

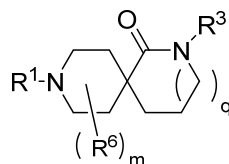
cardiac arrest to epilepsy. In addition, there are preliminary reports indicating similar involvement in the chronic neurodegeneration of Huntington's, Parkinson's and Parkinson's related conditions such as dyskinesia and L-dopa induced dyskinesia and Alzheimer's diseases. Activation of the NMDA receptor has been shown to be responsible for post-stroke
5 convulsions, and, in certain models of epilepsy, activation of the NMDA receptor has been shown to be necessary for the generation of seizures. Neuropsychiatric involvement of the NMDA receptor has also been recognized since blockage of the NMDA receptor Ca^{++} channel by the animal anesthetic PCP (phencyclidine) produces a psychotic state in humans similar to schizophrenia (reviewed in Johnson, K. and Jones, S., 1990). Further, NMDA receptors have
10 also been implicated in certain types of spatial learning.

The NMDA receptor is believed to consist of several protein chains embedded in the postsynaptic membrane. The first two types of subunits discovered so far form a large extracellular region, which probably contains most of the allosteric binding sites, several
15 transmembrane regions looped and folded so as to form a pore or channel, which is permeable to Ca^{++} , and a carboxyl terminal region. The opening and closing of the channel is regulated by the binding of various ligands to domains (allosteric sites) of the protein residing on the extracellular surface. The binding of the ligands is thought to affect a conformational change in the overall structure of the protein which is ultimately reflected in the channel opening, partially opening, partially closing, or closing.

20 A need continues to exist in the art for novel and more specific and/or potent compounds that are capable of modulating NMDA receptors, and provide pharmaceutical benefits. In addition, a need continues to exist in the medical arts for orally deliverable forms of such compounds.

SUMMARY

The present disclosure includes compounds that can be NMDA modulators. More specifically, the present disclosure provides ~~In one aspect of the present disclosure, there is provided~~ a compound represented by:



or a pharmaceutically acceptable salt and/or stereoisomer thereof, wherein

R^1 is independently selected from the group consisting of H, $-C_1-C_6$ alkyl, $-C(O)-C_1-C_6$ alkyl, $-C(O)-O-C_1-C_6$ alkyl, and $-S(O)_w-C_1-C_6$ alkyl, wherein C_1-C_6 alkyl is optionally substituted by one, two or three substituents each independently selected from R^P ;

q is 0, 1, 2, or 3;

5 w is 0, 1 or 2;

R^6 , if present, is independently, for each occurrence, selected from the group consisting of H, $-C_1-C_6$ alkyl, hydroxyl, and halogen, wherein C_1-C_6 alkyl is optionally substituted by one, two or three substituents each independently selected from R^P ;

m is 0, 1, 2, 3, or 4;

10 R^3 is selected from the group consisting of H, $-C_1-C_6$ alkyl, $-C(O)-R^{31}$, and $-C(O)-O-R^{32}$, wherein C_1-C_6 alkyl is optionally substituted by one, two or three substituents each independently selected from R^P ;

R^{31} is selected from the group consisting of H, $-C_1-C_6$ alkyl, and $-C_3-C_6$ cycloalkyl, wherein C_1-C_6 alkyl is optionally substituted by one, two or three substituents each
15 independently selected from R^P , and C_3-C_6 cycloalkyl is optionally substituted by one, two or three substituents each independently selected from R^Q ;

R^{32} is selected from the group consisting of $-C_1-C_6$ alkyl, and $-C_3-C_6$ cycloalkyl, wherein C_1-C_6 alkyl is optionally substituted by one, two or three substituents each independently selected from R^P , and C_3-C_6 cycloalkyl is optionally substituted by one, two or three
20 substituents each independently selected from R^Q ;

R^P is independently, for each occurrence, selected from the group consisting of $-C(O)NR^aR^b$, $-NR^aR^b$, hydroxyl, $-SH$, and halogen;

R^Q is independently, for each occurrence, selected from the group consisting of $-C(O)NR^aR^b$, $-NR^aR^b$, $-C_1-C_3$ alkyl, hydroxyl, and halogen; and

25 R^a and R^b are each independently, for each occurrence, selected from the group consisting of H, $-C_1-C_3$ alkyl, phenyl, and benzyl, wherein each C_1-C_3 alkyl, phenyl, and benzyl is optionally substituted by one, two or three substituents each independently selected from the group consisting of hydroxyl, C_1-C_3 alkyl, and halogen.

