



- (51) **International Patent Classification:**
C07D 405/12 (2006.01) *A61P 25/24* (2006.01)
A61K 31/496 (2006.01)
- (21) **International Application Number:**
PCT/CA2013/000560
- (22) **International Filing Date:**
13 June 2013 (13.06.2013)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
61/659,425 13 June 2012 (13.06.2012) US
61/754,197 18 January 2013 (18.01.2013) US
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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, 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, KM, ML, MR, NE, SN, TD, TG).

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))

(54) **Title:** FORMS OF VILAZODONE AND PROCESSES FOR THE PREPARATION THEREOF

(57) **Abstract:** Vilazodone hydrochloride benzyl alcohol solvates are provided as well as processes for the preparation thereof.



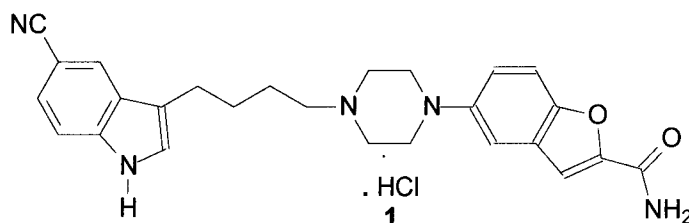
FORMS OF VILAZODONE AND PROCESSES FOR THE PREPARATION THEREOF

TECHNICAL FIELD

5 The present invention relates to a solvate of Vilazodone and processes for the preparation thereof.

BACKGROUND

10 Vilazodone hydrochloride, 1, has the chemical name 2-benzofurancarboxamide, 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-, hydrochloride (1:1). It is marketed in the U.S. as Viibryd® and is indicated for the treatment of major depressive disorder.



15 US Patent 5,532,241 and WO 00/72832 teach 1-[4-(5-Cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine, physiologically acceptable salts thereof, processes for preparation thereof and uses in treating certain medical disorders.

20 US Patent 7,834,020 discloses crystalline modifications of the hydrochloride of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine, crystalline modification of the dihydrochloride of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine and amorphous 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride which are suitable in particular for the preparation of solid medicaments for the treatment or prevention of depressive disorders, anxiety disorders, bipolar
25 disorders, mania, dementia, substance-related disorders, sexual dysfunctions, eating disorders, obesity, fibromyalgia, sleeping disorders, psychiatric disorders, cerebral infarct, tension, for the therapy of side-effects in the treatment of

hypogonadism, secondary amenorrhea, premenstrual syndrome and undesired puerperal lactation.

SUMMARY

5 The present invention relates, at least in part, to a crystalline benzyl alcohol solvate of vilazodone hydrochloride wherein the molar ratio of vilazodone hydrochloride to benzyl alcohol is approximately 1:0.5. The present invention also relates, at least in part, to a crystalline benzyl alcohol solvate of vilazodone hydrochloride wherein the molar ratio of vilazodone hydrochloride to benzyl alcohol is approximately 1:1. The crystalline solvates of the present invention may have advantages relative to other known forms of vilazodone hydrochloride, including chemical stability, polymorphic stability and/or varying solubility.

10 In illustrative embodiments of the present invention, there is provided a crystalline benzyl alcohol solvate of vilazodone hydrochloride.

15 In illustrative embodiments of the present invention, there is provided a crystalline benzyl alcohol solvate of vilazodone hydrochloride described herein wherein the molar ratio of vilazodone hydrochloride to benzyl alcohol is approximately 1:0.5.

20 In illustrative embodiments of the present invention, there is provided a Form APO-I of vilazodone hydrochloride benzyl alcohol solvate.

 In illustrative embodiments of the present invention, there is provided a Form APO-I of vilazodone hydrochloride benzyl alcohol solvate described herein characterized by a PXRD diffractogram comprising peaks, in terms of degrees 2-theta, at approximately 9.5, 10.6, 13.5, 15.6, 22.3, and 26.1.

25 In illustrative embodiments of the present invention, there is provided a Form APO-I of vilazodone hydrochloride benzyl alcohol solvate described herein characterized by a PXRD diffractogram comprising peaks, in terms of degrees 2-theta, at approximately 5.3, 9.5, 10.6, 11.2, 13.5, 14.6, 15.6, 17.5, 19.1, 20.5, 22.3, 24.5 and 26.1.

30 In illustrative embodiments of the present invention, there is provided a Form APO-I of vilazodone hydrochloride benzyl alcohol solvate described herein

characterized by a PXRD diffractogram substantially similar to the PXRD diffractogram as depicted in Figure 1.

In illustrative embodiments of the present invention, there is provided a Form APO-I of vilazodone hydrochloride benzyl alcohol solvate described herein
5 characterized by a PXRD diffractogram as depicted in Figure 1.

In illustrative embodiments of the present invention, there is provided a Form APO-I of vilazodone hydrochloride benzyl alcohol solvate described herein characterized by a 1% KBr FTIR spectrum comprising peaks, in terms of cm^{-1} , at approximately 2216, 1676, 1607, 1579, 1443 and 1380.

10 In illustrative embodiments of the present invention, there is provided a Form APO-I of vilazodone hydrochloride benzyl alcohol solvate described herein characterized by a 1% KBr FTIR spectrum comprising peaks, in terms of cm^{-1} , at approximately 3228, 2216, 1676, 1607, 1579, 1472, 1443 and 1380.

In illustrative embodiments of the present invention, there is provided a Form
15 APO-I of vilazodone hydrochloride benzyl alcohol solvate described herein characterized by a FTIR spectrum substantially similar to the FTIR spectrum as depicted in Figure 2.

In illustrative embodiments of the present invention, there is provided a Form
20 APO-I of vilazodone hydrochloride benzyl alcohol solvate described herein characterized by a FTIR spectrum as depicted in Figure 2.

In illustrative embodiments of the present invention, there is provided a pharmaceutical formulation comprising a Form APO-I vilazodone hydrochloride benzyl alcohol solvate described herein and a pharmaceutically acceptable excipient.

25 In illustrative embodiments of the present invention, there is provided a process for preparation of vilazodone hydrochloride benzyl alcohol solvate, the process comprising: i. preparing a first APO-I-preparation-mixture of vilazodone free base and a first APO-I-preparation-solvent, the first
30 APO-I-preparation-solvent comprising benzyl alcohol; ii. treating the first APO-I-preparation mixture with hydrochloric acid; and iii. crystallizing the benzyl alcohol solvate of vilazodone hydrochloride.

In illustrative embodiments of the present invention, there is provided a process for preparation of vilazodone hydrochloride benzyl alcohol solvate described herein wherein the vilazodone hydrochloride benzyl alcohol solvate is Form APO-I.

5 In illustrative embodiments of the present invention, there is provided a process for preparation of vilazodone hydrochloride benzyl alcohol solvate described herein wherein the first APO-I-preparation-solvent further comprises dimethylformamide, acetic acid or mixtures thereof.

10 In illustrative embodiments of the present invention, there is provided a process for preparation of vilazodone hydrochloride benzyl alcohol solvate described herein wherein the hydrochloric acid is provided as a solution in an organic solvent.

