(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 January 2016 (28.01.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/012470 A1

(51) International Patent Classification:
C07D 417/14 (2006.01) *A61K 31/506* (2006.01)
A61K 31/427 (2006.01) *A61P 31/12* (2006.01)

(21) International Application Number:
PCT/EP2015/066695

(22) International Filing Date:
22 July 2015 (22.07.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/CN2014/083010 25 July 2014 (25.07.2014) CN
PCT/CN2015/082814 30 June 2015 (30.06.2015) CN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

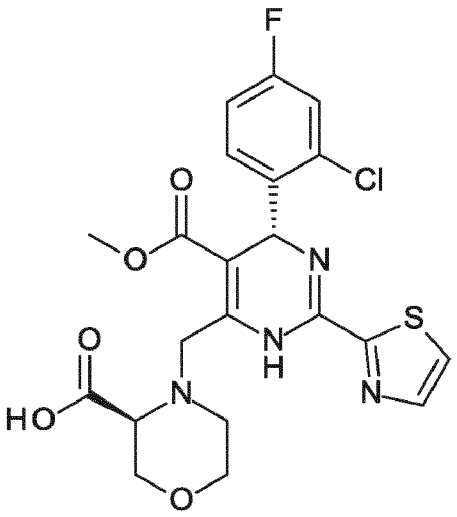
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

[Continued on next page]

(54) Title: NEW AMORPHOUS AND CRYSTALLINE FORMS OF (3S)-4-[[(4R)-4-(2-CHLORO-4-FLUORO-PHENYL)-5-METHOXYCARBONYL-2-THIAZOL-2-YL-1, 4-DIHYDROPYRIMIDIN-6-YL]METHYL]MORPHOLINE-3-CARBOXYLIC ACID



(I)

(57) Abstract: The present invention relates to a novel amorphous and crystalline form of compound (I) (3S)-4-[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1, 4- dihydropyrimidin-6-yl]methyl]morpholine-3-carboxylic acid and pharmaceutical compositions comprising the amorphous or crystalline forms or tautomers thereof disclosed herein, which may be used for the treatment or prophylaxis of a viral disease in a patient relating to hepatitis B infection or a disease caused by hepatitis B infection.

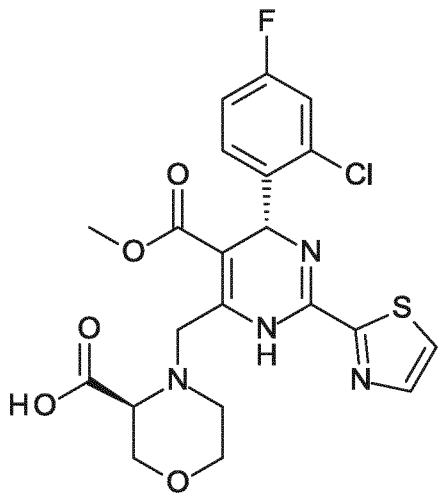
WO 2016/012470 A1

Published:

— *with international search report (Art. 21(3))*

New amorphous and crystalline forms of (3S)-4-[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1, 4-dihydropyrimidin-6-yl]methyl]morpholine-3-carboxylic acid

The present invention relates to novel amorphous and crystalline forms of compound (I),



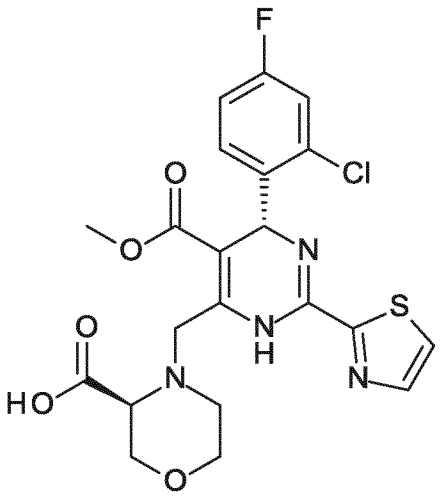
(I),

(3S)-4-[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1, 4-dihydropyrimidin-6-yl]methyl]morpholine-3-carboxylic acid and pharmaceutical compositions comprising the amorphous or crystalline forms or tautomers thereof disclosed herein, which may be used for the treatment or prophylaxis of a viral disease in a patient relating to hepatitis B infection or a disease caused by hepatitis B infection.

BACKGROUAND OF THE INVENTION

Hepatitis B is recognized as a chronic viral disease of the liver which is characterized by liver disease. Inhibitors of hepatitis B virus (HBV) are useful to limit the establishment and progression of infection by HBV as well as in diagnostic assays for HBV.

WO2014/037480 A1 disclosed HBV inhibitor compound (I), (3S)-4-[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1, 4-dihydropyrimidin-6-yl]methyl]morpholine-3-carboxylic acid. Compound (I) simultaneously has tautomer as compound (Ia), (3S)-4-[[(6R)-6-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,6-dihydropyrimidin-4-yl]methyl]morpholine-3-carboxylic acid. The compound (I) and its tautomer, compound (Ia), have rapid transforming speed at ambient temperature, which exist as the structure of (3S)-4-[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1, 4-dihydropyrimidin-6-yl]methyl]morpholine-3-carboxylic acid at ambient temperature. Compound (I) and compound (Ia) are shown below:



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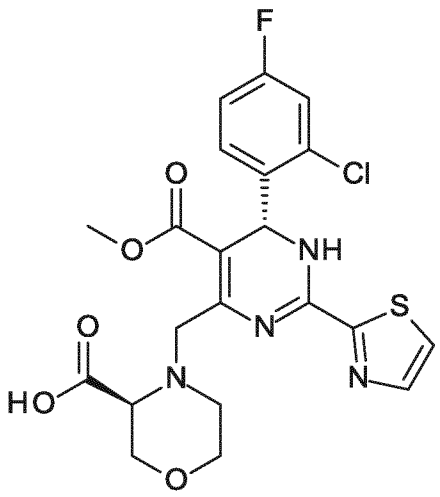


(Ia).

Solid form is a term to describe how one compound exists as solid state which includes amorphous, polymorph, salt, co-crystal, etc. It has fundamental influences on the physicochemical properties such as solubility, chemical stability, physical stability, powder properties, etc.

Methyl sulfonic acid (MSA) is a commonly used counterion for salt formation in pharmaceutical industry (Salt and Cocrystal Form Selection in Preclinical Development Handbook. Wiley-Interscience, Hoboken. 2008, 455-481). The MSA salt of compound (I) was identified and used at the early research stage. However, serious chemical stability issue of this MSA salt was observed, limiting the developability of compound (I) dramatically. As an action

of risk mitigation, comprehensive studies were conducted. Several novel crystalline solid forms were synthesized and characterized, showing significantly improved stability compared with MSA salt. These novel crystalline forms enhanced the developability of compound (I) fundamentally. At the same time, amorphous form of compound (I) was also synthesized and showed amazing stability although amorphous is generally considered as metastable solid form.

The present disclosure relates generally to novel solid forms of compound (I), and processes to make the forms.

SUMMARY OF THE INVENTION

The present invention relates to polymorphs, amorphous, salts, co-crystals and methods for the synthesis of selective production of amorphous and crystalline forms of (3S)-4-[[(4R)-4-(2-chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1, 4-dihydropyrimidin-6-yl]methyl]morpholine-3-carboxylic acid.

In one aspect, provided herein is an amorphous or crystalline form of compound (I) or salts, solvates or combination thereof. The XRPD pattern of amorphous form is shown in FIG. 1.

In another aspect, the amorphous or crystalline form of compound (I) is Form A, Form B, Form C, Form D, Form E, Form F, Form G, Form H, Form L, Form M, Form N, Form P, Form Q or a combination thereof.

In another embodiment, the crystalline form is Form A that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 7.77°±0.1°, 8.22°±0.1°, 19.71°±0.1°, 19.99°±0.1°, 24.77°±0.1° and 25.68°±0.1°.

In a further embodiment, the crystalline form is Form A that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 7.77°±0.1°, 8.22°±0.1°, 9.10°±0.1°, 9.81°±0.1°, 11.33°±0.1°, 12.60°±0.1°, 14.31°±0.1°, 19.71°±0.1°, 19.99°±0.1°, 21.56°±0.1°, 21.97°±0.1°, 22.46°±0.1°, 23.22°±0.1°, 24.77°±0.1°, 25.68°±0.1°, 26.10°±0.1°, 27.47°±0.1° and 28.22°±0.1°.

In a further embodiment, the crystalline form is Form A that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 2.

In a further embodiment, the crystalline form is Form A which is a hydrate of compound (I). In a further embodiment, Form A is a monohydrate, bihydrate, trihydrate, tetrahydrate, pentahydrate or hexahydrate of compound (I). In a further embodiment, the water content of Form A is from 0.5% to 10%, particularly from 2.5% to 4.5%.

In a further embodiment, the crystalline form is Form A with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak with onset temperature at 39°C±3°C.

In another embodiment, the crystalline form is Form B that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 8.42°±0.1°, 19.62°±0.1°, 20.42°±0.1°, 23.03°±0.1°, 25.51°±0.1° and 26.65°±0.1°.

In a further embodiment, the crystalline form is Form B that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 8.42°±0.1°, 9.34°±0.1°, 11.72°±0.1°, 12.63°±0.1°, 18.67°±0.1°, 19.62°±0.1°, 20.42°±0.1°, 23.03°±0.1°, 24.04°±0.1°, 25.51°±0.1°, 25.99°±0.1°, 26.65°±0.1°, 27.74°±0.1° and 28.36°±0.1°.

In a further embodiment, the crystalline form is Form B that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 5.

In a further embodiment, the crystalline form is Form B which is an anhydrous form of compound (I).

In another embodiment, the crystalline form is Form C that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 17.04°±0.1°, 20.93°±0.1°, 21.28°±0.1°, 22.56°±0.1°, 24.17°±0.1° and 24.38°±0.1°.

In a further embodiment, the crystalline form is Form C that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 9.65°±0.1°, 12.58°±0.1°, 14.89°±0.1°, 17.04°±0.1°, 19.40°±0.1°, 20.93°±0.1°, 21.28°±0.1°, 22.56°±0.1°, 23.67°±0.1°, 24.17°±0.1°, 24.38°±0.1° and 24.81°±0.1°.

In a further embodiment, the crystalline form is Form C that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 6.

In a further embodiment, the crystalline form is Form C which is a co-crystal of monohydrate of compound (I) and tetrafluoroborate of compound (I).

In a further embodiment, the crystalline form is Form C with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak with onset temperature at 171°C±3°C.

In a further embodiment, the crystalline form is Form C with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak substantially the same as shown in FIG.7.

In another embodiment, the crystalline form is Form D that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 15.74°±0.1°, 17.20°±0.1°, 20.46°±0.1°, 23.43°±0.1°, 28.38°±0.1° and 30.88°±0.1°.

In a further embodiment, the crystalline form is Form D that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 15.74°±0.1°, 17.20°±0.1°, 20.46°±0.1°, 21.96°±0.1°, 23.43°±0.1°, 24.76°±0.1°, 28.38°±0.1°, 30.88°±0.1°, 31.72°±0.1°, 32.80°±0.1°, 33.55°±0.1° and 37.17°±0.1°.

In a further embodiment, the crystalline form is Form D with the X-ray crystal structure showed in FIG. 9.

In a further embodiment, the crystalline form is Form D that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 10.

In a further embodiment, the crystalline form is Form D with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak with onset temperature at 216°C±3°C.

In a further embodiment, the crystalline form is Form D with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak substantially the same as shown in FIG.11.

In another embodiment, the crystalline form is Form E that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 7.39°±0.1°, 7.96°±0.1°, 9.82°±0.1°, 20.74°±0.1°, 22.50°±0.1°, 23.82°±0.1°, 24.69°±0.1° and 26.20°±0.1°.

In a further embodiment, the crystalline form is Form E that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 7.39°±0.1°, 7.96°±0.1°, 9.82°±0.1°, 12.22°±0.1°, 16.92°±0.1°, 20.02°±0.1°, 20.74°±0.1°, 21.65°±0.1°, 22.50°±0.1°, 23.82°±0.1°, 24.69°±0.1°, 26.20°±0.1°, 27.76°±0.1° and 28.92°±0.1°.

In a further embodiment, the crystalline form is Form E that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 13.

In a further embodiment, the crystalline form is Form E with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak with onset temperature at 136°C±3°C.

In a further embodiment, the crystalline form is Form E with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak substantially the same as shown in FIG.14.

In another embodiment, the crystalline form is Form F that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 11.73°±0.1°, 20.87°±0.1°, 21.80°±0.1°, 23.15°±0.1°, 27.03°±0.1° and 28.58°±0.1°.

In a further embodiment, the crystalline form is Form F that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 11.02°±0.1°, 11.73°±0.1°, 14.89°±0.1°, 18.36°±0.1°, 20.87°±0.1°, 21.80°±0.1°, 23.15°±0.1°, 24.44°±0.1°, 25.35°±0.1°, 27.03°±0.1°, 28.58°±0.1°, 32.21°±0.1°, 33.52°±0.1° and 39.03°±0.1°.

In a further embodiment, the crystalline form is Form F that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 16.

In a further embodiment, the crystalline form is Form F with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak with onset temperature at 141°C±3°C.

In a further embodiment, the crystalline form is Form F with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak substantially the same as shown in FIG.17.

In another embodiment, the crystalline form is Form G that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 9.85°±0.1°, 12.32°±0.1°, 17.37°±0.1°, 23.07°±0.1°, 24.86°±0.1°, 25.31°±0.1° and 28.48°±0.1°.

In a further embodiment, the crystalline form is Form G that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 6.81°±0.1°, 8.20°±0.1°, 9.85°±0.1°, 12.32°±0.1°, 15.01°±0.1°, 17.37°±0.1°, 19.35°±0.1°, 21.19°±0.1°, 22.42°±0.1°, 23.07°±0.1°, 24.86°±0.1°, 25.31°±0.1°, 26.57°±0.1°, 28.48°±0.1° and 35.38°±0.1°.

In a further embodiment, the crystalline form is Form G that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 19.

In a further embodiment, the crystalline form is Form G with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak with onset temperature at 152°C±3°C.

In a further embodiment, the crystalline form is Form G with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak substantially the same as shown in FIG.20.

In another embodiment, the crystalline form is Form H that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 7.88°±0.1°, 18.31°±0.1°, 19.94°±0.1°, 21.49°±0.1°, 23.12°±0.1°, 23.91°±0.1°, 25.69°±0.1° and 26.83°±0.1°.

In a further embodiment, the crystalline form is Form H that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 7.88°±0.1°, 13.23°±0.1°, 14.42°±0.1°, 17.69°±0.1°, 18.31°±0.1°, 19.94°±0.1°, 21.49°±0.1°, 23.12°±0.1°, 23.91°±0.1°, 25.69°±0.1° and 26.83°±0.1°.

In a further embodiment, the crystalline form is Form H that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 22.

In a further embodiment, the crystalline form is Form H with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak with onset temperature at 136°C±3°C.

In a further embodiment, the crystalline form is Form H with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak substantially the same as shown in FIG.23.

In a further embodiment, the crystalline form is Form D, Form E, Form F, Form G or Form H, which is a hydrochloride salt of compound (I).

In another embodiment, the crystalline form is Form L that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 5.29°±0.1°, 15.86°±0.1°, 18.99°±0.1°, 20.88°±0.1°, 22.96°±0.1° and 23.30°±0.1°.

In a further embodiment, the crystalline form is Form L that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 5.29°±0.1°, 10.56°±0.1°, 10.95°±0.1°, 15.86°±0.1°, 18.99°±0.1°, 20.88°±0.1°, 21.19°±0.1°, 21.71°±0.1°, 22.96°±0.1°, 23.30°±0.1°, 25.02°±0.1°, 26.84°±0.1°, 28.29°±0.1° and 32.36°±0.1°.

In another embodiment, the crystalline form is Form L that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 30.

In a further embodiment, the crystalline form is Form L with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak with onset temperature at 160°C±3°C.

In a further embodiment, the crystalline form is Form L with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak substantially the same as shown in FIG.31.

In a further embodiment, the crystalline form is Form L is an ethylsulfate of compound (I).

In a further embodiment, the crystalline form is Form L with the X-ray crystal structure showed in FIG. 33.

In another embodiment, the crystalline form is Form M that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 6.24°±0.1°, 8.57°±0.1°, 13.64°±0.1°, 14.53°±0.1°, 16.50°±0.1°, 17.18°±0.1°, 19.47°±0.1° and 22.11°±0.1°.

In a further embodiment, the crystalline form is Form M that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 6.24°±0.1°, 8.57°±0.1°, 9.80°±0.1°, 13.64°±0.1°, 14.53°±0.1°, 16.50°±0.1°, 17.18°±0.1°, 19.47°±0.1°, 22.11°±0.1°, 25.23°±0.1°, 28.11°±0.1° and 29.39°±0.1°.

In a further embodiment, the crystalline form is Form M that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 34.

In a further embodiment, the crystalline form is Form M with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak with onset temperature at 59°C±3°C.

In a further embodiment, the crystalline form is Form M with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak substantially the same as shown in FIG. 35.

In another embodiment, the crystalline form is Form N that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 4.62°±0.1°, 9.22°±0.1°, 18.50°±0.1°, 19.05°±0.1°, 23.14°±0.1° and 23.88°±0.1°.

In a further embodiment, the crystalline form is Form N that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 4.62°±0.1°, 9.22°±0.1°, 11.81°±0.1°, 13.10°±0.1°, 13.83°±0.1°, 17.44°±0.1°, 18.50°±0.1°, 19.05°±0.1°, 20.63°±0.1°, 21.98°±0.1°, 23.14°±0.1°, 23.88°±0.1°, 25.61°±0.1°, 27.85°±0.1°, 29.31°±0.1° and 39.07°±0.1°.

In a further embodiment, the crystalline form is Form N that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 37.

In a further embodiment, the crystalline form is Form N with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak with onset temperature at 63°C±3°C.

In a further embodiment, the crystalline form is Form N with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak substantially the same as shown in FIG.38.

In another embodiment, the crystalline form is Form P that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 11.27°±0.1°, 12.18°±0.1°, 17.57°±0.1°, 18.01°±0.1°, 22.38°±0.1° and 23.16°±0.1°.

In a further embodiment, the crystalline form is Form P that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 7.23°±0.1°, 11.27°±0.1°, 12.18°±0.1°, 15.51°±0.1°, 16.46°±0.1°, 17.57°±0.1°, 18.01°±0.1°, 21.18°±0.1°, 22.38°±0.1°, 23.16°±0.1°, 24.44°±0.1°, 29.59°±0.1° and 31.83°±0.1°.

In a further embodiment, the crystalline form is Form P that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 40.

In a further embodiment, the crystalline form is Form P with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak with onset temperature at 230°C±3°C.

In a further embodiment, the crystalline form is Form P with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak substantially the same as shown in FIG. 41.

In another embodiment, the crystalline form is Form Q that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 11.04°±0.1°, 12.77°±0.1°, 16.33°±0.1°, 16.71°±0.1°, 18.06°±0.1° and 20.65°±0.1°.

In a further embodiment, the crystalline form is Form Q that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 4.35°±0.1°,

9.96°±0.1°, 11.04°±0.1°, 12.77°±0.1°, 15.04°±0.1°, 16.33°±0.1°, 16.71°±0.1°, 18.06°±0.1°, 20.65°±0.1°, 22.19°±0.1°, 23.76°±0.1°, 25.36°±0.1°, 26.64°±0.1°, 29.34°±0.1° and 30.26°±0.1°.

In a further embodiment, the crystalline form is Form Q that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 43.

In a further embodiment, the crystalline form is Form Q with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak with onset temperature at 191°C±3°C.

In a further embodiment, the crystalline form is Form Q with a differential scanning calorimetry (DSC) thermogram comprising endothermic peak substantially the same as shown in FIG.44.

In a further embodiment, the crystalline form is Form M, Form N, Form P or Form Q, which is a calcium salt of compound (I).

In another aspect, provided herein is a pharmaceutical composition comprising the amorphous or crystalline form disclosed herein; and a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

In another aspect, provided herein is the use of the amorphous or crystalline form disclosed herein or the pharmaceutical composition for the manufacture of a medicament for the treatment or prophylaxis of a viral disease in a patient.

In another aspect, the viral disease disclosed herein is hepatitis B infection or a disease caused by hepatitis B infection.

In another aspect, provided herein is a method for the treatment or prophylaxis of hepatitis B infection or a disease caused by hepatitis B infection, which method comprises administering an therapeutically effective amount of the amorphous or crystalline form or the pharmaceutical composition disclosed herein.

The relative peak height of X-ray powder diffraction (XRPD) pattern depends on many factors related to sample preparation and geometric shapes of the instrument, however peak

position is insensitive to experimental details. In some embodiments, the crystalline form disclosed herein characterized by XRPD pattern with some listed peak positions essentially can also be characterized by XRPD pattern provided in the appended drawings of the present invention. According to the state of the instrument for the experiment, the error margin in 2-theta of the characteristic peaks is $\pm 0.1^{\circ}$.

Similarly, the relative peak height of differential scanning calorimetry (DSC) depends on many factors related to sample preparation and geometric shapes of the instrument, however peak position is insensitive to experimental details. In some embodiments, the crystalline form disclosed herein characterized by DSC thermogram with some listed peak positions essentially can also be characterized by DSC thermogram provided in the appended drawings of the present invention. According to the state of the instrument for the experiment, the error margin in the melting peaks is $\pm 3^{\circ}C$.

Similarly, the weight loss and corresponding temperature of thermal gravimetric analysis (TGA) depends on many factors related to sample preparation and geometric shapes of the instrument. In some embodiments, the crystalline form disclosed herein characterized by TGA thermogram with some listed weight losses essentially can also be characterized by TGA thermogram provided in the appended drawings of the present invention.

Whenever a number disclosed in the invention with "±" stands for a numerical range with a lower limit and an upper limit, any number falling within the rage between lower limit and upper limit is disclosed.

As used herein, the term "relative intensity" refers to the intensity of a peak with respect to the intensity of the strongest peak in the XRPD pattern which is regarded as 100%.

As used herein, the term "combination" refers to a crystalline form containing a tautomer thereof, or a crystalline form containing one or more other crystalline forms or amorphous form.

As used herein, the term "peak" refers to a feature, in a spectrum and/or data presented in a graph, that one skilled in the art would recognize as not attributable to background noise.

The terms "pharmaceutical composition" is used interchangeably and denote a mixture or solution comprising a therapeutically effective amount of an active pharmaceutical ingredient together with pharmaceutically acceptable excipients to be administered to a mammal, e.g., a human in need thereof.

The term "therapeutically effective amount" denotes an amount of a compound or molecule of the present invention that, when administered to a subject, (i) treats or prevents the particular disease or condition, (ii) attenuates, ameliorates or eliminates one or more symptoms of the particular disease or condition or (iii) prevents or delays the onset of one or more symptoms of the particular disease or condition described herein. The therapeutically effective amount will vary depending on the compound, the disease state being treated, the severity of the disease treated, the age and relative health of the subject, the route and form of administration, the judgement of the attending medical or veterinary practitioner, and other factors.

Pharmaceutical composition or medicament contain the amorphous or crystalline forms of the compound (I) of the invention and a therapeutically inert carrier, diluent or excipient, as well as methods of using the amorphous or crystalline forms of compound (I) of the invention to prepare such compositions and medicaments.

The amorphous or crystalline forms of compound (I) of the invention may be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal and epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

The amorphous or crystalline forms of compound (I) of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

An embodiment, therefore, includes a pharmaceutical composition comprising an amorphous or crystalline form of compound (I). In a further embodiment includes a pharmaceutical composition comprising a compound of Formula I, or a stereoisomer or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or excipient.

The amorphous or crystalline form of compound (I) of the invention can be used together with interferon, pegylated interferons, Lamivudine, Adefovir dipivoxil, Entecavir, Telbivudine, and Tenofovir disoproxil for the treatment or prophylaxis of HBV.

ABBREVIATIONS

$[Bmim]BF_4$	1-Butyl-3-methylimidazolium tetrafluoroborate
DSC	Differential scanning calorimetry
DVS	Dynamic vapor sorption
EtOAc	Ethyl Acetate
FWHM	Full Width at Half Maxima
H_2SO_4	Sulfuric acid
H_3PO_4	Phosphoric acid
HCl	Hydrochloric acid
MeOH	Methanol
MIBK	Methyl isobutyl ketone
Pos.	Position
Rel. Int.	Relative Intensity
TGA	Thermal gravimetric analysis

wt%	Weight%
XRPD	X-ray powder diffraction

DESCRIPTION OF THE FIGURES

FIG. 1 X-ray powder diffraction pattern for Amorphous Form

FIG. 2 X-ray powder diffraction pattern for Form A

FIG. 3 DSC thermogram of Form A

FIG. 4 TGA diagram of Form A

FIG. 5 X-ray powder diffraction pattern for Form B

FIG. 6 X-ray powder diffraction pattern for Form C

FIG. 7 DSC thermogram of Form C

FIG. 8 TGA diagram of Form C

FIG. 9 X-ray crystal structure of Form C

FIG. 10 X-ray powder diffraction pattern for Hydrochloride Salt Form D

FIG. 11 DSC thermogram of Hydrochloride Salt Form D

FIG. 12 TGA diagram of Hydrochloride Salt Form D

FIG. 13 X-ray powder diffraction pattern for Hydrochloride Salt Form E

FIG. 14 DSC thermogram of Hydrochloride Salt Form E

FIG. 15 TGA diagram of Hydrochloride Salt Form E

FIG. 16 X-ray powder diffraction pattern for Hydrochloride Salt Form F

FIG. 17 DSC thermogram of Hydrochloride Salt Form F

FIG. 18 TGA diagram of Hydrochloride Salt Form F

FIG. 19 X-ray powder diffraction pattern for Hydrochloride Salt Form G

FIG. 20 DSC thermogram of Hydrochloride Salt Form G

FIG. 21 TGA diagram of Hydrochloride Salt Form G

FIG. 22 X-ray powder diffraction pattern for Hydrochloride Salt Form H

FIG. 23 DSC thermogram of Hydrochloride Salt Form H

FIG. 24 TGA diagram of Hydrochloride Salt Form H

FIG. 25 Omitted

FIG. 26 Omitted

FIG. 27 Omitted

FIG. 28 Omitted

FIG. 29 Omitted

FIG. 30 X-ray powder diffraction pattern for Ethylsulfate Form L

FIG.31 DSC thermogram of Ethylsulfate Form L

FIG.32 TGA diagram of Ethylsulfate Form L

FIG. 33 X-ray crystal structure of Ethylsulfate Form L

FIG. 34 X-ray powder diffraction pattern for Calcium Salt Form M

FIG. 35 DSC thermogram of Calcium Salt Form M

FIG. 36 TGA thermogram of Calcium Salt Form M

FIG. 37 X-ray powder diffraction pattern for Calcium Salt Form N

FIG. 38 DSC thermogram of Calcium Salt Form N

FIG. 39 TGA thermogram of Calcium Salt Form N

FIG. 40 X-ray powder diffraction pattern for Calcium Salt Form P

FIG. 41 DSC thermogram of Calcium Salt Form P

FIG. 42 TGA diagram of Calcium Salt Form P

FIG. 43 X-ray powder diffraction pattern for Calcium Salt Form Q

FIG. 44 DSC thermogram of Calcium Salt Form Q

FIG. 45 TGA diagram of Calcium Salt Form Q

FIG. 46 X-ray powder diffraction pattern for Mesylate Form J

FIG. 47 DSC thermogram of Mesylate Form J

FIG. 48 TGA diagram of Mesylate Form J

EXAMPLES

The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention.

Example 1

Preparation of Amorphous Form of compound (I)

The 500mg/mL acetone solution of compound (I) was added into water drop-wise to form solid precipitation.

The residual solid was isolated and analysed using XRPD analysis. The result is shown in FIG. 1.

Experimental condition:

XRPD: PANalytical EMPYREAN X-ray powder diffractometer with Cu-Kα radiation using 40KV tube voltage and 40mA tube currentScan range was from 4 to 40 degree 2- theta. The step size was 0.0525° at a scanning speed of 6.66°/min.

Example 2

Preparation of Hydrate Form, Form A of compound (I).

40 mg of amorphous form of compound (I) as prepared in Example 1 was weighed and transferred to a 2-mL vial. 1 mL 0.1M H_3PO_4 was added to form slurry. The vial was mounted to a shaker and kept shaking for 1 day at room temperature. The slurry was examined periodically by polarized light microscope.

After 1 day, the slurry was removed from the vial and transferred to a 1.5mL centrifuge tube and centrifuged at 12000rpm for 5 minutes. The supernatant was removed and the residual solid was analysed using XRPD. The XRPD pattern is shown in FIG. 2. Major peaks and their related intensities in the XRPD pattern are shown in Table 1.

Experimental conditions:

XRPD: PANalytical EMPYREAN X-ray powder diffractometer with Cu-Kα radiation using 40KV tube voltage and 40mA tube current. Scan range was from 4 to 40 degree 2-theta. The step size was 0.0525° at a scanning speed of 6.66°/min.

DSC analysis: TA Q2000, 25-250°C, heating rate 10°C/min.

TGA analysis: TA Q5000, 25-350°C, heating rate 10°C/min.

Table 1. X-Ray Powder Diffraction peaks of Form A of compound (I)

Pos. [°2Th.]	Height [cts]	FWHM Left [°2Th.]	d-spacing [Å]	Rel. Int. [%]
7.770	1969	0.053	11.3689	98.2
8.218	2005	0.071	10.7509	100.0
9.099	461	0.124	9.7108	23.0
9.807	511	0.071	9.0117	25.5
11.326	461	0.053	7.8066	23.0
11.906	112	0.071	7.4275	5.6
12.423	337	0.053	7.1195	16.8
12.605	436	0.071	7.0171	21.7
14.307	393	0.071	6.1856	19.6
14.686	380	0.107	6.0270	19.0
15.593	70	0.107	5.6785	3.5
16.517	126	0.071	5.3629	6.3
17.089	379	0.071	5.1844	18.9
17.658	210	0.071	5.0186	10.5
18.037	201	0.071	4.9141	10.0
18.500	163	0.071	4.7921	8.1
18.947	95	0.071	4.6800	4.8
19.708	1662	0.124	4.5011	82.9
19.993	1022	0.071	4.4375	51.0
20.610	115	0.107	4.3061	5.7
21.221	276	0.124	4.1835	13.8
21.561	490	0.089	4.1181	24.5
21.969	410	0.089	4.0426	20.4
22.461	391	0.089	3.9551	19.5
22.778	371	0.089	3.9009	18.5
23.220	423	0.071	3.8276	21.1
23.961	128	0.071	3.7109	6.4
24.446	128	0.071	3.6384	6.4
24.767	950	0.089	3.5919	47.4

25.186	223	0.053	3.5330	11.1
25.679	1208	0.107	3.4664	60.3
26.101	400	0.089	3.4113	20.0
26.453	178	0.071	3.3667	8.9
27.072	246	0.107	3.2911	12.3
27.469	391	0.089	3.2444	19.5
27.700	277	0.071	3.2178	13.8
28.216	434	0.089	3.1602	21.6
28.727	208	0.071	3.1051	10.4
29.760	110	0.142	2.9997	5.5
30.456	139	0.053	2.9327	6.9
31.221	271	0.089	2.8625	13.5
31.963	81	0.071	2.7978	4.1
32.492	158	0.107	2.7534	7.9
32.917	178	0.107	2.7188	8.9
33.404	109	0.107	2.6803	5.4
34.465	30	0.142	2.6001	1.5
34.998	76	0.142	2.5618	3.8
35.802	46	0.107	2.5061	2.3
36.344	72	0.107	2.4699	3.6
37.660	83	0.213	2.3866	4.2
39.054	54	0.142	2.3046	2.7

DSC and TGA results shown in FIG. 3 and FIG. 4.

