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WO-A1-2010/118354
WO-A1-2014/036897
CN-A- 101 048 381
CN-B- 101 222 922

DESCRIPTION

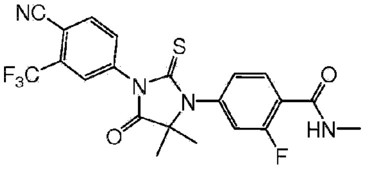
FIELD OF THE INVENTION

[0001] The present invention relates to crystal form I of (S)-4-(3-(4-(2,3-dihydroxypropoxy)phenyl)-4,4-dimethyl-5-carbonyl-2-thioimidazolin-1-yl)-2-(trifluoromethyl)benzonitrile and a preparation method thereof.

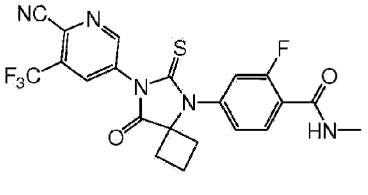
BACKGROUND OF THE INVENTION

[0002] Prostate cancer (PCa) is a malignant tumor that occurs in the prostate tissue of man, and is the result of abnormal growth of prostate acinar cells. The differentiation and growth of normal prostate epithelial cells as well as the development of prostate cancer all depend on androgen, which is mainly (about 80-90%) synthesized in testis. Synthetic androgen binds to the androgen receptor (AR) after entering the cells, causing dissociation of heat shock protein (HSP) from AR, then the AR enters the nucleus and activates multiple downstream genes, including prostate-specific antigen (PSA). Early prostate cancer is sensitive to androgen, orchiectomy (castration) thus can significantly inhibit the development of prostate cancer. However, the castration surgery is effective for a certain period of time, many patients undergo the transformation of androgen-dependent to androgen-independent during a period of time after castration. The prostate cancer of these patients develops into the androgen independent prostate cancer (AIPC), and the anti-androgen therapy is no longer effective to them. The occurrence of AIPC still has an important relationship with the activation of AR signaling pathway in PCa cells.

[0003] The first-generation drugs, which aim at inhibiting AR activity, include Bicalutamide (or Casodex) and Flutamide. The second-generation AR antagonist drugs for AIPC therapy include MDV3100 and ARN-509. MDV3100 is the first second-generation non-steroidal AR antagonist drug in the world, and was approved by the FDA at the end of August 2012. The affinity of MDV-3100 to AR is 5-8 times higher than that of bicalutamide. MDV-3100 can inhibit the growth of AIPC in mouse and human by inhibiting AR activity, and has no effect of promoting tumor cell growth.

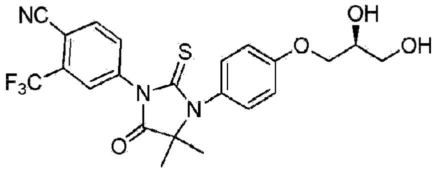


MDV-3100



ARN-509

[0004] WO2014036897A1 discloses novel AR antagonists, comprising a compound of formula (I). The activity *in vitro* of this compound is slightly better than that of MDV-3100, and the hERG inhibition rate is further improved (IC50: 24.83 μM). The inhibition half lives of this compound toward five major subtypes of CYP450 are all greater than 50 μM. The *in vivo* exposure of this compound in rats is comparable to that of MDV-3100, and the *in vivo* exposure of this compound in dogs is more than six times than that of MDV-3100 at the same dose and in the same solvent. The compound of formula (I) has only one chiral center. The chiral starting material is easy to obtain, and the synthesis difficulty is greatly reduced. In addition, the compound of formula (I) has no AR agonist activity at 3 μM and 10 μM, and the ratio of drug concentration in brain tissue to drug concentration in plasma in mice is much lower than that of MDV-3100 compound, and the possibility of epileptic side effect is smaller. Therefore, the compound of formula (I) has a broad clinical prospect.

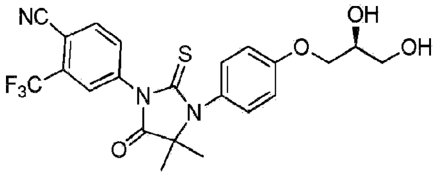


(I)

[0005] However, WO2014036897A1 does not further investigate the crystal form of this compound. It is known to those skilled in the art that the crystal structure of the pharmaceutically active ingredient often affects the chemical stability of the drug. Different crystallization conditions and storage conditions can lead to changes in the crystal structure of the compound, and sometimes accompanying production of other crystal forms. In general, an amorphous drug product does not have a regular crystal structure, and often has other defects, such as poor product stability, smaller particle size, difficult filtration, easy agglomeration, and poor liquidity. Therefore, it is necessary to improve the various properties of the above compound. There is a need to find a new crystal form with high purity and good chemical stability.

SUMMARY OF THE INVENTION

[0006] The present invention provides a new crystal form of (S)-4-(3-(4-(2,3-dihydroxypropoxy)phenyl)-4,4-dimethyl-5-carbonyl-2-thioimidazolin-1-yl)-2-(trifluoromethyl)benzonitrile (as shown in formula (I)),



(I) .

[0007] A series of crystal products of the compound of formula (I) have been obtained under various crystallization conditions, and X-ray diffraction and differential scanning calorimetry (DSC) measurements have been conducted on the obtained crystal products. It was found that a stable crystal form, which is referred to as crystal form I, can be obtained under normal crystallization conditions. The DSC spectrum of crystal form I of the present application shows a melting endothermic peak at about 157°C. The X-ray powder diffraction spectrum, which is obtained by using Cu-Ka radiation and represented by 2θ angle and interplanar distance (d value), is shown in Figure 1, in which there are characteristic peaks at 8.89 (9.94), 9.97 (8.87), 11.22 (7.88), 14.28 (6.20), 15.17 (5.83), 15.51 (5.71), 16.77 (5.28), 19.91 (4.46), 21.13 (4.20), 22.48 (3.95), 24.06 (3.70), and 26.37 (3.38).

[0008] The present invention also provides a method for preparing crystal form I of (S)-4-(3-(4-(2,3-dihydroxypropoxy)phenyl)-4,4-dimethyl-5-carbonyl-2-thioimidazolin-1-yl)-2-(trifluoromethyl)benzonitrile, comprising the following steps of:

1. 1) adding any crystal form or amorphous form of the compound of formula (I) into an appropriate amount of organic solvent, heating the solution until it is clear, and then cooling it to precipitate a crystal, wherein the solvent is selected from any one of esters, ketones, nitriles, and ethers, or a mixed solvent thereof; preferably, the solvent has 5 or less carbon atoms.
2. 2) filtering the crystal, then washing and drying it.

