(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 February 2002 (07.02.2002)

PCT

(10) International Publication Number
WO 02/009758 A3

(51) International Patent Classification[7]: A61K 45/06, A61P 31/00

(21) International Application Number: PCT/IN01/00139

(22) International Filing Date: 31 July 2001 (31.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/222,201	1 August 2000 (01.08.2000)	US
09/640,947	19 August 2000 (19.08.2000)	US
PCT/IN00/00111	21 November 2000 (21.11.2000)	IN
60/286,291	25 April 2001 (25.04.2001)	US
09/850,669	7 May 2001 (07.05.2001)	US
PCT/IN01/00100	8 May 2001 (08.05.2001)	IN

(71) Applicant *(for all designated States except US)*: **WOCKHARDT LIMITED** [IN/IN]; Wockhardt Towers, Bandra-Kurla Complex, Bandra (East), Mumbai 400 051 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DE SOUZA, Noel, J.** [IN/IN]; Wockhardt Research Centre, D-4, MIDC, Chikalthana, Aurangabad 431 210 (IN). **PATEL, Mahesh, V.** [IN/IN]; Wockhardt Research Centre, D-4, MIDC, Chikalthana, Aurangabad 431 210 (IN). **GUPTE, Shrikant, V.** [IN/IN]; Wockhardt Research Centre, D-4, MIDC, Chikalthana, Aurangabad 431 210 (IN). **UPADHYAY, Dilip, J.** [IN/IN]; Wockhardt Research Centre, D-4, MIDC, Chikalthana, Aurangabad 431 210 (IN). **SHUKLA, Milind, C.** [IN/IN]; Wockhardt Research Centre, D-4, MIDC, Chikalthana, Aurangabad 431 210 (IN). **CHATURVEDI, Nishith, C.** [US/IN]; Wockhardt Research Centre, D-4, MIDC, Chikalthana, Aurangabad 431 210 (IN). **BHAWSAR, Satish, B.** [IN/IN]; Wockhardt Research Centre, D-4, MIDC, Chikalthana, Aurangabad 431 210 (IN). **NAIR, Sheela, C.** [IN/IN]; Wockhardt Research Centre, D-4, MIDC, Chikalthana, Aurangabad 431 210 (IN). **JAFRI, Mohammed, A.** [IN/IN]; Wockhardt Research Centre, D-4, MIDC, Chikalthana, Aurangabad 431 210 (IN). **KHORAKIWALA, Habil, F.** [IN/IN]; Wockhardt Research Centre, D-4, MIDC, Chikalthana, Aurangabad 431 210 (IN).

(74) Agent: **DE SOUZA, Noel, J.**; Wockhardt Research Centre, D-4, MIDC, Chikalthana, Aurangabad 431 210 (IN).

(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, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, 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, TR), OAPI patent (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:
27 December 2002

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.

WO 02/009758 A3

(54) Title: INHIBITORS OF CELLULAR EFFLUX PUMPS OF MICROBES

(57) Abstract: Compounds are described which are efflux pump inhibitors of cellular efflux pumps of microbes. Also described are methods of preparing such compounds, methods of using such efflux pump inhibitor compounds and pharmaceutical compositions which include such compounds.

INTERNATIONAL SEARCH REPORT

Int[illegible]onal Application No
PCT/IN 01/00139

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61P31/00

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)
EPO-Internal, PAJ, WPI Data, BIOSIS, 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.
X	EP 0 300 735 A (CHINOIN) 25 January 1989 (1989-01-25) claim 1 page 4, line 49-51 page 5, line 12-40 --- -/--	1-20,22, 31-47, 50,54, 56-58

[X] Further documents are listed in the continuation of box C.

