

(19) **DANMARK**

(10) **DK/EP 3515924 T3**



(12)

## Oversættelse af europæisk patentskrift

Patent- og  
Varemærkestyrelsen

- 
- (51) Int.Cl.: **C 07 F 9/6558 (2006.01)** **A 61 K 31/675 (2006.01)** **A 61 P 9/00 (2006.01)**
- (45) Oversættelsen bekendtgjort den: **2022-03-21**
- (80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2021-12-15**
- (86) Europæisk ansøgning nr.: **17771436.7**
- (86) Europæisk indleveringsdag: **2017-09-21**
- (87) Den europæiske ansøgnings publiceringsdag: **2019-07-31**
- (86) International ansøgning nr.: **EP2017073858**
- (87) Internationalt publikationsnr.: **WO2018055016**
- (30) Prioritet: **2016-09-22 WO PCT/EP2016/072562**
- (84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**
- (73) Patenthaver: **Idorsia Pharmaceuticals Ltd, Hegenhaimermattweg 91, 4123 Allschwil, Schweiz**
- (72) Opfinder: **LEUENBERGER, Daniel, c/o Idorsia Pharmaceuticals Ltd., Hegenhaimermattweg 91, 4123 Allschwil, Schweiz**  
**REBER, Stefan, c/o Idorsia Pharmaceuticals Ltd., Hegenhaimermattweg 91, 4123 Allschwil, Schweiz**  
**VON RAUMER, Markus, c/o Idorsia Pharmaceuticals Ltd., Hegenhaimermattweg 91, 4123 Allschwil, Schweiz**
- (74) Fuldmægtig i Danmark: **Plougmann Vingtoft A/S, Strandvejen 70, 2900 Hellerup, Danmark**
- (54) Benævnelse: **KRYSTALLINSKE FORMER**
- (56) Fremdragne publikationer:  
**WO-A1-2009/069100**  
**BALDONI DANIELA ET AL: "A New Reversible and Potent P2Y12 Receptor Antagonist (ACT-246475): Tolerability, Pharmacokinetics, and Pharmacodynamics in a First-in-Man Trial", CLINICAL DRUG INVESTIGATION, ADIS INTERNATIONAL, AUCKLAND, NZ, vol. 34, no. 11 1 November 2014 (2014-11-01), pages 807-818, XP009500681, ISSN: 1173-2563, DOI: 10.1007/S40261-014-0236-8 Retrieved from the Internet: URL: <http://link.springer.com/10.1007/s40261-014-0236-8> [retrieved on 2014-10-21] cited in the application**  
**EVA CAROFF ET AL: "4-((R)-2-[[6-((S)-3-Methoxypyrrolidin-1-yl)-2-phenylpyrimidin-4-carbonyl]amino]-3-phosphonopropionyl)piperazine-1-carboxylic Acid Butyl Ester (ACT-246475) and Its Prodrug (ACT-281959), a Novel P2Y12 Receptor Antagonist with a Wider Therapeutic Window in the Rat Than Clopidogrel", JOURNAL OF MEDICINAL CHEMISTRY, vol. 58, no. 23, 10 December 2015 (2015-12-10), pages 9133-9153, XP055414260, ISSN: 0022-2623, DOI: 10.1021/acs.jmedchem.5b00933 cited in the application**



## DESCRIPTION

**[0001]** The invention relates to novel crystalline forms of 4-((*R*)-2-{[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester hydrochloride (hereinafter also referred to as "COMPOUND·HCl"), processes for the preparation thereof, pharmaceutical compositions comprising said crystalline forms, pharmaceutical compositions comprising 4-((*R*)-2-{[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester (hereinafter also referred to as "COMPOUND") wherein COMPOUND is obtained from said crystalline forms of COMPOUND·HCl, pharmaceutical compositions prepared from such crystalline forms of COMPOUND·HCl, use of the crystalline forms of COMPOUND·HCl as P2Y<sub>12</sub> receptor antagonists in the treatment of various P2Y<sub>12</sub> receptor-mediated diseases and disorders and use of COMPOUND as P2Y<sub>12</sub> receptor antagonist in the treatment of various P2Y<sub>12</sub> receptor-mediated diseases and disorders wherein COMPOUND is obtained from said crystalline forms of COMPOUND·HCl.

### **Background of the invention:**

**[0002]** The circulation of blood from and to organs guarantees the supply of oxygen, nutrients, as well as the disposal of catabolic products. Therefore, the integrity of blood vessels is essential at all times. When the vascular integrity is compromised, a highly efficient repair mechanism is activated at the site of injury resulting in the formation of a repair seal to prevent further blood loss. This fundamental biological process is defined as hemostasis. Thrombosis is the result of a pathological deviation of one or several components involved in hemostasis leading to uncontrolled platelet thrombus formation and vessel occlusion. Platelets have been described to contribute to hemostasis and thrombosis since their discovery (Coller BS, Historical perspective and future directions in platelet research. J Thromb Haemost. 2011;9 Suppl 1:374-395). More recently, atherosclerotic lesions in combination with occlusive platelet thrombi have been found in patients with ischemic cardiac death (Davies MJ et al., Intramyocardial platelet aggregation in patients with unstable angina suffering sudden ischemic cardiac death. Circulation. 1986;73:418-427).

**[0003]** Inhibition of platelet aggregation is recognized as an effective strategy for the prevention of thrombosis in patients with atherosclerotic disease in the coronary (Jneid H et al., 2012 accf/aha focused update of the guideline for the management of patients with unstable angina/non-st-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): A report of the american college of cardiology foundation/american heart association task force on practice guidelines. J Am Coll Cardiol. 2012;60:645-681; O'Gara PT et al., 2013 accf/aha guideline for the management of st-elevation myocardial infarction: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. Circulation. 2013;127:e362-425), peripheral (Jagroop IA et

al., The effect of clopidogrel, aspirin and both antiplatelet drugs on platelet function in patients with peripheral arterial disease. *Platelets*. 2004;15:117-125; Matsagas M et al., The effect of a loading dose (300 mg) of clopidogrel on platelet function in patients with peripheral arterial disease. *Clin Appl Thromb Hemost*. 2003;9:115-120), and cerebrovascular circulation (Liu F et al., P2Y<sub>12</sub> receptor inhibitors for secondary prevention of ischemic stroke. *Expert Opin Pharmacother*. 2015;16:1149-1165). Inhibition of P2Y<sub>12</sub> as an antiplatelet approach was validated in multiple clinical studies. Several P2Y<sub>12</sub> antagonists have been demonstrated to effectively reduce the risk of adverse cardiovascular events in patients with acute coronary syndromes (ACS) and patients undergoing percutaneous coronary intervention (PCI) (Cattaneo M, The platelet P2Y<sub>12</sub> receptor for adenosine diphosphate: Congenital and drug-induced defects. *Blood*. 2011;117:2102-2112; Thomas MR et al., The future of P2Y<sub>12</sub> receptor antagonists. *Platelets*. 2015;26:392-398; Wiviott SD et al., Clinical evidence for oral antiplatelet therapy in acute coronary syndromes. *Lancet*. 2015;386:292-302; Wallentin L, P2Y<sub>12</sub> inhibitors: Differences in properties and mechanisms of action and potential consequences for clinical use. *Eur Heart J*. 2009;30:1964-1977). In current treatment guidelines, P2Y<sub>12</sub> antagonists define the cornerstone therapy for patients with ACS (Jneid H et al., 2012 accf/aha focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): A report of the american college of cardiology foundation/american heart association task force on practice guidelines. *J Am Coll Cardiol*. 2012;60:645-681; O'Gara PT et al., 2013 accf/aha guideline for the management of ST-elevation myocardial infarction: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. *Circulation*. 2013;127:e362-425).

**[0004]** Three indirect P2Y<sub>12</sub> antagonists of the thienopyridine family, which block the ADP-induced platelet activation and aggregation, have reached the market: the orally active ticlopidine, clopidogrel and prasugrel. In addition, two direct P2Y<sub>12</sub> antagonists, which do not require metabolic activation and therefore display faster on- and offset of action, have received market approval: the nucleotide analogues ticagrelor and cangrelor.

**[0005]** 4-((*R*)-2-([6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-amino)-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester is a potent, reversible, and selective P2Y<sub>12</sub> receptor antagonist (Caroff E et al., *J. Med. Chem.* 2015;58:9133-9153; WO 2009/069100). Its hydrochloride salt was used as a powder in a first-in-man clinical trial (Baldoni et al., *Clinical Drug Investigation* 2014;34:807-818).

**[0006]** Despite the fact that many attempts failed to crystallize COMPOUND·HCl from several solvents in a mono-phase solvent system, it surprisingly has been found that a crystallization took place in certain heterogeneous solvent systems. The obtained crystalline forms of COMPOUND·HCl may have advantageous properties in view of the potential use of COMPOUND·HCl or COMPOUND as active pharmaceutical ingredient. Such advantages may include higher purity; better storage stability; better flow properties; less hygroscopicity; better reproducibility in manufacturing (for example better filtration parameters, better reproducibility

of formation, and/or better sedimentation); and/or defined morphology. Such crystalline forms of COMPOUND·HCl may be particularly suitable in a process of manufacturing certain pharmaceutical compositions.

### Description of the Figures

#### [0007]

Fig. 1 shows the X-ray powder diffraction diagram of COMPOUND·HCl in the crystalline form 1, wherein the X-ray powder diffraction diagram is displayed against Cu K $\alpha$  radiation. The X-ray diffraction diagram shows peaks having a relative intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensities given in parenthesis) at the indicated angles of refraction 2theta (selected peaks from the range 3-30° 2theta with relative intensity larger or equal than 10% are reported): 4.0° (100%), 5.0 (60%), 5.9° (23%), 11.7° (10%), 15.3° (13%), 19.3° (15%), 19.7° (11%), and 20.7° (10%).

Fig. 2 shows the X-ray powder diffraction diagram of COMPOUND·HCl in the crystalline form 2, wherein the X-ray powder diffraction diagram is displayed against Cu K $\alpha$  radiation. The X-ray diffraction diagram shows peaks having a relative intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensities given in parenthesis) at the indicated angles of refraction 2theta (selected peaks from the range 3-30° 2theta with relative intensity larger or equal than 10% are reported): 5.2° (100%), 6.8° (26%), 8.0° (14%), 10.3° (66%), 10.8° (66%), 12.7° (10%), 15.4° (18%), 16.2° (13%), 20.3° (40%), 20.5° (28%), and 21.7° (13%).

