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(54) Title: MIRABEGRON DIMETHYL SULPHOXIDE SOLVATE AND ITS USE FOR THE TREATMENT OF OVERACTIVE BLADDER

(57) Abstract: The present invention provides mirabegron dimethyl sulphoxide, processes for its preparation, a pharmaceutical composition comprising it, and its use for the treatment of overactive bladder. The present invention also provides processes for the preparation of mirabegron using mirabegron dimethyl sulphoxide solvate.



WO 2015/040573 A1

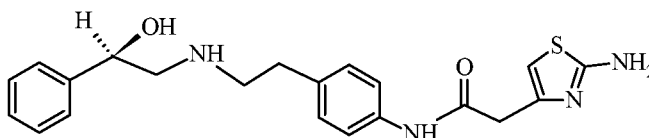
MIRABEGRON DIMETHYL SULPHOXIDE SOLVATE AND ITS USE FOR THE TREATMENT OF OVERACTIVE BLADDER

Field of the Invention

The present invention provides mirabegron dimethyl sulphoxide, processes for its preparation, a pharmaceutical composition comprising it, and its use for the treatment of overactive bladder. The present invention also provides processes for the preparation of mirabegron using mirabegron dimethyl sulphoxide solvate.

Background of the Invention

Mirabegron is a beta-3 adrenergic agonist disclosed in U.S. Patent No. 6,346,532. It is chemically designated as 2-(2-aminothiazol-4-yl)-N-[4-[2-[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]acetamide, and has the structure depicted by Formula I.



Formula I

Mirabegron is marketed in the United States under the brand name Myrbetriq[®] for the treatment of overactive bladder with symptoms of urinary incontinence, urgency, and urinary frequency.

The discovery of new polymorphic forms and solvates of a pharmaceutically useful compound provides new opportunities to improve the performance characteristics of a pharmaceutical product.

Polymorphs of mirabegron are disclosed in U.S. Patent No. 7,342,117, PCT Publication No. WO 2012/156998, and IP.com disclosure No. IPCOM000228561D.

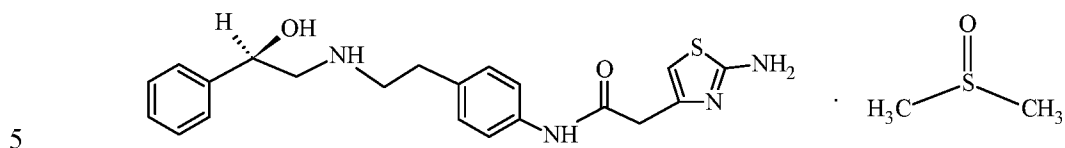
Solvates of mirabegron are not disclosed in the literature. The present invention provides mirabegron dimethyl sulphoxide solvate.

Summary of the Invention

The present invention provides mirabegron dimethyl sulphoxide solvate, processes for its preparation, a pharmaceutical composition comprising it, and its use for the treatment of overactive bladder. The mirabegron dimethyl sulphoxide solvate of the present invention is stable, easily reproducible, and is suitable for the preparation of

pharmaceutical compositions. The present invention also provides processes for the preparation of mirabegron by desolvation of the mirabegron dimethyl sulphoxide solvate.

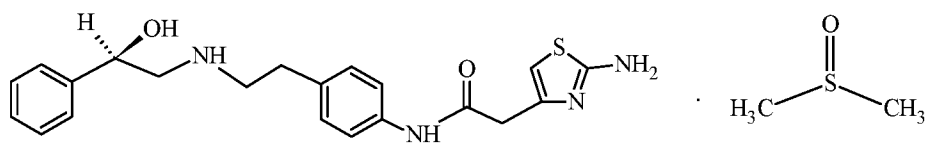
A first aspect of the present invention provides the mirabegron dimethyl sulphoxide solvate of Formula II:



Formula II

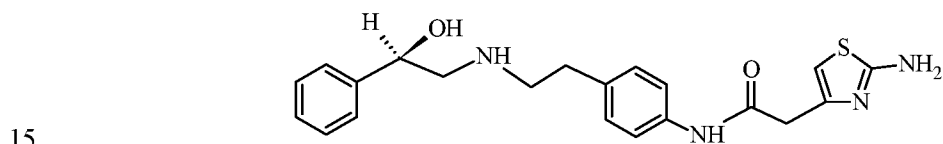
characterized by X-ray diffraction peaks at d-spacings of 5.14, 4.95, 4.45, 4.32, and 3.39 Å.

