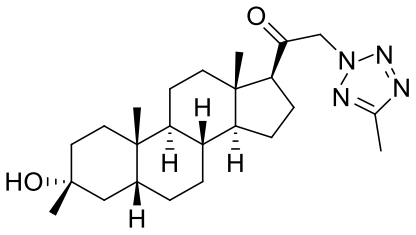
[10] New and improved neuroactive steroids are needed that act as modulating agents for brain excitability, as well as agents for the prevention and treatment of CNS-related diseases. The compounds, compositions, and methods described herein are directed toward this end.

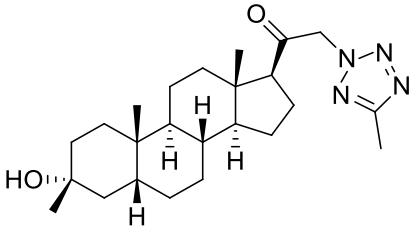
Summary

[10a] In an aspect of the present disclosure, there is provided a compound of the formula



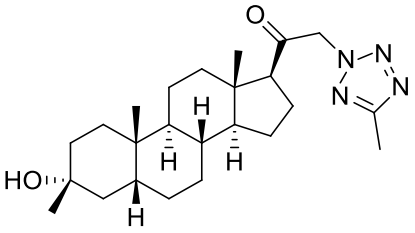
.

[10b] In another aspect of the present disclosure, there is provided a pharmaceutically acceptable salt of a compound of the formula



.

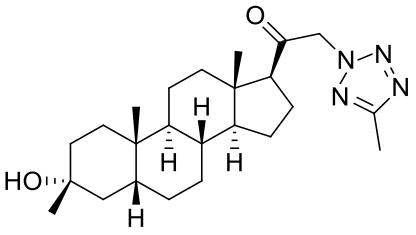
[10c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound of the formula



, and

a pharmaceutically acceptable excipient.

[10d] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable salt of a compound of the formula



, and

a pharmaceutically acceptable excipient.

[10e] In a further aspect of the present disclosure, there is provided a compound, the pharmaceutically acceptable salt, or the pharmaceutical composition disclosed herein, for use in inducing sedation and/or anesthesia in a subject.

[10f] In another aspect of the present disclosure, there is provided a compound, the pharmaceutically acceptable salt, or the pharmaceutical composition disclosed herein, for use in treating essential tremor in a subject.

[10g] In a further aspect of the present disclosure, there is provided a compound, the pharmaceutically acceptable salt, or the pharmaceutical composition disclosed herein, for use in treating seizure in a subject.

[10h] In another aspect of the present disclosure, there is provided a compound, the pharmaceutically acceptable salt, or the pharmaceutical composition disclosed herein, for use in treating epilepsy or status epilepticus in a subject.

[10i] In a further aspect of the present disclosure, there is provided a use of a compound, the pharmaceutically acceptable salt, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for inducing sedation and/or anesthesia in a subject.

[10j] In another aspect of the present disclosure, there is provided a use of a compound, the pharmaceutically acceptable salt, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating essential tremor in a subject.

[**10k]** In a further aspect of the present disclosure, there is provided a use of a compound, the pharmaceutically acceptable salt, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating seizure in a subject.

[10l] In another aspect of the present disclosure, there is provided a use of a compound, the pharmaceutically acceptable salt, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating epilepsy or status epilepticus in a subject.

[10m] In a further aspect of the present disclosure, there is provided a compound, the pharmaceutically acceptable salt, or the pharmaceutical composition disclosed herein, for use in treating a disorder related to GABA function in a subject.

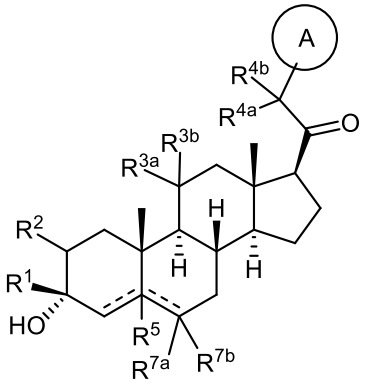
[**10n]** In another aspect of the present disclosure, there is provided a compound, the pharmaceutically acceptable salt, or the pharmaceutical composition disclosed herein, for use in treating a CNS-related disorder in a subject.

[**10o]** In a further aspect of the present disclosure, there is provided a use of a compound, the pharmaceutically acceptable salt, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a disorder related to GABA function in a subject.

[10p] In another aspect of the present disclosure, there is provided a use of a compound, the pharmaceutically acceptable salt, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a CNS-related disorder in a subject.

[11] Provided herein are C21-substituted neuroactive steroids designed, for example, to act as GABA modulators. In certain examples, such compounds are envisioned to be useful as therapeutic agents for the inducement of anesthesia and/or sedation in a subject. In some examples, 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).