Fig. 3 shows the X-ray powder diffraction diagram of COMPOUND·HCl in the crystalline form 3, wherein the X-ray powder diffraction diagram is displayed against Cu K $\alpha$  radiation. The X-ray diffraction diagram shows peaks having a relative intensity, as compared to the most intense peak in the diagram, of the following percentages (relative peak intensities given in parenthesis) at the indicated angles of refraction 2theta (selected peaks from the range 8-30° 2theta with relative intensity larger or equal than 10% are reported): 5.5° (100%), 7.2 (43%), 11.0° (51%), 11.5° (45%), 13.0° (10%), 14.4° (15%), 16.6° (51%), 18.1° (39%), 18.5° (27%), 21.1° (32%), 22.0° (37%), 23.1° (17%), 24.3° (16%) and 26.1° (10%).

In the X-ray diffraction diagrams of Fig. 1 to Fig. 3 the angle of refraction 2theta (2 $\theta$ ) is plotted on the horizontal axis and the counts on the vertical axis.

For avoidance of any doubt, the above-listed peaks describe the experimental results of the X-ray powder diffraction shown in Figures 1 to 3. It is understood that, in contrast to the above peak list, only a selection of characteristic peaks is required to fully and unambiguously characterize COMPOUND·HCl in the respective crystalline form of the present invention.

Fig. 4 shows the gravimetric vapour sorption behaviour in the range of 20 to 75% RH at 25°C (coming from low %RH and going to high %RH, i.e., sorption cycle) of COMPOUND·HCl in the crystalline form 1 as obtained from Example 1A.

Fig. 5 shows the gravimetric vapour sorption behaviour in the range of 20 to 75% RH at 25°C (coming from high %RH and going to low %RH, i.e., desorption cycle) of COMPOUND·HCl in the crystalline form 2 as obtained from Example 2.

Fig. 6 shows the gravimetric vapour sorption behaviour in the range of 20 to 75% RH at 25°C (coming from low %RH and going to high %RH, i.e., sorption cycle) of COMPOUND·HCl in the crystalline form 3 as obtained from Example 3A.

**[0008]** In the gravimetric vapour sorption diagrams of Figs. 4, 5, and 6 the relative humidity (% RH) is plotted on the horizontal axis and the mass change (% dm, dry basis) on the vertical axis.

### Detailed Description of the Invention

#### **[0009]**

- 1) A first embodiment of the invention relates to a crystalline form of 4-((*R*)-2-[[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-amino]-3-phosphonopropionyl)-piperazine-1-carboxylic acid butyl ester hydrochloride (COMPOUND·HCl), characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction  $2\theta$ : 4.0°, 5.0°, and 15.3° (form 1).

It is understood, that the crystalline forms according to embodiment 1) comprise COMPOUND·HCl in form of the hydrochloric acid (hydrochloride) salt. Furthermore, said crystalline form may comprise non-coordinated and / or coordinated solvent (especially non-coordinated and / or coordinated water). Coordinated solvent (especially coordinated water) is used herein as term for a crystalline solvate (especially a crystalline hydrate). For the avoidance of doubt, in this application the term "crystalline hydrate" encompasses non-stoichiometric hydrates. Likewise, non-coordinated solvent is used herein as term for physisorbed or physically entrapped solvent (definitions according to Polymorphism in the Pharmaceutical Industry (Ed. R. Hilfiker, VCH, 2006), Chapter 8: U.J. Griesser: The Importance of Solvates). It is further understood, that the crystalline form may contain different amounts of coordinated water as a function of relative humidity and that the X-ray powder diffraction diagram may thus vary with relative humidity. Crystalline form 1 in particular comprises about 0 to 3% of coordinated and/or non-coordinated water. Crystalline form 2 in particular comprises about 5 to 10% of coordinated and/or non-coordinated water. Crystalline form 3 in particular comprises about 2.5 to 8% of coordinated and/or non-coordinated water.

- 2) Another embodiment relates to a crystalline form of COMPOUND·HCl according to embodiment 1), characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction  $2\theta$ : 4.0°, 5.0°, 11.7°, 15.3°, and 19.3°.
- 3) Another embodiment relates to a crystalline form of COMPOUND·HCl according to embodiment 1), characterized by the presence of peaks in the X-ray powder diffraction

diagram at the following angles of refraction  $2\theta$ :  $4.0^\circ$ ,  $5.0^\circ$ ,  $5.9^\circ$ ,  $11.7^\circ$ ,  $15.3^\circ$ ,  $16.9^\circ$ ,  $19.3^\circ$ ,  $19.7^\circ$ , and  $20.7^\circ$ .

4. 4) Another embodiment relates to a crystalline form of COMPOUND·HCl according to embodiment 1), which essentially shows the X-ray powder diffraction pattern as depicted in Fig. 1.
5. 5) Disclosed herein is a crystalline form of COMPOUND·HCl according to embodiment 1), characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction  $2\theta$ :  $5.2^\circ$ ,  $6.8^\circ$ , and  $10.3^\circ$ .
6. 6) Also disclosed herein is a crystalline form of COMPOUND·HCl according to embodiment 1), characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction  $2\theta$ :  $5.2^\circ$ ,  $6.8^\circ$ ,  $10.3^\circ$ ,  $10.8^\circ$ , and  $15.4^\circ$ .
7. 7) Also disclosed herein is a crystalline form of COMPOUND·HCl according to embodiment 1), characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction  $2\theta$ :  $5.2^\circ$ ,  $6.8^\circ$ ,  $8.0^\circ$ ,  $10.3^\circ$ ,  $10.8^\circ$ ,  $12.7^\circ$ ,  $15.4^\circ$ ,  $16.2^\circ$ ,  $20.3^\circ$ , and  $21.7^\circ$ .
8. 8) Also disclosed herein is a crystalline form of COMPOUND·HCl according to embodiment 1), which essentially shows the X-ray powder diffraction pattern as depicted in Fig. 2.
9. 9) Also disclosed herein is a crystalline form of COMPOUND·HCl according to embodiment 1), characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction  $2\theta$ :  $5.5^\circ$ ,  $11.0^\circ$ , and  $16.6^\circ$ .
10. 10) Also disclosed herein is a crystalline form of COMPOUND·HCl according to embodiment 1), characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction  $2\theta$ :  $5.5^\circ$ ,  $7.2^\circ$ ,  $11.0^\circ$ ,  $11.5^\circ$ , and  $16.6^\circ$ .
11. 11) Also disclosed herein is a crystalline form of COMPOUND·HCl according to embodiment 1), characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction  $2\theta$ :  $5.5^\circ$ ,  $7.2^\circ$ ,  $11.0^\circ$ ,  $11.5^\circ$ ,  $14.4^\circ$ ,  $16.6^\circ$ ,  $18.1^\circ$ ,  $21.1^\circ$ , and  $22.0^\circ$ .
12. 12) Also disclosed herein is a crystalline form of COMPOUND·HCl according to embodiment 1), which essentially shows the X-ray powder diffraction pattern as depicted in Fig. 3.
13. 13) Also disclosed herein is a crystalline form, such as an essentially pure crystalline form, of 4-((R)-2-{[6-((S)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester hydrochloride (COMPOUND·HCl) obtainable by:
  1. a. addition of aq. 33% HCl (5.1 vol.) to a solution of butyl 4-((R)-3-(diethoxyphosphoryl)-2-(6-((S)-3-methoxypyrrolidin-1-yl)-2-phenylpyrimidine-4-carboxamido)propanoyl)piperazine-1-carboxylate in a mixture of DCM and THF (5.5 vol.);
  2. b. stirring for 4 to 12h at a temperature of 20 to  $30^\circ\text{C}$ ;
  3. c. addition of water (8.2 vol.) and DCM (8.2 vol.) at a temperature of 20 to  $30^\circ\text{C}$ ;
  4. d. separation of layers and extraction with DCM (8.2 vol.);
  5. e. removal of solvent by distillation at  $T_i = 50^\circ\text{C}$ , addition of acetone (8.7 vol.) and further removal of solvent by distillation at  $T_i = 50^\circ\text{C}$  until a final amount of 7.0 vol.

remains;

6. f. addition of acetone (18.5 vol.) at  $T_i = 50^\circ\text{C}$ ;
  7. g. addition of water (0.5 vol.) at  $T_i = 50^\circ\text{C}$  within 30 min and stirring at  $T_i = 56^\circ\text{C}$  for 3.5h;
  8. h. cooling to 20 to  $30^\circ\text{C}$  within 2h and stirring at 20 to  $30^\circ\text{C}$  for 1.5h; and
  9. i. isolation of the obtained solid residue.
14. 14) Also disclosed herein is a crystalline form of COMPOUND·HCl according to embodiment 13), characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction  $2\theta$ :  $4.0^\circ$ ,  $5.0^\circ$ , and  $15.3^\circ$ .
  15. 15) Also disclosed herein is a crystalline form of COMPOUND·HCl according to embodiment 13), characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction  $2\theta$ :  $4.0^\circ$ ,  $5.0^\circ$ ,  $11.7^\circ$ ,  $15.3^\circ$ , and  $19.3^\circ$ .
  16. 16) Also disclosed herein is a crystalline form of COMPOUND·HCl according to embodiment 13), characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction  $2\theta$ :  $4.0^\circ$ ,  $5.0^\circ$ ,  $5.9^\circ$ ,  $11.7^\circ$ ,  $15.3^\circ$ ,  $16.9^\circ$ ,  $19.3^\circ$ ,  $19.7^\circ$ , and  $20.7^\circ$ .
  17. 17) Also disclosed herein is a crystalline form of COMPOUND·HCl according to embodiment 13), which essentially shows the X-ray powder diffraction pattern as depicted in Fig. 1.
  18. 18) Also disclosed herein is the crystalline form of COMPOUND·HCl according to any one of embodiments 1) to 4), obtainable by the process of embodiment 13).
  19. 19) Also disclosed herein is a crystalline form, such as an essentially pure crystalline form, of 4-((*R*)-2-{[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester hydrochloride (COMPOUND·HCl) obtainable by:
    1. a) equilibration of a sample of COMPOUND·HCl in a crystalline form according to any one of embodiments 1) to 4) at  $\text{RH} > 90\%$  and at about RT; and
    2. b) equilibration of the obtained sample at about  $\text{RH} = 40\%$  and at about RT.