A second aspect of the present invention provides a process for the preparation of the mirabegron dimethyl sulphoxide solvate of Formula II:



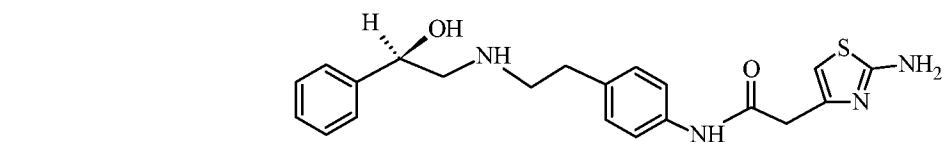
Formula II

comprising contacting mirabegron of Formula I with dimethyl sulphoxide in the presence of a solvent.



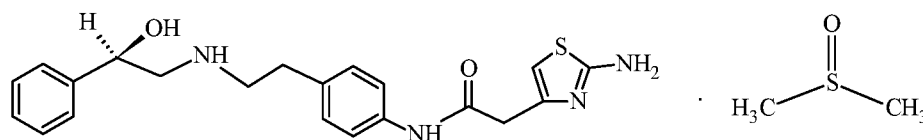
Formula I

A third aspect of the present invention provides a process for the preparation of mirabegron of Formula I:



Formula I

comprising desolvation of the mirabegron dimethyl sulphoxide solvate of Formula II.

**Formula II**

A fourth aspect of the present invention provides a pharmaceutical composition comprising the mirabegron dimethyl sulphoxide solvate of Formula II and one or more
5 pharmaceutically acceptable carriers, diluents, or excipients.

A fifth aspect of the present invention provides the use of the mirabegron dimethyl sulphoxide solvate of Formula II for the treatment of overactive bladder with symptoms of urinary incontinence, urgency, and urinary frequency.

Other objects, features, advantages, and aspects of the present invention will
10 become apparent to those skilled in the art from the description provided herein.

Brief Description of the Figures

Figure 1: X-ray Powder Diffraction (XRPD) pattern of the mirabegron dimethyl sulphoxide solvate of Formula II.

Figure 2: Differential Scanning Calorimetry (DSC) thermogram of the mirabegron
15 dimethyl sulphoxide solvate of Formula II.

Figure 3: Thermogravimetric Analysis (TGA) of the mirabegron dimethyl sulphoxide solvate of Formula II.

Detailed Description of the Invention

Various embodiments and variants of the present invention are described
20 hereinafter.

The term “contacting”, as used herein, includes dissolving, slurring, stirring, or combinations thereof.

The term “about”, as used herein, refers to a variation of up to $\pm 5\%$ in the value of a parameter, such as temperature or stirring time.

25 Mirabegron dimethyl sulphoxide solvate of Formula II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 17.25 (d-spacing at 5.14 Å), 17.92 (4.95 Å), 19.97 (4.45 Å), 20.58 (4.32 Å), and 26.28 (3.39 Å) ± 0.2 degrees 2 θ . It may be

further characterized by an XRPD pattern having peaks at 3.73 (23.71 Å), 9.94 (8.90 Å), 21.42 (4.15 Å), 21.85 (4.07 Å), and 22.94 (3.88 Å) $\pm$ 0.2 degrees 2 θ . Table 1 summarizes the d-spacing values in Å, and the corresponding 2 θ values in degrees 2 θ , of the mirabegron dimethyl sulphoxide solvate of Formula II.

5 Table 1: XRPD peaks of mirabegron dimethyl sulphoxide solvate

d-spacing [Å]	Pos. [°2 θ]	Rel. Int. [%]
23.71	3.73	35.47
11.90	7.43	4.20
8.90	9.94	34.36
8.56	10.33	9.93
7.41	11.94	12.56
6.88	12.87	5.92
6.17	14.35	3.51
5.70	15.54	17.39
5.51	16.10	7.16
5.14	17.25	79.04
5.05	17.57	34.61
4.95	17.92	80.93
4.77	18.59	30.41
4.70	18.88	38.11
4.58	19.36	20.56
4.45	19.97	100
4.32	20.58	78.31
4.15	21.42	26.62
4.07	21.85	47.93
3.97	22.40	56.35
3.88	22.94	54.84
3.77	23.64	27.43
3.71	23.97	16.60
3.66	24.33	36.13
3.59	24.77	19.29
3.54	25.16	22.72
3.50	25.42	28.39
3.47	25.68	11.29
3.39	26.28	69.78
3.27	27.30	27.39
3.18	27.70	23.27
3.10	28.01	11.60
3.22	28.83	10.01
3.06	29.22	28.56
2.99	29.88	18.13
2.90	30.87	10.65
2.86	31.32	17.42
2.83	31.63	21.78
2.78	32.20	9.63

2.71	33.03	10.45
2.65	33.84	13.26
2.61	34.39	14.20
2.56	35.01	11.40
2.52	35.57	6.29
2.48	36.25	7.74
2.41	37.32	7.00
2.35	38.30	8.44
2.27	39.73	10.62

The mirabegron dimethyl sulphoxide solvate of Formula II may also be characterized by a DSC thermogram having endotherms at about 91.50°C and about 93.68°C.