Example 3

Preparation of Anhydrous Form, Form B of compound (I).

Form B was formed by using Form A as prepared in Example 2 either after dehydration at high temperature (>70°C) or low humidity (0% RH), and characterized by XRPD pattern shown in FIG. 5. Major peaks and their related intensities in the XRPD pattern are shown in Table 2.

Experimental condition:

XRPD: PANalytical EMPYREAN X-ray powder diffractometer with Cu-Kα radiation. Tube voltage was 45KV and tube current was 40mA. Scan range was from 3 to 40 degree 2-theta. The step size was 0.013° at a scanning speed of 10°/min.

Table 2. X-Ray Powder Diffraction peaks of Form B of compound (I)

Pos. [°2Th.]	Height [cts]	FWHM Left [°2Th.]	d-spacing [Å]	Rel. Int. [%]
8.419	8777	0.102	10.5025	100.0
9.343	1261	0.128	9.4656	14.4
9.783	702	0.128	9.0408	8.0
11.716	1730	0.128	7.5536	19.7
12.628	1550	0.205	7.0099	17.7
14.454	523	0.205	6.1283	6.0
14.960	826	0.179	5.9220	9.4
17.525	584	0.205	5.0606	6.7
18.666	1064	0.154	4.7538	12.1
19.622	2890	0.154	4.5243	32.9
20.418	3283	0.179	4.3498	37.4
21.674	529	0.205	4.1004	6.0
22.380	791	0.358	3.9726	9.0
23.031	2237	0.179	3.8618	25.5
24.043	1332	0.205	3.7014	15.2
25.512	3084	0.166	3.4916	35.1
25.992	1104	0.205	3.4281	12.6
26.648	2869	0.256	3.3452	32.7
27.744	918	0.307	3.2155	10.5

28.362	884	0.358	3.1469	10.1
31.532	539	0.512	2.8373	6.1

Example 4

Preparation of Form C of compound (I).

10 mg of Form A of compound (I) as prepared in Example 2 was weighed and transferred to a 1-mL vial. 300 μL MeOH was added to form a clear solution followed by adding 20 wt% [Bmim]BF_4. The clear solution was evaporated slowly to induce precipitation at room temperature.

The solid was isolated for XRPD analysis, DSC analysis and TGA analysis.

The XRPD pattern of Form C of compound (I) is shown in FIG. 6. Major peaks and their related intensities in the XRPD pattern are shown in Table 3 below.

Experimental conditions:

XRPD: PANalytical EMPYREAN X-ray powder diffractometer with Cu-Kα radiation. Tube voltage was 45KV and tube current was 40mA. Scan range was from 3 to 40 degree 2-theta. The step size was 0.013° at a scanning speed of 10°/min.

DSC analysis: TA Q2000, 25-200°C, heating rate 10°C/min.

TGA analysis: TA Q5000, 25-300°C, heating rate 10°C/min.

Table 3. X-Ray Powder Diffraction peaks of Form C of compound (I).

Pos. [°2Th.]	Height [cts]	FWHM Left [°2Th.]	d-spacing [Å]	Rel. Int. [%]
6.609	83	0.614	13.3739	5.3
9.654	446	0.102	9.1615	28.4
12.576	313	0.102	7.0390	20.0
14.893	326	0.102	5.9487	20.8

17.043	490	0.102	5.2027	31.3
17.814	271	0.154	4.9794	17.3
18.181	299	0.205	4.8796	19.1
18.754	291	0.102	4.7317	18.6
19.399	436	0.154	4.5759	27.8
20.927	710	0.102	4.2451	45.4
21.281	533	0.154	4.1753	34.0
22.560	866	0.128	3.9414	55.3
23.671	316	0.154	3.7588	20.2
24.169	976	0.102	3.6825	62.3
24.380	1567	0.128	3.6510	100.0
24.805	394	0.205	3.5894	25.1
26.193	210	0.409	3.4023	13.4
27.294	279	0.154	3.2675	17.8
28.036	273	0.102	3.1828	17.4
34.764	125	0.256	2.5806	8.0

DSC and TGA results shown in FIG. 7 and FIG. 8 indicate Form C of compound (I) has an onset melting temperature at 171°C.

FIG. 9 shows the X-ray structure of Form C of compound (I), indicating that Form C is a monohydrate of co-crystal formed by compound (I) and its tetrafluoroborate with a molar ratio 1:2. The single crystal X-ray intensity data were collected at 173K using a Bruker APEX-II CCD diffractometer (Cu-Kα radiation, λ= 1.54178 Å). The crystal data and structure refinement is shown in Table 4.

Table 4. Crystal data and structure refinement of Form C of compound (I).

Empirical formula	$C_{63}H_{63}BCl_3F_7N_{12}O_{16}S_3$
Formula weight	1590.59
Temperature	173 K
Wavelength	154178Å
Crystal system, space	Monoclinic, $P2_1$

group	
Unit cell dimensions	a=9.64200(10) Å b= 43.3018(6) Å c= 16.5186(2) Å Alpha=90.00 deg. Beta= 95,5800(10) deg. Gamma= 90.00 deg.
Volume	6864.19(15) $Å^3$
Z, Calculated density	4, 1.539 mg/mm^3
Absorption coefficient	2.902mm^{-1}
F(000)	3280.0
Crystal size	0.2×0.2×0.1 mm^3
Theta range for data collection	2.04 to 65.05 deg.
Limiting indices	-10≤ h ≤11 -47≤ k ≤50 -19≤ l ≤18
Reflections collected/unique	23412/18350[R(int)=0.0441]
Completeness	92.1%
Refinement method	Full matrix least squares on F^2
Data/ restraints/ parameters	18350/3 /1904
Goodness-of-fit on F2	1.074
Final R indices [I>2sigma(I)]	R1= 0.0591 wR2=0.1459
Absolute structure Flack	0.044(10)
Largest diff. peak and hole	1.58/-0.61 $e.A^{-3}$

Example 5

Preparation of Hydrochloride Salt Form D of compound (I).

50mg of Form A of compound (I) as prepared in Example 2 was dissolved in 1mL EtOAc. 0.1N HCl solution in EtOAc was added at a molar ratio 2:1 (HCl: compound A) and mixed well. The solution was stirred at room temperature overnight to generate precipitation.

The solid precipitate was isolated for XRPD analysis, DSC analysis and TGA analysis.

The XRPD pattern of hydrochloride salt Form D of compound (I) is shown in FIG. 10. Major peaks and their related intensities in the XRPD pattern are shown in Table 5.

Experimental conditions:

XRPD: PANalytical EMPYREAN X-ray powder diffractometer with Cu-Kα radiation. Tube voltage was 45KV and tube current was 40mA. Scan range was from 3 to 40 degree 2-theta. The step size was 0.013° at a scanning speed of 10°/min.

DSC analysis: TA Q2000, 25-300°C, heating rate 10°C/min.

TGA analysis: TA Q5000, 25-300°C, heating rate 10°C/min.

Table 5. X-Ray Powder Diffraction peaks of hydrochloride salt Form D of compound (I).

Pos. [°2Th.]	Height [cts]	FWHM Left [°2Th.]	d-spacing [Å]	Rel. Int. [%]
15.743	259	0.102	5.6291	45.8
17.201	368	0.128	5.1554	65.0
20.459	402	0.154	4.3412	71.1
21.956	225	0.205	4.0483	39.8
23.435	565	0.154	3.7961	100.0
24.762	91	0.307	3.5956	16.2
28.376	334	0.154	3.1453	59.1
30.878	416	0.179	2.8960	73.6
31.721	98	0.512	2.8209	17.4

32.803	178	0.205	2.7302	31.6
33.548	131	0.409	2.6713	23.3
37.170	110	0.205	2.4189	19.5

DSC and TGA results shown in FIG. 11 and FIG. 12 indicate hydrochloride salt Form D of compound (I) has an onset melting temperature at 216°C.

Example 6

Preparation of Hydrochloride Salt Form E of compound (I).

50mg of Form A of compound (I) as prepared in Example 2 was dissolved in 1mL MeOH/H_2O (19/1, v/v). Equal molar 0.1N HCl solution in MeOH/H_2O (19/1, v/v) was added and mixed well. The solution was stirred at room temperature overnight to generate precipitation.

The solid precipitate was isolated for XRPD analysis, DSC analysis and TGA analysis.

The XRPD pattern of hydrochloride salt Form E of compound (I) is shown in FIG. 13. Major peaks and their related intensities in the XRPD pattern are shown in Table 6.

Experimental conditions:

XRPD: PANalytical EMPYREAN X-ray powder diffractometer with Cu-Kα radiation. Tube voltage was 45KV and tube current was 40mA. Scan range was from 3 to 40 degree 2-theta. The step size was 0.013° at a scanning speed of 10°/min.

DSC analysis: TA Q2000, 25-250°C, heating rate 10°C/min.

TGA analysis: TA Q5000, 25-250°C, heating rate 10°C/min.

Table 6. X-Ray Powder Diffraction peaks of hydrochloride salt Form E of compound (I).

Pos. [°2Th.]	Height [cts]	FWHM Left [°2Th.]	d-spacing [Å]	Rel. Int. [%]
7.387	189	0.077	11.9673	100.0
7.956	186	0.102	11.1134	98.3

9.817	123	0.179	9.0095	65.2
12.218	68	0.154	7.2440	35.8
16.922	57	0.154	5.2396	30.1
20.023	71	0.154	4.4347	37.5
20.739	136	0.154	4.2831	71.7
21.652	79	0.154	4.1044	41.6
22.500	124	0.205	3.9517	65.5
23.817	150	0.154	3.7362	79.5
24.688	179	0.179	3.6063	94.7
26.205	111	0.154	3.4008	58.7
27.759	84	0.205	3.2138	44.1
28.917	40	0.614	3.0877	20.9

DSC and TGA results shown in FIG. 14 and FIG. 15 indicate hydrochloride salt Form E of compound (I) has an onset melting temperature at 136°C.

Example 7

Preparation of Hydrochloride Salt Form F of compound (I).

300 mg of Form A of compound (I) as prepared in Example 2 was suspended in 3.0 mL acetone. 100 µL of 0.1 N HCl solution was added to form a clear solution. 5 mL heptane was added to the solution over 10 hours. The mixture was stirred for 24 hours to generate precipitation.

The solid precipitate was isolated for XRPD analysis, DSC analysis and TGA analysis

The XRPD pattern of hydrochloride salt Form F of compound (I) is shown in FIG. 16. Major peaks and their related intensities in the XRPD pattern are shown in Table 7.

Experimental conditions:

XRPD: PANalytical EMPYREAN X-ray powder diffractometer with Cu-Kα radiation. Tube voltage was 45KV and tube current was 40mA. Scan range was from 3 to 40 degree 2-theta. The step size was 0.013° at a scanning speed of 10°/min.

DSC analysis: TA Q2000, 25-200°C, heating rate 10°C/min.

TGA analysis: TA Q5000, 25-200°C, heating rate 10°C/min.

Table 7. X-Ray Powder Diffraction peaks of hydrochloride salt Form F of compound (I).

Pos. [°2Th.]	Height [cts]	FWHM Left [°2Th.]	d-spacing [Å]	Rel. Int. [%]
11.022	157	0.102	8.0278	26.0
11.729	231	0.077	7.5454	38.4
14.891	107	0.154	5.9496	17.7
18.359	154	0.205	4.8326	25.6
20.869	437	0.128	4.2567	72.5
21.797	181	0.102	4.0775	30.0
23.146	602	0.102	3.8429	100.0
24.439	141	0.205	3.6424	23.5
25.352	91	0.307	3.5132	15.1
27.027	373	0.128	3.2992	61.9
28.577	531	0.128	3.1237	88.2
32.212	57	0.256	2.7790	9.4
33.525	101	0.205	2.6731	16.8
39.025	97	0.358	2.3081	16.2

DSC and TGA results shown in FIG. 17 and FIG. 18 indicate hydrochloride salt Form F of compound (I) has an onset melting temperature at 141°C .

Example 8

Preparation of Hydrochloride Salt Form G of compound (I).

100 mg Form A of compound (I) as prepared in Example 2 was weighed and transferred to a 5-mL vial. 4 mL 0.1 N HCl solution was added to form slurry and stirred for 4 days before the solid was isolated.

The solid was isolated for XRPD analysis, DSC analysis and TGA analysis.

The XRPD pattern of hydrochloride salt Form G of compound (I) is shown in FIG. 19. Major peaks and their related intensities in the XRPD pattern are shown in Table 8.

Experimental conditions:

XRPD: PANalytical EMPYREAN X-ray powder diffractometer with Cu-Kα radiation. Tube voltage was 45KV and tube current was 40mA. Scan range was from 3 to 40 degree 2-theta. The step size was 0.013° at a scanning speed of 10°/min.

DSC analysis: TA Q2000, 25-250°C, heating rate 10°C/min.

TGA analysis: TA Q5000, 25-300°C, heating rate 10°C/min.

Table 8. X-Ray Powder Diffraction peaks of hydrochloride salt Form G of compound (I).

Pos. [°2Th.]	Height [cts]	FWHM Left [°2Th.]	d-spacing [Å]	Rel. Int. [%]
6.808	334	0.102	12.9841	10.3
8.203	343	0.102	10.7794	10.6
9.853	946	0.077	8.9769	29.1
12.317	418	0.102	7.1863	12.9
15.013	116	0.614	5.9015	3.6
17.365	719	0.102	5.1069	22.1
19.351	293	0.205	4.5870	9.0
21.194	317	0.409	4.1921	9.8
22.417	221	0.307	3.9661	6.8
23.066	539	0.154	3.8559	16.6
24.857	3254	0.154	3.5821	100.0
25.309	596	0.128	3.5192	18.3

26.567	235	0.307	3.3552	7.2
28.478	367	0.179	3.1343	11.3
35.376	81	0.819	2.5374	2.5

DSC and TGA results shown in FIG. 20 and FIG. 21 indicate hydrochloride salt Form G of compound (I) has an onset melting temperature at 152°C.

Example 9

Preparation of Hydrochloride Salt Form H of compound (I).

40 mg of amorphous form of compound (I) as prepared in Example 1 was weighed and transferred to a 2-mL vial. 1 mL 0.1 N HCl was added to form slurry. The vial was mounted to a shaker and kept shaking for 1 day at room temperature. After 1 day, the slurry was removed from the vial, transferred to a 1.5mL centrifuge tube and centrifuge at 12000rpm for 5 minutes. The supernatant was removed and the residual solid was analysed using XRPD analysis, DSC analysis and TGA analysis.

The XRPD pattern of hydrochloride salt Form H of compound (I) is shown in FIG. 22. Major peaks and their related intensities in the XRPD pattern are shown in Table 9.

Experimental conditions:

XRPD: Bruker D8 Advance X-ray diffractometer with Cu-Kα radiation. Tube voltage was 40KV and tube current was 40mA. Scan range was from 4 to 40 degree 2-theta. The step size was 0.05° at a scanning speed of 3°/min.

DSC analysis: TA Q2000, 25-300°C, heating rate 10°C/min.

TGA analysis: TA Q5000, 25-300°C, heating rate 10°C/min.

Table 9. X-Ray Powder Diffraction peaks of hydrochloride salt Form H of compound (I).

Pos. [°2Th.]	Intensity[count]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]

7.883	421	0.253	11.2062	92.5
13.226	162	0.182	6.6888	35.5
14.423	187	0.325	6.1362	41
17.693	162	0.247	5.0088	35.7
18.306	262	0.244	4.8424	57.5
19.941	305	0.154	4.4489	66.9
21.489	305	0.597	4.1319	67.1
23.124	276	0.226	3.8433	60.7
23.912	455	0.219	3.7184	100
25.693	411	0.356	3.4645	90.4
26.832	302	0.779	3.3200	66.4

DSC and TGA results shown in FIG. 23 and FIG. 24 indicate hydrochloride salt Form H of compound (I) has an onset melting temperature at 136°C.

Example 10

Omitted

Example 11

Omitted

Example 12

Preparation of Ethylsulfate Form L of compound (I).

100 mg Form A of compound (I) as prepared in Example 2 was dissolved with 3.3 mL EtOAc and then 0.5 mL 0.2 M H_2SO_4 solution in EtOAc was added. The resulting solution was stirred for 24 hours to form solid precipitation.

The solid was isolated for XRPD analysis, DSC analysis and TGA analysis.

The XRPD pattern of ethylsulfate Form L of compound (I) is shown in FIG. 30. Major peaks and their related intensities in the XRPD pattern are shown in Table 12.

Experimental conditions:

XRPD: PANalytical EMPYREAN X-ray powder diffractometer with Cu-Kα radiation. Tube voltage was 45KV and tube current was 40mA. Scan range was from 3 to 40 degree 2-theta. The step size was 0.013° at a scanning speed of 10°/min.

DSC analysis: TA Q2000, 25-200°C, heating rate 10°C/min.

TGA analysis: TA Q5000, 25-250°C, heating rate 10°C/min.

Table 12. X-Ray Powder Diffraction peaks of ethylsulfate Form L of compound (I)

Pos. [°2Th.]	Height [cts]	FWHM Left [°2Th.]	d-spacing [Å]	Rel. Int. [%]
5.293	2578	0.128	16.6977	100.0
9.960	451	0.128	8.8809	17.5
10.560	618	0.128	8.3779	24.0
10.948	611	0.102	8.0814	23.7
14.278	494	0.128	6.2032	19.2
15.859	1142	0.256	5.5885	44.3
18.993	1919	0.115	4.6727	74.4
20.880	911	0.128	4.2546	35.3
21.186	852	0.128	4.1938	33.0
21.713	803	0.128	4.0930	31.2
22.961	1584	0.128	3.8734	61.5
23.304	1061	0.179	3.8171	41.2
24.032	481	0.128	3.7032	18.7
25.022	814	0.128	3.5589	31.6
26.842	642	0.154	3.3216	24.9
28.289	578	0.128	3.1548	22.4

30.770	188	0.409	2.9058	7.3
32.357	577	0.205	2.7669	22.4
34.661	146	0.614	2.5881	5.7
36.653	238	0.307	2.4518	9.2
37.521	253	0.205	2.3971	9.8

DSC and TGA results shown in FIG. 31 and FIG. 32 indicate ethylsulfate Form L of compound (I) has an onset melting temperature at 160°C.

FIG. 33 shows the X-ray structure of ethylsulfate Form L. The single crystal X-ray intensity data were collected at 173(2) K using a Bruker APEX-II CCD diffractometer (Cu-Kα radiation, λ= 1.54178 Å). The crystal data and structure refinement is shown in Table 13.

Table 13. Crystal data and structure refinement of ethylsulfate Form L of compound (I).

Empirical formula	$C_{23}H_{26}ClFN_4O_9S_2$
Formula weight	621.05
Temperature	293 (2) K
Wavelength	154178Å
Crystal system, space group	Orthorhombic $P2_12_12_1$
Unit cell dimensions	a=9.1289(2) Å b= 9.2128(2) Å c= 33.3938(7) Å Alpha=90.00 deg. Beta= 90.00 deg. Gamma= 90.00 deg.
Volume	2808.51(10) $Å^3$
Z, Calculated density	4, 1.469 mg/mm^3
Absorption coefficient	3.160mm^{-1}
F(000)	1288.0
Crystal size	0.1×0.1×0.09 mm^3
Theta range for data	2.65 to 69.15 deg.

collection	
Limiting indices	-10≤ h ≤11 -11≤ k ≤11 -39≤ l ≤38
Reflections collected/unique	14180/4983[R(int)=0.0469]
Completeness	98.5%
Refinement method	Full matrix least squares on F^2
Data/ restraints/ parameters	18350/3 /1904
Goodness-of-fit on F2	0.814
Final R indices [I>2sigma(I)]	R1= 0.0371 wR2=0.1039
Absolute structure Flack	0.000(14)
Largest diff. peak and hole	0.32/-0.36 $e.A^{-3}$

Example 13

Preparation of Calcium Salt Form M of compound (I).

40mg of Form A of compound (I) as prepared in Example 2 was dissolved in MeOH/H_2O (19/1, v/v). Equal molar 0.1M $Ca(OH)_2$ solution in MeOH/H_2O (19/1, v/v) was added and mixed well. The solution was stirred at room temperature overnight to generate precipitation.

The solid precipitate was isolated for XRPD analysis, DSC analysis and TGA analysis.

The XRPD pattern of calcium salt Form M of compound (I) is shown in FIG. 34. Major peaks and their related intensities in the XRPD pattern are shown in Table 14.

Experimental conditions:

XRPD: PANalytical EMPYREAN X-ray powder diffractometer with Cu-Kα radiation. Tube voltage was 45KV and tube current was 40mA. Scan range was from 3 to 40 degree 2-theta. The step size was 0.013° at a scanning speed of 10°/min.

DSC analysis: TA Q2000, 25-200°C, heating rate 10°C/min.

TGA analysis: TA Q5000, 25-300°C, heating rate 10°C/min.

Table 14. X-Ray Powder Diffraction peaks of calcium salt Form M of compound (I).

Pos. [°2Th.]	Height [cts]	FWHM Left [°2Th.]	d-spacing [Å]	Rel. Int. [%]
6.237	394	0.064	14.1721	65.5
8.568	601	0.102	10.3208	100.0
9.797	60	0.614	9.0280	10.0
13.644	257	0.102	6.4901	42.8
14.532	109	0.154	6.0957	18.2
16.503	114	0.409	5.3717	18.9
17.178	194	0.102	5.1621	32.3
19.467	111	0.307	4.5599	18.5
22.108	120	0.256	4.0209	20.0
25.232	91	0.409	3.5297	15.1
28.105	48	0.614	3.1750	7.9
29.390	68	0.307	3.0391	11.4

DSC and TGA results shown in FIG. 35 and FIG. 36 indicate Calcium Salt Form M of compound (I) has an onset melting temperature at 59°C.

Example 14

Preparation of Calcium Salt Form N of compound (I).

40mg of calcium salt Form M of compound (I) as prepared in Example 13 was heated up to 110°C, held for 5 min and cooled down to room temperature.

The solid was isolated for XRPD analysis, DSC analysis and TGA analysis.

The XRPD pattern of calcium salt Form N of compound (I) is shown in FIG. 37. Major peaks and their related intensities in the XRPD pattern are shown in Table 15.

Experimental conditions:

XRPD: PANalytical EMPYREAN X-ray powder diffractometer with Cu-Kα radiation. Tube voltage was 45KV and tube current was 40mA. Scan range was from 3 to 40 degree 2-theta. The step size was 0.013° at a scanning speed of 10°/min.

DSC analysis: TA Q2000, 25-200°C, heating rate 10°C/min.

TGA analysis: TA Q5000, 25-300°C, heating rate 10°C/min.

Table 15. X-Ray Powder Diffraction peaks of calcium salt Form N of compound (I).

Pos. [°2Th.]	Height [cts]	FWHM Left [°2Th.]	d-spacing [Å]	Rel. Int. [%]
4.617	1542	0.064	19.1385	99.0
9.215	746	0.064	9.5968	47.9
11.809	320	0.154	7.4942	20.5
13.100	555	0.102	6.7582	35.6
13.834	544	0.102	6.4017	34.9
14.352	143	0.205	6.1717	9.2
17.440	566	0.102	5.0853	36.4
18.503	914	0.102	4.7953	58.7
19.052	1557	0.115	4.6583	100.0
20.627	165	0.307	4.3061	10.6
21.984	364	0.128	4.0433	23.4
23.145	912	0.102	3.8430	58.6
23.884	898	0.141	3.7257	57.7
25.612	252	0.256	3.4782	16.2
27.849	474	0.154	3.2036	30.5
29.314	173	0.409	3.0468	11.1

31.831	100	0.409	2.8114	6.4
39.069	221	0.256	2.3056	14.2

DSC and TGA results shown in FIG. 38 and FIG. 39 indicate Calcium Salt Form N of compound (I) has a onset melting temperature at 63°C.

Example 15

Preparation of Calcium Salt Form P of compound (I).

40mg calcium salt Form N of compound (I) as prepared in Example 14 was weighed and dispersed in water to form slurry and stirred for 1 hour at room temperature.

The solid was isolated for XRPD analysis, DSC analysis and TGA analysis.

The XRPD pattern of calcium salt Form P of compound (I) is shown in FIG. 40. Major peaks and their related intensities in the XRPD pattern are shown in Table 16.

Experimental conditions:

XRPD: PANalytical EMPYREAN X-ray powder diffractometer with Cu-Kα radiation. Tube voltage was 45KV and tube current was 40mA. Scan range was from 3 to 40 degree 2-theta. The step size was 0.013° at a scanning speed of 10°/min.

DSC analysis: TA Q2000, 25-275°C, heating rate 10°C/min.

TGA analysis: TA Q5000, 25-325°C, heating rate 10°C/min.

Table 16. X-Ray Powder Diffraction peaks of calcium salt Form P of compound (I).

Pos. [°2Th.]	Height [cts]	FWHM Left [°2Th.]	d-spacing [Å]	Rel. Int. [%]
7.232	51	0.307	12.2241	9.4
11.270	301	0.102	7.8513	55.5
12.177	491	0.090	7.2684	90.4
15.505	91	0.154	5.7151	16.7

16.464	81	0.205	5.3844	15.0
17.573	170	0.102	5.0469	31.2
18.015	543	0.077	4.9241	100.0
21.176	97	0.307	4.1957	17.9
22.379	180	0.230	3.9729	33.2
23.163	390	0.154	3.8401	71.9
24.443	37	0.614	3.6419	6.8
29.590	95	0.307	3.0190	17.6
31.834	45	0.614	2.8111	8.3

DSC and TGA results shown in FIG. 41 and FIG. 42 indicate Calcium Salt Form P of compound (I) has an onset melting temperature at 230°C.

Example 16

Preparation of Calcium Salt Form Q of compound (I).

20mg calcium salt Form N of compound (I) as prepared in Example 14 was weighed and mounted on the DVS (dynamic vapour sorption) intrinsic from SMS (Surface Measurement Systems Co. Ltd.) and run the method shown in Table 17.

Table 17. The testing parameters of DVS.

Parameters	Value
Temperature	25°C
Sample size	10-20mg
Gas and flow rate	N_2, 200mL/min
dm/dt	0.002%/min
Min. dm/dt stability duration	10 min
Max. equilibrium time	180 min
RH range	95%RH–0% RH–95%RH
RH step size	10% (90%RH–0% RH–90%RH)

	5% (90%RH–95% RH–90%RH)

After the DVS test, the solid was analysed using XRPD, DSC analysis and TGA analysis. The XRPD pattern of calcium salt Form Q of compound (I) is shown in FIG. 43. Major peaks and their related intensities in the XRPD pattern are shown in Table 18.

Experimental conditions:

XRPD: PANalytical EMPYREAN X-ray powder diffractometer with Cu-Kα radiation. Tube voltage was 45KV and tube current was 40mA. Scan range was from 3 to 40 degree 2-theta. The step size was 0.013° at a scanning speed of 10°/min.

DSC analysis: TA Q2000, 25-260°C, heating rate 10°C/min.

TGA analysis: TA Q5000, 25-300°C, heating rate 10°C/min.

Table 18. X-Ray Powder Diffraction peaks of calcium salt Form Q of compound (I).

Pos. [°2Th.]	Height [cts]	FWHM Left [°2Th.]	d-spacing [Å]	Rel. Int. [%]
4.353	222	0.077	20.3019	29.1
9.960	103	0.307	8.8806	13.4
11.038	509	0.102	8.0157	66.7
12.772	269	0.128	6.9315	35.2
15.039	177	0.154	5.8912	23.1
16.331	405	0.128	5.4280	53.0
16.708	763	0.077	5.3064	100.0
18.056	607	0.115	4.9131	79.6
20.650	536	0.128	4.3014	70.2
22.193	170	0.205	4.0057	22.2
23.763	133	0.205	3.7445	17.4
25.358	185	0.154	3.5124	24.2
26.639	87	0.512	3.3463	11.4
29.336	128	0.205	3.0446	16.8
30.260	81	0.307	2.9537	10.7

31.977	67	0.307	2.7989	8.8
37.826	34	0.614	2.3785	4.4

DSC and TGA results shown in FIG. 44 and FIG. 45 indicating Calcium Salt Form Q of compound (I) has an onset melting temperature at 191°C.

Example 17

Preparation of Hydrate Form, Form A of compound (I).

1 kg of compound (I) crude product was dissolved into 1.875 L actone, the resulting mixture was added dropwise into 15L water at 25°C. Then 90g of seed was added into reaction mixture, the resulting mixture was stirred at 25°C for 3 days. The solid was collected by filtration and washed twice with 5 L water and dried in a vaccum oven at 55°C for 7 days.

The water content of final product was determined using Karl Fischer Coulometric titration. The result of water content was 2.5%.

Example 18

Preparation of Hydrate Form, Form A of compound (I).

2 kg of compound (I) crude product was dissolved into 3.75 L actone, the resulting mixture was added dropwise into 30L water at 25°C. Then 180g of seed was added into reaction mixture, the resulting mixture was stirred at 25°C for 3 days. The solid was collected by filtration and washed twice with 10 L water and dried in a vaccum oven at 55°C for 7 days.

The water content of final product was determined using Karl Fischer Coulometric titration. The result of water content was 3.9%.

Example 19

Preparation of Hydrate Form, Form A of compound (I).

2 kg of compound (I) crude product was dissolved into 3.75 L actone, the resulting mixture was added dropwise into 30L water at 25°C. Then 18g of seed was added into reaction mixture, the resulting mixture was stirred at 25°C for 3 days. The solid was collected by filtration and washed twice with 10 L water and dried in a vaccum oven at 55°C for 7 days.

The water content of final product was determined using Karl Fischer Coulometric titration. The result of water content was 4.5%.

Example AA

Preparation of Mesylate Form J of compound (I).

40mg of compound (I) was dissolved by MIBK to form a clear solution. Equal molar methylsulfonic acid was added as 0.1 M solution in MIBK. The mixture was heated at 45°C-50°C for 2h. The resulted suspension was cooled to room temperature over 1 h and maintained at room temperature for 30 min.

The solid was collected by filtration, washed with MIBK and analysed using XRPD analysis, DSC analysis and TGA analysis.

The XRPD pattern of mesylate Form J of compound (I) is shown in FIG. 46. Major peaks and their related intensities in the XRPD pattern are shown in Table 10 below.

Experimental conditions:

XRPD: Bruker D8 Advance X-ray diffractometer with Cu-Kα radiation. Tube voltage was 40KV and tube current was 40mA. Scan range was from 4 to 40 degree 2-theta. The step size was 0.05° at a scanning speed of 3°/min.

DSC analysis: TA Q2000, 25-300°C, heating rate 10°C/min.

TGA analysis: TA Q5000, 25-400°C, heating rate 10°C/min.

