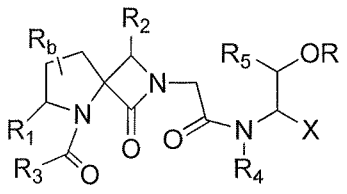
S, wherein the heteroaryl ring may be optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl and phenyl; and

R^c and R^d are each independently selected from the group consisting of H, C_1-C_6 alkyl, or phenyl, or R^c and R^d together with the nitrogen to which they are attached, form heterocyclyl including from 4 to 6 ring atoms; wherein the heterocyclyl includes not more than two ring heteroatoms (including the nitrogen atom attached to R^c and R^d), and the second ring heteroatom, when present, is independently selected from the group consisting of N, NH, N(C1-C3 alkyl), O, and S; and wherein the heterocyclyl is optionally substituted with from 1-3 substituents independently selected from the group consisting of halogen, cyano, oxo, and C_1-C_6 alkyl.

In one aspect of the present disclosure, there is provided a compound represented by formula I:



(I)

or a pharmaceutically acceptable salt, a stereoisomer, or an N-oxide thereof, wherein

R_b is selected from the group consisting of H, halogen, hydroxyl, cyano and C_1-C_6alkyl;

R is H, C_1-C_6 alkyl or –C(O)-C_1-C_6alkyl;

R_1 is H or C_1-C_6 alkyl;

R_2 is H or C_1-C_6 alkyl;

R_3 is selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, -O-C_1-C_6 alkylene-phenyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, phenyl, and heteroaryl including from 5 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C_1-C_3 alkyl), O, and S; wherein R_3 is optionally substituted with one, two, or three substituents independently selected from the group consisting of amino, protected amino, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, phenyl (optionally substituted by one, two, or three substituents each independently selected from R^a), benzyl (optionally substituted by one, two, or three substituents each independently selected from R^a), and -C_1-C_6 alkylene-C_3-C_6 cycloalkyl

(optionally substituted by one, two or three substituents independent selected from halogen and C_1-C_6 alkyl);

R^a is selected from the group consisting of halogen, C_1-C_6alkyl (optionally substituted by one, two or three halogens), C_3-C_6 cycloalkyl (optionally substituted by one, two or three halogens), and C_1-C_6 alkoxy (optionally substituted by one, two or three halogens);

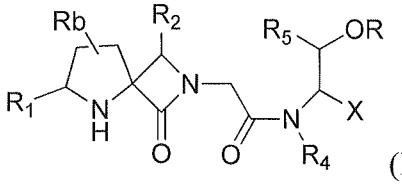
R_4 is H or C_1-C_6 alkyl;

R_5 is H or C_1-C_6 alkyl;

X is selected from the group consisting of H, C_1-C_6 alkyl, -OH, C_1-C_6 alkoxy, $-CO_2H$, $-C(O)NR^cR^d$, and heteroaryl including from 5 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C_1-C_3 alkyl), O, and S, wherein the heteroaryl ring may be optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl and phenyl; and

R^c and R^d are each independently selected from the group consisting of H, C_1-C_6 alkyl, and phenyl, or R^c and R^d together with the nitrogen to which they are attached, form heterocyclyl including from 4 to 6 ring atoms; wherein the heterocyclyl includes not more than two ring heteroatoms (including the nitrogen atom attached to R^c and R^d), and the second ring heteroatom, when present, is independently selected from the group consisting of N, NH, N(C_1-C_3 alkyl), O, and S; and wherein the heterocyclyl is optionally substituted with from 1-3 substituents independently selected from the group consisting of halogen, cyano, oxo, and C_1-C_6 alkyl.

Also provided herein, at least in part, are compounds that are NMDA modulators, for example, partial agonists of NMDA. For example, disclosed herein are compounds represented by the formula:



(II)

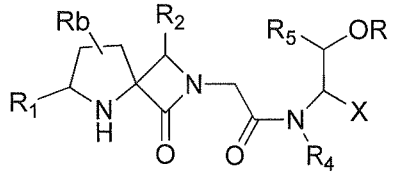
and pharmaceutically acceptable salts, stereoisomers, and N-oxides thereof, wherein

R_b is selected from the group consisting of H, halogen, hydroxyl, cyano and C_1-C_6alkyl;

independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl and phenyl; and

R^c and R^d are each independently selected from the group consisting of H, C_1-C_6 alkyl, or phenyl, or R^c and R^d together with the nitrogen to which they are attached, form heterocyclyl including from 4 to 6 ring atoms; wherein the heterocyclyl includes not more than two ring heteroatoms (including the nitrogen atom attached to R^c and R^d), and the second ring heteroatom, when present, is independently selected from the group consisting of N, NH, N(C1-C3 alkyl), O, and S; and wherein wherein the heterocyclyl is optionally substituted with from 1-3 substituents independently selected from the group consisting of halogen, cyano, oxo, and C_1-C_6 alkyl.