[0009] In a preferred embodiment, the solvent in step 1) is a single solvent selected from ethyl acetate, acetone, isopropyl acetate, tetrahydrofuran, and acetonitrile, and is acetone/isopropyl ether, ethyl acetate/n-hexane, ethyl acetate/isopropyl ether, or ethyl acetate/methyl *tert*-butyl ether; preferably ethyl acetate/isopropyl ether. The ratio of the two is not particularly limited, preferably between 1:10 and 10:1, and the volume ratio is 1:1 in an embodiment of the present invention.

[0010] The recrystallization method is not particularly limited, and can be carried out by a conventional recrystallization process. For example, the material, *i.e.,* the compound of formula (I), can be dissolved in an organic solvent under heating, then the solution is cooled slowly to precipitate a crystal. After the completion of crystallization, the desired crystal can be obtained via filtering and drying. In particular, the crystal obtained by filtration is usually dried in a vacuum under reduced pressure at a heating condition of about 30 to 100°C, preferably 40 to 60°C, to remove the recrystallization solvent.

[0011] The resulting crystal form of the compound of formula (I) is determined by differential scanning calorimetry (DSC) and X-ray diffraction spectrum. Meanwhile, the residual solvent in the obtained crystal is also determined.

[0012] Crystal form I of the compound of formula (I) prepared according to the method of the present invention does not contain or contains only a relatively low content of residual solvent, which meets the requirement of the National Pharmacopoeia concerning the limitation of the residual solvent of drug products. Therefore, the crystal of the present invention is suitable for use as pharmaceutical active ingredient.

[0013] The research results show that crystal form I of the compound of formula (I) prepared according to present invention is stable under conditions of lighting, high temperature and high humidity. Crystal form I is also stable under conditions of grinding, pressure and heating, which meets the production, transportation and storage requirements of drug products. The preparation process thereof is stable, repeatable and controllable, which is suitable for industrial production.

[0014] In another aspect, the present invention provides a pharmaceutical composition comprising the crystal form I of the compound of formula (I), wherein the pharmaceutical composition comprises a crystal form of the compound of formula (I) and a pharmaceutically acceptable carrier.

[0015] In another aspect, the present invention relates to the crystal form I of the compound of formula (I) of the present invention or the pharmaceutical composition of the present invention for use in the treatment of prostate cancer.

DESCRIPTION OF THE DRAWINGS

[0016]

Figure 1 shows the X-ray powder diffraction spectrum of crystal form I of the compound of formula (I).

Figure 2 shows the DSC spectrum of crystal form I of the compound of formula (I).

Figure 3 shows the X-ray powder diffraction spectrum of crystal form II of the compound of formula (I).

Figure 4 shows the DSC spectrum of crystal form II of the compound of formula (I).

Figure 5 shows the X-ray powder diffraction spectrum of crystal form III of the compound of formula (I).

Figure 6 shows the DSC spectrum of crystal form III of the compound of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

[0017] The present invention is illustrated by the following examples in detail. The examples of the present invention are merely intended to describe the technical solution of the present invention, and should not be considered as limiting the scope of the present invention.

[0018] Test instruments used in the experiments

1. 1. DSC spectrum
   Instrument type: Mettler Toledo DSC 1 Staree System
   Purging gas: Nitrogen
   Heating rate: 10.0°C/min
   Temperature range: 40-250°C
2. 2. X-ray diffraction spectrum
   Instrument type: Bruker D8 Focus X-ray powder diffractometer
   Ray: monochromatic Cu-Kα ray (λ=1.5406)
   Scanning mode: θ/2θ, Scanning range: 2-40°
   Voltage: 40 KV, Electric current: 40 mA

Example 1

[0019] The compound of formula (I) (1.0 g, 2.09 mmol) (prepared according to the method provided in WO2014036897A1) was added to a 25 ml one-necked flask, followed by addition of 4.0 ml of ethyl acetate. The mixture was heated to reflux until the solution was clear. The solution was continuously refluxed for 10 minutes, then cooled to precipitate a crystal under stirring. The mixture was filtered and dried to obtain a solid (560 mg, yield: 56.0%). The X-ray powder diffraction spectrum of the crystal sample is shown in Figure 1, in which there are characteristic peaks at about 8.89 (9.94), 9.97 (8.87), 11.22 (7.88), 14.28 (6.20), 15.17 (5.83), 15.51 (5.71), 16.77 (5.28), 19.91 (4.46), 21.13 (4.20), 22.48 (3.95), 24.06 (3.70), and 26.37 (3.38). The DSC spectrum is shown in Figure 2, having a sharp melting endothermic peak at 157°C. The crystal form was defined as crystal form I.

Example 2

[0020] The compound of formula (I) (1.0 g, 2.09 mmol) (prepared according to Example 1) was added to a 25 ml one-necked flask, followed by addition of 4.0 ml of acetone. The mixture was heated to reflux until the solution was clear. The solution was continuously refluxed for 10 minutes, then cooled to precipitate a crystal under stirring. The mixture was filtered and dried to obtain a solid (438 mg, yield: 43.8%). The product was identified as crystal form I after studying and comparing the X-ray diffraction and DSC spectra.

Example 3

[0021] The compound of formula (I) (1.0 g, 2.09 mmol) (prepared according to Example 1) was added to a 25 ml one-necked flask, followed by addition of 4.0 ml of ethyl acetate. The mixture was heated to reflux until the solution was clear, then 4.0 ml of n-hexane was added dropwise. The mixture was continuously refluxed for 10 minutes, then cooled to precipitate a crystal under stirring. The mixture was filtered and dried to obtain a solid (711 mg, yield: 71.1%). The product was identified as crystal form I after studying and comparing the X-ray diffraction and DSC spectra.

Example 4

[0022] The compound of formula (I) (1.0 g, 2.09 mmol) (prepared according to Example 1) was added to a 25 ml one-necked flask, followed by addition of 5.0 ml of ethyl acetate. The mixture was heated to reflux until the solution was clear, then 5.0 ml of isopropyl ether was added dropwise. The mixture was continuously refluxed for 10 minutes, then cooled to precipitate a crystal under stirring. The mixture was filtered and dried to obtain a solid (678 mg, yield: 67.8%). The product was identified as crystal form I after studying and comparing the X-ray diffraction and DSC spectra.

