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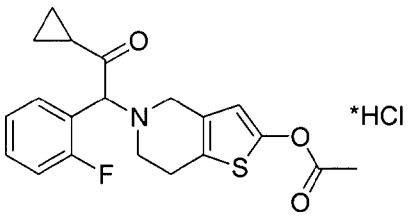
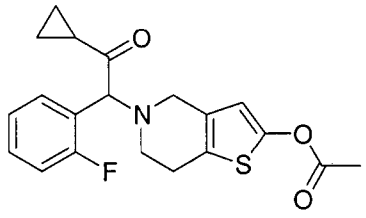
Declarations under Rule 4.17:

[Continued on next page]

(54) Title: A METHOD FOR THE PREPARATION OF PRASUGREL HYDROCHLORIDE IN POLYMORPHOUS FORM B



(I)



(II)

(57) Abstract: The invention relates to a method for the manufacture of 5-[2-cyclopropyl-l-(2- fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate hydrochloride of formula I (prasugrel hydrochloride) in crystalline form B, wherein prasugrel base of formula II is dissolved or suspended in an organic solvent and reacted with hydrogen chloride dissolved in an organic solvent or in water at a temperature in the range of -20 °C to 75°C and crystallized, optionally after addition of a co-solvent.

WO 2011/069473 A1

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

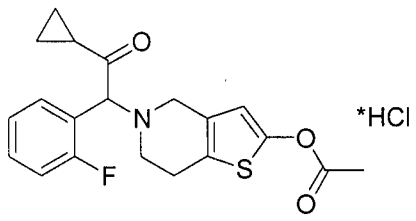
Published:

— *with international search report (Art. 21(3))*

A method for the preparation of prasugrel hydrochloride in polymorphous form B

Technical Field

The subject of the invention relates to a new method for the manufacture of 5-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate hydrochloride (of formula I), known under the non-proprietary name prasugrel hydrochloride, in polymorphous form B.



(I)

Background Art

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

The patent of the Sankyo Company no. EP 1 298 132 describes prasugrel hydrochloride and maleate. Prasugrel hydrochloride, referred to as crystal A here, was prepared by reaction of the base in acetone with 36% hydrochloric acid at 25 °C. Crystals of prasugrel hydrochloride with the melting point of 133 to 136 °C were obtained. By reacting again with 36% hydrochloric acid in the same solvent but at an increased temperature (40 °C), hydrochloride referred to as crystal B1 with the melting point of 166 to 174 °C was obtained. The same procedure; however, after inoculation with crystal B1, provided hydrochloride with the melting point of 165 to 178 °C, crystal B2 here.

Another patent application of Sankyo, EP 2 003 136, characterizes 2 crystalline forms of prasugrel hydrochloride with physical and analytical methods. Form B of the hydrochloride in accordance with this application is prepared as in the previous case from the base in acetone

by addition of 36% HCl at an increased temperature (52 °C here) and after inoculation. At the same time, this application also refers to a polymorphous form of prasugrel base.

The general patent application of Sandoz no. WO 2008/000418 describes preparation of various hydrochlorides of pharmaceutically active substances by means of in situ generated HCl from trialkyl silyl chlorides. Form B of prasugrel hydrochloride was also prepared by this method and characterized with physical and analytical methods.

The newly published application no. WO 2009/062044 (Reddy Laboratories) describes new crystalline forms C, D, E of prasugrel hydrochloride, as well as its amorphous form. Form C in accordance with this patent was produced by conversion of the prasugrel base with aqueous hydrochloric acid in 2-butanol at 40 °C or 28 °C. Form D was prepared by a reaction of the base dissolved in i-propylalcohol with HCl in the same solvent at 40 °C.

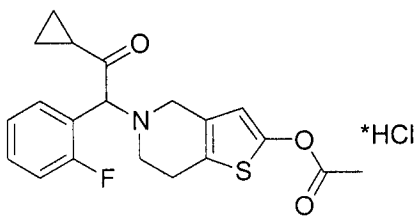
Form D was obtained by a reaction of the base dissolved in ethyl acetate with HCl in the same solvent at 40 °C. The amorphous product was obtained by evaporation of the i-propylalcohol solution of the hydrochloride.

