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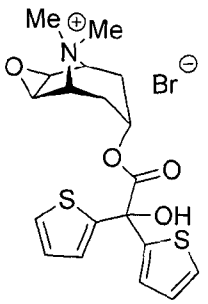
(54) Title: MIXED SOLVATE OF TIOTROPIUM BROMIDE AND A METHOD OF ITS PREPARATION



·x$CH_2(OH)CH(OH)CH_3$
·xCH_3CH_2OH

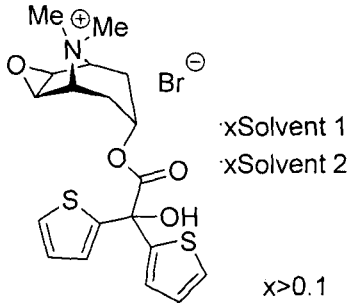
(V)

(57) Abstract: Mixed solvate of propyleneglycol/ethanol solvate of tiotropium bromide of formula V contains ethanol in the range of 3,000 to 40,000 ppm and propyleneglycol in the range of 3,000 to 40,000 ppm. An additional solution provides a method of preparing the solvate of tiotropium bromide, wherein a form of tiotropium bromide, selected from an anhydrous form, hydrate, solvate, or mixed solvate, is dissolved in a mixture of propyleneglycol and ethanol at a temperature in the range of from 40°C to the boiling point of the solvent, the formed solution is cooled down and the precipitated solvate is isolated. The solvate of tiotropium bromide is used in preparing an inhalation therapeutic formulation.

Mixed solvate of tiotropium bromide and a method of its preparation

Technical Field

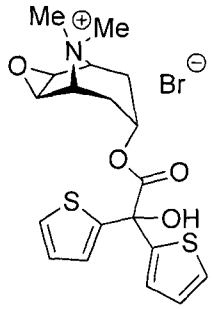
The invention relates to mixed solvates of tiotropium bromide of structure **I** and a method of their preparation. The invention includes a new solvate of tiotropium bromide as a combination of two solvents in amounts exceeding 0.1 equivalent of the solvent relatively to the molecule of tiotropium bromide.



(I)

Background Art

Tiotropium bromide of structure **II** is a trade name for 6-alpha,7-alpha-epoxy-8-methyl-8-azabicyclo(3.2.1)oct-3-endo-yl-di-2-thienyl) glycolate of methylbromide. Tiotropium bromide, first described in patent EP0418716, is a selective, competitive, reversible antagonist of cholinergic receptors with a long-lasting action. Contrary to the structurally close ipratropium, it selectively blocks muscarinic receptors M1 and M3, whereas M2 receptors are blocked shortly. It has significant bronchodilatation effects. It is in particular used in the therapy of chronic obstructive pulmonary disease (COPD) and in the therapy of asthma. The therapeutical dosing of the active substance is small (in micrograms), in the form of a powder applied by means of an inhalation appliance.

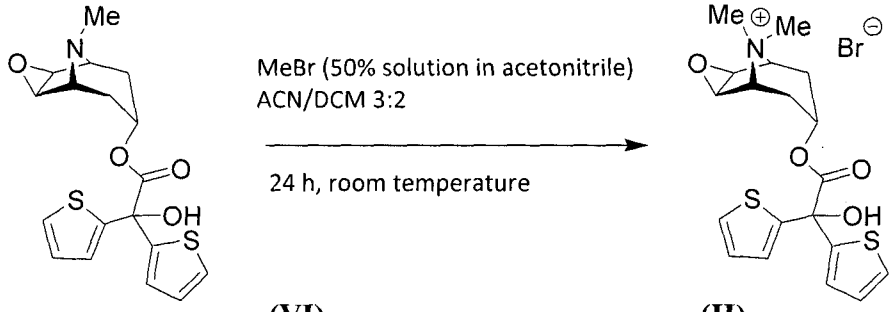


(II)

Concerning polymorphy, tiotropium bromide is a very interesting substance with many functional groups (ester group, hydroxyl group, thienyl, quaternary ammonium salt) capable to interact (hydrogen bonds, Van der Waals interactions, π-π stacking), which readily forms solvates, co-crystals, and various polymorphic forms.

A process of preparing tiotropium bromide was first published in patent EP0418716. It describes a reaction of scopine di(2-thienyl) glycolate of formula **VI** with methyl bromide (a 50% solution in anhydrous acetonitrile) in a mixture of the solvents dichloromethane and acetonitrile (Scheme 1). Subsequent recrystallization was carried out in an unspecified mixture of methanol and acetone and a white crystalline product with melting point 217 to 218°C was obtained.

Scheme 1

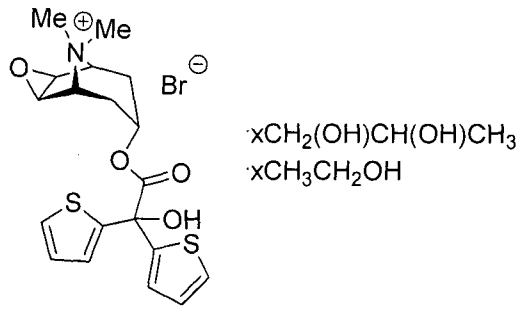


(VI) (II)

Tiotropium bromide monohydrate (EP 1 326 862) and anhydrous, or desolvated, forms of tiotropium bromide (EP 1 401 445, EP 1 682 542, EP 1 881 980) have been described in the literature. Also known are solvated forms (EP 1 879 888, EP 1 966 196, WO2010101538, WO201 101588), an amorphous form (EP 1 869 035), and a cocrystal with urea (EP 2 084 157).

Disclosure of Invention

This invention provides mixed propyleneglycol/ethanol solvate of tiotropium bromide of formula **V**

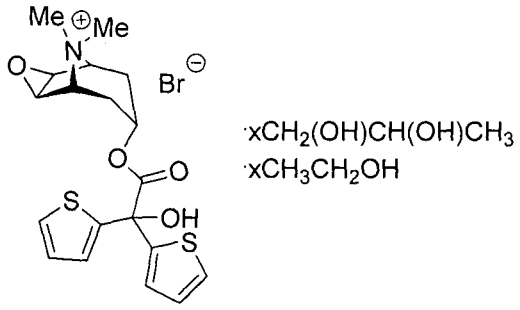


(V)

and a method of its preparation. This solvate can be used in preparing an inhalation therapeutic formulation for therapy of chronic obstructing pulmonary disease (COPD) and for therapy of asthma.

Detailed Description of Invention

This invention provides mixed propyleneglycol/ethanol solvate of tiotropium bromide of formula **V**



(V)

The mixed solvate prepared according to this invention shows the following characteristic reflections in the powder X-ray record, measured using CuKa radiation: 13.66; 15.55; 18.36; 20.16, 21.65 +/- 0.2° 2Th.

Additionally, the mixed solvate according to this invention shows the following further characteristic reflections in the powder X-ray record: of 10.17; 11.30; 16.54; 21.16; 23.90; 27.30; 29.90, 30.26 +/- 0.2° 2Th.

The solvate of tiotropium bromide prepared according to this invention contains ethanol in the range of 3,000 to 40,000 ppm and propyleneglycol in the range of 3,000 to 40,000 ppm. The contents of residual solvents were determined by gas chromatography.

The mixed solvate according to this invention can be prepared by dissolving the known forms of tiotropium bromide, for instance anhydrous forms, hydrates, and solvates and/or the known mixed solvates in a mixture of ethanol/propyleneglycol at an elevated temperature in the range between 40°C and the boiling point of the solvent; the resulting solution is cooled down and the precipitated solvate is isolated.

In a preferable embodiment of preparing the solvate according to this invention, a solvate of tiotropium bromide selected from the dichloromethane/acetonitrile solvate and/or the methanol/acetone solvate is used, dissolved in a mixture of propyleneglycol and ethanol at temperature in the range of 60 to 80°C; and the formed solution is cooled down to a temperature in the range of -5 to 10°C and the precipitated solvate is isolated.

The separated crude solvate is then dried at normal pressure or under vacuum at temperatures lower than the decomposition temperature of the mixed solvate, typically at temperatures in the range of 20 to 35°C.

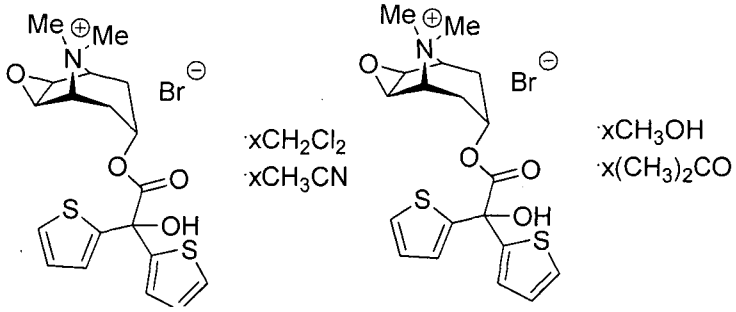
Before being used into a medicine form, the obtained solvate is then micronized to a particle size of 0-5 μm (analyzed by SEM - particle size).

Strict rules of registration authorities as regards the type (toxicity) of solvent specify the limits for solvents that can be found in a pharmaceutical product, either in the form of a solvate or as a residual solvent.

One-type solvates described in the patent literature (EP 1 879 888, EP 1 966 196, WO2010101538, WO201 101588) can represent a risk in terms acceptability, due to high amounts of a single solvent in the solvated form of tiotropium bromide, as well as to possible high toxicity of solvents in the described solvates.

On the contrary, mixed solvates can be an interesting compromise, wherein, in case of using pharmaceutically acceptable solvents, a lower portion of solvent would be declared since the same number of cavities in the solvate lattice is occupied by the same amount, however, of two or more types of solvents in case of the mixed solvate.

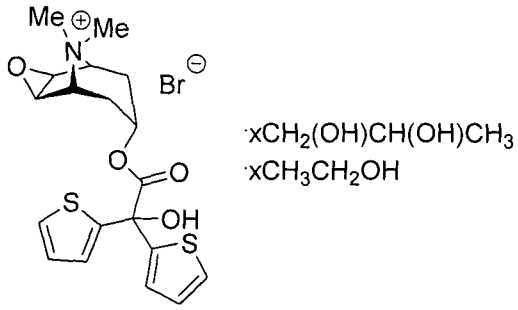
Our reproduction of the preparation of tiotropium bromide according to patent EP 0 418 716 by reaction of scopine di(2-thienyl) glycolate with methyl bromide (a 50% solution in anhydrous acetonitrile) in a mixture of the solvents dichloromethane and acetonitrile, followed by subsequent recrystallization in an unspecified mixture of methanol and acetone, resulted in formation of mixed solvates of tiotropium bromide, in particular of dichloromethane/acetonitrile solvate of formula **III** and methanol-acetone solvate of formula **IV.**



(III **(IV)**

However, the two mixed solvates lack utility in pharmaceutics because the toxic solvents, such as dichloromethane, acetonitrile, methanol, belong to class 2, the amount of which in a pharmaceutical product is limited due to toxicity associated with these solvents.

In a study of preparation of mixed solvates from various solvents, we have selected, as the most appropriate candidate from the prepared mixed solvates, propyleneglycol (propane-1 ,2-diol)-ethanol solvate of formula **V,** which meets the conditions of both lower amount of the two solvents and low toxicity of the selected solvents for formation of the mixed solvate.



(V)

Brief Description of Drawings

Figure 1a. X-ray powder record of dichloromethane/acetonitrile solvate of Example 1.

Figure 1b. DSC thermogram of dichloromethane/acetonitrile solvate of Example 1.

Figure 1c. TGA record of dichloromethane/acetonitrile solvate of Example 1.

Figure 2b. DSC thermogram of dichloromethane/acetonitrile solvate of Example 2.

Figure 2c. TGA record of dichloromethane/acetonitrile solvate of Example 2.

Figure 3a. X-ray powder record of methanol/acetone solvate of Example 3.

Figure 3b. DSC thermogram of methanol/acetone solvate of Example 3.

Figure 3c. TGA record of methanol/acetone solvate of Example 3.

Figure 4b. DSC thermogram of methanol/acetone solvate of Example 4.

