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(54) Titre : FORME CRISTALLINE DE BISULFATE INHIBITEUR DE KINASE JAK ET PROCEDE DE PREPARATION CORRESPONDANT

(54) Title: CRYSTALLINE FORM OF JAK KINASE INHIBITOR BISULFATE AND A PREPARATION METHOD THEREOF

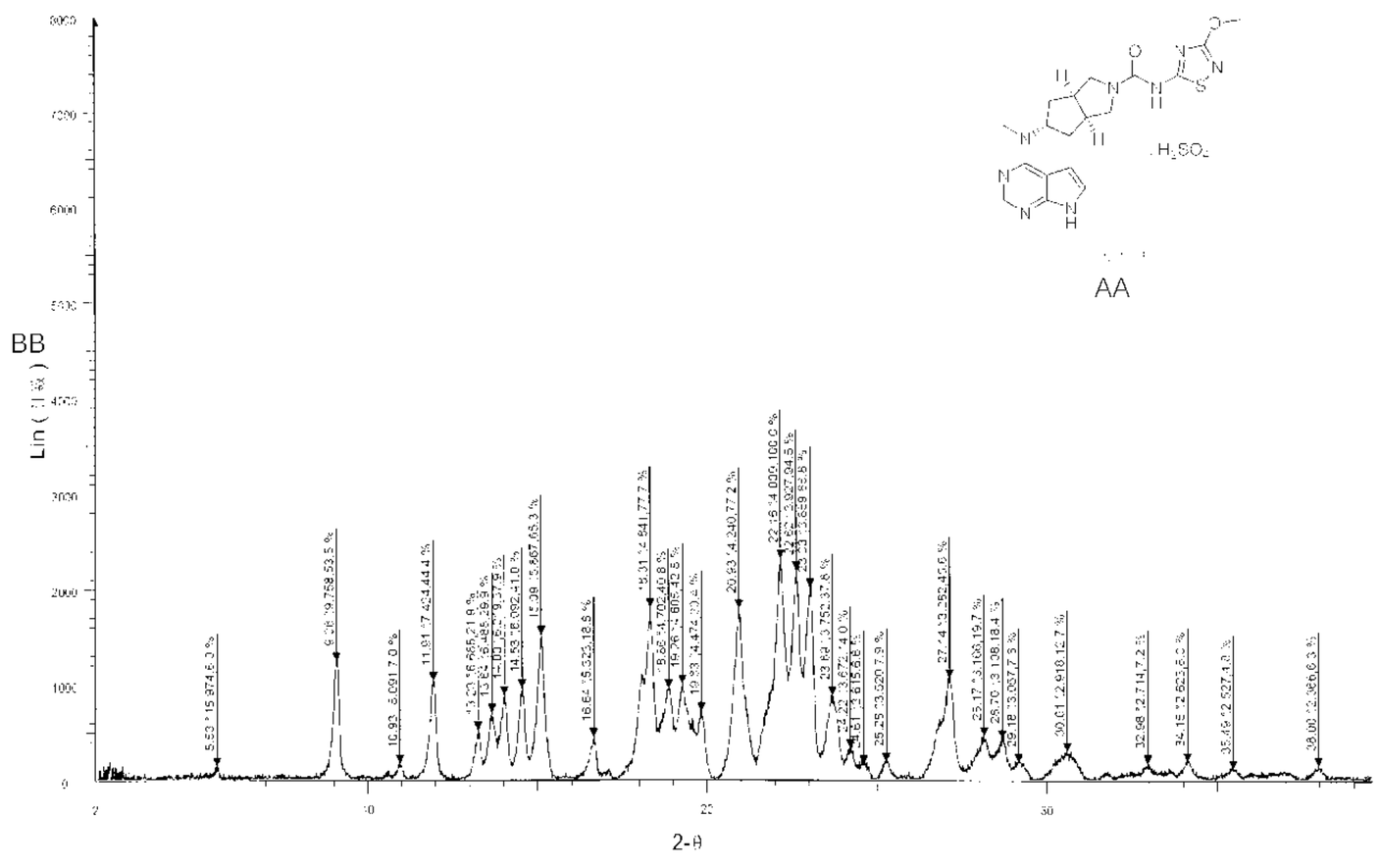


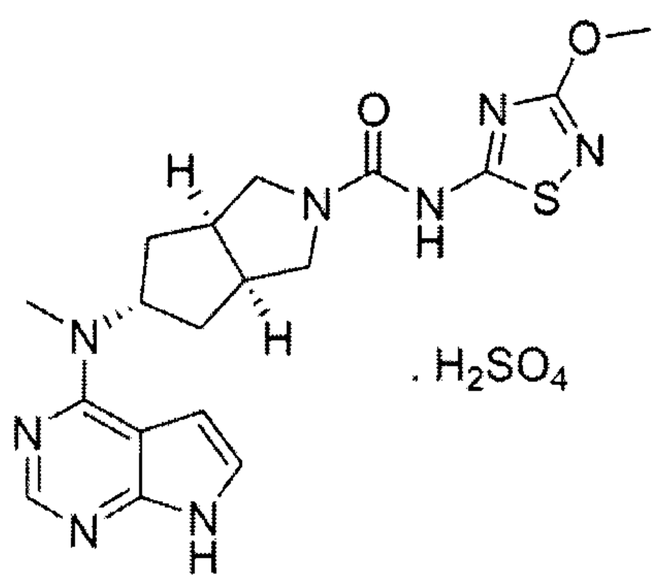
図 1 / Fig. 1

AA Formula (I)
BB Lin (count)

(57) Abrégé/Abstract:
The present invention relates to a crystal form of JAK kinase inhibitor bisulfate and a preparation method thereof. In particular, the present invention relates to a type II crystal of (3aR,5s,6aS)-N-(3-methoxy-1,2,4-thiadiazole-5-yl)-5-(methyl(7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)hexahydrocyclopenta[c]pyrrole-2(1H)-formamide bisulfate and a preparation method thereof. The preparation method comprises crystallizing any crystal forms or amorphous compound of formula (I) solid in a single organic solvent or a mixed organic solvent to obtain a type II crystal form of a compound of formula (I). The type II crystal form of compound of formula (I) obtained by the present invention has a good crystal stability and chemical stability, and the used crystal-solvent has a low toxicity and residue, which can be better used in clinical treatment.

