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CA 2855923 A1 2013/05/30

(21) 2 855 923

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2012/11/14
(87) Date publication PCT/PCT Publication Date: 2013/05/30
(85) Entrée phase nationale/National Entry: 2014/05/14
(86) N° demande PCT/PCT Application No.: IN 2012/000748
(87) N° publication PCT/PCT Publication No.: 2013/076738
(30) Priorité/Priority: 2011/11/15 (IN3909/CHE/2011)

(51) Cl.Int./Int.Cl. *C07D 277/56* (2006.01)

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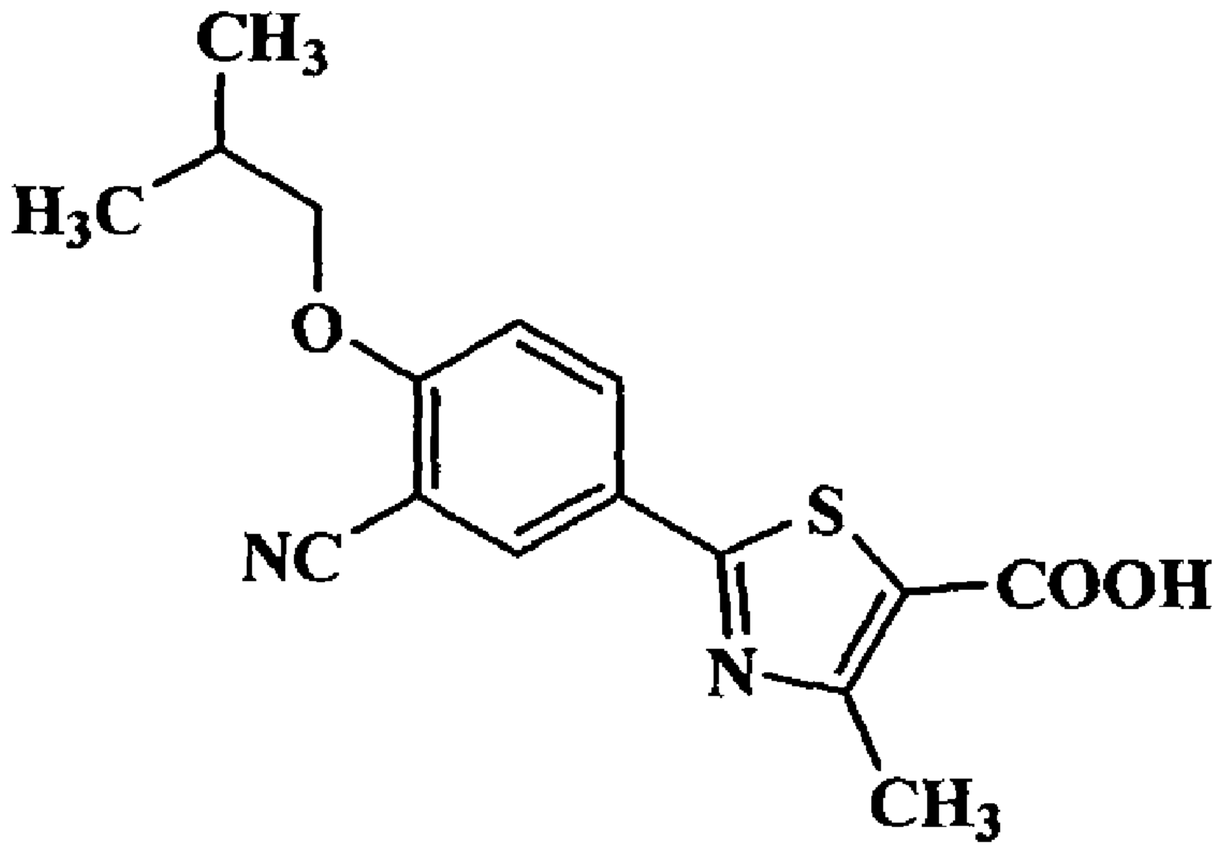
(54) Titre : PROCEDE DESTINE A LA PREPARATION DE POLYMORPHES DU FEBUXOSTAT
(54) Title: PROCESS FOR THE PREPARATION OF FEBUXOSTAT POLYMORPHS



Formula-I

(57) Abrégé/Abstract:
The present invention relates to an improved process for the preparation of Febuxostat Form-K. The present invention also relates to a novel crystalline form M_1 of Febuxostat. [Formula I]

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 May 2013 (30.05.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/076738 A3

(51) **International Patent Classification**:
C07D 277/56 (2006.01)

(21) **International Application Number**:
PCT/IN2012/000748

(22) **International Filing Date**:
14 November 2012 (14.11.2012)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
3909/CHE/2011 15 November 2011 (15.11.2011) IN

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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, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, 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, 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, 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, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

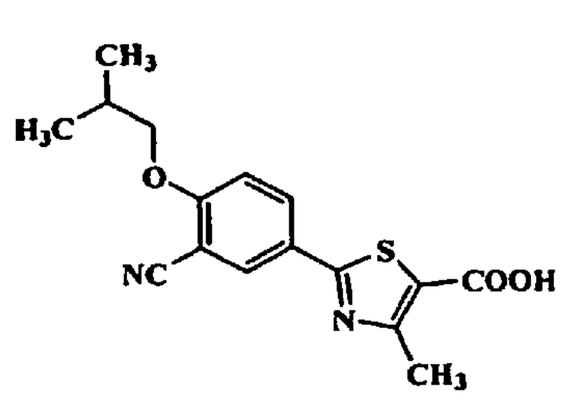
— *of inventorship (Rule 4.17(iv))*

Published:

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

(88) **Date of publication of the international search report**:
10 October 2013

(54) **Title**: PROCESS FOR THE PREPARATION OF FEBUXOSTAT POLYMORPHS



Formula-I

(57) **Abstract**: The present invention relates to an improved process for the preparation of Febuxostat Form-K. The present invention also relates to a novel crystalline form M_1 of Febuxostat. [Formula I]

WO 2013/076738 A3

PROCESS FOR THE PREPARATION OF FEBUXOSTAT POLYMORPHS

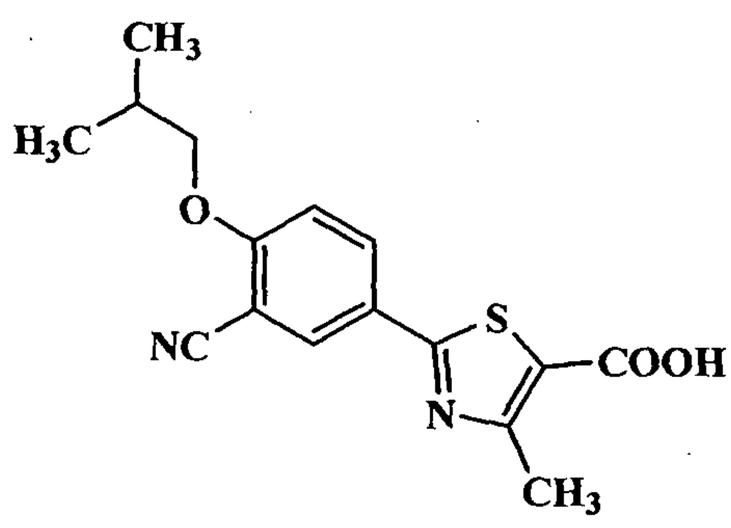
This application claims priority to Indian patent application number 3909/CHE/2011 dated on Nov 15, 2011.

FIELD OF THE INVENTION:

The present invention relates to novel crystalline Form of Febuxostat, i.e. 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, denominated as Form-M_1. Present invention also relates to process for the preparation of Febuxostat Form K.

BACKGROUND OF THE INVENTION:

Febuxostat, i.e. 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid of Formula-I is approved by USFDA for the treatment of hyperuricemia in patients with gout under the brand name of ULORIC. ULORIC is recommended at 40 mg or 80 mg once daily.



Formula-I

Febuxostat and its pharmaceutically acceptable salts were first disclosed in United States patent publication US 5,614,520. This patent also discloses process for the preparation of Febuxostat.

US 6225474 discloses crystalline Forms A, B, C, D, G and amorphous form of Febuxostat. This patent also discloses method of producing crystalline Forms A, B, C, D, G and amorphous Form of Febuxostat.

Crystalline Forms F1, F2, F10, R, R1, R2, R3, R4 and R5 of Febuxostat are disclosed in US 20100317702, WO 2011107911 and WO 2011080651.

CN 101817801 discloses crystalline Form-K characterized by powder X-ray diffraction pattern having peaks at 5.65, 7.91, 11.52, 12.77, 14.29, 15.42, 16.75, 17.44, 18.14, 18.39, 20.47, 20.98, 22.23, 23.31, 23.81, 24.45, 25.89, 26.08, 28.92, 31.26 and 34.41±0.2 2θ.

The present invention provides stable and industrially scalable crystalline form of Febuxostat and an improved process for the preparation of Febuxostat crystalline Form-K.

OBJECT AND SUMMARY OF THE INVENTION:

Principle object of the present invention is to provide novel crystalline Form-M_1 of Febuxostat, i.e. 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid. Another object of the present invention also provides an improved process for the preparation of Febuxostat crystalline Form-K.

One aspect of the present invention provides, a process for the preparation of Febuxostat crystalline Form-M_1 comprising the steps of:

a) dissolving Febuxostat in an ester solvent,
b) spray drying the solution, and
c) isolating the crystalline Form-M_1.

One more aspect of the present invention is to provide an improved process for the preparation of crystalline Form-K of Febuxostat comprising the steps of:

a) dissolving Febuxostat in an ester solvent,
b) evaporating the solvent by agitated thin film dryer (ATFD), and
c) isolating Febuxostat crystalline Form-K.

Another aspect of the present invention is to provide an improved process for the preparation of crystalline Form-K of Febuxostat comprising the steps of:

a) dissolving Febuxostat in an ester solvent at 50-80 °C,
b) removing the solvent at same temperature, and

c) isolating Febuxostat crystalline Form-K.