Example 5

[0023] The compound of formula (I) (1.0 g, 2.09 mmol) (prepared according to Example 1) was added to a 25 ml one-necked flask, followed by addition of 5.0 ml of ethyl acetate. The mixture was heated to reflux until the solution was clear, then 5.0 ml of methyl *tert*-butyl ether was added dropwise. The mixture was continuously refluxed for 10 minutes, then cooled to precipitate a crystal under stirring. The mixture was filtered and dried to obtain a solid (682 mg, yield: 68.2%). The product was identified as crystal form I after studying and comparing the X-ray diffraction and DSC spectra.

Example 6

[0024] The compound of formula (I) (1.0 g, 2.09 mmol) (prepared according to Example 1) was added to a 25 ml one-necked flask, followed by addition of 6.0 ml of isopropyl acetate. The mixture was heated to reflux until the solution was clear. The solution was continuously refluxed for 10 minutes, then cooled to precipitate a crystal under stirring. The mixture was filtered and dried to obtain a solid (612 mg, yield: 61.2%). The product was identified as crystal form I after studying and comparing the X-ray diffraction and DSC spectra.

Example 7

[0025] The compound of formula (I) (1.0 g, 2.09 mmol) (prepared according to Example 1) was added to a 25 ml one-necked flask, followed by addition of 5.0 ml of acetone. The mixture was heated to reflux until the solution was clear, then 5.0 ml of water was added dropwise. The mixture was continuously refluxed for 10 minutes, then cooled to precipitate a crystal under stirring. The mixture was filtered and dried to obtain a solid (476 mg, yield: 47.6%). The product was identified as crystal form I after studying and comparing the X-ray diffraction and DSC spectra.

Example 8

[0026] The compound of formula (I) (1.0 g, 2.09 mmol) (prepared according to Example 1) was added to a 25 ml one-necked flask, followed by addition of 5.0 ml of acetone. The mixture was heated to reflux until the solution was clear, then 5 ml of isopropyl ether was added dropwise. The mixture was continuously refluxed for 10 minutes, then cooled to precipitate a crystal under stirring. The mixture was filtered and dried to obtain a solid (521 mg, yield: 52.1%). The product was identified as crystal form I after studying and comparing the X-ray diffraction and DSC spectra.

Example 9

[0027] The compound of formula (I) (1.0 g, 2.09 mmol) (prepared according to Example 1) was added to a 25 ml one-necked flask, followed by addition of 2.0 ml of tetrahydrofuran. The mixture was heated to reflux until the solution was clear. The solution was continuously refluxed for 10 minutes, then cooled to precipitate a crystal under stirring. The mixture was filtered and dried to obtain a solid (327 mg, yield: 32.7%). The product was identified as crystal form I after studying and comparing the X-ray diffraction and DSC spectra.

Example 10

[0028] The compound of formula (I) (1.0 g, 2.09 mmol) (prepared according to Example 1) was added to a 25 ml one-necked flask, followed by addition of 2.0 ml of acetonitrile. The mixture was heated to reflux until the solution was clear. The solution was continuously refluxed for 10 minutes, then cooled to precipitate a crystal under stirring. The mixture was filtered and dried to obtain a solid (242 mg, yield: 24.2%). The product was identified as crystal form I after studying and comparing the X-ray diffraction and DSC spectra.

Example 11

[0029] The entire procedure of Example 44 of WO2014036897A1 was repeated. (*R*)-4-(3-(4-

((2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)phenyl)-4,4-dimethyl-5-oxo-2-t hioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile (2.2 g, 4.20 mmol) was dissolved in 100 mL of acetic acid, followed by addition of 50 mL of water. The reaction solution was warmed up to 70°C, and stirred for 1 hour. Then, the reaction solution was concentrated under reduced pressure to remove acetic acid, added with 100 mL of water and 100 mL of ethyl acetate, and left to stand and separate. The organic phase was washed with saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel chromatography to obtain a crystal of compound I (1.1 g, 55.0%). The crystal sample was identified not crystal form I after studying and comparing the X-ray diffraction and DSC spectra, then it was defined as crystal form III herein.

Example 12

[0030] The compound of formula (I) (1.0 g, 2.09 mmol) (prepared according to Example 1) was added to a 25 ml one-necked flask, followed by addition of 5.0 ml of methanol. The mixture was heated to reflux until the solution was clear. The solution was continuously refluxed for 10 minutes, then cooled to precipitate a crystal under stirring. The mixture was filtered and dried to obtain a solid (516 mg, yield: 51.6%). This crystal has characteristic peaks at about 4.63 (19.06), 7.37 (11.99), 9.25 (9.55), 10.91 (8.11), 11.48 (7.70), 12.40 (7.13), 13.05 (6.78), 13.73 (6.45), 15.03 (5.89), 16.04 (5.52), 16.96 (5.22), 17.87 (4.96), 19.03 (4.66), 19.45 (4.56), 20.59 (4.31), 21.87 (4.06), 22.50 (3.95), 23.11 (3.85), 23.53 (3.78), 23.96 (3.71), 25.43 (3.50), 27.00 (3.30), 27.60 (3.23), and 29.77 (3.00). The DSC spectrum is shown in Figure 2, having a sharp melting endothermic peak at 119°C. The crystal form was defined as crystal form II.

Example 13

[0031] The compound of formula (I) (0.5 g, 1.04 mmol) (prepared according to Example 1) and the compound of formula (I) (0.5 g, 1.04 mmol) (prepared according to Example 11) were added to a 25 ml one-necked flask, followed by addition of 4.0 ml of ethyl acetate-isopropyl ether (v:v = 1:1). The mixture was pulped at room temperature, then filtered and dried to obtain a solid (872 mg, yield: 87.2%). The product was identified as crystal form I after studying and comparing the X-ray diffraction and DSC spectra. It can be seen that crystal form III can be transformed into crystal form I at room temperature, confirming that crystal form I is more stable.

Example 14

[0032] The compound of formula (I) (0.5 g, 1.04 mmol) (prepared according to Example 1) and the compound of formula (I) (0.5 g, 1.04 mmol) (prepared according to Example 12) were added to a 25 ml one-necked flask, followed by addition of 4.0 ml of ethyl acetate-isopropyl ether (v:v = 1:1). The mixture was pulped at room temperature, then filtered and dried to obtain a solid (850 mg, yield: 85.0%). The product was identified as crystal form I after studying and comparing the X-ray diffraction and DSC spectra. It can be seen that crystal form II can be transformed into crystal form I at room temperature, confirming that crystal form I is more stable.

