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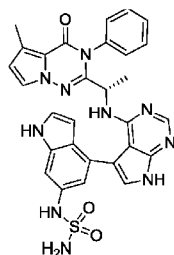
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(54) Title: ADDITION SALTS OF N-[4-(4-{{(1S)-1-(5-METHYL-4-OXO-3-PHENYL-3,4-DIHYDROPYRROLO[2,1-F][1,2,4]TRIAZIN-2-YL)ETHYL}AMINO}-7H-PYRROLO[2,3-D]PYRIMIDIN-5-YL)-1H-INDOL-6-YL]SULFAMIDE



(I)

(57) Abstract: The present invention is directed to crystalline addition salts of (I) N-[4-(4-{{(1S)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl}amino}-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1 H-indol-6-yl]sulfamide with sulfonic acid derivatives, chosen from methanesulfonic acid, ethanesulfonic acid and benzenesulfonic acid, or pharmaceutically acceptable solvates thereof.



ADDITION SALTS OF *N*-[4-(4-[[[(1S)-1-(5-METHYL-4-OXO-3-PHENYL-3,4-DIHYDROPYRROLO[2,1-F][1,2,4]TRIAZIN-2-YL)ETHYL]AMINO]-7H-PYRROLO[2,3-D]PYRIMIDIN-5-YL)-1H-INDOL-6-YL]SULFAMIDE

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### Field of the invention

The present invention is directed to novel crystalline, stable and pharmaceutically acceptable, addition salts of *N*-[4-(4-[[[(1S)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide with sulfonic acid derivatives, in particular with methanesulfonic acid, ethanesulfonic acid and benzenesulfonic acid, or pharmaceutically acceptable solvates thereof. The invention is also directed to pharmaceutical compositions comprising the salts, methods of using them to treat respiratory diseases associated with inhibition of Phosphoinositide 3-Kinase (PI3K), and processes and intermediates useful for preparing such salts.

15

### Background of the invention

WO 2014/060432 discloses pyrrolotriazinone derivatives as potent PI3Ks inhibitors. Although these compounds have shown adequate pharmacological activity, some of the compounds exemplified in this International Patent Application present a complex polymorphic landscape with numerous crystalline forms, and many of these compounds cannot be formulated for effective delivery by inhalation as a dry powder. Delivery by inhalation as a dry powder is challenging. It requires careful control of the particle size of the powder which is to be inhaled, and careful control of the particle size distribution. Further, it is important to avoid particle agglomeration or aggregation. In addition, when preparing pharmaceutical compositions and formulations for use in drug powder inhalers, it is highly desirable to have a crystalline form of a therapeutic agent that is neither hygroscopic nor deliquescent and which has a relatively high melting point (i.e. greater than about 150 °C) thereby allowing the material to be micronized without significant decomposition or loss of crystallinity.

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Although the *N*-[4-(4-[[[(1S)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide

disclosed in WO 2014/060432 has shown adequate pharmacological behaviour, it has proved difficult to obtain it in the form of a salt which is crystalline, not hygroscopic nor deliquescent and which has a relatively high melting point to enable micronization.

- 5 So far no crystalline salt of any of the compounds disclosed in WO 2014/060432 having the desired properties has been reported.

Accordingly, there is a need for PI3Ks inhibitors, which are physically and chemically stable, with relative high melting point and which do not exhibit polymorphism. This would  
10 allow the material to be further manipulated, e.g. by drying, milling or by micronization without significant decomposition, loss of crystallinity or exhibiting any change in polymorphism to prepare pharmaceutical compositions and formulations.

## 15 **Summary of the invention**

It has now been found that addition salts of *N*-[4-(4-{{(1S)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl}amino}-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide with sulfonic acid derivatives, in particular with methanesulfonic acid, ethanesulfonic acid and benzenesulfonic acid, or pharmaceutically acceptable solvates  
20 thereof, are stable and can be obtained in a crystalline form which has a relatively high melting point and does not exhibit any change in polymorphism.

