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(71) Applicant: **ZENTIVA, K.S.** [CZ/CZ]; U Kabelovny 130, 102 37 Praha 10 (CZ).

(72) Inventors: **ZVATORA, Pavel**; Rude Armady 300, 798 03 Plumlov (CZ). **DAMMER, Ondrej**; Novotneho 975, 253 01 Hostivice (CZ). **KREJCIK, Lukas**; Moravanska 474, 190 17 Praha-Vinor (CZ). **TKADLECOVA, Marcela**; Galandova 1239, 163 00 Praha 6 (CZ). **HERT, Jakub**; Slejnicka 1, 160 00 Praha 6 (CZ).

(74) Agents: **JIROTKOVA, Ivana** et al.; Rott, Ruzicka & Guttmann, Vinohradska 37, 120 00 Praha 2 (CZ).

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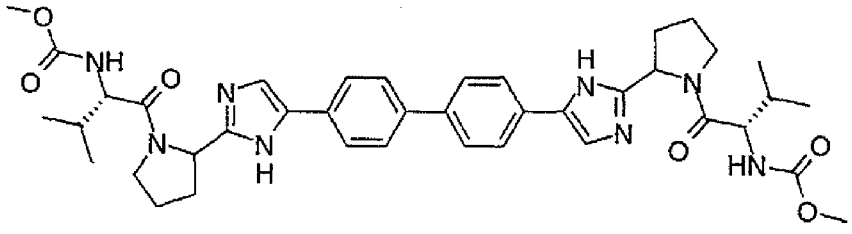
(54) Title: SOLID FORMS OF DACLATASVIR



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(57) Abstract: Salts of methyl [(1*S*)-2-{(2-*S*)-4-[4-(2'-{2-[(1*S*)-2-{(2*S*)-3-[(methoxycarbonyl)amino]-2- methylbutanoyl } -4-pyrrolidinyl]-1H-imidazol-4-yl } -2-biphenylyl)-1H-imidazol-1-yl] -3 - pyrrolidinyl}-1-methyl-2-oxo-2- butanyl]carbamate-daclatasvir of formula (I) in the solid state with an acid from the group consisting of hydrochloric, hydrobromic, sulphuric, 2-naphthalenesulfonic, toluenesulfonic, methanesulfonic, benzenesulfonic, maleic and fumaric acid. Preparation of the salts of daclatasvir with acids.

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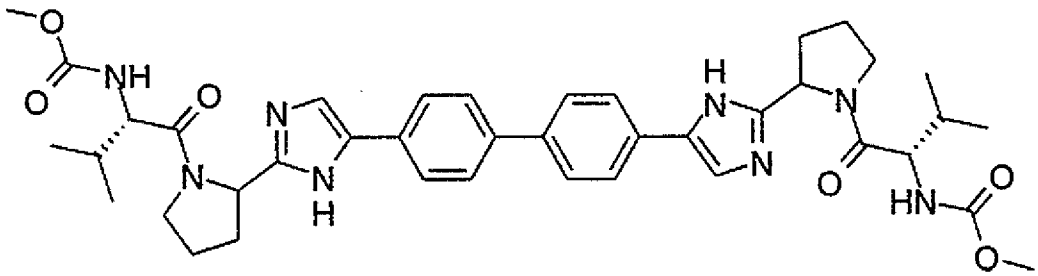
Solid forms of Daclatasvir

Technical Field

The invention relates to new solid forms of Methyl [(2*S*)-1-{(2*S*)-2-[4-(4'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-pyrrolidinyl]-1H-imidazol-4-yl}-4-biphenylyl)-1H-imidazol-2-yl]-1-pyrrolidinyl}-3-methyl-1-oxo-2-butanyl]carbamate of formula I,



(I)

known as daclatasvir, and methods of their preparation.

Background Art

Methyl [(2*S*)-1-{(2*S*)-2-[4-(4'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3--methylbutanoyl}-2-pyrrolidinyl]-1H-imidazol-4-yl}-4-biphenylyl)-1H-imidazol-2-yl]-1--pyrrolidinyl}-3-methyl-1-oxo-2-butanyl]carbamate, which is known as daclatasvir (CAS no. 1009119-64-5) belongs to the group of antiviral agents suitable for the treatment of hepatitis C. Daclatasvir dihydrochloride has been approved under the trade name Daklinza by the organization *European Medicines Agency* (EMA) for hepatitides of C type.

Preparation of this molecule and its isolation in a crystalline form as daclatasvir dihydrochloride was described in the patent applications WO 2008/021927 and WO 2009/020828.

Disclosure of Invention

The invention provides new solid forms of daclatasvir in the form of pharmaceutically acceptable salts with inorganic and organic acids and methods of their preparation. These salts are prepared by reaction of daclatasvir in the basic form (formula I) with selected acids in a suitable solvent or mixtures of solvents.

The prepared new solid forms have suitable physical-chemical characteristics for use in the pharmaceutical industry and formulation of new dosage forms.

Brief Description of Drawings

Figure 1. X-Ray powder pattern of the prepared daclatasvir free base (according to Example 1)

Figure 2. DSC record of the prepared daclatasvir free base (according to Example 1)

Figure 3. X-Ray powder pattern of the amorphous form of daclatasvir dihydrochloride (according to Example 2)

Figure 4. DSC record of the amorphous form of daclatasvir dihydrochloride (according to Example 2)

Figure 5. X-Ray powder pattern of the amorphous form of daclatasvir dihydrochloride (according to Example 3)

Figure 6. DSC record of the amorphous form of daclatasvir dihydrochloride (according to Example 3)

Figure 7. X-Ray powder pattern of daclatasvir dihydrobromide (according to Example 4)

Figure 8. DSC record of daclatasvir dihydrobromide (according to Example 4)

Figure 9. X-Ray powder pattern of daclatasvir disulfate (according to Example 5)

Figure 10. DSC record of daclatasvir disulfate (according to Example 5)

Figure 11. X-Ray powder pattern of daclatasvir naphthalene sulfonate (according to Example 6)

Figure 12. DSC record of daclatasvir naphthalene sulfonate (according to Example 6)

Figure 13. ^{1}H NMR spectrum of daclatasvir naphthalene sulfonate (according to Example 6)

Figure 14. X-Ray powder pattern of daclatasvir tosylate (according to Example 7)

Figure 15. DSC record of the amorphous form of aclatasvir tosylate (according to Example 7)

Figure 16. ^{1}H NMR spectrum of daclatasvir tosylate (according to Example 7)

Figure 17. X-Ray powder pattern of daclatasvir mesylate (according to Example 8)

Figure 18. DSC record of the amorphous form of daclatasvir mesylate (according to Example 8)

Figure 19. ^{1}H NMR spectrum of daclatasvir mesylate (according to Example 8)

Figure 20. X-Ray powder pattern of daclatasvir besylate (according to Example 9)

Figure 21. DSC record of the amorphous form of daclatasvir besylate (according to Example 9)

Figure 22. ^{1}H NMR spectrum of daclatasvir besylate (according to Example 9)

Figure 23. X-Ray powder pattern of daclatasvir maleate (according to Example 10)

Figure 24. DSC record of the amorphous form of daclatasvir maleate (according to Example 10)

Figure 25. ^{1}H NMR spectrum of daclatasvir maleate (according to Example 10)

Figure 26. X-Ray powder pattern of daclatasvir maleate (according to Example 11)

Figure 27. DSC record of the amorphous form of daclatasvir maleate (according to Example 11)

Figure 28. ^{1}H NMR spectrum of daclatasvir maleate (according to Example 11)

Figure 29. X-Ray powder pattern of daclatasvir fumarate (1:1) (according to Example 12)

Figure 30. DSC record of the amorphous form of daclatasvir fumarate (1:1) (according to Example 12)

Figure 31. ^{1}H NMR spectrum of daclatasvir fumarate (1:1) (according to Example 12)

Figure 32. X-Ray powder pattern of daclatasvir fumarate (1:2) (according to Example 13)

Figure 33. DSC record of the amorphous form of daclatasvir fumarate (1:2) (according to Example 13)

Figure 34. ^{1}H NMR spectrum of daclatasvir fumarate (1:2) (according to Example 13)

Detailed description of the invention

Salts of pharmaceutically active substances generally have higher solubility and bioavailability than their corresponding basic forms.

Although preparation of a salt by a reaction of an acid and base is a well-known method, it is always a problem to obtain the desired salts in the solid phase and in a purity corresponding to the demands for their pharmaceutical use. Biological availability greatly depends on whether a crystalline or amorphous product is obtained. An amorphous product is usually more readily soluble, it cannot often be obtained in the required quality and it is also often unstable. Conversely, compared to the amorphous form, a crystalline product is often stable, its required purity is easier to achieve and it dissolves more slowly. Mixtures of the amorphous and crystalline solid phase may represent a solution to the problem.

This invention provides salts of daclatasvir in the solid phase in amorphous forms, in a crystalline form, or in a mixed amorphous and crystalline form.

The invention provides novel solid forms of daclatasvir with hydrochloric acid, hydrobromic acid, sulfuric acid, maleic acid, benzenesulfonic acid, toluenesulfonic acid,

naphthalenesulfonic acid and methanesulfonic acid in variable molar ratios. According to the invention, the molar ratios of 2:1, 1:1 and 1:2 are preferred.

The novel solid forms of daclatasvir with these acids can be prepared in adequate ratios and yields with high chemical purity in a crystalline form, amorphous form, or in a mixture of amorphous and crystalline forms.

These novel solid forms can be both anhydrous and/or non-solvated, and they can have the form of hydrates/solvates of the respective solvents.

The prepared new solid forms of daclatasvir may have various internal arrangements (polymorphism) with different physical-chemical properties depending on the conditions of their preparation. For this reason, the invention relates to individual crystals or their mixtures in any ratios.

These novel solid forms are suitable for preparation of daclatasvir with a high chemical purity.

Preparation of the novel solid forms of daclatasvir (formula (I)) is performed by reaction of the free base with hydrochloric acid, hydrobromic acid, sulfuric acid, maleic acid, benzenesulfonic acid, toluenesulfonic acid, naphthalenesulfonic acid or methanesulfonic acid. The reaction is conducted in a suitable solvent, which can be ketones, esters, ethers, amides, nitriles or organic acids, alcohols, aliphatic and aromatic hydrocarbons, chlorinated hydrocarbons, water or their mixtures. Aliphatic C_1-C_4 alcohols, esters or their mixtures are preferred. The most commonly used solvents are ethyl acetate, methanol, ethanol, water or their mixtures.

The final product is typically precipitated or crystallized at temperatures in the range of –30°C to the boiling point of the solvent.

In this invention, an amorphous form of daclatasvir dihydrochloride is preferred, which, due to its amorphous character, has higher solubility and bioavailability than the corresponding crystalline form. The prepared amorphous forms of daclatasvir dihydrochloride show a high glass transition temperature, which makes them sufficiently stable for use in dosage forms. It has been found out that during storage of amorphous daclatasvir dihydrochloride at the temperature of 80°C and relative air humidity of 75% for at least three days no changes of its amorphous purity or changes of the amorphous character of the sample occur.

Out of the prepared crystalline forms, daclatasvir maleate and daclatasvir fumarate are preferred. These crystalline forms of daclatasvir can be prepared and isolated with high chemical purity.

The prepared novel solid forms of daclatasvir can be used as an alternative of the crystalline form of daclatasvir dihydrochloride for the composition of a new medicinal product.

Crystalline daclatasvir dihydrochloride was prepared according to the procedure disclosed in a patent (WO 2009/020828). The free base of daclatasvir was prepared by neutralization of daclatasvir dihydrochloride with the use of a solution of sodium hydroxide according to the procedure described in Example 1.

The X-ray powder pattern of the free base of daclatasvir (prepared according to Example 1) is shown in Fig. 1.

The DSC record of the free base of daclatasvir (prepared according to Example 1) is shown in Fig. 2. According to this example the glass transition temperature of the free base of daclatasvir is 121°C.

The X-ray powder pattern of the amorphous form of daclatasvir dihydrochloride (prepared according to Example 2) is shown in Fig. 3.

The DSC record of daclatasvir dihydrochloride (prepared according to Example 2) is shown in Fig. 4. According to this example the glass transition temperature of daclatasvir dihydrochloride is 191°C.

The X-ray powder pattern of the amorphous form of daclatasvir dihydrochloride (prepared according to Example 3) is shown in Fig. 5.

The DSC record of daclatasvir dihydrochloride (prepared according to Example 3) is shown in Fig. 6. According to this example the glass transition temperature of daclatasvir dihydrochloride is 187°C.

The X-ray powder pattern of the amorphous form of daclatasvir dihydrobromide (prepared according to Example 4) is shown in Fig. 7.

The DSC record of daclatasvir dihydrobromide (prepared according to Example 4) is shown in Fig. 8. According to this example the glass transition temperature of daclatasvir dihydrobromide is 183°C.

The X-ray powder pattern of the amorphous form of daclatasvir dihydrobromide (prepared according to Example 5) is shown in Fig. 9.

The DSC record of daclatasvir disulphate (prepared according to Example 5) is shown in Fig. 10. According to this example the glass transition temperature of daclatasvir disulphate is 176°C.

The crystalline form of daclatasvir naphtalene sulfonate (1:1) is characterized by the reflections presented in Table 1. Table 1 includes reflections whose relative intensity value is higher than 1 percent. The characteristic diffraction peaks of daclatasvir tosylate in accordance

with this invention are: 5.0; 6.3; 10.2; 13.7; 18.6 and 21.0 ± 0.2 ° 2-theta. The X-ray powder pattern is shown in Fig. 11.

Table 1

Pos. [°2Th.]	d [Å]	Rel. Int. [%]
5.03	17.563	90.1
5.86	15.072	67.7
6.25	14.125	64.2
8.23	10.732	15.1
9.06	9.748	11.3
10.18	8.686	28.4
10.49	8.429	26.8
12.64	6.998	10.6
13.30	6.652	40.7
13.66	6.477	52.7
14.05	6.300	27.3
14.61	6.058	38.0
14.99	5.904	33.6
15.40	5.748	21.9
18.58	4.771	35.3
19.31	4.594	28.2
19.86	4.468	22.4
20.99	4.229	100.0
21.92	4.052	17.0
22.67	3.918	18.6
23.18	3.835	10.4
23.87	3.725	11.7
25.63	3.473	17.2
26.77	3.328	13.1
27.94	3.191	10.8

In this case, the melting point of daclatasvir naphthalene sulfonate (1:1) (Figure 12) is 97°C and 223°C (DSC).

Figure 13 shows an example of ^{1}H NMR spectrum of the prepared daclatasvir naphtalene sulfonate (prepared according to Example 6).

The crystalline form of daclatasvir tosylate (1:1) is characterized by the reflections presented in Table 2. Table 2 includes reflections whose relative intensity value is higher than 1 percent. The characteristic diffraction peaks of daclatasvir tosylate in accordance with this invention are: 5.0; 6.3; 10.2; 13.7; 18.6 and 21.0 ± 0.2 ° 2-theta. The X-ray powder pattern is shown in Fig. 14.

Table 2

Pos. [°2Th.]	d [Å]	Rel. Int. [%]
5.03	17.563	90.1
5.86	15.072	67.7
6.25	14.125	64.2
8.23	10.732	15.1
9.06	9.748	11.3
10.18	8.686	28.4
10.49	8.429	26.8
12.64	6.998	10.6
13.30	6.652	40.7
13.66	6.477	52.7
14.05	6.300	27.3
14.61	6.058	38.0
14.99	5.904	33.6
15.40	5.748	21.9
18.58	4.771	35.3
19.31	4.594	28.2
19.86	4.468	22.4
20.99	4.229	100.0
21.92	4.052	17.0
22.67	3.918	18.6
23.18	3.835	10.4
23.87	3.725	11.7

25.63	3.473	17.2
26.77	3.328	13.1
27.94	3.191	10.8

In this case, the melting point of daclatasvir tosylate (1:1) (Figure 15) is 122°C and 234°C (DSC).

Figure 16 shows an example of the ^{1}H NMR spectrum of the prepared daclatasvir tosylate (prepared according to Example 7).

The X-ray powder pattern of daclatasvir mesylate (prepared according to Example 8) is shown in Fig. 17.

The DSC record of daclatasvir mesylate (prepared according to Example 8) is shown in Fig. 18. According to this example, the glass transition temperature of daclatasvir mesylate is 103°C.

Figure 19 shows an example of ^{1}H NMR spectrum of the prepared daclatasvir mesylate (prepared according to Example 8).

The X-ray powder pattern of daclatasvir besylate (prepared according to Example 9) is shown in Fig. 20.

The DSC record of daclatasvir besylate (prepared according to Example 9) is shown in Fig. 21. According to this example the glass transition temperature of daclatasvir besylate is 108°C.

Figure 22 shows an example of the ^{1}H NMR spectrum of the prepared daclatasvir besylate (prepared according to Example 9).

The crystalline form of daclatasvir maleate (1:1) is characterized by the reflections presented in Table 3. Table 3 includes reflections whose relative intensity value is higher than 1 percent. The characteristic diffraction peaks of daclatasvir maleate in accordance with this invention are: 9.1; 15.8; 17.9; 21.5; 24.7 and 26.3 ± 0.2 ° 2-theta. The X-ray powder pattern is shown in Fig. 23.

Table 3

Pos. [°2Th.]	d [Å]	Rel. Int. [%]
4.21	20.985	5.2
8.37	10.553	31.8
9.13	9.679	100.0
12.92	6.848	15.4

13.49	6.558	9.1
14.25	6.211	26.0
15.81	5.601	43.3
16.91	5.241	13.7
17.94	4.941	34.5
18.71	4.739	23.7
19.29	4.599	7.5
20.10	4.414	8.8
20.99	4.230	6.2
21.53	4.124	34.6
23.12	3.844	18.2
24.65	3.608	25.6
26.32	3.383	12.4
28.08	3.175	5.1
29.50	3.025	2.2
30.64	2.915	1.9
32.22	2.776	2.3
33.39	2.681	2.0

In this case, the melting point of daclatasvir maleate (1:1) (Figure 24) is 165°C (DSC).

Figure 25 shows an example of ^{1}H NMR spectrum of the prepared daclatasvir maleate (prepared according to Example 10).

The crystalline form of daclatasvir maleate (1:2) is characterized by the reflections presented in Table 4. Table 4 includes reflections whose relative intensity value is higher than 1 percent. The characteristic diffraction peaks of daclatasvir maleate in accordance with this invention are: 9.0; 15.6; 17.8; 21.4; 23.0 and 24.5 ± 0.2 ° 2-theta. The X-ray powder pattern is shown in Fig. 26.

Table 4

Pos. [°2Th.]	d [Å]	Rel. Int. [%]
4.11	21.469	18.0
8.31	10.629	35.3
9.02	9.795	100.0
12.61	7.013	19.5
13.20	6.700	11.5
13.98	6.331	25.2
15.57	5.687	56.4
16.74	5.293	20.8
17.77	4.987	40.0
18.62	4.761	26.3
19.94	4.450	9.7
21.38	4.153	41.1
22.20	3.999	7.9
22.54	3.941	12.3
22.97	3.869	34.8
24.55	3.623	32.7
26.30	3.388	16.4
28.05	3.179	7.2
29.59	3.016	2.8
30.47	2.932	2.1

In this case, the melting point of daclatasvir maleate (1:2) (Figure 27) is 166°C (DSC).

