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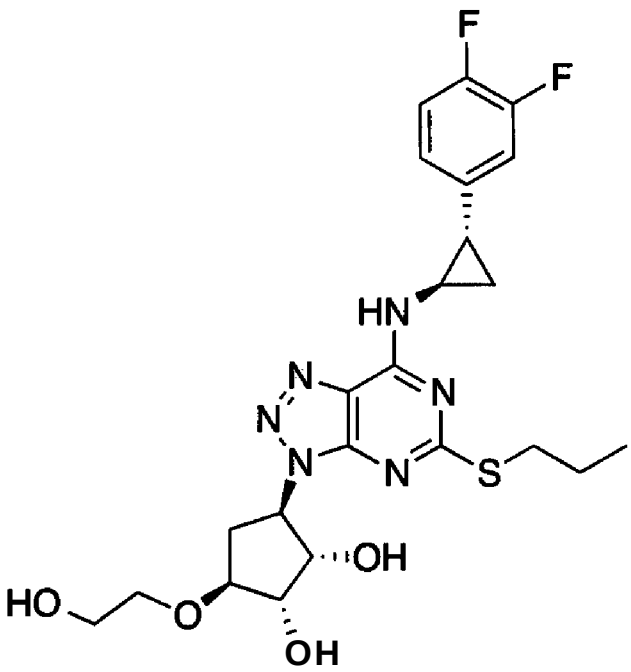
(54) Title: NOVEL PHARMACEUTICAL SOLID FORMS OF (lS,2S,3R,5S)-3-[7-[(lR,2S)-2-(3,4DIFLUOROPHENYL)CYCLOPROPYL-AMINO]-5<PROPYLTHIO)-3H41,2,3]TRIAZOLO[4,5-D]PYRIMIDIN-3YL]-5-(2-HYDROXYETHOXY)CYCLOPENTANE-L,2-DIOL



(I)

(57) Abstract: Solid state structures of (1S,2S,3R,5S)-3-[7-[lR,2S)-2-(3,4-Difluorophenyl)cyclopropyl-amino]-5- (propylthio)-3H-[l,23]triazolo[4,5-d]pyrimidin- 3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol (hereafter referred to as Ticagrelor) in the form of a stable 3-hydroxy-2-naphthoic acid co-crystal solid form as well as a 1,4-dioxane solvate, and processes for the preparation thereof.

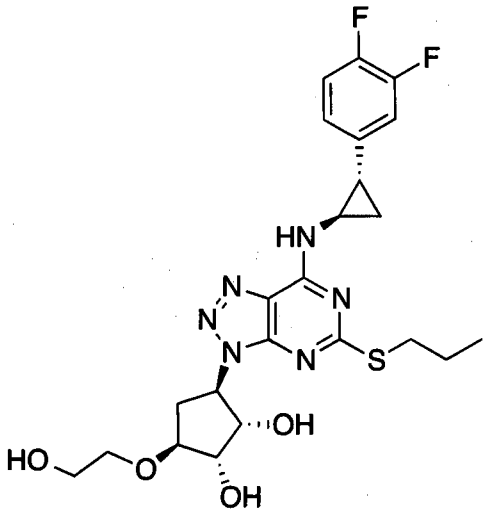
NOVEL PHARMACEUTICAL SOLID FORMS OF (IS,2S,3/?,5S)-3-[7-[(IR,2S)-2-(3,4-DIFLUOROPHENYL)CYCLOPROPYLAMINO]-5-(PROPYLTHIO)- 3H-[l,2,3]TRIAZOLO[4,5-D]PYRIM IDIN-3-YL]-5-(2-HYDROXYETHOXY)CYCLOPENTANE-l,2-DIOL

Technical Field

The present invention relates to novel solid forms of ticagrelor (I) as well as to methods of preparation. The specific solid forms claimed are a dioxane solvate and a cocrystal of ticagrelor derived from 3-hydroxy-2-naphthoic acid.

Background Art

The compound (IS,2S,3R,5S)-3-[7-[(l/?,2S)-2-(3 ,4-Difluorophenyl)cyclopropylamino]-5-(propylthio)-3H-[l,2 ,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-l,2-diol (also known as Ticagrelor) of formula I



(I)

is known to be a platelet aggregation inhibitor that is indicated for the prevention of thrombotic events in patients with myocardial infarction. Details of the synthetic method for isolating ticagrelor can be found in WO 00/34283. At least four anhydrous polymorphs of ticagrelor are known in the prior art and further details about these can be found in EP1289992. In addition, a number of cocrystals of ticagrelor are described in the prior art, specifically in WO2011067571. Studies [Nawarskas and Clark, *Cardiology in Review,* **19**(2), March/April 2011, 95-100] have shown that in patients with acute coronary syndrome, treatment with ticagrelor when compared to clopidogrel

significantly reduces mortality rate from vascular ialments, heart attack or stroke. When compared to clopidogrel, ticagrelor represents a new class of platelet inhibitor. Unlike clopidogrel, ticagrelor is a not a thienopyridine but best described as a cyclopentyl-triazolo-pyrimidine.

Ticagrelor is a low solubility, low permeability active pharmaceutical ingredient (API) and categorised as a class IV compound under the Biopharmaceutical Classification System (BCS). Such APIs are typically subjected to salt formation so as to improve their solubility and hence bioavailability. Another option, and an increasingly popular one, is to form a co-crystal of the API. A co-crystal is defined herein as a distinct solid form of the API that consists of a stoichiometric ratio of the API and a guest molecule (also known as a coformer) to give a periodically repeating crystal form. Co-crystals typically provide distinct physicochemical properties with respect to the reference API. Co-crystals offer great utility as they modify the physicochemical properties of the API without affecting the chemical structure of the API. Moreover co-crystallisation does not depend on the presence of ionisable functional groups, and this contrasts with the requirements for salt formation. Co-crystals are known to dissociate in solution at a rate faster than the time it takes for the API to reach the active site. Thus the therapeutic effect is delivered by the API alone with the cocrystal having rapidly dissociated by the time it is placed in water.

Unless there are issues with the bioavailability of the solid dosage form, those trained in the art will know that crystalline solid forms of APIs are preferred over amorphous forms since crystalline forms are thermodynamically stable and offer more predictable processing and storage conditions. The obvious caveat that goes with this of course relates to the problem of enhancing the solubility and bioavailability of the API, which favours the amorphous form. Neither polymorphs nor cocrystals of the API are obvious prior to extensive crystallisation experiments. Indeed those familiar with the art will be familiar with previous literature examples of attempted cocrystallisation experiments that have instead led to new polymorphs of the API or cases of disappearing polymorphs of the API after characterisation of supposedly stable new crystal forms.

Methods of preparing and characterising cocrystals are now extensively described in the literature. For example see: Trask *et al. Chem. Commun.,* **2004,** 890-891; and O. Almarsson, M.J. Zaworotko, *Chem. Commun.,* **2004,** 1889-1896; T. Friscic and W. Jones, *J. Pharmacy. Pharmacology,* **2010,** 62, 1547-1559. These methods as well as other methods known to those skilled in the art may be used to prepare cocrystals of ticagrelor preferentially containing a coformer molecule with at least one carboxylic acid group, or more preferentially a coformer belonging to the general class of

compounds known as hydroxybenzoic acids, or even more preferentially a coformer such as 3-hydroxy-2-naphthoic acid.

