



(51) International Patent Classification:

A61K 31/33 (2006.01) A61K 31/16 (2006.01)
A61K 31/166 (2006.01) A61K 31/7056 (2006.01)

(21) International Application Number:

PCT/US2023/010055

(22) International Filing Date:

03 January 2023 (03.01.2023)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/296,137	03 January 2022 (03.01.2022)	US
63/314,466	27 February 2022 (27.02.2022)	US
63/345,002	23 May 2022 (23.05.2022)	US
63/394,565	02 August 2022 (02.08.2022)	US
63/384,988	25 November 2022 (25.11.2022)	US

(71) Applicant: ENGRAIL THERAPEUTICS, INC.

[US/US]; 12750 High Bluff Drive, Suite 190, San Diego,
California 92130 (US).

(72) Inventors: **VADODARIA, Krishna**; c/o Engrail Therapeutics, Inc., 12750 High Bluff Drive, Suite 190, San Diego, California 92130 (US). **VANOVER, Kimberly**; c/o Engrail Therapeutics, Inc., 12750 High Bluff Drive, Suite 190, San Diego, California 92130 (US). **SERRATS, Jordi**; c/o Engrail Therapeutics, Inc., 12750 High Bluff Drive, Suite 190, San Diego, California 92130 (US). **SUDARSAN, Vikram**; c/o Engrail Therapeutics, Inc., 12750 High Bluff Drive, Suite 190, San Diego, California 92130 (US). **GARVEY, David**; c/o Engrail Therapeutics, Inc., 12750 High Bluff Drive, Suite 190, San Diego, California 92130 (US).

(74) Agent: **JONES, Marya**; 75 Main Street, Suite 203, Millburn, New Jersey 07041 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS,

(54) Title: DEUTERATED ORGANIC COMPOUNDS AND USES THEREOF

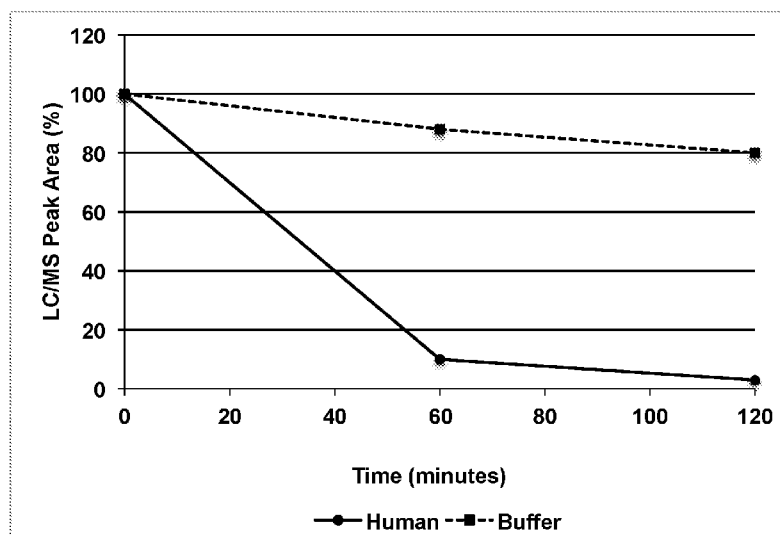


Figure 1

(57) Abstract: Provided are compounds of Formula I, described herein, processes for their preparation, their use as pharmaceuticals, and pharmaceutical compositions comprising them and intermediates used in their preparation. Compounds of Formula I are useful, for instance, in modulating dopamine neurotransmission and treating disorders that may benefit from the same, such as schizophrenia and depression.



RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS,
ZA, ZM, ZW.

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

Published:

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

DEUTERATED ORGANIC COMPOUNDS AND USES THEREOF

[0001] This application claims priority to U.S. Provisional Application No. 63/296,137 filed January 3, 2022, U.S. Provisional Application No. 63/314,466 filed February 27, 2022, U.S. Provisional Application No. 63/345,002 filed May 23, 2022, U.S. Provisional Application No. 63/394,565 filed August 2, 2022, and U.S. Provisional Application No. 63/384,988 filed November 25, 2022, the contents of each of which are hereby incorporated by reference in their entireties.

FIELD

[0002] Provided are compounds of Formula I, described below, processes for their preparation, their use as pharmaceuticals, and pharmaceutical compositions comprising them and intermediates used in their preparation. Compounds of Formula I are useful, for instance, in modulating dopamine neurotransmission and treating disorders that may benefit from the same, such as schizophrenia and depression.

BACKGROUND

[0003] Dopamine is involved in a variety of central nervous system functions, including voluntary movement, feeding, affect, reward, sleep, attention, working memory, and learning. Dopaminergic dysfunction can lead to diseases such as schizophrenia and depression.

[0004] When released from presynaptic terminals, dopamine activates members of a family of G protein-coupled dopamine receptors D1-D5. Dopamine receptors (D1-D5) are divided into two groups, the D1-like (D1 and D5) and the D2-like (D2, D3, and D4). Activation of D1-like receptors activates adenylyl cyclase and increases cAMP levels. D2-like receptors are inhibitory. Activation of D2-like receptors inhibits activation of adenylyl cyclase.

[0005] D1-like receptors are found postsynaptically on dopamine-receptive cells, while D2-like dopamine receptors are expressed both postsynaptically on dopamine target cells and presynaptically on dopaminergic neurons.

[0006] Antipsychotics are used to manage psychosis, in particular schizophrenia. A hallmark of antipsychotics is D2 receptor antagonism. D2 receptor antagonism is effective in

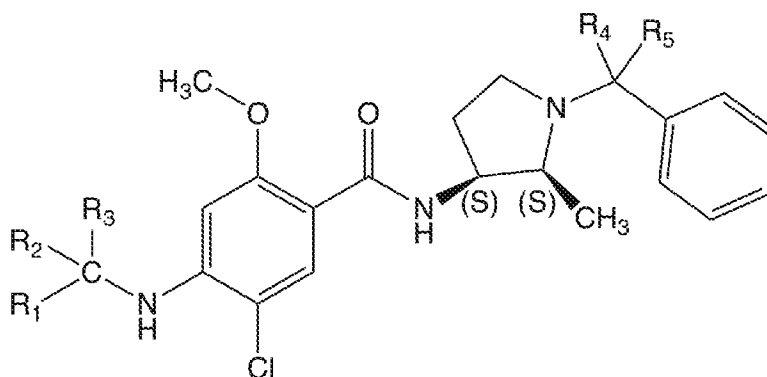
reducing positive symptoms of schizophrenia (for instance, hallucinations and delusions), but often also produces extrapyramidal side effects, including parkinsonism, akathisia, and tardive dyskinesia, increases prolactin, and may exacerbate negative symptoms of schizophrenia (for instance, loss of interest and motivation in life and activities, social withdrawal, and anhedonia). Many psychotic patients also suffer from depression, which may be left untreated by current medications.

[0007] In addition to effects on dopamine receptors, such as D2, D3, and D4, antipsychotics may also have effects on serotonin receptors, such as 5-HT1A, 5-HT2A, 5-HT2C, 5-HT6, and 5-HT7. Interacting with dopamine and serotonin receptors may be beneficial, for instance, resulting in reduced extrapyramidal motor side effects (EPS) liability. However, multi-target drugs may also result in undesirable off-target side effects.

[0008] Because imbalances in dopamine can lead to a variety of disorders and current medications may not be able to effectively modulate dopamine levels and may have undesirable side effects, new compounds that can modulate dopamine neurotransmission are needed, as are methods of treating diseases that involve imbalances in dopamine.

BRIEF SUMMARY

[0009] Provided is a compound of Formula I:



Formula I,

wherein:

R₁, R₂, R₃, R₄, and R₅ are independently selected from H and D; and
at least one of R₁, R₂, and R₃ is D;
in free or salt form.

[0010] Further provided are pharmaceutical compositions comprising compounds of Formula I, processes for preparing compounds of Formula I, and pharmaceutical uses of compounds of Formula I, for instance, as an anti-anhedonic agent and to treat schizophrenia and depression.

[0011] Further areas of applicability of the present invention will become apparent from the detailed description provided hereinafter. It should be understood that the detailed description and specific examples, while indicating preferred embodiments of the invention, are intended for purposes of illustration only and are not intended to limit the scope of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] Figure 1 shows disappearance of the compound of Example 1 (A1) in human hepatocytes.

[0013] Figure 2 shows extended brain enrichment of the compound of Example 1 (A1) in rats following a single PO dose of 0.5 mg/kg compared to plasma levels.

[0014] Figure 3 shows extended brain enrichment of the compound of Example 1 (A1) in rats following a single PO dose of 5 mg/kg compared to plasma levels.

[0015] Figure 4 shows D2 receptor occupancy of the compound of Example 1 (A1) when administered orally at a dose of 2.5 mg/kg to rats.

[0016] Figure 5A shows response bias in the probabilistic reward task for the compound of Example 1 (A1) when administered at doses of 0.5, 1, and 2.5 mg/kg to rats.

[0017] Figure 5B shows discriminability in the probabilistic reward task for the compound of Example 1 (A1) when administered at doses of 0.5, 1, and 2.5 mg/kg to rats.

[0018] Figure 6 shows D2 receptor occupancy of cis (S,S) nemonapride and the compound of Example 1 (A1) when administered orally at a dose of 2.5 mg/kg to rats.

[0019] Figure 7 shows a pharmacokinetic:pharmacodynamic model for the compound of Example 1 (A1).

[0020] Figure 8 shows average plasma concentration (ng/ml) in rats of cis (S,S) nemonapride and the compound of Example 1 (A1) following single oral administration of 2.5 mg/kg.

[0021] Figure 9 shows average brain concentration (ng/ml) in rats of cis (S,S) nemonapride and the compound of Example 1 (A1) following single oral administration of 2.5 mg/kg.

[0022] Figure 10 shows average plasma concentration (ng/ml) in rats of T1 and the compound of Example 1 (A1) following single oral administration of 0.5 mg/kg.

[0023] Figure 11 shows average brain concentration (ng/ml) in rats of T1 and the compound of Example 1 (A1) following single oral administration of 0.5 mg/kg.

[0024] Figure 12 shows average plasma concentration (ng/ml) in rats of T1 and the compound of Example 1 (A1) following single oral administration of 5 mg/kg.

[0025] Figure 13 shows average brain concentration (ng/ml) in rats of T1 and the compound of Example 1 (A1) following single oral administration of 5 mg/kg.

DETAILED DESCRIPTION

[0026] The following description of the preferred embodiment(s) is merely exemplary in nature and is in no way intended to limit the invention, its application, or uses.

[0027] In the event of a conflict in a definition in the present disclosure and that of a cited reference, the present disclosure controls.

[0028] D2- and D3- receptors are expressed both postsynaptically on dopamine target cells and presynaptically on dopamine neurons. Dopamine receptors are mainly located on non-dopamine neurons. Dopamine receptors on dopamine neurons are called autoreceptors. Autoreceptors contribute to regulating dopamine neuron activity and controlling the synthesis, release, and uptake of dopamine.

[0029] Presynaptic D2-like dopamine autoreceptors regulate dopamine release. A low dose of a D2-like receptor antagonist may preferentially block presynaptic autoreceptors and increase dopamine release, while a high dose may block postsynaptic receptors and decrease dopamine neurotransmission. Relatively high occupancy of D2-like receptors has been associated with antipsychotic effects, while lower occupancy has been associated with antidepressant effects.

[0030] Anhedonia is a core symptom of major depressive disorder (MDD) and is associated with inadequate response to approved selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) and psychotherapy (e.g., cognitive

behavioral therapy (CBT)) and neurostimulation (e.g., transcranial magnetic stimulation (TMS)). There remains a need for effective treatment of MDD characterized by anhedonia. Despite a range of available therapies, up to 50% of people suffering from MDD fail to respond to treatments, and only about 30% of patients fully recover after receiving currently available antidepressants and treatment outcomes are even poorer for MDD individuals with anhedonia.

[0031] Depletion of dopamine/catecholamines induces symptoms of depression and anhedonia. Increasing dopamine neurotransmission can alleviate symptoms of depression and anhedonia. However, while a high dose of a dopamine D2/D3 agonist may activate dopamine post-synaptic receptors, it can also be poorly tolerated (e.g., nausea/vomiting). Low dose of a dopamine D2/D3 receptor antagonist may preferentially block pre-synaptic dopamine autoreceptors and increase dopamine release without being poorly tolerated.

[0032] Besides MDD, anhedonia also plays a role in bipolar disorder, schizophrenia, post-traumatic stress disorder, and substance use disorder. Despite its role in many disorders, there are no approved medications to treat anhedonia.

[0033] The IUPAC name of nemonapride is $(\pm)$ -*cis-N*-(1-Benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide. Nemonapride is described in U.S. Patent No. 4,210,660 as a strong central nervous system depressant, in particular a strong antipsychotic.

[0034] Nemonapride is a dopamine D2/D3/D4 receptor antagonist. Nemonapride is approved in Japan and South Korea for treatment of schizophrenia. Nemonapride is supplied as 3 mg and 10 mg tablets. The approved daily dose of nemonapride for schizophrenia is 9 to 36 mg given orally in divided doses after meals. The dose can be increased up to 60 mg daily.

[0035] The nemonapride prescribing information indicates that the elimination half-life when nemonapride 3 mg and 6 mg was administered orally to healthy adults was 2.3 to 4.5 hours. Urinary metabolites of nemonapride result from debenzylation and N-demethylation. See Emilace package insert.

[0036] In addition to being a dopamine D2/D3/D4 receptor antagonist, nemonapride is also a 5-HT_{1A} agonist and has been reported to bind to 5-HT_{2A}.

[0037] When a drug is used as a mixture of stereoisomers, it is not possible to predict what properties (e.g., biological target, pharmacokinetics) each stereoisomer has, especially a drug that has multiple biological targets.

[0038] Compounds of Formula I disclosed herein are selective D2/D3/D4 receptor antagonists. D2/D3/D4 postsynaptic receptor antagonism reduces psychosis, particularly in schizophrenia, by reducing dopamine neurotransmission. A low dose of a D2/D3/D4 receptor antagonist may selectively block presynaptic autoreceptors resulting in increased dopamine release and enhanced dopamine neurotransmission. Moreover, antagonism of D3 receptors can have important implications for diseases related to mesolimbic and mesocortical dopamine systems given the enrichment of D3 receptors in the ventral striatum, thalamus, hippocampus, and cortex, dopaminergic brain areas involved in decision making and reward processing, relative to antagonism of D2 receptors alone. Given that D3 receptors have a higher affinity for dopamine compared to D2 receptors, increased dopamine release may preferentially activate D3 receptors. Additionally, by selectively blocking D2-like receptors but not D1-like receptors, increased dopamine release by a low dose of a D2/D3/D4 receptor antagonist may preferentially activate postsynaptic D1-like receptors, enriched in cortex, thereby improving cognition and negative symptoms of schizophrenia. Antagonism of D4 receptors, enriched in the frontal cortex and amygdala, among other brain areas, may also play a role in emotion processing. Selective D2/D3/D4 receptor antagonists limit off target interactions. Off target interactions may contribute to side effects in drugs that are not as selective.

[0039] Pharmacokinetics of deuterated compounds disclosed herein are beneficial. The deuterated compound of Example 1 shows extended brain enrichment compared to plasma levels of the compound. The enrichment in the brain persists up to 24 hours. That feature allows for higher receptor occupancy with less frequent dosing and may be associated with fewer peripheral side effects. The brain:plasma exposure supports once-daily dosing. In contrast, nemonapride is taken in multiple doses per day.

[0040] Data in the examples indicate that D2/D3 receptor occupancy levels of the deuterated compound of Example 1 in anti-anhedonic range may be achieved with relatively low and once daily dosing.

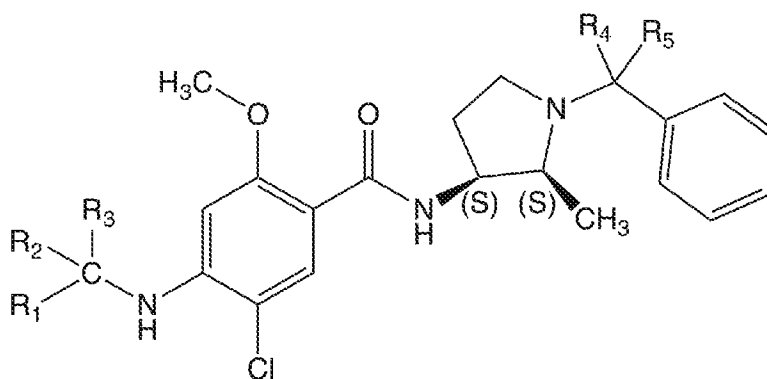
[0041] In addition, Example 6 shows that a compound of Formula I (the deuterated compound of Example 1) has enriched and retained brain levels compared to its non-deuterated analog and higher receptor occupancy levels at 4, 8, and 24 hours. For instance, Figure 9 shows that at 8 hours, brain levels of the compound of Example 1 (A1) are over double levels of cis (S,S) nemonapride measured. As discussed above, the deuterated compound of Example 1 also

shows extended brain enrichment compared to plasma levels of the compound. Enriched brain levels, higher receptor occupancy levels, and extended brain enrichment compared to plasma levels are beneficial features that allow for higher and more sustained receptor occupancy with less frequent dosing and may be associated with fewer peripheral side effects. Receptor occupancy levels can be maintained in a desired range with a convenient dosing regime.

[0042] Further, Example 8 shows that a compound of Formula I (the deuterated compound of Example 1) has enriched and retained brain levels compared to another *cis* (S,S) nemonapride deuterated derivative.

[0043] Compounds that are D2/D3/D4 receptor antagonists modulate dopamine neurotransmission and are therefore useful in treating disorders involving dopamine signaling pathways, for instance, disorders involving D2, D3, and/or D4 receptors.

[0044] Provided is a compound of Formula I:



Formula I,

wherein:

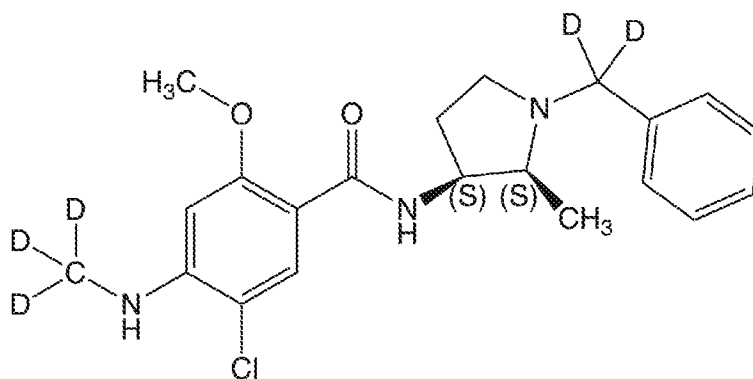
R₁, R₂, R₃, R₄, and R₅ are independently selected from H and D; and

at least one of R₁, R₂, and R₃ is D;

in free or salt form.

[0045] Further provided are compounds of Formula I as follows:

- 1.1 Formula I, wherein the compound is in pharmaceutically acceptable salt form.
- 1.2 Formula I, wherein the compound is in free form.
- 1.3 Any of Formula I, 1.1, or 1.2, wherein R₁, R₂, and R₃ are D.
- 1.4 Any of Formula I or 1.1-1.3, wherein R₄ and R₅ are D.
- 1.5 Any of Formula I or 1.1-1.4, wherein each of R₁, R₂, R₃, R₄, and R₅ are D.
- 1.6 Any of Formula I or 1.1-1.5, wherein the compound is:



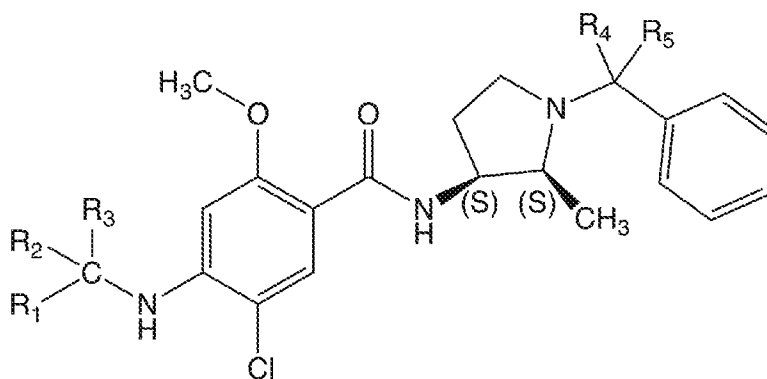
in free or salt form, e.g., in free or pharmaceutically acceptable salt form, e.g., in free form.