Figure 4c. TGA record of methanol/acetone solvate of Example 4.

Figure 5a. X-ray powder record of propyleneglycol/ethanol solvate of Example 5.

Figure 5b. DSC thermogram of propyleneglycol/ethanol solvate of Example 5.

Figure 5c. TGA record of propyleneglycol/ethanol solvate of Example 5.

Figure 6b. DSC thermogram of propyleneglycol/ethanol solvate of Example 6.

Figure 6c. TGA record of propyleneglycol/ethanol solvate of Example 6.

Examples

Melting points were measured on the Kofler block.

The samples in the following Examples were characterized by the methods of X-ray powder diffraction, differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA). The amounts of solvents were determined by GC.

Measuring parameters of X-ray powder diffraction: The diffraction patterns were measured on an X'PERT PRO MPD PANalytical diffractometer with a graphite monochromator, radiation used CuKa (λ = 0.1542 nm (1.542 A)), excitation voltage: 45 kV, anode current: 40 mA, measured range: 2 to 40° 2Θ, step size: 0.01 ° 2Θ. The measuring was performed on a flat powder sample, which was placed on a Si plate. The primary optics was adjusted using programmable divergence diaphragms with the irradiated sample area 10 mm, Soller diaphragms 0.02 rad, and a ¼ anti-scattering diaphragm. The secondary optics was adjusted using an X'Celerator detector with the maximum opening of the detection aperture, the Soller diaphragms 0.02 rad, and a 5.0 mm anti-scattering diaphragm.

Differential scanning calorimetry (DSC) records were measured on a DSC Pyris 1 instrument from Perkin Elmer. Weight of the sample in a standard Al pan was 3 to 4 mg; heating rate 10°C/min. The temperature program used included stabilization at temperature 50°C for 1 minute and heating to 250°C at heating rate 10°C/min. Nitrogen 4.0 N_2 at flow rate 20 ml/min was used as a purge gas.

Thermogravimetric analysis (TGA) records were measured on a TGA 6 instrument from Perkin Elmer. Weight of the sample in a corundum crucible was 15 to 19 mg; heating rate 10°C/min. The temperature program used included stabilization at temperature 20°C for 1 minute and heating to 250°C with heating rate 10°C/min. Nitrogen 4.0 N_2 at flow rate 20 ml/min was used as a purge gas.

Gas chromatography (GC):

Method A: Monitoring of propyleneqlvcol

Propyleneglycol was determined by gas chromatography on an Agilent 7890 instrument with FI detection.

Chromatographic conditions:

Capilllary column: DB-624 (30 m; 0.53 mm ID; 3.0 μm df) or equivalent;

Temperature program: 70°C - 2 min, gradient 10°C /min to 170°C - 0 min,

Carrier gas: *helium for chromatography R*; 35 cm/s, constant flow rate

Injection: 1 µl

Injector: 200°C, split ratio 5 : 1

Detector: FID, 260°C

Evaluation:

The content of propyleneglycol expressed in ppm was evaluated by the method of external standard according to the formula:

$$x = \frac{A_x^{test} \times m_x^{ref}}{A_x^{ref} \times m_x^{test}} \times 5000 \text{ , wherein}$$

A_x^{test} area of the propyleneglycol peak in the chromatogram of the tested sample;

A_x^{ref} area of the propyleneglycol peak inn the chromatogram of the reference sample;

m_x^{ref} weight of propyleneglycol in a storage solution in mg;

m_x^{test} weight of the tested sample in mg.

Method B: Monitoring of the following solvents: methanol, ethanol, acetonitrile, acetone, dichloromethane.

Determination of these residual solvents was performed by the method of head-space gas chromatography using a PerkinElmer Autosystem XL instrument with FI detection and a TurboMatrix 40 head-space autosampler.

Chromatographic conditions:

Capillary column: CP Sil 5 CB (30 m * 0.32 mm × 3.0 µm) or equivalent;

Temperature program: 40°C - 3 min, gradient 20°C /min to 160°C - 2 min;

Carrier gas: *helium for chromatography R;* 1.6 ml/min

Injector: split flow rate 4.0 ml/min, 165°C

Detector: FID, 300°C, Range: 1, Attn: -3

Evaluation:

The content of residual solvents expressed in % was evaluated by the method of external standard according to the formula:

$$x = \frac{A_x^{test} \cdot m_x^{ref}}{A_x^{ref} \cdot m_x^{test}} \times 0{,}2$$, wherein

A_x^{test} ... peak area of an individual residual solvent in the chromatogram of the tested sample;

A_x^{ref} ... *peak* area of an individual residual solvent in the chromatogram of the reference sample;

m_x^{ref} ...weight of an individual residual solvent in the basic solution in mg;

m_x^{test} ...weight of the tested sample in mg.

Reference examples according to the procedure of patent EP0418716:

Preparation of dichloromethane/acetonitriie solvate of tiotropium bromide (III)

Example 1

15.0 g of scopine di(2-thienyl)glycolate (39.7 mmol) was dissolved in 150 ml of a mixture of dichloromethane (60 ml) and acetonitrile (90 ml) at 55°C; the solution was cooled to 33°C and 35.0 g of 55% MeBr in acetonitrile (5.1 equivalent) was added. The solution was stirred and left to cool down freely without stirring still for 24 hours. The formed crystalline product was filtered, washed with 60 ml of dichloromethane, and dried in a vacuum oven at 35°C for 6 hours. 20.3 g of white crystals were obtained, HPLC purity 99.55%. The content of solvents (determined by GC): dichloromethane 61,000 ppm, acetonitrile 9,700 ppm.

X-ray powder diffraction - Diffraction peaks of dichloromethane/acetonitriie solvate

Pos. [°2Th.]	d [A] = 0.1 nm	Rel. Int. [%]
9.90	8.925	55.5

11.05	8.002	9.8
13.36	6.621	53.2
15.24	5.809	72.3
16.11	5.496	61.1
18.06	4.908	66.2
19.89	4.460	100.0
21.04	4.220	35.6
21.46	4.138	59.9
23.17	3.835	39.8
23.60	3.767	61.7
23.79	3.737	35.4
24.64	3.611	38.3
24.98	3.563	53.9
26.12	3.409	15.4
30.15	2.962	60.3
32.60	2.745	97.8

The thermogram of differential scanning calorimetry (DSC) contains a minor endotherm of T_{onSeti} = 160.2°C, $\mathbf{T_{peak1}}$ = 169.8°C, and a major endotherm of $\mathbf{T_{onSet2}}$ = 226.3°C, $\mathbf{T_{peak2}}$ = 228.4°C; the thermogravimetric analysis (TGA) record shows 9.2% of the solvent.

The X-ray powder record is shown in the Annex in Figure **1a,** the DSC thermogram is in Figure **1b,** and the TGA record is in Figure **1c.**

Example 2

2.0 g of scopine di(2-thienyl)glycolate (5.3 mmol) was dissolved in 20 ml of a mixture of dichloromethane (8 ml) and acetonitrile (12 ml) at 55°C. The solution was cooled down to 33°C and 5.46 g of 55% MeBr in acetonitrile (5.1 equivalents) was added. The solution was stirred and left to cool freely without stirring still for 48 hours. The formed crystalline product was filtered, washed with 30 ml of dichloromethane, and dried in a vacuum oven at 35°C for 6 hours. 2.65 g of white crystals were obtained,

HPLC purity 99.60%. The content of solvents (determined by GC): dichloromethane 69,000 ppm, acetonitrile 8,200 ppm.

The X-ray record was identical to the X-ray diffraction pattern from Example 1.

The DSC thermogram contains a minor endotherm of T_{onset1} = 157.9°C, T_{peak1} = 164.8°C, and a major endotherm of T_{onset2} = 227.4°C, T_{peak2} = 228.9°C; the scan of the thermogravimetric analysis (TGA) shows 8.6 % of the solvent.

DSC thermogram is shown in the Annex in Figure **2b** and TGA scan is in Figure **2c.**

Preparation of methanol/acetone solvate of tiotropium bromide (IV)

(recrystallization according to the procedure of patent EP 0 418 716)

Example 3

5.0 g of tiotropium bromide (dichloromethane/acetonitrile solvate) was dissolved in 42 ml of a mixture methanol (24 ml) /acetone (18 ml) = 4/3 (57 % MeOH) at 60°C. The solution was cooled to -10 °C within 90 min and further stirred at this temperature for 3.5 hours. The recrystallized product was filtered, washed with a minimum amount of ice-cold acetone, and dried under vacuum at 87°C for 17 hours. 3.46 g of white crystals were obtained; yield 69%, HPLC purity 99.90%. The content of solvents (determined by GC): methanol 23,000 ppm, acetone 4,500 ppm.

X-ray powder diffraction - Diffraction peaks of methanol/acetone solvate

Pos. [°2Th.]	d [A] = 0.1 nm	Rel. Int. [%]
6.88	12.831	25.2
10.04	8.806	33.9
11.14	7.937	27.5
13.54	6.536	62.7
13.65	6.481	95.6
15.47	5.724	66.8
18.20	4.870	67.5
20.04	4.427	75.6
21.55	4.121	100.0

23.70	3.751	12.6
24.24	3.668	27.2
24.78	3.590	17.6
25.25	3.524	27.5
26.10	3.41 1	17.1
27.33	3.261	34.0
28.13	3.170	18.3
30.96	2.886	14.5
32.14	2.783	20.0
33.33	2.686	13.9

The thermogram of differential scanning calorimetry (DSC) contains a minor endotherm of T_{onset1} = 134.6°C, T_{peak1} = 139.2°C, and a major endotherm of T_{onset2} = 227.0°C, T_{peak2} = 230.3°C; the record of the thermogravimetric analysis (TGA) shows 4.1% of the solvent.

The X-ray powder record is shown in the Annex in Figure 3a, DSC record is in Figure 3b, and TGA scan is in Figure 3c.

Example 4

490 mg of tiotropium bromide (dichloromethane/acetonitrile solvate) was dissolved in 5 ml of a mixture methanol (2 ml) /acetone (3 ml) = 4/3 (40 % MeOH) at 75°C. The solution was cooled to 0°C within 60 min and further stirred at this temperature for 1.5 hour. The crystalline product was filtered, washed with a minimum amount of acetone, and dried at 111°C for 22 hours. 160 mg of white crystals were obtained; yield 33%, HPLC purity 99.80%. The content of solvents (determined by GC): methanol 15,900 ppm, acetone 12,000 ppm.

The X-ray record of the sample from Example 4 was similar to the diffraction pattern from Example 3.

The thermogram of the differential scanning calorimetry (DSC) for Example 4 contains a minor endotherm of T_{onset1} = 113.8°C, T_{peak1} = 122.2°C, and a major endotherm

of T_{onset2} = 228.5°C, T_{peak2} = 231.7°C; the record of the thermogravimetric analysis (TGA) shows 3.8% of the solvent.

The DSC records are shown in the Annex in Figures **4b,** TGA scans are in Figures **4c.**

Working examples according to the invention

Preparation of propyleneglycol/ethanol solvate of tiotropium bromide (V)

Example 5

5.0 g of tiotropium bromide (dichloromethane/acetonitrile solvate) was dissolved in 100 ml of a mixture propyleneglycol (40 ml) /ethanol (60 ml) = 2/3 at 80°C. The solution was cooled to 5°C within 90 minutes and further stirred at this temperature for 18 hours. The crystals were filtered, washed with a minimum amount of ethanol, and dried in a vacuum oven at 0.04 MPa (400 mbar) at laboratory temperature for 0.5 hour; then dried freely. 4.09 g of white crystals were obtained; yield 82%, HPLC purity 99.84%. The content of solvents (determined by GC): ethanol 35,000 ppm, propyleneglycol 14,000 ppm.

