

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
2 March 2006 (02.03.2006)

PCT

(10) International Publication Number
WO 2006/023460 A3

(51) International Patent Classification:

C07D 409/14 (2006.01) C07D 401/12 (2006.01)
C07D 401/14 (2006.01) A61K 31/4535 (2006.01)
C07D 417/14 (2006.01) A61K 31/4545 (2006.01)

(21) International Application Number:

PCT/US2005/029024

(22) International Filing Date: 15 August 2005 (15.08.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/601,779 16 August 2004 (16.08.2004) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:

US 60/601,779 (CIP)
Filed on 16 August 2004 (16.08.2004)

(71) Applicant (for all designated States except US): **THERAVANCE, INC.** [US/US]; 901 Gateway Boulevard, South San Francisco, California 94080 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MAMMEN, Mathai** [CA/US]; 5 Barcelona Circle, Redwood City, CA 94065 (US). **MISCHKI, Trevor** [CA/CA]; 1353 Ambridge Way, Ottawa, Ontario K2C 3T3 (CA). **HUGHES, Adam** [GB/US]; 1221 Judson Street, Belmont, California 94002 (US). **JL, Yu-Hua** [CN/US]; 700 Freeport Lane, Redwood City, California 94065 (US).

(74) Agents: **HAGENAH, Jeffrey A.** et al.; THERAVANCE, INC., 901 Gateway Boulevard, South San Francisco, California 94080 (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, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US (patent), 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, IS, IT, LT, LU, LV, 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:

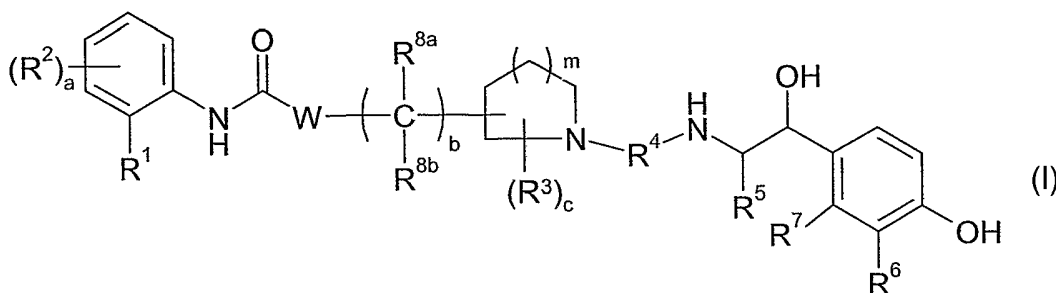
- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:

6 April 2006

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: COMPOUNDS HAVING β_2 ADRENERGIC RECEPTOR AGONIST AND MUSCARINIC RECEPTOR ANTAGONIST ACTIVITY



(57) Abstract: This invention provides compounds of formula I wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^{8a} , R^{8b} , W, a, b, c and m are as defined in the specification, or a pharmaceutically acceptable salt or solvate or stereoisomer thereof. The compounds of this invention possess both β_2 adrenergic receptor agonist and muscarinic receptor antagonist activity. Accordingly, such compounds are expected to be useful as therapeutic agents for treating pulmonary disorders, such as chronic obstructive pulmonary disease and asthma.

WO 2006/023460 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/029024

A. CLASSIFICATION OF SUBJECT MATTER
 C07D409/14 C07D401/14 C07D417/14 C07D401/12 A61K31/4535
 A61K31/4545

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, PAJ, BIOSIS, EMBASE, 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.
Y	WO 03/024439 A (GLAXO GROUP LIMITED; BOX, PHILIP, CHARLES; COE, DIANE, MARY; LOOKER, B) 27 March 2003 (2003-03-27) page 1; claims	1-46
Y	WO 03/072539 A (GLAXO GROUP LIMITED; BLAKE, KEITH; COE, DIANE, MARY; PROCOPIOU, PANAYI) 4 September 2003 (2003-09-04) page 1; claims	1-46
Y	WO 02/076933 A (GLAXO GROUP LIMITED; BIGGADIKE, KEITH; FIELD, RITA; GUNTRIP, STEPHEN,) 3 October 2002 (2002-10-03) page 1; claims	1-46
	----- -/--	

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents :

<p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*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)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p>	<p>*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</p> <p>*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</p> <p>*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.</p> <p>*Z* document member of the same patent family</p>
--	--