Table 10 X-Ray Powder Diffraction peaks of mesylate Form J of compound (I).

Pos. [°2Th.]	Intensity[count]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
5.577	486	0.248	15.8325	100.0
9.490	220	0.191	9.3116	23.2
10.104	172	0.281	8.7478	12.7
10.688	442	0.252	8.2711	90.9
14.484	237	0.326	6.1107	48.8
16.615	217	0.113	5.3312	44.7
17.083	375	0.248	5.1864	77.2
18.017	427	0.222	4.9195	87.8
18.630	156	0.114	4.7589	32.2
19.214	367	0.214	4.6156	75.4
19.740	170	0.219	4.4938	35.0
20.908	144	0.186	4.2453	29.7
21.638	279	0.217	4.1037	57.4
22.514	404	0.509	3.9460	83.2
23.945	392	0.298	3.7133	80.7
26.310	164	0.115	3.3846	33.7
26.923	203	0.201	3.3089	41.7
28.121	176	0.198	3.1707	36.3
30.574	163	0.298	2.9217	33.5
34.925	135	0.439	2.5670	27.7

DSC and TGA results shown in FIG. 47 and FIG. 48 indicate mesylate Form J of compound (I) has an onset melting temperature at 134°C.

Example AB

Chemical stability of solid forms

40mg compound (I) with different solid forms were stored in stability chamber with temperature and humidity controlled as 40°C and 75%RH respectively. After 1 month, the

samples were analyzed by HPLC method (described in Example AD) to check their chemical purity and compared with their initial value. According to the results shown in Table 11, the new discovered forms show much better stability than the original Form J as prepared in Example AA.

Table 11 Chemical stability data of different solid forms of compound (I)

Samples	Purity, %	
	Initial	40°C/RH75%, 1 Month
Example AA, Form J of compound (I)	98.8	12.3
Example 1, Amorphous of compound (I)	99.1	97.3
Example 2, Form A of compound (I)	98.8	98.8
Example 4, Form C of compound (I)	99.3	95.9
Example 13 Form M of compound (I)	96.9	96.0
Example 14 Form N of compound (I)	95.6	92.7
Example 8, Form G of compound (I)	99.3	99.3

Example AC

Equilibrium aqueous solubility

Aqueous solubility was determined by suspending 10mg compound in different bio-relevant media including SGF, FaSSIF and FeSSIF. The suspension was equilibrated at 25 °C for 24 hours then the final pH was measured. The suspension was then filtered through a 0.22um PVDF filter into a 2-mL HPLC vial. The quantitation was conducted by HPLC (described in Example AD) with reference to a standard solution. The solubility results of selected novel solid forms in this invention are shown in Table 12 which showed good aqueous solubility higher than 0.5mg/mL.

Table 12 Aqueous solubility of different solid forms

Samples	SGF	FaSSIF	FeSSIF

	S, mg/mL	Final pH	S, mg/mL	Final pH	S, mg/mL	Final pH
Example 1, Amorphous of compound (I)	>21.3	1.4	17.7	5.3	>40.7	4.9
Example 2, Form A of compound (I)	7.0	1.4	4.0	5.8	4.4	5.0
Example 4, Form C of compound (I)	0.8	2.0	3.7	6.0	2.0	5.0
Example 13 Form M of compound (I)	4.6	6.2	4.5	6.8	9.7	6.5
Example 14 Form N of compound (I)	3.6	8.1	6.1	6.9	7.2	6.0
Example 8, Form G of compound (I)	1.5	1.9	6.7	5.1	11.1	4.9

Example AD

HPLC method for chemical purity and assay test

HPLC condition is disclosed here in Table 13.

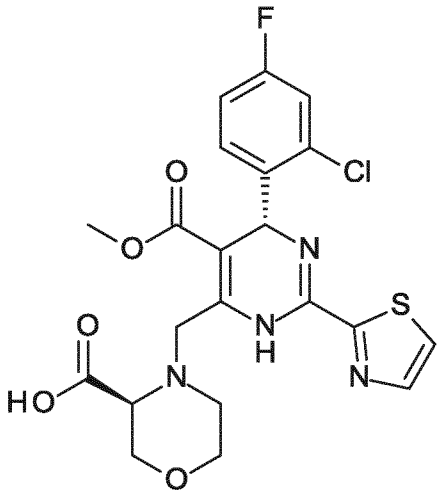
Table 13 HPLC conditions for chemical purity and assay test

Instrument	Agilent 1260 series HPLC system with DAD detector
Column	Waters XSELECT CSH C18(3.5μm,4.6 × 150 mm)
Oven temperature	30°C
Mobile phase	A: 0.1% TFA in water B: 0.1% TFA in ACN
Gradient program	Time (min) A% B% 0.00 80 20 15.00 50 50 18.00 10 90 20.00 10 90 20.01 80 20 25.00 80 20
Flow rate	0.8 mL/min
Detector	UV 300 nm
Injection Volume	10μL
Nominal concentration	0.3mg/mL

Diluent	ACN: Water=1:1, v/v

CLAIMS

1. An amorphous or crystalline form of compound (I):



(I)

or salts, solvates or combination thereof.

2. An amorphous or crystalline form according to claim 1, wherein the form is amorphous form, Form A, Form B, Form C, Form D, Form E, Form F, Form G, Form H, Form L, Form M, Form N, Form P, Form Q or a combination thereof.

3. A crystalline form according to claim 1 or 2, wherein the crystalline form is Form A that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 7.77°±0.1°, 8.22°±0.1°, 19.71°±0.1°, 19.99°±0.1°, 24.77°±0.1° and 25.68°±0.1°.

4. A crystalline form according to claim 3, wherein the crystalline form is Form A that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 7.77°±0.1°, 8.22°±0.1°, 9.10°±0.1°, 9.81°±0.1°, 11.33°±0.1°, 12.60°±0.1°, 14.31°±0.1°, 19.71°±0.1°, 19.99°±0.1°, 21.56°±0.1°, 21.97°±0.1°, 22.46°±0.1°, 23.22°±0.1°, 24.77°±0.1°, 25.68°±0.1°, 26.10°±0.1°, 27.47°±0.1° and 28.22°±0.1°.

5. A crystalline form according to claim 3 or 4, wherein the crystalline form is Form A that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 2.

6. A crystalline form according to any one of claims 3 to 5, wherein the crystalline Form A is a hydrate of compound (I) with water content of 0.5% to 10%, particularly 2.5% to 4.5%.

7. A crystalline form according to claim 1 or 2, wherein the crystalline form is Form B that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 8.42°±0.1°, 19.62°±0.1°, 20.42°±0.1°, 23.03°±0.1°, 25.51°±0.1° and 26.65°±0.1°.

8. A crystalline form according to claim 7, wherein the crystalline form is Form B that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 8.42°±0.1°, 9.34°±0.1°, 11.72°±0.1°, 12.63°±0.1°, 18.67°±0.1°, 19.62°±0.1°, 20.42°±0.1°, 23.03°±0.1°, 24.04°±0.1°, 25.51°±0.1°, 25.99°±0.1°, 26.65°±0.1°, 27.74°±0.1° and 28.36°±0.1°.

9. A crystalline form according to claim 7 or 8, wherein the crystalline form is Form B that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 5.

10. A crystalline form according to any one of claims 7 to 9, wherein the crystalline Form B is an anhydrous form of compound (I).

11. A crystalline form according to claim 1 or 2, wherein the crystalline form is Form C that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 17.04°±0.1°, 20.93°±0.1°, 21.28°±0.1°, 22.56°±0.1°, 24.17°±0.1° and 24.38°±0.1°.

12. A crystalline form according to claim 11, wherein the crystalline form is Form C that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 9.65°±0.1°, 12.58°±0.1°, 14.89°±0.1°, 17.04°±0.1°, 19.40°±0.1°, 20.93°±0.1°, 21.28°±0.1°, 22.56°±0.1°, 23.67°±0.1°, 24.17°±0.1°, 24.38°±0.1° and 24.81°±0.1°.

13. A crystalline form according to claim 11 or 12, wherein the crystalline form is Form C that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 6.

14. A crystalline form according to any one of claims 11 to 13, wherein the crystalline Form C is a co-crystal of monohydrate of compound (I) and tetrafluoroborate of compound (I).

15. A crystalline form according to claim 1 or 2, wherein the crystalline form is Form D that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 15.74°±0.1°, 17.20°±0.1°, 20.46°±0.1°, 23.43°±0.1°, 28.38°±0.1° and 30.88°±0.1°.

16. A crystalline form according to claim 15, wherein the crystalline form is Form D that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 15.74°±0.1°, 17.20°±0.1°, 20.46°±0.1°, 21.96°±0.1°, 23.43°±0.1°, 24.76°±0.1°, 28.38°±0.1°, 30.88°±0.1°, 31.72°±0.1°, 32.80°±0.1°, 33.55°±0.1° and 37.17°±0.1°.

17. A crystalline form according to claim 15 or 16, wherein the crystalline form is Form D that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 10.

18. A crystalline form according to claim 1 or 2, wherein the crystalline form is Form E that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 7.39°±0.1°, 7.96°±0.1°, 9.82°±0.1°, 20.74°±0.1°, 22.50°±0.1°, 23.82°±0.1°, 24.69°±0.1° and 26.20°±0.1°.

19. A crystalline form according to claim 18, wherein the crystalline form is Form E that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 7.39°±0.1°, 7.96°±0.1°, 9.82°±0.1°, 12.22°±0.1°, 16.92°±0.1°, 20.02°±0.1°, 20.74°±0.1°, 21.65°±0.1°, 22.50°±0.1°, 23.82°±0.1°, 24.69°±0.1°, 26.20°±0.1°, 27.76°±0.1° and 28.92°±0.1°.

20. A crystalline form according to claim 18 or 19, wherein the crystalline form is Form E that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 13.

21. A crystalline form according to claim 1 or 2, wherein the crystalline form is Form F that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 11.73°±0.1°, 20.87°±0.1°, 21.80°±0.1°, 23.15°±0.1°, 27.03°±0.1° and 28.58°±0.1°.

22. A crystalline form according to claim 21, wherein the crystalline form is Form F that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 11.02°±0.1°, 11.73°±0.1°, 14.89°±0.1°, 18.36°±0.1°, 20.87°±0.1°, 21.80°±0.1°, 23.15°±0.1°, 24.44°±0.1°, 25.35°±0.1°, 27.03°±0.1°, 28.58°±0.1°, 32.21°±0.1°, 33.52°±0.1° and 39.03°±0.1°.

23. A crystalline form according to claim 21 or 22, wherein the crystalline form is Form F that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 16.

24. A crystalline form according to claim 1 or 2, wherein the crystalline form is Form G that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 9.85°±0.1°, 12.32°±0.1°, 17.37°±0.1°, 23.07°±0.1°, 24.86°±0.1°, 25.31°±0.1° and 28.48°±0.1°.

25. A crystalline form according to claim 24, wherein the crystalline form is Form G that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 6.81°±0.1°, 8.20°±0.1°, 9.85°±0.1°, 12.32°±0.1°, 15.01°±0.1°, 17.37°±0.1°, 19.35°±0.1°, 21.19°±0.1°, 22.42°±0.1°, 23.07°±0.1°, 24.86°±0.1°, 25.31°±0.1°, 26.57°±0.1°, 28.48°±0.1° and 35.38°±0.1°.

26. A crystalline form according to claim 24 or 25, wherein the crystalline form is Form G that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 19.

27. A crystalline form according to claim 1 or 2, wherein the crystalline form is Form H that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 7.88°±0.1°, 18.31°±0.1°, 19.94°±0.1°, 21.49°±0.1°, 23.12°±0.1°, 23.91°±0.1°, 25.69°±0.1° and 26.83°±0.1°.

28. A crystalline form according to claim 27, wherein the crystalline form is Form H that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 7.88°±0.1°, 13.23°±0.1°, 14.42°±0.1°, 17.69°±0.1°, 18.31°±0.1°, 19.94°±0.1°, 21.49°±0.1°, 23.12°±0.1°, 23.91°±0.1°, 25.69°±0.1° and 26.83°±0.1°.

29. A crystalline form according to claim 27 or 28, wherein the crystalline form is Form H that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 22.

30. A crystalline form according to any one of claims 15 to 29, wherein the crystalline Form D, Form E, Form F, Form G or Form H is a hydrochloride salt of compound (I).

31. A crystalline form according to claim 1 or 2, wherein the crystalline form is Form L that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 5.29°±0.1°, 15.86°±0.1°, 18.99°±0.1°, 20.88°±0.1°, 22.96°±0.1° and 23.30°±0.1°.

32. A crystalline form according to claim 31, wherein the crystalline form is Form L that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 5.29°±0.1°, 10.56°±0.1°, 10.95°±0.1°, 15.86°±0.1°, 18.99°±0.1°, 20.88°±0.1°, 21.19°±0.1°, 21.71°±0.1°, 22.96°±0.1°, 23.30°±0.1°, 25.02°±0.1°, 26.84°±0.1°, 28.29°±0.1° and 32.36°±0.1°.

33. A crystalline form according to claim 31 or 32, wherein the crystalline form is Form L that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 30.

34. A crystalline form according to any one of claims 31 to 33, wherein the crystalline Form L is an ethylsulfate of compound (I).

35. A crystalline form according to claim 1 or 2, wherein the crystalline form is Form M that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 6.24°±0.1°, 8.57°±0.1°, 13.64°±0.1°, 14.53°±0.1°, 16.50°±0.1°, 17.18°±0.1°, 19.47°±0.1° and 22.11°±0.1°.

36. A crystalline form according to claim 35, wherein the crystalline form is Form M that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 6.24°±0.1°, 8.57°±0.1°, 9.80°±0.1°, 13.64°±0.1°, 14.53°±0.1°, 16.50°±0.1°, 17.18°±0.1°, 19.47°±0.1°, 22.11°±0.1°, 25.23°±0.1°, 28.11°±0.1° and 29.39°±0.1°.

37. A crystalline form according to claim 35 or 36, wherein the crystalline form is Form M that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 34.

38. A crystalline form according to claim 1 or 2, wherein the crystalline form is Form N that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 4.62°±0.1°, 9.22°±0.1°, 18.50°±0.1°, 19.05°±0.1°, 23.14°±0.1° and 23.88°±0.1°.

39. A crystalline form according to claim 38, wherein the crystalline form is Form N that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 4.62°±0.1°, 9.22°±0.1°, 11.81°±0.1°, 13.10°±0.1°, 13.83°±0.1°, 17.44°±0.1°, 18.50°±0.1°, 19.05°±0.1°, 20.63°±0.1°, 21.98°±0.1°, 23.14°±0.1°, 23.88°±0.1°, 25.61°±0.1°, 27.85°±0.1°, 29.31°±0.1° and 39.07°±0.1°.

40. A crystalline form according to claim 38 or 39, wherein the crystalline form is Form N that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 37.

41. A crystalline form according to claim 1 or 2, wherein the crystalline form is Form P that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 11.27°±0.1°, 12.18°±0.1°, 17.57°±0.1°, 18.01°±0.1°, 22.38°±0.1° and 23.16°±0.1°.

42. A crystalline form according to claim 41, wherein the crystalline form is Form P that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 7.23°±0.1°, 11.27°±0.1°, 12.18°±0.1°, 15.51°±0.1°, 16.46°±0.1°, 17.57°±0.1°, 18.01°±0.1°, 21.18°±0.1°, 22.38°±0.1°, 23.16°±0.1°, 24.44°±0.1°, 29.59°±0.1° and 31.83°±0.1°.

43. A crystalline form according to claim 40 or 41, wherein the crystalline form is Form P that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 40.

44. A crystalline form according to claim 1 or 2, wherein the crystalline form is Form Q that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 11.04°±0.1°, 12.77°±0.1°, 16.33°±0.1°, 16.71°±0.1°, 18.06°±0.1° and 20.65°±0.1°.

45. A crystalline form according to claim 44, wherein the crystalline form is Form Q that exhibits an X-ray powder diffraction (XRPD) pattern with characteristic peaks expressed in degrees 2-theta at 4.35°±0.1°, 9.96°±0.1°, 11.04°±0.1°, 12.77°±0.1°, 15.04°±0.1°, 16.33°±0.1°,

16.71°±0.1°, 18.06°±0.1°, 20.65°±0.1°, 22.19°±0.1°, 23.76°±0.1°, 25.36°±0.1°, 26.64°±0.1°, 29.34°±0.1° and 30.26°±0.1°.

46. A crystalline form according to claim 44 or 45, wherein the crystalline form is Form Q that exhibits an X-ray powder diffraction (XRPD) pattern shown in FIG. 43.

47. A crystalline form according to any one of claims 35 to 46, wherein the crystalline Form M, Form N, Form P or Form Q is a calcium salt of compound (I).

48. A pharmaceutical composition comprising the amorphous or crystalline form of anyone of the claims 1 to 47 and a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

49. The use of the amorphous or crystalline form of any one of claims 1 to 47 or the pharmaceutical composition of claim 48 for the manufacture of a medicament for the treatment or prophylaxis of a viral disease in a patient.

50. The use according to claim 49, wherein the viral disease is hepatitis B infection or a disease caused by hepatitis B infection.

51. A method for the treatment or prophylaxis of hepatitis B infection or a disease caused by hepatitis B infection, which method comprises administering an therapeutically effective amount of the amorphous or crystalline form as defined in any one of claims 1 to 47 or the pharmaceutical composition of claim 48.

52. The invention as hereinbefore described.

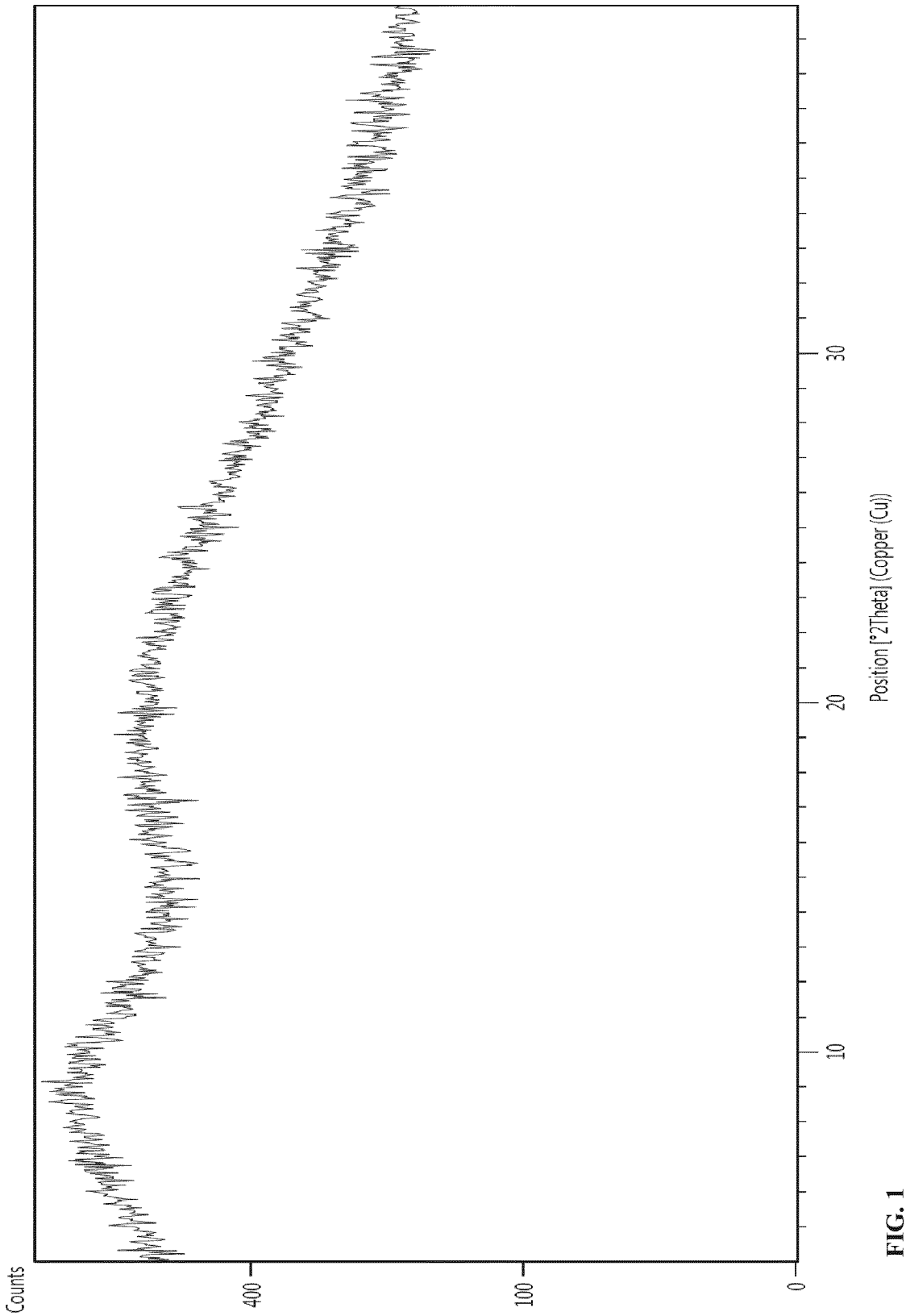


FIG. 1

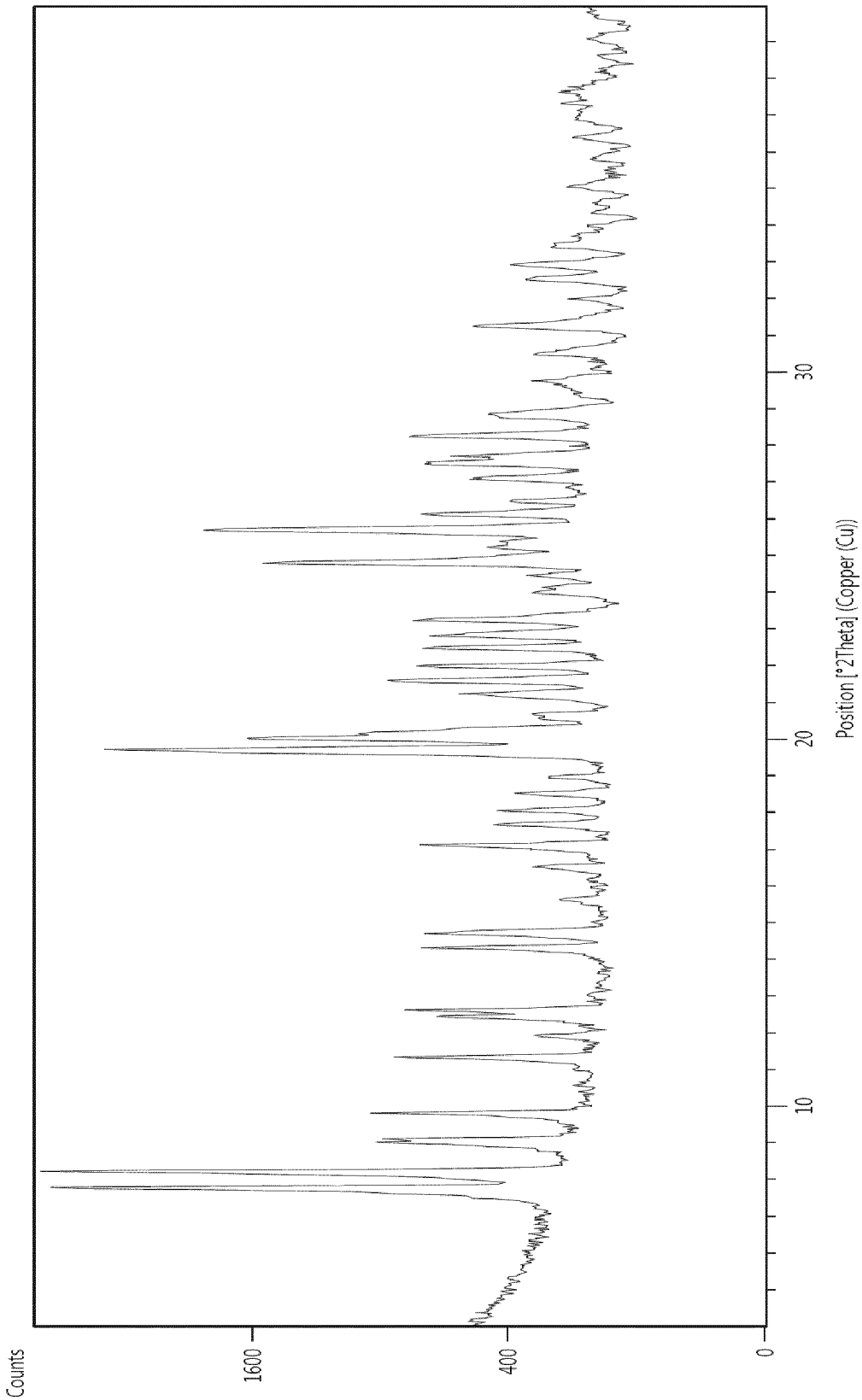


FIG. 2

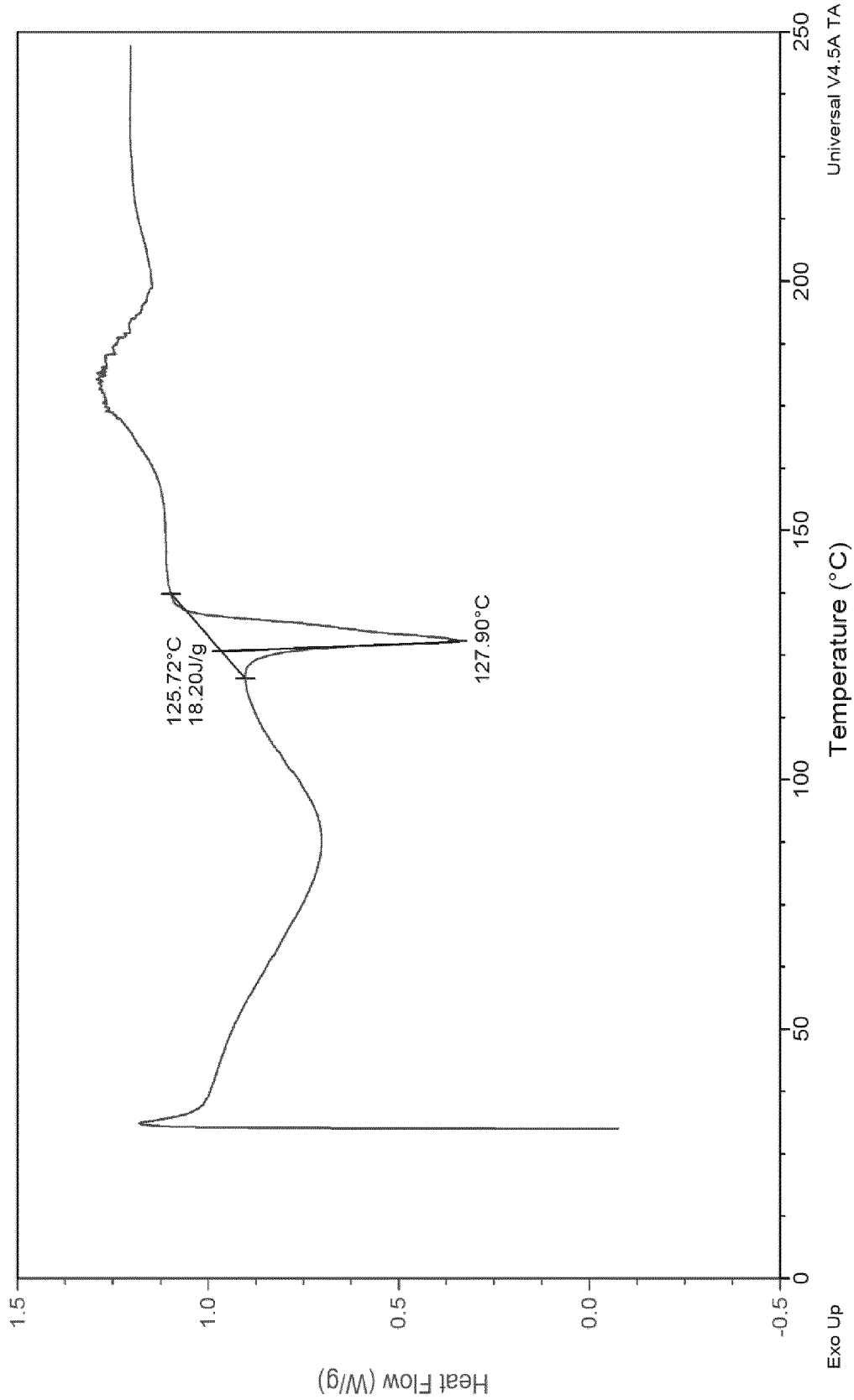

125.72°C
18.20J/g
127.90°C
Heat Flow (W/g)
Temperature (°C)
Exo Up
Universal V4.5A TA
1.5
1.0
0.5
0.0
-0.5
0
50
100
150
200
250

FIG. 3

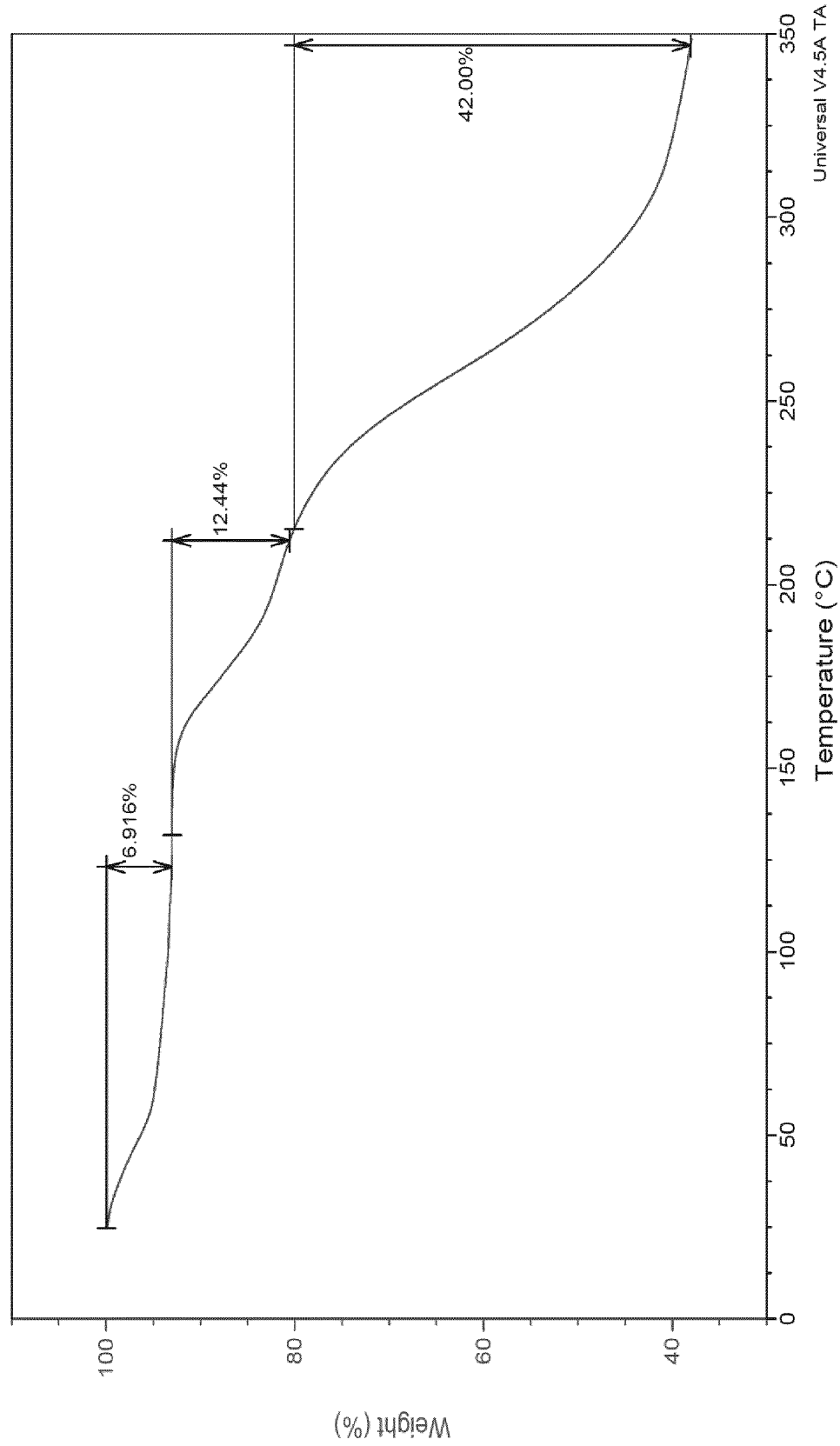

Weight (%)
100
80
60
40
0
50
100
150
200
250
300
350
Temperature (°C)
Universal V4.5A TA
6.916%
12.44%
42.00%

