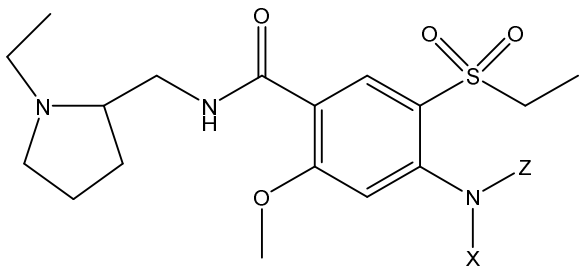
though it has also been demonstrated to bind 5-HT_{2B} and HT_{7a} receptors with low double digit nM K_i. This ability of amisulpride to bind 5-HT receptors is thought to result in amisulpride's ability to treat symptoms of depression (sometimes noted in schizophrenia patients). Interestingly, compared to other antipsychotics, amisulpride is not noted to have any activity at the 5-HT_{2a} receptor.

Despite the unique activities of amisulpride, amisulpride has low ability to cross blood brain barrier (BBB) to interact with the receptors in the brain. In a 2014 study, passive diffusion of amisulpride across a PAMPA membrane (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

In one aspect, the present disclosure refers to a compound having a structure of Formula IA:

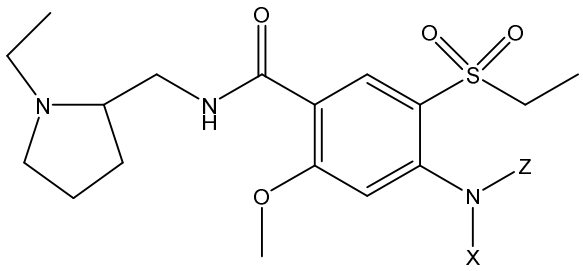


Formula IA

pharmaceutically acceptable salts and stereoisomers thereof, wherein:

X and Z are the same or different and independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroarylalkyl, and heteroaryl, optionally the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroarylalkyl, and heteroaryl groups are further substituted with one or more substitution groups selected from the group consisting of halogens, chlorine, bromine, fluorine, amines, hydroxy groups, carboxylic acids, nitro groups, carbonyl, alkyl, and aryl groups; with the proviso that at least one of X and Z is not hydrogen.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having a structure of Formula IA:

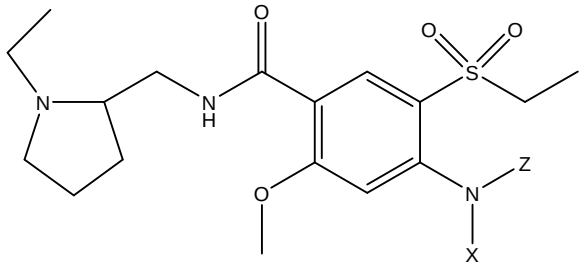


Formula IA

pharmaceutically acceptable salts and stereoisomers thereof, wherein:

X and Z are the same or different and independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroarylalkyl, and heteroaryl, optionally the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroarylalkyl, and heteroaryl groups are further substituted with one or more substitution groups selected from the group consisting of halogens, chlorine, bromine, fluorine, amines, hydroxy groups, carboxylic acids, nitro groups, carbonyl, alkyl, and aryl groups; with the proviso that at least one of X and Z is not hydrogen.

In yet another aspect, the present disclosure refers to use of a therapeutically effective amount of a compound having a structure of Formula IA:



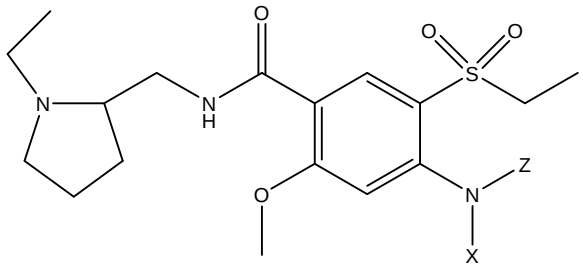
Formula IA

pharmaceutically acceptable salts and stereoisomers thereof, wherein:

X and Z are the same or different and independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl,

heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroarylalkyl, and heteroaryl, optionally the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroarylalkyl, and heteroaryl groups are further substituted with one or more substitution groups selected from the group consisting of halogens, chlorine, bromine, fluorine, amines, hydroxy groups, carboxylic acids, nitro groups, carbonyl, alkyl, and aryl groups; with the proviso that at least one of X and Z is not hydrogen, in the manufacture of a medicament for delivery into the brain of a subject; wherein the level of dopamine and/or serotonin and/or α2 receptor antagonist in brain is higher than the level of amisulpride when amisulpride is to be administered to the subject at a comparable dose.

