

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
8 October 2009 (08.10.2009)

PCT

(10) International Publication Number
WO 2009/123714 A3

(51) International Patent Classification:

C07D 241/04 (2006.01) A61K 31/496 (2006.01)
C07D 403/06 (2006.01) A61P 25/20 (2006.01)

(21) International Application Number:

PCT/US2009/002019

(22) International Filing Date:

1 April 2009 (01.04.2009)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/072,697 2 April 2008 (02.04.2008) US

(71) Applicant (for all designated States except US): ARENA PHARMACEUTICALS, INC. [US/US]; 6166 Nancy Ridge Drive, San Diego, CA 92121-3223 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): KRISHNAN, Ashwin, M. [US/US]; 11023 Cedarcrest Way, San Diego, CA 92121 (US). GHARBAOUI, Tawfik [MA/US]; 2340 Lomica Place, Escondido, CA 92029 (US).

(74) Agent: GODDARD, Christine, A.; Fish & Richardson P.C., 66 South Sixth Street, Suite 3300, P.O. Box 1022, Minneapolis, Minnesota 55440-1022 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(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, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

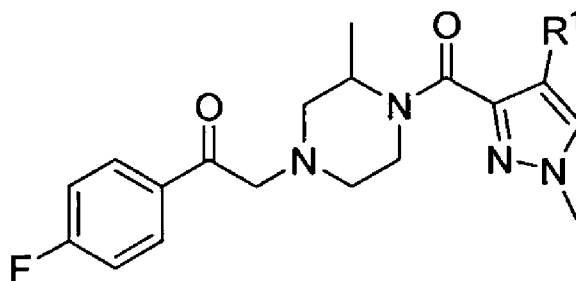
Published:

- 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:

28 January 2010

(54) Title: PROCESSES FOR THE PREPARATION OF PYRAZOLE DERIVATIVES USEFUL AS MODULATORS OF THE 5-HT_{2A} SEROTONIN RECEPTOR



(I)

(57) Abstract: The present invention relates to processes for preparing pyrazole derivatives of Formula (I) and salts and pharmaceutical compositions of the salts thereof, useful as modulators of 5-HT_{2A} serotonin receptor activity. The present invention also relates to intermediates used in the processes, and their preparation. The present invention also relates to salts of compounds of Formula (I) and pharmaceutical compositions thereof.

WO 2009/123714 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/002019

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D241/04 C07D403/06 A61K31/496 A61P25/20

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)

C07D A61K A61P

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)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2008/042388 A (ARENA PHARM INC [US]; XIONG YIFENG [US]; CHERRIER MARTIN C [US]; CHOI) 10 April 2008 (2008-04-10) Abstract; claims; pages 21-22, compounds 6, 9; pages 70-71, examples 1.45 and 1.46 (i.e. synthesis of the TFA salts of compounds 6 and 9) in combination with example 1.40 (page 68) and example 1.1, step C (page 56).	1-11, 14-38
A	WO 01/29008 A (ARENA PHARM INC [US]; TRIPOS INC [US]; BEHAN DOMINIC P [US]; BEELEY NI) 26 April 2001 (2001-04-26) Abstract; claims, examples.	1-11, 14-38
	----- -/-- -----	

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 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 2009

Date of mailing of the international search report

14/12/2009

Name and mailing address of the ISA/

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

Authorized officer

Weisbrod, Thomas

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/002019

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>VASILEVSKY ET AL.: "Study of the Heterocyclization of vic-Substituted Hydrazides of Acetylenylpyrazolecarboxylic Acids into N-Amino Pyrazolopyridinones" J. HETEROCYCL. CHEM., vol. 39, 2002, pages 1229-1233, XP002535542</p> <p>Page 1230, right column: scheme 4 and the sentence following scheme 4; page 1233: references [8], [9].</p> <p style="text-align: center;">-----</p>	1-11, 14-38
A	<p>DATABASE BEILSTEIN [Online] BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002535545</p> <p>Database accession no. 5926580 (BRN) the whole document</p> <p>-& VASILEVSKII; SHVARTSBERG: "Oxidative Iodination of Substituted N-Methylpyrazoles" BULL. ACAD. SCI. USSR (ENGLISH TRANSLATION), vol. 29, no. 5, 1980, pages 778-784, XP002535543</p> <p>Page 778, last paragraph, second sentence: (IXa) from (VIIIa); page 780, table 1, entry 4: (IXa).</p> <p style="text-align: center;">-----</p>	1-11, 14-38
A	<p>JEON ET AL.: "The synthesis of a new pyrazolylimidazolinone via 1,3-dipolar cycloaddition reaction of N-methyl sydnone with methyl propiolate" BULL. KOREAN CHEM. SOC., vol. 19, no. 7, 1998, pages 725-726, XP002535544</p> <p>Page 725, scheme 2, conversion of 4 to 5, and steps d and e starting from compound 6.</p> <p style="text-align: center;">-----</p>	1-11, 14-38

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/002019

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. 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.:

see annex

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-11, 14-38 (all complete)

directed to processes for preparing compounds (I), (II) and the salts thereof; subject-matter relating to a hydrochloride of a compound (I); and directed to a hydrobromide of a compound (II).

2. claim: 12 (part)

directed to a process for preparing a compound (III) wherein the R2 leaving group is different from 1H-imidazol-1-yl.

3. claims: 12 (part) and 13, 39-40 (all complete)

directed to a process for preparing a compounds (III) wherein R2 is 1H-imidazol-1-yl; and compounds (III) with such (R2)1H-imidazol-1-yl group.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2009/002019

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008042388 A	10-04-2008	AR 063100 A1	30-12-2008
		AU 2007305235 A1	10-04-2008
		CA 2664398 A1	10-04-2008
		CL 28592007 A1	06-06-2008
		EP 2066641 A1	10-06-2009
		PA 8749401 A1	09-02-2009
WO 0129008 A	26-04-2001	AU 1201001 A	30-04-2001
		CA 2387031 A1	26-04-2001
		CN 1411448 A	16-04-2003
		EP 1244632 A1	02-10-2002
		MX PA02003792 A	06-09-2004
		US 6150393 A	21-11-2000