~~In another aspect of the present disclosure, there is provided a compound selected from
30 the group consisting of any one of Compounds AA to AH, or a pharmaceutically acceptable salt and/or a stereoisomer thereof.~~

when q is 2 or 3:

w is 0, 1 or 2;

m is 0, 1, 2, 3, or 4;

R³¹ is selected from the group consisting of H, -C₁-C₆alkyl, and -C₃-C₆cycloalkyl, wherein C₁-C₆alkyl is optionally substituted by one, two or three substituents each independently selected from R^P, and C₃-C₆cycloalkyl is optionally substituted by one, two or three substituents each independently selected from R^Q;

20 R³² is selected from the group consisting of -C₁-C₆alkyl, and -C₃-C₆cycloalkyl, wherein
C₁-C₆alkyl is optionally substituted by one, two or three substituents each independently
selected from R^P, and C₃-C₆cycloalkyl is optionally substituted by one, two or three
substituents each independently selected from R^Q;

25 R^p is independently, for each occurrence, selected from the group consisting of
-C(O)NR^aR^b, -NR^aR^b, hydroxyl, -SH, and halogen;

R^Q is independently, for each occurrence, selected from the group consisting of
-C(O)NR^aR^b, -NR^aR^b, -C₁-C₃alkyl, hydroxyl, and halogen; and

R^a and R^b are each independently, for each occurrence, selected from the group consisting of H, -C₁-C₃alkyl, phenyl, and benzyl, wherein each C₁-C₃alkyl, phenyl, and benzyl is optionally substituted by one, two or three substituents each independently selected from the group consisting of hydroxyl, C₁-C₃alkyl, and halogen; and

5 when q is 1:

R¹ is independently selected from the group consisting of -C(O)-C₁-C₆alkyl and -S(O)_w-C₁-C₆alkyl, wherein each C₁-C₆alkyl and C₁-C₃alkyl is optionally substituted by one, two or three substituents each independently selected from R^P;

w is 0, 1, or 2;

10 R⁶, if present, is independently, for each occurrence, selected from the group consisting of H, -C₁-C₆alkyl, hydroxyl, and halogen, wherein C₁-C₆alkyl is optionally substituted by one, two or three substituents each independently selected from R^P;

m is 0, 1, 3, or 4;

15 R³ is selected from the group consisting of H, -C₁-C₆alkyl, -C(O)-R³¹, and -C(O)-O-R³², wherein C₁-C₆alkyl is optionally substituted by one, two or three substituents each independently selected from R^P;

R³¹ is selected from the group consisting of H, -C₁-C₆alkyl, and -C₃-C₆cycloalkyl, wherein C₁-C₆alkyl is optionally substituted by one, two or three substituents each independently selected from R^P, and C₃-C₆cycloalkyl is optionally substituted by one, two or three substituents each independently selected from R^Q;

20 R³² is selected from the group consisting of -C₁-C₆alkyl, and -C₃-C₆cycloalkyl, wherein C₁-C₆alkyl is optionally substituted by one, two or three substituents each independently selected from R^P, and C₃-C₆cycloalkyl is optionally substituted by one, two or three substituents each independently selected from R^Q;

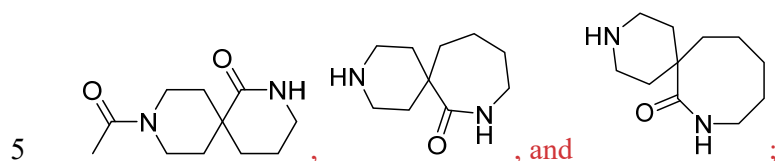
25 R^P is independently, for each occurrence, selected from the group consisting of -C(O)NR^aR^b, -NR^aR^b, hydroxyl, -SH, and halogen;

R^Q is independently, for each occurrence, selected from the group consisting of -C(O)NR^aR^b, -NR^aR^b, -C₁-C₃alkyl, hydroxyl, and halogen; and

30 R^a and R^b are each independently, for each occurrence, selected from the group consisting of H, -C₁-C₃alkyl, phenyl, and benzyl, wherein each C₁-C₃alkyl, phenyl, and benzyl

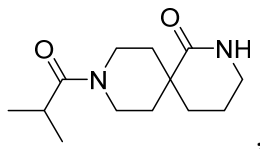
is optionally substituted by one, two or three substituents each independently selected from the group consisting of hydroxyl, C₁-C₃alkyl, and halogen.

