

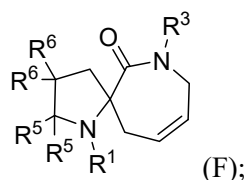
cardiac arrest to epilepsy. In addition, there are preliminary reports indicating similar involvement in the chronic neurodegeneration of Huntington's, Parkinson's and Parkinson's related conditions such as dyskinesia and L-dopa induced dyskinesia and Alzheimer's diseases. Activation of the NMDA receptor 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
25 specifically, the present disclosure provides a compound having the formula:



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

5 R^1 is independently selected from the group consisting of H, -C₁-C₄alkyl, -C(O)-C₁-C₄alkyl, -S(O)_w-C₁-C₄alkyl, and -C(O)-O-C₁-C₄alkyl, wherein C₁-C₄alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S;

w is 0, 1 or 2;

R^5 is independently selected for each occurrence from the group consisting of H, -C₁-C₄alkyl, and halogen, wherein C₁-C₄alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S;

10 R^6 is independently selected for each occurrence from the group consisting of H, -C₁-C₄alkyl, and halogen, wherein C₁-C₄alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S;

15 R^3 is selected from the group consisting of H, -C₁-C₄alkyl, -C₁-C₄alkyl-phenyl, -C(O)-R³¹, and -C(O)-O-R³², wherein C₁-C₄alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S, and phenyl is optionally substituted with one, two, or three substituents each independently selected from R^T;

20 R^{31} is selected from the group consisting of H, -C₁-C₄alkyl, -C₃-C₆cycloalkyl, and phenyl, wherein C₁-C₄alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S, and phenyl is optionally substituted with one, two, or three substituents each independently selected from R^T;

R^{32} is selected from the group consisting of H, -C₁-C₄alkyl, -C₃-C₆cycloalkyl, and phenyl, wherein C₁-C₄alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S, and phenyl is optionally substituted with one, two, or three substituents each independently selected from R^T; and

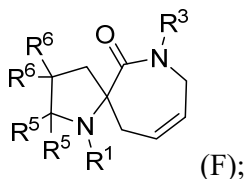
25 R^a and R^b are each independently for each occurrence selected from the group consisting of H, phenyl, and -C₁-C₄alkyl; or R^a and R^b taken together with the nitrogen

to which they are attached form a 4-6 membered heterocyclic ring, wherein C₁-C₄alkyl is optionally substituted with one, two, or three substituents each independently selected from -C₁-C₃alkoxy, hydroxyl, and halogen;

5 R^S is independently, for each occurrence, selected from the group consisting of -C(O)NR^aR^b, -NR^aR^b, hydroxyl, -C(O)-O-R^a, phenyl, and halogen, wherein each phenyl is optionally substituted with one, two, or three substituents each independently selected from the group consisting of -C₁-C₃alkoxy and halogen; and

R^T is independently, for each occurrence selected from the group consisting of -C(O)NR^aR^b, -NR^aR^b, -C₁-C₃alkoxy, hydroxyl, and halogen.

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



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

15 R¹ is independently selected from the group consisting of -C₁-C₄alkyl, -C(O)-C₁-C₄alkyl, -S(O)_w-C₁-C₄alkyl, and -C(O)-O-C₁-C₄alkyl, wherein C₁-C₄alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S; w is 0, 1 or 2;

R⁵ is independently selected for each occurrence from the group consisting of H, -C₁-C₄alkyl, and halogen, wherein C₁-C₄alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S;

20 R⁶ is independently selected for each occurrence from the group consisting of H, -C₁-C₄alkyl, and halogen, wherein C₁-C₄alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S;

25 R³ is selected from the group consisting of H, -C₁-C₄alkyl, -C₁-C₄alkyl-phenyl, -C(O)-R³¹, and -C(O)-O-R³², wherein C₁-C₄alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S, and phenyl is optionally substituted with one, two, or three substituents each independently selected from R^T;

R^{31} is selected from the group consisting of H, -C₁-C₄alkyl, -C₃-C₆cycloalkyl, and phenyl, wherein C₁-C₄alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S , and phenyl is optionally substituted with one, two, or three substituents each independently selected from R^T ;

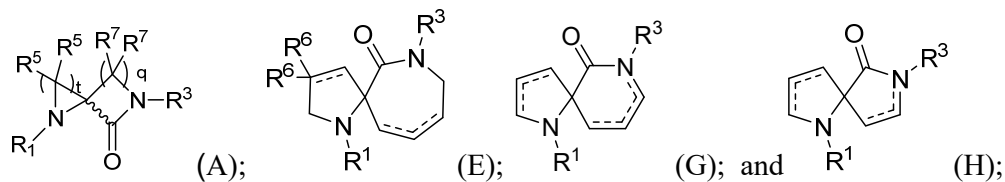
5 R^{32} is selected from the group consisting of H, -C₁-C₄alkyl, -C₃-C₆cycloalkyl, and phenyl, wherein C₁-C₄alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S , and phenyl is optionally substituted with one, two, or three substituents each independently selected from R^T ; and

