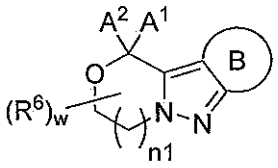
[007] Depressive disorders include major depressive disorder and dysthymia, and are associated with depressed mood (sadness), poor concentration, insomnia, fatigue, appetite disturbances, excessive guilt and thoughts of suicide.

[008] Anxiety disorders are disorders characterized by fear, worry, and uneasiness, usually generalized and unfocused as an overreaction to a situation. Anxiety disorders differ in the situations or types of objects that induce fear, anxiety, or avoidance behavior, and the associated cognitive ideation. Anxiety differs from fear in that anxiety is an emotional response to a perceived future threat while fear is associated with a perceived or real immediate threat. They also differ in the content of the associated thoughts or beliefs.

SUMMARY

[009] While medications exist for some aspects of these diseases, there remains a need for effective treatments for various neurological and psychiatric disorders, including mood disorders such as bipolar and related disorders, psychosis and schizophrenia. For example, while mood stabilizers such as lithium and valproate, antidepressants and antipsychotic drugs are used to treat mood disorders, more effective medications are necessary. And current antipsychotics may be successful in treating the positive symptoms of schizophrenia but fare less well for the negative and cognitive symptoms. Additionally, current antidepressants are typically effective only for a proportion of patients suffering from depression.

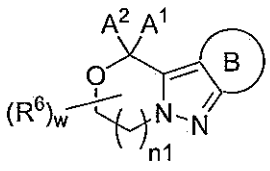
[010] In some examples, the present disclosure encompasses the insight that compounds of Formula (I):



(I)

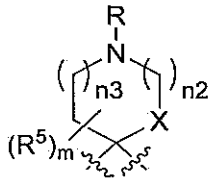
and pharmaceutically acceptable salts thereof, wherein Ring B, A^1, A^2, R^6, w and n1 are defined and described herein, are useful for treating a variety of neurological and psychiatric disorders, such as those described herein.

[011] Also described herein are methods for the treatment of various neurological and psychiatric disorders using the compounds and compositions provided herein. In one aspect, the present invention refers to a compound of Formula (I):



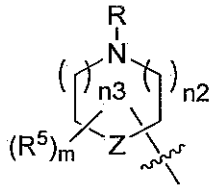
(I),

or a pharmaceutically acceptable salt thereof, wherein: Ring B is a 6-membered aromatic ring, which ring is unsubstituted or substituted with 1 to 4 substituents independently selected from halo, -OH, $-NH_2$, $-CH_3$, $-CH_2F$, $-CHF_2$ and $-CF_3$; or is a 5- or 6-membered heteroaromatic ring having 1 to 3 ring heteroatoms independently selected from O, N and S, which ring is unsubstituted or substituted with 1 to 3 substituents independently selected from halo, -OH, $-NH_2$, $-CH_3$, $-CH_2F$, $-CHF_2$ and $-CF_3$; A^1 is -H or C_{1-3} alkyl; and A^2 is $-C(R^7)(R^8)-(CH_2)_p-N(R^9)R^{10}$; or A^1 and A^2, together with the carbon atom to which they are attached, form



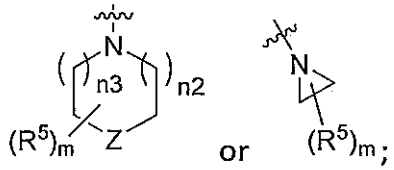
;

m is 0, 1 or 2; n1 is 1 or 2; n2 is 0 or 1; n3 is 0 or 1; p is 0 or 1; R is -H or C_1-C_3 alkyl; or R is $-CH_2$-(X), $-CH_2CH_2$-(X), $-CH_2$-(Z) or $-CH_2CH_2$-(Z); each instance of R^5 independently is halo, $-CH_3$ or ethyl; each instance of R^6 independently is halo or $-CH_3$; R^7 is -H or C_1-C_3 alkyl; R^8 is -H or C_1-C_3 alkyl which is unsubstituted or substituted with C_3-C_6 cycloalkyl; R^9 is -H, C_1-C_4 alkyl or C_3-C_6 cycloalkyl; and R^{10} is -H or C_1-C_3 alkyl; or R^9 and R^8, together with the atoms to which they are attached, form



;

or R^9 and R^{10}, together with the nitrogen atom to which they are attached, form

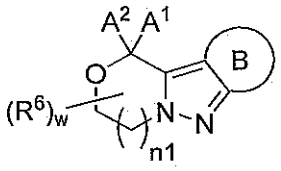


w is 0, 1 or 2; X is CH or CH_2; and Z is CH, CH_2 or O. In another aspect, the present invention refers to a composition comprising the compound of the present invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle. In yet another aspect, the present invention refers to the use of the compound according to the present invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a neurological or psychiatric disorder in a patient. In another aspect, the present invention refers to a compound according to the present invention for use in therapy, or a pharmaceutically acceptable salt thereof, wherein the compound or salt is to be used as analgesic or a cognitive enhancer.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

1. General Description of Compounds of the Invention:

[012] In some embodiments, the present invention provides a compound of Formula (I):



(I),

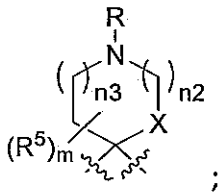
or a pharmaceutically acceptable salt thereof, wherein:

Ring B is a 6-membered aromatic ring, which ring unsubstituted or substituted with 1 to 4 substituents independently selected from halo, -OH, $-NH_2$, $-CH_3$, $-CH_2F$, $-CHF_2$ and $-CF_3$; or is a 5- or 6-membered heteroaromatic ring having 1 to 3 ring heteroatoms independently selected from O, N and S, which ring is unsubstituted or substituted with 1 to 3 substituents independently selected from halo, -OH, $-NH_2$, $-CH_3$, $-CH_2F$, $-CHF_2$ and $-CF_3$;

A^1 is -H or C_{1-3} alkyl; and

A^2 is $-C(R^7)(R^8)-(CH_2)_p-N(R^9)R^{10}$;

or A^1 and A^2, together with the carbon atom to which they are attached, form



;

m is 0, 1 or 2;

n1 is 1 or 2;

n2 is 0 or 1;

n3 is 0 or 1;

p is 0 or 1;

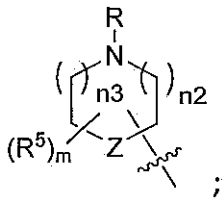
R is -H or C_1-C_3 alkyl; or R is $-CH_2$-(X), $-CH_2CH_2$-(X), $-CH_2$-(Z) or $-CH_2CH_2$-(Z);

R^8 is -H or C_1-C_3 alkyl which is unsubstituted or substituted with C_3-C_6 cycloalkyl;

R^9 is -H, C_1-C_4 alkyl or C_3-C_6 cycloalkyl; and

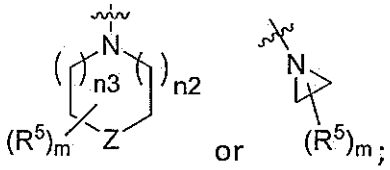
R^{10} is -H or C_1-C_3 alkyl;

or R^9 and R^8, together with the atoms to which they are attached, form



;

or R^9 and R^{10}, together with the nitrogen atom to which they are attached, form



;

w is 0, 1 or 2;

X is CH or CH_2; and

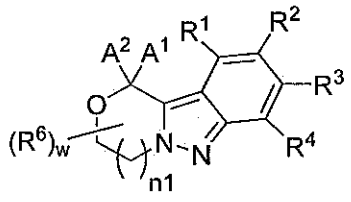
Z is CH, CH_2 or O.

2. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein A^1 is -H.

3. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein w is 0.

4. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein n1 is 1 or 2.

5. The compound of claim 1 of Formula (I-1):

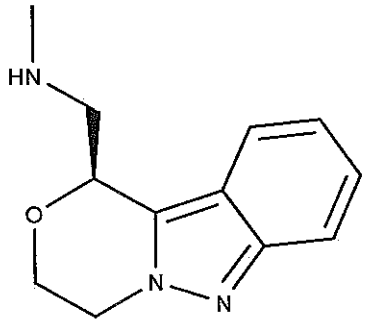


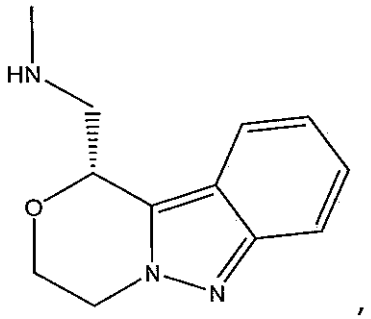
(I-1),

or a pharmaceutically acceptable salt thereof, wherein:

R^1, R^2, R^3 and R^4 are independently -H, halo, -OH, $-NH_2$, $-CH_3$, $-CH_2F$, $-CHF_2$ or $-CF_3$.

19. The compound of claim 18, or a pharmaceutically acceptable salt thereof, selected from:

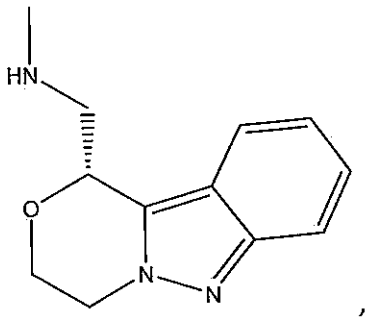


or


,

or a mixture thereof.

20. The compound of claim 19, wherein the compound is



,

or a pharmaceutically acceptable salt thereof.

21. A composition comprising the compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

22. The composition according to claim 21, wherein said composition is a pharmaceutically acceptable composition.

23. Use of the compound according to any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a neurological or psychiatric disorder in a patient.

24. The use according to claim 23, wherein the neurological or psychiatric disorder is depression, pyschosis, suicidality, bipolar disorder, pain, schizophrenia, obsessive compulsive disorder, addiction, social disorder, attention deficit hyperactivity disorder, an anxiety disorder, autism, cognitive impairment, acute suicidality, suicide ideation, suicidal thinking or suicidal behavior.

25. The use according to claim 24, wherein the neurological or psychiatric disorder is depression.

26. The use according to claim 25, wherein the depression is treatment-resistant depression (TRD), major depressive disorder (MDD), unipolar depression, bipolar depression or depression associated with another disease or disorder.

27. A compound according to claim 1 for use in therapy, or a pharmaceutically acceptable salt thereof, wherein the compound or salt is to be used as analgesic or a cognitive enhancer.

28. The use according to claim 23 for treating major depressive disorder without increasing the risk of suicidal thinking and/or behavior.