In a further aspect of the present disclosure, there is provided a compound represented by formula II:



(II)

or a pharmaceutically acceptable salt, a stereoisomer, or an N-oxide thereof, wherein

R_b is selected from the group consisting of H, halogen, hydroxyl, cyano and C_1-C_6alkyl;

R is H, C_1-C_6 alkyl or –C(O)-C_1-C_6alkyl;

R_1 is H or C_1-C_6 alkyl;

R_2 is H or C_1-C_6 alkyl;

R_4 is H or C_1-C_6 alkyl;

R_5 is H or C_1-C_6 alkyl;

X is selected from the group consisting of H, C_1-C_6 alkyl, -OH, C_1-C_6 alkoxy, -CO_2H, -C(O)N$R^c R^d$, and heteroaryl including from 5 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C_1-C_3 alkyl), O, and S, wherein the heteroaryl ring may be optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl and phenyl; and

R^c and R^d are each independently selected from the group consisting of H, C_1-C_6 alkyl, and phenyl, or R^c and R^d together with the nitrogen to which they are attached, form heterocyclyl

including from 4 to 6 ring atoms; wherein the heterocyclyl includes not more than two ring heteroatoms (including the nitrogen atom attached to R^c and R^d), and the second ring heteroatom, when present, is independently selected from the group consisting of N, NH, N(C_1-C_3 alkyl), O, and S; and wherein the heterocyclyl is optionally substituted with from 1-3 substituents independently selected from the group consisting of halogen, cyano, oxo, and C_1-C_6 alkyl.

[0009] In another aspect of the present disclosure, there is provided a pharmaceutically acceptable compositions comprising a disclosed compound, and a pharmaceutically acceptable excipient. For example, such compositions may be suitable for oral or intravenous administration to a patient.

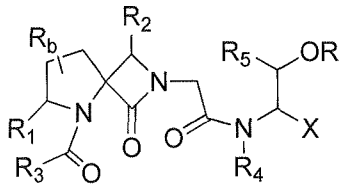
[0009a] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for treating depression, Alzheimer's disease, attention deficit disorder, schizophrenia, or anxiety, in a patient in need thereof.

[0010] The present disclosure also relates to a method of treating a condition selected from the group consisting of autism, anxiety, depression, bipolar disorder, attention deficit disorder, attention deficit hyperactivity disorder (ADHD), schizophrenia, a psychotic disorder, a psychotic symptom, social withdrawal, obsessive-compulsive disorder, phobia, post-traumatic stress syndrome, a behavior disorder, an impulse control disorder, a substance abuse disorder, a sleep disorder, a memory disorder, a learning disorder, urinary incontinence, multiple system atrophy, progressive supra-nuclear palsy, Friedrich's ataxia, Down's syndrome, fragile X syndrome, tuberous sclerosis, olivio-ponto-cerebellar atrophy, cerebral palsy, drug-induced optic neuritis, ischemic retinopathy, diabetic retinopathy, glaucoma, dementia, AIDS dementia, Alzheimer's disease, Huntington's chorea, spasticity, myoclonus, muscle spasm, Tourette's syndrome, epilepsy, cerebral ischemia, stroke, a brain tumor, traumatic brain injury, cardiac arrest, myelopathy, spinal cord injury, peripheral neuropathy, acute neuropathic pain, and chronic neuropathic, in a patient in need thereof is provided. Such methods may comprise administering to the patient a pharmaceutically effective amount of a disclosed compound or pharmaceutically acceptable salts, stereoisomers, N-oxides, and hydrates thereof.

[0011] In some embodiments, a contemplated method includes treating depression. For example, depression may include one or more of major depressive disorder, dysthymic disorder, psychotic depression, postpartum depression, seasonal affective disorder, bipolar

What is claimed is:

1. A compound represented by formula I:



(I)

or a pharmaceutically acceptable salt, a stereoisomer, or an N-oxide thereof, wherein

R_b is selected from the group consisting of H, halogen, hydroxyl, cyano and C_1-C_6alkyl;

R is H, C_1-C_6 alkyl or –C(O)-C_1-C_6alkyl;

R_1 is H or C_1-C_6 alkyl;

R_2 is H or C_1-C_6 alkyl;

R_3 is selected from the group consisting C_1-C_6 alkyl, C_1-C_6 alkoxy, -O-C_1-C_6 alkylene-phenyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, phenyl, and heteroaryl including from 5 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C_1-C_3 alkyl), O, and S; wherein R_3 is optionally substituted with one, two, or three substituents independently selected from the group consisting of amino, protected amino, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, phenyl (optionally substituted by one, two, or three substituents each independently selected from R^a), benzyl (optionally substituted by one, two, or three substituents each independently selected from R^a), and -C_1-C_6 alkylene-C_3-C_6 cycloalkyl (optionally substituted by one, two or three substituents independent selected from halogen and C_1-C_6 alkyl);