10 R^a and R^b are each independently for each occurrence selected from the group consisting of H and phenyl; or R^a and R^b taken together with the nitrogen to which they are attached form a 4-6 membered heterocyclic ring, wherein C₁-C₄alkyl is optionally substituted with one, two, or three substituents each independently selected from -C₁-C₃alkoxy, hydroxyl, and halogen;

15 R^S is independently, for each occurrence, selected from the group consisting of -C(O)NR^aR^b, -NR^aR^b, hydroxyl, -C(O)-O-R^a, phenyl, and halogen, wherein each phenyl is optionally substituted with one, two, or three substituents each independently selected from the group consisting of -C₁-C₃alkoxy and halogen; and

R^T is independently, for each occurrence selected from the group consisting of -C(O)NR^aR^b, -NR^aR^b, -C₁-C₃alkoxy, hydroxyl, and halogen.

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



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

w is 0, 1 or 2;

25 R^5 is independently selected for each occurrence from the group consisting of H, -C₁-C₆alkyl, and halogen, wherein C₁-C₆alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S ;

R⁶ is independently selected for each occurrence from the group consisting of H, -C₁-C₆alkyl, and halogen, wherein C₁-C₆alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S; or

5 R⁵ and R⁶, or two R⁵ moieties, when present on adjacent carbons, form a 3-membered carbocyclic ring taken together with the adjacent carbons to which they are attached, optionally substituted by one or two substituents independently selected from the group consisting of halogen, hydroxyl, -C₁-C₃alkyl, -C₁-C₃alkoxy, -C(O)NR^aR^b, and -NR^aR^b;

10 R⁷ is independently selected for each occurrence from the group consisting of H, -C₁-C₆alkyl, phenyl, and halogen, wherein C₁-C₆alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S, and phenyl is optionally substituted with one, two, or three substituents each independently selected from the group consisting of -C(O)NR^aR^b, -NR^aR^b, -C₁-C₃alkyl, -C₁-C₃alkoxy, and hydroxyl;

R³ is selected from the group consisting of H, -C₁-C₆alkyl, phenyl, -C(O)-R³¹, and -C(O)-O-R³², wherein:

15 phenyl is optionally substituted with one, two, or three substituents each independently selected from R^T; and

C₁-C₆alkyl is optionally substituted with one, two, or three substituents each independently selected from the group consisting of -C(O)NR^aR^b, -NR^aR^b, hydroxyl, -SH, phenyl, -O-CH₂-phenyl, and halogen, wherein each phenyl is substituted with one, two, or three substituents each independently selected from the group consisting of -C₁-C₃alkoxy and halogen;

20

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

25

R³² is selected from the group consisting of H, -C₁-C₆alkyl, -C₃-C₆cycloalkyl, and phenyl, wherein C₁-C₆alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S, and phenyl is optionally substituted with one, two, or three substituents each independently selected from R^T; and

30

R^a and R^b are independently, for each occurrence, selected from the group consisting of H, and -C(O)-O-CH₂-phenyl, ; or R^a and R^b taken together with the nitrogen to which they are attached form a 4-6 membered heterocyclic ring, wherein phenyl is optionally substituted with one, two, or three substituents each independently selected from -C₁-C₃alkyl, -C₁-C₃alkoxy, hydroxyl, and halogen;

R^S is independently, for each occurrence, selected from the group consisting of -C(O)NR^aR^b, -NR^aR^b, hydroxyl, -SH, phenyl, -O-CH₂-phenyl, and halogen, wherein each phenyl is optionally substituted with one, two, or three substituents each independently selected from the group consisting of -C₁-C₃alkoxy and halogen;

R^T is independently, for each occurrence, selected from the group consisting of -C(O)NR^aR^b, -NR^aR^b, -C₁-C₃alkyl, -C₁-C₃alkoxy, hydroxyl, and halogen; and

wherein

for Formula A:

R¹ is independently selected from the group consisting of H, -C₁-C₆alkyl, -C(O)-C₁-C₆alkyl, and -S(O)_w-C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with one, two, or three substituents each independently selected from the group consisting of -C(O)NR^aR^b, -NR^aR^b, hydroxyl, -SH, phenyl, -O-CH₂-phenyl, and halogen, wherein each phenyl is substituted with one, two, or three substituents each independently selected from the group consisting of -C₁-C₃alkoxy and halogen;

t is 2 or 5, and q is 2, 3, 4, or 5; or,

t is 4, and q is 3, 4, or 5; or

t is 3 and q is 3;

for Formula E:

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 with one, two, or three substituents each independently selected from R^S;

== is either a single or double bond;

a double bond is present in the 5-membered ring, and only one R⁶ is present;

the one double bond in the 7-membered ring is present between the α and β ring carbons or the β and γ ring carbons, with respect to the spiro junction;

for Formula G:

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

$==$ is either a single or double bond;

there is one double bond in the 5-membered ring;

there is one double bond in the 6-membered ring;

10 if the double bond in the 6-membered ring is a $C=N$ bond, then R^3 is absent; and

for Formula H:

15 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 with one, two, or three substituents each independently selected from R^S ;

