FUSED PYRROLIDINE PSYCHOPLASTOGENS AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Serial No. 63/387,225, filed on December 13, 2022, and U.S. Provisional Application Serial No. 63/290,037, filed on December 15, 2021, each of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

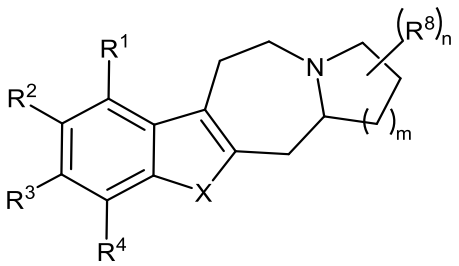
[0002] Described herein are compounds, methods of making such compounds, pharmaceutical compositions and medicaments comprising such compounds, and methods of using such compounds for the treatment of conditions, diseases, or disorders that would benefit from promoting neuronal growth and/or improving neuronal structure.

BACKGROUND OF THE INVENTION

[0003] Altered synaptic connectivity and plasticity has been observed in the brains of individuals with neurological diseases and disorders. Psychoplastogens promote neuronal growth and improve neuronal architecture through mechanisms involving the activation of AMPA receptors, the tropomyosin receptor kinase B (TrkB), and the mammalian target of rapamycin (mTOR). Modulators of these biological targets, such as, for example, ketamine, scopolamine, N,N-dimethyltryptamine (DMT), and rapastinel have demonstrated psychoplastogenic properties. For example, ketamine is capable of rectifying deleterious changes in neuronal structure that are associated with neurological diseases and disorders. Such structural alterations include, for example, the loss of dendritic spines and synapses in the prefrontal cortex (PFC) as well as reductions in dendritic arbor complexity. Furthermore, pyramidal neurons in the PFC exhibit top-down control over areas of the brain controlling motivation, fear, and reward. Psychedelic psychoplastogens have demonstrated antidepressant, anxiolytic, and anti-addictive effects of in the clinic.

SUMMARY

[0003a] In an aspect of the present disclosure, there is provided a compound of Formula (IA):



Formula (IA)

or a pharmaceutically acceptable salt or solvate thereof,

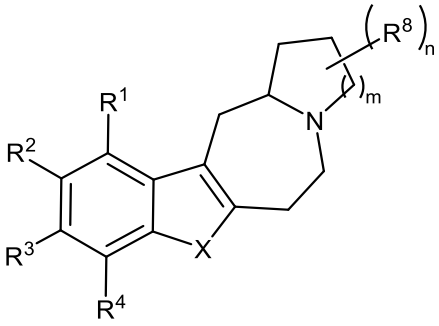
wherein

- X is NR^7, O or $S(=O)_x$;
  - x is 0, 1, or 2;
- each of R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, $-OR^a$, cyano, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

  or any of R^1 and R^2, R^2 and R^3, or R^3 and R^4 are taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring;
- R^7 is hydrogen, alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- R^a is hydrogen, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- each R^8 is independently halogen, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- m is 0, 1, 2 or 3; and
- n is 0, 1, 2, 3, 4, 5, 6, or 7;

provided that when X is NH, m is 2, and R^1-R^4 are hydrogen, then R^8 is not ethyl.

[0003b] In another aspect of the present disclosure, there is provided a compound of Formula (IB):



Formula (IB)

