

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
24 February 2005 (24.02.2005)

PCT

(10) International Publication Number  
**WO 2005/016867 A3**

(51) International Patent Classification<sup>7</sup>: **C07C 233/55**,  
C07D 209/18, 317/60, 217/14, C07C 237/22, C07D  
215/36, C07C 235/38, C07D 333/60, C07C 235/24, A61K  
31/196, 31/33

Essex CM19 5AW (GB). **SMITH, Ian, Edward, David**  
[GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage  
Hertfordshire SG1 2NY (GB).

(21) International Application Number:  
PCT/GB2004/003516

(74) Agent: **THORNLEY, Rachel, Mary**; GlaxoSmithKline,  
Corporate Intellectual Property (CN925.1), 980 Great West  
Road, Brentford Middlesex TW8 9GS (GB).

(22) International Filing Date: 13 August 2004 (13.08.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
0319126.9 14 August 2003 (14.08.2003) GB

(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.

(71) Applicant (*for all designated States except US*):  
**SMITHKLINE BEECHAM CORPORATION**  
[US/US]; One Franklin Plaza, PO Box 7929, Philadelphia,  
Pennsylvania 19101 (US).

(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).

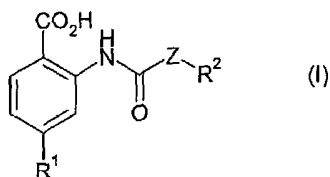
(72) Inventors; and  
(75) Inventors/Applicants (*for US only*): **CAMPBELL,  
Mathew** [GB/GB]; GlaxoSmithKline, Gunnels Wood  
Road, Stevenage Hertfordshire SG1 2NY (GB). **HAT-  
LEY, Richard, Jonathan** [GB/GB]; GlaxoSmithKline,  
Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY  
(GB). **HEER, Jag, Paul** [GB/GB]; GlaxoSmithKline,  
New Frontiers Science Park South, Third Avenue, Harlow  
Essex CM19 5AW (GB). **MASON, Andrew, McMur-  
trie** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road,  
Stevenage Hertfordshire SG1 2NY (GB). **PINTO, Ivan,  
Leo** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road,  
Stevenage Hertfordshire SG1 2NY (GB). **RAHMAN,  
Shahzad, Sharooq** [GB/GB]; GlaxoSmithKline, New  
Frontiers Science Park South, Third Avenue, Harlow

Published:  
— with international search report

(88) Date of publication of the international search report:  
31 March 2005

*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: ANTHRANILIC ACID DERIVATIVES AND THEIR USE AS ACTIVATORS OF THE HM74A RECEPTOR



(57) Abstract: Therapeutically active anthranilic acid derivatives of Formula (I) wherein R<sup>1</sup>, R<sup>2</sup> and Z are as defined in the specification, processes for the preparation of said derivatives, pharmaceutical formulations containing the active compounds and the use of the compounds in therapy, particularly in the treatment of diseases in which under-activation of the HM74A receptor contributes to the disease or in which activation of the receptor will be beneficial, are disclosed.

WO 2005/016867 A3

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB2004/003516

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
IPC 7	C07C233/55	C07D209/18
	C07D215/36	C07C235/38
	A61K31/33	
C07D317/60		
C07D217/14		
C07C237/22		
C07D333/60		
C07C235/24		
A61K31/196		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols)		
IPC 7 C07C C07D		
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, BEILSTEIN Data, CHEM ABS Data, WPI Data, PAJ		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/34909 A1 (CENTRE INTERNATIONAL DE RECHERCHES DERMATOLOGIQUES GALDERMA (C.I.R.D.) 13 August 1998 (1998-08-13)  claims 3-7; examples 13,14 page 12, line 41 - page 13, line 5	1-3,8, 13,14, 20,21, 23,24, 29,30,33
X	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; OGANESYAN, EDUARD TONIKOVICH ET AL: "Derivatives of 6-methoxychromonyl-3-acrylanilide showing antiallergic activity" XP002311348 retrieved from STN Database accession no. 1997:53544 abstract  -/--	1-3,8, 10,13, 20,21, 23,24,29
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <span style="margin-left: 200px;"><input checked="" type="checkbox"/> Patent family members are listed in annex.</span>		
° 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
20 December 2004		04/01/2005
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		Seufert, G

## INTERNATIONAL SEARCH REPORT

 International Application No  
 RU/GB2004/003516

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	& RU 2 051 914 C1 (PYATIGORSKII FARMATSEVTICHESKII INSTITUT, TAJIKISTAN) 10 January 1996 (1996-01-10) ----- DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; EJIRI, KATSUJI ET AL: "Preparation of 3,4-dihydro-2H-benzopyran derivatives as allergy inhibitors and their pharmaceutical compositions" XP002311349 retrieved from STN Database accession no. 1988:94385 abstract & JP 62 132879 A2 (KURARAY CO., LTD., JAPAN) 16 June 1987 (1987-06-16) -----	1-3,8, 10,13, 14,20, 21,23, 24,29,33
X	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MATSUO, KYOKO ET AL: "Preparation of 3,4-dihydro-2H-benzopyrans and their use as pharmaceuticals" XP002311350 retrieved from STN Database accession no. 1991:81586 abstract & JP 02 215778 A2 (KURARAY CO., LTD., JAPAN; YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD.) 28 August 1990 (1990-08-28) -----	1-3,8, 10,13, 14,20, 21,23, 24,29,33
X	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; FUJISAWA, SHINICHI ET AL: "Preparation and formulation of chromone derivatives as allergy inhibitors" XP002311351 retrieved from STN Database accession no. 1991:122061 abstract & JP 02 255672 A2 (TSUMURA AND CO., JAPAN) 16 October 1990 (1990-10-16) -----	1-4,7,8, 10,13, 14,20, 21,23, 24,29,32
X	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; OGANESYAN, E. T. ET AL: "Synthesis and antiallergic activity of 3-(3-chromonyl)acrylic acid derivatives" XP002311352 retrieved from STN Database accession no. 1996:26942 abstract -----	1-3,8, 10,13, 14,20, 21,23, 24,29,33