Figure 28 shows an example of ^{1}H NMR spectrum of the prepared daclatasvir maleate (prepared according to Example 11).

The crystalline form of daclatasvir fumarate (1:1) is characterized by the reflections presented in Table 5. Table 5 includes reflections whose relative intensity value is higher than 1 percent. The characteristic diffraction peaks of daclatasvir fumarate in accordance with this invention are: 8.1; 11.7; 15.1; 20.3; 22.7 and 24.4 ± 0.2 ° 2-theta. The X-ray powder pattern is shown in Fig. 29.

Table 5

Pos. [°2Th.]	d [Å]	Rel. Int. [%]
7.44	11.874	15.4
8.15	10.845	100.0
9.99	8.845	9.3
11.13	7.944	42.2
11.71	7.552	69.2
12.95	6.832	18.1
14.63	6.049	11.8
15.12	5.854	44.0
15.37	5.760	35.6
16.88	5.249	22.2
18.42	4.813	9.8
18.73	4.733	10.7
19.93	4.451	64.1
20.29	4.374	77.8
21.33	4.163	11.7
21.88	4.059	7.3
22.65	3.922	26.5
23.91	3.719	14.7
24.41	3.644	24.3
25.24	3.526	9.0
26.32	3.383	19.2
27.07	3.291	18.9
28,34	3.146	4.6
29.61	3.014	7.6

In this case, the melting point of daclatasvir fumarate (1:1) (Figure 30) is 112°C and 179°C (DSC).

Figure 31 shows an example of ^{1}H NMR spectrum of the prepared daclatasvir fumarate (prepared according to Example 12).

The crystalline form of daclatasvir fumarate (1:2) is characterized by the reflections presented in Table 6. Table 6 includes reflections whose relative intensity value is higher than 1 percent.

The characteristic diffraction peaks of daclatasvir fumarate in accordance with this invention are: 6.6; 8.2; 13.0; 15.4 and 20.5 ± 0.2 ° 2-theta. The X-ray powder pattern is shown in Figure 32.

Table 6

Pos. [°2Th.]	d [Å]	Rel. Int. [%]
6.60	13.378	31.4
7.56	11.680	19.5
8.23	10.730	76.6
10.02	8.823	7.5
11.31	7.814	7.4
11.82	7.484	25.4
12.48	7.089	54.6
13.00	6.804	87.6
14.16	6.250	20.5
15.41	5.747	100.0
20.52	4.325	65.8
23.40	3.798	17.0
24.59	3.617	9.5
25.37	3.508	5.6
26.47	3.365	17.0
27.22	3.274	9.6
28.72	3.106	14.4

In this case, the melting point of daclatasvir fumarate (1:1) (Figure 33) is 154°C and 200°C (DSC).

Figure 34 shows an example of ^{1}H NMR spectrum of the prepared daclatasvir fumarate (prepared according to Example 13).

The invention is clarified in a more detailed way using the embodiment examples below. These examples, which illustrate the preparation of the novel solid forms of daclatasvir in accordance with the invention, only have an illustrative character and do not restrict the scope of the invention in any respect.

Experimental part

X-ray powder diffraction

The diffractograms were obtained using an X'PERT PRO MPD PANalytical powder diffractometer, used radiation CuKα (λ=1.542 Å), excitation voltage: 45 kV, anode current: 40 mA, measured range: 2 - 40° 2θ, increment: 0.01° 2θ at the dwell time at a reflection of 0.5 s, the measurement was carried out with a flat sample with the area/thickness of 10/0.5 mm. For the correction of the primary array 0.02 rad Soller slits, a 10mm mask and a 1/4° fixed anti-dispersion slit were used. The irradiated area of the sample is 10 mm, programmable divergence slits were used. For the correction of the secondary array 0.02 rad Soller slits and a 5.0 anti-dispersion slit were used.

Infrared spectroscopy

ATR (Ge – single reflection) infrared spectra of the powder samples were measured with an infrared spectrometer (Nicolet Nexus, Thermo, USA) equipped with a DTGS KBr detector, in the measurement range of 600-4000 cm^{-1} and the spectral resolution of 4.0 cm^{-1}. The data were obtained at 64 spectrum accumulations. The OMNIC 6.2 software was used to process the spectra.

Differential Scanning Calorimetry (DSC)

The records of the novel solid forms of daclatasvir were measured with the Discovery DSC device made by TA Instruments. The sample charge in a standard Al pot (40 μL) was between 4-5 and 5 mg and the heating rate was 5°C/min. The temperature program that was used consists of 1 min of stabilization at the temperature of 0°C and then of heating up to 220°C at the heating rate of 5°C/min (Amplitude = 0.8°C and Period = 60 s). As the carrier gas 5.0 N_2 was used at the flow of 50 ml/min.

^1H NMR

For the structural characterization ^1H NMR spectroscopy at 250 MHz by Bruker Avance 250 was used. As the solvent deuterated D6-dimethyl sulfoxide was used and the measurements were carried out at the temperature of 303 K. As the internal reference with 0.00 ppm trimethylsilane (TMS) was used.

Examples

Example 1

Preparation of the free base of daclatasvir

Crystalline daclatasvir dihydrochloride was prepared according to the procedure disclosed in a patent (WO 2009/020828). The free base of daclatasvir was prepared by suspending 500 mg of daclatasvir dihydrochloride ($n = 6.45 \cdot 10^{-4}$ mol) in 30 ml of ethyl acetate. 2.3 ml of an aqueous solution of NaOH ($n = 1.29 \cdot 10^{-3}$ mol), which was prepared by dissolving 180 mg of NaOH in 8 ml of water, was added to this suspension. The obtained solution was thoroughly shaken. The organic solvent layer was separated from the aqueous phase, washed with 8 ml of water. After another removal of the aqueous phase, 50 mg of anhydrous sodium sulfate was added to the organic solution, the solution was filtered and evaporated on a rotary vacuum evaporator. Further, it was separated by neutralization of daclatasvir dihydrochloride with a solution of sodium hydroxide with subsequent isolation of the product in an ethyl acetate solution. After evaporation of the organic solvent, free base of daclatasvir was obtained. Yield 432.3 mg (95%). HPLC purity 98%. Glass transition temperature 121°C (DSC). X-ray powder pattern in Fig. 1.

Example 2

Preparation of an amorphous form of daclatasvir dihydrochloride by precipitation

Methyl [(2*S*)-1-{(2*S*)-2-[4-(4'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methyl--butanoyl}-2-pyrrolidinyl]-1H-imidazol-4-yl}-4-biphenylyl)-1H-imidazol-2-yl]-1-pyrrolidinyl}-3-methyl-1-oxo-2-butanyl]carbamate (free base of daclatasvir) in the amount of 300 mg ($4.06 \cdot 10^{-4}$ mol) was dissolved in 10 ml of isopropyl alcohol. 242 µl ($8.53 \cdot 10^{-4}$ mol) of anhydrous hydochloric acid in isopropyl alcohol (16.3 %) was added to this solution. The mixture was stirred at the room temperature for 30 min. Then, 9 ml of tert-butyl methyl ether was added to this solution and the resulting suspension was stirred at the room temperature for 2 hours. The separated solid fraction was filtered off. The resulting product was left to dry in a vacuum drier at the temperature of 40°C and the pressure of 20 kPa for 12 hours. Yield

277 mg (85%). HPLC purity 98.3%. X-ray powder pattern in Fig. 3. Glass transition temperature according to DSC 191°C.

Example 3

Preparation of an amorphous form of daclatasvir dihydrochloride by solvent evaporation

Crystalline daclatasvir dihydrochloride prepared according to Example 1 in the amount of 300 mg was dissolved in 1.5 ml of methanol at 40°C. The resulting solution was filtered and evaporated in a vacuum evaporator at the temperature of 45°C and pressure of 2 kPa. The resulting product was left to dry in a vacuum drier at the temperature of 40 °C and the pressure of 20 kPa for 12 hours. HPLC purity 98.0%. X-ray powder pattern in Fig. 5. Glass transition temperature according to DSC 187C.

Example 4

Preparation of daclatasvir dihydrobromide

Methyl [(2*S*)-1-{(2*S*)-2-[4-(4'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methyl--butanoyl}-2-pyrrolidinyl]-1H-imidazol-4-yl}-4-biphenylyl)-1H-imidazol-2-yl]-1-pyrrolidinyl}-3-methyl-1-oxo-2-butanyl]carbamate (free base of daclatasvir) in the amount of 103.3 mg ($1.40 \cdot 10^{-4}$ mol) was dissolved in 4 ml of ethyl acetate. 30.6 µl ($2.71 \cdot 10^{-4}$ mol) of hydrobromic acid (48 %) was added to this solution. The mixture was stirred at the room temperature for 2 hours. Then, the solution was left to freely evaporate at the room temperature. HPLC purity 95.4 %. X-ray powder pattern in Fig. 7Figure 6. Glass transition temperature according to DSC 183°C.

Example 5

Preparation of daclatasvir disulphate

Methyl [(2*S*)-1-{(2*S*)-2-[4-(4'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methyl--butanoyl}-2-pyrrolidinyl]-1H-imidazol-4-yl}-4-biphenylyl)-1H-imidazol-2-yl]-1-pyrrolidinyl}-3-methyl-1-oxo-2-butanyl]carbamate (free base of daclatasvir) in the amount of 102.6 mg ($1{,}39 \cdot 10^{-4}$ mol) was dissolved in 4 ml of ethyl acetate. 15.0 µl ($2{,}54 \cdot 10^{-4}$ mol) of sulphuric acid (96 %) was added to this solution. The mixture was stirred at the room temperature for 2 hours. Then, the solution was left to freely evaporate at the room temperature. HPLC purity 97.6%. X-ray powder pattern in Fig. 9. Glass transition temperature according to DSC 176°C.

Example 6

Preparation of daclatasvir naphthalene sulfonate

Methyl [(2*S*)-1-{(2*S*)-2-[4-(4'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methyl--butanoyl}-2-pyrrolidinyl]-1H-imidazol-4-yl}-4-biphenylyl)-1H-imidazol-2-yl]-1-pyrrolidinyl}-3-methyl-1-oxo-2-butanyl]carbamate (free base of daclatasvir) in the amount of 98.39 mg ($1.33 \cdot 10^{-4}$ mol) was dissolved in 4 ml of ethyl acetate. 39.91 mg ($1.42 \cdot 10^{-4}$ mol) of 2-naphthalenesulfonic acid (70 %) was added to this solution. The mixture was stirred at the room temperature for 2 hours. Then, the solution was left to freely evaporate at the room temperature. HPLC purity 96.3%. X-ray powder pattern in Fig. 11. Melting point in accordance with DSC $Tmp_1 = 97°C$ and $Tmp_1 = 223°C$.

Example 7

Preparation of daclatasvir tosylate

Methyl [(2*S*)-1-{(2*S*)-2-[4-(4'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methyl--butanoyl}-2-pyrrolidinyl]-1H-imidazol-4-yl}-4-biphenylyl)-1H-imidazol-2-yl]-1-pyrrolidinyl}-3-methyl-1-oxo-2-butanyl]carbamate (free base of daclatasvir) in the amount of

125.1 mg ($1.69 \cdot 10^{-4}$ mol) was dissolved in 4 ml of ethyl acetate. 30.33 mg ($1.74 \cdot 10^{-4}$ mol) of toluenesulfonic acid (99 %) was added to this solution. The mixture was stirred at the room temperature **for 2 hours**. Then, the solution was left to freely evaporate at the room temperature. HPLC purity 98 %. X-ray powder pattern in Fig. 14. Melting point in accordance with DSC Tmp_1 = 122°C and Tmp_2 = 234°C.

Example 8

Preparation of daclatasvir mesylate

Methyl [(2*S*)-1-{(2*S*)-2-[4-(4'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methyl--butanoyl}-2-pyrrolidinyl]-1H-imidazol-4-yl}-4-biphenylyl)-1H-imidazol-2-yl]-1-pyrrolidinyl}-3-methyl-1-oxo-2-butanyl]carbamate (free base of daclatasvir) in the amount of 98.39 mg ($1.33 \cdot 10^{-4}$ mol) was dissolved in 4 ml of ethyl acetate. 13.79 mg ($1.74 \cdot 10^{-4}$ mol) of methanesulfonic acid (99 %) was added to this solution. The mixture was stirred at the room temperature for 2 hours. Then, the solution was left to freely evaporate at the room temperature. HPLC purity 97.3%. X-ray powder pattern in Fig. 17. Glass transition temperature according to DSC 103°C.

Example 9

Preparation of daclatasvir besylate

Methyl [(2*S*)-1-{(2*S*)-2-[4-(4'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methyl--butanoyl}-2-pyrrolidinyl]-1H-imidazol-4-yl}-4-biphenylyl)-1H-imidazol-2-yl]-1-pyrrolidinyl}-3-methyl-1-oxo-2-butanyl]carbamate (free base of daclatasvir) in the amount of 101.3 mg ($1.37 \cdot 10^{-4}$ mol) was dissolved in 4 ml of ethyl acetate. 21.32 mg ($1.74 \cdot 10^{-4}$ mol) of benzenesulfonic acid (99 %) was added to this solution. The mixture was stirred at the room temperature for 2 hours. Then, the solution was left to freely evaporate at the room temperature. HPLC purity 97.7%. X-ray powder pattern in Fig. 20. Glass transition temperature according to DSC 108°C.

Example 10

Preparation of daclatasvir maleate (1:1)

Methyl [(2*S*)-1-{(2*S*)-2-[4-(4'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methyl--butanoyl}-2-pyrrolidinyl]-1H-imidazol-4-yl}-4-biphenylyl)-1H-imidazol-2-yl]-1-pyrrolidinyl}-3-methyl-1-oxo-2-butanyl]carbamate (free base of daclatasvir) in the amount of 98.45 mg ($1.33 \cdot 10^{-4}$ mol) was dissolved in 4 ml of ethyl acetate. 15.64 mg ($1.33 \cdot 10^{-4}$ mol) of maleic acid (99 %) was added to this solution. The mixture was stirred at the room temperature for 2 hours. Then, the solution was left to freely evaporate at the room temperature. HPLC purity 98.9%. X-ray powder pattern in Fig. 23. Melting point in accordance with DSC 165°C.

Example 11

Preparation of daclatasvir maleate (1:2)

Methyl [(2*S*)-1-{(2*S*)-2-[4-(4'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methyl--butanoyl}-2-pyrrolidinyl]-1H-imidazol-4-yl}-4-biphenylyl)-1H-imidazol-2-yl]-1-pyrrolidinyl}-3-methyl-1-oxo-2-butanyl]carbamate (free base of daclatasvir) in the amount of 103.6 mg ($1.40 \cdot 10^{-4}$ mol) was dissolved in 4 ml of ethyl acetate. 32.9 mg ($2.81 \cdot 10^{-4}$ mol) of maleic acid (99 %) was added to this solution. The mixture was stirred at the room temperature for 2 hours. Then, the solution was left to freely evaporate at the room temperature. HPLC purity 98.8%. X-ray powder pattern in Fig. 26. Melting point in accordance with DSC 166°C.

Example 12

Preparation of daclatasvir fumarate (1:1)

Methyl [(2*S*)-1-{(2*S*)-2-[4-(4'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methyl--butanoyl}-2-pyrrolidinyl]-1H-imidazol-4-yl}-4-biphenylyl)-1H-imidazol-2-yl]-1-pyrrolidinyl}-3-methyl-1-oxo-2-butanyl]carbamate (free base of daclatasvir) in the amount of

104.3 mg (1.41 $\cdot 10^{-4}$ mol) was dissolved in 4 ml of ethyl acetate. 21.32 mg ($1.41 \cdot 10^{-4}$ mol) of fumaric acid (99 %) was added to this solution. The mixture was stirred at the room temperature for 2 hours. Then, the solution was left to freely evaporate at the room temperature. HPLC purity 98.5%. X-ray powder pattern in Fig. 29. Melting point in accordance with DSC Tmp_1 = 112°C and Tmp_2 = 179°C.

Example 13

Preparation of daclatasvir fumarate (1:2)

Methyl [(2*S*)-1-{(2*S*)-2-[4-(4'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methyl--butanoyl}-2-pyrrolidinyl]-1H-imidazol-4-yl}-4-biphenylyl)-1H-imidazol-2-yl]-1-pyrrolidinyl}-3-methyl-1-oxo-2-butanyl]carbamate (free base of daclatasvir) in the amount of 99.8 mg (1.35 $\cdot 10^{-4}$ mol) was dissolved in 4 ml of ethyl acetate. 31.67 mg ($2.70 \cdot 10^{-4}$ mol) of fumaric acid (99 %) was added to this solution. The mixture was stirred at the room temperature for 2 hours. Then, the solution was left to freely evaporate at the room temperature. HPLC purity 98.3%. X-ray powder pattern in Fig. 32. Melting point in accordance with DSC Tmp_1 = 154°C and Tmp_2 = 200°C.

Claims

1. Salts of daclatasvir in the solid state with an acid selected from the group consisting of hydrochloric, hydrobromic, sulphuric, 2-naphthalenesulfonic, toluenesulfonic, methanesulfonic, benzenesulfonic, maleic and fumaric acids.

2. A salt of daclatasvir according to claim 1 with hydrochloric acid in the solid state, which exhibits a characteristic amorphous halo in the X-ray powder pattern.

3. The salt of daclatasvir according to claim 2 with hydrochloric acid in the solid state according to claim 1, characterized in that it exhibits a glass transition temperature Tg > 180°C.

4. A salt of daclatasvir according to claim 1 with hydrobromic acid in the solid phase.

5. The salt of daclatasvir with hydrobromic acid according to claim 4, which exhibits a characteristic amorphous halo in the X-ray powder pattern.

6. The salt of daclatasvir according to claim 4 with hydrobromic acid according to claim 4, characterized in that it exhibits a glass transition temperature Tg > 180°C.

7. A salt of daclatasvir according to claim 1 with sulphuric acid in the solid phase.

8. The salt of daclatasvir with sulphuric acid according to claim 7, which exhibits a characteristic amorphous halo in the X-ray powder pattern.

9. The salt of daclatasvir with sulphuric acid according to claim 7, characterized in that it exhibits a glass transition temperature Tg > 170°C.

10. A salt of daclatasvir according to claim 1 with 2-naphthalenesulfonic acid in the solid phase.

11. The salt of daclatasvir with 2-naphthalenesulfonic acid according to claim 10, which exhibits the following characteristic reflections in the X-ray powder pattern: 4.5; 10.5; 13.7; 15.1; 18.9 and 21,6 ± 0.2 ° 2-theta.

12. The salt of daclatasvir with 2-naphtalenesulfonic acid according to claim 10 in a crystalline form, which exhibits a peak at 97°C and a peak at 223°C in the DSC record.

