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Declarations under Rule 4.17:

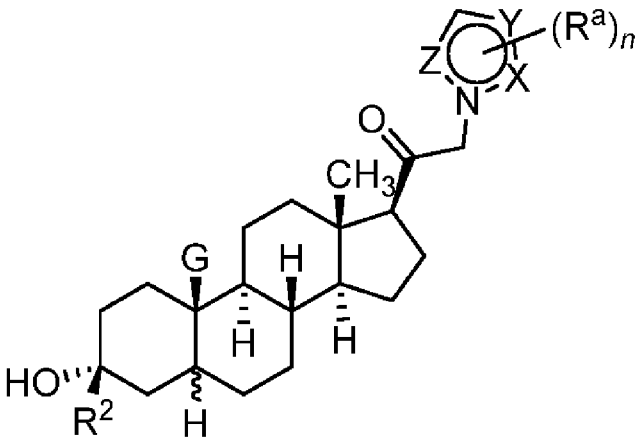
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

[Continued on next page]

(54) Title: NEUROACTIVE STEROIDS, COMPOSITIONS, AND USES THEREOF

(57) Abstract: Described herein are neuroactive steroids of the Formula (I): (I) or a pharmaceutically acceptable salt thereof; wherein R^1, R^2, R^a, G, X, Y, Z, and *n* are as defined herein. Such compounds are envisioned, in certain embodiments, to behave as GABA modulators. Also provided are pharmaceutical compositions comprising a compound described herein and methods of use and treatment, *e.g.*, such for inducing sedation and/or anesthesia.



(I)

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Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
3 November 2016

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A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/56; A61K 31/58; A61K 31/565 (2016.01)
CPC - A61K 31/56; A61K 31/58; A61K 31/565; C07J 1/00; C07J 1/0003; C07J 1/0007 (2016.05)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 31/56; A61K 31/58; A61K 31/565 (2016.01)
CPC - A61K 31/56; A61K 31/58; A61K 31/565; C07J 1/00; C07J 1/0003; C07J 1/0007 (2016.05)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/171; 514/176; 514/182; IPC(8) - A61K 31/56; A61K 31/58; A61K 31/565 (2016.01); CPC - A61K 31/56; A61K 31/58; A61K 31/565; C07J 1/00; C07J 1/0003; C07J 1/0007 (2016.05) (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, STN, PubChem, Google Patents, Google Scholar
Search terms used: steroid 3-hydroxy 3-methyl 18-methyl pyrrole methoxy

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/056181 A1 (SAGE THERAPEUTICS INC) 18 April 2013 (18.04.2013) entire document	1, 8-11, 14, 15, 17, 28, 32-35, 43, 46-66
A	US 6,143,736 A (UPASANI et al) 07 November 2000 (07.11.2000) entire document	1, 8-11, 14, 15, 17, 28, 32-35, 43, 46-66
A	US 6,277,838 B1 (UPASANI et al) 21 August 2001 (21.08.2001) entire doucment	1, 8-11, 14, 15, 17, 28, 32-35, 43, 46-66

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 June 2016	29 AUG 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Extra Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 8-11, 14, 15, 17, 28, 32-35, 43, 46-66

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

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Continued from Box No. III Observations where unity of invention is lacking

Claims 1, 8-11, 14, 15, 17, 28, 32-35, 43, and 46-66 have been analyzed subject to the restriction that the claims read on the compound of the Formula (I) as described in the Lack of Unity of Invention (See Box IV). The claims are restricted to a compound of the Formula (I): or a pharmaceutically acceptable salt thereof, wherein: each X, Y, and Z is CH; G is –C(R3a)(R3b)(OR1); R1 is C1 alkyl; R2 is C1 alkyl; each of R3a and R3b is independently H; Ra is absent; n is 0.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-66 are drawn to compounds of the Formula (I), compositions thereof, methods thereof, and kits thereof.

The first invention of Group I+ is restricted based on the proviso that the compound is not selected from a compound of Table 1 and is restricted to a compound of the Formula (I): or a pharmaceutically acceptable salt thereof, wherein: each X, Y, and Z is CH; G is –C (R3a)(R3b)(OR1); R1 is C1 alkyl; R2 is C1 alkyl; each of R3a and R3b is independently H; Ra is absent; n is 0; compositions thereof; methods thereof; and kits thereof. It is believed that claims 1, 8-11, 14, 15, 17, 28, 32-35, 43, and 46-66 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would a compound of the Formula (I): or a pharmaceutically acceptable salt thereof, wherein: X is CH, Y and Z is independently N; G is –C(R3a)(R3b)(OR1); R1 is aryl; R2 is C6 alkoxy; each of R3a and R3b is independently C6 alkyl; Ra is nitro; n is 3; compositions thereof; methods thereof; and kits thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables G, Ra, R2, X, Y, Z, and n.