Thus, the present invention provides pharmaceutically acceptable crystalline addition salts of *N*-[4-(4-{{(1S)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl}amino}-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide with sulfonic acid derivatives selected from methanesulfonic acid, ethanesulfonic acid and benzenesulfonic acid, and pharmaceutically acceptable solvates thereof.  
25

The invention also provides a pharmaceutical composition comprising a salt of the invention and a pharmaceutically acceptable carrier. The invention further provides  
30 pharmaceutical compositions as defined above and a therapeutically effective amount of one or more other therapeutic agents. The invention further provides combinations comprising a salt of the invention and a therapeutically effective amount of one or more other therapeutic agents.

The invention also provides a method of treatment of a pathological condition or disease susceptible to amelioration by inhibition of Phosphoinositide 3-Kinase (PI3K), in particular wherein the pathological condition or disease is a respiratory disease; more in particular  
5 wherein the pathological condition or disease is selected from asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchiectasis, cough, idiopathic pulmonary fibrosis and sarcoidosis; comprising administering a therapeutically effective amount of a salt of the invention.

10 The invention also provides a method of treatment of a pathological condition or disease susceptible to amelioration by inhibition of Phosphoinositide 3-Kinase (PI3K), in particular wherein the pathological condition or disease is as defined before, comprising administering a therapeutically effective amount of a pharmaceutical composition comprising a salt of the invention and a pharmaceutically-acceptable carrier, or a  
15 pharmaceutical composition comprising a salt of the invention, a pharmaceutically-acceptable carrier and a therapeutically effective amount of one or more other therapeutic agents.

The invention also provides a method of treatment of a pathological condition or disease  
20 susceptible to amelioration by inhibition of Phosphoinositide 3-Kinase (PI3K), in particular wherein the pathological condition or disease is as defined before, comprising administering a therapeutically effective amount of a combination comprising a salt of the invention and one or more other therapeutic agents.

25 The invention also provides a salt of the invention as described herein, a pharmaceutical composition comprising a salt of the invention and a pharmaceutically acceptable carrier, a pharmaceutical composition as defined above together with a therapeutically effective amount of one or more other therapeutic agents or combination of a salt of the invention together with a therapeutically effective amount of one or more other therapeutic agents,  
30 for use in the treatment of a pathological condition or disease susceptible to amelioration by inhibition of Phosphoinositide 3-Kinase (PI3K); in particular wherein the pathological condition or disease is a respiratory disease; more in particular wherein the pathological condition or disease is selected from asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchiectasis, cough, idiopathic pulmonary fibrosis and  
35 sarcoidosis.

The invention also provides the use of the salt of the invention, a pharmaceutical composition comprising a salt of the invention and a pharmaceutically acceptable carrier, a pharmaceutical composition as defined above together with a therapeutically effective amount of one or more other therapeutic agents or a combination of a salt of the invention together with one or more other therapeutic agents, for the manufacture of a formulation or medicament for treating the above mentioned pathological conditions or diseases.

### Brief description of Figures

10 Figure 1 illustrates the X-Ray Powder Diffraction (XRPD) diffractogram of *N*-[4-(4-[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide methanesulfonate.

15 Figure 2 illustrates the Differential Scanning Calorimetry (DSC) thermogram of *N*-[4-(4-[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide methanesulfonate.

20 Figure 3 illustrates the Gravimetric Vapour Sorption (GVS) isotherm of *N*-[4-(4-[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide methanesulfonate.

25 Figure 4 illustrates the Proton Nuclear Magnetic Resonance (<sup>1</sup>H-NMR) spectrum of *N*-[4-(4-[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide methanesulfonate.

Figure 5 illustrates the X-Ray Powder Diffraction (XRPD) diffractogram of *N*-[4-(4-[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide ethanesulfonate.

30 Figure 6 illustrates the Differential Scanning Calorimetry (DSC) thermogram of *N*-[4-(4-[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide ethanesulfonate.

