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(54) Title: PROCESS FOR PREPARING FORM I OF RIMONABANT

(57) Abstract: The present invention describes new process for the preparation of Form I of Rimonabant through the intermediate formation of the corresponding acid addition salt.



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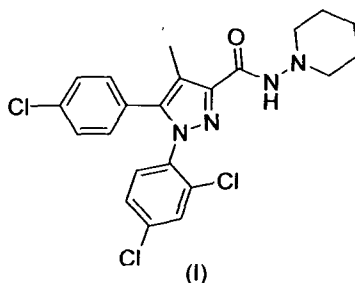
PROCESS FOR PREPARING FORM I OF RIMONABANT**FIELD OF THE INVENTION**

The present invention describes new process for the preparation of Form I of Rimonabant.

5 BACKGROUND OF THE INVENTION

Obese patients are at higher risk for coronary artery disease, hypertension, hyperlipidemia, and diabetes mellitus, among other diseases and thus their risk of morbidity and mortality increases. Due to many complex pathophysiological components which lead to obesity, the disease remains a challenging and significant clinical problem. Cannabinoids acting via cannabinoid receptors stimulate food intake and a particularly attractive antiobesity target is the cannabinoid CB₁ receptor, which has also been shown to play a role in reinforcing reward. (*I.A. Sorbera et al., Drugs of Future 2005; 30(2): 128-137*). Rimonabant has been approved in Europe for the treatment of obesity. The agent also exhibited efficacy in phase III clinical trials and hold promise in the treatment of smoking cessation.

Rimonabant is 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)pyrazole-3-carboxamide, having structural formula I.



It is developed by Sanofi, as a CB₁ antagonist, as a potential treatment for obesity, smoking cessation, Alzheimer's disease, Parkinson's disease etc. This compound is disclosed in EP 0656354 which is incorporated by reference in their entirety.

The therapeutic applications of Rimonabant has been described in US 6344474, US 6642258, WO 0158450, WO 0185092, WO 0318060, WO 0382256 etc. which are also incorporated in their entirety as reference.

WO 03040105 (Sanofi) discloses one new crystalline form of Rimonabant designating it as Form II, which also states the earlier form disclosed in EP 0656354 is the Form I. It also states that the new form, Form II can be obtained by particular crystallization conditions, and the Form II is more stable than the Form I. This

application also differentiates the Form II from the earlier disclosed Form I through difference in XRD & IR data. The application also described that the Form II can be obtained from the Form I by dissolving Form I in suitable solvent like methyl cyclohexane containing 1-10 % water or acetonitrile or acetone etc. in the hot state and subsequently cooling the mixture to obtain the crystals of Form II. This application is also hereby incorporated as reference in its entirety.

Recently, crystalline forms III, IV, V and an amorphous form of Rimonabant was disclosed in EP 1816125. US 20080070949 (Cipla) discloses new polymorphic form, Form C of Rimonabant as well as the amorphous form.

The process for preparing Form I of Rimonabant as disclosed in EP 0656354, involves crystallization from either isopropyl ether or by cooling of a medium containing the product in methyl cyclohexane. As can be very well appreciated by any person skilled in the art, use of both the solvents is not very viable commercially, isopropyl ether for its flammable properties and methyl cyclohexane for its cost as well as difficulty in handling in commercial scale, due to electrostatic charge formation and consequent ignition.

Therefore, there is a need to develop an alternate process for preparing the Form I of Rimonabant which is cheap, commercially viable and uses as little solvents as possible. We herein below disclose such a process.

EMBODIMENTS OF THE INVENTION

Accordingly, the present invention provides new process for preparing Form I of Rimonabant.

In an embodiment is provided a process for preparing Form I which is cheap, commercially viable and uses minimum amount of solvent.

The above and other embodiments are described in more details below.

DESCRIPTION OF FIGURE

Figure 1: IR peaks of Rimonabant Form I prepared according to the invention.

Figure 2: XRD peaks of Rimonabant Form I prepared according to the invention.

DESCRIPTION OF INVENTION

The present invention thus provides an improved process for preparing Form I of Rimonabant.

The process according to the present invention involves following steps.

(1) converting Rimonabant base (Forms II, III, IV-VI, amorphous, solvated, hydrated etc.) into acid addition salt of Rimonabant, using a suitable acid in suitable solvents

and or water; The reaction temperature is preferably maintained at 25-100 °C; preferably the solvent used are water miscible solvents;

(2) adding the reaction mixture to a suitable base, optionally in suitable solvent and or water at 25-100 °C; preferably, the solvents used are water miscible solvents

5 Suitable salts which can be prepared from the Rimonabant includes but are not limited to suitable inorganic salts such as halides, nitrates, sulfates, bisulfates, phosphates, hexafluorophosphates and the like; organic salts such as oxalate, maleate, succinate, fumarate, tartarate, sulfonates such as mesylate, besylate, tosylate, triflate, trifluoroacetate, perchlorate, benzoates, napsylates and the like; borates such as
10 tetrafluoroborate, tetraphenylborate; antimonates such as hexafluoroantimonate and the like.

Suitable solvents which can be used in either step (1) or (2) above may be independently selected from water or suitable water miscible solvents such as suitable alcohols, ethers, suitable ketones, DMF, DMSO and the like or their suitable mixtures.