13. A salt of daclatasvir according to claim 1 with toluenesulfonic acid in the solid phase.

14. The salt of daclatasvir with toluenesulfonic acid according to claim 13, which exhibits the following characteristic reflections in the X-ray powder pattern: 5.0; 6.3; 10.2; 13.7; 18.6 and 21.0 ± 0.2 ° 2-theta.

15. The salt of daclatasvir with toluenesulfonic acid according to claim 13 in a crystalline form, which exhibits a peak at 122°C and a peak at 234°C in the DSC record.

16. A salt of daclatasvir according to claim 1 with methanesulfonic acid in the solid phase.

17. The salt of daclatasvir with methanesulfonic acid according to claim 16, which exhibits a characteristic amorphous halo in the X-ray powder pattern.

18. The salt of daclatasvir with methanesulfonic acid according to claim 16, characterized in that it exhibits a glass transition temperature Tg > 100°C.

19. A salt of daclatasvir according to claim 1 with benzenesulfonic acid in the solid phase.

20. The salt of daclatasvir with benzenesulfonic acid according to claim 19, which exhibits a characteristic amorphous halo in the X-ray powder pattern.

21. The salt of daclatasvir with benzenesulfonic acid according to claim 19, characterized in that it exhibits a glass transition temperature Tg > 106°C.

22. A salt of daclatasvir according to claim 1 with maleic acid in the solid phase.

23. The salt of daclatasvir with one molar equivalent of maleic acid according to claim 22, which exhibits the following characteristic reflections in the X-ray powder pattern: 9.1; 15.8; 17.9; 21.5; 24.7 and 26.3 ± 0.2 ° 2-theta.

24. The salt of daclatasvir with one molar equivalent of maleic acid according to claim 22 in a crystalline form, which exhibits a peak at 165°C in the DSC record.

25. The salt of daclatasvir with two molar equivalents of maleic acid according to claim 22, which exhibits the following characteristic reflections in the X-ray powder pattern: 9.0; 15.6; 17.8; 21.4; 23.0 and 24.5 ± 0.2 ° 2-theta.

26. The salt of daclatasvir with two molar equivalents of maleic acid according to claim 22 in a crystalline form, which exhibits a peak at 166°C in the DSC record.

27. A salt of daclatasvir according to claim 1 with fumaric acid in the solid phase.

28. The salt of daclatasvir with one molar equivalent of fumaric acid according to claim 27, which exhibits the following characteristic reflections in the X-ray powder pattern: 8.1; 11.7; 15.1; 20.3; 22.7 and 24.4 ± 0.2 ° 2-theta.

29. The salt of daclatasvir with one molar equivalent of fumaric acid according to claim 27 in a crystalline form, which exhibits a peak at 112°C and a peak at 179°C in the DSC record.

30. The salt of daclatasvir with two molar equivalent of fumaric acid according to claim 27, which exhibits the following characteristic reflections in the X-ray powder pattern: 6.6; 8.2; 13.0; 15.4 and 20.5 ± 0.2 ° 2-theta.

31. The salt of daclatasvir with two molar equivalents of fumaric acid according to claim 27 in a crystalline form, which exhibits a peak at 154°C and a peak at 200°C in the DSC record.

32. A process for preparing solid forms of salts of daclatasvir as defined in claims 2, 4, 7, 10, 13, 16, 19, 22 and 27, characterized in that methyl [(2*S*)-1-{(2*S*)-2-[4-(4'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-pyrrolidinyl]-1H-imidazol-4-yl}-4-biphenylyl)-1H-imidazol-2-yl]-1-pyrrolidinyl}-3-methyl-1-oxo-2- butanyl]-carbamate - daclatasvir is mixed with an acid from the group consisting of hydrochloric, hydrobromic, sulphuric, 2-naphthalenesulfonic, toluenesulfonic, methanesulfonic, benzenesulfonic, maleic and fumaric acids and with a solvent.