ABSTRACT:

The present invention relates to a crystal form of JAK kinase inhibitor bisulfate and a preparation method thereof. In particular, the present invention relates to a type II crystal of (3*aR*,5*s*,6*aS*)-*N*-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidine-4-yl)amino)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-formamide bisulfate and a preparation method thereof. The preparation method comprises crystallizing any crystal forms or amorphous compound of formula (I) solid in a single organic solvent or a mixed organic solvent to obtain a type II crystal form of a compound of formula (I). The type II crystal form of compound of formula (I) obtained by the present invention has a good crystal stability and chemical stability, and the used crystal solvent has a low toxicity and residue, which can be better used in clinical treatment.



Formula (I)

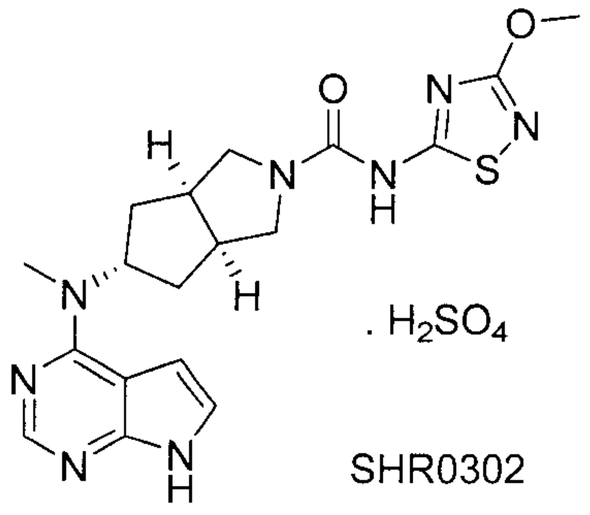
CRYSTALLINE FORM OF JAK KINASE INHIBITOR BISULFATE AND A PREPARATION METHOD THEREOF

FIELD OF THE INVENTION

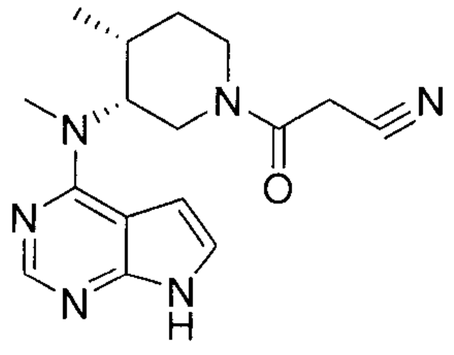
The present invention relates to crystal form II of (3*aR*,5*s*,6*aS*)-*N*-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidine-4-yl)amino)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-formamide bisulfate and the preparation and use thereof. The compound of formula (I) prepared according to the method of the present invention can be used for the treatment of arthritis.

BACKGROUND OF THE INVENTION

Arthritis is the most common chronic diseases in the world, there are many causes of arthritis, and the causes of joint damage are also different. Currently, Tofacitinib (CP-690550) is a novel oral JAK (Janus Kinase) pathway inhibitor developed by Pfizer Inc., and Tofacitinib is the first-in-class drug developed for rheumatoid arthritis treatment. Based on the structure of tofacitinib, a series of JAK inhibitor compounds, which are in vitro and in vivo active and highly absorbable, have been developed, see WO2013091539. The compounds disclosed in WO2013091539 were screened and prepared to salts in which (3*aR*,5*s*,6*aS*)-*N*-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidine-4-yl)amino)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-formamide bisulfate of formula (I) was obtained, its preparation method was disclosed in PCT patent application no. PCT/CN2014/076794 (an application previously filed by the applicant).



SHR0302



tofacitinib

Formula (I)

It is well known that the crystal structure of the pharmaceutically active ingredient often affects the chemical stability of the drug. Different crystallization conditions and storage conditions may lead to the change in the crystal structure of the compound, and sometimes the accompanying production of other forms of crystal form. The compound of formula (I) was dissolved in methanol, and then part of the solvent was evaporated to precipitate a crystal, which was called as crystal form I, see Chinese Patent Application No. 201410529863.8. In the subsequent study, we surprisingly find that the compound

also has another crystal form. When the salt is refluxed in a multisolvent system to produce a crystal transformation, or crystallized in a variety of solvents, another crystal is obtained, which is defined as crystal form II herein. Through the influence factors of crystal form and the special stability test, it is find that the crystal stability of crystal form II is good, and this crystal form is the most easily obtained and is stable. Its preparation process is controllable and repeatable, so it is more suitable for the industrial production.

SUMMARY OF THE INVENTION

The purpose of the present invention is to provide a stable crystal form of bisulfate (the compound of formula (I)) as a JAK inhibitor and the preparation method thereof.

The inventor has tested a series of crystal products of the compound of formula (I) obtained under various conditions by X-ray diffraction and differential scanning calorimetry (DSC) test. It was found that a stable crystal form of the compound of formula (I), which is called as crystal form II, can be obtained under the crystallization condition according to the present invention. DSC spectrum of crystal form II of the compound of formula (I) according to the present application shows a melting endothermic peak at about 218°C. The X-ray powder diffraction spectrum, which is obtained by using Cu-Ka radiation and represented by 2θ angle and interplanar distance (d value), is shown in Figure 1 in which there are characteristic peaks at 8.96 (9.87), 11.80 (7.50), 13.12 (6.74), 13.53 (6.54), 13.89 (6.37), 14.42 (6.14), 14.98 (5.91), 16.52 (5.36), 18.20 (4.87), 18.75 (4.73), 19.15 (4.63), 19.72 (4.50), 20.82 (4.26), 22.05 (4.03), 22.52 (3.95), 22.92 (3.88), 23.58 (3.77) and 27.04 (3.30).

In the preparation method of crystal form II of the present invention, the existing form of the compound of formula (I) used as a starting material is not particularly limited, and any crystal form or amorphous solid may be used. The preparation method of crystal form II of the compound of formula (I) of the present invention comprising:

using some lower organic solvents, preferably the polar organic solvents with fewer carbon atoms and higher volatility, which can be used as crystallization solvents, such as alcohols, ketones, esters, halogenated hydrocarbons or the mixture thereof; more preferably, methanol, ethanol, isopropanol, ethyl acetate, acetone, dichloromethane or the mixture thereof as the crystallization solvents. The crystallization solvent can be a single solvent or a mixed solvent comprising the solvents mentioned above.

Specifically, the present invention provides the preparation method of crystal form II of the compound of formula (I) comprising the following steps of:

(1) dissolving

(3*aR*,5*s*,6*aS*)-*N*-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidine-4-yl)amino)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-formamide into an organic solvent, then adding concentrated sulfuric acid dropwise, filtering the solution and precipitating a crystal; or dissolving a solid of the compound of formula (I) into an appropriate amount of organic solvent under heating, then cooling the solution to precipitate a crystal;

(2) filtering the crystal, then washing and drying it.