The X-ray powder diffraction - diffraction peaks of propyleneglycol/ethanol solvate

Pos. [°2Th.]	d [A] = 0.1 nm	Rel. Int. [%]
10.17	8.695	16.8
11.30	7.821	19.7
13.66	6.478	50.2
15.55	5.694	50.3
16.54	5.356	15.2
18.36	4.829	100.0
20.16	4.401	78.5
21.16	4.196	55.4
21.65	4.102	90.0
23.38	3.803	16.0
23.90	3.720	32.0

24.20	3.675	37.4
24.93	3.569	31.0
25.33	3.513	36.3
26.24	3.393	42.1
27.30	3.264	38.1
28.07	3.177	27.5
29.90	2.986	18.1
30.26	2.951	21.0
32.19	2.779	24.0
34.53	2.596	12.3

The thermogram of the differential scanning calorimetry (DSC) contains a minor endotherm of T_{onset1} = 150.0°C, T_{peak1} = 152.6°C, and a major endotherm of T_{onset2} = 227.2°C, T_{peak2} = 230.2°C; the record of the thermogravimetric analysis (TGA) shows 6.2% of the solvent.

The X-ray powder record is shown in the Annex in Figure **5a,** DSC record is in Figure **5b,** and TGA scan is in Figure **5c.**

Example 6

2.0 g of tiotropium bromide (dichloromethane solvate) was dissolved in 40 ml of a mixture propyleneglycol (16 ml) / ethanol (24 ml) = 2/3 at 80°C. The solution was cooled to 5°C within 90 minutes and stirred at this temperature for 2 hours. The reaction mixture was cooled to 0°C and stirred at this temperature for 2 hours. The crystals were filtered, washed with a minimum amount of ethanol, dried in a vacuum oven at 0.03 to 0.04 MPa (300 to 400 mbar) at laboratory temperature for 0.5 hour and then dried freely. 1.61 g of white crystals were obtained, yield 81%, HPLC purity 99.6%. The content of solvents (determined by GC): ethanol 30,000 ppm, propyleneglycol 35,000 ppm.

The X-ray record was identical to the X-ray diffraction pattern from Example 5.

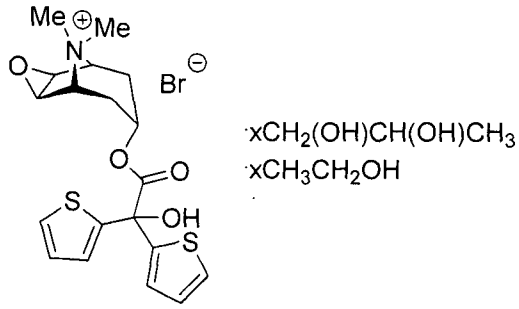
The thermogram of the differential scanning calorimetry (DSC) contains a minor endotherm of T_{onset1} = 154.3°C, T_{peak1} = 162.6°C, and a major endotherm of T_{onset2} =

222.3°C, T_{peak2} = 225.3°C; the record of the thermogravimetric analysis (TGA) shows 7.6 % of the solvent.

The DSC record is shown in the Annex in Figure **6b,** and TGA scan is in Figure **6c.**

Claims

1) Mixed propyleneglycol/ethanol solvate of tiotropium bromide of formula **V**



V

2) The solvate of tiotropium bromide according to claim 1, showing the following characteristic peaks in the powder X-ray record, measured using radiation CuKa: 13.66; 15.55; 18.36; 20.16, 21.65 +/- 0.2° 2Th.

3) The solvate of tiotropium bromide according to claims 1 or 2, showing the following additional characteristic peaks in the powder X-ray record, measured using radiation CuKa: 10.17; 11.30; 16.54; 21.16; 23.90; 27.30; 29.90, 30.26 +/- 0.2° 2Th.

4) The solvate of tiotropium bromide according to claims 1, 2 or 3, characterized in that it contains ethanol in the range of 3,000 to 40,000 ppm.

5) The solvate of tiotropium bromide according to any one of the preceding claims, characterized in that it contains propyleneglycol in the range of 3,000 to 40,000 ppm.

6) A method of preparing the solvate of tiotropium bromide according to claims 1 to 5, characterized in that a form of tiotropium bromide, selected from an anhydrous form, hydrate, solvate, or mixed solvate, is dissolved in a mixture of propyleneglycol and ethanol at a temperature in the range of from 40°C to the boiling point of the solvent, and the formed solution is cooled down and the precipitated solvate is isolated.

7) The method according to claim 6, characterized in that a solvate of tiotropium bromide selected from dichloromethane/acetonitrile solvate and/or methanol/acetone solvate is dissolved in a mixture of propyleneglycol and

ethanol at a temperature in the range of from 60 to 80°C, the formed solution is cooled down and the precipitated solvate is isolated.

8) The method according to claim 6, characterized in that the solution is cooled down to a temperature in the range of from -5 to 10°C.

9) Use of the solvate of tiotropium bromide according to claims 1 to 5 for preparing an inhalation therapeutic formulation.

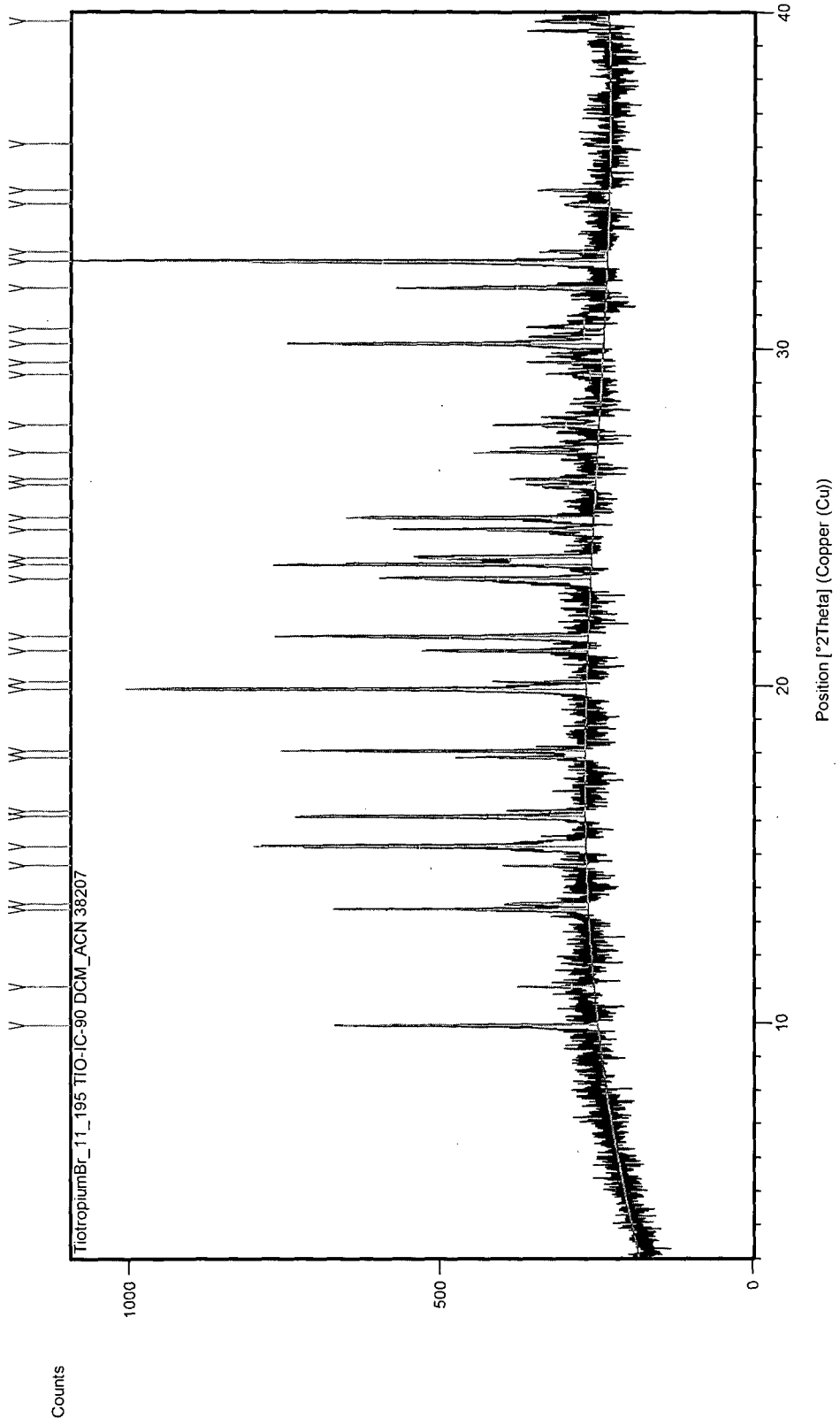
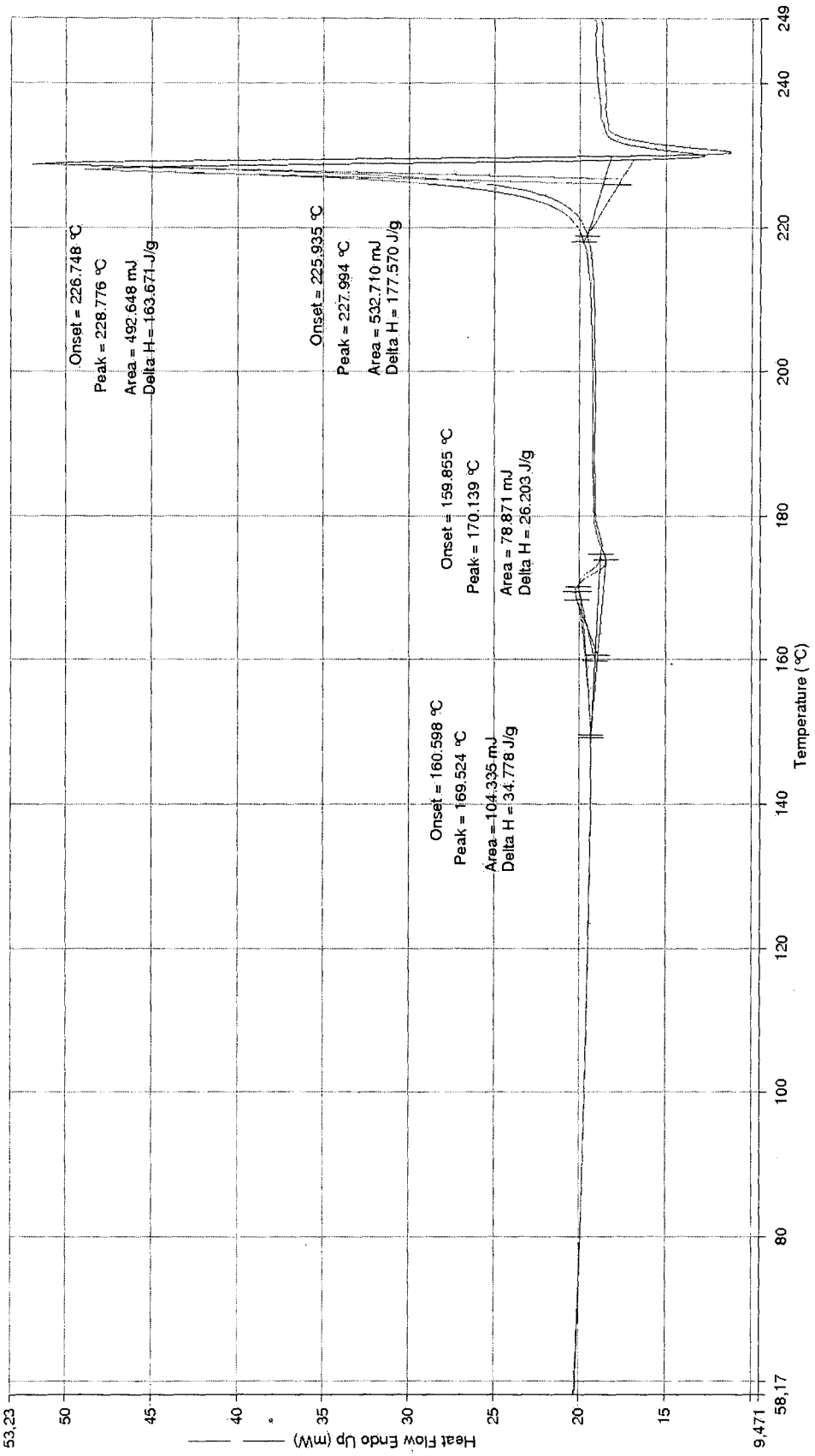