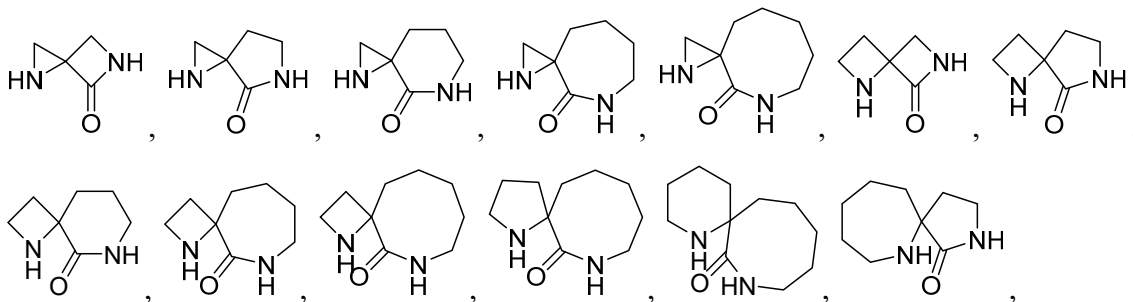
$==$ is either a single or double bond;

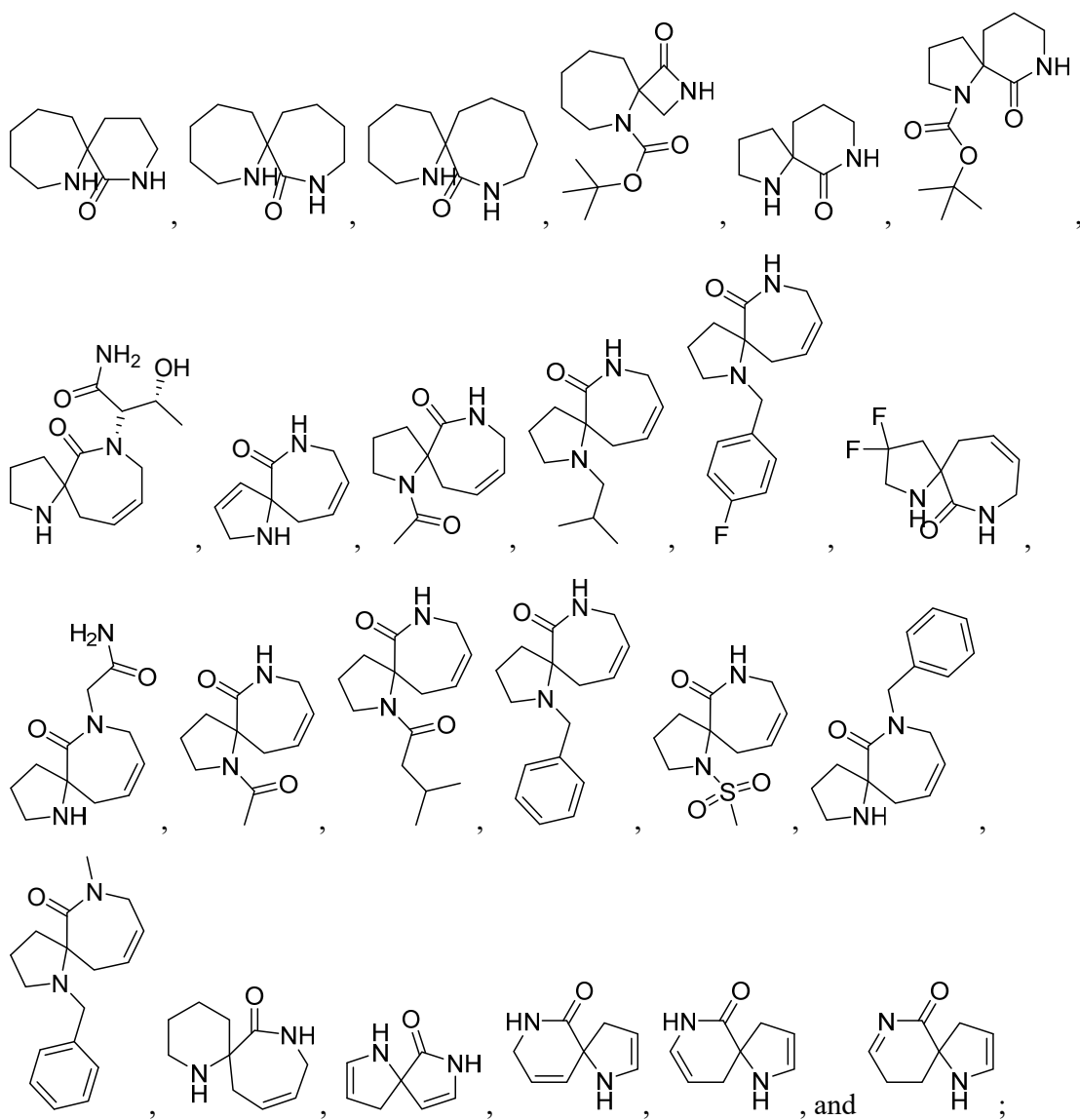
there is one double bond in the ring without a carbonyl group;

there is one double bond in the ring with a carbonyl group; and

20 if the double bond in the ring with a carbonyl group is a $C=N$ bond, then R^3 is absent.

