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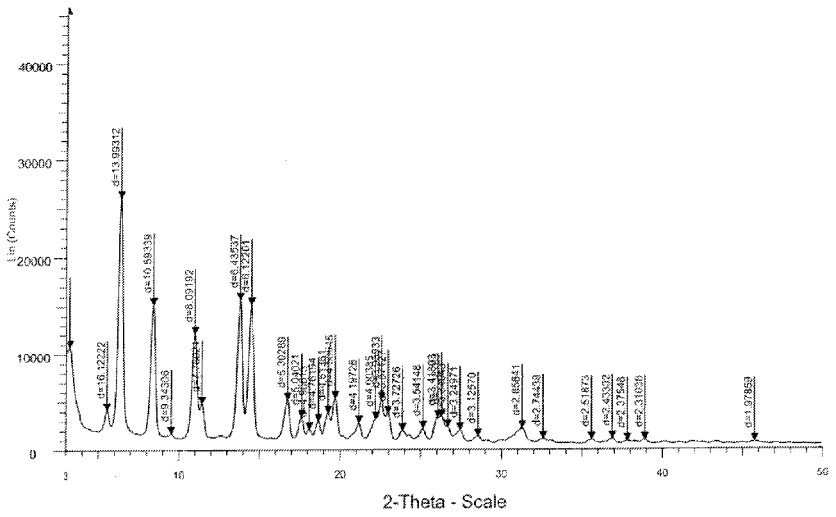
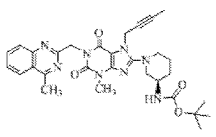


Figure 1



Formula-V

(57) Abstract: The present invention provides novel crystalline forms B1 & B2 of linagliptin intermediate of structural formula V and methods for production of novel crystalline form of linagliptin intermediate represented by the following structural formula V.

[Continued on next page]

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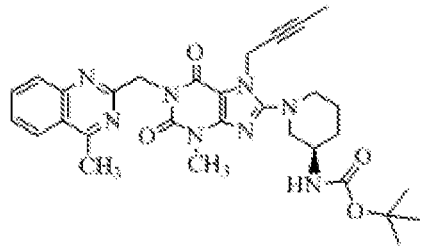
CRYSTALLINE LINAGLIPTIN INTERMEDIATE AND PROCESS FOR PREPARATION OF LINAGLIPTIN

Related Application:

This application claims the benefit of priority of our Indian patent application IN 201741034292 filed on September 27, 2017 which is incorporated herein by reference.

TECHNICAL FIELD

The present invention relates to a method for production of linagliptin via a novel crystalline form of lingliptin intermediate. More particularly the present invention relates to novel crystalline form of linagliptin intermediate and methods for production of novel crystalline form of linagliptin intermediate represented by the following structural formula V.



Formula-V

BACKGROUND AND PRIOR ART OF THE DISCLOSURE

TRADJENTA is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1.1). Linagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. It is chemically designated as 1H-purine-2,6-dione, 8-[(3R)-3-amino-l- piperidinyl] -7-(2-butyn- 1 -yl)-3 ,7-dihydro-3 -methyl- 1 -[(4-methyl-2-quinazolinyl)methyl].

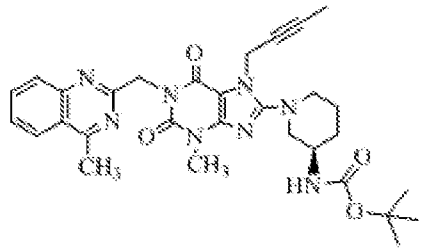
Linagliptin was disclosed in U.S. Pat. No. 7,407,955. Linagliptin, chemically 1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2quinazolinyl)methyl].

Crystalline forms A, B, C, D, E and anhydrous form A/B of Linagliptin are disclosed in US 9,266,888.

SUMMARY OF THE INVENTION

Aspects of the present application provide a safe, simpler & economical process for the preparation of novel crystalline form of Linagliptin intermediate of Formula V and a novel process for the preparation of anhydrous form A/B of Linagliptin. Each step of the process disclosed herein are contemplated both in the context of the multistep sequences described and individually.

One aspect of the present invention is novel crystalline form B1 Linagliptin intermediate of **Formula V.**



Formula-V

In another aspect of the present invention, the novel crystalline form B1 Linagliptin intermediate of **Formula V** is further characterized by PXRD having few prominent 2-theta values 3.14±0.2, 6.31±0.2, 8.33±0.2, 10.92±0.2, 13.74±0.2, 14.45±0.2, 19.67±0.2 and the PXRD pattern in accordance with the Figure-1.

In another aspect of the present invention, is novel crystalline form B1 Linagliptin intermediate of **Formula V** is further characterized by DSC having endotherms at around 53.87 °C & 163 °C and the DSC pattern in accordance with the Figure-2.

In another aspect of the present invention, the novel crystalline form B1 Linagliptin intermediate of **Formula V** is further characterized by FT-IR and the FT-IR pattern is in accordance with the Figure-3.

In another aspect of the present invention, the novel crystalline form B2 Linagliptin intermediate of **Formula V** is further characterized by PXRD having few prominent 2-theta values at 3.43± 0.2, 8.10± 0.2, 9.96± 0.2 & 17.02 ± 0.2 degrees 2θ and the PXRD pattern in accordance with the Figure-4.

In another aspect of the present invention, is novel crystalline form B2 Linagliptin intermediate of **Formula V** is further characterized by DSC having endotherm at around 168.69 °C and the DSC pattern in accordance with the Figure-5.

According to another aspect of the present invention provides process for the preparation of anhydrous form A/B of Linagliptin.

Characterization techniques:

FT-IR, DSC and PXRD techniques were used for characterising the co-crystal. The infrared spectroscopy, presents a great quantity of information about the chemical bonds and interaction. It is a fast analysis method, non-destructive.

The Powder X-ray diffraction is one of the most used techniques to determine different crystalline structures. This technique can distinguish the presence of a new crystallographic motif, which can be a polymorph or a co-crystal. It is a non-destructive method and presents diffractions patterns unique for each structure.

The differential scanning calorimetry is a characterization method based on the heat of reaction involved in different thermal events. For the pharmaceutical industry, the DSC is mostly used to obtain melting points of the API and thus, determine its purity.

Instrumental parameters:

DSC was performed on a Discovery DSC (TA instruments). About 3-5 mg of sample placed in crimped aluminium sample pan to be positioned on auto sampler. The temperature range was from 30-350 °C @ 10 °C/min. Samples were purged by a stream of nitrogen flowing at 50 mL/min.

Equilibrate: 30 °C

Ramp: 10 °C/min

Range: 30 °C -350 °C

The FT-IR spectrum (Fourier transform R spectroscopy) was recorded using the Fisher Scientific (NICOLET-iS50-FTIR), equipped with a KBr splitter and a DTGS KBr detector. The spectrum was recorded in the range of 4000 cm-1 to 400 cm-1

The powder X-ray powder diffractogram (XRPD) was obtained by using the instrument XRD BRUKER D8 ADVANCE, equipped with LYNXEYE detector with 40mA current intensity and 40kV voltage.