15 Suitable alcohols may be selected from (C₁-C₆)alcohols such as methanol, ethanol, isopropanol, butanol and the like; suitable ethers may be (C₁-C₆) ethers such as dimethyl ether, diethyl ether, methyl ethyl ether and the like dioxane, tetrahydrofuran; suitable ketones may be selected from (C₁-C₄) ketones such as dimethyl ketone, methyl ethyl ketone and the like;

20 Suitable bases may be selected from alkali or alkaline earth metal carbonates, bicarbonates or alkali metal hydroxides, ammonia, organic bases such as triethyl amine, pyridine and the like. The base is preferably taken in excess.

The base thus obtained was cooled gradually, filtered and washed with water and dried to obtain Rimonabant Form I. The Rimonabant Form 1 obtained by the
25 process of the present invention has residual solvents less than 1%, preferably less than 0.5%

The process is described below by the following non-limiting examples, which are provided for illustrative purposes only. It is well appreciated that suitable variations, alterations etc. may be carried out by persons skilled in the art to further optimize the
30 processes of the present invention as disclosed hereinafter, and such modifications/alterations are to be construed as being a part of the present invention. Therefore, these examples should not be construed to limit the scope of the invention in any way.

Example 1

Preparation of Form I of Rimonabant

i) Preparation of Rimonabant Hydrochloride

Crystalline Rimonabant (15 gm) was dissolved in ethyl acetate (100 ml) and stirred at 25-30 °C. To the reaction mass HCl gas dissolved in methanol was added drop wise at room temperature until the pH of the reaction mixture was 2-3. The resulting precipitate was stirred at 25-30 °C for 1 hours and filtered. The solid was washed with ethyl acetate and dried under vacuum at 55-60 °C to obtain Rimonabant hydrochloride (14 gm)

ii) Preparation of Rimonabant form I

Rimonabant hydrochloride (10 gm) obtained above was suspended in water (15 ml) at 50-100 °C. In another flask a solution of Potassium carbonate (0.5 gm) in 10 ml of water was prepared at 50-100 °C. To the flask containing potassium carbonate was added the suspension of the Rimonabant hydrochloride and further stirred for half an hour. The mixture was gradually cooled to room temperature. It was filtered, and washed with water, dried till constant weight when 9.0 g Rimonabant form-1 was obtained.

Melting point: 155-157 °C

The crystalline polymorph Form I of Rimonabant is characterized by X-ray diffraction pattern with 2θ peaks (±0.2°) at about, 9.181, 10.757, 11.7, 12.319, 13.078, 14.081, 16.120, 16.400, 16.840, 17.861, 18.439, 18.961, 19.420, 20.239, 20.719, 21.280, 22.118, 22.841, 23.860, 24.860, 25.299, 26.160, 27.239, 27.763, 28.520, 30.501, 33.518, 34.080, 35.598, 35.800, 38.761.

The IR peaks are provided in Figure 1 and matches well with those disclosed in prior art.

Example 2

i) Preparation of Rimonabant Hydrochloride:-

Crystalline Rimonabant (10 gm) was dissolved in ethyl acetate (100 ml) and stirred at 25-30 °C. To the reaction mass HCl gas dissolved in isopropyl alcohol was added drop wise at room temperature until the pH of the reaction mass was 2-3. The resulting precipitate was stirred at 25-30 °C for 2 hours and filtered. The solid was washed with ethyl acetate and dried under vacuum at 55-60 °C to obtain Rimonabant hydrochloride (10 gm).

The crystalline Rimonabant hydrochloride obtained was characterized by X-ray diffraction pattern with 2θ peaks (±0.2°) at about 9.559, 10.379, 11.681, 13.079,

13.699, 14.400, 14.721, 15.121, 15.602, 16.520, 17.119, 17.701, 18.242, 18.500, 19.140, 20.761, 21.340, 21.741, 22.160, 23.540, 24.139, 24.420, 25.301, 25.760, 26.439, 26.839, 27.220, 28.500, 29.680, 30.520, 35.061, 39.101.

M.P.: 238-245 °C

5 ii) Preparation of Rimonabant form I:-

Rimonabant hydrochloride (10 gm) was suspended in water (15 ml) at 50-100 °C. While in other flask was taken Potassium carbonate (0.5 gm) in 10 ml of water at 50-100 °C. To this flask, added the suspension of the Rimonabant hydrochloride and further stirred for half an hour. Gradually cooled to room temperature. The precipitate
10 was filtered and washed with water. Dried the filtrate till constant weight was obtained. Melting point: 155-157 °C; DSC: Onset Peak: 154.7°C-156.3 °C;

The Rimonabant Form I prepared was characterised by X-ray diffraction pattern with 2θ peaks (±0.2°) at about 9.181,10.757,11.7,12.319,13.078, 14.081, 16.120, 16.400, 16.840, 17.861, 18.439, 18.961, 19.420,20.239, 20.719, 21.280, 22.118,
15 22.841, 23.860, 24.860, 25.299, 26.160, 27.239, 27.763, 28.520, 30.501, 33.518, 34.080, 35.598, 35.800, 38.761.