-/--

## INTERNATIONAL SEARCH REPORT

 International Application No  
 PCT/GB2004/003516

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	& KHIMIKO-FARMATSEVTICHESKII ZHURNAL , 29(10), 22-4 CODEN: KHfZAN; ISSN: 0023-1134, 1995, ----- DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; HASHIMOTO, KINJI ET AL: "Naphthalene derivatives" XP002311353 retrieved from STN Database accession no. 1986:33908 abstract & JP 60 139646 A2 (OTSUKA PHARMACEUTICAL FACTORY, INC., JAPAN) 24 July 1985 (1985-07-24) -----	1-3,8,9, 13,14, 20,21, 23,24,29
X	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TSUCHIYA, NAOKI ET AL BENZOIC ACID, 2-'3--1-OXO-2- PROPENYL!AMINO!- (9CI): "Preparation of anthranilic acid derivatives as preventive or therapeutic agents" XP002311354 retrieved from STN Database accession no. 2000:84754 abstract & WO 00/05198 A1 (TEIJIN LIMITED, JAPAN) 3 February 2000 (2000-02-03) -----	1-4,8,9, 20,21, 23,24,29
X	DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002311355 Database accession no. BRN 352950 abstract & NARANG ET AL.: J. INDIAN CHEM. SOC., 13, 1936, page 260, 262, -----	1-6, 15-17
X	DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002311356 Database accession no. BRN 3431044 abstract & LIPOWITSCH: ZH. OBSHCH. KHIM., 23, 1953, page 811, 813, ----- -/--	1-3,8

## INTERNATIONAL SEARCH REPORT

 International Application No  
 PCT/GB2004/003516

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TUNARU, SORIN ET AL: "PUMA-G and HM74 are receptors for nicotinic acid and mediate its anti- lipolytic effect" XP002311357 retrieved from STN Database accession no. 2003:155314 cited in the application abstract & NATURE MEDICINE (NEW YORK, NY, UNITED STATES) , 9(3), 352-355 CODEN: NAMEFI; ISSN: 1078-8956, 2003, -----	1-33
A	WO 02/084298 A (PIKE NICHOLAS BRIAN ; WISE ALAN (GB); GLAXO GROUP LTD (GB); FOORD STEV) 24 October 2002 (2002-10-24) cited in the application the whole document -----	1-33
A	US 3 855 285 A (HOLLAND G) 17 December 1974 (1974-12-17) column 1, line 6 - line 37 table in column 19, compounds 39 and 40 -----	1-33
P,X	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XU, SHIPING ET AL: "Preparation of coumarincarboxamides as TGF-.beta. inhibitors" XP002311358 retrieved from STN Database accession no. 2004:490719 abstract & WO 2004/050082 A1 (INSTITUTE OF MATERIA MEDICA, CHINESE ACADEMY OF MEDICAL SCIENCES, PEOP) 17 June 2004 (2004-06-17) -----	1-4,7,8, 10,13, 14,20, 21,23, 24, 29-31,33

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB2004/003516

## Box 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:  

Although claims 27 and 28 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.
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 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:

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.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB2004/003516

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9834909	A1	13-08-1998	FR 2759368 A1	14-08-1998
			AU 718198 B2	06-04-2000
			AU 6626598 A	26-08-1998
			CA 2253221 A1	13-08-1998
			EP 0901462 A1	17-03-1999
			JP 11507960 T	13-07-1999
			US 6326510 B1	04-12-2001
			-----	
RU 2051914	C1	10-01-1996	NONE	
-----				
JP 62132879	A2	16-06-1987	JP 1874464 C	26-09-1994
			JP 5088229 B	21-12-1993
			JP 62132879 A	16-06-1987
-----				
JP 2215778	A2	28-08-1990	JP 2215778 A	28-08-1990
-----				
JP 2255672	A2	16-10-1990	JP 2255672 A	16-10-1990
-----				
JP 60139646	A2	24-07-1985	JP 1651663 C	30-03-1992
			JP 3014296 B	26-02-1991
			JP 60139646 A	24-07-1985
-----				
WO 0005198	A1	03-02-2000	AT 278661 T	15-10-2004
			AU 750670 B2	25-07-2002
			AU 4800499 A	14-02-2000
			CA 2337098 A1	03-02-2000
			CN 1319086 T	24-10-2001
			DE 69920923 D1	11-11-2004
			EP 1101755 A1	23-05-2001
			US 2003232811 A1	18-12-2003
			US 6649656 B1	18-11-2003
			-----	
WO 02084298	A	24-10-2002	EP 1377834 A2	07-01-2004
			WO 02084298 A2	24-10-2002
-----				
US 3855285	A	17-12-1974	US 3856951 A	24-12-1974
-----				
WO 2004050082	A1	17-06-2004	NONE	
-----				