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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 April 2001 (12.04.2001)

PCT

(10) International Publication Number
WO 01/25219 A3

(51) International Patent Classification[7]: C07D 241/04, A61K 31/496, A61P 25/22, C07D 401/06, 403/06

(21) International Application Number: PCT/EP00/09722

(22) International Filing Date: 5 October 2000 (05.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9923748.9 7 October 1999 (07.10.1999) GB

(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ALVARO, Giuseppe** [IT/IT]; Glaxo Wellcome SpA, Via Alessandro Fleming 2, I-37135 Verona (IT). **DI FABIO, Romano** [IT/IT]; Glaxo Wellcome SpA, Via Alessandro Fleming 2, I-37135 Verona (IT). **GIOVANNINI, Riccardo** [IT/IT]; Glaxo Wellcome SpA, Via Alessandro Fleming 2, I-37135 Verona (IT). **GUERCIO, Giuseppe** [IT/IT]; Glaxo Wellcome SpA, Via Alessandro Fleming 2, I-37135 Verona (IT). **ST-DENIS, Yves** [CA/IT]; Glaxo Wellcome SpA, Via Alessandro Fleming 2, I-37135 Verona (IT). **URSINI, Antonella** [IT/IT]; Glaxo Wellcome SpA, Via Alessandro Fleming 2, I-37135 Verona (IT).

(74) Agent: **FILLER, Wendy, Anne**; GlaxoSmithKline, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, 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.

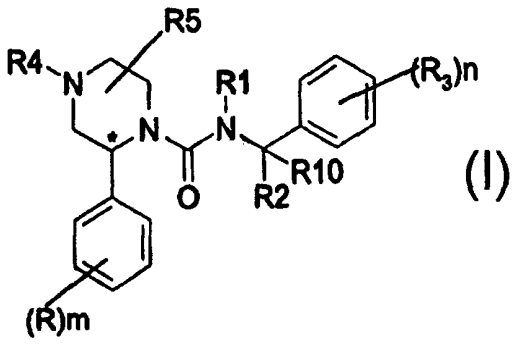
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR,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

Published:
— *with international search report*

(88) Date of publication of the international search report:
13 December 2001

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: PIPERAZINE COMPOUNDS



(57) Abstract: The present invention relates to piperazine derivatives of formula (I) wherein R represents a halogen atom or a C_{1-4} alkyl group; R_1 represents hydrogen or a C_{1-4} alkyl group; R_2 represents hydrogen, a C_{1-4} alkyl, C_{2-6} alkenyl or a C_{3-7} cycloalkyl group; or R_1 and R_2 together with nitrogen and carbon atom to which they are attached respectively represent a 5-6 membered heterocyclic group; R_3 represents a trifluoromethyl, a C_{1-4} alkyl, a C_{1-4} alkoxy, a trifluoromethoxy or a halogen group; R_4 represents hydrogen, a $(CH_2)qR_7$ or a $(CH_2)rCO(CH_2)pR_7$ group; R_5 represents hydrogen, a C_{1-4} alkyl or a COR_6 group; R_6 represents hydrogen, hydroxy, amino, methylamino, dimethylamino a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms; R_7 represents hydrogen, hydroxy or NR_8R_9 wherein R_8 and R_9 represent independently hydrogen or C_{1-4} alkyl optionally substituted by hydroxy, or by amino; R_{10} represents hydrogen, a C_{1-4} alkyl I group or R_{10} together with R_2 represents a C_{3-7} cycloalkyl group; m is zero or an integer from 1 to 3; n is zero or an integer from 1 to 3; both p and r are independently zero or an integer from 1 to 4; q is an integer from 1 to 4; provided that, when R_1 and R_2 together with nitrogen and carbon atom to which they are attached respectively represent a 5 to 6 membered heterocyclic group, i) m is 1 or 2; ii) when m is 1, R is not fluorine and iii) when m is 2, the two substituents R are not both fluorine,and pharmaceutically acceptable salts and solvates thereof.

WO 01/25219 A3

INTERNATIONAL SEARCH REPORT

Inter. ɔnal Application No
PCT/EP 00/09722

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D241/04 A61K31/496 A61P25/22 C07D401/06 C07D403/06

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 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)
CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 308 387 A (ANDERS K.K.BJÖRK) 29 December 1981 (1981-12-29) column 1 -column 11; example 35 ---	1,15-18
A	DAVID T. DAVIES: "SYNTHESIS A. BIOLOGICAL ACTIVITY OF A SERIES OF PIPERAZIN-2,3-DIONES" JOURNAL OF ANTIBIOTICS., vol. XLII, no. 3, 1989, pages 367-73, XP002164668 JAPAN ANTIBIOTICS RESEARCH ASSOCIATION. TOKYO., JP ISSN: 0021-8820 page 367; examples 5C,5D -----	1,15

☐ 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	Date of mailing of the international search report
4 April 2001	20/04/2001

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	Francois, J

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. ...nal Application No
PCT/EP 00/09722

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4308387 A	29-12-1981	AT 380685 B	25-06-1986
		AT 219383 A	15-11-1985
		AT 376666 B	27-12-1984
		AT 683479 A	15-05-1984
		AU 529260 B	02-06-1983
		AU 5198479 A	19-06-1980
		BE 879528 A	21-04-1980
		CA 1130807 A	31-08-1982
		CH 643247 A	30-05-1984
		DE 2941880 A	30-04-1980
		DK 442779 A,B,	21-04-1980
		ES 485188 A	16-05-1980
		FI 793238 A,B,	21-04-1980
		FR 2439187 A	16-05-1980
		GB 2037745 A,B	16-07-1980
		HK 57184 A	03-08-1984
		IT 1207269 B	17-05-1989
		JP 1482061 C	27-02-1989
		JP 55057572 A	28-04-1980
		JP 63026756 B	31-05-1988
		LU 81807 A	25-01-1980
		NL 7907741 A,B,	22-04-1980
		NO 793315 A,B,	22-04-1980
		NZ 191867 A	14-06-1983
		SE 448730 B	16-03-1987
		SE 7908701 A	21-04-1980
		SG 7384 G	08-02-1985
		US 4385057 A	24-05-1983
		US 4447433 A	08-05-1984