Especially, the first equilibration step requires about 3 days and the second equilibration step requires about 1 day.

20. 20) Also disclosed herein is a crystalline form of COMPOUND·HCl according to embodiment 19), characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction  $2\theta$ :  $5.2^\circ$ ,  $6.8^\circ$ , and  $10.3^\circ$ .
21. 21) Also disclosed herein is a crystalline form of COMPOUND·HCl according to embodiment 19), characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction  $2\theta$ :  $5.2^\circ$ ,  $6.8^\circ$ ,  $10.3^\circ$ ,  $10.8^\circ$ , and  $15.4^\circ$ .
22. 22) Also disclosed herein is a crystalline form of COMPOUND·HCl according to embodiment 19), characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction  $2\theta$ :  $5.2^\circ$ ,  $6.8^\circ$ ,  $8.0^\circ$ ,  $10.3^\circ$ ,  $10.8^\circ$ ,  $12.7^\circ$ ,  $15.4^\circ$ ,  $16.2^\circ$ ,  $20.3^\circ$ , and  $21.7^\circ$ .
23. 23) Also disclosed herein is a crystalline form of COMPOUND·HCl according to embodiment 19), which essentially shows the X-ray powder diffraction pattern as depicted in Fig. 2.

24. 24) Also disclosed herein is the crystalline form of COMPOUND·HCl according to any one of embodiments 5) to 8), obtainable by the processes of embodiment 19).
25. 25) Also disclosed herein is a crystalline form, such as an essentially pure crystalline form, of 4-((*R*)-2-{[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester hydrochloride (COMPOUND·HCl) obtainable by:
1. a) equilibration of a sample of COMPOUND·HCl in a crystalline form according to any one of embodiments 5) to 8) in a dry nitrogen gas stream at about RT; and
  2. b) equilibration of the obtained sample at about RH = 40% and at about RT.

Especially, the first equilibration step requires about 1 day for a 100 mg sample at a gas stream of about 400 mL/min and the second equilibration step requires about 1 day.

26. 26) Also disclosed herein is a crystalline form of COMPOUND·HCl according to embodiment 25), characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction  $2\theta$ : 5.5°, 11.0°, and 16.6°.
27. 27) Also disclosed herein is a crystalline form of COMPOUND·HCl according to embodiment 25), characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction  $2\theta$ : 5.5°, 7.2°, 11.0°, 11.5°, and 16.6°.
28. 28) Also disclosed herein is a crystalline form of COMPOUND·HCl according to embodiment 25), characterized by the presence of peaks in the X-ray powder diffraction diagram at the following angles of refraction  $2\theta$ : 5.5°, 7.2°, 11.0°, 11.5°, 14.4°, 16.6°, 18.1°, 21.1°, and 22.0°.
29. 29) Also disclosed herein is a crystalline form of COMPOUND·HCl according to embodiment 25), which essentially shows the X-ray powder diffraction pattern as depicted in Fig. 3.
30. 30) Also disclosed herein is the crystalline form of COMPOUND·HCl according to any one of embodiments 9) to 12), obtainable by the processes of embodiment 25).
31. 31) Another embodiment relates to a crystalline form of COMPOUND·HCl according to any one of embodiments 1) to 4), which essentially shows a gravimetric moisture sorption profile (sorption cycle) as depicted in Fig. 4, wherein the gravimetric moisture sorption profile is measured at 25°C.
- Also disclosed herein is a crystalline form of COMPOUND·HCl according to any one of embodiments 13) to 18), which essentially shows a gravimetric moisture sorption profile (sorption cycle) as depicted in Fig. 4, wherein the gravimetric moisture sorption profile is measured at 25°C.
32. 32) Also disclosed herein is a crystalline form of COMPOUND·HCl according to any one of embodiments 5) to 8) or 19) to 24), which essentially shows a gravimetric moisture sorption profile (desorption cycle) as depicted in Fig. 5, wherein the gravimetric moisture sorption profile is measured at 25°C.
33. 33) Also disclosed herein is a crystalline form of COMPOUND·HCl according to any one of embodiments 9) to 12) or 25) to 30), which essentially shows a gravimetric moisture sorption profile (sorption cycle) as depicted in Fig. 6, wherein the gravimetric moisture sorption profile is measured at 25°C.
34. 34) A process for the preparation of COMPOUND·HCl in a crystalline form according to

any one of embodiments 1) to 4), wherein the process comprises the following steps:

1. a. addition of acetone (10 to 30 vol.) to a solution comprising COMPOUND·HCl and a non-polar solvent (0.5 to 3.0 vol.; 0.5 to 3.0 L per kg COMPOUND·HCl) at 45 to 60°C, wherein the non-polar solvent is selected from (C<sub>1-2</sub>)chloroalkane;
  2. b. addition of water (0.3 to 0.7 vol.) at 45 to 60°C;
  3. c. stirring of the mixture under cooling from a temperature of 45 to 60°C to a temperature at or below 30°C for at least 1h; and
  4. d. isolation of the obtained crystalline material.
35. 35) A process according to embodiment 34), wherein the amount of added acetone in step a. is about 20 vol..
36. 36) A process according to any one of embodiments 34) or 35), wherein the amount of the non-polar solvent in step a. is 1.0 to 2.0 vol. and wherein the non-polar solvent is dichloromethane.
37. 37) A process according to any one of embodiments 34) to 36), wherein the amount of the added water in step b. is 0.4 to 0.6 vol. (and especially 0.5 vol.).
38. 38) A process according to any one of embodiments 34) to 37), wherein the mixture is stirred in step c. between 1 and 4h at a temperature of 45 to 60°C and is subsequently cooled to a temperature between 20 and 30°C (especially 25°C) during 1 to 2h.
39. 39) A process according to any one of embodiments 34) to 38), wherein the isolation in step d. is done by filtration.
40. 40) A process according to any one of embodiments 34) to 39), wherein the solution comprising COMPOUND·HCl and a non-polar solvent used in step a. is obtained by a process comprising the steps:
1. a. coupling of (S)-6-(3-methoxypyrrolidin-1-yl)-2-phenylpyrimidine-4-carboxylic acid, or a salt thereof (especially a sodium salt thereof), with butyl (*R*)-4-(2-amino-3-(diethoxyphosphoryl)propanoyl)piperazine-1-carboxylate in the presence of an amide coupling agent;
  2. b. extraction with a solvent mixture comprising  
  
(C<sub>1-2</sub>)chloroalkane (especially dichloromethane); and  
  
water or an aqueous solution of an inorganic salt (especially an aqueous sodium hydrogencarbonat solution)
  3. c. addition of aqueous hydrochloric acid and stirring of the mixture;
  4. d. extraction with a solvent mixture comprising  
  
(C<sub>1-2</sub>)chloroalkane (especially dichloromethane); and  
  
water or an aqueous solution of an inorganic salt (especially water); and
  5. e. removal of solvents until the amount of (C<sub>1-2</sub>)chloroalkane equals 0.5 to 3.0 L per kg (especially 1.0 to 2.0 L per kg) COMPOUND·HCl.

**[0010]** Based on the dependencies of the different embodiments 1) to 40) as disclosed hereinabove, the following embodiments are thus possible and intended and herewith specifically disclosed in individualised form:

1, 2+1, 3+1, 4+1, 31+1, 31+2+1, 31+3+1, 31+4+1, 34, 35+34, 36+34, 36+35+34, 37+34, 37+35+34, 37+36+34, 37+36+35+34, 38+34, 38+35+34, 38+36+34, 38+36+35+34, 38+37+34, 38+37+35+34, 38+37+36+34, 38+37+36+35+34, 39+34, 39+35+34, 39+36+34, 39+36+35+34, 39+37+34, 39+37+35+34, 39+37+36+34, 39+37+36+35+34, 39+38+34, 39+38+35+34, 39+38+36+34, 39+38+36+35+34, 39+38+37+34, 39+38+37+35+34, 39+38+37+36+34, 39+38+37+36+35+34, 40+34, 40+35+34, 40+36+34, 40+36+35+34, 40+37+34, 40+37+35+34, 40+37+36+34, 40+37+36+35+34, 40+38+34, 40+38+35+34, 40+38+36+34, 40+38+36+35+34, 40+38+37+34, 40+38+37+35+34, 40+38+37+36+34, 40+38+37+36+35+34, 40+39+34, 40+39+35+34, 40+39+36+34, 40+39+36+35+34, 40+39+37+34, 40+39+37+35+34, 40+39+37+36+34, 40+39+37+36+35+34, 40+39+38+34, 40+39+38+35+34, 40+39+38+36+34, 40+39+38+36+35+34, 40+39+38+37+34, 40+39+38+37+35+34, 40+39+38+37+36+34, 40+39+38+37+36+35+34;

in the list above the numbers refer to the embodiments according to their numbering provided hereinabove whereas "+" indicates the dependency from another embodiment. The different individualised embodiments are separated by commas. In other words, "36+35+34" for example refers to embodiment 36) depending on embodiment 35), depending on embodiment 34), i.e. embodiment "36+35+34" corresponds to embodiment 34) further characterised by the features of the embodiments 35) and 36).

**[0011]** For avoidance of any doubt, whenever one of the above embodiments refers to "peaks in the X-ray powder diffraction diagram at the following angles of refraction  $2\theta$ ", said X-ray powder diffraction diagram is obtained by using combined Cu K $\alpha$ 1 and K $\alpha$ 2 radiation, without K $\alpha$ 2 stripping; and it should be understood that the accuracy of the  $2\theta$  values as provided herein is in the range of  $\pm 0.1$ - $0.2^\circ$ . Notably, when specifying an angle of refraction  $2\theta$  (2 $\theta$ ) for a peak in the invention embodiments and the claims, the  $2\theta$  value given is to be understood as an interval from said value minus  $0.2^\circ$  to said value plus  $0.2^\circ$  ( $2\theta \pm 0.2^\circ$ ); and preferably from said value minus  $0.1^\circ$  to said value plus  $0.1^\circ$  ( $2\theta \pm 0.1^\circ$ ).