FIG. 4

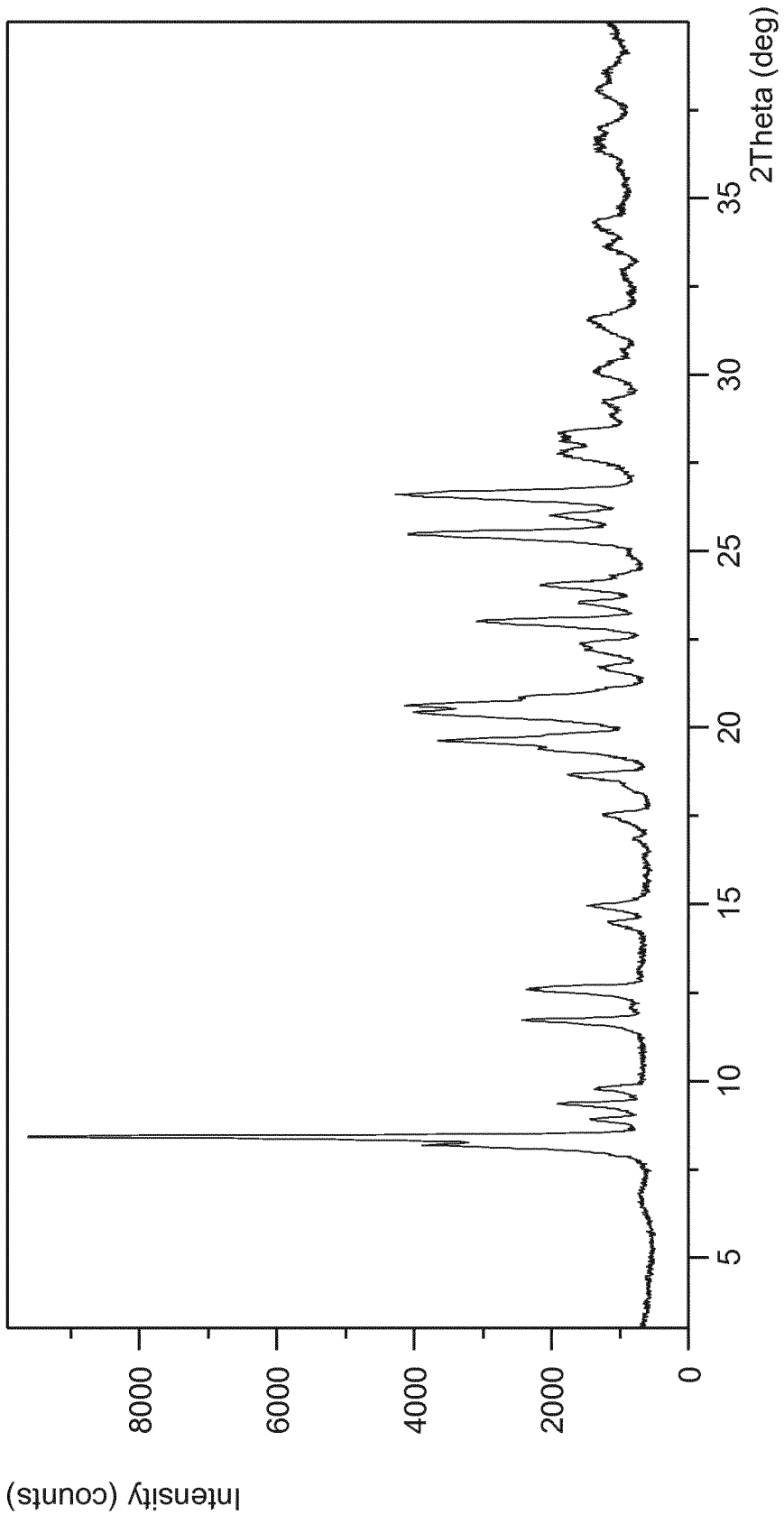

Intensity (counts)
0
2000
4000
6000
8000
5
10
15
20
25
30
35
2Theta (deg)

FIG. 5

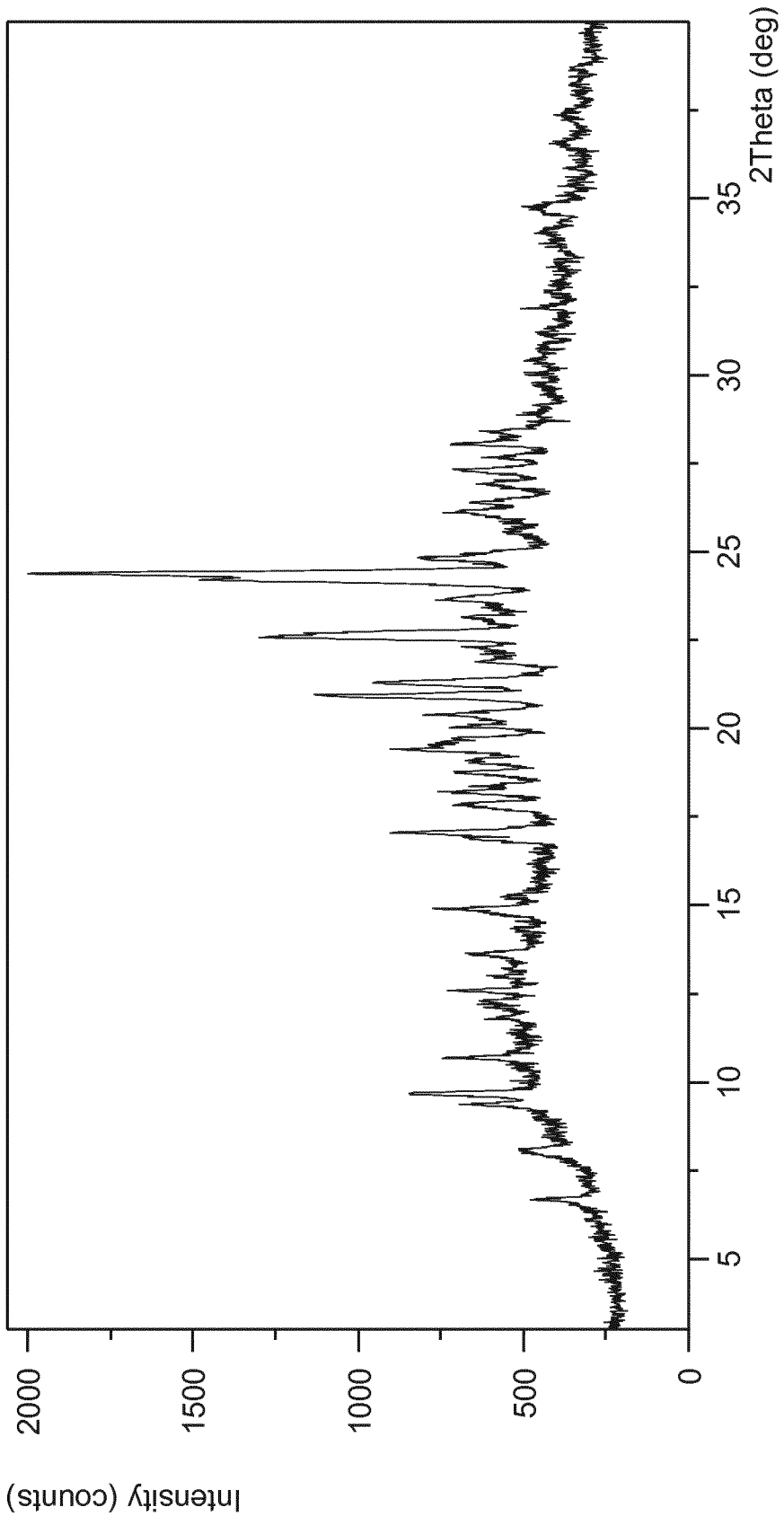

Intensity (counts)
2000
1500
1000
500
0
5
10
15
20
25
30
35
2Theta (deg)

FIG. 6

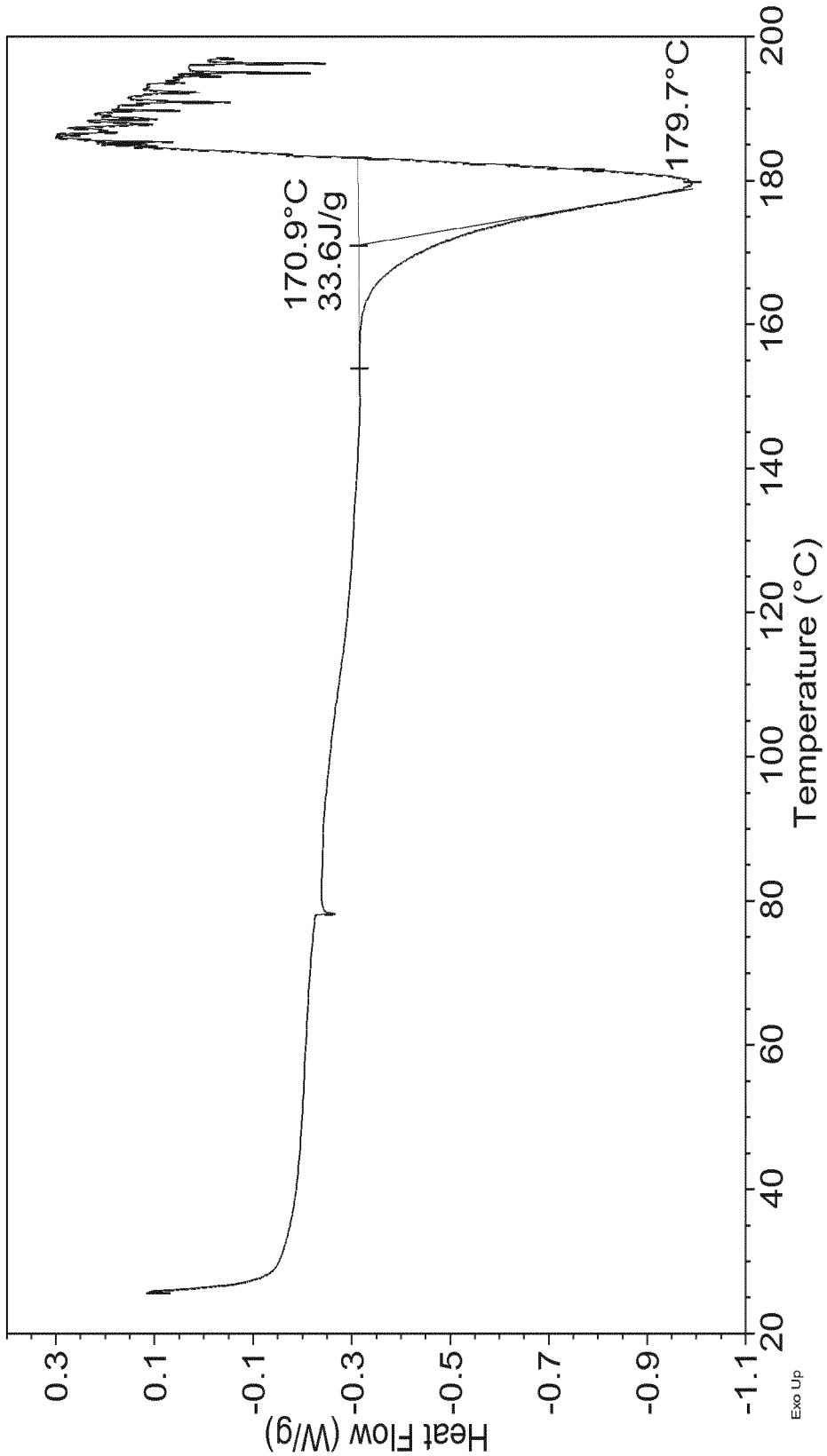

170.9°C
33.6J/g
179.7°C
Heat Flow (W/g)
Exo Up
Temperature (°C)
0.3
0.1
-0.1
-0.3
-0.5
-0.7
-0.9
-1.1
20
40
60
80
100
120
140
160
180
200

FIG. 7

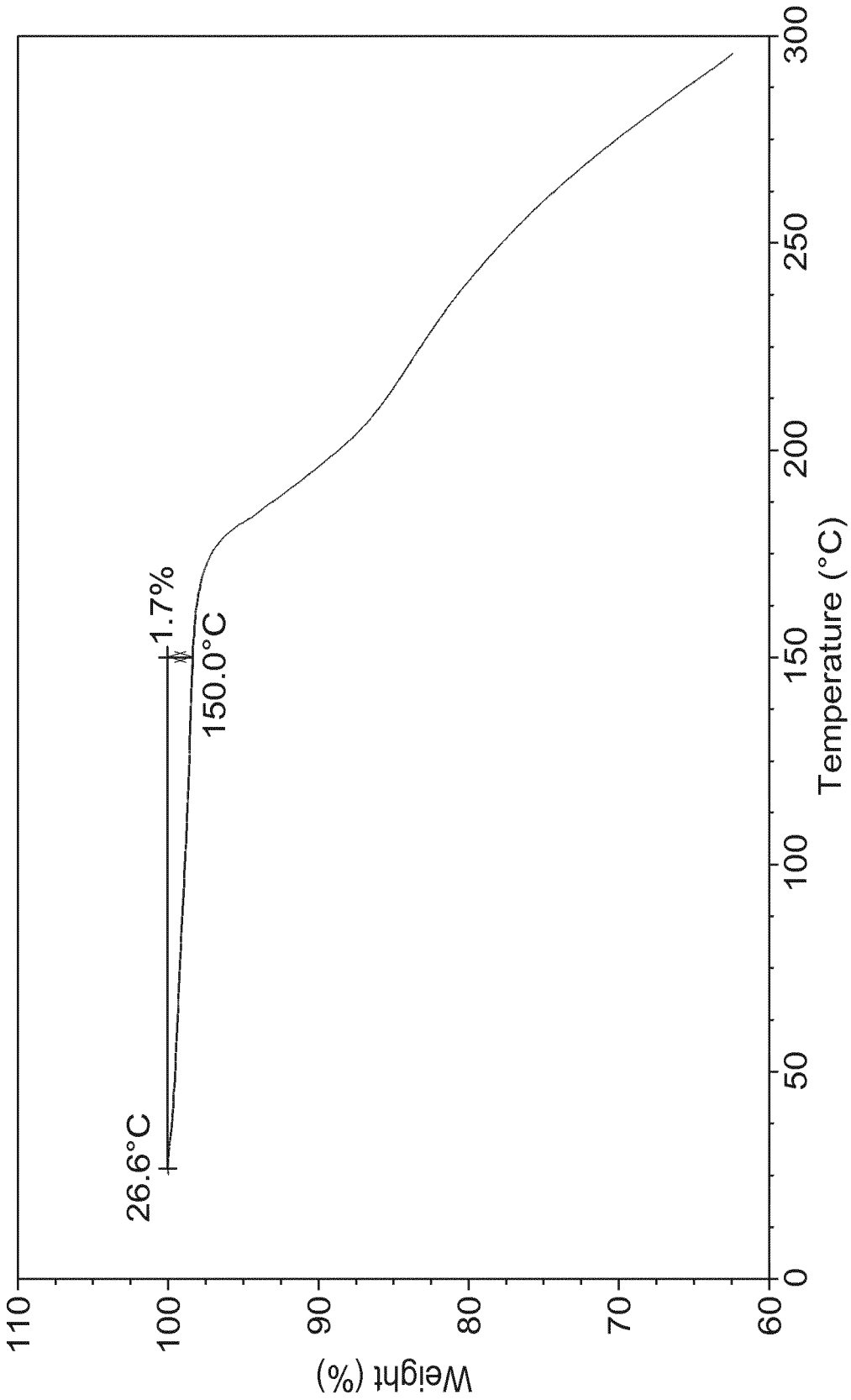

26.6°C
1.7%
150.0°C
Weight (%)
Temperature (°C)
110
100
90
80
70
60
0
50
100
150
200
250
300

FIG. 8

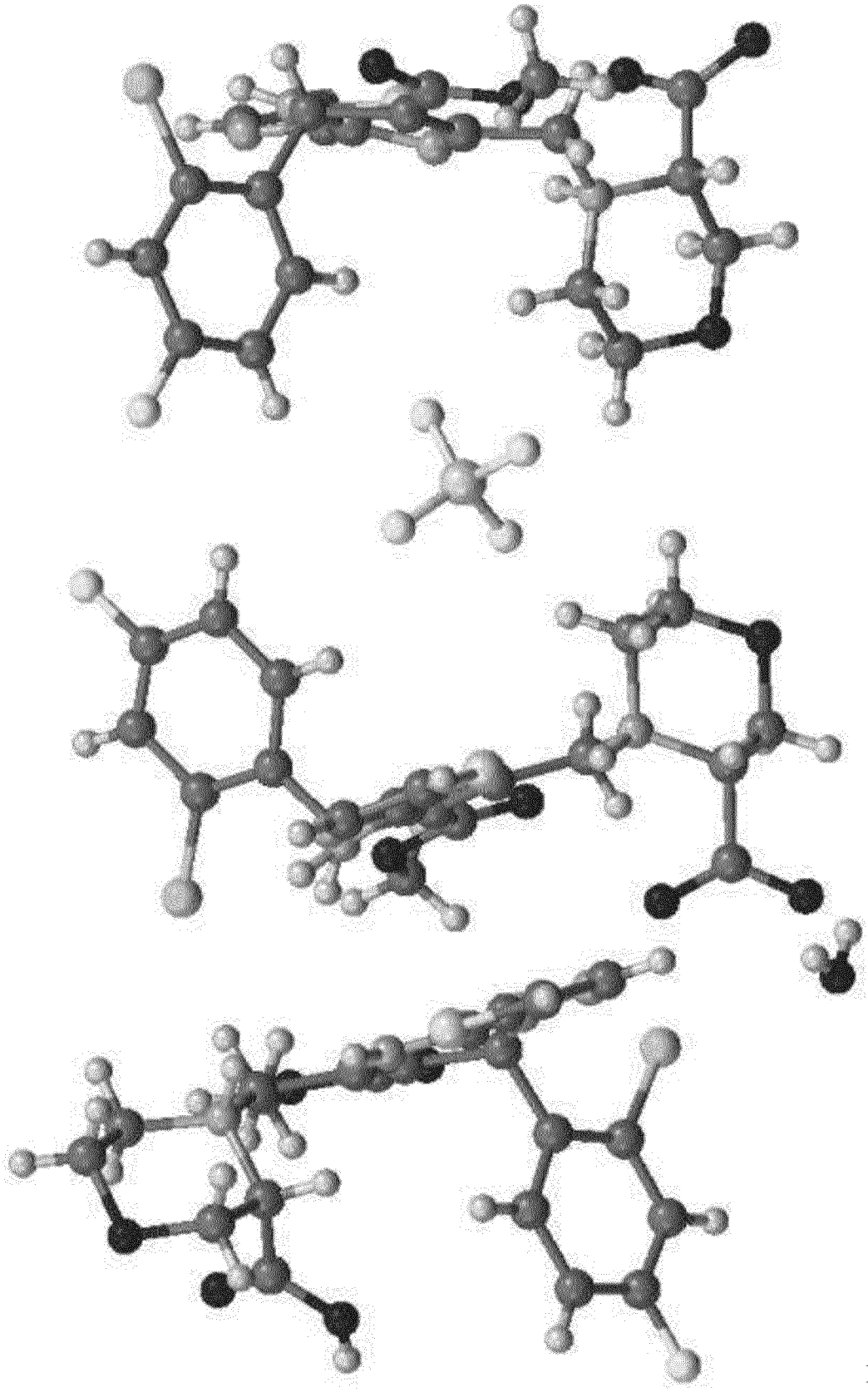


FIG. 9

FIG. 9 X-ray

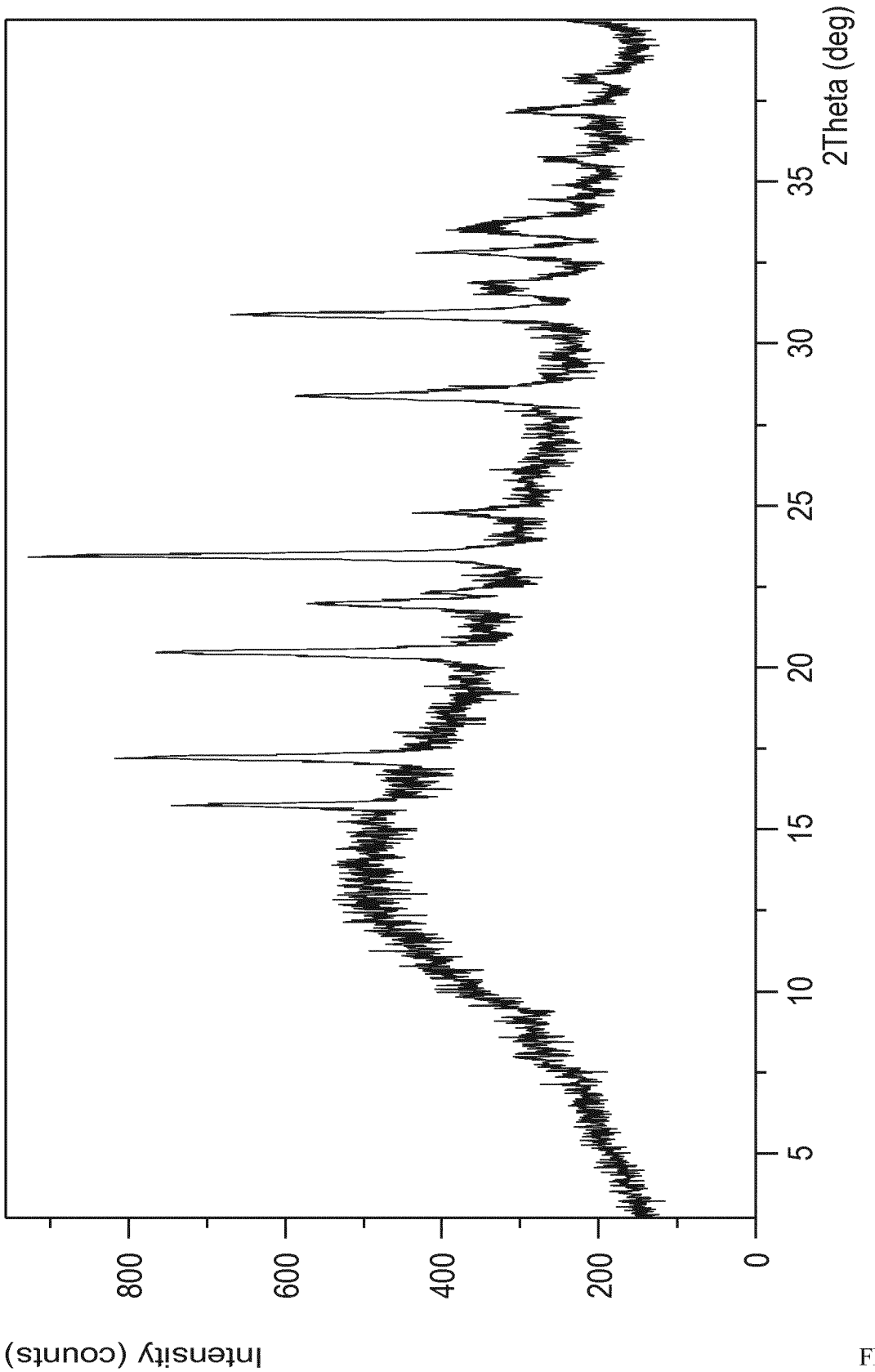


FIG. 10

FIG. 10 X

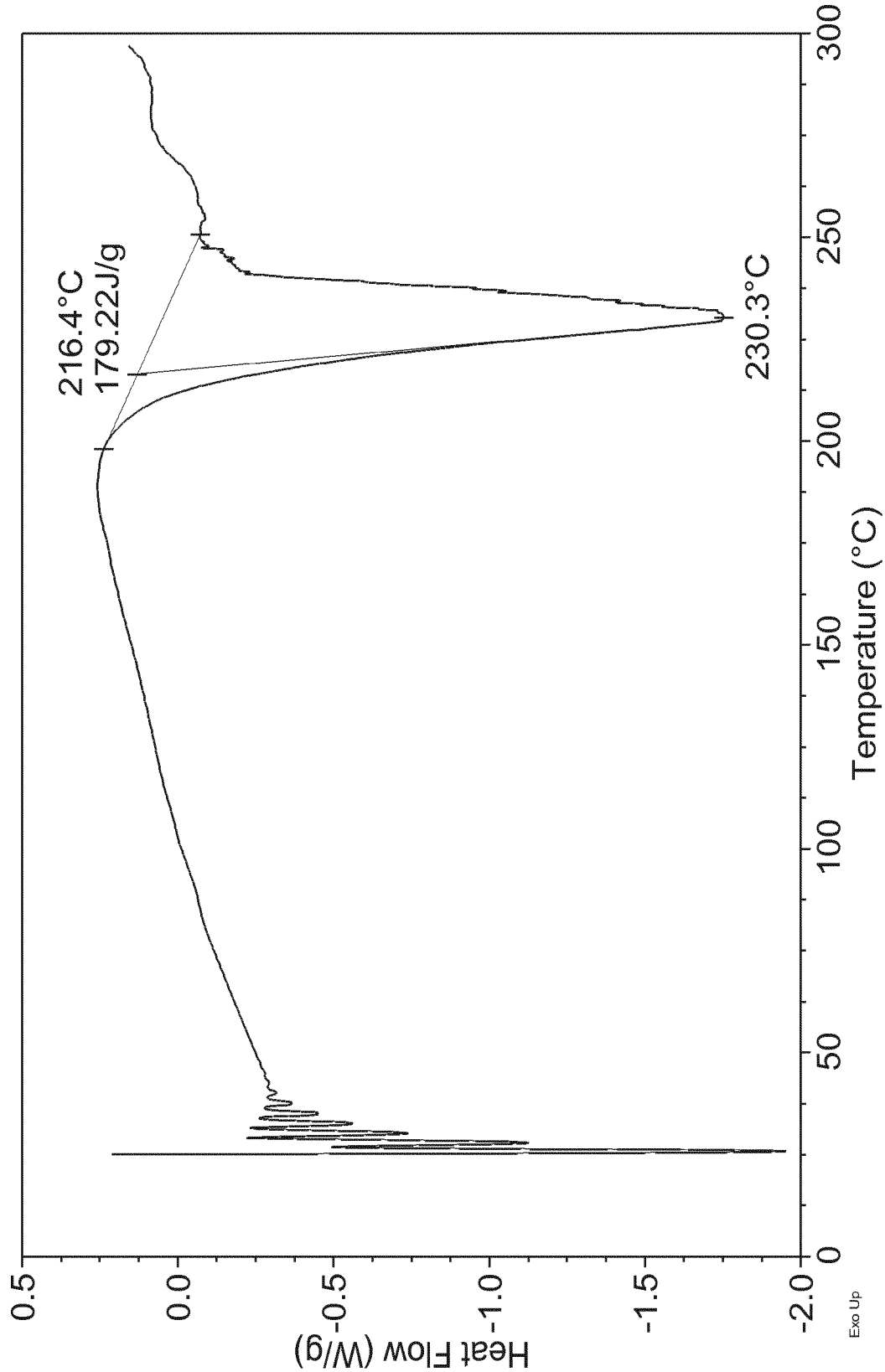

216.4°C
179.22J/g
230.3°C
Heat Flow (W/g)
Temperature (°C)
Exo Up
0.5
0.0
-0.5
-1.0
-1.5
-2.0
0
50
100
150
200
250
300

FIG. 11

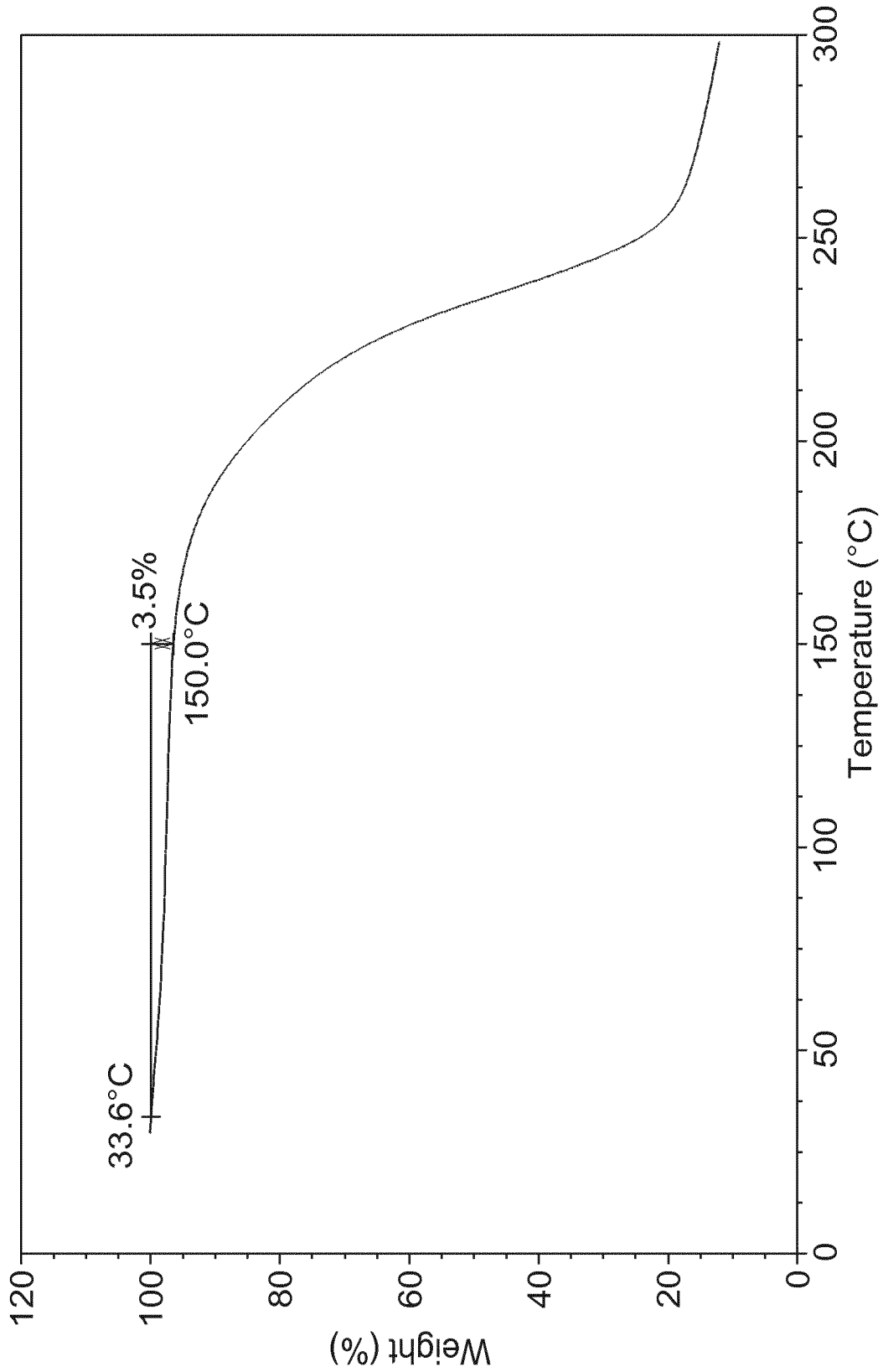

120
100
80
60
40
20
0
Weight (%)
0
50
100
150
200
250
300
Temperature (°C)
33.6°C
3.5%
150.0°C