- 1.7 Any of Formula I or 1.1-1.6, wherein the designation of deuterium (i.e., D) at a position means that position has a significantly greater than natural abundance of deuterium at that position (e.g., greater than 0.1%, or greater than 0.5%, or greater than 1%, or greater than 5%). Any atom not designated as a particular isotope is present at natural isotopic abundance.
- 1.8 Any of Formula I or 1.1-1.7, wherein the compound, in free or salt form (e.g., pharmaceutically acceptable salt form), has greater than 50% incorporation of deuterium (i.e., D) at one or more positions (e.g., at all positions) designated as deuterium (i.e., D), e.g., greater than 60%, or greater than 70%, or greater than 80%, or greater than 90%, or greater than 95%, or greater than 96%, or greater than 97%, or greater than 98%, or greater than 99%. For instance, any of Formula I or 1.1-1.7, wherein the compound, in free or salt form (e.g., pharmaceutically acceptable salt form), has greater than 50% incorporation of deuterium (i.e., D) at each position designated as deuterium (i.e., D), e.g., greater than 60%, or greater than 70%, or greater than 80%, or greater than 90%, or greater than 95%, or greater than 96%, or greater than 97%, or greater than 98%, or greater than 99%.
- 1.9 Any of Formula I or 1.1-1.8, wherein the compound is substantially stereoisomerically pure. For instance, wherein the compound has a stereoisomeric excess of greater than 90%, e.g., a stereoisomeric excess equal to or greater than 95%, e.g., a stereoisomeric excess equal to or greater than 96%, e.g., a stereoisomeric excess equal to or greater than 97%, e.g., a stereoisomeric excess equal to or greater than 98%, e.g., a stereoisomeric excess equal to or greater than

99%. For instance, wherein the compound is substantially diastereomerically and/or enantiomerically pure, e.g., wherein the compound is substantially diastereomerically and enantiomerically pure.

- 1.10 Any of Formula I or 1.1-1.9, wherein the compound is substantially diastereomerically pure. For instance, wherein the compound has a diastereomeric excess of greater than 90%, e.g., a diastereomeric excess equal to or greater than 95%, e.g., a diastereomeric excess equal to or greater than 96%, e.g., a diastereomeric excess equal to or greater than 97%, e.g., a diastereomeric excess equal to or greater than 98%, e.g., a diastereomeric excess equal to or greater than 99%.
- 1.11 Any of Formula I or 1.1-1.10, wherein the compound is substantially enantiomerically pure. For instance, wherein the compound has an enantiomeric excess of greater than 90%, e.g., an enantiomeric excess equal to or greater than 95%, e.g., an enantiomeric excess equal to or greater than 96%, e.g., an enantiomeric excess equal to or greater than 97%, e.g., an enantiomeric excess equal to or greater than 98%, e.g., an enantiomeric excess equal to or greater than 99%.
- 1.12 Any of Formula I or 1.1-1.11, wherein the compound has the stereochemical configuration as shown in Formula I.
- 1.13 Any of Formula I or 1.1-1.12, wherein the compound is in a pharmaceutical composition with a pharmaceutically acceptable carrier. For instance, any of Formula I or 1.1-1.12, wherein an effective amount of the compound is in a pharmaceutical composition with a pharmaceutically acceptable carrier.

[0046] Further provided is a pharmaceutical composition (Composition 1) comprising a compound of Formula I (e.g., any of Formula 1.1-1.13):



Formula I,

wherein:

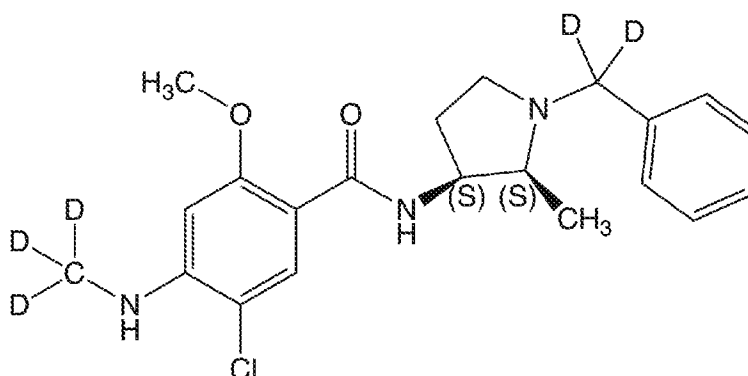
R_1 , R_2 , R_3 , R_4 , and R_5 are independently selected from H and D; and

at least one of R_1 , R_2 , and R_3 is D;

in free or pharmaceutically acceptable salt form.

[0047] Further provided is Composition 1 as follows:

- 1.1 Composition 1, wherein the composition comprises a pharmaceutically acceptable carrier.
- 1.2 Composition 1 or 1.1, wherein the composition comprises the compound, in free or pharmaceutically acceptable salt form, as described in any of Formula I or 1.1-1.13 *vide supra*.
- 1.3 Any of Composition 1, 1.1, or 1.2, wherein the compound is in free form.
- 1.4 Any of Composition 1 or 1.1-1.3, wherein the compound of Formula I is:



in free or pharmaceutically acceptable salt form, e.g., in free form.

- 1.5 Any of Composition 1 or 1.1-1.4, wherein the designation of deuterium (i.e., D) at a position means that position has a significantly greater than natural abundance of deuterium at that position (e.g., greater than 0.1%, or greater than 0.5%, or

greater than 1%, or greater than 5%). Any atom not designated as a particular isotope is present at natural isotopic abundance.

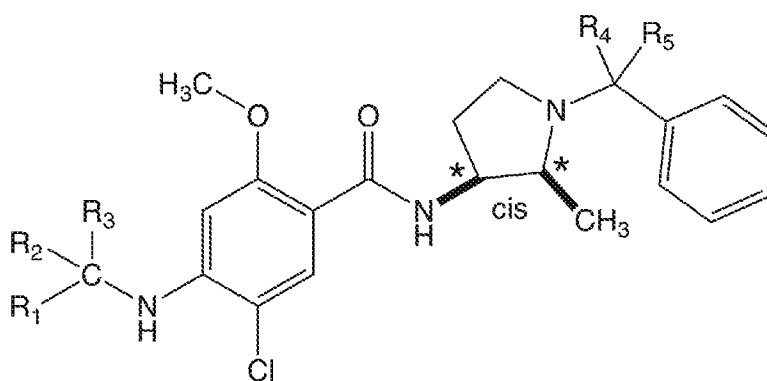
- 1.6 Any of Composition 1 or 1.1-1.5, wherein the compound of Formula I, in free or pharmaceutically acceptable salt form, has greater than 50% incorporation of deuterium (i.e., D) at one or more positions (e.g., at all positions) designated as deuterium (i.e., D), e.g., greater than 60%, or greater than 70%, or greater than 80%, or greater than 90%, or greater than 95%, or greater than 96%, or greater than 97%, or greater than 98%, or greater than 99%. For instance, any of Composition 1 or 1.1-1.5, wherein the compound of Formula I, in free or pharmaceutically acceptable salt form, has greater than 50% incorporation of deuterium (i.e., D) at each position designated as deuterium (i.e., D), e.g., greater than 60%, or greater than 70%, or greater than 80%, or greater than 90%, or greater than 95%, or greater than 96%, or greater than 97%, or greater than 98%, or greater than 99%.
- 1.7 Any of Composition 1 or 1.1-1.6, wherein the composition is in oral or parenteral dosage form, e.g., oral dosage form, for instance, a tablet, capsule, solution, or suspension, for instance, a capsule or tablet.
- 1.8 Any of Composition 1 or 1.1-1.7, wherein the composition comprises a therapeutically effective amount of the compound of Formula I, in free or pharmaceutically acceptable salt form, e.g., a therapeutically effective amount of the compound of Formula I, in free or pharmaceutically acceptable salt form, for the prophylaxis or treatment of a disorder disclosed herein, e.g., a therapeutically effective amount of the compound of Formula I, in free or pharmaceutically acceptable salt form, for use in any of the methods disclosed herein.
- 1.9 Any of Composition 1 or 1.1-1.8, wherein the composition is substantially free of any other stereoisomeric form of Formula I. For instance, any of Composition 1 or 1.1-1.8, wherein the composition is substantially free of any other diastereomeric and/or enantiomeric form of Formula I, e.g., wherein the composition is substantially free of any other diastereomeric and enantiomeric form of Formula I.

- 1.10 Any of Composition 1 or 1.1-1.9, wherein the composition comprises less than 10% w/w (weight/weight) of any other stereoisomeric form of Formula I, e.g., less than 5% w/w of any other stereoisomeric form of Formula I, e.g., less than 4% w/w of any other stereoisomeric form of Formula I, e.g., less than 3% w/w of any other stereoisomeric form of Formula I, e.g., less than 2% w/w of any other stereoisomeric form of Formula I, e.g., less than 1% w/w of any other stereoisomeric form of Formula I.
- 1.11 Any of Composition 1 or 1.1-1.10, wherein the composition comprises less than 10% w/w of any other diastereomeric form of Formula I, e.g., less than 5% w/w of any other diastereomeric form of Formula I, e.g., less than 4% w/w of any other diastereomeric form of Formula I, e.g., less than 3% w/w of any other diastereomeric form of Formula I, e.g., less than 2% w/w of any other diastereomeric form of Formula I, e.g., less than 1% w/w of any other diastereomeric form of Formula I.
- 1.12 Any of Composition 1 or 1.1-1.11, wherein the composition comprises less than 10% w/w of any other enantiomeric form of Formula I, e.g., less than 5% w/w of any other enantiomeric form of Formula I, e.g., less than 4% w/w of any other enantiomeric form of Formula I, e.g., less than 3% w/w of any other enantiomeric form of Formula I, e.g., less than 2% w/w of any other enantiomeric form of Formula I, e.g., less than 1% w/w of any other enantiomeric form of Formula I.
- 1.13 Any of Composition 1 or 1.1-1.12, wherein the compound has the stereochemical configuration as shown in Formula I.
- 1.14 Any of Composition 1 or 1.1-1.13, wherein the composition comprises 1-60 mg of the compound of Formula I. For instance, any of Composition 1 or 1.1-1.13, wherein the composition comprises 1-10 mg, e.g., 1-9 mg (e.g., 1-8 mg) of the compound of Formula I. For instance, any of Composition 1 or 1.1-1.13, wherein the composition comprises 3 mg or 10 mg of the compound of Formula I. For instance, any of Composition 1 or 1.1-1.13, wherein the composition comprises 1 mg to less than 3 mg (e.g., 2 mg) of the compound of Formula I.

- 1.15 Any of Composition 1 or 1.1-1.14, wherein the composition is for once, twice, or three times daily dosing. For instance, any of Composition 1 or 1.1-1.14, wherein the composition is for once daily dosing.

[0048] Further provided are methods of prophylaxis or treatment of a central nervous system disorder (e.g., a brain disorder), for instance, a central nervous system disorder (e.g., a brain disorder) that benefits from modulating dopamine, in a patient in need thereof, wherein the method comprises administering to the patient a compound of Formula I, in free or pharmaceutically acceptable salt form (e.g., any of Formula I or 1.1-1.13 *vide supra*), or a pharmaceutical composition comprising a compound of Formula I, in free or pharmaceutically acceptable salt form (e.g., Formula 1.13 or any of Composition 1 or 1.1-1.15 *vide supra*), or a compound of Formula Ia or Compound A, in free or pharmaceutically acceptable salt form (*vide infra*), or a pharmaceutical composition comprising a compound of Formula Ia or Compound A, in free or pharmaceutically acceptable salt form (*vide infra*). Further provided are methods of prophylaxis or treatment of a central nervous system disorder (e.g., a brain disorder) that benefits from D2 receptor antagonism, D3 receptor antagonism, and/or D4 receptor antagonism in a patient in need thereof, wherein the method comprises administering to the patient a compound of Formula I, in free or pharmaceutically acceptable salt form (e.g., any of Formula I or 1.1-1.13 *vide supra*), or a pharmaceutical composition comprising a compound of Formula I, in free or pharmaceutically acceptable salt form (e.g., Formula 1.13 or any of Composition 1 or 1.1-1.15 *vide supra*), or a compound of Formula Ia or Compound A, in free or pharmaceutically acceptable salt form (*vide infra*), or a pharmaceutical composition comprising a compound of Formula Ia or Compound A, in free or pharmaceutically acceptable salt form (*vide infra*). For instance, provided are methods as described below.

[0049] Provided is a method (Method 1) for treatment or prophylaxis of a disorder (e.g., a brain disorder) in a patient in need thereof, wherein the method comprises administering to the patient an effective amount of a compound of Formula Ia:



Formula Ia,

wherein:

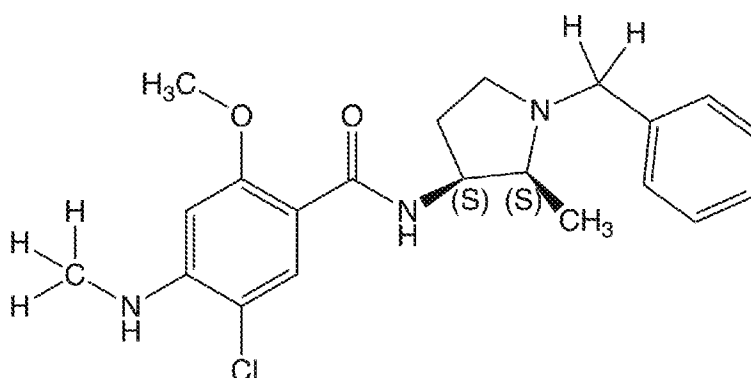
the compound of Formula Ia has cis stereochemistry at the two stereocenters marked with asterisks in the drawing,

R_1 , R_2 , R_3 , R_4 , and R_5 are independently selected from H and D;

in free or pharmaceutically acceptable salt form.

[0050] Further provided is Method 1 as follows:

- 1.1 Method 1, wherein the method comprises administering ($\pm$)-*cis*-*N*-(1-Benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide (i.e., nemonapride), in free or pharmaceutically acceptable salt form, wherein ($\pm$)-*cis*-*N*-(1-Benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide does not show optical rotation in chloroform. For instance, wherein the method comprises administering ($\pm$)-*cis*-*N*-(1-Benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide (i.e., nemonapride), in free form, wherein ($\pm$)-*cis*-*N*-(1-Benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide does not show optical rotation in chloroform.
- 1.2 Method 1, wherein the method comprises administering an effective amount of Compound A:

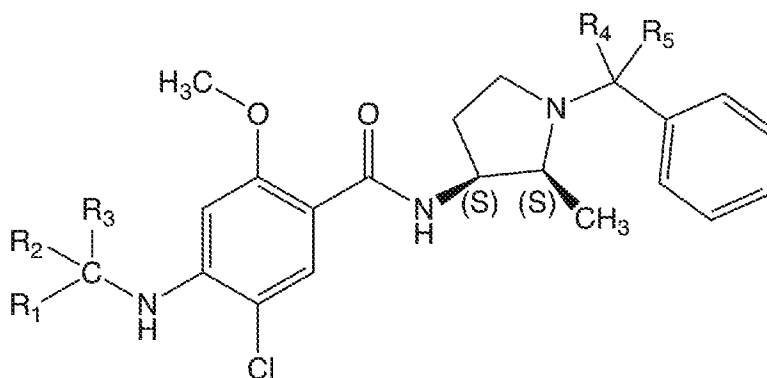


Compound A,

in free or pharmaceutically acceptable salt form. For instance, wherein the effective amount of Compound A, in free or pharmaceutically acceptable salt form, has a stereoisomeric excess of greater than 90%, e.g., a stereoisomeric excess equal to or greater than 95%, e.g., a stereoisomeric excess equal to or greater than 96%, e.g., a stereoisomeric excess equal to or greater than 97%, e.g., a stereoisomeric excess equal to or greater than 98%, e.g., a stereoisomeric excess equal to or greater than 99%. For instance, wherein the effective amount of Compound A, in free or pharmaceutically acceptable salt form, is substantially diastereomerically and/or enantiomerically pure, e.g., wherein the effective amount of Compound A, in free or pharmaceutically acceptable salt form, is substantially diastereomerically and enantiomerically pure. For instance, wherein the effective amount of compound A, in free or pharmaceutically acceptable salt form, has a diastereomeric and/or enantiomeric excess of greater than 90%, e.g., a diastereomeric and/or enantiomeric excess equal to or greater than 95%, e.g., a diastereomeric and/or enantiomeric excess equal to or greater than 96%, e.g., a diastereomeric and/or enantiomeric excess equal to or greater than 97%, e.g., a diastereomeric and/or enantiomeric excess equal to or greater than 98%, e.g., a diastereomeric and/or enantiomeric excess equal to or greater than 99%. For instance, wherein the effective amount of compound A, in free or pharmaceutically acceptable salt form, has a diastereomeric and enantiomeric excess of greater than 90%, e.g., a diastereomeric and enantiomeric excess equal to or greater than 95%, e.g., a diastereomeric and enantiomeric excess equal to or greater than 96%, e.g., a diastereomeric and enantiomeric excess equal to or

greater than 97%, e.g., a diastereomeric and enantiomeric excess equal to or greater than 98%, e.g., a diastereomeric and enantiomeric excess equal to or greater than 99%.

- 1.3 Method 1, wherein the method comprises administering a compound of Formula I:



Formula I,

wherein:

R_1 , R_2 , R_3 , R_4 , and R_5 are independently selected from H and D; and

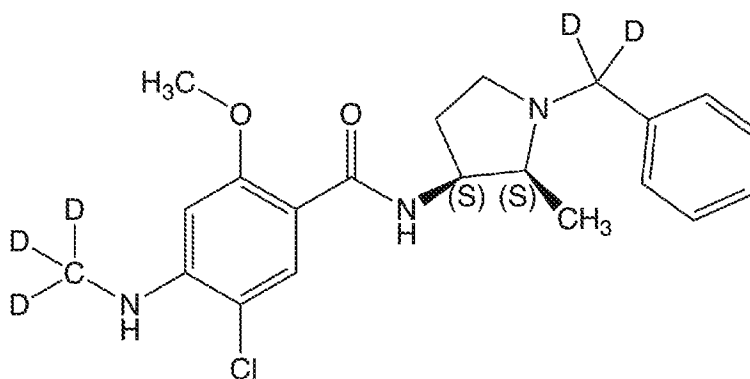
at least one of R_1 , R_2 , and R_3 is D;

in free or pharmaceutically acceptable salt form.

- 1.4 Method 1.3, wherein R_1 , R_2 , R_3 , R_4 , and R_5 are D.
- 1.5 Method 1.3 or 1.4, wherein the method comprises administering to the patient a compound of Formula I, in free or pharmaceutically acceptable salt form, as described in any of Formula I or 1.1-1.13 *vide supra*. For instance, Method 1.3 or 1.4, wherein the method comprises administering to the patient a pharmaceutical composition comprising a compound of Formula I, in free or pharmaceutically acceptable salt form, as described in any of Composition I or 1.1-1.15 *vide supra*.
- 1.6 Any of Method 1.3-1.5, wherein the effective amount of the compound of Formula I, in free or pharmaceutically acceptable salt form, has a stereoisomeric excess of greater than 90%, e.g., a stereoisomeric excess equal to or greater than 95%, e.g., a stereoisomeric excess equal to or greater than 96%, e.g., a stereoisomeric excess equal to or greater than 97%, e.g., a stereoisomeric excess equal to or greater than 98%, e.g., a stereoisomeric excess equal to or greater than 99%. For instance, wherein the effective amount of the compound of Formula I,

in free or pharmaceutically acceptable salt form, is substantially diastereomerically and/or enantiomerically pure, e.g., wherein the effective amount of the compound of Formula I, in free or pharmaceutically acceptable salt form, is substantially diastereomerically and enantiomerically pure. For instance, wherein the effective amount of the compound of Formula I, in free or pharmaceutically acceptable salt form, has a diastereomeric and/or enantiomeric excess of greater than 90%, e.g., a diastereomeric and/or enantiomeric excess equal to or greater than 95%, a diastereomeric and/or enantiomeric excess equal to or greater than 96%, a diastereomeric and/or enantiomeric excess equal to or greater than 97%, e.g., a diastereomeric and/or enantiomeric excess equal to or greater than 98%, e.g., a diastereomeric and/or enantiomeric excess equal to or greater than 99%. For instance, wherein the effective amount of the compound of Formula I, in free or pharmaceutically acceptable salt form, has a diastereomeric and enantiomeric excess of greater than 90%, e.g., a diastereomeric and enantiomeric excess equal to or greater than 95%, e.g., a diastereomeric and enantiomeric excess equal to or greater than 96%, e.g., a diastereomeric and enantiomeric excess equal to or greater than 97%, e.g., a diastereomeric and enantiomeric excess equal to or greater than 98%, e.g., a diastereomeric and enantiomeric excess equal to or greater than 99%.