Drawings

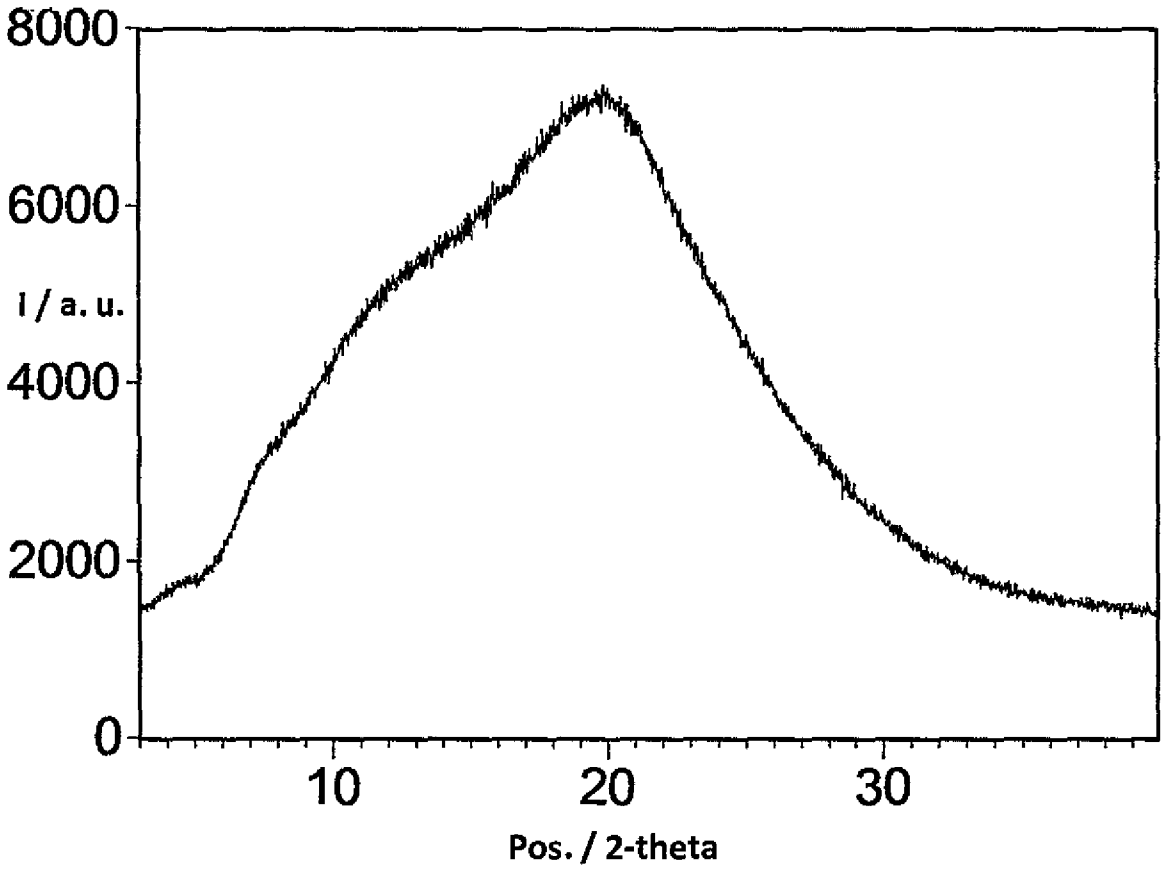


Figure 1

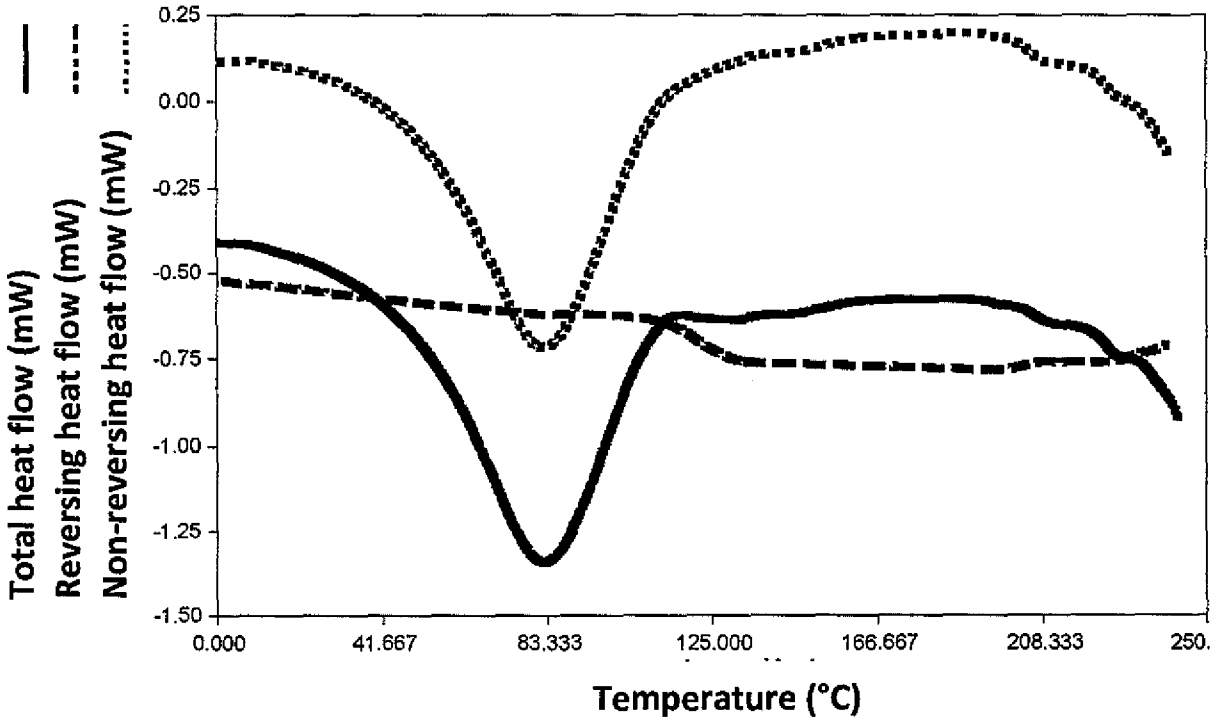


Figure 2

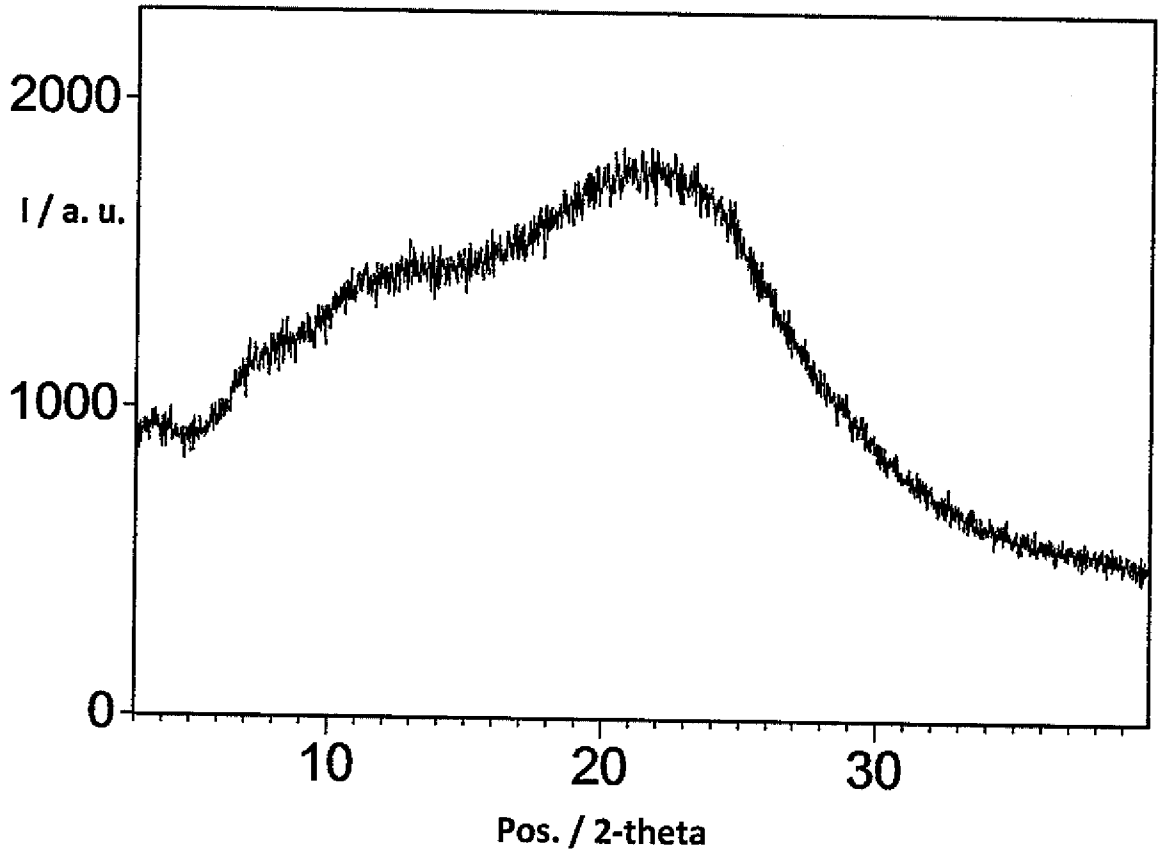


Figure 3

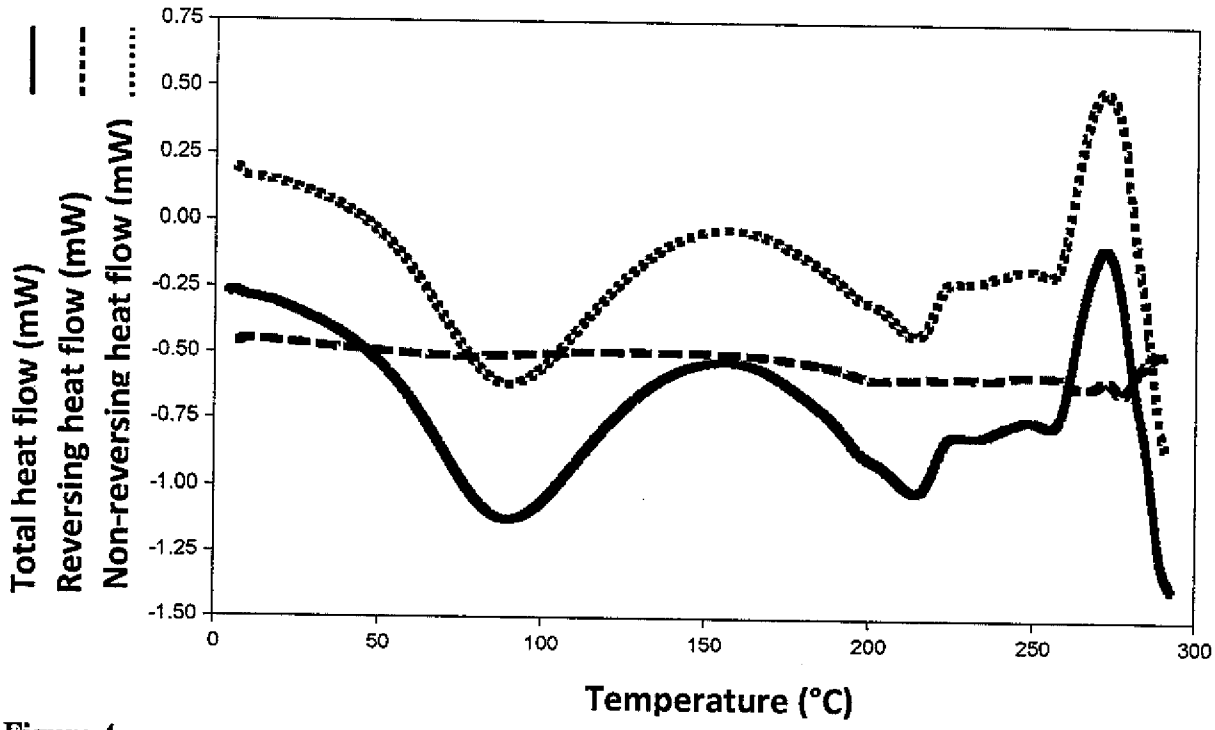


Figure 4

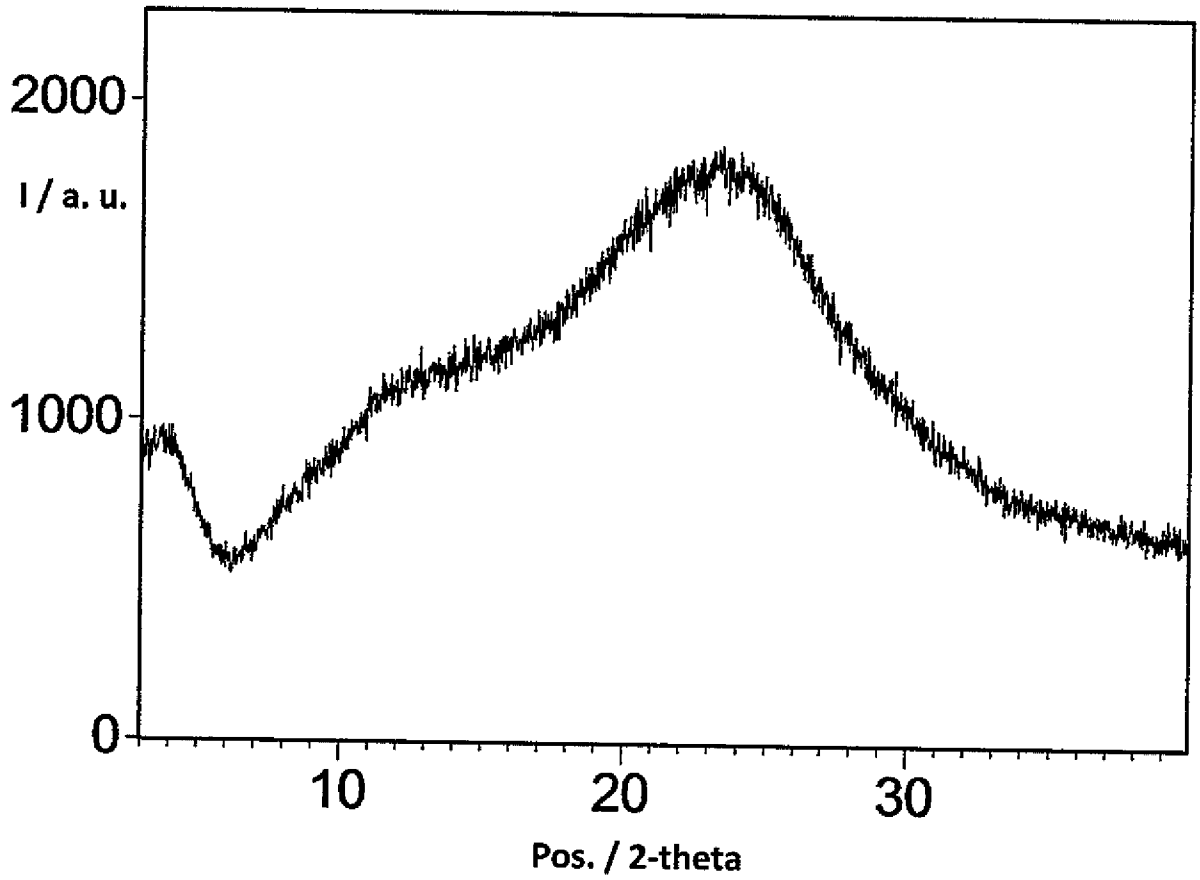


Figure 5

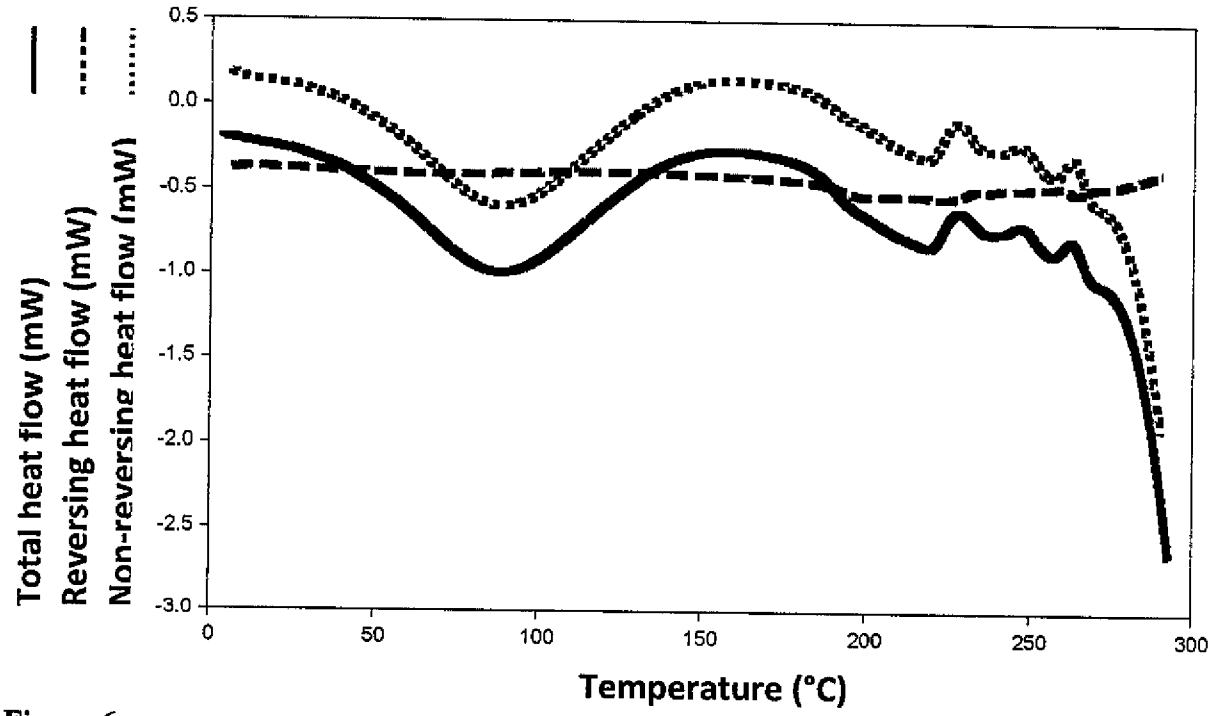


Figure 6

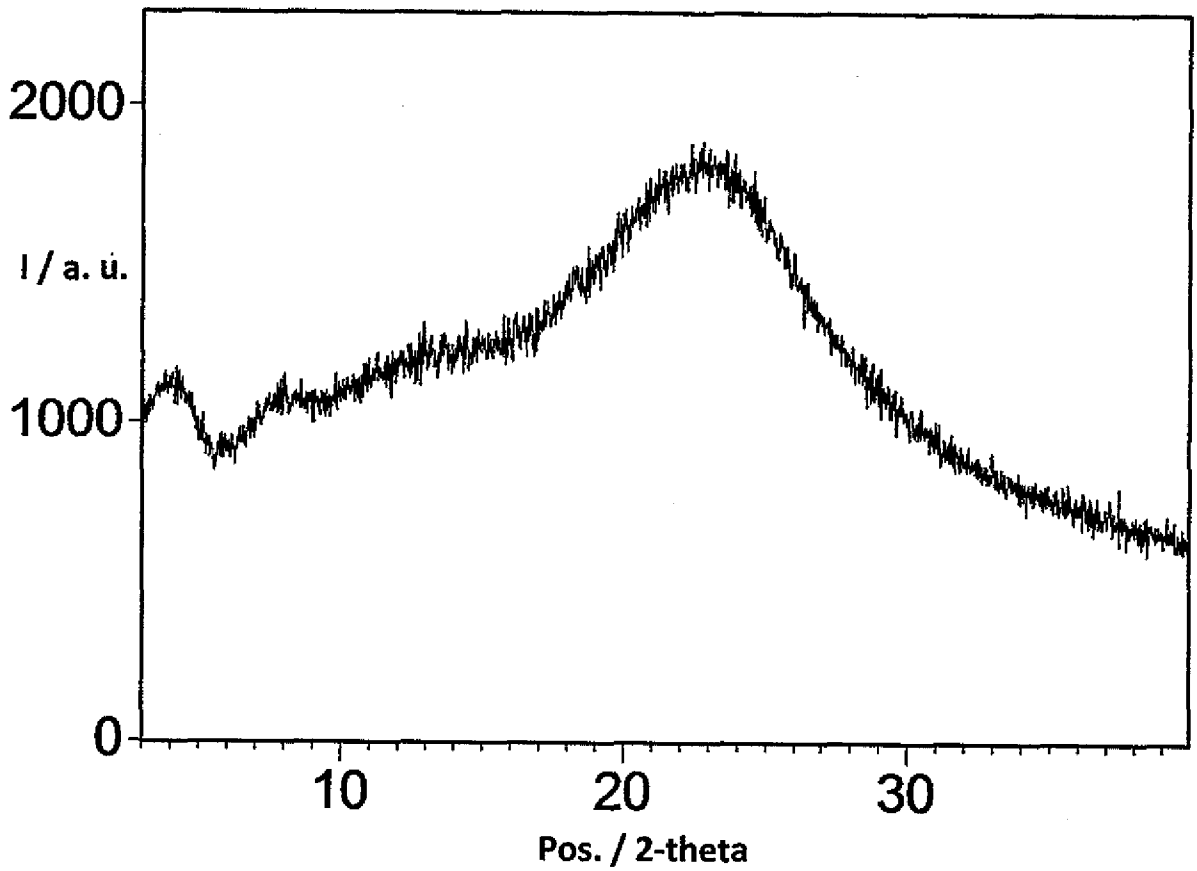


Figure 7

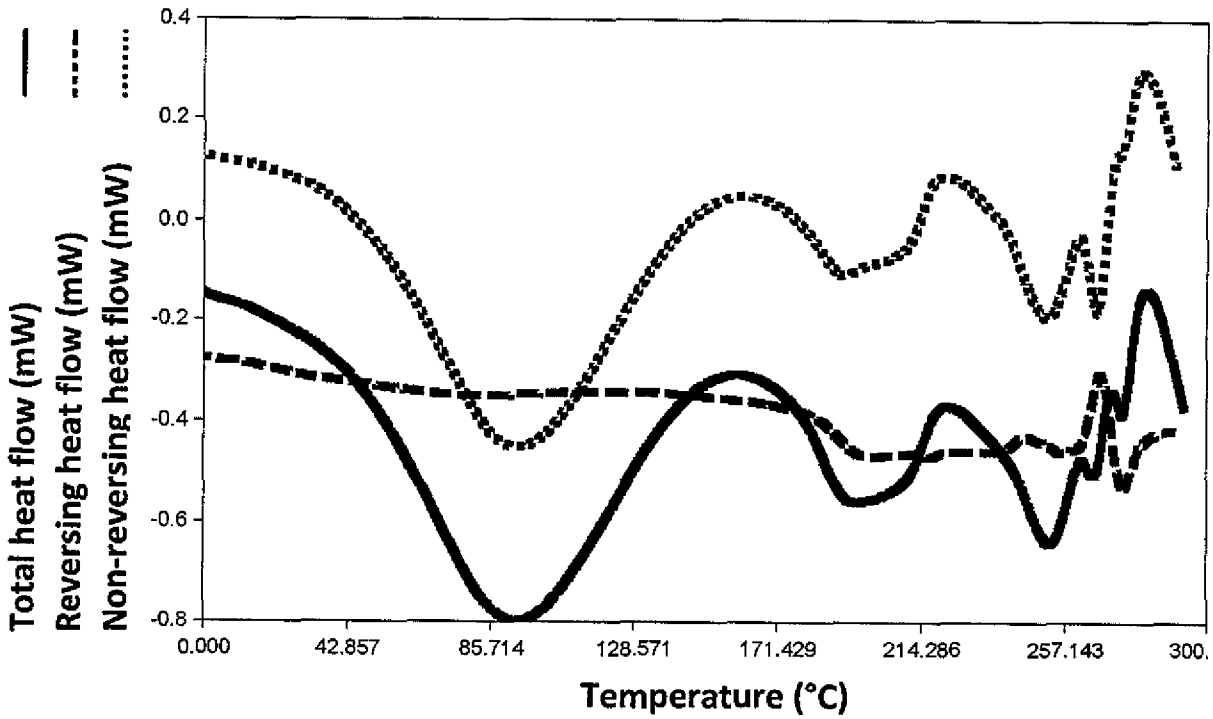


Figure 8

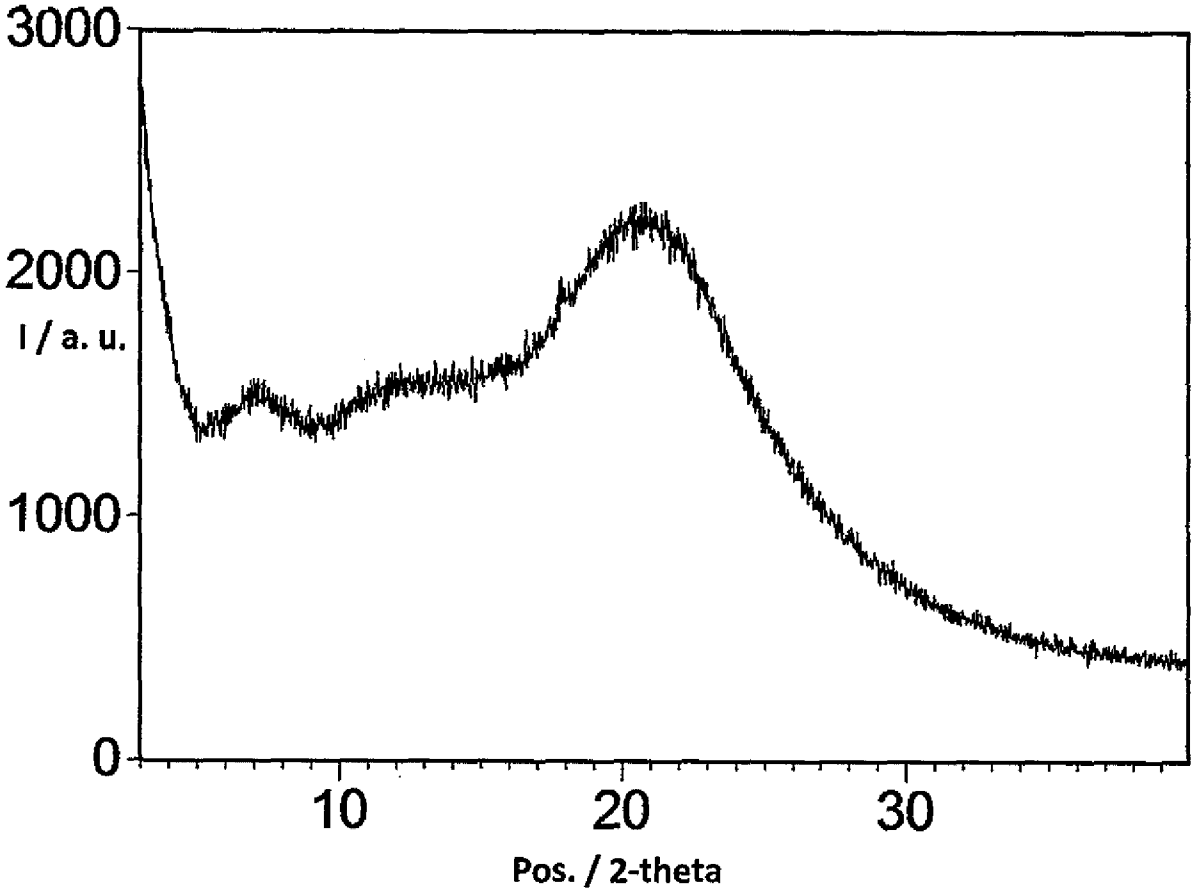


Figure 9