R^a is selected from the group consisting of halogen, C_1-C_6alkyl (optionally substituted by one, two or three halogens), C_3-C_6 cycloalkyl (optionally substituted by one, two or three halogens), and C_1-C_6 alkoxy (optionally substituted by one, two or three halogens);

R_4 is H or C_1-C_6 alkyl;

R_5 is H or C_1-C_6 alkyl;

X is selected from the group consisting of H, C_1-C_6 alkyl, -OH, C_1-C_6 alkoxy, -CO_2H, -C(O)N$R^c$$R^d$, and heteroaryl including from 5 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C_1-C_3 alkyl), O, and S, wherein the heteroaryl ring may be optionally substituted with one, two, or three substituents

independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl and phenyl; and

R^c and R^d are each independently selected from the group consisting of H, C_1-C_6 alkyl, and phenyl, or R^c and R^d together with the nitrogen to which they are attached, form heterocyclyl including from 4 to 6 ring atoms; wherein the heterocyclyl includes not more than two ring heteroatoms (including the nitrogen atom attached to R^c and R^d), and the second ring heteroatom, when present, is independently selected from the group consisting of N, NH, N(C_1-C_3 alkyl), O, and S; and wherein the heterocyclyl is optionally substituted with from 1-3 substituents independently selected from the group consisting of halogen, cyano, oxo, and C_1-C_6 alkyl.

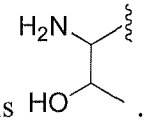
2. The compound of claim 1, wherein R_1 is H.

3. The compound of claim 1 or 2, wherein R_2 is H.

4. The compound of any one of claims 1-3, wherein R_3 is C_1-C_6 alkyl.

5. The compound of any one of claims 1-3, wherein R_3 is methyl.

6. The compound of any one of claims 1-3, wherein R_3 is C_1-C_6 alkyl substituted with one, two or three substituents each selected from the group consisting of amino, protected amino, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, phenyl (optionally substituted by one, two, or three substituents each independently selected from R^a), benzyl (optionally substituted by one two or three substituents each independently selected from R^a), and -C_1-C_6 alkylene-C_3-C_6 cycloalkyl (optionally substituted by one, two or three substituents independently selected from halogen and C_1-C_6 alkyl).

7. The compound of any one of claims 1-3, wherein R_3 is 

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8. The compound of any one of claims 1-3, wherein R_3 is heteroaryl including from 5 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C_1-C_3 alkyl), O, and S; which heteroaryl is optionally substituted with one, two, or three substituents independently selected from the group consisting of amino, protected amino, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, phenyl (optionally substituted by one, two or three substituents each independently selected from R^a), benzyl (optionally substituted by one two or three substituents each independently selected from R^a), and -C_1-C_6 alkylene-C_3-C_6

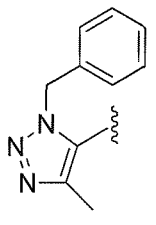
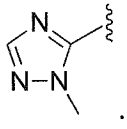
cycloalkyl (optionally substituted by one, two or three substituents independently selected from halogen and C_1-C_6 alkyl).

9. The compound of any one of claims 1-3, wherein R_3 is heteroaryl including from 5 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C_1-C_3 alkyl), O, and S; which heteroaryl is optionally substituted with one, two, or three substituents independently selected from the group consisting of C_1-C_6 alkyl and benzyl (optionally substituted by one two or three substituents each independently selected from R^a).

10. The compound of any one of claims 1-3, wherein R_3 is heteroaryl including from 5 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C_1-C_3 alkyl), O, and S; which heteroaryl is optionally substituted with one, two, or three substituents independently selected from the group consisting of $-CH_3$ and benzyl.

11. The compound of any one of claims 1-3, wherein R_3 is -O-C_1-C_6 alkylene-phenyl, which is optionally substituted with one, two, or three substituents independently selected from the group consisting of amino, protected amino, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, phenyl (optionally substituted by one, two or three substituents each independently selected from R^a), benzyl (optionally substituted by one two or three substituents each independently selected from R^a), and -C_1-C_6 alkylene-C_3-C_6 cycloalkyl (optionally substituted by one, two or three substituents independently selected from halogen and C_1-C_6 alkyl).

