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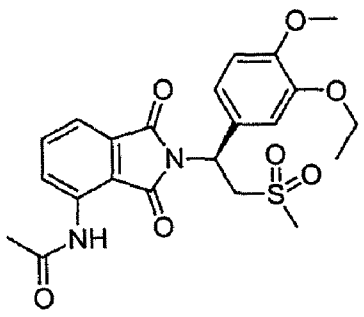

(I)

(57) Abstract: The present invention relates to amorphous apremilast of formula I, (*S*)-2-[1-(3-ethoxy-4- methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, in particular to preparation methods of amorphous apremilast from a solvate of apremilast with tetrahydrofuran, their characterization and use in a pharmaceutical composition.

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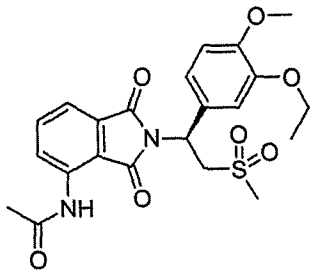
A preparation method of amorphous apremilast

Field of the Invention

The invention relates to amorphous apremilast of formula **I**, *(S)*-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione,



(I)

in particular to preparation methods of amorphous apremilast from a solvate of apremilast with tetrahydrofuran, their characterization and use in a pharmaceutical composition.

Background Art

Apremilast is a novel inhibitor of phosphodiesterase PDE-4, i.e. a representative of a drug group that has tried to assert itself mainly in the treatment of the chronic obstructive pulmonary disease so far. Apremilast causes inhibition of antiinflammatory cytokines and chemokines (TNF-α, IL-23, CXCL9 or CXCL10). Unlike biological substances exerting a neutralizing action onto already expressed antiinflammation factors, apremilast directly interferes with the production of leukotriene LTB4, inducible NO synthases (iNOS) or metalloproteinases (MMP). It represents a new small molecule for oral administration.

Apremilast in an optically pure form was first described in the patent application WO2003080049 by means of ^{1}H, ^{13}C NMR and chiral HPLC. An experiment conducted according to an example included in this application provided apremilast form B. This form is described with the use of X-ray powder diffraction and thermal methods in the following patent application WO2009120167, which describes forms A to G and an amorphous form. There, forms A, B and F are described as pure polymorphic forms of apremilast, forms C, D, E and G as solvates of apremilast (form C - toluene, form D - dichloromethane, form E - acetonitrile, form G - ethyl acetate). In the patent application WO2009120167, form C is presented as a toluene solvate that contains 3 molar equivalents of toluene per one mol of

apremilast. A reproduction of form C provided a form that corresponds to the pattern of form C of the patent application WO2009120167 with its X-ray powder pattern, but with the use of the thermal methods and ^{1}H NMR measurement the content of toluene was determined to be 0.5 molar equivalent. So according to our conclusions it is the toluene hemisolvate of apremilast.

In the patent application WO2009120167, form D is presented as a dichloromethane solvate that contains 2.5 molar equivalents of dichloromethane per one mol of apremilast. A reproduction of form D provided a form that corresponds to the pattern of form D of the patent application WO2009120167 with its X-ray powder pattern again, but with the use of the thermal methods and ^{1}H NMR measurement the content of dichloromethane was determined to be 1 molar equivalent. So according to our conclusions it is a dichloromethane solvate of apremilast in the molar ratio of 1 : 1.

In the patent application WO2009120167, form E is presented as an acetonitrile solvate and form G as an ethyl acetate solvate. Both these solvates are characterized in the patent application with the X-ray powder pattern and the records of the thermal methods.

The patent application WO2009120167 in its description mentions that another form, form H was also prepared, but there are no other more detailed data.

The patent application PV 2015-277 describes crystalline form I-1 of apremilast as a tetrahydrofuran solvate of apremilast. It includes characterization of this form by means of XRPD and thermal methods as well as preparation of this form.

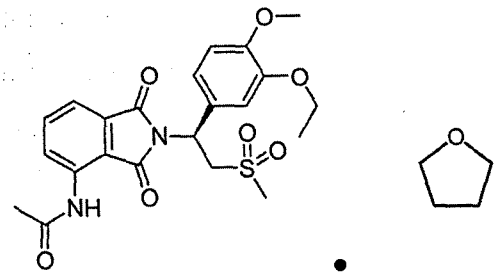
Disclosure of the Invention

Apremilast is a substance that is very poorly soluble in water. So the main effort is focused on finding a form that would be soluble in water as much as possible, thus showing the highest bioavailability of the drug in the organism. Amorphous apremilast is such a form.

The object of this invention are preparation methods of amorphous apremilast from crystalline form I-1 of apremilast. Amorphous apremilast can be prepared from crystalline form I-1 in several ways, e.g. by drying in a vacuum drier, precipitation or spray drying. The amorphous form of apremilast obtained this way is advantageously used in a pharmaceutical composition.

Detailed description of the Invention

This invention relates to preparation methods of amorphous apremilast from crystalline form I-1 (THF solvate of apremilast) of formula **II** and its use in a pharmaceutical formulation.



(II)

Crystalline form I-1 of apremilast exhibits an easy preparation procedure, high crystallinity and high purification capacity, which makes it suitable for use for preparation of highly pure apremilast. For the preparation of the amorphous form of apremilast from crystalline form I-1 several preparation methods can be used.

The amorphous form of apremilast can be prepared by drying of crystalline form I-1 of apremilast in vacuum. For the drying, temperatures in the range of 60°C to 100°C and vacuum in the range of 1 to 50 kPa can be used for at least 5 hours. Ideally, the drying is carried out at the temperature of 80°C and vacuum of 10 kPa for 20 to 30 hours.
The amorphous form of apremilast prepared this way exhibits the glass transition temperature of 71 to 74°C (DSC).

Another approach to the preparation of amorphous apremilast from crystalline form I-1 is spray drying. The removal of the solvent with the use of spray drying was carried out by means of a BUCHI B290 laboratory spray drier. Carrier gas flow 40 m^3/h, inlet temperature 120°C, outlet temperature 55°C, solution dosage rate 20%, aspirator 85%, condensation loop temperature 0°C.
A DSC analysis determined the glass transition temperature of amorphous apremilast prepared by the spray drying of 73 to 77°C.

