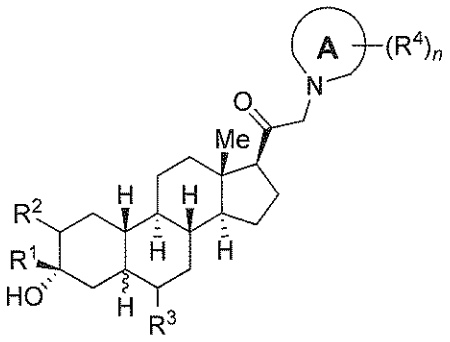
Summary

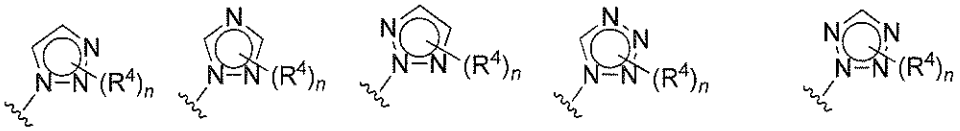
The present disclosure is based, in part, on the desire to provide novel 19-nor (i.e., C19 desmethyl) compounds, e.g., related to progesterone, deoxycorticosterone, and their metabolites, with good potency, pharmacokinetic (PK) properties, oral bioavailability, formulatability, stability, safety, clearance and/or metabolism. One key feature of the compounds as described herein is disubstitution at the C3 position (e.g., with one substituent being a 3α hydroxy moiety. The inventors envision disubstitution at C-3 will eliminate the potential for oxidation of the hydroxy moiety to the ketone, prevent further metabolism, and reduce the potential for secondary elimination pathways, such as glucuronidation. The inventors further envision the overall effect of C3 disubstitution should be of improving the overall PK parameters and reducing potential toxicities and side effects, which may allow, in certain embodiments, administration orally and/or chronically. Another key feature of the compounds as described herein is the presence of a hydrogen at the C19 position ("19-nor") rather than a methyl group. The inventors envision 19-nor compounds, as compared to their C19-methyl counterparts, will have improved physical properties, such as improved solubility. The inventors envision futher enhancement of solubility, for example, when the AB ring system is in the *cis* configuration.

Thus, in one aspect, provided herein are 19-nor C3,3-disubstituted C21-triazole and tetrazole steroids of Formula (**I**):



(**I**)

and pharmaceutically acceptable salts thereof; wherein A is selected from the group:



(A-1) , (A-2) , (A-3) , (A-4) , and (A-5) ; R^1 is C_1-C_6 haloalkyl (e.g. CHF_2, CH_2F) or C_1-C_6 alkyl (e.g., CH_3, CH_2CH_3, heteroalkyl, e.g., CH_2OCH_3, $CH_2OCH_2CH_3$); R^2 and R^3 is independently selected from H, halo (e.g., F), C_1-C_6 alkyl (e.g., CH_3) or alkoxy (e.g., OCH_3, OCH_2CH_3); R^4 is halo (e.g., Cl, F), cyano, nitro, $-S(O)_xR^a$, $-NR^bR^c$, C_1-C_6 alkyl (e.g., CH_3, CF_3), C_1-C_6 alkoxy, $-C(O)R^a$, $-C(O)OR^a$, or $-C(O)NR^bR^c$; R^a is H, aryl, heteroaryl, or C_1-C_6 alkyl; each R^b and R^c is independently H, $-S(O)_xR^a$, $-C(O)R^a$, C_1-C_6 alkyl, or C_1-C_6 alkoxy, or R^b and R^c taken together with the atom to which they are attached form a ring; *n* is an integer from 0 to 2; and x is an integer from 0 to 2; wherein when A is (A-1) or (A-2), then R^1 is selected from: $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CBr_3$, $-CHBr_2$, $-CH_2Br$, or C_1-C_6 alkyl; or when A is (A-3) or (A-5), R^1 is $-CH_3$, $-CH_2F$, $-CH_2OCH_3$, or $-CHF_2$, and *n* is 0, then at least one of R^2 and R^3 is not H.

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

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

Compounds of the present invention 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.

Thus, in another aspect, provided is a use of an effective amount of a compound of the present invention, 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 certain embodiments, the present disclosure relates to 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 invention. In certain embodiments, the CNS–related 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, 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 intramuscularly. In certain embodiments, the compound is administered chronically.

In another aspect, provided is a use of an effective amount of a compound of the Formula (**I**) in the manufacture of a medicament, for inducing sedation and/or anesthesia.

In a further aspect, provided is a use of an effective amount of a compound of the Formula (**I**) in the manufacture of a medicament, for treating seizure.

In yet another aspect, provided is a use of an effective amount of a compound of the Formula (**I**) in the manufacture of a medicament, for treating epilepsy.

In another aspect, provided is a use of an effective amount of a compound of the Formula (**I**) in the manufacture of a medicament, for treating status epilepticus (SE).

In another aspect, provided is a use of a therapeutically effective amount 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 a disorder (e.g., a disorder as described herein, e.g., a disorder related to GABA function).

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

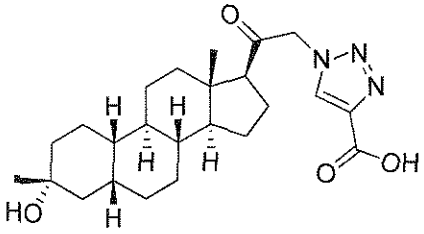
Definitions

Chemical Definitions

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

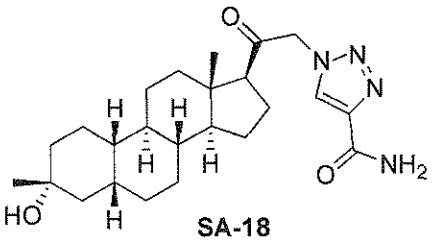
version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, 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.

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) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric



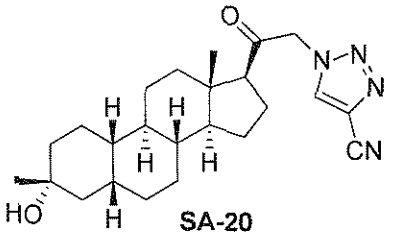
SA-17

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SA-18

, and



SA-20

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21. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt thereof of any one of the preceding claims, and a pharmaceutically acceptable excipient.

22. Use of an effective amount of a compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament, for treating a CNS–related disorder in a subject in need thereof.

23. The use of claim 22, 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.

24. The use of claim 22, wherein the CNS-related disorder is depression (e.g., post-partum depression).

25. The use of claim 22, wherein the CNS-related disorder is tremor (e.g., essential tremor).

26. The use of claim 22, wherein the CNS-related disorder is an eating disorder (e.g., anorexia nervosa, bulimia nervosa, binge-eating disorder, cachexia).

27. The use of claim 21 wherein the compound is to be administered orally, subcutaneously, intravenously, or intramuscularly.

28. The use of claim 22 wherein the compound is to be administered chronically.

29. Use of an effective amount of a compound of the Formula (**I**) in the manufacture of a medicament, for inducing sedation and/or anesthesia.

30. Use of an effective amount of a compound of the Formula (**I**) in the manufacture of a medicament, for treating seizure.

31. Use of an effective amount of a compound of the Formula (**I**) in the manufacture of a medicament, for treating epilepsy.

32. Use of an effective amount of a compound of the Formula (**I**) in the manufacture of a medicament, for treating status epilepticus (SE).

33. The use of claim 32, 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).

34. Use of a therapeutically effective amount 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 a disorder (e.g., a disorder as described herein, e.g., a disorder related to GABA function).