TiotropiumBr_11_195 TIO-IC-90 DCM_ACN 38207
Counts
1000
500
0
10
20
30
40
Position [°2Theta] (Copper (Cu))

Figure 1a

Figure 1b


Onset = 226.748 °C
Peak = 228.776 °C
Area = 492.648 mJ
Delta H = 163.671 J/g
Onset = 225.935 °C
Peak = 227.994 °C
Area = 532.710 mJ
Delta H = 177.570 J/g
Onset = 139.855 °C
Peak = 170.139 °C
Area = 78.871 mJ
Delta H = 26.203 J/g
Onset = 160.598 °C
Peak = 169.524 °C
Area = 104.335 mJ
Delta H = 34.778 J/g
Heat Flow Endo Up (mW)
Temperature (°C)
53,23
9,471
58,17
50
45
40
35
30
25
20
15
100
80
120
140
160
180
200
220
240
249

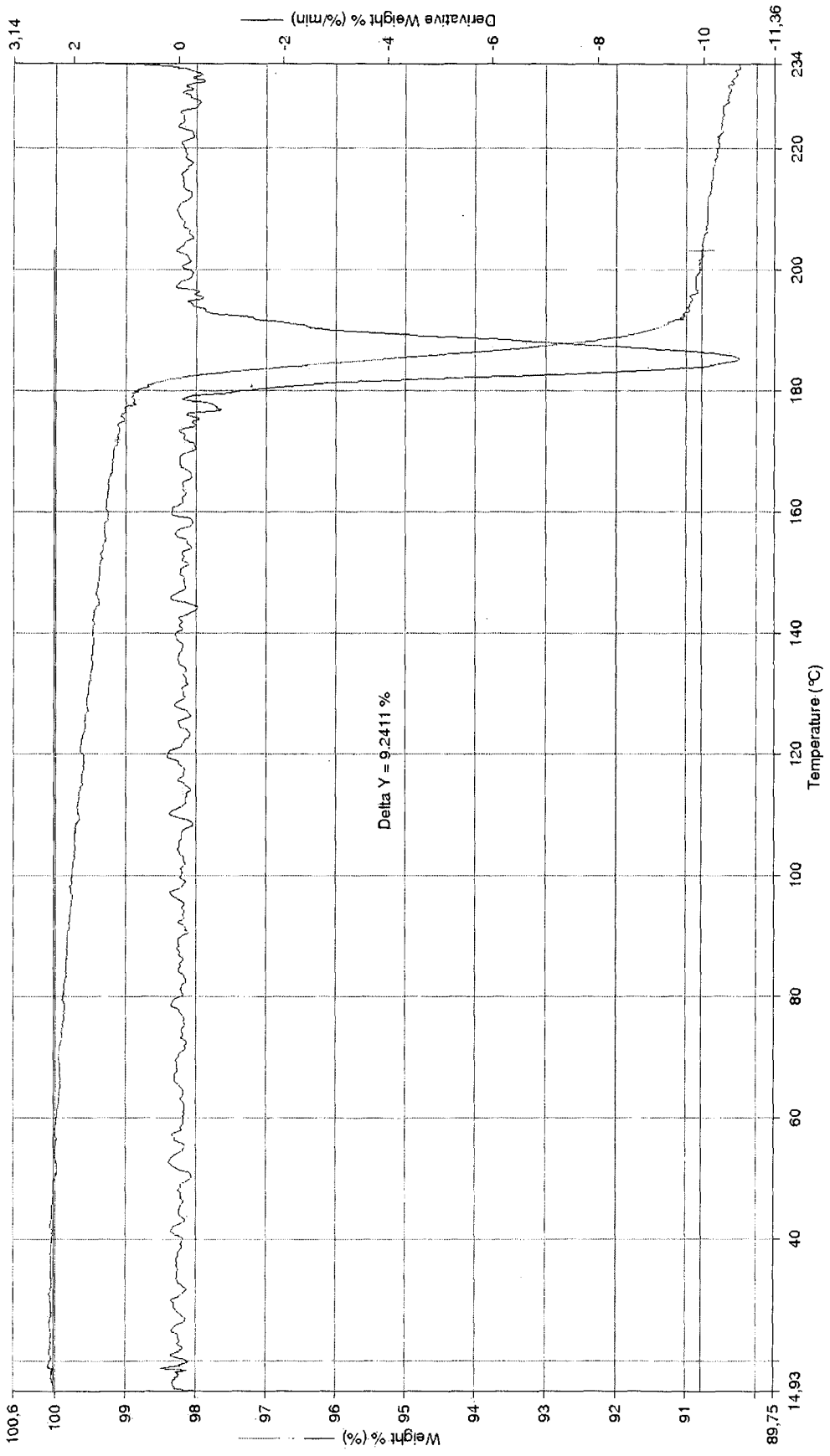
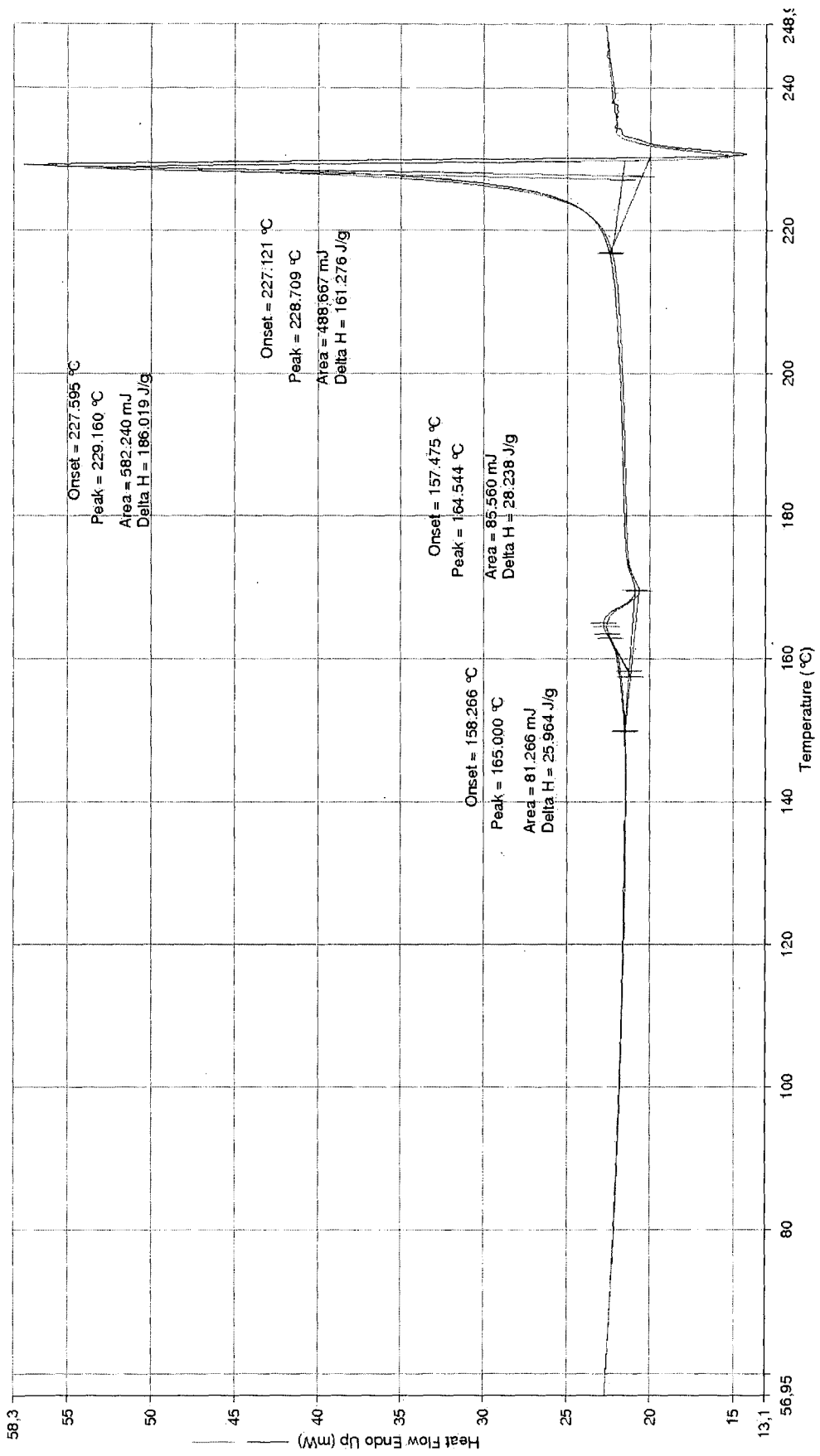

Derivative Weight % (%/min)
3,14
2
0
-2
-4
-6
-8
-10
-11,36
Weight % (%)
100,6
100
99
98
97
96
95
94
93
92
91
89,75
14,93
Delta Y = 9.2411 %
234
220
200
180
160
140
120
100
80
60
40
Temperature (°C)

Figure 1c

Figure 2b


Onset = 227.595 °C
Peak = 229.160 °C
Area = 582.240 mJ
Delta H = 186.019 J/g
Onset = 227.121 °C
Peak = 228.709 °C
Area = 488.667 mJ
Delta H = 161.276 J/g
Onset = 157.475 °C
Peak = 164.544 °C
Area = 85.560 mJ
Delta H = 28.238 J/g
Onset = 158.266 °C
Peak = 165.000 °C
Area = 81.266 mJ
Delta H = 25.964 J/g
Heat Flow Endo Up (mW)
Temperature (°C)
58,3
55
50
45
40
35
30
25
20
15
13,1
56,95
80
100
120
140
160
180
200
220
240
248,

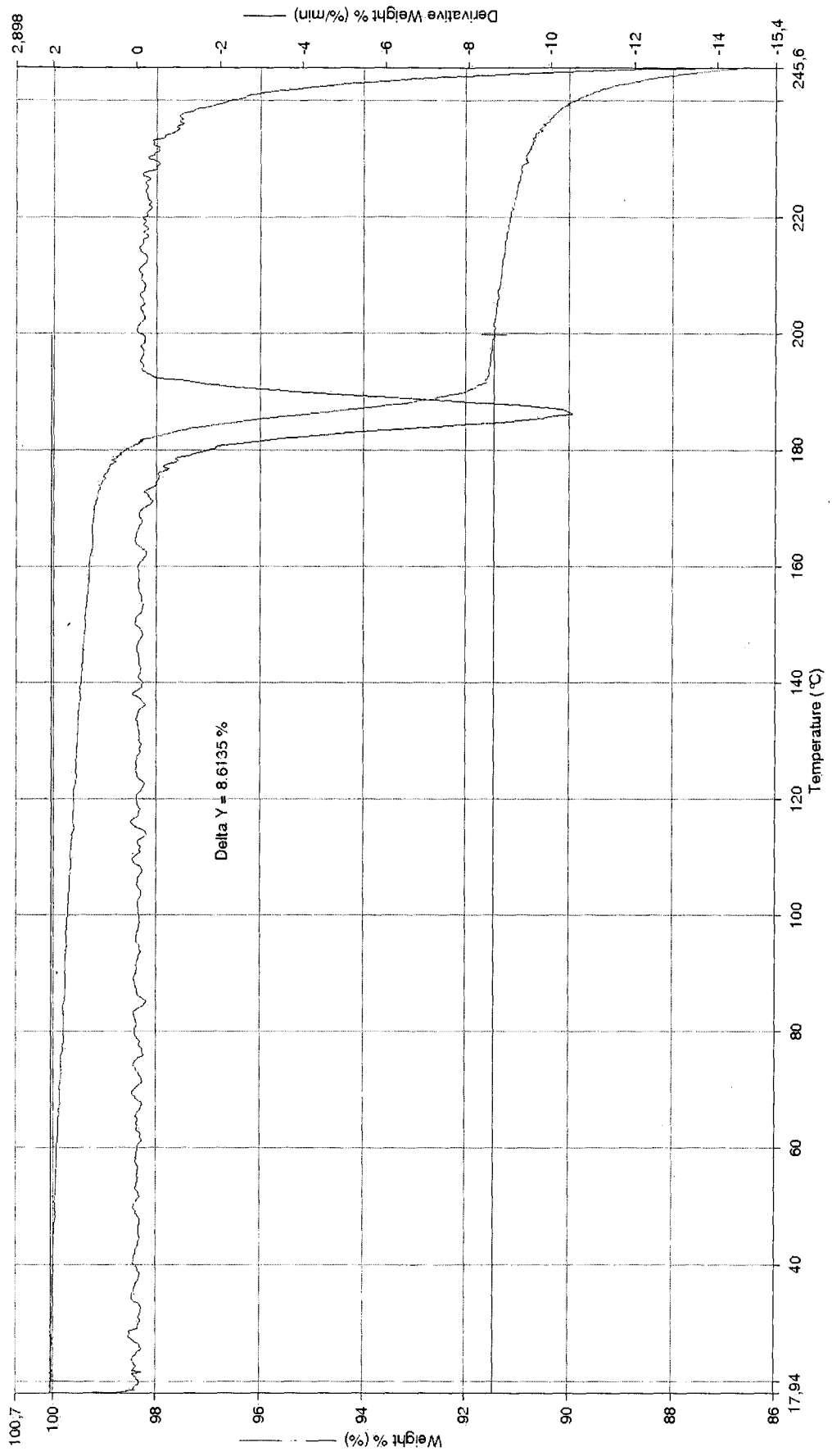

Derivative Weight % (%/min)
2,898
2
0
-2
-4
-6
-8
-10
-12
-14
-15,4
245,6
220
200
180
160
140
120
100
80
60
40
17,94
Temperature (°C)
Delta Y = 8.6135 %
Weight % (%)
100,7
100
98
96
94
92
90
88
86

