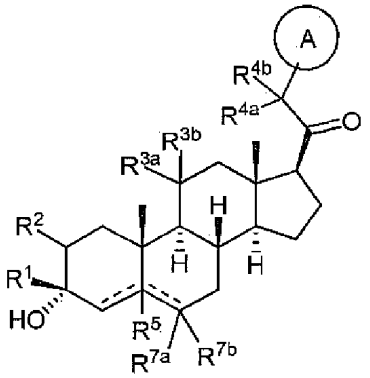
[10] New and improved neuroactive steroids are needed that act as modulating agents for brain excitability, as well as agents for the prevention and treatment of CNS-related diseases. The compounds, compositions, and methods described herein are directed toward this end.

Summary

[11] Provided herein are C21-substituted neuroactive steroids designed, for example, to act as GABA modulators. In certain embodiments, such compounds are envisioned to be useful as therapeutic agents for the inducement of anesthesia and/or sedation in a subject. In some embodiments, such compounds are envisioned to be useful as therapeutic agents for treating a CNS-related disorder (*e.g.*, sleep disorder, a mood disorder such as depression, a schizophrenia spectrum disorder, a convulsive disorder, a disorder of memory and/or cognition, a movement disorder, a personality disorder, autism spectrum disorder, pain, traumatic brain injury, a vascular disease, a substance abuse disorder and/or withdrawal syndrome, or tinnitus) in a subject in need (*e.g.*, a subject with Rett syndrome, Fragile X syndrome, or Angelman syndrome).

The present disclosure provides a compound of Formula (**I**):

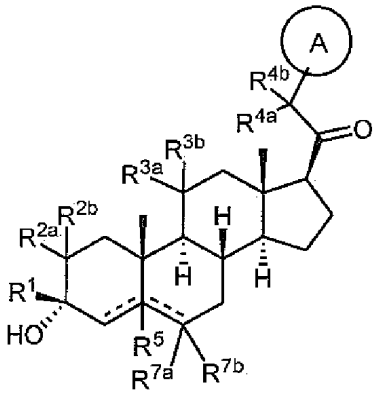


(**I**)

or a pharmaceutically acceptable salt thereof; wherein: ring A is substituted or unsubstituted carbocyclyl, heterocyclyl, aryl, or heteroaryl; R^1 is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, or substituted or unsubstituted C_{3-6} carbocylyl; R^2 is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocylyl, or $-OR^{A2}$, wherein R^{A2} is hydrogen or substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted

C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocylyl; R^{3a} is hydrogen or $-OR^{A3}$, wherein R^{A3} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocylyl, and R^{3b} is hydrogen; or R^{3a} and R^{3b} are joined to form an oxo (=O) group; R^{4a} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or $-OR^{A4}$, wherein R^{A4} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocylyl, and R^{4b} is hydrogen or substituted or unsubstituted C_{1-6} alkyl; R^{4a} and R^{4b} are joined to form an oxo (=O) group; or R^{4a} and R^{4b} together with the carbon atom to which they are attached form a ring (e.g., a 3-6-membered ring (e.g., carbocycyl or heterocyclyl ring). R^{7a} is hydrogen or halogen; R^{7b} is hydrogen; R^5 is absent or hydrogen; and ------ represents a single or double bond, wherein when one of ------ is a double bond, the other ------ is a single bond; and when one of the ------ is a double bond, R^5 is absent.

In one aspect, provided is a compound of the Formula (**I**):



(**I**)

or a pharmaceutically acceptable salt thereof;

wherein:

Ring A is carbocyclyl, heterocyclyl, aryl, or heteroaryl;

R^1 is hydrogen, C_{1-5} haloalkyl (e.g., C_{1-3} haloalkyl), C_{1-5} alkyl (e.g., C_{1-3} alkyl), C_{2-6} alkenyl, or C_{3-6} carbocylyl;

each of R^{2a} and R^{2b} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocylyl, or $-OR^{A2}$, wherein R^{A2} is hydrogen or C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-6} carbocylyl;