Figure 7 illustrates the Gravimetric Vapour Sorption (GVS) isotherm of *N*-[4-(4-[[[(1S)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide ethanesulfonate.

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Figure 8 illustrates the Proton Nuclear Magnetic Resonance (<sup>1</sup>H-NMR) spectrum of *N*-[4-(4-[[[(1S)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide ethanesulfonate.

10 Figure 9 illustrates the X-Ray Powder Diffraction (XRPD) diffractogram of *N*-[4-(4-[[[(1S)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide ethanesulfonate type A polymorph.

15 Figure 10 illustrates the X-Ray Powder Diffraction (XRPD) diffractogram of *N*-[4-(4-[[[(1S)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide ethanesulfonate type B polymorph.

20 Figure 11 illustrates the X-Ray Powder Diffraction (XRPD) overlapped diffractogram of the type A and type B polymorphs of *N*-[4-(4-[[[(1S)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide ethanesulfonate.

25 Figure 12 illustrates the X-Ray Powder Diffraction (XRPD) diffractogram of *N*-[4-(4-[[[(1S)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide benzenesulfonate.

Figure 13 illustrates the Differential Scanning Calorimetry (DSC) thermogram of *N*-[4-(4-[[[(1S)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide benzenesulfonate.

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Figure 14 illustrates the Gravimetric Vapour Sorption (GVS) isotherm of *N*-[4-(4-[[[(1S)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide benzenesulfonate.

5 Figure 15 illustrates the Proton Nuclear Magnetic Resonance (<sup>1</sup>H-NMR) spectrum of *N*-[4-(4-[[[(1S)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide benzenesulfonate.

## 10 Detailed description of the invention

When describing the salts, compositions, combinations and methods of the invention, the following terms have the following meanings, unless otherwise indicated.

15 The term "therapeutically effective amount" refers to an amount sufficient to effect treatment when administered to a patient in need of treatment.

The term "treatment" as used herein refers to the treatment of a disease or medical condition in a human patient which includes:

20 (a) preventing the disease or medical condition from occurring, i.e., prophylactic treatment of a patient;

(b) ameliorating the disease or medical condition, i.e., causing regression of the disease or medical condition in a patient;

25 (c) suppressing the disease or medical condition, i.e., slowing the development of the disease or medical condition in a patient; or

(d) alleviating the symptoms of the disease or medical condition in a patient.

30 The term "addition salt" of the compound *N*-[4-(4-[[[(1S)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide also encompasses all solvates and co-crystals thereof.

35 The term "solvate" refers to a complex or aggregate formed by one or more molecules of a solute, i.e. a salt of the invention or a pharmaceutically-acceptable salt thereof, and one

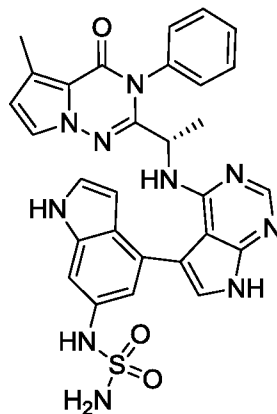
or more molecules of a solvent. Such solvates are typically crystalline solids having a substantially fixed molar ratio of solute and solvent. Representative solvents include by way of example, water, ethanol, isopropanol and the like. When the solvent is water, the solvate formed is a hydrate.

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The term co-crystal refers to a solid that is crystalline single phase material composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts.

10 The term “pharmaceutically (or physiologically) acceptable carrier (or diluent)” refers to a carrier or diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound.

15 *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide, which has the structure of formula (I), as well as a process for its manufacture, is described in the International Patent Application No. WO 2014/060432.



Formula (I)

20

One embodiment of the present invention refers to a pharmaceutically acceptable crystalline addition salt of *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide with sulfonic acid derivatives selected from methanesulfonic acid, ethanesulfonic acid and benzenesulfonic acid, or pharmaceutically acceptable solvates thereof.

