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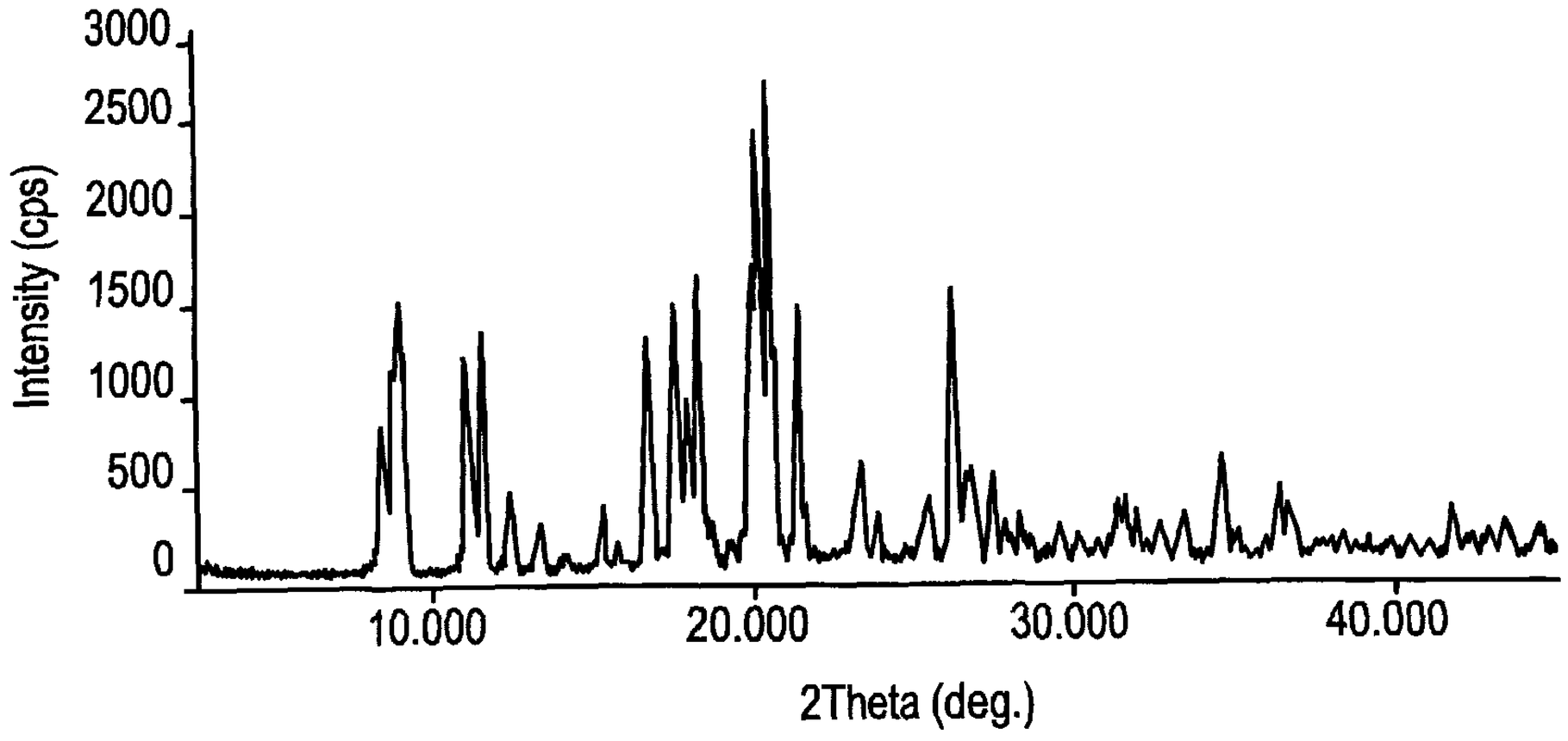
(54) Titre : DIHYDRATE-II D'OLANZAPINE: SON PROCEDE DE PREPARATION ET SON UTILISATION
(54) Title: OLANZAPINE DIHYDRATE-II A PROCESS FOR ITS PREPARATION AND USE THEREOF



(57) Abrégé/Abstract:
The present invention relates to novel dihydrate form of 2-methyl-4-(4-methyl-1-piperazinyl)-10Hthieno[2,3-b][1,5]benzodiazepine (hereinafter referred to as Olanzapine dihydrate-II), a process for its preparation and its conversation to Olanzapine Form-II. The present invention also relates to compositions containing Olanzapine dihydrate II and the use of Olanzapine dihydrate II and compositions containing Olanzapine dihydrate II for treating disorders of the central nervous system.

