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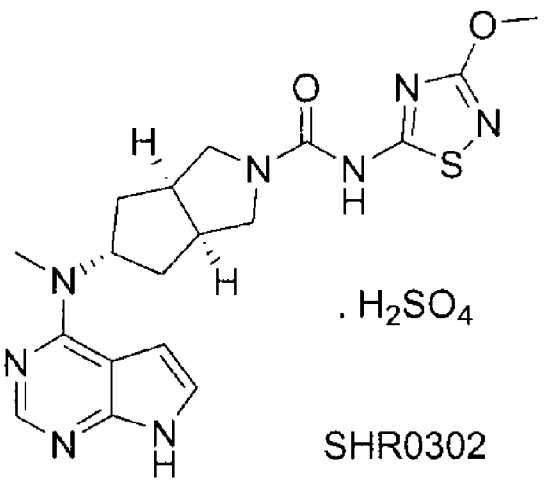
(54) Titre : FORME CRISTALLINE DE BISULFATE D'INHIBITEUR DE JAK ET SON PROCEDE DE PREPARATION
(54) Title: CRYSTAL FORM OF BISULFATE OF JAK INHIBITOR AND PREPARATION METHOD THEREFOR



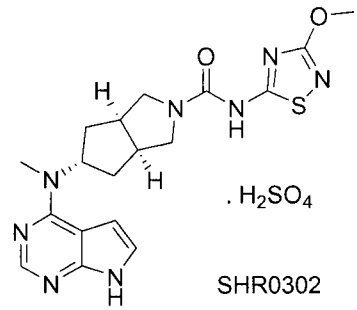
(I)

(57) Abrégé/Abstract:
Provided is an I-type crystal of a JAK (Janus Kinase) inhibitor (3aR,5s,6aS)-N-(3-methoxyl-1,2,4-thiadiazole-5-yl)-5-(methyl(7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)hexahydrocyclopenta[c]pyrrole-2(1H)-formamide bisulfate represented by formula (I), and a preparation method therefor. The preparation method comprises crystallizing any crystal form of or amorphous compound solid of formula (I) in a single organic solvent to obtain the I-type crystal; this crystal has excellent crystal stability and chemical stability, and the crystal solvent used is low in toxicity and residues, making the compound better applicable to clinical treatment.

(see formula I)

ABSTRACT:

Provided is an I-type crystal of a JAK (Janus Kinase) inhibitor (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 represented by formula (I), and a preparation method therefor. The preparation method comprises crystallizing any crystal form of or amorphous compound solid of formula (I) in a single organic solvent to obtain the I-type crystal; this crystal has excellent crystal stability and chemical stability, and the crystal solvent used is low in toxicity and residues, making the compound better applicable to clinical treatment.



SHR0302

(I)

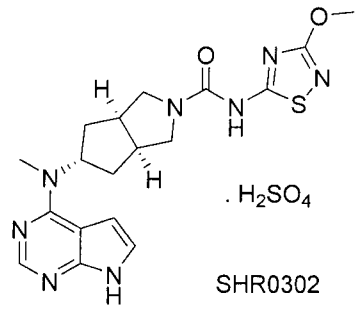
CRYSTAL FORM OF BISULFATE OF JAK INHIBITOR AND PREPARATION METHOD THEREFOR

FIELD OF THE INVENTION

The present invention relates to crystal form I 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 method 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 joint damages caused by arthritis 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. Since tofacitinib was produced in Pfizer's laboratories, the drug was highly expected to be a blockbuster drug. The success of the drug will be a big victory for the widely criticized research and development business of Pfizer. The results of clinical Phase III trials showed that the efficacy of tofacitinib of Pfizer was significantly better than that of methotrexate.



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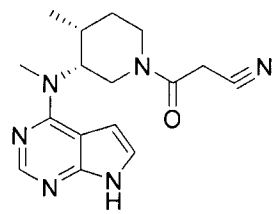

tofacitinib

formula (I)

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). The compound of formula (I) is expected to be a preferred compound of JAK inhibitors, and has

important study significance for the treatment of rheumatic and rheumatoid arthritis.

