



(51) International Patent Classification:
C07D 405/12 (2006.01)

(21) International Application Number:
PCT/IB2013/050881

(22) International Filing Date:
1 February 2013 (01.02.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
281/DEL/2012 1 February 2012 (01.02.2012) IN

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(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).

Published:

— with international search report (Art. 21(3))

(54) Title: PROCESS FOR THE PREPARATION OF VILAZODONE OR ITS PHARMACEUTICALLY ACCEPTABLE SALTS

(57) Abstract: The present invention relates to a process for the preparation of vilazodone or its pharmaceutically acceptable salts. The present invention further provides a crystalline form of vilazodone free base.



WO 2013/114338 A1

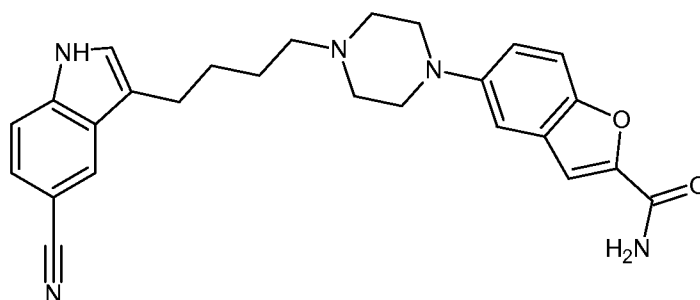
PROCESS FOR THE PREPARATION OF VILAZODONE OR ITS PHARMACEUTICALLY ACCEPTABLE SALTS

Field of the Invention

The present invention relates to a process for the preparation of vilazodone or its
5 pharmaceutically acceptable salts. The present invention further provides a crystalline form of vilazodone free base.

Background of the Invention

Vilazodone is chemically described as 5-{4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl}-1-benzofuran-2-carboxamide of Formula I.



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FORMULA I

Vilazodone is indicated for the treatment of a major depressive disorder (MDD).

Processes for the preparation of vilazodone are described in U.S. Patent Nos. 5,532,241 and 7,799,916, and European Patent No. EP 0 648 767.

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Summary of the Invention

The present invention relates to a process for the preparation of vilazodone or its pharmaceutically acceptable salts.

Brief Description of the Drawings

Figure 1 depicts the X-Ray Powder Diffraction Pattern (XRPD) of the vilazodone free
20 base obtained according to Example 1.

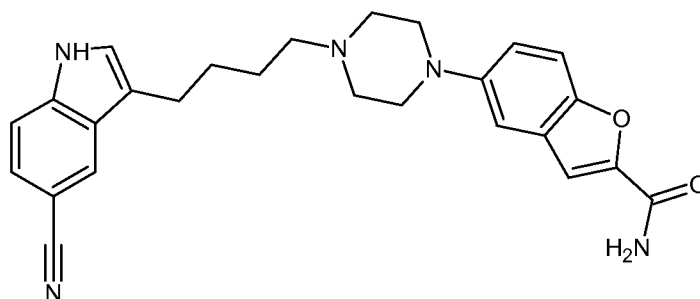
Figure 1A provides the table of values for the XRPD pattern depicted in Figure 1.

Figure 2 depicts the X-Ray Powder Diffraction Pattern (XRPD) of the vilazodone free base obtained according to Example 3.

Figure 2A provides the table of values for the XRPD pattern depicted in Figure 2.

Detailed Description of the Invention

An aspect of the present invention provides a process for the preparation of 5-{4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl}-1-benzofuran-2-carboxamide of Formula I

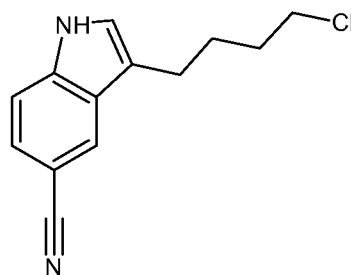


5

FORMULA I

or its pharmaceutically acceptable salts which comprises:

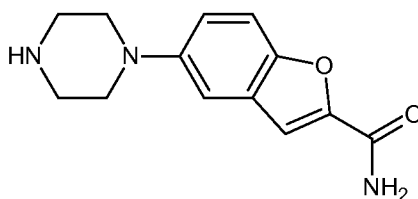
- a) reacting 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula II



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FORMULA II

with 5-(piperazin-1-yl)-1-benzofuran-2-carboxamide of Formula III

**FORMULA III**

in the presence of a base and solvent;

- b) isolating the compound of Formula I from the reaction mixture thereof; and

15

- c) optionally converting the compound of Formula I to its pharmaceutically acceptable salts.

