(19) DANMARK

(10) DK/EP 3250554 T3

Patent- og Varemærkestyrelsen

(12) Oversættelse af europæisk patentskrift

(51) Int.Cl.: *C 07 D 231/14 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2022-06-27**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2022-05-18**

(86) Europæisk ansøgning nr.: **16704029.4**

(86) Europæisk indleveringsdag: **2016-01-28**

(87) Den europæiske ansøgnings publiceringsdag: **2017-12-06**

(86) International ansøgning nr.: **FI2016050054**

(87) Internationalt publikationsnr.: **WO2016120530**

(30) Prioritet: **2015-01-30 FI 20150033**

(84) Designerede stater: **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**

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(54) Benævnelse: **Carboxamidderivat og diastereomerer deraf i stabil, krystallinsk form**

(56) Fremdragne publikationer:
**WO-A1-2011/051540**
**WO-A1-2012/143599**
**CAIRA: "Crystalline Polymorphism of Organic Compounds", TOPICS IN CURRENT CHEMISTRY, SPRINGER, BERLIN, DE, vol. 198, 1998, pages 163-208, XP008166276, ISSN: 0340-1022**
**NAVEEN CHHABRA ET AL: "A review of drug isomerism and its significance", INTERNATIONAL JOURNAL OF APPLIED AND BASIC MEDICAL RESEARCH, vol. 3, no. 1, 2013, page 16, XP055257960, ISSN: 2229-516X, DOI: 10.4103/2229-516X.112233**

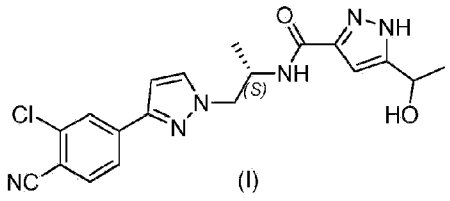
# DESCRIPTION

## Field of the invention

**[0001]** The present disclosure relates to solid crystalline forms of the diastereomers of pharmaceutical compound N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)-propan-2-yl)-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide (I), and to methods for preparing such crystalline forms.

## Background of the invention

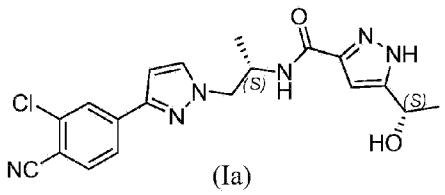
**[0002]** The compound N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)-propan-2-yl)-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide (I) and manufacture thereof have been disclosed in WO 2011/051540. Compound (I) is a potent androgen receptor (AR) modulator useful in the treatment of cancer, particularly AR dependent cancer such as prostate cancer, and other diseases where AR antagonism is desired. Compound (I) is represented by the structure:




(I)

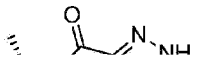
**[0003]** As the hydrogen atom of the pyrazole ring may exist in tautomeric equilibrium between the 1- and 2-position, it is recognized by the skilled person that the above structure and the chemical name "N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)-propan-2-yl)-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide (I) ," as referred to herein, is inclusive of the tautomer of compound (I), namely N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)-propan-2-yl)-3-(1-hydroxyethyl)-1H-pyrazole-5-carboxamide.

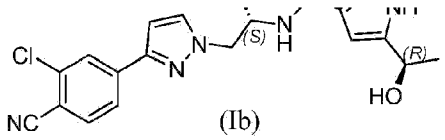
**[0004]** In addition to the chiral carbon atom shown in the chemical structure above, compound (I) has another chiral carbon atom with hydroxy group attached therein. Therefore, compound (I) has two diastereomers, namely N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((S)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ia)




(Ia)

and N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((R)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ib).





(Ib)

**[0005]** Due to the tautomeric equilibrium of the hydrogen atom between the 1- and 2-position in the pyrazole ring, the chemical name of diastereomers (Ia) and (Ib) are inclusive of the tautomers of (Ia) and (Ib), similarly to compound (I) as explained above.

**[0006]** Compounds (Ia) and (Ib) are also potent androgen receptor (AR) modulators useful in the treatment of cancer, particularly AR dependent cancer such as prostate cancer, and other diseases where AR antagonism is desired.

**Summary of the invention**

**[0007]** It has now been found that diastereomers (Ia) and (Ib) can be obtained in a stable and substantially pure crystalline form by crystallization under certain conditions.

**[0008]** Thus, the present invention provides crystalline form I' of N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((S)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ia) having an X-ray powder diffraction pattern comprising characteristic peaks at 9.3, 15.7, 17.0, 24.1 and 25.1 ± 0.15 degrees 2-theta measured using Cu filled X-ray tube.

**[0009]** The present invention further provides crystalline form I' of N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((S)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ia) having an X-ray powder diffraction pattern comprising characteristic peaks at 9.3, 11.4, 11.5, 13.6, 14.7, 14.9, 15.7, 16.1, 17.0, 17.7, 18.5, 19.1, 20.5, 21.5, 22.1, 22.6, 23.2, 23.6, 24.1, 25.1, 26.2 and 27.2 ± 0.15 degrees 2-theta measured using Cu filled X-ray tube .

**[0010]** The present invention further provides crystalline form I" of N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((R)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ib) having an X-ray powder diffraction pattern comprising characteristic peaks at 9.2, 10.9, 15.1, 15.8 and 22.1 ± 0.15 degrees 2-theta measured using Cu filled X-ray tube.

**[0011]** The present invention further provides crystalline form I" of N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((R)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ib) having an X-ray powder diffraction pattern comprising characteristic peaks at 7.9, 9.2, 10.9, 13.2, 14.8, 15.1, 15.5, 15.8, 16.9, 18.4, 20.2, 20.5, 21.8, 22.1 and 24.3 ± 0.15 degrees 2-theta measured using Cu filled X-ray tube.

**[0012]** The present invention further provides a process for preparing crystalline form I' or I" of N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5 -((S)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ia) or N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-

2-yl)-5-((R)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ib), respectively, comprising

1. a) mixing N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((S)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ia) or N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((R)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ib) with a mixture of acetonitrile and water;
2. b) heating the mixture from step a) to form a solution;
3. c) cooling the solution from step b) to about 0-50 °C; and
4. d) isolating the crystalline form.

## Brief description of the drawings

**[0013]**

Figure 1 shows the X-ray powder diffraction pattern of the crystalline form I of compound (I) obtained in Reference Example 1.

