

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
12 June 2003 (12.06.2003)

PCT

(10) International Publication Number
WO 2003/047558 A3

(51) International Patent Classification⁷: **A61P 25/28**,
A61K 31/00

(21) International Application Number:
PCT/IB2002/004805

(22) International Filing Date: 29 October 2002 (29.10.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/336,583 3 December 2001 (03.12.2001) US

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, 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, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): GENSET S.A. [FR/FR]; Route Nationale 7, F-91000 Evry (FR).

(72) Inventor; and

(75) Inventor/Applicant (*for US only*): MOSER, Paul [GB/FR]; 28 rue du Fort, 1, Le Clos Saint Lubin, F-78590 Noisy le Roi (FR).

(74) Common Representative: GENSET S.A.; c/o De Luca, Giampiero, Serono International S.A., Intellectual Property, 12, chemin des Aulx, CH-1228 Plan-Les-Ouates (CH).

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:
25 March 2004

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.

(54) Title: TREATMENT OF CNS DISORDERS USING D-AMINO ACID OXIDASE AND D-ASPARTATE OXIDASE INHIBITORS

(57) Abstract: The present invention relates to compounds that are inhibitors of D-amino acid oxidase, D-aspartate oxidase, or g34872; methods of treating CNS disorders including spinocerebellar ataxia, CAG repeat disorders, and other ataxic disorders using the compounds; and pharmaceutically acceptable compositions that contain the inhibitors are disclosed.



WO 2003/047558 A3

INTERNATIONAL SEARCH REPORT

Int Application No
PCT/IB 02/04805

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P25/28 A61K31/00

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

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	WO 01 09118 A (PRENDERGAST PATRICK T) 8 February 2001 (2001-02-08) page 10, line 21-31; page 11, line 32 - page 12, line 2; page 41, line 15-20; page 43, line 9-11; ---	1
X	WO 99 65516 A (KARPUJ MARCELLA V ;YEDA RES & DEV (IL); STEINMAN LAWRENCE (US)) 23 December 1999 (1999-12-23) page 9, line 31 - page 10, line 10; claim 1, 3, 8 ---	1
X	EP 0 950 406 A (NIIGATA UNIVERSITY) 20 October 1999 (1999-10-20) page 3, '0008!; claim 8, 9 ---	1
	--- -/--	

☒ 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

"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

7 July 2003

Date of mailing of the international search report

13. 01. 04

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Borst, M

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/IB 02/04805

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LARSON JEFFREY L ET AL: "The toxicity of repeated exposures to rolipram, a type IV phosphodiesterase inhibitor, in rats." PHARMACOLOGY & TOXICOLOGY, vol. 78, no. 1, 1996, pages 44-49, XP009013100 ISSN: 0901-9928 table I	1
X	PHANJOO A L ET AL: "Double-blind comparative multicentre study of fluvoxamine and mianserin in the treatment of major depressive episode in elderly people" ACTA PSYCHIATRICA SCANDINAVICA 1991 DENMARK, vol. 83, no. 6, 1991, pages 476-479, XP009013266 ISSN: 0001-690X page 478, paragraph entitled "Side effects"	1
X	WO 00 11952 A (PRO NEURON INC ;VON BORSTEL REID W (US)) 9 March 2000 (2000-03-09) page 9, last paragraph - page 16, second paragraph	1
A	GISPERT S ET AL: "Localization of the candidate gene D-amino acid oxidase outside the refined I-cM region of spinocerebellar ataxia 2." AMERICAN JOURNAL OF HUMAN GENETICS. UNITED STATES OCT 1995, vol. 57, no. 4, October 1995 (1995-10), pages 972-975, XP009013160 ISSN: 0002-9297 the whole document	1
A	BEERS M H ET AL.: "The Merck Manual, 17th ed." 1999, MERCK RESEARCH LABORATORIES, WHITEHOUSE STATION, N.J. XP002246495 page 1464-1465)	1
P,X	WO 02 066 672 A (CHUMAKOV ILYA ;GENSET SA (FR); COHEN DANIEL (FR)) 29 August 2002 (2002-08-29) cited in the application page 14, second paragraph	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 02/04805

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.: 1 (part)
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. ☒ Claims Nos.: 1 (part)
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:

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 (part)

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. Claim : 1 (part)

DAO or DDO inhibitors according to Formula I (aryl amino carboxylic acid esters or amides with the aminoalkyl group (A-NH-R4) attached to the carboxyl group)

2. Claim : 1 (part)

DAO or DDO inhibitors according to Formula Ia (amino aryl caboxylic acid esters or amides with the amino(-alkyl) group (W-NHR2) attached to the aromatic ring)

3. Claim : 1 (part)

DAO or DDO inhibitors according to part of Formula Ib ((carbocyclic aryl ring formed by A, G, K, J, E and substituted either directly or via an alkyl- or aminogroup (W) with an alk(en)yl-, alkoxy-, amino-, amido-, carboxy-, sulfonyl- or phosphonyl-group (R1))

4. Claim : 1 (part)

DAO or DDO inhibitors according to part of Formula Ib ((heterocyclic aryl ring formed by A, G, K, J, E and substituted either directly or via an alkyl- or aminogroup (W) with an alk(en)yl-, alkoxy-, amino-, amido-, carboxy-, sulfonyl- or phosphonyl-group (R1))