Probably the most valuable preparation method of amorphous apremilast from crystalline form I-1 of apremilast is precipitation of a solution of apremilast to an antisolvent.

The glass transition temperature of the amorphous form of apremilast prepared with the use of the process of precipitation to an antisolvent determined with the use of a DSC analysis was in the range of 76 to 80°C.

The preparation of the amorphous form from crystalline form I-1 of apremilast using the process of precipitation to an antisolvent comprises the following steps:

a/ dissolution and/or dispersion of apremilast in a solvent;

b/ addition of a solution of apremilast to an antisolvent;

c/ removal of the solvents from the mixture from step b/.

For the dissolution of form I-1 of apremilast in step a/ R-OH alcohols, R-CO-R ketones, R-COOR esters or their mixtures can be generally used while the substituent R can be a C1 to C4 carbon chain. Acetone can be advantageously used as a very good solvent. This dissolution can occur at any temperature, but preferably at 20 to 25°C.

Step b/, addition of a solution of apremilast to the antisolvent requires intensive stirring and a temperature range of preferably -5 to 10°C. A volume ratio of the solvents (solvent from step a/ to the antisolvent from step b/) can be used that is in the range of 1 : 5 to 1 : 30, however preferably a ratio in the range of 1 : 10 to 1 : 20.

As the antisolvent in step b/ organic solvents can be used that apremilast is poorly soluble in, e.g. R-O-R ethers (where the substituent R can be a C2 to C5 carbon chain), hydrocarbons (e.g. pentane, heptane) or water. Water can be advantageously used as a very good antisolvent for the preparation of amorphous apremilast.

The removal of the solvents in step c/ and isolation of amorphous apremilast can be accomplished by means of filtration, centrifugation or evaporation of the solvents.

The prepared amorphous apremilast can be dried under standard conditions e.g. in a conventional vacuum drier. Amorphous apremilast is physically and chemically stable, i.e. it does not change its solid form and it does not chemically degrade in any way.

The amorphous form of apremilast was also proved by means of X-ray powder diffraction (Fig. 1), where a classical amorphous halo was registered.

An advantage of using crystalline form I-1 of apremilast as an intermediate product consists in a high purification capability of this form. This form crystallizes well and substantially removes impurities from apremilast. When the crude form I-1 was obtained by a reaction, the chemical purity was 96.12% (HPLC), after one crystallization, the HPLC chemical purity increased to 99.29%. It also surprisingly has a significant influence on increasing the optical purity, which is increased from the original 99.05% to 100% (HPLC) during one recrystallization of form I-1 from tetrahydrofuran. The method of preparation of the amorphous form of apremilast from crystalline form I-1 does not have any impact on the chemical or optical purity of the product. Thus, the chemical and optical purity of the final product (amorphous apremilast) is equal to the chemical and optical purity of the input substance (crystalline form I-1 of apremilast).

The amorphous form of apremilast prepared with the use of the method according to this invention can be used for the preparation of pharmaceutical compositions, especially solid drug forms, e.g. tablets. Such pharmaceutical mixtures can contain at least one excipient from the group of fillers (e.g. lactose), binders (e.g. microcrystalline cellulose), disintegrants (e.g. sodium salt of croscarmellose), lubricants (e.g. magnesium stearate), surfactants etc. These tablets can be coated with common coating compounds, e.g. polyvinyl alcohol or polyethylene glycol.

To verify the concept, tablets containing the apremilast THF solvate and the amorphous form were produced. For the THF solvate the method of wet granulation with subsequent fluid drying was used, amorphous apremilast was processed using the direct mixing method, which was followed by the production of tablets. Examples of the said compositions and the description of the production procedures are included in the experimental part. Subsequent analysis confirmed that no polymorphic change of the active pharmaceutical ingredient (API) had occurred and during the production process the chemical purity of both the forms of the API had been preserved.

The term "laboratory temperature" refers, for the purposes of the text below and above, to the temperature range from 22 to 26°C.

Brief description of the Drawings

Fig. 1: XRPD pattern of the amorphous form of apremilast

Fig. 2: DSC record of the amorphous form of apremilast prepared by drying in a vacuum drier

Fig. 3: DSC record of the amorphous form of apremilast prepared by spray drying

Fig. 4: DSC record of the amorphous form of apremilast prepared by precipitation into an antisolvent

Fig. 5: XRPD pattern of crystalline form I-1

Fig. 6: DSC record of crystalline form I-1

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

Examples

For the synthesis of apremilast, the procedure disclosed in the patent application WO2003080049 was used.

Example 1

Preparation of form I-1 of apremilast

Apremilast (100 mg, 0.22 mmol) was dissolved in 0.4 ml of tetrahydrofuran under moderate reflux conditions (60°C to 75°C). The clear solution was left to slowly cool down to the laboratory temperature and subsequently was put in a fridge or freezer to crystallize. The produced crystals were aspirated and dried in a vacuum drier at 40°C for 6 hours. The amount of 80 mg of crystalline form I-1 of apremilast was obtained in the molar ratio - apremilast : tetrahydrofuran = 2 : 1 (^{1}H NMR) at the chemical purity of 99.97% (HPLC), optical purity 100% (HPLC). The ^{1}H and ^{13}C NMR spectra confirmed the structure of apremilast. The XRPD pattern and DSC record confirmed crystalline form I-1.

^{1}H NMR (500 MHz, dmso-*d6*): δ 1.32 (t, *J* = 6.9 Hz, 3H); 1.76 (m, 2H, *THF*); 2.19 (s, 3H); 3.02 (s, 3H); 3.60 (m, 2H, *THF*); 3.73 (s, 3H); 4.02 (qua, *J* = 7.0 Hz, 2H); 4.14 (dd, *J* = 14.3 Hz, *J* = 4.5 Hz, 1H); 4.34 (dd, *J* = 14.3 Hz, *J* = 10.5 Hz, 1H); 5.78 (dd, *J* = 10.4 Hz, *J* = 4.2

Hz, 1H); 6.96 (m, 2H); 7.07 (m, 1H); 7.57 (m, J = 7.4 Hz, 1H); 7.79 (t, J = 7.9 Hz, 1H); 8.44 (d, J = 8.4 Hz, 1H); 9.71 (s, 1H).