15 In illustrative embodiments of the present invention, there is provided a process for preparation of vilazodone hydrochloride benzyl alcohol solvate described herein wherein the organic solvent is isopropanol.

20 In illustrative embodiments of the present invention, there is provided a process for preparation of vilazodone hydrochloride benzyl alcohol solvate described herein further comprising maintaining the crystallized benzyl alcohol solvate of vilazodone hydrochloride in a suspension at a temperature of about 30°C to about 40°C.

25 In illustrative embodiments of the present invention, there is provided a crystalline benzyl alcohol solvate of vilazodone hydrochloride described herein wherein the molar ratio of vilazodone hydrochloride to benzyl alcohol is approximately 1:1.

30 In illustrative embodiments of the present invention, there is provided a Form APO-II of vilazodone hydrochloride benzyl alcohol solvate.

In illustrative embodiments of the present invention, there is provided a Form APO-II of vilazodone hydrochloride benzyl alcohol solvate described herein characterized by a PXRD diffractogram comprising peaks, in terms of degrees 2-theta, at approximately 10.5, 13.3, 15.8, 19.5, 21.2 and 24.7.

In illustrative embodiments of the present invention, there is provided a Form APO-II of vilazodone hydrochloride benzyl alcohol solvate described herein characterized by a PXRD diffractogram comprising peaks, in terms of degrees 2-theta, at approximately 9.2, 10.5, 13.3, 15.8, 18.6, 19.5, 20.2, 21.2, 22.3, 23.3, 24.7 and 25.4.

In illustrative embodiments of the present invention, there is provided a Form APO-II of vilazodone hydrochloride benzyl alcohol solvate described herein characterized by a PXRD diffractogram substantially similar to the PXRD diffractogram as depicted in Figure 3.

In illustrative embodiments of the present invention, there is provided a Form APO-II of vilazodone hydrochloride benzyl alcohol solvate described herein characterized by a PXRD diffractogram as depicted in Figure 3.

In illustrative embodiments of the present invention, there is provided a Form APO-II of vilazodone hydrochloride benzyl alcohol solvate described herein characterized by a 1% KBr FTIR spectrum comprising peaks, in terms of cm^{-1} , at approximately 3237, 2923, 2584, 2210, 1678, 1605, 1575, 1471, 1444, 1367 and 1231.

In illustrative embodiments of the present invention, there is provided a Form APO-II of vilazodone hydrochloride benzyl alcohol solvate described herein characterized by a 1% KBr FTIR spectrum comprising peaks, in terms of cm^{-1} , at approximately 3237, 2584, 2210, 1678, 1605, 1575, 1367 and 1231.

In illustrative embodiments of the present invention, there is provided a Form APO-II of vilazodone hydrochloride benzyl alcohol solvate described herein characterized by a FTIR spectrum substantially similar to the FTIR spectrum as depicted in Figure 4.

In illustrative embodiments of the present invention, there is provided a Form APO-II of vilazodone hydrochloride benzyl alcohol solvate described herein characterized by a FTIR spectrum as depicted in Figure 4.

In illustrative embodiments of the present invention, there is provided a pharmaceutical formulation comprising a Form APO-II vilazodone hydrochloride

benzyl alcohol solvate described herein and a pharmaceutically acceptable excipient.

In illustrative embodiments of the present invention, there is provided a process for preparation of Form APO-II of vilazodone hydrochloride benzyl alcohol solvate, the process comprising: i. preparing a first APO-II-preparation-mixture of vilazodone free base and a first APO-II-preparation-solvent, the first APO-II-preparation-solvent comprising benzyl alcohol; ii. treating the first APO-II-preparation-mixture with hydrochloric acid to produce a second APO-II-preparation-mixture; iii. heating the second APO-II-preparation-mixture to a temperature of from about 80°C to about 100°C; and iv. crystallizing the Form APO-II vilazodone hydrochloride benzyl alcohol solvate.

In illustrative embodiments of the present invention, there is provided a process for preparation of Form APO-II of vilazodone hydrochloride benzyl alcohol solvate described herein wherein the first APO-II-preparation-solvent is selected from the group consisting of benzyl alcohol, dimethylformamide, acetic acid and mixtures thereof.

In illustrative embodiments of the present invention, there is provided a process for preparation of Form APO-II of vilazodone hydrochloride benzyl alcohol solvate described herein wherein the second APO-II-preparation-mixture is heated to a temperature of from about 90°C to about 100°C.

In illustrative embodiments of the present invention, there is provided a process for preparation of Form APO-II of vilazodone hydrochloride benzyl alcohol solvate described herein further comprising maintaining the crystallized Form APO-II vilazodone hydrochloride benzyl alcohol solvate in a suspension at a temperature of from about 30°C to about 40°C.

In illustrative embodiments of the present invention, there is provided a process for preparation of Form APO-II of vilazodone hydrochloride benzyl alcohol solvate comprising heating a third APO-II-preparation-mixture comprising Form APO-I of vilazodone hydrochloride benzyl alcohol solvate and benzyl alcohol to a temperature of from about 80 °C to about 100 °C.

Other aspects and features of the present invention will become apparent to those ordinarily skilled in the art upon review of the following description of specific embodiments of the invention in conjunction with the accompanying figures.

5 **BRIEF DESCRIPTION OF THE DRAWINGS**

In drawings which illustrate embodiments of the invention,

Figure 1 is a powder X-ray diffraction (PXRD) diffractogram of APO-I

Figure 2 is a Fourier Transform Infrared (FTIR) spectrum of APO-I

Figure 3 is a powder X-ray diffraction (PXRD) diffractogram of APO-II

10 Figure 4 is a Fourier Transform Infrared (FTIR) spectrum of APO-II

DETAILED DESCRIPTION

When used in reference to a diffractogram, a spectrum and/or data presented in a graph, the term “substantially similar” means that the subject
15 diffractogram, spectrum and/or data presented in a graph encompasses all diffractograms, spectra and/or data presented in graphs that vary within acceptable boundaries of experimentation that are known to a person of skill in the art. Such boundaries of experimentation will vary depending on the type of the subject diffractogram, spectrum and/or data presented in a graph, but will
20 nevertheless be known to a person of skill in the art.

When used in reference to a peak in a PXRD diffractogram, the term “approximately” means that the peak may vary by ± 0.2 degrees 2-theta of the subject value.

When used in reference to a peak in a FTIR spectrum, the term
25 “approximately” means that the peak may vary by $\pm 5 \text{ cm}^{-1}$ of the subject value.

As used herein when referring to a diffractogram, spectrum and/or to data presented in a graph, the term “peak” refers to a feature that one skilled in the art would recognize as not attributing to background noise.

Depending on the nature of the methodology applied and the scale
30 selected to display results obtained from an X-ray diffraction analysis, an intensity of a peak obtained may vary quite dramatically. For example, it is

possible to obtain a relative peak intensity of 1% when analyzing one sample of a substance, but another sample of the same substance may show a much different relative intensity for a peak at the same position. This may be due, in part, to the preferred orientation of the sample and its deviation from the ideal random sample orientation, sample preparation and the methodology applied. Such variations are known and understood by a person of skill in the art.

The acceptable daily intake (ADI) for benzyl alcohol and its equivalents (benzoic acid, benzoate salts, benzaldehyde, benzyl acetate and benzyl benzoate) has been established by the World Health Organization at 5 mg/kg (JECFA, 2001).