5. Claim : 1 (part)

DAO or DDO inhibitors according to Formula II and IIa (hydroxy- or keto-carboxylic acids)

6. Claim : 1 (part)

DAO or DDO inhibitors according to Formula III (5 to 8 membered heterocycle with a keto- or carboxyl(amide) group directly attached to the ring)

7. Claim : 1 (part)

DAO or DDO inhibitors according to Formula IV (6-membered carbo- or heterocycle with a keto- or carboxyl(amide) group directly attached to the ring)

8. Claim : 1 (part)

DAO or DDO inhibitors according to Formula V+Va-c and VI

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

((alpha-amino acid esters or amides))

9. Claim : 1 (part)

DAO or DDO inhibitors according to page 61-64; table 2, page
94-102 not falling under formula I-VI

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1 (part)

The present claim is directed to the therapeutic use of compounds which are defined in terms of a functionality, ie the inhibition of DAO or DDO, for the treatment of ataxic disorders.

According to the description (page 50ff) the term "DAO or DDO inhibitor" as used in claim 1 refers to inhibitors for the enzymatic activity of DAO or DDO having a certain K_i and includes the compounds according to formula I (page 51), II (page 54), III (page 56), IV (page 57), V (page 58), VI (page 61) as well as the exemplified further compounds (page 61-64; table 2, page 94-102). In a further passage of the description (page 64, last paragraph - page 69, fourth paragraph) it is stated that inhibitors of DAO or DDO expression also form part of the invention.

Methods of determining inhibition of DAO or DDO enzymatic activity are described in the application (page 62-64) either directly or by reference to prior art publications. Similarly, methods for determining DAO or DDO expression are disclosed in the description (page 64, last paragraph - page 65, penultimate paragraph).

Moreover, in vivo tests for determining antipsychotic and possibly antiataxic activity of test compounds are disclosed (page 73-80).

However, the application on file fails to provide support (Article 6 PCT) for the alleged cause-effect relationship between the functionality of the compounds, ie the inhibition of DAO/DDO activity, on the one hand, and the envisaged therapeutic indication, ie the ataxic disorders, on the other hand. The application does not present a mechanism of action establishing a link between the DAO/DDO inhibition and the ataxic disorders to be treated, nor does it show an antiataxic effect for any of the compounds out of the extremely large number of possible structures falling within the term DAO/DDO inhibitors.

Additionally, Larson Jeffrey L et al., "The toxicity of repeated exposures to rolipram, a type IV phosphodiesterase inhibitor, in rats", Pharmacology & Toxicology, 1996, vol. 78, nr. 1, pg. 44-49 (cf. table I) as well as Phanjoo A L et al., "Double-blind comparative multicentre study of fluvoxamine and mianserin in the treatment of major depressive episode in elderly people", Acta Psychiatrica Scandinavica, 1991, vol. 83, nr. 6, pg. 476-479 (page 478, paragraph entitled "Side effects") report ataxic side effects caused for rolipram and fluvoxamine, which are DAO/DDO inhibitors exemplified in the description on file (cf. page 54).

In view of the lacking evidence for a cause-effect relationship linking the DAO/DDO inhibitory functionality to the ataxic disorders and in view of the contradicting reports of the prior art, it is to be concluded that the application does not provide sufficient support (Article 6 PCT) for the functional definition "DAO or DDO inhibitor" in combination with the therapeutic indication of ataxic disorders as defined in claim 1 on file.

Because of this lack of support (Article 6 PCT) it would have been justified not to perform a search at all for the subject-matter claimed.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Nevertheless, in order to provide the Applicant with prior art relevant to the application, a search will be carried out with the searchable subject-matter restricted to the compounds which are defined in terms of their structure in the description. Those are the compounds according to formula I (page 51), formula II (page 54), formula III (page 56), formula IV (page 57), formula V (page 58), formula VI (page 61) as well as the exemplified further compounds (page 61-64; table 2, page 94-102).

As the application fails to disclose structural definitions for the inhibitors of DAO or DDO expression a search for this aspect is not possible.

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/IB 02/04805

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0109118 A	08-02-2001	AU 6462500 A	19-02-2001
WO 9965516 A	23-12-1999	AU 4823999 A	05-01-2000
EP 0950406 A	20-10-1999	JP 3012923 B	28-02-2000
		JP 11209304 A	03-08-1999
		AU 733910 B	31-05-2001
		AU 1319199 A	12-08-1999
		CA 2260311 C	17-12-2002
		US 6355690 B	12-03-2002
WO 0011952 A	09-03-2000	US 2001005719 A	28-06-2001
		AU 753203 B	10-10-2002
		AU 6021999 A	21-03-2000
		BR 9913319 A	22-05-2001
		CA 2341700 A	09-03-2000
		CN 1328417 T	26-12-2001
		EP 1109453 A	27-06-2001
		HU 0103255 A	29-04-2002
		JP 2002523434 T	30-07-2002
		US 2001016576 A	23-08-2001
		US 2002049182 A	25-04-2002
		ZA 200101565 A	15-05-2002
WO 02066672 A	29-08-2002	CA 2433866 A	29-08-2002
		US 2003185754 A	02-10-2003
		US 2003166554 A	04-09-2003