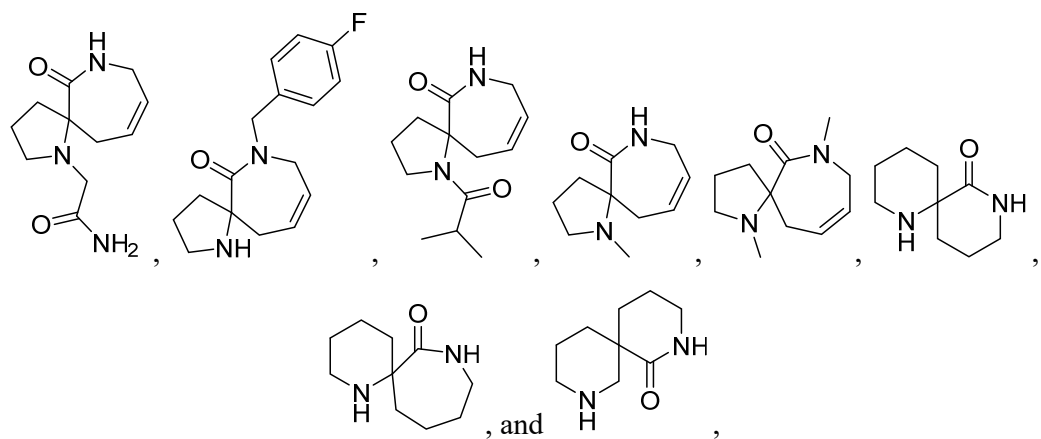
In one aspect of the present disclosure, there is provided a compound selected from the group consisting of:





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

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



or a pharmaceutically acceptable salt and/or stereoisomer thereof.

In another aspect of the present disclosure, there is provided a pharmaceutical
 5 composition comprising the compound disclosed herein, and a pharmaceutically acceptable
 excipient.

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.

5 In another aspect of the present disclosure, there is provided a use of a compound 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 in the manufacture of a medicament for treating neuropathic pain in a patient in need thereof.

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

15 In another aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for treating a cognitive impairment disorder in a patient in need thereof.

In a further aspect of the present disclosure, there is provided a compound disclosed
20 herein, or the pharmaceutical composition disclosed herein, 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.

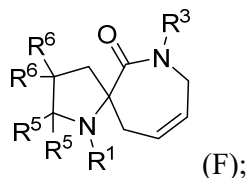
Also provided herein are pharmaceutically acceptable compositions comprising a
25 disclosed compound, and a pharmaceutically acceptable excipient. Such compositions can be suitable for administration to a patient orally, parenterally, topically, intravaginally, intrarectally, sublingually, ocularly,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

In one example, 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 disorder or
5 syndrome, a behavior disorder, an impulse control disorder, a substance abuse disorder, a sleep disorder, a cognitive impairment disorder such as a memory disorder or 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, Rett syndrome, cerebral palsy, drug-induced optic neuritis, ischemic retinopathy,
10 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, fibromyalgia, acute neuropathic pain, and chronic neuropathic pain, in a patient in need thereof is provided. Such methods may comprise administering to a patient a
15 therapeutically effective amount of a disclosed compound, or a pharmaceutically acceptable salt, a stereoisomer, and/or an N-oxide thereof, or a pharmaceutical composition including a disclosed compound, or a pharmaceutically acceptable salt, a stereoisomer, and/or an N-oxide thereof.

In various examples, a method of this disclosure includes treating depression. In

What is claimed is:

1. A compound represented by



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

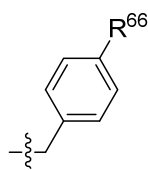
- 5 R^1 is independently selected from the group consisting of -C₁-C₄alkyl, -C(O)-C₁-C₄alkyl, -S(O)_w-C₁-C₄alkyl, and -C(O)-O-C₁-C₄alkyl, wherein C₁-C₄alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S;
w is 0, 1 or 2;
- 10 R^5 is independently selected for each occurrence from the group consisting of H, -C₁-C₄alkyl, and halogen, wherein C₁-C₄alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S;
- R^6 is independently selected for each occurrence from the group consisting of H, -C₁-C₄alkyl, and halogen, wherein C₁-C₄alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S;
- 15 R^3 is selected from the group consisting of H, -C₁-C₄alkyl, -C₁-C₄alkyl-phenyl, -C(O)-R³¹, and -C(O)-O-R³², wherein C₁-C₄alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S, and phenyl is optionally substituted with one, two, or three substituents each independently selected from R^T;
- 20 R^{31} is selected from the group consisting of H, -C₁-C₄alkyl, -C₃-C₆cycloalkyl, and phenyl, wherein C₁-C₄alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S, and phenyl is optionally substituted with one, two, or three substituents each independently selected from R^T;
- 25 R^{32} is selected from the group consisting of H, -C₁-C₄alkyl, -C₃-C₆cycloalkyl, and phenyl, wherein C₁-C₄alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S, and phenyl is optionally substituted with one, two, or three substituents each independently selected from R^T; and

