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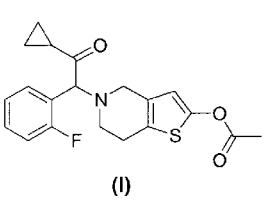
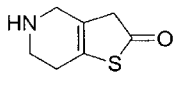
(54) **Title**: METHOD OF PRODUCING HIGHLY PURE PRASUGREL AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF



(I)



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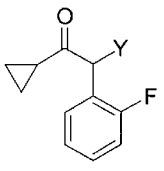

(XV)

(57) **Abstract**: A method for the production of 5-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]- 4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate of formula (I) or its salts, characterized in that the compound of formula (III) in the form of a salt with an arene sulfonic acid is reacted with the compound of formula (XV), wherein Y means: chlorine, bromine, or an OR^4 group, wherein R^4 means an alkane sulfonic group or arene sulfonic group, in an organic solvent in the presence of an inorganic base or organic base, to give, after addition of an acetylating reagent and organic base to the reaction mixture, the compound of formula (I), which, after addition of a co-solvent, is crystallized from the reaction mixture, and the compound of formula (I) is optionally purified by crystallization and optionally converted to a salt by reaction with an organic or inorganic acid in a suitable solvent. (Formulae (I), (III), (XV)

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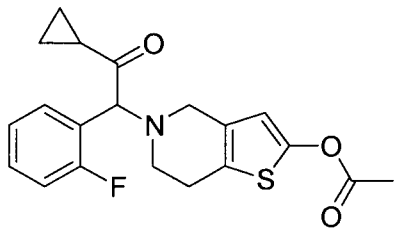
A method of producing highly pure prasugrel and its new pharmaceutically acceptable salts

Technical Field

The invention relates to a new method for the production of the well-known substance reducing blood coagulation, prasugrel of formula I, in high purity



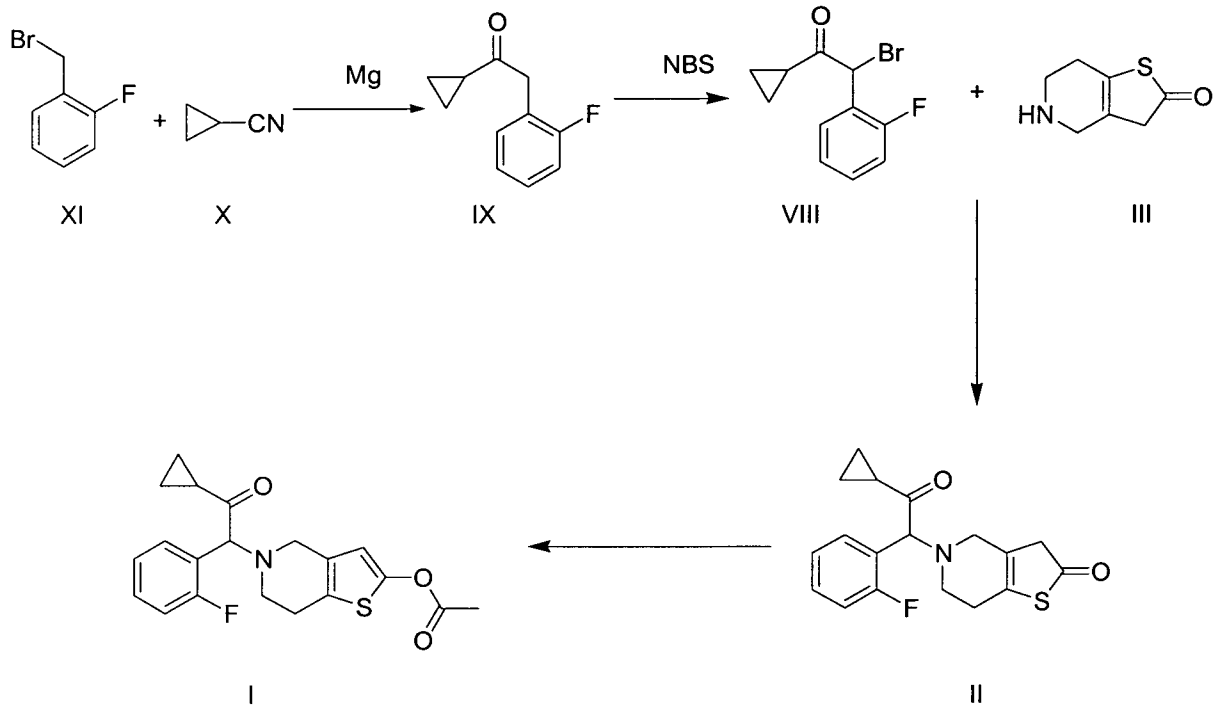
I

Background Art

Prasugrel, a method for the preparation thereof and its use as an anti-aggregation substance in patients endangered by vessel clogging with a blood clot was first described in the patent no. EP 0 542 411.

Production of prasugrel in accordance with this patent can be summarized in Scheme 1.

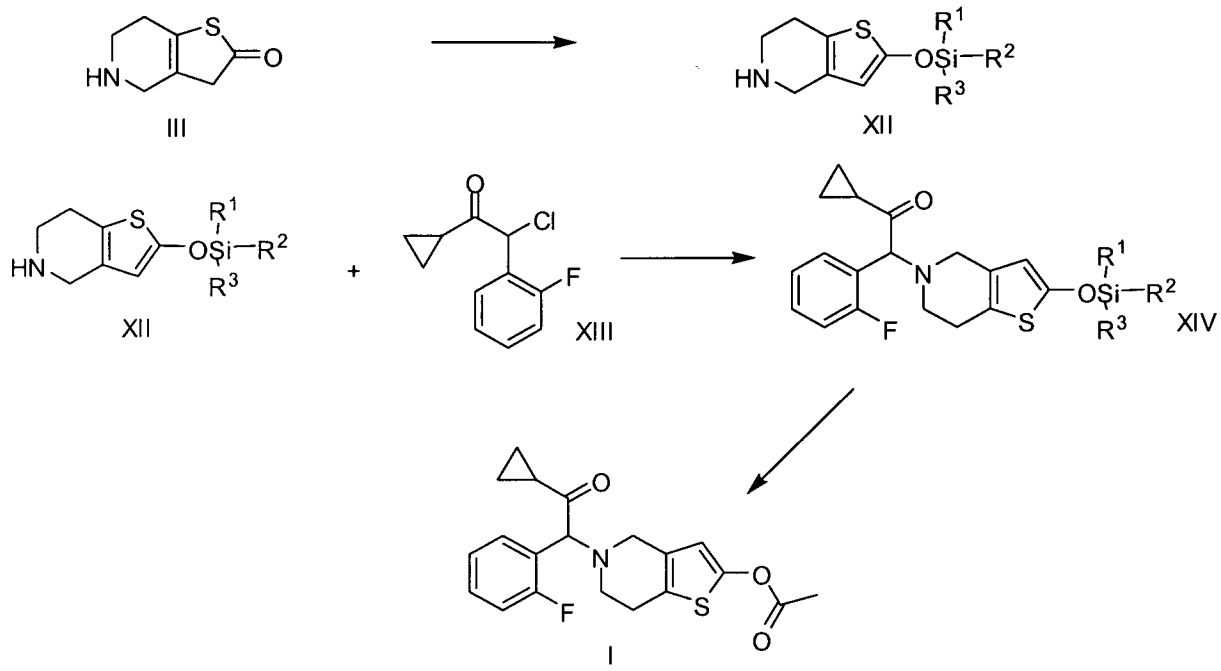
Scheme 1



According to this document a Grinard reagent prepared from 2-fluorobenzylbromide (XI) reacts with cyclopropylcyanide (X) in ether and provides the compound (IX). The compound (IX) is brominated with bromine in CCl_4 or with N-bromosuccinimide (NBS) in the presence of dibenzoylperoxide to a bromo derivative (VIII). This is subject to nucleophilic substitution by the compound (III), producing the compound (II), which is obtained in the yield of 35% after chromatographic purification and crystallization from diisopropyl ether. In the above mentioned substitution the compound of formula III is used in the hydrochloride form, from which the free base is released in situ by the action of potash. The compound (II) is transformed to the final prasugrel (I) by reaction with acetanhydride in the presence of NaH in DMF. The yield of this stage after chromatographic purification and crystallization from diisopropyl ether is 65%.