Treatment of the compound of Formula II and the compound of Formula III may be carried out in the presence of a base and solvent. The solvent may be selected from a group consisting of water, organic solvent, or a mixture thereof. Suitable organic solvents may be selected from a group consisting of alcohol, ketone, nitrile, amide, aromatic or aliphatic hydrocarbon, or dimethyl sulfoxide. Suitable alcoholic solvents may include methanol, 2-propanol, or 1-propanol. Suitable nitrile solvents may include acetonitrile. Suitable amide solvents may include N-methylpyrrolidone or dimethylformamide. Suitable ketonic solvents may include acetone or methyl isobutyl ketone. Suitable aromatic hydrocarbon solvents may include toluene. Preferable solvents may include water alone or in combination with 2-propanol, 1-propanol, dimethylformamide, or toluene. The treatment of the compound of Formula II and the compound of Formula III may be carried out in the presence of only water without using any other solvent.

The base may be selected from a group consisting of organic base or inorganic base. A suitable organic base may include triethylamine, diisopropylamine, diisopropylethylamine, 4-dimethylaminopyridine, pyrrolidine, or N-methyl morpholine. A preferable organic base includes triethylamine. A suitable inorganic base may include hydroxides or carbonates and bicarbonates of alkali or alkaline metal. Suitable carbonates or bicarbonates of alkali or alkaline metal may include sodium carbonate, potassium carbonate, magnesium carbonate, sodium bicarbonate, or potassium bicarbonate. A preferable inorganic base includes potassium carbonate. Treatment of the compound of Formula II and the compound of Formula III may be carried out in the presence of alkali metal halides, for example, sodium iodide.

The treatment of the compound of Formula II and the compound of Formula III may be carried out at a temperature of about 5°C to about 110°C, preferably at about 15°C to about 90°C. The treatment of the compound of Formula II and the compound of Formula III may be carried for about 2 hours to about 35 hours, preferably for about 5 hours to about 30 hours.

The vilazodone free base of Formula I prepared by the present invention may be converted to its pharmaceutically acceptable salt before isolation. The vilazodone free

base of Formula I may be isolated by filtration, concentration, precipitation, cooling, centrifugation, decantation, or a combination thereof.

Vilazodone free base obtained by the present invention can be converted to its pharmaceutically acceptable salt, for example hydrochloric acid salt, by any of the method
5 known in the art. The vilazodone hydrochloride salt may be isolated by filtration, decantation, or a combination thereof.

Another aspect of the present invention provides a crystalline form of vilazodone free base.

Crystalline form of vilazodone free base has substantially the same XRPD (X-Ray
10 Powder Diffraction Pattern) pattern as depicted in Figure 1 or Figure 2. The crystalline form of vilazodone free base is characterized by an XRPD pattern having interplanar spacing (d) values substantially at 6.41, 5.14, 4.79, 4.43, 4.27, 4.17, 4.06, and 3.69 ± 0.2 Å. The crystalline form of vilazodone free base is further characterized by an XRPD
15 pattern having interplanar spacing (d) values substantially at 15.35, 12.05, 10.02, 8.07, 6.63, 6.41, 5.85, 5.55, 5.14, 4.79, 4.63, 4.43, 4.27, 4.17, 4.06, 3.85, 3.69, 3.54, 3.33, 3.20, 3.11, 3.03, 2.95, 2.89, 2.82, 2.70, 2.61, 2.52, and 2.32 ± 0.2 Å.

XRPD of the samples were determined by using Panalytical X'Pert Pro X-Ray Powder Diffractometer in the range 3-40 degree 2 theta and under tube voltage and current of 45 Kv and 40 mA respectively. Copper radiation of wavelength 1.54 angstrom and
20 Xceletor detector were used.

