ability to treat symptoms of depression (sometimes noted in schizophrenia patients), improve cognition, and may explain amisulpride's ability to treat negative symptoms of schizophrenia. Interestingly, compared to other antipsychotics, amisulpride is not noted to have any activity at the 5-HT_{2a} receptor.

[0006] Despite the unique properties of amisulpride, the drug has low ability to cross the blood brain barrier (BBB) to interact with the receptors in the brain. In a 2014 study, passive diffusion of amisulpride across a PAMPA membrane (measured as P_e) was the lowest of 30 psychiatric drugs tested. Thus, dosing of amisulpride is high, typically 400 to 800 mg/d (though up to 1,200 mg/day is not uncommon). Such a high dose may cause adverse effects to the treated subjects.

Summary

[0006a] In an aspect, there is provided the use of a therapeutically effective amount of an amisulpride derivative or a pharmaceutical composition thereof, in the manufacture of a medicament for delivering a dopamine and/or serotonin (e.g., 5-HT2a, 5-HT_7) and/or alpha-2 adrenergic (α2) receptor antagonist to the brain of a subject.

[0006b] In another aspect, there is provided the use of a therapeutically effective amount of an amisulpride derivative or pharmaceutical compositions thereof, individually or in combination with other CNS active agents, in the manufacture of a medicament for antagonizing dopamine and/or serotonin (e.g., 5-HT2a, 5-HT_7) and/or α2 receptor in a subject.

[0006c] In another aspect, there is provided the use of a therapeutically effective amount of an amisulpride derivative or pharmaceutical compositions thereof, individually or in combination with other CNS active agents, in the manufacture of a medicament for treating one or more conditions responsive to modulation of dopamine and/or serotonin (e.g., 5-HT2a, 5-HT_7) and/or α2 receptor in a subject.

[0006d] In another aspect, there is provided a pharmaceutical composition, characterized by comprising an amisulpride derivative, and pharmaceutically acceptable carriers.

[0007] Provided herein are uses of amisulpride derivatives and pharmaceutical compositions thereof. In certain embodiments, the amisulpride derivatives disclosed

herein are dopamine and/or serotonin antagonists. In certain examples, the amisulpride derivatives disclosed herein have improved membrane (e.g., BBB) permeability compared to amisulpride. In certain examples, the amisulpride derivatives can act as central nervous system (CNS) dopamine and/or serotoninantagonists. These amisulpride derivatives have structures of Formula IA, Formula IB or Formula IC disclosed herein, including pharmaceutically acceptable salts thereof, stereoisomers thereof (e.g., Formula IA-S, Formula IA-R, Formula IB-S, Formula IB-R, Formula IC-S, and Formula IC-R), or deuterated analogs of structures of Formula IA, Formula IB, Formula IC, Formula IA-S, Formula IA-R, Formula IB-S, Formula IB-R, Formula IC-S, or Formula IC-R.

[0008] Provided herein is a unit dose of an amisulpride derivative disclosed herein, the unit dose comprises a pharmaceutical composition comprising a therapeutically effective amount of the amisulpride derivative, and the therapeutically effective amount being about 10 mg to about 250 mg, about 10 mg to about 225 mg, about 10 mg to about 200 mg, about 10 mg to about 175 mg, about 10 mg to about 150 mg, about 10 mg to about 125 mg, about 10 mg to about 100 mg, about 10 mg to about 75 mg, about 10 mg to about 50 mg, about 10 mg to about 25 mg, about 25 mg to about 250 mg, about 25 mg to about 225 mg, about 25 mg to about 200 mg, about 25 mg to about 175 mg, about 25 mg to about 150 mg, about 25 mg to about 125 mg, about 25 mg to about 100 mg, about 25 mg to about 75 mg, about 25 mg to about 50 mg, about

50 mg to about 250 mg, about 50 mg to about 225 mg, about 50 mg to about 200 mg, about 50 mg to about 175 mg, about 50 mg to about 150 mg, about 50 mg to about 125 mg, about 50 mg to about 100 mg, about 50 mg to about 75 mg, about 75 mg to about 250 mg, about 75 mg to about 225 mg, about 75 mg to about 200 mg, about 75 mg to about 175 mg, about 75 mg to about 150 mg, about 75 mg to about 125 mg, about 75 mg to about 100 mg, about 100 mg to about 250 mg, about 100 mg to about 225 mg, about 100 mg to about 200 mg, about 100 mg to about 175 mg, about 100 mg to about 150 mg, about 100 mg to about 125 mg, about 125 mg to about 250 mg, about 125 mg to about 225 mg, about 125 mg to about 200 mg, about 125 mg to about 175 mg, about 125 mg to about 150 mg, about 150 mg to about 250 mg, about 150 mg to about 225 mg, about 150 mg to about 200 mg, about 150 mg to about 175 mg, about 175 mg to about 250 mg, about 175 mg to about 225 mg, about 175 mg to about 200 mg, about 200 mg to about 250 mg, about 200 mg to about 225 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, or about 250 mg.