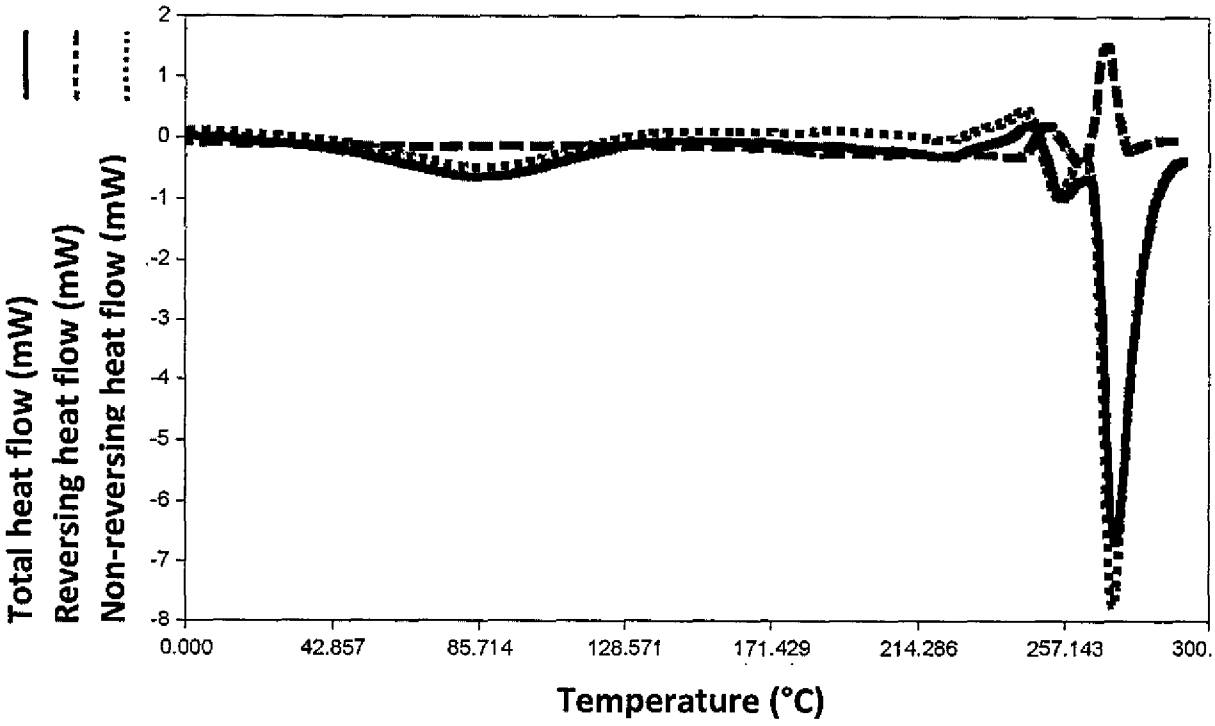


Figure 10

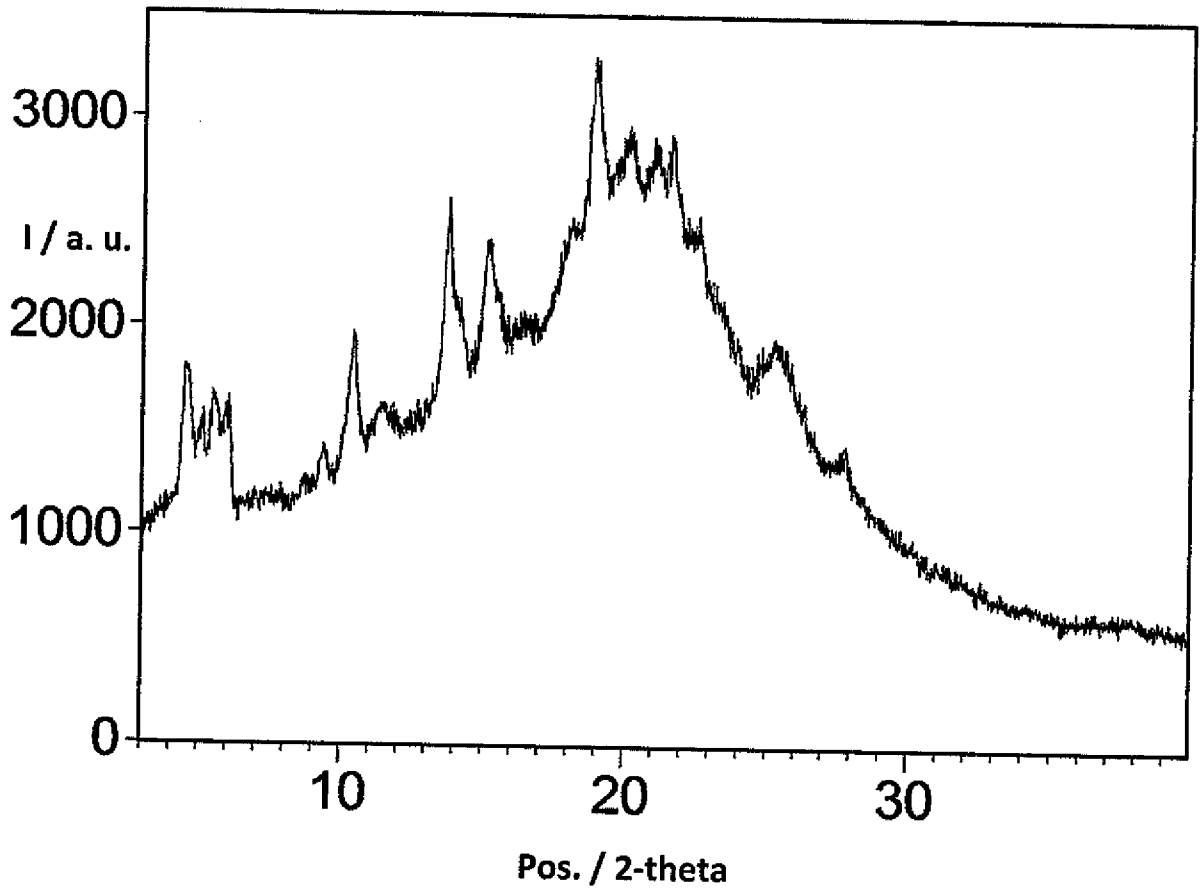


Figure 11

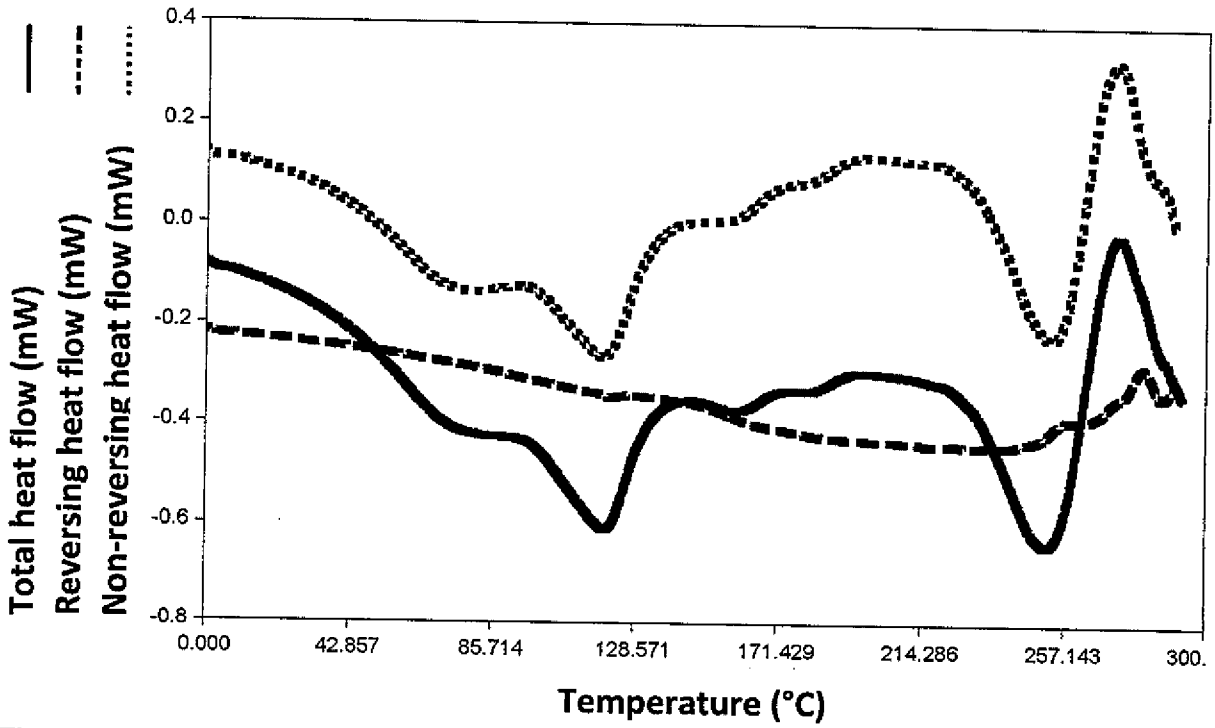


Figure 12

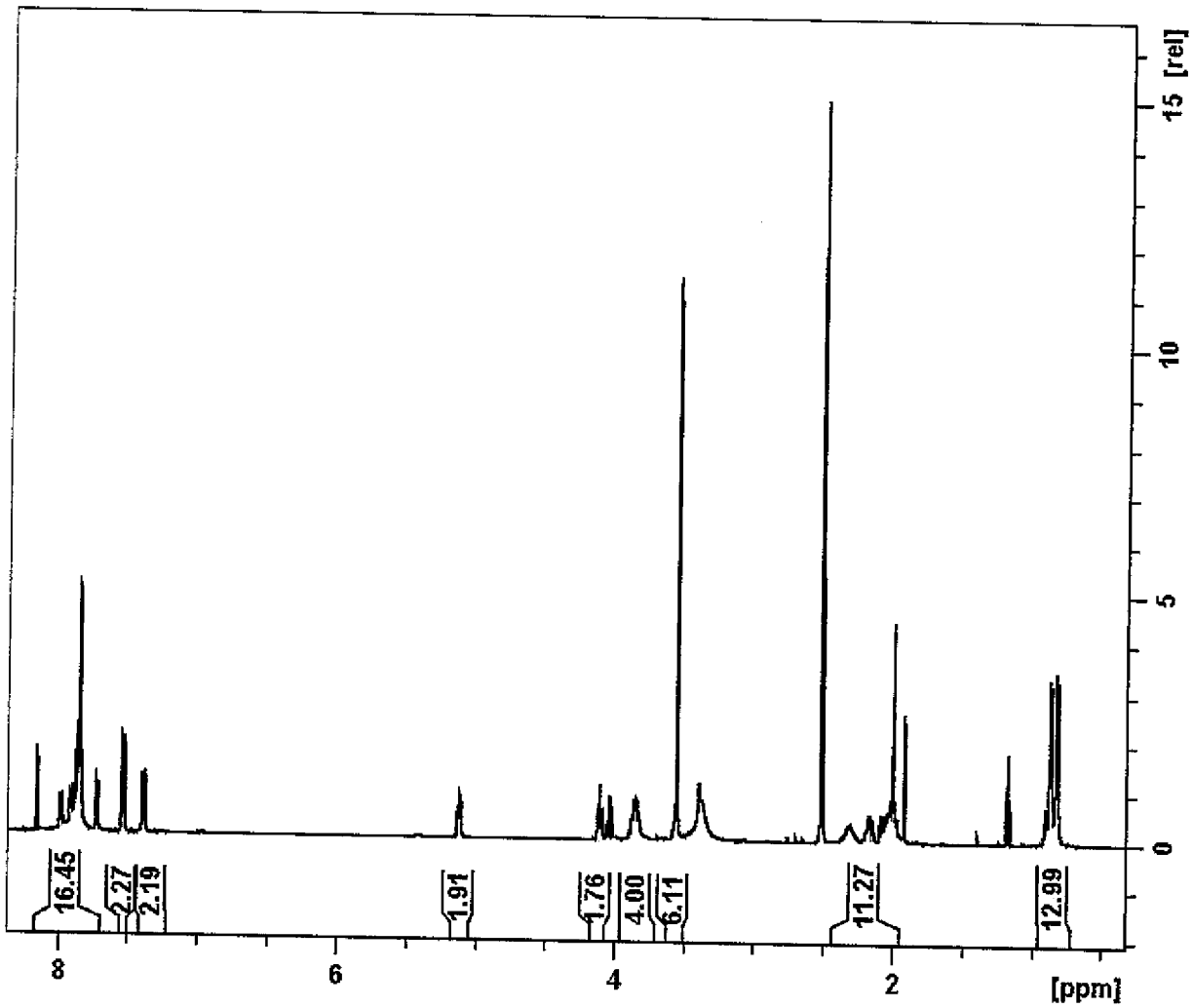


Figure 13

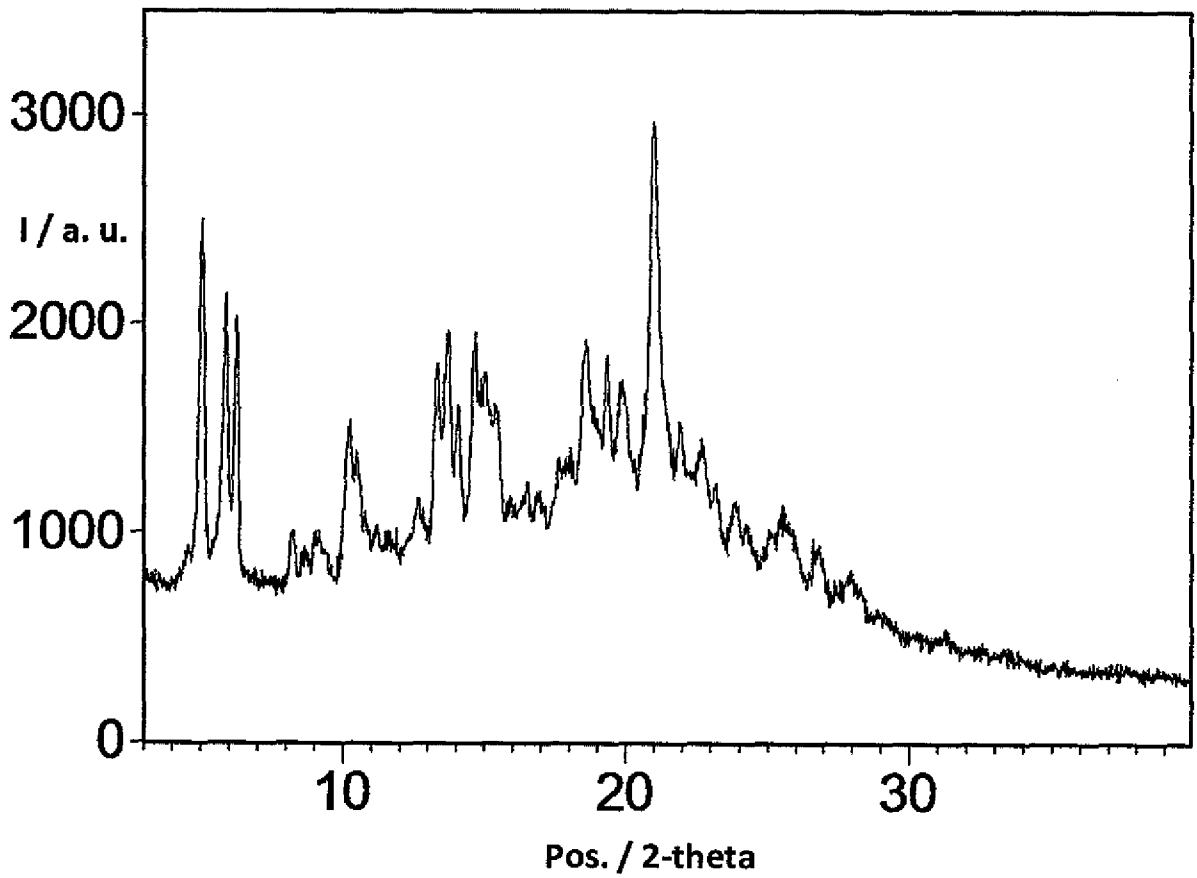


Figure 14

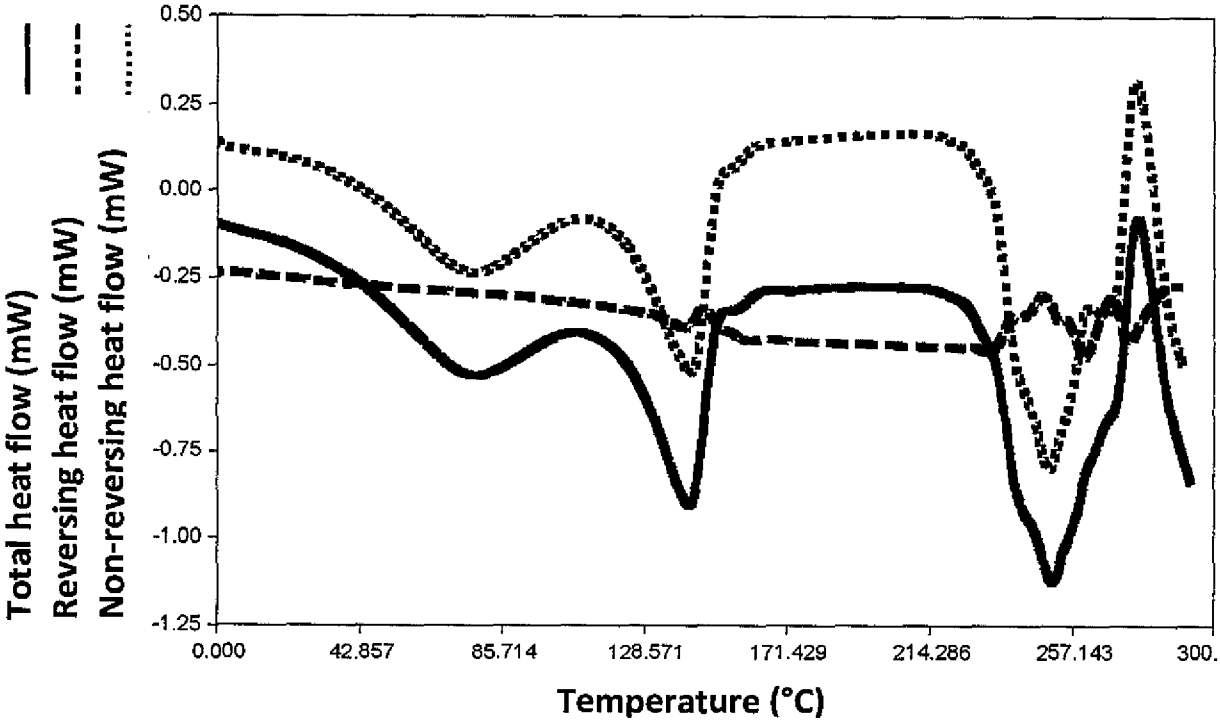


Figure 15

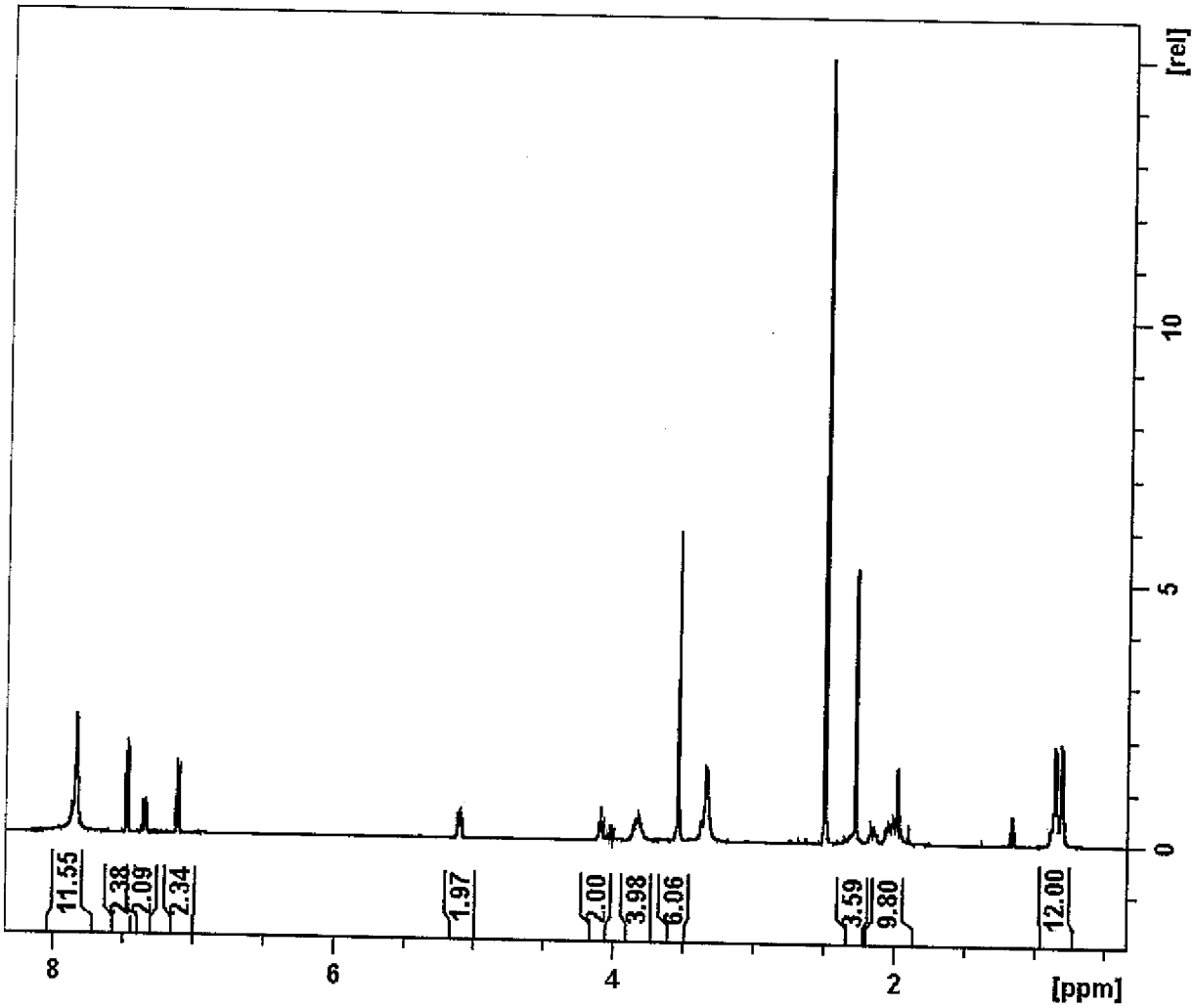


Figure 16

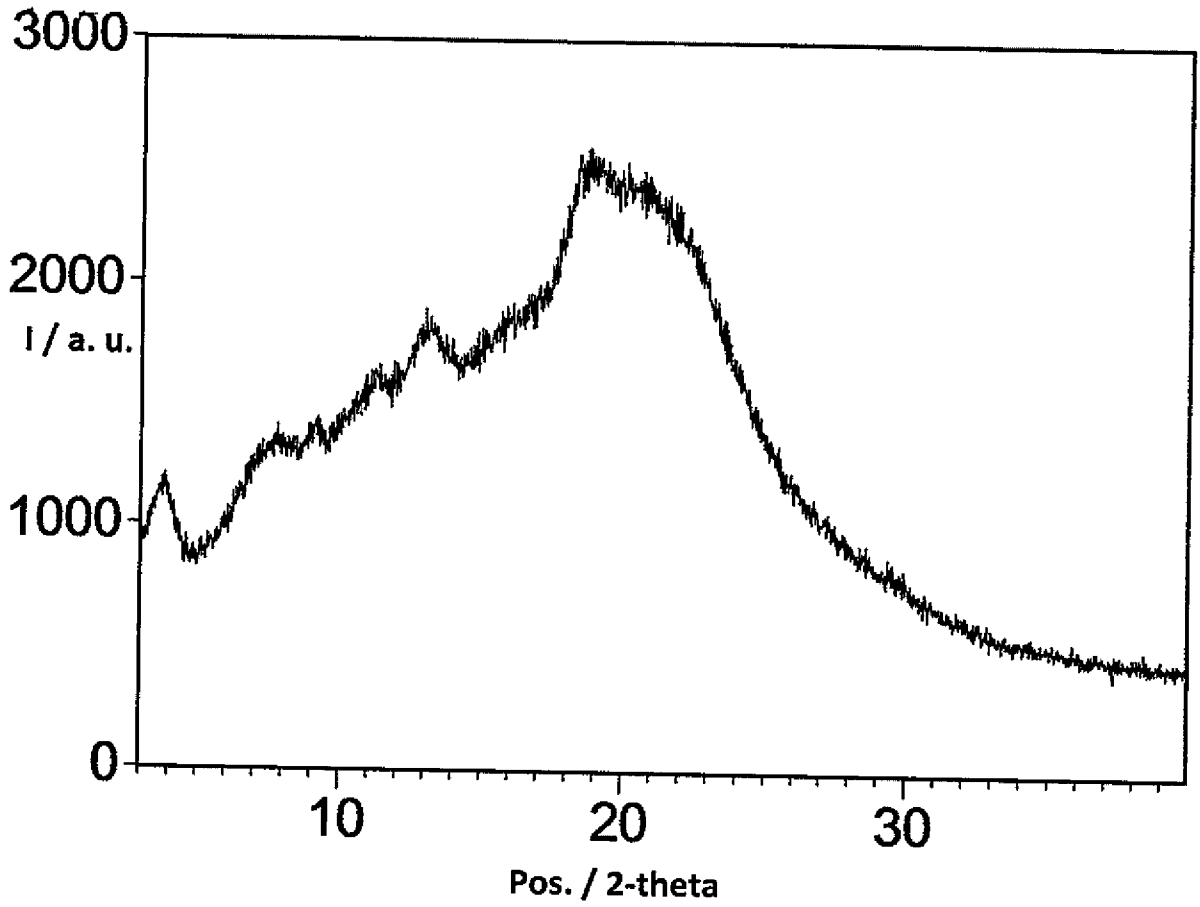


Figure 17

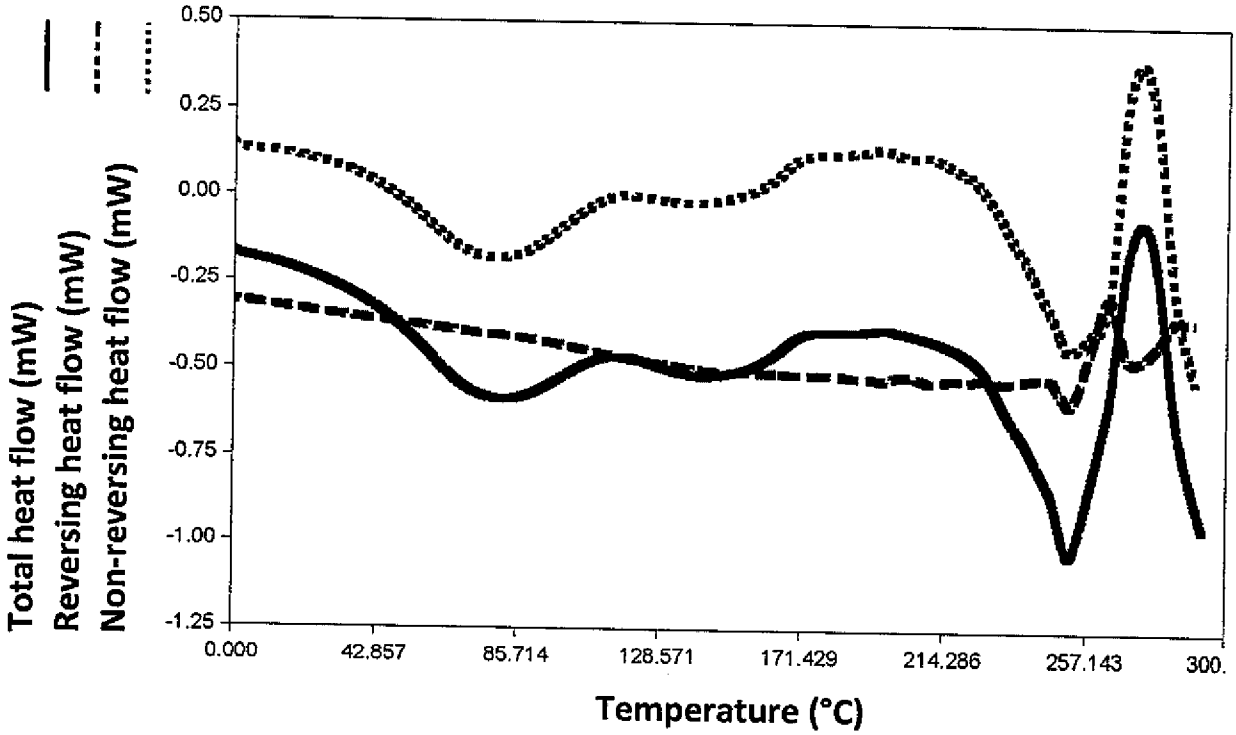


Figure 18