Description of the invention

The present invention relates to the solid state structures of (IS,2S,3R,5S)-3-[7-[(l/?,2S)-2-(3,4-Difluorophenyl)cyclopropylamino]-5-(propylthio)-3H-[l,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-l,2-diol (hereafter referred to as Ticagrelor) in the form of a stable co-crystal solid form as well as a 1,4-dioxane solvate. By the appropriate use of the anhydrous or solvated forms of the API, it is possible to modulate and ensure consistency in the physicochemical properties of the active pharmaceutical ingredient. According to EP1289992, ticagrelor has four polymorphs of which Form I is the most stable with a melting point of 146-152 °C. However Form II is used in the drug product and this polymorph is known to have a melting point in the range 136-139°C. Forms I and II interconvert upon heating/cooling and this is illustrated in Figure 2.

The present invention relates to a 1,4-dioxane solvate of ticagrelor.

More specifically the invention relates to the crystalline form of the 1,4-dioxane solvate of ticagrelor which has the characteristic X-ray powder diffraction (XRPD) peaks listed in Table 1 and the XRPD diffraction pattern shown in Figure 3. The 1,4-dioxane solvate of ticagrelor was characterised by gas chromatographic residual solvent analysis, which showed that there was approximately 24.37% of 1,4-dioxane by mass, suggesting a 2:1 molar stoichiometric ratio of l,4-dioxane:ticagrelor. The characteristic X-ray powder diffraction peaks for 1,4-dioxane solvate of ticagrelor are 5,1; 15,3; 17,2; 19,3; 20,4; 25,6 a 30,8 ± 0,2° 2Θ. The HPLC-determined purity of the solvate (98.4%) is comparable to that of ticagrelor Form II (98.8%). The 1,4-dioxane solvate of ticagrelor has a greater stability than ticagrelor Form II as illustrated by a melting point approximately 14°C higher. Differential Scanning Calorimetry (DSC) measurements have shown that the solvate melts at an onset temperature of approximately 148 °C (Figure 4) when compared to the onset of melting for Form II ticagrelor at 134 °C.

Table 1: Table of diffraction peaks for the 1,4-dioxane solvate of ticagrelor.

Pos. [°2Th.]	d-spacing [A]	Rel. Int. [%]
5,08	17,375	100,0
9,40	9,402	0,7
10,16	8,702	1,2
10,59	8,351	1,2
14,70	6,020	1,6
15,27	5,797	2,8
17,23	5,141	2,5
19,32	4,591	3,7
20,42	4,345	18,6
25,62	3,475	2,5
30,87	2,894	6,6
33,43	2,679	0,8
34,40	2,605	1,1

Characteristic peaks: 5,1; 15,3; 17,2; 19,3; 20,4; 25,6 a 30,8 ± 0,2° 2-theta.

According to the present invention is provided a process for preparation of 1,4-dioxane solvate which comprises a crystallization of ticagrelor solution or suspension in 1,4-dioxane in the temperature in the range of 20-101 °C for sufficient time to convert to the crystalline solvate. Temperature is optimally in the range of 30-101°C and the most optimally by heating to 50 °C followed by precipitation by cooling to room temperature. It means the temperature in the range of 18-25°C. For preparation of the solvate can be used all known forms of ticagrelor, for example form I or form II, III or IV as described in EP1289992. The amorphous form could be also used.

The ticagrelor 3-hydroxy-2-naphthoic acid cocrystal has the characteristic XRPD peaks listed in Table 2 and XRPD diffraction pattern is shown in Figure 5. The characteristic X-ray powder diffraction peaks for the cocrystal are 3,6; 7,2; 9,3; 14,3; 16,2; 18,7 a 24,5 ± 0,2° 2Θ. The cocrystal has an onset of melting of 136 °C, which is approximately 2 °C higher than the onset of melting for ticagrelor Form II. The HPLC purity of the cocrystal is also high at 97.9%. One of the advantageous of formulating ticagrelor as a cocrystal can be seen in its polymorphic behavior relative to ticagrelor API. Polymorphism, the ability of a compound to crystallize in more than one crystal form represents a major challenge to the pharmaceutical industry when it occurs unexpectedly. A case in point is Ritonavir (Norvir), an antiretroviral drug from the protease inhibitor class that is used to treat HIV infection and AIDS. The chemical structure of the API in the original Norvir capsules was known to exhibit conformational polymorphism, with the different polymorphs exhibiting different physical properties. The therapeutically active polymorph of Ritonavir used in the original formulation was the metastable polymorph, which readily converted to the stable polymorph [Bauer *et al, Pharmaceutical*

Research, **18**(6), 2001, 859-866.] exhibiting poor solubility and poor bioavailability. This polymorphic transformation was not foreseen by the developers of Norvir and caused significant challenges. In the case of Ticagrelor, a similar challenge exists. Namely, the polymorphic Form II used in the drug product is a metastable form, which readily transforms via a reversible temperature induced phase transition to the thermodynamically more stable Form I upon heating. In a similar light to Ritonavir, Ticagrelor also exhibits significant conformational flexibility, making it susceptible to polymorphic changes as a function of crystallisation conditions (principally the temperature and solvent). The cocrystal of ticagrelor and 3-hydroxy-2-naphthoic acid allows for better control of the solid state properties as it is not susceptible to polymorphic changes as a function of temperature and solvent (the latter being limited by time and availability). As far as the temperature-induced polymorphic behavior of the cocrystal is concerned, Figure 6 shows the DSC trace of the cocrystal which exhibits only one endotherm corresponding to the melting point of the cocrystal. Moreover, the cocrystal was shown not to be polymorphic - within the limitations of manual crystallisation techniques - as a function of the crystallisation solvent according to the results of extensive solution crystallisation experiments using different solvents. This is illustrated by Figure 7, which shows identical PXRD patterns of the cocrystal when crystallized ticagrelor is crystallised with 1 equivalent of 3-hydroxy-2-naphthoic acid from suitable solvent at temperature in the range of 20-65°C. As suitable common solvents are used for example water, nitromethane, ethanol, propanol, diethylether, 2-butanol, cyclohexane, dichloromethane, acetone, methylethylketone, 1,2-dimethyoxyethane, ethylformate, methylacetate, propylacetate, isopropylacetate, trichloroethylene, tetrahydrofuran (THF) or acetonitrile or their mixtures. For preparation of the cocrystal can be used all known forms of ticagrelor, for example form I or form II, III or IV as described in EP1289992. The amorphous form could be also used.

The final added benefit of formulating ticagrelor as a cocrystal relates to the superior water sorption stability of the cocrystal relative to the API at elevated % relative humidity values. According to Figure 8, at a relative humidity value of 80% (25 °C isotherm), the cocrystal has a water content of 3.2% by mass and this compares to 3.7% for Ticagrelor Form II. At 90% relative humidity, the cocrystal was found to have a water content of approximately 13.2% by mass when compared to 16.8% for Ticagrelor Form II. Both samples are stable to water uptake up to 60% relative humidity.

Table 2: Table of diffraction peaks for the ticagrelor 3-hydroxy-2-naphthoic acid cocrystal.