Example 15

[0033] The sample of crystal form I prepared in Example 1 was spread flat in the air to test its stability under conditions of lighting (4500 Lux), heating (40°C, 60°C), and high humidity (RH 75%, RH 90%). Samplings were carried out on Day 5 and Day 10. The purity as detected by HPLC is shown in Table 1.

Table 1. Stability comparison of the sample of crystal form I of the compound of formula (I)

Batch number	Time (day)	Lighting	40°C	60°C	RH 75%	RH 90%
Crystal form I	0	99.93%	99.93%	99.93%	99.93%	99.93%
	5	99.91%	99.91%	99.92%	99.89%	99.92%
	10	99.91%	99.91%	99.90%	99.91%	99.92%

[0034] The results of the stability study showed that the sample of crystal form I of the compound of formula (I) had good stability when it was spread flat in the air under conditions of lighting, high temperature and high humidity.

Example 16

[0035] Crystal form I of the compound of formula (I) prepared according to the method of Example 1 was ground, heated and pressed. The results showed that the crystal form is stable. The detailed experimental data are shown in Table 2 below.

Table 2. Special stability study of crystal form I of the compound of formula (I)

Batch number	Treatment Process	Experimental procedure	Crystal form	DSC peak
S011204130515G	Grinding treatment for 10 minutes	1 g of the sample of crystal form I of the compound of formula (I) was ground for 10 minutes in a mortar under nitrogen atmosphere.	Crystal form I	158.26°C
S011204130515H	Heating treatment	1 g of the sample of crystal form I of the compound of	Crystal form I	158.17°C

Batch number	Treatment Process	Experimental procedure	Crystal form	DSC peak
	for 3 hours at 80°C	formula (I) was spread flat and heated at 80°C for 3 hours.		
S011204130515P	Pressing treatment	The sample of crystal form I of the compound of formula (I) was pressed to a slice.	Crystal form I	158.33°C

Example 17

[0036] The sample of crystal form I of the compound of formula (I) prepared according to Example 1 was spread flat in the air to test its stability during long-term storage at room temperature (25°C, RH 60%). The detailed experimental data are shown in Table 3 below.

Table 3. Stability test of the sample of crystal form I of the compound of formula (I) under reserving condition at room temperature

Batch number	Time (month)	Crystal form	Purity (%)
S011204130515	0	Crystal form I	99.93
	6	Crystal form I	99.93
	12	ND	99.93
	24	ND	99.93
	36	Crystal form I	99.94

[0037] The sample was placed under conditions of 25°C, RH 60% for a long period of time, and regular sampling was carried out to determine the purity. The results showed that the crystal form of the sample is stable, and there is no significant change in purity, indicating that the sample is stable after placing for 36 months under such conditions.

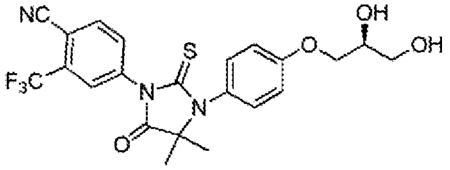
REFERENCES CITED IN THE DESCRIPTION

Patent documents cited in the description

- WO2014036897A1 **[0004] [0005] [0019] [0029]**

Patentkrav

1. Krystalform I af en forbindelse fra formlen (I), **kendetegnet ved, at** krystallen har et pulver-røntgendiffraktionsspektrum, der opnås ved at bruge Cu-Ka-stråling og er repræsenteret af en 2θ vinkel og interplanær afstand, som vist i Figur 1, hvori der er karakteristiske spidsværdier ved omkring 8,89 (9,94), 9,97 (8,87), 11,22 (7,88), 14,28 (6,20), 15,17 (5,83), 15,51 (5,71), 16,77 (5,28), 19,91 (4,46), 21,13 (4,20), 22,48 (3,95), 24,06 (3,70) og 26,37 (3,38),



(I)

2. En fremgangsmåde til fremstilling af krystalformen I af forbindelsen i formel (I) i henhold til krav 1, som omfatter følgende trin til:

1) tilføjelse af enhver krystalform eller amorf form af en forbindelse i formlen (I) i en passende mængde organisk opløsningsmiddel, opvarmning af opløsningen, indtil den er klar, og derefter afkøling for at udfælde en krystal, hvori det organiske opløsningsmiddel er valgt ud fra enhver af estere, ketoner, nitriler og ætere, som har 5 eller færre kulfiberatomer, eller et blandet opløsningsmiddel derudfra;
2) filtrering af krystallen og derefter vask og tørring af den.

3. Fremgangsmåden i henhold til krav 2, **kendetegnet ved, at** opløsningsmidlet i trin 1) er et enkelt opløsningsmiddel, der er valgt fra ethylacetat, acetone, isopropylacetat, tetrahydrofuran og acetonitril, og et blandet opløsningsmiddel, der er valgt fra acetone/isopropylæter, ethylacetat/n-hexan, ethyl/isopropylæter og ethylacetat/methyl *tert*-butyl æter, fortrinsvis ethylacetat/isopropylæter.

4. Fremgangsmåden i henhold til krav 3, hvori volumenforholdet for det blandede opløsningsmiddel er mellem 1:10 og 10:1, fortrinsvis 1:1.

5. En farmakologisk sammensætning, der omfatter fremstilling af krystalformen I af forbindelsen i formel (I) i henhold til krav 1, og en farmakologisk acceptabel bærer.

6. Krystalformen I af forbindelsen i formel (I) i henhold til krav 1 eller den farmakologisk sammensætning i henhold til krav 5 til brug ved behandling af prostatakræft.