or a pharmaceutically acceptable salt or solvate thereof,

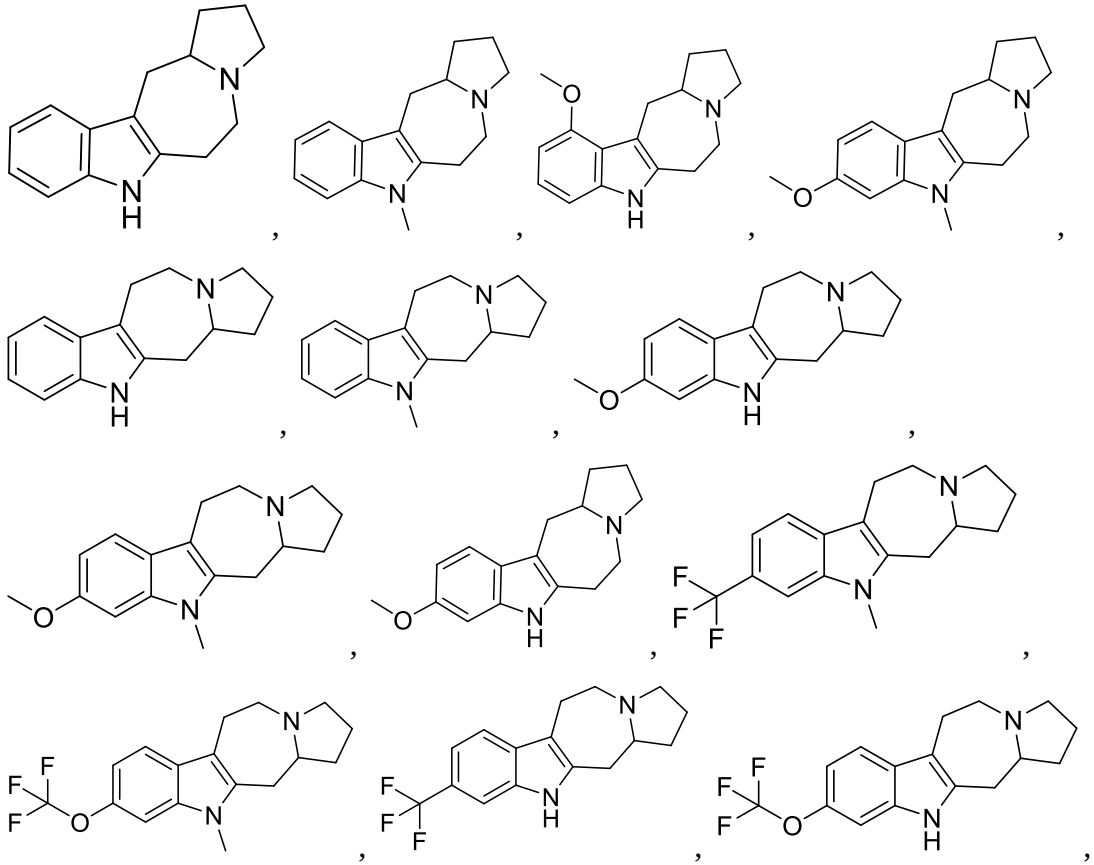
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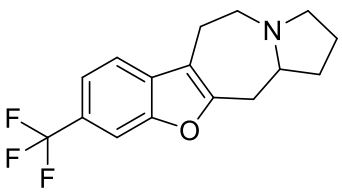
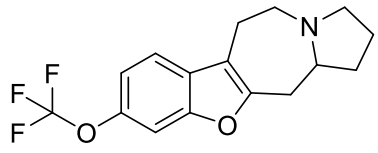
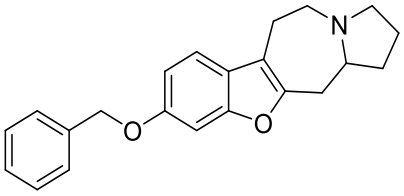
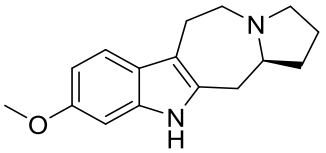
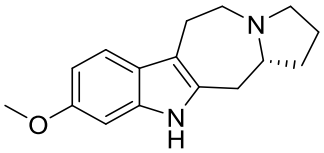
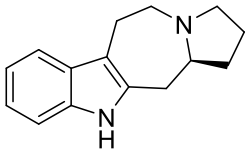
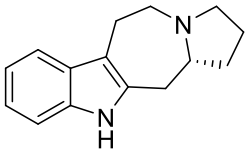
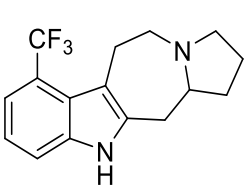
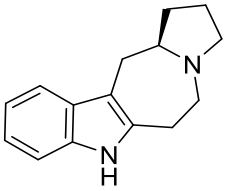
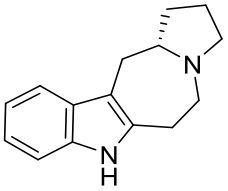
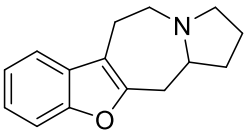
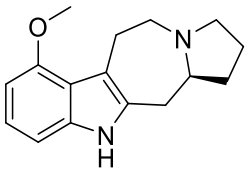
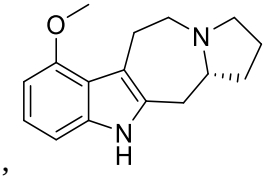
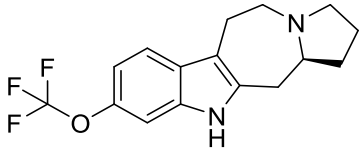
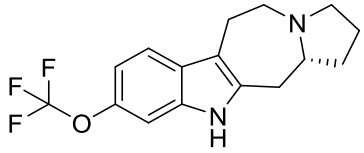
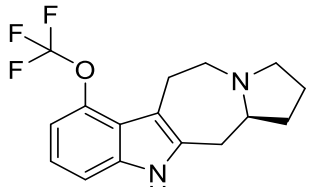
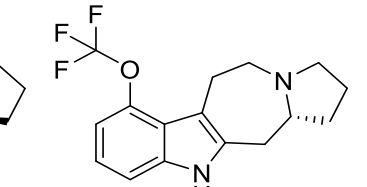
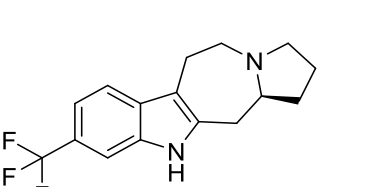
- X is NR^7, O or $S(=O)_x$;
  - x is 0, 1, or 2;

- each of R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, -OR^a, cyano, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

  or any of R^1 and R^2, R^2 and R^3, or R^3 and R^4 are taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring;
- R^7 is hydrogen, alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- R^a is hydrogen, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- each R^8 is independently halogen, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- m is 0, 1, 2 or 3; and
- n is 0, 1, 2, 3, 4, 5, 6, or 7.