FIG. 12

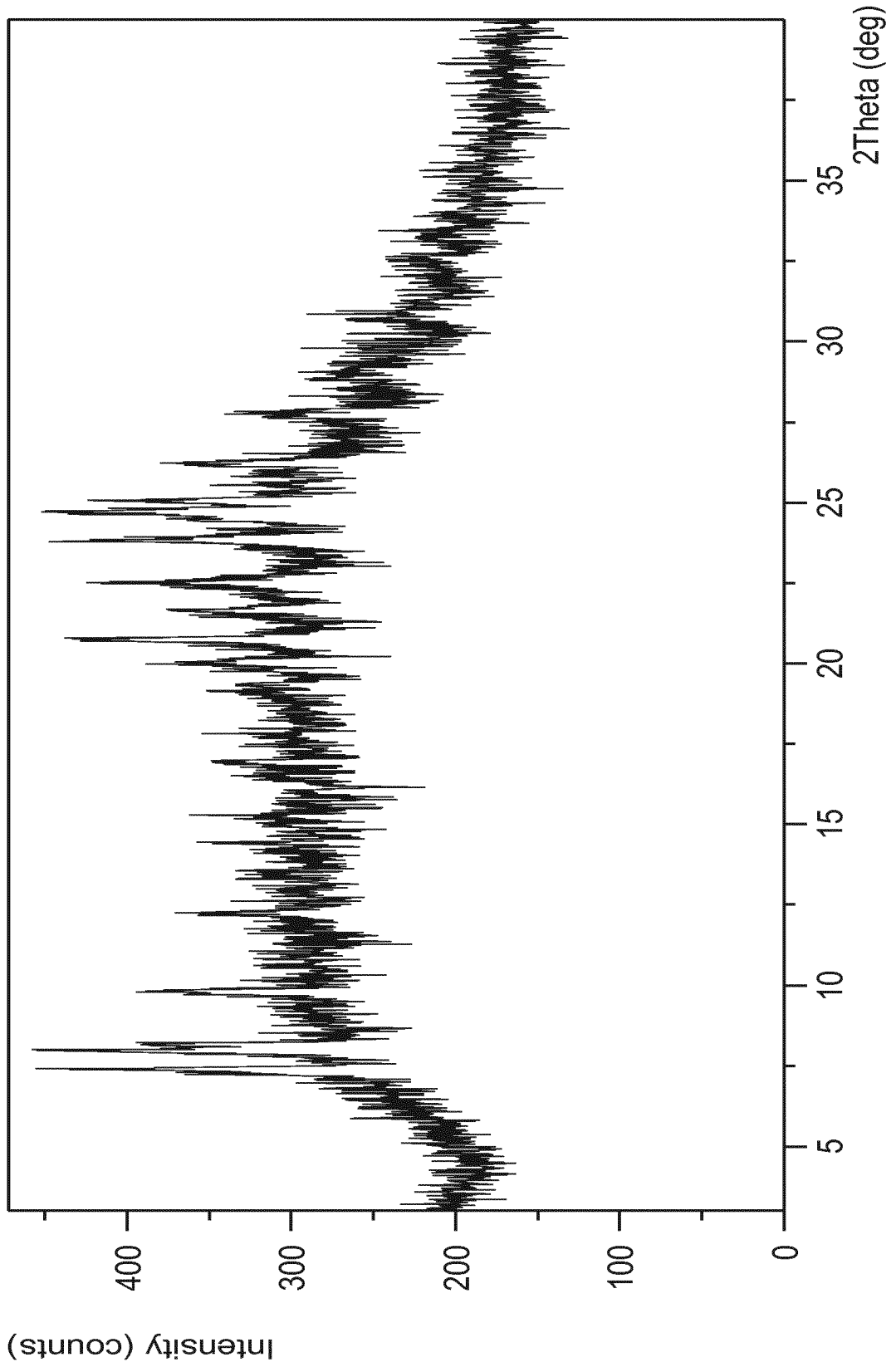

Intensity (counts)
0
100
200
300
400
5
10
15
20
25
30
35
2Theta (deg)

FIG. 13

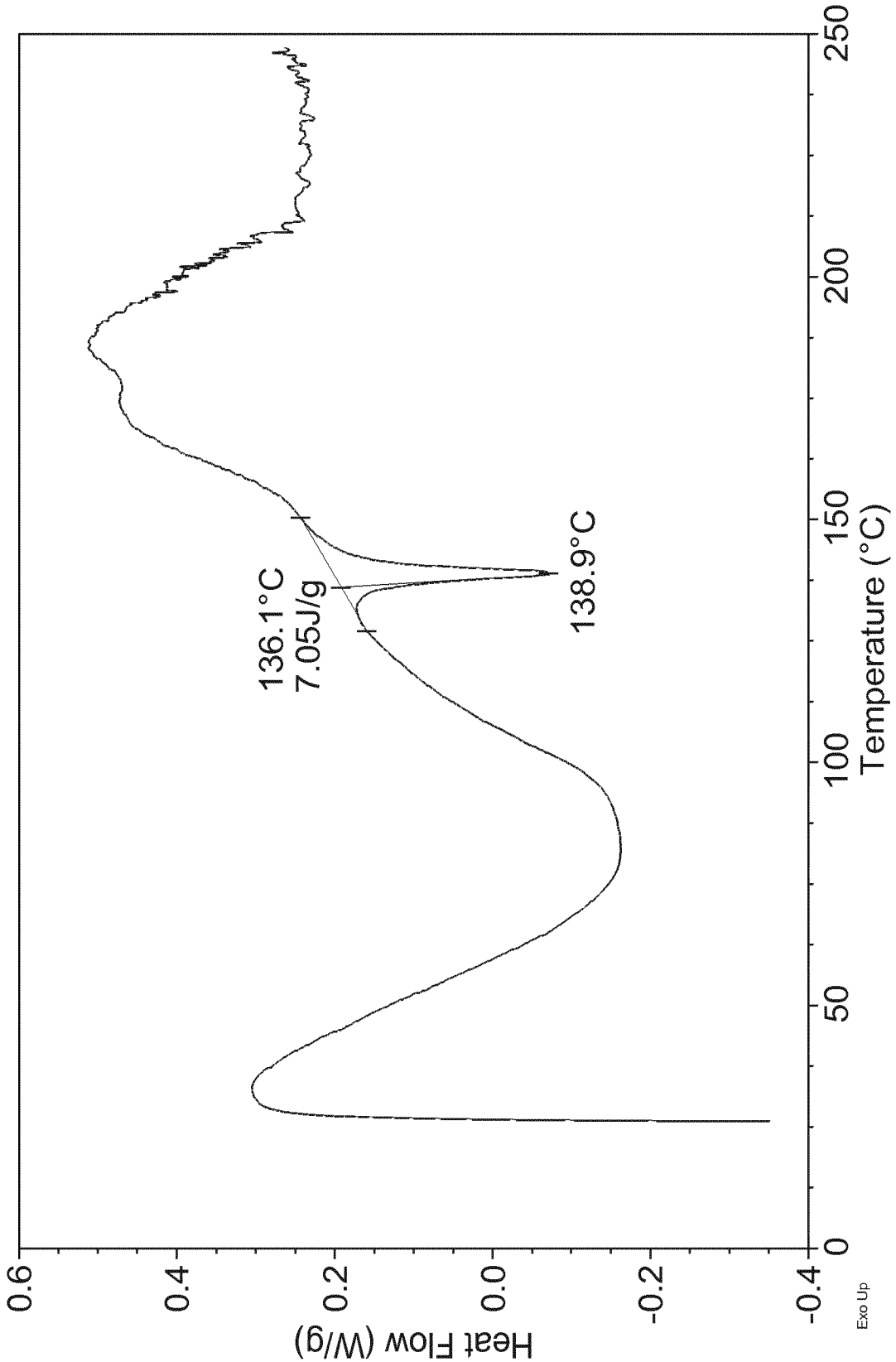

136.1°C
7.05J/g
138.9°C
Heat Flow (W/g)
Temperature (°C)
Exo Up
0.6
0.4
0.2
0.0
-0.2
-0.4
0
50
100
150
200
250

FIG. 14

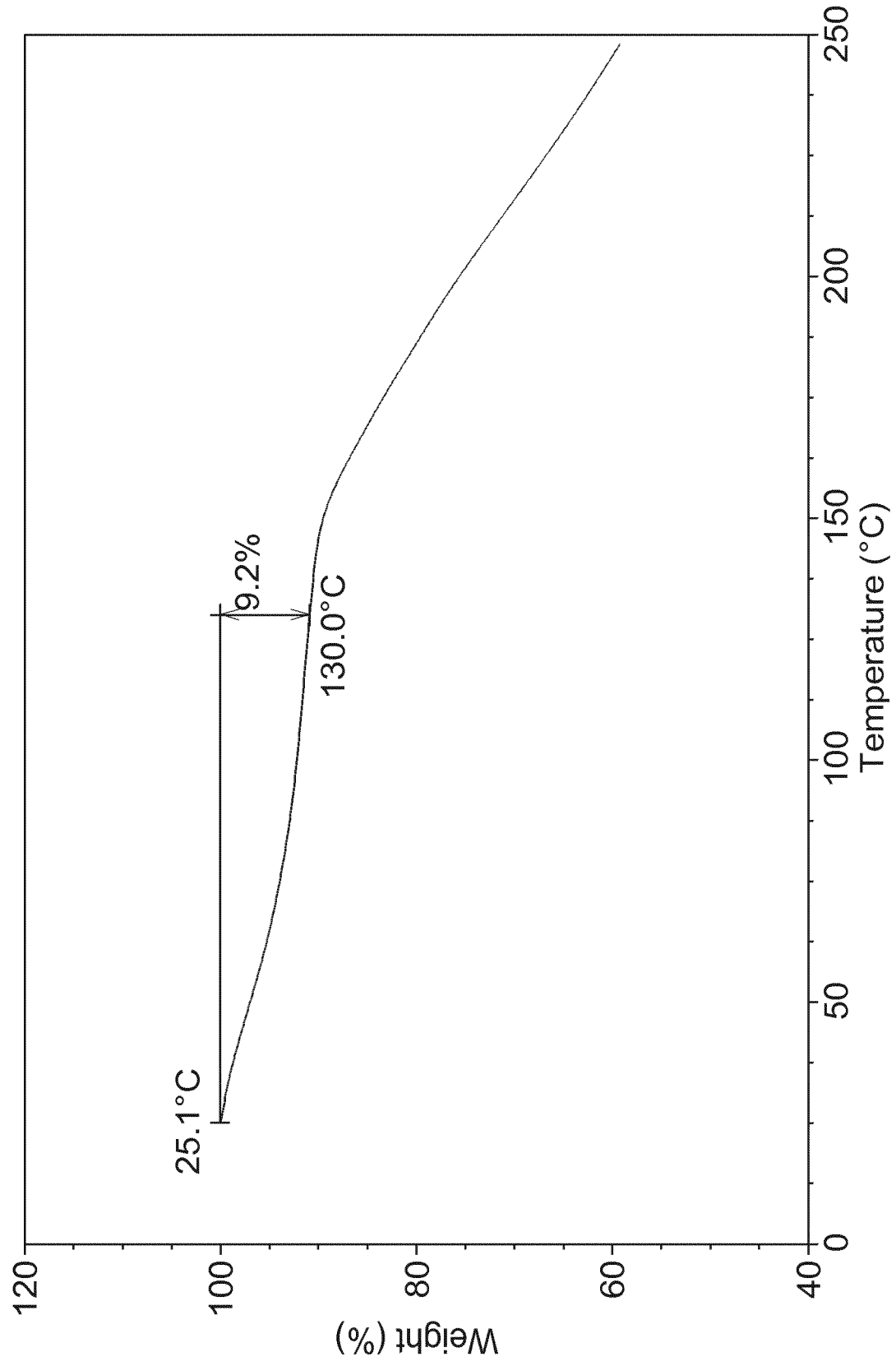

120
100
80
60
40
Weight (%)
0
50
100
150
200
250
Temperature (°C)
25.1°C
9.2%
130.0°C

FIG. 15

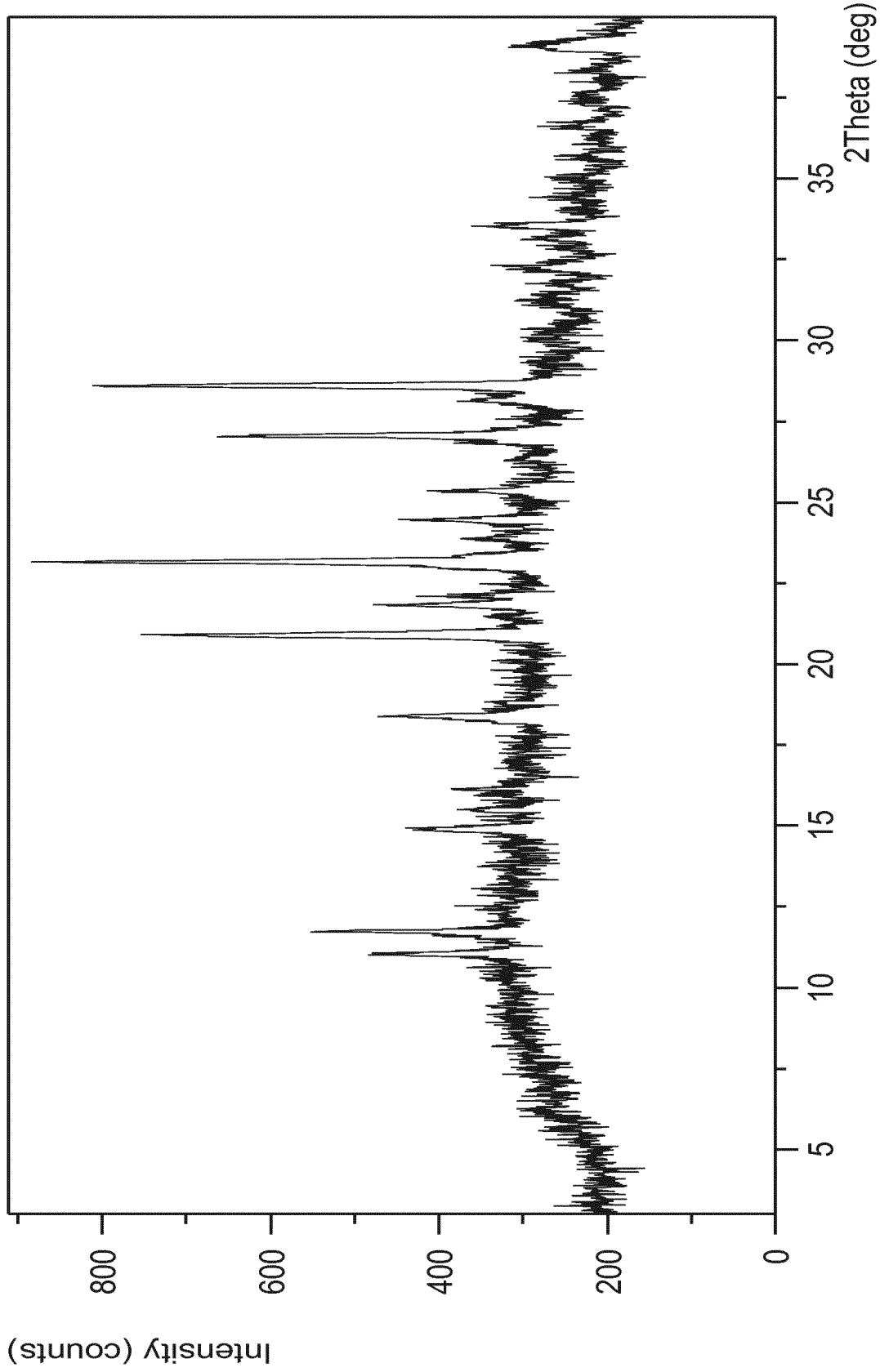

Intensity (counts)
0
200
400
600
800
5
10
15
20
25
30
35
2Theta (deg)

FIG. 16

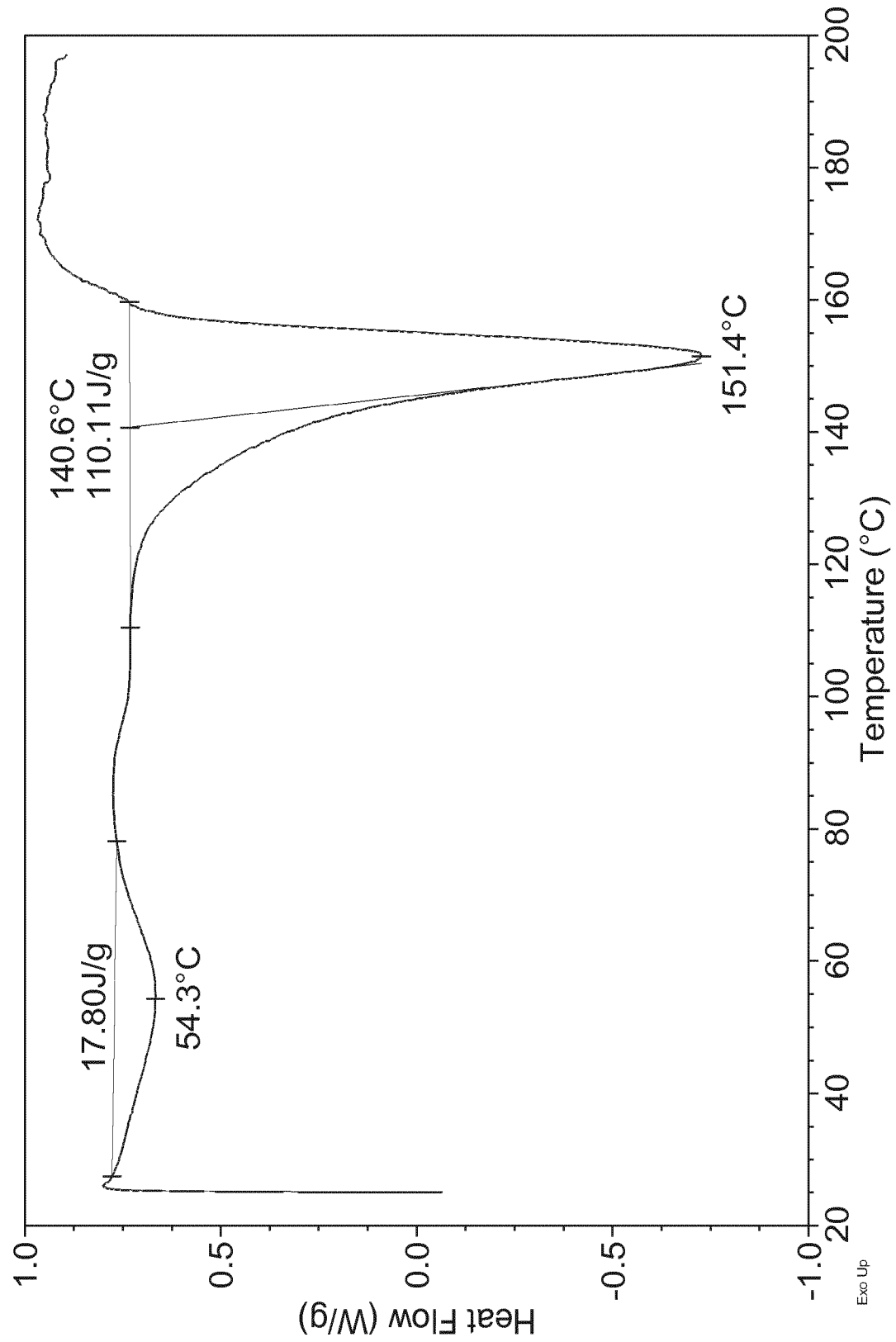

1.0
0.5
0.0
-0.5
-1.0
Heat Flow (W/g)
Exo Up
20
40
60
80
100
120
140
160
180
200
Temperature (°C)
17.80J/g
54.3°C
140.6°C
110.11J/g
151.4°C

FIG. 17

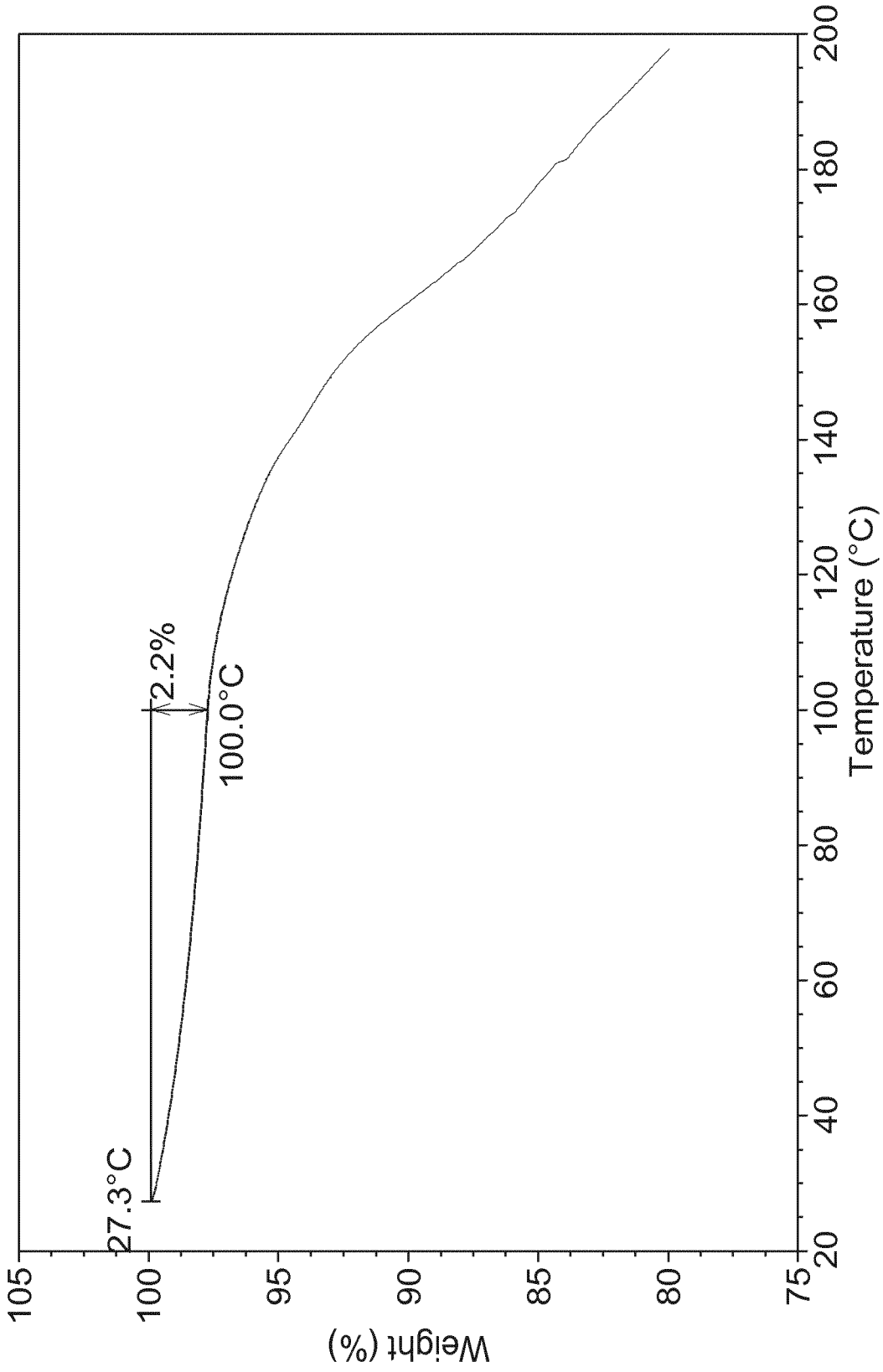

105
100
95
90
85
80
75
Weight (%)
20
40
60
80
100
120
140
160
180
200
Temperature (°C)
27.3°C
2.2%
100.0°C

FIG. 18

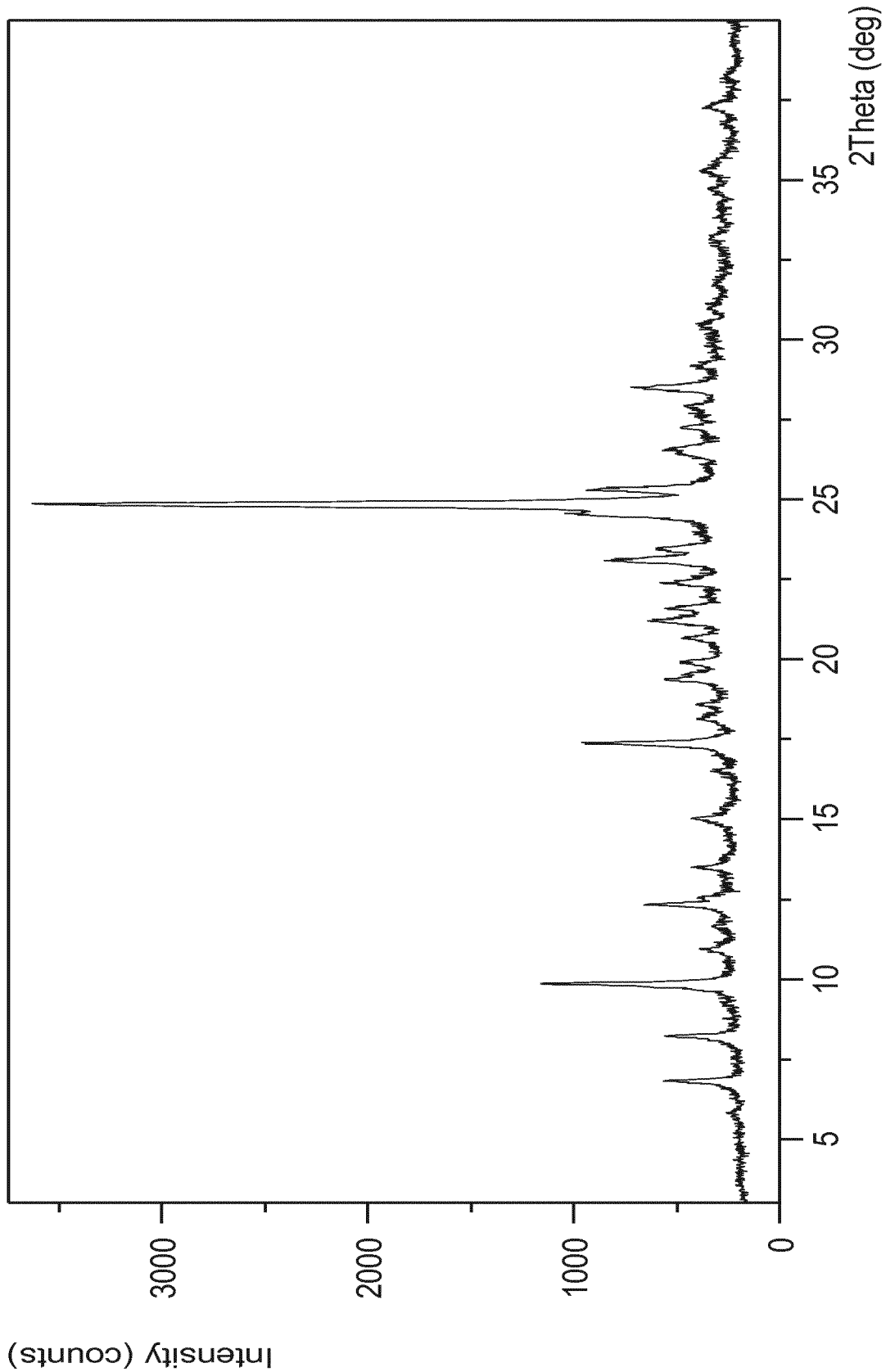

Intensity (counts)
3000
2000
1000
0
5
10
15
20
25
30
35
2Theta (deg)