In the following section, embodiments are described by way of examples to illustrate the process of invention. Several variants of these examples would be evident to persons ordinarily skilled in the art.

Example 1: Preparation of 5-{4-[4-(5-Cyano-1H-Indol-3-yl)Butyl]Piperazin-1-yl}-1-
25 Benzofuran-2-Carboxamide

3-(4-Chlorobutyl)-1H-indole-5-carbonitrile (34.2 g) was added to acetonitrile (300 mL). Sodium iodide (33.1 g) was added to the reaction mixture. The reaction mixture was heated to 80°C to 85°C and maintained for 60 minutes. The reaction mixture was cooled to 60°C. 5-(Piperazin-1-yl)-1-benzofuran-2-carboxamide (30 g) and triethylamine
30 (18.6 g) were added to the reaction mixture. The reaction mixture was heated to 80°C to 83°C for 18 hours. The reaction mixture was cooled to 20°C to 30°C. The reaction

mixture was added to water (300 mL), dichloromethane (300 mL), and sodium thiosulphate (7.5 g). Concentrated hydrochloric acid (15 mL) was added to the reaction mixture and stirred for 1.5 hours at 20°C to 30°C. The solid obtained was filtered and washed with dichloromethane (80 mL) and deionized water (150 mL). The reaction mixture was added to ethyl acetate (600 mL) and water (300 mL). Triethyl amine (20 g) was added to the reaction mixture. The reaction mixture was heated to 70°C to 75°C. The layers obtained were separated and the organic layer was washed with water (100 mL). The organic layer was recovered under vacuum. 2-Propanol (60 mL) was added to the reaction mixture and stirred at 20°C to 30°C for 1 hour. The reaction mixture was filtered, washed with 2-propanol (30 mL) and dried under vacuum at 45°C to 50°C for 12 hours to obtain the title compound having XRPD as depicted in Figure 1.

Yield: 44.0 g.

Example 2: Preparation of 5-{4-[4-(5-Cyano-1H-Indol-3-yl)Butyl]Piperazin-1-yl}-1-Benzofuran-2-Carboxamide

Potassium carbonate (11.3 g) was added to water (100 mL) and stirred for 10 minutes. 5-Piperazin-1-ylbenzofuran-2-carboxamide (20 g) and 3-(4-chlorobutyl)indole-5-carbonitrile (20.9 g) were added to the reaction mixture. The reaction mixture was heated to 98°C to 100°C and maintained for 5 hours. The reaction mixture was cooled to 50°C. Water (200 mL) was added to the reaction mixture. The solid obtained was filtered and dried in an air oven at 50°C to 55°C for 10 hours to 12 hours to obtain the title compound.

Yield: 18.0 g.

Example 3: Preparation of 5-{4-[4-(5-Cyano-1H-Indol-3-yl)Butyl]Piperazin-1-yl}-1-Benzofuran-2-Carboxamide

Potassium carbonate (28.2 g) was added to water (250 mL) and stirred for 10 minutes. 5-Piperazin-1-ylbenzofuran-2-carboxamide (50 g), 3-(4-chlorobutyl)indole-5-carbonitrile (52.3 g), and 2-propanol (250 mL) were added to the reaction mixture. The reaction mixture was heated to 80°C to 85°C and maintained for 24 hours. The reaction mixture was cooled to 30°C. Water (500 mL), dichloromethane (500 mL), and hydrochloric acid (3N; 200 mL) were added to the reaction mixture and filtered. The solid obtained was dissolved in ethyl acetate (1000 mL), triethylamine (50 mL), and water (100 mL) at 80°C to 83°C. The reaction mixture was filtered and the organic layer was

separated and recovered. The residue was treated with 2-propanol (150 mL) and filtered. The solid obtained was dried under vacuum at 45°C to 50°C to obtain the title compound having XRPD as depicted in Figure 2.

Yield: 57.5 g.