Example 2

Preparation of the amorphous form of apremilast by drying in a vacuum drier

Crystalline form I-1 of apremilast (10 g) with the chemical purity of 99.97% (HPLC) and optical purity of 100% (HPLC) was dried in a vacuum drier at 80°C and the pressure of 10 kPa for 24 hours. The product (9.9 g) was identified with the use of XRPD as the amorphous form and DSC confirmed the glass transition temperature of the amorphous substance of 71.5°C (**Fig. 2**). The chemical as well as optical purity were verified by means of HPLC.

Example 3

Preparation of the amorphous form of apremilast by spray drying

10 g of crystalline form I-1 of apremilast was dosed into a 250ml round flask with a ground joint. This quantity was dissolved in 200 ml of acetone under stirring in a magnetic stirrer at 25°C. The solution was stirred for 20 minutes, and after this time period the solvent was evaporated using the BUCHI B290 spray drier. This way, the amount of 9.8 g of the product was obtained. The XRPD pattern confirmed the amorphous form and the glass transition temperature was 75.3°C (DSC, **Fig. 3**). The chemical (99.97%) as well as optical (100%) purity were verified by means of HPLC.

Example 4

Preparation of the amorphous form of apremilast by precipitation

Apremilast (form I-1, 10 g) with the chemical purity of 99.97% (HPLC) was dissolved at the laboratory temperature in 20 ml of acetone. The clear solution was stirred for approx. 15 minutes and subsequently it was continuously added to 250 ml of icy water (0°C) by dripping during 5 minutes. During the adding, the reaction mixture was stirred vigorously. After addition of all the solution of apremilast, the reaction mixture was stirred for another 3 hours at 0°C. The obtained solid fraction was filtered and dried in a vacuum drier at 40°C and 10 kPa overnight. The amount of 8.7 g of the amorphous form of apremilast was obtained with the glass transition temperature of 77.2°C (DSC, **Fig. 4**). The amorphous form was further checked by XRPD. The chemical as well as optical purity were verified by means of HPLC.

Example 5

Preparation of the amorphous form of apremilast by precipitation

Crystalline form I-1 of apremilast (10 g) was dissolved in 30 ml of acetone at the laboratory temperature. The clear solution was stirred for approx. 15 minutes at the laboratory temperature and subsequently it was continuously added to 300 ml of icy water (0°C) by dripping during 5 minutes. During the adding, the reaction mixture was stirred vigorously. After addition of all the solution of apremilast, the reaction mixture was stirred for 10 minutes at 0°C. The obtained solid fraction was filtered and dried in a vacuum drier at 40°C and 10 kPa overnight. The amount of 8.1 g of the amorphous form of apremilast was obtained with the glass transition temperature of 78.9°C (DSC). The amorphous form was checked by XRPD. The chemical (99.97%) as well as optical (100%) purity were verified by means of HPLC.

Example 6

Tablet containing apremilast 30 mg (THF solvate) produced using the wet granulation method

The composition of the tablet is presented in Table no. 1

Table no. 1:

Composition	Contents of substances in one tablet (mg)	Percentage of ingredients (%)
Apremilast THF solvate	30.0	9.8
Lactose monohydrate	171.0	56.0
Microcrystalline cellulose	54.9	18.0
Sodium salt of croscarmellose	40.0	13.2
Polyvinyl pyrrolidone	6.1	2.0
Magnesium stearate	3.0	1.0
Total	**305.0**	**100.0**

Lactose monohydrate (28 wt.%), microcrystalline cellulose (10 wt.%), sodium salt of croscarmellose (6.6%wt.), apremilast THF solvate (9.8 wt.%) and polyvinyl pyrrolidone (2 wt.%) were homogenized in a granulator, being wetted with purified water at the same time.

Immediately after the granulation step, the obtained granulate was dried in a fluid granulation device at the drying temperature of 60°C. The dried granulate was sieved through a sieve with the mesh size of 0.8 mm. The remaining fractions of the auxiliary substances were admixed to the granulate: Lactose monohydrate (28 wt.%), microcrystalline cellulose (8 wt.%), sodium salt of croscarmellose (6.6 wt.%) and magnesium stearate (1 wt.%). Tablets were molded from the obtained tabletting matter.

Example 7:

Tablet containing apremilast 30 mg in the amorphous form produced using the direct mixing method

The composition of the tablet is presented in Table no. 2

Table no. 2:

Composition	Contents of substances in one tablet (mg)	Percentage of ingredients (%)
Amorphous apremilast	30.0	9.8
Lactose monohydrate	171.0	56.1
Microcrystalline cellulose	97.9	32.1
Sodium salt of croscarmellose	3.1	1.0
Magnesium stearate	3.0	1.0
Total	**305.0**	**100.0**

Before the preparation of the tablets, apremilast in the amorphous form was sieved through a sieve with the mesh size of 125 μm. The following auxiliary substances were added to the sieved apremilast: lactose monohydrate, microcrystalline cellulose and sodium salt of croscarmellose. The said ingredients were homogenized for 15 min. In the next step, magnesium stearate was added to the mixture and the mixture was further homogenized for 3 min. Tablets were molded from the obtained tabletting matter.

List of analytical methods

Measurement parameters of XRPD: The diffractograms were measured using an X'PERT PRO MPD PANalytical diffractometer, used radiation CuKα (λ=0.1542 nm (1.542 Å)),

excitation voltage: 45 kV, anode current: 40 mA, measured range: 2 - 40° 2θ, increment: 0.02° 2θ, the measurement was carried out on a flat powder sample that was applied on a Si plate. For the setting of the primary optical equipment programmable divergence slits with the irradiated area of the sample of 10 mm, 0.02 rad Soller slits and a ¼° anti-diffusion slit were used. For the setting of the secondary optical equipment an X'Celerator detector with maximum opening of the detection slot, 0.02 rad, Soller slits and a 5.0 mm anti-diffusion slit were used.