The patent application no. WO 2009/066326 of MSM Laboratories describes prasugrel fumarate, benzene sulphonate, p-roluene sulphonate and malate.

Helm published the patent application no. WO 2009/098142, which encompasses salts of alkyl sulfonic and aryl sulfonic acids with improved chemical stability.

Disclosure of Invention

The subject of the invention provides a new method for the manufacture of 5-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate hydrochloride of formula I, known under the non-proprietary name prasugrel hydrochloride, in polymorphous form B.

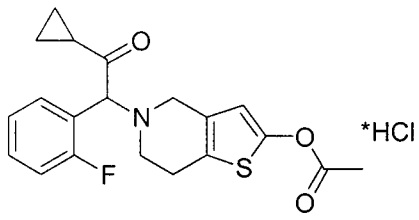


(I)

The manufacturing method of prasugrel hydrochloride, form B, according to this invention leads to a high yield of the product with a pure polymorphous form with high chemical purity.

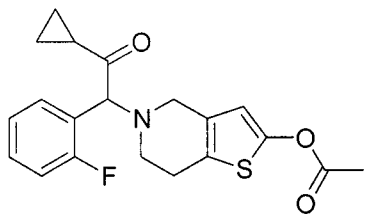
Detailed description of the invention

The subject of the invention provides a new method for the manufacture of 5-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate hydrochloride (formula I), known under the non-proprietary name prasugrel hydrochloride, in polymorphous form B



(I)

which comprises a process in which the base of prasugrel of formula II is dissolved or suspended in an organic solvent and reacted with hydrogen chloride, dissolved in an organic solvent or in water at a temperature of the solvent in the range of -20 °C to 75 °C, and further crystallized at the same temperature and/or after addition of a co-solvent or after cooling. The resulting product is separated and dried.



(II)

The prasugrel base is dissolved or suspended in an organic solvent, which is selected from the group of acetic acid esters and C1 to C5 alcohols or their mixtures. To the solution or suspension hydrogen chloride dissolved in a solvent selected from the group of acetic acid esters, C1 to C5 alcohols and water or their mixtures is added dropwise.

For the preparation of prasugrel hydrochloride 0.8 to 1.1 hydrogen chloride equivalents are used. The reaction and subsequent crystallization is carried out at a temperature in the range of from -20 °C to the boiling point of the solvent.

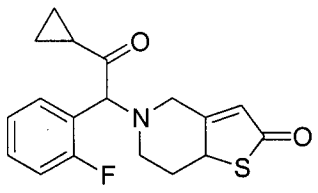
It is suitable, in some embodiments, to add a co-solvent after the reaction with hydrogen chloride, which co-solvent can be an acetic acid ester, especially ethyl or i-propyl acetate. After addition of hydrogen chloride it is also suitable to inoculate the reaction mixture with crystals of the hydrochloride of form B.

In accordance with this invention prasugrel hydrochloride of form B is prepared in this manner, which is characterized by the X-ray diffraction pattern which is presented in fig. 2a in the annex, and by the DSC record which is presented in fig. 2b in the annex.

Prasugrel hydrochloride prepared in accordance with this invention is characterized by high chemical purity, higher than 96%.

In a preferable embodiment of this invention prasugrel base is dissolved in ethyl acetate or 2-propyl acetate and reacted with hydrogen chloride in ethanol at the temperature of 25 °C and hydrochloride of form B is obtained in a yield higher than 80% and in a higher chemical purity than 99%.

The method of this invention has the advantage that the production of the hydrochloride and its crystallization is carried out at a lower temperature of 20 to 25 °C as compared to the hitherto known process of preparation from acetone at 40 °C; in practice, this represents considerable energy savings. In addition, the method of this invention also minimizes production of the decomposition product of the compound of formula III. Thus, a product with very high purity suitable for pharmaceutical use is obtained in a very high yield.