A similar procedure can be inferred from the patent of the Ube Company no. US 5 874 581, which is indicated in Scheme 2.

Scheme 2



Reaction of thienopyridin-2-one (III) with trialkylsilylchloride in an organic solvent in the presence of trialkylamine provides a silylated enol ether (XII), which reacts with the compound (XIII) to the compound (XIV). The final prasugrel of formula I is then prepared from the substance (XIV) by deprotection and subsequent acetylation with acetanhydride in the presence of dimethylaminopyridine. The compound of formula III is used in the form of p-toluene sulfonate in this method.

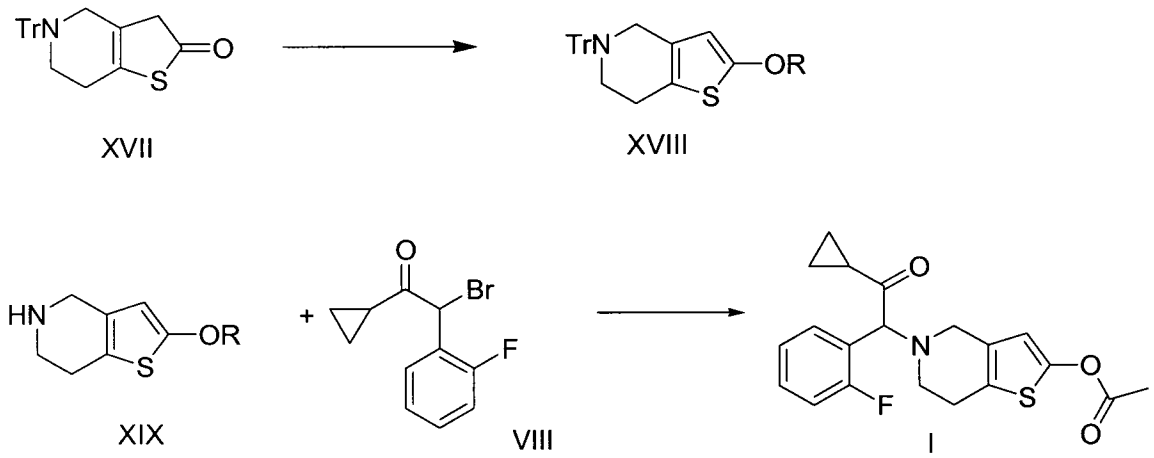
Another patent application of the Ube Company, WO2007/114526, describes an improved and more specific preparation method of prasugrel, which issues from Scheme 2. *tert*-Butyldimethylsilylchloride is used as the silylation agent and the compound of formula XII, wherein R^1 and R^2 are methyl groups and R^3 is the *tert*-butyl group, is prepared in dichloromethane in the presence of triethylamine. Then it reacts with the compound of formula XIII without isolation. The compound XIV, wherein R^1, R^2 and R^3 have the same meaning as mentioned above, is obtained in the yield of 83.7%. The compound of formula XIV is deprotected in situ and acetylated in acetonitrile in the presence of triethylamine and dimethylaminopyridine to prasugrel of formula I, which, after crystallization from the reaction mixture after addition of water, provided the product in the yield of 87%.

The patent of the Sankyo Company no. EP 1 298 132 describes prasugrel hydrochloride and maleate; in another patent application, EP 2 003 136, 2 crystalline forms of prasugrel hydrochloride are characterized with physical analytic methods. At the same time this application also deals with the polymorph form of the prasugrel base. The general patent application no. EP 0 785 205 describes production of various hydrochlorides of pharmaceutically active substances by means of HCl generated in situ from trialkylsilylchlorides. Prasugrel hydrochloride was also prepared by this method and characterized with physical analytic methods.

Another patent application, WO 2009/066326, describes prasugrel fumarate, benzene sulfonate, p-toluene sulfonate and malate.

The newly published application no. WO 2009/062044 describes new crystalline forms C, B, E of prasugrel hydrochloride, as well as its amorphous form. This application also relates to a new preparation method of prasugrel, which is indicated in Scheme 3.

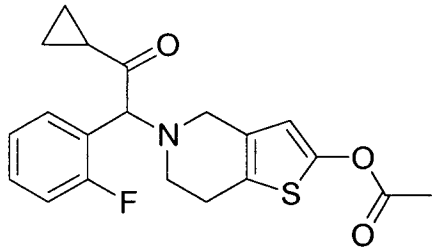
Scheme 3



From thienopyridone, protected by a trityl group on the nitrogen atom (compound of formula XVII), the compound of formula XVIII is prepared by the action of acetanhydride or acetyl chloride, which, after deprotection of the trityl group, provides the intermediate of formula XIX. A reaction of the compound XIX with the bromide of formula VIII in the presence of a base then provides prasugrel of formula I.

Disclosure of Invention

The invention provides a new method for the production of 5-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate, known under the non-proprietary name prasugrel, of formula I and its salts.

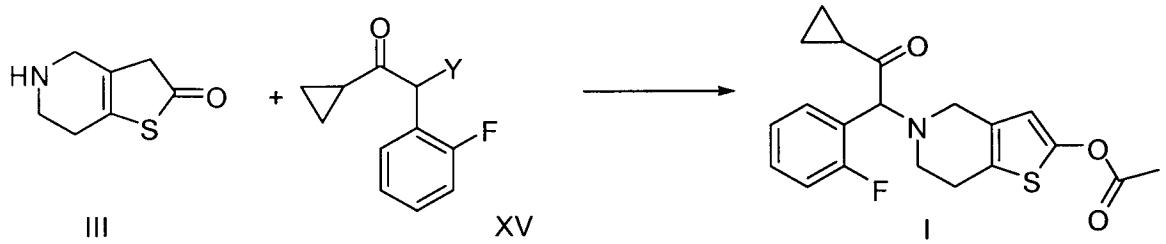


I

As compared to the known methods the production method in accordance with the invention provides the possibility of preparing a technologically feasible procedure, which provides prasugrel in a high yield and high purity. It uses a simple approach without the necessity to use protecting groups.

The production method according to this invention, which is indicated in Scheme 4, makes use of the new finding that if 4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2(3H)-one of formula III is used in the form of a salt with an aryl sulfonic acid, such as p-toluene sulfonic acid, the yield of the reaction will be considerably higher as compared to the formerly known use of the compound of formula III in the hydrochloride form.