[X] 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	Date of mailing of the international search report
3 October 2002	17/10/2002

Name and mailing address of the ISA	Authorized officer
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	Peeters, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	A.M.DHOPLE, M.A.IBANEZ: "In vivo susceptibility of mycobacterium leprae to ofloxacin either singly or in combination with rifampicin and rifabutin" ARZNEIMITTEL-FORSCHUNG, vol. 44, no. 4, 1994, pages 563-565, XP001108849 page 563 page 564, column 1 page 565, column 1	1,2,4,5, 7-9,11, 12,17, 18,20, 29, 31-33, 41,42, 44-47
X	WO 97 24128 A (BAYER) 10 July 1997 (1997-07-10) claims 1-5,10 page 3, line 1-14 page 9, line 1-12	1,2,4,5, 7-9,11, 12, 17-20, 31-33, 41,42, 44-47
X	E.M.MATEU-DE-ANTONIO, M.MARTIN: "In vitro efficacy of several antimicrobial combinations against Brucella canis and Brucella melitensis strains isolated from dogs" VETERINARY MICROBIOLOGY, vol. 45, no. 1, 1995, pages 1-10, XP001112917 page 1 page 3 -page 4 page 7 -page 8	1,2,4,5, 7-9,11, 12,17, 22, 27-29, 31-33, 41,42, 44-49
X	H.C.NEU, N.X.CHIN: "In vitro activity of fleroxacin in combination with other antimicrobial agents" AMERICAN JOURNAL OF MEDICINE, vol. 94, no. 3A, 1993, pages 9S-16S, XP008008698 page 9S page 11S page 13S page 15S	1,2,4,5, 7-9,11, 12, 17-20, 23,25, 29, 31-33, 41,42, 44-47

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	N.X.CHIN, H.C.NEU: "Combination of ofloxacin and other antimicrobial agents" JOURNAL OF CHEMOTHERAPY (FLORENCE), vol. 2, no. 6, 1990, pages 343-347, XP008008692 page 343 page 345 page 346, column 2	1,2,4,5, 7-9,11, 12,17, 18,20, 29, 31-33, 41,42, 44-47
X	P.VAN DER AUWERA E.A.: "Comparative in vitro activity of CI934, a new fluoroquinolone, alone and in combination with coumermycin, against gram-positive bacteria" DRUGS UNDER EXPERIMENTAL AND CLINICAL RESEARCH, vol. 13, no. 3, 1987, pages 125-132, XP008008697 page 125	1,2,4,5, 7-9,11, 12, 17-20, 24,32, 33,41, 42,44-47

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 01/00139

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. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

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 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.:

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

Continuation of Box I.1

Although claims 1-31 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.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

---

Continuation of Box I.2

Present claims 1-20,45-47 relate to a product/compound/method defined by reference to a desirable characteristic or property, namely: "antimicrobial agent"

The claims cover all products/compounds/methods 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 products/compounds/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, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/compound/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.

Present claims 1-35,37,39,41-49,51,52,54 relate to an extremely large number of possible compounds/products/methods. 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/products/methods claimed. 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 4-oxo-quinoline-3-carboxylic acid and derivatives as described in claims 36,38,40,50,53,55-58 optionally in combination with the compounds mentioned in claims 49,52 and 54, with due regard to the general idea underlying the present application.

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

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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/IN 01/00139

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 300735 A	25-01-1989	HU 47844 A2	28-04-1989
		AT 81458 T	15-10-1992
		AU 609676 B2	02-05-1991
		AU 1914788 A	27-01-1989
		CN 1031797 A	22-03-1989
		DE 3875295 D1	19-11-1992
		DE 3875295 T2	25-02-1993
		EP 0300735 A1	25-01-1989
		ES 2043827 T3	01-01-1994
		GR 3006560 T3	30-06-1993
		HK 71093 A	30-07-1993
		IL 87144 A	12-04-1994
		JP 1090125 A	06-04-1989
		RU 2030913 C1	20-03-1995
		US 4904647 A	27-02-1990
WO 9724128 A	10-07-1997	US 5753269 A	19-05-1998
		AU 709478 B2	26-08-1999
		AU 1334297 A	28-07-1997
		BR 9612325 A	13-07-1999
		CA 2193597 A1	28-06-1997
		CN 1209065 A	24-02-1999
		EP 0869795 A1	14-10-1998
		JP 2000502703 T	07-03-2000
		NZ 326061 A	29-11-1999
		WO 9724128 A1	10-07-1997