(III)

Brief Description of Drawings

Figure 1a – X-ray powder diffraction pattern of prasugrel hydrochloride of form A

Figure 1b – DSC record of prasugrel hydrochloride of form A

Figure 2a – X-ray powder diffraction pattern of prasugrel hydrochloride of form B

Figure 2b – DSC record of prasugrel hydrochloride of form B

Specific working examples

Melting points were measured on a Kofler block.

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

The DSC records were measured in a Pyris 1 device (Perkin Elmer). The charge of the sample was 3 to 4 mg, heating rate 10 °C/min
Temperature programme:

1) 1 minute at 50 °C
2) 50 to 200 °C at the rate of 10°C/minute (except prasugrel HCL 50 to 250 °C at the rate of 10 °C/min).

Carrier gas: N_2 20 ml/min.

Samples of prasugrel and its salts in the following examples were evaluated with HPLC by means of the following procedure:
The HPLC determination was performed in an octadecyl column (250x4.6 mm; 5 μm) at the temperature of 30 °C with UV detection at 228 nm. Gradient elution with a phosphate buffer (0.01 M KH_2PO_4 pH 2.2) with acetonitrile at the flow rate of 1.0 ml/min with the following gradient: 0 min 80 % of the buffer; 40 min 10 % of the buffer (linear gradient); 45 min 10 % of the buffer, was used for the separation. The equilibration time of the column was 10 minutes. The injected volume was 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

Preparation of prasugrel hydrochloride of form B

Prasugrel base (1.324 g; 3.545 mmol) is dissolved in isopropyl acetate (13 ml) at a temperature of up to 45 °C and cooled to the room temperature. To this solution a solution of HCl in ethanol (0.753 g containing 0.123 g of HCl) is added dropwise under stirring. The reaction mixture was stirred at the room temperature for 1 hour. The separated crystalline substance was aspirated and dried freely in air. 1.28 g of prasugrel hydrochloride of form B was obtained (88.1%) with the melt. point = 165.8 to 168.2 °C. HPLC: purity 99.8%; content of the compound of formula III 0.1%.

X-ray analysis

Table 2: Characteristic peaks of prasugrel hydrochloride of form B

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
8.01	11.028	27.1
12.88	6.870	15.2
13.52	6.545	41.4
14.52	6.095	100.0
16.17	5.476	27.0
22.01	4.035	47.7
25.57	3.481	47.0
27.28	3.267	16.2
28.17	3.165	10.7
29.27	3.049	11.8

The X-ray powder diffraction pattern is presented in fig. 2a, the DSC record is in fig. 2b in the annex.

Example 2

Preparation of prasugrel hydrochloride of form B

Prasugrel base (1.430 g, 3.83 mmol) is dissolved in ethyl acetate at 40 °C and left to cool down to the room temperature. To the prasugrel solution a 16.3% solution of hydrogen chloride in ethanol (1 equivalent) is added dropwise. The solution is inoculated and left to crystallize under stirring at the temperature of 20 to 25 °C for 2 hours. By aspiration 1.32 g (84 %) of white crystals of form B are obtained with the melt. point: 165 to 167 °C. HPLC purity: 99.5 %; content of the compound of formula III 0.1%; X-Ray and DSC are equal to the measurements mentioned in Example 1.

Example 3

Preparation of prasugrel hydrochloride of form B

To a suspension of prasugrel base (1.627 g; 4.357 mmol) in ethanol (5 ml) 1 equivalent of HCl in an ethanol solution is added dropwise; to the resulting solution 28 ml of ethyl acetate are added, the mixture is inoculated with B form crystals and stirred at the room temperature. The separated white crystals are aspirated, producing 1.54 g (86.5%) of prasugrel hydrochloride of form B with the melt. point: 167 to 168 °C. HPLC: 96.4 %; X-Ray and DSC are equal to the measurements mentioned in Example 2.