The present invention encompasses the solvates isolated in pure form or when admixed with other materials, for example other isomers and/or polymorphic forms and/or salt forms or any other material.

Solvates have some variability in the exact molar ratio of their components depending on a variety of conditions understood to a person of skill in the art.

For example, a molar ratio of components within a solvate provides a person of skill in the art information as to the general relative quantities of the components of the solvate and in many cases the molar ratio may vary by about plus or minus 20% from a stated range. For example, a molar ratio of 1:1 is understood to include the ratio 1:0.8 as well as 1:1.2 as well as all of the individual ratios in between.

In one embodiment, the present invention comprises vilazodone hydrochloride benzyl alcohol solvate wherein the ratio of vilazodone hydrochloride to benzyl alcohol is approximately 1:0.5.

An illustrative PXRD diffractogram of Form APO-I vilazodone hydrochloride benzyl alcohol solvate obtained according to the conditions given in Example 7 is shown in Figure 1. According to Figure 1, the Form APO-I vilazodone hydrochloride benzyl alcohol solvate may have a reflection ("peak") at any one or more of the values expressed in degrees 2-theta given in Table 1. Although values are given in the tables below, the solvate may be defined by the claimed peaks and a particular claim may be limited to one peak only, or several peaks. The Form APO-I vilazodone hydrochloride benzyl alcohol solvate does

not have to include all or even many of the peaks listed in Table 1. Some illustrative and non-limiting possible observations regarding relative intensities of the peaks are set out in Table 1.

Table 1	
Form APO-I vilazodone hydrochloride benzyl alcohol solvate	
Peak (degrees 2-theta)	Relative Intensity (%)
5.28	44.27
9.48	61.83
10.11	15.87
10.58	71.22
11.17	14.15
12.99	20.33
13.32	31.42
13.46	57.12
14.58	10.51
15.63	57.80
16.40	5.70
16.55	10.69
17.46	39.56
17.62	30.81
17.78	16.93
18.26	11.15
19.06	24.20
20.50	30.16
21.60	8.23
22.30	75.74
23.12	20.12
23.81	12.73
24.52	40.29
25.17	7.20
26.12	100.00
26.61	31.54

5 An illustrative FTIR spectrum of Form APO-I vilazodone hydrochloride benzyl alcohol solvate obtained according to the conditions given in Example 7 is shown in Figure 2. According to Figure 2, the Form APO-I vilazodone hydrochloride benzyl alcohol solvate may have an absorption band ("peak") at any one or more of the values expressed in cm^{-1} given in Table 2. Some illustrative and non-limiting possible observations regarding peak intensity (% Transmission) of the peaks are set out in Table 2.

Table 2	
Form APO-I vilazodone hydrochloride benzyl alcohol solvate	
Peak (cm^{-1})	Intensity (% Transmission)
3377.5	46.10
3228.4	40.75
3191.8	43.65
2945.0	65.30
2867.9	70.59
2667.1	67.97
2589.1	65.74
2451.3	74.75
2216.3	47.22
1675.8	9.95
1606.9	37.51
1579.2	40.22
1471.9	53.30
1443.2	42.70
1400.8	56.47
1380.2	38.64
1263.0	60.29
1232.6	41.00
1175.5	62.31

In an embodiment, the present invention relates to a process for preparation of vilazodone hydrochloride benzyl alcohol solvate comprising:

- i. preparing a first APO-I-preparation-mixture of vilazodone free base and a first APO-I-preparation-solvent, the first APO-I-preparation-solvent comprising benzyl alcohol;
- ii. treating the first APO-I-preparation-mixture with hydrochloric acid; and
- iii. crystallizing the benzyl alcohol solvate of vilazodone hydrochloride.

In an embodiment, the first APO-I-preparation-mixture is a solution or a suspension. The first APO-I-preparation-solvent may be benzyl alcohol alone or may further comprise acetic acid, DMF or mixtures thereof. In a particular embodiment, the first APO-I-preparation-solvent is benzyl alcohol.

Crystallizing the benzyl alcohol solvate may be induced by cooling and/or seeding. Following crystallization, a suspension may be formed and the suspension may be maintained at a temperature of about 30°C to about 40°C prior to isolation of the crystals.

The hydrochloric acid may be provided as a gas or as a solution in an organic or aqueous solvent. The organic solvent may be isopropanol.

In one embodiment, the present invention comprises vilazodone hydrochloride benzyl alcohol solvate wherein the molar ratio of vilazodone hydrochloride to benzyl alcohol is approximately 1:1.

An illustrative PXRD diffractogram of Form APO-II vilazodone hydrochloride benzyl alcohol solvate obtained according to the conditions given in Example 10 is shown in Figure 3. According to Figure 3, the Form APO-II vilazodone hydrochloride benzyl alcohol solvate may have a reflection ("peak") at any one or more of the values expressed in degrees 2-theta given in Table 3. Although values are given in the tables below, the solvate may be defined by the claimed peaks and a particular claim may be limited to one peak only, or several peaks. The Form APO-II vilazodone hydrochloride benzyl alcohol solvate does not have to include all or even many of the peaks listed in Table 3. Some

illustrative and non-limiting possible observations regarding relative intensities of the peaks are set out in Table 3.

Table 3	
Form APO-II vilazodone hydrochloride benzyl alcohol solvate	
Peak (degrees 2-theta)	Relative Intensity (%)
5.26	11.52
9.24	12.76
9.99	3.90
10.51	20.57
10.88	7.74
12.70	15.46
13.32	47.84
13.79	6.11
14.38	9.10
14.87	8.94
15.80	46.89
16.16	9.40
16.56	12.23
17.15	7.91
18.55	22.48
19.47	47.02
20.25	32.54
21.18	67.13
21.59	7.10
22.34	31.78
22.70	7.42
23.31	26.15
23.75	11.36
24.68	100.00
25.41	51.96
26.61	23.73
27.57	21.88

Table 3	
Form APO-II vilazodone hydrochloride benzyl alcohol solvate	
Peak (degrees 2-theta)	Relative Intensity (%)
29.98	18.09

An illustrative FTIR spectrum of Form APO-II vilazodone hydrochloride benzyl alcohol solvate obtained according to the conditions given in Example 10 is shown in Figure 4. According to Figure 4, the Form APO-II vilazodone hydrochloride benzyl alcohol solvate may have an absorption band ("peak") at any one or more of the values expressed in cm^{-1} given in Table 4. Some illustrative and non-limiting possible observations regarding peak intensity (% Transmission) of the peaks are set out in Table 4.