In one example, provided is 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

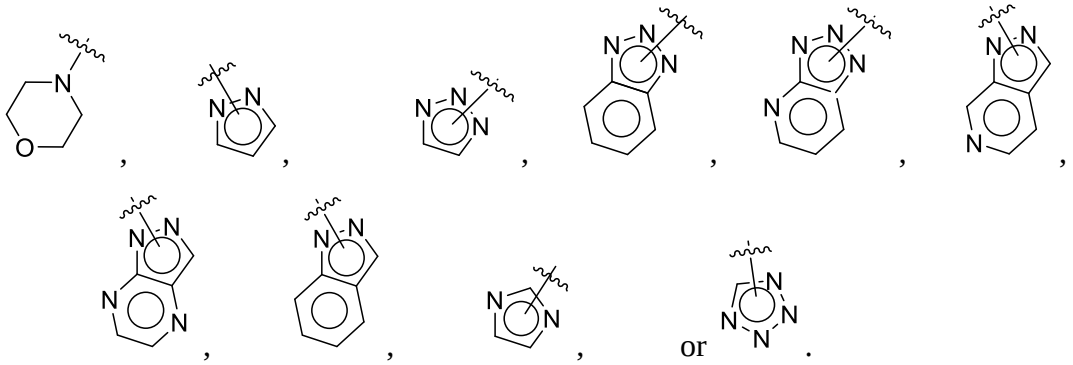
C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocylyl; R^{3a} is hydrogen or $–OR^{A3}$, wherein R^{A3} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} 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 an example, A is Ring A is substituted or unsubstituted nitrogen containing heterocyclyl, or nitrogen containing heteroaryl. In an example, A is attached through a nitrogen atom. In an example, A is monocyclic heteroaryl or heterocylcyl, for example, a substituted monocyclic heteroaryl. In an example, A is bicyclic heteroaryl, for example, a substituted bicyclic heteroaryl. Exemplary substituents are described herein.

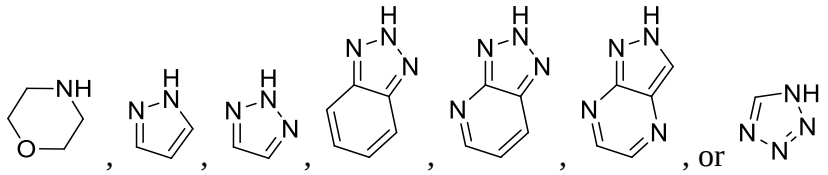
In an example, ring A is substituted carbocyclyl, heterocyclyl, aryl, or heteroaryl, for example, a substituted heterocyclyl or heteroaryl. In some examples, the heterocyclyl or heteroaryl is attached through a nitrogen atom. In an example, A is a substituted heterocyclyl linked through a nitrogen atom.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

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

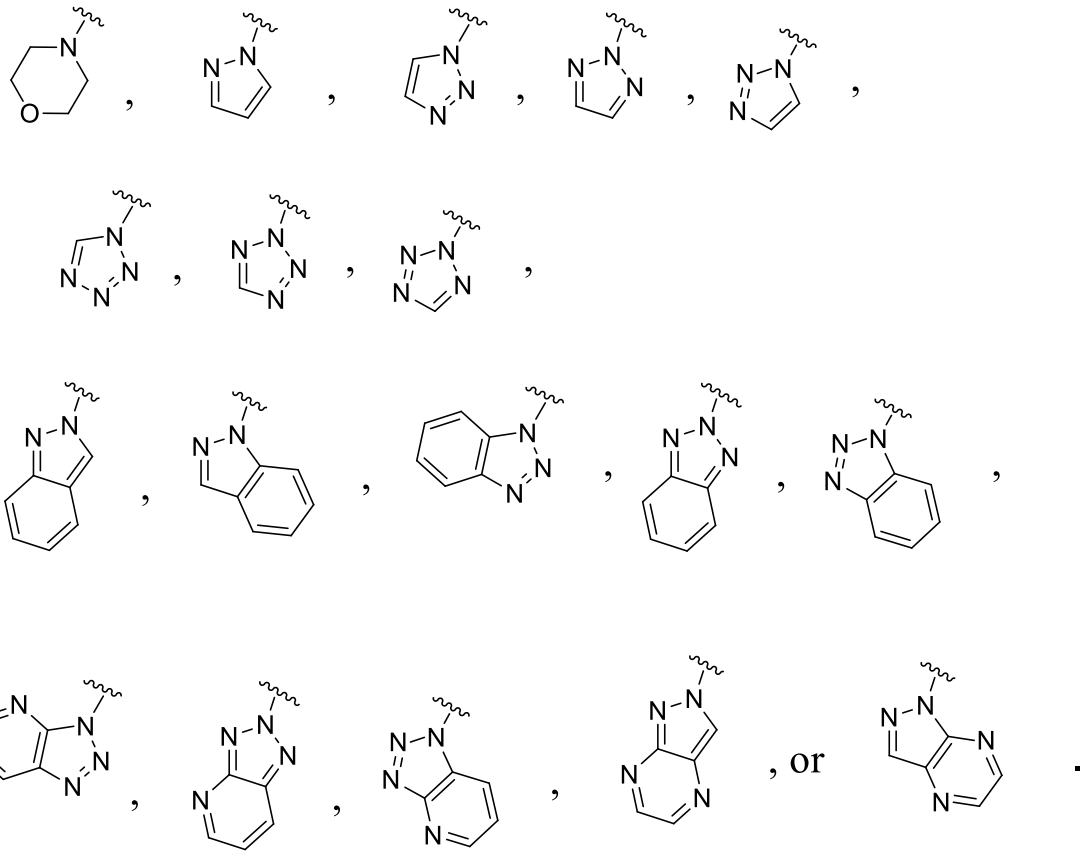
In an example, A is substituted or unsubstituted and is selected from:



