



(11) **EP 3 889 143 B9**

(12) **CORRECTED EUROPEAN PATENT SPECIFICATION**

(15) Correction information:
Corrected version no 1 (W1 B1)
Corrections, see
Claims FR 10

(51) International Patent Classification (IPC):
C07D 307/87 (2006.01)

(52) Cooperative Patent Classification (CPC):
C07D 307/87

(48) Corrigendum issued on:
05.10.2022 Bulletin 2022/40

(86) International application number:
PCT/CN2019/110807

(45) Date of publication and mention
of the grant of the patent:
22.06.2022 Bulletin 2022/25

(87) International publication number:
WO 2020/108117 (04.06.2020 Gazette 2020/23)

(21) Application number: **19891658.7**

(22) Date of filing: **12.10.2019**

(54) **METHOD FOR PREPARING ESCITALOPRAM BIS-HYDROXYNAPHTOATE CRYSTAL FORM A**

VERFAHREN ZUR HERSTELLUNG VON
ESCITALOPRAM-BIS-HYDROXYNAPHTOAT-KRISTALLFORM A

PROCÉDÉ DE PRÉPARATION D'UNE FORME CRISTALLINE A D'ESCITALOPRAM
BIS-HYDROXYNAPHTOATE

(84) Designated Contracting States:
**AL AT BE BG CH CY CZ DE DK EE ES FI FR GB
GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO
PL PT RO RS SE SI SK SM TR**

(72) Inventors:
• **XU, Wei**
Shanghai 201203 (CN)
• **CHEN, Xi**
Shanghai 201203 (CN)
• **GU, Hong**
Shanghai 201203 (CN)

(30) Priority: **26.11.2018 CN 201811212608**

(43) Date of publication of application:
06.10.2021 Bulletin 2021/40

(74) Representative: **Altmann Stöbel Dick**
Patentanwälte PartG mbB
Theodor-Heuss-Anlage 2
68165 Mannheim (DE)

(73) Proprietors:
• **Zhejiang Huahai Pharmaceutical Co., Ltd.**
Taizhou, Zhejiang 317024 (CN)
• **Shanghai Aobo Pharmtech, Inc., Ltd.**
Shanghai 201203 (CN)

EP 3 889 143 B9

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

Description

[0001] The present application claims the priority of Chinese Patent Application No. 201811212608.5, entitled "A NEW PROCESS FOR PREPARING HIGH-PURITY ESCITALOPRAM PAMOATE", filed on October 18, 2018 before China National Intellectual Property Administration.

FIELD OF INVENTION

[0002] The present application belongs to the technical field of medicine, and particularly relates to a method for preparing Escitalopram pamoate ((S)-(+)- 1-(3-(dimethylamino)propyl)-1-(4- fluorophenyl)-1,3-dihydro-5-cyanoisobenzofuran pamoate) crystal form A.

BACKGROUND OF THE INVENTION

[0003] The chemical name of escitalopram is: (S)-(+)-1-(3-(dimethylamino)propyl)-1-(4-fluorophenyl)-1,3-dihydro-5-cyanoisobenzofuran. Escitalopram oxalate was developed jointly by U.S. Forest Laboratories, Inc. and Lundbeck Inc., Denmark. It was first launched in Euro-American countries such as Switzerland in March 2002 and approved by FDA in August 2002. Escitalopram, a serotonin reuptake inhibitor (SSRI), has a unique serotonin isomeric sites binding mechanism and is highly selective for serotonin receptors, thus being used for the treatment of major depression and the maintenance treatment of depression.

[0004] Patients with major depression are usually insubordinate, so it is difficult to evaluate whether a patient has received the accurate dose of the medicine or not. Thus, it is necessary to formulate escitalopram oxalate as a type of salt with low solubility and slow release by replacing acid radical.

[0005] The patent documents, WO2018171589, WO2018223970 and EP0347066 disclose an escitalopram pamoate crystal form A and the preparation method thereof. In EP0347066 the solvent used is methanol and the starting materials are escitalopram and pamoic acid.

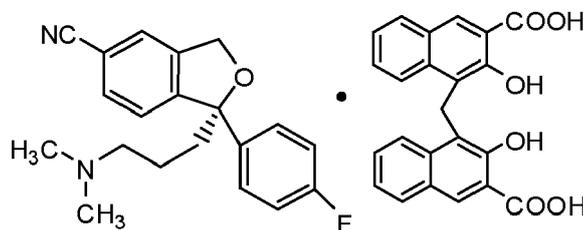
[0006] Methanol, the solvent used in the above method for preparing escitalopram pamoate, has certain toxicity. Therefore, it is a technical problem to be solved for those skilled in the art to prepare escitalopram pamoate by using less toxic or even non-toxic solvent.