Yet another aspect of the present invention is to provide an improved process for the preparation of crystalline Form-K of Febuxostat comprising the steps of:

a) dissolving Febuxostat in an ester solvent at 50-80 °C,
b) removing the solvent at same temperature,
c) adding hydrocarbon solvent, and
d) isolating Febuxostat crystalline Form-K.

BRIEF DESCRIPTION OF THE DRAWINGS:

Further objects of the present invention together with additional features contributing thereto and advantages accruing there from will be apparent from the following description of preferred embodiments of the invention which are shown in the accompanying drawing figures wherein :

Figure 1 illustrates the powder X-ray diffraction pattern of Febuxostat Form-M_1.
Figure 2 illustrates DSC thermogram of Febuxostat Form-M_1.
Figure 3 illustrates the powder X-ray diffraction pattern of Febuxostat Form-K
Figure 4 illustrates DSC thermogram of Febuxostat Form-K.
Figure 5 illustrates TGA thermogram of Febuxostat Form-K.
Figure 6 illustrates thermal ellipsoid plot of Febuxostat Form-K with atomic numbering scheme.
Figure 7 illustrates powder X-ray diffraction patterns of Febuxostat Form-K (Experimental and Simulated pattern).

DETAILED DESCRIPTION OF THE INVENTION:

The present invention relates to novel crystalline Form-M_1 of Febuxostat, i.e. 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid.

Instrumentation

Powder X-ray Diffraction (PXRD)

The said polymorph of the present invention is characterized by their X-ray powder diffraction pattern. Thus, the X-ray diffraction patterns of said polymorphs of the invention were measured on 1) ***PANalytical, X'Pert PRO*** powder diffractometer equipped with goniometer of θ/θ configuration and ***X'Celerator*** detector and 2) ***Bruker AXS D8 Discover*** powder X-ray diffractometer equipped with a goniometer of θ/2θ configuration, Vario1 monochromator and ***Lynx-Eye*** detector. The Cu-anode X-ray tube was operated at 40kV and 30mA. The experiments were conducted over the 2θ range of 2.0°-50.0°, 0.030° step size and 50 seconds step time.

Differential Scanning Calorimetry (DSC)

The DSC measurements were carried out on TA Q1000 of TA instruments. The experiments were performed at a heating rate of 10.0 °C/min over a temperature range of 30 – 300 °C purging with nitrogen at a flow rate of 50 mL/min. Standard aluminum crucibles covered by lids with three pin holes were used.

Thermo gravimetric Analysis (TGA)

TGA/DTA was recorded using the instrument TA Q5000 of TA instruments. The experiments were performed at a heating rate of 10.0 °C/min over a temperature range of 30 – 300 °C purging with nitrogen at a flow rate of 25 mL/min.

The main aspect of the present invention is to provide novel crystalline Form-M_1 of Febuxostat.

In one embodiment, crystalline Febuxostat Form M_1 is characterized by the powder X-ray diffraction having characteristic peaks 6.13, 9.06, 12.29, 17.44 and 25.81±0.2° 2θ.

In another embodiment, crystalline Form-M_1 of Febuxostat is further characterized by the Powder X-ray diffraction as depicted in Figure 1.

In one more embodiment, crystalline Form-$M_1$of Febuxostat is further characterized by the DSC thermogram as depicted in Figure 2.

Another aspect of the present invention provides a process for the preparation of Febuxostat crystalline Form-M_1 comprising the steps of:

a) dissolving Febuxostat in an ester solvent,
b) spray drying the clear solution, and
c) isolating the crystalline Form-M_1.

In one embodiment, the ester solvent used herein is Ethyl acetate.

In another embodiment, the input Febuxostat used herein is selected from the group consisting of but not limited to crystalline or amorphous form or any solvate.

According to present invention Febuxostat crystal is dissolved in ester solvent such as ethyl acetate at 50 – 60 °C and cooled to room temperature. The obtained solution optionally filtered to remove any undissolved particulate, and the clear solution is subjected to spray drying in a buchi mini spray dryer (Model B-290) to obtain crystalline Febuxostat Form-M_1.

One more aspect of the present invention is to provide an improved process for the preparation of crystalline Form-K of Febuxostat comprising the steps of:

a) dissolving Febuxostat in an ester solvent,
b) evaporating the solvent by agitated thin film dryer (ATFD), and
c) isolating Febuxostat crystalline Form-K.

In one embodiment, the ester solvent used herein is Ethyl acetate.

In another embodiment, the input Febuxostat used herein is selected from the group consisting of but not limited to crystalline or amorphous form or any solvate.

According to present invention Febuxostat is dissolved in ester solvent such as ethyl acetate at 50 – 60 °C and cooled to room temperature. The obtained solution optionally

filtered to remove any undissolved particulate, and the clear solution is evaporated on agitated thin film dryer (ATFD) instrument, at 50 °C under reduced pressure (120 mm-Hg) to obtain Febuxostat Form-K.

Another aspect of the present invention is to provide an improved process for the preparation of crystalline Form-K of Febuxostat comprising the steps of:

a) dissolving Febuxostat in an ester solvent at 50 – 80 °C,
b) removing the solvent at same temperature, and
c) isolating Febuxostat crystalline Form-K.

In one embodiment, the ester solvent used herein is Ethyl acetate.

In one more embodiment, the solvent removed in step b, is at temperature 70 – 80 °C.

In one more embodiment, the input Febuxostat used herein is selected from the group consisting of but not limited to crystalline or amorphous form or any solvate.

According to present invention Febuxostat is dissolved in ester solvent such as ethyl acetate at 50 – 60 °C, cooled to room temperature (25 – 30 °C). The resulting solution is filtered through hyflow to remove any undissolved particulate and the solution was heated to 70 – 80 °C. The solvent was distilled out at the same temperature under reduced pressure to obtain Febuxostat Form-K.

Yet another aspect of the present invention is to provide an improved process for the preparation of crystalline Form-K of Febuxostat comprising the steps of:

a) dissolving Febuxostat in an ester solvent
b) removing the solvent,
c) adding hydrocarbon solvent, and
d) isolating Febuxostat crystalline Form-K.

In one embodiment, the ester solvent used herein is Ethyl acetate.

In one more embodiment, the solvent removed in step b, is at temperature 70 – 80 °C.

In another embodiment, hydrocarbon solvents used herein are selected from cyclohexane and toluene.

In one more embodiment, the input Febuxostat used herein is selected from the group consisting of but not limited to crystalline or amorphous form or any solvate.

According to present invention Febuxostat is dissolved in ester solvent such as ethyl acetate at 50 – 60 °C, cooled to room temperature (25 – 30 °C). The resulting solution is filtered through hyflow to remove any undissolved particulate and the solution was heated to 70 – 80 °C. The solvent is distilled out at the same temperature under reduced pressure and hydrocarbon solvents such as toluene or cyclohexane is added to the residue. The resulting is slurred, filtered and dried to obtain Febuxostat Form-K.

Yet another aspect of the present invention is to provide an improved process for the preparation of crystalline Form-K of Febuxostat comprising the steps of:

a) dissolving Febuxostat in an ester solvent at 50 – 80 °C,
b) filtering the reaction mass,
c) maintaining the filtrate for 30-120 minutes at same temperature,
d) removing the solvent,
e) adding hydrocarbon solvent, and
f) isolating Febuxostat crystalline Form-K.

In one embodiment, the ester solvent used herein is Ethyl acetate.

In one more embodiment, the reaction mass is filtered to separate any undissolved particulate.

In one more embodiment, the filtrate is maintained for 30-120 minutes, preferably 60-90 minutes at 50 – 80 °C.

In one more embodiment, at step d, the solvent is removed at a temperature of 30 – 70 °C under reduced pressure.

In another embodiment, hydrocarbon solvent used herein is selected from cyclohexane and toluene.

In one more embodiment, the input Febuxostat used herein is selected from the group consisting of but not limited to crystalline or amorphous form or any solvate.

Yet another aspect of the present invention is to provide an improved process for the preparation of crystalline Form-K of Febuxostat comprising the steps of:

a) dissolving Febuxostat in one or more organic solvents,
b) adding a base to the reaction mixture,
c) removing the solvent,
d) adding water and neutralizing with acid,
e) adding one or more ester solvents,
f) optionally adding hydrocarbon solvent, and
g) isolating Febuxostat crystalline Form-K.

In one embodiment, the organic solvent is selected from ethanol, methanol, isopropanol, tetrahydrofuran or mixtures thereof.

In one more embodiment, base is selected from alkali or alkali earth metal hydroxides like sodium hydroxide or potassium hydroxide, preferably sodium hydroxide.

In one more embodiment, acid used in this invention for the neutralization is selected from acetic acid, formic acid, hydrochloric acid, sulfuric acid or phosphoric acid.

In another embodiment, the ester solvent used herein is Ethyl acetate.

In another embodiment, hydrocarbon solvents used herein are selected from cyclohexane or toluene.

In one more embodiment, the input Febuxostat used herein is selected from the group consisting of but not limited to crystalline or amorphous form or any solvate.

According to the present invention Febuxostat is dissolved in organic solvents such as ethanol and tetrahydrofuran at 25 – 30 °C. To this base such as sodium hydroxide is added and the solvent is distilled out at 60 – 70 °C. The reaction mass is cooled to 25 – 30 °C and water is added. This is neutralized with hydrochloric acid and ester solvent like ethyl acetate is added. The reaction mass is completely distilled out at 75 – 80 °C under reduced pressure and cooled to 25 – 30 °C. To the solid mass cyclohexane is added and filtered. The resulting solid is dried to obtain Febuxostat crystalline Form-K.