Figure 2 shows the X-ray powder diffraction pattern of the crystalline form I' of compound (Ia) obtained in Example 4.

Figure 3 shows the X-ray powder diffraction pattern of the crystalline form I" of compound (Ib) obtained in Example 7.

## Detailed description of the invention

**[0014]** Crystalline form I of compound (I), crystalline form I' of compound (Ia) and crystalline form I" of compound (Ib) have been characterized by X-ray powder diffraction (XRPD) studies.

**[0015]** Accordingly, in one aspect, the present disclosure provides crystalline form I' of N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((S)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ia) having an X-ray powder diffraction pattern comprising characteristic peaks at 9.3, 15.7, 17.0, 24.1 and 25.1 ± 0.15 degrees 2-theta.

**[0016]** In another aspect, the present disclosure provides crystalline form I" of N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((R)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ib) having an X-ray powder diffraction pattern comprising characteristic peaks at 9.2, 10.9, 15.1, 15.8 and 22.1 ± 0.15 degrees 2-theta.

**[0017]** In yet another aspect, the present disclosure provides crystalline form I' of N-((S)-1-(3-

(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((S)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ia) having an X-ray powder diffraction pattern comprising characteristic peaks at 9.3, 11.4, 11.5, 13.6, 14.7, 14.9, 15.7, 16.1, 17.0, 17.7, 18.5, 19.1, 20.5, 21.5, 22.1, 22.6, 23.2, 23.6, 24.1, 25.1, 26.2 and 27.2 ± 0.15 degrees 2-theta.

**[0018]** In yet another aspect, the present disclosure provides crystalline form I" of N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5 -((R)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ib) having an X-ray powder diffraction pattern comprising characteristic peaks at about 7.9, 9.2, 10.9, 13.2, 14.8, 15.1, 15.5, 15.8, 16.9, 18.4, 20.2, 20.5, 21.8, 22.1 and 24.3 ± 0.15 degrees 2-theta.

**[0019]** According to still another aspect, the present disclosure provides crystalline form I' of N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5 -((S)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ia) having an X-ray powder diffraction pattern substantially as illustrated in Figure 2.

**[0020]** According to still another aspect, the present disclosure provides crystalline form I" of N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5 -((R)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ib) having an X-ray powder diffraction pattern substantially as illustrated in Figure 3.

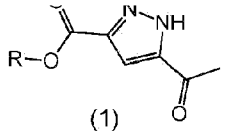
**[0021]** It is recognized by the skilled person that the X-ray powder diffraction pattern peak positions referred to herein can be subject to variations of +/- 0.15 degrees 2-theta according to various factors such as temperature, concentration, and instrumentation used.

**[0022]** According to still another aspect, the present disclosure provides a process for preparing crystalline form I' or I" of N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((S)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ia) or N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5 -((R)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ib), respectively, comprising

1. a) mixing N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((S)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ia) or N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((R)-1-hydroxyethyl)- 1H-pyrazole-3-carboxamide (Ib) with a mixture of acetonitrile and water;
2. b) heating the mixture from step a) to form a solution;
3. c) cooling the solution from step b) to about 0-50 °C; and
4. d) isolating the crystalline form.

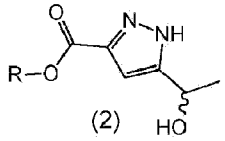
**[0023]** Also described herein is a process for the manufacture of diastereomer (Ia) or (Ib) comprising

1. a) reducing compound of formula (1)



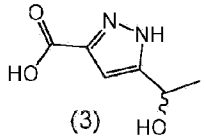
(1)

wherein R is H or $C_{1-6}$ alkyl, with a ketoreductase enzyme to obtain compound of formula (2) in optically active form, wherein R is as defined above;



(2)

2. b) optionally protecting the hydroxyl group of compound of formula (2);
3. c) in case R is an $C_{1-6}$ alkyl, subjecting the compound of formula (2), wherein the hydroxyl group is optionally protected, to cleavage of the ester bond to obtain compound (3);



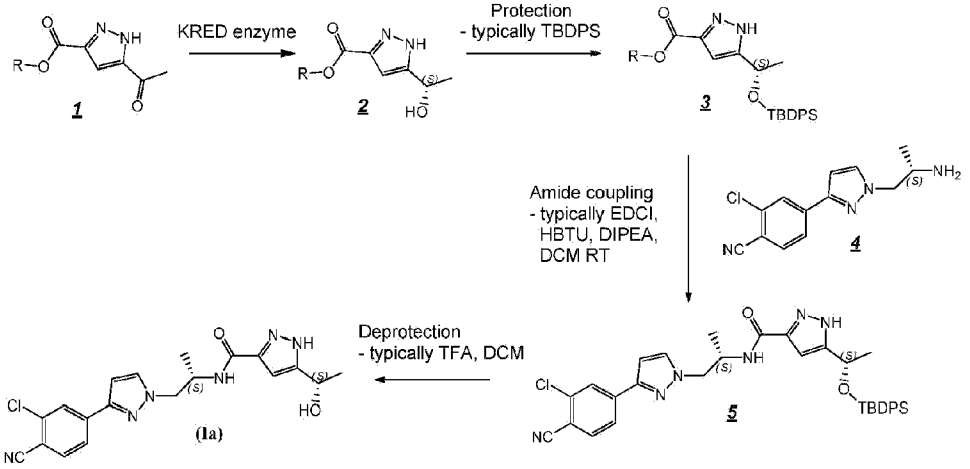
(3)

wherein the hydroxyl group is optionally protected; and

4. d) treating compound (3), wherein the hydroxyl group is optionally protected, with (S)-4-(1-(2-aminopropyl)-1H-pyrazol-3-yl)-2-chlorobenzonitrile, and, in case the hydroxyl group is protected, deprotecting the hydroxyl group, to obtain compound (Ia) or (Ib).

**[0024]** Compound (I) can be synthetized using the procedures described in WO 2011/051540.

**[0025]** Pure diastereomers (Ia) and (Ib) can be suitably synthetized, for example, using ketoreductase enzymes (KREDs) for both S- and R-selective reduction of compound 1 to compound 2 as shown in Scheme 1, wherein R is H or $C_{1-6}$ alkyl.