Pos. [°2Th.]	d-spacing [A]	Rel. Int. [%]
3,58	24,654	95,6
5,19	17,025	13,2
7,15	12,353	51,0
9,33	9,472	100,0
13,43	6,586	19,2
14,33	6,178	36,7
16,22	5,459	52,7
18,70	4,741	51,1
19,44	4,563	5,1
20,54	4,321	5,1
21,59	4,113	13,1
22,93	3,876	6,1
24,50	3,631	34,7
25,32	3,514	12,4
25,78	3,453	7,1
26,49	3,363	6,7
29,00	3,040	9,4

Characteristic peaks: 3,6; 7,2; 9,3; 14,3; 16,2; 18,7 a 24,5 ± 0,2° 2-theta.

In a further aspect of invention, the solvate and the cocrystal according to this invention could be used directly to the pharmaceutical composition or as an intermediate for preparation of a pharmaceutically accepted form.

Brief Description of Drawings:

Figure 1: XRPD pattern of ticagrelor Form II.

Figure 2: DSC trace for ticagrelor Form II.

Figure 3: XRPD pattern of the 1,4-dioxane solvate of ticagrelor.

Figure 4: DSC trace for the 1,4-dioxane solvate of ticagrelor.

Figure 5: XRPD pattern of the ticagrelor 3-hydroxy-2-naphthoic acid cocrystal.

Figure 6: DSC trace for the ticagrelor 3-hydroxy-2-naphthoic acid cocrystal.

Figure 7: Overlay of the PXRD patterns from crystallisations of ticagrelor 3-hydroxy-2-naphthoic acid cocrystal in different solvents. The overlay illustrates lack of polymorphism for the cocrystal.

Figure 8: Comparison of the sorption-desorption isotherms (25 °C) for a) Ticagrelor 3-hydroxy-2-naphthoic acid and b) Ticagrelor Form II.

Examples

In the following examples samples were evaluated with the X-ray diffraction analysis using the following procedure:

The diffraction pattern was obtained in an X' PERT PRO MPD PANalyticai powder diffracto meter with a graphite monochromator, radiation used CuKct (λ=1.542 **A),** excitation voltage: 45 kV, anode 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 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 HCI 50-250 °C at the rate of 10 °C/min).

Carrier gas: N_2 20 ml/min.

An amount of solvent was evaluated with Gas chromatography (GC) in a Agilent 7890 with FI detection

Chromatographic conditions:

Capillary column:	DB-624 (30 m, 0.53 mm ID, 3.0 μηι df) or equivalent
Temperature program:	70 °C - 2 min, gradient 10 °C /min to 170 °C - 0 min,
Carrier gas:	*helium*
Injection:	1 μI
Injector:	200 °C, split ratio 5:1

Detector: FID, 260 °C

Example 1: Method for the preparation of ticagrelor 1,4-dioxane solvate

700mg of Ticagrelor was placed in a 50ml round-bottomed flask. To this was added 15 ml of 1,4-Dioxane. The contents of the flask were heated to 50 ° C. The contents of the flask were allowed to cool to 30 ° C before heating once again to 50 ° C. After cooling down to room temperature one final time, approximately 40ml of the solvent was distilled off. The contents of the flask were then stirred for 2 hours in an ice-bath until crystallisation was induced. Yield: 664 mg (94.86 % of the theoretical maximum). HPLC Purity: 98.4%.

The sample was characterised with powder X-ray and list of characteristic peaks is given in Table 1.

Example 2: Method for the preparation of ticagrelor 3-hydroxy-2-naphthoic acid cocrystal

Approximately 870mg of Ticagrelor Form II was placed inside a 100ml capacity round-bottomed flask. To this was added 312mg (lmol equiv.) of 3-hydroxy-2-naphthoic acid. The flask was fitted with an air condenser and thermometer. To the contents of the flask was added 50ml of MeOH. The resulting suspension was heated to a temperature of 50 ° C. The contents of the flask were allowed to cool down to 40 ° C and then heated once again to 50 ° C under reflux. A condenser for distillation was attached to the round-bottomed flask and the suspension heated to approximately 60 ° C so as to distil approximately 90% of the methanol by volume. The thick suspension that remained was stirred and allowed to cool under an ice-bath for 1 hour. Rapid precipitation was observed. Yield: 1.15g (97.29% of the theoretical maximum). HPLC Purity: 97.9% .

The sample was characterised with powder X-ray and list of characteristic peaks is given in Table 2.

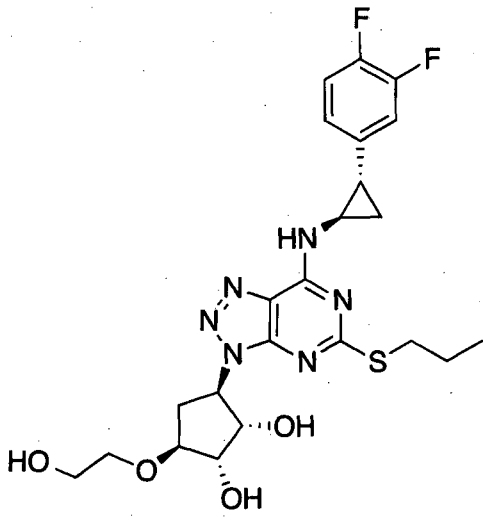
Example 3: Preparation of ticagrelor 3-hydroxy-2-naphthoic acid cocrystal from a range of solvents via slurrying

Approximately 40mg of Ticagrelor Form II was placed inside a 1ml capacity vial. To this was added 14.34mg (lmol equiv.) of 3-hydroxy-2-naphthoic acid. To the vial was added 1ml of one of the following solvents to create a saturated suspension: Water, nitromethane, ethanol, propanol, diethylether, 2-butanol, cyclohexane, dichloromethane, acetone, methylethylketone, 1,2-

dimethyoxyethane, ethylformate, methylacetate, propylacetate, isopropylacetate, trichloroethylene, THF or acetonitrile. The contents of the vial were placed inside a HLC Thermomixer (Model No: MHR 23). The temperature of the slurry was kept constant at 35 °C and agitation of 900rpm for 9 days so as to investigate any solvent induced polymorphic transformations. The crystalline samples were evaluated with X-ray powder diffractions. Patterns from all samples comply with X-ray pattern measured in Example 2. In Figure 7 is shown patterns from chosen solvents.

Claims

1. A solvate of Ticagrelor of formula (I)



(I)

with 1,4-dioxane.

2. A solvate as claimed in claim 1, characterised by an X-ray powder diffraction pattern measured using CuKa, containing specific peaks of high intensity at : 5,1; 15,3; 17,2; 19,3; 20,4; 25,6 a 30,8 ± 0,2° 2-theta.

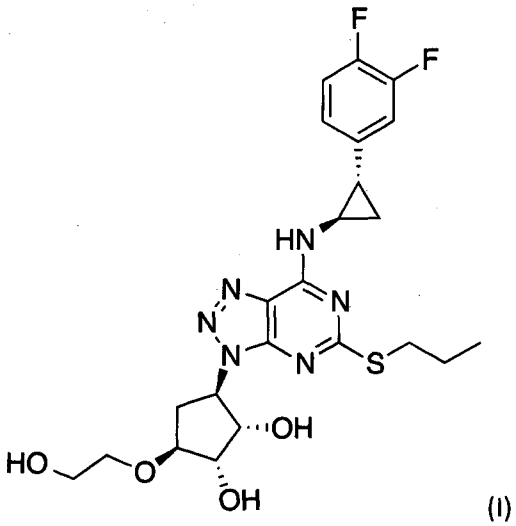
3. A solvate as claimed in claim 1 or 2, characterised in that a mass of 1,4 dioxane is in the 2:1 molar stoichiometric ratio.