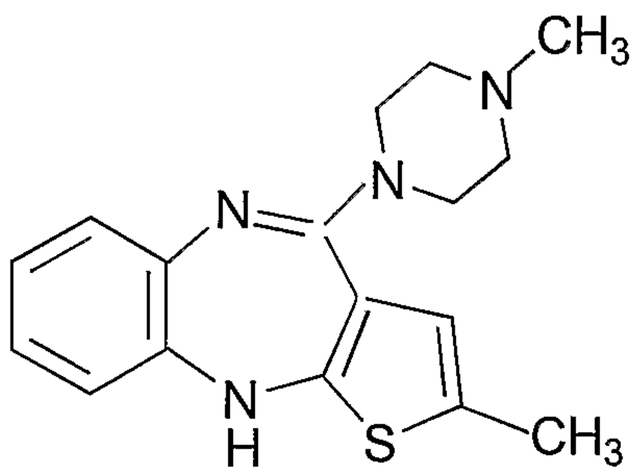
OLANZAPINE DIHYDRATE-II A PROCESS FOR ITS PREPARATION AND USE THEREOF

Field of Invention

The present invention relates to novel dihydrate form of 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-b][1,5]benzodiazepine (hereinafter referred to as Olanzapine dihydrate-II), a process for its preparation and its conversion to Olanzapine Form-II. The present invention also relates to compositions containing Olanzapine dihydrate II and the use of Olanzapine dihydrate II and compositions containing Olanzapine dihydrate II for treating disorders of the central nervous system.

Background of Invention

Olanzapine is represented by the following structure:



Olanzapine is useful for treating psychotic patients and patients with mild-anxiety states. Preparation of Olanzapine and its acid addition salts, having pharmaceutical properties, particularly in the treatment of disorders of the central nervous system is disclosed in U.S. 5,229,382.

EP 733635B1 discloses Olanzapine Form-II and designates the product obtained according to the process described in U.S. 5,229,382 as Olanzapine Form-I characterizing both Form-I and Form-II with their XRD patterns.

EP 831098B1 discloses Olanzapine Form-II as the most stable anhydrous form of Olanzapine, providing a stable anhydrous formulation with pharmaceutically desired characteristics. The patent further discloses that substantially pure Olanzapine Form-II, which can be prepared using an Olanzapine dihydrate. In addition to this, the patent discloses the preparation of a series of dihydrates of Olanzapine namely Dihydrate B, Dihydrate D and Dihydrate E characterized by their XRD pattern which serve as intermediates for the preparation of Olanzapine Form-II.

The present invention hence provides a novel Olanzapine dihydrate-II, which is useful in the preparation of Olanzapine Form-II. The Olanzapine dihydrate-II is prepared using an eco-friendly process. Conversion of Olanzapine dihydrate-II to

Olanzapine Form-II, is specially advantageous since the novel Olanzapine dihydrate-II is prepared in water and subsequently dried to provide Olanzapine Form-II, thus providing assurance that the Form-II material is substantially free from all organic solvent residues.

Summary of the Invention

The present invention is directed to novel Olanzapine dihydrate-II.

The present invention further provides an eco-friendly and a commercially viable process for the preparation of novel Olanzapine dihydrate-II, comprising stirring Olanzapine form-I with water, followed by filtration and drying to afford the novel Olanzapine dihydrate –II.

The present invention also provides a process for the conversion of novel Olanzapine dihydrate-II to Olanzapine Form-II comprising further drying of Olanzapine dihydrate-II to constant weight, thereby yielding Olanzapine Form-II.

The present invention also provides for the use of Olanzapine dihydrate-II for treating disorders of the central nervous system and for the use of Olanzapine dihydrate-II in compositions.

Brief Description Of Accompanying Drawings

Fig 1 is an X Ray Powder Diffractogram of novel Olanzapine dihydrate-II.

Fig 2 is an Infrared Absorption Spectrum of Olanzapine dihydrate-II.

Fig 3 is a Differential Scanning Calorimetry Thermogram of Olanzapine dihydrate-II.

Fig 4 is an X Ray Powder Diffractogram of Olanzapine Form-II obtained from novel Olanzapine dihydrate –II.

Detailed Description Of The Invention

The Olanzapine dihydrate-II of the present invention can be prepared by the treatment of Form I of 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-b][1,5]benzodiazepine i.e. Olanzapine Form-I with water by stirring at 25 – 35°C for 72 to 120 hours. Subsequent filtration and drying the product renders the desired Olanzapine dihydrate-II. The drying can be achieved under vacuum at 25-50°C for 1 – 2 hours, in an oven at 60-70°C for 1-2 hours, or air-drying at ambient temperature for 5-24 hours. This isolated Olanzapine dihydrate-II on further drying in oven at 60-70°C, to constant weight, renders Olanzapine Form-II.

The novel Olanzapine dihydrate-II of the present invention is well distinguished from the crystal modifications reported in the prior art.

The Form-I used in the preparation of Olanzapine dihydrate-II can be prepared as per the process disclosed in U.S. 5,229,382, Indian Patent Application No. 709/MAS/2000 or PCT Application No. WO 02/18390A1, the subject matter of which is incorporated herein by reference.