DRAWINGS

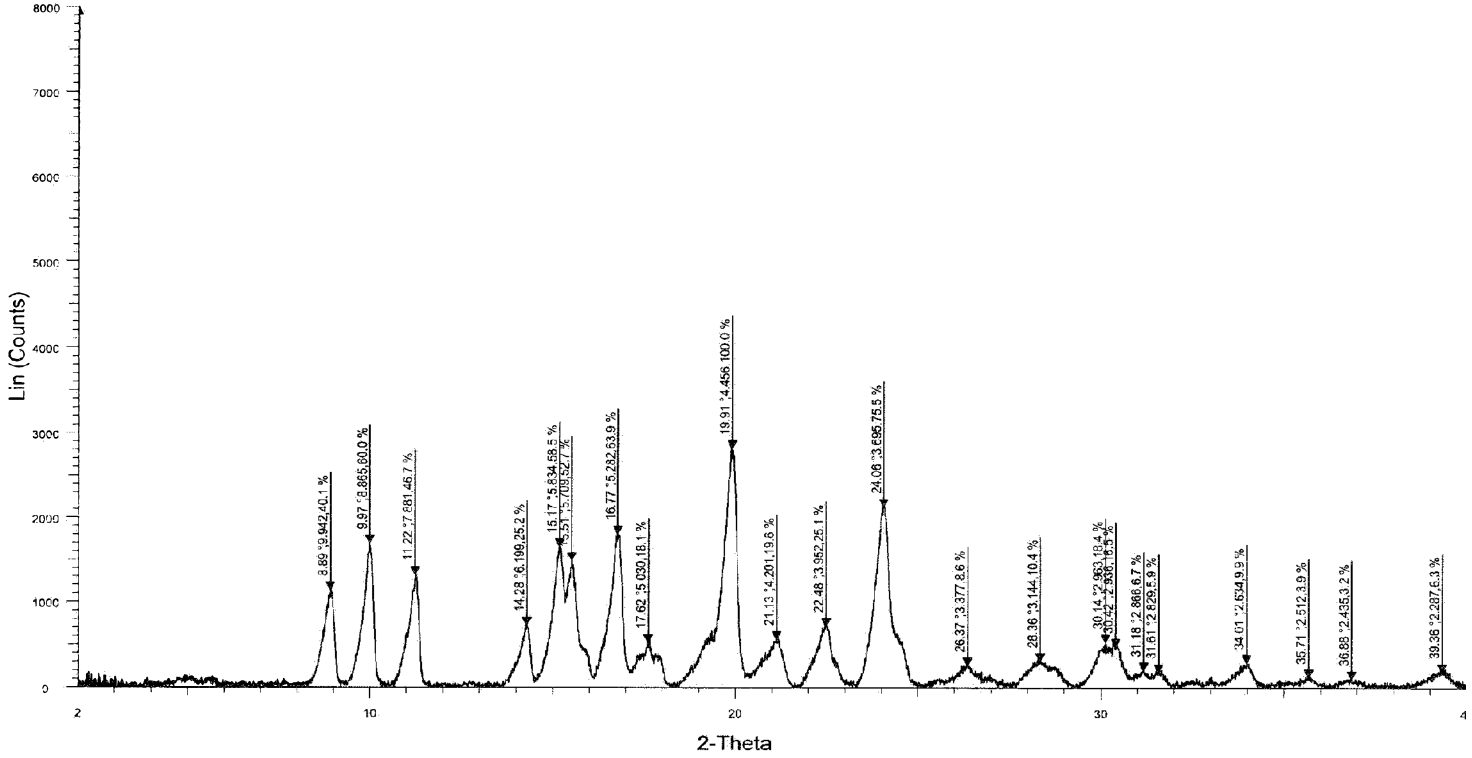
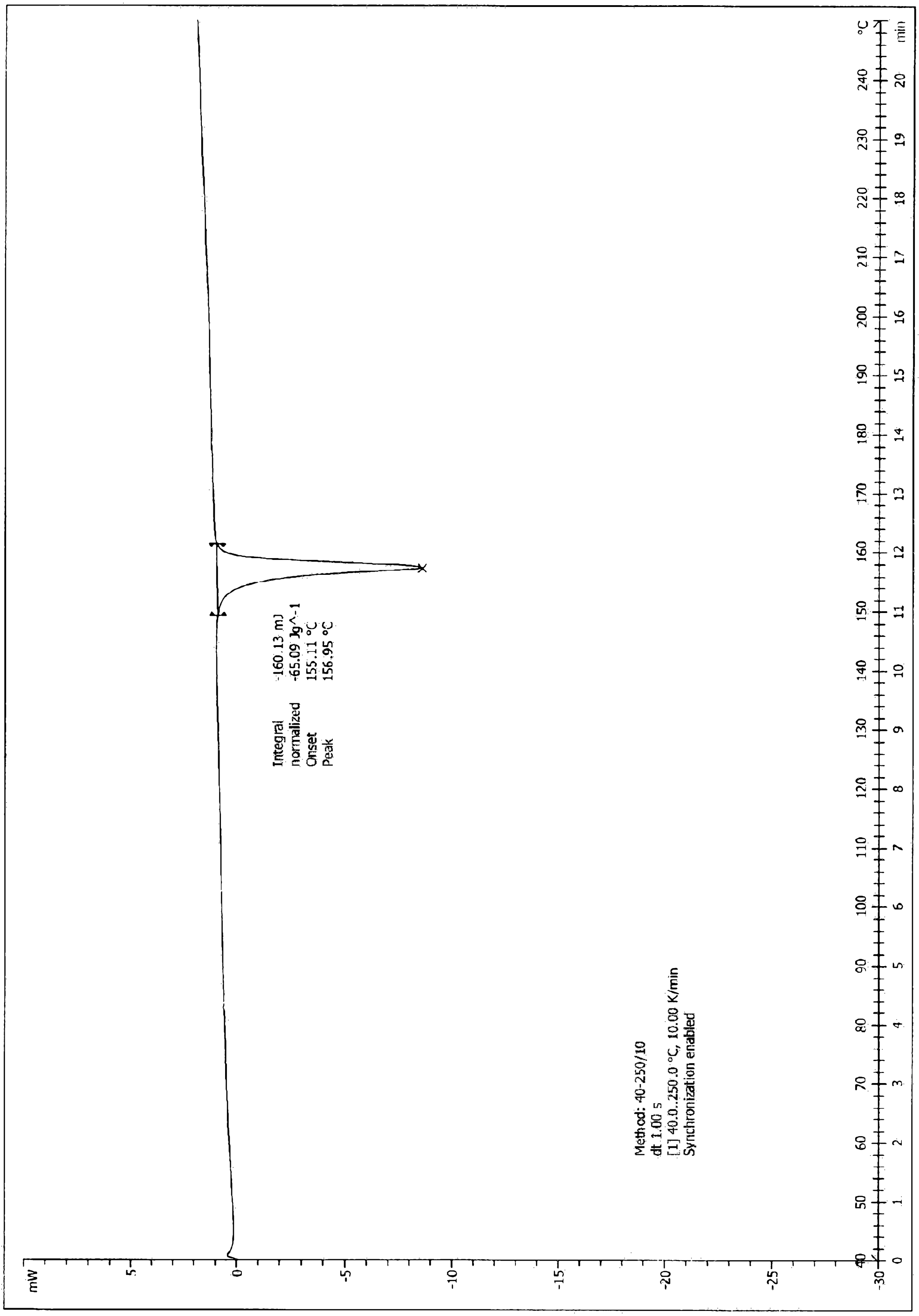