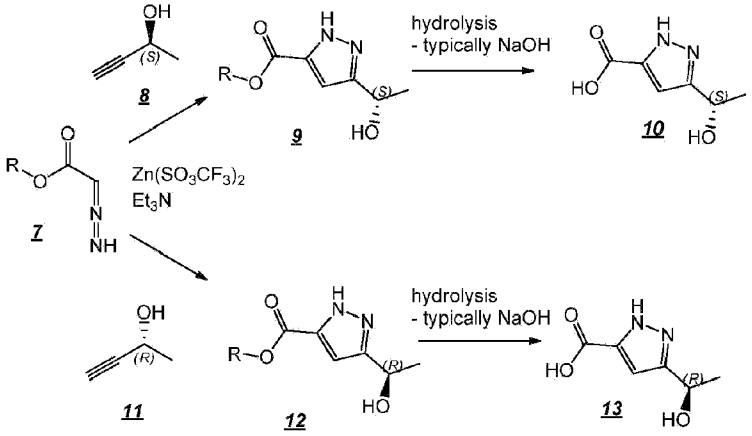

**Scheme 1.**

**[0026]** For example, Codexis KRED-130 and KRED -NADH-110 enzymes are useful for

obtaining excellent stereoselectivity, even stereospecificity. In Scheme 1 the starting material 1 is preferably an ester (R= $C_{1-6}$ alkyl), for example ethyl ester (R=ethyl), such as to facilitate extraction of the product into the organic phase as the compound where R=H has a tendency to remain in the water phase. Intermediate 2 can be protected, preferably with silyl derivatives such as *tert*-butyldiphenylsilyl, in order to avoid esterification in amidation step. In the case of R=$C_{1-6}$ alkyl, ester hydrolysis is typically performed before amidation step, preferably in the presence of LiOH, NaOH or KOH. Amidation from compound 3 to compound 5 is suitably carried out using EDCI HBTU, DIPEA system but using other typical amidation methods is also possible. Deprotection of 5 give pure diastereomers (Ia) and (Ib).

**[0027]** Pyrazole ring without NH substitution is known tautomerizable functionality and is described here only as single tautomer but every intermediate and end product here can exist in both tautomeric forms at the same time.

**[0028]** The stereochemistry of the compounds can be confirmed by using optically pure starting materials with known absolute configuration as demonstrated in Scheme 2, wherein R=H or $C_{1-6}$ alkyl, preferably alkyl, for example ethyl. The end products of Scheme 2 are typically obtained as a mixture of tautomers at +300K $^1$H-NMR analyses in DMSO.




**Scheme 2.** Synthesis pathway to stereoisomers by using starting materials with known absolute configuration

**[0029]** The crystalline forms I, I' and I" of compounds (I), (Ia) and (Ib), respectively, can be prepared, for example, by dissolving the compound in question in an acetonitrile:water mixture having volume ratio from 85:15 to 99:1, such as from 90:10 to 98:2, for example 95:5, under heating and slowly cooling the solution until the crystalline form precipitates from the solution. The concentration of the compound in the acetonitrile:water solvent mixture is suitably about 1 kg of the compound in 5-25 liters of acetonitrile:water solvent mixture, for example 1 kg of the compound in 10-20 liters of acetonitrile:water solvent mixture. The compound is suitably dissolved in the acetonitrile:water solvent mixture by heating the solution, for example near to the reflux temperature, for example to 60-80 °C, for example to 75 °C, under stirring and filtering if necessary. The solution is suitably then cooled to 0-50 °C, for example to 5-35 °C, for

example to RT, over 5 to 24 hours, for example over 6 to 12 hours, and stirred at this temperature for 3 to 72 hours, for example for 5 to 12 hours. The obtained crystalline product can then be filtered, washed, and dried. The drying is suitably carried out in vacuum at 40 to 60 °C, for example at 55 °C, for 1 to 24 hours, such as for 2 to 12 hours, for example 2 to 6 hours.

**[0030]** The crystalline forms I, I' and I" of compounds (I), (Ia) and (Ib), respectively, are useful as medicaments and can be formulated into pharmaceutical dosage forms, such as tablets and capsules for oral administration, by mixing with pharmaceutical excipients known in the art.

**[0031]** The disclosure is further illustrated by the following examples.

**Reference Example 1. Crystallization of N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)-propan-2-yl)-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide (I)**

**[0032]** N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)-propan-2-yl)-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide (I) (5 g), 71.25 ml of acetonitrile, and 3.75 ml of distilled water were charged to a flask, and the mixture was heated up to 75 °C. The mixture was slowly cooled down to RT and stirred at RT for 3 days. The solid obtained was filtered and washed twice with acetonitrile:water (9.5 ml:0.5 ml). The product was dried under vacuum at 40 °C and finally at 60°C to obtain 4.42 g of crystalline title compound (yield of 88 %) which was used in X-ray diffraction study.

**Reference Example 2. X-ray diffraction study of crystalline compound (I)**

**[0033]** The crystalline form of compound (I) obtained in Example 1 was analysed by X-ray powder diffraction method. The measurements were performed with the X-ray powder diffractometer PANalytical X'Pert PRO at room temperature using Cu filled X-ray tube (45kV × 40mA) as the X-ray source, a fixed 1° anti-scatter slit, a programmable divergence slit with 5.0 mm irradiated length and the real time multiple strip detector X'Celerator. Data collection was done in 0.008° steps at a scan speed of 1°/min in the range of 3-80° 2θ. The crystalline form was characterized by an X-ray powder diffraction pattern as shown in Figure 1 and exhibiting characteristic peaks at about the following 2-theta values:

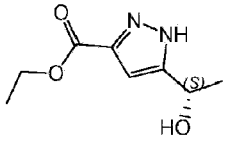
| Angle 2-theta ° |
|---|
| 6.4 |
| 8.5 |
| 9.6 |
| 9.7 |
| 10.4 |
| 12.8 |

| Angle 2-theta ° |
|---|
| 13.6 |
| 14.9 |
| 15.9 |
| 16.6 |
| 16.9 |
| 18.7 |
| 19.2 |
| 21.8 |
| 24.3 |
| 25.5 |

**Example 3. Synthesis of N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)-propan-2-yl)-5-((S)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ia)**