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 changes in the crystal structure of the compound, and sometimes the accompanying production of other forms of crystal form. In general, an amorphous drug product does not have a regular crystal structure, and often has other defects such as poor product stability, smaller particle size, difficult filtration, easy agglomeration, and poor liquidity. Thus, it is necessary to improve the various properties of the above product. It is need to search a new crystal form with high purity and good chemical stability.

SUMMARY OF THE INVENTION

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

The inventor has tested a series of crystal products of the compound of formula (I) obtained under various crystallization conditions by X-ray diffraction and differential scanning calorimetry (DSC) measurement. It was found that a stable crystal form of the compound of formula (I), which is referred as crystal form I, can be obtained under the normal crystallization condition. DSC spectrum of crystal form I of the compound of formula (I) according to the present application shows a melting endothermic peak at about 220°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 6.38 (13.85), 10.38 (8.51), 10.75 (8.23), 14.49 (6.11), 15.07 (5.88), 15.58 (5.69), 16.23 (5.46), 17.84 (4.97), 18.81 (4.72), 19.97 (4.44), 20.77 (4.27), 22.12 (4.02), 23.19 (3.83), 24.12 (3.69), 25.51 (3.49), 26.62 (3.35), 27.38 (3.26), 28.56 (3.12), and 29.91 (2.99).

In the preparation method of crystal form I 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 I of the compound of formula (I) of the present invention comprises:

using some lower organic solvents, preferably alcohols having 3 or less carbon atoms, and more preferably methanol as recrystallization solvents.

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

(1) dissolving a solid of the compound of formula (I) in any form into an appropriate amount of organic solvent under heating, then evaporating part of the

solvent;

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

In a preferred embodiment of the present invention, the organic solvent in step (1) is an alcohol having 3 or less carbon atoms, further preferably, the organic solvent is methanol.

The recrystallization method is different from the conventional recrystallization method. Any form of the compound of formula (I) is dissolved into an organic solvent under heating, and then part of the solvent is evaporated at atmospheric pressure; after completion of crystallization, the resulting crystal was filtered and dried to obtain the desired crystal. The crystal obtained by filtration is usually dried in vacuum at about 30~100°C, preferably 40~60°C, to remove the recrystallization solvent.

The crystal form of the obtained 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 I of the compound of formula (I) prepared according to the method of the invention does not contain or contains only a relatively low content of residual solvent, which meets the requirement of the national pharmacopoeia concerning the limitation of the residual solvent of drug products. Thus the crystal of the present invention can be suitably used as a pharmaceutically active ingredient.

The present invention is further to provide a pharmaceutical composition comprising crystal form I of the compound of formula (I) and at least one 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 I in the pharmaceutical composition of the present invention is 0.5 mg~200 mg.

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

DESCRIPTION OF THE DRAWINGS

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

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

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

Figure 4 shows the DSC spectrum of 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^e 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: The sample of the compound of formula (I) was prepared according to the method of Example 2 of PCT patent application no. PCT/CN2014/076794

Preparation 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 of formula (I)

140 g (0.34 mol) 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, 350 g of anhydrous methanol and 2.0 kg of dichloromethane were added in a 10 L reaction flask and stirred suspendedly. 34.8 g (0.36 mol) of sulfuric acid was slowly added dropwise at room temperature, then the reaction solution was clear and stirred for 30 min. Insolubles were

removed by filtration, the filtrate was concentrated under reduced pressure to dryness to obtain 135 g~168 g of the desired product, yield: 80~90%.

MS m/z (ESI):415.1651[M+1].

^{1}H NMR (400MHz, DMSO-d_6): δ 12.75 (s, 1H), 11.04 (s, 1H), 8.37 (s, 1H), 7.41-7.42 (t, 1H), 6.89 (s, 1H), 5.15-5.19 (m, 1H), 3.89 (s, 3H), 3.68-3.70 (m, 2H), 3.38-3.40 (m, 2H), 3.29 (s, 3H), 2.95 (s, 2H), 2.09-2.16 (m, 2H), 1.92-1.97 (m, 2H).