- 5 The mirabegron dimethyl sulphoxide solvate of Formula II may also be characterized by an XRPD pattern, a DSC thermogram, and a TGA as depicted in Figures 1-3, respectively.

Mirabegron used for the preparation of the mirabegron dimethyl sulphoxide solvate of Formula II may be obtained by the methods known in the literature, such as those described in U.S. Patent No. 7,342,117 and PCT Publication No. WO 2012/156998 which are incorporated herein by reference.

The preparation of the mirabegron dimethyl sulphoxide solvate of Formula II is carried out by contacting mirabegron of Formula I with dimethyl sulphoxide at a temperature of about 20°C to the reflux temperature of the solvent. The preparation of the mirabegron dimethyl sulphoxide solvate of Formula II may also be carried out using a solvent selected from the group comprising of aromatic hydrocarbons, alkyl acetates, and mixtures thereof. Examples of aromatic hydrocarbons include toluene and xylene. Examples of alkyl acetates include ethyl acetate, propyl acetate, isopropyl acetate, and *t*-butyl acetate.

20 The preparation of the mirabegron dimethyl sulphoxide solvate of Formula II may also be carried out by stirring the reaction mixture at a temperature of about 20°C to about 40°C for about 15 minutes to about 4 hours.

Isolation of the mirabegron dimethyl sulphoxide solvate of Formula II may be accomplished by crystallization, concentration, precipitation, cooling, filtration, centrifugation, or a combination thereof, followed by drying. Any suitable method of

drying may be employed such as drying under reduced pressure, vacuum tray drying, air drying, or a combination thereof. Drying is carried out at a temperature of about 20°C to about 40°C for about 30 minutes to about 20 hours.

5 In an embodiment of the present invention, the mirabegron dimethyl sulphoxide solvate of Formula II is prepared by dissolving mirabegron in a mixture of dimethyl sulphoxide and an aromatic hydrocarbon solvent, stirring the reaction mixture for about 15 minutes to about 2 hours at a temperature of about 20°C to about 40°C, followed by isolation.

10 In another embodiment of the present invention, the mirabegron dimethyl sulphoxide solvate of Formula II is prepared by dissolving mirabegron in a mixture of dimethyl sulphoxide and an alkyl acetate solvent, stirring the reaction mixture for about 15 minutes to about 2 hours at a temperature of about 20°C to about 40°C, followed by isolation.

15 In the preferred embodiments of the present invention, the mirabegron dimethyl sulphoxide solvate of Formula II is prepared by using a mixture of dimethyl sulphoxide with toluene, or a mixture of dimethyl sulphoxide with *t*-butyl acetate as a solvent.

The desolvation of the mirabegron dimethyl sulphoxide solvate is carried out by stirring a reaction mixture containing the mirabegron dimethyl sulphoxide solvate in a solvent selected from the group comprising of water, chlorinated hydrocarbons, alcohols, ketones, and mixtures thereof at a temperature of about 0°C to about 50°C. Examples of chlorinated hydrocarbons include dichloromethane and chloroform. Examples of alcohols include methanol, ethanol, iso-propanol, and butanol. Examples of ketones include acetone, dimethyl ketone, ethyl methyl ketone, and methyl iso-butyl ketone.

20

25 In one embodiment of the present invention, the desolvation of the mirabegron dimethyl sulphoxide solvate of Formula II is carried out by contacting the mirabegron dimethyl sulphoxide solvate of Formula II with water at a temperature of about 25°C to about 35°C. The reaction mixture is stirred for about 30 minutes to about 2 hours, filtered, and the solid obtained is dried at a temperature of about 40°C to about 50°C under vacuum.

30 In another embodiment of the present invention, the desolvation of the mirabegron dimethyl sulphoxide solvate of Formula II is carried out by contacting the mirabegron dimethyl sulphoxide solvate of Formula II with acetone at a temperature of about 0°C to

about 10°C. The reaction mixture is stirred for about 30 minutes to about 2 hours, filtered, and the solid obtained is dried at a temperature of about 20°C to about 40°C under vacuum.

Polymorphs and pseudomorphs of the mirabegron dimethyl sulphoxide solvate of Formula II are also included within the scope of the present invention.