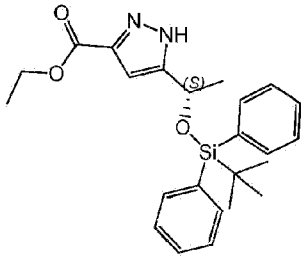
**[0034]**

1. a) Ethyl-5-((S)1-hydroxyethyl)-1H-pyrazole-3-carboxylate



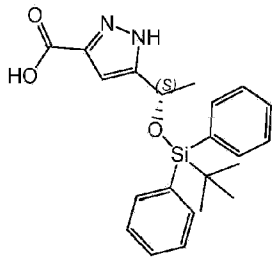
$MgSO_4$ ×7$H_2O$ (341 mg), NADP monosodium salt (596 mg), D(+)-glucose (9.26 g) and optimized enzyme CDX-901 lyophilized powder (142 mg) were added to 0.2 mM of $KH_2PO_4$ buffer (pH 7.0, 709 ml) to prepare solution I. To this solution I was added solution II which contained ethyl-5-acetyl-1H-pyrazole-3-carboxylate (8.509 g; 46.70 mmol), EtOH (28 ml) and KRED-130 (NADPH ketoreductase, 474 mg). The mixture was agitated at 30-32°C for 5.5 h (monitoring by HPLC) and allowed to cool to RT. The mixture was evaporated to smaller volume and the residue was agitated with diatomaceous earth and filtered. The mother liquid was extracted with 3x210 ml of EtOAc and dried. The solution was filtered through silica (83 g) and evaporated to dryness to give 7.40 g of the title compound. The optical purity was 100 % ee.

2. b) Ethyl 5-((S)-1-((tert-butyldiphenylsilyl)oxy)ethyl)-1H-pyrazole-3-carboxylate



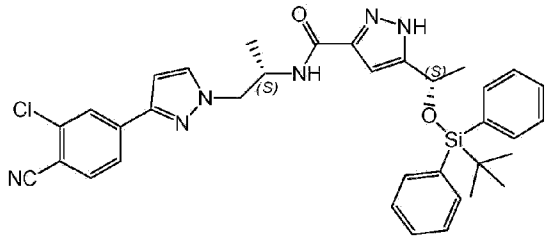
Diphenyl-*tert*-butyl chlorosilane (7.48 g, 27.21 mmol) was added in 26 ml of DMF to a mixture of compound of Example 3(a) (5.00 g, 27.15 mmol) and imidazole (2.81 g, 41.27 mmol) in DMF (50 ml) at RT. The mixture was stirred at RT for 24 h. Saturated aqueous $NaHCO_3$ (56 ml) and water (56 ml) were added and the mixture was stirred at RT for 20 min. The mixture was extracted with 2×100 ml of EtOAc. Combined organic phases were washed with water (1×100 ml, 1x50 ml), dried ($Na_2SO_4$), filtered and concentrated to give 10.92 g of crude title compound.

3. c) 5-((S)-1-((tert-Butyldiphenylsilyl)oxy)ethyl)-1H-pyrazole-3-carboxylic acid



2 M NaOH (aq) (38.8 ml; 77.5 mmol) was added to a solution of the compound of Example 3(b) (10.9 g, 25.8 mmol) in 66 ml of THF. The mixture was heated up to reflux temperature. Heating was continued for 2.5 h and THF was removed in vacuum. Water (40 ml) and EtOAc (110 ml) were added. Clear solution was obtained after addition of more water (10 ml). Layers were separated and aqueous phase was extracted with 100 ml of EtOAc. Combined organic phases were dried ($Na_2SO_4$), filtered and concentrated to give 9.8 g of the title compound.

4. d) 5-((S)-1-((tert-Butyldiphenylsilyl)oxy)ethyl)-N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-1H-pyrazole-3-carboxamide



Under nitrogen atmosphere HBTU (0.84 g; 2.22 mmol), EDCI×HCl (3.26 g; 17.02 mmol) and (S)-4-(1-(2-aminopropyl)-1H-pyrazol-3-yl)-2-chlorobenzonitrile (3.86 g; 14.80 mmol) were added to a mixture of crude compound of Example 3(c) (8.68g; purity 77.4 area-%) and DIPEA (2.20 g; 17.02 mmol) in DCM (50 ml). The mixture was stirred at RT for 46 h (6 ml of DCM was added after 20 h). The mixture was washed with 3x20 ml of water, dried ($Na_2SO_4$), filtered and concentrated to give 13.7 g of crude title compound.

5. e) N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((S)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ia)

TBAF hydrate ($Bu_4NF \times 3H_2O$; 2.34 g; 7.40 mmol) in 10 ml of THF was added to the solution of the compound of Example 3(d) (9.43 g; 14.79 mmol) in THF (94 ml) at 0 °C under nitrogen atmosphere. Stirring was continued at RT for 21.5 h and the mixture was concentrated. DCM (94 ml) was added to the residue and the solution was washed with 3x50 ml of water, dried ($Na_2SO_4$), filtered and concentrated. Crude product was purified by flash chromatography (EtOAc/*n*-heptane) to give 2.1 g of the title compound. $^1$H-NMR

(400MHz; d6-DMSO; 300K): Major tautomer (~85 %): δ 1.11 (d, 3H), 1.39 (d, 3H), 4.24-4.40 (m, 2H), 4.40-4.50 (m, 1H), 6.41(s, 1H), 6.93 (d, 1H), 7.77-7.82 (m, 1H), 7.88-8.01 (m, 2H), 8.08 (s, 1H), 8.19 (d, 1H), 13.02 (broad s, 1H). Minor tautomer (~15 %) δ 1.07-1.19 (m, 3H), 1.32-1.41 (m, 3H), 4.24-4.40 (m, 2H), 4.40-4.50 (m, 1H), 6.80 (broad s, 1H), 6.91-6-94 (m, 1H), 7.77-7.82 (m, 1H), 7.88-8.01 (m, 2H), 8.05-8.09 (m, 1H), 8.31 (d, 1H), 13.10 (broad s, 1H).

**Example 4. Crystallization of N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((S)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ia)**

**[0035]** N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((S)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ia) (5.00 g; 12.54 mmol) was mixed with 47.5 ml of ACN and 2.5 ml of water. The mixture was heated until compound (Ia) was fully dissolved. The solution was allowed to cool slowly to RT to form a precipitate. The mixture was then further cooled to 0 °C and kept in this temperature for 30 min. The mixture was filtered and the precipitate was dried under vacuum to obtain 4.50 g of crystalline title compound which was used in the X-ray diffraction study.

