



- (51) **International Patent Classification:**
C07D 405/12 (2006.01) *C07D 405/06* (2006.01)
A61K 31/496 (2006.01)
- (21) **International Application Number:** PCT/IB2013/052729
- (22) **International Filing Date:** 5 April 2013 (05.04.2013)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
1187/MUM/2012 12 April 2012 (12.04.2012) IN
1784/MUM/2012 21 June 2012 (21.06.2012) IN
- (71) **Applicant: ALEMBIC PHARMACEUTICALS LIMITED** [IN/IN]; Alembic Research Centre (arc), Patent Cell, Alembic Road, Gujarat, Vadodara 390003 (IN).
- (72) **Inventor; and**
- (71) **Applicant : JAYARAMAN, Venkat Raman** [IN/IN]; Alembic Research Centre (arc), Patent Cell, Alembic Road, Gujarat, Vadodara 390003 (IN).
- (72) **Inventors: RATHOD, Dhiraj;** Alembic Research Centre (arc), Patent Cell, Alembic Road, Gujarat, Vadodara 390003 (IN). **VOHRA, Irfan;** Alembic Research Centre (arc), Patent Cell, Alembic Road, Gujarat, Vadodara 390003 (IN). **BHUJADE, Vinayak;** Alembic Research Centre (arc), Patent Cell, Alembic Road, Gujarat, Vadodara 390003 (IN). **MODI, Viral;** Alembic Research Centre (arc), Patent Cell, Alembic Road, Gujarat, Vadodara 390003 (IN). **GANDHI, Ojas;** Alembic Research Centre (arc), Patent Cell, Alembic Road, Gujarat, Vadodara 390003 (IN). **BUDH, Mayur;** Alembic Research Centre (arc), Patent Cell, Alembic Road, Gujarat, Vadodara 390003 (IN).
- (74) **Agent: PATEL, Bhavik;** Alembic Research Centre (ARC), Patent Cell, Alembic Road, Gujarat, Vadodara 390003 (IN).

- (81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, 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, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, 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, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i))
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

- (88) **Date of publication of the international search report:**
9 January 2014

(54) **Title:** PROCESS FOR THE PREPARATION OF VILAZODONE HYDROCHLORIDE AND ITS AMORPHOUS FORM

(57) **Abstract:** The present invention relates to a process for the preparation of vilazodone hydrochloride directly from the corresponding carboxylic acid ester derivative by aminolysis. Also part of the invention is a polymorphic form of vilazodone, a process for preparation of novel pure amorphous form of vilazodone hydrochloride and polymorphs of ethyl 5-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)benzofuran-2- carboxylate.



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/052729

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07D405/12 A61K31/496 C07D405/06
 ADD.

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 practicable, search terms used)
 EPO-Internal, 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.
X,P	BIN HU ET AL: "Scale-Up Synthesis of Antidepressant Drug Vilazodone", ORGANIC PROCESS RESEARCH & DEVELOPMENT, vol. 16, no. 9, 21 September 2012 (2012-09-21), pages 1552-1557, XP055061951, ISSN: 1083-6160, DOI: 10.1021/op300171m entry 8; page 1554; table 3 page 1555, left-hand column, paragraph 3 ----- -/--	1-6

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 application or patent 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>"&" document member of the same patent family</p>
---	---

Date of the actual completion of the international search 16 August 2013	Date of mailing of the international search report 20/11/2013
--	---

Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Österle, Carmen
--	--

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2013/052729

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HEINRICH T ET AL: "Synthesis and Structure-Activity Relationship in a Class of Indolebutylpiperazines as Dual 5-HT1A Receptor Agonists and Serotonin Reuptake Inhibitors", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 47, no. 19, 1 January 2004 (2004-01-01), pages 4684-4692, XP002388367, ISSN: 0022-2623, DOI: 10.1021/JM040793Q	22,23
A	scheme 2, step c) page 4689, right-hand column, last paragraph - page 4690, left-hand column, paragraph 1 page 4690, left-hand column, paragraph 1	1-6,24
X	-----	
X	EP 0 648 767 A1 (MERCK PATENT GMBH [DE]) 19 April 1995 (1995-04-19)	22,23
A	page 9; example 4 page 8, line 49 - line 50 page 11; example 9	1-6,24
E	-----	
E	WO 2013/078361 A1 (ASSIA CHEMICAL IND LTD [IL]; TEVA PHARMA [US]; LEKSIC EDISLAV [HR]; PA) 30 May 2013 (2013-05-30) General procedures B and C; page 33	1-5,22
A	-----	
A	SORBERA L A ET AL: "VILAZODONE HYDROCHLORIDE", DRUGS OF THE FUTURE, PROUS SCIENCE, ES, vol. 26, no. 3, 1 January 2001 (2001-01-01), pages 247-252, XP009035003, ISSN: 0377-8282, DOI: 10.1358/DOF.2001.026.03.611242 the whole document	1-6, 22-24
A	-----	
A	CN 102 267 985 A (SHANGHAI INST PHARM IND) 7 December 2011 (2011-12-07) the whole document	1-6, 22-24
A	-----	
A	WO 02/102794 A2 (MERCK PATENT GMBH [DE]; BATHE ANDREAS [DE]; HELFERT BERND [DE]; NEUENF) 27 December 2002 (2002-12-27) cited in the application the whole document	1-6, 22-24
A	-----	
A	CN 102 219 783 A (TIANJIN HANKANG PHARMACEUTICAL BIOTECHNOLOGY CO LTD) 19 October 2011 (2011-10-19) the whole document	1-6, 22-24
A	-----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2013/052729

Box No. 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:

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 No. 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:

see additional sheet

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 fees, this Authority did not invite payment of additional fees.