SUMMARY OF THE INVENTION

[0007] Through continuous research, the inventor of the present invention found a novel method for preparing escitalopram pamoate crystal form A by using water and ethanol as the solvent, thereby overcoming the problem of solvent toxicity in the prior art, the method is environment-friendly without pollution. Further, the escitalopram pamoate crystal form A prepared by the method has a purity over 99.5%.

[0008] Specific scheme is as follows:

The present invention provides a method for preparing an escitalopram pamoate crystal form A, comprising dissolving escitalopram oxalate in a reaction solvent (mixed solvent of water and ethanol) to obtain an escitalopram oxalate solution; and adding a solution of a pamoate salt dropwise to precipitate escitalopram pamoate crystal form A



formula I.

[0009] In some embodiments of the present invention, X-ray powder diffraction spectrum of crystal form A of the compound of formula I has characteristic peaks at $8.9 \pm 0.2^\circ$, $11.3 \pm 0.2^\circ$, $13.2 \pm 0.2^\circ$, $18.4 \pm 0.2^\circ$, $20.6 \pm 0.2^\circ$ and $21.9 \pm 0.2^\circ$.

[0010] In some embodiments of the present invention, the reaction solvent is water.

[0011] In some embodiments of the present invention, dissolving is carried out at a temperature of 0-70°C.

[0012] In some embodiments of the present invention, dissolving is carried out at a temperature of is 25-35°C.

[0013] In some embodiments of the present invention, the pamoate salt is disodium pamoate.

[0014] In some embodiments of the present invention, a solvent of the pamoate salt solution is a mixed solvent of water and ethano with a mixing ratio of water and ethanol in the mixed solvent of 7:3-3:7, preferably 1.2:1-1:1.2, more preferably 1:1.

[0015] In some embodiments of the present invention, during adding the solution of the pamoate salt dropwise, a temperature of escitalopram oxalate solution is 25-35°C. In some embodiments of the present invention, during adding the solution of the pamoate salt dropwise, the temperature of escitalopram oxalate solution is 30°C. In some embodiments of the present invention, a mass ratio of escitalopram oxalate and the pamoate salt is 1:0.9-1:1.2.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] In order to illustrate the examples of the present application and the technical solution of the prior art more clearly, the following is a brief description of the drawings that need to be used in the examples and the prior art. It is obvious that the drawings in the following description are only some of the examples of the present invention and according to these drawings, other drawings can be obtained by those skilled in the art without any inventive efforts.

Figure 1 is an XRPD spectrum of escitalopram pamoate crystal form A prepared according to Example 1.

Figure 2 is a HPLC spectrum of escitalopram pamoate crystal form A prepared according to Example 1.

Figure 3 is the relevant datas of the HPLC spectrum of escitalopram pamoate crystal form A prepared according to Example 1.

DETAILED DESCRIPTION OF THE INVENTION

[0017] In order to make the technical problems, technical solutions and beneficial effects of the present application more clear, the application is further explained below in combination with specific examples. In the following examples, unless otherwise indicated, specific conditions of all of the test methods are generally carried out according to the conventional conditions or conditions recommended by manufacturers; raw materials and reagents are commercially available or prepared by using published information.

[0018] The data of X-ray powder diffraction used in the present application is determined by BRUKER D8 Advance from BRUKER Corp., Germany using Cu-K α radiation; voltage and current: 40 kV, 40 mA; goniometer: Vertical goniometer, radius: 280mm; slit: DS=2°, SS=1/2°, mask=15mm, RS=5.0mm; detector: LYNXEYE detector; scan patterns: continuous scan; scan range: 3-40°; count time per step: 0.2s; total scan time: 390s.