R^a and R^b are each independently for each occurrence selected from the group consisting of H and phenyl; or R^a and R^b taken together with the nitrogen to which they are attached form a 4-6 membered heterocyclic ring, wherein C_1 - C_4 alkyl is optionally substituted with one, two, or three substituents each independently selected from - C_1 - C_3 alkoxy, hydroxyl, and halogen;

R^S is independently, for each occurrence, selected from the group consisting of - $C(O)NR^aR^b$, - NR^aR^b , hydroxyl, - $C(O)-O-R^a$, phenyl, and halogen, wherein each phenyl is optionally substituted with one, two, or three substituents each independently selected from the group consisting of - C_1 - C_3 alkoxy and halogen; and

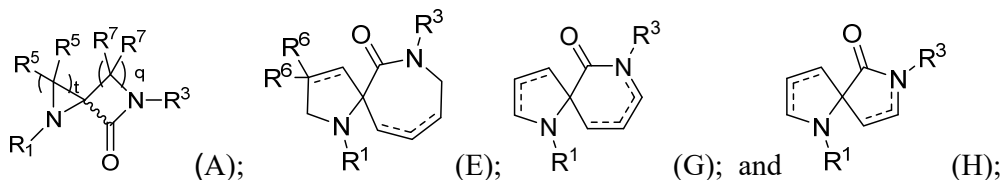
R^T is independently, for each occurrence selected from the group consisting of - $C(O)NR^aR^b$, - NR^aR^b , - C_1 - C_3 alkoxy, hydroxyl, and halogen.

2. The compound of claim 1, wherein R^1 is H, methyl or - CH_2 -phenyl optionally substituted by halogen.
3. The compound of claim 1, wherein R^1 is - $C(O)-C_1$ - C_4 alkyl.
4. The compound of claim 3, wherein R^1 is - $C(O)CH(CH_3)_2$.
5. The compound of claim 1, wherein R^1 is - $CH_2C(O)NH_2$.
6. The compound of any one of claims 1-5, wherein each of R^5 and R^6 is H.

7. The compound of any one of claims 1-6, wherein R^3 is H, methyl or  ;

wherein R^{66} is selected from the group consisting of H, F and - C_1 - C_3 alkoxy.

8. A compound represented by a formula selected from the group consisting of:



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

w is 0, 1 or 2;

R⁵ is independently selected for each occurrence from the group consisting of H, -C₁-C₆alkyl, and halogen, wherein C₁-C₆alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S;

5 R⁶ is independently selected for each occurrence from the group consisting of H, -C₁-C₆alkyl, and halogen, wherein C₁-C₆alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S; or

R⁵ and R⁶, or two R⁵ moieties, when present on adjacent carbons, form a 3-membered carbocyclic ring taken together with the adjacent carbons to which they are attached, optionally substituted by one or two substituents independently selected from the group consisting of halogen, hydroxyl, -C₁-C₃alkyl, -C₁-C₃alkoxy, -C(O)NR^aR^b, and -NR^aR^b;

10 R⁷ is independently selected for each occurrence from the group consisting of H, -C₁-C₆alkyl, phenyl, and halogen, wherein C₁-C₆alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S, and phenyl is optionally substituted with one, two, or three substituents each independently selected from the group consisting of -C(O)NR^aR^b, -NR^aR^b, -C₁-C₃alkyl, -C₁-C₃alkoxy, and hydroxyl;

15 R³ is selected from the group consisting of H, -C₁-C₆alkyl, phenyl, -C(O)-R³¹, and -C(O)-O-R³², wherein:

20 phenyl is optionally substituted with one, two, or three substituents each independently selected from R^T; and

C₁-C₆alkyl is optionally substituted with one, two, or three substituents each independently selected from the group consisting of -C(O)NR^aR^b, -NR^aR^b, hydroxyl, -SH, phenyl, -O-CH₂-phenyl, and halogen, wherein each phenyl is substituted with one, two, or three substituents each independently selected from the group consisting of -C₁-C₃alkoxy and halogen;

25 R³¹ is selected from the group consisting of H, -C₁-C₆alkyl, -C₃-C₆cycloalkyl, and phenyl, wherein C₁-C₆alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S, and each of C₃-C₆cycloalkyl and phenyl is optionally substituted with one, two, or three substituents each independently selected from R^T;

30

R³² is selected from the group consisting of H, -C₁-C₆alkyl, -C₃-C₆cycloalkyl, and phenyl, wherein C₁-C₆alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S, and phenyl is optionally substituted with one, two, or three substituents each independently selected from R^T; and

5 R^a and R^b are independently, for each occurrence, selected from the group consisting of H, and -C(O)-O-CH₂-phenyl, ; or R^a and R^b taken together with the nitrogen to which they are attached form a 4-6 membered heterocyclic ring, wherein phenyl is optionally substituted with one, two, or three substituents each independently selected from -C₁-C₃alkyl, -C₁-C₃alkoxy, hydroxyl, and halogen;

10 R^S is independently, for each occurrence, selected from the group consisting of -C(O)NR^aR^b, -NR^aR^b, hydroxyl, -SH, phenyl, -O-CH₂-phenyl, and halogen, wherein each phenyl is optionally substituted with one, two, or three substituents each independently selected from the group consisting of -C₁-C₃alkoxy and halogen;

