} - RFU\text{ low control})} * 100\%$$

iii. Calculate EC50 by fitting % activation against log of compound concentrations with Hill equation using XLfit.

The exemplary compounds of the application were found to be 5-HT2A agonists. The results of representative compounds are presented as EC50 provided in Table 1.

Table 1: Effect of compounds of Formula I (I-28) and its metabolite targeting on human 5-HT2A (h5-HT2A) receptor under agonist mode:

Compound ID #	h5-HT2A EC50 [nM]	RFU @ 10 mM EC50 [nM]
Psilocin	75.2	308
I-28 (Example 1)	964.52	302
I-45 (Metabolite of I-28)	74.85	316
I-46 (Example 1)	72.64	287

II. Results & Discussion

Exemplary compound of Formula I, I-46, 1-28, and the metabolite of I-28 (I-45) were evaluated functionally using FLIPR assay for their effect on h5-HT2A receptor under agonist mode. EC_{50} (nM) concentrations are illustrated in Table 1. This assay confirms that either the compounds of the application and/or their major metabolites are effective agonists of the target human 5-HT2A receptors. Specifically, in this example, the metabolite of the I-28 prodrug is the active agonist of the target human 5-HT2A receptor.

Example 6: Human 5-HT2A: Radioligand Binding Assay

II. 1. Materials and Instruments:

Materials	Vendor	Cat#
Ketanserin Hydrochloride, [Ethylene-3H]-	PerkinElmer	NET791250UC
Ketanserin	MedChemExpress	HY-10562
Bovine Serum Albumin (BSA)	Sigma	A1933
Calcium chloride ($CaCl_2$)	Sigma	C5670
Tris(hydroxymethyl)aminomethane (Tris)	Alfa Aesar	A18494
Polyethylenimine, branched (PEI)	Sigma	408727

II. 2. Instrumentation and Consumables:

Item	Supplier	Cat#
Microbeta² Microplate Counter	PerkinElmer	2450-0060
UniFilter-96 GF/B	PerkinElmer	6005177
TopSeal	Biotss	SF-800
MicroBeta Filtermate-96	PerkinElmer	D961962
Seven Compact pH meter	Mettler Toledo	S220
Ultrapure Water Meter	Sichuan Ulupure	UPH-III-20T
Benchtop Centrifuge	Hunan Xiangyi	L550
Microplate Shaker	Allsheng	MX100-4A
384-Well Polypropylene Microplate	Labcyte	PP-0200
96 Round Well Plate	Corning	3799
96 Round Deep Well Plate	Axygen	P-DW-11-C
Echo	LABCYTE	550

II. 3 Experiment Procedure:

i. Prepare the assay buffer following the table below;

Reagent	Concentration
Tris	50 mM
$CaCl_2$	4 mM
BSA	0.1% (w/v)

Adjust pH to 7.4 followed by 0.2 uM sterile filtration

ii. Preparation of 8 doses of reference and test compounds starting from 10 mM stock solution as requested by 5-fold serial dilutions with 100%;

iii. Prepare (v/v) DMSO: a. Add 50 μl/well of 0.5% (v/v) PEI to UniFilter-96 GF/B plates. Seal the plates and incubate at 4° C. for 3 hrs; b. After incubation, wash the plates 3 times with ice-cold wash buffer (50 mM Tris, pH7.4);

iv. Preparation of assay plates: a. Dilute cell membrane with assay buffer and add 330 μl/well to 96 round deep well plates to reach a concentration of 20 μg/well; b. Prepare 8 concentrations of reference or test compounds and add 110 μl/well to 96 round deep well plates; c. Dilute [3H]-ketanserin with assay buffer to 5 nM (5× final concentration) and add 110 μl/well to 96 round deep well plates.

v. Centrifuge the plate at 1000 rpm for 30 secs and then agitate at 600 rpm, R.T. for 5 min.

vi. the plates and incubate the plate at 27° C. for 90 min.

vii. Stop the incubation by vacuum filtration onto GF/B filter plates followed by 4 times washing with ice-cold wash buffer (50 mM Tris, pH7.4).

viii. Dry the plates at 37° C. for 45 min.

ix. Seal the filter plates and add 40 μl/well of scintillation cocktail.

X. Read the plate by using a Microbeta2 microplate counter.

Data Analysis:

For reference and exemplary test compounds of the application, the results are expressed as % Inhibition, using the normalization equation: N=100−100×(U−C2)/(C1−C2), where U is the unknown value, C1 is the average of high controls, and C2 is the average of low controls. The IC50 is determined by fitting percentage of inhibition as a function of compound concentrations with Hill equation using XLfit.

Results and Discussion

The results of potential competition binding properties of the exemplary prodrug compound (I-28) of the application

and its metabolite (I-45) targeting the human 5-hydroxytryptamine receptor 2 A (5-HT2A) are summarized in Table 2. The results of exemplary compounds of the application are presented as IC_{50} provided in Table 2.

TABLE 2

Effect of exemplary compounds of Formula 1 using Radioligand binding assay on human 5-HT2A receptor

Compound ID#	h5-HT2A IC_{50} [nM]
Psilocin	112.3
I-28 (Example 1)	515.6
I-45 (Metabolite of I-28)	351.7
I-46 (Example 1)	106.5

Exemplary compounds of Formula I were evaluated using radioligand binding assay on human 5-HT2A receptor. EC_{50} (nM) concentrations are illustrated in Table 2. This assay confirms that compounds or metabolites of the application are effective ligands of the target human 5-HT2A receptors. Specifically, the metabolite of the exemplary compound (I-28) demonstrates greater binding affinity at the target receptor.

Example 7: Human, Rat and Mouse Liver Microsomes Stability

Objective

The objective of this study was to estimate in vitro metabolic stability of I-12 in pooled human, male rat and male mouse liver microsomes. The concentrations of parent compounds in reaction systems were evaluated by LC-MS/MS for estimating the stability in pooled human, male rat and male mouse liver microsomes. The in vitro intrinsic clearances of test compounds were determined as well.