Mirabegron dimethyl sulphoxide solvate of Formula II may be administered as part of a pharmaceutical composition for the treatment of overactive bladder. Accordingly, in a further aspect, there is provided a pharmaceutical composition comprising mirabegron dimethyl sulphoxide solvate of Formula II, one or more pharmaceutically acceptable carriers, diluents, or excipients, and optionally other therapeutic ingredients. Pharmaceutical compositions comprising mirabegron dimethyl sulphoxide solvate of Formula II may be administered orally, topically, parenterally, by inhalation or spray, rectally, or in the form of injectables. The injectable compositions may include intravenous, intramuscular, subcutaneous, and parenteral injections, as well as use of infusion techniques.

In the foregoing section, embodiments are described by way of examples to illustrate the processes of invention. However, these are not intended in any way to limit the scope of the present invention. Variants of the examples that would be evident to persons ordinarily skilled in the art are within the scope of the present invention.

EXAMPLES

Method

The X-ray powder diffraction (XRPD) pattern was recorded using a PANalytical[®] X'pert PRO with X'celerator[®] as the detector.

The DSC was recorded using a Mettler-Toledo[®] 821e. Data collection parameters: Scanning rate: 10°C/minute; Temperature: 30°C to 300°C.

The TGA was recorded using a TA Instruments[®] Q500.

The NMR spectrum was recorded using a Bruker[®] Avance III 400 MHz NMR spectrometer.

Example 1: Preparation of mirabegron dimethyl sulphoxide solvate**Method A:**

Mirabegron (1.5 g) was suspended in a mixture of dimethyl sulphoxide (1.0 mL) and toluene (2 mL). The reaction mixture was stirred for about 30 minutes at a temperature of about 25°C to about 35°C. The reaction mixture was diluted with toluene (5 mL). The solid obtained was filtered, washed with toluene (40 mL), and dried in a vacuum tray dryer at a temperature of about 25°C to about 35°C for about 16 hours to obtain the mirabegron dimethyl sulphoxide solvate.

Yield: 1.79 g

¹H-NMR (DMSO-*d*₆, 400 MHz) δ (in ppm): 1.80 (1H, s), 2.53 (6H, s), 2.59-2.67 (4H, m), 2.69-2.79 (2H, m), 3.44 (2H, s), 4.58-4.61 (1H, m), 5.23 (1H, s), 6.29 (1H, s), 6.89 (2H, s), 7.10-7.12 (2H, d), 7.18-7.23 (1H, m), 7.27-7.33 (4H, m), 7.48-7.50 (2H), 10.00 (1H, s).

Method B:

Mirabegron (4.5 g) was suspended in a mixture of dimethyl sulphoxide (3 mL) and *t*-butyl acetate (45 mL). The reaction mixture was stirred at a temperature of about 25°C to about 35°C for about 3 hours. The solid obtained was filtered, washed with *t*-butyl acetate (30 mL), and dried in a vacuum tray dryer at a temperature of about 25°C to about 35°C for about 3 hours to obtain the mirabegron dimethyl sulphoxide solvate.

Yield: 5.18 g

Example 2: Preparation of mirabegron by desolvation of the mirabegron dimethyl sulphoxide solvate

Method A:

Water (15 mL) was added to mirabegron dimethyl sulphoxide solvate (500 mg) at about 25°C to about 35°C. The reaction mixture was stirred for about 1 hour. The solid obtained was filtered and dried under vacuum at about 45°C for about 3 hours to obtain mirabegron.

Yield: 0.37 g

Method B:

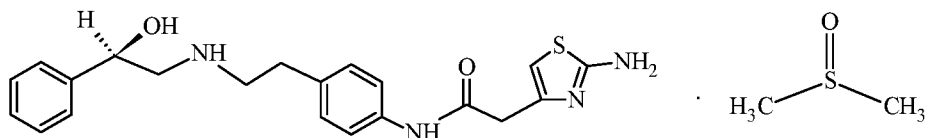
Acetone (10 mL) was added to mirabegron dimethyl sulphoxide solvate (500 mg). The reaction mixture was stirred for about 1 hour at about 0°C to about 5°C. The solid

obtained was filtered and dried under vacuum at about 25°C to about 35°C for about 2 hours to obtain mirabegron.

Yield: 0.31 g.

We claim:

- 1 1. Mirabegron dimethyl sulphoxide solvate of Formula II

**Formula II**

- 4 characterized by X-ray diffraction peaks at d-spacing of 5.14, 4.95, 4.45, 4.32, and 3.39 Å.

- 1 2. The mirabegron dimethyl sulphoxide solvate of claim 1 further characterized by X-
2 ray diffraction peaks at d-spacing of 23.71, 8.90, 4.15, 4.07, and 3.88 Å.

