(51) International Patent Classification: A61K 31/495

(21) International Application Number: PCT/GB2005/000119

(22) International Filing Date: 14 January 2005 (14.01.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0400802.5 14 January 2004 (14.01.2004) GB


(72) Inventors:


(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, [Continued on next page])

(54) Title: DOPAMINE UPTAKE INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL DISEASE

(57) Abstract: Treatment of diseases and disorders related to altered neuronal excitability, especially migraine prophylaxis, mood stabilisation and convulsions, in particular the treatment of convulsions due to epilepsy, also treatment of depression or psychomotor retardation in subjects prone to seizures. Dopamine uptake inhibitors are employed, especially benzhydroxy-ethyl piperazine derivatives, including GBR12909, GBR12935, GBR13069, GBR13098, GBR13119 and pharmaceutically acceptable salts thereof.
Published:
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report: 15 September 2005

For two-letter codes and other abbreviations, refer to the “Guidance Notes on Codes and Abbreviations” appearing at the beginning of each regular issue of the PCT Gazette.
INTERNATIONAL SEARCH REPORT

PCT/GB2005/000119

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/495

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 7 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, PAJ

C. DOCUMENTS CONSIDERED TO BE RELevANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>P,X</td>
<td>CLINCKERS R ET AL: &quot;Anticonvulsant action of GBR-12909 and citalopram against acute experimentally induced limbic seizures&quot; NEUROPHARMACOLOGY, Pergamon Press, Oxford, GB, vol. 47, no. 7, December 2004 (2004−12), pages 1053−1061, XP004650289 ISSN: 0028−3908 abstract page 1054, left-hand column, line 38 - right-hand column, line 2 page 1057, left-hand column, paragraph 3 page 1058, left-hand column, paragraph 2 - right-hand column, paragraph 1 page 1060, left-hand column, paragraph 2 - right-hand column, paragraph 2</td>
<td>1−20</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of box C. Patent family members are listed in 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 document 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 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

*X* document of particular relevance; the claimed invention cannot be considered to involve an inventive step where 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: 11 May 2005

Date of mailing of the international search report: 04/07/2005

Name and mailing address of the ISA:

European Patent Office, P.B. 5818 Patentlaan 2 NL−2280 HV Rijswijk Tel. (+31)−70 340−2800, Fax. (+31)−70 940−3016

Authorized officer:

Tudor, M

Form: PCT/ISA/10 (second sheet) (January 2004)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>SOGAARD U ET AL: &quot;A tolerance study of single and multiple dosing of the selective dopamine uptake inhibitor GBR 12909 in healthy subjects.&quot; INTERNATIONAL CLINICAL PSYCHOPHARMACOLOGY, OCT 1990, vol. 5, no. 4, October 1990 (1990-10), pages 237-251, XP009047476 ISSN: 0268-1315 abstract page 250, paragraph 2</td>
<td>1,2,4, 7-17,19, 20</td>
</tr>
<tr>
<td>X</td>
<td>ANDERSEN P H: &quot;THE DOPAMINE UPTAKE INHIBITOR GBR-12909 SELECTIVITY AND MOLECULAR MECHANISM OF ACTION&quot; EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 166, no. 3, 1989, pages 493-504, XP002327585 ISSN: 0014-2999 abstract page 494, left-hand column, paragraph 2 page 501, right-hand column, paragraph 2 page 502, left-hand column, paragraph 3 - right-hand column, paragraph 2 page 503, right-hand column, paragraph 2</td>
<td>1,2,4, 7-12,16, 17,19</td>
</tr>
<tr>
<td>Category</td>
<td>Citation of document, with indication, where appropriate, of the relevant passages</td>
<td>Relevant to claim No.</td>
</tr>
<tr>
<td>----------</td>
<td>---------------------------------------------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>X</td>
<td>HANSARD MATTHEW J ET AL: &quot;Dopamine, but not norepinephrine or serotonin, reuptake inhibition reverses motor deficits in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated primates.&quot; THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS. DEC 2002, vol. 303, no. 3, December 2002 (2002-12), pages 952-958, XP002327586 ISSN: 0022-3565 page 952, right-hand column, paragraph 2 - page 953, left-hand column, paragraph 1 page 953, left-hand column, paragraph 4 - right-hand column, paragraph 1 page 955, left-hand column, paragraph 3 page 955, left-hand column, paragraph 8 - right-hand column, line 22 page 957, left-hand column, paragraph 3 - right-hand column, line 6</td>
<td>1,2,4, 7-12,16, 17,19</td>
</tr>
</tbody>
</table>
INTERNATIONAL SEARCH REPORT
PCT/GB2005/000119

Box 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. [x] Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
   Although claims 16-20 are directed to a method of treatment of the human or animal body, the search has been carried out and based on the alleged effects of the compound or composition.

2. [x] 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:
   see FURTHER INFORMATION sheet PCT/ISA/210

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 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:

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 an additional fee, this Authority did not invite payment of any additional fee.

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.
- [ ] No protest accompanied the payment of additional search fees.
Continuation of Box II.1

Although claims 16-20 are directed to a method of treatment of the human or animal body, the search has been carried out and based on the alleged effects of the compound or composition.

----

Continuation of Box II.2

Present claims 1-8 and 13-20 relate to compounds and a method defined by reference to a desirable characteristic or property, namely the inhibition of dopamine reuptake. The claims cover all compounds and methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds and methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, said claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds and method by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compound benzylhydroxyethyl piperazine and derivatives thereof, in particular, GBR12909, GBR12935, GBR13069, GBR12098 and GBR13119.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.