[0019] The HPLC detection conditions used in the present application are as follows:

Instrument: High performance liquid chromatograph equipped with an UV detector

Chromatographic column:	Waters Symmetry C18 100×4.6mm, 3.5 μ m
Mobile phase A	3.54g/L sodium hydrogen phosphate solution, pH is adjusted to 7.0 with phosphoric acid
Mobile phase B	Methanol: Acetonitrile = 1: 1 (V/V)
Mobile phase	Mobile phase A: Mobile phase B =55: 45 (% V/V)
Detection wavelength:	230nm
Flow rate:	1.2mL/min
Sample size:	10 μ L
Column temperature:	40°C
Run time:	25min

Example 1: preparation of escitalopram pamoate crystal form A

[0020] 900ml of water was added to 35g of escitalopram oxalate sample, and was heated to 60°C to completely dissolve it; 500ml of water was added to 36.6g of disodium pamoate to completely dissolve it at room temperature, then 500ml of anhydrous ethanol was added and was mixed well. A water/ethanol mixed solution of disodium pamoate was added dropwise to escitalopram oxalate solution at 30°C. A solid was obtained immediately with good dispersion. After the addition was complete, the mixture was continuously stirred for 2h and then filtered. The filter cake was washed with

EP 3 889 143 B9

500ml of water, filtered with suction for 10 min and dried under vacuum. 59.5g of escitalopram pamoate crystal form A sample was obtained. XRPD spectrum thereof was shown in Figure 1; HPLC spectrum was shown in Figure 2 and 3; the purity was 99.87% by HPLC.

5 Example 2: preparation of escitalopram pamoate crystal form A

10 **[0021]** 25ml of water was added to 500mg of escitalopram oxalate sample, and was heated to 30°C to completely dissolve it; 12.5ml of water was added to 520g of disodium pamoate to completely dissolve it at room temperature, then 12.5ml of anhydrous ethanol was added and was mixed well. A water/ethanol mixed solution of disodium pamoate was added dropwise to escitalopram oxalate solution at 30°C. A solid was obtained immediately with good dispersion. After the addition was complete, the mixture was continuously stirred for 2h and then filtered. The filter cake was washed with 50ml of water, filtered with suction for 10 min and dried under vacuum. 850mg of escitalopram pamoate crystal form A was obtained. The purity was 99.86% by HPLC.

15 Example 3: preparation of escitalopram pamoate crystal form A

20 **[0022]** 140ml of water was added to 5g of escitalopram oxalate sample, and was heated to 60°C to completely dissolve it; 25ml of water was added to 5.2g of disodium pamoate to completely dissolve it at room temperature, then 25ml of anhydrous ethanol was added and was mixed well. A water/ethanol mixed solution of disodium pamoate was added dropwise to escitalopram oxalate solution at 30°C. A solid was obtained immediately with good dispersion. After the addition was complete, the mixture was continuously stirred for 2h and then filtered. The filter cake was washed with 50ml of water, filtered with suction for 10 min and dried under vacuum. 8.5g of escitalopram pamoate crystal form A sample was obtained. The purity was 99.81% by HPLC.

25 Example 4

30 **[0023]** 400ml of water was added to 15g of escitalopram oxalate sample, and was heated to 60°C to completely dissolve it; 200ml of water was added to 14.9g of disodium pamoate, and then 100ml of anhydrous ethanol was added and was mixed well. The solid was completely dissolved at room temperature. A water/ethanol mixed solution of disodium pamoate was added dropwise to escitalopram oxalate solution at 30°C. A solid was obtained immediately with a small amount of agglomeration. After the addition was complete, the agglomeration was obvious. The mixture was continuously stirred for 2h and then filtered. The filter cake was washed with 50ml of water, filtered with suction for 10 min and dried under vacuum. 25.5g of escitalopram pamoate crystal form A sample was obtained. The purity was 99.74% by HPLC.

35 Example 5

40 **[0024]** 400ml of water was added to 15g of escitalopram oxalate sample, and was heated to 60°C to completely dissolve it; 200ml of water was added to 14.9g of disodium pamoate, and then 100ml of anhydrous ethanol was added and was mixed well. The solid was completely dissolved at room temperature. A water/ethanol mixed solution of disodium pamoate was added dropwise to escitalopram oxalate solution at 30°C. A solid was obtained immediately with a small amount of agglomeration. After the addition was complete, the agglomeration was obvious. The mixture was continuously stirred for 2h and then filtered. The filter cake was washed with 50ml of water, filtered with suction for 10 min and dried under vacuum. 25.5g of escitalopram pamoate crystal form A sample was obtained. The purity was 99.71% by HPLC.