Date of the actual completion of the international search 7 February 2006	Date of mailing of the international search report 16/02/2006
---	---

Name and mailing address of the ISA/ 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	Authorized officer Frelon, D
---	--

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/029024

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/042164 A (THERAVANCE, INC; MORAN, EDMUND, J; JACOBSEN, JOHN, R; LEADBETTER, MICH) 22 May 2003 (2003-05-22) abstract; claims	1-46
Y	EP 0 286 242 A (GLAXO GROUP LIMITED) 12 October 1988 (1988-10-12) page 3; claims	1-46
Y	CH 686 869 A5 (SEPRACOR, INC) 31 July 1996 (1996-07-31) abstract; claims	1-46
Y	WO 99/64031 A (ADVANCED MEDICINE, INC; GRIFFIN, JOHN, H; MORAN, EDMUND, J; CHOI, SEOK) 16 December 1999 (1999-12-16) abstract; claims	1-46
Y	WO 01/42212 A (ADVANCED MEDICINE, INC; MAMMEN, MATHAI; OARE, DAVID) 14 June 2001 (2001-06-14) page 2 - page 3; claims	1-46
Y	WO 01/42213 A (ADVANCED MEDICINE, INC; MAMMEN, MATHAI; OARE, DAVID) 14 June 2001 (2001-06-14) abstract; claims	1-46
A,P	WO 2004/074246 A (THERAVANCE INC; MAMMEN, MATHAI; DUNHAM, SARAH; HUGHES, ADAM; LEE, TAE) 2 September 2004 (2004-09-02) the whole document	1-46

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/029024

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 34-37 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/US2005/029024

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03024439	A	27-03-2003	BR 0212455 A	19-10-2004
			CA 2458534 A1	27-03-2003
			CN 1585633 A	23-02-2005
			EP 1425001 A1	09-06-2004
			HU 0401619 A2	29-11-2004
			JP 2005511508 T	28-04-2005
			MX PA04002405 A	31-05-2004
			NO 20041041 A	21-04-2004
			US 2005075394 A1	07-04-2005

WO 03072539	A	04-09-2003	AU 2003210428 A1	09-09-2003
			EP 1478620 A1	24-11-2004
			JP 2005519083 T	30-06-2005
			US 2005209338 A1	22-09-2005

WO 02076933	A	03-10-2002	EP 1370521 A1	17-12-2003
			JP 2004538259 T	24-12-2004
			US 2004157830 A1	12-08-2004

WO 03042164	A	22-05-2003	BR 0213795 A	07-12-2004
			CA 2466962 A1	22-05-2003
			CN 1585742 A	23-02-2005
			EP 1446379 A1	18-08-2004
			HU 0401876 A2	28-12-2004
			JP 2005509024 T	07-04-2005
			NO 20041817 A	04-05-2004

EP 0286242	A	12-10-1988	JP 1085964 A	30-03-1989
			US 4937268 A	26-06-1990

CH 686869	A5	31-07-1996	NONE	

WO 9964031	A	16-12-1999	AT 302748 T	15-09-2005
			AU 4336899 A	30-12-1999
			AU 4337699 A	30-12-1999
			AU 4423499 A	30-12-1999
			AU 4426599 A	30-12-1999
			AU 4543599 A	30-12-1999
			AU 4543999 A	30-12-1999
			AU 4549199 A	30-12-1999
			AU 4551599 A	30-12-1999
			AU 4552099 A	30-12-1999
			AU 4557099 A	30-12-1999
			AU 4672799 A	30-12-1999
			AU 4674799 A	30-12-1999
			AU 4675199 A	30-12-1999
			AU 4675299 A	30-12-1999
			AU 4675399 A	30-12-1999
			AU 4675499 A	30-12-1999
			AU 4677699 A	10-01-2000
			AU 4818199 A	30-12-1999
			AU 5203999 A	30-12-1999
			BR 9910832 A	16-10-2001
			CA 2318055 A1	16-12-1999
			CA 2318192 A1	16-12-1999
			CA 2318286 A1	16-12-1999
			CA 2318894 A1	16-12-1999
			CA 2319068 A1	16-12-1999

