(19) World Intellectual Property Organization

International Bureau



(43) International Publication Date 15 March 2007 (15.03.2007)

(10) International Publication Number WO 2007/030721 A3

(51) **International Patent Classification:** *C07D 205/08* (2006.01) *A61P 3/04* (2006.01) *A61K 31/397* (2006.01)

(21) International Application Number:

PCT/US2006/035060

(22) International Filing Date:

8 September 2006 (08.09.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/715,919 8 September 2005 (08.09.2005) US 60/832,430 20 July 2006 (20.07.2006) US

- (71) Applicant (for all designated States except BB, US): TEVA PHARMACEUTICAL INDUSTRIES LTD. [IL/IL]; 5 Basel Street, Ro. Box 3190, 49131 Petah Tiqva (IL).
- (71) Applicant (for BB only): TEVAPHARMACEUTICALS USA, INC. [US/US]; 1090 Horsham Road, Ro. Box 1090, North Wales, PA 19454 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): KANSAL, Vinod,

Kumar [IN/IN]; House No. 1396, Sector 14, Faridabad, Haryana (IN). AHMAD, Suhail [IN/IN]; J-267, Sarita Vihar, New Delhi 110044 (IN). TYAGI, Bhupendra [IN/IN]; 815/16 Andra Nagar Colony, Dehradun, Uttaranchal 248006 (IN). GUPTA, Nitin [IN/IN]; 1542, Sector 37, Noida, Uttar Pradesh (IN). PERLMAN, Nurit [IL/IL]; 4 Moshe Dayan St., 44539 Kfar Saba (IL).

- (74) Agents: BRAINARD, Charles, R. et al.; Kenyon & Kenyon LLR One Broadway, New York, NY 10004-1050 (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, HN, HR, HU, ID, IL, IN, IS, **JP**, KE, KG, KM, KN, KR **KR**, KZ, LA, LC, LK, LR, LS, LT, LU, LV,LY,MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, **TJ**, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, 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,

[Continued on next page]

(54) Title: PROCESSES FOR THE PREPARATION OF (3R,4S)-4-((4-BENZYLOXY)PHENYL)-1-(4-FLUO-ROPHENYL)-3-((S)-3-(4-FLUOROPHENYL)-3-HYDROXYPROPYL)-2-AZETIDINONE, AN INTERMEDIATE FOR THE SYNTHESIS OF EZETIMIBE

(57) Abstract: The invention encompasses (3R,4S)-4-((4-benzyloxy)phenyl)-1-(4-fluorophenyl)-3- (3-(4-fluorophenyl)-3-oxopropyl)-2-azetidinone (Compound 2a). The invention further encompasses processes tor preparing Compound 2a from Compound 1. The invention also encompasses processes for preparing a compound having Formula (A) from a compound having the formula (B); wherein R is selected from the group consisting of: H or a hydroxyl protecting group. The invention also encompasses processes for preparing Compound 2a, preferably to form Compound 2a-Form 01. Also included are processes for preparing ezetimibe from Compound 2a-Form 01 or Compound 2a prepared according to the invention, compositions containing such ezetimibe, and methods for reducing cholesterol using such compositions.



WO 2007/030721 A3



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

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

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.

INTERNATIONAL SEARCH REPORT

International application No PCT/US2006/035060

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D205/08 A61K3

A61K31/397

A61P3/04

According to International Patent Classification (IPC) orto 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 , BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUM	ENTS CONSIDERED TO BE RELEVANT			
Category *	Citation of document, with indication, where appropriate of the relevant passages	Relevant to claim No		
χ	WU G ET AL: "A NOVEL ONE-STEP DIASTEREO-	1-8,72,		
	AND ENANTIOSELECTIVE FORMATION OF	73,75-81		
	TRANS-AZETIDINONES AND ITS APPLICATION TO			
	THE TOTAL SYNTHESIS OF CHOLESTEROL			
	ABSORPTION INHIBITORS"			
	JOURNAL OF ORGANIC CHEMISTRY, AMERICAN			
	CHEMICAL SOCIETY. EASTON, US,			
	vol. 64, 1999, pages 3714-3718,			
	XP002296009			
	ISSN: 0022-3263			
Υ	page 3717, right-hand column; example 9	9-41,74		
Α	the whole document	42,54		
Χ	US 5 886 171 A (WU GUANG-ZHONG [US] ET AL)	1-8,72,		
	23 March 1999 (1999-03-23)	73,75-81		
Υ	column 20; example 5	9-41,74		
	columns 21-22; example 7			
Α	the whole document	42,54		
	Made hand made from hand			
	_/	1		