**Example 5. X-ray diffraction study of crystalline compound (Ia)**

**[0036]** The crystalline form of compound (Ia) obtained in Example 4 was analysed by X-ray powder diffraction method as described in Example 2. The crystalline form was characterized by an X-ray powder diffraction pattern as shown in Figure 2 and exhibiting characteristic peaks at about the following 2-theta values:

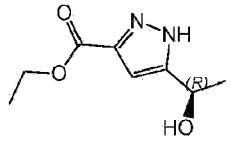
| Angle 2-theta ° |
|---|
| 9.3 |
| 11.4 |
| 11.5 |
| 13.6 |
| 14.7 |
| 14.9 |
| 15.7 |
| 16.1 |
| 17.0 |
| 17.7 |
| 18.5 |
| 19.1 |

| Angle 2-theta ° |
|---|
| 20.5 |
| 21.5 |
| 22.1 |
| 22.6 |
| 23.2 |
| 23.6 |
| 24.1 |
| 25.1 |
| 26.2 |
| 27.2 |

**Example 6. Synthesis of N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)-propan-2-yl)-5-((R)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ib)**

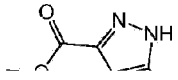
**[0037]**

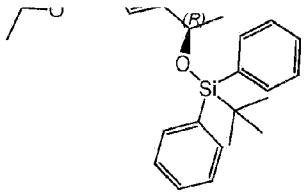
1. a) Ethyl-5-((R)-1-hydroxyethyl)-1H-pyrazole-3-carboxylate




Potassium dihydrogen phosphate buffer (*Solution I*) was prepared by dissolving potassium dihydrogen phosphate (11.350 g, 54.89 mmol) to water (333 ml) and adjusting pH of the solution to 7.0 by addition of 5 M solution of NaOH. $MgSO_4 \times 7\ H_2O$ (1.650 g), NAD monosodium salt (0.500 g), D(+)-glucose (10.880 g) and optimised enzyme CDX-901 lyophilised powder (0.200 g) were added to *Solution I.* To this solution (*Solution II*) were added KRED-NADH-110 (0.467 g), ethyl-5-acetyl-1H-pyrazole-3-carboxylate (10.00 g; 54.89 mmol) and 2-methyltetrahydrofuran (16 ml). The mixture was agitated at 30° C for 11 h and allowed to cool to RT overnight. The pH of the mixture was kept at 7 by addition of 5 M solution of NaOH. The mixture was evaporated to a smaller volume. The evaporation residue was agitated for 10 min with diatomaceous earth (40 g) and activated charcoal (0.54 g), and filtered. Material on the filter was washed with water (40 ml) and the washings were combined with the filtrate. Layers were separated and aqueous phase was extracted with EtOAc (450 ml and 2x270 ml). Combined organic phases were dried over $Na_2SO_4$, filtered and evaporated to dryness to give 9.85 g of the title compound (100 % ee).

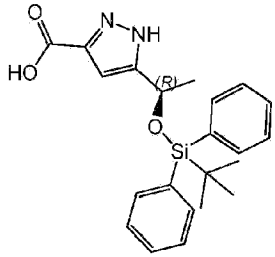
2. b) Ethyl-5-((R)-1-((tert-butyldiphenylsilyl)oxy)ethyl)-1H-pyrazole-3-carboxylate





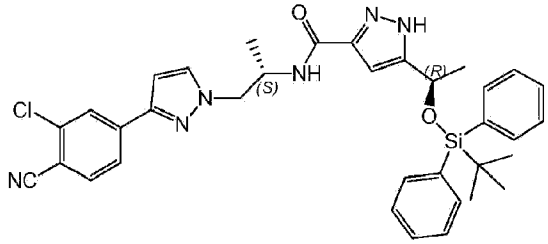
Imidazole (5.32 g; 78.08 mmol) was added to a DCM (67 ml) solution of the compound of Example 6(a) (9.85 g; 53.48). The mixture was stirred until all reagent was dissolved and tert-butyldiphenyl chlorosilane (13.21 ml; 50.80 mmol) was added to the mixture. The mixture was stirred for 1.5 h, 70 ml of water was added and stirring was continued for 15 min. Layers were separated and organic phase was washed with 2x70 ml of water and dried over $Na_2SO_4$, filtered and concentrated to give 22.07 g of crude title compound.

3. c) 5-((R)-1-((tert-Butyldiphenylsilyl)oxy)ethyl)-1H-pyrazole-3-carboxylic acid



Compound of Example 6(b) (11.3 g; 26.74 mmol; theoretical yield from the previous step) was dissolved in 34 ml of THF and 50 ml of 2 M NaOH (aq.) was added. The mixture was heated under reflux temperature for 70 min. The mixture was extracted with 2x55 ml of EtOAc and combined organic phases were washed with brine, dried over $Na_2SO_4$, filtered and concentrated. Evaporation residue was triturated in 250 ml of n-heptane, filtered and dried to give 17.58 g of crude title compound.

4. d) 5-((R)-1-((tert-Butyldiphenylsilyl)oxy)ethyl)-N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-1H-pyrazole-3-carboxamide



A mixture of the compound of Example 6(c) (11.14 g; 26.75 mmol; theoretical yield from the previous step), 91 ml of DCM, HBTU (1.52 g; 4.01 mmol), EDCI×HCl (5.90 g; 30.76 mmol), (S)-4-(1-(2-aminopropyl)-1H-pyrazol-3-yl)-2-chlorobenzonitrile (6.97 g; 26.75 mmol) and DIPEA (3.98 g; 30.76 mmol) was stirred at RT for 3 h and at 30° C for 22 h. The mixture was washed with 2x90 ml of 0.5 M HCl and 4x90 ml of water, dried over $Na_2SO_4$, filtered and concentrated. Crude product was purified by flash column chromatography (n-heptane-EtOAc) to give 16.97 g of title compound.