Example 4

Preparation of prasugrel hydrochloride of form A

Prasugrel base (2.55 g; 6.82 mmol) is dissolved in ethyl methyl ketone (25) ml at a temperature of up to 35 °C and cooled down in a water + ice bath to 0 °C. Under stirring and at the temperature of 0°C A solution of HCl in ethanol (1.45 ml containing 0.237 g HCl) is added dropwise to this solution under stirring at the temperature 0 °C. The reaction mixture was stirred at the temperature of 0 °C for 1 hour. The separated crystalline substance was aspirated and dried freely in air. 2.26 g of prasugrel hydrochloride of form A (80.7%) were obtained with the melt. point = 122 to 124 °C. HPLC: purity 99.3%.

X-ray analysis

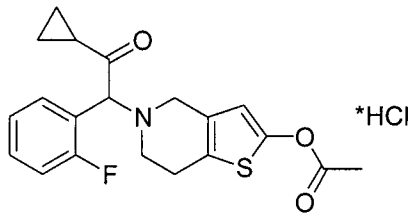
Table 1: Characteristic peaks of prasugrel hydrochloride of form A

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
8.33	10.600	59.9
11.94	7.407	41.5
12.55	7.045	23.4
12.88	6.869	18.4
13.24	6.681	45.8
15.52	5.705	100.0
18.52	4.786	12.7
20.41	4.348	16.0
20.72	4.283	27.7
25.29	3.518	40.4
26.68	3.339	39.0
27.31	3.263	15.6
28.35	3.146	10.1

The X-ray powder diffraction pattern is presented in fig. 1a, the DSC record is in fig. 1b in the annex.

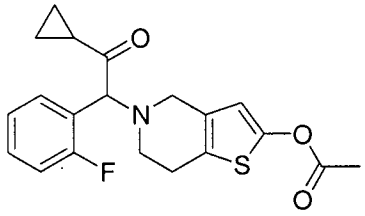
Claims

1. A method for the manufacture of prasugrel hydrochloride of formula I



(I)

in crystalline form B, characterized in that prasugrel base of formula II



(II)

is dissolved or suspended in an organic solvent and reacted with hydrogen chloride dissolved in an organic solvent or in water, at a temperature in the range of -20 °C to 75 °C and crystallized, optionally after addition of a co-solvent.

2. The method according to claim 1, characterized in that prasugrel base is dissolved or suspended in a solvent elected from the group consisting of acetic acid esters and C1 to C5 alcohols and their mixtures.

3. The method according to claims 1 or 2, characterized in that the suspension or solution of prasugrel base is reacted with 0.8 to 1.1 equivalents of hydrogen chloride dissolved in a solvent selected from the group consisting of acetic acid esters, C1 to C5 alcohols and water and their mixtures.

4. The method according to claims 1 to 3, characterized in that the reaction with hydrogen chloride and crystallization are carried out at a temperature in the range of from -20 °C to the boiling point of the solvent.

5. The method according to claims 1 to 4, characterized in that the reaction with hydrogen chloride and crystallization are carried out at a temperature of 0 to +30 °C.

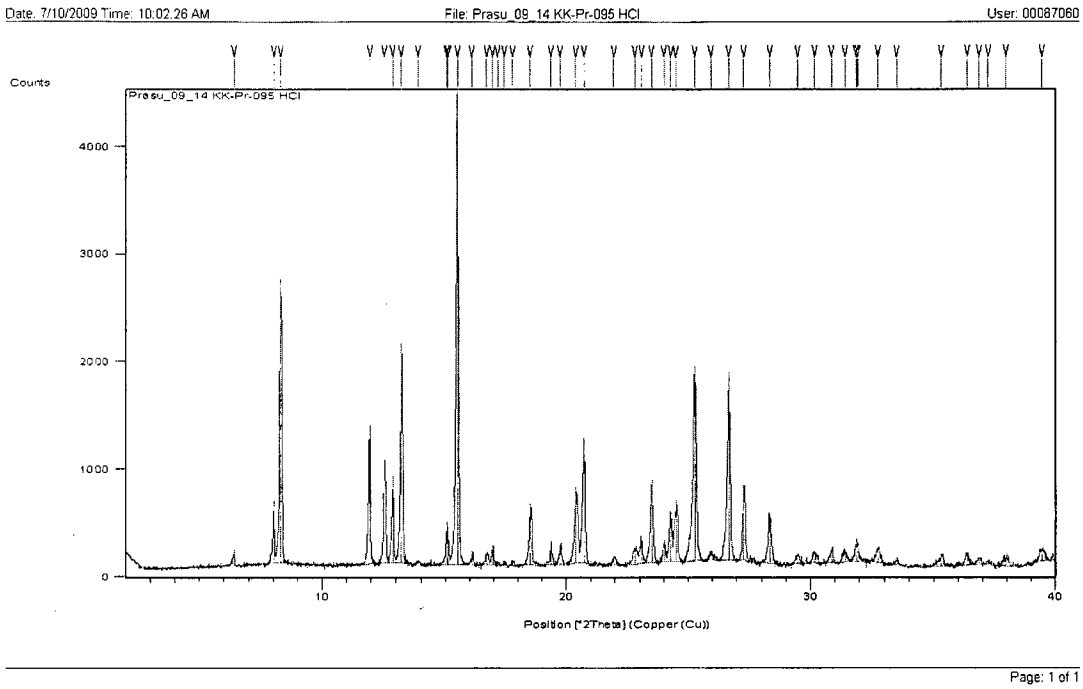
6. The method according to claims 1 to 5, characterized in that, after the reaction with hydrogen chloride, an acetic acid ester is added to the mixture as a co-solvent.