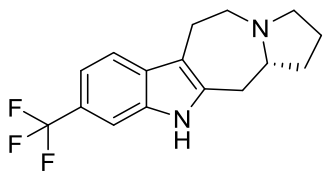
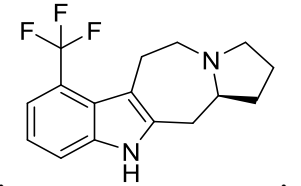
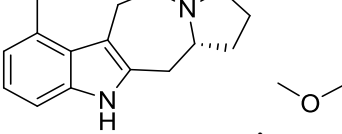
[0003c] In a further aspect of the present disclosure, there is provided a compound that is:




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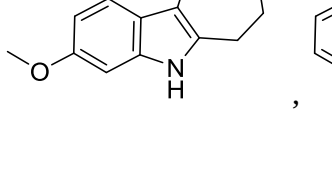
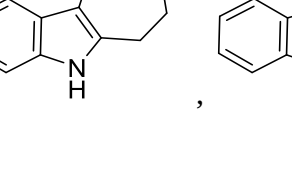
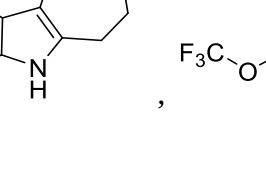
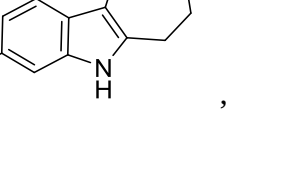
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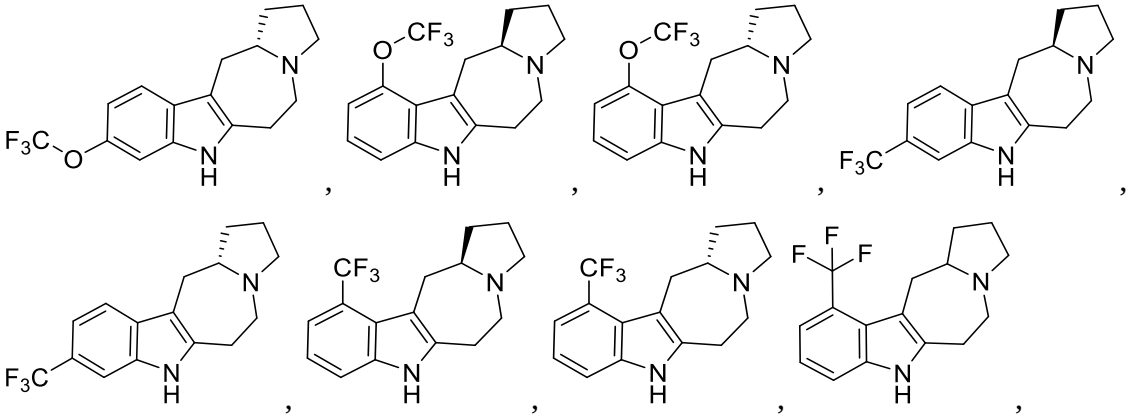
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or a pharmaceutically acceptable salt or solvate thereof.

[0003d] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0003e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or any pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for promoting neuronal growth in a mammal.

[0003f] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or any pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for improving neuronal structure in a mammal.

[0003g] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or any pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a disease or disorder in a mammal that is mediated by the action of 5-hydroxytryptamine (5-HT) at 5-hydroxytryptamine receptor 2A (5-HT_{2A}).

[0003h] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or any pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a disease or disorder in a mammal that is mediated by the loss of synaptic connectivity, plasticity, or a combination thereof.

[0003i] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or any pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a neurological disease or disorder in a mammal.

[0003j] In another aspect of the present disclosure, there is provided a compound disclosed herein, or any pharmaceutically acceptable salt or solvate thereof, for use in therapy.

[0004] In some examples, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:

(i) R^5 and R^{6a} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring;

(ii) R^5 and R^{6b} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring; or

(iii) R^{6a} and R^{6b} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring; and

provided that when X is NH, R^{6a} is hydrogen, and each of R^1, R^2, R^3 and R^4 is hydrogen, then R^5 and R^{6b} are not taken together with the atoms to which they are attached to form a 6-membered heterocyclic ring substituted by ethyl or ethylidene.

[0005] In one example, provided herein is a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0006] In some examples, the compounds disclosed herein, or a pharmaceutically acceptable salt thereof, are formulated for administration to a mammal by intravenous administration, subcutaneous administration, oral administration, inhalation, nasal administration, dermal administration, or ophthalmic administration. In some examples, the compound disclosed herein, or a pharmaceutically acceptable salt thereof, is in the form of a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion.