Scheme 4



III XV I

Y in Scheme 4 means a halogen such as chlorine, bromine, or an OR^4 group, wherein R^4 means an alkane sulfonic group, such as the methane sulfonic group, or an arene sulfonic group such as p-toluene sulfonic group.

In a preferred embodiment of the invention the compound of formula III is reacted with the compound of formula XV with trialkylamine in an organic solvent; the resulting product is acetylated in situ by addition of acetanhydride. Prasugrel of formula I then crystallizes from the reaction mixture by addition of a co-solvent. To obtain highly pure prasugrel crude prasugrel is re-crystallized from an organic solvent by addition of a co-solvent.

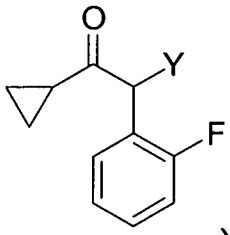
Highly pure prasugrel was used to prepare new stable salts that are suitable for use in medical dosage forms, such as hydrobromide, hydroiodide, hydrogen sulfate, cyclamate, ethane sulfonate and the salt with 2-naphthalene sulfonic acid.

Detailed description of the invention

The procedure for producing prasugrel of formula I according to the invention, which is indicated in Scheme 4, makes use of the finding about a remarkable increase of the reaction yield if 4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2(3H)-one of formula III is used in the form of a salt with an aryl sulfonic acid, such as p-toluene sulfonic acid, as compared to the formerly known use of the compound of formula III in the hydrochloride form.

Y in Scheme 4 means a halogen such as chlorine, bromine, or an OR^4 group, wherein R^4 means an alkane sulfonic group such as the methane sulfonic group or an arene sulfonic group such as p-toluene sulfonic or benzene sulfonic groups.

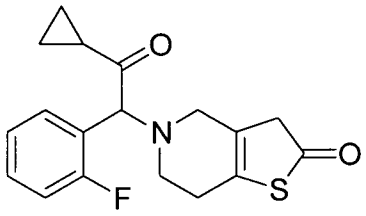
In a preferred embodiment of the invention the compound of formula III is reacted with the compound of formula XV, wherein Y means a halogen such as chlorine, bromine, or an OR^4 group, wherein R^4 means an alkane sulfonic group such as the methane sulfonic group or an arene sulfonic group such as p-toluene sulfonic or benzene sulfonic groups in an organic solvent such as acetonitrile, dimethylformamide or acetone in the presence of an inorganic base such as sodium, potassium or caesium carbonates or sodium, potassium or caesium hydrogen carbonates, or in the presence of an organic base such as a trialkylamine, e.g. triethylamine or ethyldiisopropylamine.



XV

The resulting product is acetylated in situ by addition of acetanhydride, preferably in the presence of dimethylaminopyridine and an organic base. Prasugrel of formula I then crystallizes from the reaction mixture by addition of a co-solvent. A co-solvent is to be understood as including water, aqueous solutions of inorganic salts, alcohols such as methanol, ethanol, propyl alcohols, acetic acid esters such as the ethyl ester, propyl esters and butyl esters of acetic acid, aliphatic hydrocarbons such as hexane or cyclohexane. The reaction is carried out at a temperature of from -20 °C to +100 °C, advantageously at a temperature of from -20 °C to +40 °C.

After addition of the co-solvent prasugrel is left to crystallize at a temperature of from -30 °C to +40 °C, conveniently at a temperature of from -30 °C to +15 °C. Thus obtained crude prasugrel contains less than 0.10 % of the compound of formula II.



II

The crude product is re-crystallized from an organic solvent such as acetonitrile, acetone or lower alcohols, e.g. methanol or ethanol, acetic acid esters such as the ethyl ester, propyl esters and butyl esters of acetic acid, by addition of a co-solvent. A co-solvent is to be understood as including water, aqueous solutions of inorganic salts, aliphatic hydrocarbons such as pentane, hexane or cyclohexane, or their mixtures. After addition of the co-solvent prasugrel is left to crystallize at a temperature of from -30 °C to +40 °C, conveniently at a temperature of from -30 °C to +15 °C. The re-crystallized product contains less than 0.10 % of the compound of formula II.

Highly pure prasugrel is then used to prepare new stable salts suitable for use in medical dosage forms, such as hydrobromide, hydroiodide, hydrogen sulfate, cyclamate, ethane sulfonate and the salt with 2-naphthalene sulfonic acid. Highly pure prasugrel is dissolved in a suitable organic solvent, such as ketones, e.g. acetone and methyl ethyl ketone, acetic acid esters, e.g. the ethyl ester, propyl esters and butyl esters of acetic acid, lower alcohols, e.g. methanol, ethanol and propyl alcohols, or in aromatic hydrocarbons such as toluene. 0.95 to 1.05 equivalents of the acid, dissolved in any of the above-mentioned solvents or in water, are added to a solution of the base. The resulting salt is left to crystallize at a temperature of from -30 °C to the boiling temperature of the solvent, conveniently at a temperature in the range of from -30 to + 25 °C.

Brief Description of Drawings

Figure 1a – X-ray powder diffraction pattern of prasugrel base
Figure 1b – DSC curve of prasugrel base

Examples

Melting points were measures on a Kofler block.

In the following examples samples of prasugrel and its salts were evaluated by X-ray diffraction analysis using the procedure mentioned below:
The diffraction pattern was obtained in an X'PERT PRO MPD PANalytical powder diffractometer with a graphite monochromator, radiation used CuKα (λ=1.542 Å), excitation voltage: 45 kV, anodic current: 40 mA, measured range: 2 - 40° 2θ, increment: 0.01° 2θ at the reflection delay of 50s; the measurement was carried out on a flat sample with the area/thickness of 10/0.5 mm.

DSC curves were measured with a Pyris 1 (Perkin Elmer) device. The sample charge was 3-4 mg, heating-up rate 10 °C/min
Temperature programme:

1) 1 minute at 50 °C

2) 50-200 °C at the rate of 10 °C/minute (except prasugrel HCl 50-250 °C at the rate of 10 °C/min).

Carrier gas: N_2 20 ml/min.

In the following examples samples of prasugrel and its salts were evaluated by means of HPLC in accordance with the procedure described below:
HPLC determination was carried out in an octadecyl column (250x4.6 mm; 5 μm) at the temperature of 30 °C with UV detection at 228 nm. For the separation gradient elution with a phosphate buffer (0.01 M KH_2PO_4 pH 2.2) was used with acetonitrile at the flow rate of 1.0 ml/min with the following gradient: 0 min 80% of buffer; 40 min 10% of buffer (linear gradient); 45 min 10% of buffer. The equilibration time of the column was 10 minutes. The spraying volume amounted to 10 μl. The capacity factor of prasugrel is 4.3. The sample was prepared by dissolution of the corresponding substance in acetonitrile to the concentration of 1 mg/ml.