- 1.7 Any of Method 1 or 1.1-1.6, wherein the compound is in free form.
- 1.8 Method 1.3, wherein the method comprises administering an effective amount of Compound B:



Compound B,

in free or pharmaceutically acceptable salt form, e.g., in free form.

- 1.9 Method 1.8, wherein the effective amount of Compound B, in free or pharmaceutically acceptable salt form, has a stereoisomeric excess of greater than 90%, e.g., a stereoisomeric excess equal to or greater than 95%, e.g., a stereoisomeric excess equal to or greater than 96%, e.g., a stereoisomeric excess equal to or greater than 97%, e.g., a stereoisomeric excess equal to or greater than 98%, e.g., a stereoisomeric excess equal to or greater than 99%. For instance, wherein the effective amount of Compound B, in free or pharmaceutically acceptable salt form, is substantially diastereomerically and/or enantiomerically pure, e.g., wherein the effective amount of Compound B, in free or pharmaceutically acceptable salt form, is substantially diastereomerically and enantiomerically pure. For instance, wherein the effective amount of compound B, in free or pharmaceutically acceptable salt form, has a diastereomeric and/or enantiomeric excess of greater than 90%, e.g., a diastereomeric and/or enantiomeric excess equal to or greater than 95%, e.g., a diastereomeric and/or enantiomeric excess equal to or greater than 96%, e.g., a diastereomeric and/or enantiomeric excess equal to or greater than 97%, e.g., a diastereomeric and/or enantiomeric excess equal to or greater than 98%, e.g., a diastereomeric and/or enantiomeric excess equal to or greater than 99%. For instance, wherein the effective amount of compound B, in free or pharmaceutically acceptable salt form, has a diastereomeric and enantiomeric excess of greater than 90%, e.g., a diastereomeric and enantiomeric excess equal to or greater than 95%, e.g., a diastereomeric and enantiomeric excess equal to or greater than 96%, e.g., a diastereomeric and enantiomeric excess equal to or greater than 97%, e.g., a diastereomeric and enantiomeric excess equal to or greater than 98%, e.g., a diastereomeric and enantiomeric excess equal to or greater than 99%.
- 1.10 Any of Method 1 or 1.3-1.9, wherein the designation of deuterium (i.e., D) at a position means that position has a significantly greater than natural abundance of deuterium at that position (e.g., greater than 0.1%, or greater than 0.5%, or greater than 1%, or greater than 5%). Any atom not designated as a particular isotope is present at natural isotopic abundance.

- 1.11 Any of Method 1 or 1.3-1.10, wherein the compound, in free or pharmaceutically acceptable salt form, has greater than 50% incorporation of deuterium (i.e., D) at one or more positions (e.g., at all positions) designated as deuterium (i.e., D), e.g., greater than 60%, or greater than 70%, or greater than 80%, or greater than 90%, or greater than 95%, or greater than 96%, or greater than 97%, or greater than 98%, or greater than 99%. For instance, any of Method 1 or 1.3-1.10, wherein the compound, in free or pharmaceutically acceptable salt form, has greater than 50% incorporation of deuterium (i.e., D) at each position designated as deuterium (i.e., D), e.g., greater than 60%, or greater than 70%, or greater than 80%, or greater than 90%, or greater than 95%, or greater than 96%, or greater than 97%, or greater than 98%, or greater than 99%.
- 1.12 Any of Method 1 or 1.1-1.11, wherein the disorder is a brain disorder. For instance, any of Method 1 or 1.1-1.11, wherein the disorder is a neuropsychiatric condition in which anhedonia is prominent.
- 1.13 Any of Method 1 or 1.1-1.12, wherein the disorder is an affective (mood) disorder or an anxiety disorder.
- 1.14 Any of Method 1 or 1.1-1.13, wherein the disorder is depression (e.g., depression associated with anhedonia), an anxiety disorder, psychosis (e.g., psychosis in neurodegenerative conditions, such as psychosis in Alzheimer's disease, Parkinson's disease, or dementia (e.g., dementia-related psychosis)), schizophrenia, schizoaffective disorder, post-traumatic stress disorder (PTSD), attention-deficit/hyperactivity disorder (ADHD), Tourette syndrome, anorexia nervosa, bulimia nervosa, binge-eating disorder, body dysmorphic disorder, obsessive compulsive disorder, addiction, bipolar disorder (including bipolar depression, bipolar mania, and bipolar disorder with mixed features), or a migraine. For instance, any of Method 1 or 1.1-1.13, wherein the anxiety disorder is panic disorder, social anxiety disorder, a phobia, or generalized anxiety disorder. Or, any of Method 1 or 1.1-1.13, wherein the method is prophylaxis or treatment of behavioral and psychological symptoms of dementia including agitation, depression, anxiety, apathy, and/or psychosis.

- 1.15 Any of Method 1 or 1.1-1.14, wherein the disorder is anhedonia or depression associated with anhedonia, suicidal ideation, anxious depression, inflammatory depression, treatment-resistant depression, dysthymia, bipolar depression, psychotic depression, or post-psychotic depression. For instance, any of Method 1 or 1.1-1.14, wherein the disorder is depression associated with anhedonia. Or, for instance, wherein the disorder is anhedonia. Or, for instance, any of Method 1 or 1.1-1.14, wherein the disorder is melancholic depression.
- 1.16 Any of Method 1 or 1.1-1.15, wherein the disorder is major depressive disorder.
- 1.17 Any of Method 1 or 1.1-1.14, wherein the disorder is a substance use disorder.
- 1.18 Any of Method 1 or 1.1-1.14, wherein the method is prophylaxis or treatment of negative symptoms of schizophrenia. Or, any of Method 1 or 1.1-1.14, wherein the method is improving cognition in schizophrenia.
- 1.19 Any of Method 1 or 1.1-1.11, wherein the compound, in free or pharmaceutically acceptable salt form, is administered as an anti-emetic.
- 1.20 Any of Method 1 or 1.1-1.19, wherein the method comprises administering 9-60 mg a day of the compound, in free or pharmaceutically acceptable salt form (i.e., 9-60 mg total daily dose of the compound, in free or pharmaceutically acceptable salt form). For instance, any of Method 1 or 1.1-1.19, wherein the method comprises administering 9-36 mg a day of the compound, in free or pharmaceutically acceptable salt form (i.e., 9-36 mg total daily dose of the compound, in free or pharmaceutically acceptable salt form).
- 1.21 Any of Method 1 or 1.1-1.20, wherein the method comprises administering an amount of the compound, in free or pharmaceutically acceptable salt form, that provides 55%-80% D2/D3 receptor occupancy, e.g., as measured by positron emission tomography. For instance, wherein the method comprises administering an amount of the compound, in free or pharmaceutically acceptable salt form, that provides about 65% D2/D3 receptor occupancy, e.g., as measured by positron emission tomography. Or, for instance, wherein the method comprises administering an amount of the compound, in free or pharmaceutically acceptable salt form, that provides about 60% D2/D3 receptor occupancy, e.g., as measured by positron emission tomography.

- 1.22 Method 1.20 or 1.21, wherein the disorder is psychosis (e.g., psychosis in neurodegenerative conditions, such as Alzheimer's disease, Parkinson's disease, and dementia (e.g., dementia-related psychosis)), schizophrenia, schizoaffective disorder, or bipolar disorder (e.g., bipolar mania).
- 1.23 Method 1.20 or 1.21, wherein the method is prophylaxis or treatment of negative symptoms of schizophrenia. Or, Method 1.20 or 1.21, wherein the method is improving cognition in schizophrenia.
- 1.24 Any of Method 1 or 1.1-1.19, wherein the method comprises administering 1-9 mg (e.g., 1-8 mg, e.g., 1.5-6 mg) a day of the compound, in free or pharmaceutically acceptable salt form (i.e., 1-9 mg total daily dose, e.g., 1-8 mg total daily dose, e.g., 1.5-6 mg total daily dose, of the compound, in free or pharmaceutically acceptable salt form). For instance, any of Method 1 or 1.1-1.19, wherein the method comprises administering 1-8 mg a day of the compound, in free or pharmaceutically acceptable salt form (i.e., 1-8 mg total daily dose of the compound, in free or pharmaceutically acceptable salt form). For instance, any of Method 1 or 1.1-1.19, wherein the method comprises administering 1-3 mg a day of the compound, in free or pharmaceutically acceptable salt form (i.e., 1-3 mg total daily dose of the compound, in free or pharmaceutically acceptable salt form). For instance, any of Method 1 or 1.1-1.19, wherein the method comprises administering 1 mg to less than 3 mg a day (e.g., 2 mg a day) of the compound, in free or pharmaceutically acceptable salt form (i.e., 1 mg to less than 3 mg total daily dose of the compound, in free or pharmaceutically acceptable salt form).
- 1.25 Any of Method 1, 1.1-1.19, or 1.24, wherein the method comprises administering an amount of the compound, in free or pharmaceutically acceptable salt form, that provides 10%-60% (e.g., 40%-60% or, e.g., 10%-55%, e.g., 10%-50%, e.g., 30%-50% or, e.g., 15%-50%, e.g., 15%-45%, e.g., 20%-40%, e.g., 10%-30%) D2/D3 receptor occupancy, e.g., as measured by positron emission tomography. Or, for instance, any of Method 1, 1.1-1.19, or 1.24, wherein the method comprises administering an amount of the compound, in free or pharmaceutically acceptable salt form, that provides $\leq 40\%$ (e.g., about 40%), e.g., $< 40\%$, D2/D3 receptor occupancy, e.g., as measured by positron emission tomography.

- 1.26 Method 1.24 or 1.25, wherein the disorder is depression (e.g., depression associated with anhedonia), an anxiety disorder, post-traumatic stress disorder (PTSD), attention-deficit/hyperactivity disorder (ADHD), Tourette syndrome, anorexia nervosa, bulimia nervosa, binge-eating disorder, body dysmorphic disorder, obsessive compulsive disorder, addiction, bipolar disorder, bipolar disorder with mixed features, or a migraine. For instance, Method 1.24 or 1.25, wherein the anxiety disorder is panic disorder, social anxiety disorder, a phobia, or generalized anxiety disorder.
- 1.27 Any of Method 1.24-1.26, wherein the disorder is anhedonia or depression associated with anhedonia, suicidal ideation, anxious depression, inflammatory depression, treatment-resistant depression, dysthymia, bipolar depression, psychotic depression, or post-psychotic depression. For instance, wherein the disorder is anhedonia or depression associated with anhedonia.
- 1.28 Any of Method 1.24-1.27, wherein the disorder is major depressive disorder.
- 1.29 Method 1.24 or 1.25, wherein the disorder is a substance use disorder.
- 1.30 Any of Method 1 or 1.1-1.29, wherein the method comprises administering a pharmaceutical composition comprising the compound, in free or pharmaceutically acceptable salt form. For instance, any of Method 1 or 1.1-1.29, wherein the method comprises administering Formula 1.13 or any of Composition 1 or 1.1-1.15 *vide supra*.
- 1.31 Any of Method 1 or 1.1-1.30, wherein the method comprises administering the compound of Formula Ia, in free or pharmaceutically acceptable salt form, once, twice, or three times a day, e.g., once a day. For instance, any of Method 1 or 1.1-1.30, wherein the method comprises administering a pharmaceutical composition comprising the compound of Formula Ia, in free or pharmaceutically acceptable salt form, once, twice, or three times a day, e.g., once a day.
- 1.32 Any of Method 1 or 1.1-1.31, wherein the method comprises administering the compound of Formula I, in free or pharmaceutically acceptable salt form, once, twice, or three times a day, e.g., once a day. For instance, any of Method 1 or 1.1-1.31, wherein the method comprises administering a pharmaceutical composition

comprising the compound of Formula I, in free or pharmaceutically acceptable salt form, once, twice, or three times a day, e.g., once a day.

- 1.33 Any of Method 1 or 1.1-1.32, wherein the method comprises administering Compound B, in free or pharmaceutically acceptable salt form, once, twice, or three times a day, e.g., once a day. For instance, any of Method 1 or 1.1-1.32, wherein the method comprises administering a pharmaceutical composition comprising Compound B, in free or pharmaceutically acceptable salt form, once, twice, or three times a day, e.g., once a day.

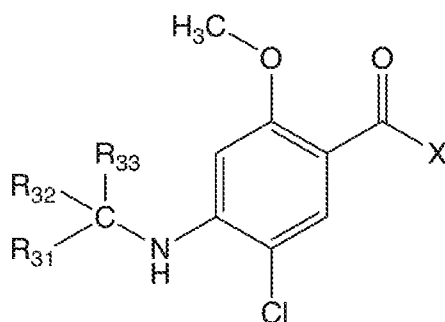
[0051] Further provided is a compound of Formula I (e.g., any of Formula 1.1-1.13) or a pharmaceutical composition disclosed herein (e.g., Formula 1.13 or any of Composition 1 or 1.1-1.15) for use in any of Method 1 or 1.1-1.33 *vide supra*.

[0052] Further provided is use of a compound of Formula I (e.g., any of Formula 1.1-1.13) or a pharmaceutical composition disclosed herein (e.g., Formula 1.13 or any of Composition 1 or 1.1-1.15) in any of Method 1 or 1.1-1.33 *vide supra*.

[0053] Further provided is use of a compound of Formula I (e.g., any of Formula 1.1-1.13) in the manufacture of a medicament (e.g., Formula 1.13 or any of Composition 1 or 1.1-1.15) for use in any of Method 1 or 1.1-1.33 *vide supra*.

[0054] Further provided are intermediate compounds of Formula II and Formula III, each in free or salt (e.g., pharmaceutically acceptable salt) form.

[0055] For instance, further provided is a compound of Formula II:



Formula II,

wherein R_{31} , R_{32} , and R_{33} are independently selected from H and D;

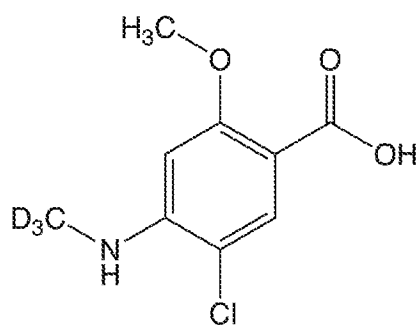
X is OH or a leaving group; and

at least one of R_{31} , R_{32} , and R_{33} are D;

in free or salt (e.g., pharmaceutically acceptable salt) form.

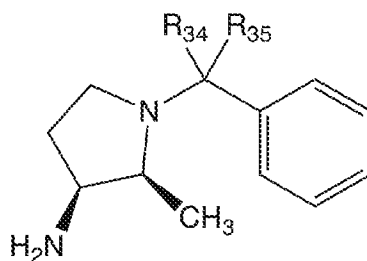
[0056] Further provided are compounds of Formula II as follows:

- 2.1 Formula II, wherein the compound is in pharmaceutically acceptable salt form.
- 2.2 Formula II or 2.1, wherein R_{31} , R_{32} , and R_{33} are D.
- 2.3 Any of Formula II, 2.1, or 2.2, wherein X is OH.
- 2.4 Any of Formula II, 2.1, or 2.2, wherein X is a leaving group (e.g., an activated ester, e.g., an O-acylisourea, or a halide). For instance, any of Formula II, 2.1, or 2.2, wherein the compound of Formula II is reacted with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.
- 2.5 Any of Formula II or 2.1-2.3, wherein the compound is:



in free or salt (e.g., pharmaceutically acceptable salt) form, e.g., in free form.

[0057] Also further provided is a compound of Formula III:



Formula III,

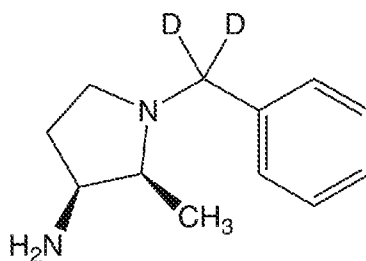
wherein:

R_{34} and R_{35} are D;

in free or salt (e.g., pharmaceutically acceptable salt) form.

[0058] Further provided are compounds of Formula III as follows:

- 3.1 Formula III, wherein the compound is in pharmaceutically acceptable salt form.
- 3.2 Formula III or 3.1, wherein the compound is:

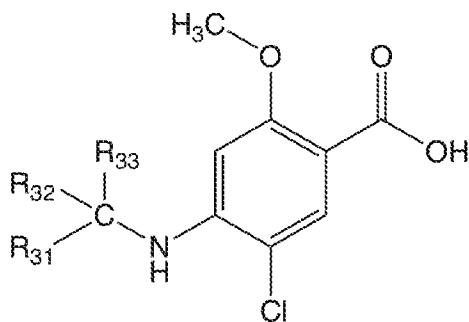


in free or salt (e.g., pharmaceutically acceptable salt) form, e.g., in free form.

[0059] Further provided is a process (Process 1) for synthesizing a compound of Formula I (e.g., any of Formula 1.1-1.13), in free or salt (e.g., pharmaceutically acceptable salt) form.

[0060] Further provided is Process 1 as follows:

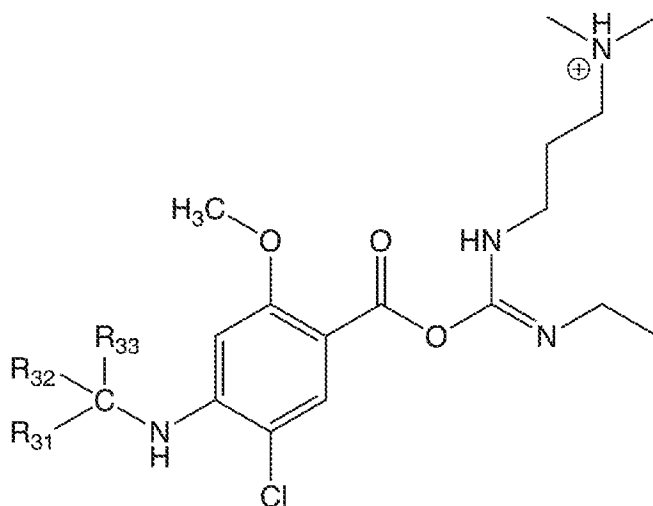
- 1.1 Process 1, wherein the process comprises reacting a compound of Formula II (e.g., any of Formula 2.1-2.5) with a compound of Formula III (e.g., any of Formula 3.1-3.2).
- 1.2 Process 1 or 1.1, wherein the process occurs in the presence of an amine (e.g., triethylamine, e.g., triethylamine and dimethylformamide).
- 1.3 Process 1, 1.1, or 1.2, wherein the process occurs in an organic solvent (e.g., dimethylformamide).
- 1.4 Any of Process 1 or 1.1-1.3, wherein the process occurs with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and hydroxybenzotriazole. For instance, any process wherein the process occurs with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, hydroxybenzotriazole, triethylamine, and dimethylformamide.
- 1.5 Any of Process 1 or 1.1-1.4, wherein the process comprises reacting a compound of Formula IIa:



Formula IIa,

wherein R_{31} , R_{32} , and R_{33} are independently selected from H and D and at least one of R_{31} , R_{32} , and R_{33} is D, in free or salt (e.g., pharmaceutically acceptable salt) form, with an activating agent (e.g., 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide).

1.6 Process 1.5, wherein the process forms a compound of Formula IIb:



Formula IIb,

wherein R_{31} , R_{32} , and R_{33} are independently selected from H and D and at least one of R_{31} , R_{32} , and R_{33} is D, in free or salt (e.g., pharmaceutically acceptable salt) form.

1.7 Process 1.6, wherein the compound of Formula IIb is formed in situ.

[0061] For compounds disclosed herein, a hydrogen atom position of a structure is considered substituted with deuterium when the abundance of deuterium at that position is enriched. The natural abundance of deuterium is about 0.02%, so a compound is “enriched” with deuterium at a specific position when the frequency of incorporation of deuterium at that position exceeds 0.02%. Therefore, for deuterated compounds disclosed herein, any position designated as deuterium (i.e., D) may be enriched with deuterium at a level of greater than 0.1%, or greater than 0.5%, or greater than 1%, or greater than 5%, such as, greater than 50%, or greater than 60%, or greater than 70%, or greater than 80%, or greater than 90%, or greater than 95%, or greater than 96%, or greater than 97%, or greater than 98%, or greater than 99%. For compounds disclosed herein, any atom not designated as a particular isotope is present at natural isotopic abundance.