[0007] In one example, described herein is a method of promoting neuronal growth in a mammal comprising administering to the mammal a compound described herein, or any pharmaceutically acceptable salt or solvate thereof.

[0008] In another example, described herein is a method of improving neuronal structure comprising administering to the mammal a compound provided herein, or a pharmaceutically acceptable salt or solvate thereof.

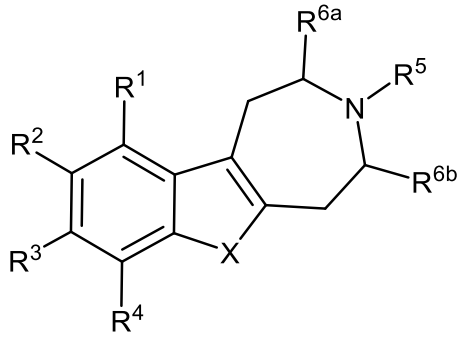
[0009] In another example, described herein is a method of method of modulating the activity of 5-hydroxytryptamine receptor 2A (5-HT_{2A}) receptor in a mammal comprising administering to the mammal a compound provided herein, or any pharmaceutically acceptable salt or solvate thereof.

[0010] In another example, described herein is a method of treating a disease or disorder in a mammal that is mediated by the action of 5-hydroxytryptamine (5-HT) at 5-hydroxytryptamine receptor 2A (5-HT_{2A}) comprising administering to the mammal a compound provided herein, or any pharmaceutically acceptable salt or solvate thereof.

[0011] In another example, described herein is a method of treating a disease or disorder in a mammal that is mediated by the loss of synaptic connectivity, plasticity, or a combination thereof

comprising administering to the mammal a compound provided herein, or a pharmaceutically acceptable salt or solvate thereof. In some examples, the disease or disorder is neurological disease or disorder.

[0012] In another example, described herein is a method for treating neurological disease or disorder in a mammal, the method comprising administering to the mammal a compound represented by the structure of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I)

wherein:

- X is NR^7, O or $S(=O)_x$;
- x is 0, 1, or 2;
- each of R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, $-OR^a$, cyano, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

  or any of R^1 and R^2, R^2 and R^3, or R^3 and R^4 are taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring;
- R^5 is hydrogen, halogen, $-OR^a$, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- each R^{6a} and R^{6b} is independently hydrogen, halogen, $-OR^a$, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

  or R^5 is taken together with R^{6a} or R^{6b} and the atoms to which they are attached to form an optionally substituted heterocyclic ring;

  or R^{6a} and R^{6b} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring;

- R^7 is hydrogen, alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted; and
- R^a is hydrogen, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

wherein

(i) R^5 and R^{6a} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring;

(ii) R^5 and R^{6b} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring; or

(iii) R^{6a} and R^{6b} are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring; and

[0013] provided that when X is NH, R^{6a} is hydrogen, and each of R^1, R^2, R^3 and R^4 is hydrogen, then R^5 and R^{6b} are not taken together with the atoms to which they are attached to form a 6-membered heterocyclic ring substituted by ethyl or ethylidene.In some examples, the neurological disease or disorder is a neurodegenerative, a neuropsychiatric, or a substance use disease or disorder.

[0014] In some examples, the neurological disease or disorder is an injury.

[0015] In some examples, the neurological disease or disorder is selected from the group consisting of an anxiety disorder, a mood disorder, a psychotic disorder, a personality disorder, an eating disorder, a sleep disorder, a sexuality disorder, an impulse control disorder, a substance use disorder, a dissociative disorder, a cognitive disorder, a developmental disorder, and a factitious disorder.

[0016] In some examples, the mammal is a human.

[0017] In any of the aforementioned examples are further examples in which an effective amount of the compound described herein, or a pharmaceutically acceptable salt thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by injection to the mammal.

[0018] In any of the aforementioned examples are further examples comprising single administrations of an effective amount of the compound, including further examples in which the compound is administered once a day to the mammal or the compound is administered to the mammal multiple times over the span of one day. In some examples, the compound is administered on a continuous dosing schedule. In some examples, the compound is administered on a continuous daily dosing schedule.

[0019] Articles of manufacture, which include packaging material, a formulation within the packaging material (e.g. a formulation suitable for topical administration), and a label that indicates that the compound or composition, or pharmaceutically acceptable salt, or solvate thereof, is used for promoting neuronal growth and/or improving neuronal structure, or for the treatment, prevention or amelioration of one or more symptoms of a disease or disorder that is associated with promoting neuronal growth and/or improving neuronal structure, are provided.

[0020] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific examples, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

[0021] The present disclosure provides non-hallucinogenic compounds useful for the treatment of a variety of neurological diseases and disorders as well as increasing neuronal plasticity.