U.S. 5,229,382, Example 1 (4) discloses preparation of Olanzapine Form-I wherein crude 4-amino-2-methyl-10*H*-thieno-[2,3b] [1,5] benzodiazepine HCl was refluxed in a mixture of N-methylpiperazine, DMSO and toluene under nitrogen atmosphere for 20 hours. The mixture was cooled to 50°C, water added and the product allowed to crystallize at 5°C overnight. The product was filtered and crystallized from acetonitrile to give 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-b][1,5] benzodiazepine which was later designated in EP 733635B1 as Olanzapine Form-I.

Indian Application, 709/MAS/2000 and WO 02/18390A1 disclose preparation of Olanzapine Form-I from Olanzapine by dissolving Olanzapine in C_1-C_3 haloalkane solvent selected from dichloromethane, 1,2-dichloroethane and chloroform, preferably dichloromethane at reflux, cooling the reaction solution, filtering the precipitate obtained by conventional methods, and drying the product to obtain the desired Olanzapine Form–I.

Olanzapine Form–I can be prepared by any other known method.

In addition to using Olanzapine dihydrate II to prepare Olanzapine Form-I, Olanzapine dihydrate II can be used as a drug and in compositions, including compositions that can be administered to mammals including humans. Pharmaceutical compositions of this invention can contain and/or comprise a therapeutically effective amount of the active ingredient, together with inorganic or organic, solid or liquid, pharmaceutically acceptable carriers or excipients, which are suitable for enteral, for example oral, parenteral or topical administration. The pharmaceutical compositions may be sterilized and/or may comprise of one or more excipients, for example preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating the osmotic pressure and/or buffers. Preferably, the compositions are formulated in unit dosage form, each dosage containing from 0.1 mg to 20 mg or 0.5 to 10 mg of active ingredient.

The dosage of Olanzapine dihydrate II depends on various factors, such as method of administration, species, age and/or individual condition. The doses to be administered daily are between 0.5 mg and about 100 mg, preferably between 1 mg to 40 mg daily for warm-blooded species.

The pharmaceutical compositions of this invention can be used to treat disorders of the central nervous system including schizophrenia and psychosis.

The present invention is described in detail with examples given below that are provided by way of illustration only and therefore, should not be construed to limit the scope of the invention.

EXAMPLES

Preparation of Olanzapine dihydrate-II

Example 1

Olanzapine Form-I (25.0 g) and water (125 ml) were stirred at 25 – 30°C for 120 hours. It was then filtered and dried under vacuum at 32 – 44°C for about 1-2 hours to render the desired Olanzapine dihydrate – II.

Yield: 27.4 g; Moisture content: 10.33%w/w. Weight loss of the product on TGA is 10.090%.

Preparation of Olanzapine Form-II

The Olanzapine dihydrate-II (5.0g) obtained as per Example 1 is dried in oven at 60-70°C to constant weight rendering Form II of Olanzapine.

Yield: 4.5 g Moisture content: 0.88% w/w. Weight loss of the product on TGA is 0.310%.

Example 2

Olanzapine Form-I (25.0 g) and water (125 ml) were stirred at 25 – 30°C for 120 hours.

Approximately ½ part of the above-obtained wet cake was dried at 65°C for 90 minutes to afford the desired Olanzapine dihydrate-II.

Yield: 14.1 g; Moisture content: 11.4 %w/w.

The remaining part was air dried for about 6-7 hours at ambient temperature, to render the desired Olanzapine dihydrate – II.

Yield: 14.3 g; Moisture content: 11.1 %w/w.

The aforementioned crystalline form in Examples 1 and 2 have been examined for their structural and analytical data viz., Powder X-Ray Diffraction,

Differential Scanning Calorimetry, Infrared Absorption Spectroscopy and moisture content. The results obtained for the example are discussed in (Fig. 1-4).

The X-Ray Diffraction Pattern set out herein for Example 1 is obtained using Rigaku D / Max-2200 X-Ray Powder Diffractometer having a copper Kα radiation source of wavelength λ=1.54 A°. The samples were scanned between 3-45 degrees 2θ.

The d values of X-Ray diffractogram for Olanzapine dihydrate-II and Olanzapine Form-II in Example-1 are herewith enclosed (Fig. 1 & Fig. 4 respectively)

Olanzapine Dihydrate – II		Olanzapine Form-II	
D value	I/I_0	d value	I/I_0
9.9949	30	10.3696	100
9.5838	45	8.6314	24
9.4007	58	7.1668	20
7.6884	42	5.7869	31
7.4184	46	5.2296	20
5.2052	46	4.4937	54
4.9678	55	4.2468	82
4.8756	34	4.1526	36
4.7767	58	4.0046	33
4.4271	37	3.7324	50
4.3881	62	3.3449	22
4.3414	92		
4.2752	100		
4.1145	50		
3.7762	20		
3.3682	56		

Detailed Description Of Accompanying Drawings

Fig. 1 is a characteristic X-Ray powder diffraction pattern of Olanzapine dihydrate-II (Vertical axis: Intensity (CPS); Horizontal axis: Two Theta (degrees). The significant d values obtained are 9.9949, 9.5838, 9.4007, 7.6884, 7.4184, 5.2052, 4.9678, 4.8756, 4.7767, 4.4271, 4.3881, 4.3414, 4.2752, 4.1145, 3.7762 and 3.3682.