5 Example 4: Preparation of 5-{4-[4-(5-Cyano-1H-Indol-3-yl)Butyl]Piperazin-1-yl}-1-Benzofuran-2-Carboxamide

Potassium carbonate (28.2 g) was added to water (250 mL) and stirred for 10 minutes. 5-Piperazin-1-ylbenzofuran-2-carboxamide (50 g), 3-(4-chlorobutyl)indole-5-carbonitrile (52.3 g), and 2-propanol (250 mL) were added to the reaction mixture. The reaction mixture was heated to 80°C to 85°C and maintained for 24 hours. The reaction mixture was cooled to 25°C to 30°C and filtered. The reaction mixture was added to dichloromethane (350 mL), methanol (350 mL), and concentrated hydrochloric acid (25 mL) at 30°C to 35°C. Water (350 mL) was added to the reaction mixture and the mixture was stirred and filtered. The solid obtained was dissolved in ethyl acetate (1000 mL), methanol (250 mL), and triethylamine (50 mL) at 80°C to 83°C. The reaction mixture was washed with water and the organic layer was recovered. The reaction mixture was treated with methanol (150 mL) and filtered. The solid obtained was dried under vacuum at 50°C to 55°C to obtain the title compound.

Yield: 64 g.

20 XRD provided

Example 5: Preparation of 5-{4-[4-(5-Cyano-1H-Indol-3-yl)Butyl]Piperazin-1-yl}-1-Benzofuran-2-Carboxamide

Potassium carbonate (5.64 g) was added to water (50 mL) and stirred for 10 minutes. 5-Piperazin-1-ylbenzofuran-2-carboxamide (10 g), 3-(4-chlorobutyl)indole-5-carbonitrile (10.45 g), and 1-propanol (50 mL) were added to the reaction mixture. The reaction mixture was refluxed at 85°C to 90°C and maintained for 11 hours. The reaction mixture was cooled to 50°C. Water (100 mL) and hydrochloric acid (4N; 40 mL) were added to the reaction mixture and filtered. Dichloromethane (150 mL), methanol (150 mL), and water (150 mL) were added to the reaction mixture. The reaction mixture was treated with activated carbon (1 g), filtered through celite, and washed with dichloromethane (50 mL) and water (50 mL). Triethylamine (10 mL) was added to the

reaction mixture, the layers obtained were separated and the organic layer was recovered under vacuum. Methanol (20 mL) was added to the reaction mixture, stirred for 1.5 hours and filtered. The solid obtained was dried at 45°C to 50°C to obtain the title compound.

Yield: 13 g.

5 Example 6: Preparation of 5-{4-[4-(5-Cyano-1H-Indol-3-yl)Butyl]Piperazin-1-yl}-1-Benzofuran-2-Carboxamide

5-Piperazin-1-ylbenzofuran-2-carboxamide (2.0 g) was added to 3-(4-chlorobutyl)indole-5-carbonitrile (1.9 g) in dimethylformamide (20 mL). Potassium carbonate (1.2 g) was added to the reaction mixture and heated to 80°C to 85°C and
10 maintained for 5 hours. The reaction mixture was cooled to 35°C and water (50 mL) was added, stirred for 2 hours, and then filtered. The solid obtained was dried under vacuum at 45°C to 50°C to obtain the title compound.

Yield: 1.0 g.

15 Example 7: Preparation of 5-{4-[4-(5-Cyano-1H-Indol-3-yl)Butyl]Piperazin-1-yl}-1-Benzofuran-2-Carboxamide

Potassium carbonate (2.8 g) was added to water (25 mL) and stirred for 10 minutes. 5-Piperazin-1-ylbenzofuran-2-carboxamide (5.0 g), 3-(4-chlorobutyl)indole-5-carbonitrile (5.7 g), and toluene (25 mL) were added to the reaction mixture and heated to 90°C to 95°C for 29 hours. The reaction mixture was cooled to 30°C, filtered and washed
20 with water (25 mL). The solid obtained was dried at 45°C to 50°C to obtain the title compound.

Yield: 7.0 g.