7. The method according to claim ~~1 to~~ 6, characterized in that the acetic acid ester is ethyl or 2-propyl ester of acetic acid.

8. The method according to claims 1 to 7, characterized in that the C1 to C5 alcohol is ethanol.

9. The method according to claims 1 to 8, characterized in that prasugrel hydrochloride is obtained in chemical purity (HPLC) higher than 96%.

10. The method according to 1 to 8, characterized in that prasugrel hydrochloride is obtained in chemical purity (HPLC) higher than 99%.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User: 00087060
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Prasu_09_14 KK-Pr-095 HCl
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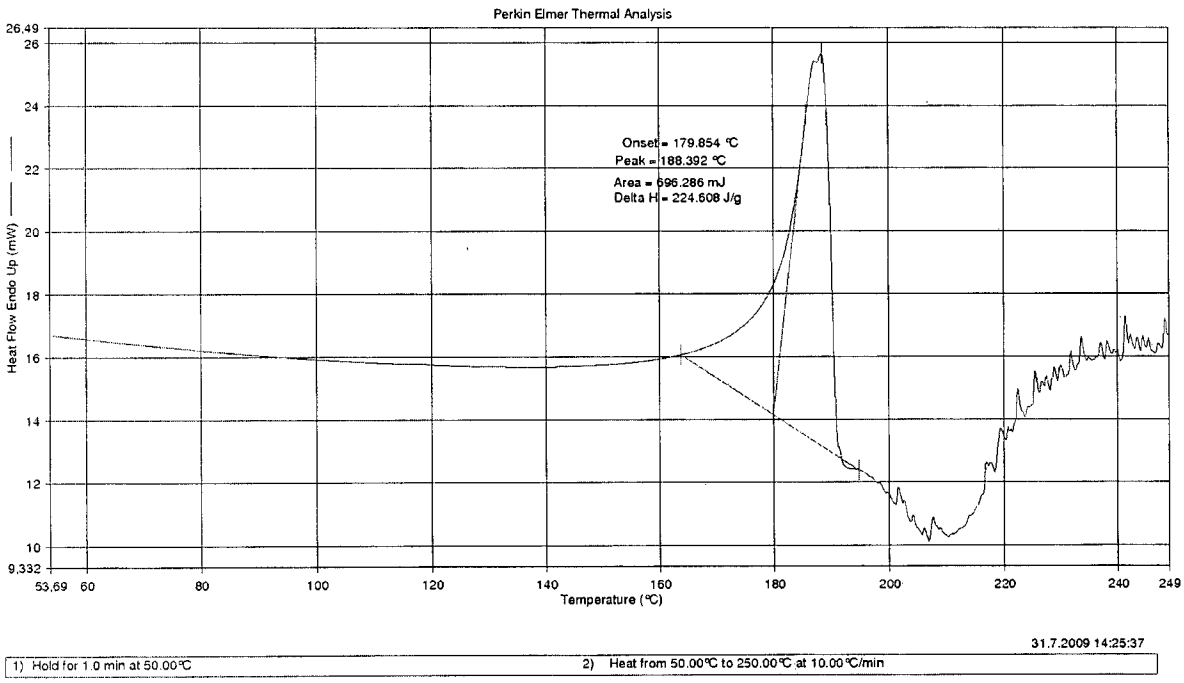
0
10
20
30
40
Position [°2Theta] (Copper (Cu))
Page: 1 of 1