Table 4	
Form APO-II vilazodone hydrochloride benzyl alcohol solvate	
Peak (cm^{-1})	Intensity (% Transmission)
3402.3	36.55
3236.6	17.70
3189.9	25.28
2922.8	44.55
2863.1	49.30
2665.2	49.22
2584.4	35.80
2210.2	27.30
1678.4	3.09
1605.0	16.44
1575.1	26.45
1471.0	34.24
1444.1	23.21
1402.5	49.73
1367.4	22.15
1260.4	39.07
1244.6	31.90

Table 4	
Form APO-II vilazodone hydrochloride benzyl alcohol solvate	
Peak (cm ⁻¹)	Intensity (% Transmission)
1231.2	23.07
1221.4	26.65

In an embodiment, the present invention relates to a process for preparation of Form APO-II of vilazodone hydrochloride benzyl alcohol solvate comprising:

- i. preparing a first APO-II-preparation-mixture of vilazodone free base and a first APO-II-preparation-solvent, the first APO-II-preparation-solvent comprising benzyl alcohol;
- ii. treating the first APO-II-preparation-mixture with hydrochloric acid to produce a second APO-II-preparation-mixture;
- iii. heating the second APO-II-preparation-mixture to a temperature of from about 80°C to about 100°C and crystallizing the vilazodone hydrochloride benzyl alcohol solvate.

In an embodiment, the first APO-II-preparation-mixture is a solution or a suspension. The first APO-II-preparation-solvent may be benzyl alcohol alone or may further comprise acetic acid, DMF or mixtures thereof. In a particular embodiment, the first APO-II-preparation-solvent is benzyl alcohol.

In an embodiment, the second APO-II-preparation-mixture is a solution or a suspension, which may or may not remain upon heating.

Crystallization of the Form APO-II benzyl alcohol solvate may occur spontaneously or may be induced by cooling and/or seeding. Following crystallization, a suspension may be formed and the suspension may be maintained at a temperature of about 30°C to about 40°C prior to isolation of the crystals.

The hydrochloric acid may be provided as a gas or as a solution in an organic or aqueous solvent. The organic solvent may be isopropanol.

In an embodiment, the present invention relates to a process for preparation of Form APO-II of vilazodone hydrochloride benzyl alcohol solvate comprising heating a third APO-II-preparation-mixture comprising Form APO-I of vilazodone hydrochloride benzyl alcohol solvate and benzyl alcohol to a temperature of from about 80°C to about 100°C. The heating may be done for a suitable period of time from a minimum time of about 3 hours.

Examples

The following examples are illustrative of some of the embodiments of the invention described herein. These examples do not limit the spirit or scope of the invention in any way.

Powder X-Ray Diffraction Analysis: The data were acquired on a PANalytical X-Pert Pro MPD diffractometer with fixed divergence slits and an X-Celerator RTMS detector. The diffractometer was configured in Bragg-Brentano geometry; data was collected over a 2-theta range of 3 to 40 using CuK α radiation at a power of 40 mA and 45 kV. CuK β radiation was removed using a divergent beam nickel filter. A step size of 0.017 degrees was used.

Fourier Transform Infrared (FTIR) Analysis: The FTIR spectrum was collected at 4 cm⁻¹ resolution using a Perkin Elmer Paragon 1100 single beam FTIR instrument. The samples were intimately mixed in an approximately 1:100 ratio (w/w) with potassium bromide using an agate mortar and pestle to a fine consistency; the mixture was compressed in a pellet die at a pressure of 4 to 6 tonnes for a time period between 2 and 5 minutes. The resulting disk was scanned 4 times versus a collected background. Data was baseline corrected and normalized.

Example 1

1-[4-(5-Cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine (1 g) was dissolved in benzyl alcohol (10 ml) under inert gas atmosphere at 20 – 25°C. To the clear solution was added HCl in isopropanol (0.55 g, 1.2 eq). The resulting suspension was stirred for 20h at 20 – 25°C. The suspension was then

heated to 35°C and maintained for 3h. The solid was filtered, washed with acetone (2 x 5 mL) and dried at about 65°C to afford 0.84 g hemi solvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with benzyl alcohol. ¹H NMR (DMSO-d₆) 11.47 (br s, 1H); 10.40 (br s, 1H); 8.10 (s, 1H); 8.05, 7.63 (br s, 2H); 7.55-7.50 (m, 2H); 7.45-7.39 (m, 3H); 7.32-7.25 (m, 2.5H); 7.23-7.20 (m, 1H); 5.10 (br s, 0.5 H); 4.49 (s, 1H); 3.75-3.70 (m, 2H); 3.6-3.56 (m, 2H); 3.25-3.08 (m, 6H); 2.78 (t, 2H); 1.79-1.68 (m, 4H).

Example 2

1-[4-(5-Cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine (1.1 g) was dissolved in benzyl alcohol (10 ml) under inert gas atmosphere at 20 – 25°C. To the clear solution was added HCl in isopropanol (0.6 g, 1.2 eq). The resulting suspension was stirred for 20h at 20 – 25°C. The suspension was heated to 35°C and maintained for 3h. The solid was filtered, washed with MTBE (2 x 5 ml) and dried at 65°C to afford 0.88 g hemi solvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with benzyl alcohol.

Example 3

1-[4-(5-Cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine (1 g) was dissolved in benzyl alcohol (10 ml) under inert gas atmosphere at 20 – 25°C. To the clear solution was added HCl in isopropanol (0.55 g, 1.2 eq). The resulting suspension was stirred for 20h at 20 – 25°C. Ethyl acetate (5 ml) was added to the suspension followed by stirring for 3h at 35°C. The solid was filtered, washed with ethyl acetate (2 x 5 ml) and dried at 65°C to afford 0.9 g hemi solvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with benzyl alcohol.

Example 4

1-[4-(5-Cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine (1 g) was dissolved in benzyl alcohol (10 ml) under inert gas atmosphere at 20 –

25°C. To the clear solution was added conc. HCl (0.31 g). The resulting suspension was stirred for 20h at 20 – 25°C. The suspension was heated to 35°C and maintained for 3h. The solid was filtered, washed with MTBE (2 x 5 ml) and dried at 65°C to afford 0.65 g hemi solvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with benzyl alcohol.

Example 5

1-[4-(5-Cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine (1 g) in benzyl alcohol (5 ml) was heated under inert gas atmosphere to 45°C. To the suspension was added HCl in isopropanol (0.55 g, 1.2 eq) followed by cooling to 20 – 25°C and stirring for about 20h. The suspension was heated to 35°C and maintained for 3 h. The solid was filtered, washed with MTBE (2 x 5 ml) and dried at 65°C to afford 0.94 g hemi solvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with benzyl alcohol.

Example 6

1-[4-(5-Cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine (1 g) was dissolved in a 1:1 mixture of DMF : benzyl alcohol (6 ml) under inert gas atmosphere at 20 – 25°C. To the clear solution was added HCl in isopropanol (0.55 g, 1.2 eq). The resulting suspension was stirred for about 20h at 20 – 25°C. The suspension was heated to 35°C and maintained for 3h. The solid was filtered, washed with MTBE (2 x 5 ml) and dried at 65°C to afford 0.9 g hemi solvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with benzyl alcohol.

Example 7

1-[4-(5-Cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine (1 g) was dissolved in a 1:1 mixture of benzyl alcohol : AcOH (6 ml) under inert gas atmosphere and heated to 45°C. To the clear solution was added HCl in isopropanol (0.83 g, 1.2 eq) and the mixture was gradually cooled to 20 – 25°C. The resulting suspension was stirred for about 20h. The suspension was heated

to 35°C and maintained for 3h. The solid was filtered, washed with MTBE (2 x 5 ml) and dried at 65°C to afford 0.95 g hemi solvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with benzyl alcohol.