5. e) N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((R)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ib)

A mixture of the compound of Example 6(d) (6.09 g; 9.56 mmol), 61 ml of THF and TBAF was stirred at 40 °C for 6.5 h. The mixture was concentrated and 61 ml of EtOAc

was added to the evaporation residue. Solution was washed with 2x50 ml of 0.5 M HCl and 4x50 ml of water, dried over $Na_2SO_4$, filtered and concentrated. Crude product was purified by flash column chromatography (n-heptane-EtOAc) to give 1.71 g of the title compound. $^1$H-NMR (400MHz; d6-DMSO; 300K): Major tautomer (~85%): δ 1.10 (d, 3H), 1.38 (d, 3H), 4.14-4.57 (m, 2H), 5.42 (d, 1H), 6.39(s, 1H), 6.86-6.98 (m, 1H), 7.74-7.84 (m, 1H), 7.86-8.02 (m, 2H), 8.08 (s, 1H), 8.21 (d, 1H), 13.04 (broad s, 1H). Minor tautomer (~ 15%) δ 0.95-1.24 (m, 3H), 1.25-1.50 (m, 3H), 4.14-4.57 (m, 2H), 4.60-4.90 (m, 1H), 5.08 (d, 1H), 6.78 (broad s, 1H), 6.86-6.98 (m, 1H), 7.77-7.84 (m, 1H), 7.86-8.02 (m, 2H), 8.02-8.12 (m, 1H), 8.32 (d, 1H), 13.11 (broad s, 1H).

**Example 7. Crystallization of N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((R)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ib)**

**[0038]** N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((R)-1-hydroxyethyl)-1H-pyrazole-3-carboxamide (Ib) (3.7 g; 9.28 mmol) was mixed with 70 ml of ACN and 3.5 ml of water. The mixture was heated to reflux temperature until compound (Ib) was fully dissolved. The solution was allowed to cool slowly. The mixture was filtered at 50 °C to obtain 6.3 mg of the precipitate. Mother liquid was cooled to 41 °C and filtered again to obtain 20.7 mg of the precipitate. Obtained mother liquid was then cooled to 36 °C and filtered to obtain 173 mg of the precipitate. The final mother liquid was cooled to RT, stirred overnight, cooled to 0 °C, filtered, washed with cold ACN:water (1:1) and dried to obtain 2.71 g of the precipitate. The precipitates were checked for optical purity and the last precipitate of crystalline title compound (optical purity 100 %) was used in the X-ray diffraction study.

**Example 8. X-ray diffraction study of crystalline compound (Ib)**

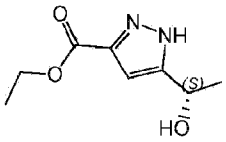
**[0039]** The crystalline form of compound (Ib) obtained in Example 7 was analysed by X-ray powder diffraction method as described in Example 2. The crystalline form was characterized by an X-ray powder diffraction pattern as shown in Figure 3 and exhibiting characteristic peaks at about the following 2-theta values:

| Angle 2-theta ° |
|---|
| 7.9 |
| 9.2 |
| 10.9 |
| 13.2 |
| 14.8 |
| 15.1 |

| Angle 2-theta ° |
|---|
| 15.5 |
| 15.8 |
| 16.9 |
| 18.4 |
| 20.2 |
| 20.5 |
| 21.8 |
| 22.1 |
| 24.3 |

**Example 9. Synthesis of Ethyl-5-((S)1-hydroxyethyl)- 1H-pyrazole-3-carboxylate**

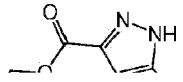
**[0040]**



**[0041]** Zinc trifluoromethanesulfonate (0.259 g; 0.713 mmol) and (S)-(-)-3-butyn-2-ol (0.25 g; 3.57 mmol) were added to 0.75 ml (5.35 mmol) of $Et_3N$ under nitrogen atmosphere. Ethyldiazoacetate (0.45 ml; 4.28 mmol) was added slowly and the mixture was heated at 100 °C for 2 h. The mixture was cooled to RT and 5 ml of water was added. The mixture was washed with 15 ml of DCM, 5 ml of water was added and phases were separated. Water phase was washed twice with DCM, all organic layers were combined, dried with phase separator filtration and evaporated to dryness to give 0.523 g of crude material. The product was purified by normal phase column chromatography (0-5 % MeOH:DCM) to give 0.165 mg of the title compound. $^1$H-NMR (400MHz; d6-DMSO; temp +300 K): Tautomer 1 (major 77%): δ 1.28 (t, 3H), 1.39 (d, 3H), 4.20-4.28 (m, 2H), (d, 1H), 4.75-4.85 (m, 1H) 5.43 (broad d, 1H), 6.54 (broad s, 1H), 13.28 (broad s, 1H). Tautomer 2 (minor 23%): δ 1.28 (t, 3H), 1.39 (d, 3H), 4.20-4.28 (m, 2H), 4.66-4.85 (m, 1H), 5.04-5.15 (broad s, 1H), 6.71 (broad s, 1H), 13.60 (broad s, 1H).

**Example 10. Ethyl-5-((R)-1-hydroxyethyl)-1H-pyrazole-3-carboxylate**

**[0042]**




**[0043]** Zinc trifluoromethanesulfonate (1.037 g; 2.85 mmol) and (R)-(+)-3-butyn-2-ol (1.00 g; 14.27 mmol) were added to 2.98 ml (21.40 mmol) of $Et_3N$ under nitrogen atmosphere. Ethyldiazoacetate (1.80 ml; 21.40 mmol) was added slowly and then refluxed for 3 h. The mixture was cooled to RT and 45 ml of water was added. The mixture was extracted with 3x50 ml of DCM, organic layers were combined, dried with phase separator filtration and evaporated to dryness to give 2.503 g of crude material which was purified by normal phase column chromatography (0-10 % MeOH:DCM) to give 0.671mg of the title compound. $^1$H-NMR (400MHz; d6-DMSO; temp +300 K): Tautomer 1 (major 78%): δ 1.28 (t, 3H), 1.39 (d, 3H), 4.18-4.35 (m, 2H), (d, 1H), 4.75-4.85 (m, 1H) 5.42 (broad d, 1H), 6.54 (s, 1H), 13.29 (broad s, 1H). Tautomer 2 (minor 22%): δ 1.28 (t, 3H), 1.39 (d, 3H), 4.18-4.35 (m, 2H), 4.66-4.85 (m, 1H), 5.09 (broad s, 1H), 6.71 (broad s, 1H), 13.61 (broad s, 1H).