4. A solvate as claimed in any one of claims 1, 2 or 3, characterised by a differential scanning calorimetry curve having an onset melting which at approximately 148°C.

5. A process for the preparation of a solvate as claimed in claim 1, wherein ticagrelor is crystallised from 1,4-dioxane at a temperature in the range of 20-101 °C.

6. A process for the preparation of a solvate as claimed in claim 5, wherein ticagrelor is crystallised from 1,4-dioxane by heating to 50 °C, followed by precipitation by cooling to room temperature.

7. A cocrystal of Ticagrelor of formula (I)



(I)

with 3-hydroxy-2-naphthoic acid.

8. A cocrystal as claimed in claim 7, characterised by an X-ray powder diffraction pattern measured using CuKa, containing specific peaks of high intensity at 3,6; 7,2; 9,3; 14,3; 16,2; 18,7 a 24,5 ± 0,2° 2-theta.

9. A cocrystal as claimed in claim 7 or 8, characterised in that a mass of 3-hydroxy-2-naphthoic acid to ticagrelor is in the 1:1 molar stoichiometric ratio.

10. A cocrystal as claimed in any one of claims 7, 8 or 9, characterised by an differential scanning calorimetry curve having an onset melting which at approximately 136°C.

11. A process for the preparation of a cocrystal as claimed in claim 7, wherein ticagrelor is crystallised with 3-hydroxy-2-naphthoic acid from a suitable solvent at a temperature in the range of 20-65°C.

12. A process as claimed in claim 11, wherein the solvent is selected from the group consisting of water, nitromethane, ethanol, propanol, diethylether, 2-butanol, cyclohexane, dichloromethane, acetone, methylethylketone, 1,2-dimethyoxyethane, ethylformate, methylacetate, propylacetate, isopropylacetate, trichloroethylene, THF and acetonitrile.

13. Use of a solvate as claimed in claim 1 for preparation of a pharmaceutical composition.

14. Use of a cocrystal as claimed in claim 7 for preparation of a pharmaceutical composition.

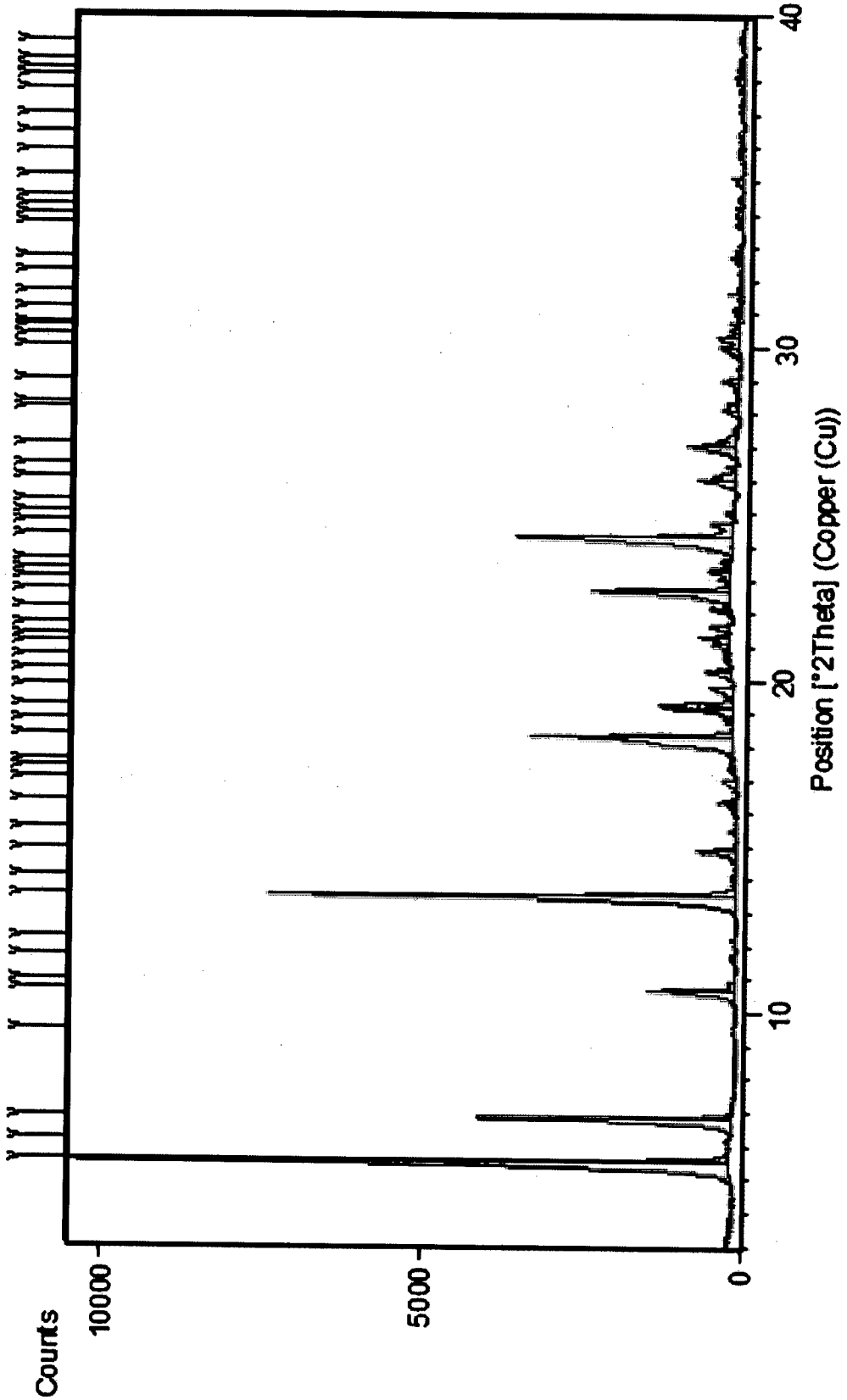
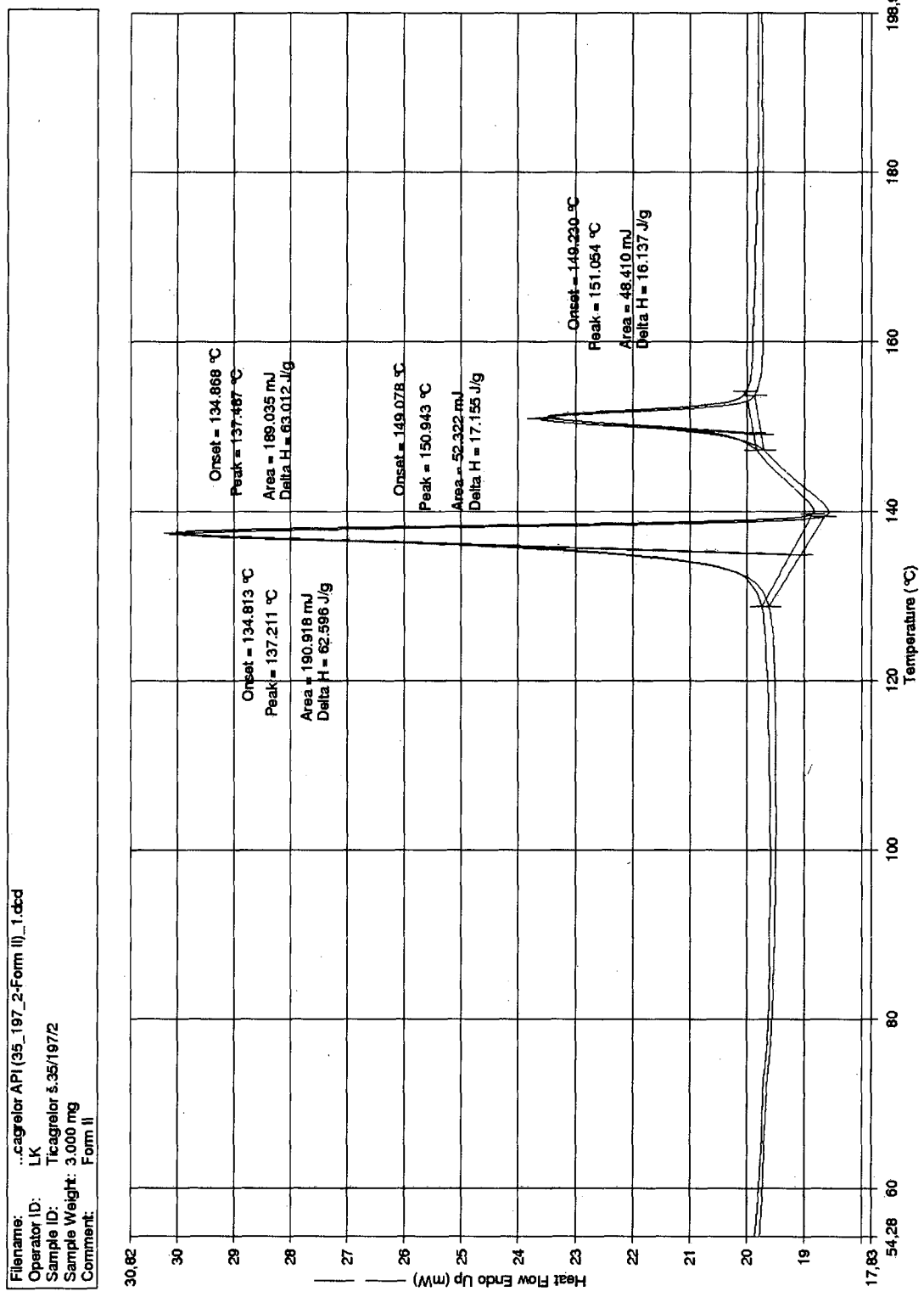