The records of differential scanning calorimetry (DSC) were measured using a Discovery DSC device made by TA Instruments. The sample charge in a standard Al pot (40 μL) was between 3 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 250°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.

Chemical purity was measured with the use of liquid chromatography (HPLC):

Device: Waters Acquity UPLC, PDA

Sample preparation: Dissolve 15.0 mg of the tested sample in 25.0 ml of 50% acetonitrile

Column: - dimension: l = 0.10 m, ϕ = 2.1 mm

- *stationary phase:* Acquity HSS C18 SB, 1.7 μm particles

- *column temperature:* 45°C.

Mobile phase: *A*: 10 mM $(NH_4)H_2PO_4$ at pH 3.0

B: acetonitrile

Gradient elution:

Time (min)	Flow (ml/min)	% A	% B
0	0.4	90	10
10	0.4	40	60
11	0.4	90	10
12	0.4	90	10

Detection: spectrophotometric 230 nm

Injection: 0.5 μl

Sample temperature: 15°C

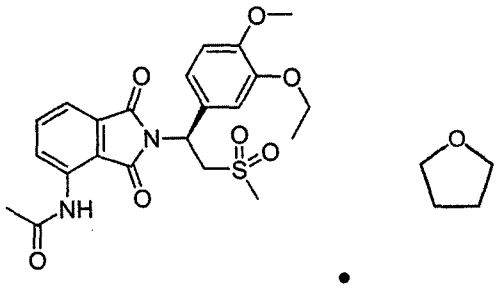
Sample concentration: 0.6 mg/ml

Optical purity was measured with the use of liquid chromatography (HPLC):

Device:	Waters Alliance HPLC, PDA
Sample preparation:	Dissolve 25.0 mg of the tested sample in 25.0 of the hexane : tetrahydrofuran mixture 80 : 20 (V/V)
Column:	- dimension: l = 0.25 m, ϕ = 4.6 mm - *stationary phase:* Chiralpak AZ-H, 5.0 μm particles - *column temperature:* 40°C.
Mobile phase:	*A*: Hexane *B*: Ethanol
Isocratic elution:	A : B 50 : 50
Flow:	1 ml/min
Detection:	spectrophotometric 230 nm
Injection:	12 μl
Sample temperature:	15°C
Sample concentration:	1.0 mg/ml

CLAIMS

1. A method for preparing amorphous apremilast from crystalline form I-1 of apremilast of formula II.



(II)

2. The method for preparing amorphous apremilast in accordance with claim 1, characterized in that it comprises the procedure of precipitation or vacuum drying or spray drying.
3. The method for preparing amorphous apremilast in accordance with claim 2, characterized in that it comprises precipitation into an antisolvent.
4. The method for preparing amorphous apremilast in accordance with claim 3, characterized in that it comprises the following steps:
   a/ dissolution and/or dispersion of apremilast in a solvent;
   b/ addition of a solution of apremilast into an antisolvent;
   c/ removal of the solvent from the mixture from step b/.
5. The method for preparing amorphous apremilast in accordance with claim 4, characterized in that for the dissolution of apremilast in step a/ the solvent is selected from the group of R-OH alcohols, R-CO-R ketones, R-COOR esters or their mixture, wherein the substituent R can be a C1 to C4 carbon chain, preferably methanol, acetone or ethyl acetate.
6. The method for preparing amorphous apremilast in accordance with claim 4, characterized in that the used antisolvent in step b/ is an R-O-R ether, wherein R can be a C2 to C5 carbon chain, aliphatic hydrocarbon, e.g. pentane, heptane or water; water is preferably used.
7. The method for preparing amorphous apremilast in accordance with claim 4, characterized in that the solvent for apremilast and the antisolvent are used in the mutual volume ratio of 1:5 to 1:30, preferably 1:10 to 1:20.

8. The method for preparing amorphous apremilast in accordance with claim 4, characterized in that to remove the solvent in step c/, filtration, centrifugation or evaporation of the solvents is used.
9. The method for preparing amorphous apremilast in accordance with claim 2, characterized in that it comprises drying in vacuum at a pressure in the range from 1 to 50 kPa and at a temperature of 60 to 100°C for at least 5 hours.
10. The method for preparing amorphous apremilast in accordance with claim 2, characterized in that it comprises removal of the solvent by spray drying.
11. The method for preparing amorphous apremilast in accordance with claims 1 to 10, characterized in that apremilast is prepared at a chemical purity higher than 99.80% by HPLC.
12. The method for preparing amorphous apremilast in accordance with claims 1 to 10, characterized in that apremilast is prepared at an optical purity higher than 99.90% by HPLC.
13. A pharmaceutical composition containing the amorphous form of apremilast prepared in accordance with claims 1 to 10, characterized in that it further contains at least one pharmaceutically acceptable excipient selected from the group of lactose, microcrystalline cellulose, sodium salt of croscarmellose, magnesium stearate, wherein the pharmaceutical composition is preferably in the tablet form.
14. A method for preparing the pharmaceutical composition defined in claim 13, characterized in that it comprises the granulation procedure.