Fig. 2 is a characteristic infrared absorption spectrum in potassium bromide of Olanzapine dihydrate-II [Vertical axis, Transmission (%); Horizontal axis: Wave number (cm^{-1})]. The characteristic peaks for Olanzapine dihydrate-II are indicated around 750.43 cm-1, 971.39 cm-1 and 1003.70 cm-1.

Fig. 3 is a characteristic of differential scanning calorimetry thermogram of Olanzapine dihydrate-II. Vertical axis: mW; Horizontal axis: Temperature (°C). The DSC thermogram exhibits a significant endo - endo pattern at 69.50-195.38°C, which is characteristic of Olanzapine dihydrate-II. The heating rate is 5°C/minute.

Fig 4 is an X ray powder diffractogram of Olanzapine Form-II obtained from novel Olanzapine dihydrate – II. (Vertical axis: Intensity (CPS); Horizontal axis: Two Theta (degrees). The significant d values obtained are 10.3696, 8.6314, 7.1668, 5.2296, 4.7869, 4.4937, 4.2468, 4.1526, 4.0046, 3.7324 and 3.5449.

The present invention therefore provides novel Olanzapine dihydrate-II and a process for the preparation thereof. The novel Olanzapine dihydrate-II of the present invention is an important intermediate for the preparation of Olanzapine Form-II, which is disclosed as the most stable anhydrous form of Olanzapine, providing a stable anhydrous formulation with pharmaceutically desired characteristics.

CLAIMS

1. Olanzapine Dihydrate-II.

2. The compound according to claim 1, which is characterized by a powder X-ray diffraction pattern (d values in A°) of about: 9.9949, 9.5838, 9.4007, 7.6884, 7.4184, 5.2052, 4.9678, 4.8756, 4.7767, 4.4271, 4.3881, 4.3414, 4.2752, 4.1145, 3.7762 and 3.3682.

3. The compound according to claim 1, characterized by infrared absorption peaks (in cm^{-1}) at about: 750.43 cm-1, 971.39 cm-1 and 1003.70 cm-1.

4. The compound according to claim 1, characterized by a DSC thermogram having endo-endo peaks at about 69.50 and 195.38°C.

5. Olanzapine Dihydrate II according to claim 1, characterized by an X-ray diffraction pattern substantially in accordance with Figure 1.

6. Olanzapine Dihydrate II according to claim 1, characterized by a differential scanning calorimetry thermogram substantially in accordance with Figure 3.

7. Olanzapine Dihydrate II according to claim 1, characterized by an infrared absorption pattern substantially in accordance with Fig. 2

8. Olanzapine Dihydrate II according to claim 5, characterized by a differential scanning calorimetry thermogram in accordance with Figure 3.

9. A process for preparing olanzapine dihydrate II which comprises the steps of:

a) stirring a mixture of Form I of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine and water at 25-35°C for 72 to 120 hours followed by isolation of product obtained; and

b) drying the product of step a) to obtain Olanzapine Dihydrate-II.

10. The process according to claim 9, wherein the product of step a) is dried under vacuum at 25-50°C for 1 – 2 hours to obtain Olanzapine Dihydrate-II.

11. The process according to claim 8, wherein the product of step a) is air-dried at ambient temperature for 5-24 hours to obtain Olanzapine Dihydrate-II.

12. The process according to claim 9, wherein the product of step a) is dried in an oven at 60-70°C for 1-2 hours to obtain Olanzapine Dihydrate-II.

13. A process for preparing Olanzapine Form-II which comprises the steps of:

a) stirring a mixture of Form I of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine and water at 25-35°C for 72-120 hours followed by isolation of product obtained;

b) drying the product of step a) to afford Olanzapine Dihydrate-II; and

c) further drying Olanzapine Dihydrate-II to constant weight to obtain Olanzapine Form II.