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



In an example A is substituted or unsubstituted and is selected from:



In an example, R^1 is hydrogen, methyl, ethyl, or propyl (e.g., methyl). In an example, R^1 is unsubstituted C_{1-3} alkyl. In an example, R^1 is substituted C_{1-6} alkyl (e.g., haloalkyl or alkoxyalkyl such as methoxymethyl).

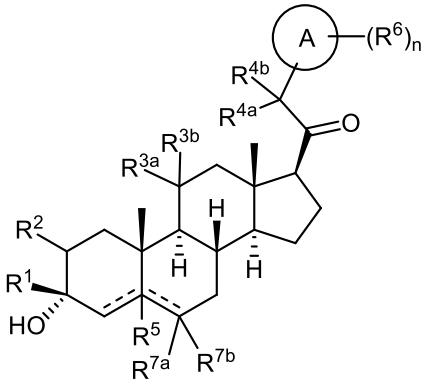
[12] In an example, at least one of R^2, R^{3a}, R^{4a} or R^{4b} is not hydrogen. For example, in an example, at least 2 of R^2, R^{3a}, R^{4a} or R^{4b} is not hydrogen.

In an example, R^2 is 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. In an example, R^2 is $–OR^{A2}$, 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, for example, hydroxyl or alkoxy.

In an example, R^{3a} is $–OR^{A3}$, 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. In an example, R^{3a} is $–OR^{A3}$, 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, for example, hydroxyl or alkoxy

In an example, R^{4a} is 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; or R^{4a} and R^{4b} are joined to form an oxo (=O) group.

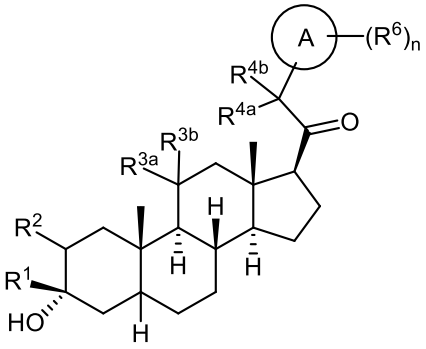
In an example, the compound is of the Formula (**I-a**):



(**I-a**)

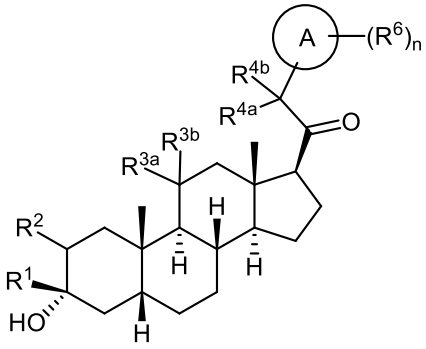
wherein: R^6 is substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocylyl, C_{1-6} haloalkyl, halogen, cyano,–OR^{A6}, -C(=O)OR^{A6}, -SR^{B6}, -S(=O)R^{B6}, or S(=O)$_2R^{B6}$, wherein R^{A6} is hydrogen or 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 C_{1-6} haloalkyl, and R^{B6} is substituted or unsubstituted C_{1-6} alkyl or substituted or unsubstituted C_{3-6} carbocylyl; and n is 0, 1, 2, or 3.

In an example, the compound is of the Formula (**I-b**):

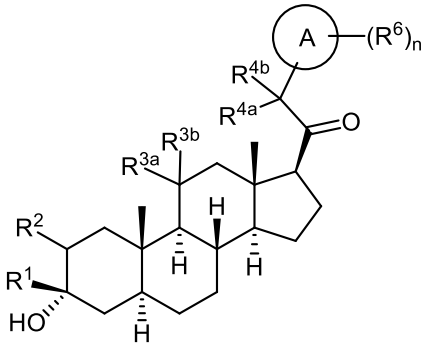


(**I-b**).