In a preferred embodiment of the present invention, the organic solvent in step (1) is selected from any one of alcohols, ketones, esters having 3 or less carbon atoms, or a mixed solvent of one or more solvents mentioned above and a halogenated hydrocarbon having 3 or less carbon atoms. Further preferably, the organic solvent is selected from methanol, ethanol, isopropanol, acetone, ethyl acetate, or a mixed solvent system such as dichloromethane/methanol, dichloromethane/methanol/ethanol, dichloromethane/methanol/isopropanol, dichloromethane/methanol/ ethyl acetate, dichloromethane/methanol/acetone.

Most preferably, the single solvent is methanol.

In another preferred embodiment of the present invention, the mixed solvent is dichloromethane/methanol/ethanol, and the ratio of the three is not particularly limited. In a preferred embodiment of the present invention, the ratio of the three is 12:3:10.

The recrystallization method is not particularly limited and can be carried out by a conventional recrystallization process. For example, any form of the compound of formula (I) can be dissolved in an organic solvent under heating, and then the solution is cooled slowly and stirred to precipitate a crystal. After the completion of crystallization, the resulting product is filtered and dried to obtain the desired crystal. The crystal obtained by filtration is usually dried in vacuum under reduced pressure at a heating temperature of about 30~100°C, preferably 40~60°C, to remove the recrystallization solvent.

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

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

The research results show that the stability of the crystal form II of the compound of formula (I) prepared by the present invention is significantly better than that of the amorphous sample under the conditions of high temperature and high humidity. Moreover, crystal form II has good stability under the conditions of grinding, pressure and heating which meets the production, transportation and storage requirements of drug products. The preparation process of crystal form II is stable, repeatable and controllable, and is suitable for industrial production.

The present invention is further to provide a pharmaceutical composition comprising crystal form II of the compound of formula (I) and at least one of pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier is selected from at least one of lactose, mannitol, microcrystalline cellulose, croscarmellose sodium, sodium carboxymethyl starch, hydroxypropyl methyl cellulose, povidone, and magnesium stearate. The content of crystal form II in the pharmaceutical composition of the present invention is 0.5 mg~200 mg.

The present invention further relates to use of crystal form II of the compound of formula (I) or pharmaceutical composition of the present invention in the preparation of a medicament for the treatment of JAK-related disease, preferably rheumatic and rheumatoid arthritis.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the X-ray powder diffraction spectrum of crystal form II of the compound of formula (I) (represented by the symbol SHR0302 in the figure).

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

Figure 3 shows the X-ray powder diffraction spectrum of the amorphous solid of the compound of formula (I).

Figure 4 shows the DSC spectrum of the amorphous solid of the compound of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

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

Test instruments used in the experiments

1. DSC spectrum

Instrument type: Mettler Toledo DSC 1 Stare^{c} System

Purging gas: Nitrogen

Heating rate: 10.0°C/min

Temperature range: 40-300°C

2. X-ray diffraction spectrum

Instrument type: D/Max-RA Japan Rigaku X-ray powder diffractometer

Rays: monochromatic Cu-Kα rays (λ=1.5418Å)

Scanning mode: θ/2θ, Angular range: 2-40°

Voltage: 40KV Electric Current: 40mA

Example 1:

1.0 g (2.4 mmol) of (3*aR*,5*s*,6*aS*)-*N*-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidine-4-yl)amino)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-formamide was added to a 50 ml erlenmeyer flask, followed by addition of 12 ml of dichloromethane and 3 ml of anhydrous methanol. The reaction mixture was stirred at room temperature, then 0.25 g (2.5 mmol) of concentrated sulfuric acid was added dropwise. After the suspension became clear, the insolubles were removed by filtration. No solid was precipitated after the filtrate was stirred for 6 hours. 10 ml of isopropanol was added, then a large amount of white solid was precipitated. The reaction mixture was stirred for another 18 hours, filtered and dried to obtain 1.138 g of a white solid in 92.1% yield. The X-ray diffraction spectrum of this crystal sample is shown in Figure 1 in which there are characteristic peaks at 8.96 (9.87), 11.80 (7.50), 13.12 (6.74), 13.53 (6.54), 13.89 (6.37), 14.42 (6.14), 14.98 (5.91), 16.52 (5.36), 18.20 (4.87), 18.75 (4.73), 19.15 (4.63), 19.72 (4.50), 20.82 (4.26), 22.05 (4.03), 22.52 (3.95), 22.92 (3.88), 23.58 (3.77) and 27.04 (3.30). The DSC spectrum is shown in Figure 2, having a melting endothermic peak at 217.24°C. The crystal form was defined as crystal form II.

Example 2

1.0 g (2.4 mmol) of (3*aR*,5*s*,6*aS*)-*N*-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidine-4-yl)amino)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-formamide was added to a 50 ml erlenmeyer flask, followed by addition of 12 ml of dichloromethane and 3 ml of anhydrous methanol. The reaction mixture was stirred at room temperature, then 0.25 g (2.5 mmol) of concentrated sulfuric acid was added dropwise. After the suspension became clear, the insolubles were removed by filtration, and the filtrate was concentrated to dryness to obtain the compound of formula (I) in an amorphous form.

The X-ray diffraction spectrum of the solid sample is shown in Figure 3 in which there are no characteristic absorption peaks of a crystal. The DSC spectrum of the solid sample is shown in Figure 4.

Example 3

1.0 g (2.4 mmol) of (3*aR*,5*s*,6*aS*)-*N*-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidine-4-yl)amino)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-formamide was added to a 50 ml erlenmeyer flask, followed by addition of 12 ml of dichloromethane and 3 ml of anhydrous methanol. The reaction mixture was stirred at room temperature, then 0.25 g (2.5 mmol) of concentrated sulfuric acid was added dropwise. After the suspension became clear, the insolubles were removed by filtration, and the filtrate was stirred for 24 hours to precipitate a crystal, filtered and dried to obtain 1.15 g of a white solid in 93.2% yield. The product was identified as crystal form II after studying and comparing the X-ray diffraction and DSC spectra.