12. The compound of any one of claims 1-3, wherein R_3 is -O-CH_2-phenyl, which is optionally substituted with one, two, or three substituents independently selected from the group consisting of amino, protected amino, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, phenyl (optionally substituted by one, two or three substituents each independently selected from R^a), benzyl (optionally substituted by one two or three substituents each independently selected from R^a), and --C_1-C_6 alkylene-C_3-C_6 cycloalkyl (optionally substituted by one, two or three substituents independently selected from halogen and C_1-C_6 alkyl).

13. The compound of any one of claims 1-3, wherein R_3 is selected from the group consisting of benzyloxy,  and  .

14. The compound of any one of claims 1-13, wherein X is -C(O)NR^cR^d.

15. The compound of claim 14, wherein R^c and R^d are each independently selected from the group consisting of H, C_1-C_6 alkyl, and phenyl.

16. The compound of claim 14, wherein R^c and R^d are both H.

17. The compound of any one of claims 1-13, wherein X is heteroaryl including from 5 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C_1-C_3 alkyl), O, and S, which heteroaryl is optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl and phenyl.

18. The compound of claim 17, wherein X is selected from the group consisting of 1,2,4-oxadiazolyl, 1,3,4- oxadiazolyl, 1,2,4-triazolyl (optionally substituted with from 1-2 independently selected C_1-C_6 alkyl), pyridyl, and pyrimidinyl.

19. The compound of any one of claims 1-18, wherein R is H.

20. The compound of any one of claims 1-18, wherein R is –C(O)-C_1-C_6alkyl.

21. The compound of claim 20, wherein R is –C(O)-CH_3.

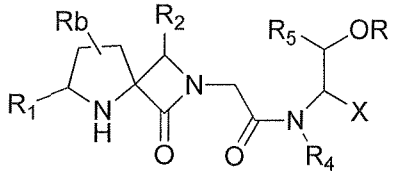
22. The compound of any one of claims 1-21, wherein R_5 is C_1-C_6 alkyl.

23. The compound of claim 22, wherein R_5 is –CH_3.

24. The compound of any one of claims 1-23, wherein R_4 is H.

25. The compound of any one of claims 1-24, wherein R_b is H.

26. A compound represented by formula II:



(II)

or a pharmaceutically acceptable salt, a stereoisomer, or an N-oxide thereof, wherein

R_b is selected from the group consisting of H, halogen, hydroxyl, cyano and C_1-C_6alkyl;

R is H, C_1-C_6 alkyl or –C(O)-C_1-C_6alkyl;

R_1 is H or C_1-C_6 alkyl;

R_2 is H or C_1-C_6 alkyl;

R_4 is H or C_1-C_6 alkyl;

R_5 is H or C_1-C_6 alkyl;

X is selected from the group consisting of H; C_1-C_6 alkyl, -OH, C_1-C_6 alkoxy, $-CO_2H$, $-C(O)NR^cR^d$, and heteroaryl including from 5 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C_1-C_3 alkyl), O, and S, wherein the heteroaryl ring may be optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl and phenyl; and

R^c and R^d are each independently selected from the group consisting of H, C_1-C_6 alkyl, and phenyl, or R^c and R^d together with the nitrogen to which they are attached, form heterocyclyl including from 4 to 6 ring atoms; wherein the heterocyclyl includes not more than two ring heteroatoms (including the nitrogen atom attached to R^c and R^d), and the second ring heteroatom, when present, is independently selected from the group consisting of N, NH, N(C_1-C_3 alkyl), O, and S; and wherein the heterocyclyl is optionally substituted with from 1-3 substituents independently selected from the group consisting of halogen, cyano, oxo, and C_1-C_6 alkyl.

27. The compound of claim 26, wherein R_1 is H.

28. The compound of claim 26 or 27, wherein R_2 is H.

29. The compound of any one of claims 26-28, wherein X is $-C(O)NR^cR^d$.

30. The compound of claim 29, wherein R^c and R^d are each independently selected from the group consisting of H, C_1-C_6 alkyl, and phenyl.

31. The compound of claim 30, wherein R^c and R^d are both H.

32. The compound of any one of claims 26-31, wherein R is H.

33. The compound of any one of claims 26-31, wherein R is $-C(O)$-C_1-C_6alkyl.

34. The compound of claim 33, wherein R is $-C(O)$-CH_3.

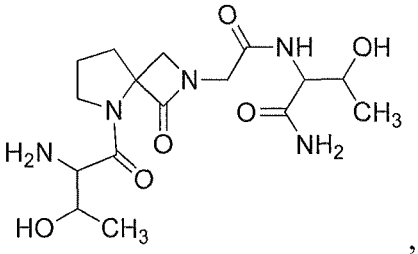
35. The compound of any one of claims 26-34, wherein R_5 is C_1-C_6 alkyl.