R^{3a} is hydrogen or $-OR^{A3}$, wherein R^{A3} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-6} carbocylyl, and R^{3b} is hydrogen; or R^{3a} and R^{3b} are joined to form an oxo (=O) group;

R^{4a} is hydrogen, C_{1-6} alkyl, or $-OR^{A4}$, wherein R^{A4} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-6} carbocylyl, and R^{4b} is hydrogen or C_{1-6} alkyl; or R^{4a} and R^{4b} are joined to form an oxo (=O) group; or R^{4a} and R^{4b} together with the carbon atom to which they are attached form a ring (e.g., a 3-6-membered ring (e.g., carbocycyl or heterocyclyl ring);

R^5 is absent or hydrogen;

each of R^{7a} and R^{7b} is independently hydrogen or halogen;

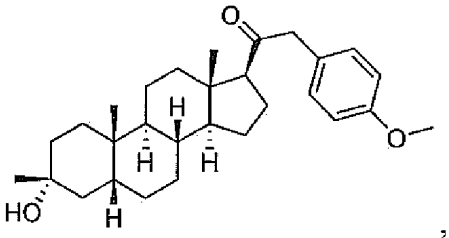
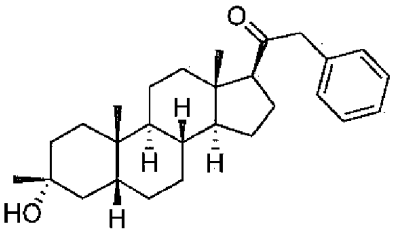
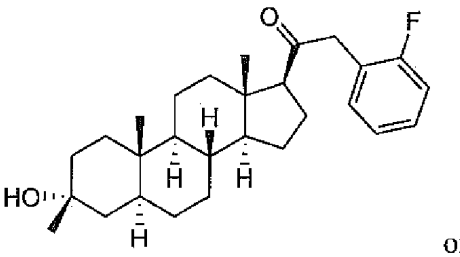
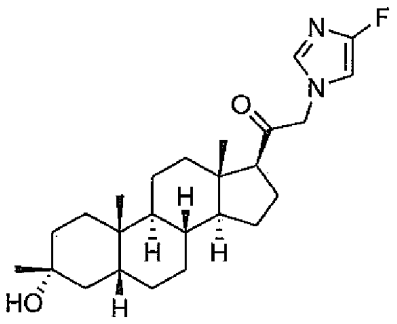
------ represents a single or double bond, wherein when one of ------ is a double bond, the other ------ is a single bond; and when one of the ------ is a double bond, R^5 is absent.

In an embodiment, A is Ring A is substituted or unsubstituted nitrogen containing heterocyclyl, or nitrogen containing heteroaryl. In an embodiment, A is attached through a nitrogen atom. In an embodiment, A is monocyclic heteroaryl or heterocylcyl, for example, a substituted monocyclic heteroaryl. In an embodiment, A is bicyclic heteroaryl, for example, a substituted bicyclic heteroaryl. Exemplary substituents are described herein.

In an embodiment, ring A is substituted carbocyclyl, heterocyclyl, aryl, or heteroaryl, for example, a substituted heterocyclyl or heteroaryl. In some embodiments, the heterocyclyl or heteroaryl is attached through a nitrogen atom. In an embodiment, A is a substituted heterocyclyl linked through a nitrogen atom. In an embodiment, A is an unsubstituted heterocyclyl linked through a nitrogen atom. In an embodiment, A is a substituted heteroaryl linked through a nitrogen atom. In an embodiment, A is an unsubstituted heteroaryl linked through a nitrogen atom.

In an embodiment, A is substituted or unsubstituted imidiaole or benzimidazole (e.g., a substituted imidazole or benzimidazole). In some embodiments the imidazole or benzimidazole is attached through a nitrogen atom.

In an embodiment, A is substituted or unsubstituted and is selected from:




or


In one aspect, provided is a pharmaceutical composition comprising a compound of the Formula (I) and a pharmaceutically acceptable excipient.

The present disclosure also provides a method of inducing sedation and/or anesthesia in a subject, comprising administering to the subject an effective amount of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof.