Yet another aspect of the present invention is to provide an improved process for the preparation of crystalline Form-K of Febuxostat comprising the steps of:

a) dissolving alkyl ester of Febuxostat in one or more organic solvents,
b) adding a base to the reaction mixture,
c) removing the solvent,
d) adding water and neutralizing with acid,
e) adding one or more ester solvents,
f) optionally adding hydrocarbon solvent, and
g) isolating Febuxostat crystalline Form-K.

In one embodiment, alkyl ester of Febuxostat is selected from methyl or ethyl ester, preferably ethyl ester.

In one more embodiment, the organic solvent is selected from ethanol, methanol, isopropanol, tetrahydrofuran or mixtures thereof.

In one more embodiment, base is selected from alkali or alkali earth metal hydroxides like sodium hydroxide or potassium hydroxide, preferably sodium hydroxide.

In one more embodiment, acid used in this invention for the neutralization is selected from acetic acid, formic acid, hydrochloric acid, sulfuric acid and phosphoric acid.

In another embodiment, the ester solvent used herein is Ethyl acetate.

In another embodiment, hydrocarbon solvents used herein are selected from cyclohexane and toluene.

According to the present invention ethyl ester of Febuxostat is dissolved in organic solvents such as ethanol and tetrahydrofuran at 25 – 30 °C. To this base such as sodium hydroxide is added and the solvent is distilled out at 60 – 70 °C. The reaction mass is cooled to 25 – 30 °C and water is added. This is neutralized with hydrochloric acid and ester solvent like ethyl acetate is added. The reaction mass is completely distilled out at 75 – 80 °C under reduced pressure and cooled to 25 – 30 °C. To the solid mass cyclohexane is added and filtered. The resulting solid is dried to obtain Febuxostat crystalline Form-K.

Yet another aspect of the present invention is to provide an improved process for the preparation of crystalline Form-K of Febuxostat comprising the steps of:

a) dissolving Febuxostat in an ester solvent,
b) partially removing the solvent,
c) adding hydrocarbon solvent, and
d) isolating Febuxostat crystalline Form-K.

In one embodiment, the ester solvent used herein is Ethyl acetate.

In another embodiment, hydrocarbon solvents used herein are selected from cyclohexane and toluene.

In one more embodiment, the input Febuxostat used herein is selected from the group consisting of but not limited to crystalline or amorphous form or any solvate.

Yet another aspect of the present invention is to provide an improved process for the preparation of crystalline Form-K of Febuxostat comprising the steps of:

a) dissolving Febuxostat in mixture of ester and hydrocarbon solvent,
b) partially removing the solvent, and
c) isolating Febuxostat crystalline Form-K.

In one embodiment, the ester solvent used herein is Ethyl acetate and hydrocarbon solvent used herein is selected from cyclohexane and toluene. The preferable mixture of solvent is mixture of ethyl acetate and toluene.

In one more embodiment, at step b, 30-70 % preferably 40-55 % of solvent is removed at a temperature of 50 – 100 °C preferably at atmospheric pressure.

In one more embodiment, Febuxostat crystalline Form K is isolated by cooling the reaction temperature to 10 -40 °C, preferably 20- 35 °C followed by filtration.

In one more embodiment, the input Febuxostat used herein is selected from the group consisting of but not limited to crystalline or amorphous form or any solvate.

Febuxostat Form K is characterized by single crystal X-ray diffraction as shown in Figure 6. The crystallographic data and atomic coordinates are incorporated respectively in Table 1 and Table 2.

Table 1: Crystallographic Data of Febuxostat Form K from single crystal X-ray diffraction.

Crystal system	Triclinic
Lattice type	Primitive
Space group	*P*-1
Lattice parameters	$a = 7.3660(15)$Å
	$b = 15.403(3)$Å
	$c = 15.721(3)$Å
	$\alpha = 90.85(3)°$
	$\beta = 96.38(3)°$
	$\gamma = 98.75(3)°$
	$V = 1751.1(6)$ Å^3
Reflections ($I > 2\ \sigma$)	4048
R-values: R, Rw	0.0777, 0.1626

Table 2: Atomic coordinates of Febuxostat Form K obtained from single crystal X-ray diffraction.

Atom	Coordinates			
	x	y	z	Ueq
S1	0.37859(14)	0.06001(6)	0.76398(6)	0.0599
S2	0.11124(14)	0.87630(7)	0.25622(7)	0.0672
O1	0.0449(5)	0.9901(2)	0.3948(2)	0.0961
O2	0.0308(5)	0.8924(2)	0.4972(2)	0.0995
O3	0.4619(4)	0.1019(2)	0.52581(18)	0.0779
O4	0.4517(5)	−0.0160(2)	0.60628(19)	0.0804
O5	0.2721(4)	0.20255(17)	1.15913(17)	0.0769
O6	0.2427(4)	0.65396(16)	−0.09539(19)	0.0729
N1	0.1411(5)	0.7189(2)	0.2993(2)	0.0708
N2	0.3579(4)	0.2249(2)	0.76064(19)	0.0549
N3	0.2567(6)	0.4085(2)	1.0843(3)	0.0868
N4	0.2208(7)	0.8748(3)	−0.1236(3)	0.1091
C1	0.4420(5)	0.0666(3)	0.5940(3)	0.0588
C2	0.4022(5)	0.1134(2)	0.6696(2)	0.0537
C3	0.3871(5)	0.2005(3)	0.6801(2)	0.0554
C4	0.3986(6)	0.2695(3)	0.6138(3)	0.0728
C5	0.3504(5)	0.1573(2)	0.8113(2)	0.0549
C6	0.3215(5)	0.1651(2)	0.9021(2)	0.0539
C7	0.3092(5)	0.2466(2)	0.9363(2)	0.052
C8	0.2890(5)	0.2566(2)	1.0228(2)	0.0519
C9	0.2837(6)	0.1845(2)	1.0765(2)	0.0602
C10	0.2909(7)	0.1027(3)	1.0403(3)	0.0818
C11	0.3104(6)	0.0934(3)	0.9550(3)	0.0749

Atom	Coordinates			
	x	y	z	Ueq
C12	0.2721(6)	0.3410(3)	1.0582(2)	0.0606
C13	0.2752(7)	0.1332(3)	1.2197(3)	0.0868
C14	0.2871(8)	0.1747(4)	1.3081(3)	0.0975
C15	0.1266(12)	0.2194(5)	1.3184(4)	0.1854
C17	0.4701(12)	0.2329(5)	1.3304(4)	0.1826
C18	0.1187(10)	0.5774(4)	– 0.2664(4)	0.1467
C19	0.3108(10)	0.4601(4)	– 0.2265(4)	0.1361
C20	0.2784(9)	0.5544(3)	– 0.2078(4)	0.0916
C21	0.2471(7)	0.5621(3)	– 0.1152(3)	0.0797
C22	0.2208(5)	0.6774(2)	– 0.0149(3)	0.0618
C23	0.2120(7)	0.8251(3)	– 0.0708(3)	0.0735
C24	0.2042(5)	0.7658(2)	– 0.0014(3)	0.0572
C25	0.2138(6)	0.6218(3)	0.0537(3)	0.0692
C26	0.1907(6)	0.6537(3)	0.1328(3)	0.0692
C27	0.1792(5)	0.7959(3)	0.0797(3)	0.0617
C28	0.1718(5)	0.7409(3)	0.1480(3)	0.059
C29	0.1449(5)	0.7708(3)	0.2339(3)	0.0613
C30	0.1120(6)	0.7622(3)	0.3716(3)	0.0748
C31	0.1088(7)	0.7132(4)	0.4537(3)	0.1013
C32	0.0904(5)	0.8488(3)	0.3604(3)	0.0699
C33	0.0547(6)	0.9132(4)	0.4225(3)	0.0736
H1	0.023(8)	1.0218(11)	0.4336(11)	0.1443
H4	0.493(7)	– 0.0369(9)	0.5654(16)	0.1208
H4a	0.386(4)	0.2419(3)	0.5579(3)	0.1092
H4b	0.301(2)	0.3039(12)	0.6172(12)	0.1092
H4c	0.5160(17)	0.3070(12)	0.6239(11)	0.1092
H7	0.3144(5)	0.2950(2)	0.9016(2)	0.0624
H10	0.2826(7)	0.0536(3)	1.0742(3)	0.0978
H11	0.3162(6)	0.0380(3)	0.9322(3)	0.0897
H13a	0.166(3)	0.0890(15)	1.2083(4)	0.104
H13b	0.379(3)	0.1022(19)	1.2145(5)	0.104
H14	0.2827(8)	0.1267(4)	1.3485(3)	0.117
H15a	0.137(5)	0.243(4)	1.3759(15)	0.278
H15b	0.124(6)	0.266(3)	1.279(4)	0.278
H15c	0.0147(13)	0.1780(13)	1.307(5)	0.278
H17a	0.468(4)	0.2881(18)	1.303(4)	0.274
H17b	0.493(5)	0.243(4)	1.3913(6)	0.274
H17c	0.5666(17)	0.205(2)	1.311(4)	0.274
H18a	0.0075(16)	0.540(2)	– 0.256(2)	0.22
H18b	0.105(5)	0.6374(12)	– 0.256(2)	0.22
H18c	0.141(4)	0.570(3)	– 0.3249(4)	0.22
H19a	0.411(5)	0.4463(13)	– 0.187(2)	0.204
H19b	0.200(2)	0.4198(5)	– 0.220(3)	0.204

Atom	Coordinates			
	x	y	z	Ueq
H19c	0.341(7)	0.4552(10)	– 0.2839(12)	0.204
H20	0.394(8)	0.599(4)	– 0.226(4)	0.15
H21a	0.347(3)	0.5419(15)	– 0.0791(7)	0.096
H21b	0.131(2)	0.5269(11)	– 0.1059(14)	0.096
H25	0.2248(6)	0.5629(3)	0.0460(3)	0.0827
H26	0.1874(6)	0.6157(3)	0.1782(3)	0.0831
H27	0.1673(5)	0.8545(3)	0.0880(3)	0.0739
H31a	– 0.0126(16)	0.708(2)	0.4718(13)	0.151
H31b	0.140(5)	0.6557(9)	0.4445(7)	0.151
H31c	0.197(4)	0.7448(13)	0.4971(7)	0.151

The experimental PXRD pattern was matched with the simulated PXRD pattern obtained from single crystal X-ray diffraction as shown in Figure 7, which shows the phase purity of Form K.