In yet another aspect, the present disclosure refers to use of a therapeutically effective amount of a compound having a structure of Formula IA:



Formula IA

pharmaceutically acceptable salts and stereoisomers thereof, wherein:

X and Z are the same or different and independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroarylalkyl, and heteroaryl, optionally the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroarylalkyl, and heteroaryl groups are further substituted with one or more substitution groups selected from the group consisting of halogens, chlorine, bromine, fluorine, amines, hydroxy groups, carboxylic acids, nitro groups, carbonyl, alkyl, and aryl groups; with the proviso that at least one of X and Z is not hydrogen,

in the manufacture of a medicament for treating one or more conditions selected from the group consisting of depression, bipolar disorder, Tourette's syndrome, Schizoaffective disorder, Parkinson's psychosis, Alzheimer's psychosis, oppositional

defiant disorder, personality disorder, childhood schizophrenia, dysthymia, treatment resistant schizophrenia, and chronic fatigue syndrome, wherein the compound is to be administered to the subject.

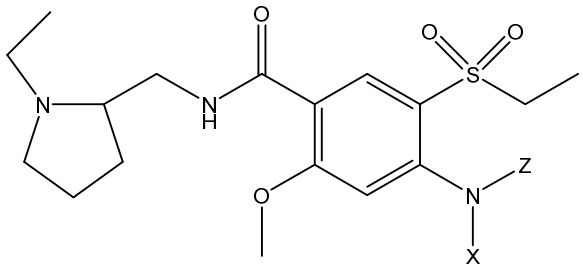
Provided herein are novel amisulpride derivatives and pharmaceutical compositions thereof. In certain examples, the amisulpride derivatives disclosed herein are dopamine and/or serotonin antagonists. In certain examples, the amisulpride derivatives disclosed herein have improved membrane (e.g., BBB)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

Also provided herein are methods for delivering a dopamine and/or serotonin (e.g., 5-HT2a) and/or alpha-2 adrenergic (α2) receptor antagonist to the brain of a subject comprising administering to the subject 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 is higher than administering to the subject amisulpride at a comparable dose.

Also provided herein are methods for antagonizing dopamine and/or serotonin (e.g., 5-HT2a) and/or α2 receptor in a subject comprising administering to a subject

What is claimed is:

1. A compound having a structure of Formula IA:

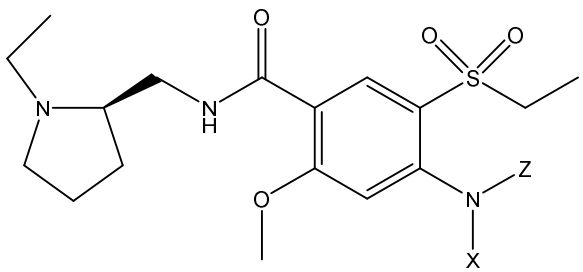


Formula IA

pharmaceutically acceptable salts and stereoisomers thereof, wherein:

X and Z are the same or different and independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroarylalkyl, and heteroaryl, optionally the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroarylalkyl, and heteroaryl groups are further substituted with one or more substitution groups selected from the group consisting of halogens, chlorine, bromine, fluorine, amines, hydroxy groups, carboxylic acids, nitro groups, carbonyl, alkyl, and aryl groups; with the proviso that at least one of X and Z is not hydrogen.

2. The compound of claim 1, wherein the compound is a stereoisomer having a structure of Formula IA-S:



Formula IA-S

and pharmaceutically acceptable salts thereof.

3. The compound of claim 1, wherein X and Z are the same or different and independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, and heteroaryl, optionally the alkyl, alkenyl, alkynyl, aryl, and heteroaryl groups are further substituted with one or more substitution groups selected from the group consisting of halogens, chlorine, bromine, fluorine, amines, hydroxy groups, carboxylic acids, nitro groups, carbonyl, alkyl, and aryl groups; with the proviso that at least one of X and Z is not hydrogen.

4. The compound of claim 2, wherein X and Z are the same or different and independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, and heteroaryl, optionally the alkyl, alkenyl, alkynyl, aryl, and heteroaryl groups are further substituted with one or more substitution groups selected from the group consisting of halogens, chlorine, bromine, fluorine, amines, hydroxy groups, carboxylic acids, nitro groups, carbonyl, alkyl, and aryl groups; with the proviso that at least one of X and Z is not hydrogen.

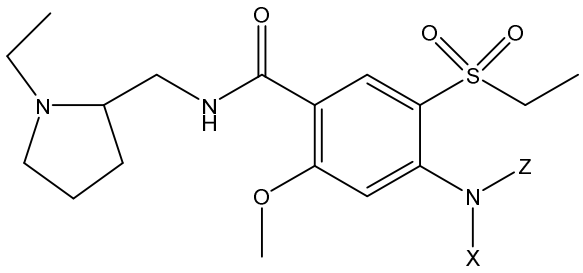
5. The compound of claim 1, wherein X is H.