Example 1

N-Ethyldiisopropylamine (1.7 ml; 9.7 mmol) is added to a suspension of 2-oxo-2,4,5,6,7a-hexahydrothieno[3,2-c]pyridine *p*-toluene sulfonate (1.52 g; 4.6 mmol) in acetonitrile (4 ml). Thus prepared solution is added to a solution of 1-cyclopropyl-2-bromo-2-(2-fluorophenyl)ethanone (1.13 g; 4.4 mmol) in acetonitrile (2 ml) and the reaction is stirred at the room temperature for 1.5 hours. Subsequently, acetanhydride (1.2 ml; 13.2 mmol), *N*-ethyldiisopropylamine (0.6 ml; 3.5 mmol) and a catalytic amount of *N,N*-dimethylaminopyridine are added to the solution. The reaction is stirred at the room temperature for 2 hours. Then, the reaction mixture is cooled down to -15 °C, 2.5 ml of water are added and the reaction is stirred at -12 to -8 °C for 2 h. The resulting white crystals are aspirated, washed with ethanol and dried in air. 0.97 g of prasugrel base (58%) are obtained, melting point: 118 - 120 °C, HPLC: purity 98.6%; content of the compound of formula II 0.08%.
The crude product obtained in this manner (0.9 g) is dissolved in acetonitrile (10.5 ml) and, after addition of 0.2 ml of acetanhydride, the mixture is stirred at the room temperature for 1 h. The mixture is then cooled down to -15 °C, water (4 ml) is added and white crystals precipitate under stirring at the temperature of -12 to -8 °C. After two hours they are aspirated, washed with ethanol and dried. 0.66 g of white

prasugrel crystals are obtained. Melting point: 120 -121 °C. HPLC: purity 99.4%; content of the compound of formula II 0.04%.

^{1}H NMR (250 MHz, CDCl3) δ (ppm): 7.47 (ddd, *J* = 14.7, 7.4, 1.7 Hz, 1H), 7.31 (m, 1H), 7.14 (m, 2H), 6.26 (s, 1H), 4.82 (s, 1H), 3.51 (m, 2H), 2.89 (m, 1H), 2.79 (m, 3H), 4.30 (m, 1H), 2.25 (s, 3H), 1.03 (m, 2H), 0.85 (m, 2H); ^{13}C NMR (250 MHz, CDCl3) δ(ppm): 207.7, 167.7, 161.3 (d, J_{CF} = 247.6 Hz), 149.5, 130.6 (d, J_{CF} = 3.5 Hz), 129.9 (d, J_{CF} = 8.4 Hz), 129.4, 125.8, 124.4 (d, J_{CF} = 3.5 Hz), 122.1 (d, J_{CF} = 14.1 Hz), 115.8 (d, J_{CF} = 22.9 Hz), 112.0, 71.6, 50.5, 48.4, 25.0, 20.6,18.3,12.0, 11.4.

X-ray analysis

Table 1: Characteristic peaks of prasugrel base:

Pos. [°2Th.]	d-spacing [A]	Rel. Int. [%]
7.65	11.553	26.1
11.15	7.933	33.6
13.36	6.624	100.0
14.62	6.053	63.2
15.06	5.880	18.2
18.76	4.726	88.1
19.22	4.614	55.0
21.38	4.153	80.1
22.73	3.909	26.7
23.32	3.811	74.2
24.24	3.669	45.1
26.89	3.313	13.3
31.29	2.856	18.3

The X-ray powder diffraction pattern is presented in the Annex in figure 1a; the DSC curve is presented in figure 1b.

Example 2

N-Ethyldiisopropylamine (1.7 ml; 9.7 mmol) is added to a suspension of 2-oxo-2,4,5,6,7a-hexahydrothieno[3,2-c]pyridine hydrochloride (0.89 g; 4.6 mmol) in acetonitrile (4 ml). Thus prepared solution is added dropwise to a solution of 1-cyclopropyl-2-bromo-2(2-fluorophenyl)ethanone (1.13 g; 4.4 mmol) in acetonitrile

(2 ml) and the reaction is stirred at the room temperature for 1.5 hours. Subsequently, acetanhydride (1.2 ml; 13.2 mmol), *N*-ethyldiisopropylamine (0.6 ml; 3.5 mmol) and a catalytic amount of *N,N*-dimethylaminopyridine are added to the solution. The reaction is stirred at the room temperature for 2 hours. Then, the reaction mixture is cooled down to -15 °C, 2.5 ml of water are added and the reaction is stirred at -12 to -8 °C for 2 hours. The resulting white crystals are aspirated, washed with ethanol and dried in air. 0.48 g of prasugrel base (29%) is obtained. Melting point: 117.5-119.5 °C, HPLC: purity 98.5%; content of the compound of formula II 0.09%.

The crude product obtained in this manner (0.45 g) is dissolved in acetonitrile (10.5 ml) and, after addition of 0.2 ml of acetanhydride, the mixture is stirred at the room temperature for 1 h. Then, the mixture is cooled down to -15 °C, water (4 ml) is added and white crystals precipitate under stirring at the temperature of -2 to -8 °C. After two hours they are aspirated, washed with ethanol and dried. 0,31 g of white crystals of prasugrel are obtained. Melting point: 120 -121 °C. HPLC: purity 99.4%; content of the compound of formula II 0.07%.

Example 3

12.22 g of 2-oxo-2,4,5,6,7a-hexahydrothieno[3,2-c]pyridine *p*-toluene sulfonate and 40 ml of acetonitrile are charged into a 250-ml three-neck flask equipped with a magnetic stirrer and a thermometer, which is closed with a calcium-chloride tube. 13.6 ml of diisopropylethylamine are added to the thick suspension under stirring and the mixture is stirred at the room temperature until a solution is produced (5-10 minutes). Then, 3-cyclopropyl-1-(2-fluorophenyl)-3-oxopropyl methane sulfonate (9.68 g) and 7.84 g of Et_4N^+Br are added to the flask. The resulting mixture is then stirred at the temperature of +22 to +25 °C for 4 to 5 hours. The reaction is monitored with TLC. After disappearance of the starting substance 10 ml of Ac_2O and 50 mg of dimethylaminopyridine are added to the reaction mixture. The reaction mixture is further stirred at the temperature of +22 to +25 °C for another 1.5 to 2 hours. The reaction is monitored with TLC in the same system. After this period the reaction mixture is cooled down to a temperature of -12 to -15 °C; 25 ml of a 20 mM aqueous solution of KH_2PO_4 are added. The mixture is inoculated and the product is left to crystallize under stirring at a temperature of -12 to -15 °C for 1.5 hours. The separated product - prasugrel base - is aspirated and washed with 20 ml of cooled

ethanol on fritted glass. The product is freely dried at the room temperature. 4.06 g (30.5%) of a crude product with the purity of 96.11% (HPLC) are obtained; content of the compound of formula II 0.08%.