Example 3

i) Preparation of Rimonabant Sulphate:-

Sulfuric acid (2.11 gm) was dissolved in methanol (50 ml) & to it was then
20 charged 10 gm of Rimonabant and stirred at 25-30 °C, till a clear solution was obtained. Distilled off the solvent in a rota vapour under vacuum and removed the traces of the solvent at 55-60 °C to obtain Rimonabant sulphate (11.6 gm).

Melting point: 115-120 °C

XRD: Amorphous pattern.

25 ii) Preparation of Rimonabant form I:-

Rimonabant sulphate (10 gm) was suspended in water (15 ml) at 50-100 °C. In another flask Potassium carbonate (0.5 gm) was dissolved in 10 ml of water at 50-100 °C. To this flask was added the suspension of the Rimonabant sulphate and further stirred for half an hour, & then gradually cooled to room temperature. The solution was
30 filtered, washed with water & dried to constant weight to obtain Form I of Rimonabant. XRD, DSC, IR matches with those reported.

Example 4

i) Preparation of Rimonabant Phosphate:-

Orthophosphoric acid (1.24 gm) was dissolved in methanol (50 ml) and to it was then charged 10 gm of Rimonabant and stirred at 25-30 °C to get clear solution. Distilled off the solvent on a rota vapour under vacuum and removed traces of the solvent at 55-60 °C to obtain Rimonabant phosphate (12.2 gm).

5 Melting point: 168-172 °C

The Rimonabant phosphate is characterized by X-ray diffraction pattern with 20 peaks ($\pm 0.2^\circ$) at about 5.501, 9.459, 10.640, 11.660, 12.860, 13.679, 15.440, 16.330, 17.161, 17.939, 19.319, 21.359, 22.480, 23.039, 23.754, 25.460, 26.261, 27.341, 29.640, 30.680, 31.161, 34.038, 34.719.

10 ii) Preparation of Rimonabant form I:-

Rimonabant phosphate (10 gm) was suspended in water (15 ml) at 50-100 °C, while in another flask Potassium carbonate (0.5 gm) was dissolved in 10 ml of water at 50-100 °C. To this flask was added the suspension of Rimonabant phosphate and further stirred for half an hour. The mixture was gradually cooled to room temperature,
15 filtered, washed with water & Dried to constant weight, to obtain the form I of Rimonabant.

XRD, DSC, IR matches with those reported.

Example 5

Preparation of Rimonabant form I:-

20 Crystalline Rimonabant (10 gm) was suspended in methanol (100 ml) and stirred at 25-30 °C. To the reaction mass added conc. HCl (1 ml) at room temperature & stirred at 55-60 °C to get a clear solution. Clear light yellow colored solution was observed. In another flask, a solution of Sodium carbonate (12 gm) in 10 ml of water was prepared at 50-100 °C. To this flask was added the solution of Rimonabant
25 hydrochloride and further stirred for half an hour. The mixture was gradually cooled to room temperature, filtered and washed with water. The residue was dried to constant weight to obtain form I of Rimonabant.

XRD, DSC, IR matches with those reported.

Example 6

30 Preparation of Rimonabant form I:-

Crystalline Rimonabant (10 gm) was suspended in ethanol (100 ml) and stirred at 25-30 °C. To the reaction mass was added conc. HCl (1 ml) at room temperature. The mixture was stirred at 55-60 °C to get clear solution. In another flask was dissolved sodium bicarbonate (12 gm) in 10 ml of water at 50-100 °C. To this flask, added the

suspension of Rimonabant hydrochloride and further stirred for half an hour, & slowly cooled to room temperature. The mixture was filtered, washed with water & dried to constant weight to obtain form I of Rimonabant.

XRD, DSC, IR matches with those reported.

5 **Example 7**

Preparation of Rimonabant form I:-

To a stirred suspension of crystalline Rimonabant (10 gm) in isopropanol (100 ml) at 25-30 °C was added conc. Sulfuric acid (2.11 gm) and stirred at 55-60 °C to get clear solution. In another flask Sodium hydroxide (12 gm) was dissolved in 10 ml of
10 water at 50-100 °C. To this flask was added the solution of the Rimonabant sulfate and further stirred for half an hour. The mixture was gradually cooled to room temperature, filtered, & washed with water. The residue was dried to constant weight to obtain form I of Rimonabant.

XRD, DSC, IR matches with those reported.

15 **Example 7**

Preparation of Rimonabant form I:-

Crystalline Rimonabant (10 gm) was suspended in acetone (100 ml) and stirred at 25-30 °C. To the reaction mass was added conc. HCl (1 ml) at room temperature & stirred at 55-60 °C to get a clear solution. In another flask potassium hydroxide (12 gm)
20 was dissolved in 10 ml of water and warmed to 50-100 °C. To this flask was added the solution of Rimonabant hydrochloride and further stirred for half an hour. The solution was gradually cooled to room temperature, filtered and washed with water. The residue was dried to constant weight to obtain form I of Rimonabant.

XRD, DSC, IR matches with those reported.

25 **Example 8**

Preparation of Rimonabant form I:-

Crystalline Rimonabant (10 gm) was suspended in THF (100 ml) and stirred at 25-30 °C. To the reaction mass was added conc. HCl (1 ml) and further stirred at 55-60 °C to get a clear solution In another flask potassium bicarbonate (12 gm) in 10 ml of
30 water was dissolved at 50-100 °C. To this flask, was added the solution of the Rimonabant hydrochloride and further stirred for half an hour. The mixture was gradually cooled to room temperature, filtered and washed with water. The residue was dried to constant weight to obtain form I of Rimonabant.