Protocol

A master solution in the "Incubation Plate" containing phosphate buffer, ultra-pure H_2O, $MgCl_2$ solution and liver microsomes was made according to Table-3. The mixture was pre-warmed at 37° C. water bath for 5 minutes.

TABLE 3

Preparation of master solution

Reagent	Stock Concentration	Volume	Final Concentration
Phosphate buffer	200 mM	200 uL	100 mM
Ultra-pure H_2O	—	106 uL	—
$MgCl_2$ solution	50 mM	40 uL	5 mM
Microsomes	20 mg/mL	10 uL	0.5 mg/mL

40 μL of 10 mM NADPH solution was added to each well. The final concentration of NADPH was 1 mM. The negative control samples were prepared by replacing NADPH with 40 μL of ultra-pure H_2O. Samples were prepared in duplicate. Negative controls were prepared in singlet.

The reaction was started with the addition of 4 μL of 200 μM exemplary test compounds of the application or control compounds to each master solution to get the final concentration of 2 μM. This study was performed in duplicate.

Aliquots of 50 μL were taken from the reaction solution at 0, 15, 30, 45 and 60 minutes. The reaction solutions were stopped by the addition of 4 volumes of cold methanol with IS (100 nM alprazolam, 200 nM imipramine, 200 nM labetalol and 2 μM ketoprofen). Samples were centrifuged at 3,220 g for 40 minutes. Aliquot of 90 μL of the supernatant was mixed with 90 μL of ultra-pure H2O and then was used for LC-MS/MS analysis.

LC/MS analysis was performed for all samples from this study using a Shimadzu liquid chromatograph separation system equipped with degasser DGU-20A5R; solvent delivery unit LC-30AD; system controller SIL-30AC; column oven CTO-30A; CTC Analytics HTC PAL System. Mass spectrometric analysis was performed using an Triple Quad™ 5500 instrument.

All calculations were carried out using Microsoft Excel. Peak area ratios of test compound to internal standard (listed in the below table) were determined from extracted ion chromatograms.

All calculations were carried out using Microsoft Excel. Peak areas were determined from extracted ion chromatograms. The slope value, k, was determined by linear regression of the natural logarithm of the remaining percentage of the parent drug vs. incubation time curve.

The in vitro half-life (in vitro t1/2) was determined from the slope value:

$$\text{in vitro } t_{1/2} = -(0.639/k)$$

Conversion of the in vitro t1/2 (min) into the in vitro intrinsic clearance (in vitro CLint, in μL/min/mg proteins) was done using the following equation (mean of duplicate determinations):

$$\text{in vitro } CL_{int} = \left(\frac{0.693}{(t_{1/2})}\right) * \left(\frac{\text{volume of incubation } (\mu L)}{\text{amount of proteins (mg)}}\right)$$

For the exemplary compounds of the application or control compound that showed an initial fast disappearance followed by a slow disappearance, only the time points that were within the initial rate were included in the calculation.

Results & Discussion

Human, rat and mouse liver microsomes contain a wide variety of drug metabolizing enzymes and are commonly used to support in vitro ADME (absorption, distribution, metabolism and excretion) studies. These microsomes are used to examine the potential first-pass metabolism by-products of orally administered drugs. Exemplary compounds of the application were evaluated for their stability in human, rat and mouse liver microsomes. A majority of the exemplary compounds of the application in three species, human, rat and mouse liver microsomes were recovered within a 60 minute time period indicating that the compounds were not rapidly cleared (see Table 4 for Exemplary compounds of Formula I).

TABLE 4

Metabolic stability of Exemplary prodrug compound of Formula 1 (1-28) and its metabolite and control compounds verapamil and psilocin in human, rat and mouse with NADPH

Example	Remaining Percentage (%) after 60 min			$t_{1/2}$ (min)			CL_{int} (μL/min/mg protein)		
ID#	Human	Rat	Mouse	Human	Rat	Mouse	Human	Rat	Mouse
Verapamil	5.37	1.37	1.73	14.21	9.70	10.25	97.5	142.92	135.18
Psilocin	70.16	62.68	96.89	117.32	89.01	141.71	11.81	15.57	9.78
Example 1 (I-28)	73.27	34.92	8.12	133.71	39.52	16.56	10.37	35.07	83.70
Metabolite (I-45)	87.08	67.47	84.40	300.48	105.6	245.20	4.61	13.12	5.65
Example 1 (I-46)	58.94	108.23	44.75	78.65	35.59	51.71	17.62	39.05	26.80

Results: The results demonstrate the exemplary compounds (I-46 and I-28) are rapidly metabolized and the metabolite of I-28 is comparable to the psilocin reference.

Example 8: In Vivo Assessment of the Pharmacokinetics of Exemplary Compound I-28 and its Metabolite I-45 in Mice

1. Formulation Preparation and Storage

Group ID	Formulation	Storage
1, 3, 5, 7 & 9	A 0.2 mg/mL formulation of the appropriate TA will be freshly prepared in saline on the day of dosing.	−80° C.
2, 4, 6, 8 & 10	A 1 mg/mL formulation of the appropriate TA will be freshly prepared in saline on the day of dosing.	

2. Sample Collection

Group ID	Blood collection time (h)	Volume/time-point
1, 3, 5, 7 & 9	0.0833, 0.25, 0.5, 1, 2, 4, 6 & 8-24	~0.03 mL (tail snip) ~0.4 mL blood via cardiac puncture
2, 4, 6, 8 & 10	0.25, 0.5, 1, 2, 4, 6, & 8-24	~0.03 mL (tail snip) ~0.4 mL blood via cardiac puncture

3. Study Details

Animals:

Male C57 BL/6 mice (25-30 g) from Charles River Labs were acclimatized for a minimum of 5 days prior to dosing. Body weights were recorded on the day of dosing.