[0022] Psychedelic compounds promote structural and functional neural plasticity in key circuits, elicit therapeutic responses in multiple neuropsychiatric disorders, and produce beneficial neurological effects that can last for months following a single administration. Compounds capable of modifying neural circuits that control motivation, anxiety, and drug-seeking behavior have potential for treating neurological diseases and disorders that are mediated by the loss of synaptic connectivity and/or plasticity. Moreover, such compounds are likely to produce sustained therapeutic effects because, for example, of the potential to treat the underlying pathological changes in circuitry.

[0023] In some embodiments, 5-HT_{2A} antagonists abrogate the neuritogenesis and spinogenesis effects of hallucinogenic compounds with 5-HT_{2A} agonist activity, e.g., DMT, LSD, and DOI, demonstrating the correlation of 5-HT_{2A} agonism and the promotion of neural plasticity (Ly et al., 2018; Dunlap et al., 2020). However, the hallucinogenic and dissociative potential of such compounds has limited the use of these compounds in the clinic for neurological diseases, such as, for example, neuropsychiatric diseases. (Ly et al., 2018)

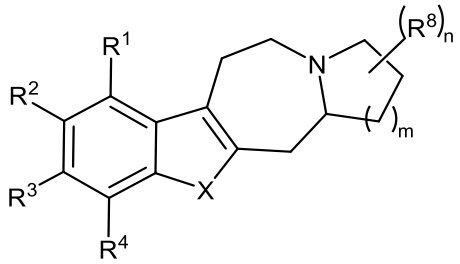
[0024] In addition, non-hallucinogenic analogs of psychedelic compounds, such as, for example, lisuride and sumatriptan, have been examined as treatments for various neurological diseases and disorders, such as, but not limited to, neurodegenerative diseases (e.g., Alzheimer's disease and Parkinson's disease) and headaches (e.g., migraines).

Certain Terminology

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (IA):



Formula (IA)

or a pharmaceutically acceptable salt or solvate thereof,

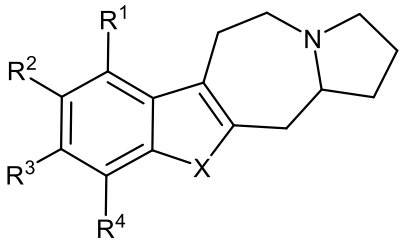
wherein

- X is NR^7, O or $S(=O)_x$;
- x is 0, 1, or 2;
- each of R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, $-OR^a$, cyano, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

  or any of R^1 and R^2, R^2 and R^3, or R^3 and R^4 are taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring;
- R^7 is hydrogen, alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- R^a is hydrogen, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- each R^8 is independently halogen, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- m is 0, 1, 2 or 3; and
- n is 0, 1, 2, 3, 4, 5, 6, or 7;

provided that when X is NH, m is 2, and R^1-R^4 are hydrogen, then R^8 is not ethyl.

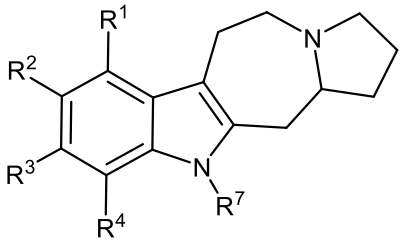
2. The compound of claim 1, wherein n is 0, m is 1, and the compound has the structure of Formula (IA-1):



Formula (IA-1)

or a pharmaceutically acceptable salt or solvate thereof.

3. The compound of claim 1 or 2, wherein X is NR^7, and the compound has the structure of Formula (IA-2):



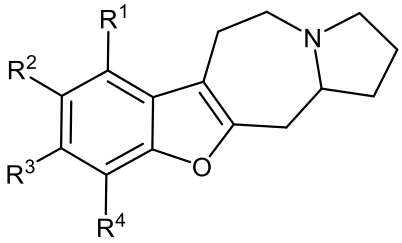
Formula (IA-2)

or a pharmaceutically acceptable salt or solvate thereof.

4. The compound of claim 3, wherein R^7 is hydrogen.

5. The compound of claim 3, wherein R^7 is methyl.

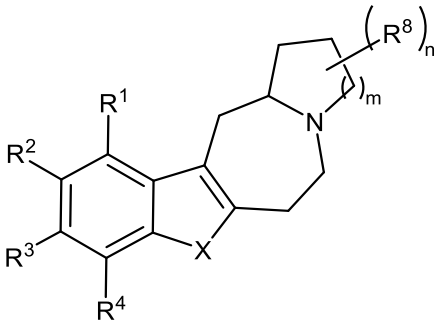
6. The compound of claim 1 or 2, wherein X is O, and the compound has the structure of Formula (IA-3):



Formula (IA-3)

or a pharmaceutically acceptable salt or solvate thereof.