Example 8: Preparation of 5-{4-[4-(5-Cyano-1H-Indol-3-yl)Butyl]Piperazin-1-yl}-1-Benzofuran-2-Carboxamide Hydrochloride

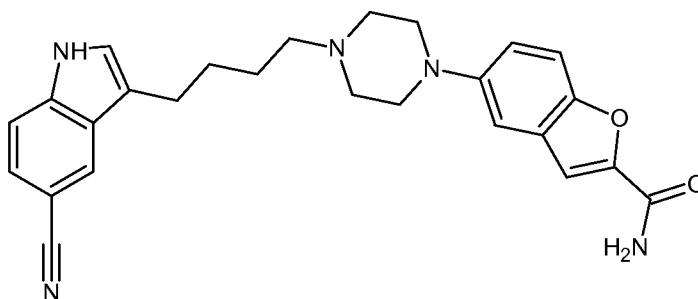
25 5-{4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl}-1-benzofuran-2-carboxamide (10.0 g) was added to 2-propanol (430 mL). The reaction mixture was heated to 80°C to 83°C. The reaction mixture was filtered. The reaction mixture was heated to 70°C to 80°C and a solution of 2-propnaolic hydrochloride (0.1N; 230 mL) was added to the reaction mixture at 70°C to 80°C in 20 minutes. The reaction mixture was
30 cooled to 25°C to 30°C and stirred for 2.5 hours. The solid obtained was filtered, washed

with diethyl ether (30 mL) and dried under vacuum at 20°C to 30°C for 12 hours to obtain the title compound.

Yield: 9.9 g.

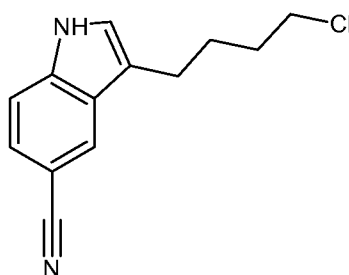
We claim:

1. A process for the preparation of 5-{4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl}-1-benzofuran-2-carboxamide of Formula I

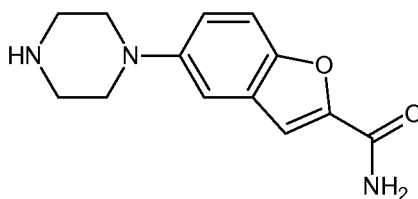
**FORMULA I**

or its pharmaceutically acceptable salts which comprises:

- a) reacting 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula II

**FORMULA II**

with 5-(piperazin-1-yl)-1-benzofuran-2-carboxamide of Formula III,

**FORMULA III**

- in the presence of base and solvent;
- b) isolating the compound of Formula I from the reaction mixture thereof; and
- c) optionally converting the compound of Formula I to its pharmaceutically acceptable salts.

- 1 2. The process according to claim 1, wherein the base is selected from a group
2 consisting of an organic base or an inorganic base.
- 1 3. The process according to claim 2, wherein the organic base is selected from
2 triethylamine, diisopropylamine, diisopropylethylamine, 4-dimethylaminopyridine,
3 pyrrolidine or N-methyl morpholine.
- 1 4. The process according to claim 3, wherein the organic base is triethylamine.
- 1 5. The process according to claim 2, wherein the inorganic base includes hydroxides
2 or carbonates and bicarbonates of alkali or alkaline metal.
- 1 6. The process according to claim 5, wherein the carbonates and bicarbonates of
2 alkali or alkaline metal is sodium carbonate, potassium carbonate, magnesium carbonate,
3 sodium bicarbonate or potassium bicarbonate.
- 1 7. The process according to claim 2, wherein the inorganic base is potassium
2 carbonate.
- 1 8. The process according to claim 1, wherein the solvent is selected from a group
2 consisting of water, organic solvent, or a mixture thereof.
- 1 9. The process according to claim 8, wherein organic solvents are selected from a
2 group consisting of alcohol, ketone, nitrile, amide, aromatic or aliphatic hydrocarbon, or
3 dimethyl sulfoxide.
- 1 10. The process according to claim 9, wherein the alcoholic solvent is methanol, 2-
2 propanol, or 1-propanol.
- 1 11. The process according to claim 9, wherein the amide solvent is N-
2 methylpyrrolidone or dimethyl formamide.
- 1 12. The process according to claim 9, wherein the ketonic solvent is acetone or methyl
2 isobutyl ketone.
- 1 13. The process according to claim 9, wherein the aromatic hydrocarbon solvent is
2 toluene.
- 1 14. The process according to claim 1, wherein the solvent is water alone or in
2 combination with 2-propanol, 1-propanol, dimethylformamide, or toluene.