Example 4

68 ml of *N*-ethyl-*N,N*-diisopropylamine (389 mmol; 2 eq.) are added to a suspension of 2-oxo-2,4,5,6,7a-hexahydrothieno[3,2-c]pyridine *p*-toluene sulfonate (66.86 g; 204.2 mmol; 1.05 eq.) in 160 ml of acetonitrile. Thus prepared solution is added dropwise to a solution of 50 g of 1-cyclopropyl-2-bromo-2(2-fluorophenyl)ethanone (194.5 mmol) and 50 ml of acetonitrile, charged in a 1L three-neck flask with a magnetic stirrer, thermometer and a dripping funnel closed with a calcium-chloride tube, such that the temperature does not exceed 30 °C, and the mixture is stirred for 30 min, being monitored with TLC (silica gel on glass, toluene : ethyl acetate 3:1). After disappearance of the starting 1-cyclopropyl-2-bromo-2(2-fluorophenyl)ethanone acetanhydride (60 ml; 3 eq.), *N*-ethyl-*N,N*-diisopropylamine and a catalytic amount of *N,N*-dimethylaminopyridine are added to the mixture and reacted for 1.5-2 h. The reaction is monitored with TLC in the same system. After this period the mixture is cooled down to -15 to -20 °C and 150 ml of water are added in portions. The mixture is left to crystallize under thorough stirring at -15 to -6 °C for 1.5 to 2 hours. The separated product - prasugrel base - is aspirated and washed with 2 × 25 ml of cooled ethanol on fritted glass and dried freely in air. 43.79 g (60.3 %) of crude prasugrel base with the purity of 99.44% (HPLC) is obtained; the content of the compound of formula II lower than 0.05%.

The crude product obtained in this manner (43 g) is dissolved in acetonitrile (480 ml), acetanhydride (8 ml) is added and, after stirring for 1 hour, cooled down to -15 °C, 200 ml of water are added in portions and the product is left to crystallize at -12 to -6 °C for two hours. By aspiration on fritted glass, washing with 2×25 ml of cooled ethanol and drying in air, 34.81 g of white crystals with the purity of 99.4% (HPLC) are obtained; the content of the compound of formula II lower than 0.05%.

Example 5

N-Ethyl-*N,N*-diisopropylamine (1.7 ml; 9.7 mmol) is added to a suspension of 2-oxo-2,4,5,6,7a-hexahydrothieno[3,2-c]pyridine hydrochloride (0.89 g; 4.6 mmol) in

acetonitrile (6 ml). 2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethylmethanesulfonate (1.18 g; 4.4 mmol) and 0.972 g (4.62 mmol) of tetraethylammonium bromide are added to the resulting solution and the reaction is stirred at the room temperature for 1.5 hours. Subsequently, acetanhydride (1.2 ml; 13.2 mmol), *N*-ethyl-*N,N*-diisopropylamine (0.6 ml; 3.5 mmol) and a catalytic quantity of *N,N*-dimethylaminopyridine are added to the reaction mixture. The reaction is stirred at the room temperature for 2 hours. The reaction mixture is cooled down to -15 °C, 2.5 ml of water are added and the reaction is stirred at -12 to -8 °C for 2 h. The resulting white crystals are aspirated, washed with ethanol and air-dried. 0.190 g of prasugrel base (12%) are obtained. Melting point: 118-120 °C, HPLC: purity 96.9%, content of the compound of formula II 0.22%.

The crude product obtained in this manner (0.150 g) is dissolved in acetonitrile (2 ml) and, after addition of 0.1 ml of acetanhydride, the mixture is stirred at the room temperature for 1 h. Then, the mixture is cooled down to -15 °C, water (2 ml) is added and white crystals precipitate under stirring at a temperature of -12 to -8 °C. After two hours they are aspirated, washed with ethanol and dried. 0.100 g of white crystals of prasugrel are obtained. Melting point: 120 -121 °C. HPLC: purity 99.6%; content of the compound of formula II 0.05%.

The X-ray powder diffraction pattern is equal to that presented in Example 1.

Example 6

N-Ethyldiisopropylamine (1.7 ml; 9.7 mmol) is added to a suspension of 2-oxo-2,4,5,6,7a-hexahydrothieno[3,2-c]pyridine *p*-toluene sulfonate (1.52 g; 4.6 mmol) in acetonitrile (6 ml). 2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethylmethanesulfonate (1.18 g; 4.4 mmol) is added to the resulting solution and the reaction is stirred at the room temperature for 1.5 hours. Subsequently, acetanhydride (1.2 ml; 13.2 mmol), *N*-ethyl-*N,N*-diisopropylamine (0.6 ml; 3.5 mmol) and a catalytic amount of *N,N*-dimethylaminopyridine are added to the solution. The reaction is stirred at the room temperature for 2 hours. Then, the reaction mixture is cooled down to -15 °C, 2.5 ml of water are added and the reaction is stirred at -12 to -8 °C for 2 h. The resulting white crystals are aspirated, washed with ethanol and air-dried. 0.52 g of prasugrel base are obtained (32%). Melting point: 116.5-119.5 °C, HPLC: purity 94%; content of the compound of formula II 0.20%.

The crude product obtained in this manner (0.47 g) is dissolved in acetonitrile (6 ml) and, after addition of 0.2 ml of acetanhydride, the mixture is stirred at the room temperature for 1 h. Then, the mixture is cooled down to -15 °C, water (2 ml) is added and white crystals precipitate under stirring at a temperature of -12 to -8 °C. After two hours they are aspirated, washed with ethanol and dried. 0.34 g of white prasugrel crystals are obtained. Melting point: 120 -121 °C.

The X-ray powder diffraction patterns is equal to that presented in Example 1.

Example 7

K_2CO_3 (4.03 g; 29.17) is added to a suspension of 2-oxo-2,4,5,6,7a-hexahydrothieno[3,2-c]pyridine *p*-toluene sulfonate (3.34 g; 10.21 mmol) in acetone (25 ml). The suspension is stirred at the room temperature for 10 minutes, then, 1-cyclopropyl-2-bromo-2(2-fluorophenyl)ethanone (2.51 g; 9.72 mmol) is added to the reaction mixture and the reaction is stirred at the room temperature for 3.5 hours. The course of the reaction is monitored with TLC (silica gel on glass; toluene : ethyl acetate; 3 : 1). After this period the undissolved fraction is filtered through a S2 fritted glass and the filtration cake is washed with 15 ml of acetone. 2.8 ml of acetanhydride (29.17 mmol) and 1.4 ml of *N*-ethyldiisopropylamine (7.78 mmol) and a catalytic amount of *N,N*-dimethylaminopyridine are added to the filtrate. The reaction mixture is stirred at the room temperature for 1.5 hours. Then, the reaction mixture is cooled down to -15 °C, 25 ml of water are added and the reaction is stirred at -12 to -8 °C for 2 h. The separated crystals are aspirated, washed with ethanol and air-dried. 2.05 g of prasugrel (56.5 %) is obtained. HPLC: purity 98.85%; content of the compound of formula II 0.05%.

Example 8

K_2CO_3 (4.03 g; 29.17) is added to a suspension of 2-oxo-2,4,5,6,7a-hexahydrothieno[3,2-c]pyridine hydrochloride (1.96 g; 10.21 mmol) in acetone (25 ml). The suspension is stirred at the room temperature for 10 minutes and then 1-cyclopropyl-2-bromo-2(2-fluorophenyl)ethanone (2.51 g; 9.72 mmol) is added to the reaction mixture and the reaction is stirred at the room temperature for 3.5 hours. The course of the reaction is monitored with TLC (silica gel on glass; toluene : ethyl acetate; 3 : 1). After this period the undissolved fraction is filtered through a S2 fritted

glass and the filtration cake is washed with 15 ml of acetone. 2.8 ml of acetanhydride (29.17 mmol) and 1.4 ml of *N*-ethyldiisopropylamine (7.78 mmol) and a catalytic amount of *N,N*-dimethylaminopyridine are added to the filtrate. The reaction mixture is stirred at the room temperature for 1.5 hours. Then, the reaction mixture is cooled down to -15 °C, 25 ml of water are added and the reaction is stirred at -12 to -8 °C for 2 h. The separated crystals are aspirated, washed with ethanol and air-dried. 1.83 g of prasugrel (50.4 %) are obtained. HPLC: purity 98.2 %; content of the compound of formula II less than 0.05%.