A further aspect of the present invention is to provide packaging conditions for the stable crystalline Form-K of Febuxostat in a way to attain the polymorphic stability, there by increasing the shelf life of the product. According to the present invention the method for packaging crystalline Febuxostat Form-K comprises of placing Febuxostat Form-K in LDPE (low density polyethylene) bag under nitrogen atmosphere, placing the sealed bag in Triple laminated aluminum liner bag with vacuumised nitrogen sealing, placing the above Triple laminated aluminum bag into the outer bag of triple laminated aluminum bag and vacuumised nitrogen sealing and enclosing the triple laminated bag in closed HDPE (high density polyethylene) drums.

The invention is illustrated with the following examples, which are provided by way of illustration only and should not be construed to limit the scope of the invention.

Experimental procedure:

Example – 1: Process for the Preparation of crystalline Febuxostat Form-M_1

5 g of Febuxostat Crystal A was dissolved in ethyl acetate (200 mL) at 50 – 60 °C and cooled to room temperature (25 – 30 °C). The resulting solution was filtered through

hyflow to remove any undissolved particulate. The clear solution was subjected to spray drying in a Buchi mini spray dryer (Model B-290). The product was collected and dried at 50 °C under vacuum for 15h. The resulted solid was identified as crystalline Febuxostat Form –M_1.

Example – 2: Process for the Preparation of crystalline Febuxostat Form-M_1

5 g of Febuxostat Crystal G was dissolved in ethyl acetate (200 mL) at 50 – 60 °C and cooled to room temperature (25 – 30 °C). The resulting solution was filtered through hyflow to remove any undissolved particulate. The clear solution was subjected to spray drying in a Buchi Mini Spray Dryer (B-290). The product was collected and dried at 50 °C under vacuum for 15h. The resulted solid was identified as crystalline febuxostat Form – M_1.

Example – 3: Process for the preparation of Febuxostat crystal Form-K

5 g of Febuxostat Crystal A was dissolved in ethyl acetate (200 mL) at 50 – 60 °C and cooled to room temperature (25 – 30 °C). The resulting solution was filtered through hyflow to remove any undissolved particulate. The clear solution was evaporated on agitated thin film dryer (ATFD) instrument, at 50 °C under reduced pressure (120 mm-Hg). The resulted solid was collected and identified as crystalline febuxostat Form K.

Example – 4: Process for the preparation of Febuxostat crystal Form-K

5g of Febuxostat Crystal G was dissolved in ethyl acetate (200 mL) at 50 – 60 °C and cooled to room temperature (25 – 30 °C). The resulting solution was filtered through hyflow to remove any undissolved particulate. The clear solution was evaporated on ATFD instrument at 65 °C under reduced pressure (120 mm-Hg). The resulted solid was collected and identified as crystalline febuxostat Form K.

Example – 5: Process for the preparation of Febuxostat crystal Form-K

5 g of Febuxostat was dissolved in ethyl acetate (200 mL) at 70 – 80 °C and the solvent was removed on rotary evaporator at same temperature under reduced pressure. The resulted solid was collected and identified as crystalline febuxostat Form K.

Example – 6: Process for the preparation of Febuxostat crystal Form-K

10 g of Febuxostat was dissolved in ethyl acetate (150 mL) at 70 – 80 °C and the solvent was removed on rotary evaporator at same temperature under reduced pressure. The resulted solid was collected and identified as crystalline febuxostat Form K.

Example – 7: Process for the preparation of Febuxostat crystal Form-K

5 g of Febuxostat was dissolved in ethyl acetate (200 mL) at 50 – 60 °C and cooled to room temperature (25 – 30 °C). The resulting solution was filtered through hyflow to remove any undissolved particulate. The solution was heated to 70 – 80 °C and the solvent was distilled out at the same temperature under reduced pressure. The resulted solid was collected and identified as crystalline febuxostat Form K.

Example – 8: Process for the preparation of Febuxostat crystal Form-K

10 g of Febuxostat was dissolved in ethyl acetate (250 mL) at 50 – 60 °C and cooled to room temperature (25 – 30 °C). The resulting solution was filtered through hyflow to remove any undissolved particulate. The solution was heated to 70 – 80 °C and the solvent was distilled out at the same temperature under reduced pressure. To the resulted solid mass 100 mL of toluene was added, slurred for 2 hours, filtered and dried over night at 50 °C under reduced pressure. The dry solid was identified as crystalline febuxostat Form K.

Example – 9: Process for the preparation of Febuxostat crystal Form-K

10 g of Febuxostat was dissolved in ethyl acetate (250 mL) at 50 – 60 °C, cooled to room temperature (25 – 30 °C). The resulting solution was filtered through hyflow to remove any undissolved particulate. The solution was heated to 70 – 80 °C and the solvent was distilled out at the same temperature under reduced pressure. To the resulted solid mass 100 mL of cyclohexane was added, slurred for 2 hours, filtered and dried over night at 50 °C under reduced pressure. The dry solid was identified as crystalline febuxostat Form K.

Example – 10: Process for the preparation of Febuxostat crystal Form-K

10 g of Febuxostat was dissolved in ethyl acetate (250 mL) at 50 – 80 °C. The resulting solution was filtered and maintained for 60-90 minutes at 50 – 80 °C. The solvent was distilled out at 40-60 °C under reduced pressure. To the resulted solid mass 100 mL of cyclohexane was added and maintained for 2 hours. The reaction mass is centrifuged and the wet material is dried at 60 °C under reduced pressure. The dry solid was identified as crystalline Febuxostat Form K.

Example – 11: Process for the preparation of Febuxostat crystal Form-K

5 g of Febuxostat was suspended in ethyl acetate (80 mL) at 25–30°C and heated to 75 – 80 °C to obtain clear solution. The clear solution was distilled at 75 – 80 °C under reduced pressure to remove 60 mL of solvent. To the resulting suspension, cyclohexane (50 mL) was added at 75 – 80 °C and stirred for 10 – 15 minutes at 75 – 80 °C. The reaction mass was further distilled to half of its volume at 70 – 80 °C under reduced pressure and filtered at 75 – 80 °C. The product was isolated and dried at 60 °C under vacuum for 12 – 15 h. The solid obtained was identified as crystalline Febuxostat Form K.

Example – 12: Process for the preparation of Febuxostat crystal Form-K

20 g of Febuxostat was suspended in EtOH (160 mL) and THF (220 mL) at 25 – 30 °C and stirred for 10 – 15 min to obtain clear solution. To this clear solution, aqueous NaOH solution (1N, 108 mL) was added slowly at 25 – 30 °C, raised the temperature to 60 °C

and stirred the reaction mass at 60 °C for 1 h. The solvent was distilled out completely under reduced pressure at 60–70 °C. The reaction mass was cooled to 25 – 30 °C, added water (100 mL) and neutralized with 1N HCl. Then ethyl acetate (400 mL) was added to the reaction mass and stirred for 10 – 15 minutes at 25–30°C. The aqueous layer was extracted using ethyl acetate (100 mL) and dried over anhydrous Na_2SO_4. The reaction mass was distilled out completely at 75 – 80 °C under reduced pressure. The solid obtained was identified as crystalline Febuxostat Form K.

Example – 13: Process for the preparation of Febuxostat crystal Form-K

20g of Febuxostat was suspended in EtOH (160 mL) and THF (220 mL) at 25–30 °C and stirred for 10 – 15 min to obtain clear solution. To this clear solution, aqueous NaOH solution (1N, 108 mL) was added slowly at 25 – 30°C, raised the temperature to 60 °C and stirred the reaction mass at 60 °C for 1h. The solvent was distilled out completely under reduced pressure at 60 – 70 °C. The reaction mass was cooled to 25 – 30 °C, added water (100 mL) and neutralized with 1N HCl. Then ethyl acetate (400 mL) was added to the reaction mass and stirred for 10 – 15 minutes at 25–30°C. The aqueous layer was extracted using ethyl acetate (100 mL) and dried over anhydrous Na_2SO_4. The reaction mass was distilled out completely at 75 – 80 °C under reduced pressure and cooled to 25 – 30°C. To the resulting solid mass, cyclohexane (100 mL) was added, slurred for 2 hours at 25–30°C and filtered. The isolated solid was dried at 60°C under vacuum for 12 – 15h. The product obtained was identified as crystalline Febuxostat Form K.

Example – 14: Process for the preparation of Febuxostat crystal Form-K

20g of ethyl ester of Febuxostat [ethyl 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylate] was suspended in EtOH (160 mL) and of THF (220 mL) at 25–30°C and stirred for 10 – 15 min to obtain clear solution. To this clear solution, aqueous NaOH solution (1N, 108 mL) was added slowly at 25 – 30°C, raised the temperature to 60°C and stirred the reaction mass at 60°C for 1h. The solvent was distilled out completely under reduced pressure at 60 – 70°C. The reaction mass was cooled to 25 – 30°C, added water (100 mL) and neutralized with 1N HCl. Then ethyl acetate (400 mL) was added to

the reaction mass and stirred for 10 – 15 minutes at 25 – 30°C. The aqueous layer was extracted using ethyl acetate (100 mL) and dried over anhydrous Na_2SO_4. The reaction mass was distilled out completely at 75 – 80 °C under reduced pressure and cooled to 25 – 30 °C. To the resulting solid mass, cyclohexane (100 mL) was added, slurred for 2 hours at 25 – 30 °C and filtered. The isolated solid was dried at 60 °C under vacuum for 12 – 15 h. The product obtained was identified as crystalline Febuxostat Form K.