- 1 15. The process according to claim 1, wherein the reaction of the compound of
2 Formula II and the compound of Formula III is carried out in the presence of only water
3 without using any other solvent.
- 1 16. The process according to claim 1, wherein the pharmaceutically acceptable salt
2 includes hydrochloride salt.
- 1 17. A crystalline form of vilazodone free base with substantially the same XRPD (X-
2 Ray Powder Diffraction Pattern) as depicted in Figure 1 or Figure 2.
- 1 18. A crystalline form of vilazodone free base characterized by an XRPD having
2 interplanar spacing (d) values substantially at 6.41, 5.14, 4.79, 4.43, 4.27, 4.17, 4.06, and
3 3.69 ± 0.2 Å.
- 1 19. The crystalline form of vilazodone free base according to claim 18 which is further
2 characterized by an XRPD having interplanar spacing (d) values substantially at 15.35,
3 12.05, 10.02, 8.07, 6.63, 6.41, 5.85, 5.55, 5.14, 4.79, 4.63, 4.43, 4.27, 4.17, 4.06, 3.85,
4 3.69 , 3.54, 3.33, 3.20, 3.11, 3.03, 2.95, 2.89, 2.82, 2.70, 2.61, 2.52, and 2.32 ± 0.2 Å.

Figure 1

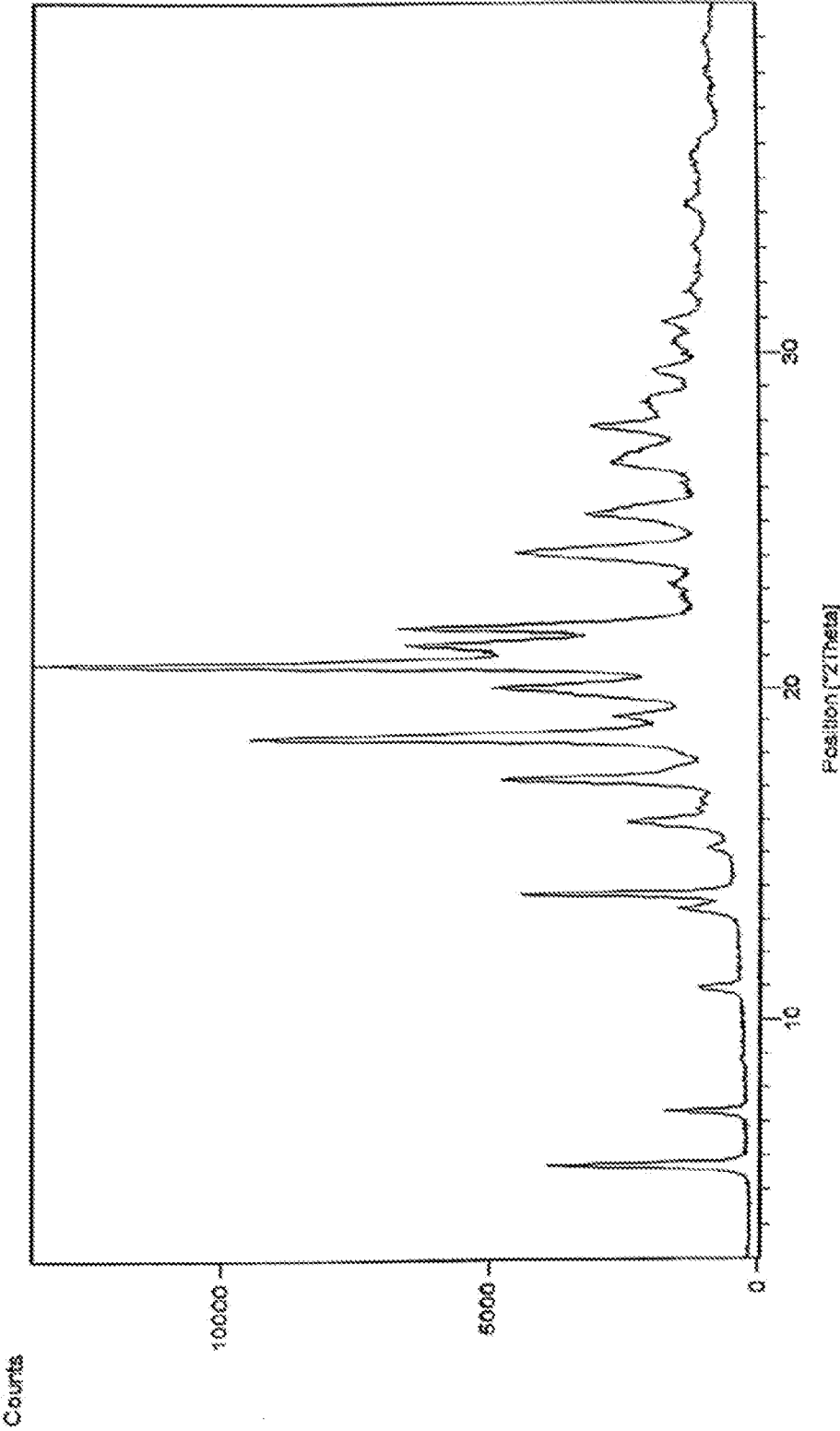


**FIGURE 1A: TABLE OF VALUES FOR THE XRPD PATTERN DEPICTED IN
FIGURE 1**

Two Theta Values	d-spacing [Å]	Rel. Int [%]
5.76	15.35	27.28
7.33	12.05	12.03
8.82	10.02	0.45
10.96	8.07	6.82
13.36	6.63	8.93
13.81	6.41	31.73
15.15	5.85	4.21
15.96	5.55	15.60
17.25	5.14	33.49
18.53	4.79	71.40
19.18	4.63	17.68
20.05	4.43	34.93
20.78	4.27	100.00
21.31	4.17	46.94
21.89	4.06	47.81
23.07	3.85	8.36
24.10	3.69	31.43
25.17	3.54	19.76
26.73	3.33	16.76
27.86	3.20	19.85
28.69	3.11	11.04
29.52	3.03	10.36
30.30	2.95	7.14
30.90	2.89	8.51
31.77	2.82	4.80
33.15	2.70	3.94
34.32	2.61	4.63
35.67	2.52	3.94
38.89	2.32	0.96