FIG. 19

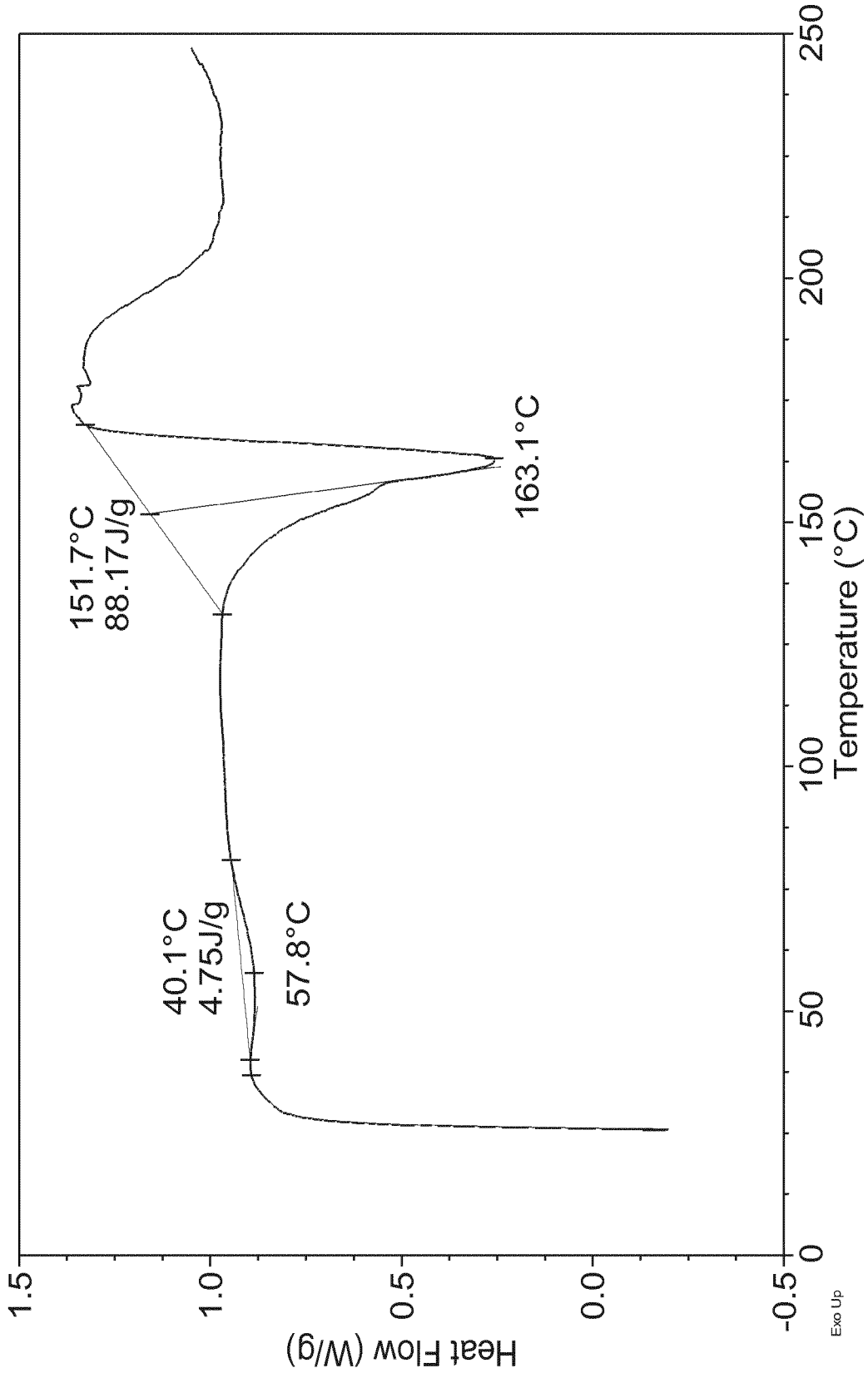

151.7°C
88.17J/g
163.1°C
40.1°C
4.75J/g
57.8°C
Heat Flow (W/g)
Temperature (°C)
Exo Up
1.5
1.0
0.5
0.0
-0.5
0
50
100
150
200
250

FIG. 20

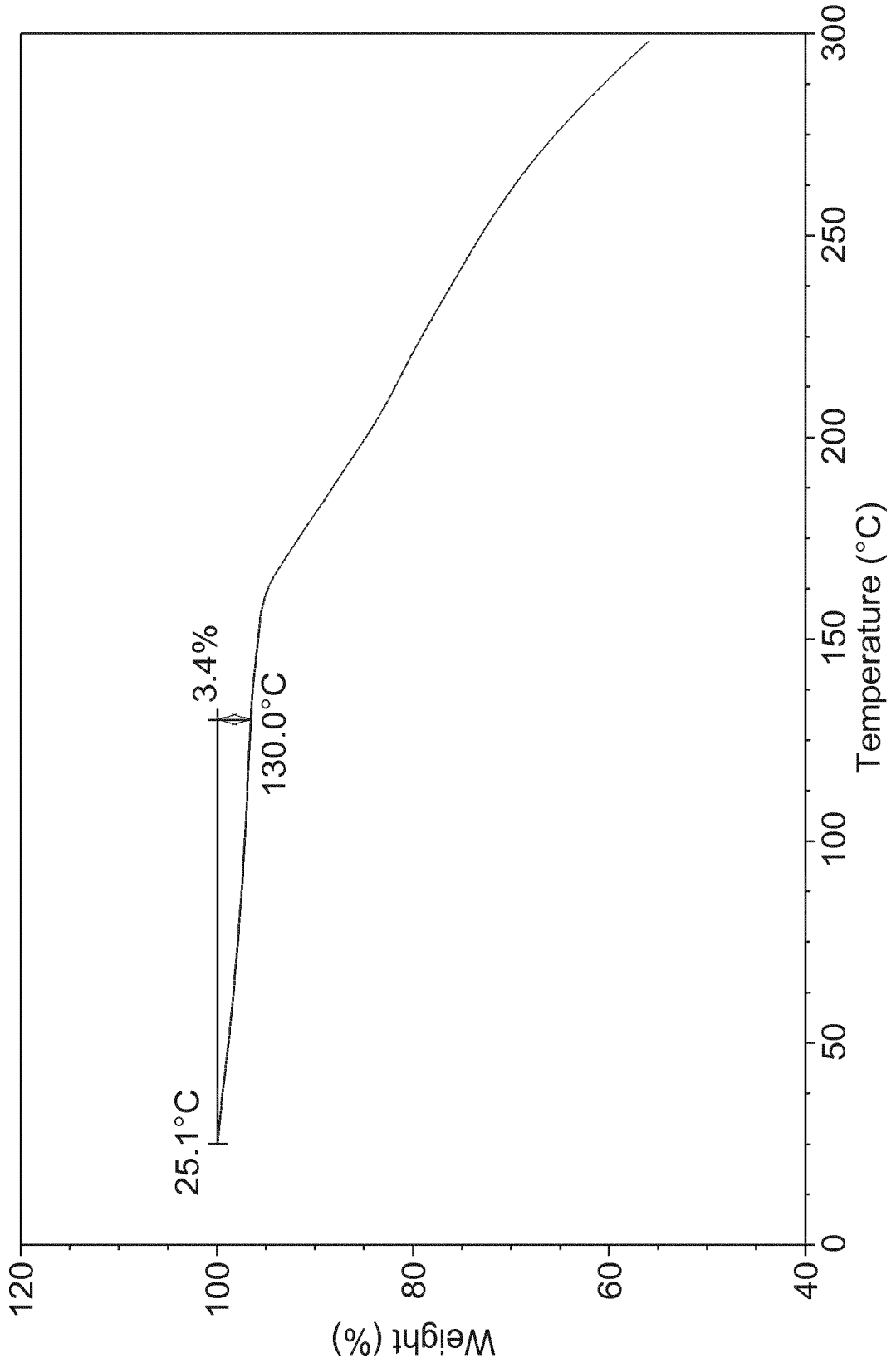

Weight (%)
120
100
80
60
40
0
50
100
150
200
250
300
Temperature (°C)
3.4%
130.0°C
25.1°C

FIG. 21

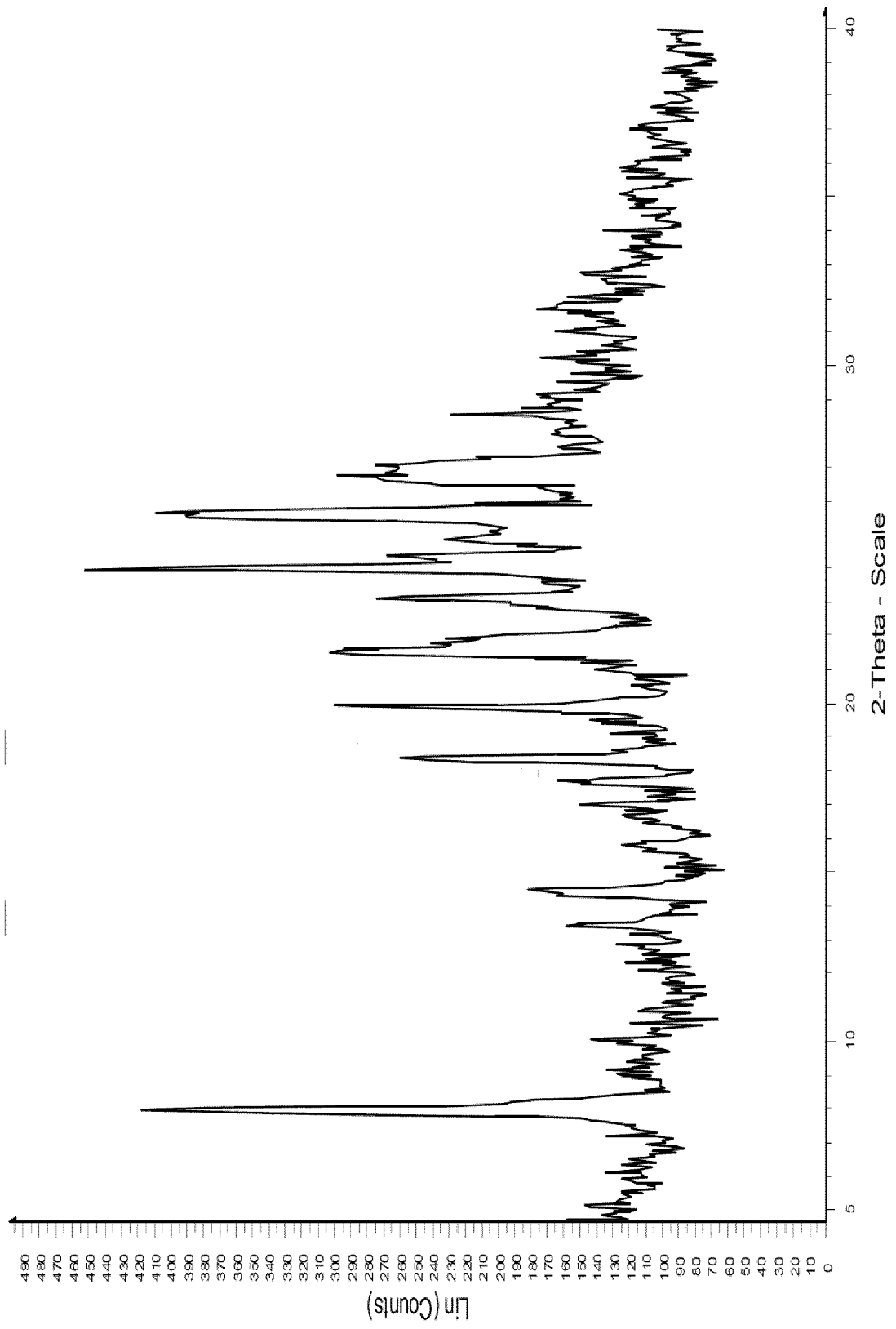


FIG. 22

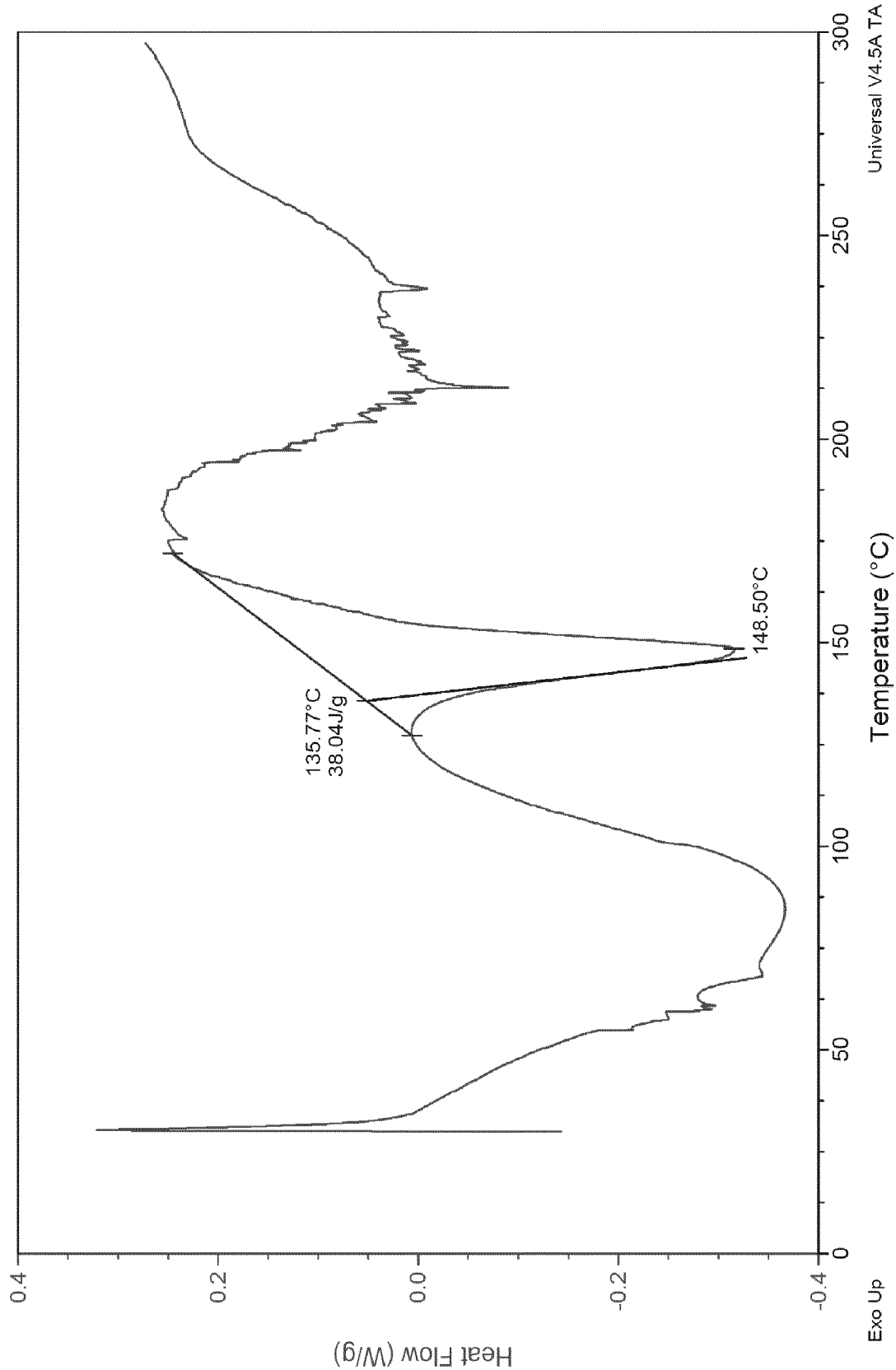

Heat Flow (W/g)
0.4
0.2
0.0
-0.2
-0.4
Exo Up
0
50
100
150
200
250
300
Temperature (°C)
Universal V4.5A TA
135.77°C
38.04J/g
148.50°C

FIG. 23

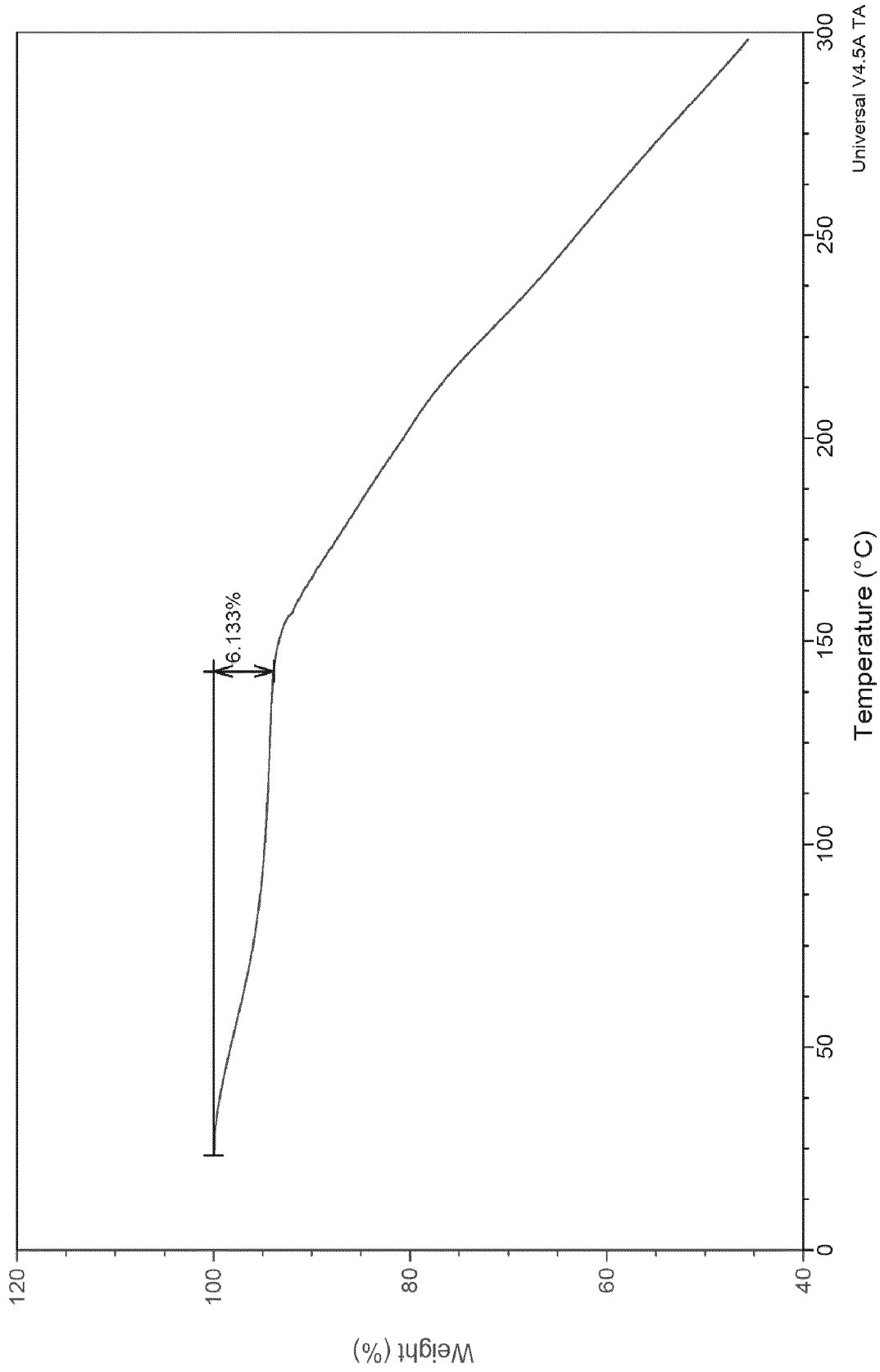

Universal V4.5A TA
Temperature (°C)
Weight (%)
6.133%
0
50
100
150
200
250
300
40
60
80
100
120

FIG. 24

FIG. 25 Omitted
FIG. 26 Omitted
FIG. 27 Omitted
FIG. 28 Omitted
FIG. 29 Omitted

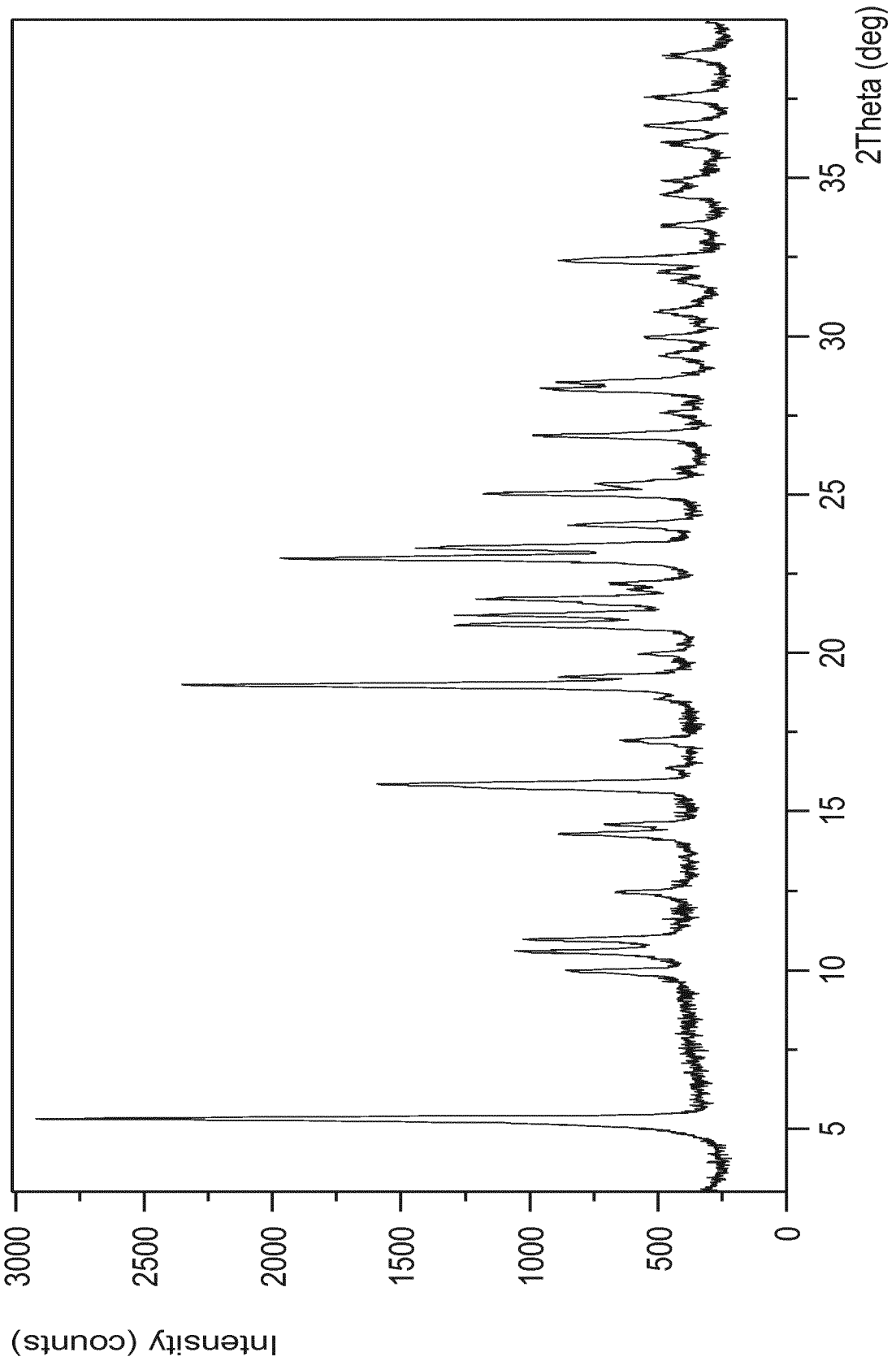

Intensity (counts)
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
2Theta (deg)

FIG. 30

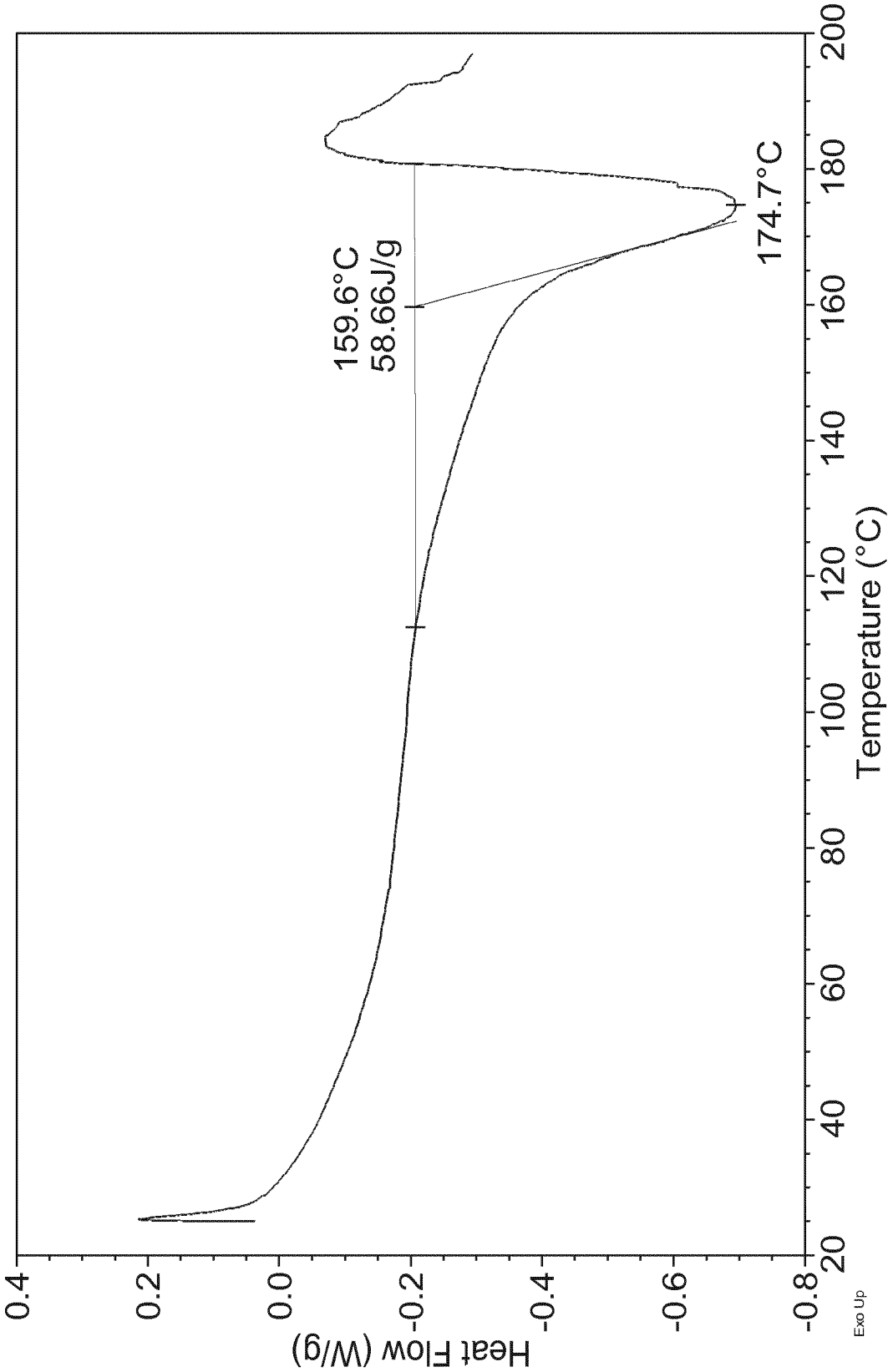

159.6°C
58.66J/g
174.7°C
Heat Flow (W/g)
Temperature (°C)
Exo Up
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
20
40
60
80
100
120
140
160
180
200

FIG. 31

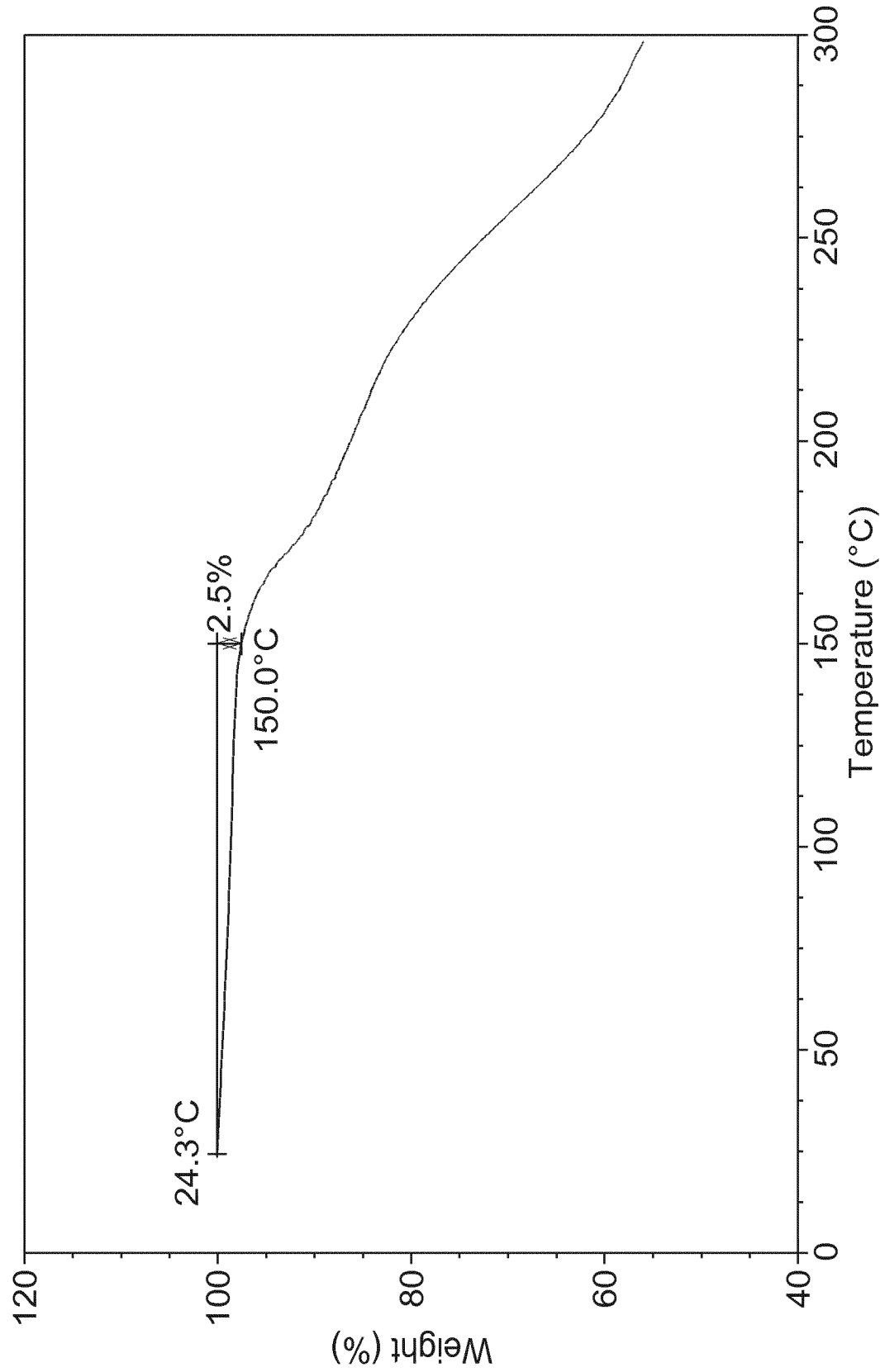

120
100
80
60
40
Weight (%)
0
50
100
150
200
250
300
Temperature (°C)
24.3°C
2.5%
150.0°C