Example – 15: Process for the preparation of Febuxostat crystal Form-K

50 g of Febuxostat was suspended in ethyl acetate (1250 mL) at 25 – 30 °C and heated to 75 – 80 °C to obtain clear solution. The resulted solution was refluxed for 1h and then cooled to 60 °C. The solvent was distilled at 60 – 35 °C under reduced pressure to leave about 400 – 500 mL of solvent. To the resulting suspension, cyclohexane (500 mL) was added at 35 °C and stirred for 1h at 25 – 30 °C and filtered. The product was isolated, dried at 60 °C under vacuum and unloaded under controlled humidity 40± 10 % RH and packed. The solid obtained was identified as crystalline Febuxostat Form K.

Example – 16: Process for the preparation of Febuxostat crystal Form-K

50 g of Febuxostat was suspended in ethyl acetate (1000 mL) and toluene (500 mL) at 25 – 30 °C and heated to 75 – 80 °C to obtain clear solution. The resulted solution was refluxed for 1h. The solution was distilled at 80 – 90 °C to leave about 700 mL of solution. The clear solution was cooled to 70 °C in 30 minutes and maintain at 70°C for further 30 minutes. The hazy solution was further cooled to 25 – 30 °C in about 1h and maintain at 25 – 30 °C for 30 minutes. The slurry was filtered, dried at 60 °C under vacuum and unloaded under controlled humidity 40± 10 % RH and packed. The solid obtained was identified as crystalline Febuxostat Form K.

Packaging:

Febuxostat Form-K was packed in LDPE bag under nitrogen atmosphere, twisted and tied with plastic fastener. It was inserted in Triple laminated aluminum liner bag with vacuumised nitrogen sealing. Both these bags were then put into the outer bag of triple

laminated aluminum bag and vacuumised nitrogen sealing. Such poly bags were further packed in HDPE drums, closed with plastic lids having rubber gasket followed by locking ring and a metal seal and labeled.

We claim:

1. An improved process for the preparation of crystalline Form-K of Febuxostat comprising the steps of:
    a) dissolving Febuxostat in an ester solvent,
    b) removing the solvent,
    c) adding hydrocarbon solvent, and
    d) isolating Febuxostat crystalline Form-K.
2. The process according to claim 1, wherein the ester solvent is ethyl acetate.
3. The process according to claim 1, wherein hydrocarbon solvent is selected from cyclohexane or toluene.
4. An improved process for the preparation of crystalline Form-K of Febuxostat comprising the steps of:
    a) dissolving Febuxostat in an ester solvent at 50 – 80 °C,
    b) filtering the reaction mass,
    c) maintaining the filtrate for 30-120 minutes at same temperature,
    d) removing the solvent,
    e) adding hydrocarbon solvent, and
    f) isolating Febuxostat crystalline Form-K.
5. The process according to claim 4, wherein the ester solvent is ethyl acetate.
6. The process according to claim 4, wherein hydrocarbon solvent is selected from cyclohexane or toluene.
7. An improved process for the preparation of crystalline Form-K of Febuxostat comprising the steps of:
    a). dissolving Febuxostat in mixture of ester and hydrocarbon solvent,
    b) partially removing the solvent, and
    c) isolating Febuxostat crystalline Form-K.
8. The process according to claim 7, wherein ester solvent is ethyl acetate.
9. The process according to claim 7, wherein hydrocarbon solvent is selected from cyclohexane or toluene.
10. The process according to claim 7, wherein mixture of solvent is mixture of ethyl acetate and toluene.

11. An improved process for the preparation of crystalline Form-K of Febuxostat comprising the steps of:
    a) dissolving Febuxostat in an ester solvent,
    b) evaporating the solvent by agitated thin film dryer (ATFD), and
    c) isolating Febuxostat crystalline Form-K.

12. The process according to claim 11, wherein the ester solvent is ethyl acetate.

13. An improved process for the preparation of pure crystalline Form-K of Febuxostat comprising the steps of:
    a) dissolving Febuxostat in an ester solvent at 50 – 80 °C,
    b) removing the solvent and
    c) isolating Febuxostat crystalline Form-K.

14. The process according to claim 13, wherein the ester solvent is ethyl acetate.

15. An improved process for the preparation of crystalline Form-K of Febuxostat comprising the steps of:
    a) dissolving Febuxostat in one or more organic solvents,
    b) adding a base to the reaction mixture,
    c) removing the solvent,
    d) adding water and neutralizing with acid,
    e) adding one or more ester solvents,
    f) optionally adding hydrocarbon solvent, and
    g) isolating Febuxostat crystalline Form-K.

16. The process according to claim 15, wherein organic solvent is selected from ethanol, methanol, isopropanol, tetrahydrofuran or mixtures thereof.

17. The process according to claim 15, wherein base is selected from alkali or alkali earth metal hydroxides.

18. The process according to claim 15, wherein acid used for the neutralization is selected from acetic acid, formic acid, hydrochloric acid, sulfuric acid or phosphoric acid.

19. The process according to claim 15, wherein ester solvent is ethyl acetate.

20. The process according to claim 15, wherein hydrocarbon solvent is selected from cyclohexane or toluene.

21. An improved process for the preparation of crystalline Form-K of Febuxostat comprising the steps of:
    a) dissolving alkyl ester of Febuxostat in one or more organic solvents,
    b) adding a base to the reaction mixture,
    c) removing the solvent,
    d) adding water and neutralizing with acid,
    e) adding one or more ester solvents,
    f) optionally adding hydrocarbon solvent, and
    g) isolating Febuxostat crystalline Form-K.
22. The process according to claim 21, wherein alkyl ester of Febuxostat is selected from methyl or ethyl ester.
23. The process according to claim 21, wherein organic solvent is selected from ethanol, methanol, isopropanol, tetrahydrofuran or mixtures thereof.
24. The process according to claim 21, wherein base is selected from alkali or alkali earth metal hydroxides.
25. The process according to claim 21, wherein acid used for the neutralization is selected from acetic acid, formic acid, hydrochloric acid, sulfuric acid or phosphoric acid.
26. The process according to claim 21, wherein ester solvent is ethyl acetate.
27. The process according to claim 21, wherein hydrocarbon solvent is selected from cyclohexane or toluene.
28. An improved process for the preparation of crystalline Form-K of Febuxostat comprising the steps of:
    a) dissolving Febuxostat in an ester solvent,
    b) partially removing the solvent,
    c) adding hydrocarbon solvent, and
    d) isolating Febuxostat crystalline Form-K.
29. The process according to claim 28, wherein ester solvent is ethyl acetate.
30. The process according to claim 28, wherein hydrocarbon solvent is selected from cyclohexane or toluene.
31. A method of packaging crystalline Febuxostat Form-K comprising:

a) placing Febuxostat Form-K in LDPE (low density polyethylene) bag under nitrogen atmosphere,

b) placing the sealed bag in triple laminated aluminum liner bag with vacuumised nitrogen sealing,

c) placing the above bag into the outer bag of triple laminated aluminum bag with vacuumised nitrogen sealing, and

d) enclosing the triple laminated bag in closed HDPE (high density polyethylene) drums.

32. Crystalline Form M_1 of Febuxostat.

33. The compound according to claim 32, wherein Form M_1 of Febuxostat is characterized by the powder X-ray diffraction having characteristic peaks 6.13, 9.06, 12.29, 17.44 and 25.81±0.2° 2θ.

34. The compound according to claim 32, wherein Form M_1 of Febuxostat is characterized by Powder X-ray diffraction as depicted in Figure 1.

35. The compound according to claim 32, herein Form M_1 of Febuxostat is characterized by the DSC thermogram as depicted in Figure 2.

36. A process for the preparation of Febuxostat crystalline Form-M_1 comprising the steps of:

a) dissolving Febuxostat in an ester solvent,

b) spray drying the clear solution, and

c) isolating the crystalline Form-M_1.