**[0044]** Abbreviations:

ACN: acetonitrile

DCM: dichloromethane

DIPEA: N,N-diisopropyl-ethyl amine

DMF: dimethylformamide

DMSO: dimethylsulfoxide

EDCI×HCl: N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride

EtOAc: ethyl acetate

EtOH: ethanol

HBTU: o-benzotriazole-N,N,N' ,N' -tetramethyl-uroniumhexafluoro-phosphate

KRED: ketoreductase (enzyme)

RT: room temperature

TFA: trifluoroacetic acid.

# REFERENCES CITED IN THE DESCRIPTION

Cited references

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**Patent documents cited in the description**


- WO2011051540A [0002] [0024]

## PATENTKRAV

**1.** Krystallinsk form I' af N-((S)-1-(3-(3-chlor-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((S)-1-hydroxyethyl)-1H-pyrazol-3-carboxamid (Ia) med et røntgendiffraktionsmønster omfattende karakteristiske toppunkter ved 9,3, 15,7, 17,0, 24,1 og 25,1 ± 0,15 grader 2-theta målt ved hjælp af et Cu-fyldt røntgenrør.

**2.** Krystallinsk form I' af N-((S)-1-(3-(3-chlor-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((S)-1-hydroxyethyl)-1H-pyrazol-3-carboxamid (Ia) ifølge krav 1, med et røntgendiffraktionsmønster omfattende karakteristiske toppunkter ved 9,3, 11,4, 11,5, 13,6, 14,7, 14,9, 15,7, 16,1, 17,0, 17,7, 18,5, 19,1, 20,5, 21,5, 22,1, 22,6, 23,2, 23,6, 24,1, 25,1, 26,2 og 27,2 ± 0,15 grader 2-theta målt ved hjælp af et Cu-fyldt røntgenrør.

**3.** Krystallinsk form I'' af N-((S)-1-(3-(3-chlor-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((R)-1-hydroxyethyl)-1H-pyrazol-3-carboxamid (Ib) med et røntgendiffraktionsmønster omfattende karakteristiske toppunkter ved 9,2, 10,9, 15,1, 15,8 og 22,1 ± 0,15 grader 2-theta målt ved hjælp af et Cu-fyldt røntgenrør.

**4.** Krystallinsk form I'' af N-((S)-1-(3-(3-chlor-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((R)-1-hydroxyethyl)-1H-pyrazol-3-carboxamid (Ib) ifølge krav 3, med et røntgendiffraktionsmønster omfattende karakteristiske toppunkter ved 7,9, 9,2, 10,9, 13,2, 14,8, 15,1, 15,5, 15,8, 16,9, 18,4, 20,2, 20,5, 21,8, 22,1 og 24,3 ± 0,15 grader 2-theta målt ved hjælp af et Cu-fyldt røntgenrør.

**5.** Fremgangsmåde til fremstilling af henholdsvis krystallinsk form I' eller I'' af N-((S)-1-(3-(3-chlor-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((S)-1-hydroxyethyl)-1H-pyrazol-3-carboxamid (Ia) eller N-((S)-1-(3-(3-chlor-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((R)-1-hydroxyethyl)-1H-pyrazol-3-carboxamid (Ib), der omfatter

a) blanding af N-((S)-1-(3-(3-chlor-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((S)-1-hydroxyethyl)-1H-pyrazol-3-carboxamid (Ia) eller N-((S)-1-(3-(3-chlor-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-5-((R)-1-hydroxyethyl)-1H-pyrazol-3-carboxamid (Ib) med en blanding af acetonitril og vand;

b) opvarmning af blandingen fra trin a) for at danne en opløsning;

c) afkøling af opløsningen fra trin b) til ca. 0-50 °C og

d) isolering af den krystallinske form.

**6.** Fremgangsmåde ifølge krav 5, hvor blandingen af acetonitril og vand har et volumenforhold fra 85:15 til 99:1.

**7.** Fremgangsmåde ifølge krav 6, hvor blandingen af acetonitril og vand har et volumenforhold fra 90:10 til 98:2.

**8.** Fremgangsmåde ifølge krav 7, hvor blandingen af acetonitril og vand har et volumenforhold på ca. 95:5.

**9.** Fremgangsmåde ifølge et hvilket som helst af kravene 5 til 8, hvor afkølingstrinnet c) foregår over 5 til 24 timer.

**10.** Fremgangsmåde ifølge krav 9, hvor afkølingstrinnet c) foregår over 6 til 12 timer.

**11.** Fremgangsmåde ifølge et hvilket som helst af kravene 5 til 10, hvor den isolerede krystallinske form tørres under vakuum ved 40 °C til 60 °C.