Fig. 1a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Delta H = 224.608 J/g
Heat Flow Endo Up (mW)
26,49
26
24
22
20
18
16
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12
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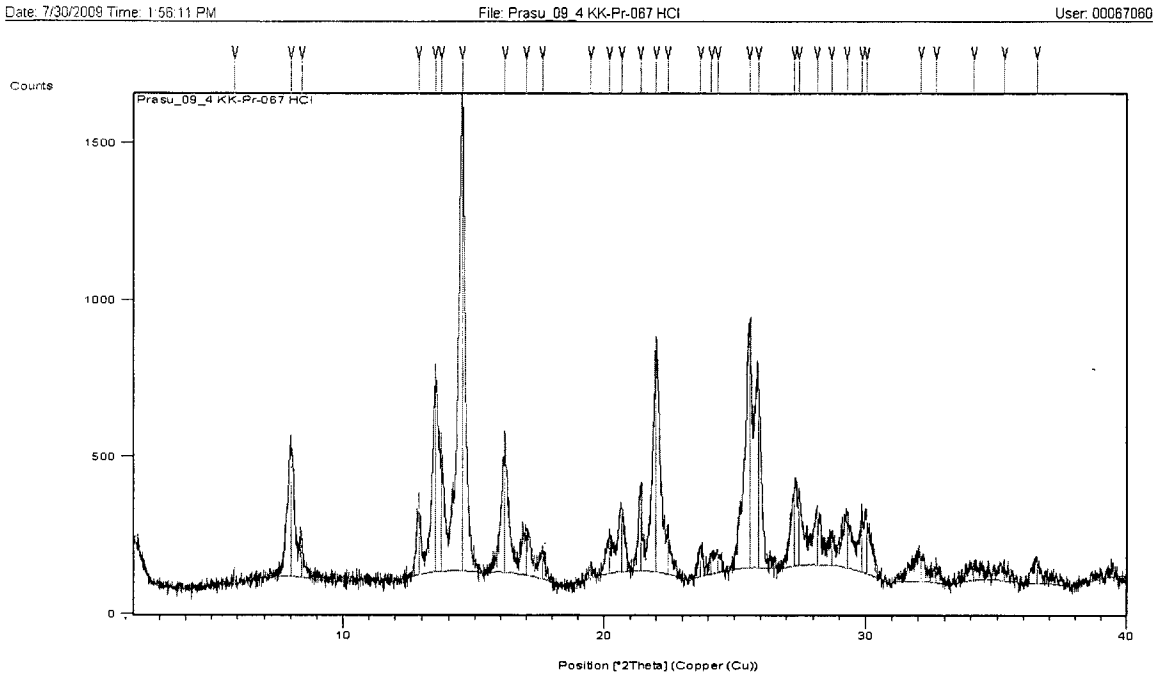
9,332
53,69
60
80
100
120
140
160
180
200
220
240
249
Temperature (°C)
31.7.2009 14:25:37
1) Hold for 1.0 min at 50.00°C
2) Heat from 50.00°C to 250.00°C at 10.00°C/min

Fig. 1b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Prasu_09_4 KK-Pr-067 HCl
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500
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10
20
30
40
Position [°2Theta] (Copper (Cu))
Page: 1 of 1