Example 2: Crystal form measurement of the sample of Example 1

The X-ray diffraction spectrum of the solid sample prepared in Example 1 is shown in Figure 3 in which there are no characteristic absorption peaks of a crystal. The DSC spectrum of this solid sample is shown in Figure 4, which has no melting characteristic absorption peak below 300°C. The product was thus identified as an amorphous solid.

Example 3

1.0 g (2.4 mmol) of the compound of formula (I) (prepared according to the method of Example 1) 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 min. About 90 ml of methanol was removed by evaporation at atmospheric pressure, and a large amount of white solid was precipitated. The mixture was filtered while it was hot, and dried to obtain 784 mg of a white solid in 78.4% yield. The X-ray diffraction spectrum of this crystal sample is shown in Figure 1 in which there are characteristic peaks at 6.38 (13.85), 10.38 (8.51), 10.75 (8.23), 14.49 (6.11), 15.07 (5.88), 15.58 (5.69), 16.23 (5.46), 17.84 (4.97), 18.81 (4.72), 19.97 (4.44), 20.77 (4.27), 22.12 (4.02), 23.19 (3.83), 24.12 (3.69), 25.51 (3.49), 26.62 (3.35), 27.38 (3.26), 28.56 (3.12) and 29.91 (2.99). The DSC spectrum of this crystal sample is shown in Figure 2, having a melting endothermic peak at 220.23°C. This crystal form was defined as crystal form I.

Example 4

The amorphous sample prepared in Example 1 and crystal form I prepared in Example 3 were spread flat in the air to test their stability under the 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. Comparison of stability of crystal form I and amorphous sample of the compound of formula (I)

Batch number	Time (Day)	Lighting	40°C	60°C	RH 75%	RH 90%
Crystal form I	0	99.45%	99.45%	99.45%	99.45%	99.45%

S011113120828	5	99.40%	99.42%	99.36%	99.42%	99.42%
	10	99.39%	99.42%	99.35%	99.40%	99.39%
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 I and the amorphous sample of the compound of formula (I) were spread flat in the air to test the 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 I is significantly better than that of the amorphous sample.

WHAT IS CLAIMED IS:

1. Crystal form I 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, wherein 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 6.38 (13.85), 10.38 (8.51), 10.75 (8.23), 14.49 (6.11), 15.07 (5.88), 15.58 (5.69), 16.23 (5.46), 17.84 (4.97), 18.81 (4.72), 19.97 (4.44), 20.77 (4.27), 22.12 (4.02), 23.19 (3.83), 24.12 (3.69), 25.51 (3.49), 26.62 (3.35), 27.38 (3.26), 28.56 (3.12) and 29.91 (2.99).

2. A method of preparing crystal form I 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 as defined in claim 1, comprising the following steps of:

1) 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 evaporating part of the solvent at atmospheric pressure to precipitate a solid, wherein the organic solvent is an alcohol having 3 or less carbon atoms;

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

3. The method according to claim 2, wherein the organic solvent in step 1) is methanol.

4. A pharmaceutical composition comprising crystal form I 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 as defined in claim 1 and a pharmaceutically acceptable carrier.

5. The pharmaceutical composition according to claim 4, wherein the content of crystal form I 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 from 0.5 mg to 200 mg.

Date reçue / Date received 2021-11-05

6. The pharmaceutical composition according to claim 4 or 5, wherein 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 I as defined in claim 1 in the preparation of a medicament for the treatment of rheumatic and rheumatoid arthritis.

8. Use of crystal form I as defined in claim 1 for the treatment of rheumatic and rheumatoid arthritis.

9. Use of the pharmaceutical composition as defined in any one of claims 4 to 6 in the preparation of a medicament for the treatment of rheumatic and rheumatoid arthritis.

