



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/135, 31/137, 31/138, 31/4462, 31/00, 31/352, 31/382, 31/335, C07C 217/00	A3	(11) International Publication Number: WO 00/02551 (43) International Publication Date: 20 January 2000 (20.01.00)
(21) International Application Number: PCT/US99/15857 (22) International Filing Date: 12 July 1999 (12.07.99) (30) Priority Data: 60/092,546 13 July 1998 (13.07.98) US (71) Applicant (for all designated States except US): NPS PHARMACEUTICALS, INC. [US/US]; Suite 240, 420 Chipeta Way, Salt Lake City, UT 84018-1256 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): MUELLER, Alan [US/US]; 2510 East Skyline Drive, Salt Lake City, UT 84108 (US). MOE, Scott [US/US]; 1979 E. Forest Creek Lane, Salt Lake City, UT 84121 (US). BALANDRIN, Manuel [US/US]; 9184 South Winter Wren Drive, Sandy, UT 84093 (US). (74) Agent: WARBURG, Richard, J.; Lyon & Lyon LLP, Suite 4700, 633 West Fifth Street, Los Angeles, CA 90071-2066 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 21 September 2000 (21.09.00)
(54) Title: METHODS AND COMPOUNDS FOR TREATING DEPRESSION (57) Abstract <p>The present invention features compounds active at both the serotonin euptake site and the N-methyl-D-aspartate (NMDA) receptor and the use of such compounds for treating different disorders. Compounds having activity at the serotonin reuptake site and the NMDA receptor ("multi-active compounds") can be used to treat different types of disorders such as depression, obsessive-compulsive disorders (OCD), sleep disorders, sexual dysfunction, and eating disorders. Preferably, the multi-active compounds are used to treat depression.</p>		

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INTERNATIONAL SEARCH REPORT

Internatic	Application No
PCT/US 99/15857	

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/135 A61K31/137 A61K31/138 A61K31/4462 A61K31/00
 A61K31/352 A61K31/382 A61K31/335 C07C217/00

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 C07C

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 practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WILKINSON A ET AL: "Alaproclate acts as a potent, reversible and noncompetitive antagonist of the NMDA receptor coupled ion flow." JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1994 DEC) 271 (3) 1314-9., XP000862851 the whole document	1,2
X	EP 0 000 322 A (ASTRA LAEKEMEDEL AB) 10 January 1979 (1979-01-10) the whole document	1-3
X	FR 2 077 916 A (DAINIPPON PHARMACEUTICAL CO) 5 November 1971 (1971-11-05) the whole document	1-3
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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- *O* document referring to an oral disclosure, use, exhibition or other means
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- *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
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Date of the actual completion of the international search

21 January 2000

Date of mailing of the international search report

19.06.00

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

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PCT/US 99/15857

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MARYANOFF ET AL: "Structure-Activity Studies on Antidepressant 2,2-Diarylethylamines" JOURNAL OF MEDICINAL CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 27, page 1067-1071 XP002083434 ISSN: 0022-2623 Table I, compounds 34,35,37 page 1067, right-hand column, last paragraph ---	1-3
X	CARNMARM, BERNT ET AL: "Antidepressant agents. V. 1,1-Dimethyl-.omega.,.omega.-diphenylalkylamines" ACTA PHARM. SUEC. (1975), 12(2), 173-82, XP000862860 the whole document ---	1-3
X	MARCUSSON J O ET AL: "INHIBITION OF U3HPAROXETINE BINDING BY VARIOUS SEROTONIN UPTAKE INHIBITORS: STRUCTURE-ACTIVITY RELATIONSHIPS" EUROPEAN JOURNAL OF PHARMACOLOGY, NL, AMSTERDAM, vol. 215, no. 2/03, page 191-198 XP002016630 ISSN: 0014-2999 abstract table 4 ---	1-3
X	WO 96 40097 A (NPS PHARMA INC) 19 December 1996 (1996-12-19) abstract page 1, line 18 -page 2, line 11	1-3
Y	page 60, line 22 -page 69 page 224 last compound claims 1-5,8-13,18-33 ---	4-6
X	WO 97 46511 A (VANWAGENEN BRADFORD C ;DELMAR ERIC G (US); MOE SCOTT T (US); SMITH) 11 December 1997 (1997-12-11) abstract page 1, line 20 -page 2, line 12	1-3
Y	page 61, line 19 -page 74 page 236 "astra compound" claims 1-27 ---	4-6
Y	NOWAK G ET AL: "Adaptation of cortical NMDA receptors by chronic treatment with specific serotonin reuptake inhibitors." EUROPEAN JOURNAL OF PHARMACOLOGY, (1998 JAN 26) 342 (2-3) 367-70., XP000862854 the whole document ---	4-6

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INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/US 99/15857

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>PAUL I A ET AL: "ADAPTATION OF THE N-METHYL-D-ASPARTATE RECEPTOR COMPLEX FOLLOWING CHRONIC ANTIDEPRESSANT TREATMENTS" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS,US,AMERICAN SOCIETY FOR PHARMACOLOGY AND, vol. 269, no. 1, page 95-102 XP002016627 ISSN: 0022-3565 the whole document</p> <p>---</p>	4-6
A	<p>WO 95 21612 A (NPS PHARMA INC ;MUELLER ALAN L (US); WAGENEN BRADFORD C VAN (US);) 17 August 1995 (1995-08-17) abstract page 1, line 1 - line 19 page 31, line 6 -page 37, line 5; claims 14-19</p> <p>-----</p>	1-6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/15857

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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:
Although claims 1-6 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-2
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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

see FURTHER INFORMATION PCT/ISA/210

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.:
1-2 partially, 3-6

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-2 (partially),3-6

Method of treating depression with a compound of structure I, such as defined in claim 3

2. Claims: 1-2(partially),7-10,17-18(partially)

Method of treating depression with a compound of structure II, such as defined in claim 7

3. Claims: 1-2(partially),11-14

Method of treating depression with a compound of structure III, such as defined in claim 11

4. Claims: 1-2(partially), 15-16,17-18(partially)

Method of treating depression with a compound of structure VII, such as defined in claim 15

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-2

Present claims 1-2 relate to a compound defined by reference to a desirable characteristic or property, namely "having NMDA IC50 of " and "serotonin reuptake IC50 of".

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search for the subject-matters of claims 1-2 is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by its pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search for the subject-matters of claims 1-2 impossible.

Furthermore, present claims 3-4 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds. 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.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds mentioned in claims 5,6 and to the general idea underlying the present invention .

Claims searched completely: 5,6
Claims searched incompletely: 3-4
Claims not searched: 1-2

The applicant's attention is drawn to the fact that claims, or parts of 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/15857

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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