Figure 2c

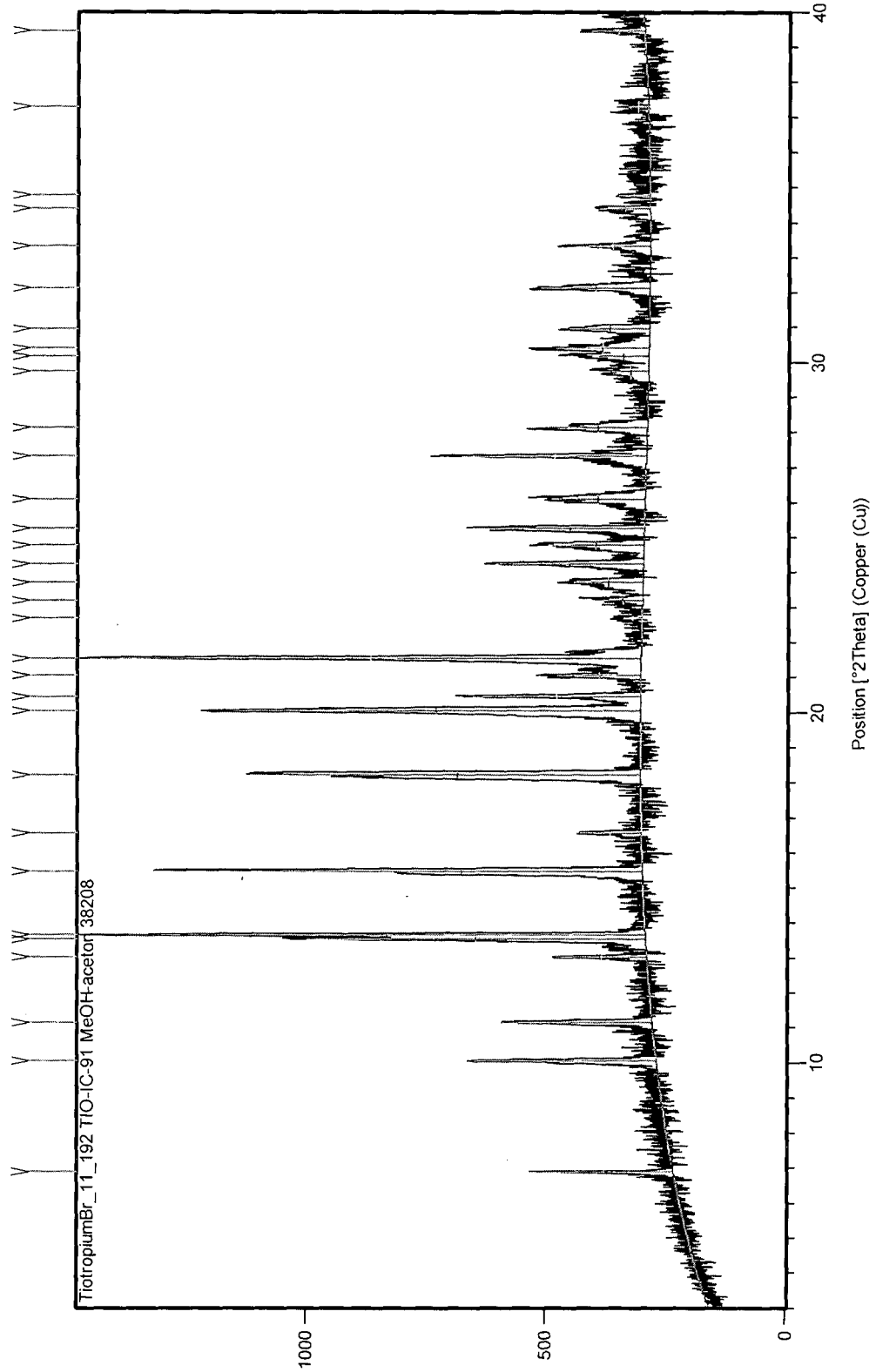
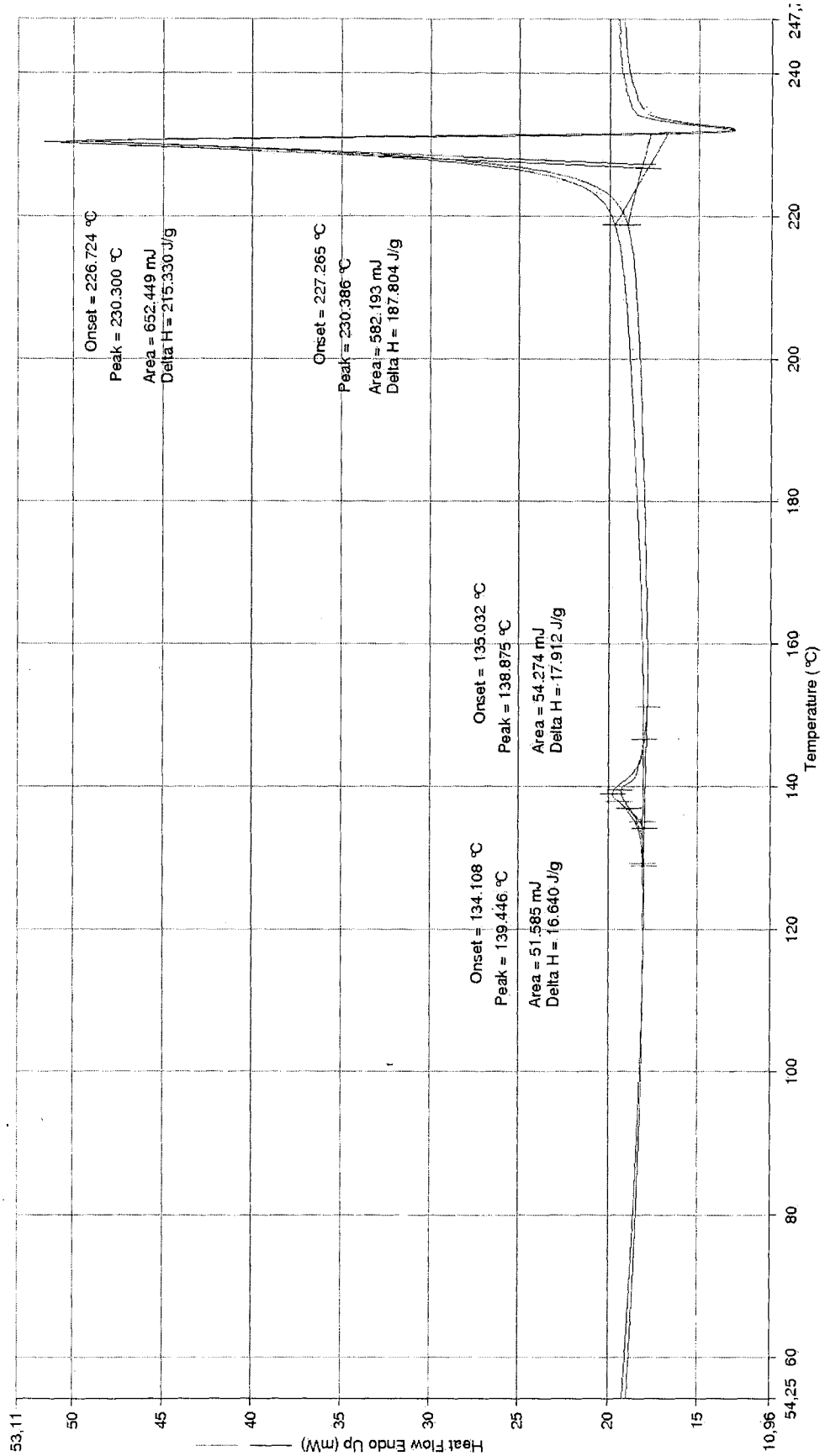

TiotropiumBr_11_192 TIO-IC-91 MeOH-aceton 38208
Counts
1000
500
0
10
20
30
40
Position [°2Theta] (Copper (Cu))

Figure 3a

Figure 3b


Onset = 226.724 °C
Peak = 230.300 °C
Area = 652.449 mJ
Delta H = 215.330 J/g
Onset = 227.265 °C
Peak = 230.386 °C
Area = 582.193 mJ
Delta H = 187.804 J/g
Onset = 135.032 °C
Peak = 138.875 °C
Area = 54.274 mJ
Delta H = 17.912 J/g
Onset = 134.108 °C
Peak = 139.446 °C
Area = 51.585 mJ
Delta H = 16.640 J/g
Heat Flow Endo Up (mW)
Temperature (°C)
53,11
10,96
54,25
247,
50
45
40
35
30
25
20
15
60
80
100
120
140
160
180
200
220
240