Figure 1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min
Integral -160.13 mJ
normalized -65.09 Jg^-1
Onset 155.11 °C
Peak 156.95 °C
Method: 40-250/10
dt 1.00 s
[1] 40.0..250.0 °C, 10.00 K/min
Synchronization enabled

Figure 2

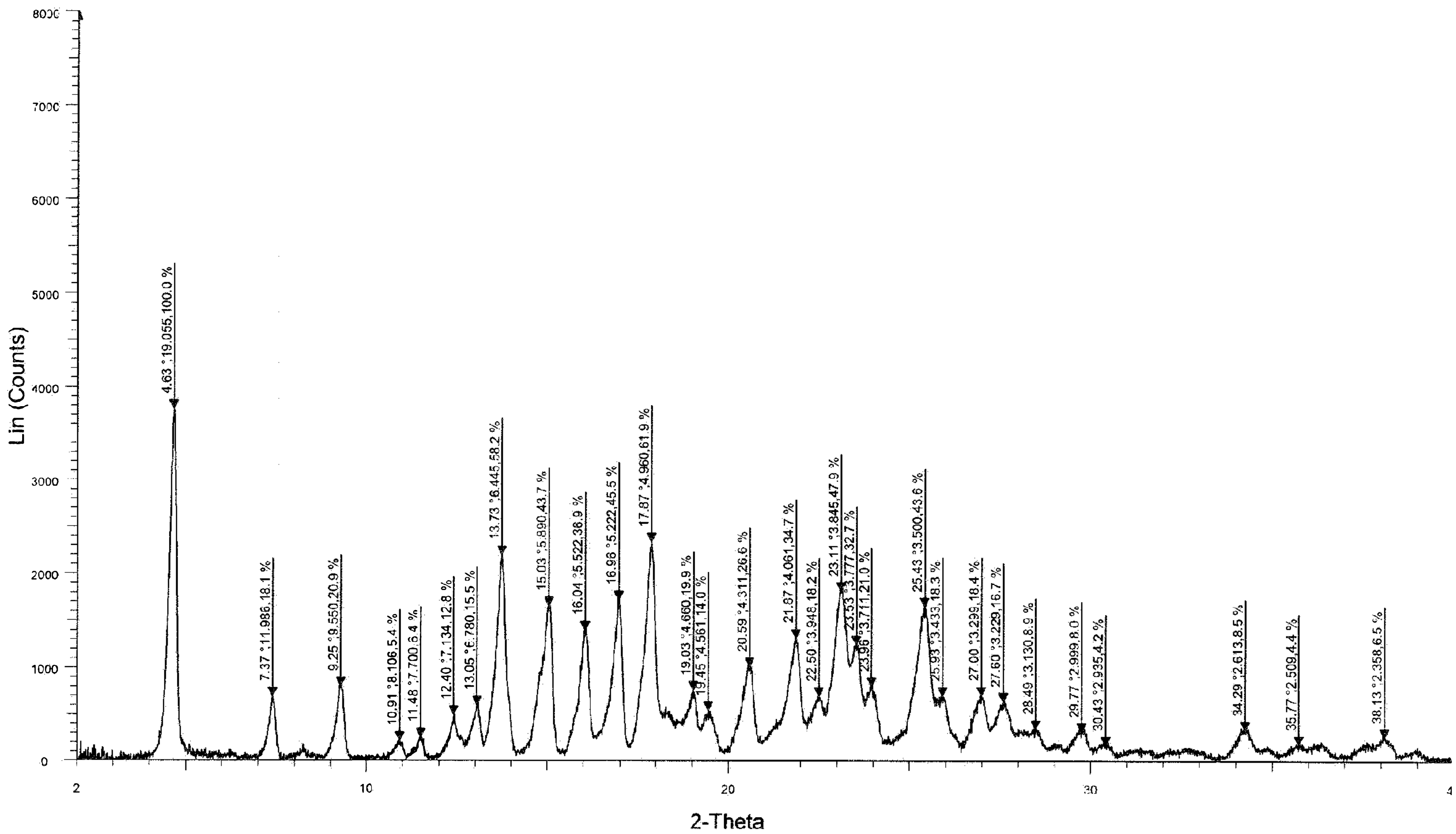
Lin (Counts)
8000
7000
6000
5000
4000
3000
2000
1000
0
2
10
20
30
4
2-Theta
4.63 °19.055,100.0 %
7.37 °11.986,18.1 %
9.25 °9.550,20.9 %
10.91 °8.106,5.4 %
11.48 °7.700,6.4 %
12.40 °7.134,12.8 %
13.05 °6.780,15.5 %
13.73 °6.445,58.2 %
15.03 °5.890,43.7 %
16.04 °5.522,36.9 %
16.98 °5.222,45.5 %
17.87 °4.960,61.9 %
19.03 °4.660,19.9 %
19.45 °4.561,14.0 %
20.59 °4.311,26.6 %
21.87 °4.061,34.7 %
22.50 °3.948,18.2 %
23.11 °3.845,47.9 %
23.53 °3.777,32.7 %
23.96 °3.711,21.0 %
25.43 °3.500,43.6 %
25.93 °3.433,18.3 %
27.00 °3.299,18.4 %
27.60 °3.229,16.7 %
28.49 °3.130,8.9 %
29.77 °2.999,8.0 %
30.43 °2.935,4.2 %
34.29 °2.613,8.5 %
35.77 °2.509,4.4 %
38.13 °2.358,6.5 %