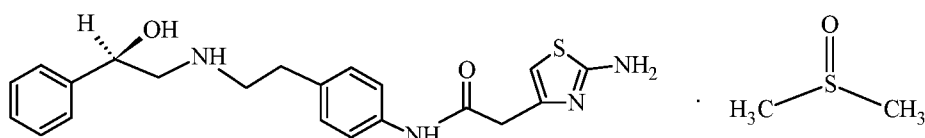
- 1 3. The mirabegron dimethyl sulphoxide solvate of Formula II characterized by an
2 XRPD pattern substantially as depicted in Figure 1.

- 1 4. The mirabegron dimethyl sulphoxide solvate of Formula II characterized by a DSC
2 thermogram having endotherms at about 91.50°C and about 93.68°C.

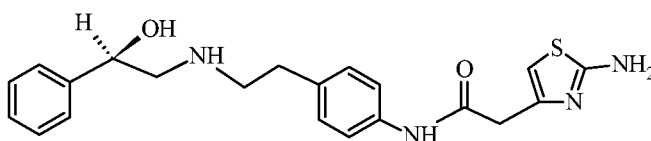
- 1 5. The mirabegron dimethyl sulphoxide solvate of Formula II characterized by a DSC
2 thermogram substantially as depicted in Figure 2.

- 1 6. The mirabegron dimethyl sulphoxide solvate of Formula II characterized by a TGA
2 substantially as depicted in Figure 3.

- 1 7. A process for the preparation of the mirabegron dimethyl sulphoxide of Formula II

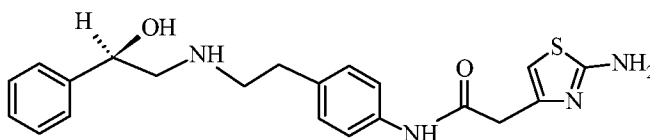
**Formula II**

- 4 comprising contacting mirabegron of Formula I

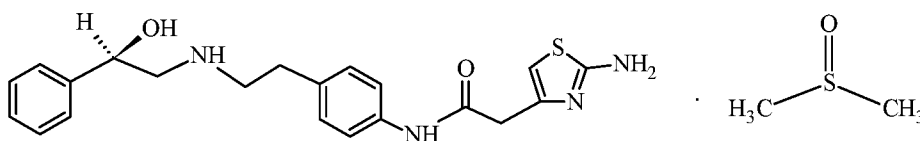
**Formula I**

- 7 with dimethyl sulphoxide in the presence of a solvent.

- 1 8. The process according to claim 7, wherein the solvent is selected from the group
2 comprising of aromatic hydrocarbons, alkyl acetates, and mixtures thereof.
- 1 9. The process according to claim 8, wherein the aromatic hydrocarbons are selected
2 from toluene and xylene.
- 1 10. The process according to claim 8, wherein the alkyl acetates are selected from
2 ethyl acetate, propyl acetate, isopropyl acetate, and *t*-butyl acetate.
- 1 11. The process according to claim 7, wherein mirabegron is contacted with dimethyl
2 sulphoxide at a temperature of about 20°C to the reflux temperature of the solvent.
- 1 12. A process for the preparation of mirabegron of Formula I

**Formula I**

- 4 comprising desolvation of the mirabegron dimethyl sulphoxide solvate of Formula II.

**Formula II**

- 1 13. The process according to claim 12, wherein the desolvation is carried out in the
2 presence of a solvent selected from the group comprising of water, chlorinated
3 hydrocarbons, alcohols, ketones, and mixtures thereof.
- 1 14. The process according to claim 13, wherein the chlorinated hydrocarbons are
2 selected from dichloromethane and chloroform.
- 1 15. The process according to claim 13, wherein the alcohols are selected from
2 methanol, ethanol, iso-propanol, and butanol.
- 1 16. The process according to claim 13, wherein the ketones are selected from acetone,
2 dimethyl ketone, ethyl methyl ketone, and methyl iso-butyl ketone.

- 1 17. A pharmaceutical composition comprising the mirabegron dimethyl sulphoxide
2 solvate of Formula II, and one or more pharmaceutically acceptable carriers, diluents, or
3 excipients.
- 1 18. Use of the mirabegron dimethyl sulphoxide solvate of Formula II for the treatment
2 of overactive bladder with symptoms of urinary incontinence, urgency, and urinary
3 frequency.

FIGURE 1: X-RAY POWDER DIFFRACTION (XRPD) PATTERN OF THE MIRABEGRON DIMETHYL SULPHOXIDE SOLVATE OF FORMULA II.