In one aspect, provided is a use of a compound of the Formula (I) in the manufacture of a medicament for inducing sedation and/or anesthesia in a subject.

The present disclosure also provides a method of administering an effective amount of a compound, a pharmaceutically acceptable salt thereof, or pharmaceutical composition of a compound of Formula (I), to a subject in need thereof, wherein the subject experiences sedation and/or anesthesia within two hours of administration.

In one aspect, provided is a use of a compound, a pharmaceutically acceptable salt thereof, or pharmaceutical composition of a compound of Formula (I), in the manufacture of a medicament for a method of administration to a subject in need thereof, wherein the subject experiences sedation and/or anesthesia within two hours of administration.

In an embodiment, the subject experiences sedation and/or anesthesia within one hour of administration.

In an embodiment, the subject experiences sedation and/or anesthesia instantaneously.

In an embodiment, the compound is administered by intravenous administration.

In an embodiment, the compound is administered chronically.

In an embodiment, the subject is a mammal. In an embodiment, the subject is a human.

In an embodiment, the compound is administered in combination with another therapeutic agent.

The present disclosure also provides a method for treating seizure in a subject, comprising administering to the subject an effective amount of a compound of the Formula (**I**) or a pharmaceutically acceptable salt thereof.

In one aspect, provided is a use of a compound of the Formula (**I**) in the manufacture of a medicament for treating seizure in a subject.

The present disclosure also provides a method for treating epilepsy or status or status epilepticus in a subject, the method comprising administering to the subject an effective amount of a compound of the Formula (**I**) or a pharmaceutically acceptable salt thereof.

In one aspect, provided is a use of a compound of the Formula (**I**) in the manufacture of a medicament for treating epilepsy or status or status epilepticus in a subject.

In an embodiment, the status epilepticus is convulsive status epilepticus (*e.g.*, early status epilepticus, established status epilepticus, refractory status epilepticus, super-refractory status epilepticus) or non-convulsive status epilepticus, (*e.g.*, generalized status epilepticus, complex partial status epilepticus).

The present disclosure also provides a method for treating disorders related to GABA function in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound, a pharmaceutically acceptable salt thereof, or pharmaceutical composition of one of a compound of the Formula (**I**).

In one aspect, provided is a use of of a compound, a pharmaceutically acceptable salt thereof, or pharmaceutical composition of one of a compound of Formula (**I**), in the manufacture of a medicament for treating disorders related to GABA function in a subject in need thereof.

The present disclosure also provides a method for treating a CNS-related disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the Formula (**I**) or a pharmaceutically acceptable salt thereof.

In one aspect, provided is a use of a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a CNS-related disorder in a subject in need thereof.

In an embodiment, the CNS-related disorder is a sleep disorder, a mood disorder such as depression, a schizophrenia spectrum disorder, a convulsive disorder, a disorder of memory and/or cognition, a movement disorder, a personality disorder, autism spectrum disorder, pain, traumatic brain injury, a vascular disease, a substance abuse disorder and/or withdrawal syndrome, or tinnitus.

In an embodiment, the subject is a subject with Rett syndrome, Fragile X syndrome, or Angelman syndrome. In an embodiment, the CNS–related disorder is a sleep disorder, an eating disorder, a mood disorder such as depression, a schizophrenia spectrum disorder, a convulsive disorder, a disorder of memory and/or cognition, a movement disorder, a personality disorder, autism spectrum disorder, pain, traumatic brain injury, a vascular disease, a substance abuse disorder and/or withdrawal syndrome, or tinnitus. In an embodiment, the CNS-related disorder is depression (e.g., post-partum depression). In an embodiment, the CNS-related disorder is

tremor (e.g., essential tremor). In an embodiment, the CNS-related disorder is an eating disorder (e.g., anorexia nervosa, bulimia nervosa, binge-eating disorder, cachexia).

In an embodiment, the compound is administered orally. In an embodiment, the compound is administered intramuscularly.

In one aspect, provided is a kit comprising a solid composition comprising a compound of Formula (**I**) and a sterile diluent.

