

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
30 August 2007 (30.08.2007)

PCT

(10) International Publication Number  
**WO 2007/098250 A3**

- (51) **International Patent Classification:**  
C07D 333/20 (2006.01)
- (21) **International Application Number:**  
PCT/US2007/004632
- (22) **International Filing Date:**  
21 February 2007 (21.02.2007)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**  
60/775,593 21 February 2006 (21.02.2006) US  
60/791,103 10 April 2006 (10.04.2006) US  
60/792,812 17 April 2006 (17.04.2006) US
- (71) **Applicant (for all designated States except BB, US):**  
**TEVA PHARMACEUTICAL INDUSTRIES LTD.**  
[IL/IL]; 5 Basel Street, P.O. Box 3190, 49131 Petah Tiqva (IL).
- (71) **Applicant (for BB only):** **TEVA PHARMACEUTICAL USA, INC.** [US/US]; 1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454 (US).
- (72) **Inventors; and**
- (75) **Inventors/Applicants (for US only):** **INI, Santiago** [IL/IL]; 51 Ruth St., 34404 Haifa (IL). **SHMUELY, Yaron** [IL/IL]; 7 Baruch Boran Road, 38303 Hedera (IL). **ABRAMOV, Mili** [IL/IL]; 83/4 Shenkin Street, Givataim (IL).
- (74) **Agents:** **BIRDE, Patrick, J.** et al; Kenyon & Kenyon LLP, 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, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, 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, 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:**  
1 November 2007  
*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:** PROCESS FOR THE PREPARATION OF (S)-(-)-N,N-DIMETHYL-3-(2-THIENYL)-3-HYDROXYPROPANAMINE, A DULOXETINE INTERMEDIATE

(57) **Abstract:** A chiral resolution process for the preparation of (S)-AT-OL, and a process for the racemization of AT-OL are provided. A one pot continuous process for preparing (S)-AT-OL or (S)-AT-OL mandelate comprising: a) converting (R) -AT-OL to (BJS) -AT-OL in a mixture of a C1-8 alcohols and a C2-8 ether in presence of an acid; b) reacting the (BJS) -AT-OL with (S) - (+) -mandelic acid in the mixture to obtain (S)-AT-OL mandelate; and c) optionally converting the (S)-AT-OL mandelate to (S)-AT-OL.



WO 2007/098250 A3

**INTERNATIONAL SEARCH REPORT**

International application No  
**PCT/US2007/004632**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D333/20

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

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, CHEM ABS Data, BEILSTEIN Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
P, X	US 2006/063943 A1 (SAKAI KENICHI [JP] ET AL) 23 March 2006 (2006-03-23) examples	1-51
Y	EP 1 506 965 A (MITSUBISHI RAYON CO [JP]) 16 February 2005 (2005-02-16) claims; examples	1-51
	----- -/--	

Further documents are listed in the continuation of Box C

See patent family annex

\* Special categories of cited documents

"A<sup>1</sup>" document defining the general state of the art which is not considered to be of particular relevance