In another aspect of the present disclosure, there is provided a compound selected from the group consisting of:



or a pharmaceutically acceptable salt and/or a stereoisomer thereof.

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



10 or a pharmaceutically acceptable salt and/or a stereoisomer thereof.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound disclosed herein, or a pharmaceutically acceptable salt and/or a stereoisomer thereof, and a pharmaceutically acceptable excipient.

15 In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt and/or a stereoisomer thereof, or the pharmaceutical composition 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.

20 In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt and/or a stereoisomer thereof, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a migraine in a patient in need thereof.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt and/or a stereoisomer thereof, or the

pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating neuropathic pain in a patient in need thereof.

In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt and/or a stereoisomer thereof, or the
5 pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating traumatic brain injury in a patient in need thereof.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a neurodevelopmental disorder related to synaptic dysfunction in a
10 patient in need thereof

In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt and/or a stereoisomer thereof, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a cognitive impairment disorder in a patient in need thereof.

5 In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt and/or a stereoisomer thereof, or the pharmaceutical composition disclosed herein, for use in treating depression, Alzheimer's disease, attention deficit disorder, schizophrenia, anxiety, migraine, neuropathic pain, traumatic
10 brain injury, neurodevelopmental disorder related to synaptic dysfunction, or cognitive impairment disorder in a patient in need thereof.

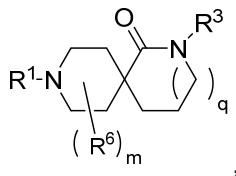
Also provided herein are pharmaceutically acceptable compositions comprising a disclosed compound, and a pharmaceutically acceptable excipient. Such compositions can be suitable for administration to a patient orally, parenterally, topically, intravaginally, intrarectally, sublingually, ocularly, transdermally, or nasally.

15 In one example, a method of treating a condition selected from the group consisting of

CLAIMS

What is claimed is:

1. A compound represented by



or a pharmaceutically acceptable salt and/or a stereoisomer thereof, wherein:

when q is 2 or 3:

R¹ is independently selected from the group consisting of H, -C₁-C₆alkyl, -C(O)-C₁-C₆alkyl, ~~-C(O)-O-C₁-C₆alkyl~~, and -S(O)_w-C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted by one, two or three ~~substitutents~~substituents each independently selected from R^P;

~~q is 0, 1, 2, or 3;~~

w is 0, 1 or 2;

R⁶, if present, is independently, for each occurrence, selected from the group consisting of H, -C₁-C₆alkyl, hydroxyl, and halogen, wherein C₁-C₆alkyl is optionally substituted by one, two or three ~~substitutents~~substituents each independently selected from R^P;

m is 0, 1, 2, 3, or 4;

R³ is selected from the group consisting of H, -C₁-C₆alkyl, -C(O)-R³¹, and -C(O)-O-R³², wherein C₁-C₆alkyl is optionally substituted by one, two or three ~~substitutents~~substituents each independently selected from R^P;

R³¹ is selected from the group consisting of H, -C₁-C₆alkyl, and -C₃-C₆cycloalkyl, wherein C₁-C₆alkyl is optionally substituted by one, two or three ~~substitutents~~substituents each independently selected from R^P, and C₃-C₆cycloalkyl is optionally substituted by one, two or three ~~substitutents~~substituents each independently selected from R^Q;

R³² is selected from the group consisting of -C₁-C₆alkyl, and -C₃-C₆cycloalkyl, wherein C₁-C₆alkyl is optionally substituted by one, two or three ~~substitutents~~substituents

each independently selected from R^P , and C_3 - C_6 cycloalkyl is optionally substituted by one, two or three ~~substitutents~~ substituents each independently selected from R^Q ;

R^P is independently, for each occurrence, selected from the group consisting of $-C(O)NR^aR^b$, $-NR^aR^b$, hydroxyl, $-SH$, and halogen;

R^Q is independently, for each occurrence, selected from the group consisting of $-C(O)NR^aR^b$, $-NR^aR^b$, $-C_1$ - C_3 alkyl, hydroxyl, and halogen; and