Figure 1

Figure 2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Comment: Form II
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Peak = 137.467 °C
Area = 189.035 mJ
Delta H = 63.012 J/g
Onset = 134.813 °C
Peak = 137.211 °C
Area = 190.918 mJ
Delta H = 62.596 J/g
Onset = 149.078 °C
Peak = 150.943 °C
Area = 52.322 mJ
Delta H = 17.155 J/g
Onset = 149.230 °C
Peak = 151.054 °C
Area = 48.410 mJ
Delta H = 16.137 J/g
Heat Flow Endo Up (mW)
Temperature (°C)
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60
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100
120
140
160
180

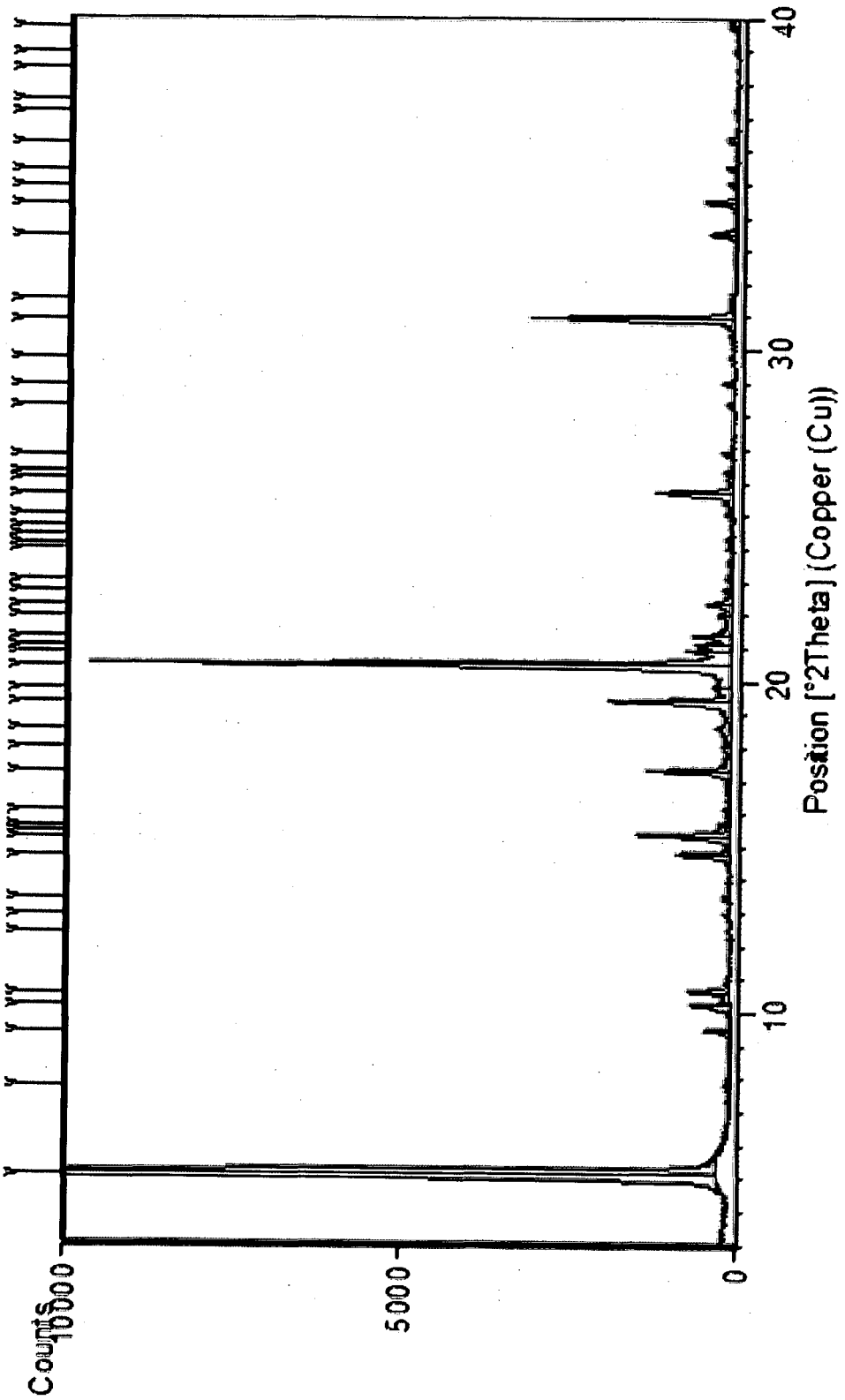


Figure 3

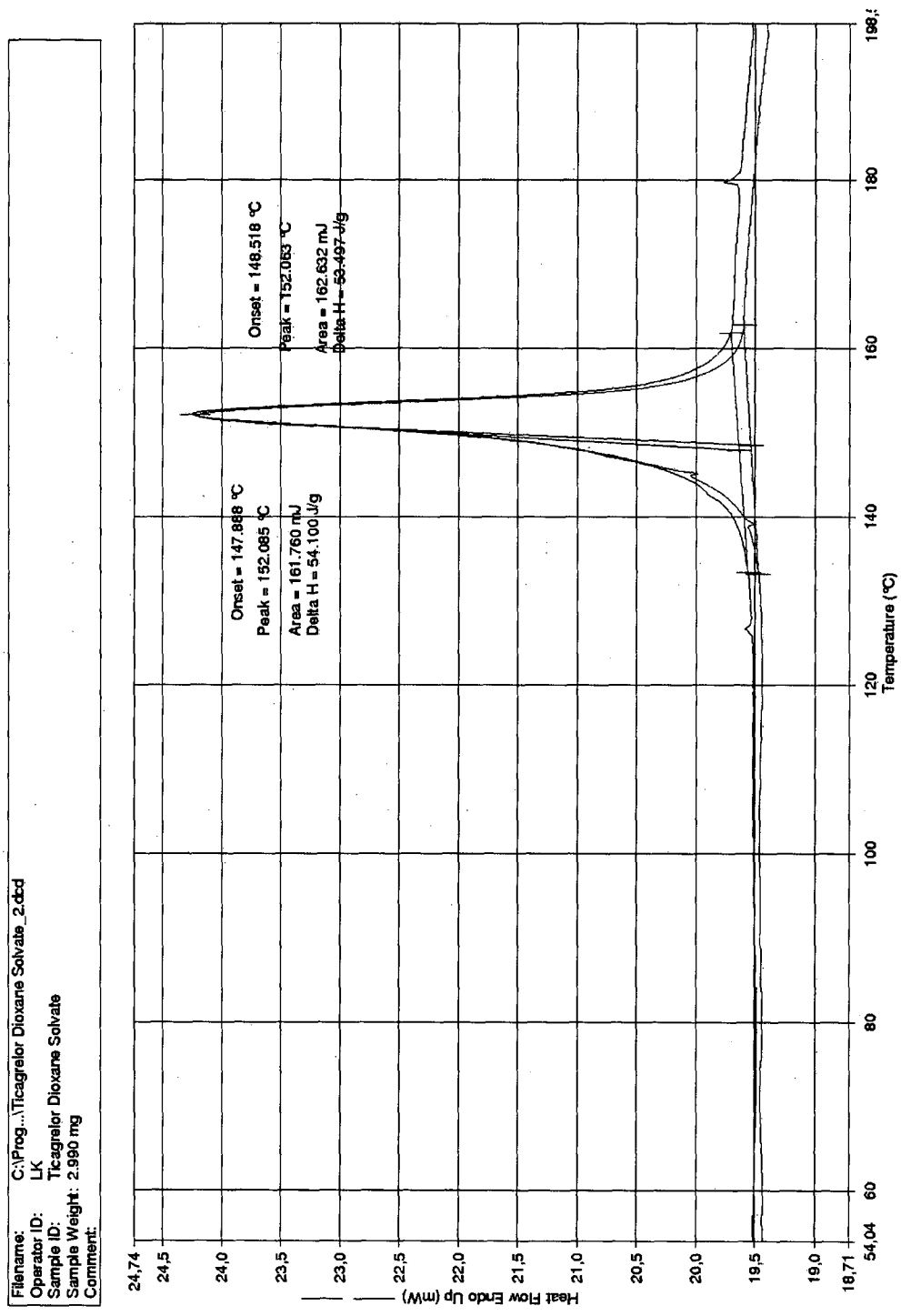

Filename: C:\Prog...\Ticagrelor Dioxane Solvate_2.dsd
Operator ID: LK
Sample ID: Ticagrelor Dioxane Solvate
Sample Weight: 2.990 mg
Comment:
Onset = 147.868 °C
Peak = 152.085 °C
Area = 161.760 mJ
Delta H = 54.100 J/g
Onset = 148.518 °C
Peak = 152.063 °C
Area = 162.632 mJ
Delta H = 54.497 J/g
Heat Flow Endo Up (mW)
Temperature (°C)
24,74
24,5
24,0
23,5
23,0
22,5
22,0
21,5
21,0
20,5
20,0
19,5
19,0
18,71
54,04
60
80
100
120
140
160
180