10. Use of the pharmaceutical composition as defined in any one of claims 4 to 6 for the treatment of rheumatic and rheumatoid arthritis.

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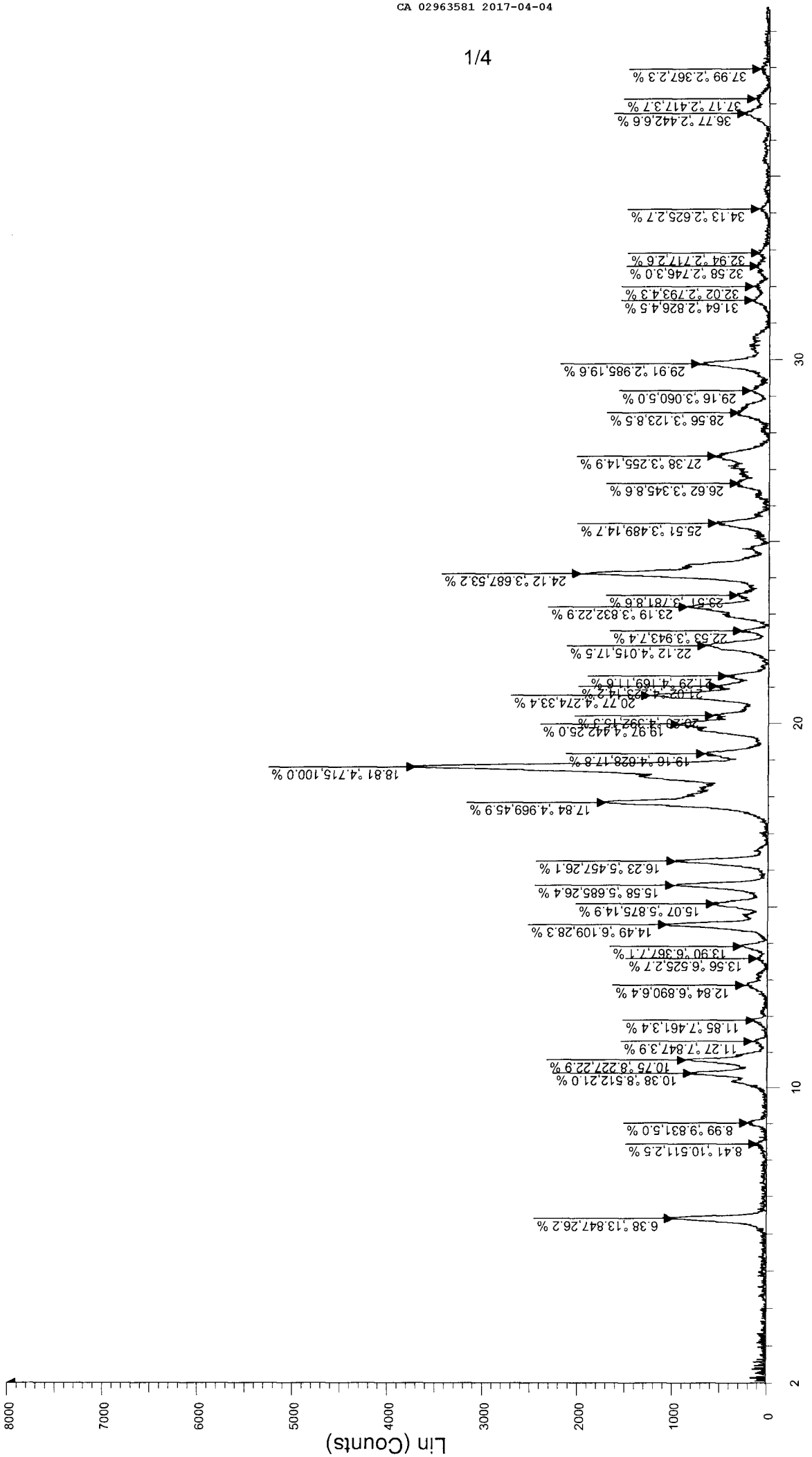
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21.29 °4.169,11.6 %
22.12 °4.015,17.5 %