The sample was arranged on a Si-Zero background Sample holder and analysed using the following parameters:

- Scanning range (°): 3.000 to 60.000
- Step size (°): 0.03
- Scan type: Locked coupled
- Scanning mode: continuous
- Count time per step (s): 0.5
- Delay time (s): 0
- Divergent slit: 0.300
- Antiscatter slit: 0.300

Advantages of present invention:

An API can exist in a variety of solid state forms, which include: polymorphs; solvates; hydrates; salts; co-crystals and amorphous forms. Each form exhibits unique physiochemical properties that can profoundly influence the bioavailability, stability, manufacturability and other performance characteristics of the Formulated API.

Crystalline forms when compared to the amorphous form often show desired unique physical and/or biological characteristics which usually contributes in the manufacture or Formulation of the active compound, to the purity levels and uniformity required for regulatory approval. Hence, it is desirable to provide the pharmaceutically active ingredient in a substantially pure, crystalline and stable form of API.

Furthermore, the provision of further crystalline forms of a pharmaceutically useful compound offers an opportunity to improve the performance profile of a pharmaceutical

product. In particular, not all solid forms of a pharmaceutically useful compound are equally suited for development of a pharmaceutical dosage form. It is therefore desirable to widen the reservoir of materials a Formulation scientist can select from, such that he can design a new dosage form of a drug having improved characteristics.

BRIEF DESCRIPTION OF THE FIGURES

In order that the disclosure may be readily understood and put into practical effect, reference will now be made to exemplary embodiments as illustrated with reference to the accompanying figures. The figures together with a detailed description below, are incorporated in and form part of the specification, and serve to further illustrate the embodiments and explain various principles and advantages, in accordance with the present disclosure wherein:

Figure 1: Illustrates the PXRD pattern of novel crystalline Linagliptin intermediate of **Formula V** as obtained from Step 2 of Example-2a.

Figure 2: Illustrates the DSC thermogram of novel crystalline Linagliptin intermediate of **Formula V** as obtained from Step 2 of Example-2a.

Figure 3: Illustrates the FT-IR of novel crystalline Linagliptin intermediate of **Formula V** as obtained from Step 2 of Example-2a.

Figure 4: Illustrates the PXRD pattern of novel crystalline Linagliptin intermediate of **Formula V** as obtained from Step 2 of Example-2b.

Figure 5: Illustrates the DSC thermogram of novel crystalline Linagliptin intermediate of **Formula V** as obtained from Step 2 of Example-2b.

Figure 6: Illustrates the DSC thermogram of anhydrous form A/B of Linagliptin as obtained from Step 3 of Example-3.

The method of analysis of the compounds represented in the figures as above are as below:

PXRD analysis

About 300 mg of powder sample was taken onto the sample holder and was tightly packed on the sample holder uniformly by means of glass slide and Powder X-ray diffraction was recorded on Bruker D8 Advance diffractometer (Bruker-AXS, Karlsruhe, Germany) using

Cu-Kα X-radiation (λ = 1.5406 Å) at 40 kV and 30 mA powder.X-ray diffraction patterns were collected over the 2θ range 3–50° at a scan rate of 1°/min.

DSC Analysis

DSC was performed on a Mettler Toledo DSC 822e module. 4-6 mg of sample was placed in crimped but vented aluminium sample pans. The temperature range was from 30-250 °C @ 10 °C/min. Samples were purged by a stream of nitrogen flowing at 80 mL/min.

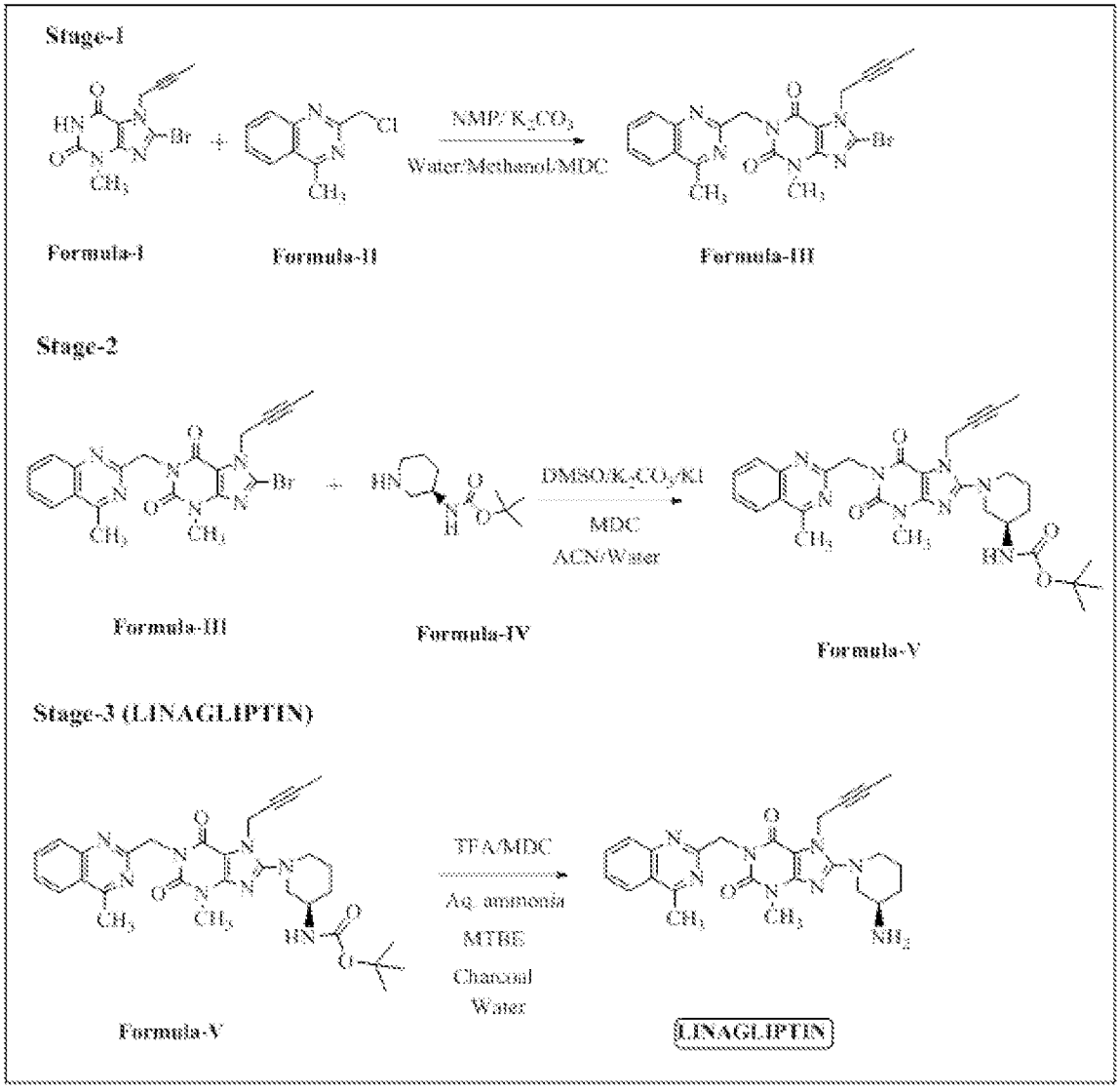
IR Analysis

IR was performed on a Fisher Scientific (NICOLET-iS50-FTIR). About 5 mg of sample was spread over the region of diamond ATR sampling station and collected the sample spectrum between 4000 cm-1 to 400 cm-1 to obtain a spectrum of suitable intensity (above 60 % transmission at 2000 cm-1).