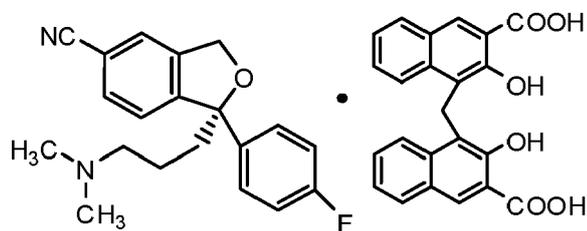
45 Example 6

50 **[0025]** 140ml of water was added to 5g of escitalopram oxalate sample, and was heated to 60°C to completely dissolve it; 50ml of water was added to 5.2g of disodium pamoate to completely dissolve it at room temperature. Disodium pamoate solution was added dropwise to escitalopram oxalate solution at 30°C. A solid was obtained immediately with a small amount of agglomeration. After the addition was complete, the agglomeration was obvious. The mixture was continuously stirred for 2h and then filtered. The filter cake was washed with 50ml of water, filtered with suction for 10 min and dried under vacuum. 8.5g of escitalopram pamoate crystal form A sample was obtained. The purity was 99.71% by HPLC.

55 **[0026]** The function of the above-mentioned examples is to explain the substantive content of the present application, it is not intended to limit the protection scope of the present application.

Claims

1. A method for preparing a crystal form A of a compound of formula I, comprising: dissolving escitalopram oxalate in a reaction solvent to obtain an escitalopram oxalate solution; and adding a solution of a pamoate salt dropwise to precipitate the crystal form A of the compound of formula I



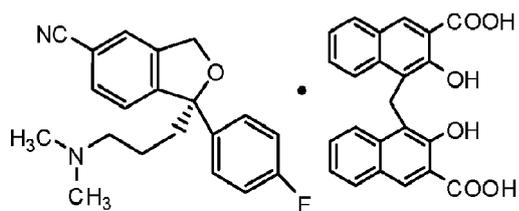
formula I,

wherein the solvent of the solution of the pamoate salt is a mixed solvent of water and ethanol.

2. The method according to claim 1, wherein the reaction solvent is water.
3. The method according to claim 1 or 2, wherein dissolving is carried out at a temperature of 0-70°C.
4. The method according to claim 3, wherein dissolving is carried out at a temperature of 25-35°C.
5. The method according to any one of claims 1-4, wherein the pamoate salt is disodium pamoate.
6. The method according to claim 1, wherein a volume ratio of water and ethanol in the mixed solvent is 7:3-3:7, preferably 1.2:1-1:1.2, more preferably 1:1.
7. The method according to any one of claims 1-6, wherein during adding the solution of the pamoate salt dropwise, a temperature of the escitalopram oxalate solution is 25-35°C.
8. The method according to claim 7, wherein during adding the solution of the pamoate salt dropwise, the temperature of the escitalopram oxalate solution is 30°C.
9. The method according to any one of claims 1-8, wherein a mass ratio of escitalopram oxalate and the pamoate salt is 1:0.9-1:1.2.
10. The method according to any one of claims 1-9, wherein the crystal form A of the compound of formula I has a X-ray powder diffraction spectrum, showing characteristic peaks at $8.9 \pm 0.2^\circ$, $11.3 \pm 0.2^\circ$, $13.2 \pm 0.2^\circ$, $18.4 \pm 0.2^\circ$, $20.6 \pm 0.2^\circ$ and $21.9 \pm 0.2^\circ$.

Patentansprüche

1. Verfahren zur Herstellung einer Kristallform A einer Verbindung der Formel I umfassend: Lösen von Escitalopramoxalat in einem Reaktionslösungsmittel unter Erhalt einer Escitalopramoxalat-Lösung und Zutropfen einer Lösung eines Pamoatsalzes zur Ausfällung der Kristallform A der Verbindung der Formel I



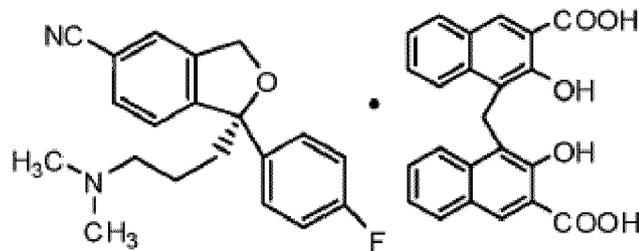
Formel I,

10 wobei das Lösungsmittel der Lösung des Pamoatsalzes ein gemischtes Lösungsmittel aus Wasser und Ethanol ist.