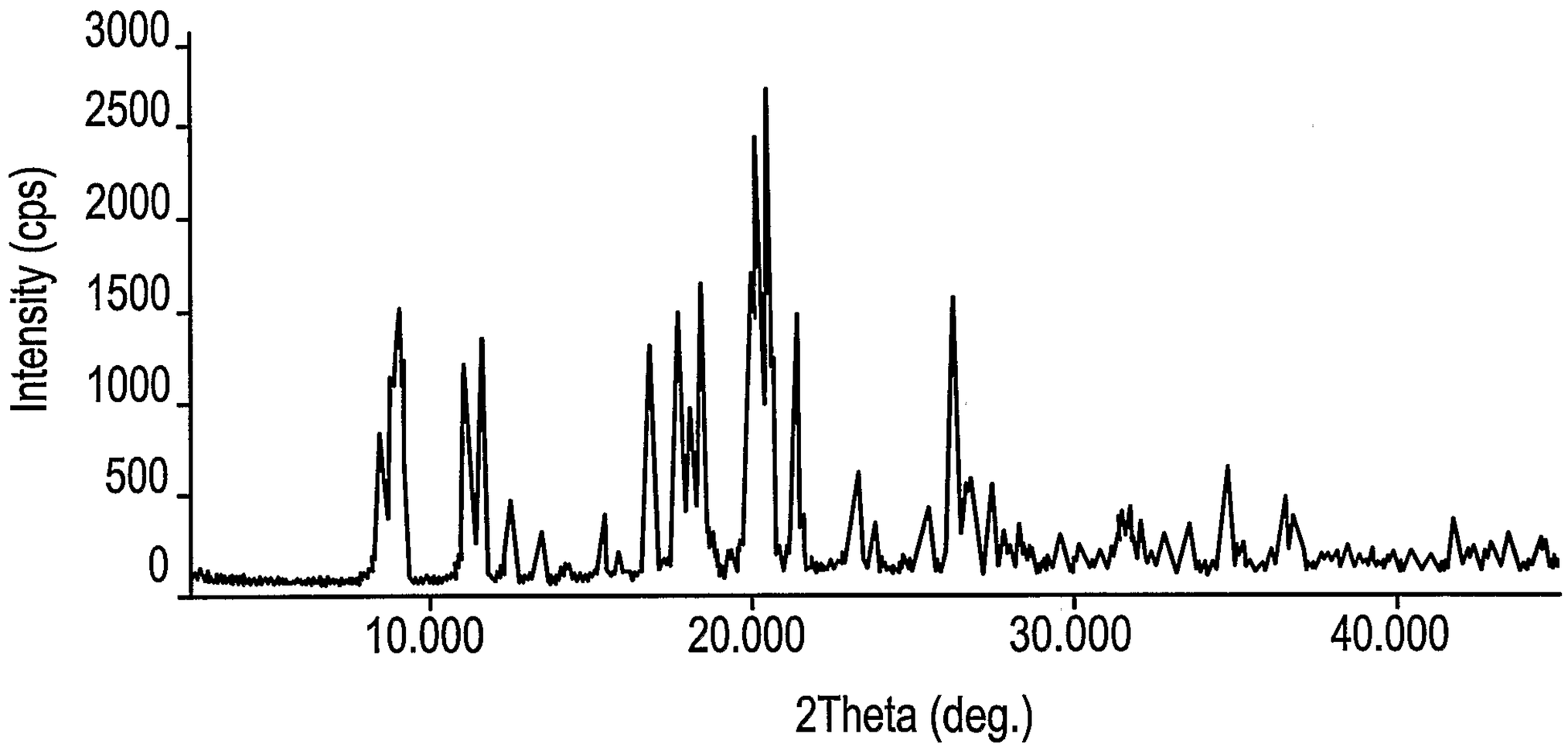
14. The process according to claim 13, wherein in step c) the Olanzapine Dihydrate-II is dried at 60-70°C in oven to constant weight.

15. A composition comprising Olanzapine Dihydrate-II according to any one of claims 1 to 8 and a pharmaceutically acceptable excipient.

16. A composition according to claim 15 for treating disorders of the central nervous system.

17. Use of Olanzapine dihydrate-II according to any one of claims 1 to 8 for preparing a medicament for treating disorders of the central nervous system.

FIG. 1


3000
2500
2000
1500
1000
500
0
Intensity (cps)
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20.000
30.000
40.000
2Theta (deg.)