[0062] Compounds disclosed herein, e.g., any of Formula I (e.g., any of Formula 1.1-1.13), Formula Ia, Formula II (e.g., any of Formula 2.1-2.5), Formula III (e.g., any of Formula 3.1-3.2), Formula IIa, Formula IIb, Compound A, and Compound B, may exist in free or salt form, e.g., as acid addition salts. As used herein, unless otherwise indicated, language such as “compound of formula” is to be understood as embracing the compound in any form, for example free or acid addition salt form, or where the compound contains an acidic substituent, in base addition salt form. Compounds of Formula I (e.g., any of Formula 1.1-1.13), Formula Ia, Compound A, and Compound B are intended for use as pharmaceuticals, therefore pharmaceutically acceptable salts are preferred. Salts which are unsuitable for pharmaceutical uses may be useful, for example, for the isolation or purification of free compounds of Formula I or Formula Ia or their pharmaceutically acceptable salts, so therefore are also included.

[0063] Isolation or purification of the stereoisomers of compounds disclosed herein, for instance, Formula I (e.g., any of Formula 1.1-1.13), Formula Ia, Formula II (e.g., any of Formula 2.1-2.5), Formula III (e.g., any of 3.1-3.2), Formula IIa, Formula IIb, Compound A, and Compound B, any in free or pharmaceutically acceptable salt form, may be achieved by conventional methods known in the art, e.g., column purification, preparative thin layer chromatography, preparative HPLC, trituration, simulated moving beds, and the like.

[0064] Pure stereoisomeric forms of the compounds and intermediates disclosed herein are isomers substantially free of other enantiomeric and diastereomeric forms of the same basic molecular structure of said compounds or intermediates. “Substantially stereoisomerically pure” includes compounds or intermediates having a stereoisomeric excess of greater than 90% (i.e., more than 90% of one isomer and less than 10% of any other possible isomer). The terms “substantially diastereomerically pure” and “substantially enantiomerically pure” should be understood in a similar way, but then having regard to the diastereomeric excess and enantiomeric excess, respectively, of the material in question.

[0065] Compounds disclosed herein, e.g., any of Formula I (e.g., any of Formula 1.1-1.13), Formula Ia, Formula II (e.g., any of Formula 2.1-2.5), Formula III (e.g., any of 3.1-3.2), Formula IIa, Formula IIb, Compound A, and Compound B, any in free or pharmaceutically acceptable salt form, may be made by using the methods as described and exemplified herein and by methods similar thereto and by methods known in the chemical art. Such methods include, but are not limited to, those described below. If not commercially available, starting materials for

these processes may be made by procedures, which are selected from the chemical art using techniques that are similar to or analogous to the synthesis of known compounds.

[0066] Pharmaceutically acceptable salts of any of Formula I (e.g., any of Formula 1.1-1.13), Formula Ia, Formula II (e.g., any of Formula 2.1-2.5), Formula III (e.g., any of 3.1-3.2), Formula IIa, Formula IIb, Compound A, and Compound B, may be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free base forms of these compounds with a stoichiometric amount of the appropriate acid in an appropriate solvent.

[0067] For methods of treatment, the word “effective amount” is intended to encompass a therapeutically effective amount to treat a specific disease or disorder.

[0068] Dosages employed in practicing the present invention will of course vary depending, e.g. on the particular disease or condition to be treated, the particular compound used, the mode of administration, and the therapy desired.

[0069] Compounds disclosed herein, e.g., any of Formula I (e.g., any of Formula 1.1-1.13), Formula Ia, Compound A, or Compound B, any in free or pharmaceutically acceptable salt form, may be administered by any suitable route, including orally, parenterally, or transdermally, but are preferably administered orally.

[0070] Pharmaceutical compositions comprising compounds disclosed herein, e.g., any of Formula I (e.g., any of Formula 1.1-1.13 or any of Composition 1 or 1.1-1.15), Formula Ia, Compound A, or Compound B, any in free or pharmaceutically acceptable salt form, may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets, capsules, solutions, suspensions, and the like.

EXAMPLES

Abbreviations

AcOH = acetic acid

Boc = tert-butyloxycarbonyl

DIAD = diisopropyl azodicarboxylate

DCM = dichloromethane

DMAP = 4-dimethylaminopyridine

DMF = dimethylformamide

EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

EtOAc or EA = ethyl acetate

h = hour(s)

HOBt = hydroxybenzotriazole

MeOH = methanol

MsCl = methanesulfonyl chloride

rt (or RT) = room temperature

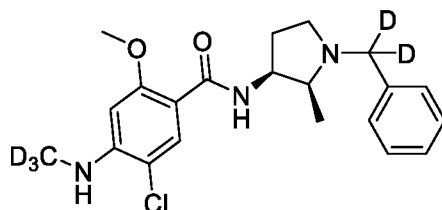
TEA = triethylamine

TFA = trifluoroacetic acid

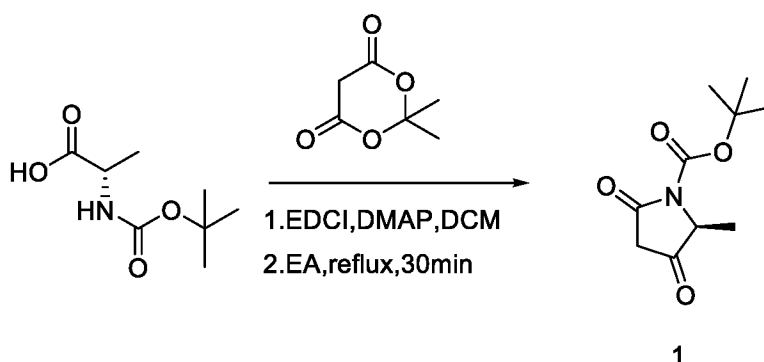
THF = tetrahydrofuran

Example 1

Synthesis of A1: 5-Chloro-N-((2S,3S)-1-(dideutero(phenyl)methyl)-2-methylpyrrolidin-3-yl)-2-methoxy-4-(trideuteromethylamino)benzamide



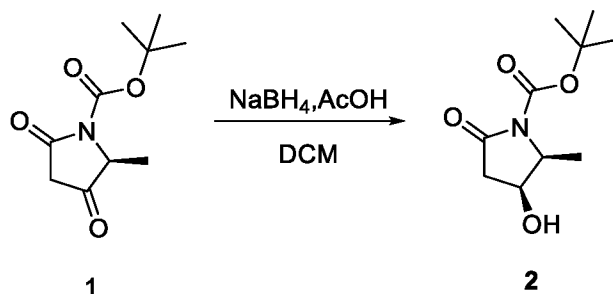
Compound 1: tert-butyl (S)-2-methyl-3,5-dioxopyrrolidine-1-carboxylate



[0071] To a stirred solution of Boc-L-alanine (25 g, 132.1 mmol), Meldrum's acid (20 g, 138.7 mmol), and DMAP (19.4 g, 158.6 mmol) in CH₂Cl₂ (250 mL) is added EDCI (30.4g, 158.6 mmol) under nitrogen at 0 °C. The resulting solution is then allowed to warm up to room temperature (rt) and stirred over 16 h. It is quenched with water (50 mL), the organic phase is washed with a cold solution of 5% KHSO₄ (300 mL x 2), water (300 mL x 1) and brine, then

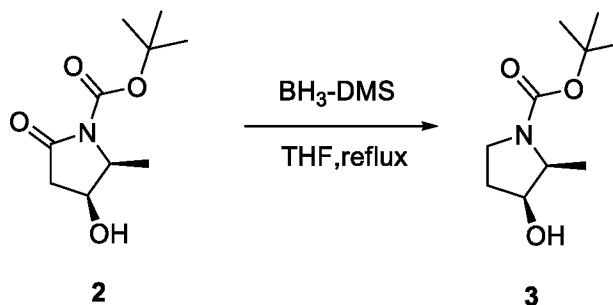
dried over anhydrous MgSO_4 , and concentrated to give the residue (40 g). EtOAc (200 mL) is added and the reaction mixture is refluxed for 30 minutes. The solution is concentrated and the residue is stirred in EtOAc (90 mL) at $-10\text{ }^\circ\text{C}$ for 2 h, then filtered, and the filter cake is collected to give the title compound as a pale yellow solid (16 g, 46% yield). ^1H NMR (400 MHz, CDCl_3) δ 4.41 (q, $J = 6.8$ Hz, 1H), 3.22 (s, 2H), 1.57 (s, 9H), 1.51 (d, $J = 6.8$ Hz, 3H). MS m/z (ESI): 158 $[\text{M}+\text{H}-56]^+$

Compound 2: tert-butyl (2S,3S)-3-hydroxy-2-methyl-5-oxo-pyrrolidine-1-carboxylate



[0072] To a stirred solution of compound **1** (13 g, 61 mmol) in dichloromethane (DCM) (130 mL) is added AcOH (65 mL) at $0\text{ }^\circ\text{C}$. Then NaBH_4 (5.77 g, 152.4 mmol) is added in three portions. The resulting solution is then allowed to warm up to room temperature and stirred over 16 h. The reaction mixture is quenched with 5% NaHCO_3 at $0\text{ }^\circ\text{C}$. It is then extracted with DCM (200 mL $\times$ 3). The combined organic layers are washed with 5% NaHCO_3 , brine, dried over anhydrous MgSO_4 , and concentrated to give the residue which is stirred in isopropyl ether to afford the title compound **2** (8 g, 61% yield). ^1H NMR (400 MHz, CDCl_3) δ 4.53-4.47 (m, 1H), 4.29-4.22 (m, 1H), 2.75-2.55 (m, 2H), 1.53 (s, 9H), 1.31 (d, $J = 6.8$ Hz, 3H). MS m/z (ESI): 160 $[\text{M}+\text{H}-56]^+$

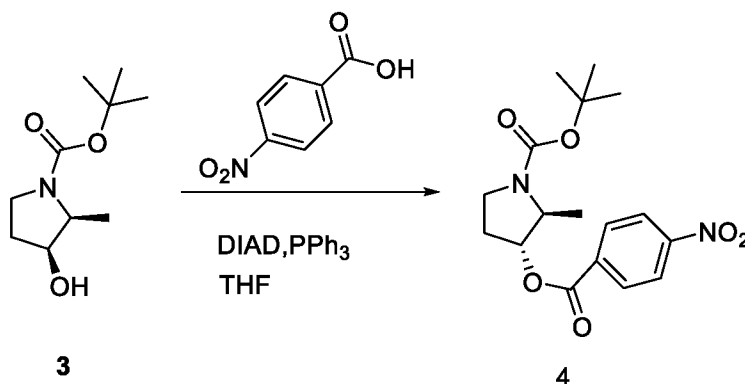
Compound 3: tert-butyl (2S,3S)-3-hydroxy-2-methyl-pyrrolidine-1-carboxylate



[0073] To a solution of compound **2** (3 g, 14 mmol) in dry THF (40 mL) is added a solution of $\text{BH}_3\text{-SMe}_2$ (21 mL, 41.8 mmol) at $0\text{ }^\circ\text{C}$ and it is stirred for 30 minutes at $0\text{ }^\circ\text{C}$. Then

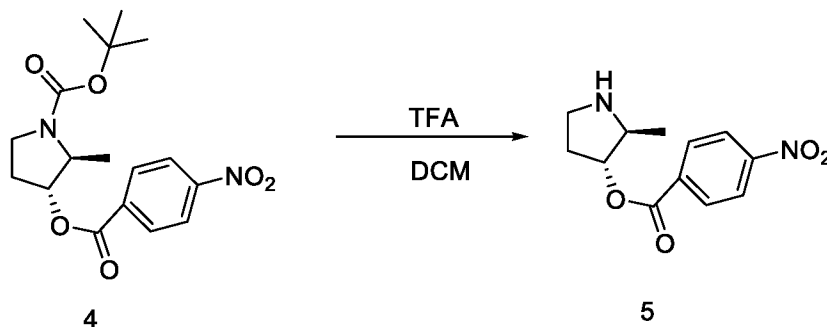
the mixture is refluxed for 4 h. The resulting mixture is cooled and quenched with saturated NH_4Cl at 0 °C. It is then extracted with EtOAc (100 ml x 3). The organic phases are dried over anhydrous MgSO_4 and concentrated to give compound **3** (2.24 g, 80% yield). ^1H NMR (400 MHz, CDCl_3) δ 4.34-4.29 (m, 1H), 3.90-3.83 (m, 1H), 3.46-3.33 (m, 2H), 2.09-1.80 (m, 2H), 1.46 (s, 9H), 1.18 (d, $J = 6.8$ Hz, 3H). MS m/z (ESI): 146 $[\text{M}+\text{H}-56]^+$

Compound 4: tert-butyl (2S,3R)-2-methyl-3-((4-nitrobenzoyl)oxy)pyrrolidine-1-carboxylate



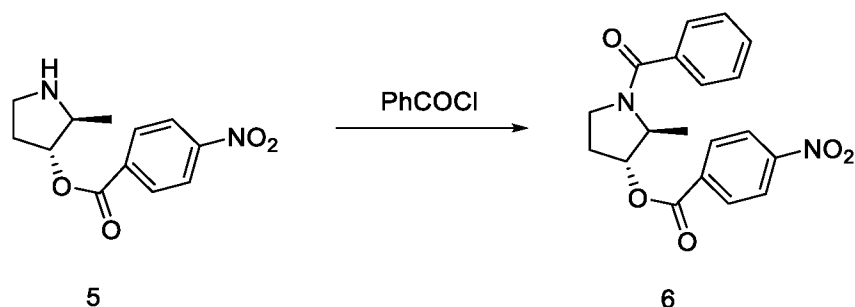
[0074] To a cold solution of compound **3** (12 g, 59.6 mmol), 4-nitrobenzoic acid (10.46 g, 62.6 mmol), and PPh_3 (16.42 g, 62.6 mmol) in dry THF (200 ml) is added diisopropyl azodicarboxylate (DIAD) (12.66 g, 62.6 mmol) for 30 minutes at 0 °C. The reaction mixture is allowed to warm room temperature for 16 h. The resulting mixture is cooled and quenched with water. The mixture is extracted with EtOAc (200 ml x 3), dried over anhydrous MgSO_4 . It is then concentrated and purified by silica gel chromatography to afford the title compound **4** (17.1 g, 81.9% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.31-8.17 (m, 4H), 5.20 (d, $J = 4$ Hz 1H), 4.17-3.86 (m, 1H), 3.59-3.46 (m, 2H), 2.35-2.11 (m, 2H), 1.48 (s, 9H), 1.28 (d, $J = 6.8$ Hz, 3H). MS m/z (ESI): 295 $[\text{M}+\text{H}-56]^+$

Compound 5: (2S,3R)-2-methylpyrrolidin-3-yl 4-nitrobenzoate



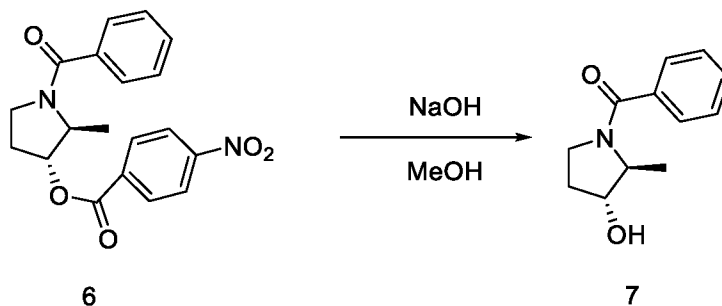
[0075] A mixture of compound **4** (16.1 g, 46 mmol) and trifluoroacetic acid (TFA) (80mL) in DCM (160 mL) is stirred at room temperature for 1 h. The reaction mixture is then concentrated to give the product **5** (11.5 g, 100% yield). MS m/z (ESI): 251 [M+H]⁺

Compound 6: (2S,3R)-1-benzoyl-2-methylpyrrolidin-3-yl 4-nitrobenzoate



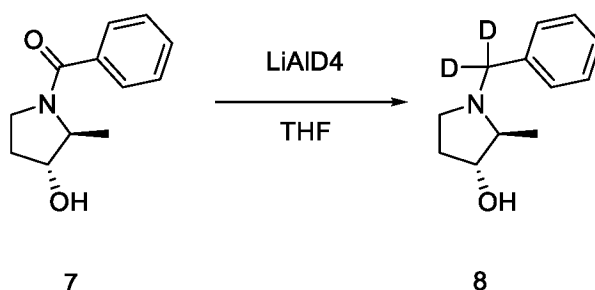
[0076] To a solution of compound **5** (11.5 g, 46 mmol) in toluene (360 ml) is added 2N NaOH (360 ml, 72 mmol), then benzoyl chloride (6.6 g, 46 mmol) in toluene (150 ml) is added at 0 °C. The mixture is separated and the aqueous phase is extracted with DCM (250 ml x 3). The organic phase is dried over MgSO₄ and concentrated to give compound **6** (14.0 g, 85.9% yield). MS m/z (ESI): 355 [M+H]⁺

Compound 7: ((2S,3R)-3-hydroxy-2-methylpyrrolidin-1-yl)(phenyl)methanone



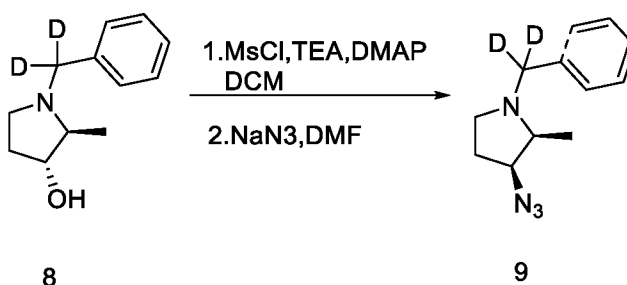
[0077] To a stirred solution of compound **6** (14g, 39.5 mmol) in MeOH (350 mL) is added 6N NaOH (6.6 ml, 39.6 mmol). The reaction mixture is stirred for 40 minutes and then concentrated under reduced pressure. The residue is diluted with DCM (200 ml) and water (100 ml), the aqueous phase is extracted with DCM (250 ml x 3). The organic phase is dried over MgSO₄ and concentrated to give the residue which is treated with petroleum ether (PE) (9 ml) and EtOAc (3 ml) to afford the title compound **7** (7.1 g, 87.6%yield). MS m/z (ESI): 206 [M+H]⁺

Compound 8: (2S,3R)-1-(dideutero(phenyl)methyl)-2-methylpyrrolidin-3-ol



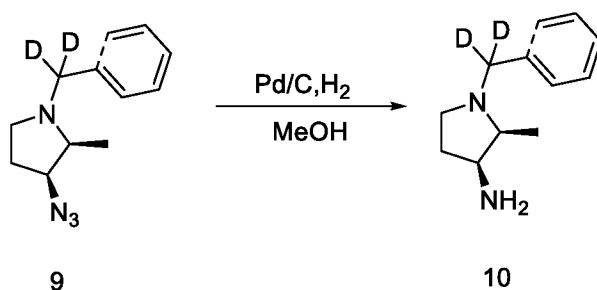
[0078] To a stirred solution of compound **7** (1.6 g, 7.8 mmol) in dry THF (30 mL) is slowly added lithium aluminum deuteride (372 mg, 7.8 mmol) in portions at -15 °C. The reaction mixture is stirred to room temperature for 18 hours. The mixture is cooled to 0 °C and quenched with 20% aqueous KOH (2 mL). The mixture is filtered and washed with diethyl ether. The combined organic phases are dried over Na₂SO₄ and concentrated to give the residue that is purified by silica gel chromatography to afford the title compound **8** (1.5 g, 99% yield). MS m/z (ESI): 194 [M+H]⁺