2. Verfahren nach Anspruch 1, wobei das Reaktionslösungsmittel Wasser ist.
- 15 3. Verfahren nach Anspruch 1 oder 2, wobei das Lösen bei einer Temperatur von 0-70 °C durchgeführt wird.
4. Verfahren nach Anspruch 3, wobei das Lösen bei einer Temperatur von 25-35 °C durchgeführt wird.
5. Verfahren nach einem der Ansprüche 1-4, wobei das Pamoatsalz Dinatriumpamoat ist.
- 20 6. Verfahren nach Anspruch 1, wobei das Volumenverhältnis von Wasser und Ethanol in dem gemischten Lösungsmittel 7:3-3:7, vorzugsweise 1,2:1-1:1,2, weiter bevorzugt 1:1, ist.
7. Verfahren nach einem der Ansprüche 1 bis 6, wobei die Temperatur der Escitaloproxalat-Lösung während des Zutropfens der Lösung des Pamoatsalzes 25-35 °C beträgt.
- 25 8. Verfahren nach Anspruch 7, wobei die Temperatur der Escitaloproxalat-Lösung während des Zutropfens der Lösung des Pamoatsalzes 30 °C beträgt.
9. Verfahren nach einem der Ansprüche 1-8, wobei ein Massenverhältnis von Escitaloproxalat und dem Pamoatsalz 1:0,9-1:1,2 ist.
- 30 10. Verfahren nach einem der Ansprüche 1-9, wobei die Kristallform A der Verbindung der Formel I ein Röntgenpulverbeugungsspektrum aufweist, das charakteristische Peaks bei $8,9 \pm 0,2^\circ$, $11,3 \pm 0,2^\circ$, $13,2 \pm 0,2^\circ$, $18,4 \pm 0,2^\circ$, $20,6 \pm 0,2^\circ$ und $21,9 \pm 0,2^\circ$ zeigt.
- 35

Revendications

- 40 1. Procédé pour la préparation d'une forme cristalline A d'un composé de formule I, comprenant : la dissolution d'oxalate d'escitalopram dans un solvant de réaction pour obtenir une solution d'oxalate d'escitalopram ; et l'ajout d'une solution d'un sel de pamoate goutte-à-goutte pour précipiter la forme cristalline A du composé de formule I



formule I,

55 le solvant de la solution du sel de pamoate étant un solvant mixte d'eau et d'éthanol.

2. Procédé selon la revendication 1, le solvant de réaction étant l'eau.

EP 3 889 143 B9

3. Procédé selon la revendication 1 ou 2, la dissolution étant mise en œuvre à une température de 0 à 70 °C.
4. Procédé selon la revendication 3, la dissolution étant mise en œuvre à une température de 25 à 35 °C.
- 5 5. Procédé selon l'une quelconque des revendications 1 à 4, le sel de pamoate étant le pamoate disodique.
6. Procédé selon la revendication 1, un rapport volumique d'eau et d'éthanol dans le solvant mixte étant de 7 : 3 à 3 : 7, préférablement de 1,2 : 1 à 1 : 1,2, plus préférablement de 1 : 1.
- 10 7. Procédé selon l'une quelconque des revendications 1 à 6, dans lequel pendant l'ajout de la solution du sel de pamoate goutte-à-goutte, une température de la solution d'oxalate d'escitalopram est de 25 à 35 °C.
8. Procédé selon la revendication 7, dans lequel pendant l'ajout de la solution du sel de pamoate goutte-à-goutte, la température de la solution d'oxalate d'escitalopram est de 30 °C.
- 15 9. Procédé selon l'une quelconque des revendications 1 à 8, un rapport en masse d'oxalate d'escitalopram et du sel de pamoate étant de 1 : 0,9 à 1 : 1,2.
- 20 10. Procédé selon l'une quelconque des revendications 1 à 9, la forme cristalline A du composé de formule I possédant un spectre de diffraction des rayons X sur poudre, présentant des pics caractéristiques à $8,9 \pm 0,2^\circ$, $11,3 \pm 0,2^\circ$, $13,2 \pm 0,2^\circ$, $18,4 \pm 0,2^\circ$, $20,6 \pm 0,2^\circ$ et $21,9 \pm 0,2^\circ$.