Example 9

K_2CO_3 (4.03 g; 29.17) is added to a suspension of 2-oxo-2,4,5,6,7a-hexahydrothieno[3,2-c]pyridine *p*-toluene sulfonate (3.34 g; 10.21 mmol) in acetonitrile (25 ml). The suspension is stirred at the room temperature for 10 minutes and then 1-cyclopropyl-2-bromo-2(2-fluorophenyl)ethanone (2.51 g; 9.72 mmol) is added to the reaction mixture and the reaction is stirred at the room temperature for 3.5 hours. The course of the reaction is monitored with TLC (silica gel on glass; toluene : ethyl acetate; 3 : 1). After this period the undissolved fraction is filtered through a S2 fritted glass and the filtration cake is washed with 15 ml of acetonitrile. 2.8 ml of acetanhydride (29.17 mmol) and 1.4 ml of *N*-ethyldiisopropylamine (7.78 mmol) and a catalytic amount of *N,N*-dimethylaminopyridine are added to the filtrate. The reaction mixture is stirred at the room temperature for 1.5 hours. Then, the reaction mixture is cooled down to -15 °C, 25 ml of water are added and the reaction is stirred at -12 to -8 °C for 2 h. The separated crystals are aspirated, washed with ethanol and air-dried. 1.98 g of prasugrel (54.4%) are obtained. HPLC: purity 98.8%; content of the compound of formula II less than 0.05%.

Example 10

K_2CO_3 (4.03 g; 29.17) is added to a suspension of 2-oxo-2,4,5,6,7a-hexahydrothieno[3,2-c]pyridine hydrochloride (1.96 g; 10.21 mmol) in acetonitrile (25 ml). The suspension is stirred at the room temperature for 10 minutes and then 1-cyclopropyl-2-bromo-2(2-fluorophenyl)ethanone (2.51 g; 9.72 mmol) is added to the reaction mixture and the reaction is stirred at the room temperature for 3.5 hours. The course of the reaction is monitored with TLC (silica gel on glass; toluene : ethyl

acetate; 3 : 1). After this period the undissolved fraction is filtered through a S2 fritted glass and the filtration cake is washed with 15 ml of acetone. 2.8 ml of acetanhydride (29.17 mmol) and 1.4 ml of *N*-ethyldiisopropylamine (7.78 mmol) and a catalytic amount of *N,N*-dimethylaminopyridine are added to the filtrate. The reaction mixture is stirred at the room temperature for 1.5 hours. Then, the reaction mixture is cooled down to -15 °C, 25 ml of water are added and the reaction is stirred at -12 to -8 °C for 2 h. The separated crystals are aspirated, washed with ethanol and air-dried. 1.67 g of prasugrel (46%) are obtained. HPLC: purity 99.0%; content of the compound of formula II less than 0.05%.

Example 11

Triethylamine (36.5 ml; 0.26 mol) is added to a suspension of 2-oxo-2,4,5,6,7a-hexahydrothieno[3,2-c]pyridine hydrochloride (50 g; 0.26 mol) in a mixture of methanol (250 ml) and acetone (250 ml). *p*-Toluene sulfonic acid monohydrate (54.6 g; 0.28 mol) is added to the solution. White crystals precipitate from the solution under stirring at a temperature of 10 °C to 15 °C. After 2 hours they are aspirated and 49.7 g of the first fraction (58%) of 2-oxo-2,4,5,6,7a-hexahydrothieno[3,2-c]pyridine *p*-toluene sulfonate (58 %) are thus obtained. By concentration of the mother liquors in a rotary vacuum evaporator to ½ the volume and cooling to 10 °C another 26.2 g (31 %) of the second fraction are obtained. The total yield of 2-oxo-2,4,5,6,7a-hexahydrothieno[3,2-c]pyridine *p*-toluene sulfonate is 89%.

Example 12

Crude prasugrel (10.19 g) prepared in accordance with Example 1 is dissolved in ethyl acetate (50 ml) at the temperature of 45 °C, activated carbon is added and the solution is filtered hot. Hexane (40 ml) is added to the hot solution. Crystals start to precipitate and the mixture is gradually cooled down to 0 °C and stirred at 0-5 °C for 2 hours. By aspiration 7.9 g (79%) of white crystals of prasugrel are obtained, melt. point: 120-121 °C; HPLC purity 99.3%.; content of the compound of formula II less than 0.05%. The X-ray powder diffraction pattern is identical with that presented in Example 1.

Example 13

Crude prasugrel (1.03 g) prepared in accordance with Example 1 is dissolved in methanol (16 ml) at the temperature of 50 °C, activated carbon is added and the solution is filtered hot. Water (6.5 ml) is added to the hot solution. Crystals start to precipitate and the mixture is gradually cooled down to 5 °C and stirred at 0-5 °C for 2 hours. By aspiration 0.77 g (77%) of white crystals are obtained, melting point: 120-121 °C; HPLC purity 99.4%; content of the compound of formula II less than 0.05%.

Example 14

Crude prasugrel (1.79 g) prepared in accordance with Example 8 is dissolved in acetone (20 ml) at the room temperature, activated carbon is added and the solution is filtered and the filtration cake is washed with another 5 ml of acetone. Water (12 ml) is added to the filtrate dropwise under cooling to the temperature of -15 to -10 °C. Crystals start to precipitate and the mixture is stirred at -5 to -10 °C for 2 h. Aspiration offers 1.53 g (85%) of white crystals, melting point: 120-121 °C; HPLC purity: 99.2%; content of the compound of formula II less than 0.05%.

Example 15

Preparation of prasugrel hydrobromide, form A

Prasugrel base (3.15 g, 8.43 mmol) is dissolved in acetone (46 ml) and the solution is cooled down to 5-10 °C. A 48% solution of hydrobromic acid (0.90 ml; 8.01 mmol) is added dropwise to the solution; the solution is inoculated and stirred at a temperature of 5-10 °C for 1 hour. The precipitated crystals are aspirated. 3.60 g (99%) of prasugrel hydrobromide, form A with the melt. point of 137-141°C are obtained.

Example 16

Preparation of prasugrel hydrobromide, form A

Prasugrel base (3.089 g; 8.27 mmol) is dissolved in acetone (46 ml) and the solution is cooled down to 5-10 °C. Toluene saturated with hydrogen bromide (0.95 eq.) is added dropwise to the solution; the solution is optionally inoculated and stirred at a temperature of 5-10 °C for 2 hours. 2.87 g of prasugrel hydrobromide (80%) are obtained. Melt. point: 134.7-136.3

The X-ray record of the product is equal to that presented in Example 15.

Example 17

Preparation of prasugrel hydrobromide, form B

1.0 g of prasugrel hydrobromide prepared in accordance with Example 14 was dissolved while hot in a mixture of 8 ml of ethanol and 25 ml of ethyl acetate. The resulting solution was filtered and left to crystallize at a temperature of +5 °C for 24 hours. The separated hydrobromide is aspirated and 0.25 g (25%) of prasugrel hydrobromide, form B are obtained; melt. point 148 -153 °C.