Example 4:

1.0 g (2.4 mmol) of (3*aR*,5*s*,6*aS*)-*N*-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidine-4-yl)amino)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-formamide was added to a 50 ml erlenmeyer flask, followed by addition of 12 ml of dichloromethane and 3 ml of anhydrous methanol. The reaction mixture was stirred at room temperature, then 0.25 g (2.5 mmol) of concentrated sulfuric acid was added dropwise. After the suspension became clear, the insolubles were removed by filtration. No solid was precipitated after the filtrate was stirred for 6 hours. 10 ml of ethanol was added, then a large amount of white solid was precipitated. The reaction mixture was stirred for another 18 hours, filtered and dried to obtain 1.17 g of a white solid in 94.9% yield. The product was identified as crystal form II after studying and comparing the X-ray diffraction and DSC spectra.

Example 5:

1.0 g (2.4 mmol) of (3*aR*,5*s*,6*aS*)-*N*-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidine-4-yl)amino)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-formamide was added to a 50 ml erlenmeyer flask, followed by addition of 12 ml of dichloromethane and 3 ml of anhydrous methanol. The reaction mixture was stirred at room temperature, then 0.25 g (2.5 mmol) of concentrated sulfuric acid was added dropwise. After the suspension became clear, the insolubles were removed by filtration. No solid was precipitated after the filtrate was stirred for 6 hours. 5 ml of ethyl acetate was added, then a large amount of white solid was precipitated. The reaction mixture was stirred for another 18 hours, filtered and dried to obtain 1.16 g of a white solid in 94.2% yield. The product was

identified as crystal form II after studying and comparing the X-ray diffraction and DSC spectra.

Example 6:

1.0 g (2.4 mmol) of (3*aR*,5*s*,6*aS*)-*N*-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidine-4-yl)amino)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-formamide was added to a 50 ml erlenmeyer flask, followed by addition of 12 ml of dichloromethane and 3 ml of anhydrous methanol. The reaction mixture was stirred at room temperature, then 0.25 g (2.5 mmol) of concentrated sulfuric acid was added dropwise. After the suspension became clear, the insolubles were removed by filtration. No solid was precipitated after the filtrate was stirred for 6 hours. 5 ml of acetone was added, then a large amount of white solid was precipitated. The reaction mixture was stirred for another 18 hours, filtered and dried to obtain 1.14 g of a white solid in 92.3% yield. The product was identified as crystal form II after studying and comparing the X-ray diffraction and DSC spectra.

Example 7

1.0 g (2.4 mmol) of (3*aR*,5*s*,6*aS*)-*N*-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidine-4-yl)amino)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)- formamide was added to a 50 ml erlenmeyer flask, followed by addition of 12 ml of dichloromethane and 3 ml of anhydrous methanol. The reaction mixture was stirred at room temperature, then 0.25 g (2.5 mmol) of concentrated sulfuric acid was added dropwise. After the suspension became clear, the insolubles were removed by filtration, and the filtrate was concentrated to dryness to obtain the compound of formula (I) in an amorphous form. The resulting sample was added to 5 ml of methanol, then the mixture was heated to reflux for 20 minutes, cooled, stirred for 2 hours to produce a crystal transformation, filtered and dried to obtain 942 mg of a white solid in 76.2% yield. The product was identified as crystal form II after studying and comparing the X-ray diffraction and DSC spectra.

Example 8

The compound of formula (I) in an amorphous form was prepared from 1.0 g (2.4 mmol) of (3*aR*,5*s*,6*aS*)-*N*-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidine-4-yl)amino)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-formamide according to the experimental method of Example 2. The resulting sample was added to 5 ml of ethanol, then the mixture was heated to reflux until the solution was clear. The solution was refluxed for another 20 minutes, cooled, stirred for 2 hours to produce a crystal transformation, filtered and dried to obtain 1.08 g of a white solid in 82.3% yield. The

product was identified as crystal form II after studying and comparing the X-ray diffraction and DSC spectra.

Example 9

The compound of formula (I) in an amorphous form was prepared from 1.0 g (2.4 mmol) of (3*aR*,5*s*,6*aS*)-*N*-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidine-4-yl)amino)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-formamide according to the experimental method of Example 2. The resulting sample was added to 5 ml of isopropanol, then the mixture was heated to reflux until the solution was clear. The solution was refluxed for another 20 minutes, cooled, stirred for 2 hours to produce a crystal transformation, filtered and dried to obtain 1.05 g of a white solid in 85.0% yield. The product was identified as crystal form II after studying and comparing the X-ray diffraction and DSC spectra.

Example 10

The compound of formula (I) in an amorphous form was prepared from 1.0 g (2.4 mmol) of (3*aR*,5*s*,6*aS*)-*N*-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidine-4-yl)amino)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-formamide according to the experimental method of Example 2. The resulting sample was added to 5 ml of ethyl acetate, then the mixture was heated to reflux until the solution was clear. The solution was refluxed for another 20 minutes, cooled, stirred for 2 hours to produce a crystal transformation, filtered and dried to obtain 1.11 g of a white solid in 90.1% yield. The product was identified as crystal form II after studying and comparing the X-ray diffraction and DSC spectra.

Example 11

The compound of formula (I) in an amorphous form was prepared from 1.0 g (2.4 mmol) of (3*aR*,5*s*,6*aS*)-*N*-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidine-4-yl)amino)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-formamide according to the experimental method of Example 2. The resulting sample was added to 5 ml of acetone, then the mixture was heated to reflux until the solution was clear. The solution was refluxed for another 20 minutes, cooled, stirred for 2 hours to produce a crystal transformation, filtered and dried to obtain 1.13 g of a white solid in 91.5% yield. The product was identified as crystal form II after studying and comparing the X-ray diffraction and DSC spectra.

Example 12

1.0 g (2.4 mmol) of the compound of formula (I) (crystal form II), which was

prepared according to the method of Chinese Patent Application No. 201410529863.8, and 100 ml of methanol were added to a 250 ml one-necked flask, and heated to reflux until the solution was clear, then the solution was refluxed for another 10 minutes, and cooled. About 90 ml of methanol was removed by evaporation under reduced pressure, then the mixture was stirred at room temperature for 4 hours, filtered and dried to obtain 842 mg of a white solid in 84.2% yield. The product was identified as crystal form II after studying and comparing the X-ray diffraction and DSC spectra.

Example 13

Crystal form II prepared in Example 1 and the amorphous sample prepared in Example 2 were spread flat in the air to test their stability in conditions of lighting (4500 Lux), heating (40°C, 60°C), and high humidity (RH 75%, RH 90%). Sampling times of 5 days and 10 days were studied, and the purity as detected by HPLC is shown in Table 1.