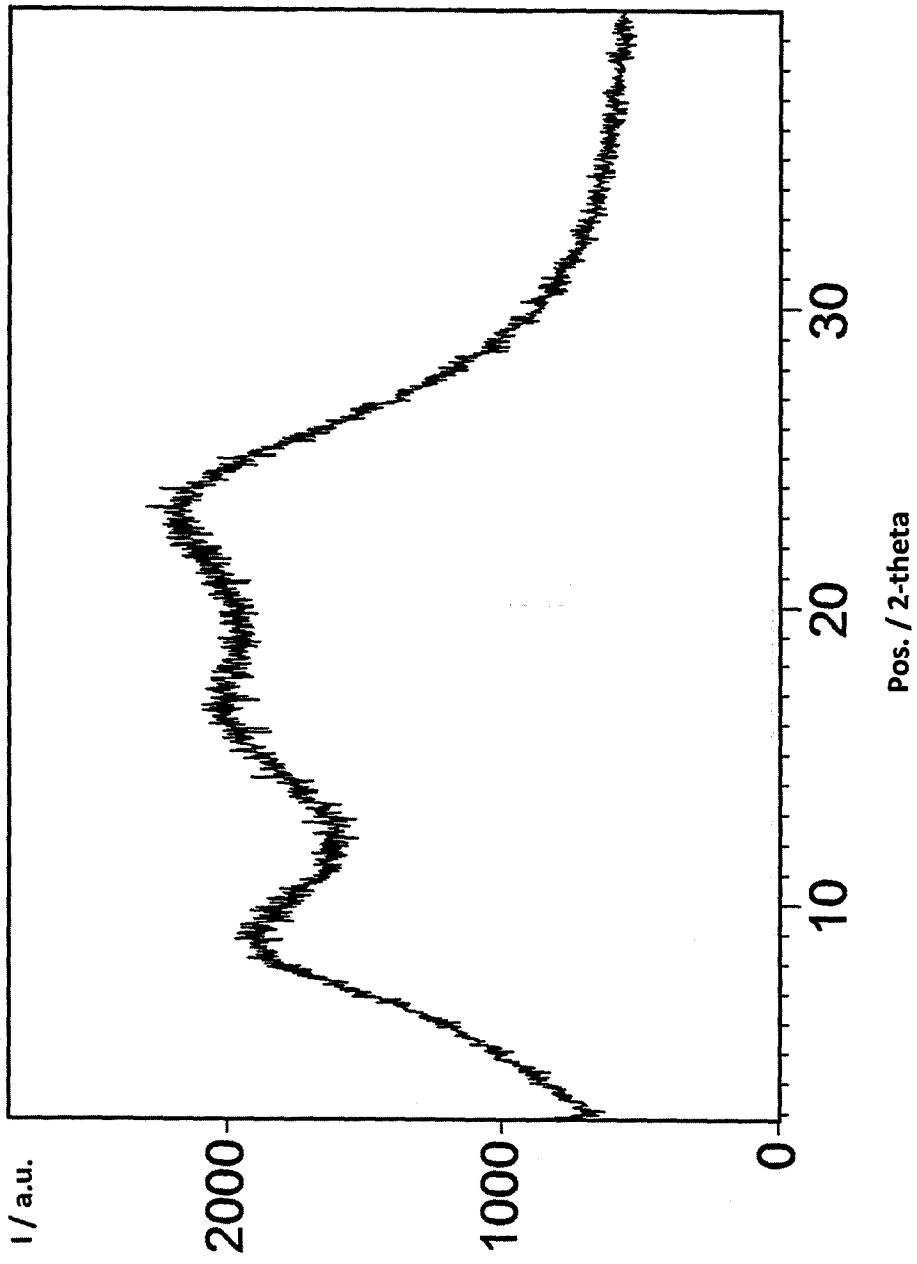


Fig. 1

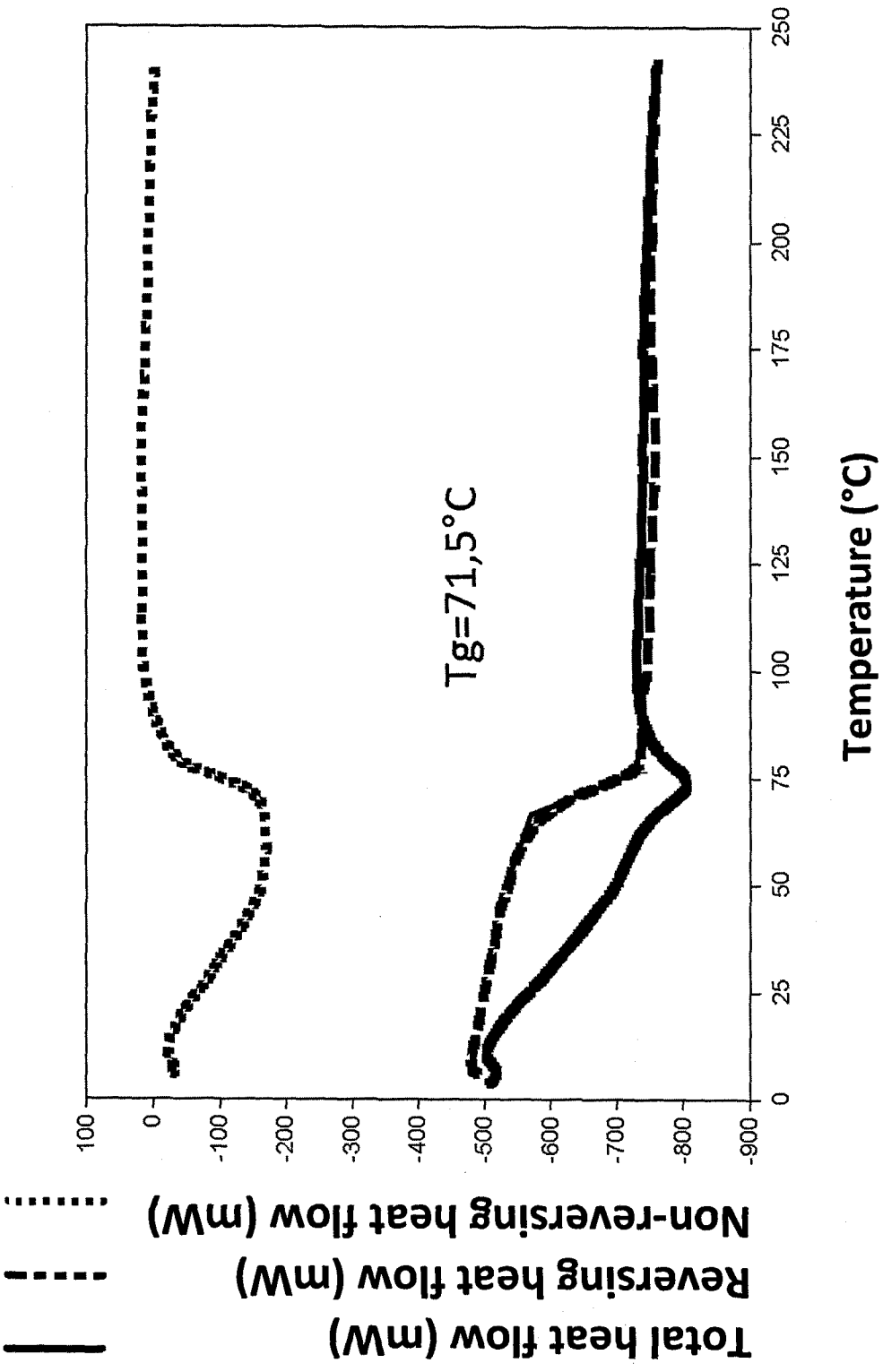

Total heat flow (mW)
Reversing heat flow (mW)
Non-reversing heat flow (mW)
Tg=71,5°C
Temperature (°C)
100
0
-100
-200
-300
-400
-500
-600
-700
-800
-900
0
25
50