7. A compound of Formula (IB):



Formula (IB)

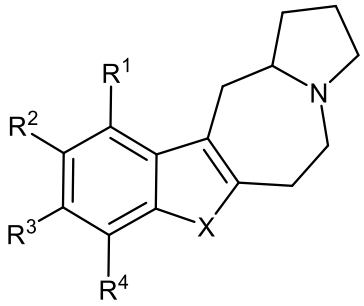
or a pharmaceutically acceptable salt or solvate thereof,

wherein

- X is NR^7, O or $S(=O)_x$;
- x is 0, 1, or 2;
- each of R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, $-OR^a$, cyano, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

  or any of R^1 and R^2, R^2 and R^3, or R^3 and R^4 are taken together with the carbon atoms to which they are attached to form an optionally substituted 5- or 6-membered ring;
- R^7 is hydrogen, alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- R^a is hydrogen, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- each R^8 is independently halogen, alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl, wherein each alkyl, heteroalkyl, aryl, arylalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;
- m is 0, 1, 2 or 3; and
- n is 0, 1, 2, 3, 4, 5, 6, or 7.

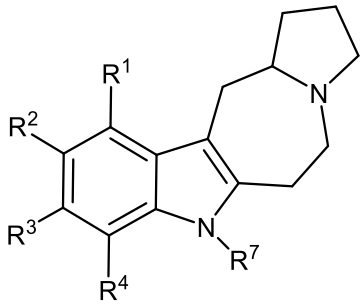
8. The compound of claim 7, wherein n is 0, m is 1, and the compound has the structure of Formula (IB-1):



Formula (IB-1)

or a pharmaceutically acceptable salt or solvate thereof.

9. The compound of claim 7 or 8, wherein X is NR^7, and the compound has the structure of Formula (IB-2):



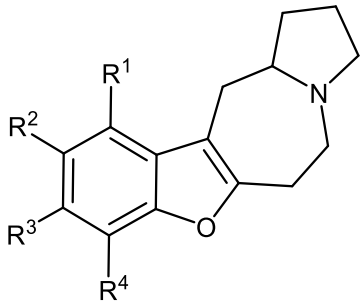
Formula (IB-2)

or a pharmaceutically acceptable salt or solvate thereof.

10. The compound of claim 9, wherein R^7 is hydrogen.

11. The compound of claim 9, wherein R^7 is methyl.

12. The compound of claim 7 or 8, wherein X is O, and the compound has the structure of Formula (IB-3):



Formula (IB-3)

or a pharmaceutically acceptable salt or solvate thereof.

13. The compound of any one of claims 1-12, wherein each of R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, $-OR^a$, cyano, or haloalkyl.

14. The compound of any one of claims 1-13, wherein each of R^1, R^2, R^3 and R^4 is hydrogen.

15. The compound of any one of claims 1-13, wherein at least one of R^1, R^2, R^3 and R^4 is halogen.

16. The compound of any one of claims 1-13, wherein at least one of R^1, R^2, R^3 and R^4 is haloalkyl.

17. The compound of any one of claims 1-13, wherein at least one of R^1, R^2, R^3 and R^4 is OR^a wherein R^a is haloalkyl.

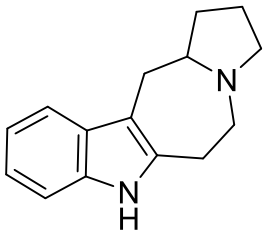
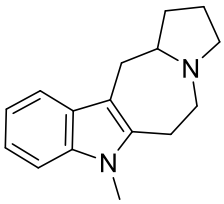
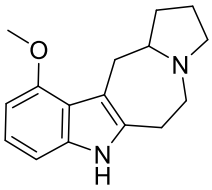
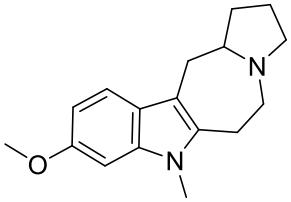
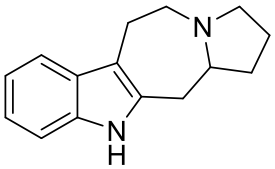
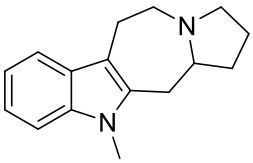
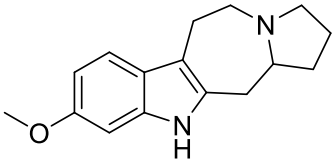
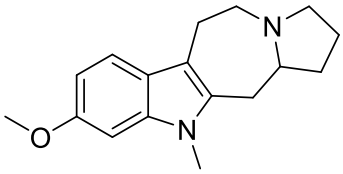
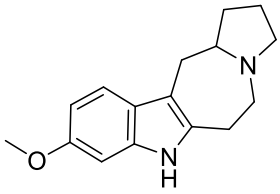
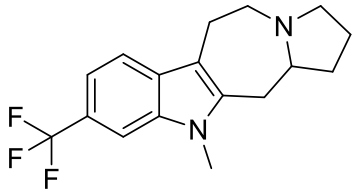
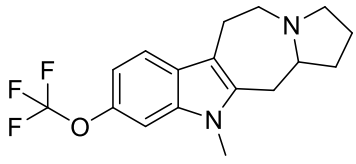
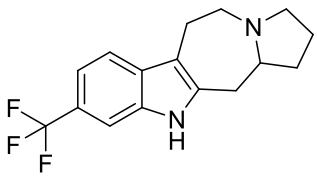
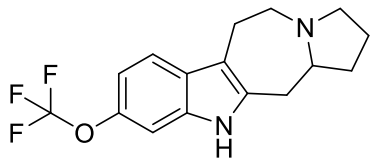
18. The compound of any one of claims 1-13, wherein at least one of R^1, R^2, R^3 and R^4 is OR^a wherein R^a is arylalkyl.