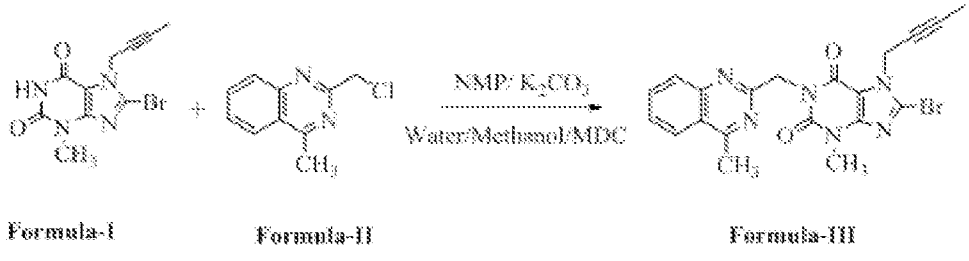
DETAILED DESCRIPTION OF THE INVENTION

The embodiments of the present invention are further described using specific examples herein after. The examples are provided for better understanding of certain embodiments of the invention and not, in any manner, to limit the scope thereof. Possible modifications and equivalents apparent to those skilled in the art using the teachings of the present description and the general art in the field of the invention shall also form the part of this specification and are intended to be included within the scope of it.

Synthetic scheme of the present invention:

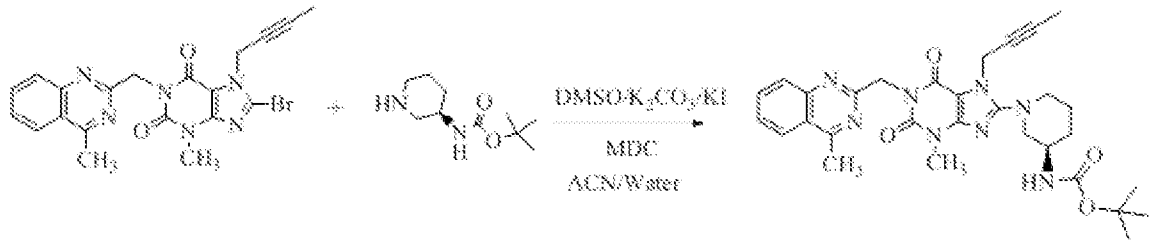


Example 1: Preparation of 8-bromo-7-(but-2-yn-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl) methyl)-3, 7-dihydro-1H-purine-2,6-dione (Formula III):



To a 3000 mL glass vessel equipped with a stirrer, condenser and a thermometer probe were added **Formula I** (100.0 g, 0.33 mol), **Formula II** (70.02 g, 0.36 mol), potassium carbonate (51.16 g, 0.37 mol) and N-Methyl-2-pyrrolidone (500.0 mL, 5.00 vol) and the mass was heated to 80±2 °C. The reaction mass was maintained at 80±2 °C under stirring for 6 to 8h. The reaction mass was cooled to 25±5 °C and water (1000 mL) was added to the reaction mass under constant stirring. The mass was filtered and the solid was washed with water (200 mL) followed by Methanol (200 mL), suck dried and dried at 45±5 °C under vacuum for 8-10h to obtain compound of Formula III as a pale yellow solid. It is further purified using a mixture of methanol and MDC.

Example 2a: Preparation of tert-butyl (R)-(1-(7-(but-2-yn-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl) piperidin -3-yl) carbamate (Formula V):



Formula-III Formula-IV Formula-V

To a 3000 mL glass vessel equipped with a stirrer, condenser and a thermometer probe were added **Formula III** (100.0 g, 0.22 mol) **Formula IV** (50.81 g, 0.25 mol), potassium iodide (3.66 g, 0.02 mol), potassium carbonate (36.65 g, 0.26 mol) and DMSO (400 mL). The mass was heated to 82±2 °C. The reaction mass was maintained at 82±2 °C under stirring for 6 - 9h. The reaction mass was cooled to 25±5 °C, MDC (400 mL) & water (600 mL) was added to the reaction mass under constant stirring for 1 to 2h. Layers were separated. Re-extracted the aqueous layer with MDC (2x200 mL). Combined the MDC layers and washed with water (200 mL). Separated the layers and partially concentrated the MDC layer to obtain the **Formula V** in MDC solution.

Purification of crude Formula V:

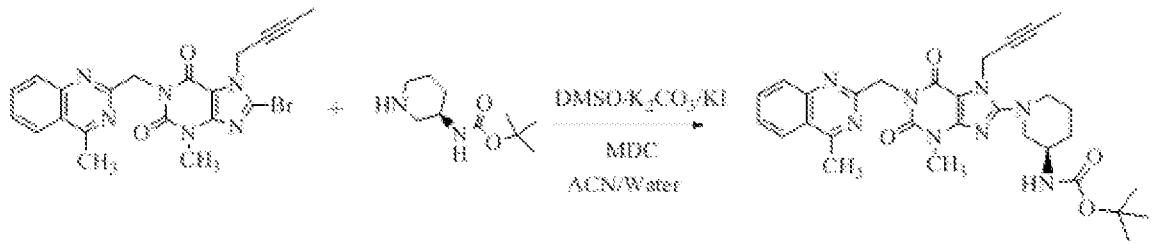
To the compound of Formula V in MDC solution was added acetonitrile and concentrated. Added another lot of acetonitrile and heated the reaction mass to 78±3 °C for 2 h. Charge water at temperature 70±5°C. Maintain at 75±5°C for 2 hours. Reaction mass was slowly cooled to 25±5°C. Stir the mass for 1 hour at 25±5°C. The resulting product was filtered off, washed with acetonitrile followed by water, suck dried and dried at 70±5 °C under vacuum for 16-18h to obtain compound of Formula V as a pale yellow solid.

The novel crystalline Linagliptin intermediate of **Formula V** which is prepared as per Example-2 is characterized by XPRD as represented in Figure-1.

The novel crystalline Linagliptin intermediate of **Formula V** which is prepared as per Example-2 is characterized by DSC as represented in Figure-2.

The novel crystalline Linagliptin intermediate of **Formula V** which is prepared as per Example-2 is characterized by FTIR as represented in Figure-3.