In an example, the compound is of the Formula (**I-c1**) or (**I-c2**):

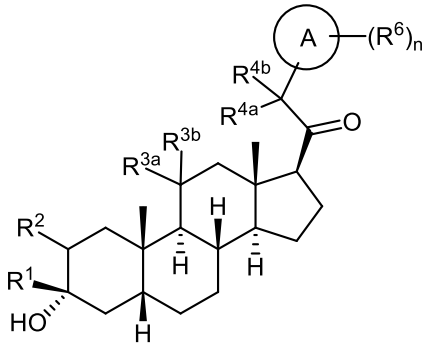


(**I-c1**)



(**I-c2**).

In an example, the compound is of the Formula (**I-c1**):



(**I-c1**)

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^6 is 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, C_{1-6} haloalkyl, halogen, cyano,–OR^{A6}, -$C(=O)OR^{A6}$, -SR^{B6}, -$S(=O)R^{B6}$, or $S(=O)_2R^{B6}$, wherein R^{A6} is hydrogen or 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 C_{1-6} haloalkyl, and R^{B6} is substituted or unsubstituted C_{1-6} alkyl or substituted or unsubstituted C_{3-6} carbocylyl; and n is 0, 1, 2, or 3.

In an example, A is a carbon bound (e.g., A linked through a carbon atom) substituted or unsubstituted 5 or 6-membered heteroaryl, or 6-membered aryl.

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

[13] In an example, R^1 is hydrogen. In an example, R^1 is substituted or unsubstituted C_{1-6} alkyl, for example, methyl.

[14] In an example, at least one of R^2, R^{3a}, R^{4a} or R^{4b} is not hydrogen. For example, in an example, at least 2 of R^2, R^{3a}, R^{4a} or R^{4b} is not hydrogen.

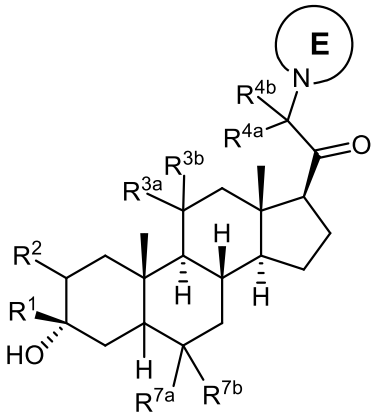
In an example, R^2 is substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocylyl, or –OR^{A2}, wherein R^{A2} is hydrogen or substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocylyl. In an example, R^2 is –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, for example, hydroxyl or alkoxy.

In an example, R^{3a} is –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. In an example, R^{3a} is $–OR^{A3}$, 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, for example, hydroxyl or alkoxy

In an example, R^{4a} is 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; or R^{4a} and R^{4b} are joined to form an oxo (=O) group.

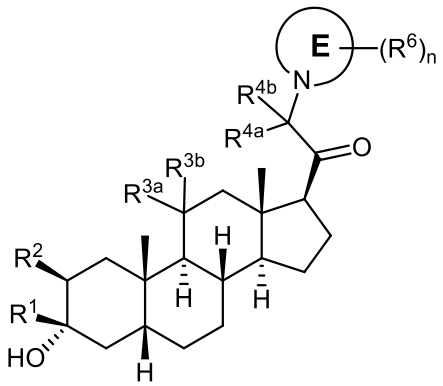
In an example, the compound is of the Formula (**II**):



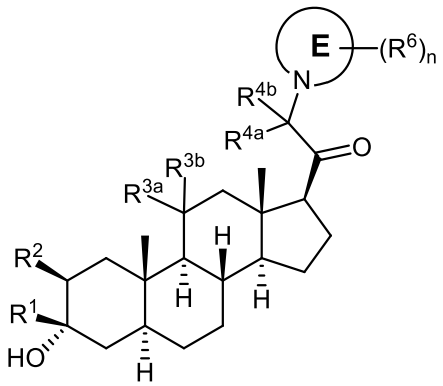
(**II**)

wherein: Ring E is substituted or unsubstituted heterocyclyl or heteroaryl.

In an example, the compound is of the Formula (**II-a1**) or (**II-a2**):



(**II-a1**)

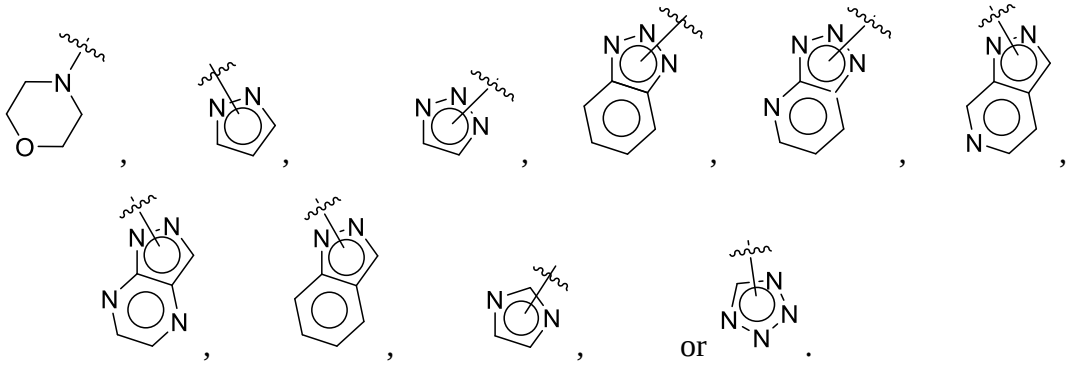


(**II-a2**).