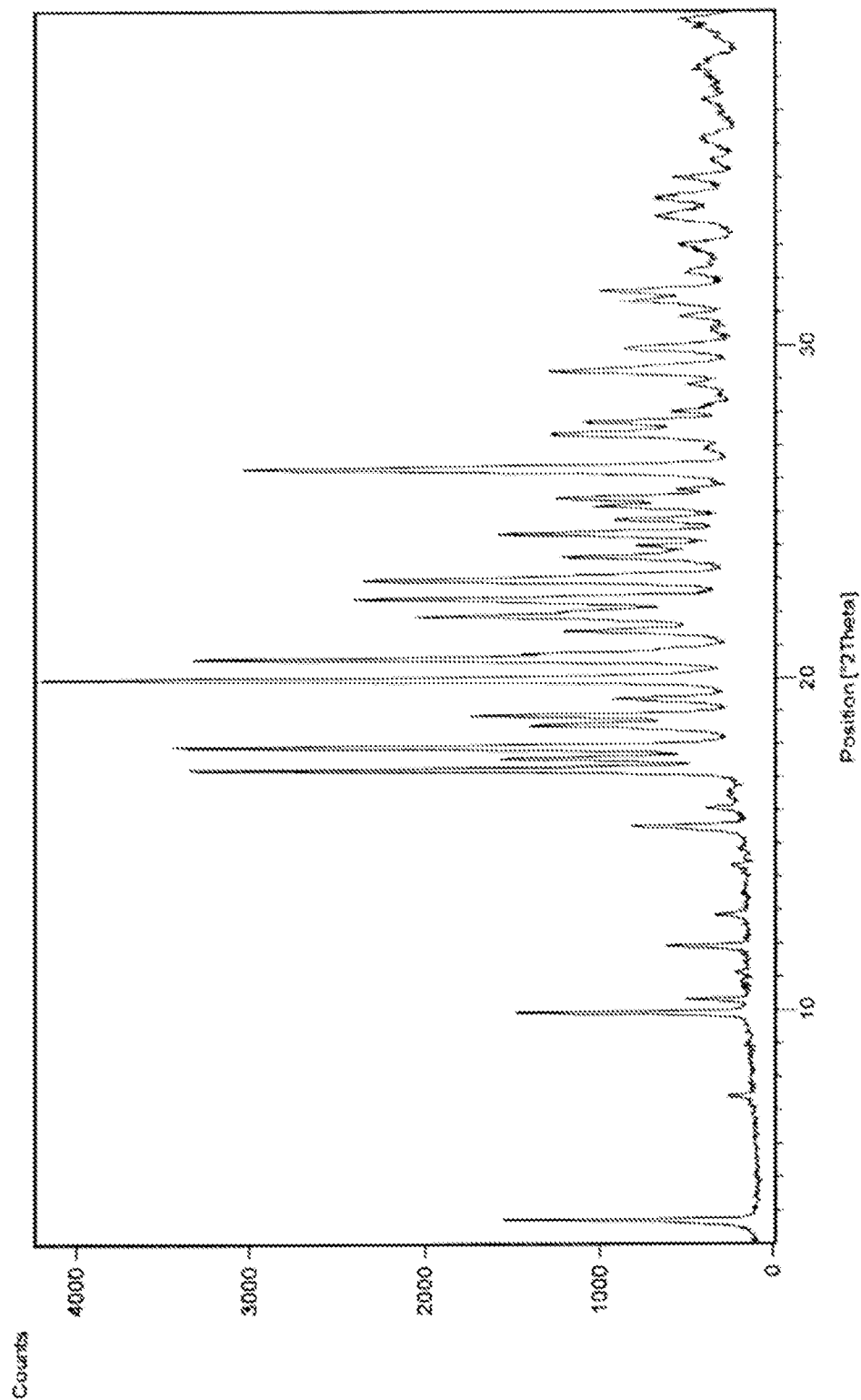


FIGURE 2: DIFFERENTIAL SCANNING CALORIMETRY (DSC) THERMOGRAM OF THE MIRABEGRON DIMETHYL SULPHOXIDE SOLVATE OF FORMULA II.