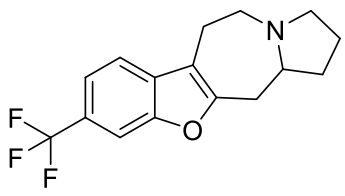
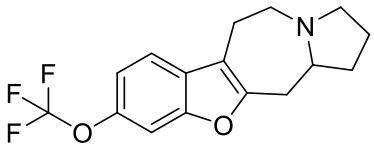
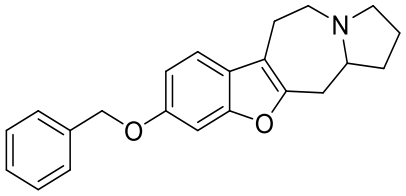
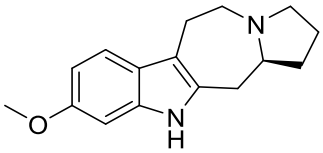
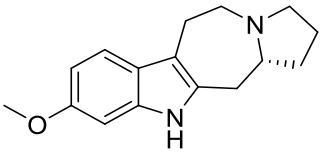
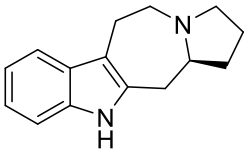
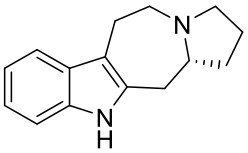
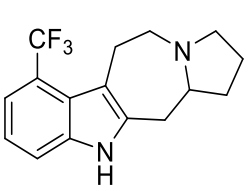
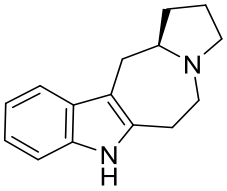
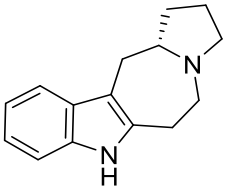
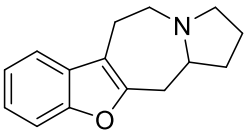
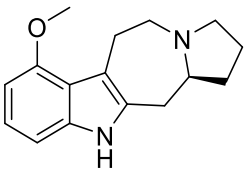
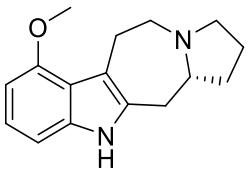
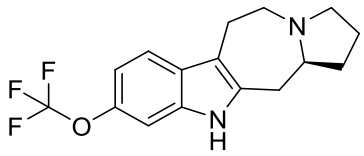
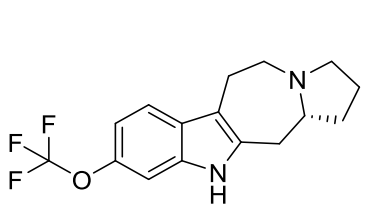
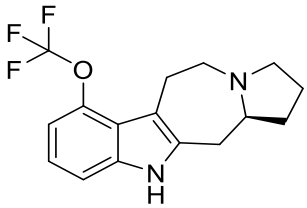
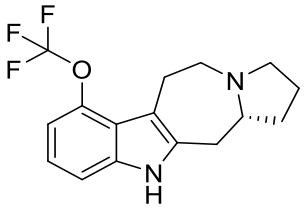
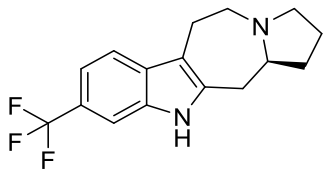
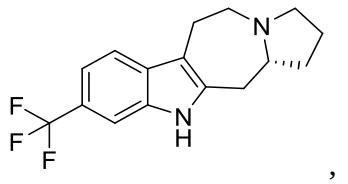
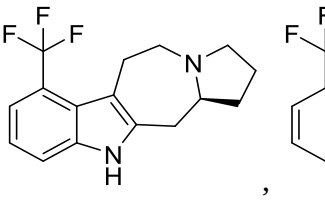
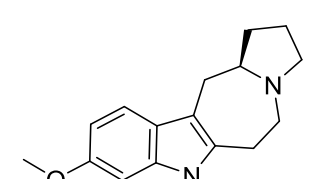
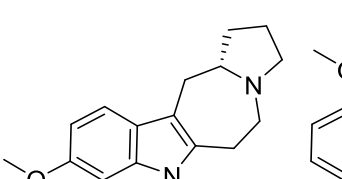
19. The compound of any one of claims 1-13, wherein at least one of R^1, R^2, R^3 and R^4 is OR^a wherein R^a is alkyl.