**[0012]** Where the plural form is used for compounds, solids, pharmaceutical compositions, diseases and the like, this is intended to mean also a single compound, solid, pharmaceutical composition, disease or the like.

**[0013]** Definitions provided herein are intended to apply uniformly to the subject matter as defined in any one of embodiments 1) to 40), and, mutatis mutandis, throughout the description and the claims unless an otherwise expressly set out definition provides a broader or narrower definition. It is well understood that a definition or preferred definition of a term or expression defines and may replace the respective term or expression independently of (and in combination with) any definition or preferred definition of any or all other terms or

expressions as defined herein.

**[0014]** The term "(C<sub>1-2</sub>)chloroalkane" refers to an alkane group containing one or two carbon atoms in which one or more (and possibly all) hydrogen atoms have been replaced with chlorine. For example a (C<sub>1-2</sub>)chloroalkane group contains one or two carbon atoms in which one to six (especially two) hydrogen atoms have been replaced with chlorine. Preferred examples of (C<sub>1-2</sub>)chloroalkane groups are dichloromethane and 1,2-dichloroethane (and especially dichloromethane).

**[0015]** The term "amide coupling agent" refers to a compound that promotes the formation of a chemical bond (amide bond) between the -COOH group of a carboxylic acid and the -NH<sub>2</sub> group of an amine. Representative examples of amide coupling agents are carbodiimides (such as dicyclohexylcarbodiimide, diisopropylcarbodiimide or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) in the presence or absence of an additive such as 1-hydroxy-benzotriazole, 1-hydroxy-7-aza-1H-benzotriazole or N-hydroxysuccinimide; phosphonium reagents (such as benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate or benzotriazol-1-yloxy-tripyrrolidino-phosphonium hexafluorophosphate); aminium reagents (such as 2-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium tetrafluoroborate, 2-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium hexafluorophosphate or 2-(7-aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium hexafluorophosphate); and 2-propanephosphonic acid anhydride; preferred is 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide in the presence of 1-hydroxy-benzotriazole.

**[0016]** The term "enantiomerically enriched" is understood in the context of the present invention to mean especially that at least 90, preferably at least 95, and most preferably at least 99 per cent by weight of the COMPOUND (or of COMPOUND·HCl) are present in form of one enantiomer of the COMPOUND (or of COMPOUND·HCl). It is understood that any reference to "COMPOUND" (or to "COMPOUND·HCl") refers to 4-((R)-2-{{6-((S)-3-methoxypyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl}-amino}-3-phosphono-propionyl)-piperazine-1-carboxylic acid (or to its HCl salt) in enantiomerically enriched or in pure form.

**[0017]** The term "essentially pure" is understood in the context of the present invention to mean especially that at least 90, preferably at least 95, and most preferably at least 99 per cent by weight of the crystals of COMPOUND·HCl are present in a crystalline form according to the present invention.

**[0018]** When defining the presence of peak in e.g. an X-ray powder diffraction diagram, a common approach is to do this in terms of the S/N ratio (S = signal, N = noise). According to this definition, when stating that a peak has to be present in a X-ray powder diffraction diagram, it is understood that the peak in the X-ray powder diffraction diagram is defined by having an S/N ratio (S = signal, N = noise) of greater than x (x being a numerical value greater than 1), usually greater than 2, especially greater than 3.

**[0019]** In the context with stating that the crystalline form essentially shows an X-ray powder diffraction pattern as depicted in Fig. 1, 2, or 3, respectively, the term "essentially" means that at least the major peaks of the diagram depicted in said figures, i.e. those having a relative intensity of more than 20%, especially more than 10%, as compared to the most intense peak in the diagram, have to be present. However, the person skilled in the art of X-ray powder diffraction will recognize that relative intensities in X-ray powder diffraction diagrams may be subject to strong intensity variations due to preferred orientation effects.

**[0020]** The term "equilibration", as used in the context of "equilibration of a sample of COMPOUND·HCl", refers to a process step of keeping a sample for an equilibration time under specific conditions, such as a specifically given relative humidity, a specifically given gas stream and/or a specifically given temperature, wherein the term "equilibration time" refers to the time that is required to obtain an essentially constant content of water in the sample. The content of water is "essentially constant" if the change in the water content is less than 5% if the sample is kept for 24 h under the given specific conditions.

**[0021]** Unless used regarding temperatures, the term "about" placed before a numerical value "X" refers in the current application to an interval extending from X minus 10% of X to X plus 10% of X, and preferably to an interval extending from X minus 5% of X to X plus 5% of X; most preferred is X. In the particular case of temperatures, the term "about" placed before a temperature "Y" refers in the current application to an interval extending from the temperature Y minus 10 °C to Y plus 10 °C, preferably to an interval extending from Y minus 3 °C to Y plus 3 °C; most preferred is Y. Room temperature means a temperature of about 25 °C.

**[0022]** Whenever the word "between" or "to" is used to describe a numerical range, it is to be understood that the end points of the indicated range are explicitly included in the range. For example: if a temperature range is described to be between 40°C and 80°C (or 40°C to 80°C), this means that the end points 40°C and 80°C are included in the range; or if a variable is defined as being an integer between 1 and 4 (or 1 to 4), this means that the variable is the integer 1, 2, 3, or 4.

**[0023]** It is understood that 4-((*R*)-2-([6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-amino)-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester hydrochloride (or COMPOUND·HCl) refers to a hydrochloride salt of COMPOUND wherein the salt contains about 1 molar equivalent of HCl per molar equivalent of COMPOUND, especially 0.98 to 1.02 molar equivalent of HCl per molar equivalent of COMPOUND and notably 1.00 molar equivalent of HCl per molar equivalent of COMPOUND.

**[0024]** The expression % w/w refers to a percentage by weight compared to the total weight of the composition considered. Likewise, the expression v/v refers to a ratio by volume of the two components considered.

**[0025]** The crystalline forms, especially the essentially pure crystalline forms, of COMPOUND·HCl according to any one of embodiments 1) to 36) can be used as

medicaments, e.g. in the form of pharmaceutical compositions for enteral (such especially oral) or parenteral administration (including topical application or inhalation).

41) Another embodiment thus relates to a crystalline form of 4-((*R*)-2-[[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-amino]-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester hydrochloride according to any one of embodiments 1) to 4) or 31) for use as a medicament.

42) Another embodiment relates to COMPOUND, or a pharmaceutically acceptable salt thereof, for use as a medicament, wherein COMPOUND, or a pharmaceutically acceptable salt thereof, is obtained from a crystalline form of COMPOUND·HCl according to any one of embodiments 1) to 4) or 31).

The term "pharmaceutically acceptable salt" refers to a salt that retains the desired biological activity of the subject compound and exhibits minimal undesired toxicological effects. Such salts include inorganic or organic acid and/or base addition salts depending on the presence of basic and/or acidic groups in the subject compound. For reference see for example 'Handbook of Pharmaceutical Salts. Properties, Selection and Use.', P. Heinrich Stahl, Camille G. Wermuth (Eds.), Wiley-VCH, 2008, and 'Pharmaceutical Salts and Co-crystals', Johan Wouters and Luc Quéré (Eds.), RSC Publishing, 2012.

The crystalline solid, especially the essentially pure crystalline solid, of COMPOUND·HCl according to any one of embodiments 1) to 4) or 31) may be used as single component or as mixture with other crystalline forms or amorphous form of COMPOUND·HCl.

The production of the pharmaceutical compositions can be effected in a manner which will be familiar to any person skilled in the art (see for example Remington, The Science and Practice of Pharmacy, 21st Edition (2005), Part 5, "Pharmaceutical Manufacturing" [published by Lippincott Williams & Wilkins]) by bringing the crystalline form of the present invention, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, pharmaceutically acceptable solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

43) A further embodiment of the invention relates to pharmaceutical compositions comprising as active ingredient a crystalline form of COMPOUND·HCl according to any one of embodiments 1) to 4) or 31), and at least one pharmaceutically acceptable carrier material.

44) A further embodiment of the invention relates to pharmaceutical compositions comprising as active ingredient COMPOUND, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier material, wherein COMPOUND, or a pharmaceutically acceptable salt thereof, is obtained from a crystalline form of COMPOUND·HCl according to any one of embodiments 1) to 4) or 31).

45) A further embodiment of the invention relates to a crystalline form of COMPOUND·HCl according to any one of embodiments 1) to 4) or 31), for use in the manufacture of a pharmaceutical composition, wherein said pharmaceutical composition comprises as active ingredient the COMPOUND·HCl, and at least one pharmaceutically acceptable carrier material.

46) A further embodiment of the invention relates to COMPOUND, or a pharmaceutically

acceptable salt thereof, for use in the manufacture of a pharmaceutical composition, wherein said pharmaceutical composition comprises as active ingredient the COMPOUND, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier material, wherein the COMPOUND is obtained from a crystalline form of COMPOUND·HCl according to any one of embodiments 1) to 4) or 31).

47) A further embodiment of the invention relates to a crystalline form of COMPOUND·HCl according to any one of embodiments 1) to 4) or 31), for use in the prevention/prophylaxis or treatment of diseases selected from the group consisting of acute arterial thrombosis.

48) A preferred embodiment of the invention relates to a crystalline form of COMPOUND·HCl according to any one of embodiments 1) to 4) or 31), for use in the prevention/prophylaxis or treatment of diseases selected from the group consisting of acute coronary syndromes, peripheral ischaemia, amaurosis, ischaemic stroke and transient ischaemic attack.

49) A most preferred embodiment of the invention relates to a crystalline form of COMPOUND·HCl according to any one of embodiments 1) to 4) or 31), for use in the prevention/prophylaxis or treatment of acute coronary syndromes.