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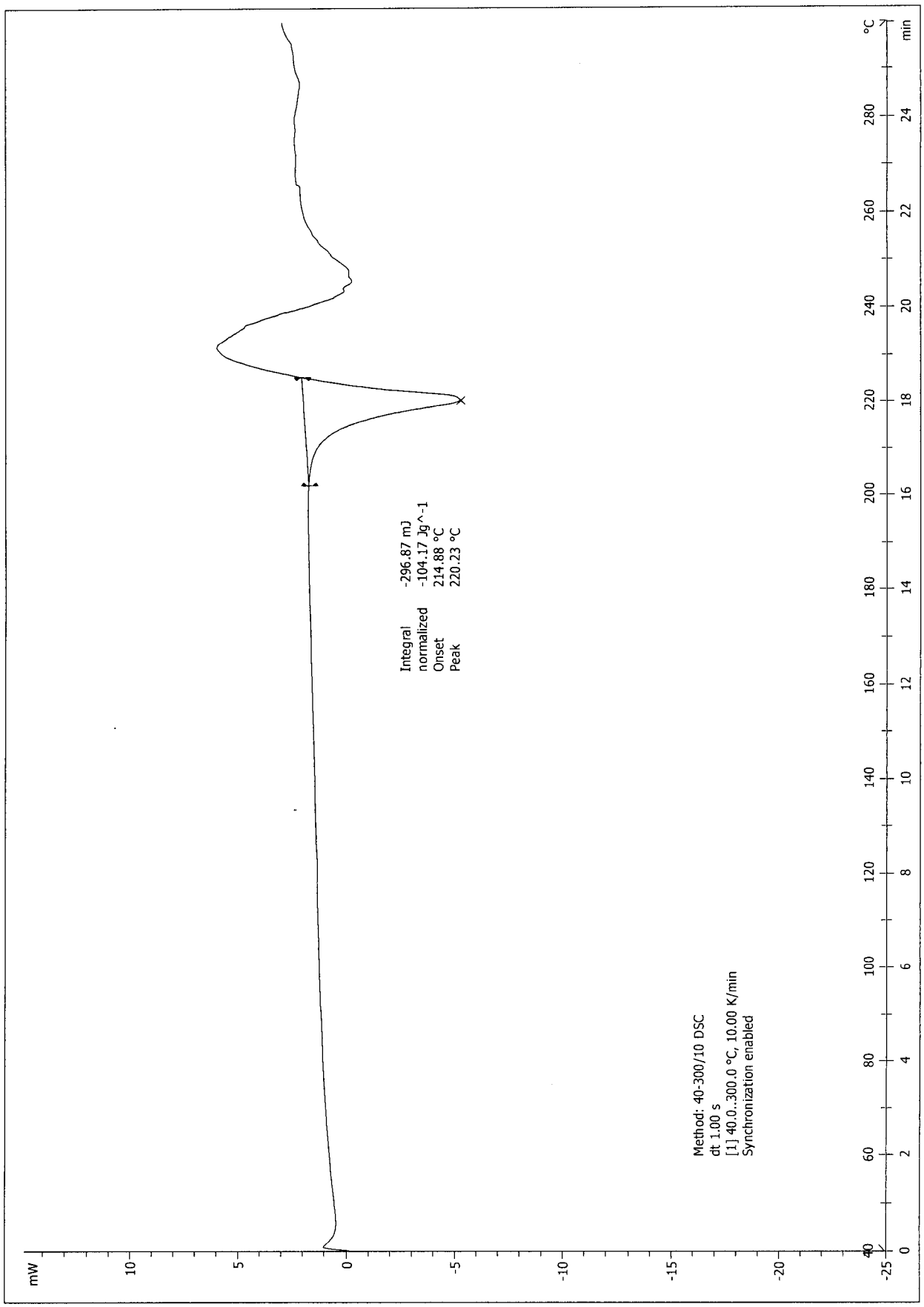
Figure 1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16
18
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22
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normalized -104.17 Jg^-1
Onset 214.88 °C
Peak 220.23 °C
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Figure 2