Compound 9: (2S,3S)-3-azido-1-(dideutero(phenyl)methyl)-2-methylpyrrolidine



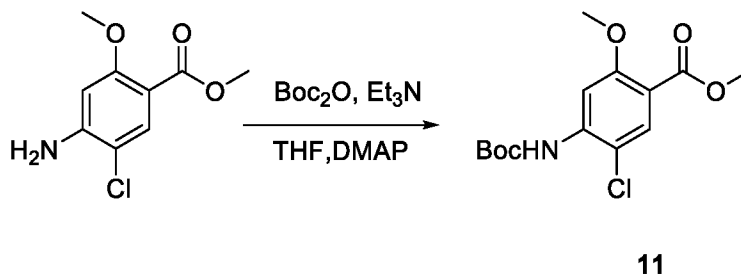
[0079] To a stirred solution of compound **8** (1.5 g, 7.8 mmol), DMAP (2.36 g, 0.78 mmol), and Et₃N (95 mg, 23.4 mmol) in dry CH₂Cl₂ at 0 °C is added MsCl (1.8 g, 15.62 mmol). The reaction mixture is stirred for 3 hours at room temperature, then quenched with saturated aqueous NaHCO₃, and the aqueous layer extracted with CHCl₃ (30 mL x 3). The combined organic phases are washed with brine and dried over anhydrous Na₂SO₄. The organic phase is concentrated under reduced pressure and the residue is diluted with DMF (40 mL) and NaN₃ (1.65 g, 23.4 mmol) is added. The reaction mixture is stirred for 16 h at 80 °C. It is quenched with water, extracted with EtOAc (100 mL x 3). The organic phases are dried over MgSO₄ and concentrated to give the residue which is purified by silica gel column chromatography to afford the title compound **9** (1.64 g, 96% yield). MS m/z (ESI): 219 [M+H]⁺ LCMS: M+1=219

Compound 10: (2S,3S)-1-(dideutero(phenyl)methyl)-2-methylpyrrolidin-3-amine



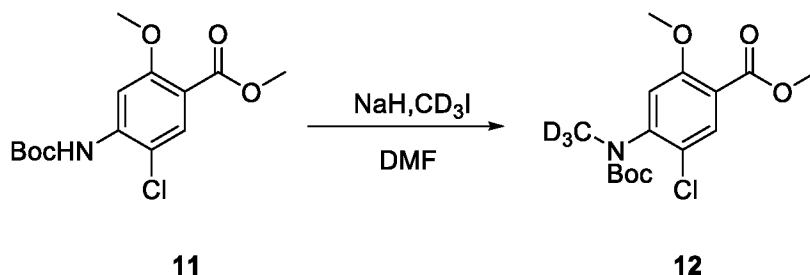
[0080] A mixture of compound **9** (1.64 g, 3 mmol) and 10% of Pd/C (182 mg) in MeOH (50 mL) is stirred under H₂ for 18 hours. The reaction mixture is filtered and the solvent evaporated under reduced pressure to afford the title compound **10** (1 g, 66% yield). MS m/z (ESI): 193 [M+H-56]⁺

Compound 11: Methyl 4-(tert-butoxycarbonylamino)-5-chloro-2-methoxybenzoate



[0081] To a mixture of methyl 4-amino-5-chloro-2-methoxybenzoate (5 g, 23.2 mmol), DMAP (1.4 g, 11.7 mmol), and triethylamine (13.2 mL) in THF (175 mL) is added Boc₂O (5.6 g, 25.5 mmol) and the reaction mixture is stirred at 38 °C for 6 h. It is concentrated to give the residue that is purified by silica gel column chromatography to afford the compound **11** (4.4 g, 60% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.71 (s, 1H), 7.72 (s, 1H), 7.62 (s, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 1.49 (s, 9H). MS m/z (ESI): 316 [M+H-56]⁺

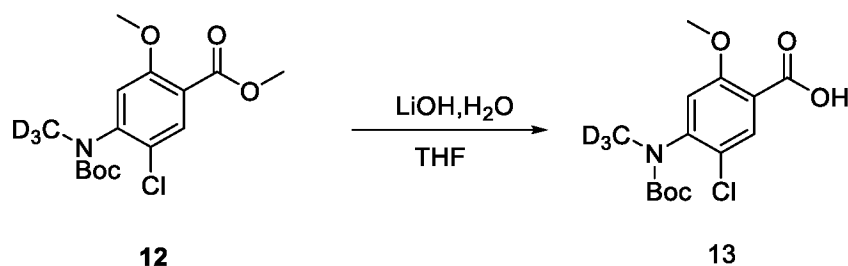
Compound 12: Methyl 4-(tert-butoxycarbonyl(trideuteriomethyl)amino)-5-chloro-2-methoxybenzoate



[0082] To a solution of compound **11** (1.96 g, 6.2 mmol) in dry DMF (40 mL) is added NaH (370 mg, 9.3 mmol) and the reaction is stirred at room temperature for 30 minutes, then

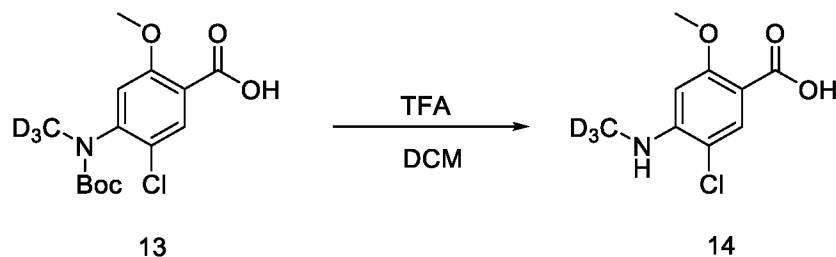
CD₃I (1.8 g, 12.4 mmol) is added and the reaction is stirred at room temperature for 3 h. The reaction is cooled to 0 °C and quenched with saturated aqueous NH₄Cl. It is extracted with EtOAc (100 mL) and the organic phase is washed with water, brine, and dried over anhydrous Na₂SO₄. The organic phase is concentrated under reduced pressure and the residue purified by silica gel column chromatography to afford the title compound **12** (2.02 g, 97.6% yield). NMR (400 MHz, CDCl₃) δ 7.86 (s, 1H), 6.85 (s, 1H), 3.90 (s, 6H), 1.36 (s, 9H). MS m/z (ESI): 277 [M+H-56]⁺

Compound 13: 4-(tert-Butoxycarbonyl(trideuteriomethyl)amino)-5-chloro-2-methoxybenzoic acid



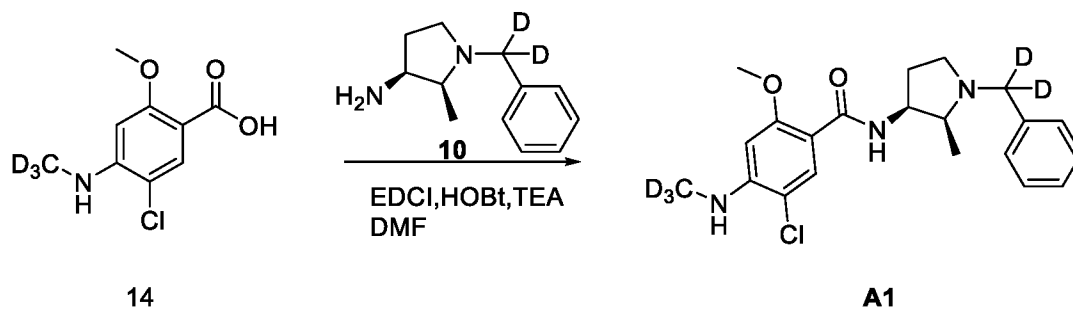
[0083] To a solution of compound **12** (1.68 g, 5.1 mmol) in THF (65 mL) and water (20 mL) is added LiOH·H₂O (844 mg, 20 mmol) and the mixture is stirred for 12 h. The reaction is acidified to pH = 3 with 1N HCl and then is extracted with EtOAc (50 mL x 3) and the combined organic phases are washed with brine and dried over anhydrous Na₂SO₄. The organic phase is concentrated under reduced pressure and the residue is purified by silica gel column chromatography to afford the title compound **13**. (1.46 g, 90% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.23 (s, 1H), 6.96 (s, 1H), 4.08 (s, 3H), 1.39 (s, 9H). MS m/z (ESI): 263 [M+H-56]⁺

Compound 14: 5-Chloro-2-methoxy-4-(trideuteriomethylamino)benzoic acid



[0084] A mixture of compound **13** (1.44g, 4.5mmol) and TFA (12 mL) in CH₂Cl₂ (25 mL) is stirred at room temperature for 1 h. The reaction mixture is concentrated to give compound **14** (0.73 g, 73.8% yield). ¹H NMR (400 MHz, DMSO-d₆) δ 7.61(s, 1H), 6.20 (s, 1H), 6.18 (s, 1H), 3.83 (s, 3H). MS m/z (ESI): 219 [M+H]⁺

A1: 5-Chloro-*N*-((2*S*,3*S*)-1-(dideutero(phenyl)methyl)-2-methylpyrrolidin-3-yl)-2-methoxy-4-(trideuteromethylamino)benzamide



[0085] A mixture of compound **10** (100 mg, 0.52 mmol), compound **14** (114 mg, 0.52 mmol), HOBT (105 mg, 0.78 mmol), EDCI (150 mg, 0.78 mmol), and TEA (158 mg, 1.56 mmol) in dry DMF (2 ml) is stirred at room temperature for 16 h. The resulting mixture is quenched with water and extracted with EtOAc (15 mL x 3), washed with brine, dried over anhydrous MgSO₄, and concentrated to give the residue which is purified by silica gel chromatography to afford the title compound **A1** (87 mg, 42.3% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.10 (s, 1H), 7.99 (s, 1H), 7.52-7.35 (m, 5H), 6.13 (s, 1H), 4.69 (s, 2H), 4.00 (s, 3H), 2.97 (s, 1H), 2.63 (s, 1H), 2.21-2.05 (m, 2H), 1.59 (s, 1H), 1.13 (s, 3H). MS m/z (ESI): 393 [M+H]⁺

Example 2 – Radioligand Binding Competition Activity on Recombinant Human Dopamine and Serotonin Receptors Using Filtration Binding Assays

[0086] Radioligand binding experiments are conducted with membrane preparations. Receptor accession numbers, cellular background, and reference compounds are listed in Table 1.

Table 1.

Receptor	Accession Number	Cell Line	Reference Tracer	Reference Competitor
D2S	NP_057658.2	CHO-K1	[³ H]-Spiperone	Risperidone
D3	AAA73929.1	CHO-K1	[³ H]-R-(+)-7-OH-DPAT	R-(+)-7-OH-DPAT
D4.4	NP_000788.2	CHO-K1	[³ H]-Spiperone	Haloperidol
5-HT1A	NP_000515.2	CHO-K1	[³ H]-8-OH-DPAT	5-HT
5-HT2A	NP_000612.1	CHO-K1	[³ H]-Ketanserin	Ketanserin
5-HT7A	NP_000863.1	CHO-K1	[³ H]-LSD	5-CT
human D2L	AAB26819.1	CHO-K1	[³ H]-Spiperone	Risperidone

[0087] The compound from Example 1 (A1) is tested for radioligand binding competition activity at human Dopamine D2S, D2L, D3, and D4.4 and Serotonin 5-HT1A, 5-HT2A, and 5-HT7A receptors and results are provided in Table 2.

Table 2. Binding

Measure	D2S	D3	D4	5-HT1A	5-HT2A	5-HT7A	D2L
Nemon-apride ^a (IC ₅₀ , nM)	0.5	0.3	0.8	2.7	10	75.7	0.95
Nemon-apride ^a (K _i , nM)	0.1	0.2	0.4	1.4	2.3	53.2	0.01
cis (S,S) nemon-apride ^b (IC ₅₀ , nM)	0.5	0.6	6.5	53.4	13	167	0.09
cis (S,S) nemon-apride ^b (K _i , nM)	0.1	0.3	3.2	26.7	2.9	117	0.01
Ex. 1 (A1, S,S) (IC ₅₀ , nM)	0.6 ^c (0.76,0.44)	0.4 ^c (0.37,0.45)	3.3 ^c (5.21,1.3)	45.0 ^c (38.1,51.8)	16.4 ^c (16.0,16.8)	100 ^c (94.4,106)	0.1
Ex. 1 (A1, S,S) (K _i , nM)	0.1	0.2	1.6	22.5	3.7	74.4	0.01

a. (±)-*cis*-N-(1-Benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide

b. N-[(2S,3S)-1-benzyl-2-methylpyrrolidin-3-yl]-5-chloro-2-methoxy-4-(methylamino)benzamide

c. Average of numbers in parentheses.

Example 3 – Agonist or Antagonist Activity on Recombinant Human Dopamine and Serotonin Receptors Using IPOne HTRF, cAMP HTRF, and GTPγS Assays

[0088] SPA ³⁵S-GTPγS experiments are conducted with membrane preparations. IP-One and cAMP HTRF assays are conducted with recombinant cell lines. Receptor accession numbers, cellular background, and reference compounds are listed in Table 3.

Table 3.

Receptor	Accession Number	Assay	Cell Line	Reference Agonist	Reference Antagonist
D2S	NP_057658.2	cAMP	CHO-K1	Quinpirole	Haloperidol
D3	AAA73929.1	GTP	CHO-K1	Dopamine	GR103691
D4.4	NP_000788.2	cAMP	CHO-K1	Dopamine	Spiperone
5-HT1A	NP_000515.2	cAMP	CHO-K1	5-CT	Not tested
5-HT2A	NP_000612.1	IPOne	CHO-K1	α-Me-5-HT	Ketanserin
5-HT7A	NP_000863.1	cAMP	CHO-K1	5-CT	Risperidone
D2L	AAB26819.1	cAMP	CHO-K1	Quinpirole	Haloperidol

[0089] The compound from Example 1 (A1) is tested for antagonist activity at human Dopamine D2S, D2L, D3, and D4.4 receptors, for agonist activity at human Serotonin 5-HT1A receptor, for agonist and antagonist activity at human Serotonin 5-HT2A receptor, and for antagonist activity at human Serotonin 5-HT7A receptor. Results are in Tables 4 and 5.

[0090] Agonist activity of test compounds is expressed as a percentage of the activity of the reference agonist at its EC₁₀₀ concentration. Antagonist activity of the test compound is expressed as a percentage of the inhibition of reference agonist activity at its EC₈₀ concentration.

Table 4. Functional Assays

Measure (IC ₅₀ , nM)	D2 (antagonist mode)	D3 (antagonist mode)	D4 (antagonist mode)	5-HT1A (agonist mode) EC ₅₀	5-HT2A (agonist mode) EC ₅₀	5-HT2A (antagonist mode) EC ₅₀	5-HT7A (antagonist mode)
Nemonapride ^a	cAMP 0.3 (D2S) cAMP 0.08 (D2L)	GTP γ S 3.0	cAMP 0.9	cAMP 14.3	IP-one 5.5	IP-one 6.5	-
cis (S,S) nemonapride ^b	cAMP 0.3 (D2S) cAMP 0.09 (D2L)	GTP γ S 7.4	cAMP 1.9	cAMP >100	IP-one 2.8	IP-one 2.4	-
Ex. 1 (A1)	cAMP 1.1 ^c (1.93, 0.26) (D2S) cAMP 0.1 (D2L)	GTP γ S 2.4 ^c (2.01, 2.76)	cAMP 15.3 ^c (24.1, 6.58)	cAMP >3000	IP-one 2.5 ^c (1.26, 5.20, 1.15)	IP-one 14.1 ^c (24, 4.26)	cAMP 2240

a. ((±)-*cis*-N-(1-Benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide)

b. N-[(2S,3S)-1-benzyl-2-methylpyrrolidin-3-yl]-5-chloro-2-methoxy-4-(methylamino)benzamide

c. Average of numbers in parentheses.

Table 5.

Measure ^a	D2 (antagonist mode)	D3 (antagonist mode)	D4 (antagonist mode)	5- HT1A (agonist mode)	5- HT2A (agonist mode)	5-HT2A (antagonist mode)	5-HT7A (antagonist mode)
Nemon- apride ^b	cAMP 97 (D2S) cAMP 86 (D2L)	GTP γ S 126	cAMP 75	cAMP 52	IP-one 48	IP-one 33	-
cis (S,S) nemon- apride ^c	cAMP 88 (D2S) cAMP 84 (D2L)	GTP γ S 117	cAMP 67	cAMP 17	IP-one 29	IP-one 52	-
Ex. 1 (A1)	cAMP 98 ^d (104,91) (D2S) cAMP 81 (D2L)	GTP γ S 129 ^d (135,123)	cAMP 89 ^d (103,75)	cAMP 0.6	IP-one 27 ^d (43,19, 36,10)	IP-one 39 ^d (32,46)	-

a. Top % Inhibition or Activation at maximal concentration

b. ((±)-*cis*-*N*-(1-Benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide)

c. *N*-[(2*S*,3*S*)-1-benzyl-2-methylpyrrolidin-3-yl]-5-chloro-2-methoxy-4-(methylamino)benzamide

d. Average of numbers in parentheses.

[0091] As shown above, the deuterated compound of Example 1 is a D2/D3/D4 antagonist.

Table 6. Functional Assays

Measure for Ex. 1 (A1)	5-HT1A (antagonist mode)	5-HT2B (antagonist mode)
EC ₅₀ (nM)	1900	3.4
E _{max}	63%	92%

Example 4 – In vitro metabolism

[0092] Study compounds are investigated in pooled cryopreserved human (mixed gender) hepatocytes. The incubations are performed using 5 μ M initial concentration and sampling at 0, 60, and 120 minute time points. The samples are analyzed using UPLC-QE-orbitrap-MS. Incubation volume: 300 μ l in 48-well plate. Number of cells: 1 million viable cells/ml. Test compound: 5 μ M (stock solution in DMSO). Incubation medium: pH 7.4, Bioreclamation IVT in vitro KHB medium. Shaking: 600 rpm. Time points: 0, 60, and 120 minutes with and without cells. Temperature: 37 °C. Sampling volume: 60 μ l. DMSO content in incubation: 0.5%. Termination of incubations: 2-fold volume of 75% acetonitrile. Control: verapamil disappearance rate.

[0093] Sample preparation for hepatocyte samples: Samples are centrifuged for 20 min at 2272 x g at room temperature and pipetted to a UPLC-plate for analysis.

[0094] Data are shown in Figure 1 and the table below. In Figure 1, the dashed line is without cells and the solid line is with cells.

Table 7.

Compound	Incubation	0 min, %	60 min, %	120 min, %
Compound from Example 1 (A1)	Human	100	10	3
	Buffer	100	88	80

Example 5 – In vivo pharmacokinetics

[0095] Group A male Sprague-Dawley (SD) rats are dosed (by PO) with test compound at 0.5 mg/kg and 5 mg/kg (N=3 animals/dose level). Blood samples are obtained at 5, 10, and 30 minutes, and 1, 2, 4, 8, and 24 hours after dosing. Following blood collection at 24 hours, brain perfusion is performed on the animals before harvesting brain tissues.

[0096] Group B male Sprague-Dawley (SD) rats are dosed (by PO) with test compound at 0.5 mg/kg and 5 mg/kg (N=9 animals/dose level). At designated timepoints (1, 4, and 8 hours), three animals from each dose group undergo blood draw followed by brain perfusion before samples are collected.

[0097] Test compound is the deuterated compound of Example 1 (A1).

[0098] Rats are surgically cannulated with femoral artery catheter for blood collection. Approximate weight of rats is 250-350 g. Water is provided ad libitum. Fasting overnight prior to oral dose. Food available 4 h post dose.

[0099] Dose formulations are 0.5% aqueous methylcellulose (4000 cps) with 0.1% TweenTM80 for PO administration. Once prepared, the suspension is vortexed/homogenized and continuously stirred until administration. Dose concentration: 0.1 mg/mL for 0.5 mg/kg dose and 1 mg/mL for 5 mg/kg dose. Route of administration: oral gavage. Dose volume: 5 mL/kg. Serial bleed: 200 µL per time point. Terminal bleed: 500 µL.

[00100] Blood samples are obtained via an automated sampling system in tubes containing potassium EDTA anticoagulant up to 24 h post dose. Plasma is obtained by centrifugation and snap frozen on dry ice within 30 minutes after collection. Aliquots of each dose formulation are taken, diluted appropriately, and analyzed at the same time with plasma samples by LC-MS/MS.

[00101] Plasma (harvested from blood samples) and brain tissues (homogenized and processed) are analyzed by LC/MS/MS. Plasma is harvested from blood via centrifugation within 30 minutes of sample collection. Brain tissue is collected after animals undergo perfusion to remove residual cardiovascular blood.

[00102] Dose solutions, plasma (harvested from blood), and brain tissues (homogenized and processed) are stored at -20 °C until analysis.

[00103] Plasma samples are thawed at room temperature before adding an organic solvent containing an internal standard to precipitate proteins.