Table 1. Comparing of stability of crystal form II and amorphous sample of the compound of formula (I)

Bach number	Time (Day)	Lighting	40°C	60°C	RH 75%	RH 90%
Crystal form II 20130107	0	99.30%	99.30%	99.30%	99.30%	99.30%
	5	99.29%	99.30%	99.20%	99.31%	99.31%
	10	99.30%	99.28%	99.15%	99.28%	99.31%
Amorphous Form 20120918	0	98.33%	98.33%	98.33%	98.33%	98.33%
	5	98.04%	97.65%	94.53%	98.32%	99.14%
	10	97.51%	96.61%	92.12%	98.16%	99.12%

After crystal form II and the amorphous sample of the compound of formula (I) were spread flat in the air to test their stability under the conditions of lighting, high temperature, high humidity, the results of the stability study showed that high humidity does not have much effect on the two examples, but under the conditions of lighting and high temperature, the stability of crystal form II is significantly better than that of the amorphous sample.

Example 14

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

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

Batch number	Treatment Process	Experiment procedure	Crystal form	DSC peak

Experiment 14.1 S011113120822G	Grinding treatment for 10 minutes	1 g of crystal form II of the compound of formula (I) was grinded for 10 minutes in a mortar under nitrogen atmosphere.	Crystal form II	DSC peak 217.98°C
Experiment 14.2 S011113120822H	Heating treatment at 80°C for 3 hours	1 g of crystal form II of the compound of formula (I) was spread flat and heated at 80°C for 3 hours.	Crystal form II	DSC peak 218.45°C
Experiment 14.3 S011113120822P	Pressing treatment	Crystal form II of the compound of formula (I) was pressed to a slice.	Crystal form II	DSC peak 217.85°C

WHAT IS CLAIMED IS:

1. Crystal form II of (3*aR*,5*s*,6*aS*)-*N*-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidine-4-yl)amino)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-formamide bisulfate, characterized in that the crystal has an X-ray powder diffraction spectrum, which is obtained by using Cu-Ka radiation and represented by 2θ angle and interplanar distance, as shown in Figure 1 in which there are characteristic peaks at about 8.96 (9.87), 11.80 (7.50), 13.12 (6.74), 13.53 (6.54), 13.89 (6.37), 14.42 (6.14), 14.98 (5.91), 16.52 (5.36), 18.20 (4.87), 18.75 (4.73), 19.15 (4.63), 19.72 (4.50), 20.82 (4.26), 22.05 (4.03), 22.52 (3.95), 22.92 (3.88), 23.58 (3.77) and 27.04 (3.30).

2. A preparation method of crystal form II of (3*aR*,5*s*,6*aS*)-*N*-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidine-4-yl)amino)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-formamide bisulfate according to claim 1, comprising the following steps of:

1) dissolving any crystal form or amorphous form of (3*aR*,5*s*,6*aS*)-*N*-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidine-4-yl)amino)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-formamide into an appropriate amount of organic solvent, then adding concentrated sulfuric acid dropwise to precipitate a crystal, or adding an anti-solvent to precipitate a crystal; or dissolving a solid of (3*aR*,5*s*,6*aS*)-*N*-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidine-4-yl)amino)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-formamide bisulfate in any crystal form or amorphous form into an appropriate amount of organic solvent under heating, then cooling the solution to precipitate a crystal, wherein the organic solvent is selected from any one of alcohols, ketones, esters having 3 or less carbon atoms, or a mixed solvent of one or more solvents mentioned above and a halogenated hydrocarbon having 3 or less carbon atoms;

2) filtering the crystal, then washing and drying it.

3. The preparation method according to claim 2, characterized in that the organic solvent in step 1) is methanol, ethanol, isopropanol, acetone, ethyl acetate, or dichloromethane/methanol, dichloromethane/methanol/ethanol, dichloromethane/methanol/isopropanol, dichloromethane/methanol/ethyl acetate, dichloromethane/methanol/acetone, preferably, the single solvent is methanol and the mixed solvent is dichloromethane/methanol/ethanol, more preferably in the volume ratio of 12:3:10.

4. A pharmaceutical composition comprising crystal form II of (3*aR*,5*s*,6*aS*)-*N*-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimi

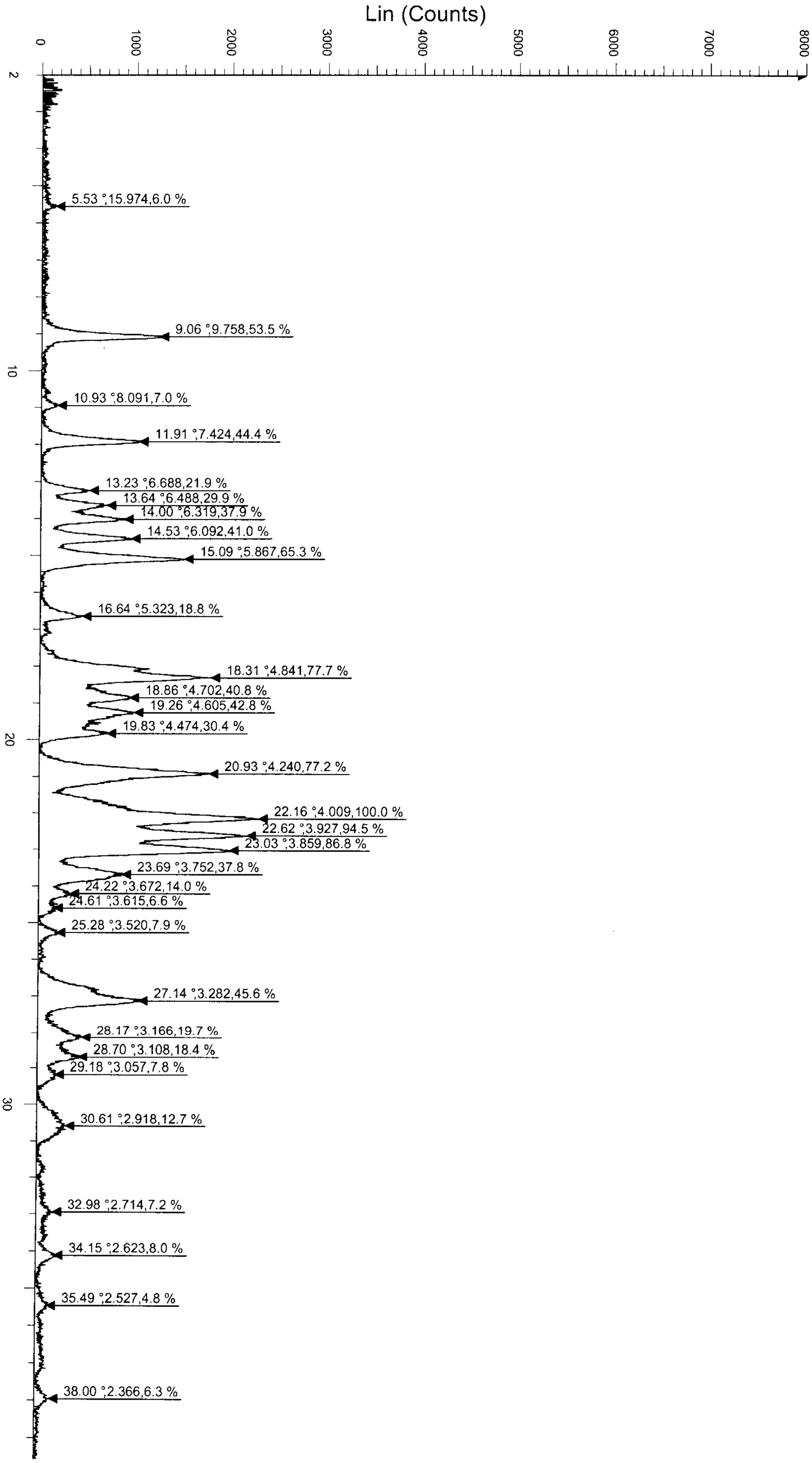
dine-4-yl)amino)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-formamide bisulfate according to claim 1 and at least one pharmaceutically acceptable carrier.