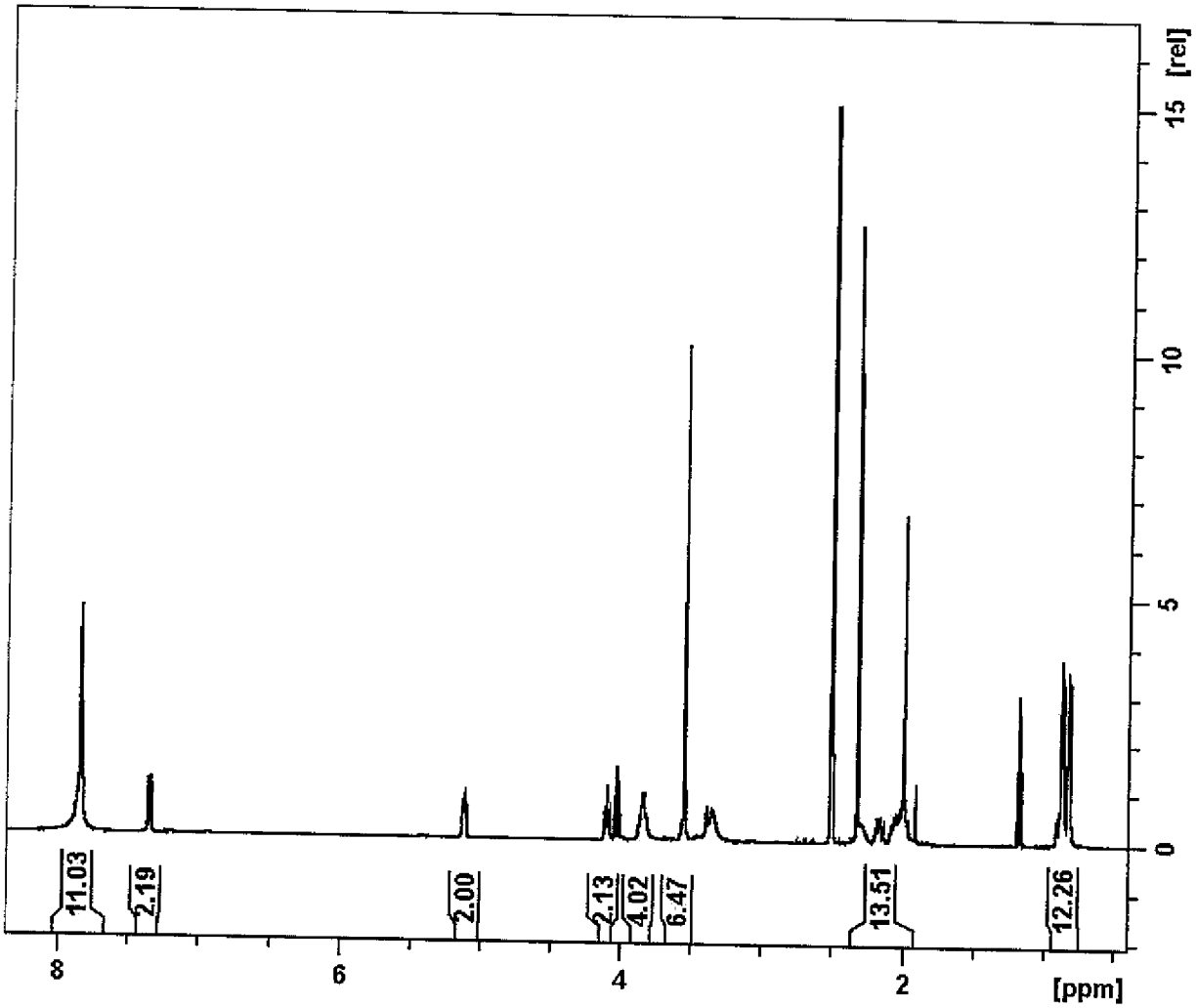


Figure 19

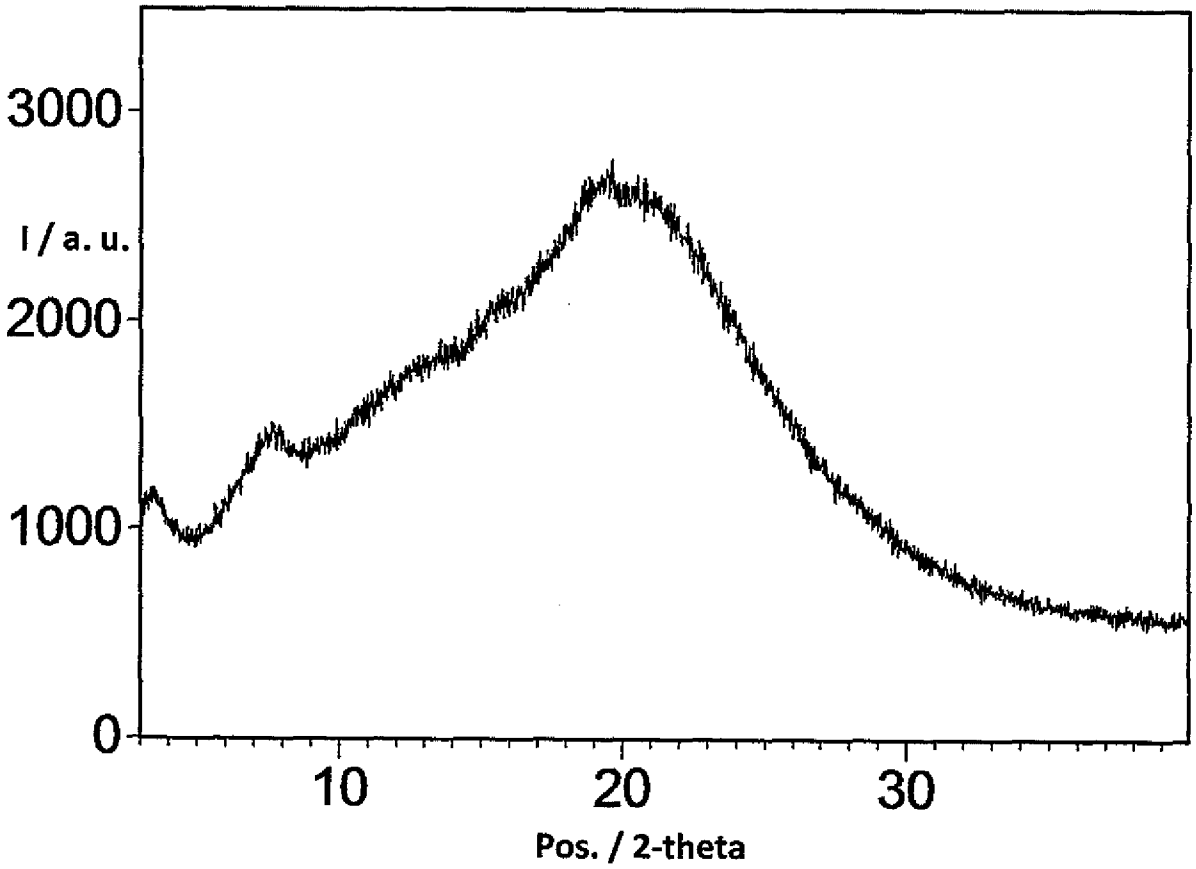


Figure 20

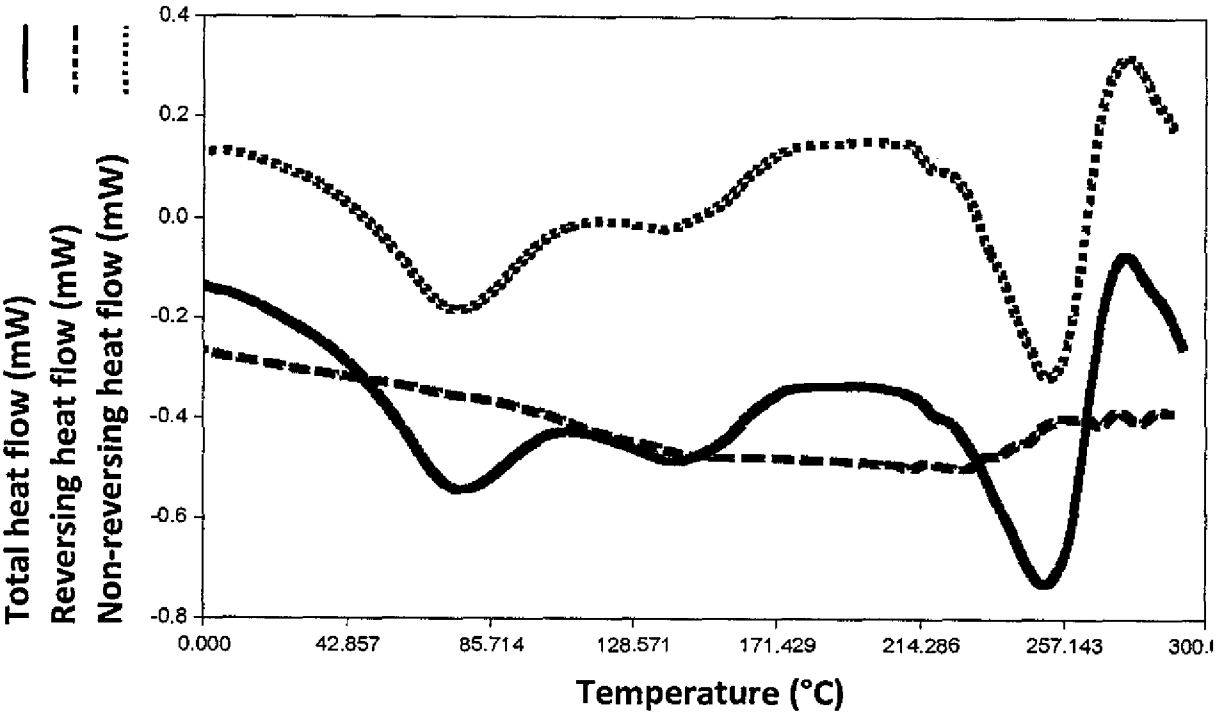


Figure 21

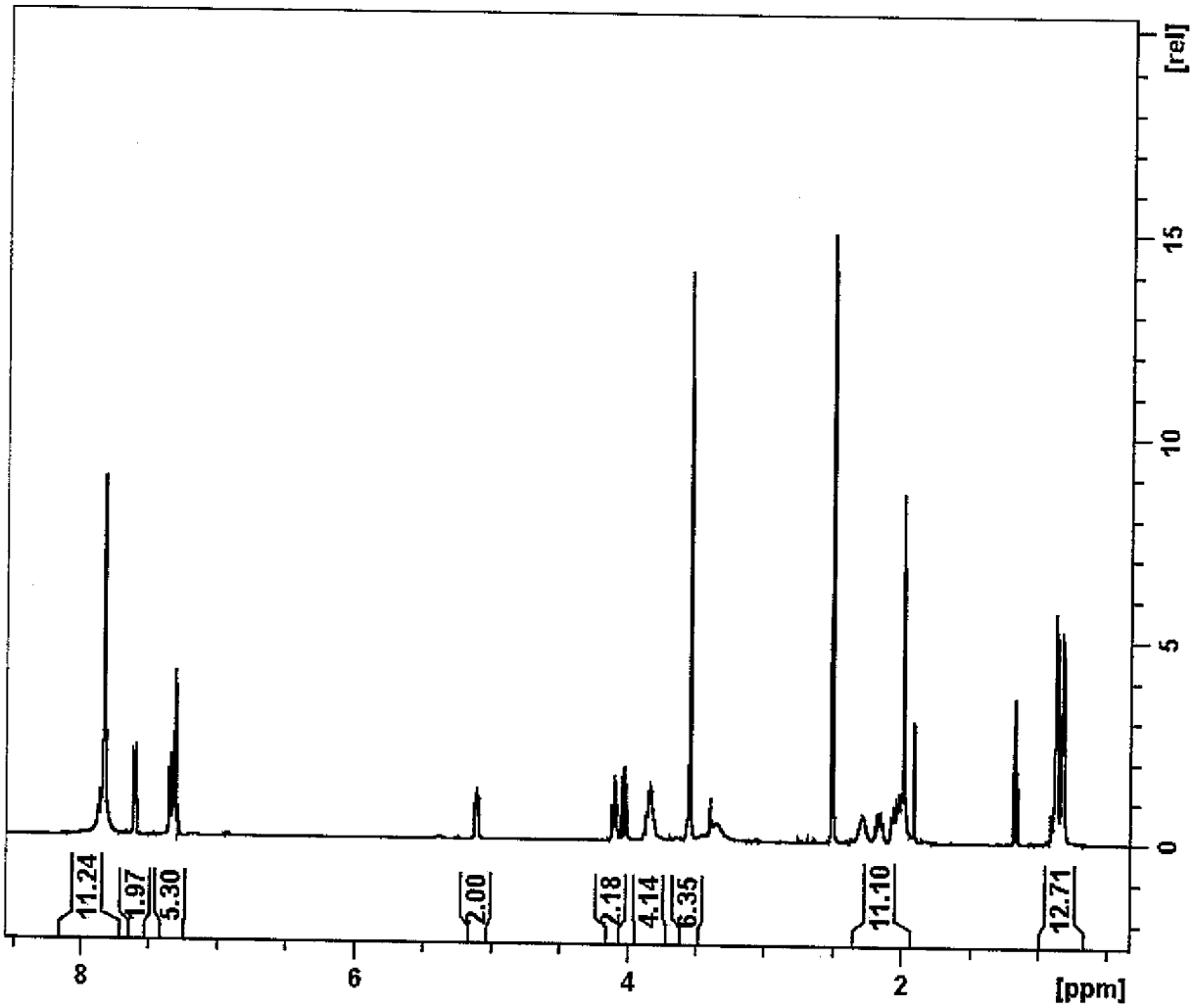


Figure 22

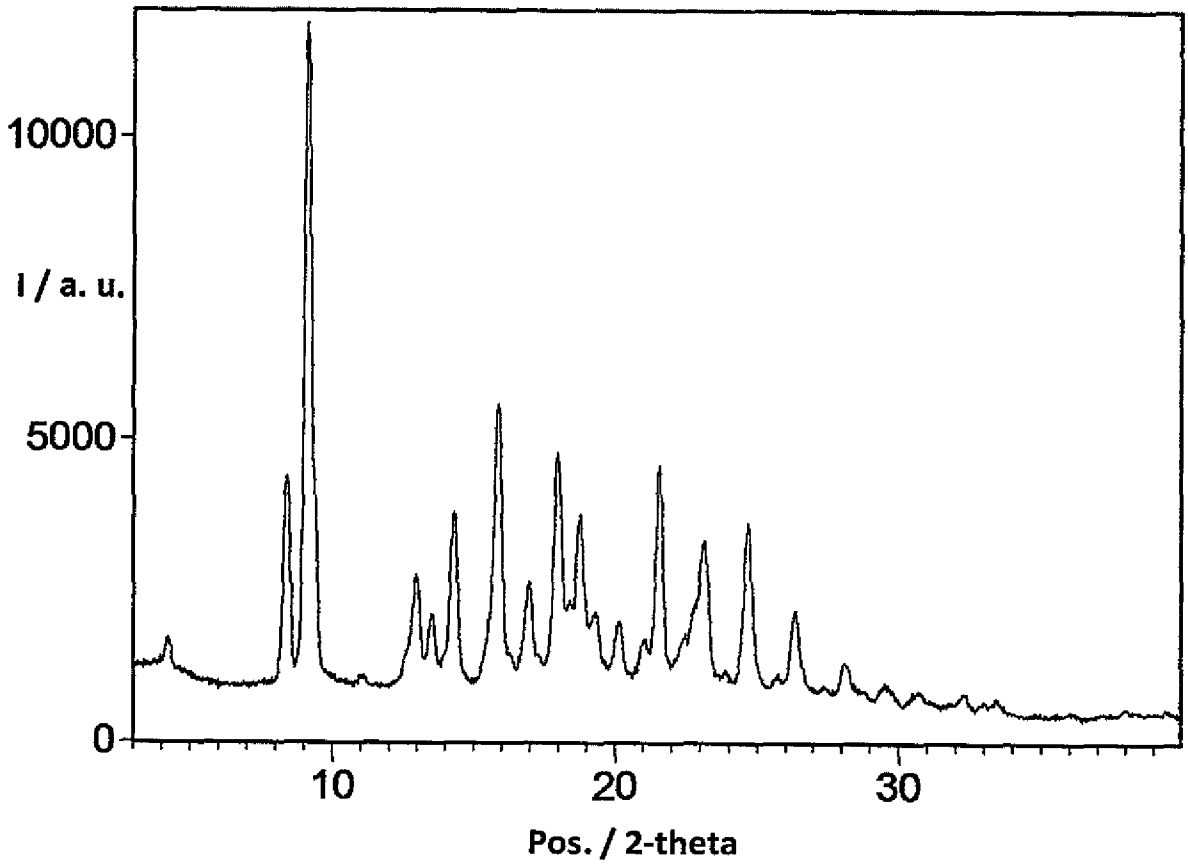


Figure 23

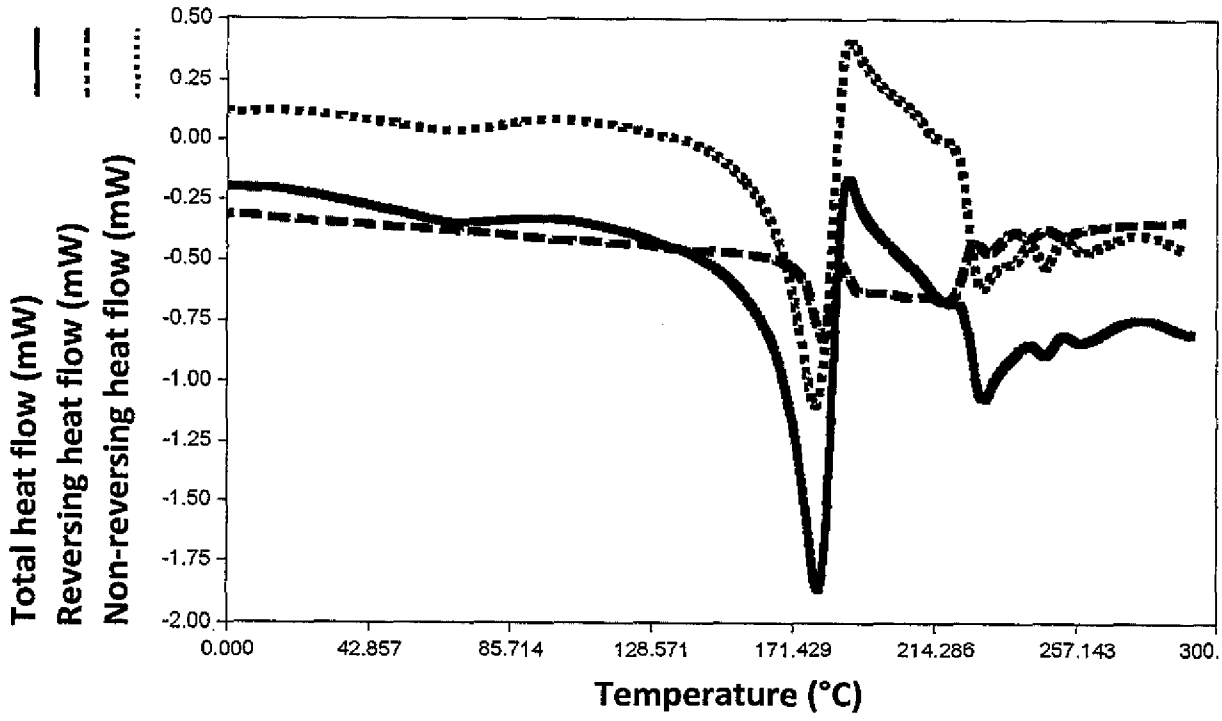


Figure 24

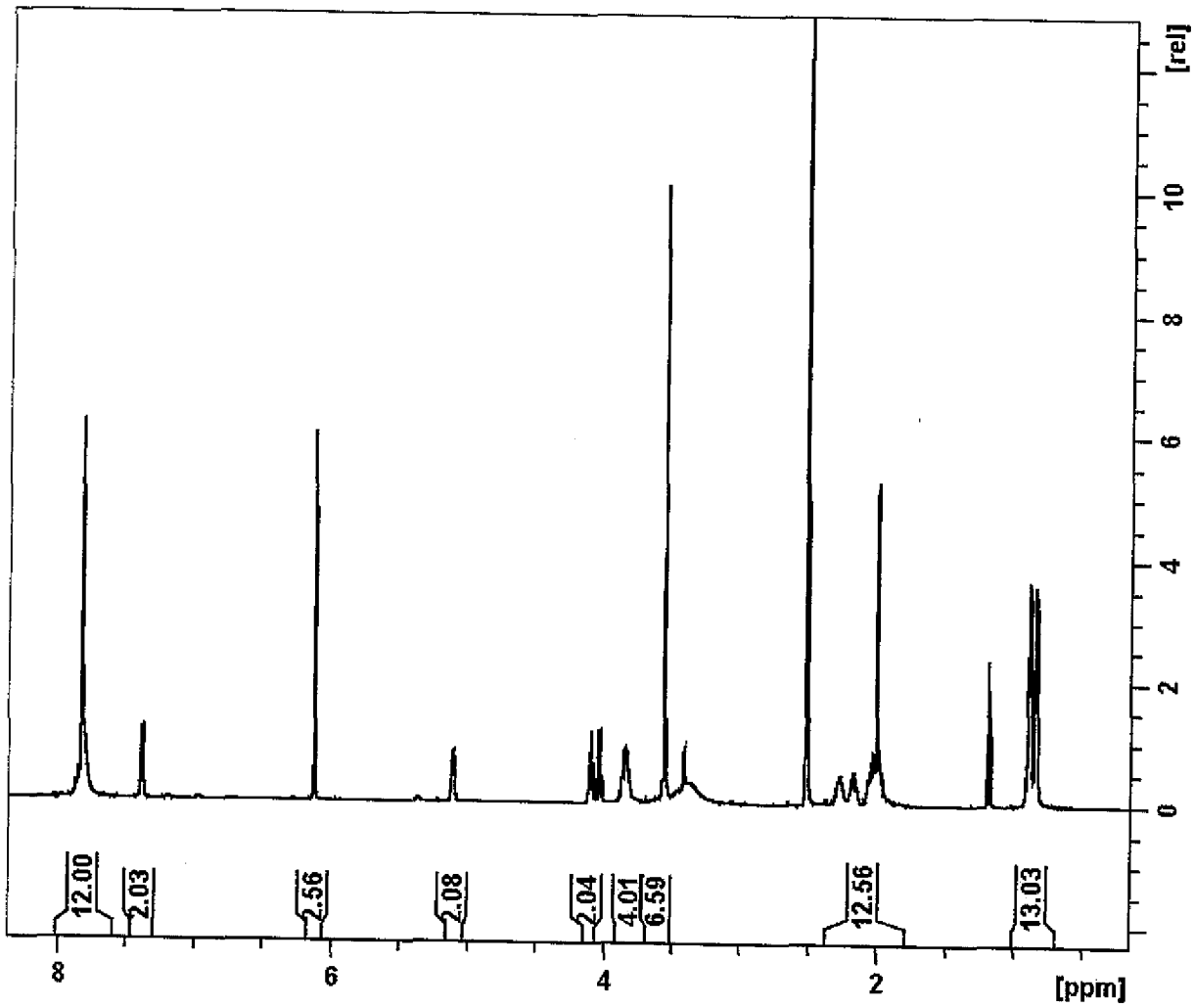


Figure 25

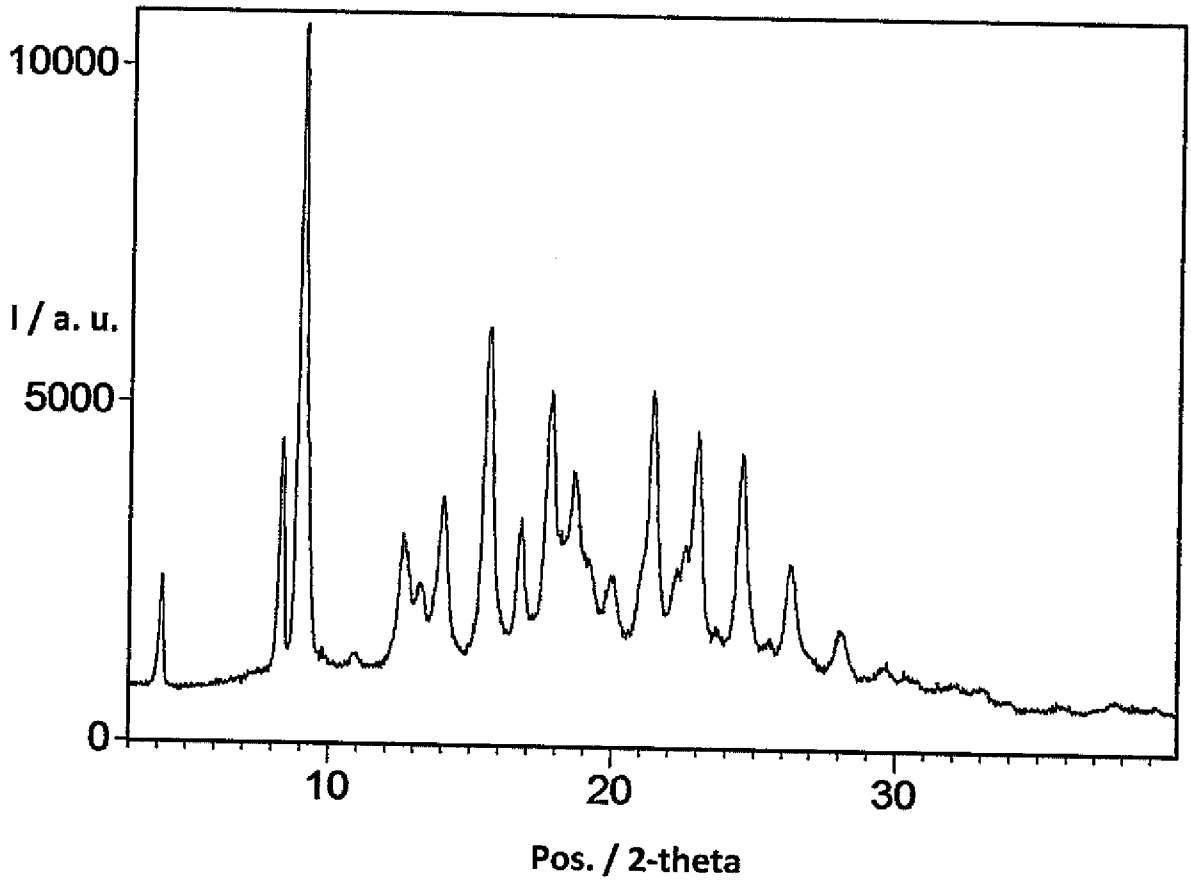


Figure 26

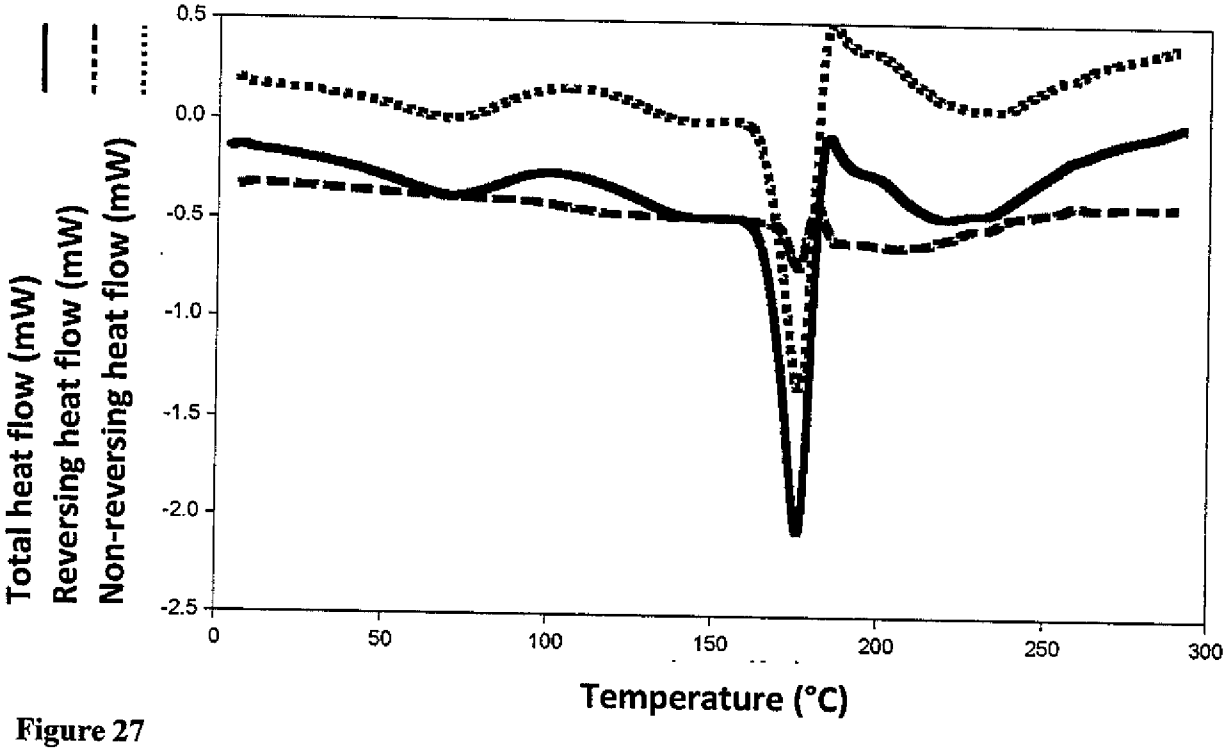


Figure 27