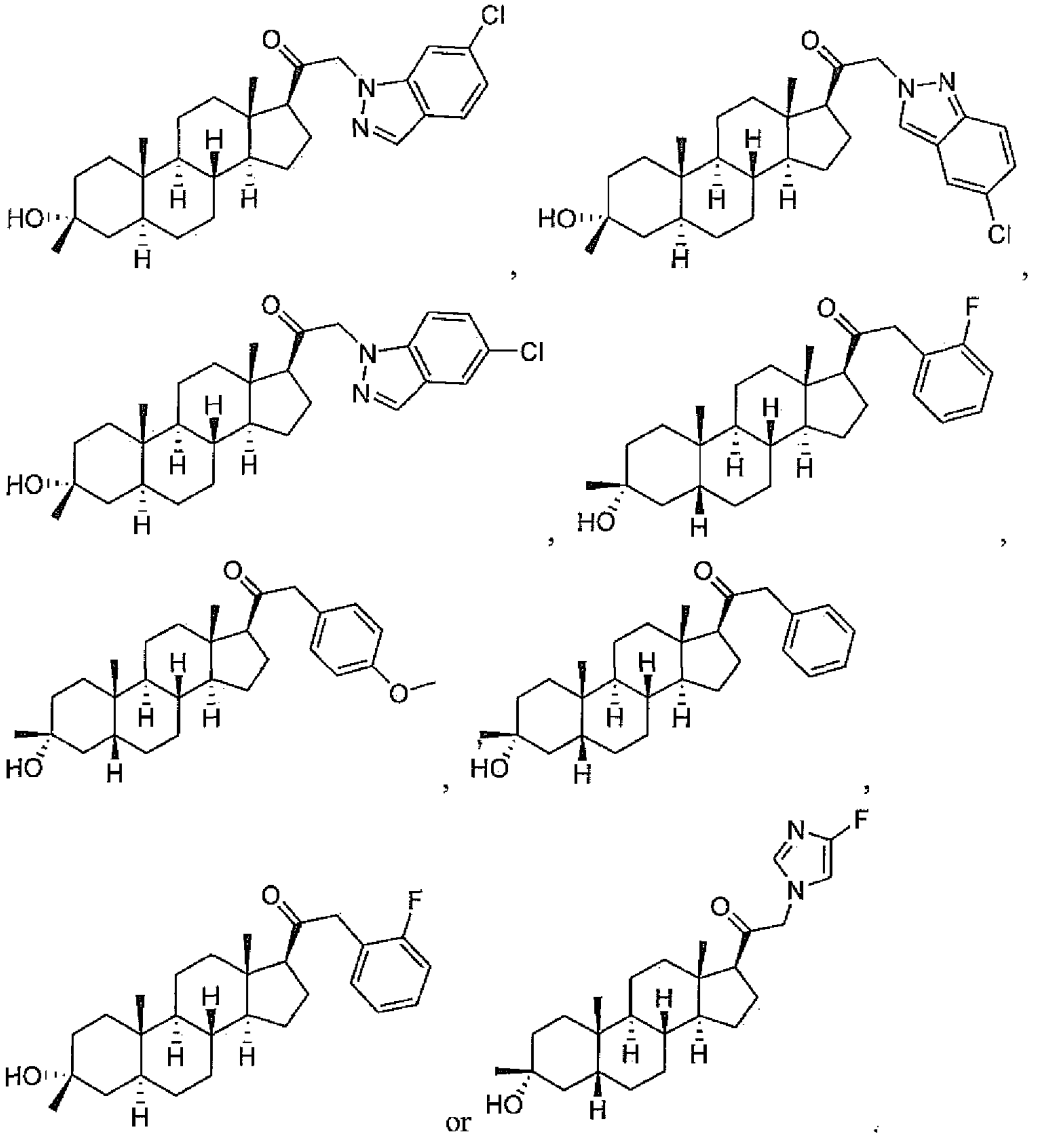
[15] The present disclosure also provides pharmaceutical compositions comprising a compound of the present disclosure and methods of use and treatment, *e.g.*, such as for inducing sedation and/or anesthesia, for treating a CNS-related disorder.