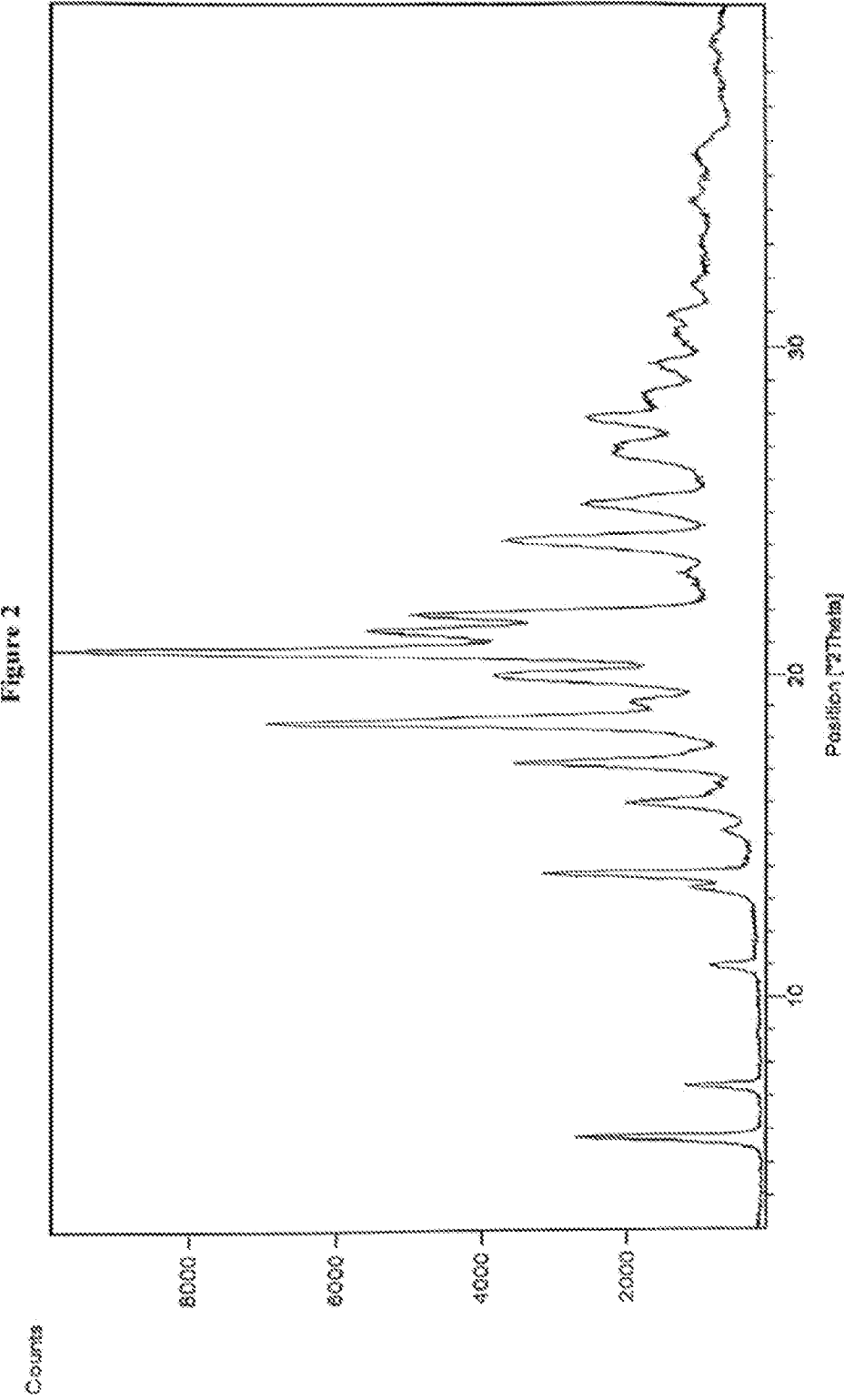


**FIGURE 2A: TABLE OF VALUES FOR THE XRPD PATTERN DEPICTED IN
FIGURE 2**

Two Theta Values	d-spacing [Å]	Rel. Int [%]
5.78	15.28	26.13
7.34	12.04	11.71
8.82	10.02	0.42
10.98	8.06	6.93
13.36	6.63	10.53
13.83	6.40	32.15
15.14	5.85	4.59
15.98	5.55	20.51
17.20	5.15	37.93
18.54	4.79	77.68
19.18	4.63	18.43
20.06	4.43	36.57
20.83	4.26	100.00
21.42	4.15	60.05
21.88	4.06	53.06
23.16	3.84	9.45
24.20	3.68	37.72
25.27	3.52	25.05
26.66	3.34	18.86
27.13	3.29	18.17
27.94	3.19	22.10
28.64	3.11	14.35
29.51	3.02	13.09
30.39	2.94	9.39
30.99	2.89	9.64
31.76	2.82	6.45
34.29	2.61	5.86
35.71	2.51	5.14
38.90	2.31	1.54

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/050881

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D405/12
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, EMBASE, WPI 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.
X	US 7 799 916 B2 (BATHE ANDREAS [DE]) 21 September 2010 (2010-09-21) cited in the application	17-19
A	column 4, line 25 - line 39 -----	1-16
X	CN 102 267 932 A (SHANGHAI INST PHARM IND) 7 December 2011 (2011-12-07)	1-16
A	paragraph [0011] - paragraph [0012] -----	17-19
X	US 5 723 614 A (BATHE ANDREAS [DE] ET AL) 3 March 1998 (1998-03-03)	1-16
A	column 5, line 54 - column 6, line 63 -----	17-19
X	US 6 509 475 B1 (BATHE ANDREAS [DE] ET AL) 21 January 2003 (2003-01-21)	1-16
A	column 3, line 7 - line 12 -----	17-19



Further documents are listed in the continuation of Box C.



See patent family annex.

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"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search

7 May 2013

Date of mailing of the international search report

15/05/2013

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INTERNATIONAL SEARCH REPORT

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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.:

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: 1-16

A process for preparing vilazodone

2. claims: 17-19

A crystalline form of vilazodone free base