36. The compound of claim 35, wherein R_5 is $-CH_3$.

37. The compound of any one of claims 26-36, wherein R_4 is H.

38. The compound of any one of claims 26-37, wherein R_b is H.

39. The compound of claim 1, wherein the compound is selected from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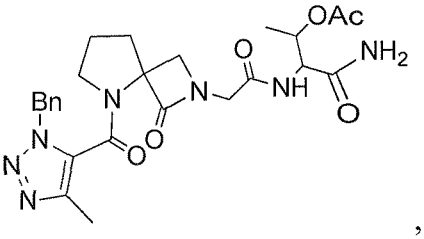
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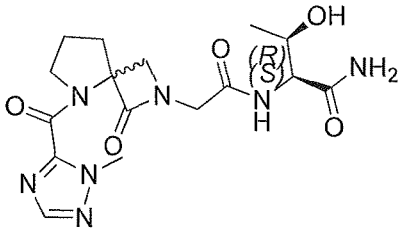
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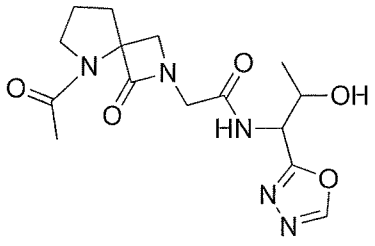
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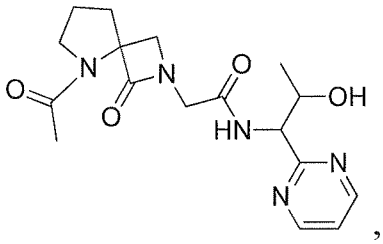
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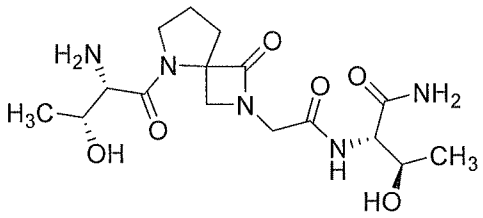
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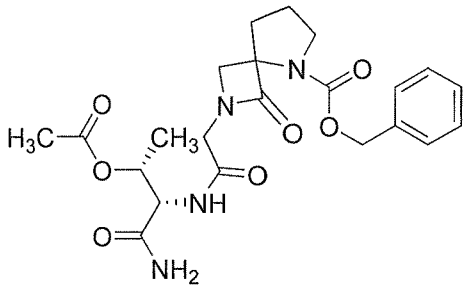
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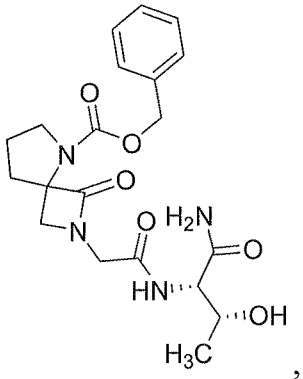
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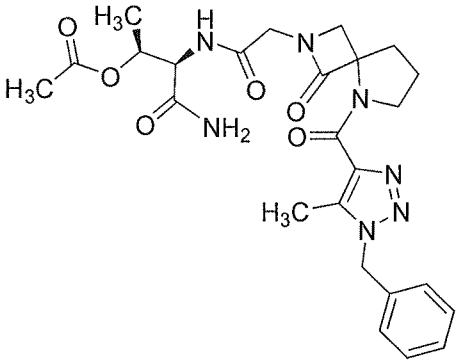
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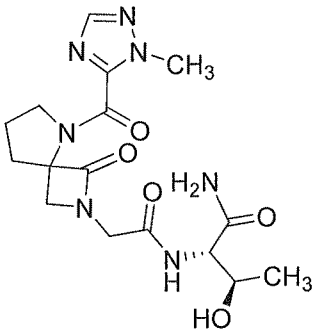
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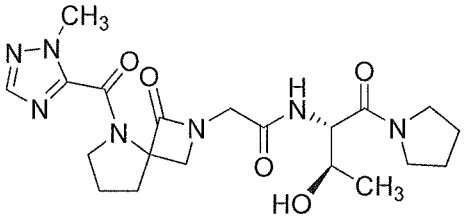
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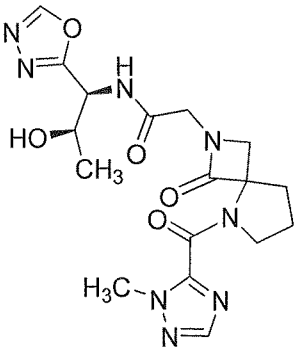
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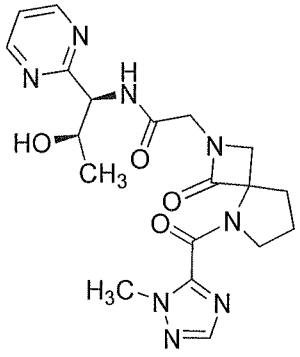
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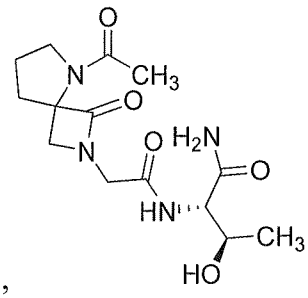
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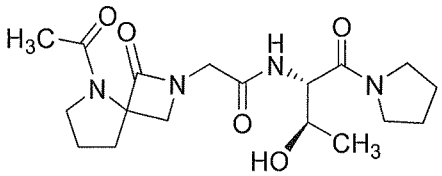