Example 18

Preparation of prasugrel hydroiodide

Prasugrel base (3.028 g; 8.11 mmol) is dissolved in acetone (16 ml) and cooled in an ice bath to 5-10 °C. A 57% solution of hydrogen iodide in water (0.95 eq.) is added dropwise to the solution, the solution is inoculated and stirred at the temperature of ca. 5 °C for 1.5 h. 2.99 g of yellowish crystals (74%) are obtained, melting point: 123-125 °C.

Example 19

Preparation of prasugrel benzene sulfonate

Prasugrel base (1.554 g; 4.16 mmol) is dissolved in acetone (15 ml) at a temperature of up to 35 °C and cooled down to the room temperature. Benzene sulfonic acid (0.625 g; 3.95 mmol) is dissolved in diethyl ether (6.2 ml) and the solution is added to the prasugrel solution. Another 8 ml of diethyl ether are added to the solution, the solution is cooled down to -10 °C, inoculated, and stirred at the temperature of -10 °C for 12 h. The precipitated crystals are aspirated, washed with diethyl ether and dried freely. 1.96 g (93%) of white crystals with the melt. point of 162.5-163.5 °C are obtained.

Example 20

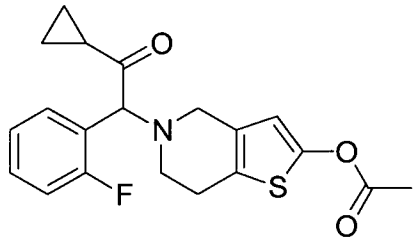
Preparation of prasugrel cyclamate

Prasugrel base (2.2 g; 5.41 mmol) is dissolved in acetone (20 ml). Cyclamic acid (0.970 g; 5.41 mmol) is dissolved in acetone (9 ml) and the solution is added to the prasugrel solution, cooled down to -10 °C, inoculated and stirred at the temperature of

-10 °C for 12 h. The precipitated crystals are aspirated, washed with acetone and dried freely. 0.730 g (45%) of white crystals with the melt. point of 162.5-163.5 °C are obtained.

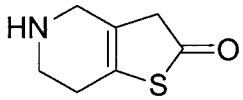
Claims:

1. A method for the production of 5-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate of formula **I**



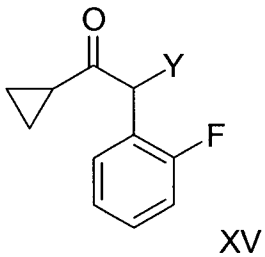
I

or its salts, characterized in that the compound of formula III,



III

in the form of a salt with an arene sulfonic acid, is reacted with the compound of formula XV



XV

wherein Y means: chlorine, bromine, or an OR^4 group wherein R^4 means an alkane sulfonic group or arene sulfonic group,

in an organic solvent in the presence of an inorganic base or organic base, to give, after addition of an acetylating reagent and organic base to the reaction mixture, the compound of formula I, which, after addition of a co-solvent, is crystallized from the reaction mixture, and the compound of formula I is optionally purified by crystallization and optionally converted to a salt by reaction with an organic or inorganic acid in a suitable solvent.

2. The method according to claim 1, characterized in that the compound of formula III is used in the form of a salt with p-toluene sulfonic acid or benzene sulfonic acid.

3. The method according to claims 1 or 2, characterized in that the compound of formula III is used in the form of a salt with p-toluene sulfonic acid.

4. The method according to any of the preceding claims, characterized in that the compound of formula XV is used wherein Y means: bromine or an OR^4 group, wherein R^4 means the methane sulfonic group.

5. The method according to any of the preceding claims, characterized in that the organic solvent used is selected from the group consisting of acetonitrile, dimethylformamide, acetone and their mixtures.

6. The method according to any of the preceding claims, characterized in that the inorganic base used is selected from the group consisting of sodium, potassium or caesium carbonates and sodium, potassium or caesium hydrogen carbonates and the organic base used is trialkylamine.

7. The method according to any of the preceding claims, characterized in that the inorganic base used is sodium or potassium carbonate and the organic base used is triethylamine or ethyldiisopropylamine.

8. The method according to any of the preceding claims, characterized in that the acetylating reagent used is acetanhydride.

9. The method according to any of the preceding claims, characterized in that the compound of formula I is crystallized from the reaction mixture by addition of a co-solvent selected from the group consisting of water, an aqueous solution of an inorganic salt, an alcohol such as methanol and ethanol and propyl alcohol, an acetic acid ester such as ethyl ester, propyl ester or butyl ester, and an aliphatic hydrocarbon such as hexane or cyclohexane.

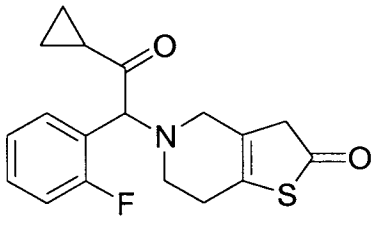
10. The method according to claim 9, characterized in that the co-solvent is selected from the group consisting of water, an aqueous solution of an inorganic salt, methanol, ethanol, an acetic acid ethyl ester, hexane and cyclohexane.

11. The method according to claim 1, characterized in that the compound I is purified by crystallization from a solvent selected from the group consisting of lower alcohols and ketones, esters and nitriles of organic acids, optionally with addition of a co-solvent.

12. The method according to claim 1, characterized in that the compound I is purified by crystallization using a co-solvent selected from the group consisting of water and aqueous solutions of inorganic salts and aliphatic hydrocarbons, preferably pentane, hexane, or cyclohexane, or their mixtures.

13. The method according to claims 1, 11 and 12, characterized in that the compound I is purified by crystallization at a temperature of -30° C to +40° C, preferably -30° C to +15° C.