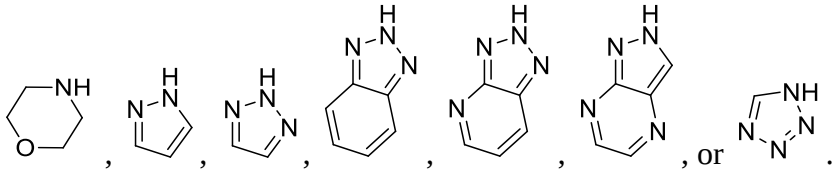
In an example, E is a ring comprising at least one nitrogen atom.

In an example, A is a ring comprising at least one nitrogen atom.

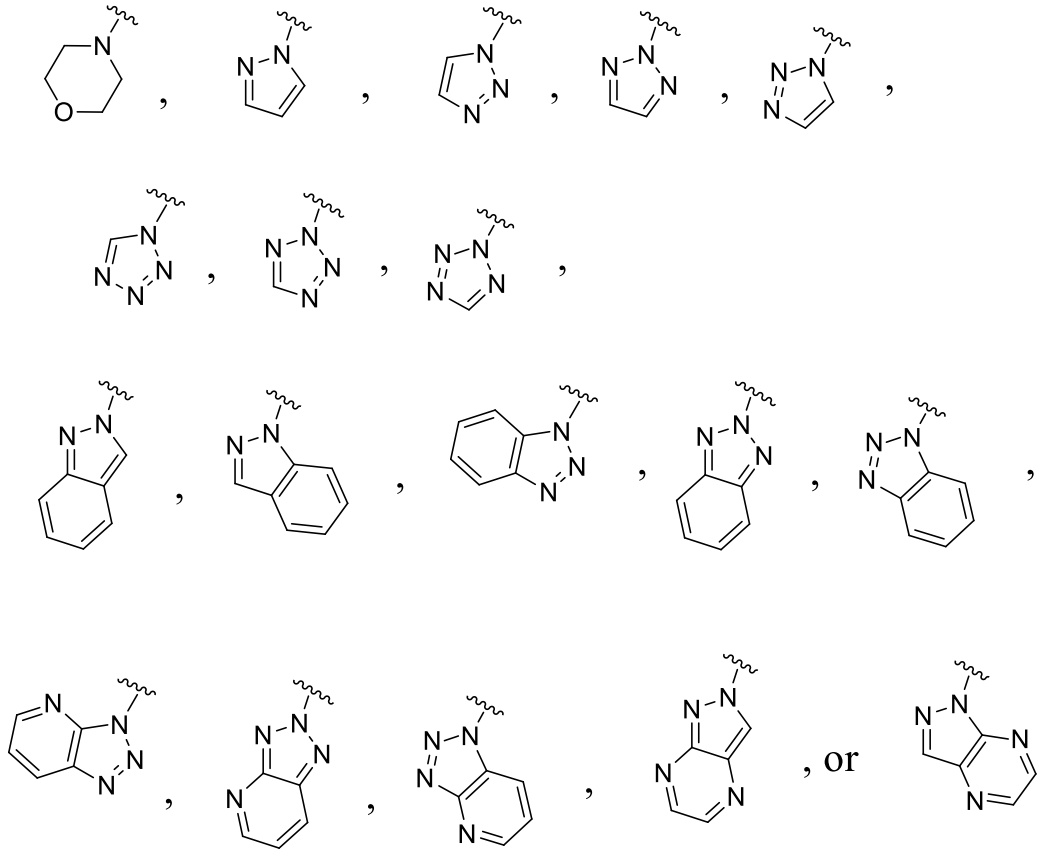
In an example, E is selected from:



In an example, E is selected from:



In an example, A is:



In an example, E is a ring comprising at least two nitrogen atoms. In an example, E is a ring comprising at least two nitrogen atoms and R^1 is substituted or unsubstituted C_{2-6} alkyl. In an example, E is a ring comprising at least two nitrogen atoms and at least one of R^2, R^{3a}, R^{4a} or R^{4b} is not hydrogen.

In an example, E is a ring comprising at least three nitrogen atoms. In an example, E is a ring comprising four nitrogen atoms.

In an example, R^1 is substituted or unsubstituted C_{2-6} alkyl.