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/029024

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9964031	A	CA 2319159 A1	16-12-1999
		CA 2319175 A1	16-12-1999
		CA 2319496 A1	16-12-1999
		CA 2319497 A1	16-12-1999
		CA 2319643 A1	16-12-1999
		CA 2319650 A1	29-12-1999
		CA 2319651 A1	16-12-1999
		CA 2319751 A1	16-12-1999
		CA 2319756 A1	16-12-1999
		CA 2320926 A1	16-12-1999
		CA 2321120 A1	16-12-1999
		CA 2321152 A1	16-12-1999
		CA 2321170 A1	16-12-1999
		CA 2321273 A1	16-12-1999
		CN 1295479 A	16-05-2001
		DE 69926861 D1	29-09-2005
		EP 1083917 A1	21-03-2001
		EP 1083893 A1	21-03-2001
		EP 1003540 A1	31-05-2000
		EP 1085887 A2	28-03-2001
		EP 1083888 A1	21-03-2001
		EP 1085889 A2	28-03-2001
		EP 1107753 A1	20-06-2001
<hr/>			
WO 0142212	A	14-06-2001	
		AT 271039 T	15-07-2004
		AT 299494 T	15-07-2005
		AU 782232 B2	14-07-2005
		AU 1951801 A	18-06-2001
		AU 783095 B2	22-09-2005
		AU 2067401 A	18-06-2001
		BR 0015963 A	06-08-2002
		CA 2392028 A1	14-06-2001
		CA 2392030 A1	14-06-2001
		CN 1407970 A	02-04-2003
		CZ 20021830 A3	16-10-2002
		DE 60012223 D1	19-08-2004
		DE 60012223 T2	25-08-2005
		DE 60021282 D1	18-08-2005
		EP 1235803 A1	04-09-2002
		EP 1235802 A1	04-09-2002
		ES 2225275 T3	16-03-2005
		ES 2243333 T3	01-12-2005
		HK 1049483 A1	18-02-2005
		HR 20020574 A2	31-08-2005
		HU 0203677 A2	28-03-2003
		JP 2003516390 T	13-05-2003
		JP 2003516391 T	13-05-2003
		NO 20022683 A	02-07-2002
		NZ 518722 A	26-03-2004
		PL 364922 A1	27-12-2004
		SK 7982002 A3	03-12-2002
		UA 73543 C2	16-09-2002
		WO 0142213 A1	14-06-2001
		US 2004029919 A1	12-02-2004
		US 2002049195 A1	25-04-2002
		ZA 200204553 A	08-09-2003
ZA 200204557 A	08-09-2003		

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/029024

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0142213	A	14-06-2001	AT 271039 T 15-07-2004
			AT 299494 T 15-07-2005
			AU 782232 B2 14-07-2005
			AU 1951801 A 18-06-2001
			AU 783095 B2 22-09-2005
			AU 2067401 A 18-06-2001
			BR 0015963 A 06-08-2002
			CA 2392028 A1 14-06-2001
			CA 2392030 A1 14-06-2001
			CN 1407970 A 02-04-2003
			CZ 20021830 A3 16-10-2002
			DE 60012223 D1 19-08-2004
			DE 60012223 T2 25-08-2005
			DE 60021282 D1 18-08-2005
			EP 1235803 A1 04-09-2002
			EP 1235802 A1 04-09-2002
			ES 2225275 T3 16-03-2005
			ES 2243333 T3 01-12-2005
			HK 1049483 A1 18-02-2005
			HR 20020574 A2 31-08-2005
			HU 0203677 A2 28-03-2003
			JP 2003516390 T 13-05-2003
			JP 2003516391 T 13-05-2003
			NO 20022683 A 02-07-2002
			NZ 518722 A 26-03-2004
			PL 364922 A1 27-12-2004
			SK 7982002 A3 03-12-2002
			UA 73543 C2 16-09-2002
			WO 0142212 A1 14-06-2001
			US 2004029919 A1 12-02-2004
			US 2002049195 A1 25-04-2002
			ZA 200204553 A 08-09-2003
			ZA 200204557 A 08-09-2003
WO 2004074246	A	02-09-2004	AU 2004213411 A1 02-09-2004
			CA 2515777 A1 02-09-2004
			EP 1594860 A2 16-11-2005
			EP 1592685 A1 09-11-2005
			EP 1615889 A2 18-01-2006
			WO 2004074276 A1 02-09-2004
			WO 2004074812 A2 02-09-2004