[00104] Brain samples are thawed and homogenized in water (3-4 volumes) and aliquots of homogenates analyzed by LC/MS/MS.

[00105] Results are shown in Figures 2 and 3.

[00106] The extended brain enrichment of the compound of Example 1 (A1) in rats following single PO doses of 0.5 mg/kg and 5 mg/kg compared to plasma levels is shown in Figure 2 and Figure 3, respectively. In each figure, average brain concentration (ng/ml) is shown as the dashed line and average plasma concentration (ng/ml) is shown as the solid line.

[00107] The plasma half-life of the compound of Example 1 (A1) at 0.5 mg/kg is about 2 hours. While plasma concentrations reduce, maximum brain concentration is reached at about 4 hours post dose.

Example 6 – Ex Vivo Radioligand Binding in Membrane Preparations to Determine Time-Course of Receptor Occupancy at Central D₂ Receptors

[00108] This study is to determine receptor occupancy at central D₂ receptors following oral administration of the deuterated compound of Example 1 (A1) at various time points (1, 2,

4, 8, and 24 hours) and the positive comparator, olanzapine (10 mg/kg, po), using [³H]raclopride and rat striatal membranes. Liquid scintillation counting is used to quantify radioactivity.

Animals

[00109] Thirty-five male Sprague-Dawley rats. Standard pelleted diet and filtered water is available ad libitum.

Drug Treatment

[00110] On day of test, animals are dosed orally with either vehicle, a single dose (2.5 mg/kg) of the deuterated compound of Example 1 (A1), olanzapine (10 mg/kg, po), or N-[(2S,3S)-1-benzyl-2-methylpyrrolidin-3-yl]-5-chloro-2-methoxy-4-(methylamino)benzamide (cis (S,S) nemonapride) (2.5 mg/kg). Rats are sacrificed at 1 (N=5 rats), 2 (N=5 rats), 4 (N=5 rats), 8 (N=5 rats), and 24 (N=5 rats) hours after drug administration or 1 hour after vehicle and olanzapine administration (N=5 rats for vehicle and N=5 rats for olanzapine). Vehicle is 0.5% methylcellulose.

Pharmacokinetics

[00111] A post-mortem blood sample (approx. 5 ml) is taken by cardiac puncture and placed into K/EDTA tubes. The post-mortem blood samples are gently inverted, centrifuged (1900 g for 5 minutes at 4°C), and 1 ml of plasma from taken for PK determination. All plasma samples are frozen and stored at -80°C.

[00112] Whole brains are removed, rinsed with saline, and blot dried. The left striatum and right striatum is dissected out and weighed before being frozen on dry ice. The striata from each hemisphere are frozen separately. The tissue is wrapped in aluminum foil, placed in bags, and stored at -20°C until the day of the assay.

[³H]Raclopride Binding

Homogenate Preparation

[00113] The striata is homogenised individually in ice-cold 50 mM Tris, pH 7.4, 120 mM NaCl, 5 mM KCl, 2 mM CaCl₂, 1 mM MgCl₂, and 10 μM pargyline using a tight-fitting homogeniser equivalent to 6.25 mg wet weight of tissue/ml and used immediately in the binding assay.

Assay

[00114] Striatal homogenates (400 μl, equivalent to 2.5 mg wet weight tissue/tube) are incubated with 50 μl of 1.6 nM [³H]raclopride and either 50 μl assay buffer (total binding) or 50

µl of 1 µM (-)-sulpiride (to define non-specific binding) for 30 minutes at 23°C. The assay buffer consists of 50 mM Tris, pH 7.4, 120 mM NaCl, 5 mM KCl, 2 mM CaCl₂, 1 mM MgCl₂, and 10 µM pargyline. The wash buffer consists of 50 mM Tris, pH 7.4. There are two tubes for the determination of total binding and two tubes for the determination of non-specific binding.

[00115] Membrane bound radioactivity is recovered by filtration under vacuum through filters, presoaked in 0.5% polyethylenimine (PEI) using a cell harvester. Filters are rapidly washed with ice-cold buffer and radioactivity determined by liquid scintillation counting.

Data Analysis

[00116] A value for specific binding (dpm) is generated by the subtraction of mean non-specific binding (dpm) from mean total binding (dpm) for each animal.

[00117] Results are shown in Figures 4, 6, 8, and 9. Figure 4 shows D2 receptor occupancy of the compound of Example 1 (A1) when administered orally at a dose of 2.5 mg/kg to rats. Compared to Figure 6, Figure 4 excludes one data point at the 1 hour time point that is later determined should be included and which is included in the Figure 6 graph.

[00118] Results in Figure 4 are expressed as mean receptor occupancy as a percentage of control taken as 0% (n = 4-5). Data is square root transformed and analyzed by one-way ANOVA with treatment as a factor. Comparisons to vehicle are by Williams' test for the deuterated compound of Example 1 (A1) and by multiple t test for olanzapine. ***p<0.001.

[00119] Figure 6 shows the deuterated compound of Example 1 (A1) has higher receptor occupancy levels at 4h, 8h, and 24h compared to N-[(2S,3S)-1-benzyl-2-methylpyrrolidin-3-yl]-5-chloro-2-methoxy-4-(methylamino)benzamide (cis (S,S) nemonapride).

[00120] Plasma pharmacokinetics between N-[(2S,3S)-1-benzyl-2-methylpyrrolidin-3-yl]-5-chloro-2-methoxy-4-(methylamino)benzamide (cis (S,S) nemonapride) and the deuterated compound of Example 1 (A1) are shown in Figure 8. In Figure 8, average data for cis (S,S) nemonapride data is shown as the solid line and average data for the deuterated compound of Example 1 (A1) is shown as the dashed line (single oral administration of 2.5 mg/kg of each compound).

[00121] The brain enrichment and retention of the compound of Example 1 (A1) in rats following single oral administration of 2.5 mg/kg compared to plasma levels is seen by comparing Figure 8 and Figure 9.

[00122] The deuterated compound of Example 1 (A1) has enriched and retained brain levels compared to N-[(2S,3S)-1-benzyl-2-methylpyrrolidin-3-yl]-5-chloro-2-methoxy-4-(methylamino)benzamide (cis (S,S) nemonapride) (see Figure 9) (single oral administration of 2.5 mg/kg of each compound).

[00123] In addition, as discussed above, Figure 6 shows the deuterated compound of Example 1 (A1) has higher receptor occupancy levels at 4h, 8h, and 24h compared to N-[(2S,3S)-1-benzyl-2-methylpyrrolidin-3-yl]-5-chloro-2-methoxy-4-(methylamino)benzamide (cis (S,S) nemonapride).

Example 7 – Touchscreen-Based Rat Probabilistic Reward Task

[00124] The Probabilistic Reward Task (PRT) uses visual discrimination methodology to quantify reward responsiveness to both identify deficits and characterize drug-induced improvements. Groups of rats are trained on the touchscreen-based PRT and exposed to asymmetrical probabilistic contingencies to generate response biases to the richly rewarded stimulus (Pizzagalli, D. et al., *Biological Psychiatry*, 2005, 57, 319-327; Kangas, B. et al., *Translational Psychiatry*, 2020, 10(1):285; Wooldridge, L. et al., *International Journal of Neuropsychopharmacology*, 2021, 24, 409-418). Next, subjects are tested with vehicle and three doses of the deuterated compound of Example 1 (A1).

Methods

Subjects

[00125] Male Sprague Dawley rats are used in the present study.

Apparatus

[00126] Details and schematics of the rodent touch-sensitive experimental chamber can be found in Kangas, B. et al., *Behavioural Pharmacology*, 2017, 28, 623-629. Briefly, a custom-built Plexiglas chamber (25x30x35 cm) is situated in a sound- and light-attenuating enclosure (40x60x45 cm). A 17" touch-sensitive screen (1739L, ELO TouchSystems, Menlo Park, CA) comprises the inside right-hand wall of the enclosure. An infusion pump (PHM-100-5, Med Associates, St. Albans, VT) outside the enclosure is used to deliver sweetened condensed milk solution into the shallow reservoir of a custom-designed aluminum receptacle. The receptacle is mounted 3 cm above the floor bars and centered on the left-hand inside wall. Both touchscreen and fluid reservoir are easily accessible to the subject. A speaker bar (NQ576AT, Hewlett-Packard, Palo Alto, CA) mounted above the touchscreen is used to emit audible feedback. All

experimental events and data collection are programmed in E-Prime Professional 2.0 (Psychology Software Tools, Inc., Sharpsburg, PA).

Procedure

Initial training

[00127] Modified response-shaping techniques are used to train rats to engage with the touchscreen (Kangas, B. et al., Journal of Neuroscience Methods, 2012, 209, 331-336). A 5x5 cm blue square on a black background is presented in different sections of the touchscreen (left, right or center), with the proviso that its lower edge always is 10 cm above the floor bars. This requires the rat to rear on its hind legs to reach the screen and make a touchscreen response with its paw. Each response is reinforced with 0.1 mL of 30% sweetened condensed milk and the delivery is paired with an 880 ms yellow screen flash and 440 Hz tone and followed by a 5-sec intertrial interval (ITI) blackout period. After responses are reliably observed with latencies <5 sec following stimulus presentation, line-length discrimination training commenced.

Line-length discrimination training

[00128] Discrete trials begin with concurrent presentation of a white line presented 5 cm above left and right response boxes. The width of the line is always 7 cm, but the length of the line is either 30 cm or 15 cm and varies in a quasi-random fashion across 100-trial sessions (50 trials of each length). Subjects learn to respond to the left or right response box depending on the length of the white line (i.e., long line = respond left, short line = respond right, or vice versa). Response box designation is counter-balanced across subjects. A correct response is reinforced as described above and is followed by a 5 sec ITI, whereas an incorrect response immediately results in a 5 sec ITI. A correction procedure (Kangas, B. et al., Journal of the Experimental Analysis of Behavior, 2008, 90, 103-112) is implemented during initial discrimination training – each incorrect trial is repeated until a correct response is made – and is discontinued after session-wide trial repeats are <5 in each trial type. Discrimination sessions continue without correction until accuracies for both line lengths are >75% correct for 3 consecutive sessions.

Probabilistic Reward Task

[00129] Following line-length discrimination training, probabilistic reinforcement schedules are introduced. Based on the human task protocol, a 3:1 rich/lean probabilistic schedule is arranged such that 60% of correct responses to one of the line lengths (e.g., long line = rich alternative) and 20% of correct responses to the other line length (e.g., short line = lean

alternative) are rewarded. Rich/lean line assignment is counterbalanced across subjects and 50 trials of each trial type are presented in a quasi-random sequence. These probabilistic contingencies are assessed across 5 consecutive sessions prior to initiation of drug testing.

PRT Drug Tests

[00130] Following the establishment of probabilistic contingencies, an acute drug testing protocol is arranged that includes intermittent maintenance sessions in which correct responses on all trials are reinforced, control sessions in which 3:1 (60%:20%) rich/lean probabilistic contingencies are arranged and, no more than once per week, a drug testing session in which vehicle or a dose of the deuterated compound of Example 1 (A1) (0.5, 1, or 2.5 mg/kg) is tested by administering it orally, 4-5 hr prior to a 3:1 (60%:20%) probabilistic session. Doses of the deuterated compound of Example 1 (A1) are tested in a mixed order across subjects using a Latin Square design. Vehicle and all doses of the deuterated compound of Example 1 (A1) are tested in all subjects.

Data Analysis

[00131] The implementation of probabilistic contingencies yields two primary dependent measures: response bias and task discriminability. These can be quantified by examining the number of Correct and Incorrect responses in rich and lean trial types using, respectively, $\log b$ and $\log d$ equations derived from signal detection theory (Kangas, B. et al., Journal of the Experimental Analysis of Behavior, 2008, 90, 103-112; Luc O. et al., Perspectives on Behavior Science, 2021, 44 (4), 517-540; McCarthy, D., Signal Detection: Mechanisms, Models, and Applications (eds Nevin, J. et al.), Behavioral Detection Theory: Some Implications for Applied Human Research, 1991 (Erlbaum, New Jersey)).

$$\log b = 0.5 * \log \left(\frac{(Rich_{Correct} + 0.5) * (Lean_{Incorrect} + 0.5)}{(Rich_{Incorrect} + 0.5) * (Lean_{Correct} + 0.5)} \right)$$

$$\log d = 0.5 * \log \left(\frac{(Rich_{Correct} + 0.5) * (Lean_{Correct} + 0.5)}{(Rich_{Incorrect} + 0.5) * (Lean_{Incorrect} + 0.5)} \right)$$

[00132] High bias values are produced by high numbers of correct responses during rich trials and incorrect responses during lean trials, which increase the $\log b$ numerator. High discriminability values are produced by high numbers of correct responses during both rich and lean trials, which increase the $\log d$ numerator. (0.5 is added to all parameters to avoid instances where no errors are made on a given trial type, which would make log transformation

impossible.) All data ($\log b$, $\log d$, accuracy, reaction time) are subject to repeated measures analysis of variance (ANOVA).

Drugs

[00133] The deuterated compound of Example 1 (A1) is dissolved in a 0.5% methylcellulose solution. Drug doses are administered orally 4-5 hr prior to the experimental session.

Results and Discussion

[00134] As shown in Figure 5A, there is response bias for rich stimulus specifically at doses of 0.5 and 1 mg/kg of the deuterated compound of Example 1 (A1).

[00135] As shown Figure 5A, administration of 0.5 and 1 mg/kg of the deuterated compound of Example 1 (A1) increases the group mean $\log b$ relative to sessions following treatment with vehicle. Administration of 2.5 mg/kg also produces group average increases, but to a lesser extent.

[00136] As shown in Figure 5B, discriminability ($\log d$) values are similar to vehicle following the doses tested. Within the context of the PRT, this comparator supports the fact that the increases in $\log b$ detailed above are not simply due to drug-induced decrements in task discriminability or overall accuracy.

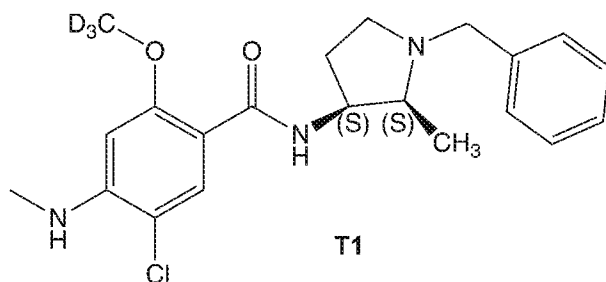
[00137] The data shows that doses of the deuterated compound of Example 1 (A1) targeting low but not high D_2 RO significantly increase reward responsiveness. This is revealed by substantive increases in response bias ($\log b$) without reductions in task discriminability ($\log d$). General linear model tests of within-subjects contrast (quadratic term) yield statistical significance across the dose-response function for the deuterated compound of Example 1 (A1) ($F[1,7]=5.69$; $p=0.048$). Paired t-test analyses of $\log b$ values confirm the statistical significance of each dose-related effect. Paired t-test analyses show that low doses are significantly different than vehicle (0.5 mg/kg: $n=8$, paired t-test $p=0.006$; Cohen's $d=1.21$ and 1 mg/kg: $n=8$, paired t-test $p=0.04$; Cohen's $d=0.75$), but not 2.5 mg/kg ($n=8$, paired t-test $p=0.1$; Cohen's $d=0.5$). $\log d$ values are not reduced at any doses tested for the deuterated compound of Example 1 (A1).

[00138] No catalepsy is observed at tested doses.

[00139] Data shows that the deuterated compound of Example 1 (A1) may reduce anhedonia at low doses without inducing extrapyramidal side effects.

[00140] Data suggests that D2/3 receptor occupancy of about 40-60% provides antianhedonic effects, D2/3 receptor occupancy of about 65-80% provides antipsychotic effects, and catalepsy emerges above 80% receptor occupancy.

Example 8



[00141] Compound T1 above is synthesized similar to Example 1 with appropriate deuterated fragment. In vivo pharmacokinetics in rats for single oral doses of 0.5 mg/kg and 5 mg/kg of T1 are determined similar to Example 5.

[00142] Group A male Sprague-Dawley (SD) rats are dosed (by PO) with test compound at 0.5 mg/kg and 5 mg/kg (N=3 animals/dose level). Blood samples are obtained at 5, 10, and 30 minutes, and 1, 2, 4, 8, and 24 hours after dosing. Following blood collection at 24 hours, brain perfusion is performed on the animals before harvesting brain tissues.

[00143] Group B male Sprague-Dawley (SD) rats are dosed (by PO) with test compound at 0.5 mg/kg and 5 mg/kg (N=9 animals/dose level). At designated timepoints (1, 4, and 8 hours), three animals from each dose group undergo blood draw followed by brain perfusion before samples are collected.

[00144] Test compound is T1 above.

[00145] Dose formulation is 0.5% aqueous methylcellulose (4000 cps) with 0.1% TweenTM80 for PO administration. Dose concentration: 0.1 mg/mL for 0.5 mg/kg dose and 1 mg/mL for 5 mg/kg dose. Dose volume: 5 mL/kg.

[00146] Pharmacokinetic data for the deuterated compound of Example 1 (A1) and T1 are in Tables 8 and 9 below and shown in Figures 10-13. Data for the deuterated compound of Example 1 (A1) is from Example 5.

Table 8. Plasma

Dose (mg/kg)	0.5		5	
Compound	T1	A1	T1	A1
C _{max} (ng/mL)	0.21	0.11	2.11	6.13
T _{max} (h)	0.69	0.56	0.83	0.28

AUC (ng•h/mL)	0.58	0.31	6.62	9.41
---------------	------	------	------	------

Table 9. Brain

Dose (mg/kg)	0.5		5	
Compound	T1	A1	T1	A1
C _{max} (ng/mL)	0.77	1.06	7.99	13.47
T _{max} (h)	4	4	1	4
AUC (ng•h/mL)	10.66	13.69	55.86	107.10
Brain/Plasma Ratio	18.50	44.58	8.44	11.38

[00147] The brain AUC of the deuterated compound of Example 1 (A1) is 2-fold higher than T1 at 5 mg/kg. The deuterated compound of Example 1 (A1) has better brain/plasma ratios than T1 at both dose levels. Figure 11 shows that at 8 hours, brain levels of the compound of Example 1 (A1) are similar to the highest levels of T1 measured, which occur at shorter time.

Example 9 – Conditioned Avoidance Response

[00148] Adult male Sprague Dawley rats are used. Risperidone (0.5 mg/kg; Sigma Aldrich) is dissolved in 10% DMSO in water and injected i.p. at a dose volume of 1 mg/kg 30 minutes prior to test. The deuterated compound of Example 1 (A1) (0.5, 2.5, and 5 mg/kg) is formulated in 0.5% methyl cellulose in water and administered orally at a dose volume of 1 mg/kg 4 hours prior to test.

[00149] The Conditioned Avoidance Response (CAR) Test is an animal model screening for antipsychotic drugs.

[00150] Dunnett's post hoc analysis reveals that risperidone (0.5 mg/kg) and the deuterated compound of Example 1 (A1) (2.5 and 5 mg/kg) significantly decrease percent avoidance as well as the number of avoidance responses compared to vehicle.

[00151] Dunnett's post hoc analysis reveals that risperidone (0.5 mg/kg) and the deuterated compound of Example 1 (A1) (5 mg/kg) increase escape failures compared to vehicle.

[00152] Rats treated acutely with the deuterated compound of Example 1 (A1) (2.5 and 5 mg/kg) show decreased avoidance responses and percent avoidance indicating potential antipsychotic activity. The deuterated compound of Example 1 (A1) (5 mg/kg) shows a slight increase in escape failures.

Example 10 – Headshake Response

[00153] Adult male Sprague Dawley rats are used. The deuterated compound of Example 1 (A1) (1, 5, and 10 mg/kg) is formulated in 0.5% methylcellulose solution and administered orally (PO) at a dose volume of 1 ml/kg 4 hours prior to test. DOI (3 mg/kg) is dissolved in saline and administered IP at a dose volume of 1 ml/kg (10 minutes prior to test).

[00154] Animals are administered vehicle, DOI, or test compound and returned to their holding cage for the appropriate pretreatment time (10 minutes for DOI and 4 hours for the deuterated compound of Example 1 (A1)), following which headshakes are recorded for 10 minutes using video cameras. The headshake response is a rapid, rhythmic shaking of the head in a radial motion. Data are analyzed by ANOVA followed by post hoc analysis where appropriate.

[00155] Dunnett's post analysis finds that, compared to vehicle, DOI significantly increases the number of headshakes. None of the doses of the deuterated compound of Example 1 (A1) have any significant effect on this measure.