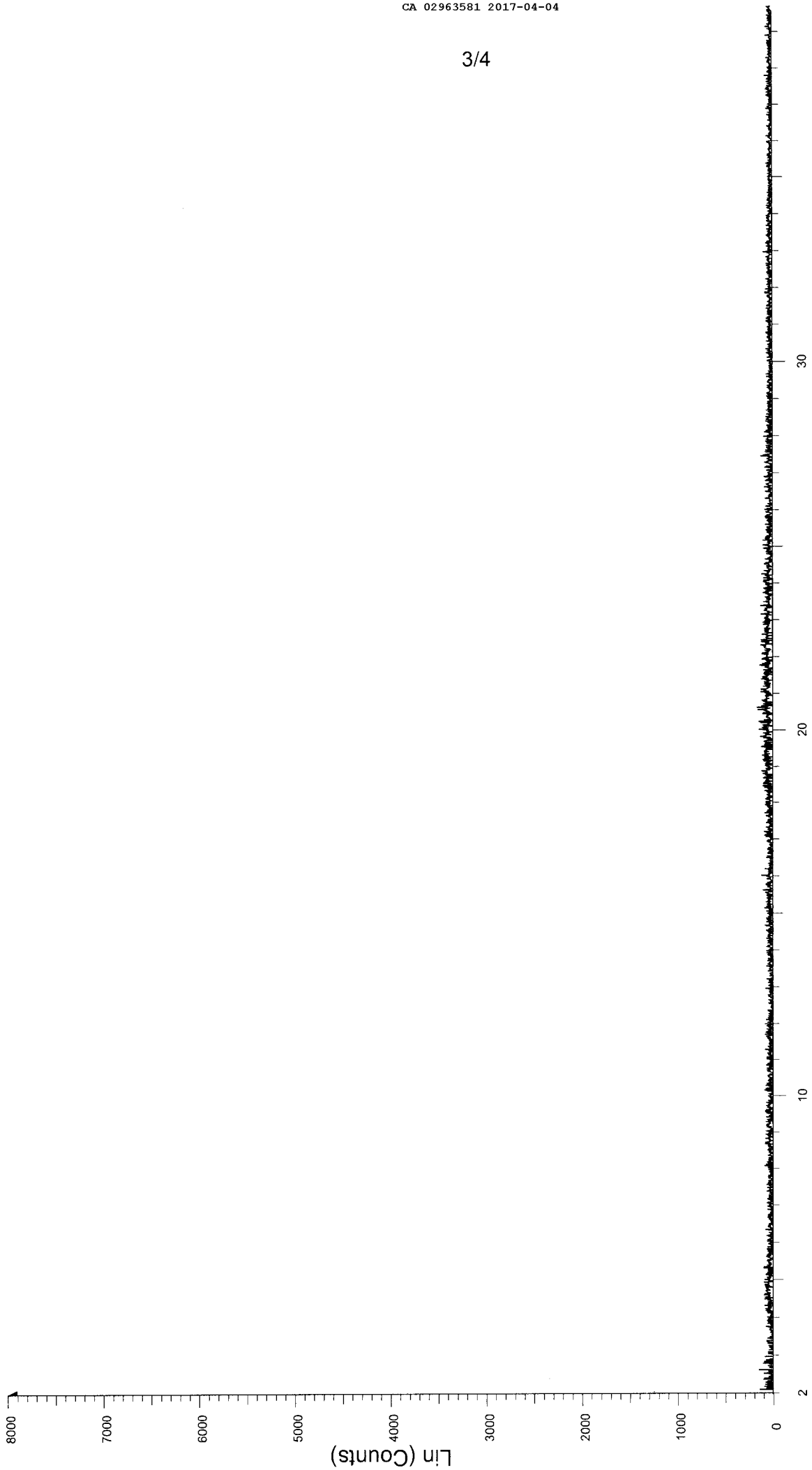
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Figure 3