37. The process according to claim 36, wherein the ester solvent is ethyl acetate.

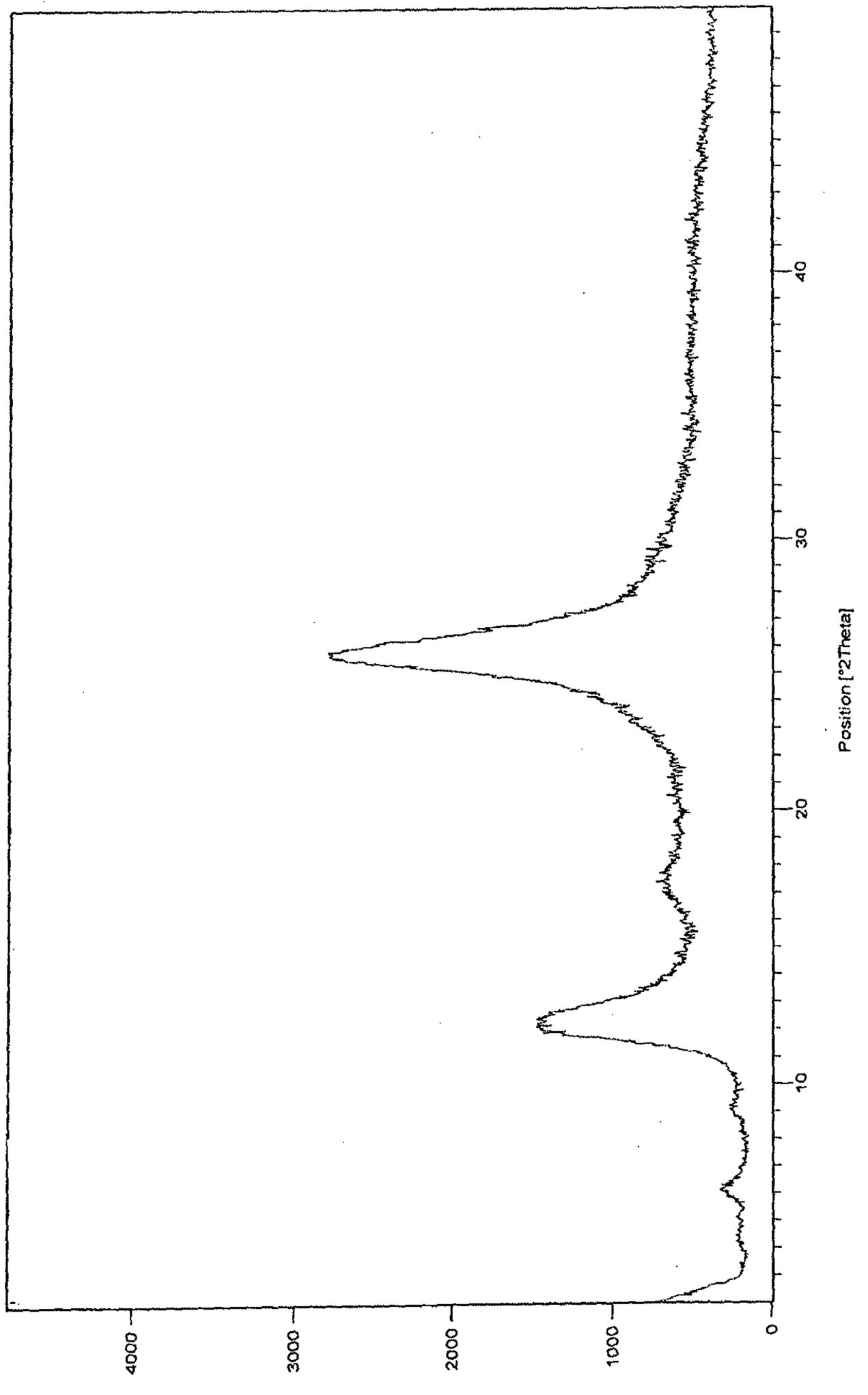
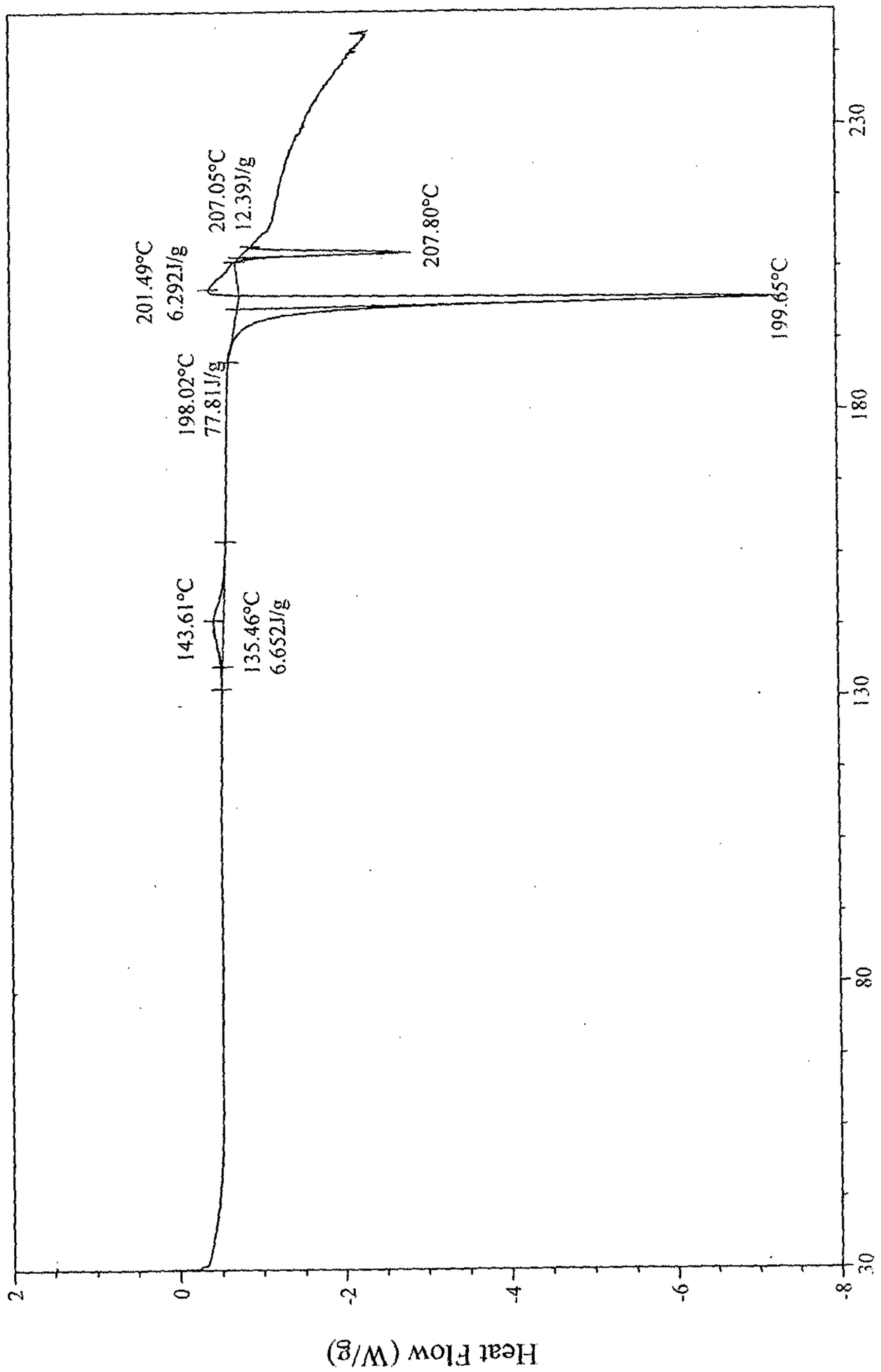


Figure 1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135.46°C
6.652J/g
Temperature (°C)
Heat Flow (W/g)

Figure 2

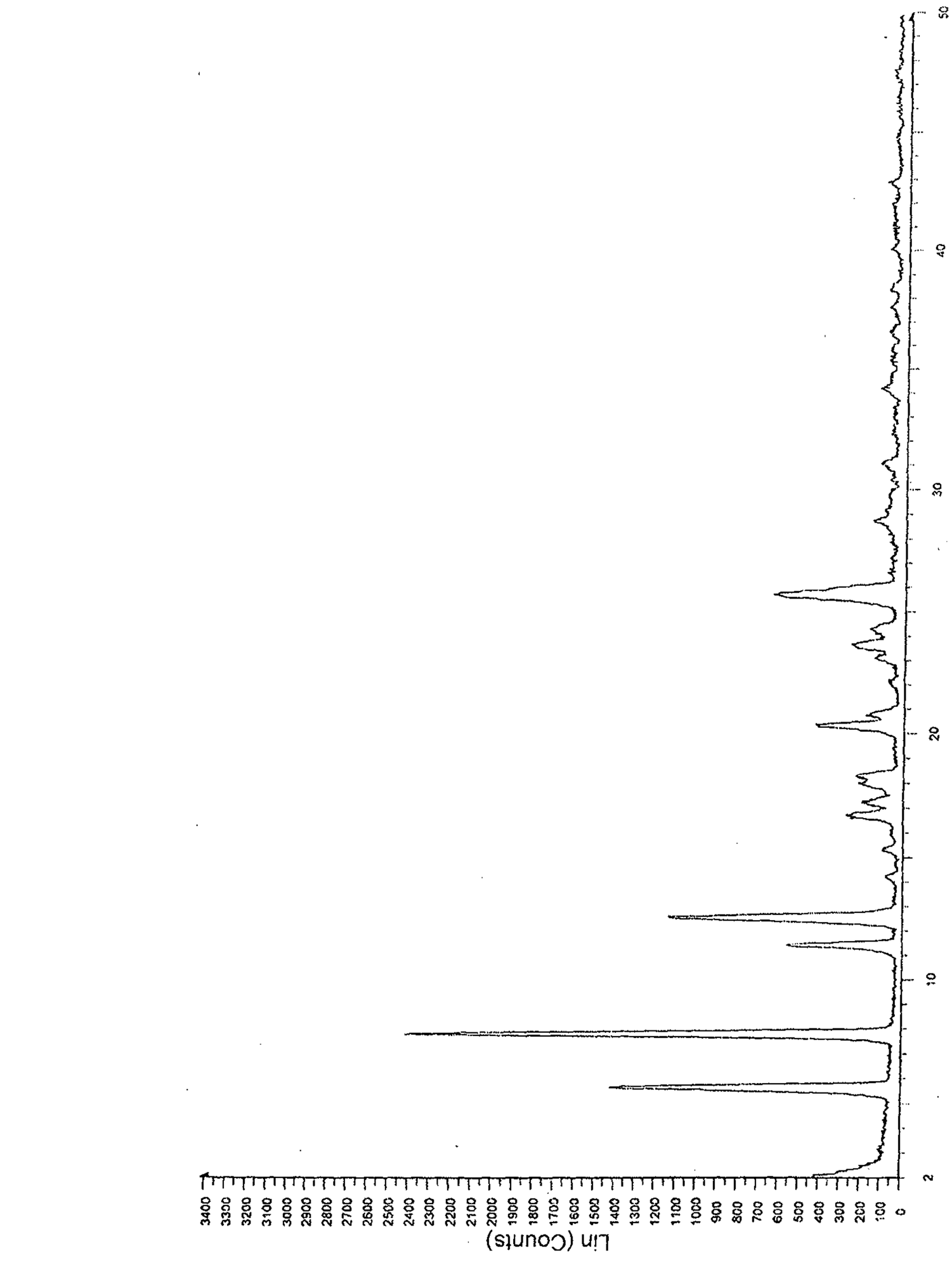
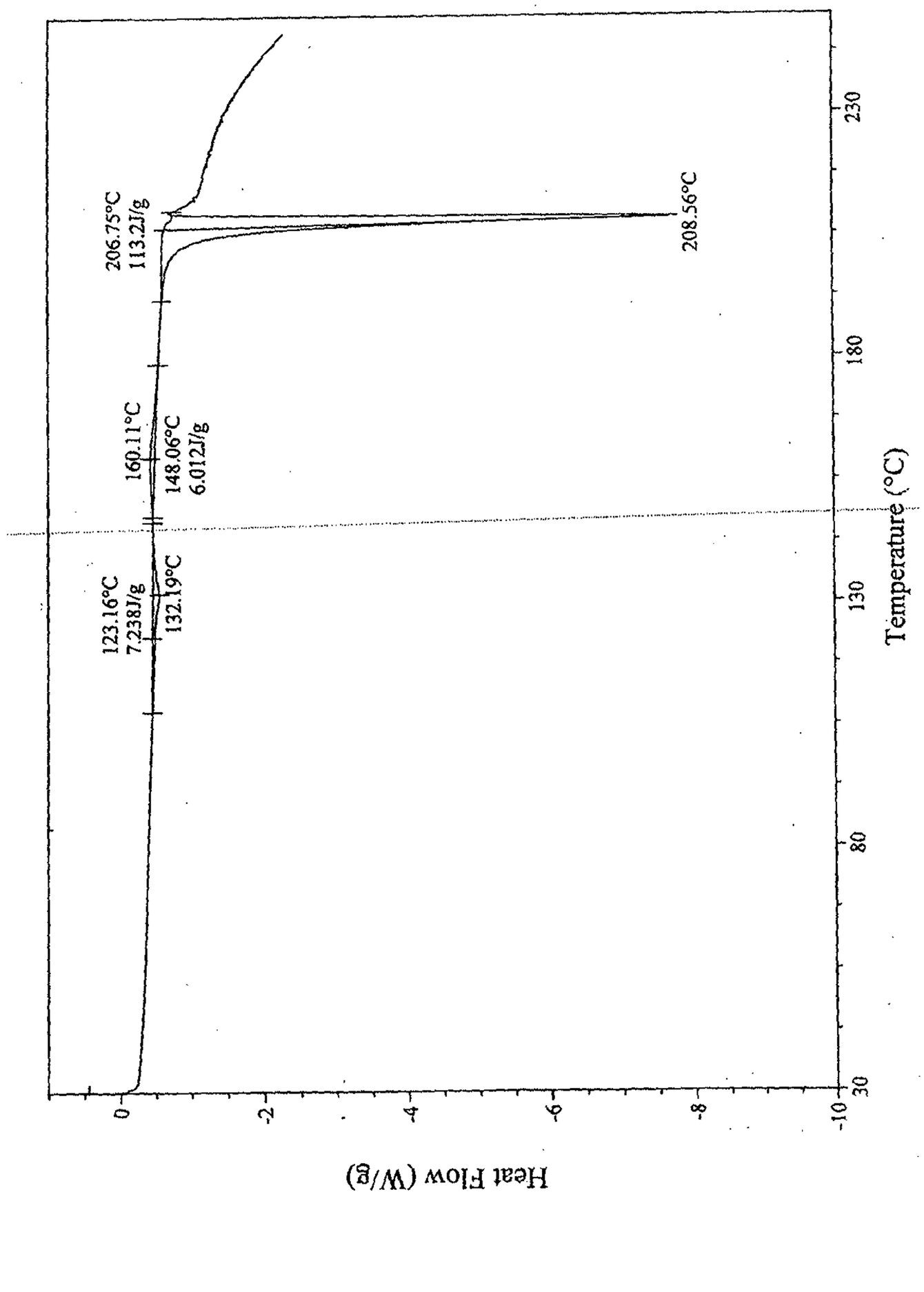