Food Restriction:

Animals dosed p.o. were deprived of food overnight and fed ~2 h following dosing.

Clinical Observations:

Animals were observed at the time of dosing and each sample collection. Any abnormalities were documented.

Dosing:

Formulations were administered intravenously (i.v.) via the tail vein or orally (p.o.) by gavage with disposable feeding needles.

Sample Collection:

Serial blood samples were collected via tail snip. Terminal blood samples were collected under isoflurane anesthesia by cardiac puncture.

Sample Processing/Storage:

All blood samples were transferred into K_2EDTA tubes on wet ice and centrifuged within 5 min (3200×g for 5 min at 4° C.) to obtain plasma. Plasma were stored at −80° C. until analysis.

Sample Retention:

4. Bioanalytical Method Development and Sample Analysis

Matrix:

Mouse Plasma.

Instrumentation:

AB Sciex QTRAP 4000 or 6500 MS/MS system equipped with an LC system with a binary pump, a solvent degasser, a thermostated column compartment and a multiplate autosampler.

5. Method Development:

i. selection of the ion transition for the test compounds (i.e. identification of the parent and product ions).

ii. optimization of mass spectrometric operating parameters.

iii. establishment of the chromatographic conditions.

iv. of an appropriate internal standard(s) (IS).

V. sample clean-up method using protein precipitation.

6. Method Qualification:

i. the determination of the quantification dynamic range using non-zero calibration standards (STDs) in singlet. The STDs consisted of a blank matrix sample (without IS), a zero sample (with IS), and at least 6 non-zero STDs covering the expected range and including the lower level of quantitation (LLOQ).

Ii. 3 injections of a system suitability sample (neat solution containing the analyte and IS) bracketing the batch.

7. Method Acceptance Criteria:

i. at least 75% of non-zero STDs were included in the calibration curve with all back-calculated concentrations within ±20% deviation from nominal concentrations (±25% for the lower level of quantification, LLOQ).

Ii. the correlation coefficient (r) of the calibration curve must be greater than or equal to 0.99.

Iii. the area ratio variation between the pre- and post-run injections of the system suitability samples is within ±25%.

8. Sample Analysis Batch;

i. 3 injections of a system suitability sample bracketing the batch.

ii. the STDs in ascending order.

iii. the study samples and the dosing solutions diluted as 3 independent dilutions into blank matrix (plasma).

iv. for more than 40 study samples in a batch, two sets of STDs bracketing the samples were utilized.

v. samples which were 25% greater than the highest calibration standard, were diluted and re-assayed along with a corresponding dilution quality control standard. Dilution standards were acceptable if they are within 25% accuracy of the target concentration.

9. PK Analysis

i. Analysis software: Phoenix® WinNonlin® 8.2 (Pharsight, Certara, Mountainview, Calif.)

ii. Analysis methods: non-compartmental analysis, linear up/log down trapezoidal rule

iii. PK parameters: C_0, $t_{1/2}$, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, CL, V_{SS}, MRT, $t_{max(po)}$, $C_{max(po)}$, F, as appropriate

10. Results and discussion

TABLE 5

Pharmacokinetic Parameters for Examples 5 (I-28) Following i.v. Administration to Male C57BL/6 mice at 1 mg/kg

Parameter	Metabolite (I-45) Alone	Example 1 (I-28) I-28	Example 1 (I-28) Metabolite (I-45) found after administration of I-28 [b]
Dose (mg/kg)	1	2.2[a]	n/a
C_0 (ng/mL)	566 ± 85.0	448 ± 411	n/a
t_{max} (h)	n/a	n/a	0.0833 ± 0.00
C_{max} (ng/mL)	n/a	n/a	379 ± 61.4
C_{max}/Dose (kg*ng/mL/mg)	n/a	n/a	379 ± 61.4
Apparent $t_{1/2}$ (h)	5.32 ± 2.99	4.92 (n = 2)	4.05 ± 2.14
$AUC_{0\text{-}tlast}$ (h*ng/mL)	178 ± 32.2	110 ± 85.9	263 ± 38.3
$AUC_{0\text{-}inf}$ (h*ng/mL)	181 ± 30.8	137 (n = 2)	265 ± 39.5
$AUC_{0\text{-}inf}$/Dose (h*kg*ng/mL/mg)	181 ± 30.8	62.1 (n = 2)	265 ± 39.5
CL (mL/h/kg)	5640 ± 895	23100 (n = 2)	n/a
$MRT_{0\text{-}inf}$ (h)	1.49 ± 0.536	0.977 (n = 2)	1.91 ± 0.594
V_{SS} (mL/kg)	8340 ± 3150	17000 (n = 2)	n/a
f_m	n/a	n/a	147 ± 21.8

(a)Dose is equimolar to 1 mg/kg of metabolite.

(b) The properties of the metabolite following dosing of the exemplary prodrug I-28.

TABLE 6

Pharmacokinetic Parameters for Examples 5 (I-28) Following p.o. Administration to Male C57BL/6 mice at 10 mg/kg.