50) A further embodiment of the invention relates to COMPOUND, or a pharmaceutically acceptable salt thereof, for use in the prevention/prophylaxis or treatment of a disease selected from the diseases according to any one of embodiments 47) to 49), wherein the COMPOUND, or a pharmaceutically acceptable salt thereof, is obtained from a crystalline form of COMPOUND·HCl according to any one of embodiments 1) to 4) or 31).

51) A further embodiment of the invention relates to a crystalline form of COMPOUND·HCl according to any one of embodiments 1) to 4) or 31), for use in the manufacture of a pharmaceutical composition for the prevention/prophylaxis or treatment of diseases selected from the group consisting of acute arterial thrombosis.

52) A preferred embodiment of the invention relates to a crystalline form of COMPOUND·HCl according to any one of embodiments 1) to 4) or 31), for use in the manufacture of a pharmaceutical composition for the prevention/prophylaxis or treatment of diseases selected from the group consisting of acute coronary syndromes, peripheral ischaemia, amaurosis, ischaemic stroke and transient ischaemic attack.

53) A most preferred embodiment of the invention relates to a crystalline form of COMPOUND·HCl according to any one of embodiments 1) to 4) or 31), for use in the manufacture of a pharmaceutical composition for the prevention/prophylaxis or treatment of acute coronary syndromes.

54) A further embodiment of the invention relates to COMPOUND, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a pharmaceutical composition for the prevention/prophylaxis or treatment of a disease selected from the diseases according to any one of embodiments 51) to 53), wherein the COMPOUND, or a pharmaceutically acceptable salt thereof, is obtained from a crystalline form of COMPOUND·HCl according to any one of embodiments 1) to 4) or 31).

55) A further embodiment of the invention relates to pharmaceutical compositions according to embodiment 43), for use in the prevention/prophylaxis or treatment of diseases selected from the group consisting of acute arterial thrombosis.

56) A preferred embodiment of the invention relates to pharmaceutical compositions according to embodiment 43), for use in the prevention/prophylaxis or treatment of diseases selected from the group consisting of acute coronary syndromes, peripheral ischaemia, amaurosis, ischaemic stroke and transient ischaemic attack.

57) A most preferred embodiment of the invention relates to pharmaceutical compositions according to embodiment 43), for use in the prevention/prophylaxis or treatment of acute coronary syndromes.

58) A further embodiment of the invention relates to pharmaceutical compositions according to embodiment 44), for use in the prevention/prophylaxis or treatment of a disease selected from the diseases according to any one of embodiments 55) to 57).

**[0026]** The present disclosure also relates to a method for the prevention/prophylaxis or treatment of a disease or disorder mentioned herein, comprising administering to a subject a pharmaceutically active amount of a crystalline form of COMPOUND·HCl according to any one of embodiments 1) to 33), or of a pharmaceutical composition according to embodiment 43).

**[0027]** The present invention also relates to a method for the prevention/prophylaxis or treatment of a disease or disorder mentioned herein, comprising administering to a subject a pharmaceutically active amount of the COMPOUND, or a pharmaceutically acceptable salt thereof, wherein the COMPOUND, or a pharmaceutically acceptable salt thereof, is obtained from a crystalline form of COMPOUND·HCl according to any one of embodiments 1) to 36), or of the pharmaceutical composition according to embodiment 47).

#### **Experimental Procedures:**

#### **Abbreviations (as used hereinbefore or hereinafter):**

**[0028]**

AP

Aqueous layer

aq.

Aqueous

Bu

	Butyl such as in n-Bu = n-butyl
conc.	Concentrated
DCM	Dichloromethane
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
eq	Equivalent(s)
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
Fig	Figure
h	Hour(s)
<sup>1</sup> H-NMR	Nuclear magnetic resonance of the proton
HOBt	1-Hydroxy-benzotriazole mono hydrate
HPLC	High performance liquid chromatography
IPC	In-process control
LC-MS	Liquid chromatography - Mass Spectrometry
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
mW	milli-Watt
min	Minute(s)
MS	Mass spectrometry
N	Normality
NMR	

	Nuclear magnetic resonance
prep.	Preparative
RH	relative humidity
RT	Room temperature
sat.	Saturated
sec	Second(s)
T <sub>e</sub>	External temperature
T <sub>i</sub>	Internal temperature
TFA	trifluoroacetic acid
THF	Tetrahydrofuran
t <sub>R</sub>	Retention time
UPLC	Ultra Performance Liquid Chromatography
UV	Ultra violet
vol.	L solvent per kg starting material
XRPD	X-ray powder diffraction

**[0029]** All solvents and reagents are used as obtained from commercial sources unless otherwise indicated.

**[0030]** Temperatures are indicated in degrees Celsius (°C). Unless otherwise indicated, the reactions take place at room temperature (RT).

**[0031]** In mixtures, relations of parts of solvent or eluent or reagent mixtures in liquid form are given as volume relations (v/v), unless indicated otherwise.

**[0032]** Compounds described in the invention are characterized by UPLC and chiral HPLC (retention time t<sub>R</sub> is given in min using the conditions listed below).

**[0033]** Analytical UPLC conditions as used in the Examples below:

UPLC analyses are performed using the following elution condition:

Analytical UPLC on YMC Triart ExRS (Part. No. TAR08S03-1003PTH) column (100mm x 3.0 mm, 3µm); Gradient of 20mM Ammonium acetate + 10 mM NH<sub>4</sub>PF<sub>6</sub> buffer / Acetonitrile 95/5 (A) and Acetonitrile / Ammonium acetate 10 mM (B) from 8% to 100% B over 19 min; flow rate 0.5 ml/min, detection at 210 nm.

**[0034]** Analytical HPLC over a chiral stationary phase are performed on a Chiralpak AD-H (4.6 X 250 mm, 5 µm) column. Typical conditions of chiral HPLC are an isocratic mixture of Hexane/Ethanol/TFA (80:20:0.1 v/v/v), at a flow rate of 0.8 mL/min., at 40 °C; detection at 247 nm.

### **X-ray powder diffraction analysis (XRPD)**

**[0035]** X-ray powder diffraction patterns were collected on a Bruker D8 Advance X-ray diffractometer equipped with a Lynxeye detector operated with CuKα-radiation in reflection mode (coupled two Theta/Theta). Typically, the X-ray tube was run at of 40kV/40mA. A step size of 0.02° (2θ) and a step time of 76.8 sec over a scanning range of 3 - 50° in 2θ were applied. The divergence slits were set to fixed 0.3°. Powders were slightly pressed into a silicon single crystal sample holder with depth of 0.5 mm and samples were rotated in their own plane during the measurement. Diffraction data are reported without application of Kα<sub>2</sub> stripping. The accuracy of the 2θ values as provided herein is in the range of +/- 0.1-0.2° as it is generally the case for conventionally recorded X-ray powder diffraction patterns.

### **Gravimetric vapour sorption (GVS) analysis**

**[0036]** Measurements were performed on an IGASORP Model HAS-036-080 moisture sorption instrument (Hiden Isochema, Warrington, UK) operated in stepping mode at 25°C. The sample was allowed to equilibrate at the starting relative humidity (RH) before starting a predefined humidity program in steps of 5% ΔRH and with a maximal equilibration time of 24 hours per step. About 20 to 30 mg of each sample was used.

### **I-Chemistry**

**[0037]** (S)-6-(3-methoxypyrrolidin-1-yl)-2-phenylpyrimidine-4-carboxylic acid, butyl (R)-4-(2-amino-3-(diethoxyphosphoryl)propanoyl)piperazine-1-carboxylate and 4-((R)-2-{[6-((S)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester (COMPOUND) can be prepared according to the procedures given in WO 2009/069100 (example 2) or Caroff E et al., J. Med. Chem. 2015;58:9133-9153.

**[0038]** (S)-6-(3-methoxypyrrolidin-1-yl)-2-phenylpyrimidine-4-carboxylic acid can be transferred into sodium (S)-6-(3-methoxypyrrolidin-1-yl)-2-phenylpyrimidine-4-carboxylate in presence of aqueous sodium hydroxide.

## **II. Preparation of crystalline forms of COMPOUND·HCl**

### **Example 1A: Preparation and characterization of COMPOUND·HCl in crystalline form 1**

**[0039]** A 15 L reactor was charged with sodium (S)-6-(3-methoxypyrrolidin-1-yl)-2-phenylpyrimidine-4-carboxylate (584 g, 1.82 mol) and 1-hydroxy-benzotriazole mono hydrate (HOBt) (274 g, 1.1 eq.). Water (1305 mL, 2.0 vol.) was added. The pH of the suspension was 5-6. Butyl (R)-4-(2-amino-3-(diethoxyphosphoryl)propanoyl)piperazine-1-carboxylate (665.7 g, 1.0 eq) was dissolved in tetrahydrofurane (THF) (1960 ml, 3.0 vol.). The solution was added to the reaction at 20 to 30 °C during 5 to 10 min. A solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) (389 g, 1.2 eq.) in water (1305 ml, 2.0 vol.) was added to the reaction at 20 to 30 °C during 15 to 30 min. The pH of the reaction stayed between 6-7. The reaction was stirred during 4 h at 20 to 30 °C. An IPC showed 93% conversion. The reaction was diluted with dichloromethane (DCM) (3265 ml, 5.0 vol.) and ½ sat. aq. sodium hydrogencarbonat solution (3265 ml, 5.0 vol.). The layers were separated. The organic layer was washed again with ½ sat. aq. sodium hydrogencarbonat solution (3265 ml, 5.0 vol.). The layers were separated. An IPC showed the complete removal of HOBt. The organic layer was washed with aq. 10% citric acid (3265 ml, 5.0 vol.). In total 3.75 L of solvents were distilled off at minimal 800 mbar and  $T_e = 75$  to 80 °C during 40 min. The residual solution was cooled to 20 to 30 °C. Aq. 32% HCl (3 L, 19 eq.) was added during 5 to 10 min at 20 to 30 °C. An IPC after 4 h of stirring showed complete hydrolysis. Water (5.2 L, 8 vol.) was added at 20 to 30 °C. The reaction was diluted with DCM (5.2 L, 8 vol.). The layers were separated. The aqueous layer was extracted again 2 x with DCM (2x 5.2 L, 8 vol.). All DCM layers were combined and filtered through a polycap 75 HD filter. In total 14 L of solvents were distilled off during 2 h at atmospheric pressure and  $T_e = 75$  to 80 °C. Acetone (21.6 L, 33 vol.) was added to the refluxing reaction mixture at  $T_e = 70$  to 75 °C. To the refluxing fine suspension water (325 mL, 0.5 vol.) was added. The fine, pale suspension was stirred at reflux during 1.5 h and a thick white slurry was obtained. The slurry was cooled to  $T_i = 25$  °C during 1 h (ramp). The solid product was isolated by filtration. The filter cake was rinsed with acetone (4.5 L, 7 vol.) and was dried by blowing nitrogen through it to give 750 g (69%) of 4-((R)-2-[[6-((S)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-amino]-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester hydrochloride as a white solid.