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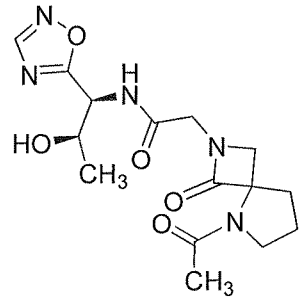
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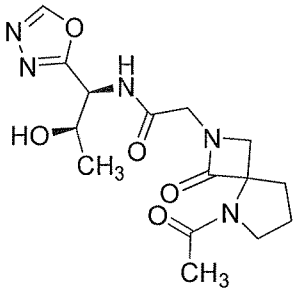
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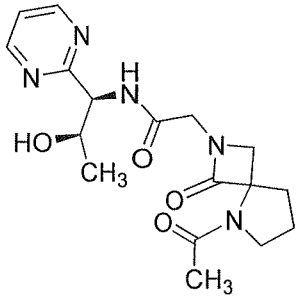
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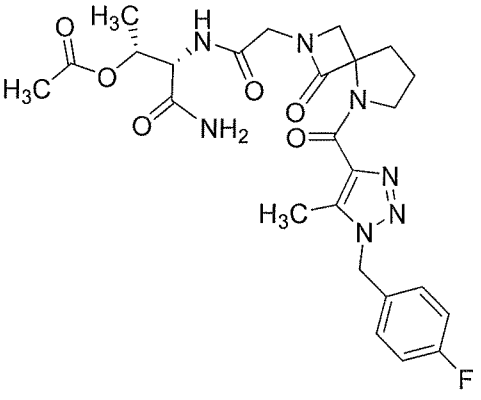
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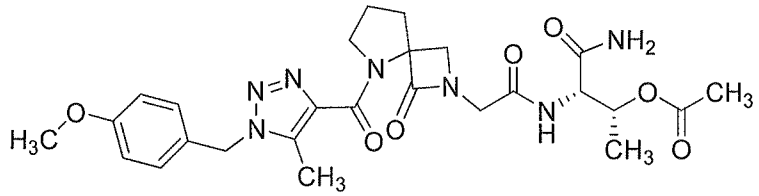
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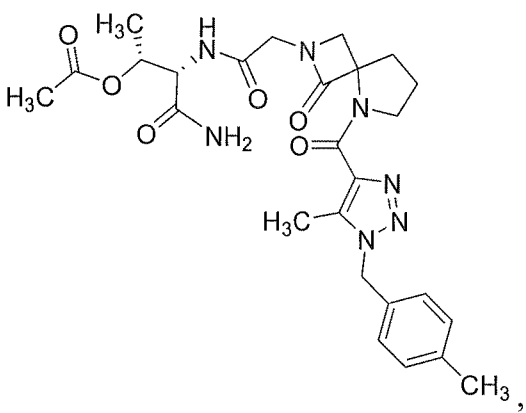
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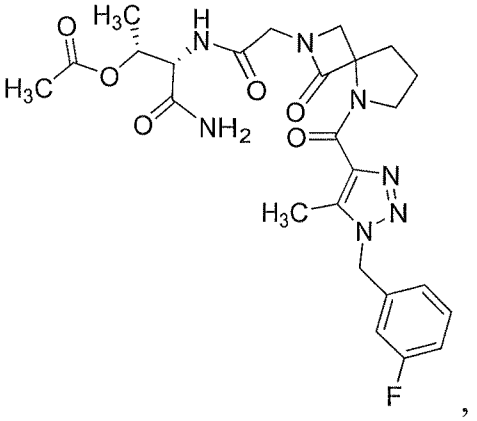
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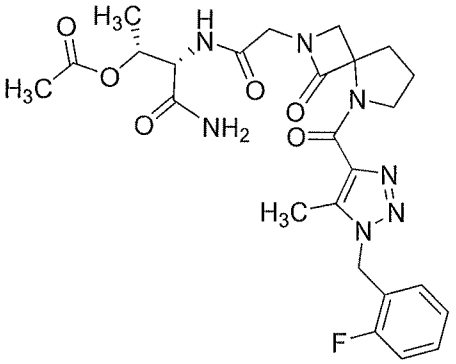
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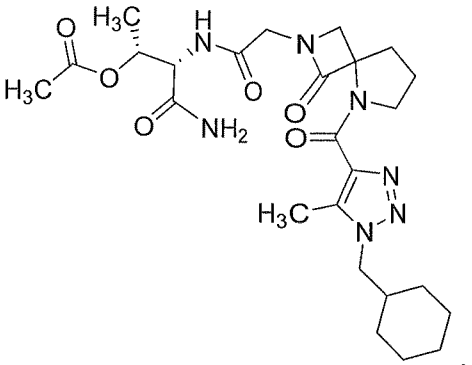
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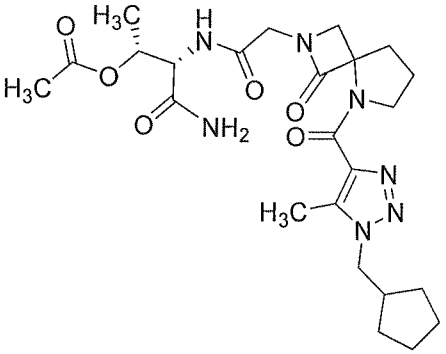
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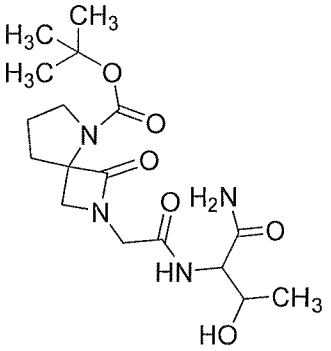
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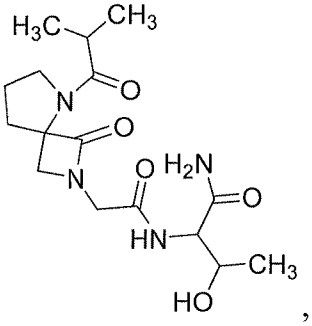
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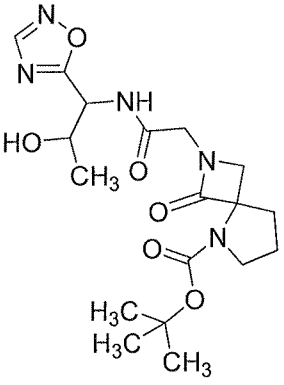
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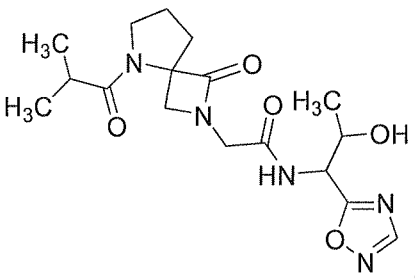
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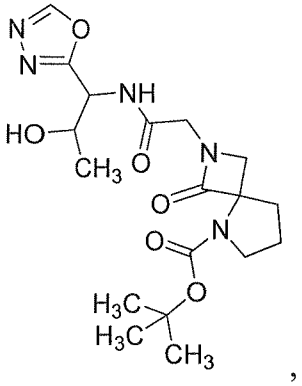
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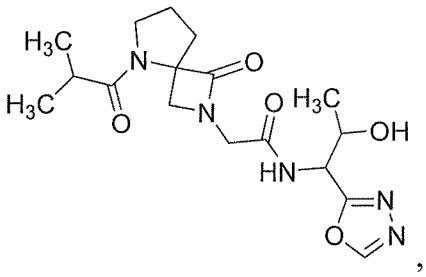

