OXYSTEROLS AND METHODS OF USE THEREOF

Related Applications

This application claims priority to U.S. Provisional Application Number 62/189,068 filed July 6, 2015, and 62/332,931 filed May 6, 2016, the contents of each of which are incorporated by reference in their entirety.

Background of the Invention

[0001] NMDA receptors are heteromeric complexes comprised of NR1, NR2, and/or NR3 subunits and possess distinct recognition sites for exogenous and endogenous ligands. These recognition sites include binding sites for glycine, and glutamate agonists and modulators. NMDA receptors are expressed in the peripheral tissues and the CNS, where they are involved in excitatory synaptic transmission. Activating these receptors contributes to synaptic plasticity in some circumstances and excitotoxicity in others. These receptors are ligand-gated ion channels that admit Ca2+ after binding of the glutamate and glycine, and are fundamental to excitatory neurotransmission and normal CNS function. Positive modulators may be useful as therapeutic agents with potential clinical uses as cognitive enhancers and in the treatment of psychiatric disorders in which glutamatergic transmission is reduced or defective (see, *e.g.,* Horak et al., J. of Neuroscience, 2004, 24(46), 10318-10325). In contrast, negative modulators may be useful as therapeutic agents with potential clinical uses in the treatment of psychiatric disorders in which glutamatergic transmission is pathologically increased (*e.g.,* treatment resistant depression).

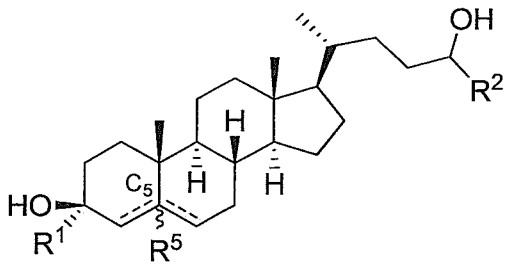
[0002] Oxysterols are derived from cholesterol and have been shown to potently and selectively modulate NMDA receptor function. New and improved oxysterols are needed that modulate the NMDA receptor for the prevention and treatment of conditions associated with NMDA expression and function. Compounds, compositions, and methods described herein are directed toward this end.

Summary

[0003] Provided herein are substituted oxysterols useful for preventing and/or treating a broad range of disorders, including, but not limited to, NMDA–mediated disorders. These compounds are expected to show improved *in vivo* potency, pharmacokinetic (PK) properties,

oral bioavailability, formulatability, stability, and/or safety as compared to other oxysterols. Further provided are pharmaceutical compositions comprising the compounds of the present disclosure, and methods of their use and treatment.

[0004] In one aspect, provided herein are compounds according to Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein: R^1 is hydrogen or C_{1-6} alkyl; R^2 is C_{1-6} alkyl, carbocyclyl, or heterocyclyl; R^5 is absent or hydrogen; and ----- represents a single or double bond, wherein when one ----- is a double bond, the other ----- is a single bond and R^5 is absent.

In some embodiments, R^1 is hydrogen.

In some embodiments, R^1 is C_{1-6} alkyl. In some embodiments, R^1 is substituted C_{1-6} alkyl. In some embodiments, R^1 is unsubstituted C_{1-6} alkyl. In some embodiments, R^1 is methyl (e.g., $-CH_3$, $-CF_3$ or $-CH_2OCH_3$), ethyl, or isopropyl. In some embodiments, R^1 is methyl (e.g., $-CH_3$) or ethyl (e.g., $-CH_2CH_3$).

In some embodiments, R^2 is C_{1-6} alkyl or carbocyclyl. In some embodiments, R^2 is substituted C_{1-6} alkyl. In some embodiments, R^2 is unsubstituted C_{1-6} alkyl. In some embodiments, R^2 is C_{1-4} alkyl. In some embodiments, R^2 is substituted C_{1-4} alkyl. In some embodiments, R^2 is unsubstituted C_{1-4} alkyl. In some embodiments, R^2 is C_{1-3} alkyl. In some embodiments, R^2 is substituted C_{1-3} alkyl. In some embodiments, R^2 is unsubstituted C_{1-3} alkyl. In some embodiments, R^2 is methyl, ethyl (e.g., $-CH_2CH_3$, $-CH_2CF_3$, $-CH(CH_3)(CF_3)$), isopropyl, tertbutyl, or cyclopropyl. In some embodiments, R^2 is haloalkyl. In some embodiments, R^2 is $-CH_2CF_3$ or $-CH(CH_3)(CF_3)$.

In some embodiments, R^1 and R^2 are C_{1-6} alkyl. In some embodiments, R^1 is C_{1-6} alkyl and R^2 is C_{1-6} alkyl, carbocyclyl, or heterocyclyl. In some embodiments, R^1 is methyl or ethyl, and R^2 is unsubstituted or substituted C_{1-6} alkyl (*e.g.*, haloalkyl). In some embodiments, R^1 is methyl or ethyl, and R^2 is carbocyclyl or heterocyclyl.

In some embodiments, ----- represents a single bond.

[0005] Provided herein is a pharmaceutical composition comprising a compound described herein (*e.g.*, a compound of Formula (I), or pharmaceutically acceptable salt thereof), and a pharmaceutically acceptable carrier.