In an example, at least one of R^2, R^{3a}, R^{4a} or R^{4b} is not hydrogen.

In an example, E is a ring comprising 2, 3 or 4 nitrogen atoms.

In an example, E is a ring selected from pyrazole, triazole, tetrazole, indazole, benzotriazole, triazolopyridine, triazolopyrazine, pyrazolopyrazine.

In an example, A is a 6-membered heterocyclyl ring (e.g., a 6-membered heterocyclyl ring comprising at least two heteroatoms).

In an example, A is a 5-6-membered heterocyclyl ring, and n is 1 or 2.

In an example, E is morpholine and n is 1 or 2.

In an example, R^1 is hydrogen or unsubstituted C_{1-6} alkyl. In an example, R^1 is or methyl. In an example, R^1 is substituted or unsubstituted C_{2-6} alkyl.

In an example, R^2 is hydrogen, $–OR^{A2}$, wherein R^{A2} is hydrogen, or substituted or unsubstituted C_{1-6} alkyl (e.g., methyl, ethyl).

In an example, R^{3a} is $–OR^{A3}$, wherein R^{A3} is hydrogen, or substituted or unsubstituted C_{1-6} alkyl (e.g., methyl).

In an example, R^{3a} and R^{3b} are joined to form an oxo (=O) group.

In an example, R^{4a} is hydrogen, or substituted or unsubstituted C_{1-6} alkyl (e.g., methyl).

In an example, R^{4b} is hydrogen, or substituted or unsubstituted C_{1-6} alkyl (e.g., methyl).

In an example, R^{4a} is hydrogen, and R^{4b} is substituted or unsubstituted C_{1-6} alkyl (e.g., methyl).

In an example, R^5 is hydrogen.

In an example, n is 0.

In an example, n is 1 and R^6 is substituted or unsubstituted C_{1-6} alkyl, C_{1-6} haloalkyl, halogen (e.g., -F, -Br, -Cl), cyano, $–OR^{A6}$, $-C(=O)OR^{A6}$, $-SR^{B6}$, $-S(=O)R^{B6}$, or $S(=O)_2R^{B6}$, wherein R^{A6} is hydrogen or substituted or unsubstituted C_{1-6} alkyl (e.g., methyl, ethyl), C_{1-6} haloalkyl (e.g., $-CF_3$), and R^{B6} is substituted or unsubstituted C_{1-6} alkyl.

In an example, n is 1 and R^6 is halogen (e.g., -F, -Br, -Cl) or cyano. In an example, n is 1 and R^6 is substituted or unsubstituted C_{1-6} alkyl (e.g., methyl). In an example, n is 1 and R^6 is C_{1-6} haloalkyl, $–OR^{A6}$, or $–C(=O)OR^{A6}$, wherein R^{A6} is hydrogen or substituted or unsubstituted C_{1-6} alkyl (e.g., methyl, ethyl), C_{1-6} haloalkyl (e.g., $-CF_3$). In an example, n is 1 and R^6 is SR^{B6}, $-S(=O)R^{B6}$, or $S(=O)_2R^{B6}$, wherein R^{B6} is substituted or unsubstituted C_{1-6} alkyl (e.g., methyl).

In an example, n is 2 and R^6 is independently selected from substituted or unsubstituted C_{1-6} alkyl, C_{1-6} haloalkyl, halogen (e.g., -F, -Br, -Cl), cyano,$–OR^{A6}$, $-C(=O)OR^{A6}$, -

SR^{B6}, $-S(=O)R^{B6}$, or $S(=O)_2R^{B6}$, wherein R^{A6} is hydrogen or substituted or unsubstituted C_{1-6} alkyl (e.g., methyl, ethyl), C_{1-6} haloalkyl (e.g., $-CF_3$), and R^{B6} is substituted or unsubstituted C_{1-6} alkyl.