FIG. 2

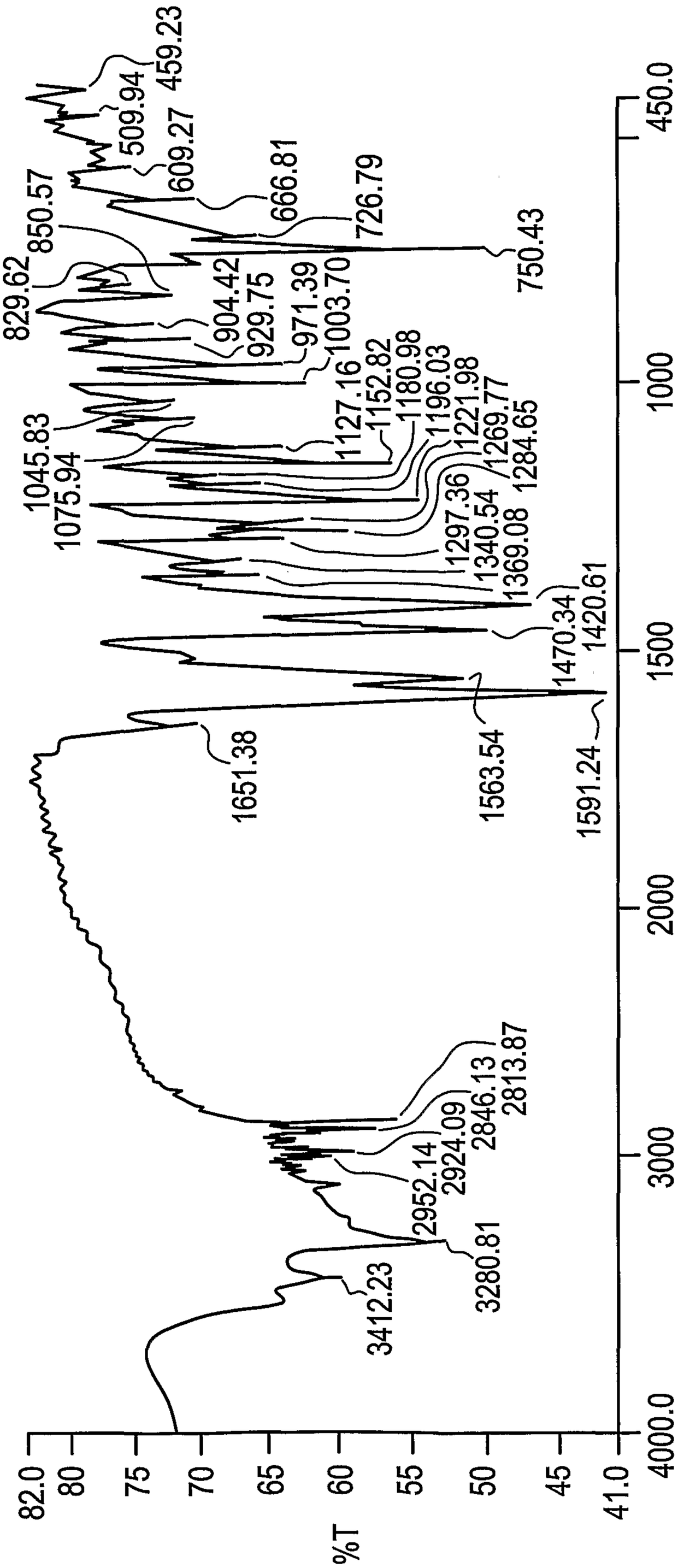

459.23
509.94
609.27
666.81
726.79
750.43
850.57
829.62
904.42
929.75
971.39
1003.70
1045.83
1075.94
1127.16
1152.82
1180.98
1196.03
1221.98
1269.77
1284.65
1297.36
1340.54
1369.08
1420.61
1470.34
1563.54
1591.24
1651.38
2813.87
2846.13
2924.09
2952.14
3280.81
3412.23
450.0
1000
1500
2000
3000
4000.0
cm-1
82.0
80
75
70
65
60
55
50
45
41.0
%T