15 R^T is independently, for each occurrence, selected from the group consisting of -C(O)NR^aR^b, -NR^aR^b, -C₁-C₃alkyl, -C₁-C₃alkoxy, hydroxyl, and halogen; and

wherein

for Formula A:

20 R¹ is independently selected from the group consisting of H, -C₁-C₆alkyl, -C(O)-C₁-C₆alkyl, and -S(O)_w-C₁-C₆alkyl, wherein C₁-C₆alkyl is optionally substituted with one, two, or three substituents each independently selected from the group consisting of -C(O)NR^aR^b, -NR^aR^b, hydroxyl, -SH, phenyl, -O-CH₂-phenyl, and halogen, wherein each phenyl is substituted with one, two, or three substituents each independently selected from the group consisting of -C₁-C₃alkoxy and halogen;

t is 2 or 5, and q is 2, 3, 4, or 5; or,

25 t is 4, and q is 3, 4, or 5; or

t is 3 and q is 3;

for Formula E:

30 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 with one, two, or three substituents each independently selected from R^S;

$\equiv$ is either a single or double bond;

a double bond is present in the 5-membered ring, and only one R^6 is present;

the one double bond in the 7-membered ring is present between the α and β ring carbons or the β and γ ring carbons, with respect to the spiro junction;

5 for Formula G:

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

$\equiv$ is either a single or double bond;

10 there is one double bond in the 5-membered ring;

there is one double bond in the 6-membered ring;

if the double bond in the 6-membered ring is a $C=N$ bond, then R^3 is absent; and

for Formula H:

15 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 with one, two, or three substituents each independently selected from R^S ;

$\equiv$ is either a single or double bond;

there is one double bond in the ring without a carbonyl group;

20 there is one double bond in the ring with a carbonyl group; and

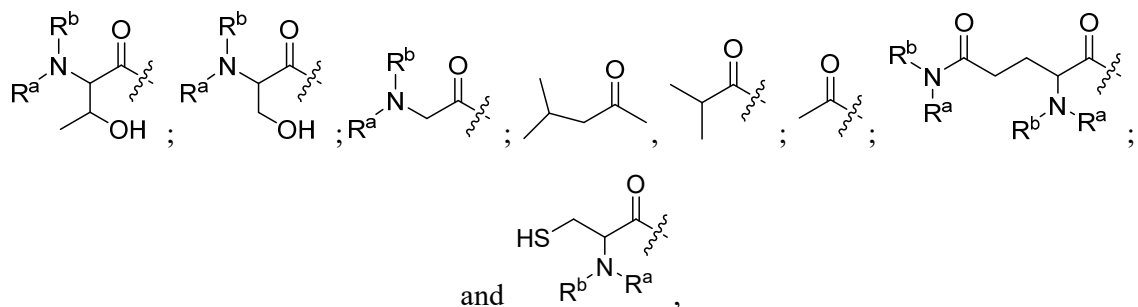
if the double bond in the ring with a carbonyl group is a $C=N$ bond, then R^3 is absent.

9. The compound of claim 8, wherein R^1 is H.

10. The compound of claim 8, wherein for Formulae E, G and H, R^1 is $-C(O)-O-tert$ -butyl.

25 11. The compound of claim 10, wherein R^1 is $-C(O)-C_1-C_6$ alkyl, wherein C_1-C_6 alkyl is optionally substituted with one, two, or three substituents each independently selected from R^S .

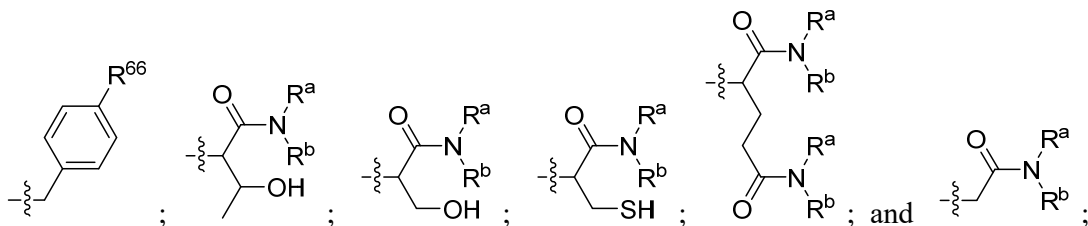
12. The compound of claim 11, wherein R^1 is selected from the group consisting of:



wherein R^a and R^b are independently, for each occurrence, H.

13. The compound of claim 8, wherein R^1 is $-C_1-C_6$ alkyl optionally substituted by one, two or three substituents independently selected from the group consisting of $-C(O)NR^aR^b$, hydroxyl, $-SH$, halogen, and phenyl, wherein phenyl is substituted by $-C_1-C_3$ alkoxy or halogen.

14. The compound of claim 13, wherein R^1 is selected from the group consisting of:



wherein R^{66} is methoxy; and R^a and R^b are independently, for each occurrence, H.