6. The compound of claim 5, wherein Z = CH_3.

7. The compound of claim 2, wherein X is H.

8. The compound of claim 7, wherein Z = CH_3.

9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having a structure of Formula IA:



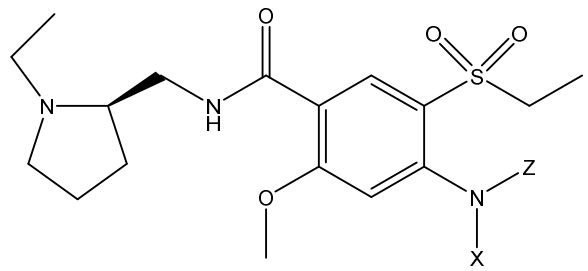
Formula IA

pharmaceutically acceptable salts and stereoisomers thereof, wherein:

X and Z are the same or different and independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl,

heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroarylalkyl, and heteroaryl, optionally the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroarylalkyl, and heteroaryl groups are further substituted with one or more substitution groups selected from the group consisting of halogens, chlorine, bromine, fluorine, amines, hydroxy groups, carboxylic acids, nitro groups, carbonyl, alkyl, and aryl groups; with the proviso that at least one of X and Z is not hydrogen.

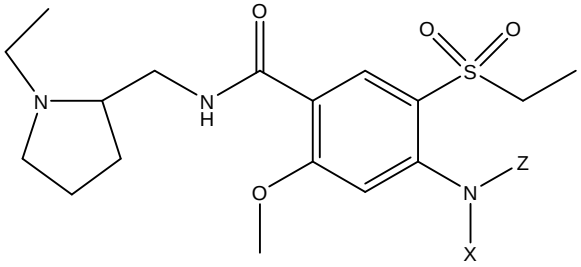
10. The pharmaceutical composition of claim 9, wherein the compound is a stereoisomer having a structure of Formula IA-S:



Formula IA-S

and pharmaceutically acceptable salts thereof.

11. Use of a therapeutically effective amount of a compound having a structure of Formula IA:



Formula IA

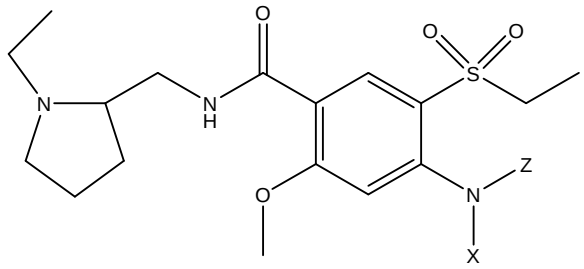
pharmaceutically acceptable salts and stereoisomers thereof, wherein:

X and Z are the same or different and independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroarylalkyl, and heteroaryl, optionally the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl,

heterocyclylalkyl, aryl, arylalkyl, heteroarylalkyl, and heteroaryl groups are further substituted with one or more substitution groups selected from the group consisting of halogens, chlorine, bromine, fluorine, amines, hydroxy groups, carboxylic acids, nitro groups, carbonyl, alkyl, and aryl groups; with the proviso that at least one of X and Z is not hydrogen,

in the manufacture of a medicament for delivery into the brain of a subject; wherein the level of dopamine and/or serotonin and/or α2 receptor antagonist in brain is higher than the level of amisulpride when amisulpride is to be administered to the subject at a comparable dose.

12. Use of a therapeutically effective amount of a compound having a structure of Formula IA:



Formula IA

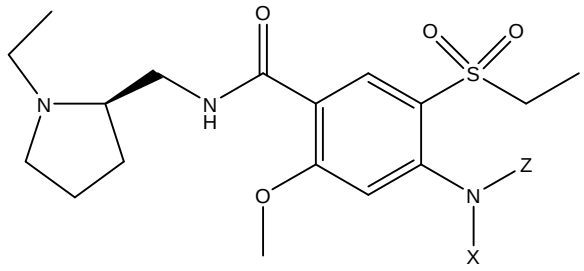
pharmaceutically acceptable salts and stereoisomers thereof, wherein:

X and Z are the same or different and independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroarylalkyl, and heteroaryl, optionally the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroarylalkyl, and heteroaryl groups are further substituted with one or more substitution groups selected from the group consisting of halogens, chlorine, bromine, fluorine, amines, hydroxy groups, carboxylic acids, nitro groups, carbonyl, alkyl, and aryl groups; with the proviso that at least one of X and Z is not hydrogen,

in the manufacture of a medicament for treating one or more conditions selected from the group consisting of depression, bipolar disorder, Tourette's syndrome, Schizoaffective disorder, Parkinson's psychosis, Alzheimer's psychosis, oppositional defiant disorder, personality disorder, childhood schizophrenia,

dysthymia, treatment resistant schizophrenia, and chronic fatigue syndrome, wherein the compound is to be administered to the subject.