**Table 1: Characterisation data for COMPOUND·HCl in crystalline form 1**

Technique	Data Summary	Remarks
XRPD	Crystalline	see Fig. 1

Technique	Data Summary	Remarks
<sup>1</sup> H-NMR	Consistent	
Elemental analysis	Corresponds	
Purity (UPLC, Area %)	98.6%	
Moisture sorption at 25°C	Profile measured from low RH to high RH	see Fig. 4

#### Example 1B: Preparation and characterization of COMPOUND·HCl in crystalline form 1

**[0040]** An enamelled reactor was charged with water (10.5 L; 1.6 vol.), sodium (S)-6-(3-methoxypyrrolidin-1-yl)-2-phenylpyrimidine-4-carboxylate (6.06 kg; 18.87 mol, 1.12 eq) and 1-hydroxy-benzotriazole mono hydrate (HOBt) (2.71 kg; 17.70 mol; 1.08 eq.). The resulting white suspension was stirred during 60 min at 21 °C. A yellow solution of butyl (R)-4-(2-amino-3-(diethoxyphosphoryl)propanoyl)piperazine-1-carboxylate (6.47 kg, 16.45 mol, 1.0 eq.) in THF (41 kg, 46.6 L, 7.2 vol.) was transferred into a stirring tank via inline filter. After addition of this solution into the reactor within 12 min at 20 °C a solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) (4.00 kg; 20.8 mol; 1.26 eq.) in water (13.5 L; 2.1 vol.) was added within 13 min at 20 °C. The reaction was stirred during 64 h at 20 °C. At 20 °C aq. 3.7% NaHCO<sub>3</sub> (32 L; 5.0 vol.) was added into the reactor followed by dichloromethane (DCM) (32 L; 5.0 vol.). The mixture was stirred during 10 min at 20 °C. After layer separation the pH of the aqueous layer (AP) was 8-9. The AP was extracted again with DCM (16 L; 2.5 vol.). The combined organic layers were charged into the reactor (total volume = 94 L) and were washed with aq. 3.7% NaHCO<sub>3</sub> (32 L; 5.0 vol.). After layer separation the pH was 10. The resulting organic layer was washed with aq. 10% citric acid (32 L; 5.0 vol.). The yellow solution was concentrated to a final volume of 5.5 vol. of butyl 4-((R)-3-(diethoxyphosphoryl)-2-(6-((S)-3-methoxypyrrolidin-1-yl)-2-phenylpyrimidine-4-carboxamido)propanoyl)piperazine-1-carboxylate at 55 °C and not below a pressure of 585 mbar. 52 L solvent were removed within 5 h.

**[0041]** The concentrated organic solution was treated with aq. 33% HCl (33 L; 5.1 vol.). The reaction mixture was stirred during 12 h at 20 to 30 °C. An IPC showed complete conversion into free phosphonate. At 20 to 30 °C water (53 L; 8.2 vol.) was added into the reactor followed by DCM (53 L; 8.2 vol.). The layers were separated. The aqueous layer was extracted 2 x with DCM (53 L; 8.2 vol.). The organic layers were combined and concentrated at T<sub>i</sub> = 50 °C and a pressure not below 900 mbar. 76 L of solvents were removed. Acetone (56 L; 8.7 vol.) was added without interrupting the distillation. The distillation was continued at T<sub>i</sub> = 50 °C until a final amount of 7 vol. remained. The pressure was not below 500 mbar. The concentrated solution was diluted with acetone (120 L; 18.5 vol.). The concentrated solution was stirred at T<sub>i</sub> = 50 °C. A white suspension was formed. Within 30 minutes the white suspension was diluted with water (3.4 L; 0.5 vol.) and was stirred during 3.5 h at T<sub>i</sub> = 56 °C. The suspension was

cooled to 20 to 30 °C within 2 h and stirred at this temperature for 1.5 h. The thick, white suspension was filtered off. The filter cake was washed twice with acetone (2x 24 L; 3.7 vol.) and was dried on the filter to give 7.67 kg of ((R)-3-(4-(butoxycarbonyl)piperazin-1-yl)-2-(6-((S)-3-methoxypyrrolidin-1-yl)-2-phenylpyrimidine-4-carboxamido)-3-oxopropyl)phosphonic acid hydrochloride.

**Table 2: Characterisation data for COMPOUND·HCl in crystalline form 1**

Technique	Data Summary	Remarks
XRPD	Crystalline	corresponds to Fig. 1
<sup>1</sup> H-NMR	Consistent	
Purity (UPLC, Area %)	99.8%	
Moisture sorption at 25°C	Profile measured from low RH to high RH	corresponds to Fig. 4

**Example 2: Preparation and characterization of COMPOUND·HCl in crystalline form 2**

**[0042]** COMPOUND·HCl in crystalline form 1 (100mg), as obtained by the process described in example 1A, was allowed to equilibrate at a relative humidity of >90% and room temperature for 3 days. The sample was then allowed to equilibrate at 40% RH and room temperature for 1 day to give COMPOUND·HCl in crystalline form 2.

**Table 3: Characterisation data for COMPOUND·HCl in crystalline form 2**

Technique	Data Summary	Remarks
XRPD	Crystalline	see Fig. 2
<sup>1</sup> H-NMR	Consistent	
Moisture sorption at 25°C	Profile measured from high RH to low RH	see Fig. 5

**Example 3A: Preparation and characterization of COMPOUND·HCl in crystalline form 3**

**[0043]** COMPOUND·HCl in crystalline form 2 (100mg), as obtained by the process described in example 2, was allowed to equilibrate in a dry nitrogen gas stream (400mL/min) at room temperature for 1 day. The sample was then allowed to equilibrate at 40% RH and room temperature for 1 day to give COMPOUND·HCl in crystalline form 3.

**Table 4: Characterisation data for COMPOUND·HCl in crystalline form 3**

Technique	Data Summary	Remarks
XRPD	Crystalline	see Fig. 3
Moisture sorption at	Profile measured from low RH to	see Fig. 6

Technique	Data Summary	Remarks
25°C	high RH	

**Example 3B: Preparation and characterization of COMPOUND·HCl in crystalline form 3 by re-crystallization**

**[0044]** An enamelled reactor was rinsed with acetone (20 L). 4-((R)-2-{{6-((S)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester hydrochloride (1.70 kg), water (1.28 L, 0.75 vol.) and acetone (8.5 L, 5 vol.) were charged and the mixture was heated to  $T_i = 40\text{ }^{\circ}\text{C}$  for 34 min. Additional acetone (17 L, 10 vol.) was added over 47 min. The mixture was further stirred for 37 min at  $T_i = 40\text{ }^{\circ}\text{C}$  and cooled to  $T_i = 20\text{ }^{\circ}\text{C}$  over 67 min. After 2 h at  $T_i = 20\text{ }^{\circ}\text{C}$  the suspension was slowly filtered over 2h and the crystalline solid was washed twice with acetone (2x 10 L, 5.9 vol.). Prolonged drying on the suction filter gave COMPOUND·HCl in crystalline form 3.

**Table 5: Characterisation data for COMPOUND·HCl in crystalline form 3**

Technique	Data Summary	Remarks
XRPD	Crystalline	corresponds to Fig. 3
$^1\text{H-NMR}$	Consistent	

## REFERENCES CITED IN THE DESCRIPTION

### Cited references

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

### Patent documents cited in the description

- [WO2009069100A](#) [0005] [0037]

## Non-patent literature cited in the description

- J Thromb Haemost, 2011, vol. 9, 1374-395 [0002]
- **DAVIES MJ et al.**Intramyocardial platelet aggregation in patients with unstable angina suffering sudden ischemic cardiac deathCirculation, 1986, vol. 73, 418-427 [0002]
- **JNEID H et al.**2012 accf/aha focused update of the guideline for the management of patients with unstable angina/non-st-elevation myocardial infarctionJ Am Coll Cardiol, 2012, vol. 60, 645-681 [0003] [0003]
- **O'GARA PT et al.**2013 accf/aha guideline for the management of st-elevation myocardial infarctionCirculation, 2013, vol. 127, e362-425 [0003] [0003]
- **JAGROOP IA et al.**The effect of clopidogrel, aspirin and both antiplatelet drugs on platelet function in patients with peripheral arterial diseasePlatelets, 2004, vol. 15, 117-125 [0003]
- **MATSAGAS M et al.**The effect of a loading dose (300 mg) of clopidogrel on platelet function in patients with peripheral arterial diseaseClin Appl Thromb Hemost, 2003, vol. 9, 115-120 [0003]
- **LIU F et al.**P2Y<sub>12</sub> receptor inhibitors for secondary prevention of ischemic strokeExpert Opin Pharmacother, 2015, vol. 16, 1149-1165 [0003]
- **CATTANEO M**The platelet P2Y<sub>12</sub> receptor for adenosine diphosphate: Congenital and drug-induced defectsBlood, 2011, vol. 117, 2102-2112 [0003]
- **THOMAS MR et al.**The future of P2Y<sub>12</sub> receptor antagonistsPlatelets, 2015, vol. 26, 392-398 [0003]
- **WIVIOTT SD et al.**Clinical evidence for oral antiplatelet therapy in acute coronary syndromesLancet, 2015, vol. 386, 292-302 [0003]
- **WALLENTIN L**P2Y<sub>12</sub> inhibitors: Differences in properties and mechanisms of action and potential consequences for clinical useEur Heart J, 2009, vol. 30, 1964-1977 [0003]
- **CAROFF E et al.**J. Med. Chem., 2015, vol. 58, 9133-9153 [0005] [0037]
- **BALDONI et al.**Clinical Drug Investigation, 2014, vol. 34, 807-818 [0005]
- The Importance of Solvates**U.J. GRIESSER**Polymorphism in the Pharmaceutical IndustryVCH20060000 [0009]
- Handbook of Pharmaceutical Salts. Properties, Selection and Use.Wiley-VCH20080000 [0025]
- Pharmaceutical Salts and Co-crystalsRSC Publishing20120000 [0025]
- Pharmaceutical Manufacturing**REMYINGTON**The Science and Practice of PharmacyLippincott Williams & Wilkins20050000 [0025]