XRD, DSC, IR matches with those reported.

Example 9**Preparation of Rimonabant form I:-**

Conc. HCl (1 ml) was added to crystalline rimonabant (10 gm) in Methanol (100 ml) and stirred at 25-30 °C. Further stirred it at 55-60 °C to get clear solution. In another flask aqueous ammonia solution (12 gm) was taken in 10 ml of water and warmed at 50-100 °C. To this flask, added the solution of Rimonabant hydrochloride and further stirred for half an hour. The solution was gradually cooled to room temperature, filtered and washed with water. The residue was dried to constant weight to obtain form I of Rimonabant.

XRD, DSC, IR matches with those reported.

Following a similar process as above, Rimonabant form I was obtained from Rimonabant sulphate & Rimonabant phosphate.

Example 10**Preparation of Rimonabant form I:-**

Crystalline Rimonabant (10 gm) was suspended in water (100 ml) and stirred at 25-30 °C. To the reaction mass was added conc. HCl (1 ml) at room temperature and further stirred at 55-100 °C. In another flask sodium carbonate (12 gm) was dissolved in 70 ml of water at 50-100 °C. To this was added the suspension of Rimonabant hydrochloride and further stirred for half an hour. The solution was gradually cooled to room temperature, filtered, washed with water. The residue was dried to constant weight to obtain form I of Rimonabant.

XRD, DSC, IR matches with those reported.

Example 11**Preparation of Rimonabant form I:-**

Crystalline Rimonabant (10 gm) was suspended in water (100 ml) and stirred at 25-30 °C. To the reaction mass was added conc. HCl (1 ml) at room temperature & stirred at 55-100 °C. In another flask sodium bicarbonate (8 gm) in 60 ml water was warmed to 50-100 °C. To this flask was added the suspension of Rimonabant hydrochloride and further stirred for half an hour. The solution was slowly cooled to room temperature and filtered, washed with water & residue dried to constant weight to obtain form I of Rimonabant.

XRD, DSC, IR matches with those reported.

Example 12**Preparation of Rimonabant form I:-**

Crystalline Rimonabant (10 gm) was suspended in water (100 ml) and stirred at 25-30 °C. To the suspension was added conc. HCl (1 ml) & stirred at 55-100 °C. In another flask Sodium hydroxide (9 gm) was dissolved in 50 ml of water at 50-100 °C. To this flask was added the suspension of the Rimonabant hydrochloride and further stirred for half an hour. The solution was gradually cooled to room temperature. The separated solid was filtered, washed with water and dried till constant weight, to obtain form I of Rimonabant.

XRD, DSC, IR matches with those reported.

Example 13

Preparation of Rimonabant form I:-

To a stirred suspension of crystalline Rimonabant (10 gm) in water (100 ml) at 25-30 °C was added conc. Sulfuric acid (2.11 gm) at room temperature & further stirred at 55-100 °C. In another flask Potassium hydroxide (12 gm) was dissolved in 100 ml of water at 50-100 °C. To this flask was added the suspension of Rimonabant sulphate and further stirred for half an hour, slowly cooled to room temperature, filtered & washed with water. The residue was dried to constant weight to obtain form I of Rimonabant.

XRD, DSC, IR matches with those reported.

Example 14

Preparation of Rimonabant form I:-

Crystalline Rimonabant (10 gm) was suspended in water (100 ml) and stirred at 25-30 °C. To the reaction mass was added conc. HCl (1 ml) and further stirred at 40-70 °C. In another flask Potassium bicarbonate (10 gm) was dissolved in 80 ml of water at 50-100 °C. To this flask was added the suspension of the Rimonabant hydrochloride and further stirred for half an hour. The mixture was gradually cooled to room temperature, filtered, washed with water & dried to constant weight to obtain form I of Rimonabant.

XRD, DSC, IR matches with those reported.

Example 15

Preparation of Rimonabant form I:-

To a stirred suspension of Rimonabant (10 gm) in water (100 ml) at 25-30 °C. was added conc. HCl (1 ml) and further stirred it at 40-100 °C. In another flask an aqueous ammonia solution (12 gm) in 10 ml of water was warmed to 50-100 °C. To this flask was added the suspension of Rimonabant hydrochloride and further stirred for

half an hour. The mixture was gradually cooled to room temperature, filtered & washed with water. The residue was dried to constant weight to obtain form I of Rimonabant. XRD, DSC, IR matches with those reported.

By processes similar to above, Rimonabant form I was obtained from

- 5 Rimonabant sulphate, phosphate etc.

Example 16

i) Preparation of Rimonabant Oxalate:-

Crystalline Oxalic acid (1.3 gm) was dissolved in methanol (100 ml) and stirred at 25-30 °C to get a clear solution. To the solution was added Rimonabant (10 gm) and
10 stirred to get a clear solution. The solvent was distilled over Rota vapour under vacuum at 50-55 °C to obtain Rimonabant oxalate (10.5 gm).