25

30

35

40

45

50

55

Commander Sample ID (Coupled TwoTheta/Theta)

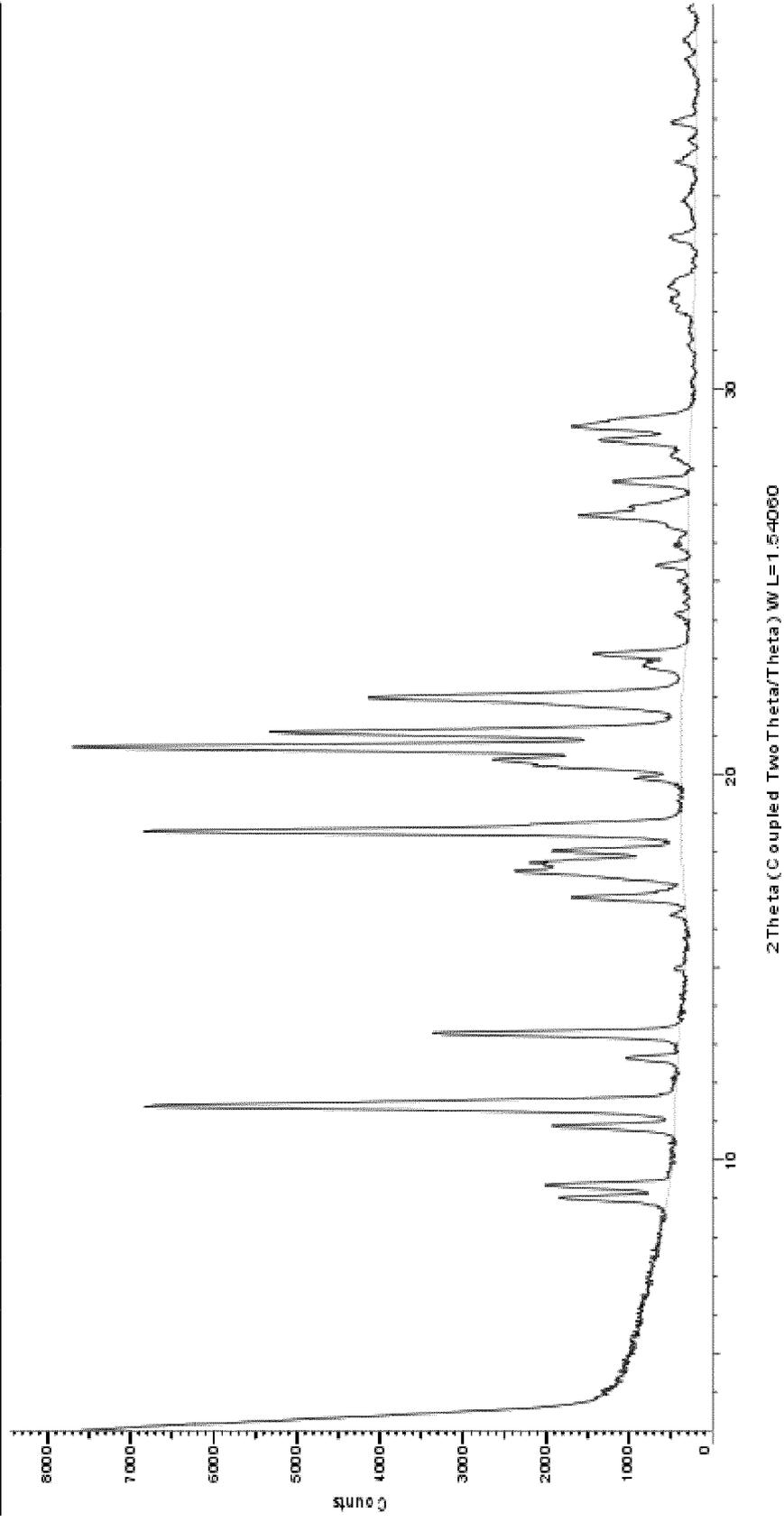


Fig. 1

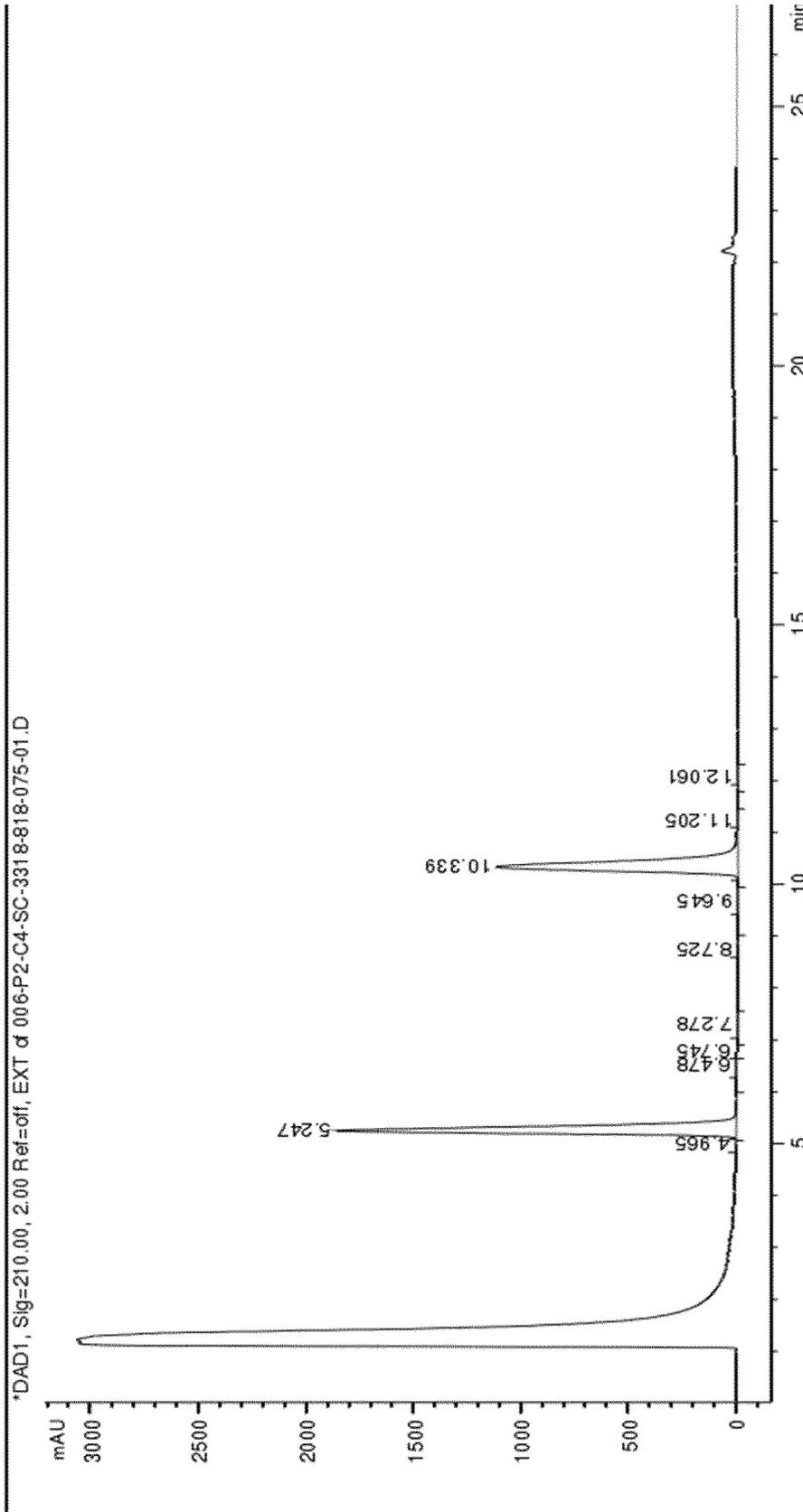


Fig. 2

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.965	MM	0.1221	1.04446	1.88142e-1	3.327e-3
2	5.247	MM	0.1501	1.66857e4	1852.83008	53.1532
3	6.478	MF	0.1660	3.77522	3.78954e-1	0.0120
4	6.745	FM	0.1443	1.30746	1.51039e-1	4.165e-3
5	7.278	MM	0.2617	12.11539	7.71501e-1	0.0386
6	8.725	MM	0.3088	3.47771	1.87712e-1	0.0111
7	9.645	MM	0.3109	6.74968	3.61817e-1	0.0215
8	10.339	MM R	0.2178	1.46668e4	1122.51965	46.7219
9	11.205	MM T	0.0954	2.28069	3.98392e-1	7.265e-3
10	12.061	MM	0.1975	8.45872	7.13640e-1	0.0269

Fig. 3

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- CN 201811212608 [0001]
- WO 2018171589 A [0005]
- WO 2018223970 A [0005]
- EP 0347066 A [0005]