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Example 8

1-[4-(5-Cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine (1 g) was dissolved in a 1:1 mixture of benzyl alcohol : DMF (6 ml) under inert gas atmosphere 20 – 25°C. To the clear solution was added HCl in isopropanol (0.49 g, 1.2 eq). The resulting suspension was stirred for about 20h at 20 – 25°C and heated to 30- 35°C and maintained for 3h. The solid was filtered, washed with 1-propanol (2 x 5 ml) and dried at 65°C to afford 0.98 g hemi solvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with benzyl alcohol.

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Example 9

1-[4-(5-Cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine (2 g) was dissolved in a 1:1 mixture of benzyl alcohol : DMF (6 ml) under inert gas atmosphere 20 – 25°C. To the clear solution was added HCl in isopropanol (0.98 g, 1.2 eq). The resulting suspension was stirred for about 20h at 20 – 25°C. The solid was filtered, washed with MTBE (2 x 10 ml) and dried at 65°C to afford 1.8 g hemi solvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with benzyl alcohol.

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Example 10

1-[4-(5-Cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine (4 g) in benzyl alcohol (36 ml) was heated to 35 – 40°C under inert gas atmosphere. The clear solution was filtered through microfiber paper and washed with benzyl alcohol (4 ml). The filtrate was stirred at 20 – 25°C for about 30 minutes. To the thin suspension was charged conc. HCl (0.91 g, 0.98 eq.) and a clear solution was obtained. Following stirring for about 10 minutes a thick

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suspension formed, which was allowed to stir at 20 – 25°C for 17 hours. The suspension was heated to about 95°C and stirred for about 6.5 hours whereupon the suspension became thin. The resulting suspension was cooled to 30 – 35°C and stirred for about 1 hour. The solid was filtered, washed with benzyl alcohol (8 ml) and MTBE (3 x 8 ml) and dried *in vacuo* at 35 – 40°C for about 3 hours to afford 4.5 g mono solvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with benzyl alcohol.

Example 11

1-[4-(5-Cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine (25 g) was suspended in benzyl alcohol (250 ml) under inert gas atmosphere. The resulting suspension was charged with conc. HCl (0.91 g, 0.98 eq.) and after addition a clear solution was obtained. Following stirring for about 10 minutes a thick suspension formed, which was allowed to stir at 20 – 25°C for 17 hours. The suspension was heated to about 95°C and stirred for about 5 hours whereupon the suspension became thin. The resulting suspension was cooled to 30 – 35°C and stirred for about 1 hour. The solid was filtered, washed with benzyl alcohol (50 ml) and MTBE (2 x 50 ml) and dried *in vacuo* at 20 – 25°C for about 3 hours to afford 31.5 g mono solvate of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride with benzyl alcohol.

Although various embodiments of the invention are disclosed herein, many adaptations and modifications may be made within the scope of the invention in accordance with the common general knowledge of those skilled in this art. Such modifications include the substitution of known equivalents for any aspect of the invention in order to achieve the same result in substantially the same way. Numeric ranges are inclusive of the numbers defining the range. Furthermore, numeric ranges are provided so that the range of values is recited in addition to the individual values within the recited range being specifically recited in the absence of the range. The word "comprising" is used herein as an

open-ended term, substantially equivalent to the phrase "including, but not limited to", and the word "comprises" has a corresponding meaning. As used herein, the singular forms "a", "an" and "the" include plural references unless the context clearly dictates otherwise. Thus, for example, reference to "a thing" includes more than one such thing. Citation of references herein is not an admission that such references are prior art to the present invention. Furthermore, material appearing in the background section of the specification is not an admission that such material is prior art to the invention. Any priority document(s) are incorporated herein by reference as if each individual priority document were specifically and individually indicated to be incorporated by reference herein and as though fully set forth herein. The invention includes all embodiments and variations substantially as hereinbefore described and with reference to the examples and drawings.

What is claimed is:

1. A crystalline benzyl alcohol solvate of vilazodone hydrochloride.
- 5 2. The crystalline benzyl alcohol solvate of vilazodone hydrochloride of claim 1 wherein the molar ratio of vilazodone hydrochloride to benzyl alcohol is approximately 1:0.5.
3. Form APO-I of vilazodone hydrochloride benzyl alcohol solvate.
- 10 4. The Form APO-I of vilazodone hydrochloride benzyl alcohol solvate of claim 3 characterized by a PXRD diffractogram comprising peaks, in terms of degrees 2-theta, at approximately 9.5, 10.6, 13.5, 15.6, 22.3, and 26.1.
- 15 5. The Form APO-I of vilazodone hydrochloride benzyl alcohol solvate of claim 3 characterized by a PXRD diffractogram comprising peaks, in terms of degrees 2-theta, at approximately 5.3, 9.5, 10.6, 11.2, 13.5, 14.6, 15.6, 17.5, 19.1, 20.5, 22.3, 24.5 and 26.1.
- 20 6. The Form APO-I of vilazodone hydrochloride benzyl alcohol solvate of claim 3 characterized by a PXRD diffractogram substantially similar to the PXRD diffractogram as depicted in Figure 1.
- 25 7. The Form APO-I of vilazodone hydrochloride benzyl alcohol solvate of claim 3 characterized by a PXRD diffractogram as depicted in Figure 1.
8. The Form APO-I of vilazodone hydrochloride benzyl alcohol solvate of any one of claims 3 to 7 characterized by a 1% KBr FTIR spectrum comprising peaks, in terms of cm^{-1} , at approximately 2216, 1676, 1607, 1579, 1443 and
30 1380.

9. The Form APO-I of vilazodone hydrochloride benzyl alcohol solvate of any one of claims 3 to 7 characterized by a 1% KBr FTIR spectrum comprising peaks, in terms of cm^{-1} , at approximately 3228, 2216, 1676, 1607, 1579, 1472, 1443 and 1380.

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10. The Form APO-I of vilazodone hydrochloride benzyl alcohol solvate of any one of claims 3 to 7 characterized by a FTIR spectrum substantially similar to the FTIR spectrum as depicted in Figure 2.

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11. The Form APO-I of vilazodone hydrochloride benzyl alcohol solvate of any one of claims 3 to 7 characterized by a FTIR spectrum as depicted in Figure 2.

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12. A pharmaceutical formulation comprising Form APO-I vilazodone hydrochloride benzyl alcohol solvate of any one of claims 3 to 11 and a pharmaceutically acceptable excipient.

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13. A process for preparation of vilazodone hydrochloride benzyl alcohol solvate, the process comprising:

- i. preparing a first APO-I-preparation-mixture of vilazodone free base and a first APO-I-preparation-solvent, the first APO-I-preparation-solvent comprising benzyl alcohol;
- ii. treating the first APO-I-preparation mixture with hydrochloric acid; and
- iii. crystallizing the benzyl alcohol solvate of vilazodone hydrochloride.

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14. The process for preparation of vilazodone hydrochloride benzyl alcohol solvate of claim 13 wherein the vilazodone hydrochloride benzyl alcohol solvate is Form APO-I.