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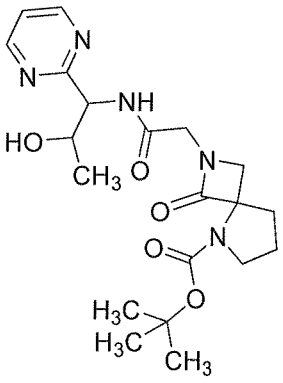

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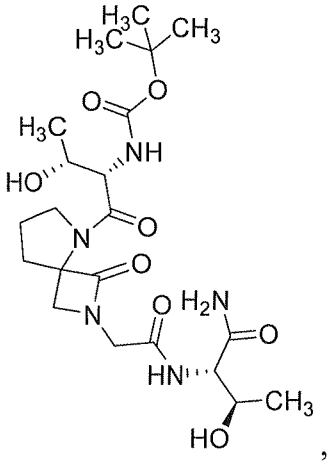
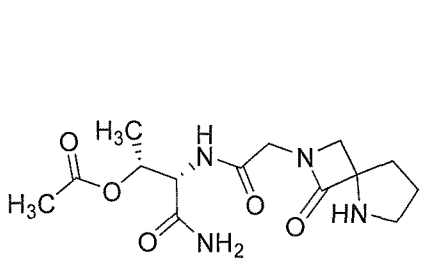


, or a

pharmaceutically acceptable salt, a stereoisomer, or an N-oxide thereof.