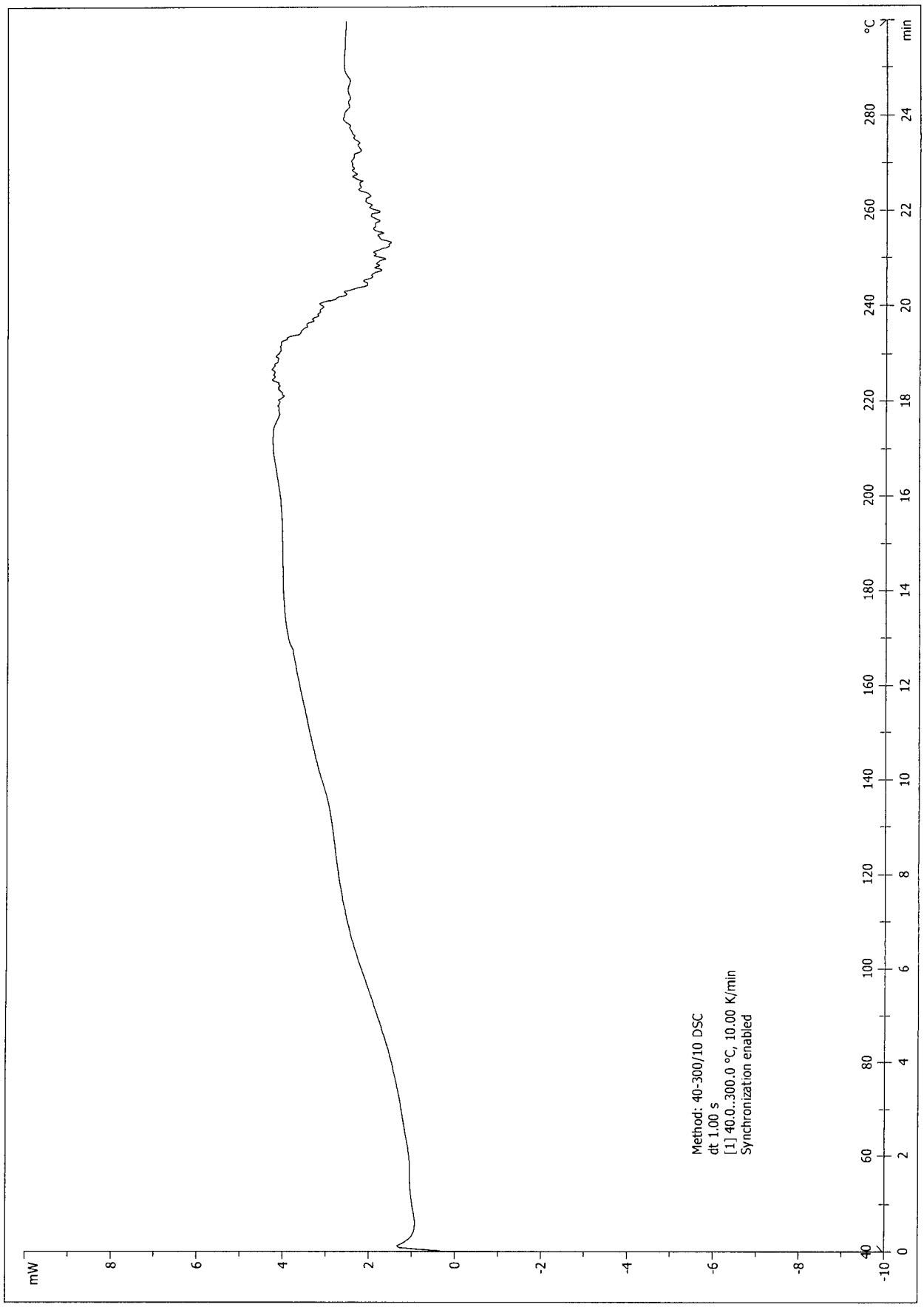
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