The crystalline oxalate salt of Rimonabant was characterized by X-ray diffraction pattern with 2θ peaks (±0.2°) at about, 5.641, 8.742, 10.041, 11.322, 11.860, 12.519, 15.419, 17.039, 18.139, 18.739, 19.600, 20.200, 21.061, 21.620, 21.979,
15 22.339, 22.920, 23.740, 23.979, 24.460, 25.001, 27.660, 28.500, 31.142, 31.421, 32.061, 32.401.

M.P.: 205-205 °C

ii) Preparation of Rimonabant form I:-

Rimonabant oxalate (10 gm) was suspended in water (15 ml) at 50-100 °C.
20 While in other flask a solution of potassium carbonate (11 gm) in 50 ml of water was warmed to 50-100 °C. To this flask was added the suspension of the Rimonabant oxalate and further stirred for half an hour. The mixture was gradually cooled to room temperature, filtered, washed with water and dried till constant weight, to obtain form I of Rimonabant.

25 XRD, DSC, IR matches with those reported.

Example 17

i) Preparation of Rimonabant Maleate:-

Crystalline maleic acid (1.25 gm) was dissolved in acetone (100 ml) and stirred at 25-30 °C to get a clear solution, Rimonabant (10 gm) was added to the solution. The
30 clear solution was stirred for half an hour at room temperature and solvent distilled off on a Rota vapour under vacuum at 50-55 °C to obtain Rimonabant maleate (10.7 gm).

The crystalline maleate salt of Rimonabant was characterized by X-ray diffraction pattern with 2θ peaks (±0.2°) at about, 9.400, 10.521, 11.962, 13.698, 15.021, 13.698, 15.021, 16.040, 17.139, 17.860, 18.277, 19.139, 19.721, 20.377,

20.880, 21.284, 21.662, 22.458, 22.983, 23.979, 24.741, 25.319, 26.101, 26.878, 27.360, 27.719, 29.640, 31.581, 33.039, 33.922.

M.P.: 63-67 °C

ii) Preparation of Rimonabant form I:-

5 Rimonabant maleate (10 gm) was suspended in water (15 ml) at 50-100 °C. While in another flask, a solution of sodium carbonate (11 gm) in 50 ml of water was warmed to 50-100 °C. To this flask was added the suspension of the Rimonabant maleate and further stirred for half an hour. The mixture was gradually cooled to room temperature, filtered, washed with water and dried till constant weight, to obtain form I
10 of Rimonabant.

XRD, DSC, IR matches with those reported.

Residual solvent:<1%

Example 18

i) Preparation of Rimonabant Succinate:-

15 Crystalline Succinic acid (1.25 gm) was dissolved in isopropanol (100 ml) and stirred at 25-30 °C to get a clear solution. To the solution was added Rimonabant (10 gm) at room temperature until the pH of the reaction mass was 2-3. The solvent was distilled over Rota vapour under vacuum at 50-55 °C to obtain Rimonabant succinate (10.7 gm)

20 The crystalline succinate salt of Rimonabant was characterized by X-ray diffraction pattern with 2θ peaks (±0.2°) at about, 7.161, 9.239, 10.420, 13.420, 14.400, 15.180, 16.021, 17.019, 17.700, 18.899, 19.921, 20.701, 21.099, 22.360, 22.801, 23.579, 24.520, 26.019, 27.159, 29.061, 29.380, 30.483, 31.401, 33.760, 34.398, 34.596, 37.940, 38.399.

25 M.P.: 105-108 °C

ii) Preparation of Rimonabant form I:-

 Rimonabant succinate (10 gm) was suspended in water (15 ml) at 50-100 °C. While in another flask Sodium bicarbonate (11 gm) in 50 ml of water was warmed to 50-100 °C. To this flask was added the suspension of the Rimonabant succinate and
30 further stirred for half an hour. The mixture was gradually cooled to room temperature, filtered, washed with water and dried till constant weight, to obtain form I of Rimonabant.

XRD, DSC, IR matches with those reported.

Residual solvent:<1%

Example 19**i) Preparation of Rimonabant Fumarate:-**

Crystalline Fumaric acid (1.25 gm) was dissolved in absolute alcohol (100 ml) and stirred at 25-30 °C to get clear solution. To the solution was added Rimonabant (10 gm) at room temperature until the pH of the reaction mass was 2-3. The solvent was distilled over Rota vapour under vacuum at 50-55 °C to obtain Rimonabant fumarate (12 gm)

The crystalline fumarate salt of Rimonabant was characterized by X-ray diffraction pattern with 2θ peaks (±0.2°) at about, 7.200, 9.200, 10.400, 13.420, 14.399, 15.140, 16.001, 16.940, 17.660, 18.981, 19.500, 20.180, 20.679, 21.060, 21.439, 22.340, 22.720, 23.580, 24.500, 25.141, 27.100, 28.679, 29.339, 30.521.

M.P.: 106-108 °C

ii) Preparation of Rimonabant form I:-

Rimonabant fumarate (10 gm) was suspended in water (80 ml) at 50-100 °C. In another flask Sodium hydroxide (6 gm) in 50 ml of water was warmed to 50-100 °C. To this flask was added the suspension of the Rimonabant fumarate and further stirred. The mixture was slowly cooled to room temperature, filtered, washed with water and dried till constant weight, to obtain form I of Rimonabant.