**Patentkrav**

1. Krystallinsk form af 4-((*R*)-2-{[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidin-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazin-1-carboxylsyre-butylesterhydrochlorid, kendetegnet ved tilstedeværelsen af toppe i
  - 5 røntgenpulverdiffraktionsdiagrammet ved følgende brydningsvinkler  $2\theta$ :  $4,0^\circ$ ,  $5,0^\circ$  og  $15,3^\circ$ .
2. Krystallinsk form af 4-((*R*)-2-{[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidin-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazin-1-carboxylsyre-
  - 10 butylesterhydrochlorid ifølge krav 1, kendetegnet ved tilstedeværelsen af toppe i røntgenpulverdiffraktionsdiagrammet ved følgende brydningsvinkler  $2\theta$ :  $4,0^\circ$ ,  $5,0^\circ$ ,  $11,7^\circ$ ,  $15,3^\circ$  og  $19,3^\circ$ .
3. Krystallinsk form af 4-((*R*)-2-{[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-
  - 15 pyrimidin-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazin-1-carboxylsyre-butylesterhydrochlorid ifølge krav 1, kendetegnet ved tilstedeværelsen af toppe i røntgenpulverdiffraktionsdiagrammet ved følgende brydningsvinkler  $2\theta$ :  $4,0^\circ$ ,  $5,0^\circ$ ,  $5,9^\circ$ ,  $11,7^\circ$ ,  $15,3^\circ$ ,  $16,9^\circ$ ,  $19,3^\circ$ ,  $19,7^\circ$  og  $20,7^\circ$ .
- 20 4. Fremgangsmåde til fremstillingen af 4-((*R*)-2-{[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidin-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazin-1-carboxylsyre-butylesterhydrochlorid i en krystallinsk form ifølge et hvilket som helst af kravene 1 til 3, hvor fremgangsmåden omfatter følgende trin:
  - a. tilsætning af acetone (10 til 30 vol.) til en opløsning omfattende 4-((*R*)-2-{[6-
    - 25 ((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidin-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazin-1-carboxylsyre-butylesterhydrochlorid og et ikke-polært opløsningsmiddel (0,5 til 3,0 vol.) ved 45 til  $60^\circ\text{C}$ , hvor det ikke-polære opløsningsmiddel er valgt fra ( $\text{C}_{1-2}$ )chloralkan;
  - b. tilsætning af vand (0,3 til 0,7 vol.) ved 45 til  $60^\circ\text{C}$ ;
  - 30 c. omrøring af blandingen under afkøling fra en temperatur på 45 til  $60^\circ\text{C}$  til en temperatur på eller under  $30^\circ\text{C}$  i mindst 1 time; og

d. isolering af det opnåede krystallinske materiale.

**5.** Fremgangsmåde ifølge krav 4, hvor mængden af det ikke-polære opløsningsmiddel i trin a. er 1,0 til 2,0 vol., og hvor det ikke-polære

5 opløsningsmiddel er dichlormethan.

**6.** Fremgangsmåde ifølge et hvilket som helst af kravene 4 eller 5, hvor blandingen omrøres i trin c. mellem 1 og 4 timer ved en temperatur på 45 til 60°C og afkøles efterfølgende til en temperatur mellem 20 og 30°C i løbet af 1 til 2

10 timer.

**7.** Krystallinsk form af 4-((*R*)-2-{[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidin-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazin-1-carboxylsyre-butylesterhydrochlorid ifølge et hvilket som helst af kravene 1 til 3, til anvendelse

15 som et medikament.

**8.** Farmaceutisk sammensætning der som aktiv ingrediens omfatter en krystallinsk form af 4-((*R*)-2-{[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidin-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazin-1-carboxylsyre-

20 butylesterhydrochlorid ifølge et hvilket som helst af kravene 1 til 3, og mindst en farmaceutisk acceptabel bærer.

**9.** Krystallinsk form af 4-((*R*)-2-{[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidin-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazin-1-carboxylsyre-

25 butylesterhydrochlorid ifølge et hvilket som helst af kravene 1 til 3, til anvendelse i fremstillingen af en farmaceutisk sammensætning, hvor nævnte farmaceutiske sammensætning som aktiv ingrediens omfatter 4-((*R*)-2-{[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidin-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazin-1-carboxylsyre-butylesterhydrochlorid, og mindst et farmaceutisk

30 acceptabelt bæremateriale.

**10.** Krystallinsk form af 4-((*R*)-2-{[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidin-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazin-1-carboxylsyre-

butylesterhydrochlorid ifølge et hvilket som helst af kravene 1 til 3, til anvendelse til forebyggelsen eller behandlingen af sygdomme valgt fra gruppen bestående af akutte koronarsyndromer, perifer iskæmi, amaurose, iskæmisk slagtilfælde og transitorisk iskæmisk anfald.

5

**11.** 4-((*R*)-2-{[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidin-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazin-1-carboxylsyre-butylester, eller et farmaceutisk acceptabelt salt deraf, til anvendelse i forebyggelsen eller behandlingen af en sygdom valgt fra gruppen bestående af akutte

- 10 koronarsyndromer, perifer iskæmi, amaurose, iskæmisk slagtilfælde og transitorisk iskæmisk anfald, hvor 4-((*R*)-2-{[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidin-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazin-1-carboxylsyre-butylester, eller et farmaceutisk acceptabelt salt deraf, er opnået fra en krystallinsk form af 4-((*R*)-2-{[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-  
15 pyrimidin-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazin-1-carboxylsyre-butylesterhydrochlorid ifølge et hvilket som helst af kravene 1 til 3.

- 12.** Krystallinsk form af 4-((*R*)-2-{[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidin-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazin-1-carboxylsyre-  
20 butylesterhydrochlorid ifølge et hvilket som helst af kravene 1 til 3, til anvendelse i fremstillingen af en farmaceutisk sammensætning til forebyggelsen eller behandlingen af sygdomme valgt fra gruppen bestående af akutte koronarsyndromer, perifer iskæmi, amaurose, iskæmisk slagtilfælde og transitorisk iskæmisk anfald.

