

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
29 December 2004 (29.12.2004)

PCT

(10) International Publication Number
WO 2004/112704 A3

(51) International Patent Classification⁷: **A61K 31/445**,
31/47, C07D 401/04, 217/22, 211/32

(21) International Application Number:
PCT/US2004/018905

(22) International Filing Date: 15 June 2004 (15.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/462,507 16 June 2003 (16.06.2003) US

(71) Applicant (for all designated States except US): **ADOL-
LOR CORPORATION** [US/US]; 700 Pennsylvania
Drive, Exton, PA 19341 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **LE BOURDON-
NEC, Bertrand** [FR/US]; 317 Ivy Lane, East Fallowfield,
PA 19320 (US). **DOLLE, Roland, E.** [US/US]; 550 Prince
Frederick Street, King of Prussia, PA 19406 (US).

(74) Agents: **CHERRY, David, A.** et al.; Woodcock Wash-
burn, LLP, One Liberty Place - 46th Floor, Philadelphia,
PA 19103 (US).

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

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, 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, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, 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, HU, IE, IT, LU, MC, NL, 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
- 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 "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.



WO 2004/112704 A3

(54) Title: SUBSTITUTED PIPERIDINE COMPOUNDS AND METHODS OF THEIR USE

(57) Abstract: Novel 3,4-disubstituted-4-aryl-piperidine compounds are disclosed. Pharmaceutical compositions containing the 3,4-disubstituted-4-aryl-piperidine compounds and methods of their pharmaceutical uses are also disclosed. The compounds disclosed are useful, *inter alia*, as antagonists of opioid receptors.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/18905

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/445, 31/47, C07D 401/04, 217/22, 211/32
 US CL : 514/307, 331; 546/139, 236, 237, 238, 239, 240

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)

U.S. : 514/307, 331; 546/139, 236, 237, 238, 239, 240

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)
 Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/30896 A1 (OKADA et al.) 18 April 2002 (18.04.2002), see entire article especially ages 45-46 compounds 77-82.	1-14, 18-25, 28-32, 34-50, 52-55
Y	US 5,159,081 A (CANTRELL et al.) 27 October 1992 (27.10.1992), see entire article.	1-14, 18-25, 28-32, 34-50, 52-55
Y	US 5,434,171 A (FRANK et al.) 18 July 1995 (18.07.1995), see entire article.	1-14, 18-25, 28-32, 34-50, 52-55

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 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

06 July 2005 (06.07.2005)

Date of mailing of the international search report

20 JUL 2005

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
 Commissioner for Patents
 P.O. Box 1450
 Alexandria, Virginia 22313-1450

Facsimile No. (703) 305-3230

Authorized officer

Celia Chang

F. Roberts for

Telephone No. 571-272-1600

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/18905

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:
Please See Continuation 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 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.: 1-14, 18-25, 34-50, 52-55 (R4-R8=ring)

Remark on Protest The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/18905

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-14, 18-20, 28-32, 34-50, 52-55 reading on claims 21-25, when R5 is (CH₂)_y(CHR₈)_j(CHR_{8a})_zW, R4 and R8 forms 4-8 membered ring, drawn to multiple heterocyclic ring core compounds, compositions and method of use.

Group II, claims 1-20, 28-50, 52-55 reading on claims 21-25, when R5 is (CH₂)_y(CHR₈)_j(CHR_{8a})_zW, R4 and R8 are independent substituents, W is COOR⁹ drawn to carboxylamido piperidine compounds, compositions and method of use.

Group III, claims 1-20, 28-50, 52-55 reading on claims 21-25, when R5 is (CH₂)_y(CHR₈)_j(CHR_{8a})_zW, R4 and R8 are independent substituents, W is CONR^{10a}R^{10b} drawn to bisamido piperidine compounds, compositions and method of use.

Group IV, claims 1-5, 16, 28-50, 52-55, R5 is SO₂R^{7d}, drawn to sulfonyl piperidine, composition and method of use.

Group V, claims 1-20, 27-50, 52-55 when R5 is (P=O)OR^{7b}OR^{7c} or W is P(=O)OR^{7b}OR^{7c}, drawn to piperidine phosphates.

Group VI, claims 51, 56-58, drawn to therapeutic method in administering multiple active ingredients.

The inventions listed as Groups I-VI do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: PCT Rule 13.2, Annex B, part I(f)v indicates that "when dealing with alternatives, if it can be shown that at least one Markush alternative is not novel over the prior art, the question of unity of invention shall be reconsidered by the examiner" In the instant case, group II, W is coor⁹ compounds are anticipated by Cantrell et al. Ca 118:124401, thus, at least one Markush alternative is not novel.

Continuation of B. FIELDS SEARCHED Item 3:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/18905

CAS-structure
EAST/WEST-image