R^a and R^b are each independently, for each occurrence, selected from the group consisting of H, $-C_1$ - C_3 alkyl, phenyl, and benzyl, wherein each C_1 - C_3 alkyl, phenyl, and benzyl is optionally substituted by one, two or three substituents each independently selected from the group consisting of hydroxyl, C_1 - C_3 alkyl, and halogen; and

when q is 1:

R^1 is independently selected from the group consisting of $-C(O)-C_1$ - C_6 alkyl and $-S(O)_w-C_1$ - C_6 alkyl, wherein each C_1 - C_6 alkyl and C_1 - C_3 alkyl is optionally substituted by one, two or three substituents each independently selected from R^P ;

w is 0, 1, or 2;

R^6 , if present, is independently, for each occurrence, selected from the group consisting of H, $-C_1$ - C_6 alkyl, hydroxyl, and halogen, wherein C_1 - C_6 alkyl is optionally substituted by one, two or three substituents each independently selected from R^P ;

m is 0, 1, 3, or 4;

R^3 is selected from the group consisting of H, $-C_1$ - C_6 alkyl, $-C(O)-R^{31}$, and $-C(O)-O-R^{32}$, wherein C_1 - C_6 alkyl is optionally substituted by one, two or three substituents each independently selected from R^P ;

R^{31} is selected from the group consisting of H, $-C_1$ - C_6 alkyl, and $-C_3$ - C_6 cycloalkyl, wherein C_1 - C_6 alkyl is optionally substituted by one, two or three substituents each independently selected from R^P , and C_3 - C_6 cycloalkyl is optionally substituted by one, two or three substituents each independently selected from R^Q ;

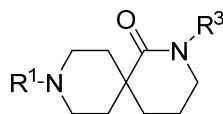
R^{32} is selected from the group consisting of $-C_1$ - C_6 alkyl, and $-C_3$ - C_6 cycloalkyl, wherein C_1 - C_6 alkyl is optionally substituted by one, two or three substituents each independently selected from R^P , and C_3 - C_6 cycloalkyl is optionally substituted by one, two or three substituents each independently selected from R^Q ;

R^P is independently, for each occurrence, selected from the group consisting of -C(O)NR^aR^b, -NR^aR^b, hydroxyl, -SH, and halogen;

R^Q is independently, for each occurrence, selected from the group consisting of -C(O)NR^aR^b, -NR^aR^b, -C₁-C₃alkyl, hydroxyl, and halogen; and

R^a and R^b are each independently, for each occurrence, selected from the group consisting of H, -C₁-C₃alkyl, phenyl, and benzyl, wherein each C₁-C₃alkyl, phenyl, and benzyl is optionally substituted by one, two or three substituents each independently selected from the group consisting of hydroxyl, C₁-C₃alkyl, and halogen.

2. The compound of claim 1, wherein the compound is represented by:



or a pharmaceutically acceptable salt and/or a stereoisomer thereof, wherein:

~~R¹ is independently selected from the group consisting of H, -C₁-C₆alkyl, -C(O)-C₁-C₆alkyl, and -C(O)-O-C₁-C₆alkyl,~~ wherein C₁-C₆alkyl is optionally substituted by one, two or three ~~substituents-substituents~~ each independently selected from R^P;

R³ is selected from the group consisting of H and -C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted by one, two or three ~~substituents-substituents~~ each independently selected from R^P;

R^P is independently, for each occurrence, selected from the group consisting of -C(O)NR^aR^b, -NR^aR^b, hydroxyl, -SH, and halogen; and

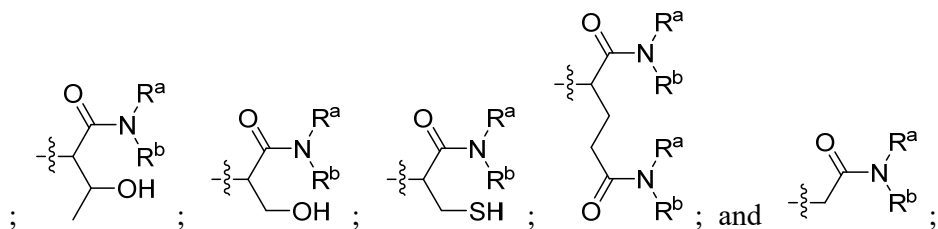
R^a and R^b are each independently, for each occurrence, selected from the group consisting of H, -C₁-C₃alkyl, phenyl, and benzyl, wherein each C₁-C₃alkyl, phenyl, and benzyl is optionally substituted by one, two or three substituents each independently selected from the group consisting of hydroxyl, C₁-C₃alkyl, and halogen.