[0009] Also provided herein are methods for delivering a dopamine and/or serotonin (e.g., 5-HT2a, 5-HT_7) and/or alpha-2 adrenergic (α2) receptor antagonist to the brain of a subject comprising administering to the subject a therapeutically effective amount of an amisulpride derivative disclosed herein or a pharmaceutical composition thereof; and the dopamine and/or serotonin and/or α2 receptor antagonist level in the brain being higher than administering to the subject amisulpride at a comparable dose. In certain examples, the method comprises administering to the subject one, two, three, or four unit doses of an amisulpride derivative disclosed herein. In certain examples, the method comprises administering to the subject one, two, three, or four unit doses of an amisulpride derivative disclosed herein once a day, once every two days, once every three days, once every four days, once every five days, once every six days, or once a week. In certain examples, the unit dose is 50 mg, 75 mg, or 100 mg. In certain examples, the method further comprising adjusting the dose of the amisulpride derivative to accomplish a striatal dopamine RO% or an average dopamine (e.g., D_2/D_3) RO% of caudate and putamen measured from a

treated subject to about 60% to about 80%, about 50% to about 85%, or about 40% to about 90%.

[0010] Also provided herein are methods for antagonizing dopamine and/or serotonin (e.g., 5-HT2a, 5-HT_7) and/or α2 receptor in a subject comprising administering to a subject a therapeutically effective amount of an amisulpride derivative disclosed herein or pharmaceutical compositions thereof, either individually or in combination with other CNS active agents. In certain examples, the method comprises administering to the subject one, two, three, or four unit doses of an amisulpride derivative disclosed herein. In certain examples, the method comprises administering to the subject one, two, three, or four unit doses of an amisulpride derivative disclosed herein once a day, once every two days, once every three days, once every four days, once every five days, once every six days, or once a week. In certain examples, the unit dose is 50 mg, 75 mg, or 100 mg. In certain examples, the method further comprising adjusting the dose of the amisulpride derivative to accomplish a striatal dopamine RO% or an average dopamine (e.g., D_2/D_3) RO% of caudate and putamen measured from a treated subject to about 60% to about 80%, about 50% to about 85%, or about 40% to about 90%.

[0011] Also provided herein are methods for treating one or more conditions responsive to modulation of dopamine and/or serotonin (e.g., 5-HT2a, 5-HT_7) and/or α2 receptor in a subject comprising administering to a subject a therapeutically effective amount of an amisulpride derivative disclosed herein or pharmaceutical compositions thereof, either individually or in combination with other CNS active agents. In certain examples, the method comprises administering to the subject one, two, three, or four unit doses of an amisulpride derivative disclosed herein. In certain examples, the method comprises administering to the subject one, two, three, or four unit doses of an amisulpride derivative disclosed herein once a day, once every two days, once every three days, once every four days, once every five days, once every six days, or once a week. In certain examples, the unit dose is 50 mg, 75 mg, or 100 mg. In certain examples, the method further comprising adjusting the dose of the amisulpride derivative to accomplish a striatal dopamine RO% or an average dopamine (e.g., D_2/D_3) RO% of caudate and putamen measured from a treated subject to about 60% to about 80%, about 50% to about 85%, or about 40% to about 90%.

[0012] Also provided herein are methods for treating one or more disorders associated with an abnormality in levels of dopamine and/or serotonin in the brain, comprising administering to a subject a therapeutically effective amount of an amisulpride derivative disclosed herein or pharmaceutical compositions thereof, either individually or in combination with other CNS active agents. In certain examples, the method comprises administering to the subject one, two, three, or four unit doses of an amisulpride derivative disclosed herein. In certain examples, the method comprises administering to the subject one, two, three, or four unit doses of an amisulpride derivative disclosed herein once a day, once every two days, once every three days, once every four days, once every five days, once every six days, or once a week. In certain examples, the unit dose is 50 mg, 75 mg, or 100 mg. In certain examples, the method further comprising adjusting the dose of the amisulpride derivative to accomplish a striatal dopamine RO% or an average dopamine (e.g., D2/D3) RO% of caudate and putamen measured from a treated subject to about 60% to about 80%, about 50% to about 85%, or about 40% to about 90%.