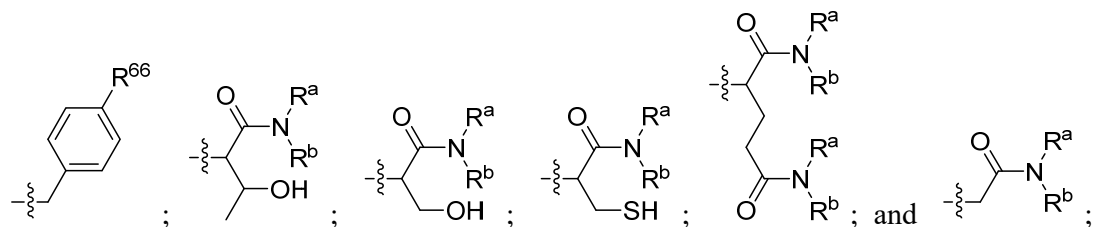
10

15. The compound of any one of claims 8-14, wherein each R^5 , R^6 and R^7 is H.

16. The compound of any one of claims 8-15, wherein R^3 is H.

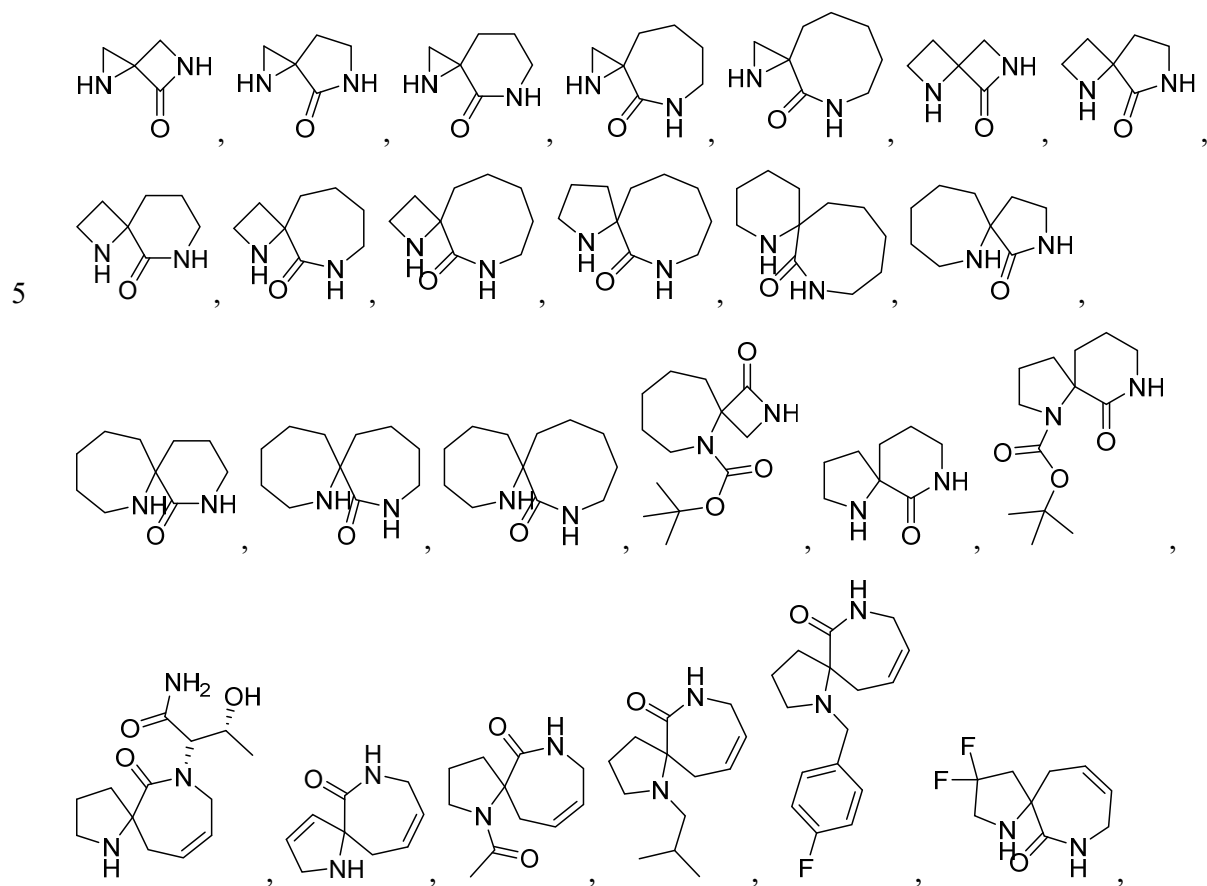
17. The compound of any one of claims 8-15, wherein R^3 is $-C_1-C_6$ alkyl optionally substituted by one, two or three substituents independently selected from the group consisting of $-C(O)NR^aR^b$, hydroxyl, $-SH$, halogen, and phenyl; wherein phenyl is optionally substituted by $-C_1-C_3$ alkoxy or halogen.