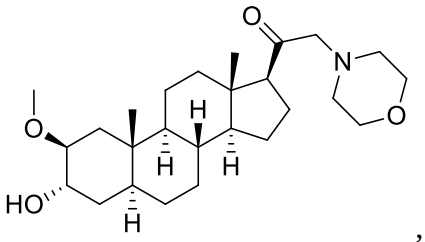
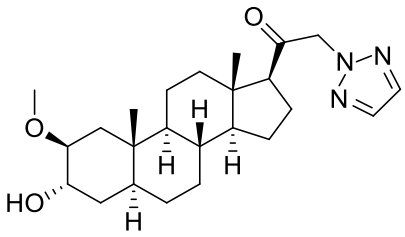
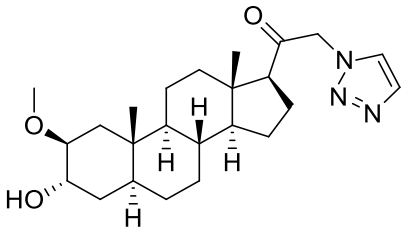
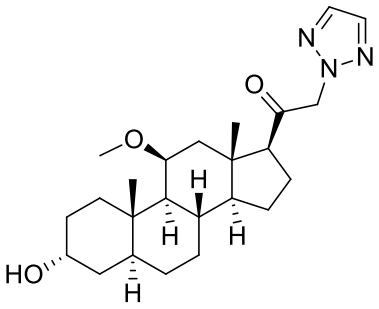
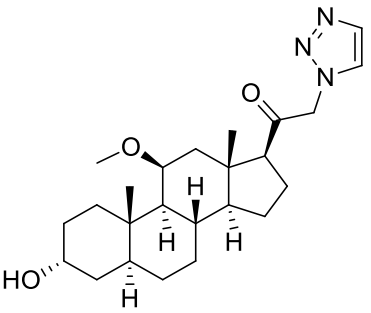
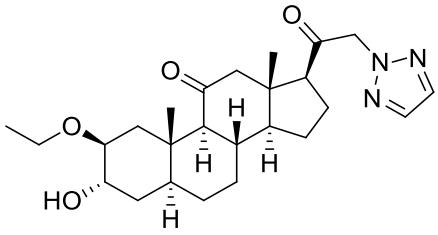
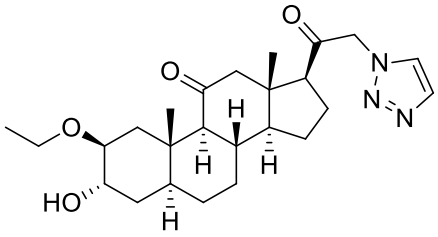
In an example, n is 2 and R^6 is independently selected from halogen (e.g., -F, -Br, -Cl). In an example, n is 2 and one of R^6 is fluorine.

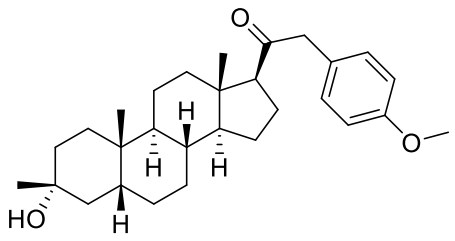
In an example, n is 0 and R^1 is substituted or unsubstituted C_{2-6} alkyl.

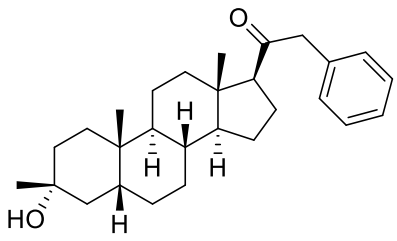
In an example, R^1 is substituted or unsubstituted C_{1-6} alkyl and at least one of R^2, R^{3a}, R^{4a} or R^{4b} is not hydrogen.

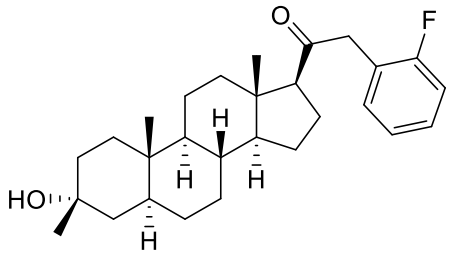
In an example, the compound is of the Formula (**II-a1**) and E is a heteroaryl ring comprising at least 3 nitrogen atoms.

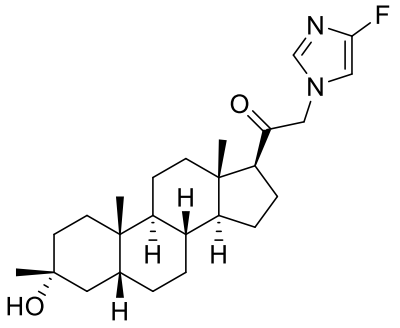
In an example, the compound is:


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or


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

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

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

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

In an example, the compound is administered chronically.

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

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

In one example, provided is 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 example, provided is 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 an example, 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).

In one example, provided is 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 example, provided is 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 an example, 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 example, the subject is a subject with Rett syndrome, Fragile X syndrome, or Angelman syndrome. In an example, 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 example, the CNS-related disorder is depression (e.g., post-partum depression). In an example, the CNS-related disorder is

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

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

In one example, 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 disclosure" or "compounds of the present invention."

[17] In another example, provided is a pharmaceutical composition comprising a compound of the present disclosure and a pharmaceutically acceptable excipient. In certain examples, the compound of the present disclosure is provided in an effective amount in the pharmaceutical composition. In certain examples, the compound of the present disclosure is provided in a therapeutically effective amount. In certain examples, 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 examples, 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, in another example, provided are 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 examples, 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 examples, the compound is administered orally, subcutaneously, intravenously, or

intramuscularly. In certain examples, the compound is administered chronically. In certain examples, the compound is administered continuously, *e.g.*, by continuous intravenous infusion.