[0013] Examples of the conditions responsive to modulation of dopamine and/or serotonin (e.g., 5-HT2a, 5-HT7) and/or α2 receptor and/or and the disorders associated with abnormality in levels of dopamine and/or serotonin in the brain include, e.g., without limitation, mental illnesses. Examples of the mental illnesses include, without limitation, schizophrenia, symptoms of schizophrenia, schizoaffective disorder, bipolar disorder, depression, obsessive-compulsive disorder, Parkinson's psychosis, Alzheimer's psychosis, oppositional defiant disorder, aggression, suicidality, hostility, personality disorders, chronic fatigue syndrome, predominantly negative symptoms of schizophrenia, Charles Bonnet Syndrome, autism, and Tourette's disorder.

Brief Description of the Drawings

[0014] Fig. 1A: Dopamine (e.g., D2/D3) %RO for 50 mg LB-102 oral administration to human subjects (n = 4).

[0015] Fig. 1B: Dopamine (e.g., D2/D3) %RO for 100 mg LB-102 oral administration to human subjects (n = 3).

[0016] Fig. 2: Plasma concentration of LB-102 (diamond), amisulpride (square), and total benzamide (triangle) after 50 mg LB-102 oral administration to human subjects (n = 4).

We claim:

1. Use of a therapeutically effective amount of an amisulpride derivative or a pharmaceutical composition thereof, in the manufacture of a medicament for delivering a dopamine and/or serotonin (e.g., 5-HT2a, 5-HT_7) and/or alpha-2 adrenergic (α2) receptor antagonist to the brain of a subject.

2. Use of a therapeutically effective amount of an amisulpride derivative or pharmaceutical compositions thereof, individually or in combination with other CNS active agents, in the manufacture of a medicament for antagonizing dopamine and/or serotonin (e.g., 5-HT2a, 5-HT_7) and/or α2 receptor in a subject.

3. Use of a therapeutically effective amount of an amisulpride derivative or pharmaceutical compositions thereof, individually or in combination with other CNS active agents, in the manufacture of a medicament for treating one or more conditions responsive to modulation of dopamine and/or serotonin (e.g., 5-HT2a, 5-HT_7) and/or α2 receptor in a subject.

4. The use of one of claims 1-3, characterized in that the amisulpride derivative is LB-102.

5. The use of any one of claims 1-4, characterized in that the dosage of the amisulpride derivative is selected from one, two, three, or four unit doses of the amisulpride derivative.

6. The use of any one of claims 1-5, characterized in that the amisulpride derivative is to be administered once a day, once every two days, once every three days, once every four days, once every five days, once every six days, or once a week.

7. The use of any one of claims 1-6, characterized in that the unit dose is 50 mg, 75 mg, or 100 mg.

8. The use of any one of claims 1-7, further comprising the dose of the amisulpride derivative to be adjusted to accomplish a striatal dopamine RO% or an average dopamine (e.g., D_2/D_3) RO % of caudate and putamen measured from a treated subject to about 60% to about 80%, about 50% to about 85%, or about 40% to about 90%.

9. The use of any one of claims 1-8, comprising:

(a) a first unit dose of the amisulpride derivative to be administered to the subject once a day for one day, two days, three days, four days, five days, six days, or a week;

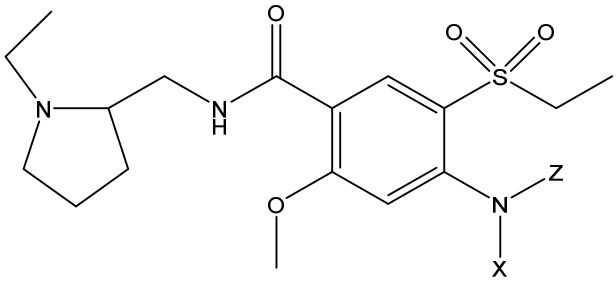
(b) a first average dopamine RO % of caudate and putamen of the subject to be obtained;

(c) a second dose of the amisulpride derivative to be administered to the subject once a day for one day, two days, three days, four days, five days, six days, or a week if a first striatal dopamine RO% or a first average dopamine (e.g., D_2/D_3) RO % of caudate and putamen of the subject is outside of a predetermined range of about 60% to about 80%, about 50% to about 85%, or about 40% to about 90%;

(d) a second striatal dopamine RO% or a second average dopamine (e.g., D_2/D_3) RO % of caudate and putamen of the subject to be obtained; and

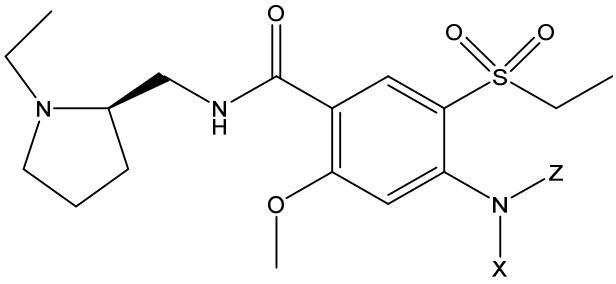
(e) steps c) and d) to be repeated until the striatal dopamine RO% or average dopamine (e.g., D_2/D_3) RO % of caudate and putamen of the subject falls within the predetermined range (e.g., about 60% to about 80%, about 50% to about 85%, or about 40% to about 90%).