Figure 3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6.012J/g
123.16°C
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132.19°C
230
180
130
Temperature (°C)
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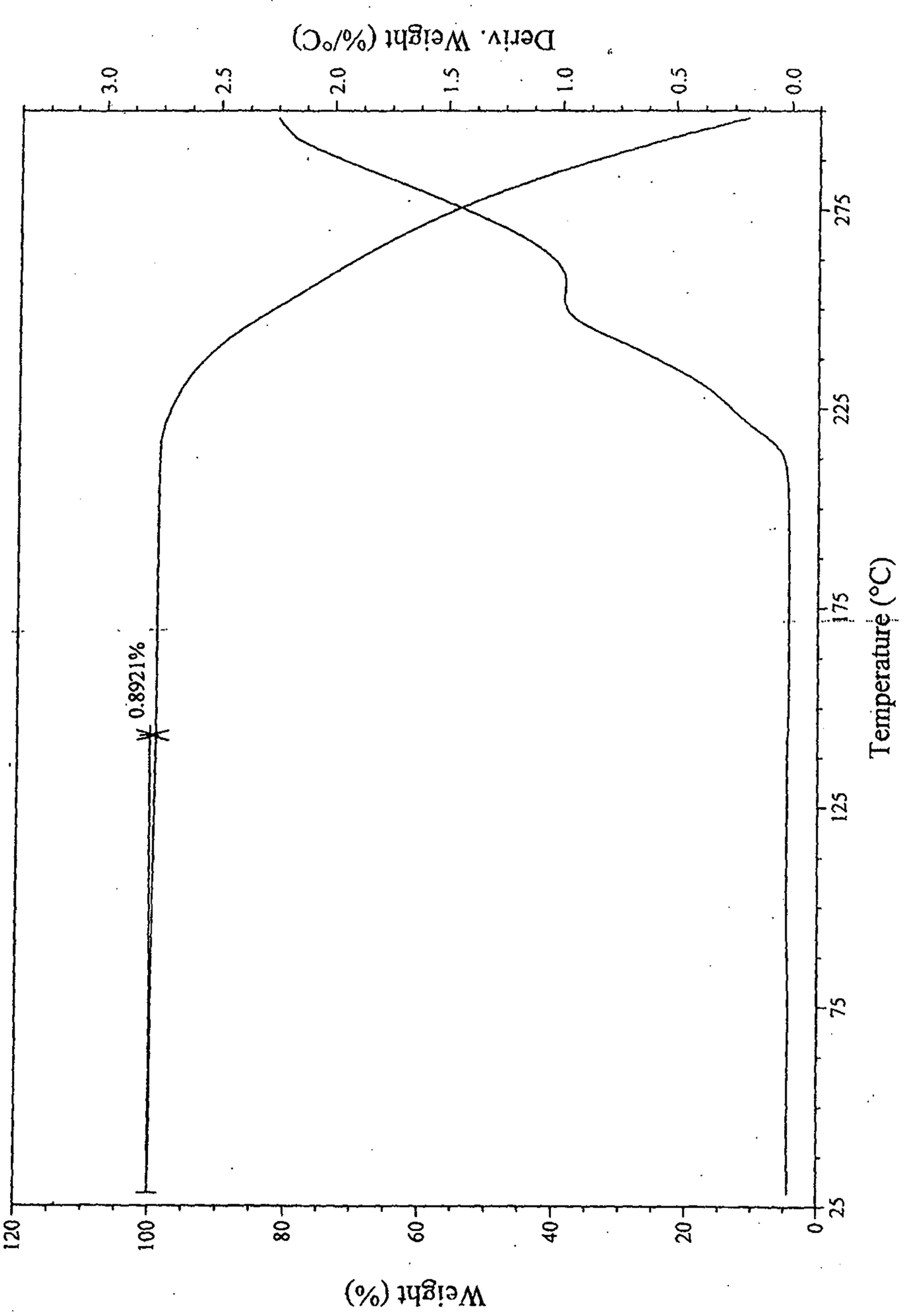
-4
-6
-8
-10
30
80
Heat Flow (W/g)

Figure 4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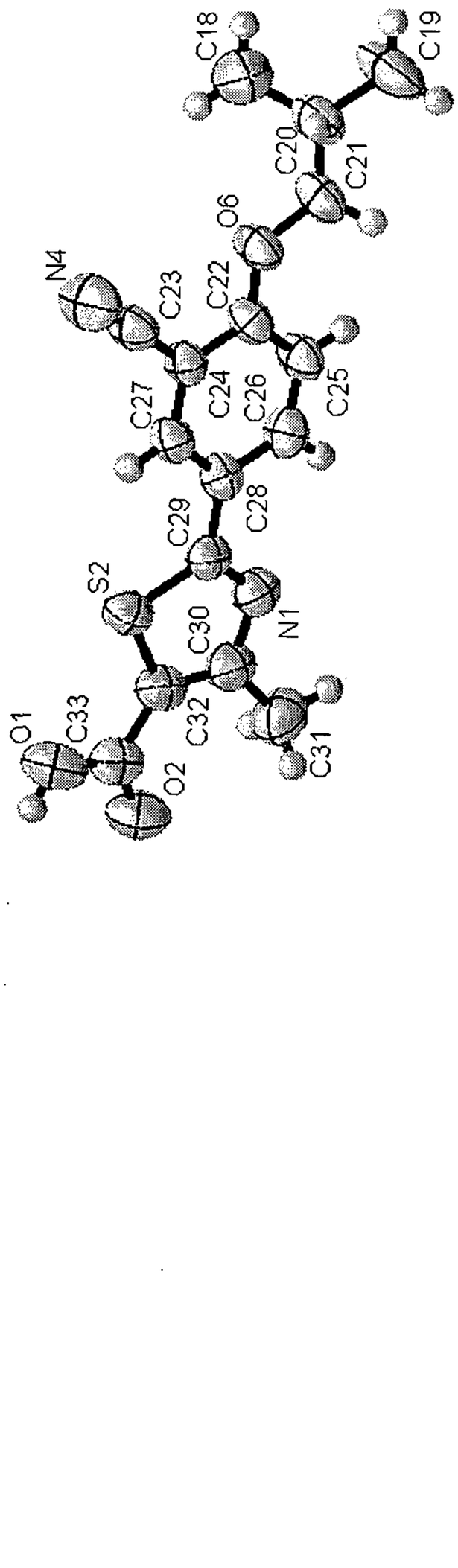
100
80
60
40
20
0
25
75
125
Weight (%)