FIG. 3

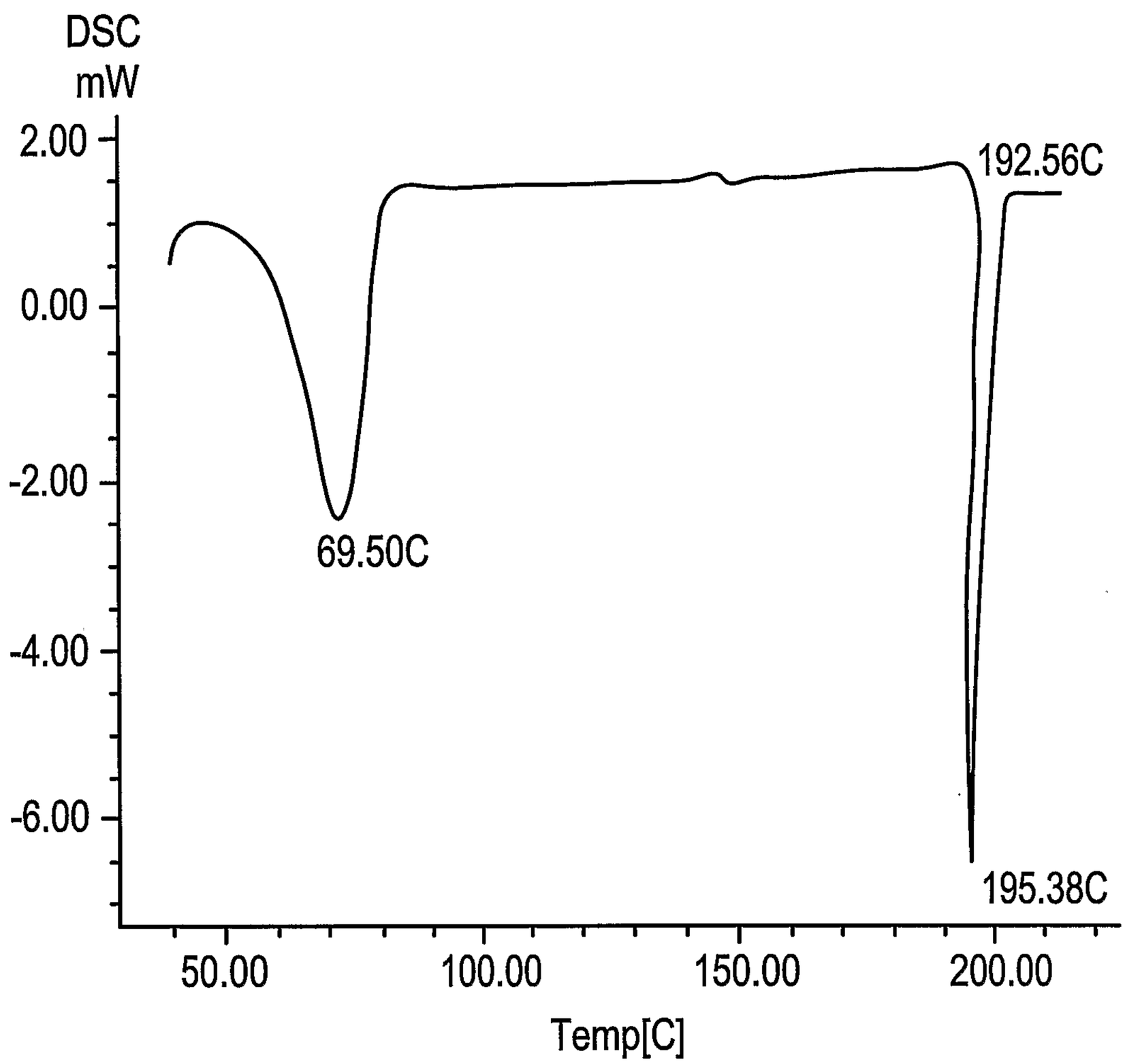
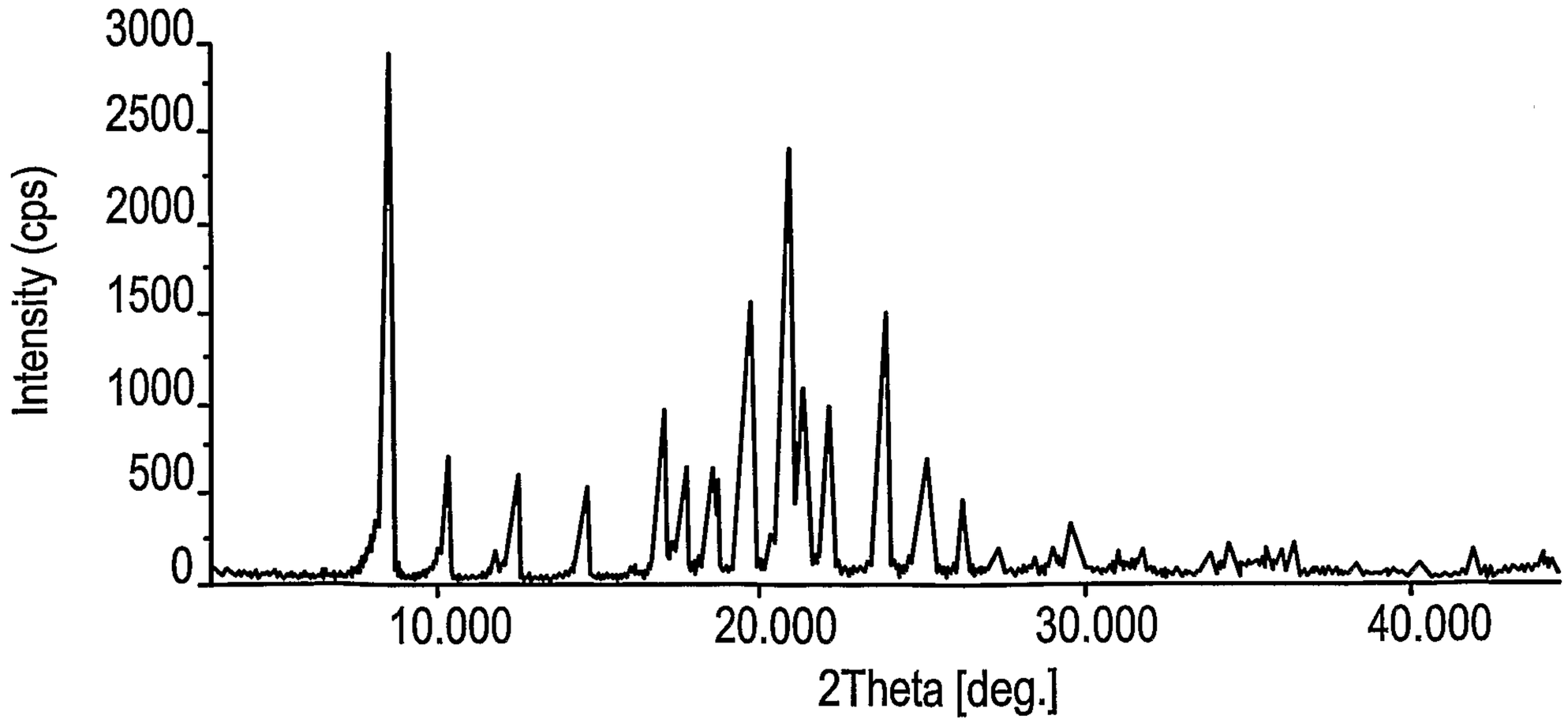