75
100
125
150
175
200
225
250

Fig. 2

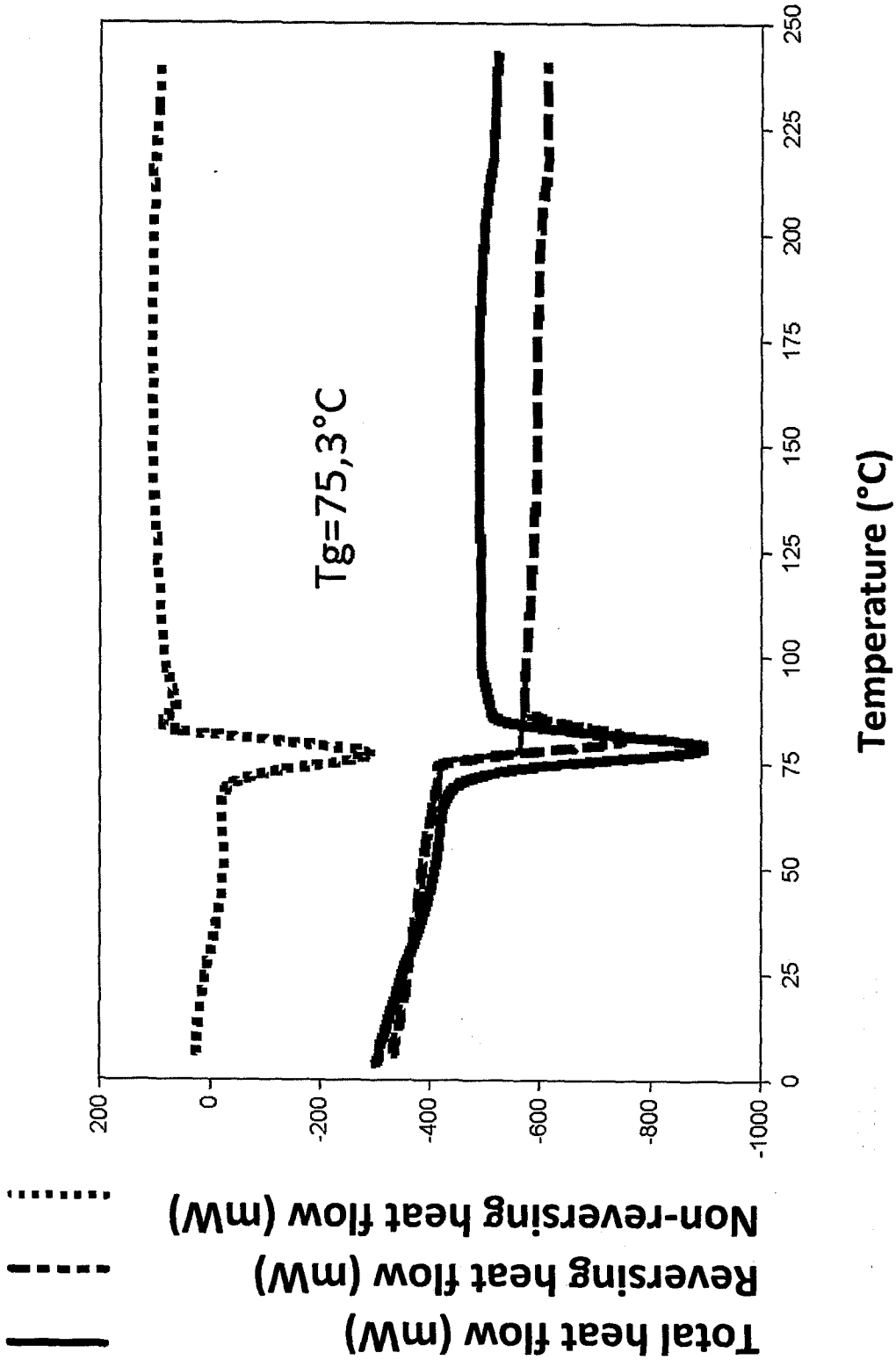

Tg=75,3°C
Total heat flow (mW)
Reversing heat flow (mW)
Non-reversing heat flow (mW)
Temperature (°C)
200
0
-200
-400
-600
-800
-1000
0
25
50
75
100
125
150
175
200
225
250