Figure 5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C23
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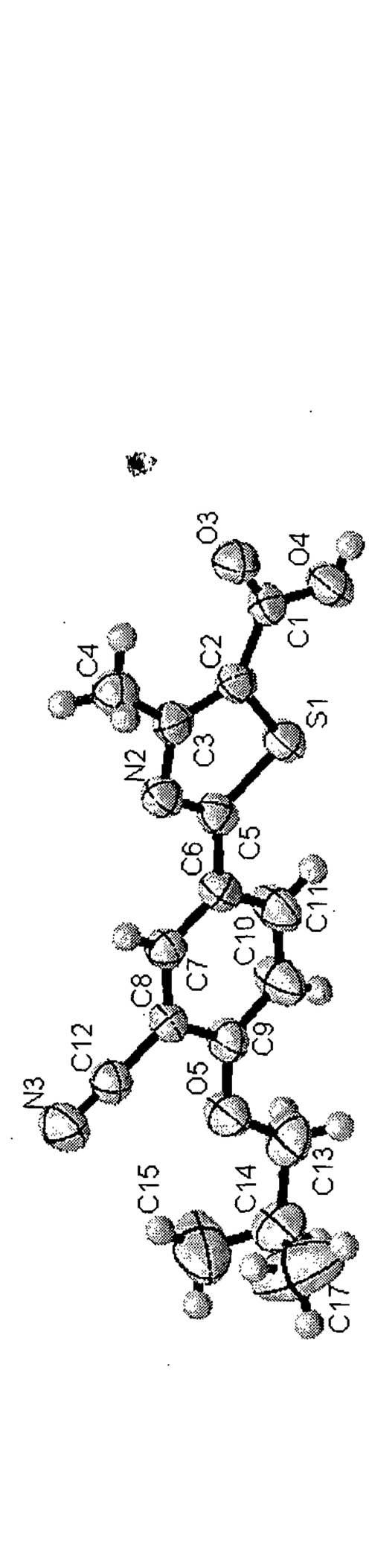
O2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C4
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O5
C15
C14
C13
C17

Figure 6

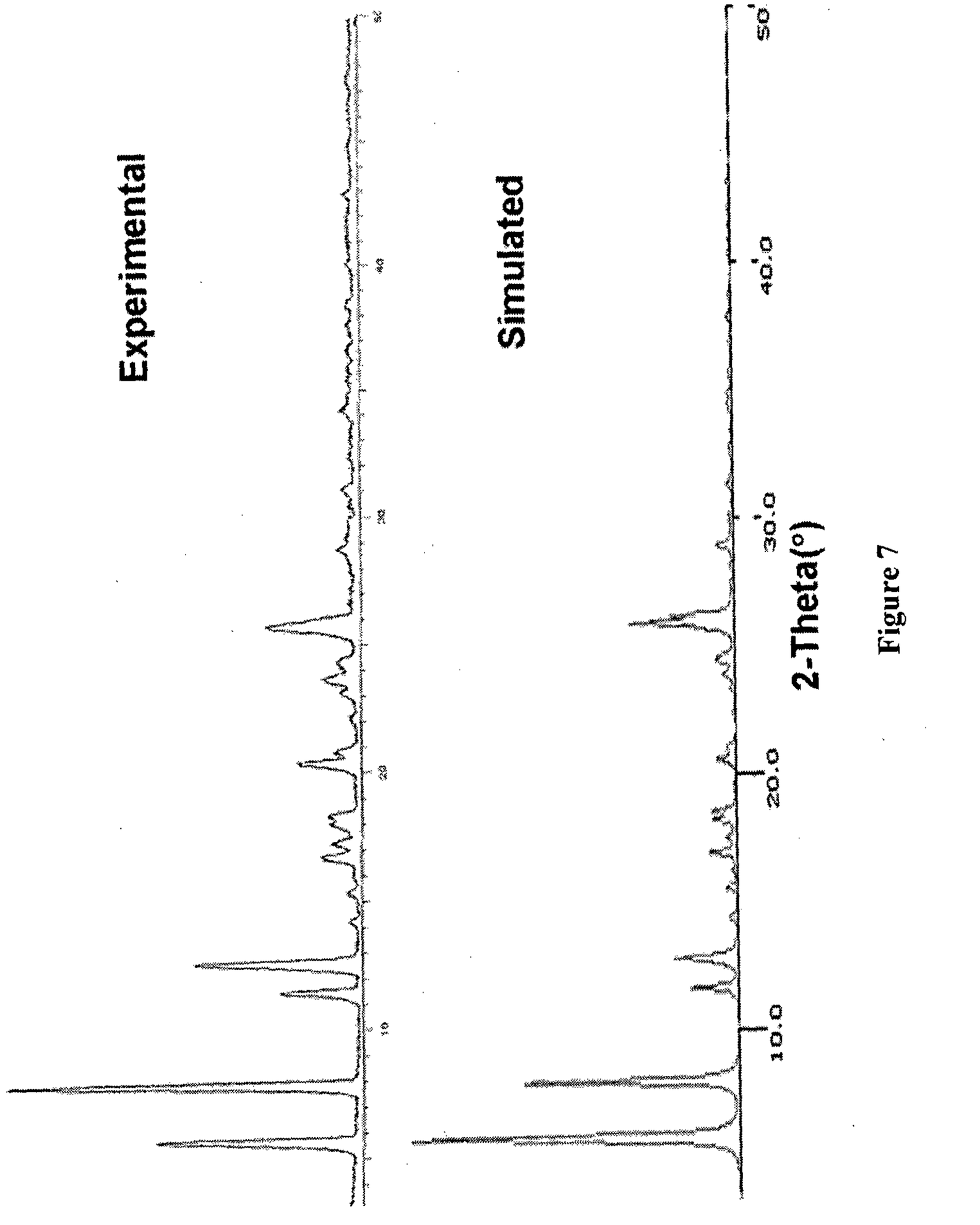
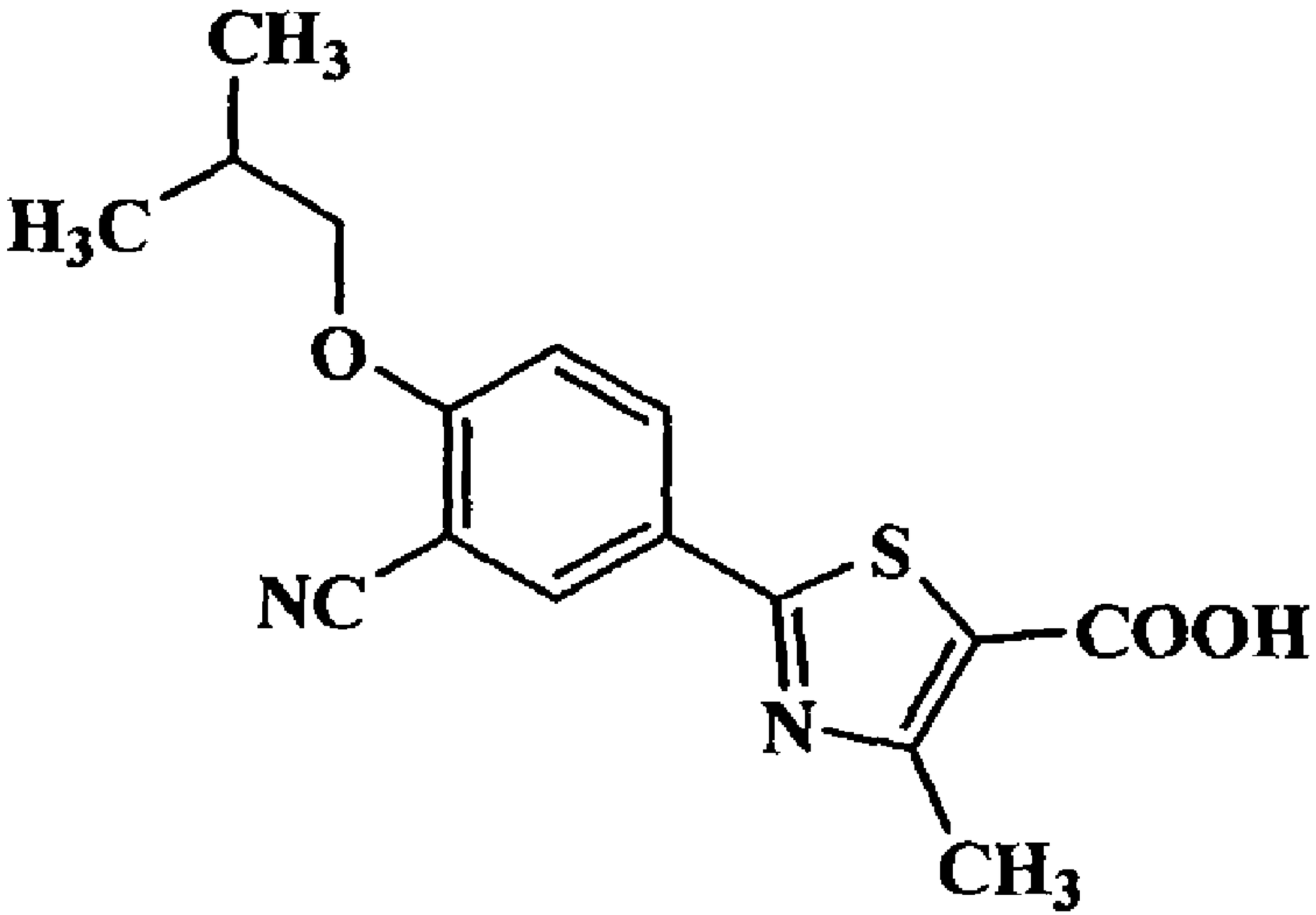


Figure 7



Formula-I