Parameter	Metabolite (I-45) Alone	Example 1 (I-28) Example 1 (I-28)	Example 1 (I-28) Metabolite (I-45) found after administration of I-28 [c]
Dose (mg/kg)	10	22[a]	n/a
t_{max} (h)	0.250 ± 0.00	2.17 ± 3.32	0.333 ± 0.144
C_{max} (ng/mL)	704 ± 128	1.06 ± 0.447	325 ± 72.5
C_{max}/Dose (kg*ng/mL/mg)	70.4 ± 12.8	0.0482 ± 0.0203	32.5 ± 7.25
Apparent $t_{1/2}$ (h)	4.52 ± 0.481	nc[b]	5.54 ± 2.18
$AUC_{0\text{-}tlast}$ (h*ng/mL)	792 ± 120	nc	530 ± 92.3
$AUC_{0\text{-}inf}$ (h*ng/mL)	795 ± 121	nc	539 ± 86.2
$AUC_{0\text{-}inf}$/Dose (h*kg*ng/mL/mg)	79.5 ± 12.1	nc	53.9 ± 8.62
$MRT_{0\text{-}inf}$ (h)	2.00 ± 0.227	nc	3.68 ± 0.478
F (%)	44.0 ± 6.70	nc	66.7 ± 11.6[d]

(a)Dose is equimolar to 10 mg/kg Metabolite.

(b)nc denotes not calculable as the terminal phase was not defined.

(c) The properties of the metabolite following dosing of the exemplary prodrug I-28.

(d)Ratio of AUCs following administration of Example 1 (I-28) relative to Metabolite.

TABLE 7

Exemplary compound I-28 and Metabolite, residual dosing solution concentrations.

Nominal I-28 concentration (mg/mL)[a]	Measured concentration (mg/mL) Example 1 (I-28)	Measured concentration (mg/mL) Metabolite, (I-45)
0.44	0.343 (n = 2)	0.0454
2.2	2.06	0.235

(a)I-28 formulation was diluted in plasma for analysis. Metabolite (Example#1 , I-45) concentration in I-28 formulation was analyzed in neat solution (DMSO) against a neat metabolite curve.

C_0 concentration extrapolated to time zero following an i.v. dose

t_{max} time at which maximum concentration is observed

C_{max} maximum observed concentration

Apparent $t_{1/2}$ apparent terminal half-life area under the concentration vs time curve from time 0 to the time of the last

$AUC_{0\text{-}tlast}$ measurable concentration

$AUC_{0\text{-}inf}$ area under the concentration vs time curve from time 0 to infinity

CL systemic clearance

$MRT_{0\text{-}inf}$ mean residence time from time zero to infinity

V_{SS} steady-state volume of distribution

F bioavailability=$(Dose^{iv}*AUC^{po})/(Dose^{po}*AUC^{iv})*100$

Example 7: Psychedelic-Like Effect of Exemplary Compounds of Formula I

The effect of different doses of exemplary compound I-28 of Formula I and its active metabolite were evaluated on head-twitch response (HTR) as a behavior-based model of psychedelic activity.

1. Protocols

Mouse Head Twitch

Male, C57 BL/6 J mice (body weight range 20-30 g) were dosed with the appropriate dose of test article, and following a 1-minute pre-treatment time, placed in individual observation chambers. Animals were visually assessed for the incidence head twitches continuously over a 1 hr period. Head twitches were defined as a rapid jerk of the head which was not elicited by an external tactile stimulus (Corne and Pickering, Psychopharmacologia, 1967, 11 (1): 65-78). Each head twitch was individually counted by a trained observer, and the data expressed as the mean±SEM of 6-10 mice per group. Mice were used in a single experiment only.

Rat Behavioural Test

Male, Sprague-Dawley rats (body weight range 250-400 g) were dosed with the appropriate dose of test article and following a 1-minute pre-treatment time, placed in locomotor activity boxes (dimensions 17" W×17" L×12" H) and continuously monitored for a 1 hr period with data collected into 10 minute time bins. Animals were visually assessed for overt behavioural signs, including behaviours characteristic of 5-HT2A receptor activation (wet dog shakes, back muscle contractions), 5-HT2A receptor activation (yawning, penile grooming) and 5-HT1 A behaviours (forepaw treading, hindlimb abduction) (Halberzettl et al, Behav Brain Res. 256: 328-345, 2013). Additional behavioural and somatic signs characteristic of 5-HT syndrome (e.g. tremor, salivation, flat body posture, core body temperature change) were also measured. Simultaneously, the spontaneous activity of

the rats was measured using an automated tracking system (Med Associates, VT, USA). Activity data collected included total distance traveled, rearing counts and ambulatory episodes. All data were expressed as the mean±SEM of 6-10 rats per group.

Drug Discrimination in the Rat

Male Sprague-Dawley rats were initially food restricted by presentation of 18-20 g food at day end (single housing). After 7 days acclimatisation to the food restriction procedure, they were trained daily to lever press for food (45 mg Bioserve pellet) in standard 2-lever operant conditioning chambers controlled by Med-PC software over a period of 1 week (Med. Associates Ins., St. Albans, Vt.). The rats were trained to lever press for food to an FR10 value (i.e 10 lever presses for a single food reward). Once stable food responding was acquired to both response levers, discrimination training began. Over a period of 20-50 training sessions, the rats were trained to associate one lever to a psilocybin training dose of 1 mg/kg SC, and the second lever to a neutral stimulus (saline, SC) (Winter et al, Pharmacol Biochem Behav. 87(4): 472-480, 2007). Training sessions lasted 30-min or until the delivery of 50 pellets and continued until the animals attained appropriate stimulus control (defined as six consecutive sessions where animals made no more than 16 lever presses before the delivery of the first reward, and at least 95% total responses on the appropriate lever). The rats continued to receive daily food ration in their home cage at day end.

Once trained, tests of substitution were conducted. On test days, both levers were designated active, i.e., every 10 th response on either lever resulted in delivery of a food pellet. Test sessions continued until 50 pellets had been obtained or 30 min had elapsed. During these sessions response rate was also measured.

Results and Discussion

FIG. 1. is a graph showing the effect of various doses of exemplary compound of Formula I, I-28, on head-twitch response (HTR) in male C57 BL6 mice. The mice were treated with compound I-28 by SC route (N=6 mice/dose), and the total number of head twitches were recorded over a 1 h period. Data is expressed as mean±SEM. The induction of head twitches elicited by 5-HT2A receptor agonists is believed to represent a behavioural proxy of their psychedelic effects. Also locomotor activity and other 5-HT receptor signs measured (FIG. 1). The metabolite of I-28 (I-45) demonstrates greater efficacy to induce head twitch than the exemplary prodrug I-28 (FIG. 2).