Figure 3

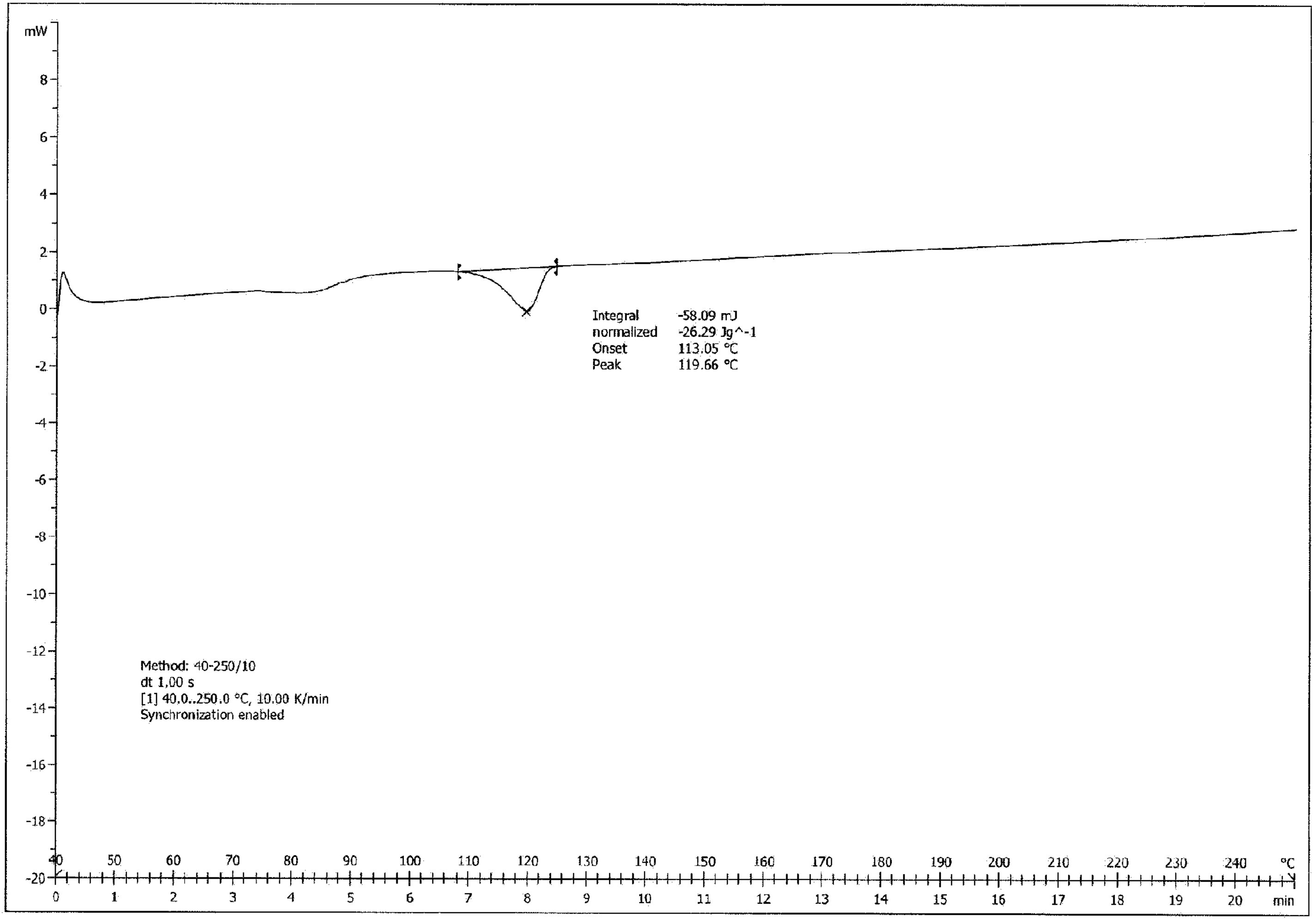
mW
8
6
4
2
0
-2
-4
-6
-8
-10
-12
-14
-16
-18
-20
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
240
°C
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
min
Integral -58.09 mJ
normalized -26.29 Jg^-1
Onset 113.05 °C
Peak 119.66 °C
Method: 40-250/10
dt 1.00 s
[1] 40.0..250.0 °C, 10.00 K/min
Synchronization enabled

Figure 4

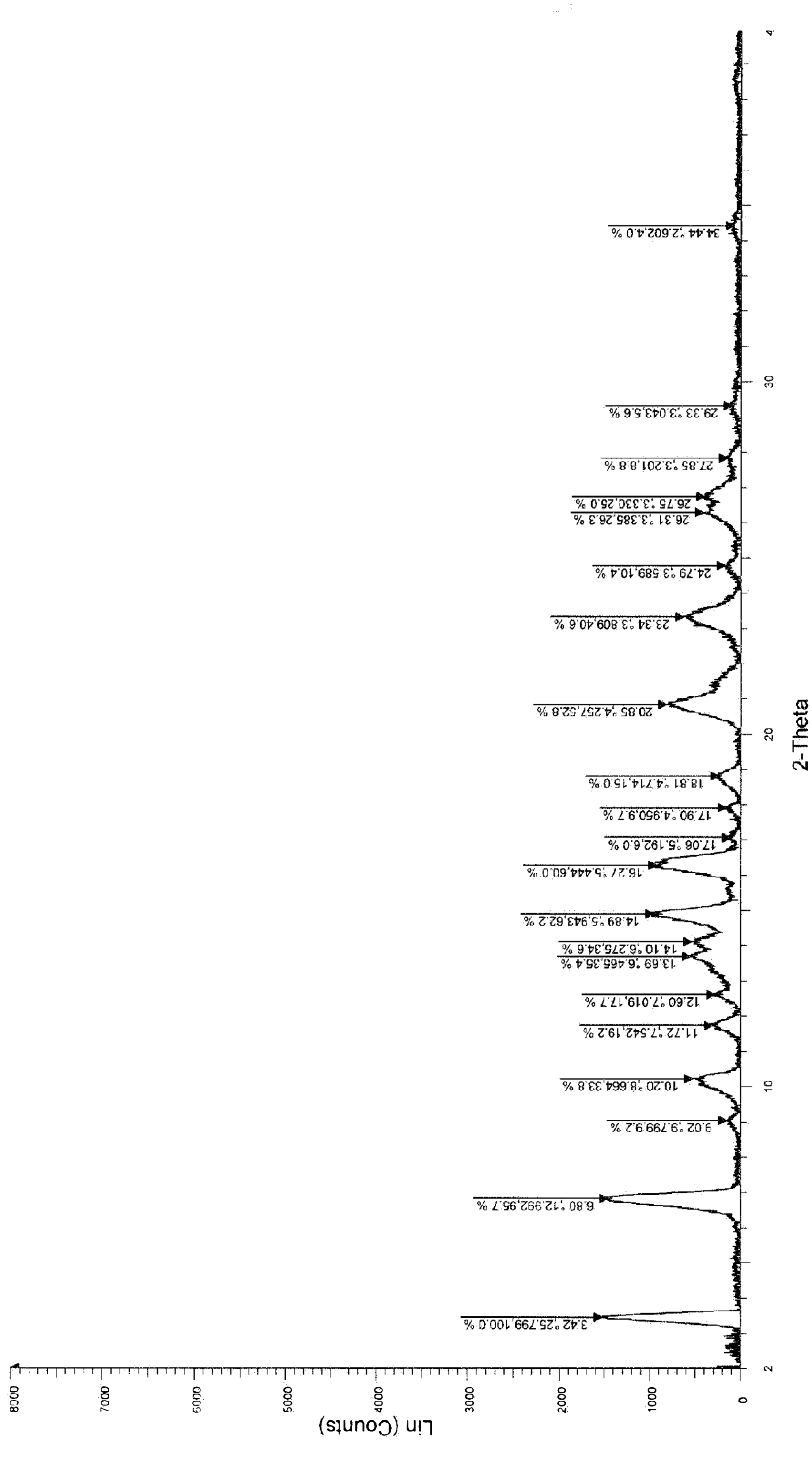
Lin (Counts)
0
1000
2000
3000
4000
5000
6000
7000
8000
2
10
20
30
4
2-Theta
3.42 °25.799,100.0 %
6.80 °12.992,95.7 %
9.02 °9.799,9.2 %
10.20 °8.664,33.8 %
11.72 °7.542,19.2 %
12.60 °7.019,17.7 %
13.69 °6.465,35.4 %
14.10 °6.275,34.6 %
14.89 °5.943,62.2 %
16.27 °5.444,60.0 %
17.06 °5.192,6.0 %
17.90 °4.950,9.7 %
18.81 °4.714,15.0 %
20.85 °4.257,52.8 %
23.34 °3.809,40.6 %
24.79 °3.589,10.4 %
26.31 °3.385,26.3 %
26.75 °3.330,25.0 %
27.85 °3.201,8.8 %
29.33 °3.043,5.6 %
34.44 °2.602,4.0 %