[00156] Acute oral administration of the deuterated compound of Example 1 (A1) (1, 5, and 10 mg/kg) shows no significant increase in the number of headshakes compared to vehicle. DOI (3 mg/kg) significantly increases headshake responses in the rats following acute i.p. injection.

Example 11 – DOI-Induced Headshake Response

[00157] Adult male Sprague Dawley rats are used. The deuterated compound of Example 1 (A1) (1, 5, and 10 mg/kg) is formulated in 0.5% methylcellulose solution and administered orally (PO) at a dose volume of 1 ml/kg 4 hours prior to test. DOI (3 mg/kg) is dissolved in saline and administered IP at a dose volume of 1 ml/kg (10 minutes prior to test). Ketanserin (1 mg/kg) is dissolved in saline and injected IP 30 minutes prior to DOI at a dose volume of 1 ml/kg.

[00158] Animals are administered vehicle, ketanserin, or test compound and returned to their holding cage for the appropriate pretreatment time (4 hours for the deuterated compound of Example 1 (A1) and 30 minutes for ketanserin). Rats are then injected with DOI and headshakes are recorded 10 minutes after DOI injection for 10 minutes using video cameras. The headshake response is a rapid, rhythmic shaking of the head in a radial motion. Data is analyzed by ANOVA followed by post hoc analysis where appropriate.

[00159] Dunnett's post analysis finds that, compared to vehicle, DOI significantly increases the number of headshakes. Ketanserin and the deuterated compound of Example 1 (A1)

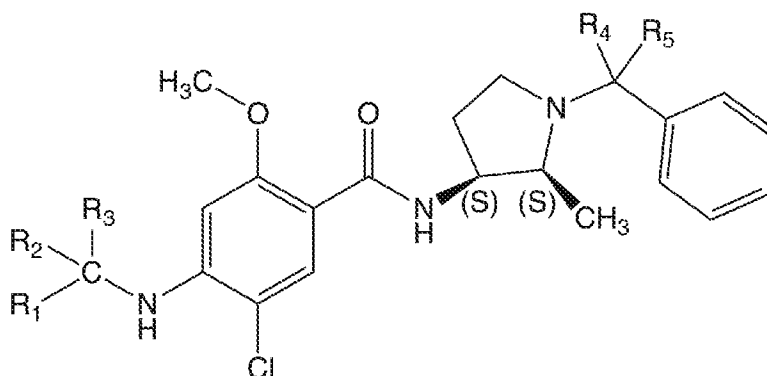
(5 and 10 mg/kg) decrease DOI-induced headshake responses. The deuterated compound of Example 1 (A1) at 1 mg/kg shows a non-significant trend to decreasing DOI-induced headshake responses ($p=0.051$, an effect is considered significant if $p<0.05$).

[00160] Acute oral administration of the deuterated compound of Example 1 (A1) (5 and 10 mg/kg) decreases DOI-induced headshakes compared to vehicle. The deuterated compound of Example 1 (A1) shows a trend to decreasing the DOI-induced headshake response. Ketanserin (1 mg/kg) also decreases the number of headshake responses induced by DOI following acute i.p. injection.

CLAIMS

What is claimed:

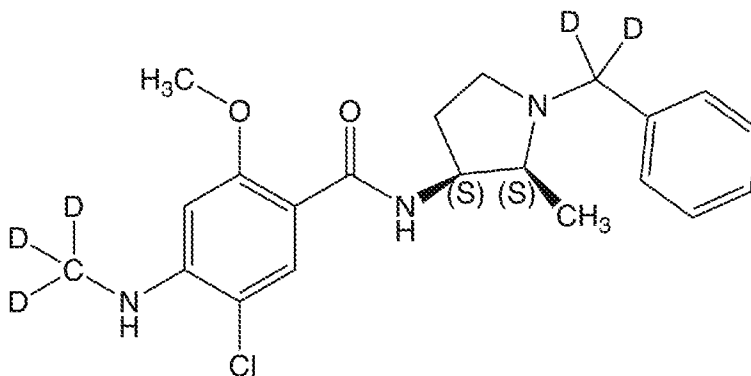
1. A compound of Formula I:



Formula I,

wherein:

- R_1 , R_2 , R_3 , R_4 , and R_5 are independently selected from H and D; and at least one of R_1 , R_2 , and R_3 is D; in free or salt form.
2. The compound according to claim 1, wherein the compound is in free form.
3. The compound according to claim 1 or 2, wherein R_1 , R_2 , and R_3 are D.
4. The compound according to any one of claims 1-3, wherein each of R_1 , R_2 , R_3 , R_4 , and R_5 are D.
5. The compound according to any one of claims 1-4, wherein the compound is:



in free or salt form.

6. The compound according to any one of claims 1-5, wherein the compound, in free or pharmaceutically acceptable salt form, has greater than 90% incorporation of deuterium at one or more positions designated as deuterium.
7. A pharmaceutical composition, wherein the pharmaceutical composition comprises a compound according to any one of claims 1-6, in free or pharmaceutically acceptable salt form, and a pharmaceutically acceptable carrier.
8. A method for treatment of a brain disorder in a patient in need thereof, wherein the method comprises administering to the patient a compound according to any one of claims 1-6, in free or pharmaceutically acceptable salt form, or a pharmaceutical composition according to claim 7.
9. The method according to claim 8, wherein the disorder is an affective disorder or an anxiety disorder.
10. The method according to claim 8, wherein the disorder is depression, an anxiety disorder, psychosis, schizophrenia, schizoaffective disorder, post-traumatic stress disorder (PTSD), attention-deficit/hyperactivity disorder (ADHD), Tourette syndrome, anorexia nervosa, bulimia nervosa, binge-eating disorder, body dysmorphic disorder, obsessive compulsive disorder, addiction, bipolar disorder, or a migraine.
11. The method according to claim 10, wherein the anxiety disorder is panic disorder, social anxiety disorder, a phobia, or generalized anxiety disorder.
12. The method according to claim 8, wherein the disorder is anhedonia, depression associated with anhedonia, suicidal ideation, anxious depression, inflammatory depression, treatment-resistant depression, dysthymia, bipolar depression, psychotic depression, or post-psychotic depression.
13. The method according to claim 8, wherein the disorder is depression associated with anhedonia.
14. The method according to claim 8, wherein the disorder is anhedonia.
15. The method according to claim 8, wherein the disorder is melancholic depression.
16. The method according to claim 8, wherein the disorder is major depressive disorder.

17. The method according to claim 8, wherein the disorder is a substance use disorder.
18. The compound according to any one of claims 1-6, in free or pharmaceutically acceptable salt form, or a pharmaceutical composition according to claim 7, for use in the treatment of a brain disorder.
19. Use of a compound according to any one of claims 1-6 in the manufacture of a medicament for treatment of a brain disorder.
20. The use according to claim 18 or 19, wherein the brain disorder is as recited in any of claims 9-17.