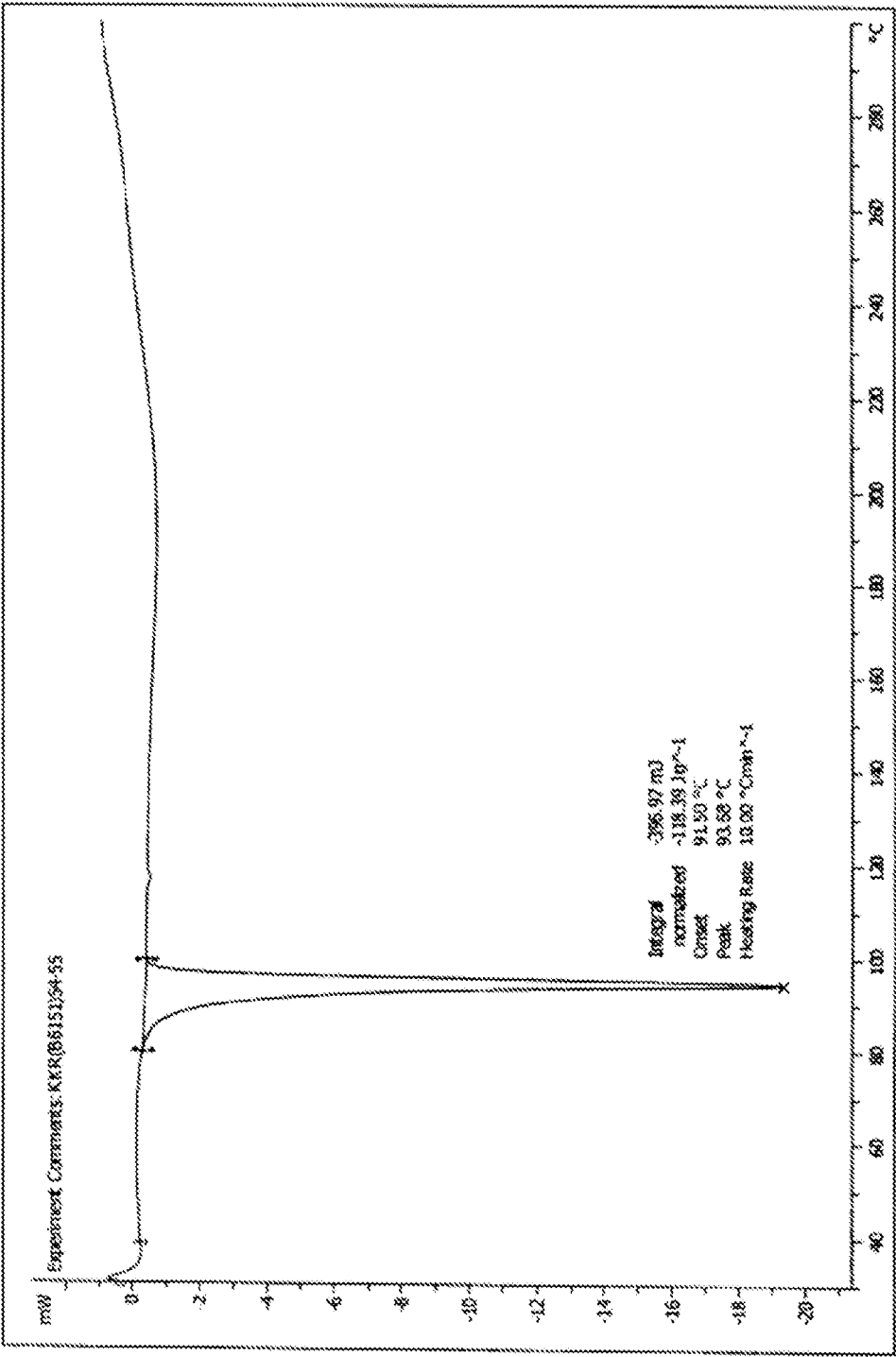
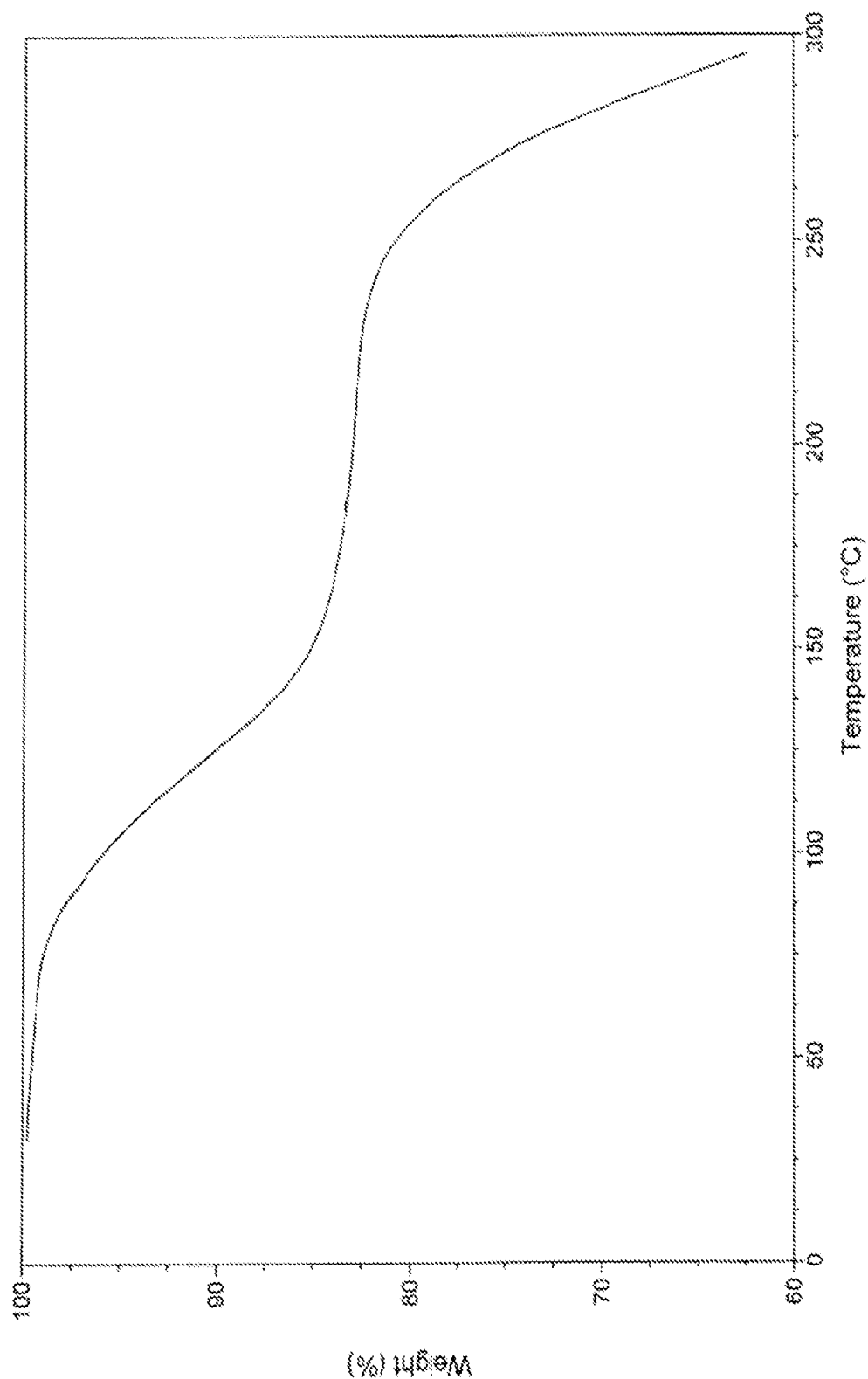