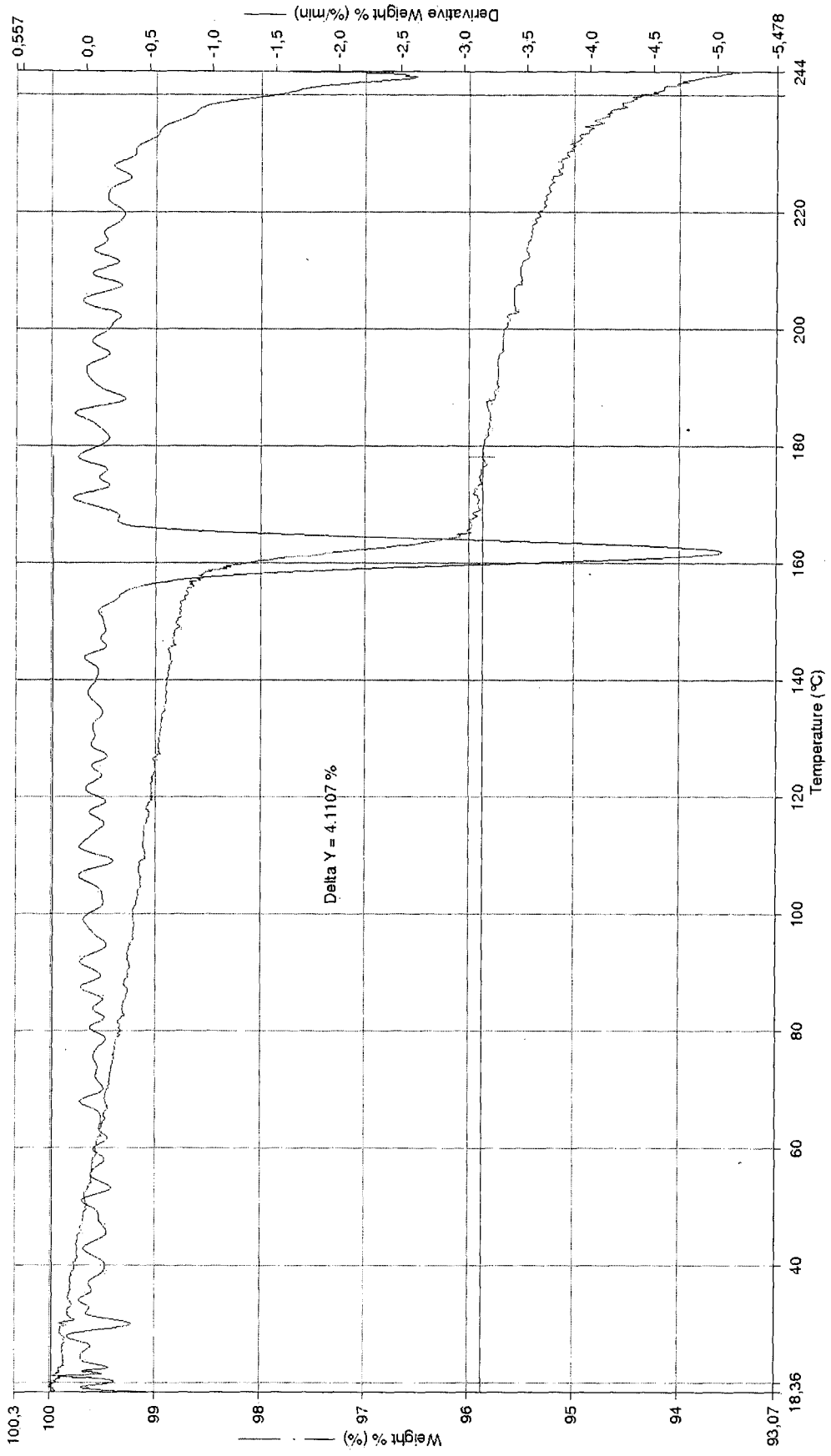

Derivative Weight % (%/min)
0,557
0,0
-0,5
-1,0
-1,5
-2,0
-2,5
-3,0
-3,5
-4,0
-4,5
-5,0
-5,478
Weight % (%)
100,3
100
99
98
97
96
95
94
93,07
18,36
Delta Y = 4.1107 %
40
60
80
100
120
140
160
180
200
220
244
Temperature (°C)

Figure 3c

Figure 4b

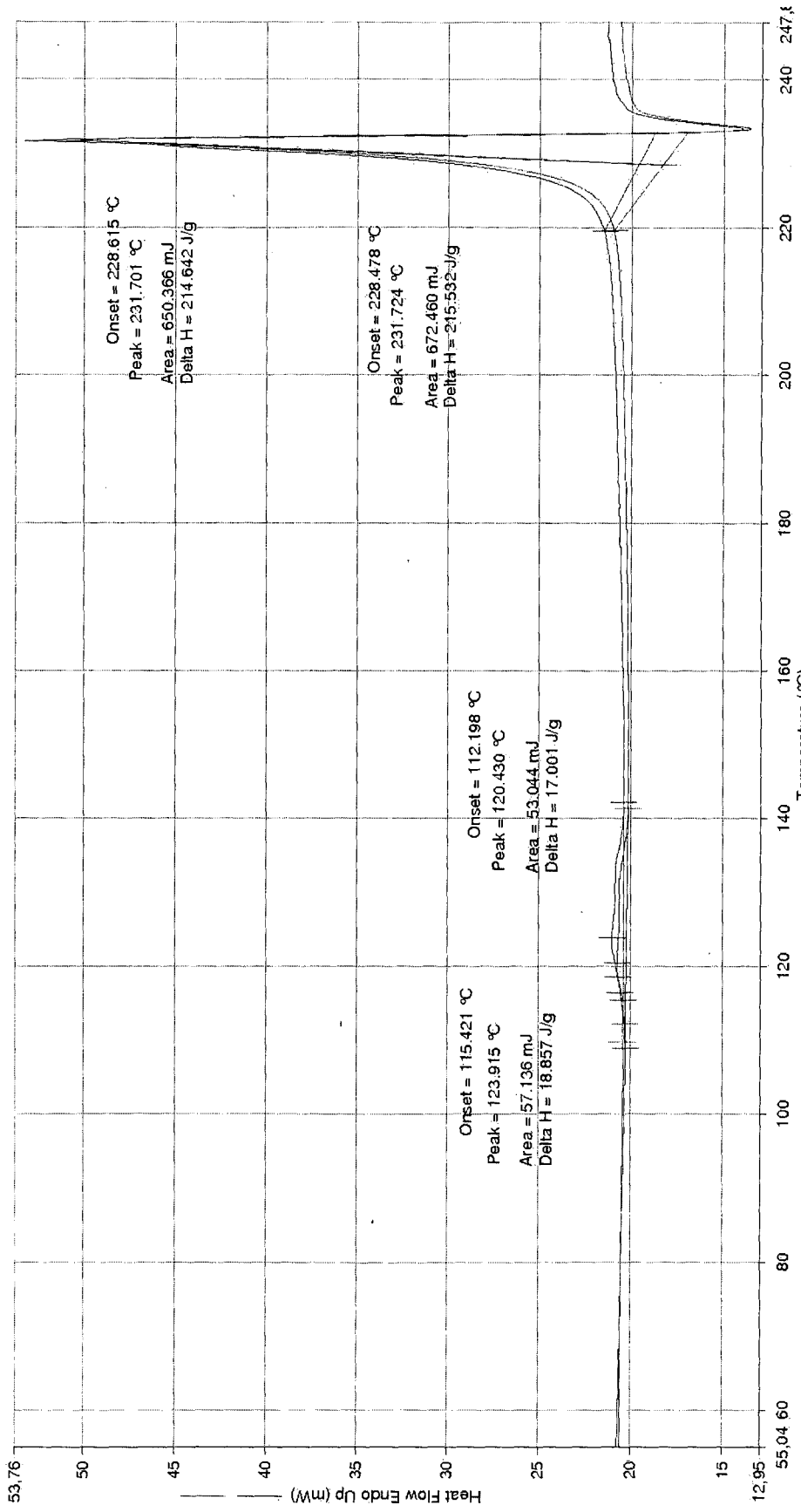
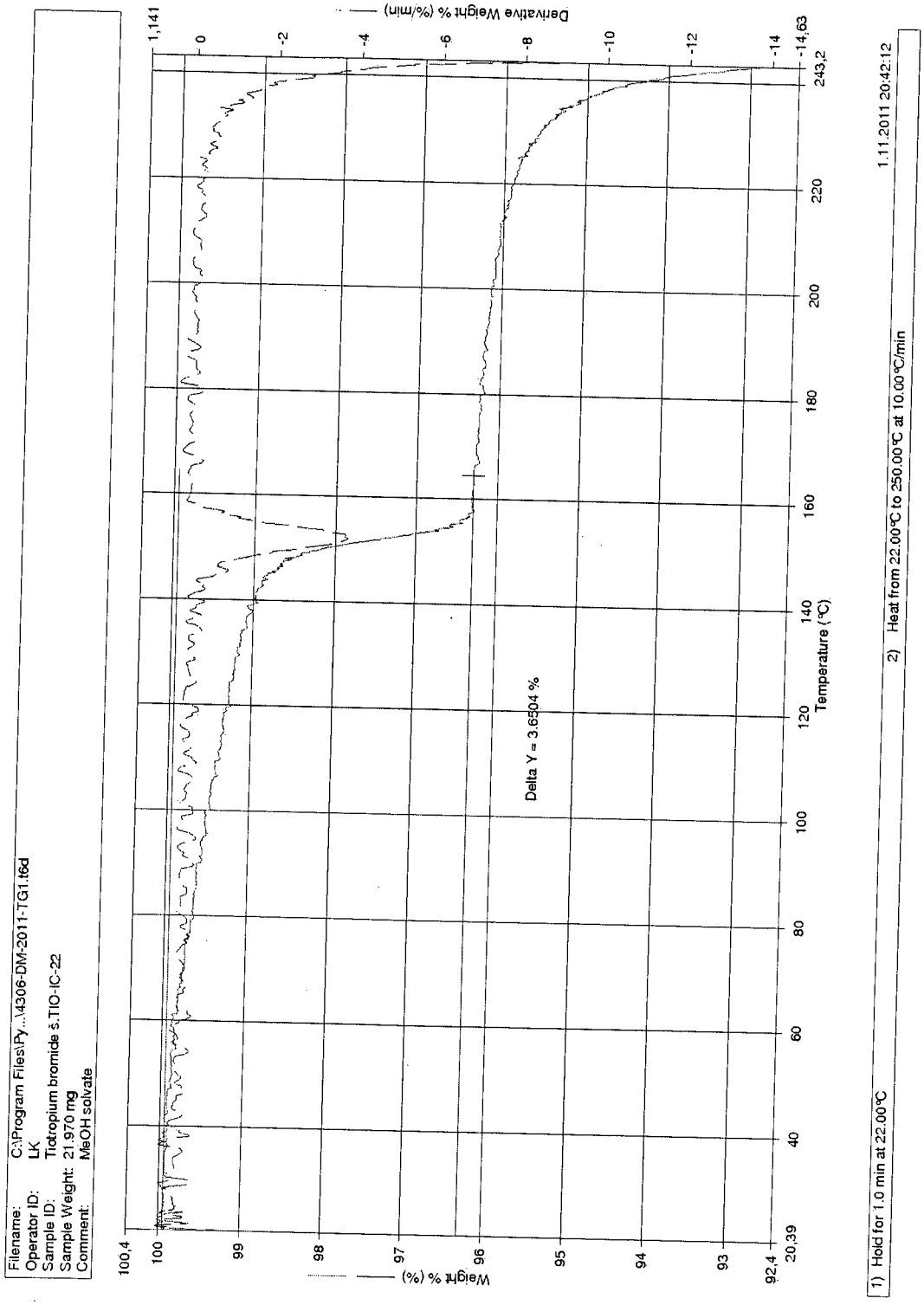

Onset = 228.615 °C
Peak = 231.701 °C
Area = 650.366 mJ
Delta H = 214.642 J/g
Onset = 228.478 °C
Peak = 231.724 °C
Area = 672.460 mJ
Delta H = 215.532 J/g
Onset = 112.198 °C
Peak = 120.430 °C
Area = 53.044 mJ
Delta H = 17.001 J/g
Onset = 115.421 °C
Peak = 123.915 °C
Area = 57.136 mJ
Delta H = 18.857 J/g
Heat Flow Endo Up (mW)
Temperature (°C)
53,76
50
45
40
35
30
25
20
15
12,95
55,04
60
80
100
120
140
160
180
200
220
240
247,

Figure 4c


Filename: C:\Program Files\Py...\4306-DM-2011-TG1.t6d
Operator ID: LK
Sample ID: Tiotropium bromide š.TIO-IC-22
Sample Weight: 21.970 mg
Comment: MeOH solvate
Weight % (%)
Derivative Weight % (%/min)
Temperature (°C)
Delta Y = 3.6504 %
1) Hold for 1.0 min at 22.00°C
2) Heat from 22.00°C to 250.00°C at 10.00°C/min
1.11.2011 20:42:12