The Groups I+ share the technical features of a compound having the core structure of the Formula (I): or a pharmaceutically acceptable salt thereof; a pharmaceutical composition comprising a compound and a pharmaceutically acceptable excipient; a method of inducing sedation and/or anesthesia in a subject, comprising administering to the subject an effective amount of a compound; a method of administering an effective amount of a compound, a pharmaceutically acceptable salt thereof, or pharmaceutical composition of a compound to a subject in need thereof, wherein the subject experiences sedation and/or anesthesia within two hours of administration; a method for treating seizure in a subject, comprising administering to the subject an effective amount of a compound; a method for treating epilepsy or status epilepticus in a subject, the method comprising administering to the subject an effective amount of a compound; a method for treating a neuroendocrine disorder or dysfunction in a subject, comprising administering to the subject an effective amount of a compound; a method for treating a neurodegenerative disease or disorder in a subject, comprising administering to the subject an effective amount of a compound; a method for treating a movement disorder or tremor in a subject, comprising administering to the subject an effective amount of a compound; a method for treating a mood disorder or anxiety disorder in a subject, comprising administering to the subject an effective amount of a compound; 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 a compound; 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; and a kit comprising a solid composition comprising a compound and a sterile diluent. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 6,277,838 B1 to Upasani et al. teach a compound having the core structure of the Formula (I): or a pharmaceutically acceptable salt thereof (Col. 15, Lns. 58-60, Example 9, 3a-Hydroxy-21-(1'-imidazolyl)-5B-3-pregnan-20-one); a pharmaceutical composition comprising a compound and a pharmaceutically acceptable excipient (Col. 34, Lns. 45-64); a method of inducing sedation and/or anesthesia in a subject (Col. 34, Lns. 63-65, Another desirable object of the compounds an methods is to induce anesthesia, particularly by intravenous administration.), comprising administering to the subject an effective amount of a compound (Col. 34, Lns. 63-65; Col. 60, Lns. 1-12); a method of administering an effective amount of a compound, a pharmaceutically acceptable salt thereof, or pharmaceutical composition of a compound to a subject in need thereof (Col. 34, Lns. 63-65; Col. 60, Lns. 1-12), wherein the subject experiences sedation and/or anesthesia within two hours of administration (Col. 34, Lns. 63-65; Col. 60, Lns. 1-12); a method for treating seizure in a subject (Abstract; Claim 1), comprising administering to the subject an effective amount of a compound (Col. 34, Lns. 45-64, Desirable objects of the compositions and methods of this invention are in the treatment of stress, anxiety, PMS, PND, and seizures; Col. 51, Table 7); a method for treating epilepsy or status epilepticus in a subject (Col. 3, Lns. 61-63, Representative disorders treated in the present invention are epilepsy...; Col. 34, Lns. 45-64), the method comprising administering to the subject an effective amount of a compound (Col. 34, Lns. 45-64, Desirable objects of the compositions and methods of this invention are in the treatment of stress, anxiety, PMS, PND, and seizures; Col. 51, Table 7); a method for treating a neuroendocrine disorder or dysfunction in a subject (Abstract; Claim 1, A method of treating or preventing stress or anxiety...; See Para. [244] of the applicants specification that describes anxiety of as symptom of a neuroendocrine disorder.), comprising administering to the subject an effective amount of a compound (Col. 34, Lns. 45-64, Desirable objects of the compositions and methods of this invention are in the treatment of stress, anxiety, PMS, PND, and seizures); a method for treating a neurodegenerative disease or disorder in a subject (Col. 3, Lns. 61-63, Representative disorders treated in the present invention are epilepsy...; Col. 34, Lns. 45-64; See Para. [245] of the applicants specification that describes epilepsy as a neurodegenerative disease.), comprising administering to the subject an effective amount of a compound (Col. 3, Lns. 61-63, Representative disorders treated in the present invention are epilepsy...; Col. 34, Lns. 45-64); a method for treating disorders related to GABA function in a subject in need thereof (Abstract, Claim 10), the method comprising administering to the subject a therapeutically effective amount of a compound, a pharmaceutically acceptable salt thereof, or pharmaceutical composition of a compound (Col. 36, Lns. 50-59 Claim 10); a method for treating a CNS-related disorder in a subject in need thereof (Abstract; Claim 1,

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A method of treating or preventing stress or anxiety, treating or preventing mood disorders...; See Para. [214] of the applicants specification that states the CNS-related disorder may be mood disorders), comprising administering to the subject an effective amount of a compound (Col. 34, Lns. 45-64).

Additionally, WO 2013/056181 A1 to Sage Therapeutics, Inc. teaches a compound having the core structure of the Formula (I): or a pharmaceutically acceptable salt thereof (Pg. 38, third shown structure;...see shown structure...); a method for treating a movement disorder or tremor in a subject (Abstract; Claims 28 and 29; Para. [00015]; Para. [00289]), comprising administering to the subject an effective amount of a compound (Abstract; Claims 28 and 29; Para. [00015]; Para. [00289]); and a kit comprising a solid composition comprising a compound and a sterile diluent (Para. [00276]).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.