Figure 5

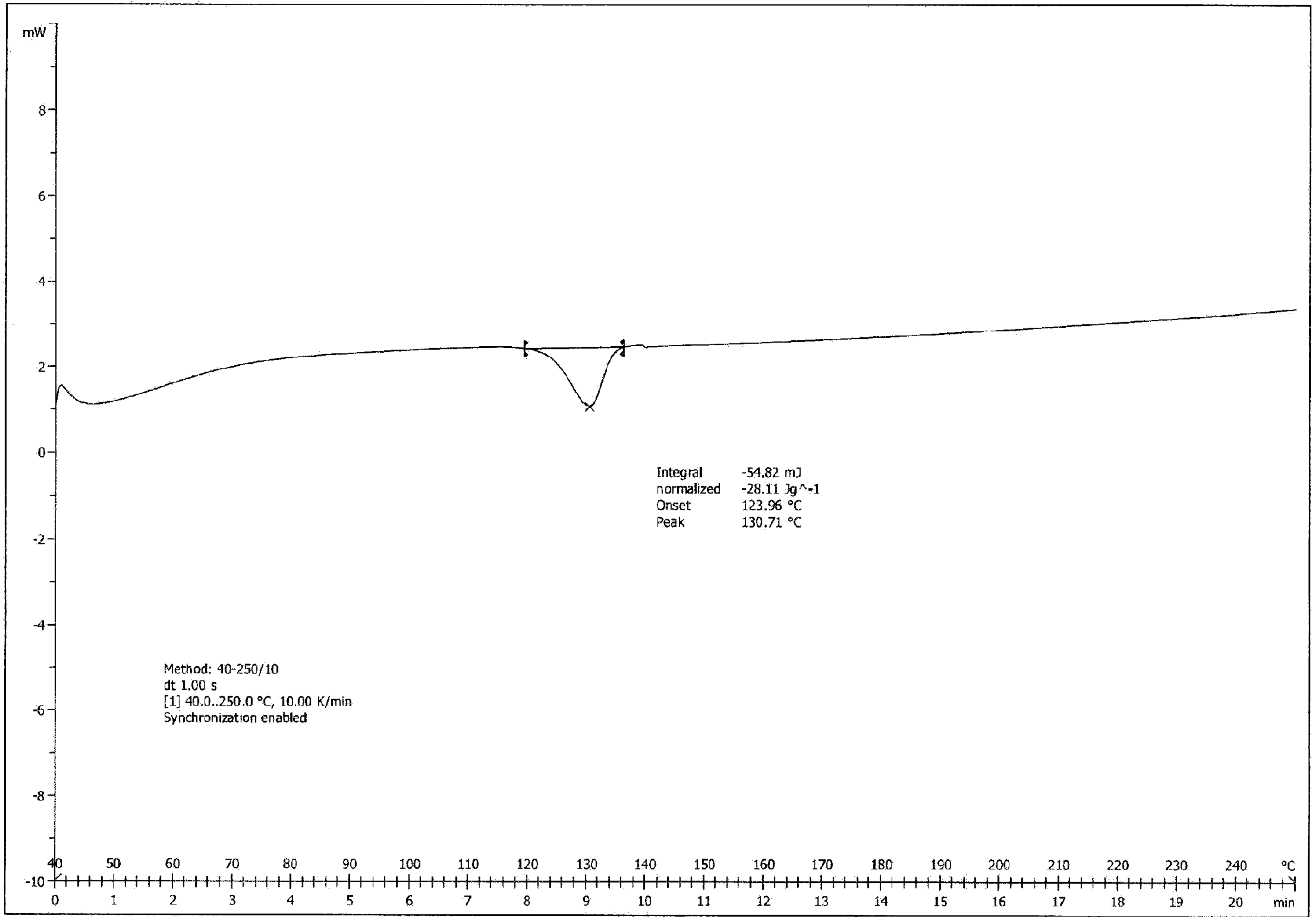
mW
8
6
4
2
0
-2
-4
-6
-8
-10
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
240
°C
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
min
Integral -54.82 mJ
normalized -28.11 Jg^-1
Onset 123.96 °C
Peak 130.71 °C
Method: 40-250/10
dt 1.00 s
[1] 40.0..250.0 °C, 10.00 K/min
Synchronization enabled

Figure 6