25

## DRAWINGS

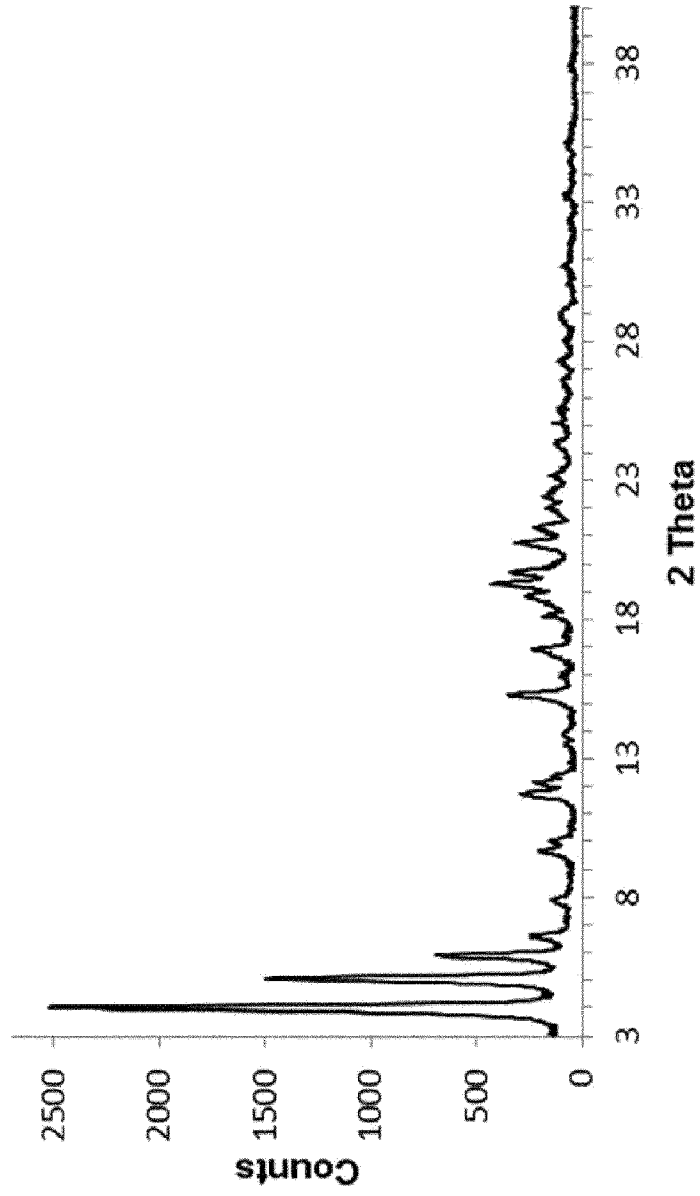


Fig. 1

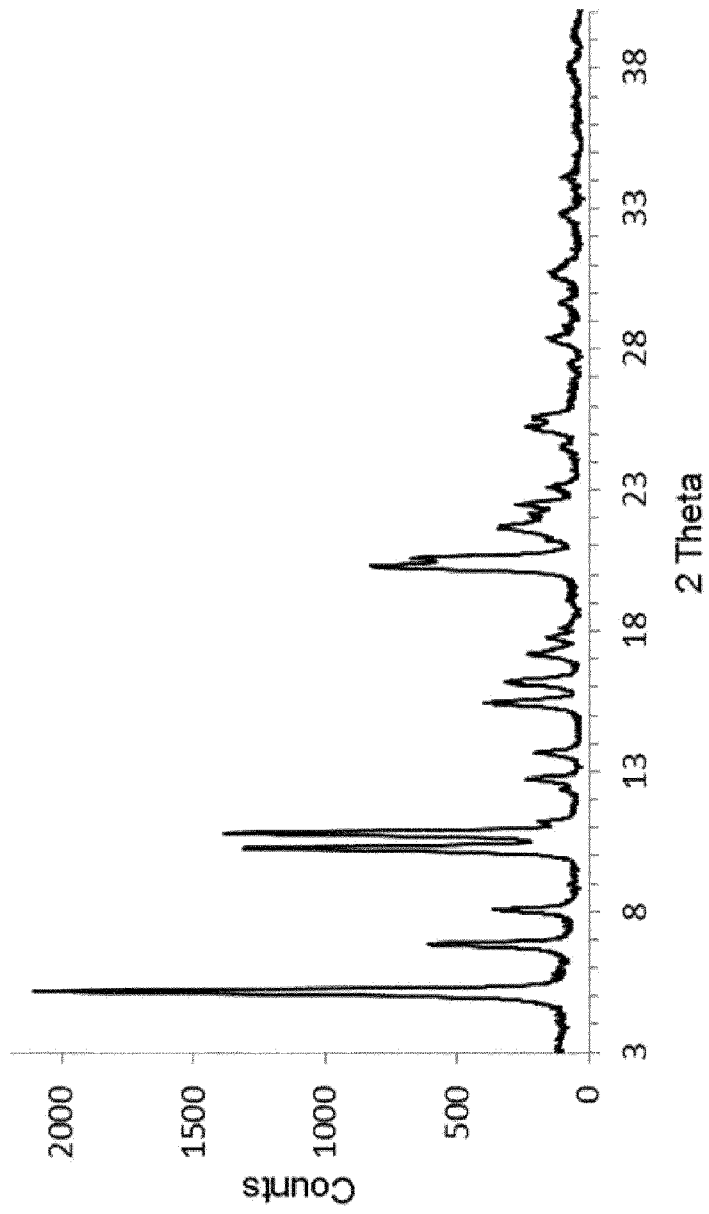


Fig. 2

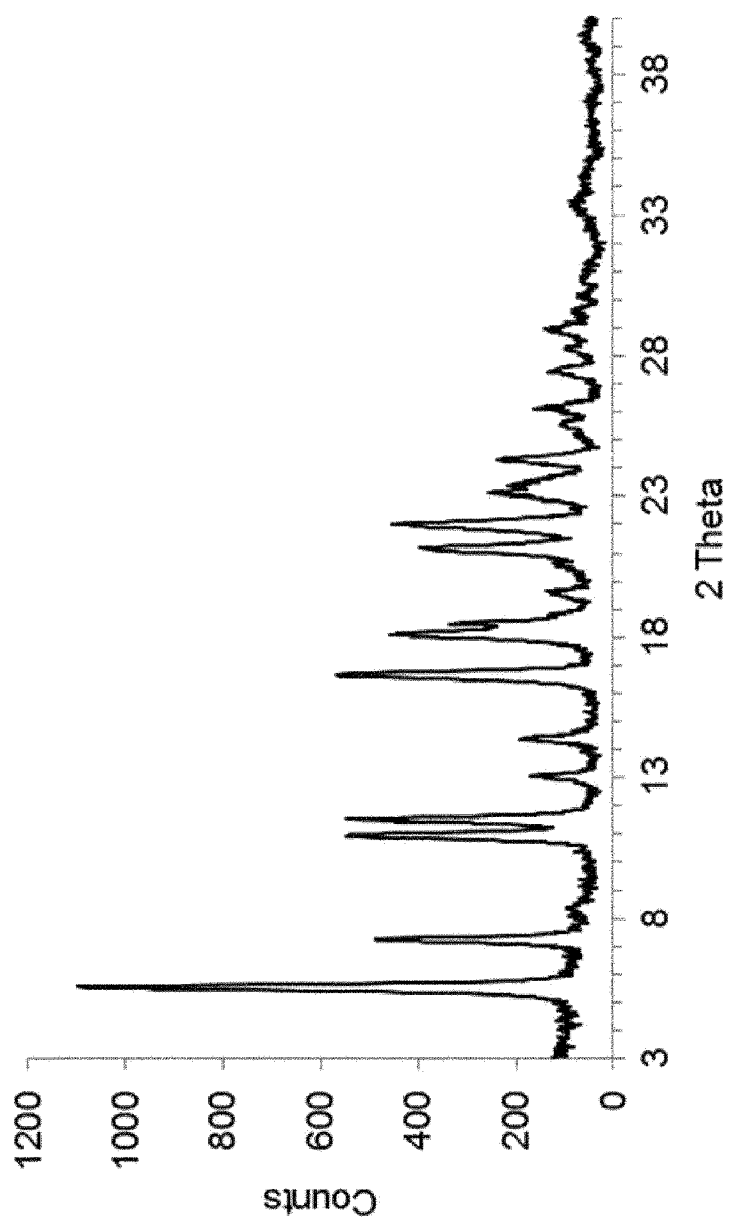


Fig. 3

Fig. 4

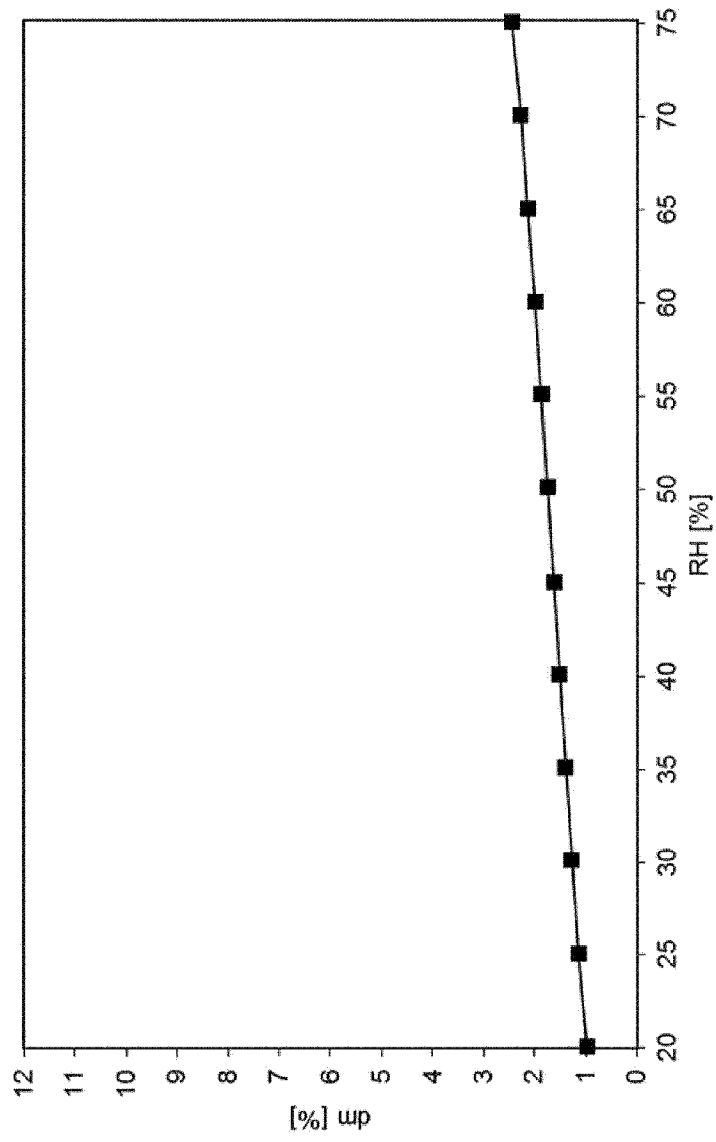


Fig. 5

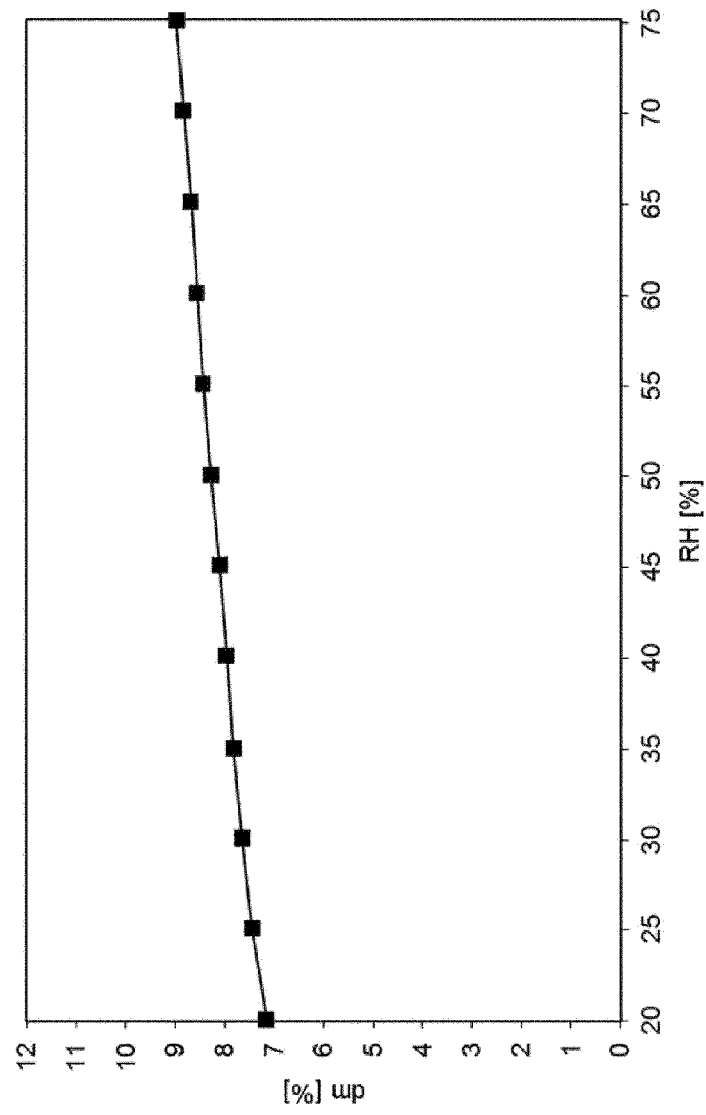


Fig. 6