Figure 4

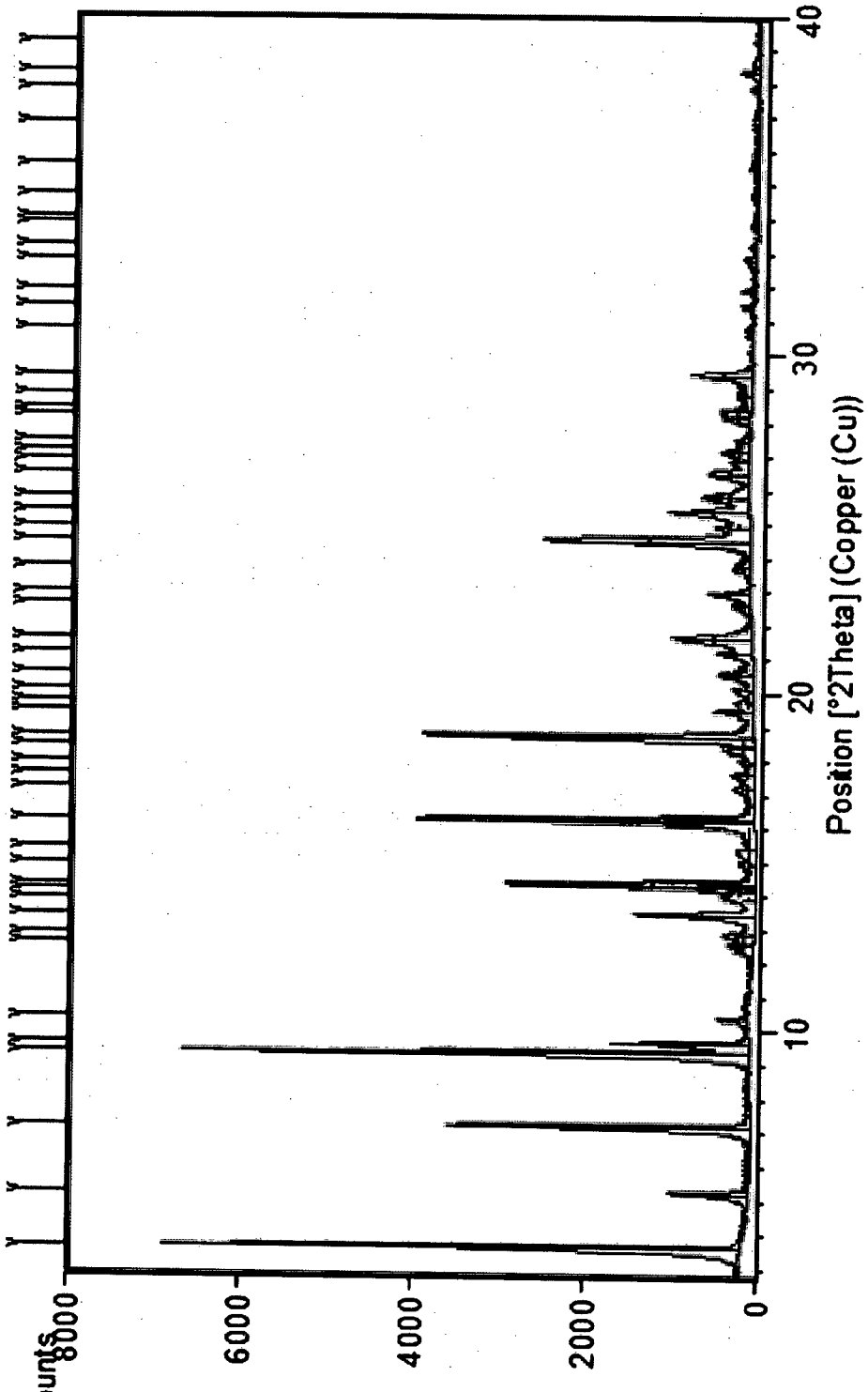

Counts
8000
6000
4000
2000
0
10
20
30
40
Position [°2Theta] (Copper (Cu))

Figure 5

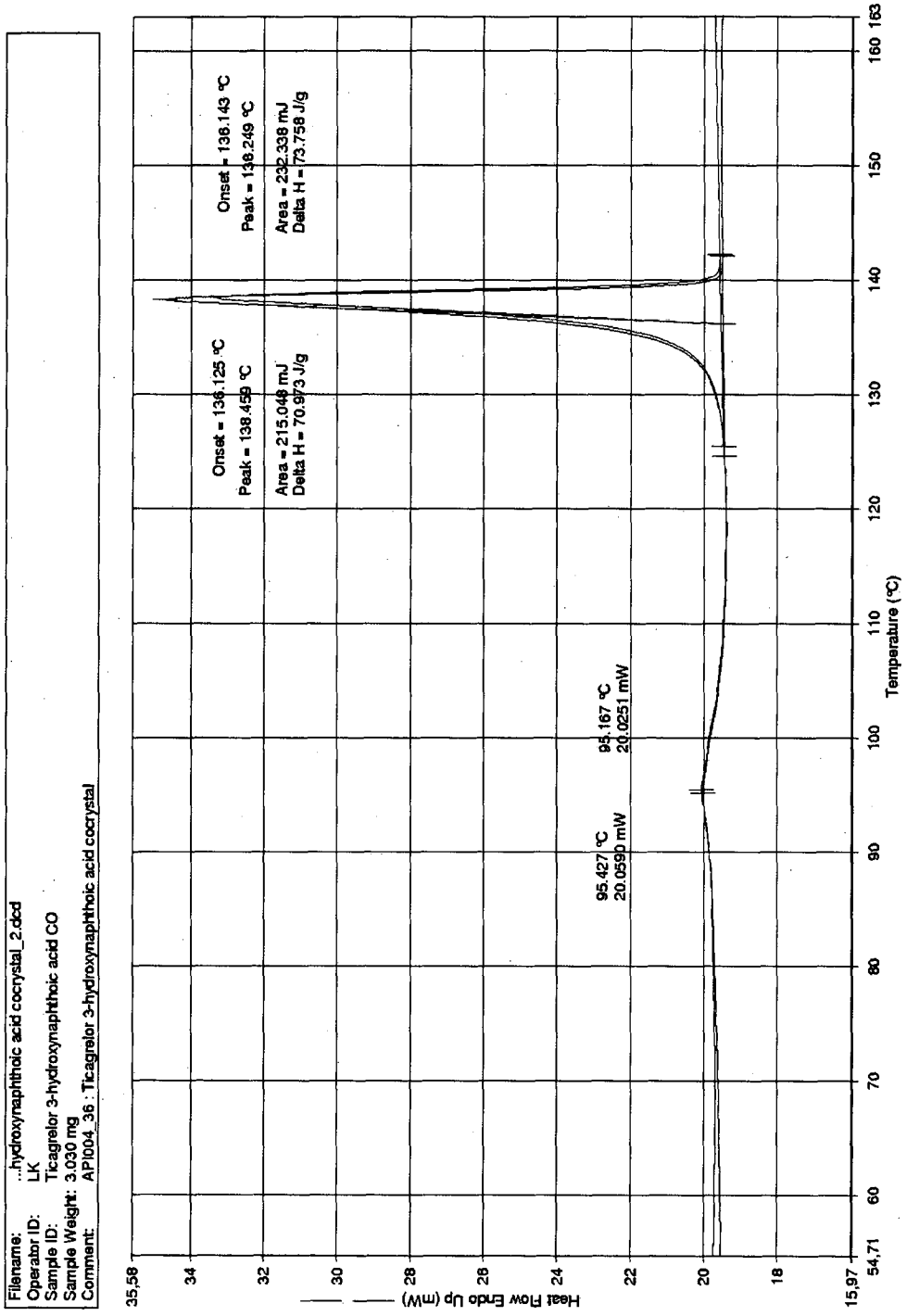

Filename: ...hydroxynaphthoic acid cocrystal_2.dcd
Operator ID: LK
Sample ID: Ticagrelor 3-hydroxynaphthoic acid CO
Sample Weight: 3.030 mg
Comment: AP1004_36 : Ticagrelor 3-hydroxynaphthoic acid cocrystal
Onset = 136.125 °C
Peak = 138.459 °C
Area = 215.048 mJ
Delta H = 70.973 J/g
Onset = 136.143 °C
Peak = 138.249 °C
Area = 232.338 mJ
Delta H = 73.758 J/g
95.427 °C
20.0590 mW
95.167 °C
20.0251 mW
Heat Flow Endo Up (mW)
Temperature (°C)
35,58
34
32
30
28
26
24
22
20
18
15,97
54,71
60
70
80
90
100
110
120
130
140
150
160
163