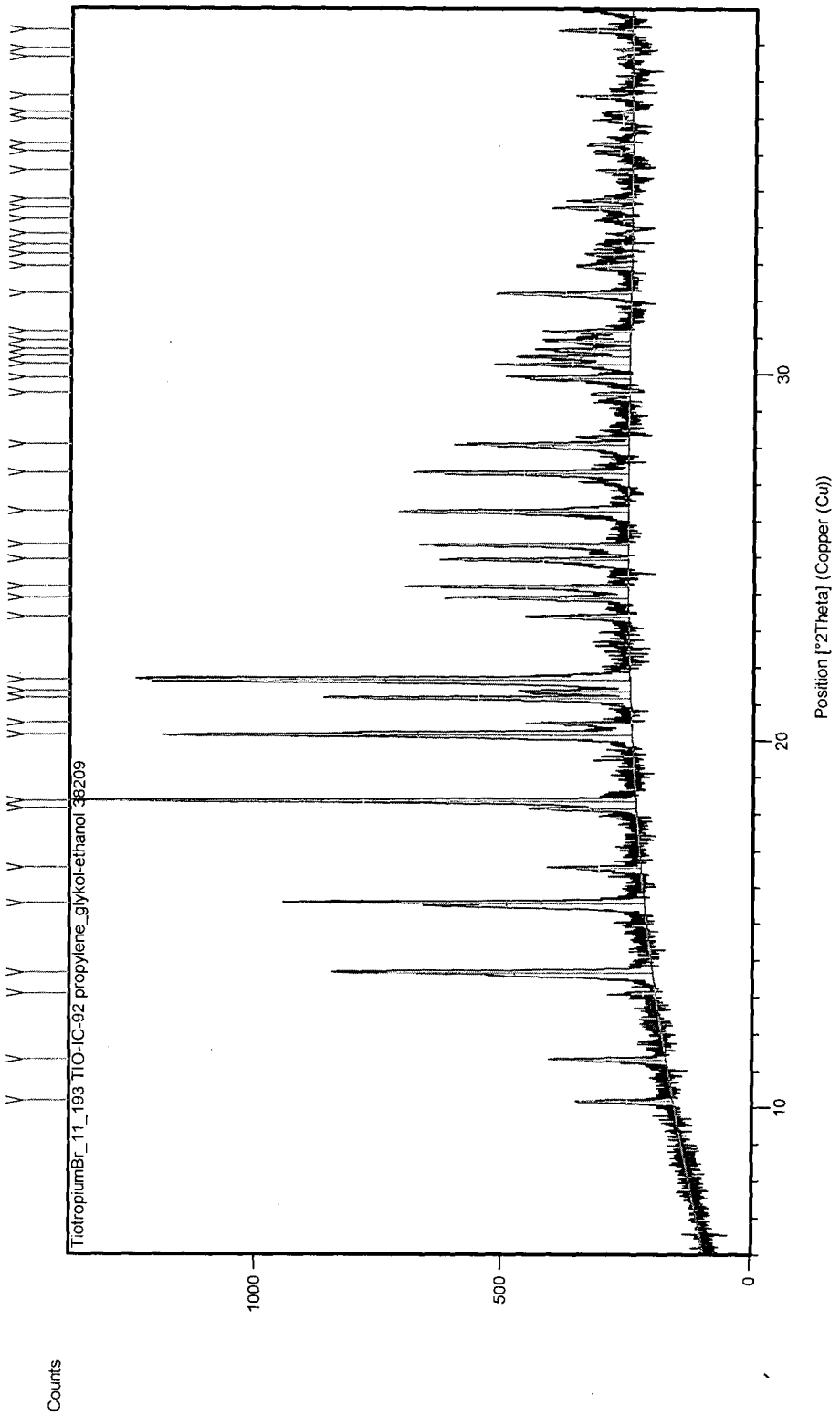
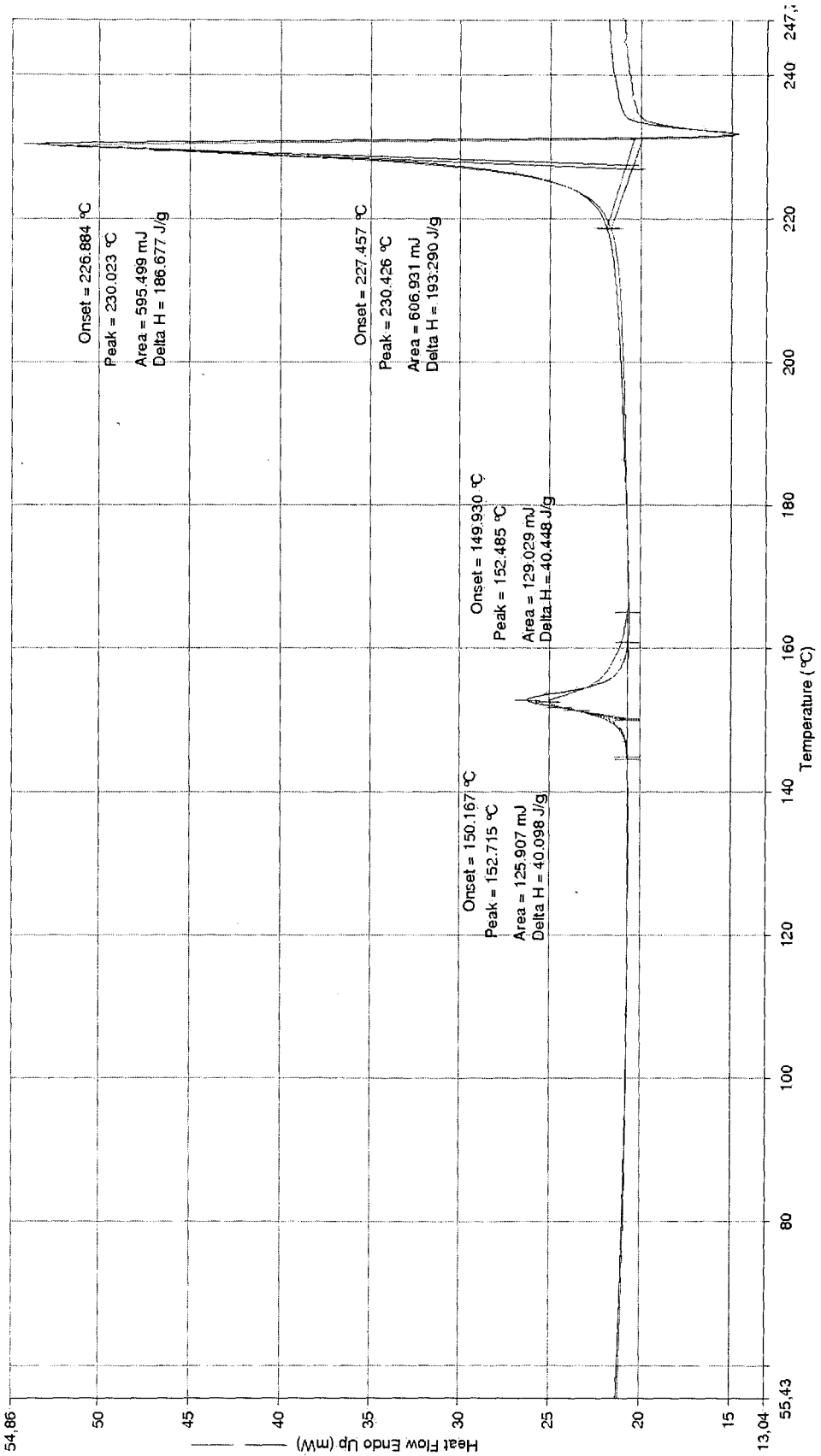

TiotropiumBr_11_193 TIO-IC-92 propylene_glykol-ethanol 38209
Counts
1000
500
0
10
20
30
Position [°2Theta] (Copper (Cu))

Figure 5a

Figure 5b


Onset = 226.884 °C
Peak = 230.023 °C
Area = 595.499 mJ
Delta H = 186.677 J/g
Onset = 227.457 °C
Peak = 230.426 °C
Area = 606.931 mJ
Delta H = 193.290 J/g
Onset = 149.930 °C
Peak = 152.485 °C
Area = 129.029 mJ
Delta H = 40.448 J/g
Onset = 150.167 °C
Peak = 152.715 °C
Area = 125.907 mJ
Delta H = 40.098 J/g
Heat Flow Endo Up (mW)
Temperature (°C)
54,86
50
45
40
35
30
25
20
15
13,04
55,43
80
100
120
140
160
180
200
220
240

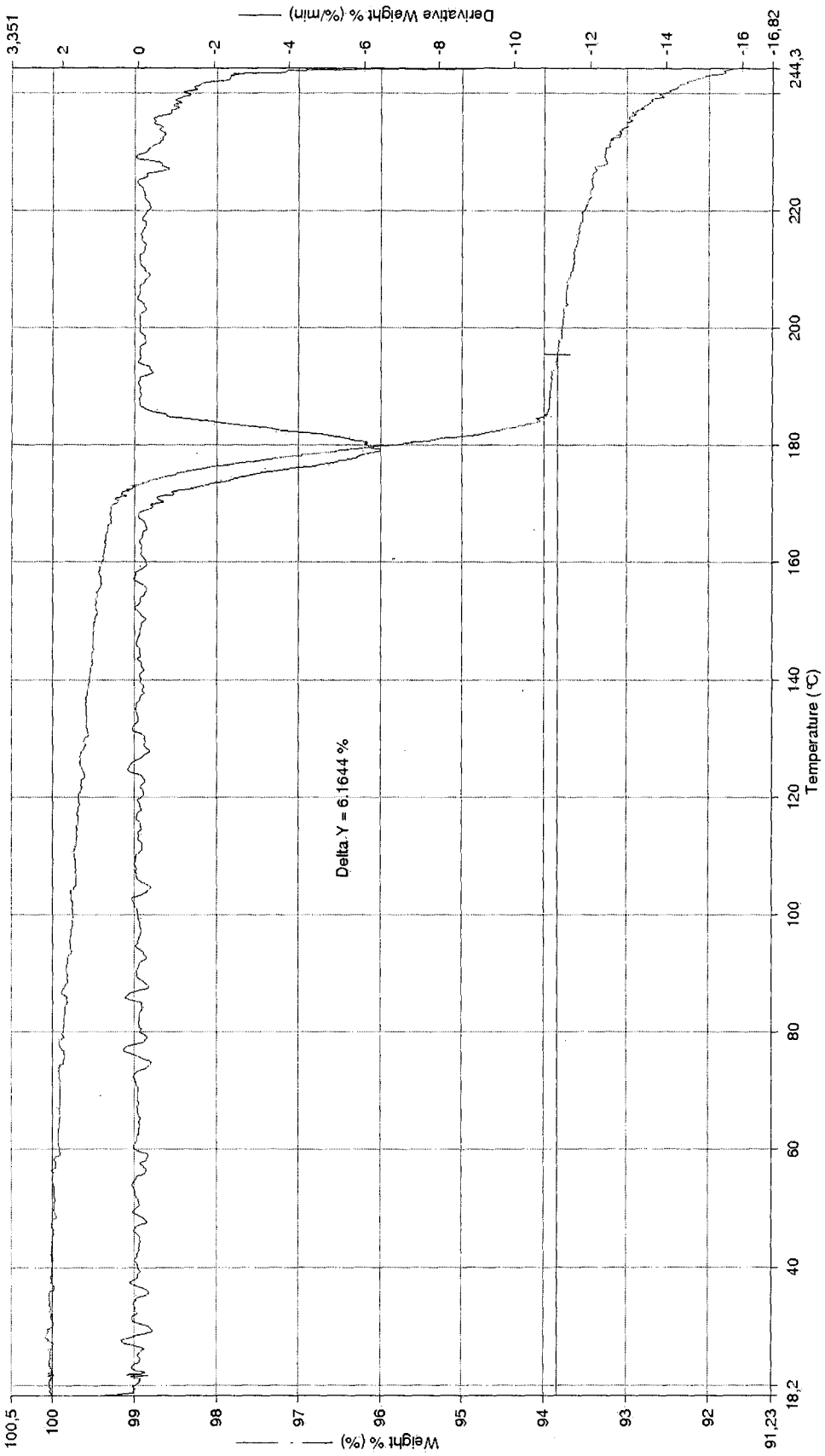

Derivative Weight % (%/min)
3,351
2
0
-2
-4
-6
-8
-10
-12
-14
-16
-16,82
Weight % (%)
100,5
100
99
98
97
96
95
94
93
92
91,23
Delta Y = 6,1644 %
18,2
40
60
80
100
120
140
160
180
200
220
244,3
Temperature (°C)