5. The pharmaceutical composition according to claim 4, characterized in that the content of crystal form II of (3*aR*,5*s*,6*aS*)-*N*-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidine-4-yl)amino)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-formamide bisulfate is 0.5 mg~200 mg.

6. The pharmaceutical composition according to claim 4, characterized in that the pharmaceutically acceptable carrier is selected from at least one of lactose, mannitol, microcrystalline cellulose, croscarmellose sodium, sodium carboxymethyl starch, hydroxypropyl methyl cellulose, povidone, and magnesium stearate.

7. Use of crystal form II according to claim 1 or the pharmaceutical composition according to any one of claims 4 to 6 in the preparation of a medicament for the treatment of JAK-related disease.

8. Use of crystal form II according to claim 1 or the pharmaceutical composition according to any one of claims 4 to 6 in the preparation of a medicament for the treatment of rheumatic and rheumatoid arthritis.


Lin (Counts)
0
1000
2000
3000
4000
5000
6000
7000
8000
2
10
20
30
2-Theta
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9.06 °,9.758,53.5 %
10.93 °,8.091,7.0 %
11.91 °,7.424,44.4 %
13.23 °,6.688,21.9 %
13.64 °,6.488,29.9 %
14.00 °,6.319,37.9 %
14.53 °,6.092,41.0 %
15.09 °,5.867,65.3 %
16.64 °,5.323,18.8 %
18.31 °,4.841,77.7 %
18.86 °,4.702,40.8 %
19.26 °,4.605,42.8 %
19.83 °,4.474,30.4 %
20.93 °,4.240,77.2 %
22.16 °,4.009,100.0 %
22.62 °,3.927,94.5 %
23.03 °,3.859,86.8 %
23.69 °,3.752,37.8 %
24.22 °,3.672,14.0 %
24.61 °,3.615,6.6 %
25.28 °,3.520,7.9 %
27.14 °,3.282,45.6 %
28.17 °,3.166,19.7 %
28.70 °,3.108,18.4 %
29.18 °,3.057,7.8 %
30.61 °,2.918,12.7 %
32.98 °,2.714,7.2 %
34.15 °,2.623,8.0 %
35.49 °,2.527,4.8 %
38.00 °,2.366,6.3 %