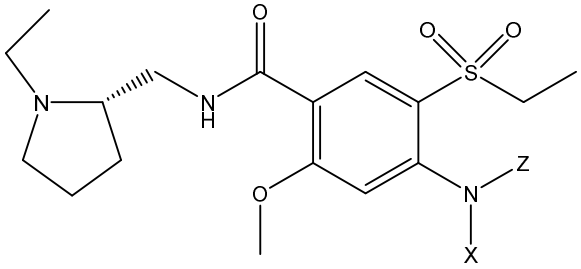
13. The use of claim 11, wherein the compound is a stereoisomer having a structure of Formula IA-S:



Formula IA-S

and pharmaceutically acceptable salts thereof.

14. The compound of claim 1, wherein the compound is a stereoisomer having a structure of Formula IA-R:



Formula IA-R

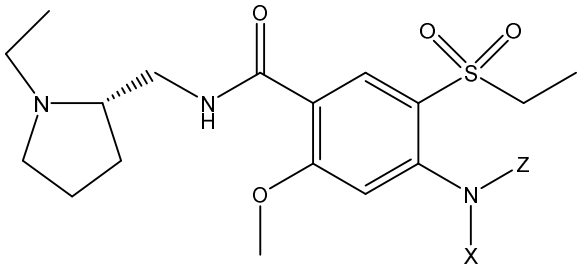
and pharmaceutically acceptable salts thereof.

15. The compound of claim 14, wherein X and Z are the same or different and independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, and heteroaryl, optionally the alkyl, alkenyl, alkynyl, aryl, and heteroaryl groups are further substituted with one or more substitution groups selected from the group consisting of halogens, chlorine, bromine, fluorine, amines, hydroxy groups, carboxylic acids, nitro groups, carbonyl, alkyl, and aryl groups; with the proviso that at least one of X and Z is not hydrogen.

16. The compound of claim 15, wherein X is H.

17. The compound of claim 16, wherein Z = CH_3.

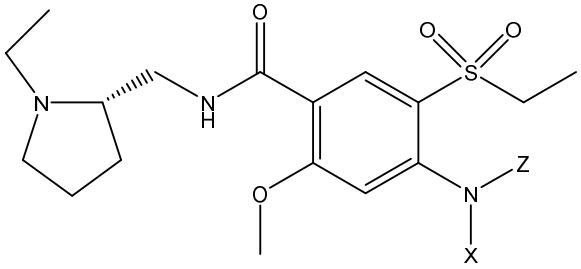
18. The pharmaceutical composition of claim 9, wherein the compound is a stereoisomer having a structure of Formula IA-R:



Formula IA-R

and pharmaceutically acceptable salts thereof.

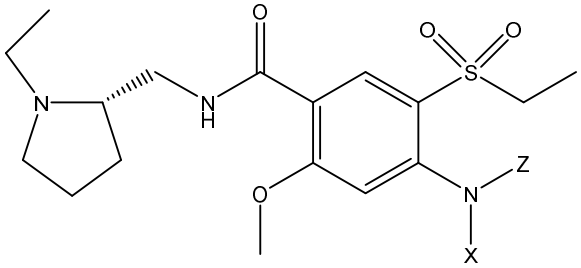
19. The use of claim 11, wherein the compound is a stereoisomer having a structure of Formula IA-R:



Formula IA-R

and pharmaceutically acceptable salts thereof.

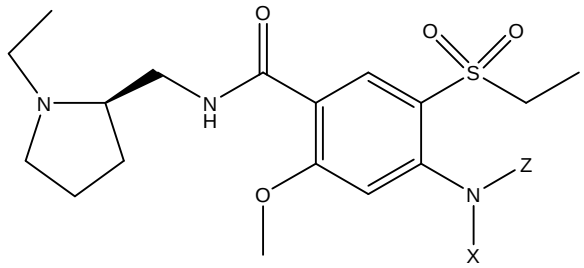
20. The use of claim 12, wherein the compound is a stereoisomer having a structure of Formula IA-R:



Formula IA-R

and pharmaceutically acceptable salts thereof.

21. The use of claim 12, wherein the compound is a stereoisomer having a structure of Formula IA-S:



Formula IA-S

and pharmaceutically acceptable salts thereof.