"E<sup>1</sup>" 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

<sup>1</sup>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

<sup>1</sup>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

<sup>1</sup>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

<sup>1</sup>&" document member of the same patent family

Date of the actual completion of the international search

23 August 2007

Date of mailing of the international search report

06/09/2007

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

**Fazzi , Raffael I a**

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2007/004632

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>DATABASE WPI Week 2004 Derwent Publications Ltd., London, GB; AN 2004-336553 XP002447780 HATAHIRA ET AL.: "Manufacture of optically active 3-(methylamino)-1-(2-thienyl )propane-1-ol useful as intermediate for pharmaceuticals, by resolving (RS)-3-(methyl amino)-1-(2-thienyl )propane- 1-ol with optically active mandelic acid" &amp; JP 2004 123596 A (YAMAKAWA CHEM IND CO LTD) 22 April 2004 (2004-04-22) abstract</p>	1-31
X	<p>WO 2004/031168 A (LONZA AG [CH]; FUCHS RUDOLF [CH]; MICHEL DOMINIQUE [CH]; BRIEDEN WALTE) 15 April 2004 (2004-04-15) cited in the application examples 1,2</p>	23-35
Y	<p>US 5 362 886 A (BERGLUND RICHARD A [US]) 8 November 1994 (1994-11-08) cited in the application examples</p>	1-51
P,X	<p>TAO, XIAO ET AL: "(R)-3-Hydroxy-N,N-dimethyl-3-(2-thienyl)p ropanamine" ACTA CRYSTALLOGRAPHICA, SECTION E: STRUCTURE REPORTS ONLINE , E62(11), 05202-05203 CODEN: ACSEBH; ISSN: 1600-5368 URL: HTTP://JOURNALS.IUCR.ORG/E/ISSUES/2006/11/ 00/CF2028/INDEX.HTML, November 2006 (2006-11), XP002447766 page 05202</p>	1-51
P,Y	<p>FUJIMA, YOSHITO ET AL: "Synthesis of (S)-3-(N-Methylamino)-1-(2-thienyl)propan- 1-ol : Revisiting Eli Lilly's Resol uti on-Racemi zati on-Recycl e Synthesi s of Duloxetine for Its Robust Processes" ORGANIC PROCESS RESEARCH &amp; DEVELOPMENT , 10(5), 905-913 CODEN: OPRDFK; ISSN: 1083-6160, 2006, XP002447767 tables</p>	1-51

V-

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2007/004632

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>SAKAI K ET AL: "Resolution of 3-(methylamino)-1-(2-thienyl)propan-1-ol a new key intermediate for dui oxeti ne, with (S)-mandei i c aci d" TETRAHEDRON: ASYMMETRY., ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 14, no. 12, 20 Oune 2003 (2003-06-20), pages 1631-1636, XP004429604 ISSN: 0957-4166 the whole document</p> <p style="text-align: center;">-----</p>	1-51
Y	<p>BOPP R J ET AL: "PRACTICAL CONSIDERATIONS FOR CHIRAL SEPARATIONS OF PHARMACEUTICAL COMPOUNDS" LC - GC, ADVANSTAR COMMUNICATIONS, CLEVELAND, OH, US, vol. 6, no. 6, 1988, page 514,516,518,520,522, XP009008342 ISSN: 0888-9090 page 516</p> <p style="text-align: center;">-----</p>	1-51

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2007/004632

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2006063943 A1	23-03-2006	NONE	
EP 1506965 A	16-02-2005	WO 03097632 A1 US 2006167278 A1	27-11-2003 27-07-2006
JP 2004123596 A	22-04-2004	NONE	
WO 2004031168 A	15-04-2004	AU 2003276066 A1	23-04-2004
US 5362886 A	08-11-1994	AT 199084 T AU 685494 B2 AU 7572094 A BR 9404045 A CA 2133899 A1 CN 1109470 A CZ 9402465 A3 DE 69426663 D1 DE 69426663 T2 DK 650965 T3 EP 0650965 A1 ES 2153850 T3 FI 944773 A GR 3035715 T3 HU 68943 A2 IL 111188 A JP 3644986 B2 JP 7188065 A NO 943825 A NZ 264633 A PH 31595 A PL 305326 A1 PT 650965 T RU 2127269 C1 TW 381090 B US 5491243 A ZA 9407839 A	15-02--2001 22-01--1998 04-05--1995 13-06--1995 13-04--1995 04-10--1995 17-05--1995 15-03--2001 21-06--2001 26-02--2001 03-05--1995 16-03--2001 13-04--1995 31-07--2001 28-08--1995 15-06--1998 11-05--2005 25-07--1995 18-04--1995 22-09--1997 03-11--1998 18-04--1995 31-05--2001 10-03--1999 01-02--2000 13-02--1996 09-04--1996