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.:
1-6, 22-24

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-6, 22-24

Process for preparing vilazodone of formula (I)

1.1. claims: 1-6, 24

Process for preparing vilazodone of formula (I) by contacting the compound of formula (II) with a source of ammonia

Process for preparing vilazodone of formula (I) by contacting the compound of formula (II) with a source of ammonia and a solvent

Process for preparing vilazodone of formula (I) from a compound of formula (II) in presence of a suitable solvent under ammonia pressure

Process for preparing vilazodone of formula (I) comprising reaction steps 1) through e).

1.2. claims: 22, 23

Process for preparing vilazodone of formula (I) by reacting a compound (VII) with a compound (VIII) to yield a compound of formula (II) in the presence of NEt₃ and Bu₄NBr

Process for preparing vilazodone of formula (I) by reacting the HBr salt of a compound (VII) with a compound (VIII) to yield a compound of formula (II)

2. claims: 7(completely); 25(partially)

Ethyl 5-(1-piperazinyl)-benzofuran-2-carboxylate dihydrochloride and its use

3. claims: 8(completely); 25(partially)

Ethyl 5-(1-piperazinyl)-benzofuran-2-carboxylate hydrobromide and its use

4. claims: 9-15

Purification of Vilazodone

5. claims: 16-18(completely); 25(partially)

Crystalline form A of Vilazodone and preparation thereof

6. claim: 19

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Preparation of amorphous Vilazodone base

7. claims: 20, 21(completely); 25(partially)

Crystalline form II of ethyl 5-(4-(4-(5-cyano-1H-indol-3-yl)
butyl)piperazin- 1-yl)benzofuran-2-carboxylate hydrochloride
and its use

8. claims: 26-32

Preparation of Vilazodone HCl salt

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2013/052729

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0648767	A1	19-04-1995	AT 153663 T 15-06-1997
			AU 679774 B2 10-07-1997
			AU 7424494 A 13-04-1995
			CA 2133152 A1 31-03-1995
			CN 1106811 A 16-08-1995
			CZ 9402370 A3 12-04-1995
			DE 4333254 A1 06-04-1995
			DK 0648767 T3 22-12-1997
			EP 0648767 A1 19-04-1995
			ES 2105454 T3 16-10-1997
			GR 3024551 T3 31-12-1997
			HU 218918 B 28-12-2000
			JP 4065034 B2 19-03-2008
			JP 4700017 B2 15-06-2011
			JP H07149762 A 13-06-1995
			JP 2007119502 A 17-05-2007
			NO 943616 A 31-03-1995
			PL 305216 A1 03-04-1995
			RU 2132848 C1 10-07-1999
			SK 118494 A3 10-05-1995
			US 5532241 A 02-07-1996
			ZA 9407622 A 16-05-1995

WO 2013078361	A1	30-05-2013	NONE

CN 102267985	A	07-12-2011	NONE

WO 02102794	A2	27-12-2002	AR 034595 A1 03-03-2004
			AT 437871 T 15-08-2009
			BR 0210495 A 17-08-2004
			CA 2451028 A1 27-12-2002
			CA 2683040 A1 27-12-2002
			CA 2782494 A1 27-12-2002
			CA 2782515 A1 27-12-2002
			CA 2782517 A1 27-12-2002
			CA 2782519 A1 27-12-2002
			CA 2782521 A1 27-12-2002
			CA 2782615 A1 27-12-2002
			CA 2782623 A1 27-12-2002
			CA 2782628 A1 27-12-2002
			CA 2782761 A1 27-12-2002
			CA 2782791 A1 27-12-2002
			CA 2782857 A1 27-12-2002
			CA 2782862 A1 27-12-2002
			CA 2782865 A1 27-12-2002
			CA 2782868 A1 27-12-2002
			CN 1516699 A 28-07-2004
			CN 101139345 A 12-03-2008
			CZ 20040026 A3 14-04-2004
			DK 1397357 T3 05-10-2009
			EC SP044943 A 26-02-2004
			EE 200400019 A 15-04-2004
			EP 1397357 A2 17-03-2004
			ES 2330314 T3 09-12-2009
			HK 1066003 A1 31-10-2008
			HK 1116165 A1 26-04-2013
			HU 0400236 A2 28-06-2004
			IL 159426 A 29-12-2011

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2013/052729

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		JP 4624667 B2	02-02-2011
		JP 2004534803 A	18-11-2004
		JP 2010132687 A	17-06-2010
		JP 2010132688 A	17-06-2010
		KR 20040012922 A	11-02-2004
		MX PA03011723 A	19-03-2004
		NZ 530642 A	29-09-2006
		PL 364576 A1	13-12-2004
		PT 1397357 E	03-11-2009
		RU 2303598 C2	27-07-2007
		SK 162004 A3	06-04-2004
		UA 76758 C2	16-02-2004
		US 2004147528 A1	29-07-2004
		US 2009023749 A1	22-01-2009
		US 2010016332 A1	21-01-2010
		US 2011183994 A1	28-07-2011
		US 2011190317 A1	04-08-2011
		US 2011294824 A1	01-12-2011
		US 2011294825 A1	01-12-2011
		US 2011312971 A1	22-12-2011
		US 2013102616 A1	25-04-2013
		WO 02102794 A2	27-12-2002
		ZA 200400329 A	15-04-2005
<p>CN 102219783 A 19-10-2011 NONE</p>			