Fig. 3

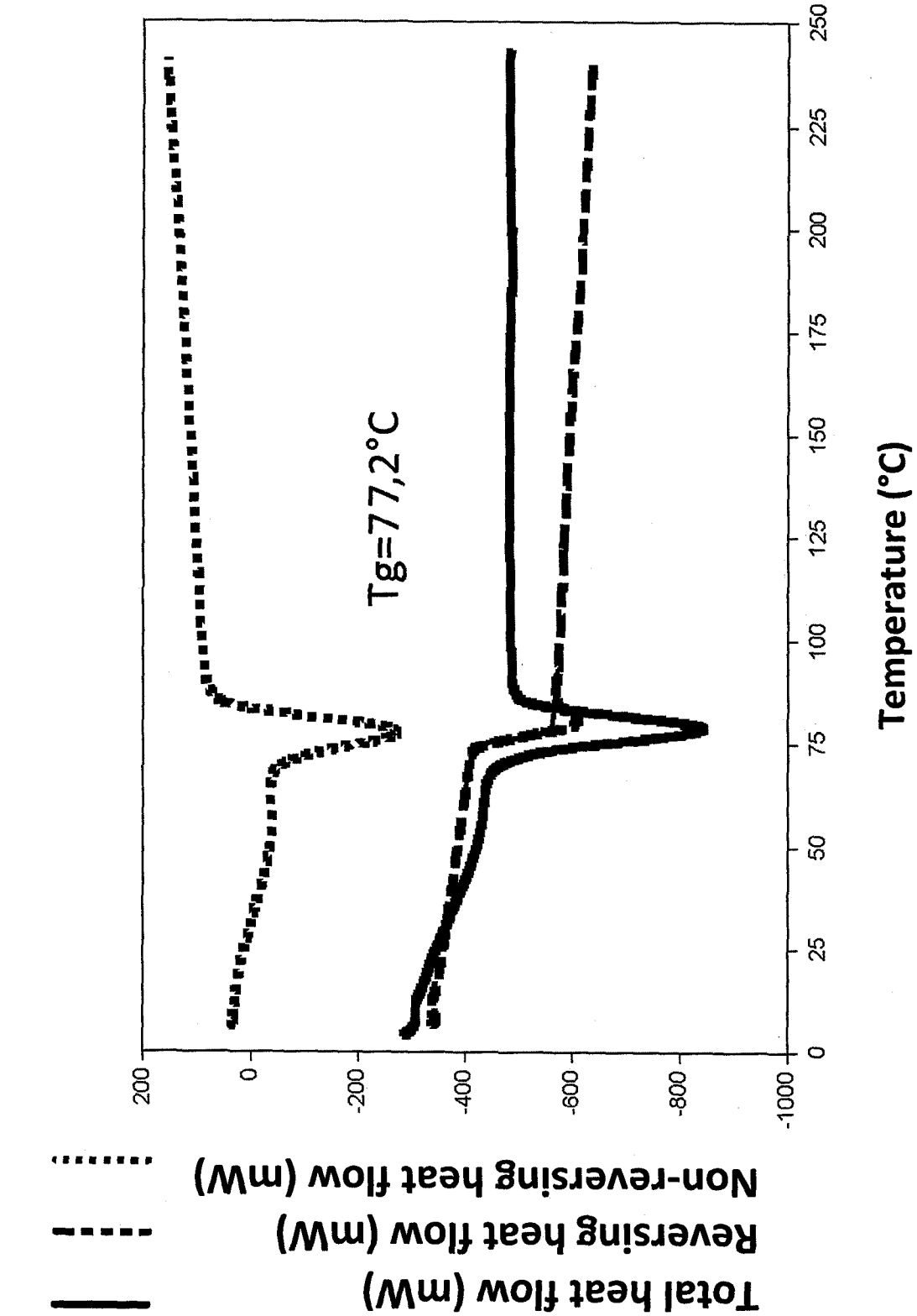

Tg=77,2°C
Total heat flow (mW)
Reversing heat flow (mW)
Non-reversing heat flow (mW)
Temperature (°C)
200
0
-200
-400
-600
-800
-1000
0
25
50
75
100
125
150
175
200
225
250