[0005a] In an aspect, provided herein is a pharmaceutical composition comprising a compound described herein, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0005b] In an aspect, provided herein is a compound described herein, or a pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof, for use in therapy.

[0006] Provided herein is a method of inducing sedation or anesthesia comprising administering to a subject an effective amount of a compound described herein (*e.g.*, a compound of Formula (I), or pharmaceutically acceptable salt thereof), or pharmaceutical composition thereof.

[0006a] In an aspect, provided herein is a use of a compound described herein, or a pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof, in the manufacture of a medicament for inducing sedation or anesthesia.

[0007] Provided herein is a method for treating or preventing a disorder described herein, comprising administering to a subject in need thereof an effective amount of a compound described herein (*e.g.*, a compound of Formula (I), or pharmaceutically acceptable salt thereof), or pharmaceutical composition thereof.

[0007a] In an aspect, provided herein is a use of a compound described herein, or a pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof , in the manufacture of a medicament for treating or preventing a disorder described herein.

[0008] In some embodiments, the disorder is a gastrointestinal (GI) disorder *e.g.,* constipation, irritable blowel syndrome (IBS), inflammatory bowel disease (IBD) (e.g., ulcerative colitis, Crohn's disease), structural disorders affecting the GI, anal disorders (*e.g.,* hemorrhoids, internal hemorrhoids, external hemorrhoids, anal fissures, perianal abscesses, anal fistula), colon polyps, cancer, colitis.

[0009] In some embodiments, the disorder is inflammatory bowel disease.

[0010] In some embodiments, the disorder is cancer, diabetes, or a sterol synthesis disorder.

[0011] Provided herein is a method for treating or preventing a CNS-related condition comprising administering to a subject in need thereof an effective amount of a compound described herein (*e.g.*, a compound of Formula (I), or pharmaceutically acceptable salt thereof), or pharmaceutical composition thereof.

[0011a] In an aspect, provided herein is a use of a compound described herein, or a pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof, in the manufacture of a medicament for treating or preventing a CNS-related condition.

[0011b] In some embodiments, the CNS-related condition is an adjustment disorder, anxiety disorder (including obsessive-compulsive disorder, posttraumatic stress disorder, and social phobia), cognitive disorder (including Alzheimer's disease and other forms of dementia), dissociative disorder, eating disorder, mood disorder (including depression (*e.g.*, postpartum depression), bipolar disorder, dysthymic disorder, suicidality), schizophrenia or other psychotic disorder (including schizoaffective disorder), sleep disorder (including insomnia), substance-related disorder, personality disorder (including obsessive-compulsive personality disorder), autism spectrum disorders (including those involving mutations to the Shank group of proteins (*e.g.*, Shank3)), neurodevelopmental disorder (including Rett syndrome, Tuberous Sclerosis complex), multiple sclerosis, sterol synthesis

or a pharmaceutically acceptable salt thereof.

23. A pharmaceutical composition comprising a compound of claim 1, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

24. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof, in the manufacture of a medicament for inducing sedation or anesthesia.

25. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof, in the manufacture of a medicament for treating or preventing a disorder described herein.

26. The use according to claim 25, wherein the disorder is a gastrointestinal (GI) disorder *e.g.,* constipation, irritable blowel syndrome (IBS), inflammatory bowel disease (IBD) (e.g., ulcerative colitis, Crohn's disease), structural disorders affecting the GI, anal disorders (*e.g.,* hemorrhoids, internal hemorrhoids, external hemorrhoids, anal fissures, perianal abscesses, anal fistula), colon polyps, cancer, colitis.

27. The use according to claim 26, wherein the disorder is inflammatory bowel disease.

28. The use according to claim 26, wherein the disorder is cancer, diabetes, or a sterol synthesis disorder.

29. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof, in the manufacture of a medicament for treating or preventing a CNS-related condition.

30. The use according to claim 29, wherein the CNS-related condition is an adjustment disorder, anxiety disorder (including obsessive-compulsive disorder, posttraumatic stress disorder, and social phobia), cognitive disorder (including Alzheimer's disease and other forms of dementia), dissociative disorder, eating disorder, mood disorder (including depression (*e.g.,* postpartum depression), bipolar disorder, dysthymic disorder, suicidality), schizophrenia or other

psychotic disorder (including schizoaffective disorder), sleep disorder (including insomnia), substance-related disorder, personality disorder (including obsessive-compulsive personality disorder), autism spectrum disorders (including those involving mutations to the Shank group of proteins (*e.g.,* Shank3)), neurodevelopmental disorder (including Rett syndrome, Tuberous Sclerosis complex), multiple sclerosis, sterol synthesis disorders, pain (including acute and chronic pain), encephalopathy secondary to a medical condition (including hepatic encephalopathy and anti-NMDA receptor encephalitis), seizure disorder (including status epilepticus and monogenic forms of epilepsy such as Dravet's disease), stroke, traumatic brain injury, movement disorder (including Huntington's disease and Parkinson's disease), vision impairment, hearing loss, and tinnitus.

31. The use according to claim 29, wherein the disorder is sterol synthesis disorder.

32. The compound of claim 1, or a pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof, for use in therapy.