Figure 1

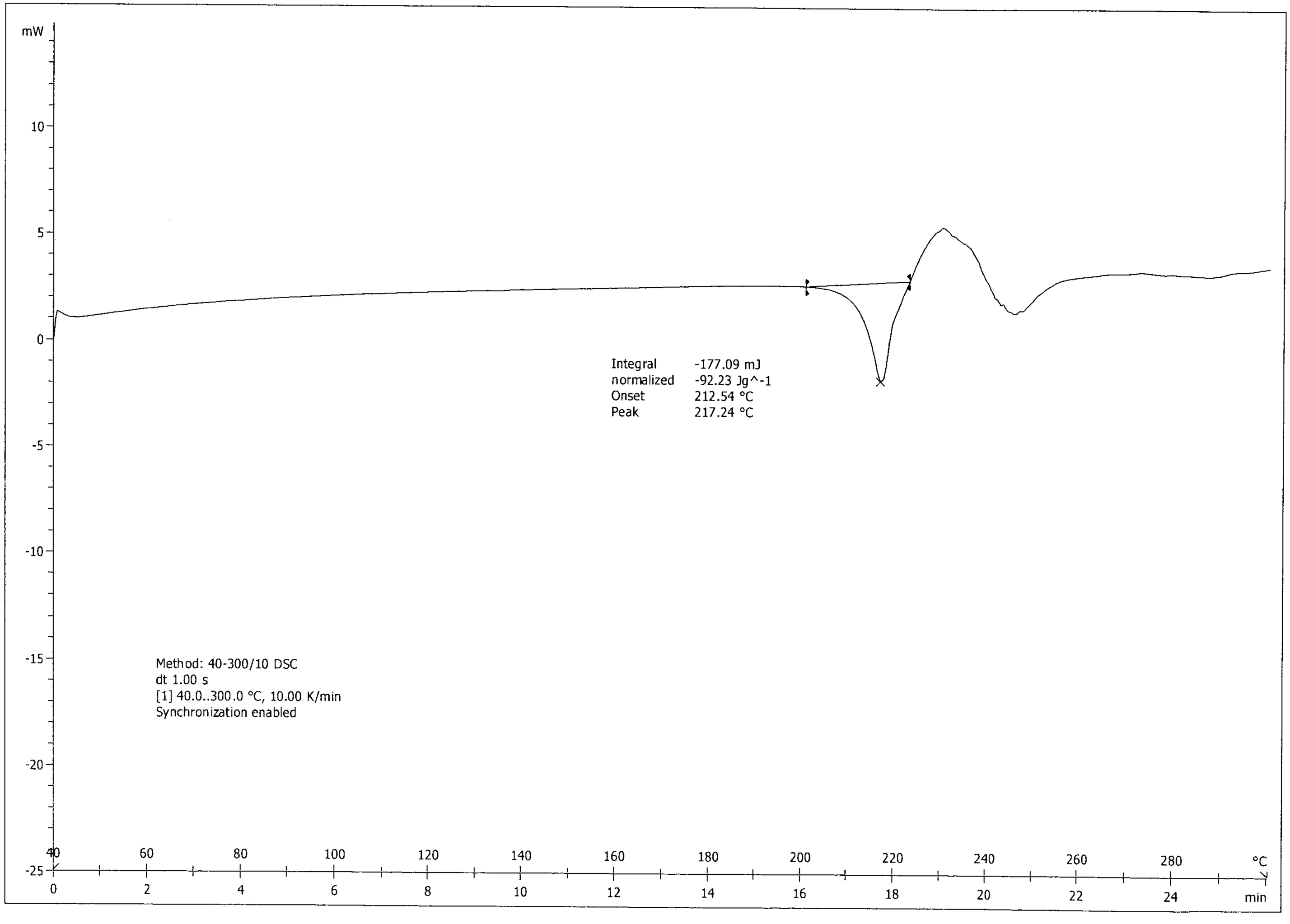


Figure 2

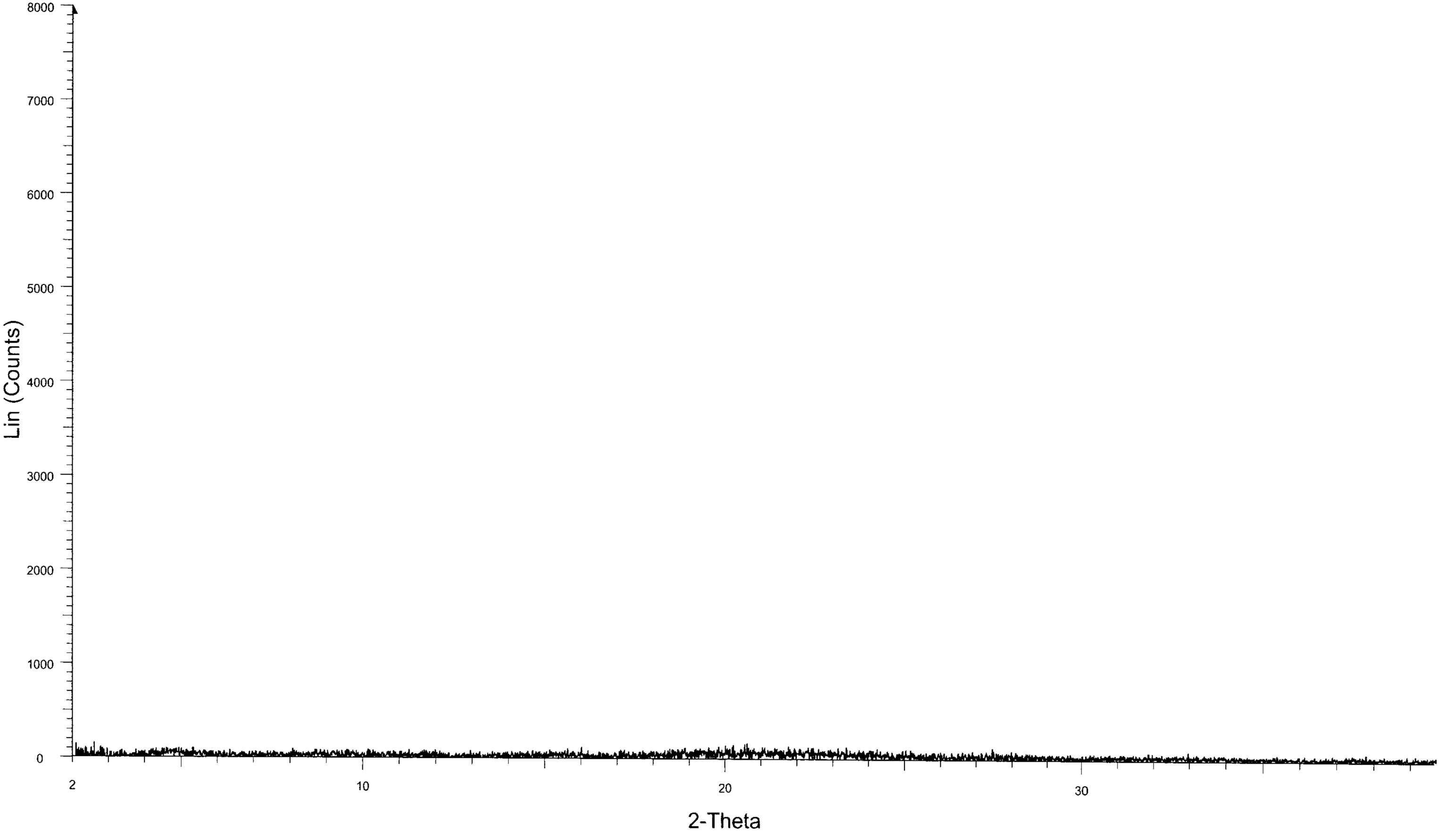


Figure 3