[20] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing **Detailed Description**, **Examples**, and **Claims**.

Definitions

Chemical definitions

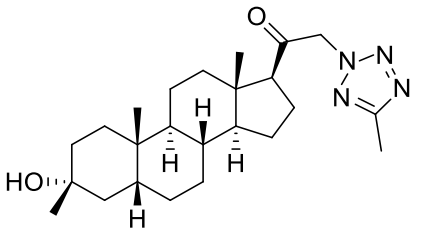
[21] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[22] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC)), supercritical fluid chromatography (SFC), and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical*

Claims

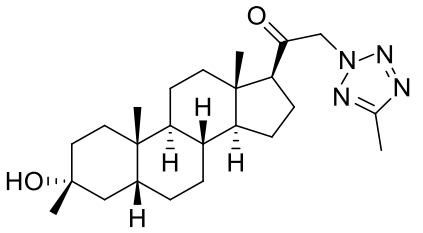
What is claimed is:

1. A compound of the formula



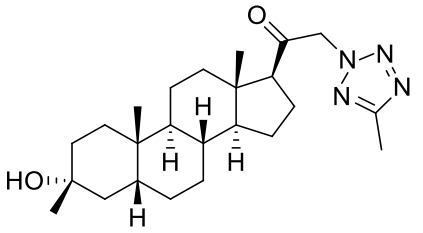
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2. A pharmaceutically acceptable salt of a compound of the formula



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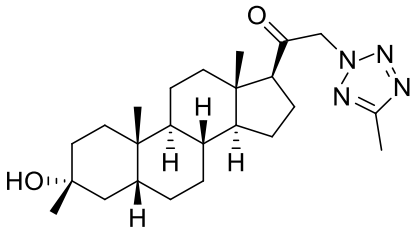
3. A pharmaceutical composition comprising a compound of the formula



, and

a pharmaceutically acceptable excipient.

4. A pharmaceutical composition comprising a pharmaceutically acceptable salt of a compound of the formula



, and

a pharmaceutically acceptable excipient.

5. The compound of claim 1, the pharmaceutically acceptable salt of claim 2, or the pharmaceutical composition of claim 3 or claim 4, for use in inducing sedation and/or anesthesia in a subject.

6. The compound of claim 1, the pharmaceutically acceptable salt of claim 2, or the pharmaceutical composition of claim 3 or claim 4, for use in treating essential tremor in a subject.

7. The compound of claim 1, the pharmaceutically acceptable salt of claim 2, or the pharmaceutical composition of claim 3 or claim 4, for use in treating seizure in a subject.

8. The compound of claim 1, the pharmaceutically acceptable salt of claim 2, or the pharmaceutical composition of claim 3 or claim 4, for use in treating epilepsy or status epilepticus in a subject.

9. Use of a compound of claim 1, a pharmaceutically acceptable salt of claim 2, or a pharmaceutical composition of claim 3 or 4, in the manufacture of a medicament for inducing sedation and/or anesthesia in a subject.

10. Use of a compound of claim 1, a pharmaceutically acceptable salt of claim 2, or a pharmaceutical composition of claim 3 or 4, in the manufacture of a medicament for treating essential tremor in a subject.

11. Use of a compound of claim 1, a pharmaceutically acceptable salt of claim 2, or a pharmaceutical composition of claim 3 or 4, in the manufacture of a medicament for treating seizure in a subject.

12. Use of a compound of claim 1, a pharmaceutically acceptable salt of claim 2, or a pharmaceutical composition of claim 3 or 4, in the manufacture of a medicament for treating epilepsy or status epilepticus in a subject.

13. The compound of claim 1, the pharmaceutically acceptable salt of claim 2, or the pharmaceutical composition of claim 3 or claim 4, for use in treating a disorder related to GABA function in a subject.

14. The compound of claim 1, the pharmaceutically acceptable salt of claim 2, or the pharmaceutical composition of claim 3 or claim 4 for use in treating a CNS-related disorder in a subject.

15. Use of a compound of claim 1, a pharmaceutically acceptable salt of claim 2, or a pharmaceutical composition of claim 3 or 4, in the manufacture of a medicament for treating a disorder related to GABA function in a subject.

16. Use of a compound of claim 1, a pharmaceutically acceptable salt of claim 2, or a pharmaceutical composition of claim 3 or 4, in the manufacture of a medicament for treating a CNS-related disorder in a subject.

17. The compound of claim 1, the pharmaceutically acceptable salt of claim 2, or the pharmaceutical composition of claim 3 or claim 4, for use according to claim 13 or claim 14, or the use according to claim 15 or claim 16, wherein the disorder is selected from the group consisting of 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 (ASD), pain, traumatic brain injury (TBI), a vascular disease, a substance abuse disorder and/or withdrawal syndrome, and tinnitus.