15. The process for preparation of vilazodone hydrochloride benzyl alcohol solvate of claim 13 or 14 wherein the first APO-I-preparation-solvent further comprises dimethylformamide, acetic acid or mixtures thereof.

5 16. The process for preparation of vilazodone hydrochloride benzyl alcohol solvate of any one of claims 13 to 15 wherein the hydrochloric acid is provided as a solution in an organic solvent.

10 17. The process for preparation of vilazodone hydrochloride benzyl alcohol solvate of claim 16 wherein the organic solvent is isopropanol.

15 18. The process for preparation of vilazodone hydrochloride benzyl alcohol solvate of any one of claims 13 to 17 further comprising maintaining the crystallized benzyl alcohol solvate of vilazodone hydrochloride in a suspension at a temperature of about 30°C to about 40°C.

20 19. The crystalline benzyl alcohol solvate of vilazodone hydrochloride of claim 1 wherein the molar ratio of vilazodone hydrochloride to benzyl alcohol is approximately 1:1.

20. Form APO-II of vilazodone hydrochloride benzyl alcohol solvate.

25 21. The Form APO-II of vilazodone hydrochloride benzyl alcohol solvate of claim 20 characterized by a PXRD diffractogram comprising peaks, in terms of degrees 2-theta, at approximately 10.5, 13.3, 15.8, 19.5, 21.2 and 24.7.

30 22. The Form APO-II of vilazodone hydrochloride benzyl alcohol solvate of claim 20 characterized by a PXRD diffractogram comprising peaks, in terms of degrees 2-theta, at approximately 9.2, 10.5, 13.3, 15.8, 18.6, 19.5, 20.2, 21.2, 22.3, 23.3, 24.7 and 25.4.

23. The Form APO-II of vilazodone hydrochloride benzyl alcohol solvate of claim 20 characterized by a PXRD diffractogram substantially similar to the PXRD diffractogram as depicted in Figure 3.

5 24. The Form APO-II of vilazodone hydrochloride benzyl alcohol solvate of claim 20 characterized by a PXRD diffractogram as depicted in Figure 3.

10 25. The Form APO-II of vilazodone hydrochloride benzyl alcohol solvate of any one of claims 20 to 24 characterized by a 1% KBr FTIR spectrum comprising peaks, in terms of cm^{-1} , at approximately 3237, 2923, 2584, 2210, 1678, 1605, 1575, 1471, 1444, 1367 and 1231.

15 26. The Form APO-II of vilazodone hydrochloride benzyl alcohol solvate of any one of claims 20 to 24 characterized by a 1% KBr FTIR spectrum comprising peaks, in terms of cm^{-1} , at approximately 3237, 2584, 2210, 1678, 1605, 1575, 1367 and 1231.

20 27. The Form APO-II of vilazodone hydrochloride benzyl alcohol solvate of any one of claims 20 to 24 characterized by a FTIR spectrum substantially similar to the FTIR spectrum as depicted in Figure 4.

28. The Form APO-II of vilazodone hydrochloride benzyl alcohol solvate of any one of claims 20 to 24 characterized by a FTIR spectrum as depicted in Figure 4.

25 29. A pharmaceutical formulation comprising Form APO-II vilazodone hydrochloride benzyl alcohol solvate of any one of claims 20 to 28 and a pharmaceutically acceptable excipient.

30 30. A process for preparation of Form APO-II of vilazodone hydrochloride benzyl alcohol solvate, the process comprising:

- i. preparing a first APO-II-preparation-mixture of vilazodone free base and a first APO-II-preparation-solvent, the first APO-II-preparation-solvent comprising benzyl alcohol;
- ii. treating the first APO-II-preparation-mixture with hydrochloric acid to produce a second APO-II-preparation-mixture;
- iii. heating the second APO-II-preparation-mixture to a temperature of from about 80°C to about 100°C; and
- iv. crystallizing the Form APO-II vilazodone hydrochloride benzyl alcohol solvate.

31. The process for preparation of Form APO-II of vilazodone hydrochloride benzyl alcohol solvate of claim 30 wherein the first APO-II-preparation-solvent is selected from the group consisting of benzyl alcohol, dimethylformamide, acetic acid and mixtures thereof.

32. The process for preparation of Form APO-II of vilazodone hydrochloride benzyl alcohol solvate of claim 30 or 31 wherein the second APO-II-preparation-mixture is heated to a temperature of from about 90°C to about 100°C.

33. The process for preparation of Form APO-II of vilazodone hydrochloride benzyl alcohol solvate of any one of claims 30 to 32 further comprising maintaining the crystallized Form APO-II vilazodone hydrochloride benzyl alcohol solvate in a suspension at a temperature of from about 30°C to about 40°C.

34. A process for preparation of Form APO-II of vilazodone hydrochloride benzyl alcohol solvate comprising heating a third APO-II-preparation-mixture comprising Form APO-I of vilazodone hydrochloride benzyl alcohol solvate and benzyl alcohol to a temperature of from about 80 °C to about 100 °C.