14. Prasugrel, containing less than 0.5% of the compound of formula II.



II

15. Prasugrel according to claim 14, containing less than 0.1% of the compound of formula II.

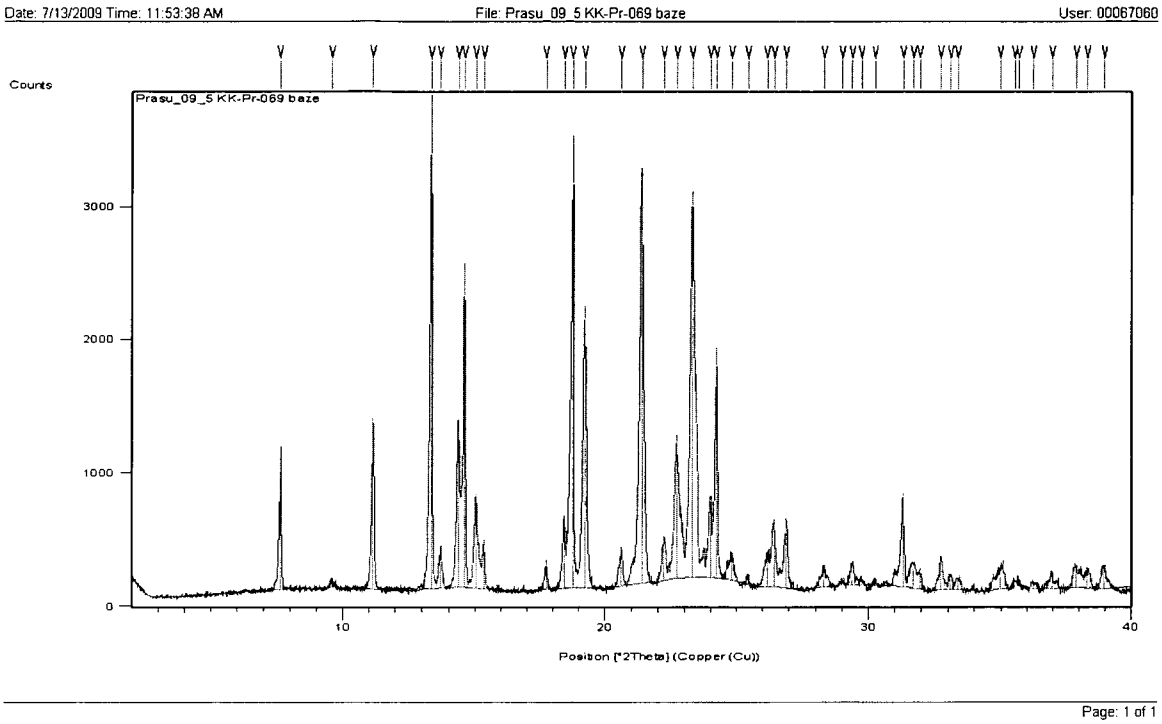
16. The method according to claims 1-13, characterized in that the compound I is converted to a salt by reaction with an acid selected from the group consisting of hydrochloric, hydrobromic, hydroiodic, sulfuric, cyclamic, ethane sulfonic, benzene sulfonic and 2-naphthalene sulfonic acids.

17. The method according to claims 1-13 and 16, characterized in that the conversion to the salt is carried out by dissolving the compound of formula I in an organic solvent, followed by addition of 0.95 to 1.05 molar equivalents of an acid selected from the group consisting of hydrochloric, hydrobromic, hydroiodic, sulfuric, cyclamic, ethane sulfonic, benzene sulfonic and 2-naphthalene sulfonic acids, and leaving the reaction mixture to crystallize at a temperature of -30 °C to the boiling point of the solvent.

18. The method according to claim 17, characterized in that the organic solvent is selected from the group consisting of ketones, preferably acetone or ethyl methyl ketone, acetic acid esters, lower alcohols, preferably methanol and ethanol, and aromatic hydrocarbons, preferably toluene.

19. The method according to claim 17, characterized in that the acid is added as a solution in an organic solvent selected from the group consisting of ketones, preferably acetone or ethyl methyl ketone, acetic acid esters, lower alcohols, preferably methanol or ethanol, aromatic hydrocarbons, preferably toluene, and water.

20. The method according to claim 17, characterized in that the crystallization is carried out at a temperature of -30 °C to +40 °C.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User: 00067060
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0
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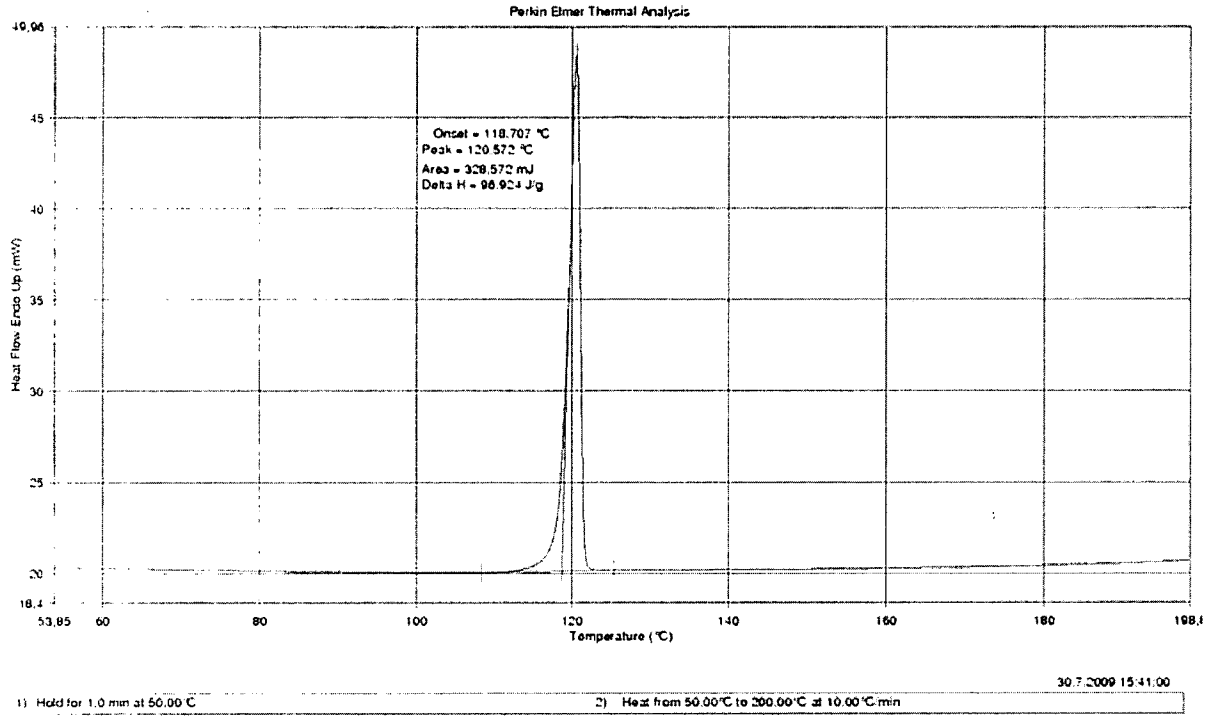
20
30
40
Position [°2Theta] (Copper (Cu))
Page: 1 of 1

Fig. 1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Delta H = 96.924 J/g
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30.7.2009 15:41:00
1) Hold for 1.0 min at 50.00 °C
2) Heat from 50.00°C to 200.00°C at 10.00°C/min

Fig. 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2010/000115

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D495/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/066326 A2 (MSN LAB LTD [IN]; SATYANARAYANA REDDY MANNE [IN]; ESWARAIAH SAJJA [IN]) 28 May 2009 (2009-05-28) cited in the application	1-13
Y	page 19; example 18 page 20; example 22 claims 1,2	16-20

X	EP 2 003 136 A1 (DAIICHI SANKYO CO LTD [JP]; UBE INDUSTRIES [JP]) 17 December 2008 (2008-12-17) cited in the application	14,15
Y	page 2, paragraph 4 page 8 - page 9; example 1 page 10; table 1 & WO 2007/114526 A1 (DAIICHI SANKYO CO LTD [JP]; UBE INDUSTRIES; INOUE TERUHIKO; NAKAMURA K) 11 October 2007 (2007-10-11)	16-20

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 March 2011	15/03/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Hoepfner, Wolfgang

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/CZ2010/000115

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009066326 A2	28-05-2009	NONE	
EP 2003136 A1	17-12-2008	AU 2007234467 A1	11-10-2007
		CA 2648503 A1	11-10-2007
		WO 2007114526 A1	11-10-2007
		KR 20080110777 A	19-12-2008
		RU 2008144008 A	20-05-2010
		US 2009203729 A1	13-08-2009