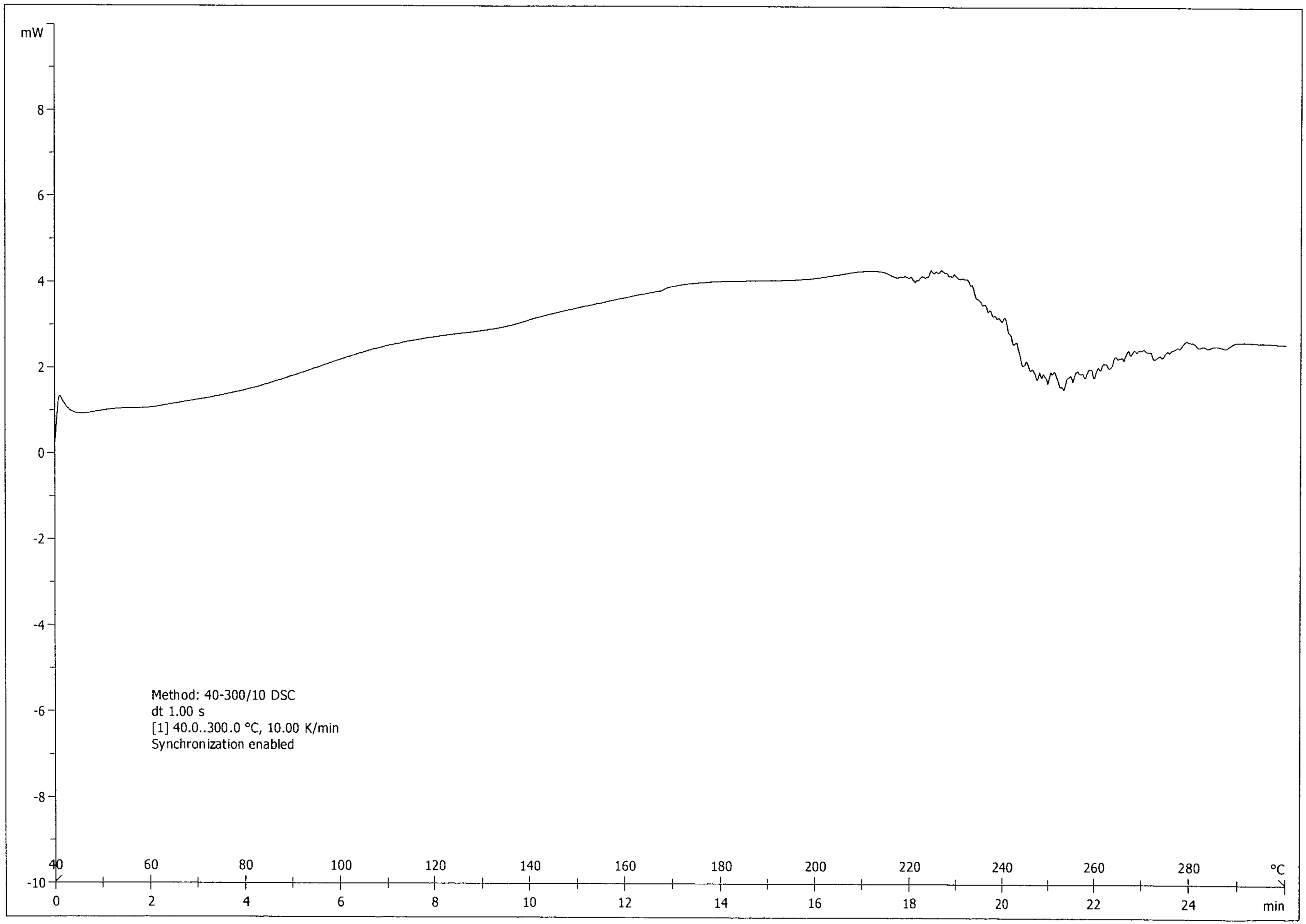
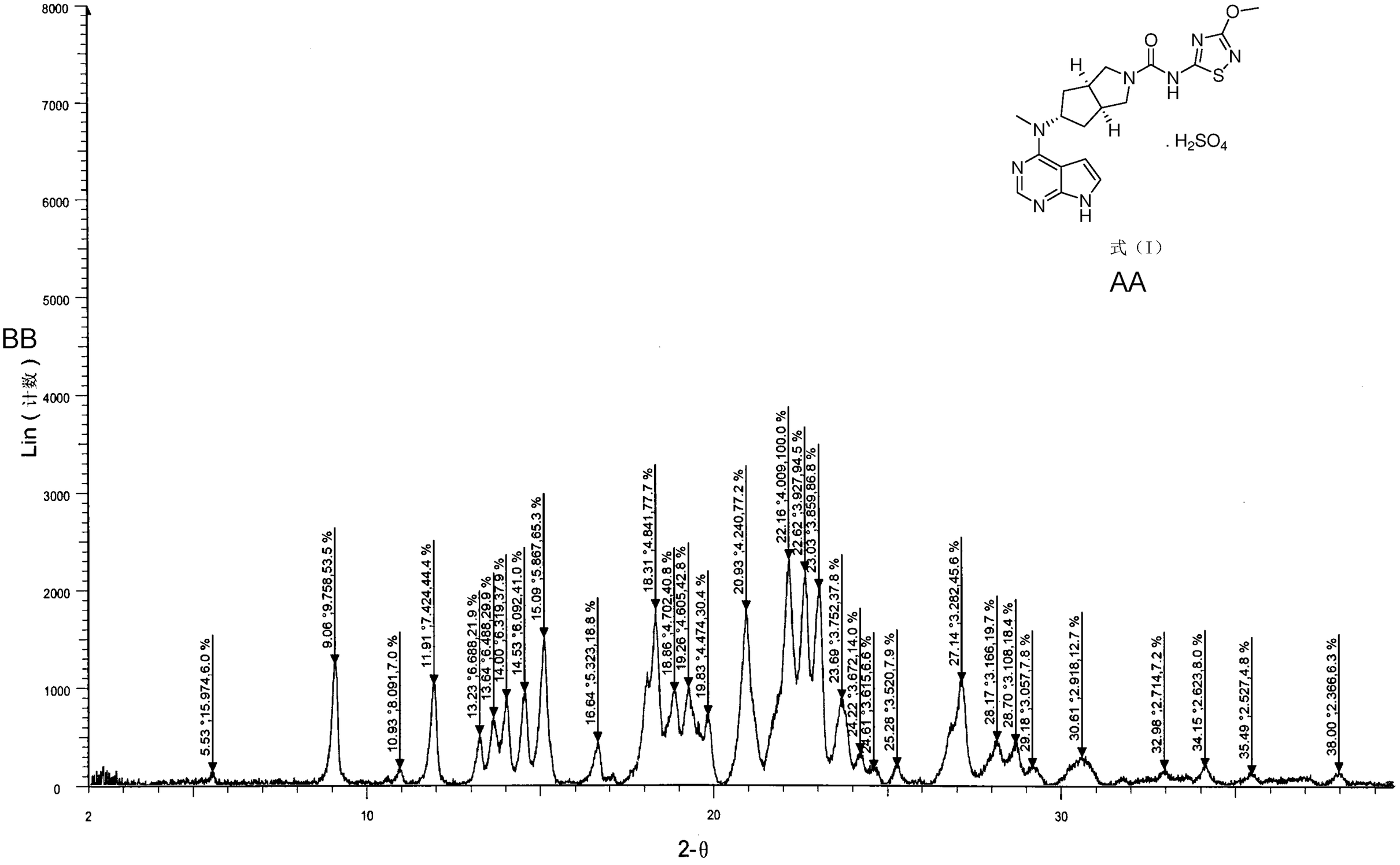


Figure 4



式（I）

AA

图 1 / Fig. 1

AA Formula (I)

BB Lin (count)