XRD, DSC, IR matches with those reported.

Residual solvent:<1%

Example 20**i) Preparation of Rimonabant Tartarate:-**

Tartaric acid (1.6 gm) was dissolved in THF (80 ml) and stirred at 25-30 °C to get clear solution. To this solution was added Rimonabant (10 gm) at room temperature until the pH of the reaction mass was 2-3. The solvent was distilled over Rota vapour under vacuum at 50-55 °C to obtain Rimonabant tartarate (12 gm)

The crystalline tartarate salt of Rimonabant was characterized by X-ray diffraction pattern with 2θ peaks (±0.2°) at about, 6.579, 9.280, 9.579, 10.442, 11.161, 13.159, 13.500, 14.280, 15.240, 16.119, 16.921, 17.760, 18.819, 19.199, 20.899, 21.320, 22.020, 22.400, 24.001, 24.540, 25.619, 26.035, 27.100, 30.879, 31.939, 32.760, 33.300, 33.960, 35.401.

M.P.: 83-86 °C

ii) Preparation of Rimonabant form I:-

Rimonabant tartarate (10 gm) was suspended in water (50 ml) at 50-100 °C. In another flask potassium hydroxide (6 gm) in 50 ml was warmed to 50-100 °C. To this flask was added the suspension of the Rimonabant tartarate and further stirred for half an hour. The mixture was gradually cooled to room temperature and filtered, washed with water and dried till constant weight, to obtain form I of Rimonabant. XRD, DSC, IR matches with those reported.

Example 21

Preparation of Rimonabant form I:-

Crystalline oxalic acid (1.3 gm) was dissolved in methanol (100 ml) and stirred at 25-30 °C. To the solution was added crystalline Rimonabant (10 gm) at room temperature & stirred at 55-60 °C to get a clear solution. In other flask Sodium carbonate (12 gm) was dissolved in 100 ml of water at 50-100 °C. To this flask was added the solution of the Rimonabant oxalate and further stirred for half an hour. The mixture was gradually cooled to room temperature and filtered, washed with water and dried till constant weight, to obtain form I of Rimonabant. XRD, DSC, IR matches with those reported.

Example 22

Preparation of Rimonabant form I:-

Crystalline oxalic acid (1.3 gm) was dissolved in absolute alcohol (80 ml) and stirred at 25-30 °C. To the solution Rimonabant (10 gm) was added at room temperature and further stirred at 55-60 °C to get a clear solution. In another flask Potassium carbonate (11 gm) was dissolved in 90 ml of water and warmed at 50-100 °C. To this flask was added the solution of the Rimonabant oxalate and further stirred for half an hour. The mixture was gradually cooled to room temperature, filtered and washed with water. The residue was dried to constant weight to obtain form I of Rimonabant. XRD, DSC, IR matches with those reported.

Example 23

Preparation of Rimonabant form I:-

Crystalline oxalic acid (1.3 gm) was dissolved in acetone (60 ml) and stirred at 25-30 °C. To the clear solution was added Rimonabant (10 gm) at room temperature. The mixture was stirred at 55-60 °C to get clear solution. In another flask Potassium hydroxide (7 gm) in 90 ml of water was warmed to 50-100 °C. To this solution was added the solution of Rimonabant oxalate and further stirred for half an hour. The

mixture was gradually cooled to room temperature, filtered, washed with water & dried till constant weight to obtain form I of Rimonabant.

XRD, DSC, IR matches with those reported.

Example 24

5 Preparation of Rimonabant form I:-

Crystalline oxalic acid (1.3 gm) was dissolved in Isopropanol (80 ml) and stirred at 25-30 °C. Rimonabant (10 gm) was added and further stirred it at 55-60 °C to get clear solution. In another flask Sodium hydroxide (8 gm) in 90 ml of water was warmed to 50-100 °C. To this solution was added the solution of the Rimonabant oxalate and further stirred for half an hour. The mixture was gradually cooled to room temperature, filtered, washed with water and dried till constant weight, to obtain form I of Rimonabant.

XRD, DSC, IR matches with those reported.

Example 25

15 Preparation of Rimonabant form I:-

Crystalline oxalic acid (1.3 gm) was dissolved in THF (90 ml) and stirred at 25-30 °C. To this solution Rimonabant (10 gm) was added at room temperature and further stirred at 55-60 °C to get a clear solution. In other flask aqueous ammonia solution (10 gm) in 90 ml warmed to 50-100 °C. To this flask was added the solution of the Rimonabant oxalate and further stirred for half an hour. The solution was slowly cooled to room temperature, filtered, washed with water and dried till constant weight, to obtain form I of Rimonabant.

XRD, DSC, IR matches with those reported.

By processes similar to those described above, Rimonabant form I may be obtained from Rimonabant maleate, succinate, tartarate, fumarate, sulfonates, triflate, trifluoroacetate, perchlorate, benzoate, napsylate, borates, antimonates etc.

Benefits of the process of the present invention:

1. The process is scalable and does not use any difficult solvents like ethers or cyclohexane;
2. The process is economical as the solvents used are either water or low cost commercially viable solvents;
3. The product obtained (Form I) is stable and obtained without any steps of crystallization etc., making the process commercially viable.