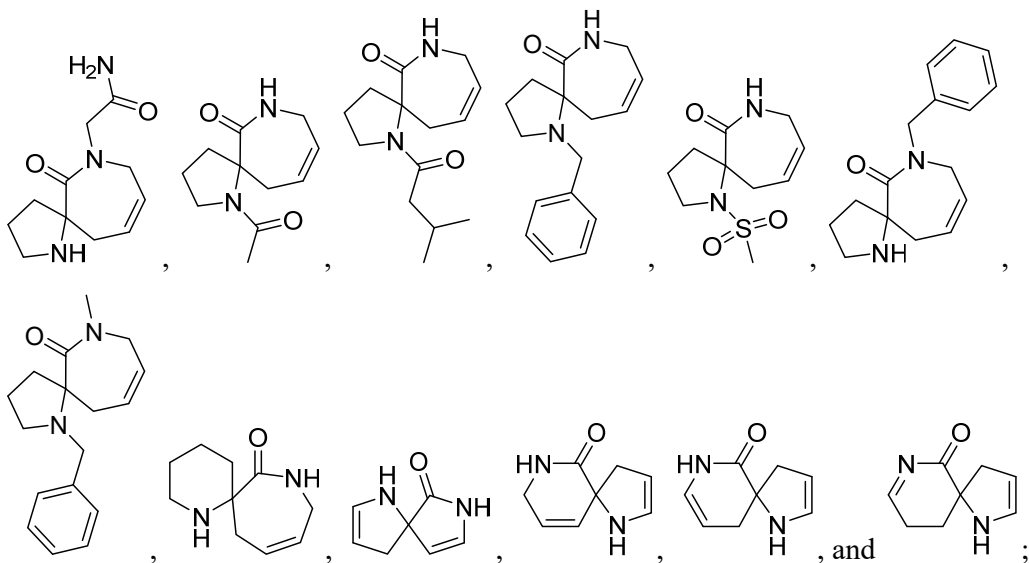
18. The compound of claim 17, wherein R^3 is selected from the group consisting of:



wherein R^{66} is methoxy or fluoro; and R^a and R^b are, for each occurrence, H.

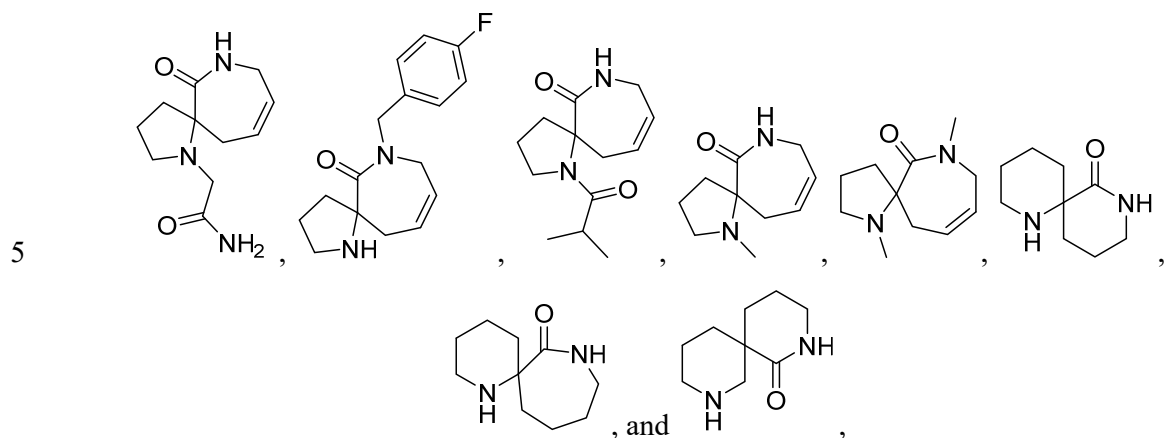
19. A compound selected from the group consisting of:





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

20. A compound selected from the group consisting of:



or a pharmaceutically acceptable salt and/or stereoisomer thereof.

21. A pharmaceutical composition comprising the compound of any one of claims 1-20, and a pharmaceutically acceptable excipient.

10 22. The pharmaceutical composition of claim 21, suitable for oral administration, parenteral administration, topical administration, intravaginal administration, intrarectal administration, sublingual administration, ocular administration, transdermal administration, or nasal administration.

23. Use of a compound of any one of claims 1-20 in the manufacture of a medicament for treating depression, Alzheimer's disease, attention deficit disorder, schizophrenia, or anxiety, in a patient in need thereof.
24. Use of a compound of any one of claims 1-20 in the manufacture of a medicament for
5 treating a migraine in a patient in need thereof.
25. Use of a compound of any one of claims 1-20 in the manufacture of a medicament for treating neuropathic pain in a patient in need thereof.
26. Use of a compound of any one of claims 1-20 in the manufacture of a medicament for treating traumatic brain injury in a patient in need thereof.
- 10 27. Use of a compound of any one of claims 1-20 in the manufacture of a medicament for treating a neurodevelopmental disorder related to synaptic dysfunction in a patient in need thereof.
28. Use of a compound of any one of claims 1-20 in the manufacture of a medicament for treating a cognitive impairment disorder in a patient in need thereof.
- 15 29. A compound of any one of claims 1-20, or the pharmaceutical composition of claim 21 or 22, 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.