DSC
mW
2.00
0.00
-2.00
-4.00
-6.00
192.56C
69.50C
195.38C
50.00
100.00
150.00
200.00
Temp[C]

FIG. 4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Intensity (cps)
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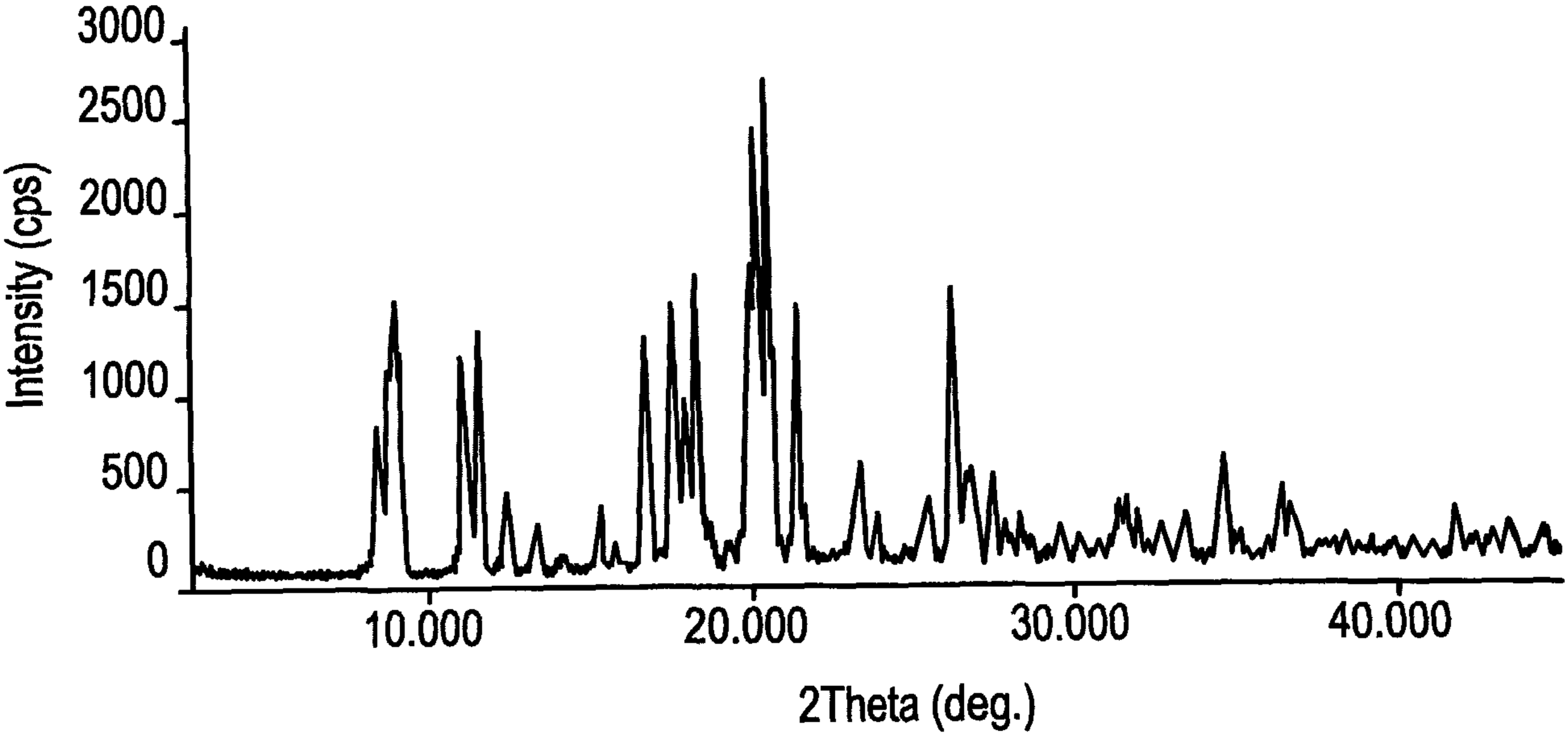
2Theta [deg.]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