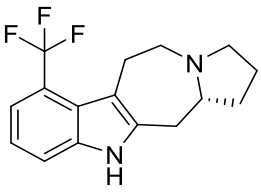
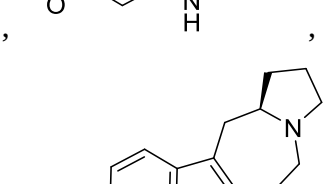
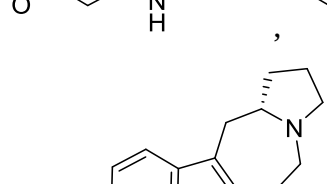
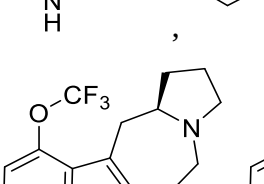
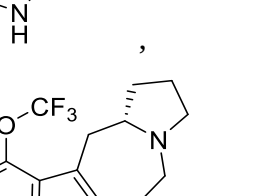
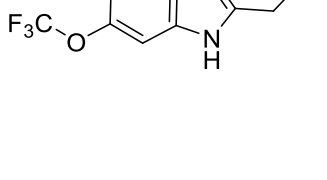
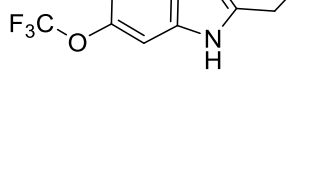
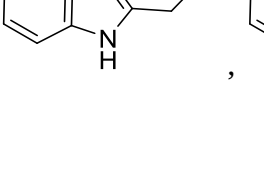
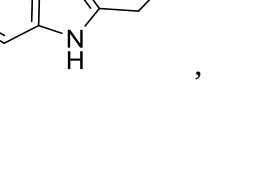
20. The compound of any one of claims 1-13, wherein at least one of R^1, R^2, R^3 and R^4 is benzyloxy, methoxy, fluoro, trifluoromethyl, or trifluoromethoxy.

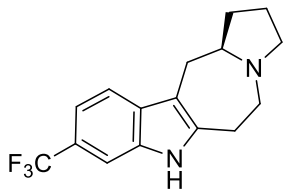
21. The compound of any one of claims 1-13, wherein R^3 is benzyloxy, methoxy, fluoro, trifluoromethyl, or trifluoromethoxy, and R^1, R^2, and R^4 are each hydrogen.

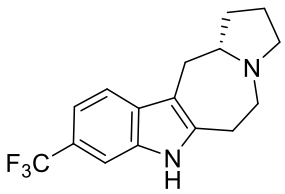
22. A compound that is:

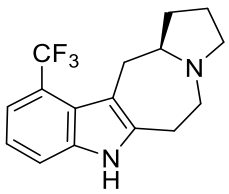

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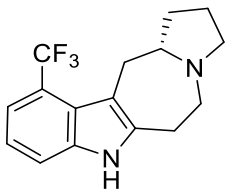

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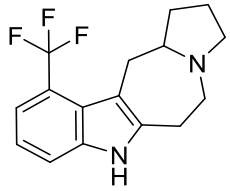
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or a pharmaceutically acceptable salt or solvate thereof.

23. A pharmaceutical composition comprising a compound of any one of claims 1-22, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

24. Use of a compound of any one of claims 1-22, or any pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for promoting neuronal growth in a mammal.

25. Use of a compound of any one of claims 1-22, or any pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for improving neuronal structure in a mammal.

26. Use of a compound of any one of claims 1-22, or any pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a disease or disorder in a mammal that is mediated by the action of 5-hydroxytryptamine (5-HT) at 5-hydroxytryptamine receptor 2A (5-HT_{2A}).

27. Use of a compound of any one of claims 1-22, or any pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a disease or disorder in a mammal that is mediated by the loss of synaptic connectivity, plasticity, or a combination thereof.

28. Use of a compound of any one of claims 1-22, or any pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a neurological disease or disorder in a mammal.

29. The use of claim 28, wherein the neurological disease or disorder is a neurodegenerative, a neuropsychiatric, or a substance use disease or disorder.

30. The use of claim 28, wherein the neurological disease or disorder is an injury.

31. The use of claim 28, wherein the neurological disease or disorder is selected from the group consisting of an anxiety disorder, a mood disorder, a psychotic disorder, a personality disorder, an eating disorder, a sleep disorder, a sexuality disorder, an impulse control disorder, a substance use disorder, a dissociative disorder, a cognitive disorder, a developmental disorder, and a factitious disorder.

32. A compound of any one of claims 1-22, or any pharmaceutically acceptable salt or solvate thereof, for use in therapy.