Figure 6

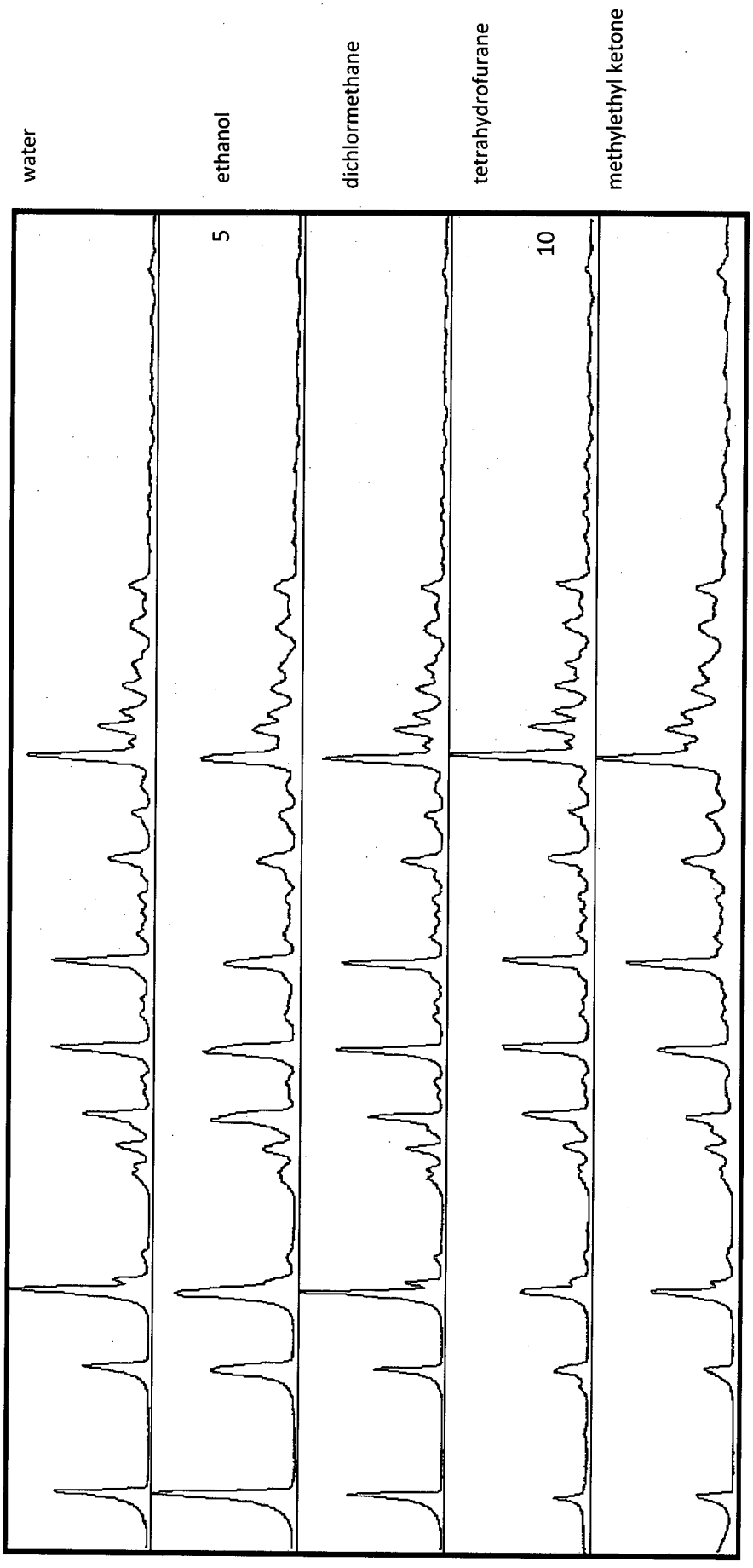
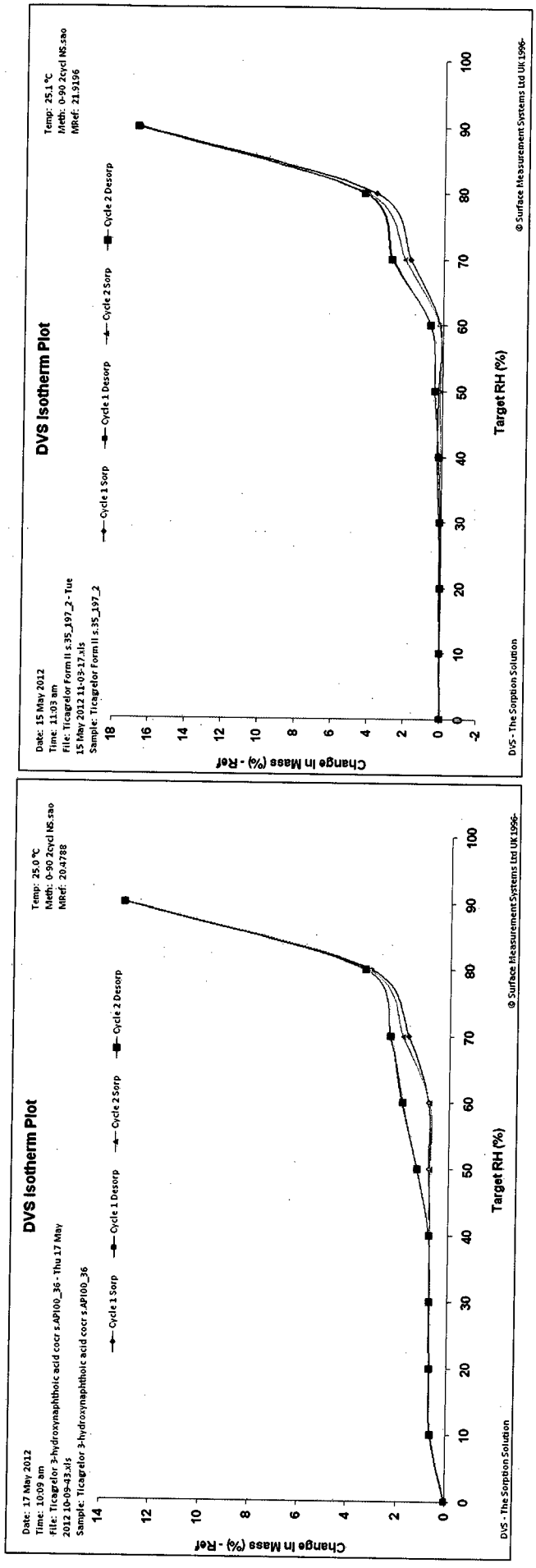

water
ethanol
dichlormethane
tetrahydrofurane
methylethyl ketone
5
10

Figure 7

Figure 8



a) Water Sorption-Desorption Isotherm for Ticagrelor Cocrystal

b) Water Sorption-Desorption Isotherm for Ticagrelor Form II

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2012/0OQ059

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/5 19 A61 P7/02
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 A61 K A61P

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 practicable, search terms used)
EPO-Internal , WPI Data, 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 QO/34283 Al (ASTRAZEN ECA UK LTD [GB] ; ASTPsAZEN ECA AB [SE] ; GUILE SIMON [GB] ; HARDER) 15 June 200Q (2000-06 - 15) cited in the appli cati on the whole document	1-6, 13
X	WO 01/92262 Al (ASTRAZEN ECA AB [SE] ; BOHLIN MARTIN [SE] ; C0SGR0VE STEVE [GB] ; LASSEN B) 6 December 200 1 (2001 - 12-06) cited in the appli cati on the whole document	1-6, 13
X	W0 2011/06757 1 Al (ASTRAZ ENECA AB [SE] ; ASTRAZEN ECA UK LTD [GB] ; C0SGR0VE STEPHEN DAVID [) 9 June 201 1 (2011-06 -09) cited in the appli cati on the whole document	1-14

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

☒ 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 application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) orwhich 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
14 May 2013	28/05/2013

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	de Nooy, Arjan

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CZ2012/00Q059

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos. :

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-6, 13

A solvate of Ticagrelor with 1,4-dioxane.

---

2. claims: 7-12, 14

A cocrystal of Ticagrelor with 3-hydroxy-2-naphthoic acid.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/CZ2012/0OQ059

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Information on patent family members

International application No
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