Example 2b: Preparation of tert-butyl (R)-(1-(7-(but-2-yn-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl) piperidin -3-yl) carbamate (Formula V):



Formula-III Formula-IV Formula-V

To a 3000 mL glass vessel equipped with a stirrer, condenser and a thermometer probe were added **Formula III** (100.0 g, 0.22 mol) **Formula IV** (50.81 g, 0.25 mol), potassium iodide (3.66 g, 0.02 mol), potassium carbonate (36.65 g, 0.26 mol) and DMSO (400 mL). The mass was heated to 82±2 °C. The reaction mass was maintained at 82±2 °C under stirring for 6 - 9h. The reaction mass was cooled to 25±5 °C, MDC (400 mL) & water (600 mL) was added to the reaction mass under constant stirring for 1 to 2h. Layers were

separated. Re-extracted the aqueous layer with MDC (2x200 mL). Combined the MDC layers and washed with water (200 mL). Separated the layers and partially concentrated the MDC layer to obtain the **Formula V** in MDC solution.

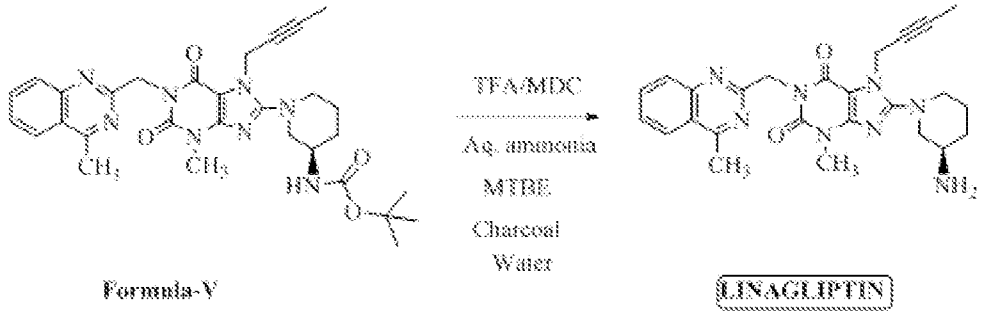
Purification of crude Formula V:

To the compound of Formula V in MDC solution was added pre-heated (60 °C) Acetonitrile (800 mL) was charged to the crude **Formula V**, heated the reaction mass to 55±5 °C and added water (500 mL). The reaction mixture was heated to 70±5 °C and stirred for 2-4 h and cooled the reaction mass slowly to room temperature. Stirred the reaction mass for 1h at 25±5 °C. The mass was filtered and the solid was washed with Acetonitrile (60 mL) followed by water (140 mL), suck dried and dried at 70±5 °C under vacuum for 16- 18h to obtain compound of Formula V as a pale yellow solid.

The novel crystalline Linagliptin intermediate of **Formula V** which is prepared as per Example-2 is characterized by XPRD as represented in Figure-4.

The novel crystalline Linagliptin intermediate of **Formula V** which is prepared as per Example-2 is characterized by DSC as represented in Figure-5.

Example 3: Preparation of Linagliptin:



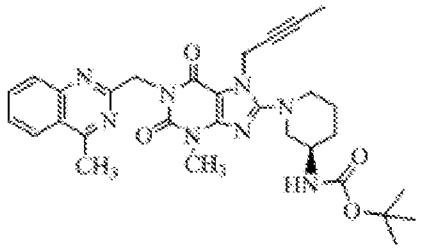
To a 3000 mL glass vessel equipped with a stirrer, condenser and a thermometer probe were added Formula V (100.0 g, 0.17 mol) and MDC (600 mL, 6.0 vol), stirred to dissolve at 25±5 °C. The reaction mixture was cooled to 20 ±5 °C and TFA (200 mL, 2.0 vol) was added slowly and warmed to 25±5 °C and stirred for 6-8h. After completion of the reaction MDC (500 mL) was added and cooled the reaction mass to 3±3 °C, water (500 mL) pre-chilled to 5±3 °C was added and adjusted pH of the reaction mass to 9 to 11 using aq.

Ammonia maintaining the reaction temperature at 5±3 °C. The reaction mass was warmed to 25±5 °C and stirred for 2 h. Layers were separated and MDC layer was preserved. The aqueous layer was re-extracted with MDC (300 mL). Combined MDC layers were treated with activated charcoal and stirred for 30 min. The reaction mass was filtered over celite bed and washed the celite bed with MDC (200 mL). Filtrate as obtained was concentrated at a temperature below 45 °C up to 3.0 vol. with respect to weight of Formula V used as input. MTBE (1200 mL) was added dropwise at 25±5 °C to the partially concentrated product and stirred for 1 h. The reaction mass was further cooled to 5±3 °C and stirred for 2 h. The product as obtained was filtered off, washed with MTBE (200 mL) and suck dried. The product was dried at 45±5 °C under vacuum for 10h to obtain Linagliptin as a pale yellow solid. The product was kept at -5±5°C for 36 h, raised the temperature to 25±5°C and hold it for 4-5 h to obtain anhydrous crystalline form A/B of Linagliptin.

The anhydrous crystalline form A/B of Linagliptin which is prepared as per Example-3 is characterized by DSC as represented in Figure-6.

CLAIMS

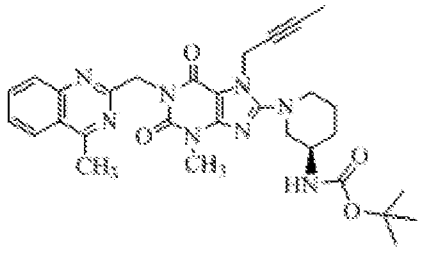
1. A crystalline form B1 of Linagliptin intermediate of **formula V**,



Formula-V

Characterised by an XPRD pattern in accordance with Figure-1.