FIG. 32

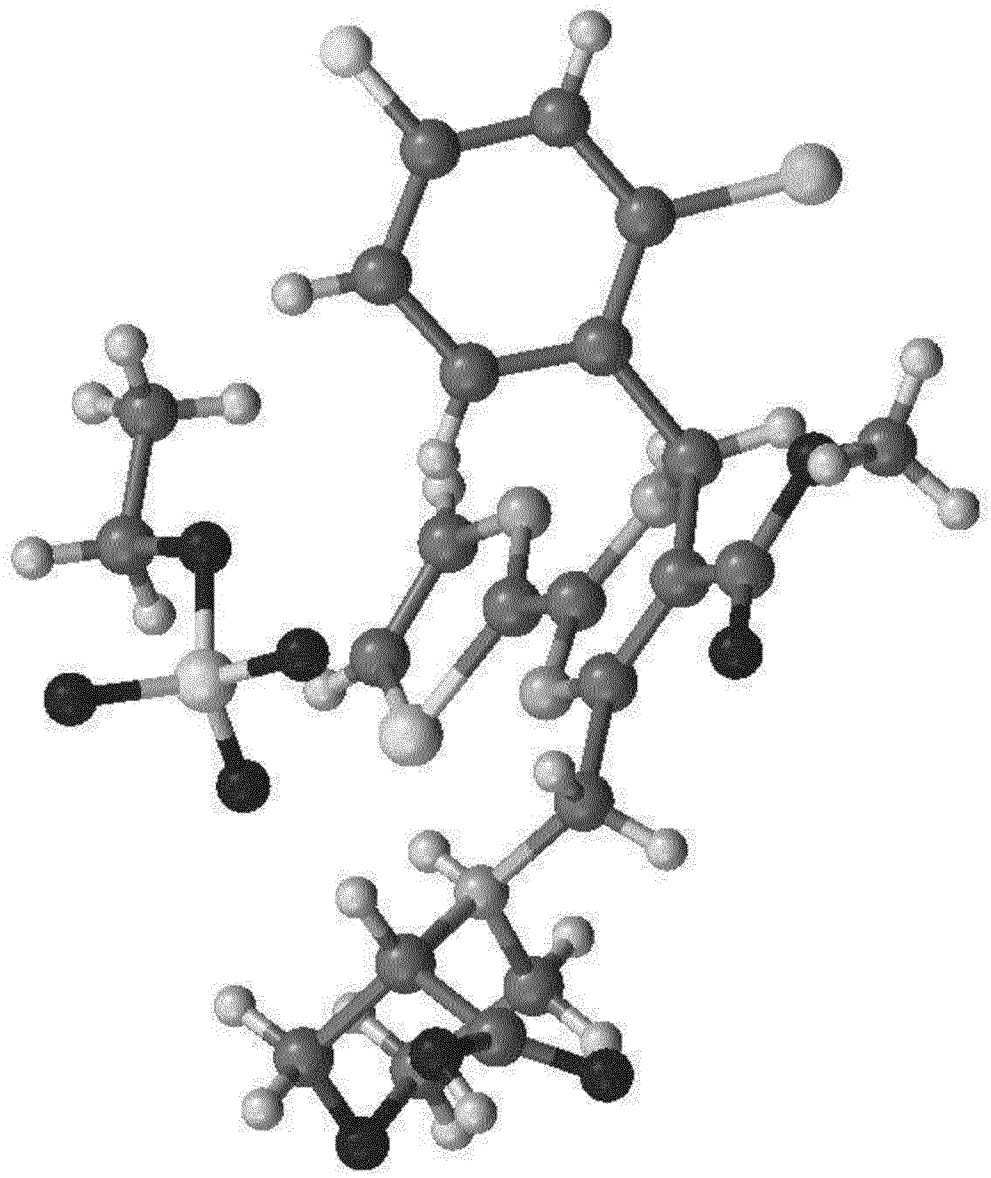


FIG. 33

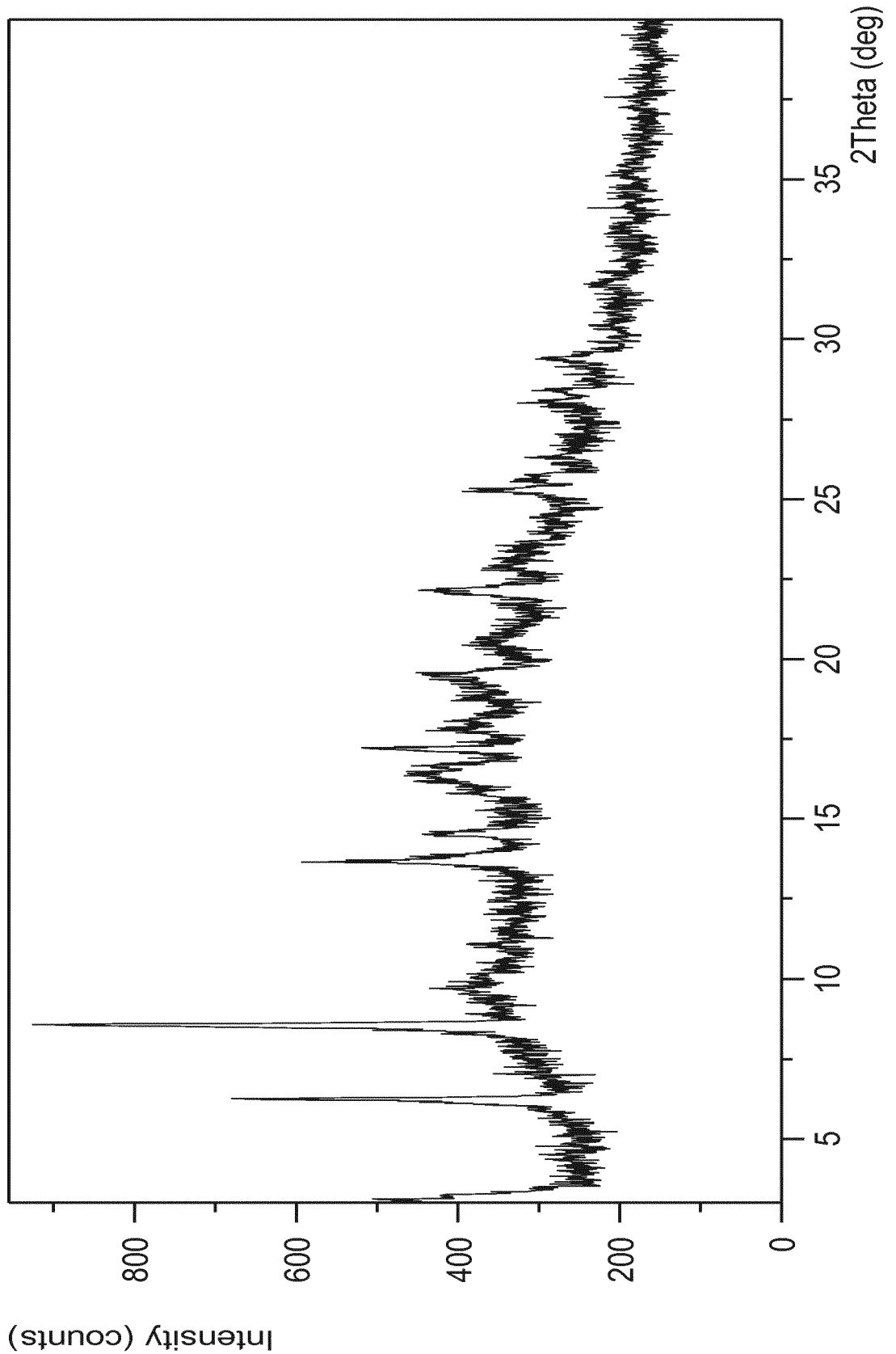

Intensity (counts)
0
200
400
600
800
5
10
15
20
25
30
35
2Theta (deg)

FIG. 34

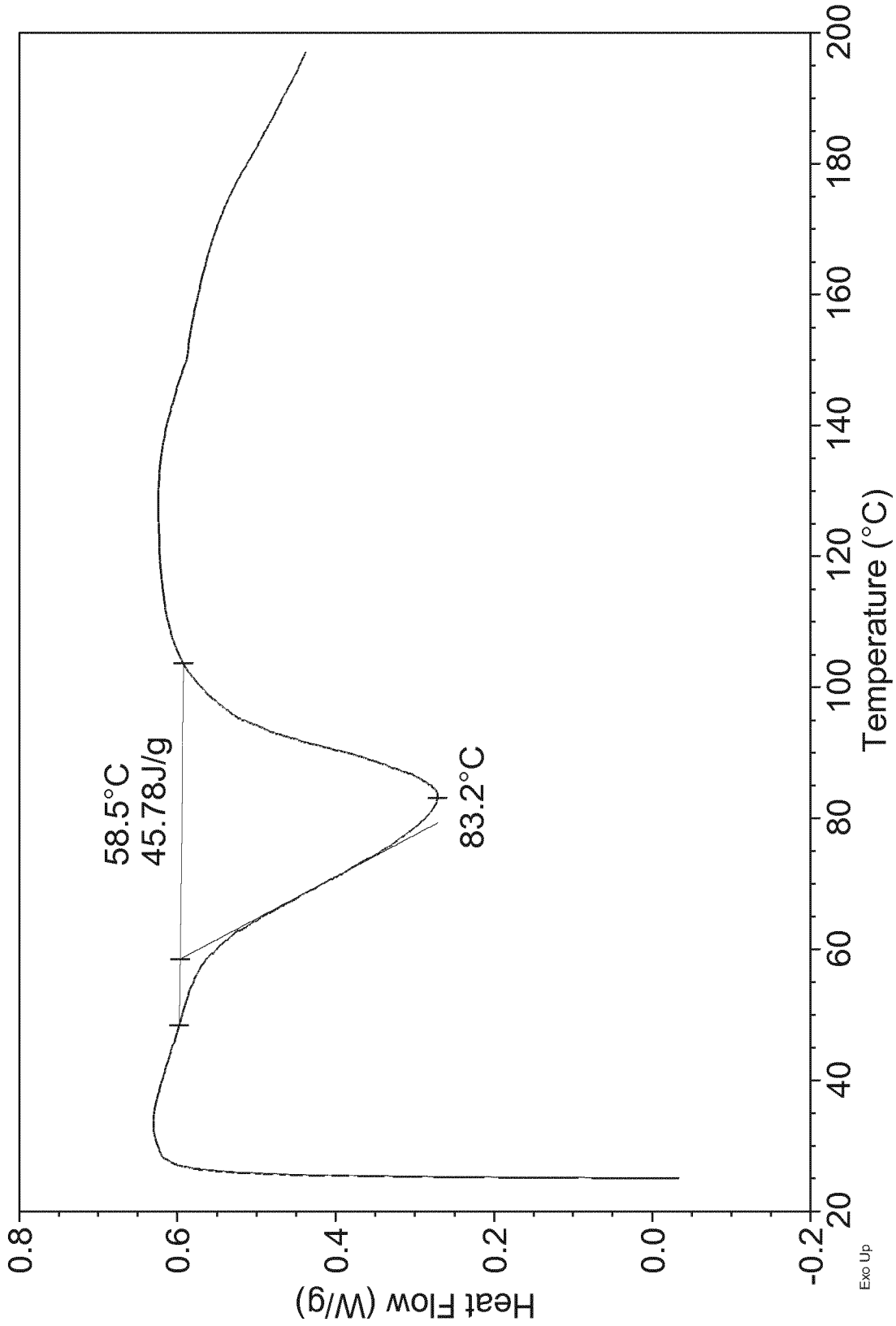

58.5°C
45.78J/g
83.2°C
Heat Flow (W/g)
Exo Up
Temperature (°C)
0.8
0.6
0.4
0.2
0.0
-0.2
20
40
60
80
100
120
140
160
180
200

FIG. 35

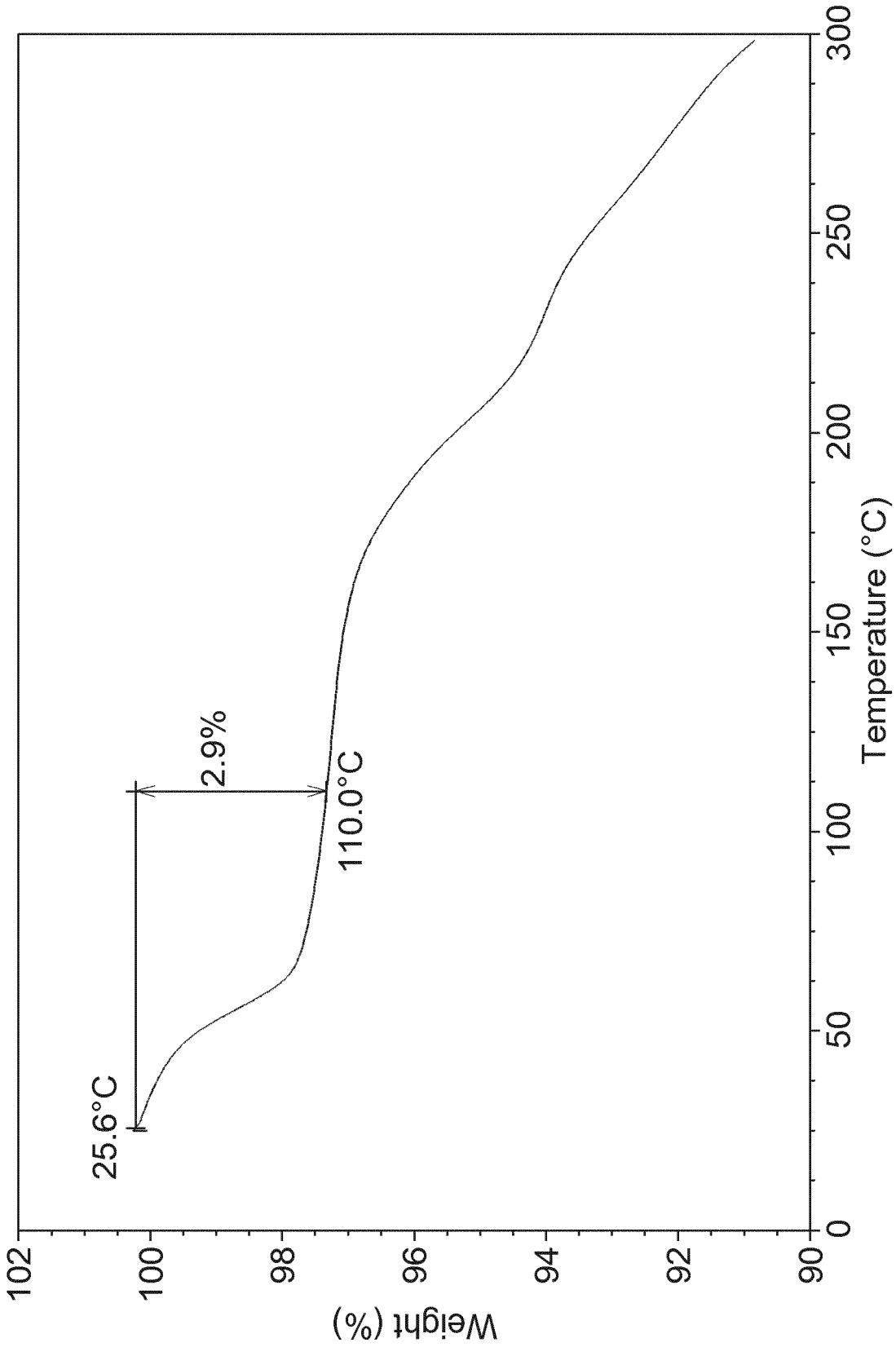


FIG. 36

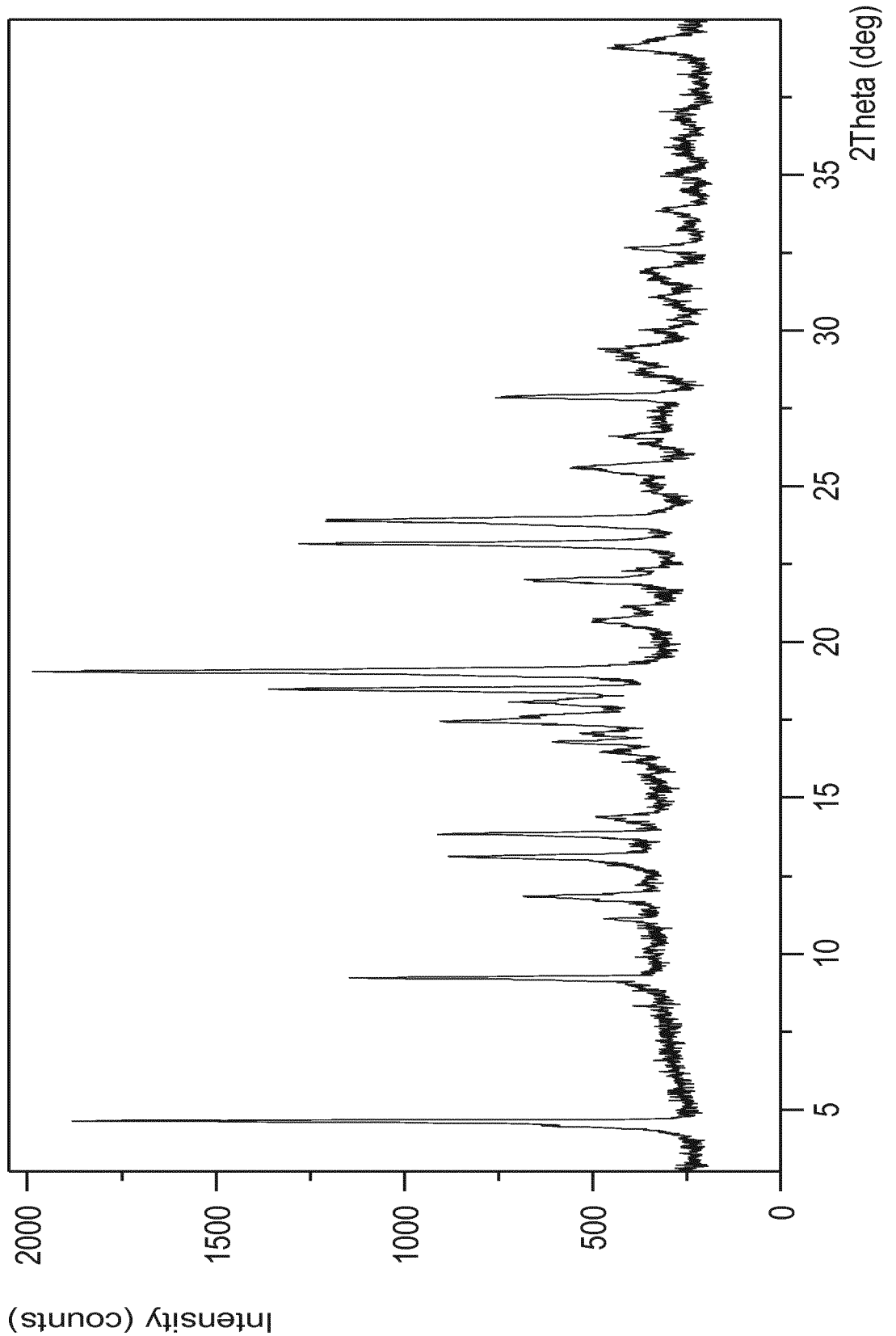

Intensity (counts)
2000
1500
1000
500
0
5
10
15
20
25
30
35
2Theta (deg)

FIG. 37

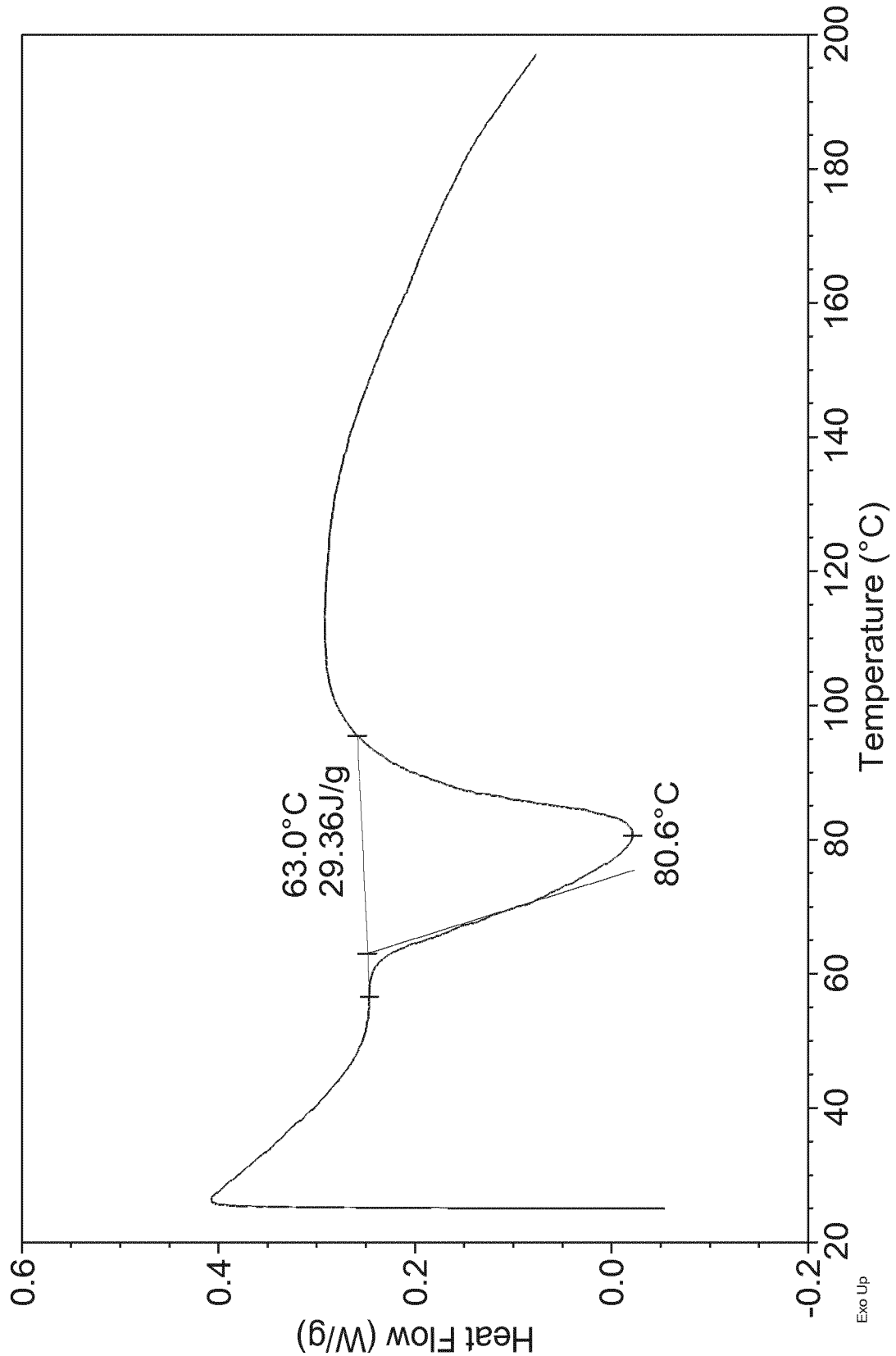

63.0°C
29.36J/g
80.6°C
Heat Flow (W/g)
Exo Up
Temperature (°C)
0.6
0.4
0.2
0.0
-0.2
20
40
60
80
100
120
140
160
180
200

FIG. 38

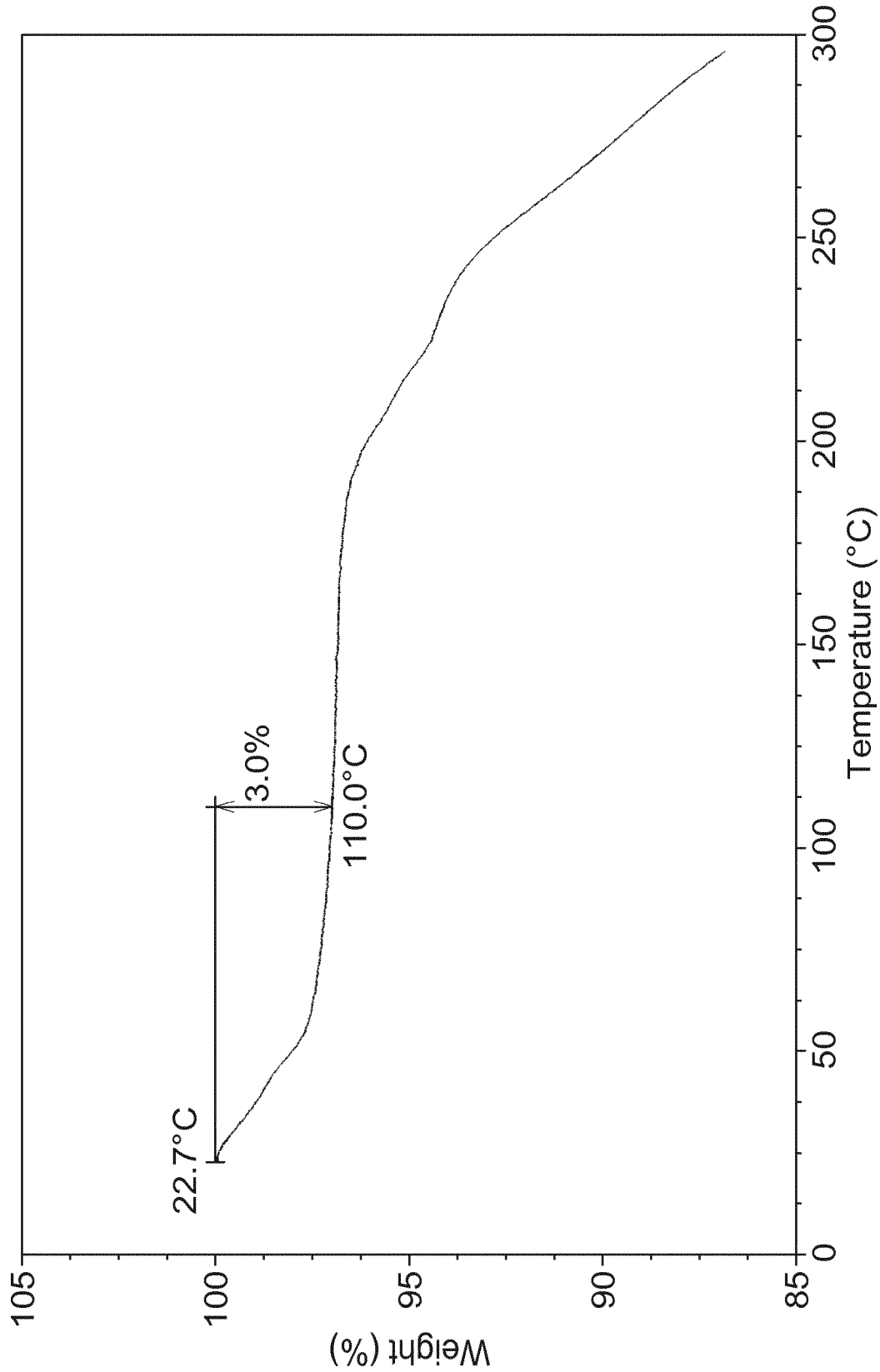

105
100
95
90
85
Weight (%)
0
50
100
150
200
250
300
Temperature (°C)
22.7°C
3.0%
110.0°C

FIG. 39

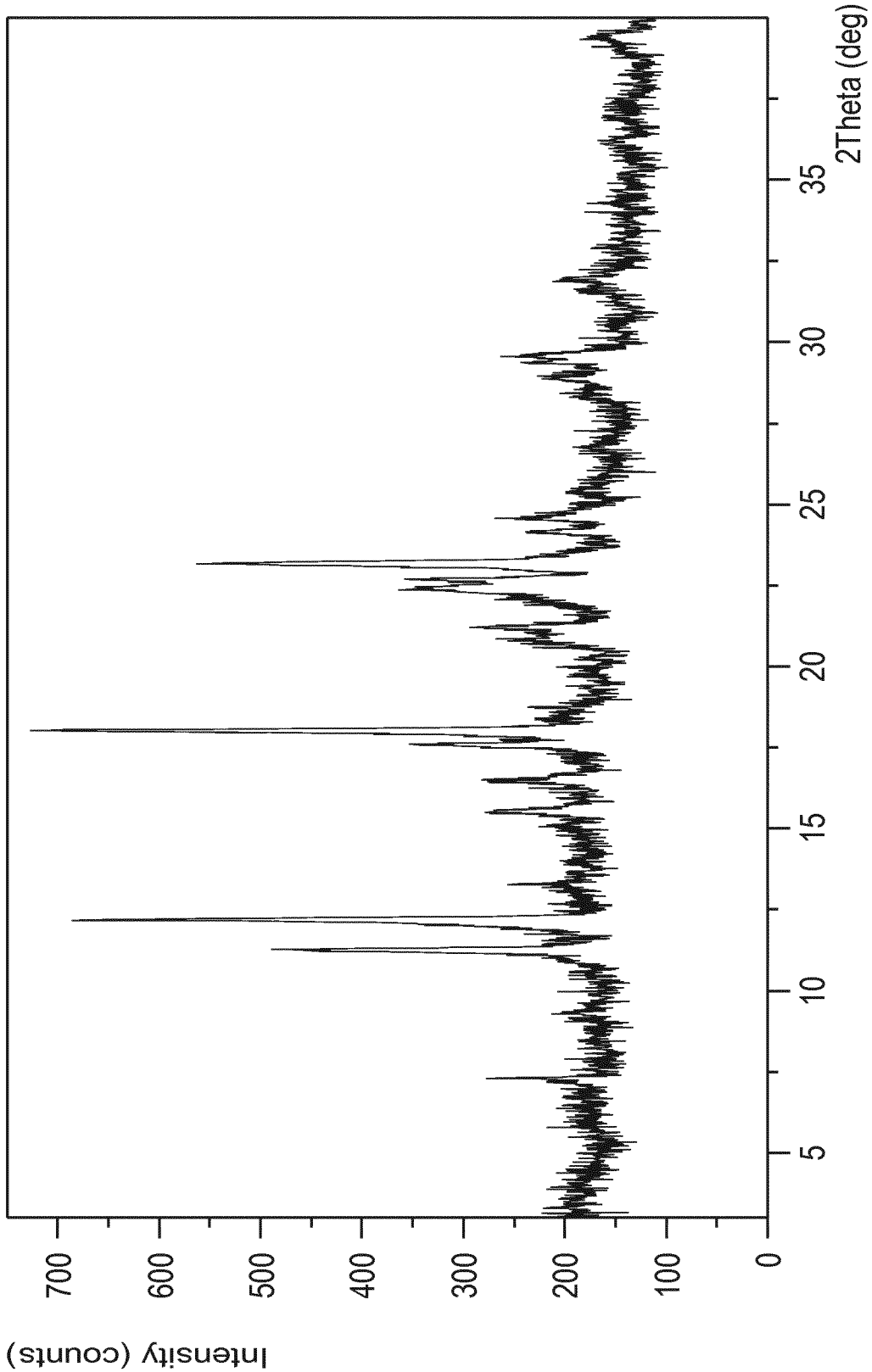

Intensity (counts)
0
100
200
300
400
500
600
700
5
10
15
20
25
30
35
2Theta (deg)