40. The compound of claim 26, wherein the compound is selected from the group consisting of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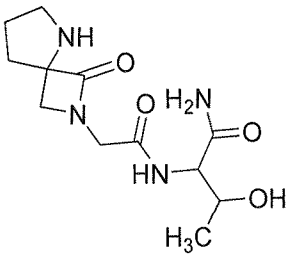
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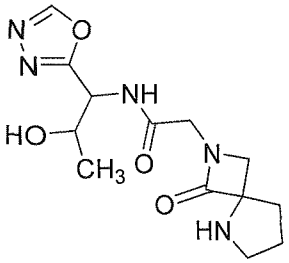
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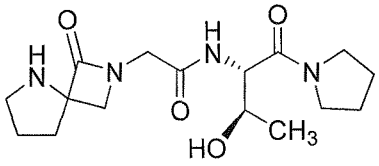
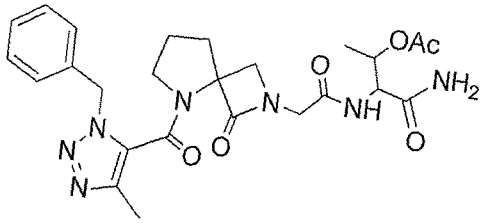
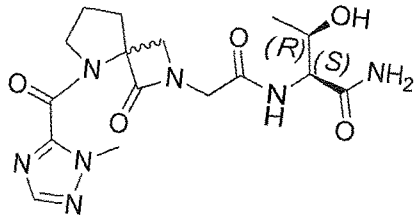
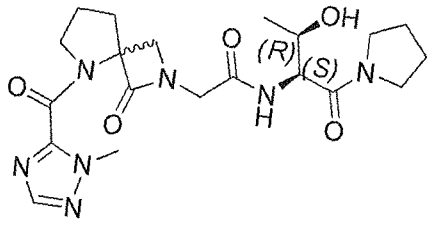
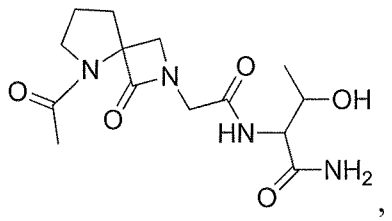

, or a pharmaceutically acceptable salt, a stereoisomer, or an N-oxide thereof.

41. The compound of claim 1, wherein the compound is selected from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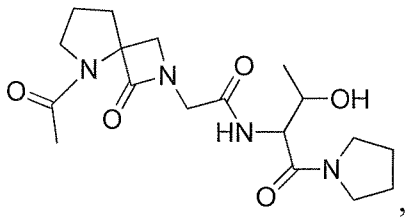
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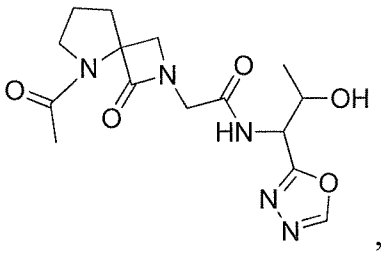
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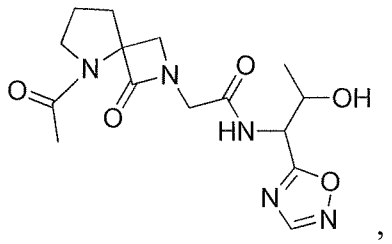
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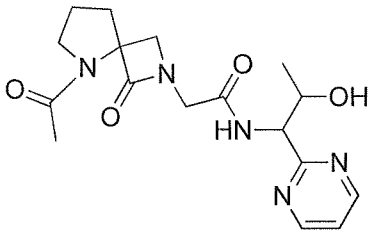
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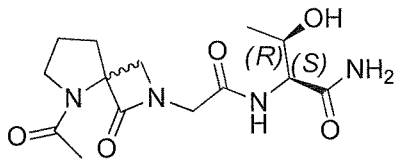
, or a pharmaceutically acceptable salt, a stereoisomer, or an N-oxide thereof.

42. A pharmaceutical composition comprising a compound of any one of claims 1-41, and a pharmaceutically acceptable excipient.

43. The pharmaceutical composition of claim 42, suitable for oral administration.

44. The pharmaceutical composition of claim 42, suitable for intravenous administration.

45. Use of a compound of any one of claims 1-41 in the manufacture of a medicament for treating depression, Alzheimer's disease, attention deficit disorder, schizophrenia, or anxiety, in a patient in need thereof.