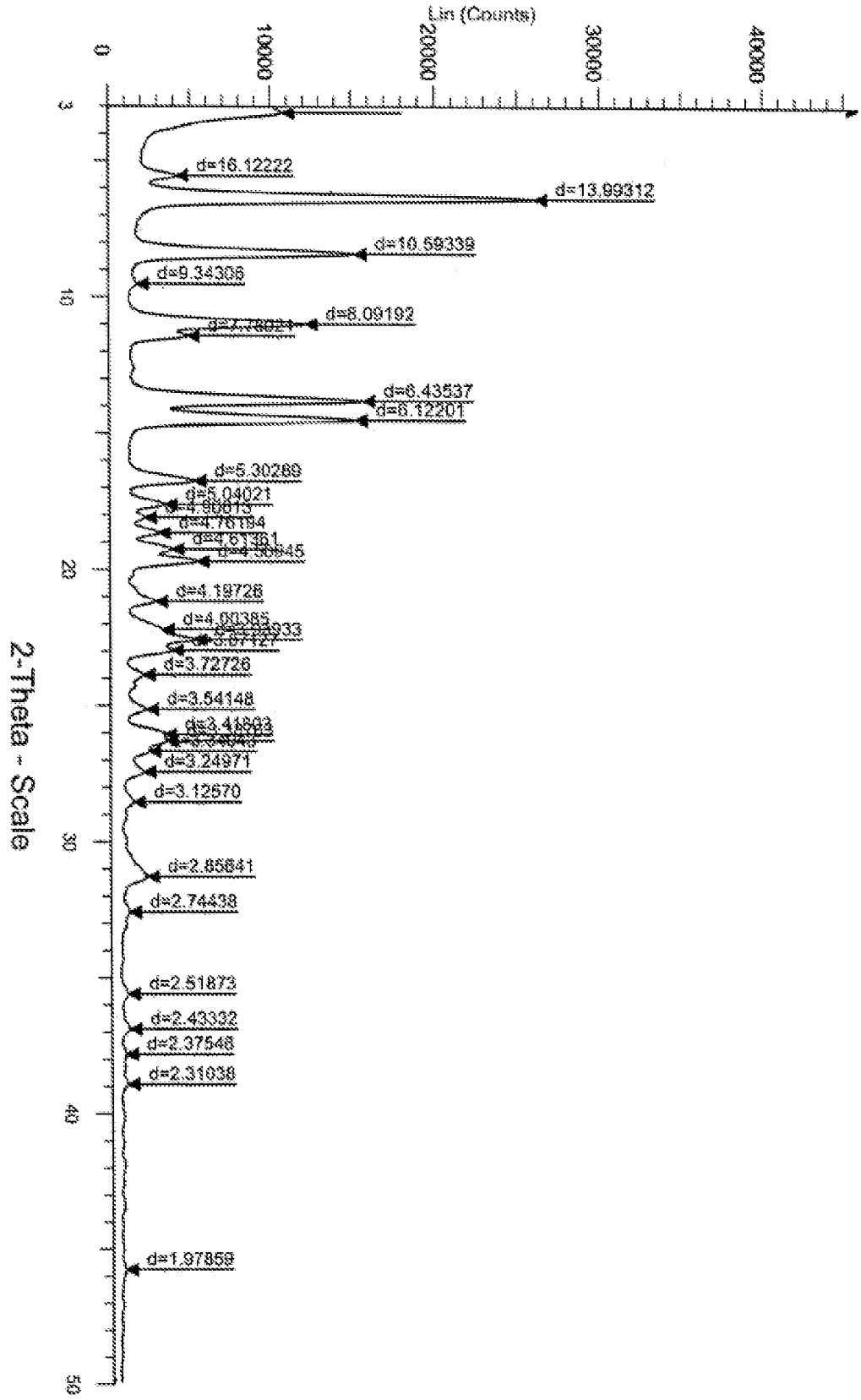
2. The crystalline form B1 of Linagliptin intermediate of **formula V**, as per claim 1 having prominent peaks at 3.14± 0.2, 6.31± 0.2, 8.34± 0.2, 10.93± 0.2, 13.75± 0.2 & 14.46 ± 0.2 degrees 2θ.
3. The crystalline form B1 of Linagliptin intermediate of **formula V**, as per claim 1 having DSC endotherms at 53.87 & 162.97 °C.
4. A process for preparation of crystalline form B1 of Linagliptin intermediate of **formula V** comprising following steps of:
   a. Heating crude linagliptin intermediate of **formula V** in a solvent.
   b. Adding a suitable anti-solvent to the reaction mass of above step at elevated temperature.
   c. Heating the reaction mass to an elevated temperature.
   d. Reaction mass was cooled and isolated the crystalline form of Linagliptin intermediate of **formula V.**
5. The process for preparation as per claim 4, wherein solvent is acetonitrile.
6. The process for preparation as per claim 4, wherein anti-solvent is water.
7. A crystalline form B2 of Linagliptin intermediate of **formula V**,



Formula-V

characterised by an XPRD pattern in accordance with Figure-1.

8. The crystalline form B2 of Linagliptin intermediate of **formula V**, as per claim 7 having prominent peaks at 3.43± 0.2, 8.10± 0.2, 9.96± 0.2 & 17.02 ± 0.2 degrees 2θ.
9. The crystalline form B2 of Linagliptin intermediate of **formula V**, as per claim 7 having DSC endotherms at 168.69 °C.
10. A process for preparation of crystalline form B2 of Linagliptin intermediate of **formula V** comprising following steps of:
    a. Treating crude linagliptin intermediate of **formula V** with preheated solvent.
    b. Adding an anti-solvent to the reaction mass of above step.
    c. Heating the reaction mass to an elevated temperature.
    d. Reaction mass was cooled and isolated the crystalline form of Linagliptin intermediate of **formula V.**
11. The process for preparation as per claim 4, wherein solvent is acetonitrile.
12. The process for preparation as per claim 4, wherein anti-solvent is water.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30000
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Figure 1

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4	8.3399	10.5934	651	58.0
5	9.4584	9.34306	68	6.1
6	10.9249	8.09192	521	46.4
7	11.3641	7.78021	202	18.0
8	13.7493	6.43537	673	59.9
9	14.4568	6.12201	653	58.1
10	16.7047	5.30289	218	19.5
11	17.5820	5.04021	141	12.6
12	18.0665	4.90613	85	7.6
13	18.6183	4.76195	123	10.9
14	19.2225	4.61361	159	14.1
15	19.6709	4.50945	225	20.1
16	21.1502	4.19726	113	10.1
17	22.1846	4.00385	133	11.8
18	22.5526	3.93933	218	19.4
19	22.9545	3.87127	156	13.9
20	23.8541	3.72726	80	7.2
21	25.1254	3.54148	88	7.9
22	26.0485	3.41803	137	12.2
23	26.2865	3.38763	142	12.6
24	26.6647	3.34043	95	8.5
25	27.4234	3.24971	82	7.3
26	28.5340	3.1257	54	4.8
27	31.2898	2.85641	90	8.0
28	32.6019	2.74438	42	3.8
29	35.6160	2.51873	38	3.4
30	36.9104	2.43332	41	3.6
31	37.8432	2.37546	31	2.8
32	38.9515	2.31038	35	3.1
33	45.8241	1.97859	27	2.4