FIG. 40

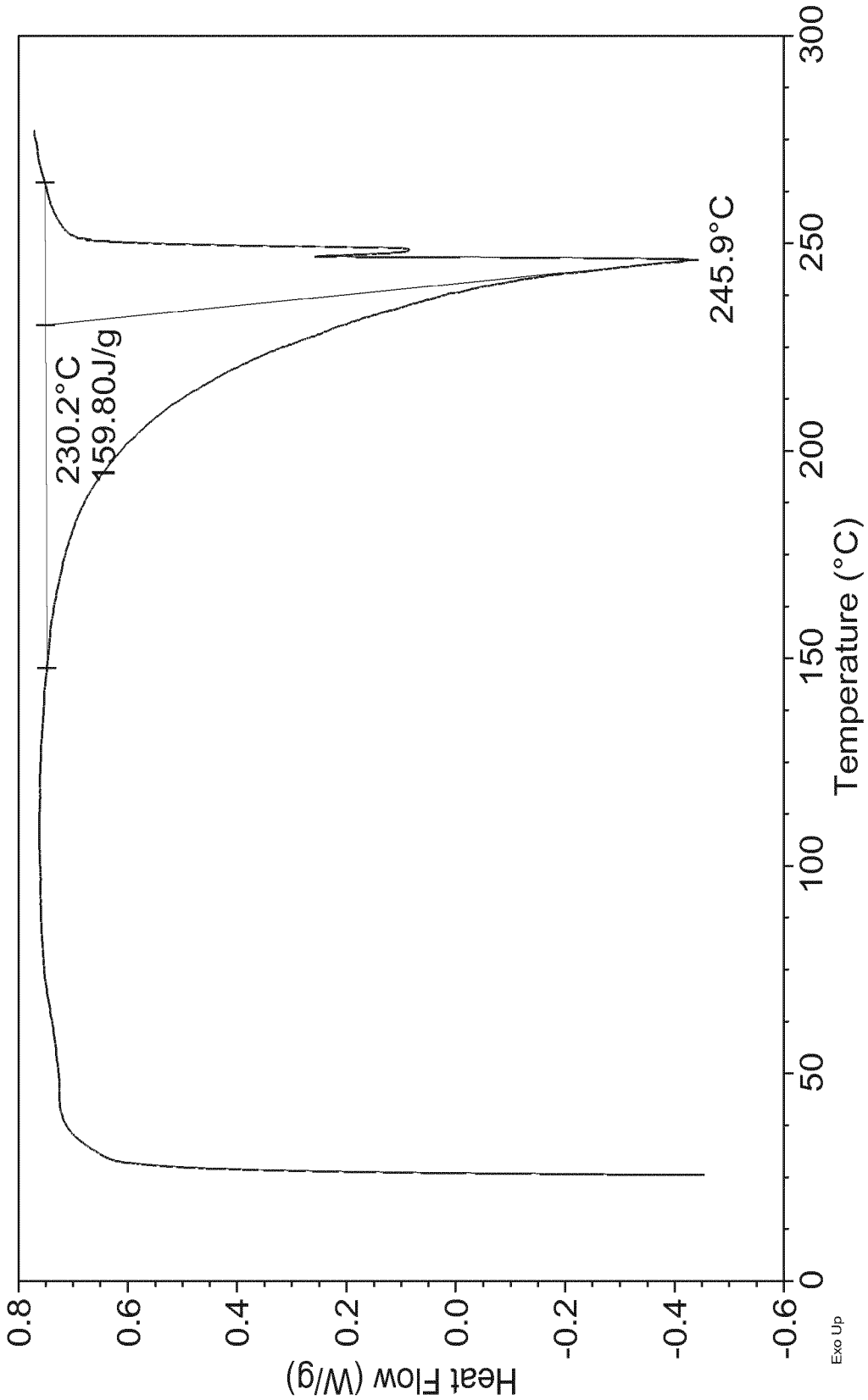

0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
Heat Flow (W/g)
Exo Up
0
50
100
150
200
250
300
Temperature (°C)
230.2°C
159.80J/g
245.9°C

FIG. 41

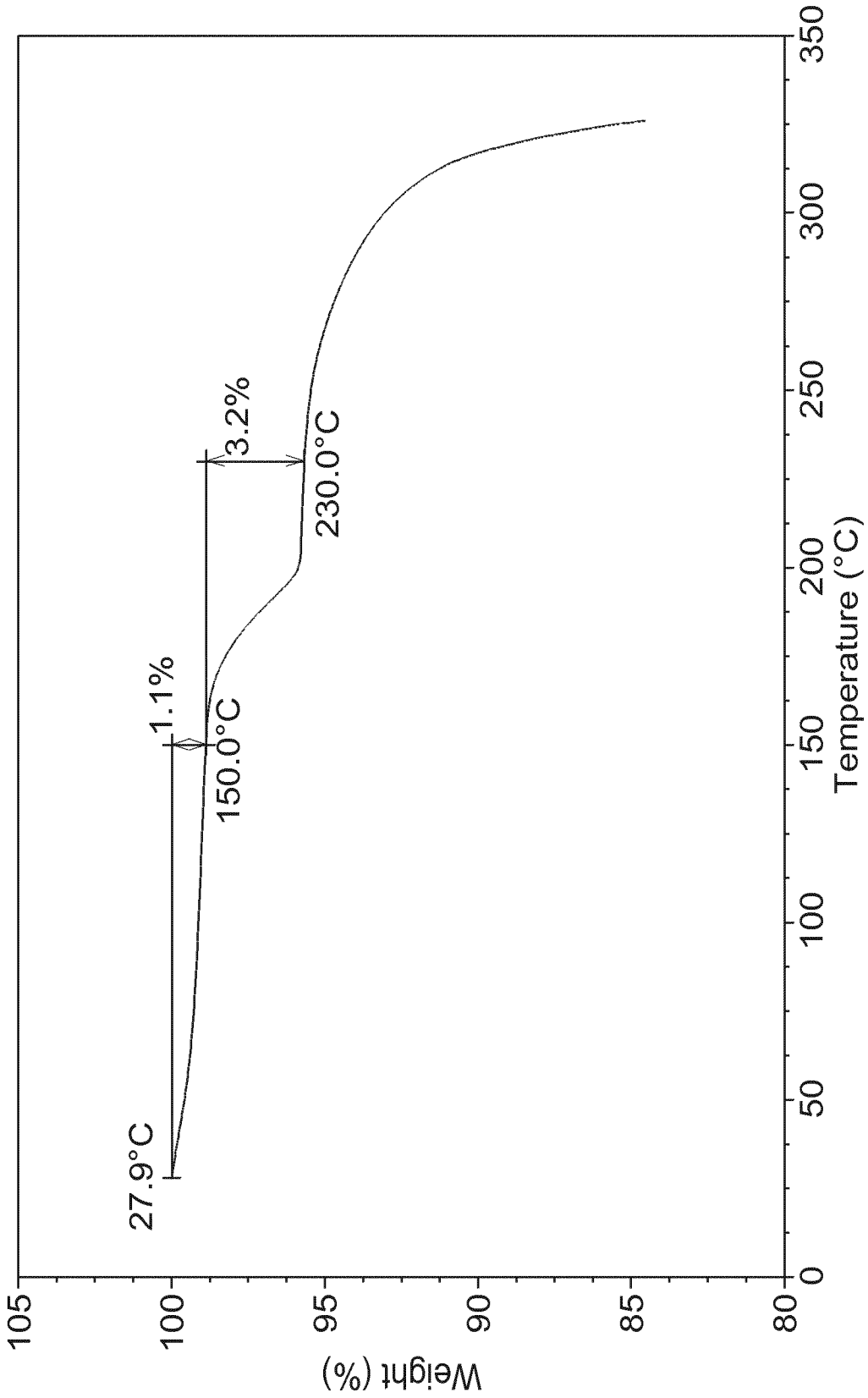

105
100
95
90
85
80
Weight (%)
0
50
100
150
200
250
300
350
Temperature (°C)
27.9°C
1.1%
150.0°C
3.2%
230.0°C

FIG. 42

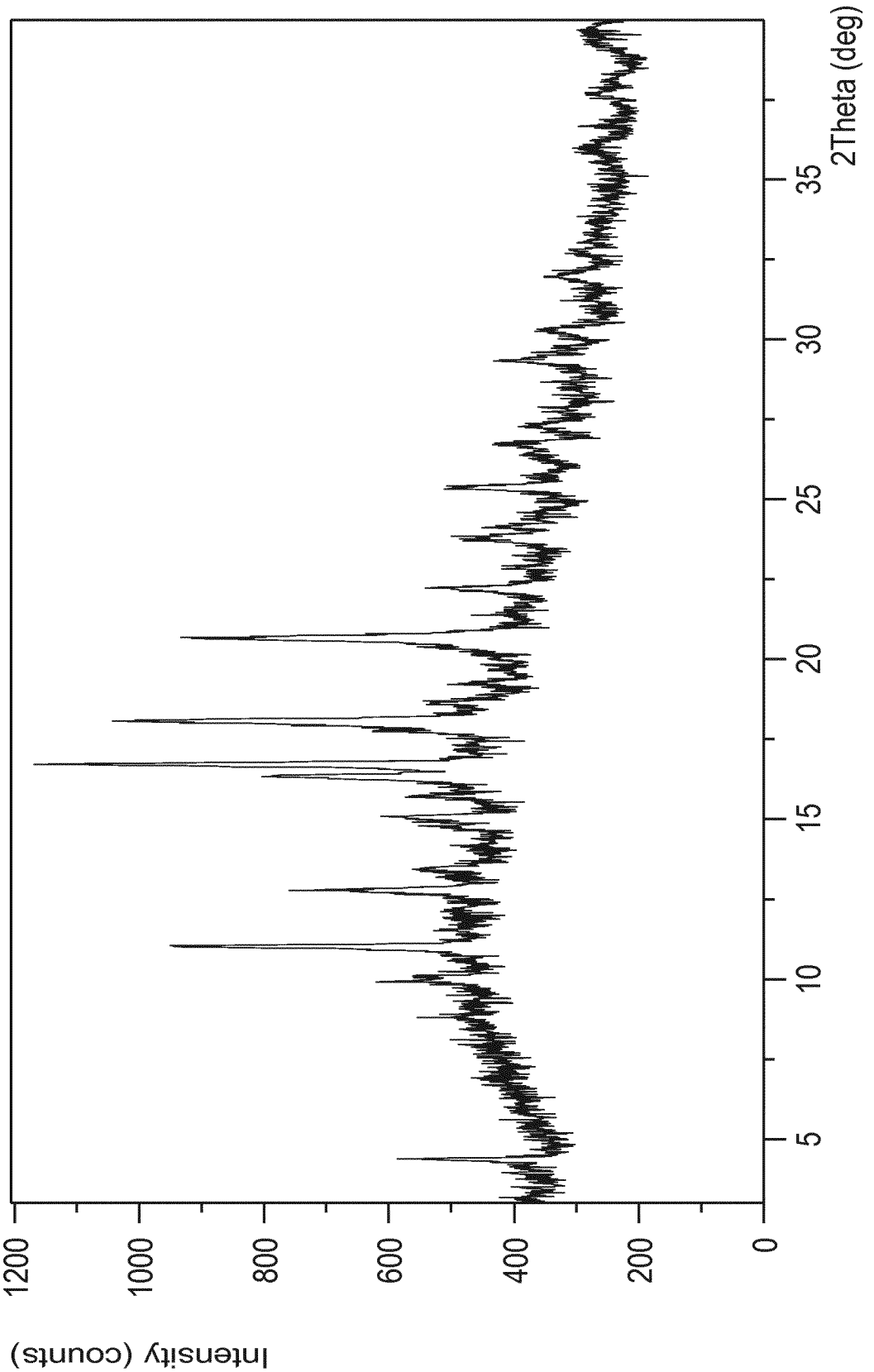

Intensity (counts)
0
200
400
600
800
1000
1200
5
10
15
20
25
30
35
2Theta (deg)

FIG. 43

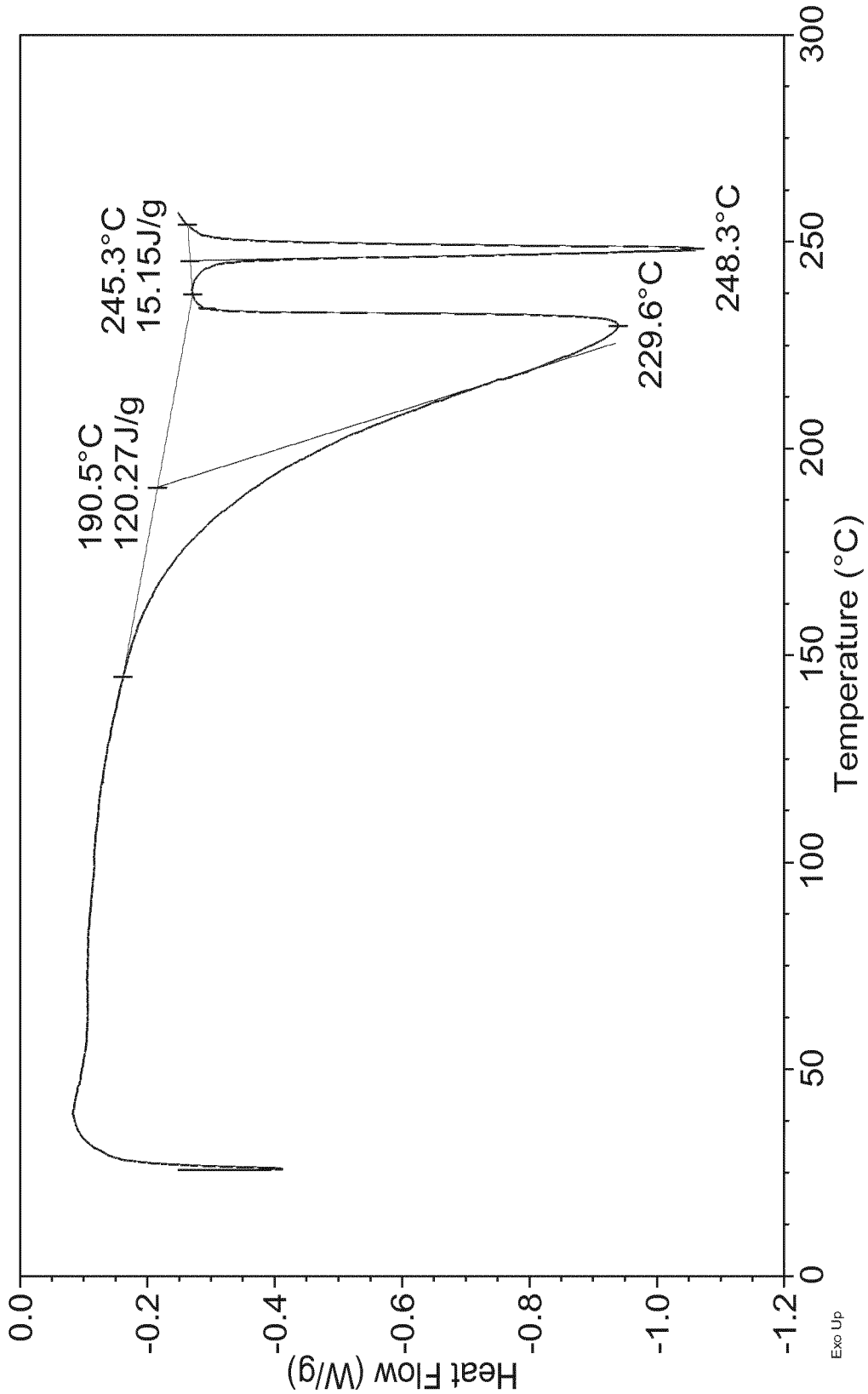

190.5°C
120.27J/g
245.3°C
15.15J/g
229.6°C
248.3°C
Heat Flow (W/g)
Temperature (°C)
Exo Up
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
0
50
100
150
200
250
300

FIG. 44

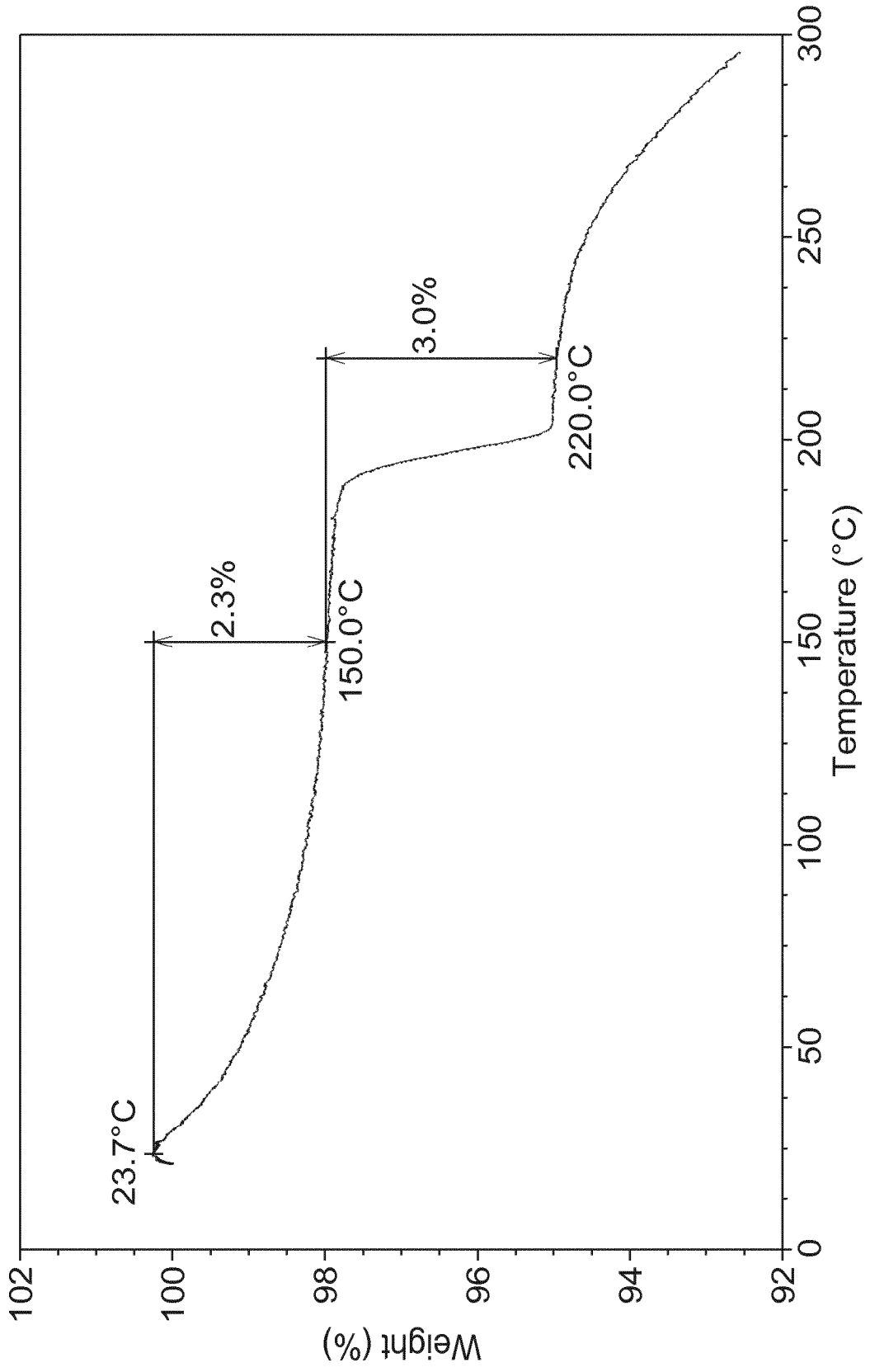

Weight (%)
Temperature (°C)
102
100
98
96
94
92
0
50
100
150
200
250
300
23.7°C
2.3%
150.0°C
3.0%
220.0°C

FIG. 45

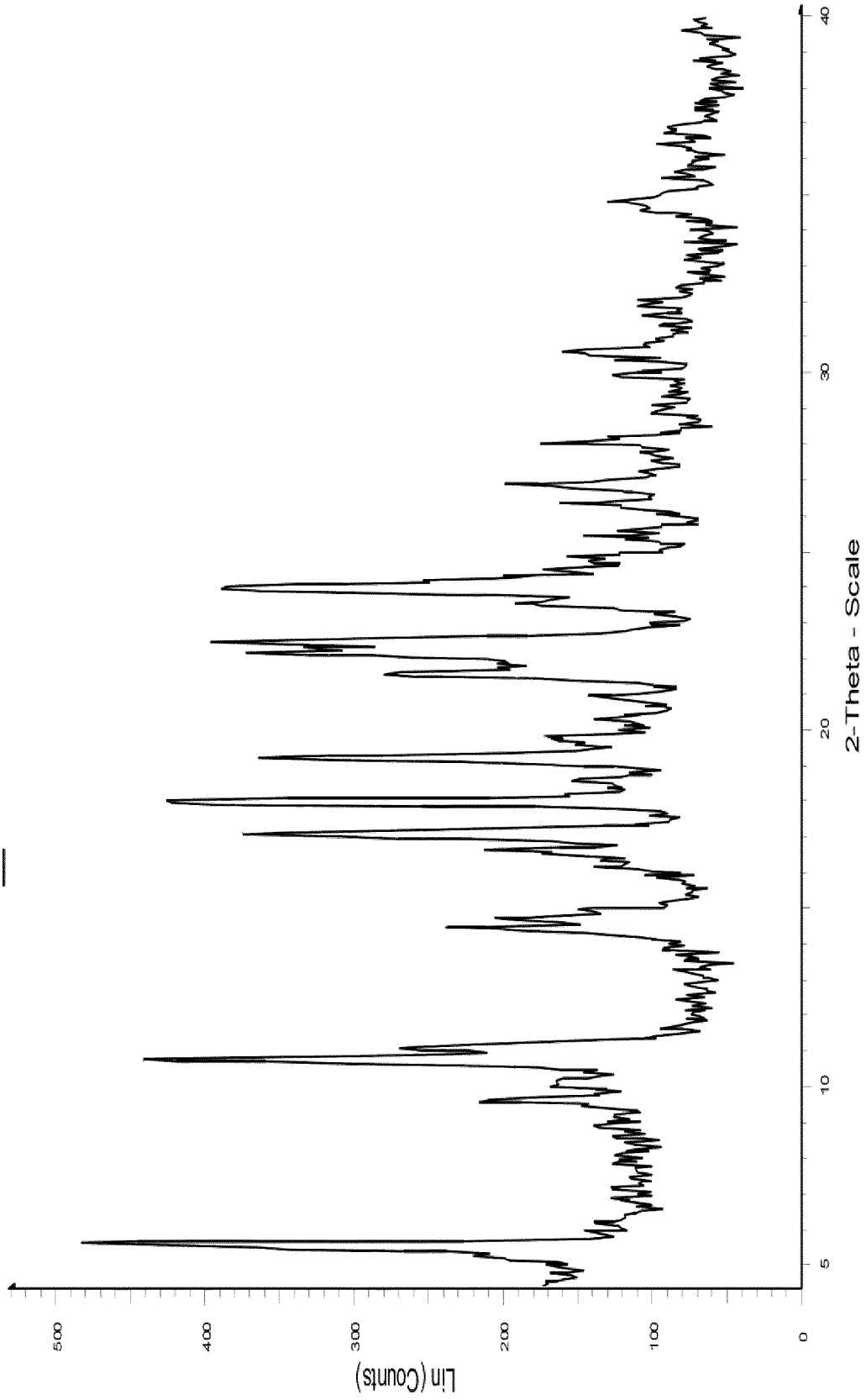


FIG. 46

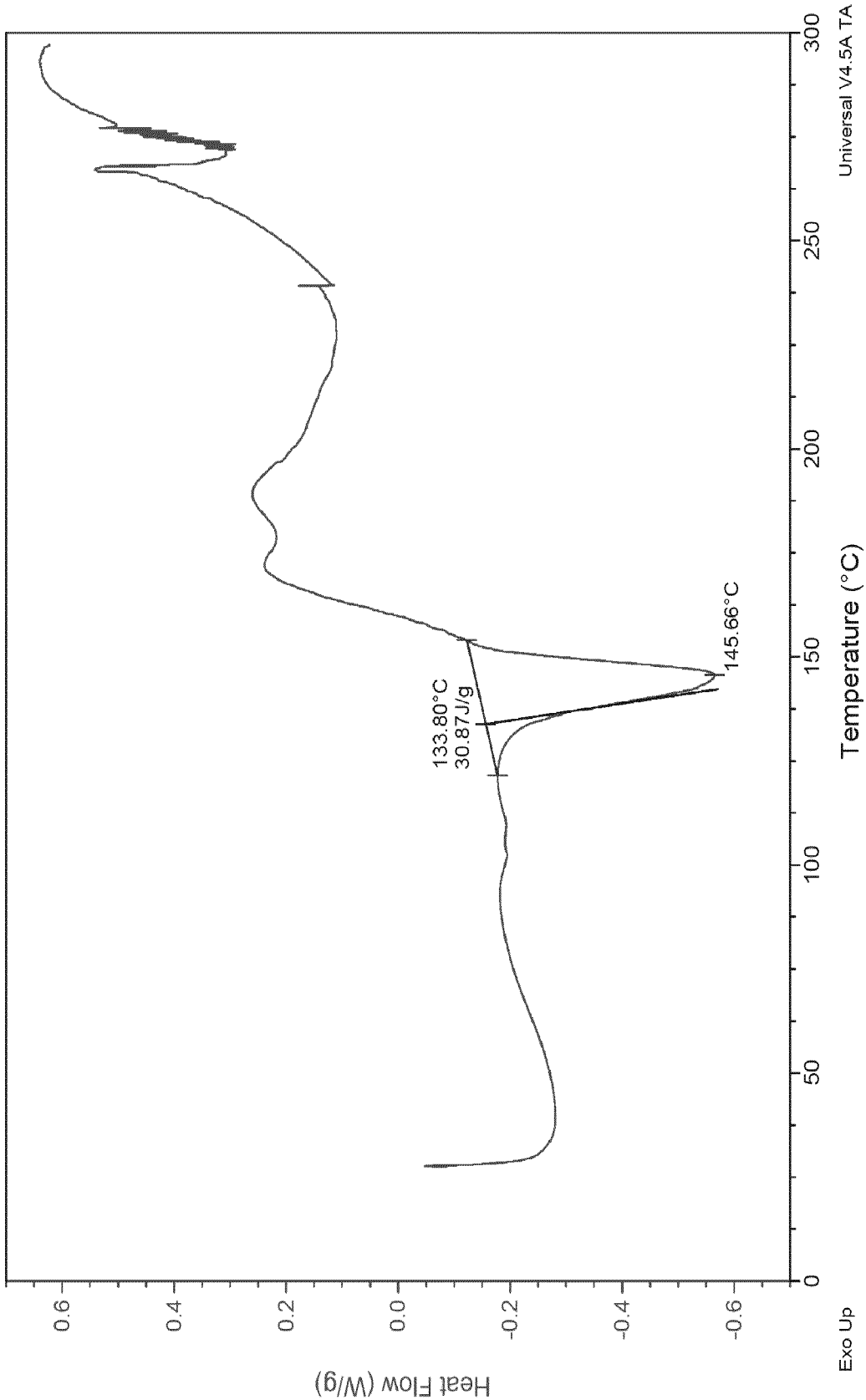

Heat Flow (W/g)
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
Exo Up
0
50
100
150
200
250
300
Temperature (°C)
Universal V4.5A TA
133.80°C
30.87J/g
145.66°C

FIG. 47

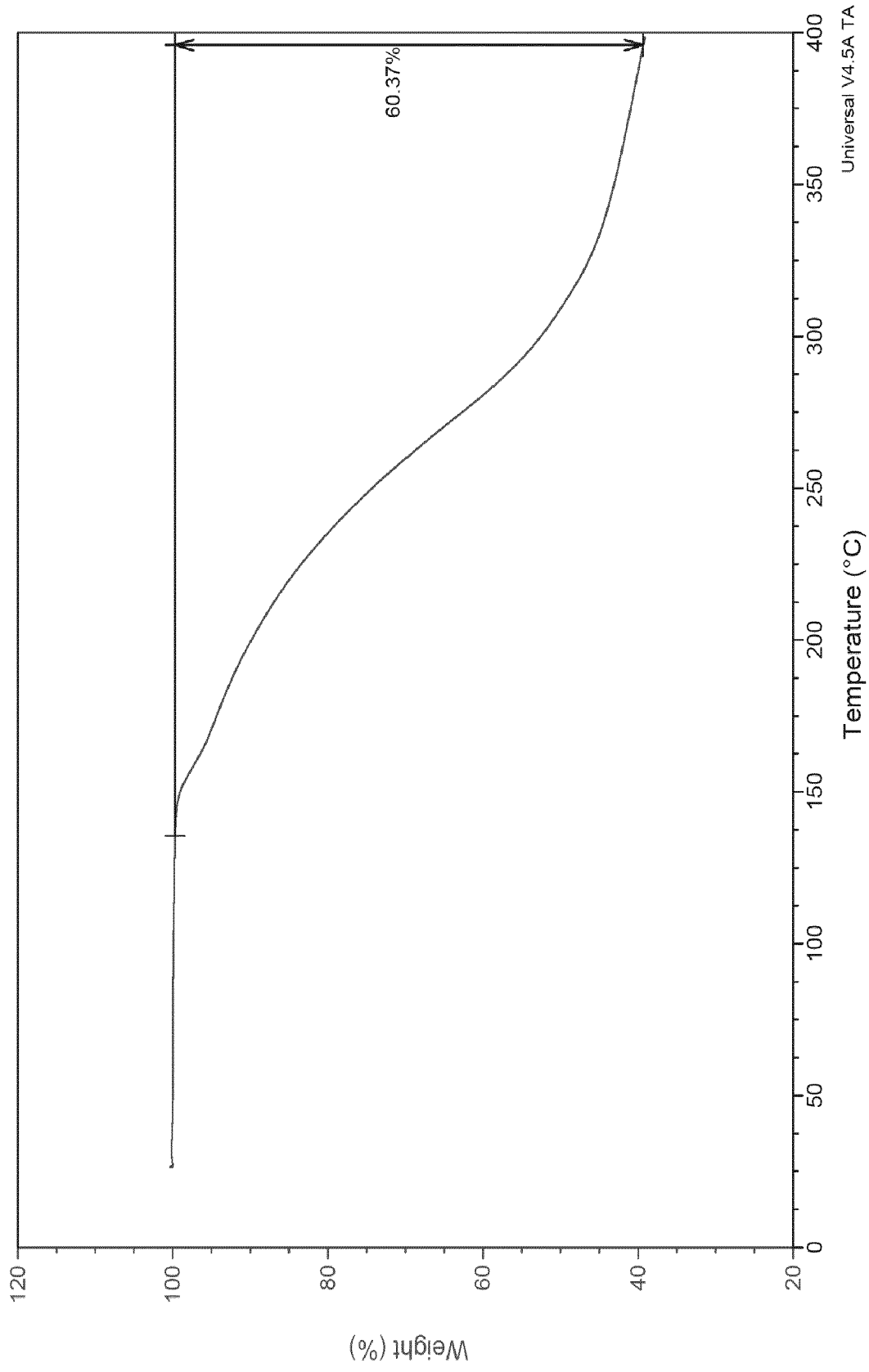

60.37%
Universal V4.5A TA
Temperature (°C)
Weight (%)
0
50
100
150
200
250
300
350
400
20
40
60
80
100
120

FIG. 48

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/066695

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D417/14 A61K31/427 A61K31/506 A61P31/12
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 A61K A61P

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, 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.
X	WO 2014/029193 A1 (SUNSHINE LAKE PHARMA CO LTD [CN]) 27 February 2014 (2014-02-27) paragraph [0002] page 92; example 7 claim 1 -----	1-52
X	WO 2014/037480 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) 13 March 2014 (2014-03-13) cited in the application pages 19,96; example 5 claim 30 -----	1-52

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 August 2015	20/08/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Samsam Bakhtiary, M

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2015/066695

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014029193 A1	27-02-2014	AU 2013305390 A1	15-01-2015
		CA 2876690 A1	27-02-2014
		CN 103626752 A	12-03-2014
		EP 2888241 A1	01-07-2015
		KR 20150044859 A	27-04-2015
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		US 2015152096 A1	04-06-2015
		WO 2014029193 A1	27-02-2014
WO 2014037480 A1	13-03-2014	AU 2013311705 A1	05-02-2015
		CA 2881322 A1	13-03-2014
		CO 7170160 A2	28-01-2015
		EP 2892893 A1	15-07-2015
		IL 236691 A	26-02-2015
		KR 20150054795 A	20-05-2015
		PE 07762015 A1	21-05-2015
		TW 201416360 A	01-05-2014
		WO 2014037480 A1	13-03-2014