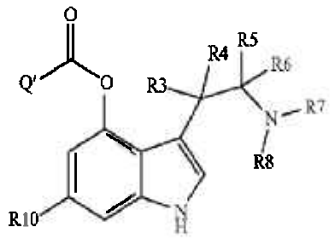
While the present application has been described with reference to examples, it is to be understood that the scope of the claims should not be limited by the embodiments set forth in the examples, but should be given the broadest interpretation consistent with the description as a whole.

All patents, patent applications and publications cited herein are hereby incorporated by reference in their entirety. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art as known to those skilled therein as of the date of the application described and claimed herein.

The invention claimed is:

1. A compound of Formula IG, or a pharmaceutically acceptable salt or solvate thereof:

(IG)



wherein

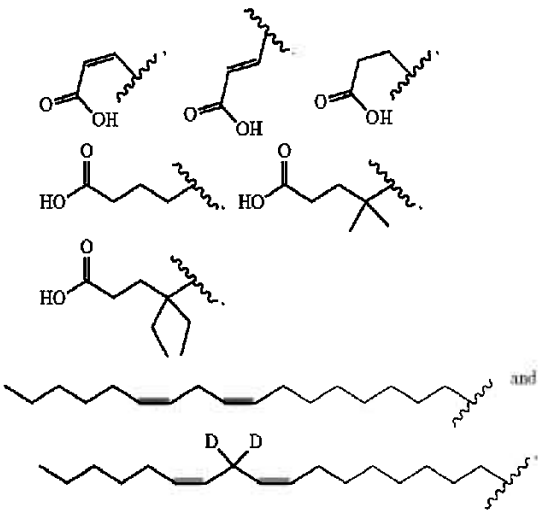
R^3, R^4, R^5 and R^6 are independently selected from the group consisting of hydrogen and deuterium;

R^7 and R^8 are independently selected from the group consisting of hydrogen, and unsubstituted C_{1-6}alkyl; or

R^7 and R^8 are taken together with the atoms to which they are attached form a 3- to 7-membered heterocyclic ring;

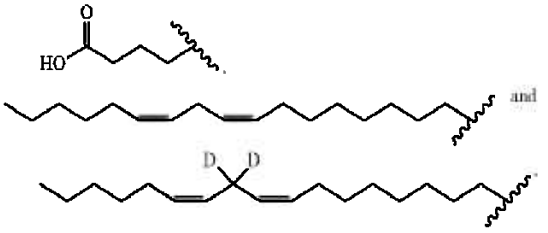
R^{10} is selected from the group consisting of hydrogen, halogen, cyano and lower alkyl; and

Q' is selected from

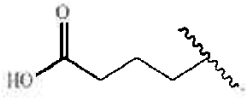


wherein one or more of R^3, R^4, R^5, R^6, R^7, R^8, and R^{10} optionally comprises deuterium.

2. The compound of claim 1, wherein Q' is selected from the group consisting of:



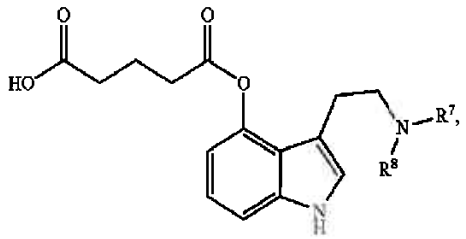
3. The compound of claim 2, wherein Q' is



4. The compound of claim 1, wherein R^3, R^4, R^5, and R^6 are hydrogen.

5. The compound of claim 3, wherein R^3, R^4, R^5, and R^6 are hydrogen.

6. The compound of claim 1 having the following structure:



wherein

R^7 and R^8 are independently selected from the group consisting of hydrogen, and unsubstituted C_{1-6}alkyl; or

R^7 and R^8 are taken together with the atoms to which they are attached form a 3- to 6-membered heterocyclic ring, or

a pharmaceutically acceptable salt or solvate thereof.

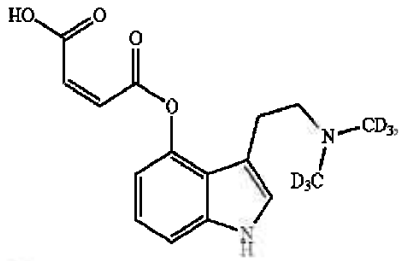
7. The compound of claim 6, wherein R^7 and R^8 are independently selected from the group consisting of hexyl, pentyl, n-butyl, iso-buty, sec-butyl, tert-butyl, n-propyl, isopropyl, ethyl, and methyl.

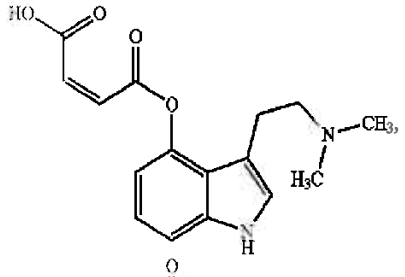
8. The compound of claim 7, wherein R^7 and R^8 are independently selected from the group consisting of n-butyl, iso-butyl, sec-butyl, tert-butyl, n-propyl isopropyl, ethyl, and methyl.

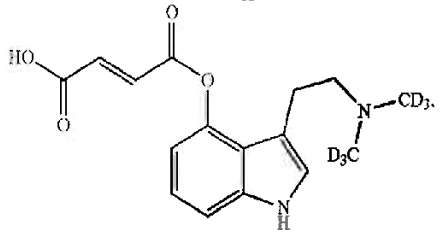
9. The compound of claim 1, wherein R^{10} is hydrogen.