Table-1

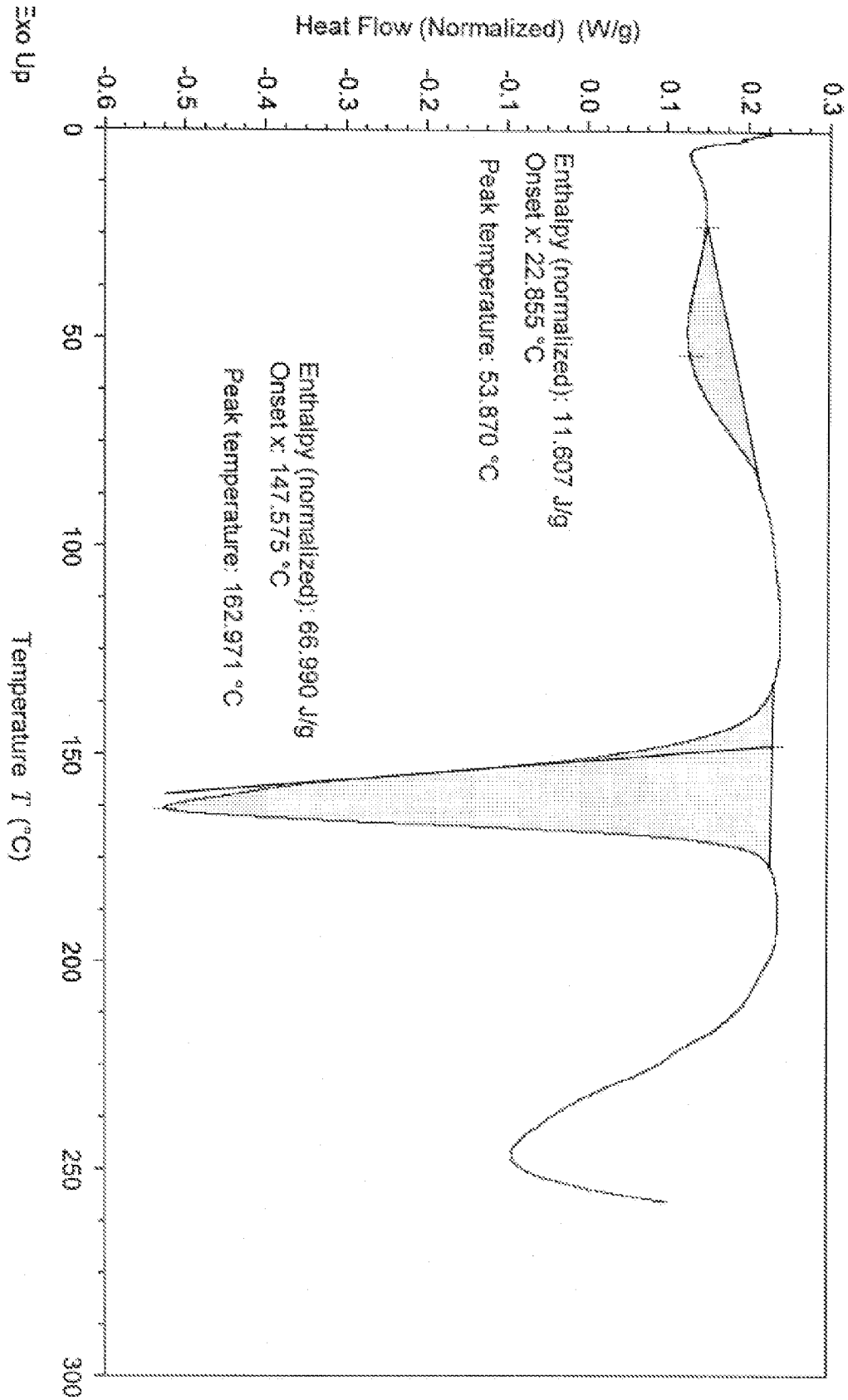
Heat Flow (Normalized) (W/g)
Exo Up
Temperature T (°C)
Enthalpy (normalized): 11.607 J/g
Onset x: 22.855 °C
Peak temperature: 53.870 °C
Enthalpy (normalized): 66.990 J/g
Onset x: 147.575 °C
Peak temperature: 162.971 °C

Figure 2

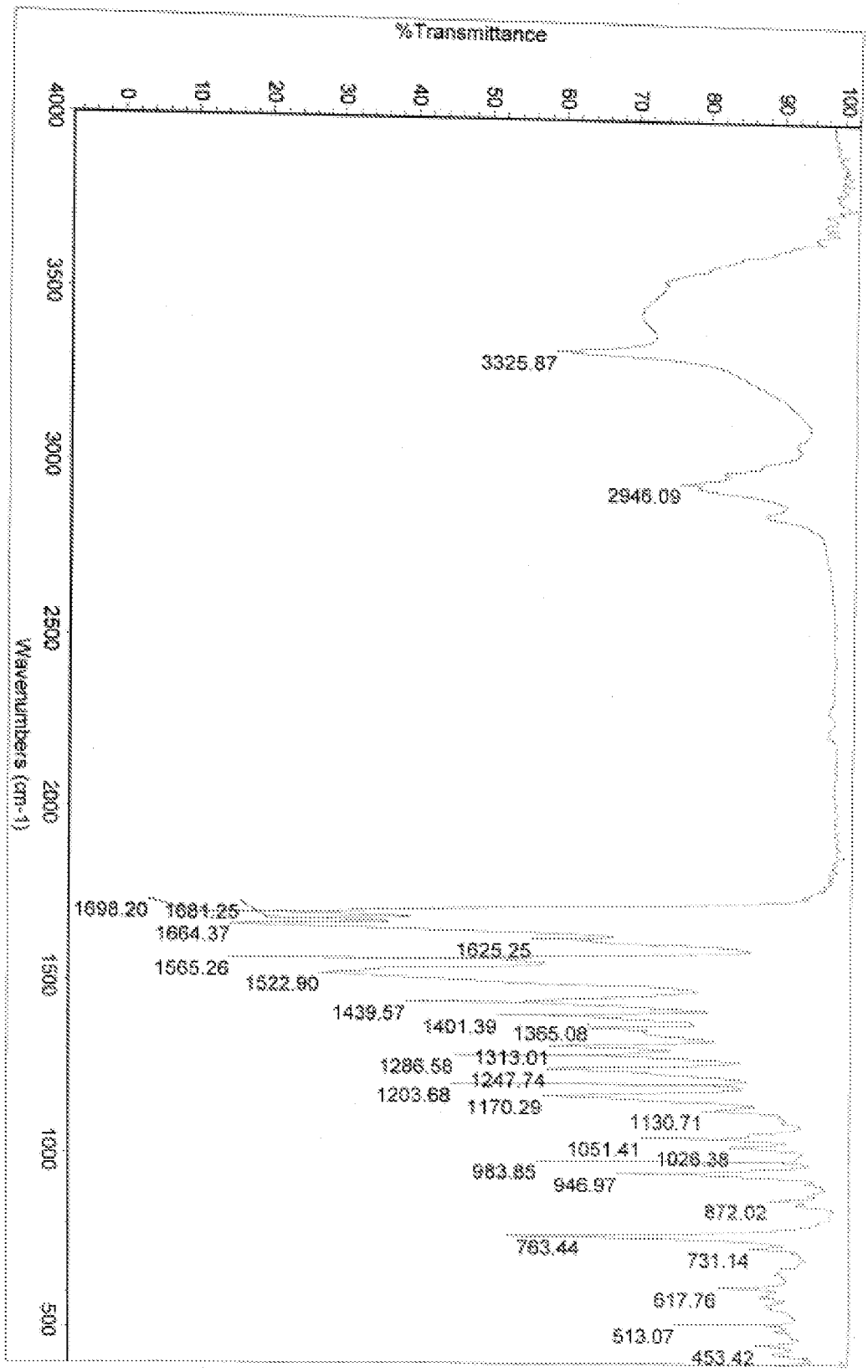
%Transmittance
0
10
20
30
40
50
60
70
80
90
100
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)
3325.87
2946.09
1698.20
1681.25
1664.37
1625.25
1565.26
1522.90
1439.57
1401.39
1365.08
1313.01
1286.59
1247.74
1203.68
1170.29
1130.71
1051.41
1029.38
983.85
946.97
872.02
763.44
731.14
617.76
513.07
453.42