We claim:

1. A process for preparing Rimonabant Form I comprising the steps of
 - i) converting Rimonabant to its corresponding acid addition salts, using a suitable acid in water or suitable water miscible solvents;
 - 5 ii) reacting the acid addition salts with a suitable base;
 - iii) isolating the Form I of Rimonabant
2. The process as claimed in claim 1, wherein the suitable acid addition salt of Rimonabant is selected from halides, nitrates, sulfates, phosphates, hexafluorophosphates; organic salts selected from oxalate, maleate, succinate,
10 fumarate, tartarate, sulfonates, triflate, trifluoroacetate, perchlorate, benzoate, napsylate, borates, antimonates
3. The process as claimed in claim 2 wherein the sulfonate salts are selected from mesylate, besylate or tosylate.
4. The process as claimed in claim 2 or 3 wherein the borates are selected from
15 tetrafluoroborate, tetraphenylborate.
5. The process as claimed in any preceding claim wherein the water miscible solvent is selected from suitable alcohols, ethers, or ketones.
6. The process as claimed in any preceding claim wherein the reaction is carried out at a temperature in the range of 25-100 °C.
- 20 7. The process as claimed in any preceding claim wherein the suitable bases are selected from alkali or alkaline earth metal carbonates, bicarbonates or alkali metal hydroxides, ammonia, organic bases selected from triethyl amine, pyridine.
8. The process as claimed in any preceding claim wherein the Rimonabant used is selected from Forms II, III, IV or other polymorphic forms known, including
25 amorphous form, solvates or hydrates or anhydrous form of Rimonabant.
9. The process as claimed in any preceding claim wherein the salts are isolated prior to conversion or used as it is in the solution to obtain Rimonabant Form I.
10. The process as claimed in any preceding claim wherein the Rimonabant Form I is isolated by suitably cooling the reaction mixture and filtering and drying the
30 residue.
11. The process as claimed in any preceding claim wherein the Rimonabant Form I has a X-ray diffraction pattern with 20 peaks ($\pm 0.2^\circ$) at about, 9.181, 10.757, 11.7, 12.319, 13.078, 14.081, 16.120, 16.400, 16.840, 17.861, 18.439,

18.961, 19.420, 20.239, 20.719, 21.280, 22.118, 22.841, 23.860, 24.860, 25.299,
26.160, 27.239, 27.763, 28.520, 30.501, 33.518, 34.080, 35.598, 35.800, 38.761.

12. The process as claimed in any preceding claim, wherein the Rimonabant Form has
IR spectra substantially as described in Figure 1.

5 13. The Rimonabant Form I having residual solvent less than 1%.

