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  A61K 31/437 (2006.01)  A61P 25/18 (2006.01)

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  62/290,864 3 February 2016 (03.02.2016) US


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Declarations under Rule 4.17:
— as to applicant’s entitlement to apply for and be granted a patent (Rule 4.1.7(H))
— as to the applicant’s entitlement to claim the priority of the earlier application (Rule 4.1.7(m))

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: 2 February 2017

(54) Title: VMAT2 INHIBITORS FOR TREATING NEUROLOGICAL DISEASES OR DISORDERS

(57) Abstract: Methods are provided herein for treating mania in mood disorders and other neurological diseases or disorders. The methods provided herein comprise administering a VMAT2 inhibitor to a subject in need thereof. A VMAT2 inhibitor useful in the methods provided herein includes (S)-2-Amino-3-methylbutyric acid (2R,3R,1 lbR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,1 lb-hexahydro-2H-pyrido[2, 1-alisoquinolin-2-yl ester.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/437 A61P25/18
ADD.

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)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category</th>
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<td>X</td>
<td>WATTS ET AL: &quot;Clinical and biochemical studies on treatment of Lesch-Nyhan syndrome&quot;. ARCHIVES OF DISEASE IN CHILDHOOD. vol. 49, 1974, pages 693-702, XP002764462. DOI : 10.1136/adc.49.9.693 abstract</td>
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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

* 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
A: document member of the same patent family

Date of the actual completion of the international search
22 November 2016

Date of mailing of the international search report
19/12/2016

Name and mailing address of the ISA/Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Cattel 1, James
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INTERNATIONAL SEARCH REPORT

**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 additional sheet

1. [X] 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 an 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.:

**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.
- [X] No protest accompanied the payment of additional search fees.
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-34, 103-120
   
   The use of VMAT2 inhibitors to treat mania and depression in mood disorders and OCD.

2. claims: 35-50
   
   The use of VMAT2 inhibitors to treat dysfunction associated with Lysch-Nyham syndrome

3. claims: 51-68
   
   The use of VMAT2 inhibitors to treat agitation in Alzheimer's disease.

4. claims: 69-84
   
   The use of VMAT2 inhibitors to treat Fragile X syndrome

5. claims: 85-102
   
   The use of VMAT2 inhibitors to treat ASD

6. claims: 121-136
   
   The use of VMAT2 inhibitors to treat chorea acanthocytosis

7. claims: 137-152
   
   The use of VMAT2 inhibitors to treat Rett syndrome
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<td>AU 2013318182 Al</td>
<td>19-03-2015</td>
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<tr>
<td></td>
<td></td>
<td>CA 2883641 Al</td>
<td>27-03-2014</td>
</tr>
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<td></td>
<td>CN 104684555 A</td>
<td>03-06-2015</td>
</tr>
<tr>
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<td></td>
<td>EP 2897615 Al</td>
<td>29-07-2015</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HK 1212232 Al</td>
<td>10-06-2016</td>
</tr>
<tr>
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<td></td>
<td>JP 2015528516 A</td>
<td>28-09-2015</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2014336386 Al</td>
<td>13-11-2014</td>
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<tr>
<td></td>
<td></td>
<td>US 2014341994 Al</td>
<td>20-11-2014</td>
</tr>
<tr>
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<td></td>
<td>US 2015004231 Al</td>
<td>01-01-2015</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2016235733 Al</td>
<td>18-08-2016</td>
</tr>
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<td></td>
<td>WO 2014047167 Al</td>
<td>27-03-2014</td>
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<tr>
<td></td>
<td></td>
<td>BR PI0718247 A2</td>
<td>07-01-2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2668689 Al</td>
<td>15-05-2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 101553487 A</td>
<td>07-10-2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK 200970461 Al</td>
<td>30-12-2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2081929 Al</td>
<td>29-07-2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2402220 T3</td>
<td>29-04-2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 5290185 B2</td>
<td>18-09-2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 20100509366 A</td>
<td>25-03-2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20090079257 A</td>
<td>21-07-2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT 2081929 E</td>
<td>15-04-2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2008167337 Al</td>
<td>10-07-2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2012077839 Al</td>
<td>29-03-2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2008058261 Al</td>
<td>15-05-2008</td>
</tr>
</tbody>
</table>