Figure 3

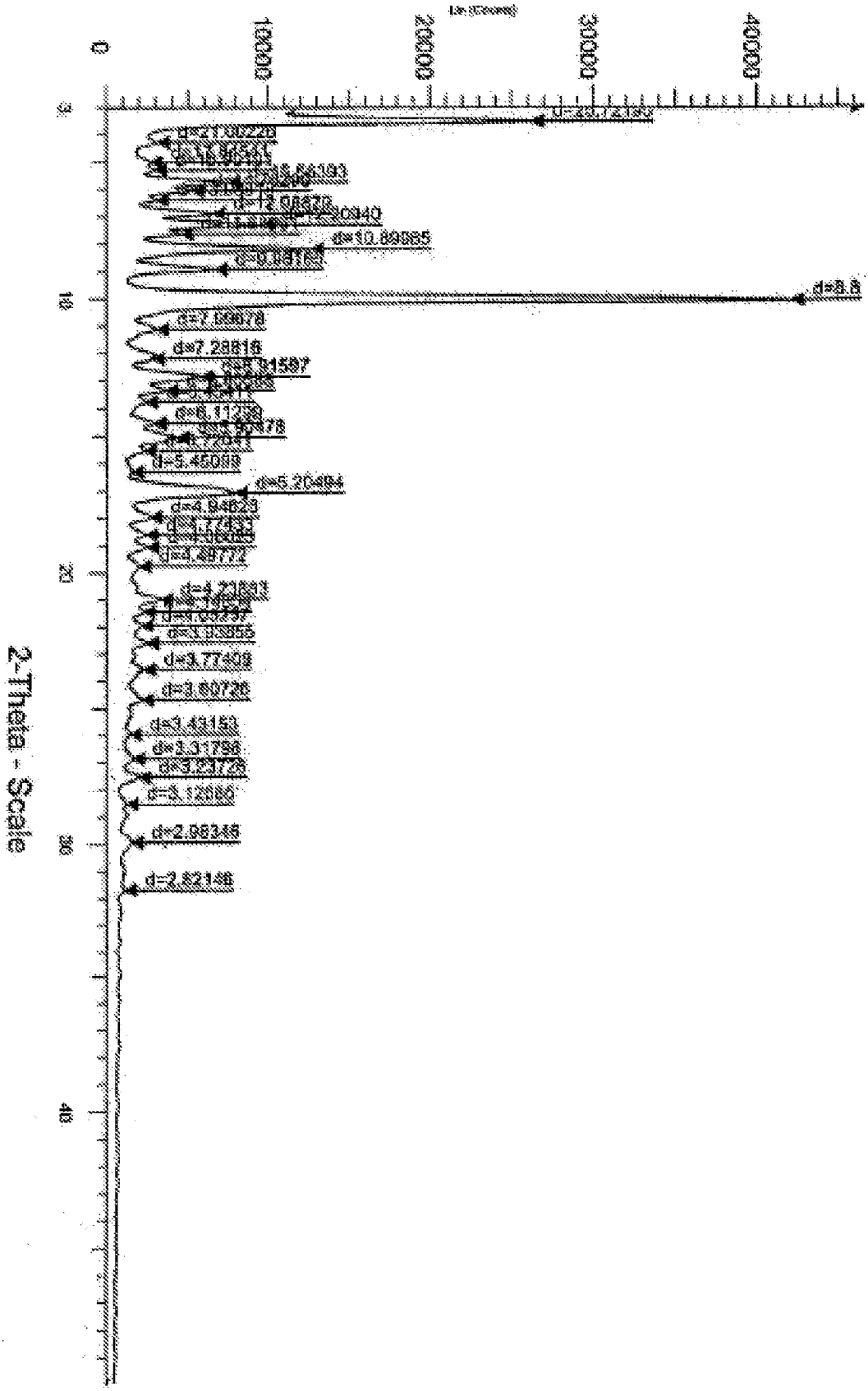
0
10000
20000
30000
40000
2-Theta - Scale
d=10.89585
d=8.8
d=7.28818
d=5.20484
d=4.94623
d=4.49772
d=3.77409
d=3.60726
d=3.31756
d=2.98346
d=2.82148

Figure 4

Num.	Gonio	d	Int	I/Imax
1	3.4322	25.722	1138	61.9
2	4.2038	21.0023	128	7.0
3	4.9479	17.8454	109	6.0
4	5.2243	16.9015	119	6.6
5	5.6738	15.5639	318	17.5
6	5.9819	14.7629	218	12.0
7	6.3135	13.9882	124	6.8
8	6.9103	12.9688	276	15.2
9	7.2345	12.2094	410	22.5
10	7.5566	11.6896	188	10.3
11	8.1050	10.8998	542	29.7
12	8.8520	9.98165	281	15.5
13	8.9569	9.87636	1821	100.0
14	11.0553	7.99670	125	6.8
15	12.1341	7.28816	114	6.3
16	12.7897	6.91597	243	13.3
17	13.2897	6.65688	169	9.2
18	13.7092	6.45411	94	5.2
19	14.4782	6.11299	117	6.4
20	14.9916	5.90478	179	9.8
21	15.4777	5.72061	80	4.4
22	16.2478	5.45099	58	3.2
23	17.0214	5.20494	336	18.5
24	17.9187	4.94626	107	5.9
25	18.5696	4.77433	94	5.2
26	19.0284	4.66023	97	5.3
27	19.7227	4.49772	77	4.2
28	20.9403	4.23881	133	7.3
29	21.4015	4.14854	88	4.8
30	21.9146	4.05257	83	4.5
31	22.5572	3.93855	98	5.4
32	23.5539	3.77409	90	4.9
33	24.6600	3.60726	84	4.6
34	25.9442	3.43153	53	2.9
35	26.8485	3.31798	61	3.3
36	27.9309	3.23726	76	4.2
37	28.5232	3.12685	44	2.4
38	29.9254	2.98346	58	3.2
39	31.6075	2.82146	39	2.2

