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(54) Title: NOVEL PROCESS FOR PREPARATION OF DULOXETINE HYDROCHLORIDE

(57) **Abstract:** An improved, safer and easy to operate on plant scale process for synthesis of duloxetine hydrochloride (1) having chiral purity greater than 99.9% that is characterized by the following: (i) preparation of racemic condensed compound (RS)-N,N-di methyl-3- (1-naphthyloxy)-3-(2-thienyl)propanamine (4) by reaction of racemic hydroxy compound (2) with 1-fluronaphthalene (3) in presence of a base such as sodamide, potassium amide or potassium bis(trimethylsilyl)amide (KHDMS) in polar aprotic solvent, (ii) optical resolution of racemic condensed compound (5a + 5b) with di-benzoyl-L-tartaric acid (7, DBTA, R = H) or di-para-anisoyl-L-tartaric acid (7, DATA, R = OCH₃) to obtain crude (S)-N,N-dimethyl-3-(1-naphthyloxy)-3-(2-thienyl)propanamine dibenzoyl tartarate salt (8a) or (S)-N,N-dimethyl-3-(1-naphthyloxy)-3-(2-thienyl)propanamine di-p-anisoyl tartarate salt (9a) respectively, (iii) optionally purification of crude tartarate salts (8a or 9a) by crystallization, (iv) optionally purification of duloxetine hydrochloride (1) by crystallization and (v) racemization of undesired (R)-N,N-di methyl-3-(1-naphthyloxy)-3-(2-thienyl)propanamine (5b) by treatment with base potassium bis(trimethylsilyl)amide (KHDMS) to obtain racemic mixture of condensed compounds (5a and 5b). A novel salt S(+)-N,N-dimethyl-3-(1-naphthyloxy)-3-(2-thienyl)propanamine dibenzoyl -(L)- tartarate (8a) and S(+)-N,N-dimethyl-3-(1-naphthyloxy)-3-(2-thienyl)propanamine di-p-anisoyl-(L)- tartarate (9a). Novel process for racemization of undesired (R)-N,N-di methyl-3-(1-naphthyloxy)-3-(2-thienyl)propanamine (5b) by treatment with KHDMS to obtain racemic mixture condensed compounds (5a and 5b).

WO 2008/107911 A3

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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, BEILSTEIN Data, WPI 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 2006/126213 A (MATRIX LAB LTD [IN]; SATYANARAYANA CHAVA [IN]; RAMANOANEYULU GORANTLA) 30 November 2006 (2006-11-30) cited in the application Scheme 4 on page 5 pages 4,5; claims 1-21; examples 1-3 -----	1-62
Y	US 6 541 668 B1 (KJELL DOUGLAS PATTON [US] ET AL) 1 April 2003 (2003-04-01) cited in the application column 5, line 49 - column 6, line 9; claim 1 Reaction Scheme A column 4, lines 24-44 ----- -/-	1-35

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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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 2006/027798 A (SUN PHARMACEUTICAL IND LTD [IN]; PATEL KARTIK SHANTILAL [IN]; PATEL NI) 16 March 2006 (2006-03-16) cited in the application page 9, line 19 - page 12, line 30 page 17, line 20 - page 18, line 5; claims 1-6,11-15; examples 1,2,4 -----	1-29, 36-62
X	WO 2006/099433 A (TEVA PHARMA [IL]; TEVA PHARMA [US]; INI SANTIAGO [IL]; ABRAMOV MILI [I] 21 September 2006 (2006-09-21) examples 1-11 -----	48-52

INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006126213 A	30-11-2006	NONE	
us 6541668 B1	01-04-2003	NONE	
WO 2006027798 A	16-03-2006	US 2007191616 A1	16-08-2007
WO 2006099433 A	21-09-2006	CA 2599475 A1	21-09-2006
		CA 2599478 A1	21-09-2006
		EP 1874754 A1	09-01-2008
		EP 1858859 A1	28-11-2007
		EP 1858873 A2	28-11-2007
		WO 2006099459 A1	21-09-2006
		WO 2006099468 A2	21-09-2006