[16] Steroids of Formula (**I**), sub-genera thereof, and pharmaceutically acceptable salts thereof are collectively referred to herein as "compounds of the present invention/disclosure."

[17] In another aspect, provided is a pharmaceutical composition comprising a compound of the present disclosure and a pharmaceutically acceptable excipient. In certain embodiments, the compound of the present disclosure is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the compound of the present disclosure is provided in a therapeutically effective amount. In certain embodiments, the compound of the present disclosure is provided in a prophylactically effective amount.

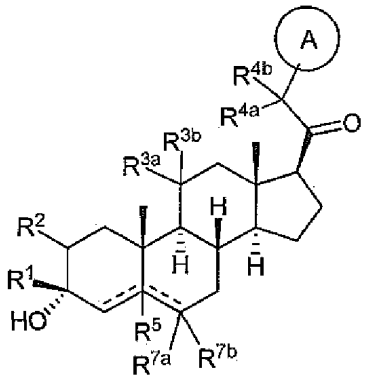
[18] Compounds of the present disclosure as described herein, act, in certain embodiments, as GABA modulators, *e.g.*, effecting the $GABA_A$ receptor in either a positive or negative manner. As modulators of the excitability of the central nervous system (CNS), as mediated by their ability to modulate $GABA_A$ receptor, such compounds are expected to have CNS-activity.

[19] Thus, the present disclosure provides methods of treating a CNS–related disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the present disclosure. In certain embodiments, the CNS–related disorder is selected from the group consisting of a sleep disorder, a mood disordersuch as depression, a schizophrenia spectrum disorder, a convulsive disorder, a disorder of memory and/or cognition, a movement disorder, a personality disorder, autism spectrum disorder, pain, traumatic brain injury, a vascular disease, a substance abuse disorder and/or withdrawal syndrome, and tinnitus. In certain embodiments, the compound is administered orally, subcutaneously, intravenously, or



50. A pharmaceutical composition comprising a compound of any one of the preceding claims and a pharmaceutically acceptable excipient.

51. Use of a compound of the Formula (I) in the manufacture of a medicament for inducing sedation and/or anesthesia in a subject:



(I)

or a pharmaceutically acceptable salt thereof;

wherein:

Ring A is carbocyclyl, heterocyclyl, aryl, or heteroaryl;

R^1 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{3-6} carbocylyl;

R^2 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocylyl, or $-OR^{A2}$, wherein R^{A2} is hydrogen or C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-6} carbocylyl;

R^{3a} is hydrogen or $-OR^{A3}$, wherein R^{A3} is hydrogen, C_{1-6} alkyl C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-6} carbocylyl, and R^{3b} is hydrogen; or R^{3a} and R^{3b} are joined to form an oxo (=O) group;

R^{4a} is hydrogen, C_{1-6} alkyl, or $-OR^{A4}$, wherein R^{A4} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-6} carbocylyl, and R^{4b} is hydrogen or C_{1-6} alkyl; R^{4a} and R^{4b} are joined to form an oxo (=O) group; or R^{4a} and R^{4b} together with the carbon atom to which they are attached form a ring (e.g., a 3-6-membered ring (e.g., carbocycyl or heterocyclyl ring).

R^{7a} is hydrogen or halogen;

R^{7b} is hydrogen;

R^5 is absent or hydrogen; and

⁻⁻⁻⁻⁻⁻ represents a single or double bond, wherein

when one of ⁻⁻⁻⁻⁻⁻ is a double bond, the other ⁻⁻⁻⁻⁻⁻ is a single bond; and

when one of the ⁻⁻⁻⁻⁻⁻ is a double bond, R^5 is absent.

52. Use of a compound, a pharmaceutically acceptable salt thereof, or pharmaceutical composition of a compound of claim 1, in the manufacture of a medicament for a method of administration to a subject in need thereof, wherein the subject experiences sedation and/or anesthesia within two hours of administration.