FIGURE 3: THERMOGRAVIMETRIC ANALYSIS (TGA) OF THE MIRABEGRON DIMETHYL SULPHOXIDE SOLVATE OF FORMULA II.



INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2014/064642

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D277/40 A61K31/426 A61P3/10
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 440 969 A1 (YAMANOUCHI PHARMA CO LTD [JP]) 28 July 2004 (2004-07-28) page 8, paragraph 0039 - paragraph 0044; claims; examples	1-18
Y	----- WO 2012/156998 A2 (REDDYS LAB LTD DR [IN]; PEDDY VISHWESHWAR [IN]; BOGE RAJESHAM [IN]) 22 November 2012 (2012-11-22) page 5, line 4 - line 11; claims; examples	1-18
Y	----- WO 2010/147830 A2 (AUSPEX PHARMACEUTICALS INC [US]; RAO TADIMETI [US]; ZHANG CHENGZHI [US]) 23 December 2010 (2010-12-23) paragraph [0030]; claims; examples ----- -/-	1-18

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

☒ See patent family annex.

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Date of the actual completion of the international search

14 October 2014

Date of mailing of the international search report

21/10/2014

Name and mailing address of the ISA/

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Gavriliu, Daniela

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2014/064642

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JULIEN DOUILLET ET AL: "Development of a solvate as an active pharmaceutical ingredient: Developability, crystallisation and isolation challenges", JOURNAL OF CRYSTAL GROWTH, vol. 342, no. 1, 1 March 2012 (2012-03-01), pages 2-8, XP55068245, ISSN: 0022-0248, DOI: 10.1016/j.jcrysgr.2011.05.023 the whole document -----	1-18
Y	A S Mckim ET AL: "Dimethyl Sulfoxide USP, PhEur in Approved Pharmaceutical Products and Medical Devices Dimethyl sulfoxide USP in dosage forms and devices", 1 January 2007 (2007-01-01), XP055146360, Retrieved from the Internet: URL: http://www.gaylordchemical.com/uploads/images/pdfs/literature/166.pdf [retrieved on 2014-10-14] the whole document -----	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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EP 1440969	A1	28-07-2004	BR	0213570 A	26-10-2004
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