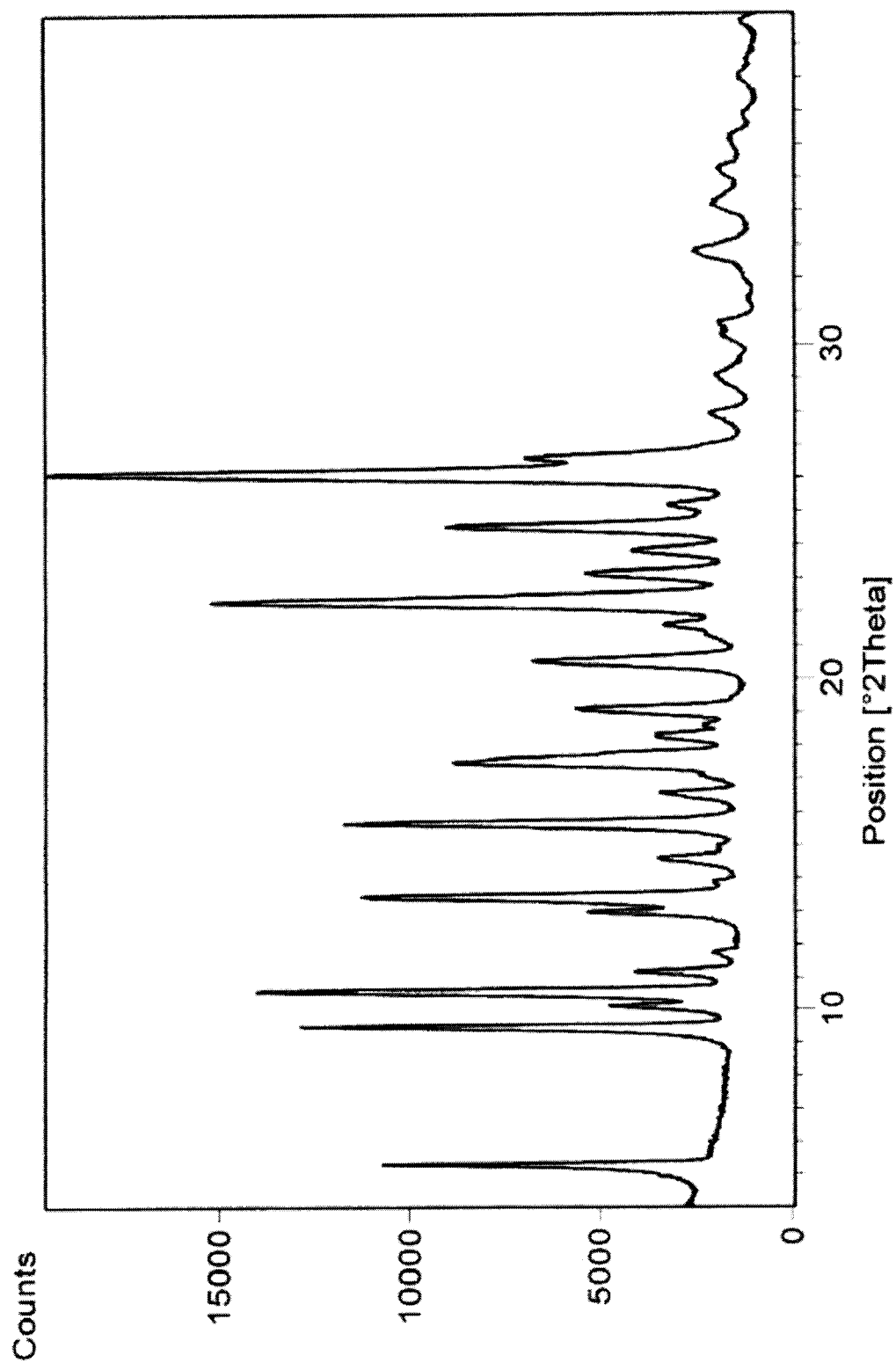
FIG. 1

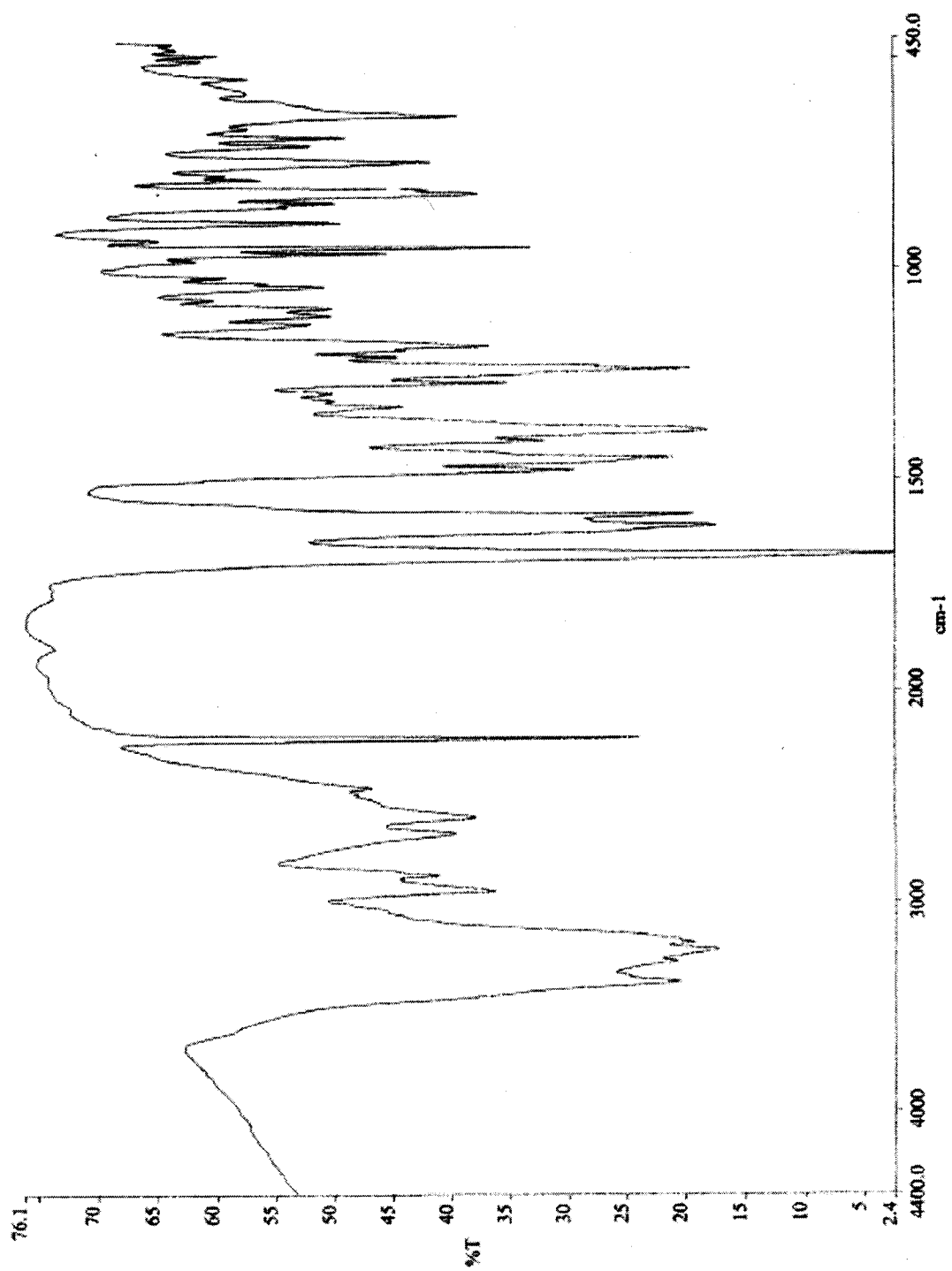
FIG. 2

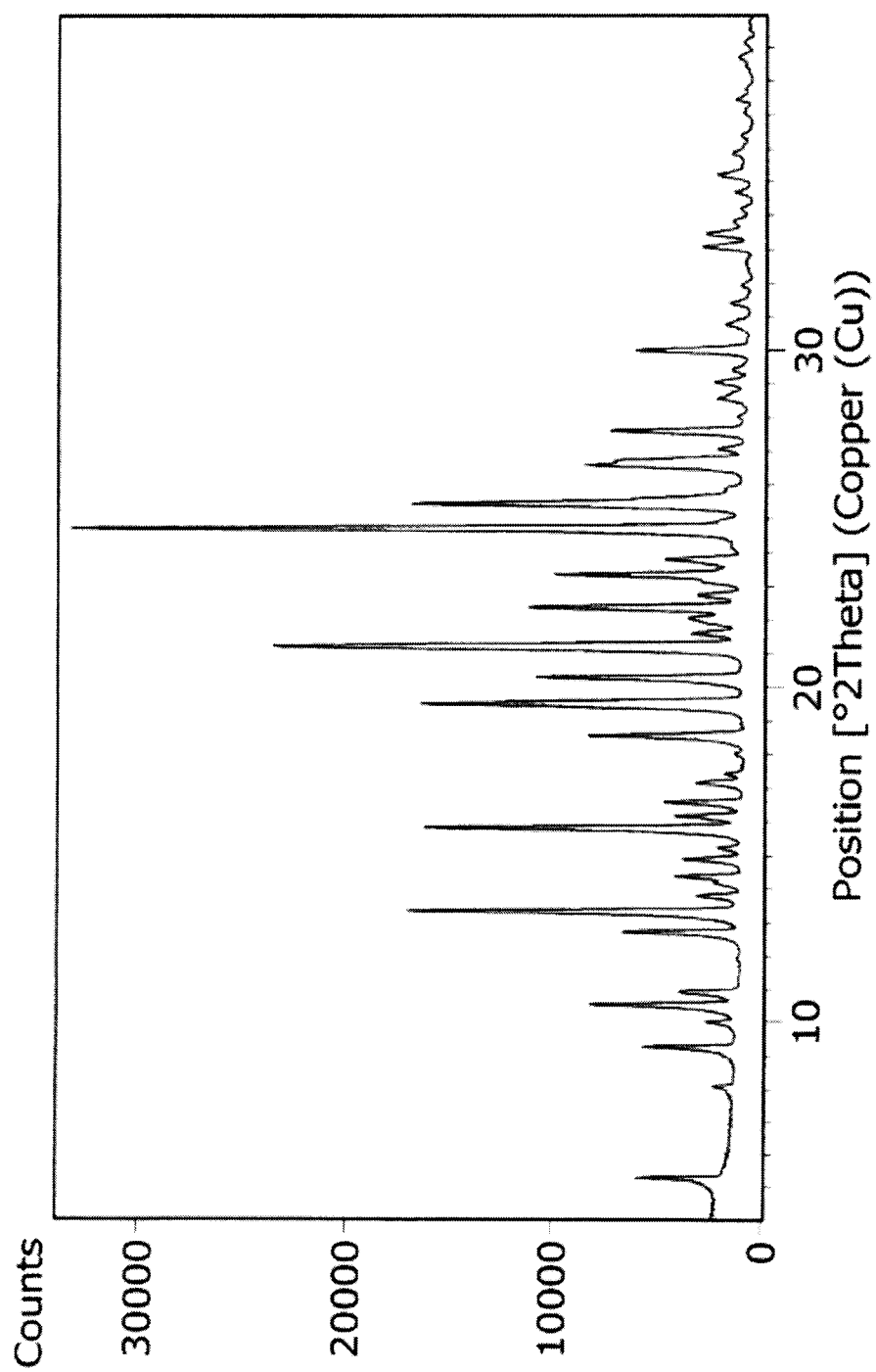
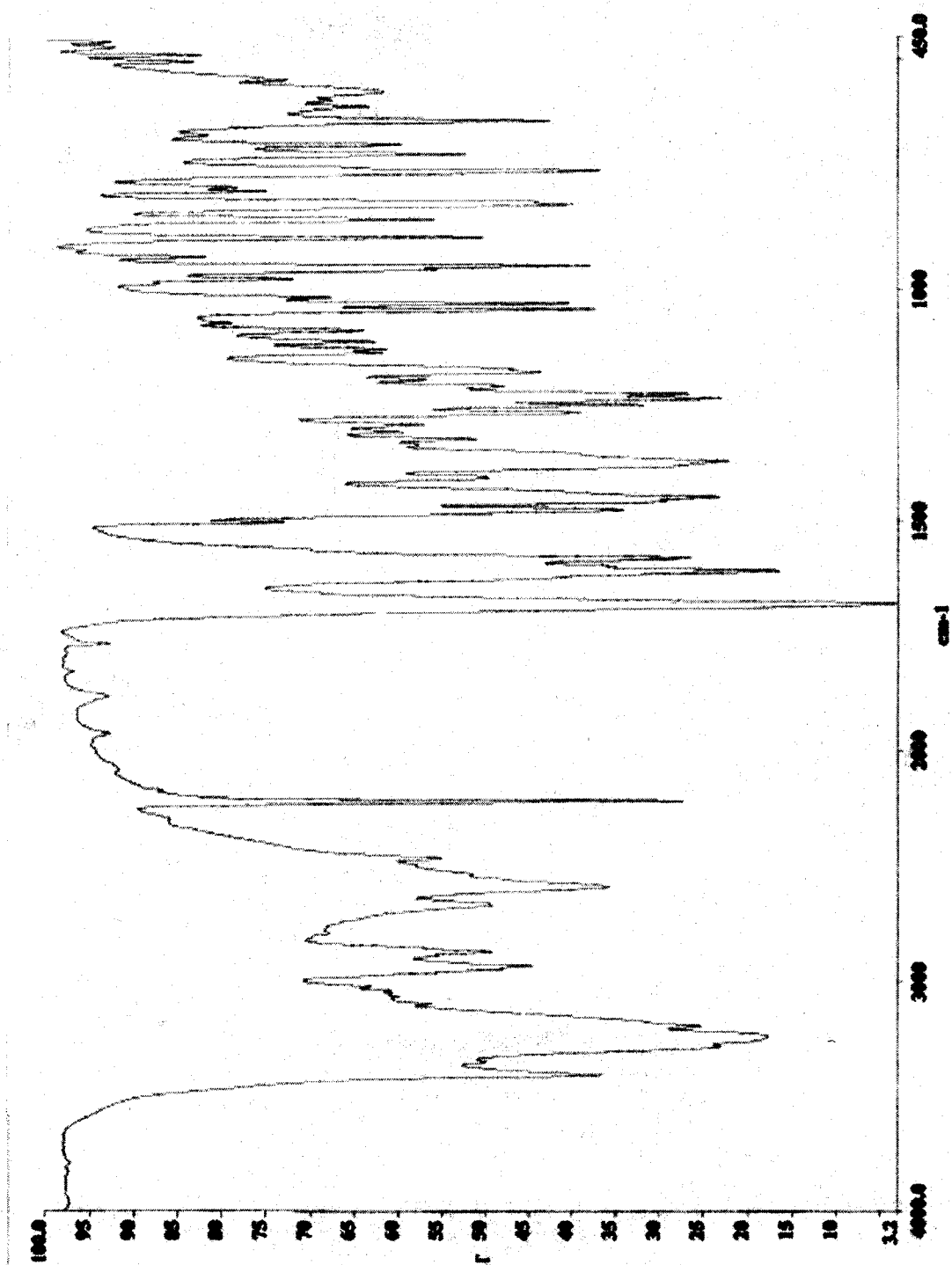
FIG. 3

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2013/000560

A. CLASSIFICATION OF SUBJECT MATTER

IPC: **C07D 405/12** (2006.01) , **A61K 31/496** (2006.01) , **A61P 25/24** (2006.01)

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)

IPC: **C07D 405/12** (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
STN, LexisNexis® TotalPatent, Canadian Patent Database [Keywords: vilazodone, solvate, benzyl alcohol]

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO02/102794, BATHE et al., 27 December 2002 (27-12-2002) (see the whole document and in particular page 2, lines 18-31; page 5, line 27 to page 6 line 30; and example 5 at page 29) -fam. member US7834020 cited in this application-	1-34
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A	US2007/0099933, HEINRICH et al., 3 May 2007 (03-05-2007) (see the whole document and in particular par. [0033], [0034],[0037], [0065])	1-34

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

☒ See patent family annex.

* Special categories of cited documents :	"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
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Date of the actual completion of the international search

16 September 2013 (16-09-2013)

Date of mailing of the international search report

11 October 2013 (11-10-2013)

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2013/000560

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