X Further documents are listed in the continuation of Box C	X See patent family annex			
* Special categories of cited documents	 1T1 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 1X1 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 "Y1 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 			
"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 pno mty claimfs) or which is cited to establish the publication date of another citation or other special reason (as specified)				
¹ O" document referring to an oral disclosure, use, exhibition or other means				
¹ P" document published prior to the international filing date but later than the priority date claimed				
Date of the actual completion of the international search	Date of mailing of the international search report			
2 February 2007	15/02/2007			
Name and mailing address of the ISA/	Authorized officer			
European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV RijSWJk Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016	Meg i do, Benigno			

INTERNATIONAL SEARCH REPORT

International application No PCT/US2006/035060

Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT						
gory* Citation of document, with indication, where appropriate, of the	e relevant passages Relevant to claim N					
US 5 856 473 A (SHANKAR BANDAR [US]) 5 January 1999 (1999-01-column 8; example 5	1 50 55 6					
	42,54					
WO 95/08532 A (SCHERING CORP [ROSENBLUM STUART B [US]; DUGAR [US]; BURNE) 30 March 1995 (19	SUNDEEP 54-73,					
page 32 - page 34; example 6	9-53,74					
WO 02/072104 A2 (MERCK & CO IN NICHTBERGER STEVEN A [US]) 19 September 2002 (2002-09-19) the whole document	C [US]; 76-81					
FU X ET AL: "Process for prep Ezetimibe intermediate by an a chemo- and enantioselective CB ketone reduction"	cid enhanced S catalyzed					
TETRAHEDRON LETTERS, ELSEVIER, NL, vol . 44, no. 4,						
20 January 2003 (2003-01-20), 801-804, XP004405139 ISSN: 0040-4039	pages					
the whole document KIYOHARU NISHIDE, MANABU NODE:	"Recent 42-53					
Development of Asymmetric Synt on the Meerwein-Ponndorf-Verley CHIRALITY,						
vol. 14, no. 10, 2002, pages 7 XP002418155 the whole document	59-767,					

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2006/035060

Patent document cited in search report		Publication date	Patent family member(s)		Publication date	
US 5886171	A	23-03-1999	NONE	3		······································
US 5856473	A	05-01-1999	NONE	3		
wo 9508532	A	30-03-1995	AT	180249	<u>Т</u>	15-06-1999
			AU	681445	B2	28-08-1997
			AU	7795294	A	10-04-1995
			CA	2172149	C	28-11-2000
			CN	1131416	A	18-09-1996
			CZ	9600839	A3	14-08-1996
			DE	10399001	I 1	12-06-2003
			DE	69418613	Dl	24-06-1999
			DE	69418613	T2	30-09-1999
			DE 1	122004000026	I 1	18-11-2004
			DK	720599	T3	08-11-1999
			EP	0720599	Al	10-07-1996
			ES	2132432	T3	16-08-1999
			FI	961300	A	21-03-1996
			GR	3030312	T3	30-09-1999
			HU	73852	A2	30-09-1996
			ΙL	110956	A	11-01-2001
			JΡ	2803908	B2	24-09-1998
			JР	8509989	T	22-10-1996
			KR	186853	Bl	01-05-1999
			LU	91050	A9	12-10-2004
			LU	91160	A9	25-11-2005
			MA	23332	Al	01-04-1995
			NL	300132	I 1	01-10-2003
			NL	300172	I 1	01-04-2005
			NO	961133	A	20-03-1996
			NZ	274041	A	19-12-1997
			PL	313589	Al	08-07-1996
			RU	2138480	Cl	27-09-1999
			SG	46208	Al	20-02-1998
			SK	35596	A3	05-02-1997
			TW	427974	В	01-04-2001
			us	5767115	A	16-06-1998
wo 02072104	A2	19-09-2002	СА	2439920	Al	19-09-2002
			EP	1389114	A2	18-02-2004
			JΡ	2004523569	T	05-08-2004