# DRAWINGS

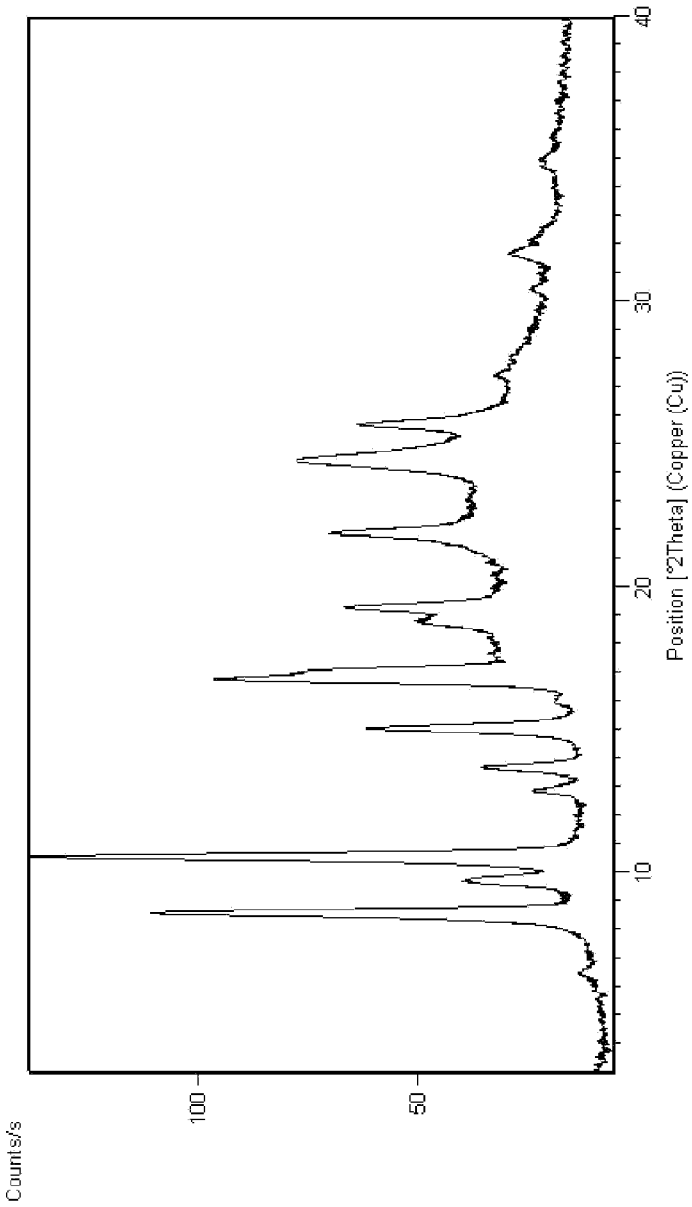


FIG. 1

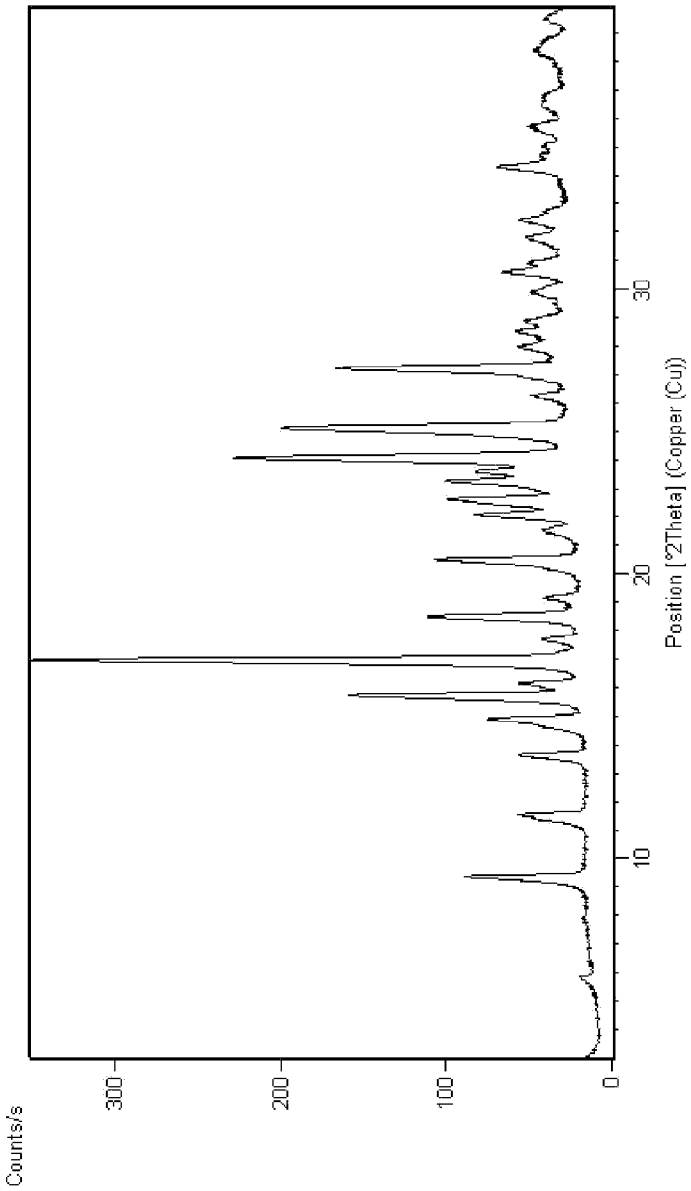


FIG. 2

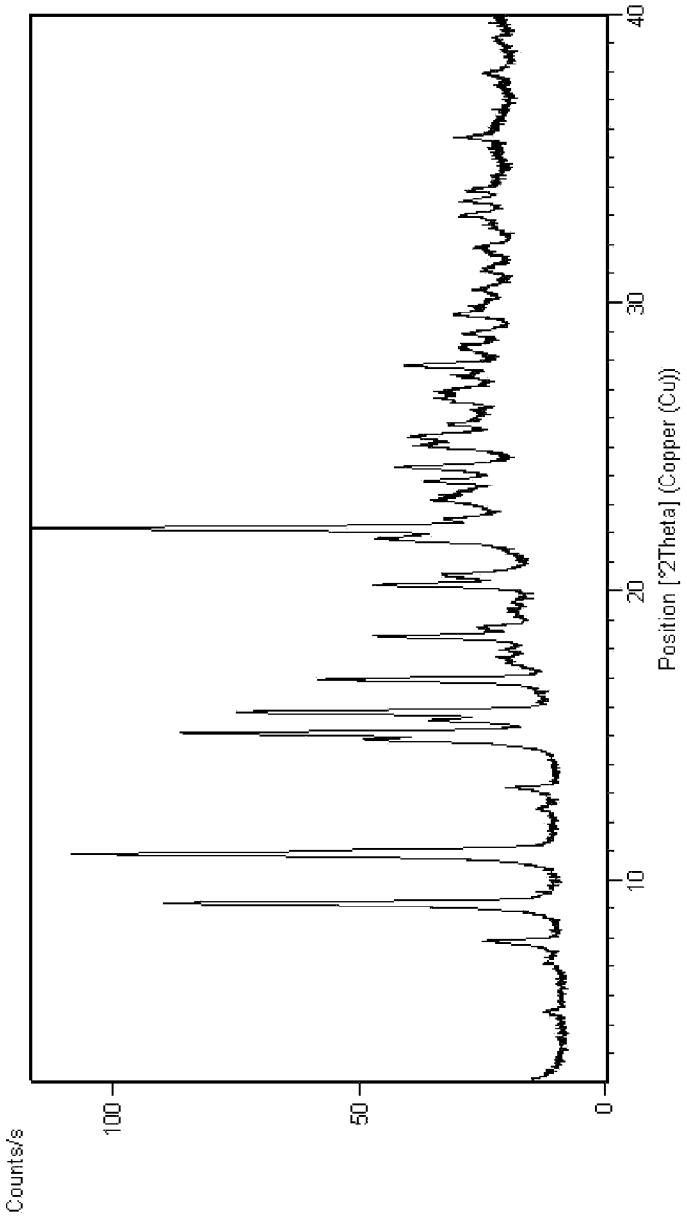


FIG. 3