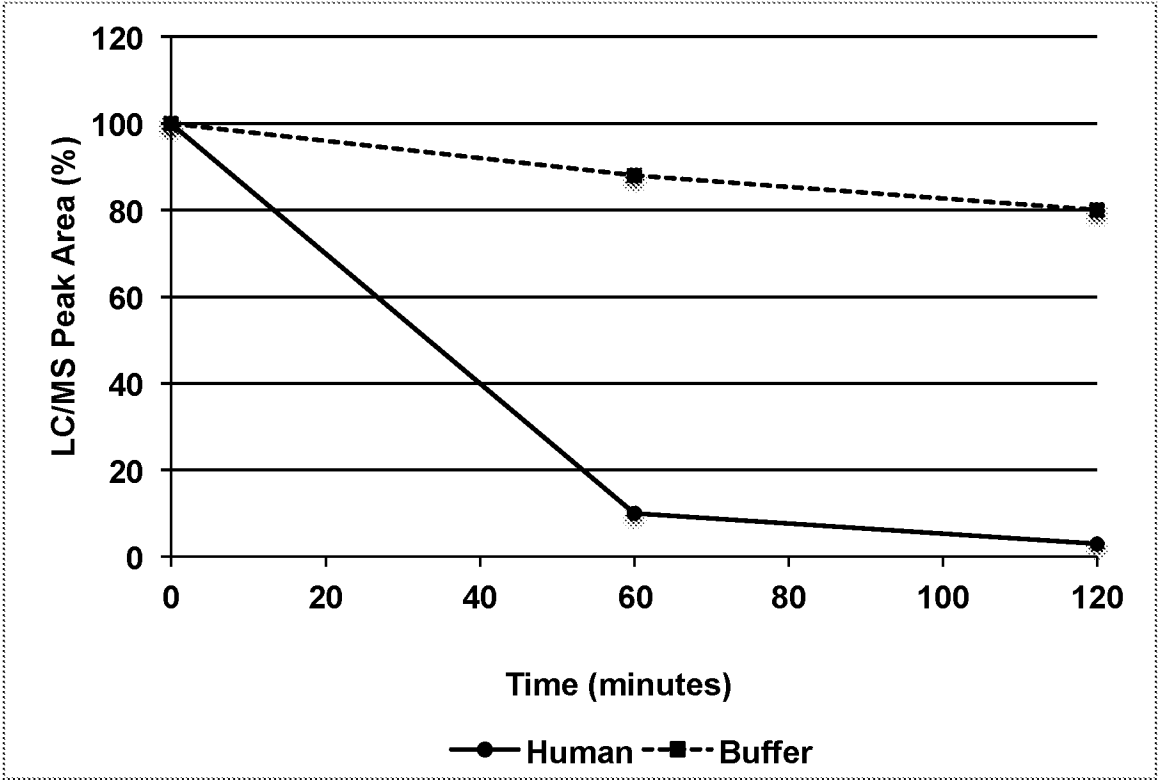


Figure 1

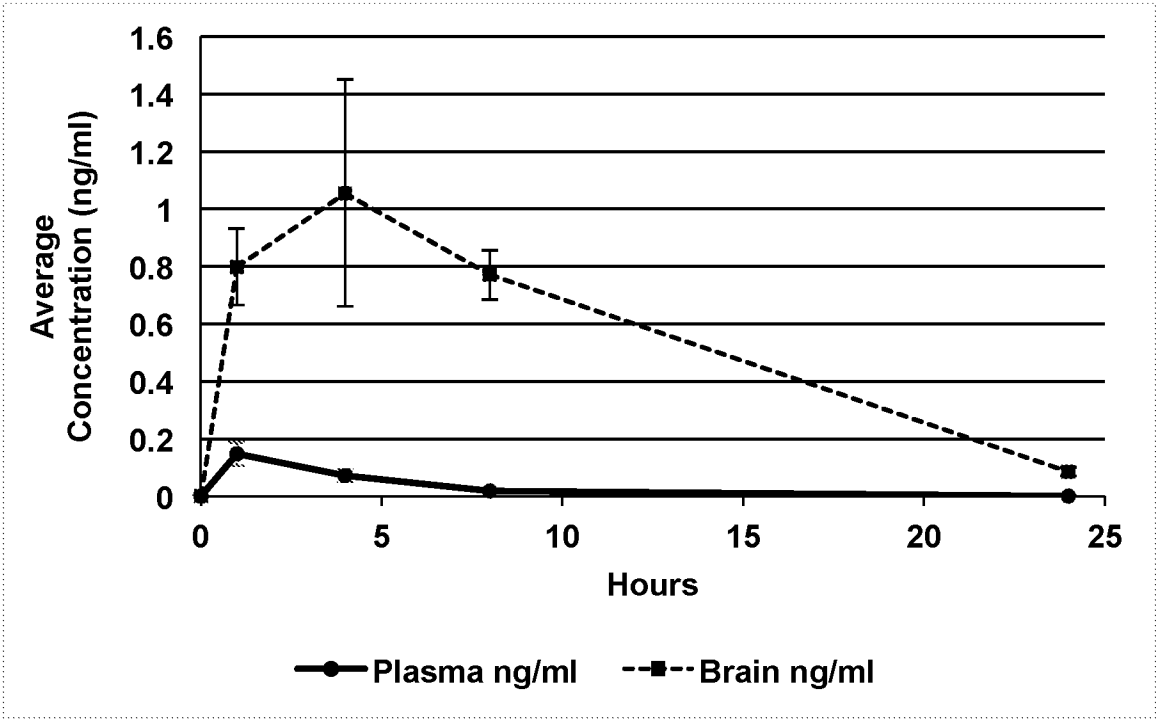


Figure 2

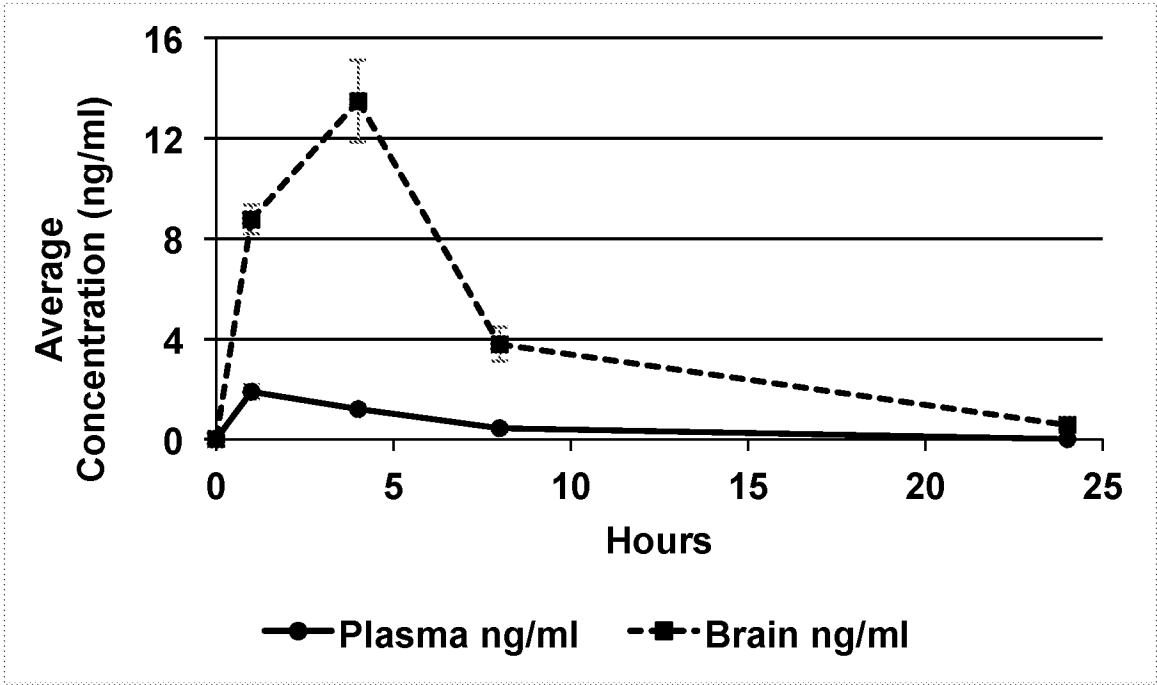


Figure 3

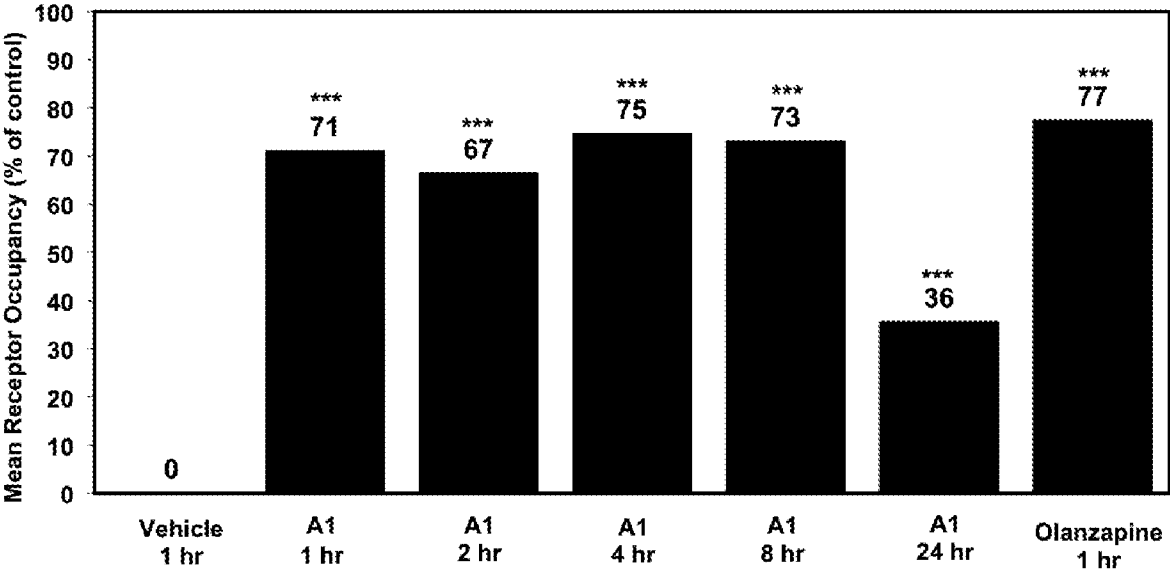


Figure 4

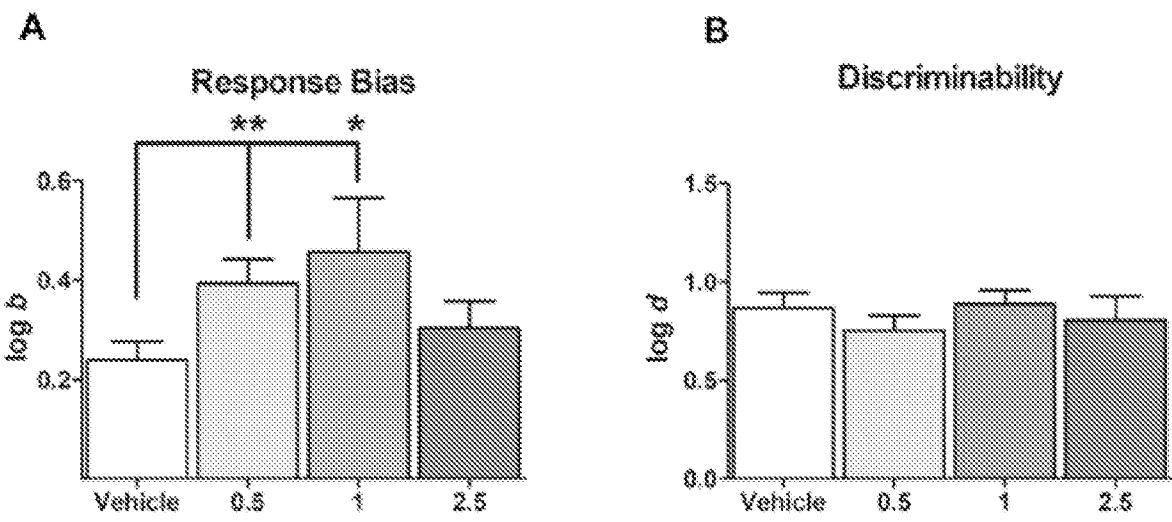


Figure 5

6/13

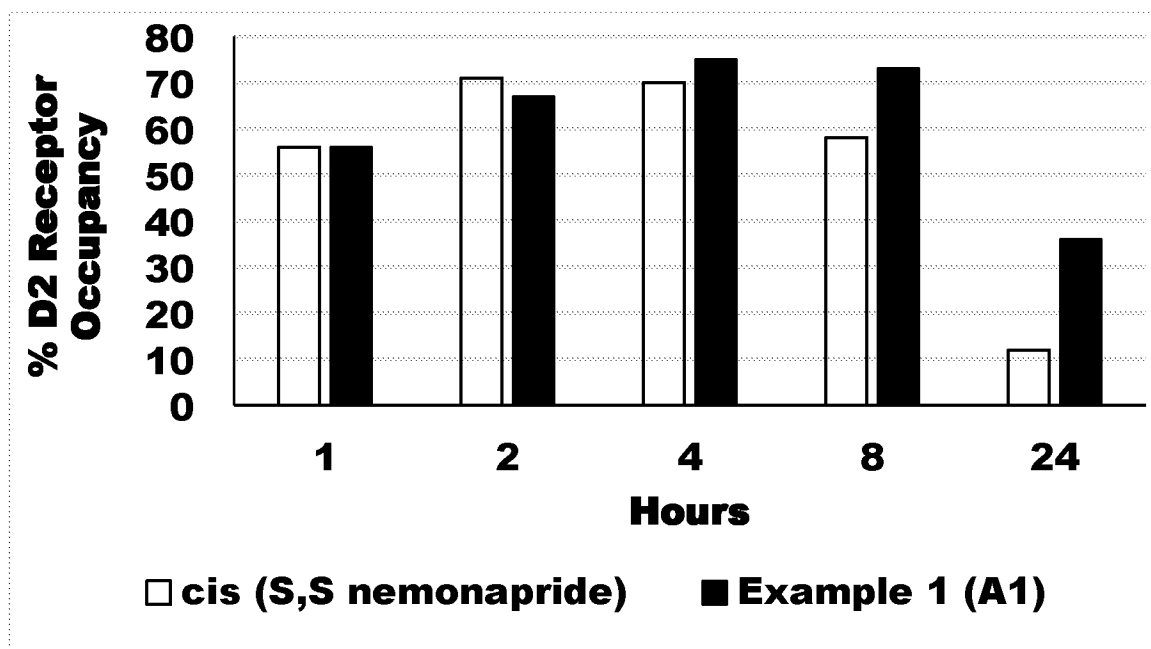


Figure 6

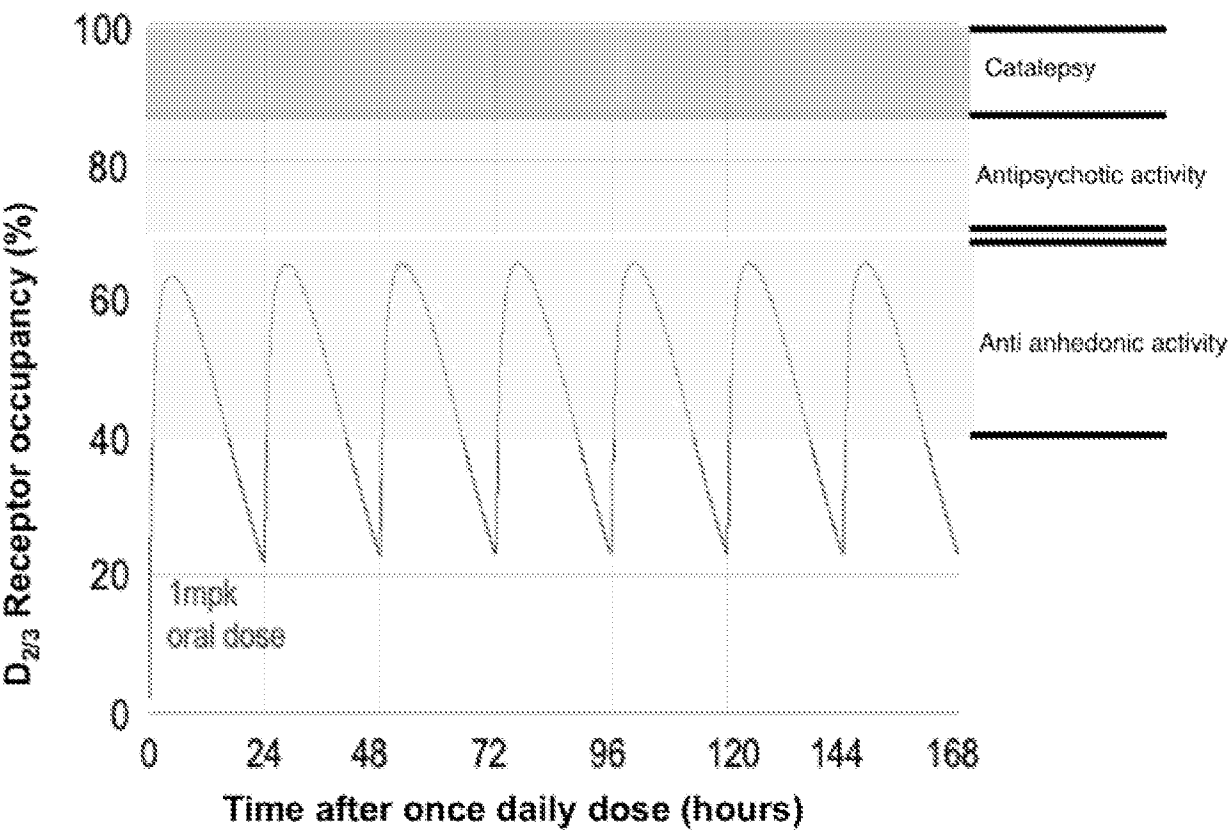


Figure 7

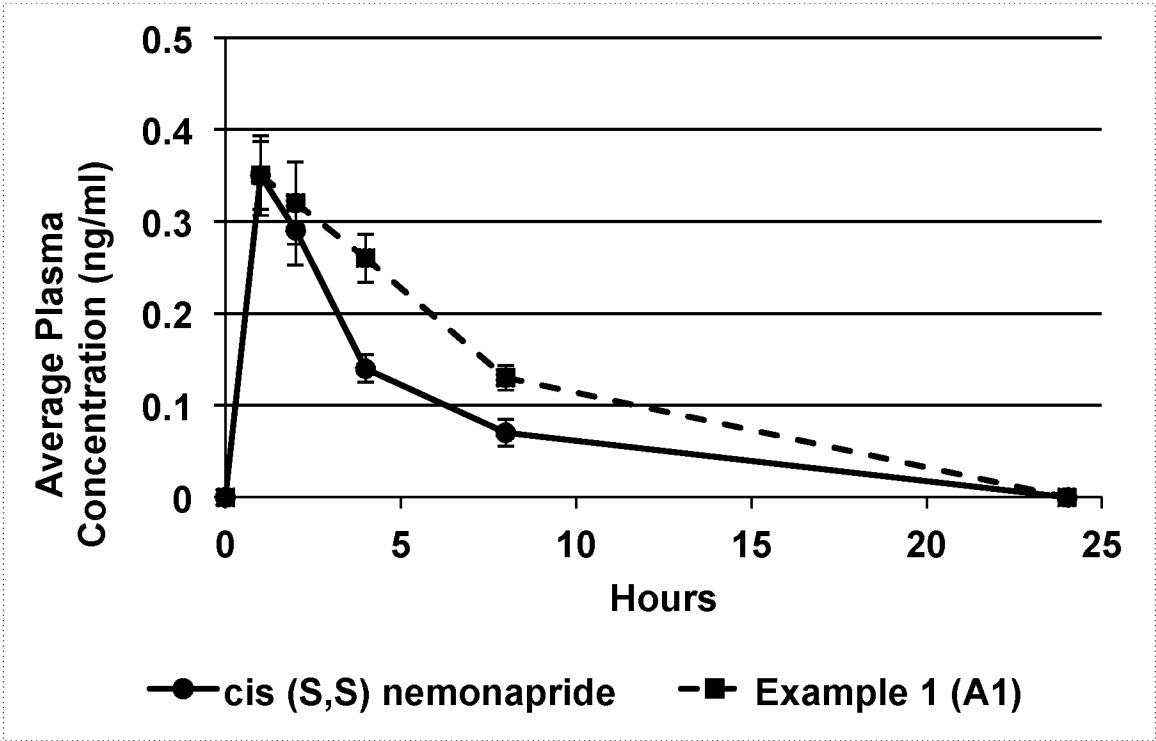


Figure 8

9/13

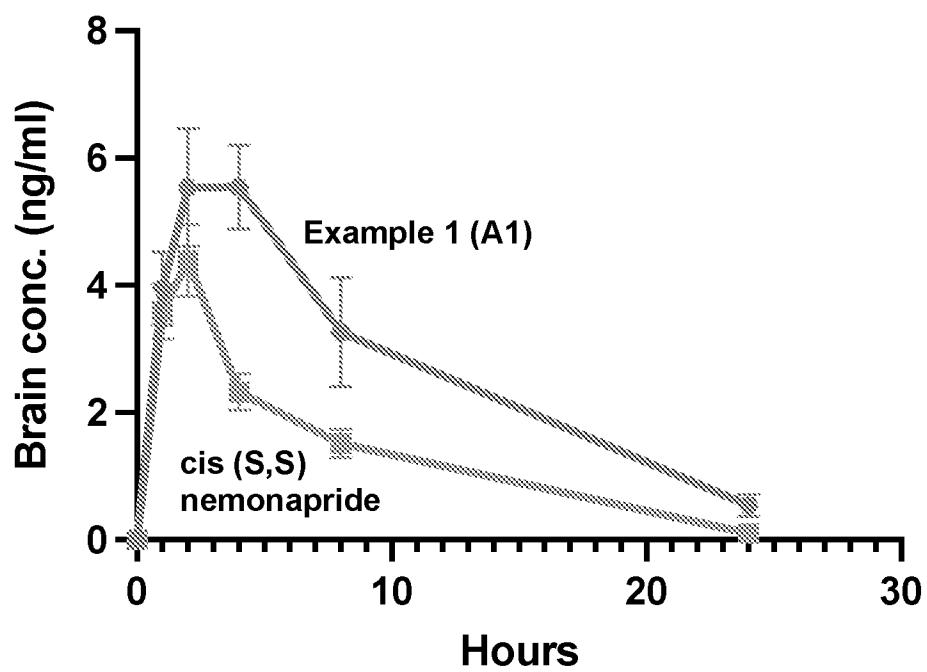


Figure 9

10/13

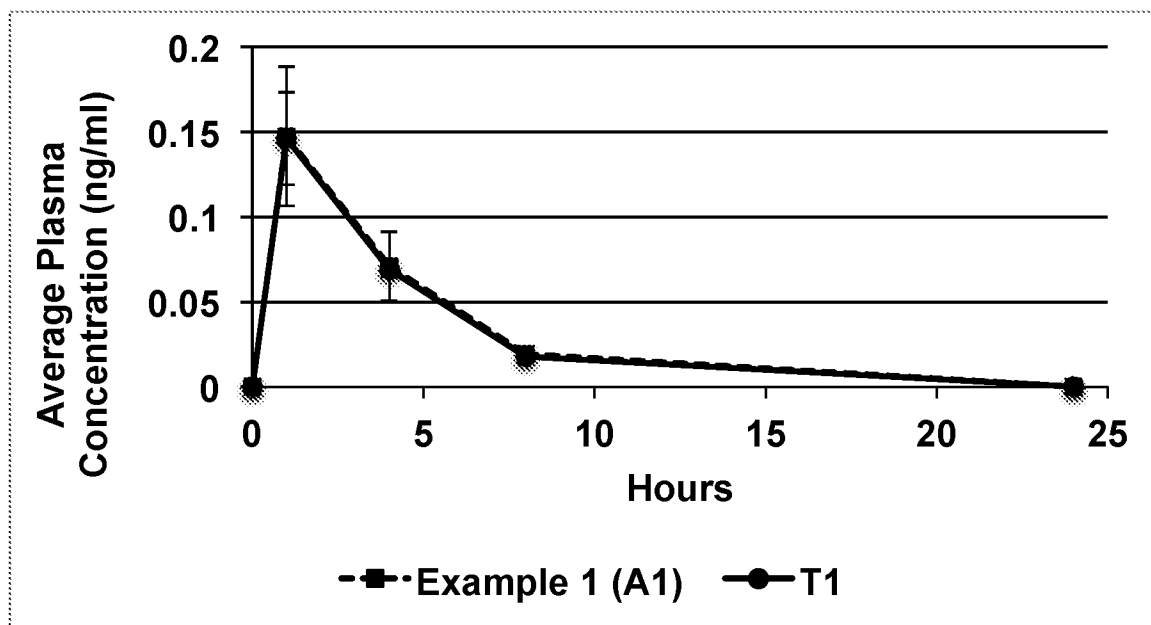


Figure 10

11/13

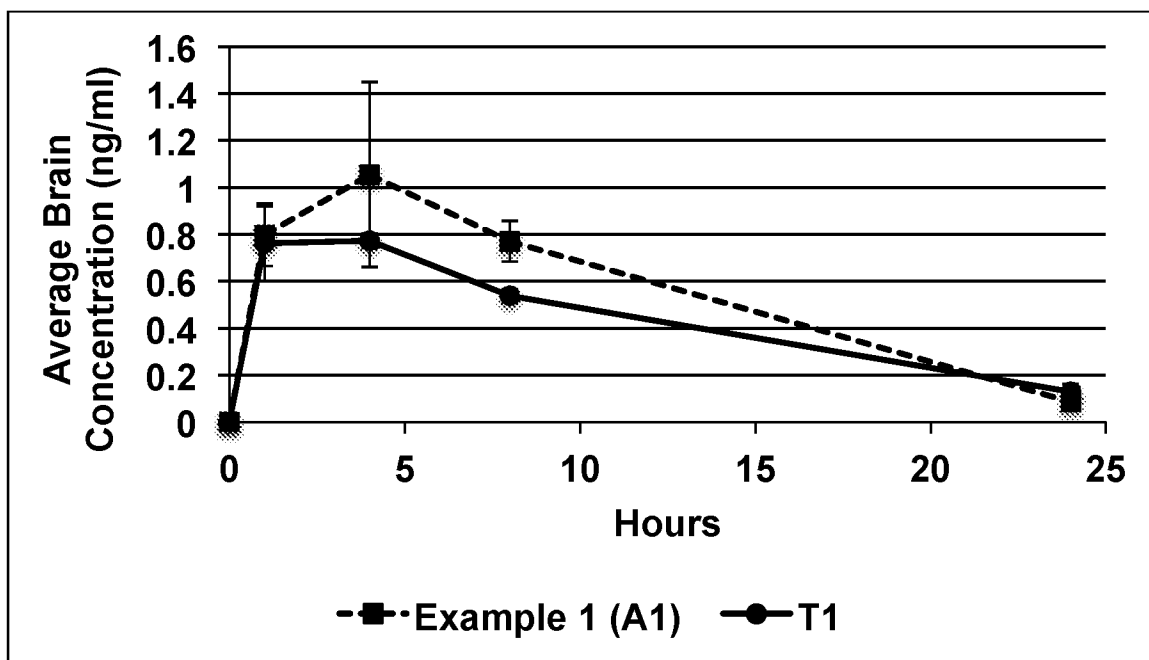


Figure 11

12/13

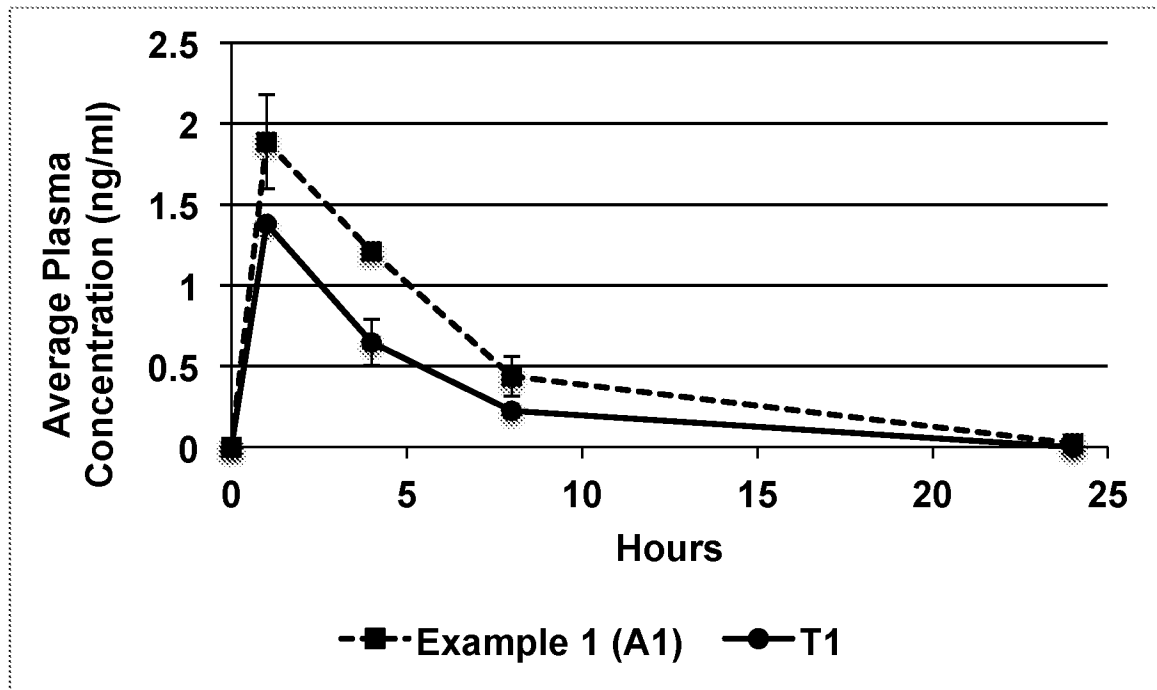


Figure 12

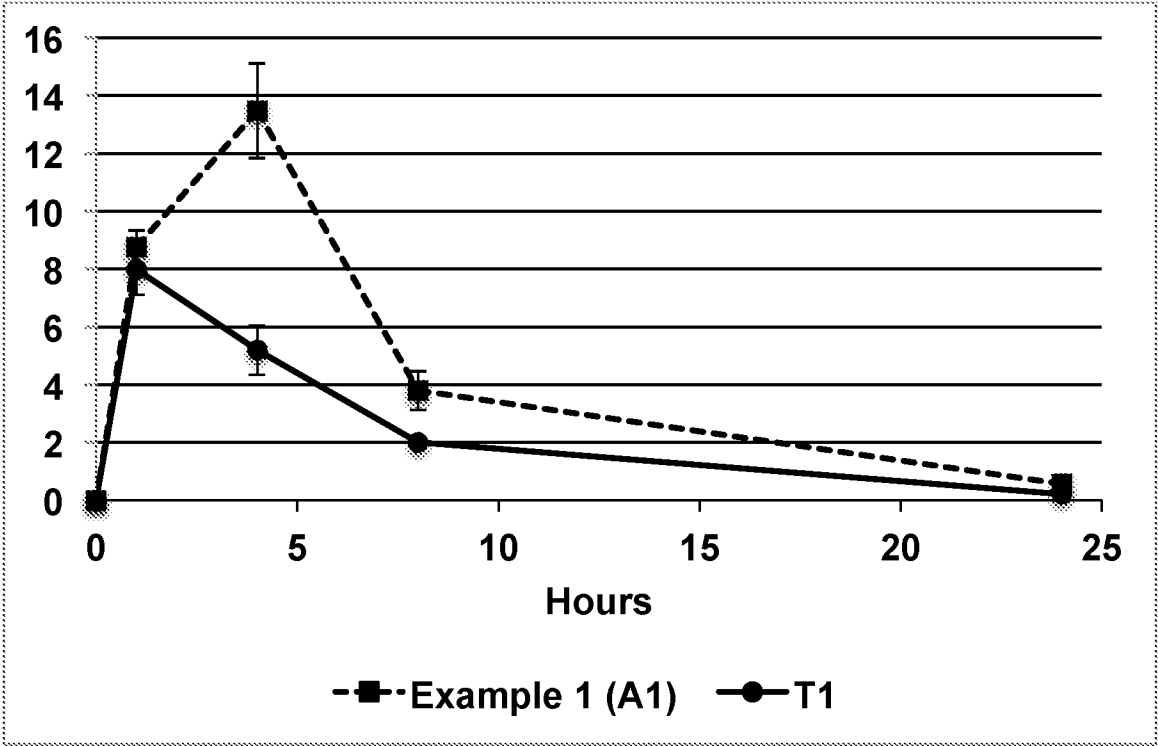


Figure 13

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 23/10055

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/33, A61K 31/166, A61K 31/16 (2023.01)
 ADD. A61K 31/7056 (2023.01)

CPC - INV. A61K 31/33, A61K 31/166, A61K 31/16
 ADD. A61K 31/7056

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"PubChem CID 4452", create date, 25 March 2005, page 2 formula	1-3
A	Tung, "The Development of Deuterium-Containing Drugs", 2014. retrieved from chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.concertpharma.com/wp-content/uploads/2014/12/IPT-0310.pdf	1-3
A	US 4,197,243 A (Murakami et al.) 08 April 1980 (08.04.1980) entire document	1-3

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
 "D" document cited by the applicant in the international application
 "E" earlier application or patent but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
 "&" document member of the same patent family

Date of the actual completion of the international search

03 March 2023

Date of mailing of the international search report

APR 28 2023

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
 P.O. Box 1450, Alexandria, Virginia 22313-1450
 Facsimile No. 571-273-8300

Authorized officer

Karl Rodriguez

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 23/10055

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 4-20
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

Remark on Protest

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