10. The compound of claim 3, wherein R^{10} is hydrogen.

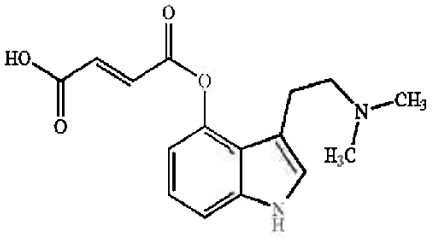
11. The compound of claim 1 selected from the group consisting of:

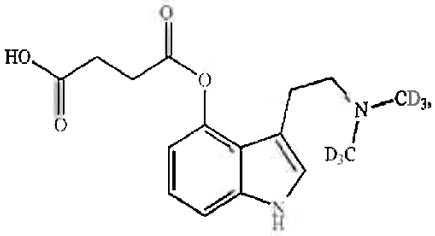


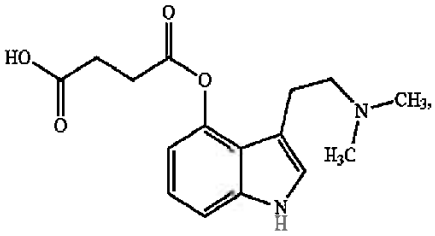


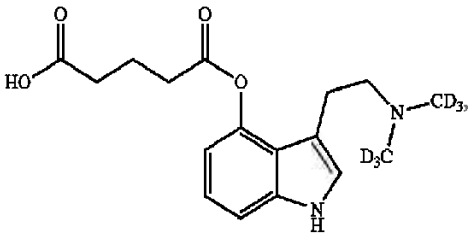


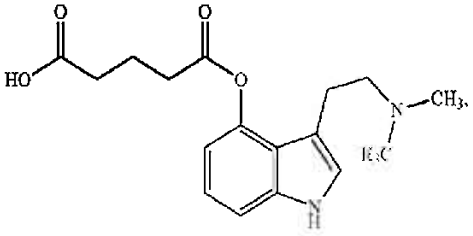
-continued

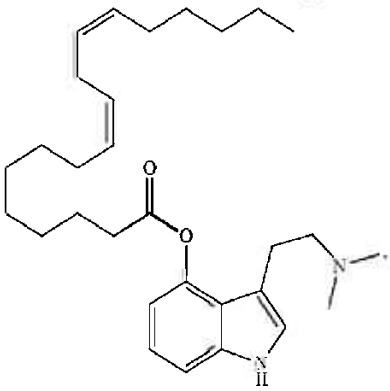


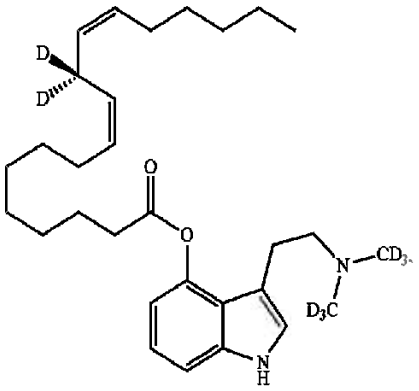


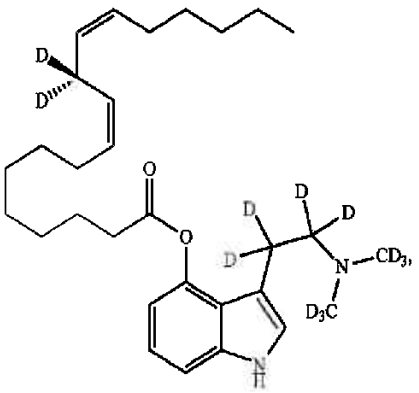


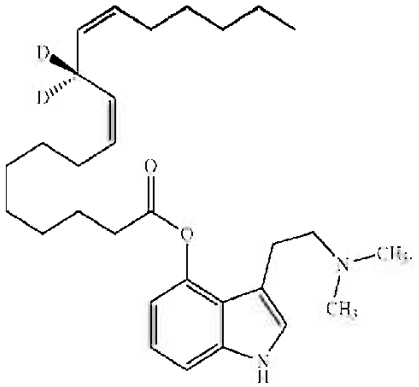


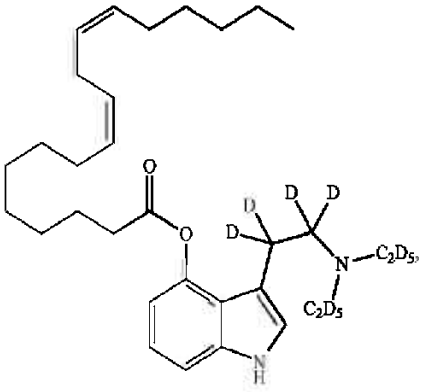


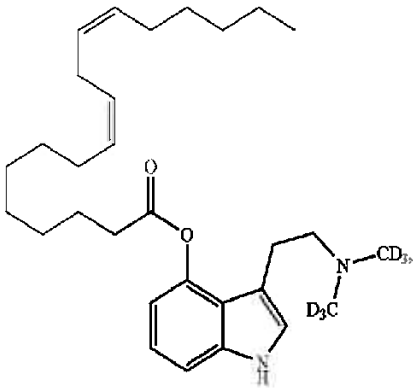