Figure 5c

Figure 6b

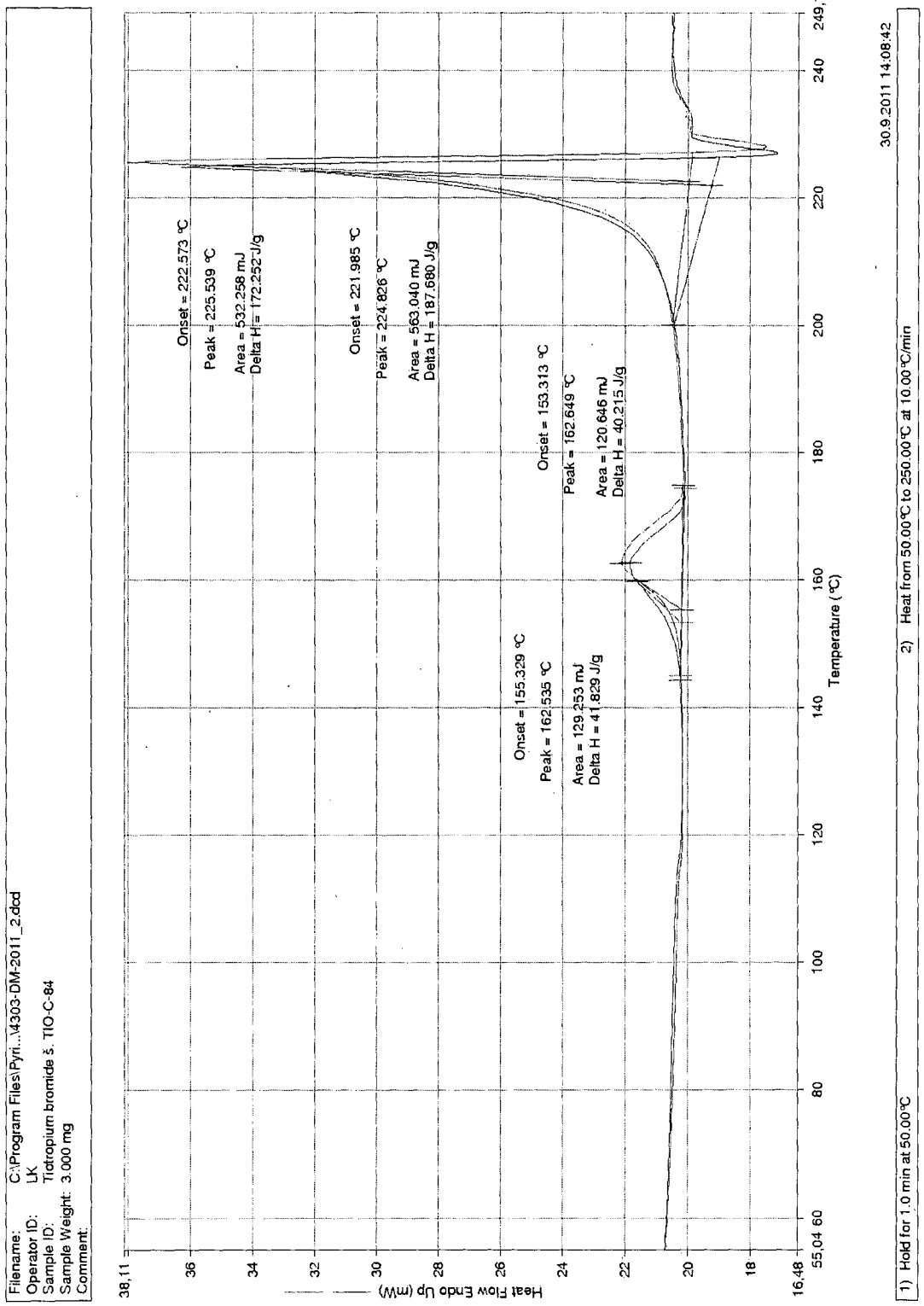
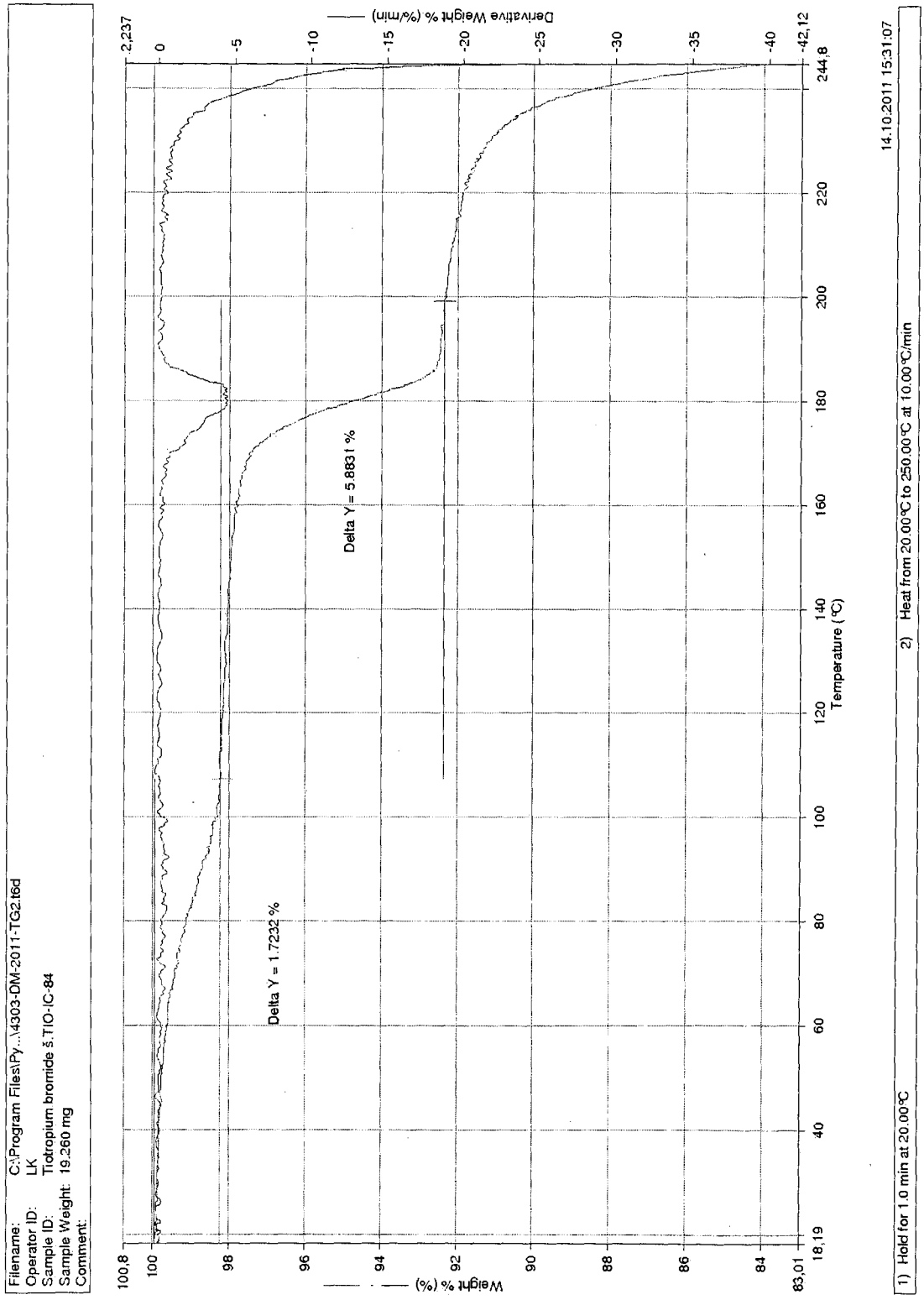

Filename: C:\Program Files\Pyri...\4303-DM-2011_2.dcd
Operator ID: LK
Sample ID: Tiotropium bromide š. TIO-C-84
Sample Weight: 3.000 mg
Comment:
Onset = 222.573 °C
Peak = 225.539 °C
Area = 532.258 mJ
Delta H = 172.252 J/g
Onset = 221.985 °C
Peak = 224.826 °C
Area = 563.040 mJ
Delta H = 187.680 J/g
Onset = 155.329 °C
Peak = 162.535 °C
Area = 129.253 mJ
Delta H = 41.829 J/g
Onset = 153.313 °C
Peak = 162.649 °C
Area = 120.646 mJ
Delta H = 40.215 J/g
Heat Flow Endo Up (mW)
Temperature (°C)
30.9.2011 14:08:42
1) Hold for 1.0 min at 50.00°C
2) Heat from 50.00°C to 250.00°C at 10.00°C/min

Figure 6c


Filename: C:\Program Files\Py...\4303-DM-2011-TG2.t6d
Operator ID: LK
Sample ID: Tiotropium bromide š.TIO-IC-84
Sample Weight: 19.260 mg
Comment:
Weight % (%)
Derivative Weight % (%/min)
Temperature (°C)
Delta Y = 1.7232 %
Delta Y = 5.8831 %
100,8
100
98
96
94
92
90
88
86
84
83,01
18,19
2,237
0
-5
-10
-15
-20
-25
-30
-35
-40
-42,12
40
60
80
100
120
140
160
180
200
220
244,8
14.10.2011 15:31:07
1) Hold for 1.0 min at 20.00°C
2) Heat from 20.00°C to 250.00°C at 10.00°C/min

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2012/0OQ121

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D451/12 A61K31/46 A61P11/00
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 , WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2006/117299 A2 (BOEHRINGER INGELHEIM INT [DE] ; BOEHRINGER INGELHEIM PHARMA [DE] ; POP M) 9 November 2006 (2006-11-09) claim 1	1-9
Y	WO 2006/117300 A2 (BOEHRINGER INGELHEIM INT [DE] ; BOEHRINGER INGELHEIM PHARMA [DE] ; MORIS) 9 November 2006 (2006-11-09) cited in the application claim 1	1-9
Y	WO 2007/075838 A2 (SICOR INC [US] ; VOLONTE ROBERTA [IT] ; DIULGHEROFF NICOLA [IT] ; SCARPIT) 5 July 2007 (2007-07-05) cited in the application the whole document	1-9

-/ -

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 February 2013	27/02/2013

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	Sahagun Krause, H

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2012/0OQ121

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2010/101538 A2 (MAHMUT BILGIC [TR]) 10 September 2010 (2010-09-10) cited in the application claims	1-9
Y	WO 02/30928 A1 (BOEHRINGER INGELHEIM PHARMA [DE]; BANHOLZER ROLF [DE]; SIEGER PETER [D) 18 April 2002 (2002-04-18) cited in the application claims	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/CZ2012/0OQ121

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		JP 2008540366 A	20-11-2008
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		PT 1881980 E	06-12-2012
		SI 1881980 TI	31-12-2012
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		CA 2606552 Al	09-11-2006
		CN 101203513 A	18-06-2008
		EP 1879888 A2	23-01-2008
		JP 2008540367 A	20-11-2008
		KR 20080007656 A	22-01-2008
		US 2006246009 Al	02-11-2006
		W0 2006117300 A2	09-11-2006
		ZA 200708175 A	25-09-2008
W0 2007075838 A2	05-07-2007	CA 2620142 Al	05-07-2007
		CN 101360744 A	04-02-2009
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		W0 2007075838 A2	05-07-2007
W0 2010101538 A2	10-09-2010	EP 2403851 A2	11-01-2012
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		AR 034389 Al	25-02-2004
		AR 068527 A2	18-11-2009
		AT 276253 T	15-10-2004
		AU 1499602 A	22-04-2002
		BG 66161 Bl	30-09-2011
		BR 0114584 A	26-08-2003
		CA 2425539 Al	11-04-2003
		CN 1469877 A	21-01-2004
		CN 1733761 A	15-02-2006
		CR 6938 A	28-10-2004
		CZ 301841 B6	07-07-2010
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		EG 24142 A	06-08-2008

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/CZ2012/0OQ121

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		EP 1326862 Al	16-07-2003
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		ES 2228965 T3	16-04-2005
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		NZ 525733 A	28-01-2005
		OA 12403 A	18-04-2006
		PE 04222002 Al	28-06-2002
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		PT 1326862 E	30-11-2004
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