Fig. 4

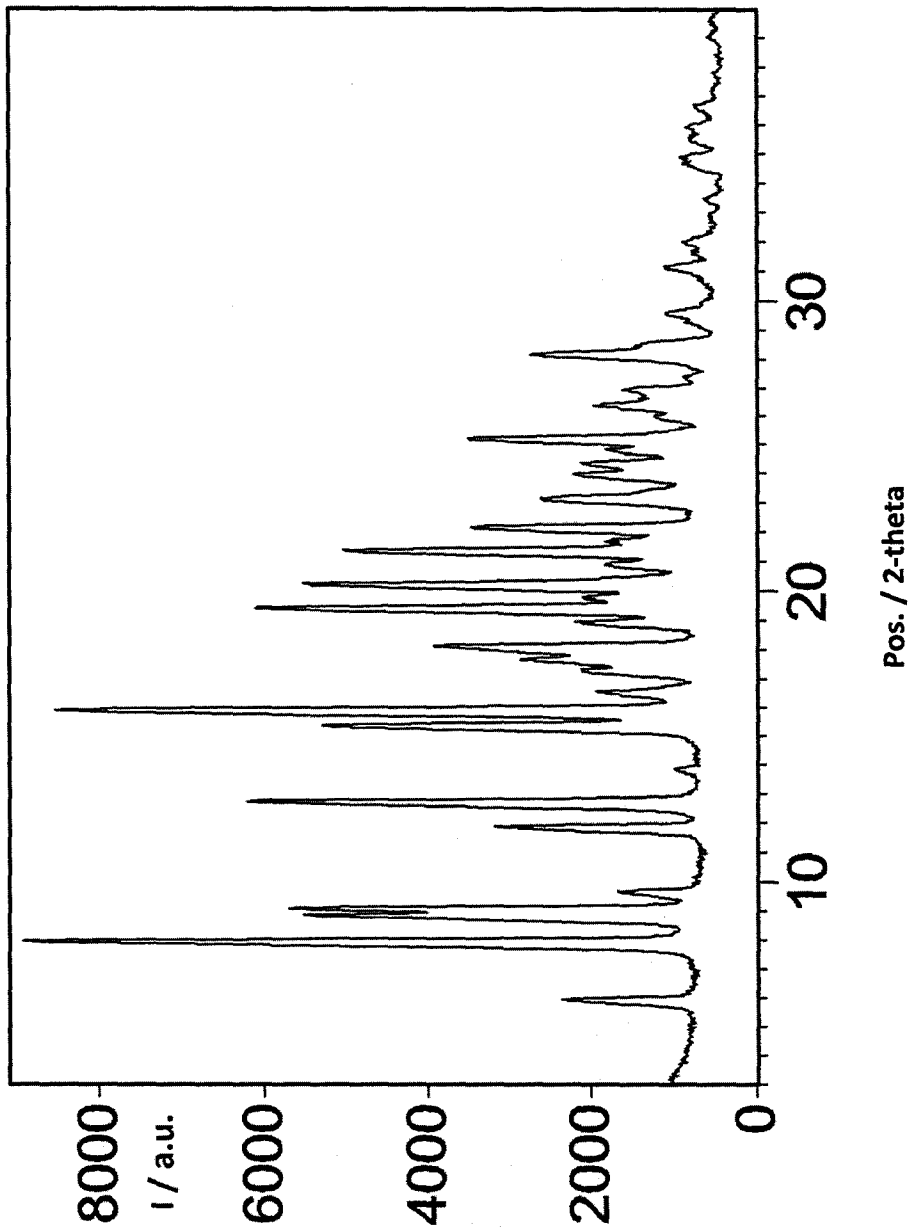


Fig. 5

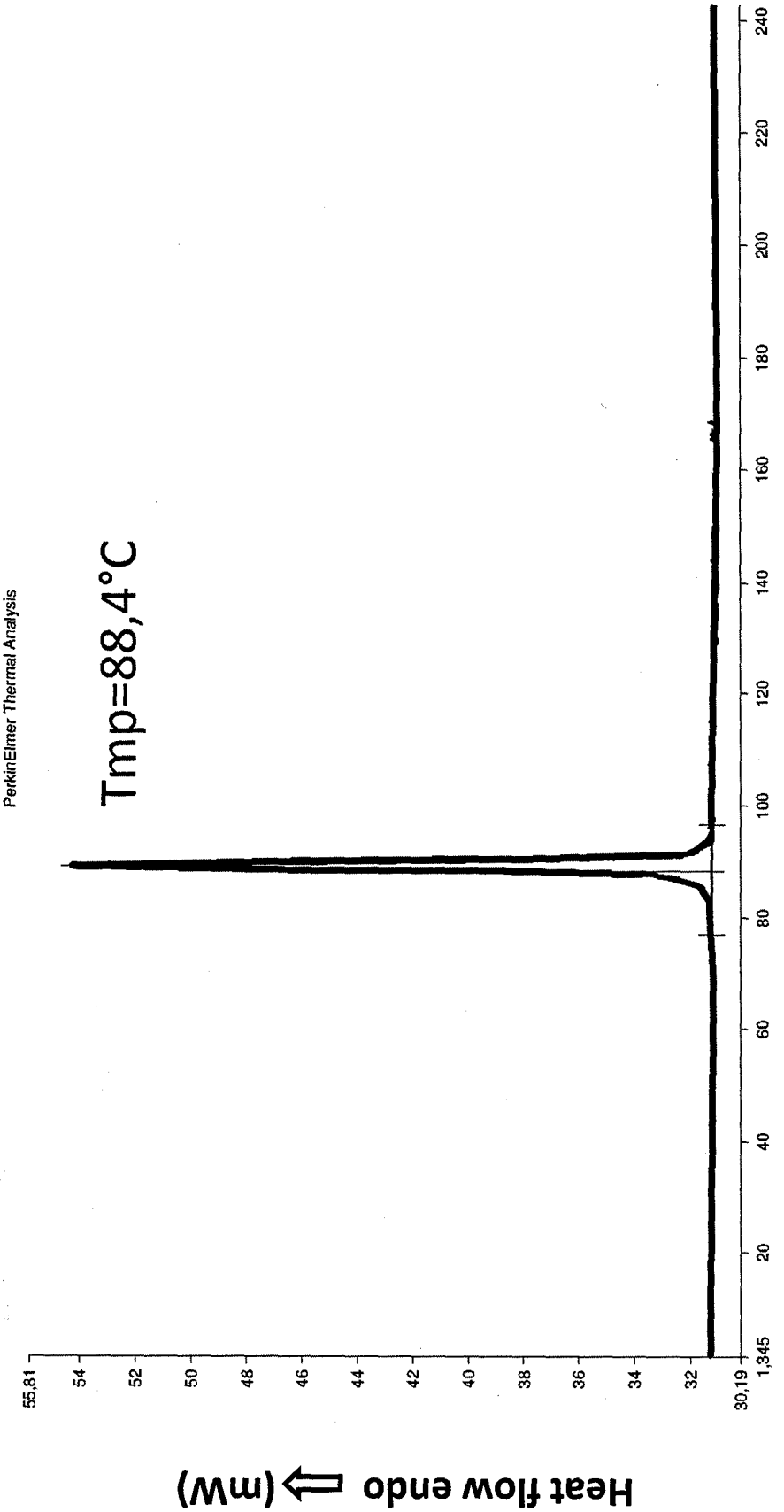

PerkinElmer Thermal Analysis
Tmp=88,4°C
Heat flow endo ⇨ (mW)
Temperature (°C)
55,81
30,19
1,345
54
52
50
48
46
44
42
40
38
36
34
32
20
40
60
80
100
120
140
160
180
200
220
240

Fig. 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2016/000132

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/48 A61K31/4035 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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2016/135755 A1 (MYLAN LABORATORIES LTD [IN]) 1 September 2016 (2016-09-01) claims 1-14	1-12
X	WO 2015/173792 A1 (MAPI PHARMA LTD [IL]) 19 November 2015 (2015-11-19) claims 4-12	1-12
X	US 2015/283249 A1 (KHERA BRIJ [IN] ET AL) 8 October 2015 (2015-10-08) paragraph [0067] paragraph [0075]	1-12
X	WO 2013/101810 A1 (CELGENE CORP [US]) 4 July 2013 (2013-07-04) claims 3-10, 21 item 4.2; page 29	13,14

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

[X] See patent family annex.

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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
30 January 2017	08/02/2017

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	Bérillon, Laurent

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INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2016/000132

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/204825 A1 (CELGENE CORP [US]) 24 December 2014 (2014-12-24) claim 2 paragraph [00335] -----	13,14
A	CN 105 111 127 A (JINAN TRIO PHARMATECH CO LTD) 2 December 2015 (2015-12-02) abstract -----	1-14

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO 2014204825 A1	24-12-2014
CN 105111127 A	02-12-2015	NONE	