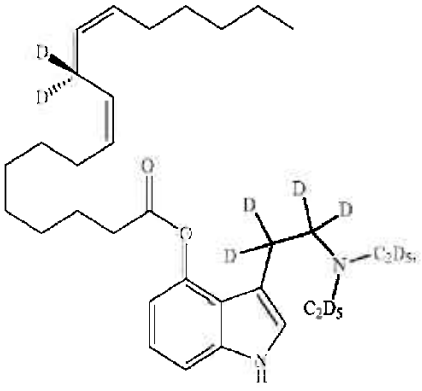


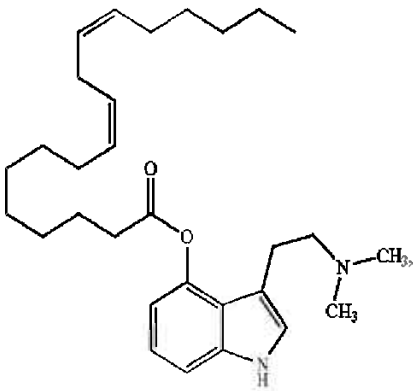


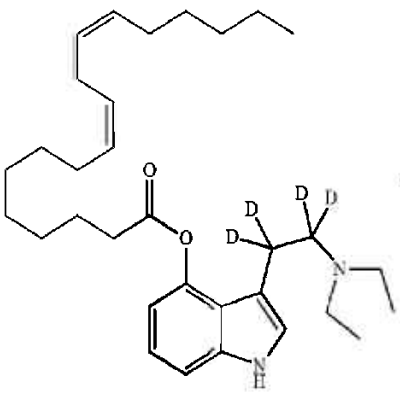




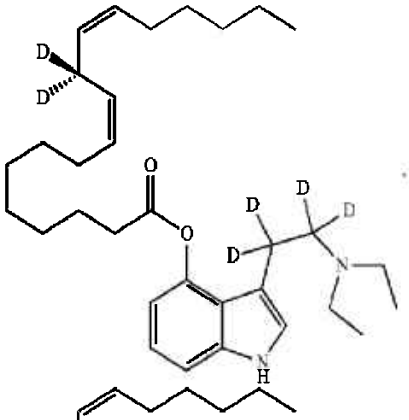




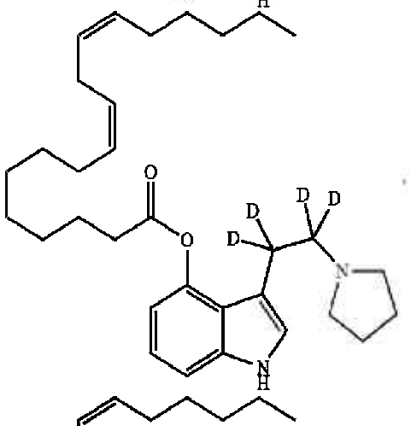


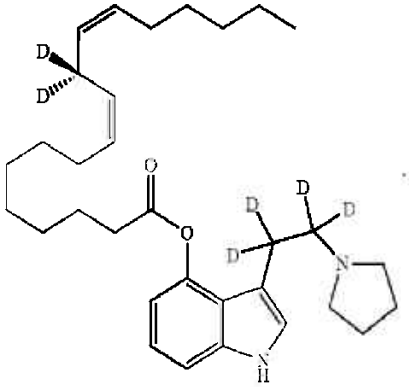


-continued



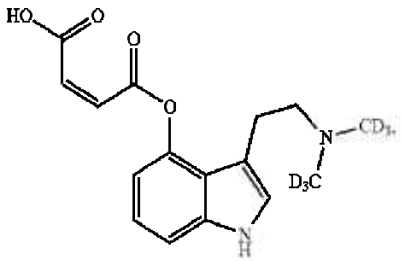
and

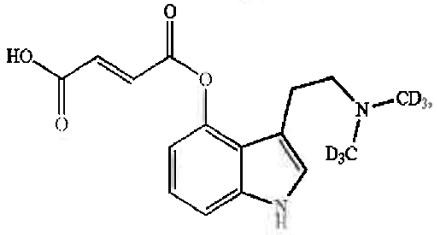




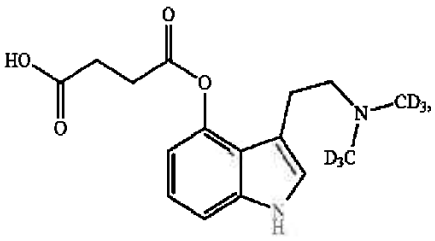
or a pharmaceutically acceptable salt or solvate thereof.

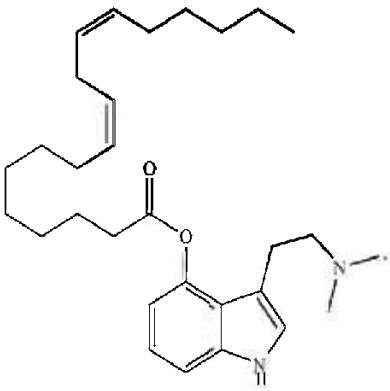
12. The compound of claim 1 selected from the group consisting of:

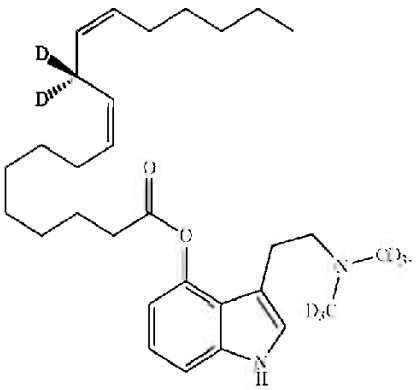


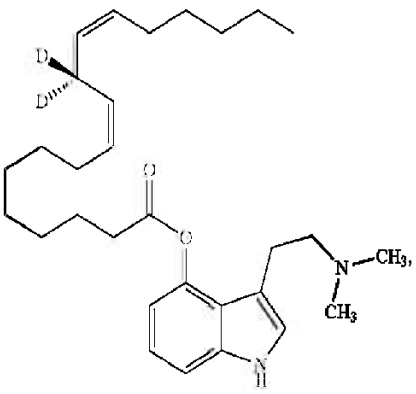


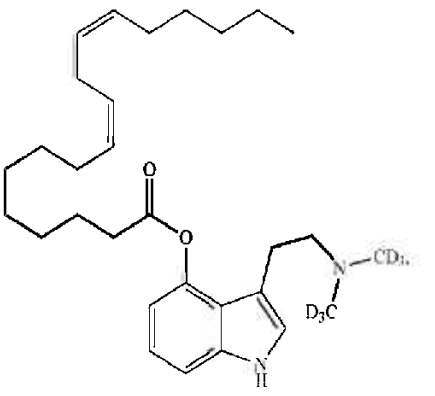
-continued



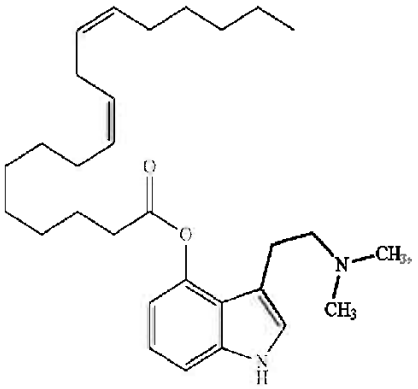


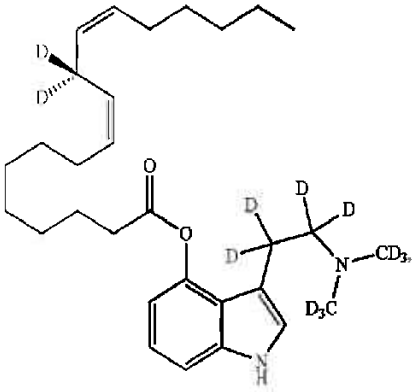


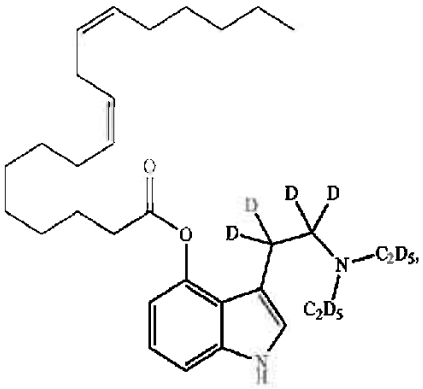


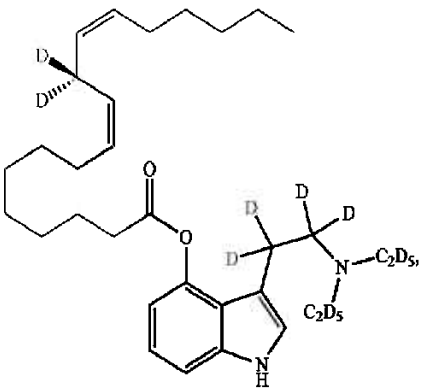


-continued

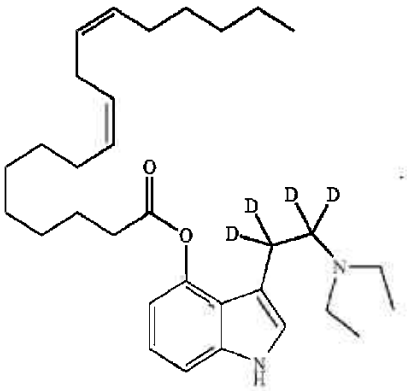


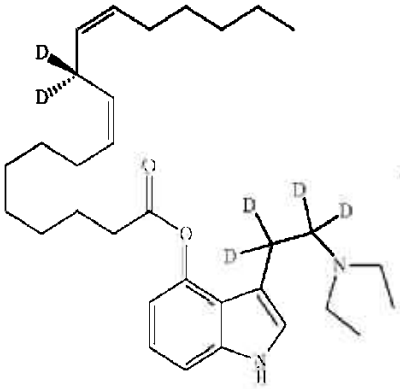


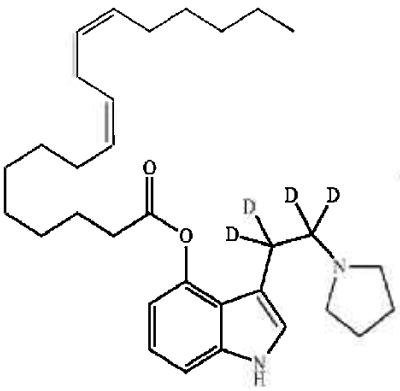




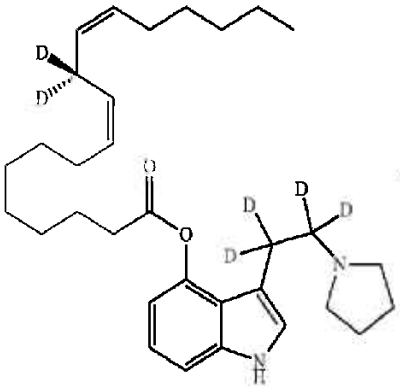
-continued





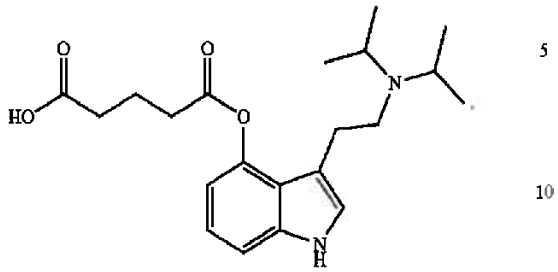


and



or a pharmaceutically acceptable salt or solvate thereof.

13. The compound of claim 1 that is:



or a pharmaceutically acceptable salt or solvate thereof.

14. A pharmaceutical composition comprising one or more compounds of claim 1, or a pharmaceutically acceptable salt and/or solvate thereof, and pharmaceutically acceptable carrier.

15. A pharmaceutical composition comprising the compound of claim 13, or a pharmaceutically acceptable salt and/or solvate thereof, and pharmaceutically acceptable carrier.

* * * * *