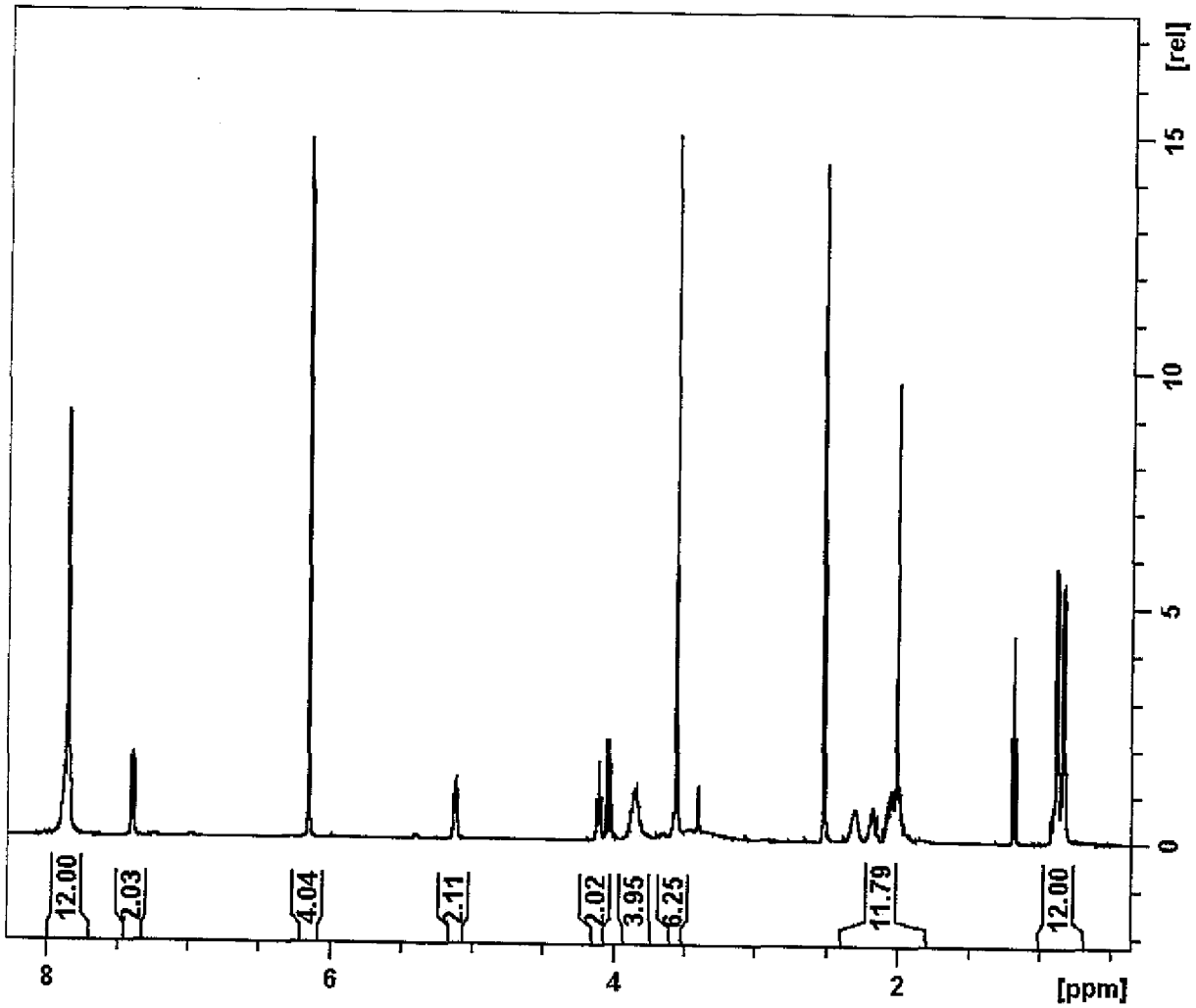


Figure 28

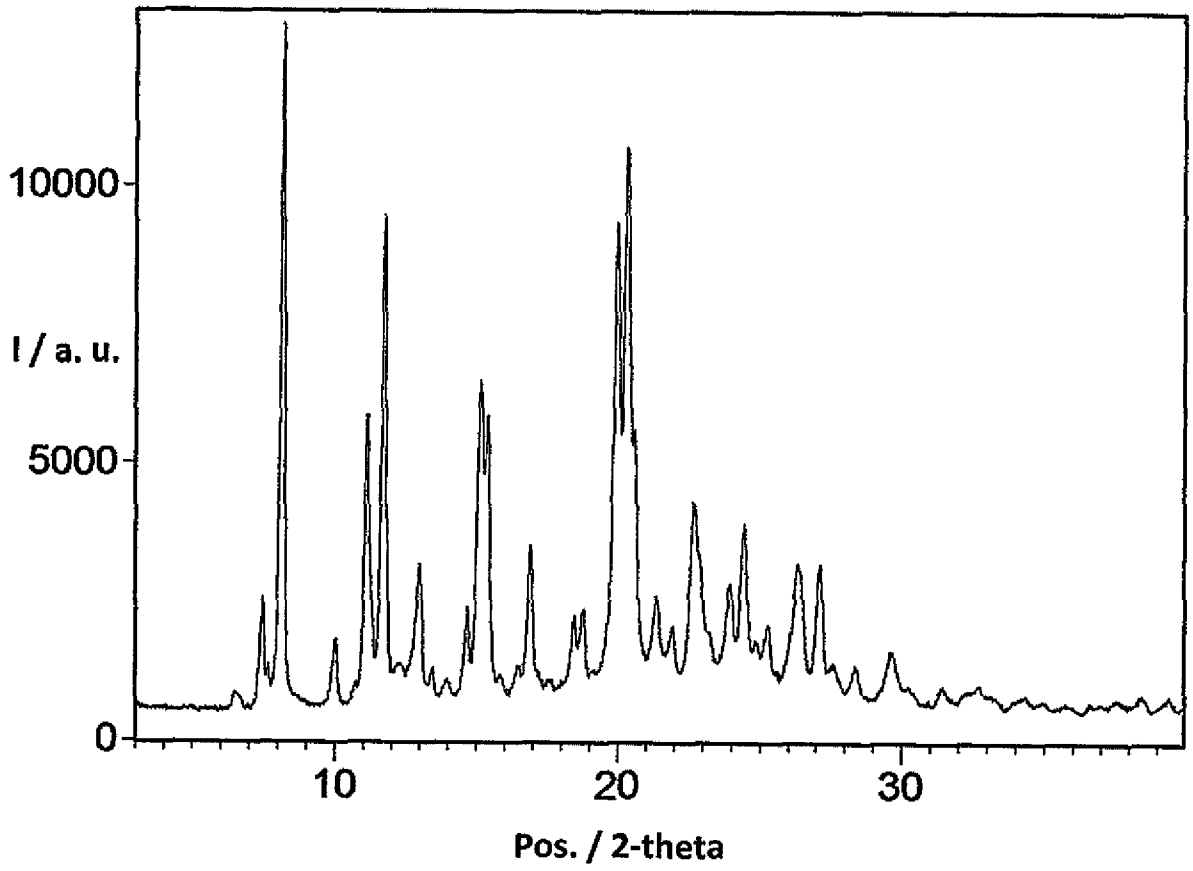


Figure 29

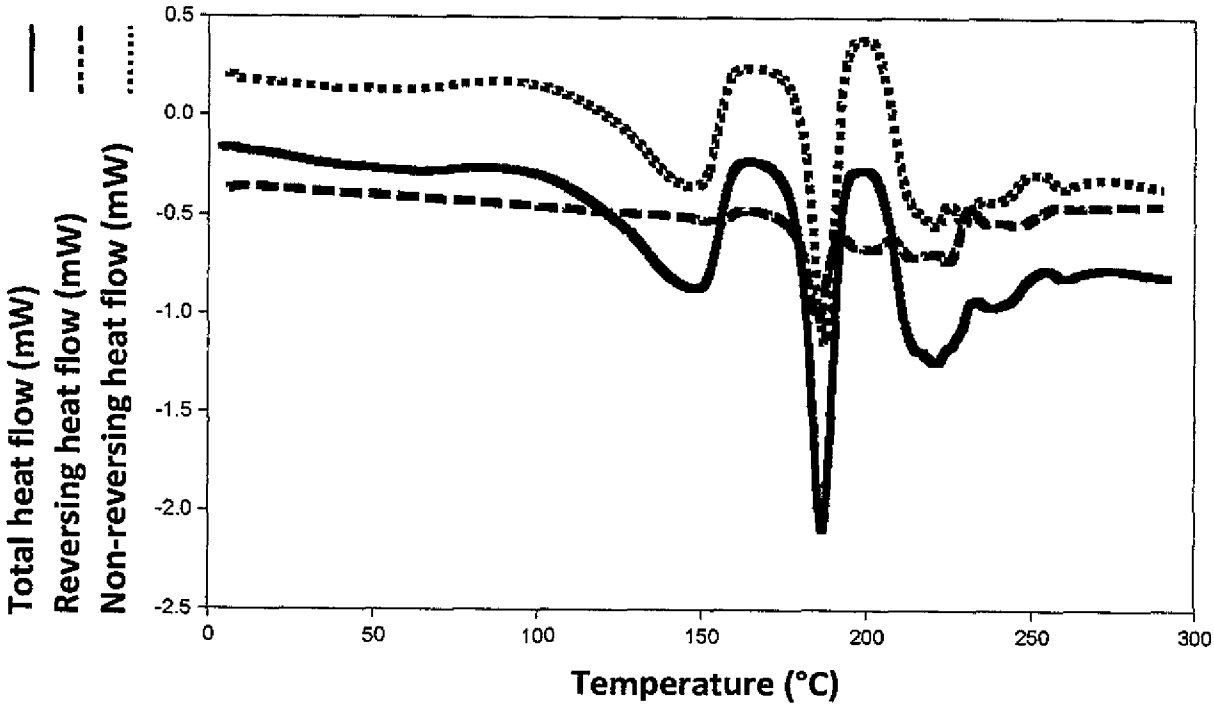


Figure 30

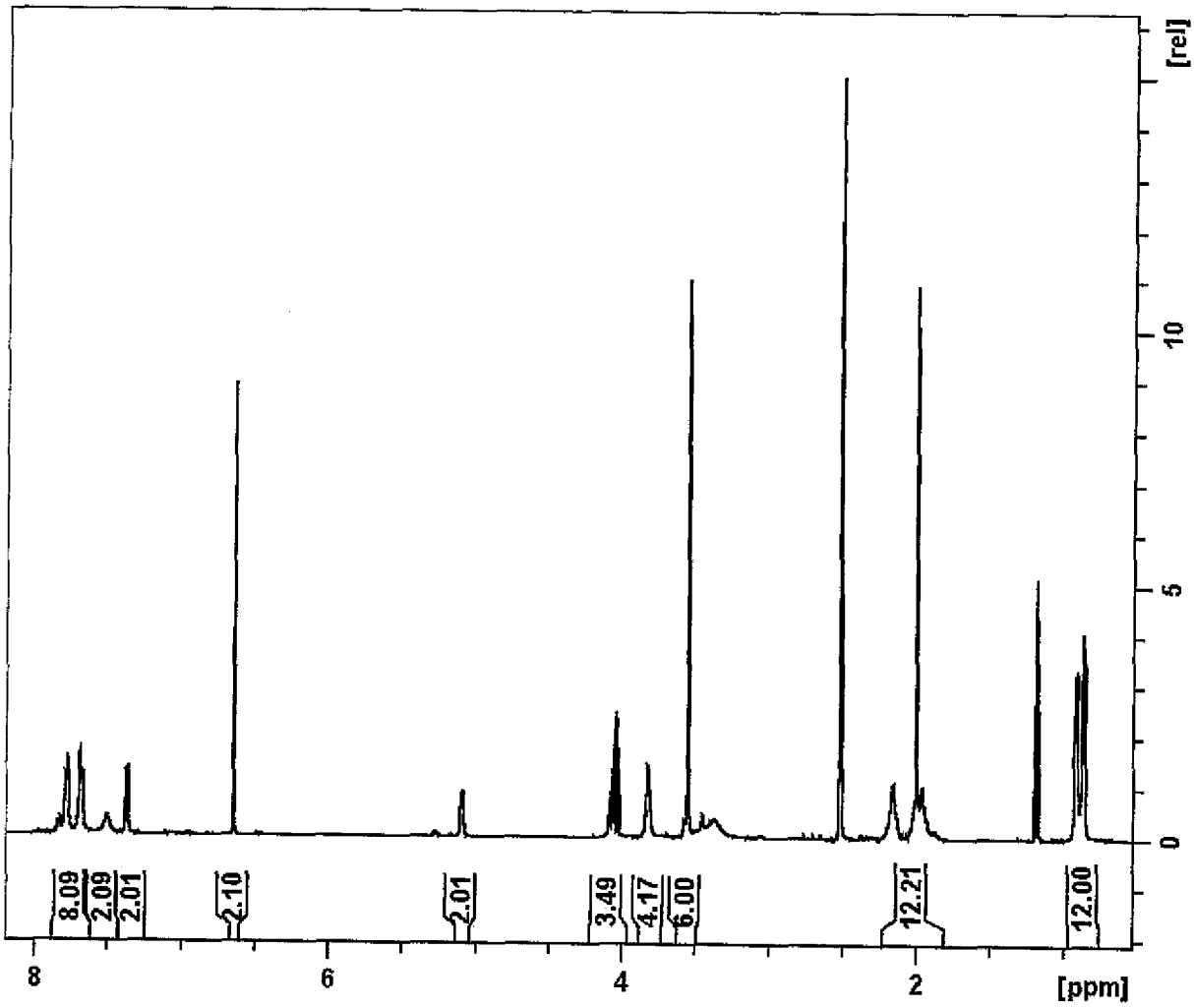


Figure 31

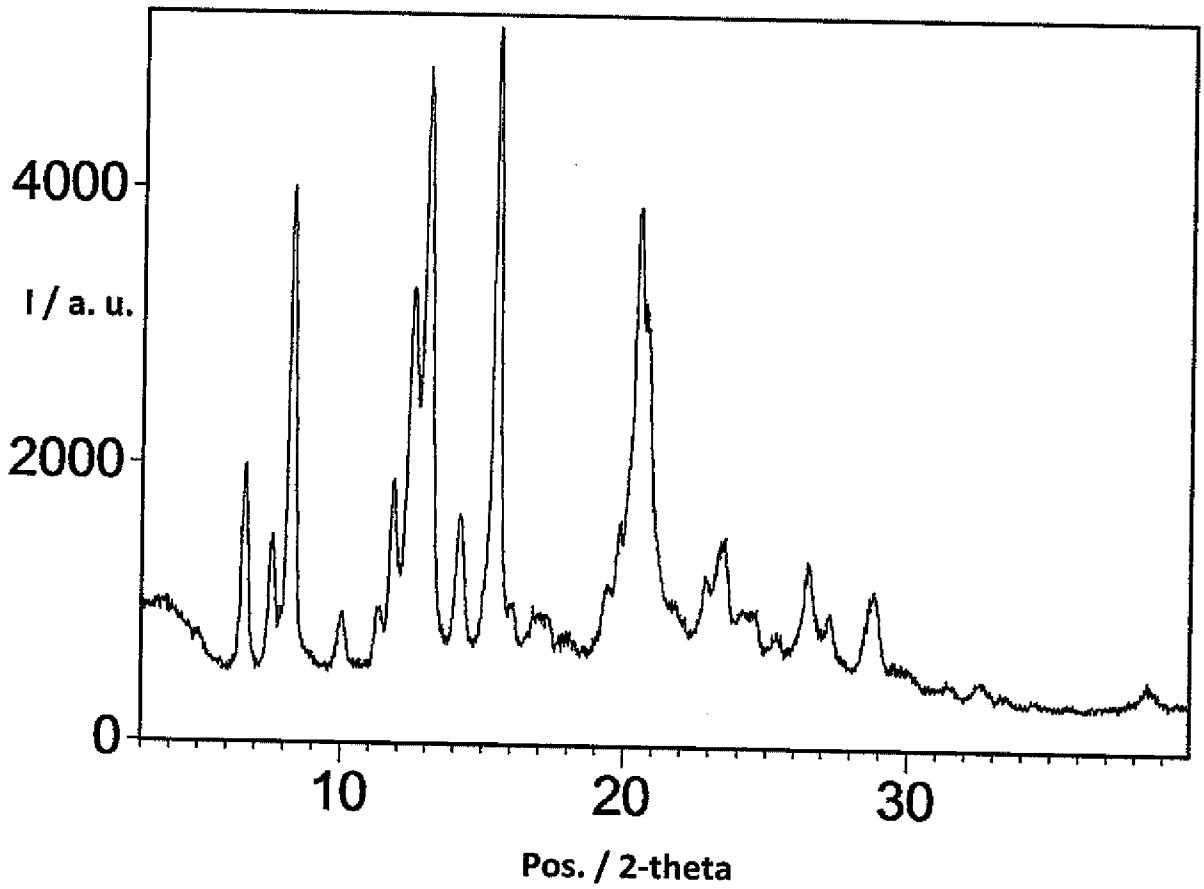


Figure 32

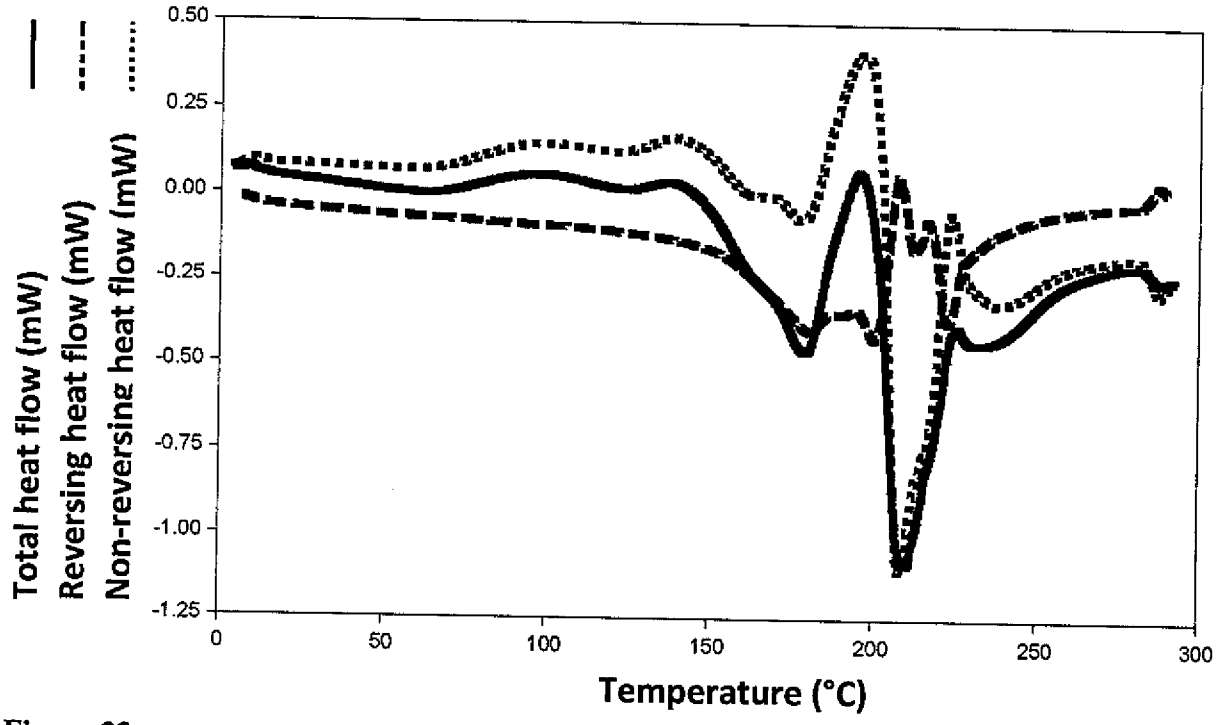


Figure 33

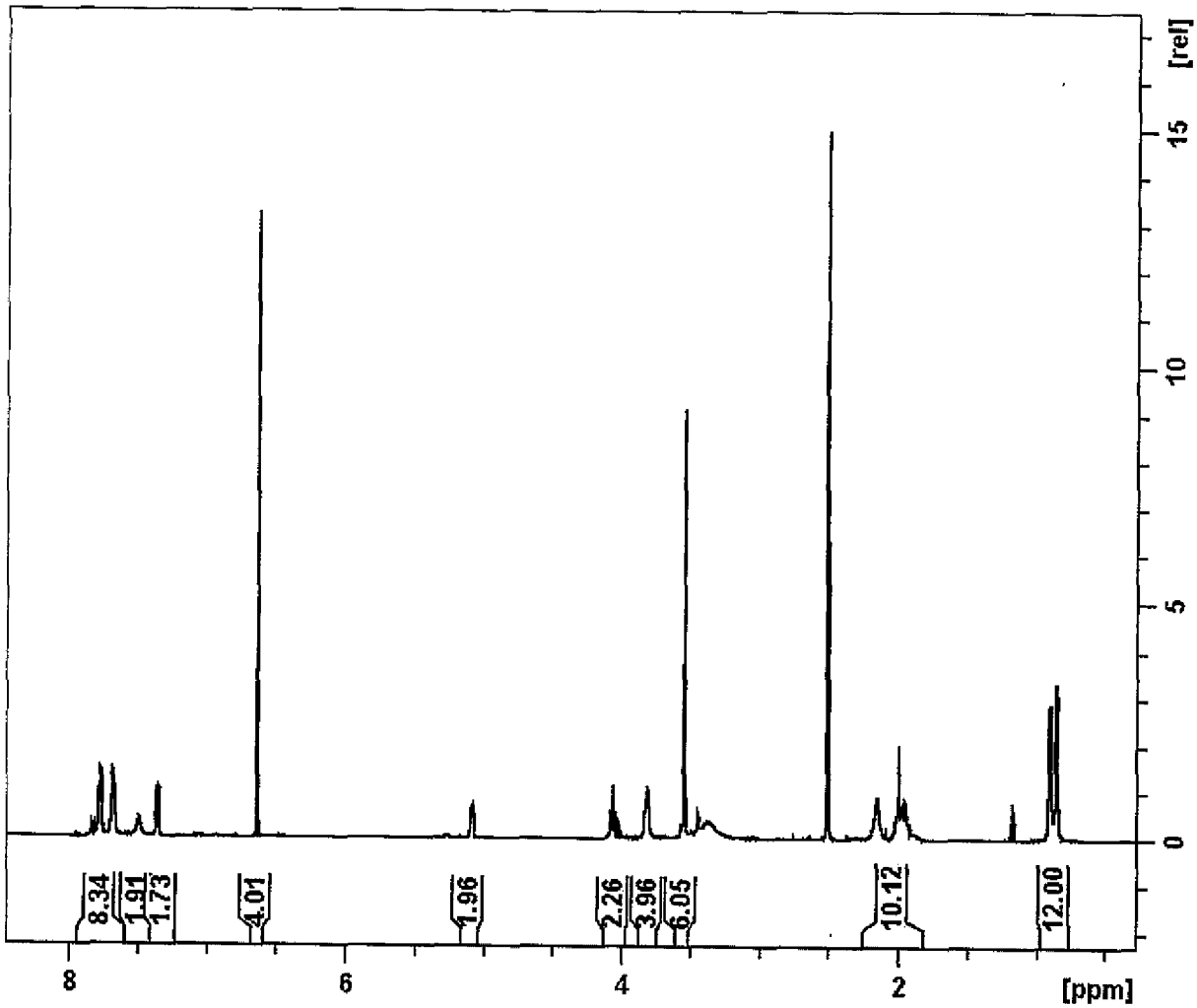


Figure 34

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2016/000058

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/14 A61K31/4178 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

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

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
20 July 2016	01/08/2016

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

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INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2016/000058

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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