Table-2

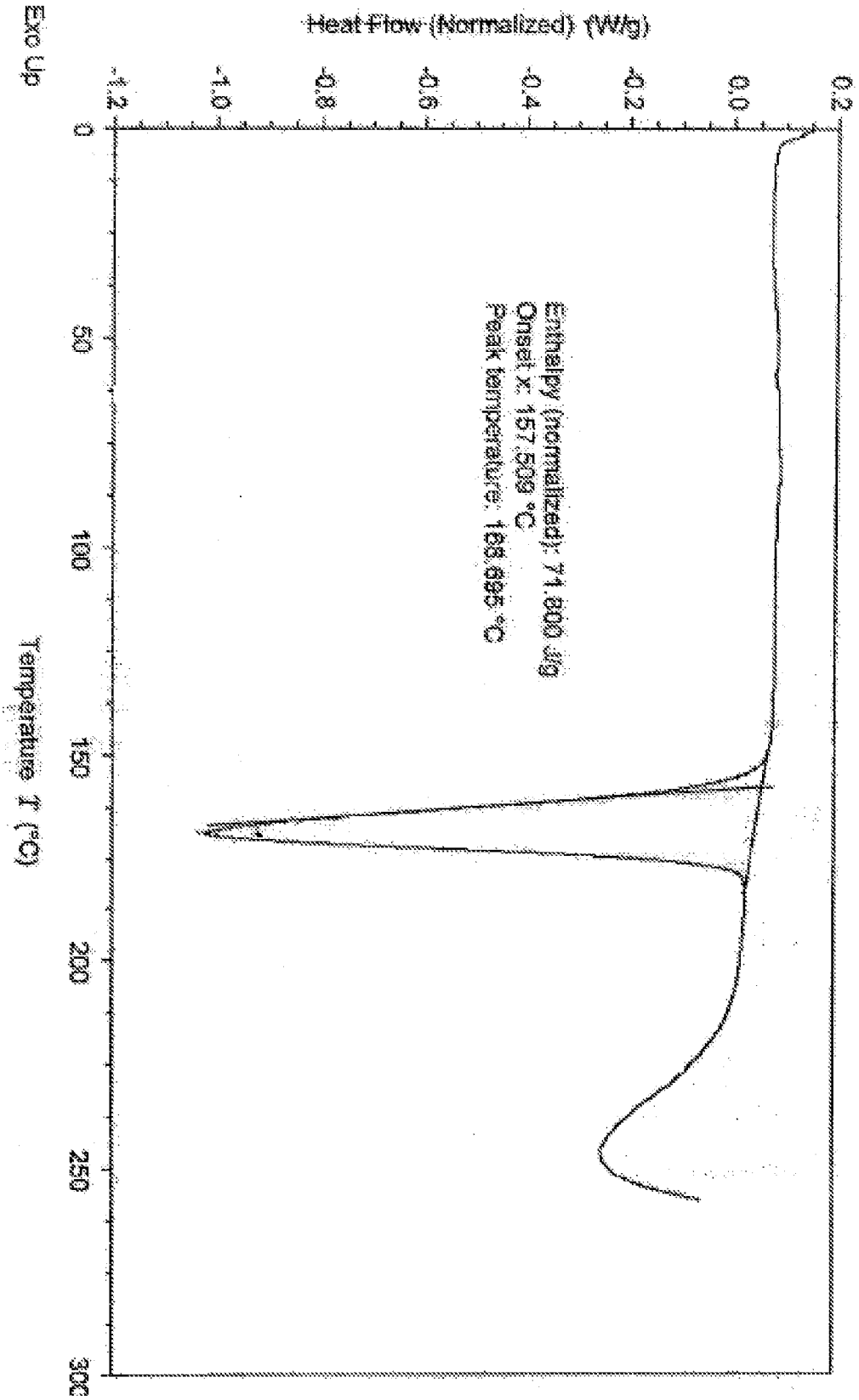
Exo Up
Heat Flow (Normalized) (W/g)
-1.2
-1.0
-0.8
-0.6
-0.4
-0.2
0.0
0.2
0
50
100
150
200
250
300
Temperature T (°C)
Enthalpy (normalized): 71.800 J/g
Onset x: 157.509 °C
Peak temperature: 165.895 °C

Figure 5

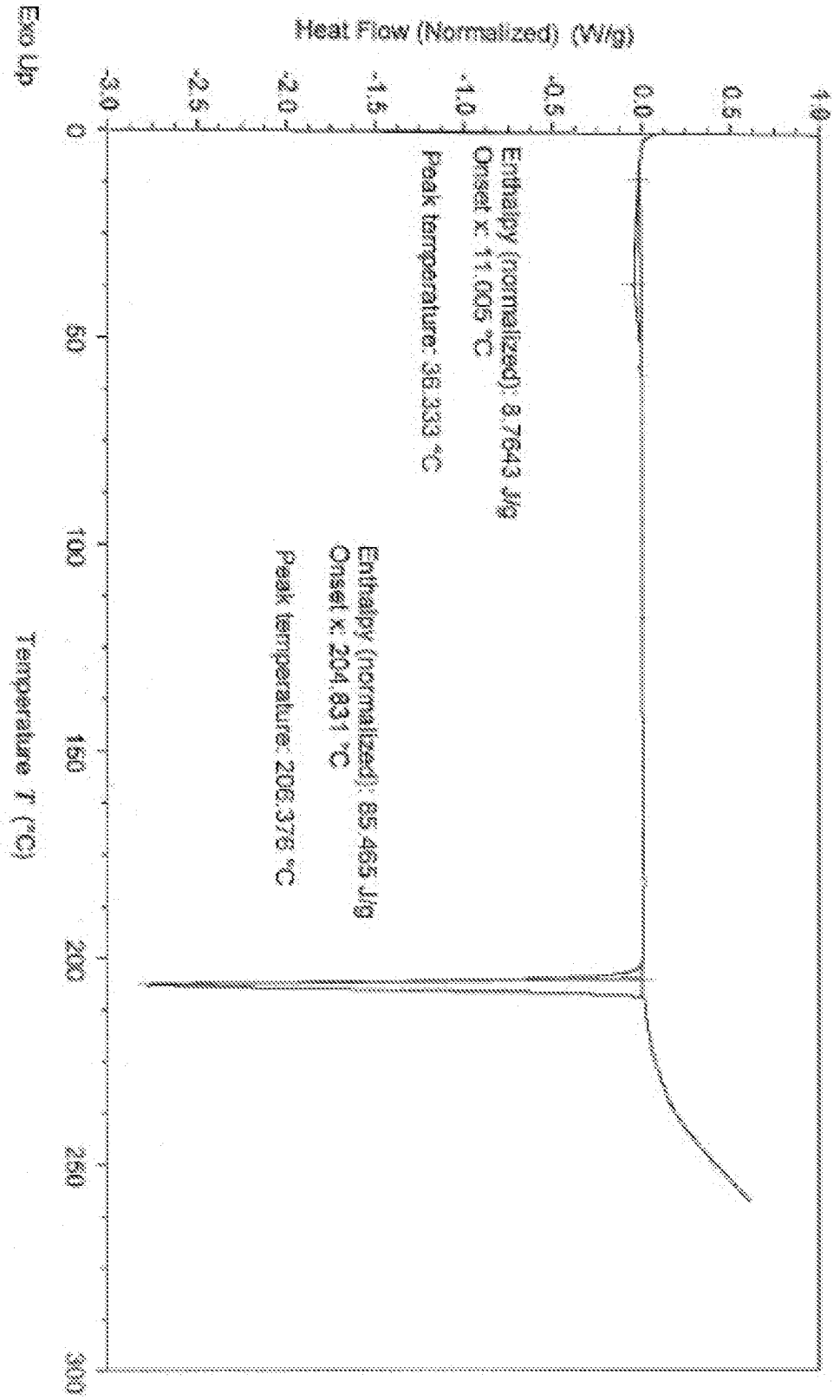
Heat Flow (Normalized) (W/g)
Exo Up
Temperature T (°C)
Enthalpy (normalized): 8.7643 J/g
Onset x: 11.005 °C
Peak temperature: 36.333 °C
Enthalpy (normalized): 85.465 J/g
Onset x: 204.831 °C
Peak temperature: 206.376 °C

Figure 6