Fig. 2a

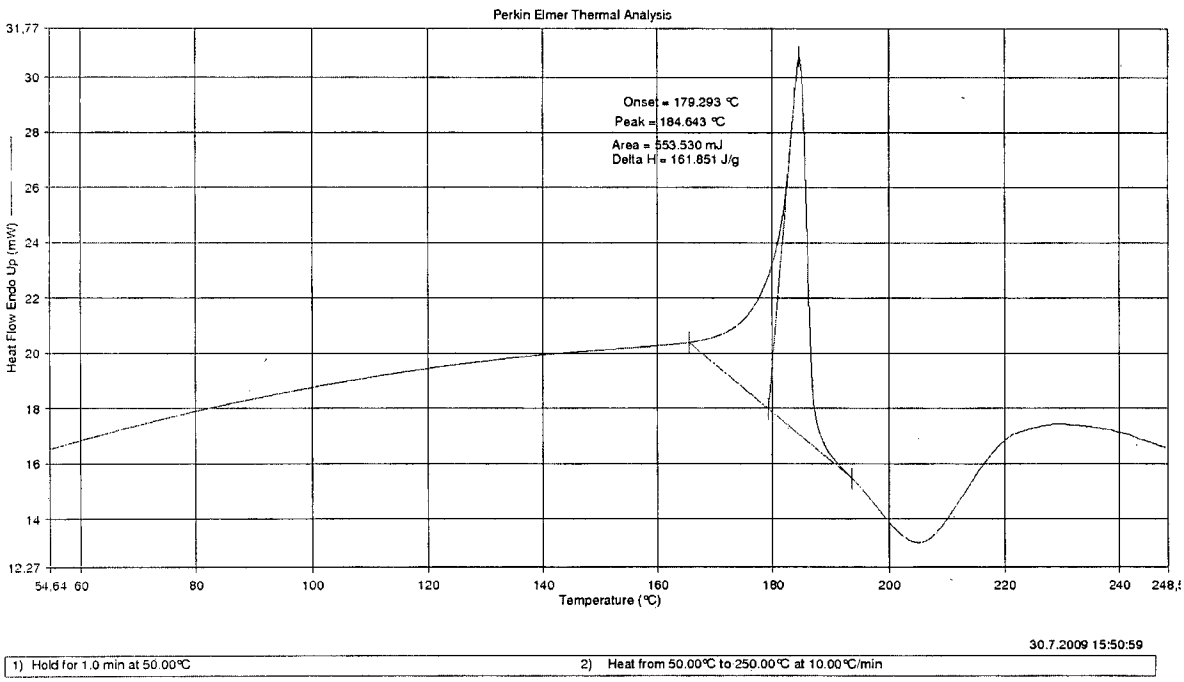
Perkin Elmer Thermal Analysis
Onset = 179.293 °C
Peak = 184.643 °C
Area = 553.530 mJ
Delta H = 161.851 J/g
Heat Flow Endo Up (mW)
31.77
30
28
26
24
22
20
18
16
14
12.27
54.64
60
80
100
120
140
160
180
200
220
240
Temperature (°C)
30.7.2009 15:50:59
1) Hold for 1.0 min at 50.00°C
2) Heat from 50.00°C to 250.00°C at 10.00°C/min

Fig. 2b

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2010/000126

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, WPI 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 2009/062044 A2 (REDDYS LAB LTD DR [IN]; REDDYS LAB INC DR [US]; PADI PRATAP REDDY [IN]) 14 May 2009 (2009-05-14) cited in the application page 26 - page 46; examples 13-18	1-10
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 example 14	1-5,9,10

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

"P" document published prior to the international filing date but later than the priority date claimed

"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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"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
30 March 2011	06/04/2011

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	Megido, Benigno

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2010/000126

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 2 003 136 A1 (DAIICHI SANKYO CO LTD [JP]; UBE INDUSTRIES [JP]) 17 December 2008 (2008-12-17) cited in the application page 3, paragraph 8 page 6, paragraphs 27,28 page 7, paragraph 54 example 1 figures 2,3	1-5,9,10
X	EP 1 298 132 A1 (SANKYO CO [JP]; UBE INDUSTRIES [JP]) 2 April 2003 (2003-04-02) cited in the application paragraph [0016]; examples 3,4,6	1,3-5,9, 10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/CZ2010/000126

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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