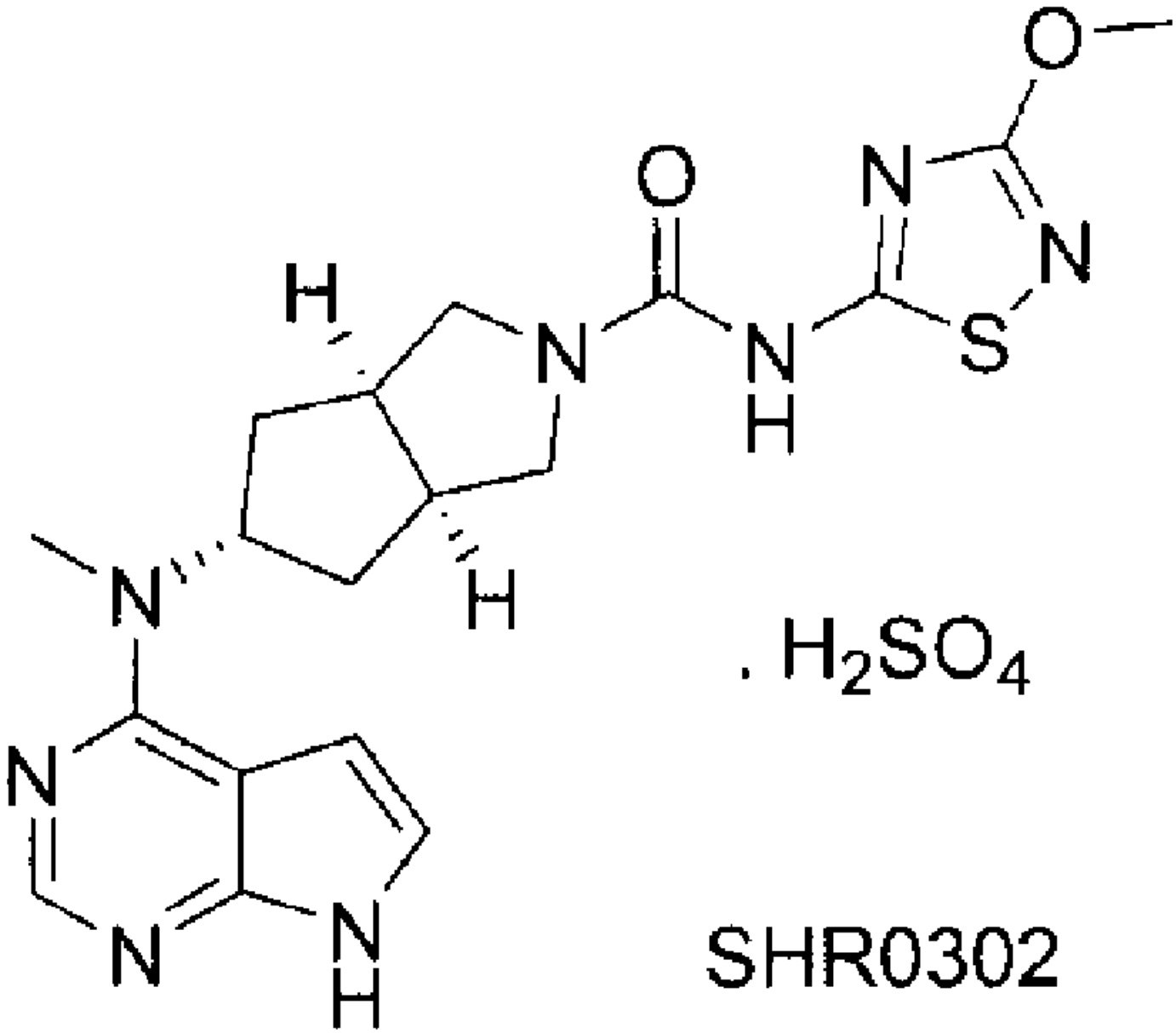
Figure 4



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