3. The compound of claim 1 or 2, wherein R¹ is -C(O)-C₁-C₄alkyl.

4. The compound of any one of claims 1-3, wherein R³ is H.

5. The compound of any one of claims 1-3, wherein R³ is -C₁-C₆alkyl optionally substituted by one, two or three substituents independently selected from R^P.

6. The compound of claim 5, wherein R³ is selected from the group consisting of:



wherein:

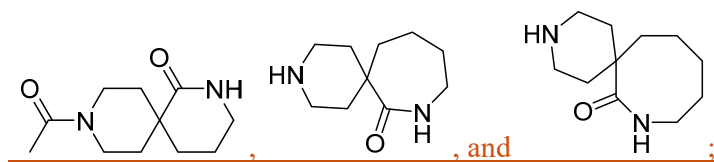
R^a and R^b are each independently selected for each occurrence from the group consisting of H and -C₁-C₃alkyl.

7. The compound of claim 6, wherein R^a and R^b are H.

8. The compound of claim 1, wherein m is 0.

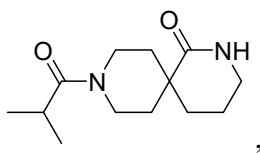
9. The compound of claim 1, wherein when q is 2 or 3, m is 1, 2 or 3; or when q is 1, m is 1 or 3, and R⁶ is F.

10. A compound selected from the group consisting of: any one of Compounds AA to AH,



or a pharmaceutically acceptable salt and/or a stereoisomer thereof.

11. A compound represented by



or a pharmaceutically acceptable salt and/or a stereoisomer thereof.

12. A pharmaceutical composition comprising the compound of any one of claims 1-11, or a pharmaceutically acceptable salt and/or a stereoisomer thereof, and a pharmaceutically acceptable excipient.

13. The pharmaceutical composition of claim 12, suitable for oral administration, parenteral administration, topical administration, intravaginal administration, intrarectal administration, sublingual administration, ocular administration, transdermal administration, or nasal administration.
14. Use of a compound of any one of claims 1-11, or a pharmaceutically acceptable salt and/or a stereoisomer thereof, or the pharmaceutical composition of claim 12 or 13, in the manufacture of a medicament for treating depression, Alzheimer's disease, attention deficit disorder, schizophrenia, or anxiety, in a patient in need thereof.
15. Use of a compound of any one of claims 1-11, or a pharmaceutically acceptable salt and/or a stereoisomer thereof, or the pharmaceutical composition of claim 12 or 13, in the manufacture of a medicament for treating a migraine in a patient in need thereof.
16. Use of a compound of any one of claims 1-11, or a pharmaceutically acceptable salt and/or a stereoisomer thereof, or the pharmaceutical composition of claim 12 or 13, in the manufacture of a medicament for treating neuropathic pain in a patient in need thereof.
17. Use of a compound of any one of claims 1-11, or a pharmaceutically acceptable salt and/or a stereoisomer thereof, or the pharmaceutical composition of claim 12 or 13, in the manufacture of a medicament for treating traumatic brain injury in a patient in need thereof.
18. Use of a compound of any one of claims 1-11, or a pharmaceutically acceptable salt and/or a stereoisomer thereof, or the pharmaceutical composition of claim 12 or 13, in the manufacture of a medicament for treating a neurodevelopmental disorder related to synaptic dysfunction in a patient in need thereof.
19. Use of a compound of any one of claims 1-11, or a pharmaceutically acceptable salt and/or a stereoisomer thereof, or the pharmaceutical composition of claim 12 or 13, in the manufacture of a medicament for treating a cognitive impairment disorder in a patient in need thereof.
20. A compound of any one of claims 1-11, or a pharmaceutically acceptable salt and/or a stereoisomer thereof, or the pharmaceutical composition of claim 12 or 13, for use in treating depression, Alzheimer's disease, attention deficit disorder, schizophrenia, anxiety, migraine, neuropathic pain, traumatic brain injury, neurodevelopmental disorder related to synaptic dysfunction, or cognitive impairment disorder in a patient in need thereof.