53. The use of claim 52, wherein the subject experiences sedation and/or anesthesia within one hour of administration.

54. The use of claim 52, wherein the subject experiences sedation and/or anesthesia instantaneously.

51. The use of claim 52, wherein the compound is to be administered by intravenous administration.

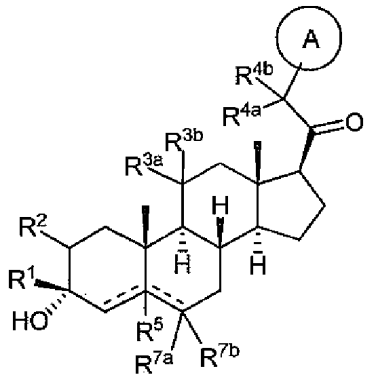
56. The use of claim 52, wherein the compound is to be administered chronically.

57. The use of claim 52, wherein the subject is a mammal.

58. The use of claim 57, wherein the subject is a human.

59. The use of claim 52, wherein the compound is to be administered in combination with another therapeutic agent.

60. Use of a compound of the Formula (I) in the manufacture of a medicament for treating seizure in a subject:



(I)

or a pharmaceutically acceptable salt thereof;

wherein:

Ring A is carbocyclyl, heterocyclyl, aryl, or heteroaryl;

R^1 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{3-6} carbocylyl;

R^2 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocylyl, or $-OR^{A2}$, wherein R^{A2} is hydrogen or C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-6} carbocylyl;

R^{3a} is hydrogen or $-OR^{A3}$, wherein R^{A3} is hydrogen, C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-6} carbocylyl, and R^{3b} is hydrogen; or R^{3a} and R^{3b} are joined to form an oxo (=O) group;

R^{4a} is hydrogen, C_{1-6} alkyl, or $-OR^{A4}$, wherein R^{A4} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-6} carbocylyl, and R^{4b} is hydrogen or C_{1-6} alkyl; R^{4a} and R^{4b} are joined to form an oxo (=O) group; or R^{4a} and R^{4b} together with the carbon atom to which they are attached form a ring (e.g., a 3-6-membered ring (e.g., carbocycyl or heterocyclyl ring).

R^{7a} is hydrogen or halogen;

R^{7b} is hydrogen;

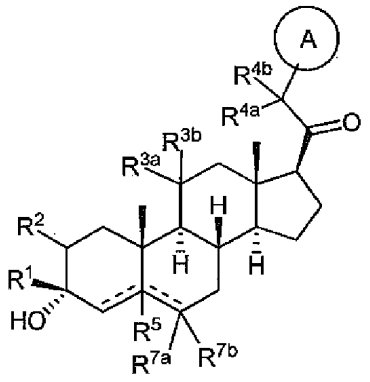
R^5 is absent or hydrogen; and

------ represents a single or double bond, wherein

when one of ------ is a double bond, the other ------ is a single bond; and

when one of the ------ is a double bond, R^5 is absent.

61. Use of a compound of the Formula (I) in the manufacture of a medicament for treating epilepsy or status or status epilepticus in a subject:



(I)

or a pharmaceutically acceptable salt thereof;

wherein:

Ring A is carbocyclyl, heterocyclyl, aryl, or heteroaryl;

R^1 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{3-6} carbocylyl;

R^2 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocylyl, or $-OR^{A2}$, wherein R^{A2} is hydrogen or C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-6} carbocylyl;

R^{3a} is hydrogen or $-OR^{A3}$, wherein R^{A3} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-6} carbocylyl, and R^{3b} is hydrogen; or R^{3a} and R^{3b} are joined to form an oxo (=O) group;

R^{4a} is hydrogen, C_{1-6} alkyl, or $-OR^{A4}$, wherein R^{A4} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-6} carbocylyl, and R^{4b} is hydrogen or C_{1-6} alkyl; R^{4a} and R^{4b} are joined to form an oxo (=O) group; or R^{4a} and R^{4b} together with the carbon atom to which they are attached form a ring (e.g., a 3-6-membered ring (e.g., carbocycyl or heterocyclyl ring).