10. Use according to any one of claims 1 to 9, characterized in that the amisulpride derivative is selected from:



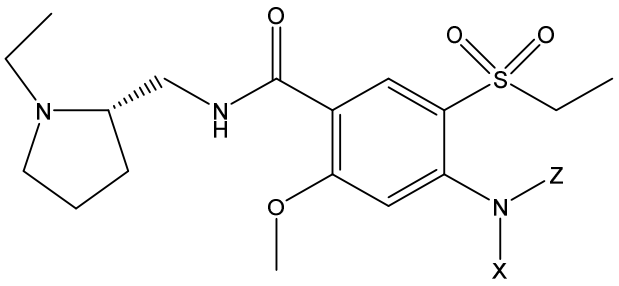
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Formula IA



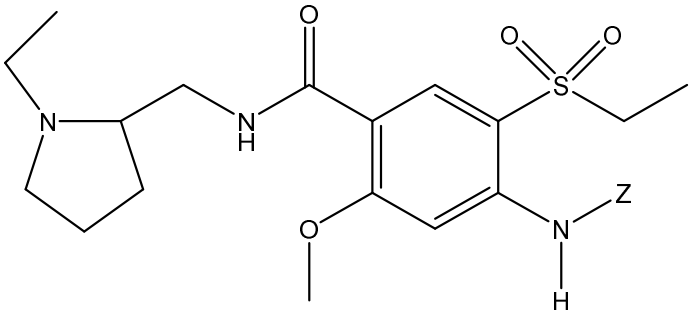
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Formula IA-R



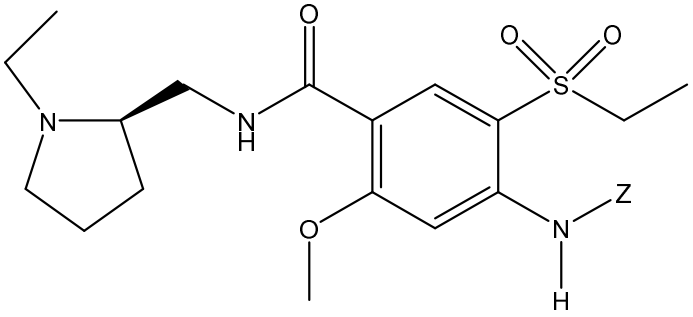
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Formula IA-S



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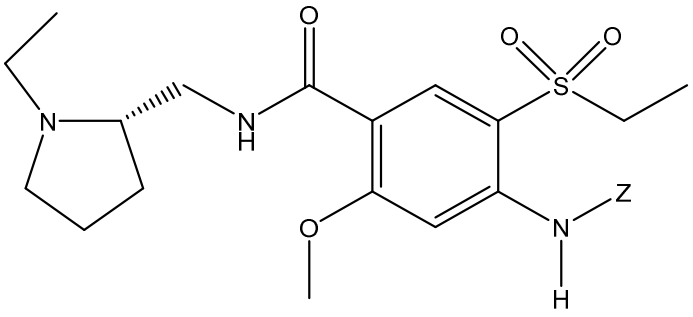
Formula IB



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Formula IB-R

or



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Formula IB-S

11. Pharmaceutical composition, characterized by comprising an amisulpride derivative, and pharmaceutically acceptable carriers.

12. Pharmaceutical composition, according to claim 11, characterized by further comprises other CNS active agents.

13. Pharmaceutical composition, according to claim 11 or 12, characterized in that it is for delivering a dopamine and/or serotonin (e.g., 5-HT2a, 5-HT7) and/or alpha-2 adrenergic (α2) receptor antagonist to the brain of a subject, and/or for antagonizing dopamine and/or serotonin (e.g., 5-HT2a, 5-HT7) and/or α2 receptor in a subject, and/or for treating one or more conditions responsive to modulation of dopamine and/or serotonin (e.g., 5-HT2a, 5-HT_7) and/or α2 receptor in a subject.

14. Use of a pharmaceutical composition, according to claim 11 or 12, in the manufacture of a medicament for delivering a dopamine and/or serotonin (e.g., 5-HT2a, 5-HT7) and/or alpha-2 adrenergic (α2) receptor antagonist to the brain of a subject, and/or in the manufacture of a medicament for antagonizing dopamine and/or serotonin (e.g., 5-HT2a, 5-HT7) and/or α2 receptor in a subject, and/or in the manufacture of a medicament for treating one or more conditions responsive to modulation of dopamine and/or serotonin (e.g., 5-HT2a, 5-HT_7) and/or α2 receptor in a subject.