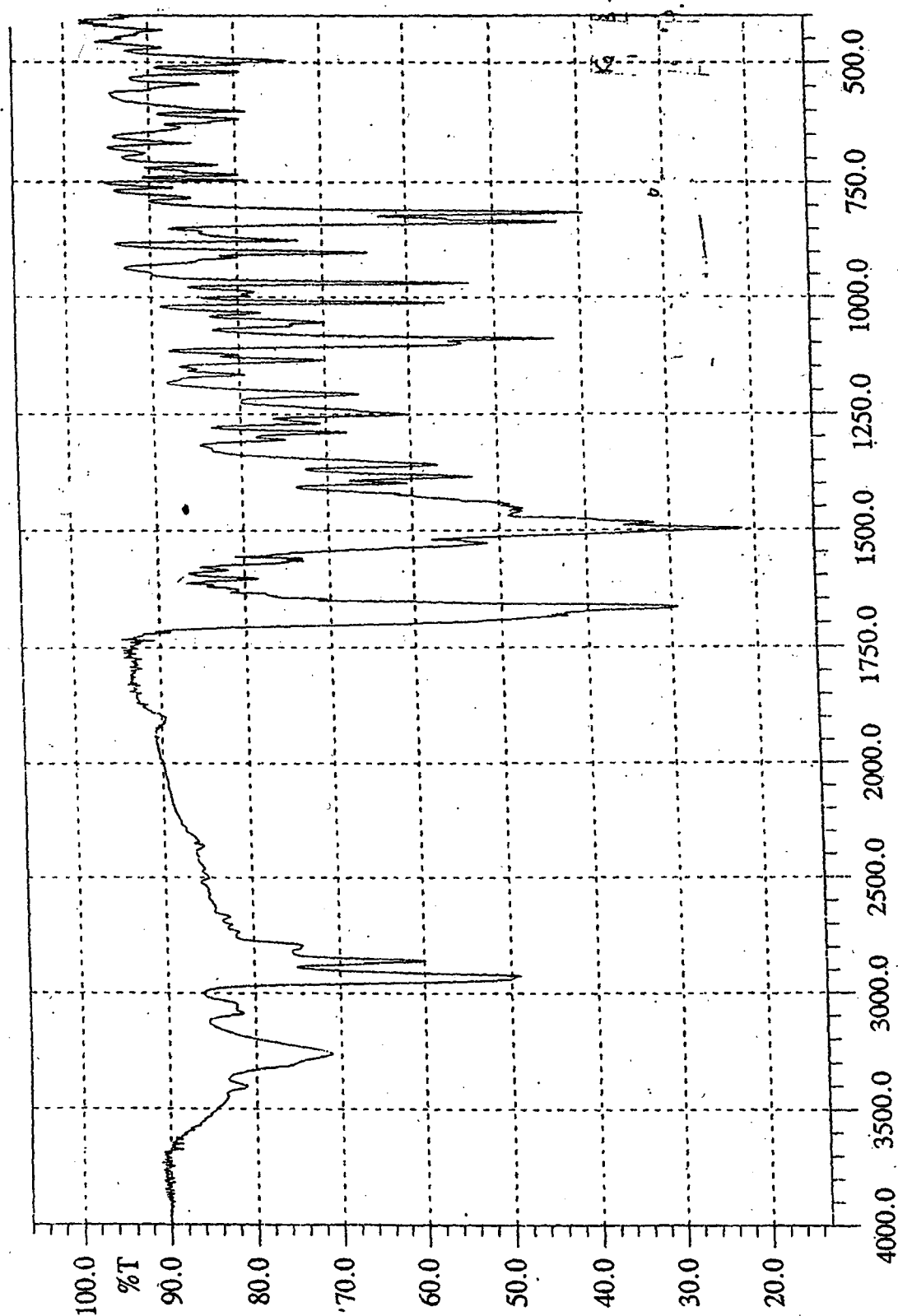


FIG-1

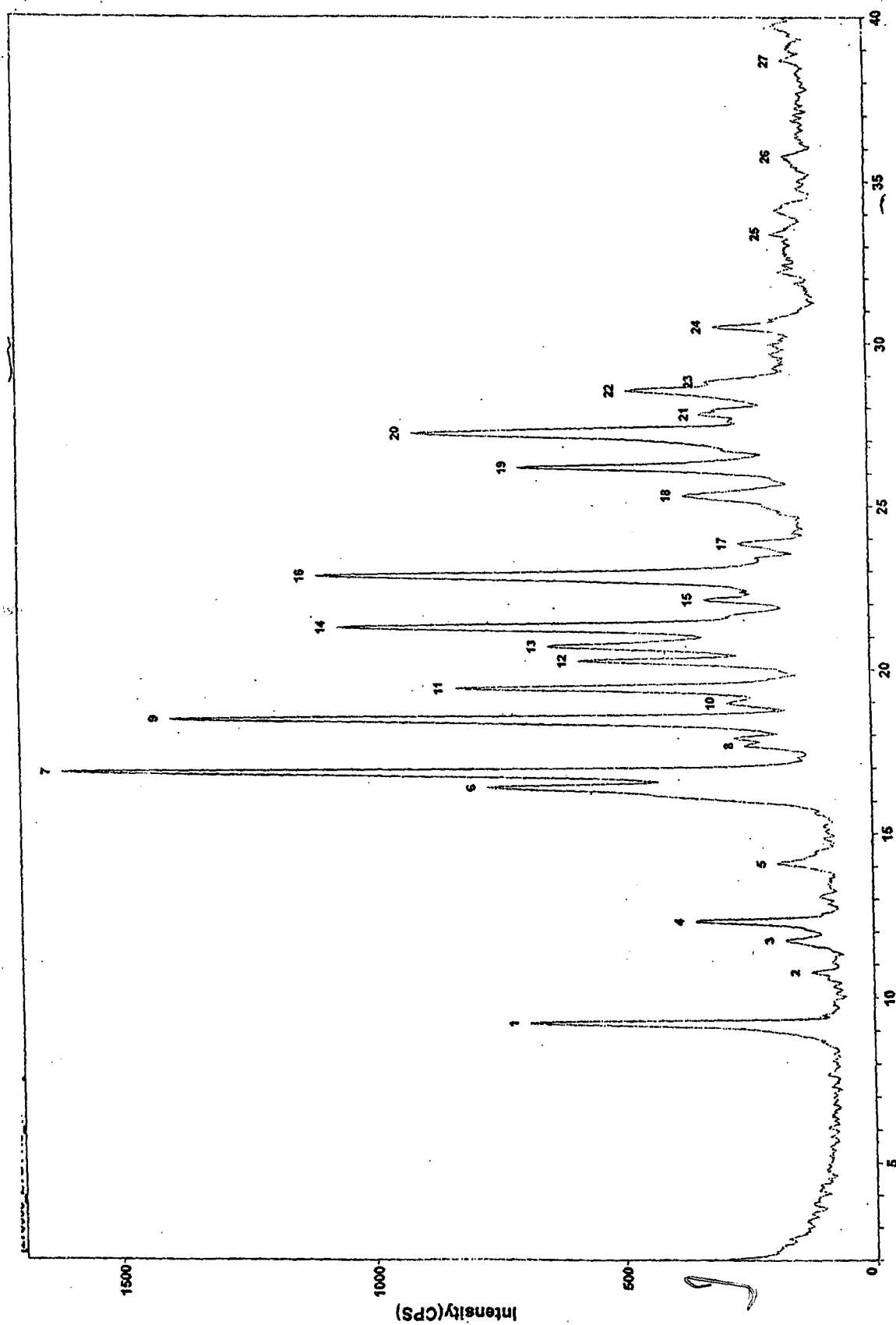


FIG II

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2009/000220

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D231/14

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, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

☒ See patent family annex.

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- *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.
- *G* document member of the same patent family

Date of the actual completion of the international search

3 September 2009

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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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