R^{7a} is hydrogen or halogen;

R^{7b} is hydrogen;

R^5 is absent or hydrogen; and

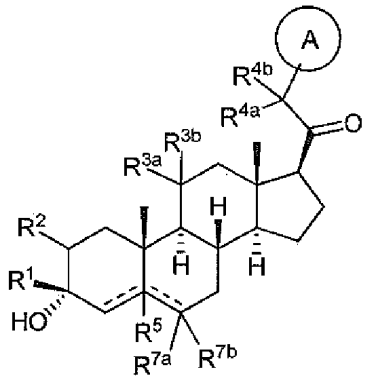
------ represents a single or double bond, wherein

when one of ------ is a double bond, the other ------ is a single bond; and

when one of the ------ is a double bond, R^5 is absent.

62. The use of claim 61, wherein the status epilepticus is convulsive status epilepticus (*e.g.*, early status epilepticus, established status epilepticus, refractory status epilepticus, super-refractory status epilepticus) or non-convulsive status epilepticus, (*e.g.*, generalized status epilepticus, complex partial status epilepticus).

63. Use of of a compound, a pharmaceutically acceptable salt thereof, or pharmaceutical composition of one of a compound of Formula (I), in the manufacture of a medicament for treating disorders related to GABA function in a subject in need thereof:



(I)

or a pharmaceutically acceptable salt thereof;

wherein:

Ring A is carbocyclyl, heterocyclyl, aryl, or heteroaryl;

R^1 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{3-6} carbocylyl;

R^2 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocylyl, or $-OR^{A2}$, wherein R^{A2} is hydrogen or C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-6} carbocylyl;

R^{3a} is hydrogen or $-OR^{A3}$, wherein R^{A3} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-6} carbocylyl, and R^{3b} is hydrogen; or R^{3a} and R^{3b} are joined to form an oxo (=O) group;

R^{4a} is hydrogen, C_{1-6} alkyl, or $-OR^{A4}$, wherein R^{A4} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{3-6} carbocylyl, and R^{4b} is hydrogen or C_{1-6} alkyl; R^{4a} and R^{4b} are joined to form an oxo (=O) group; or R^{4a} and R^{4b} together with the carbon atom to which they are attached form a ring (e.g., a 3-6-membered ring (e.g., carbocycyl or heterocyclyl ring).

R^{7a} is hydrogen or halogen;

R^{7b} is hydrogen;

R^5 is absent or hydrogen; and

------ represents a single or double bond, wherein

when one of ------ is a double bond, the other ------ is a single bond; and

when one of the ------ is a double bond, R^5 is absent.

64. Use of a compound of any of the preceding claims, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a CNS-related disorder in a subject in need thereof.

65. The use of claim 64, wherein the CNS-related disorder is a sleep disorder, a mood disorder, a schizophrenia spectrum disorder, a convulsive disorder, a disorder of memory and/or cognition, a movement disorder, a personality disorder, autism spectrum disorder, pain, traumatic brain injury, a vascular disease, a substance abuse disorder and/or withdrawal syndrome, or tinnitus.

66. The use of claim 64, wherein the compound is to be administered orally.

67. The use of claim 64, wherein the compound is to be administered intramuscularly.

68. The use of claim 64, wherein the subject is a subject with Rett syndrome, Fragile X syndrome, or Angelman syndrome.

69. The use of claim 64, wherein the CNS–related disorder is a sleep disorder, an eating disorder, a mood disorder, a schizophrenia spectrum disorder, a convulsive disorder, a disorder of memory and/or cognition, a movement disorder, a personality disorder, autism spectrum disorder, pain, traumatic brain injury, a vascular disease, a substance abuse disorder and/or withdrawal syndrome, or tinnitus.

70. The use of claim 64, wherein the CNS-related disorder is depression (e.g., post-partum depression).

71. The use of claim 64, wherein the CNS-related disorder is tremor (e.g., essential tremor).

72. The use of claim 64, wherein the CNS-related disorder is an eating disorder (e.g., anorexia nervosa, bulimia nervosa, binge-eating disorder, cachexia).

73. A kit comprising a solid composition comprising a compound of Formula (I):