25



In a particular embodiment of the present invention the addition salt is *N*-[4-(4-((1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide methanesulfonate, or  
5 pharmaceutically acceptable solvates thereof.

Preferably *N*-[4-(4-((1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide  
methanesulfonate contains 1 molar equivalent of *N*-[4-(4-((1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide per molar equivalent of the methanesulfonic acid.  
10

Typically, methanesulfonic acid (CAS RN 75-75-2) is a colourless liquid with the molecular formula CH<sub>4</sub>O<sub>3</sub>S (molecular weight of 96.11 g/mol). Salts of methanesulfonic acid are  
15 known as methanesulfonates, mesitates (International Nonproprietary Name or INN) or mesylates (United States Adopted Name or USAN).

In another particular embodiment of the present invention the *N*-[4-(4-((1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide methanesulfonate has an XRPD pattern with at  
20 least one peak at 2θ of 22.3±0.1.

In another particular embodiment of the present invention the *N*-[4-(4-((1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide methanesulfonate has an XRPD pattern  
25 comprising peaks at 2θ of 8.1±0.1, 9.6±0.1, 13.1±0.1, 15.9±0.1, 16.6±0.1, 17.5±0.1, 19.1±0.1, 22.3±0.1, 22.8±0.1, 23.5±0.1, 24.1±0.1 and 24.6±0.1.

In another particular embodiment of the present invention the *N*-[4-(4-((1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide methanesulfonate has an XRPD pattern  
30 comprising peaks at 2θ of 8.1±0.1, 8.7±0.1, 9.6±0.1, 10.1±0.1, 10.4±0.1, 11.2±0.1, 12.1±0.1, 12.2±0.1, 13.1±0.1, 13.5±0.1, 15.3±0.1, 15.9±0.1, 16.0±0.1, 16.6±0.1, 16.7±0.1, 17.5±0.1, 17.7±0.1, 18.4±0.1, 19.1±0.1, 19.6±0.1, 20.6±0.1, 20.8±0.1, 21.8±0.1,

22.3±0.1, 22.8±0.1, 23.2±0.1, 23.5±0.1, 24.1±0.1, 24.6±0.1, 25.5±0.1, 26.0±0.1, 26.7±0.1, 28.2±0.1, 28.7±0.1, 30.1±0.1, 30.6±0.1, 31.9±0.1, 32.4±0.1, 33.0±0.1 and 39.8±0.1.

In another particular embodiment of the present invention the *N*-[4-(4-{{(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl}amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide methanesulfonate has an XRPD pattern substantially as shown in Figure 1.

In a particular embodiment of the present invention the addition salt is *N*-[4-(4-{{(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl}amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate, or pharmaceutically acceptable solvates thereof.

Preferably *N*-[4-(4-{{(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl}amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate contains 1 molar equivalent of *N*-[4-(4-{{(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl}amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide per molar equivalent of the ethanesulfonic acid.

Typically, ethanesulfonic acid (CAS RN 594-45-6) is a colourless liquid with the molecular formula C<sub>2</sub>H<sub>6</sub>O<sub>3</sub>S (molecular weight of 110.13 g/mol). Salts of ethanesulfonic acid are known as ethanesulfonates, esilates (International Nonproprietary Name or INN) or esylates (United States Adopted Name or USAN).

In another particular embodiment of the present invention the *N*-[4-(4-{{(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl}amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate has an XRPD pattern with at least one peak at 2θ of 7.3±0.1.

In another particular embodiment of the present invention the *N*-[4-(4-{{(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl}amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate has an XRPD pattern with at least one peak at 2θ of 19.5±0.1.

In another particular embodiment of the present invention the *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate has an XRPD pattern comprising peaks at  $2\theta$  of  $7.3\pm 0.1$ ,  $8.7\pm 0.1$ ,  $8.9\pm 0.1$ ,  $10.0\pm 0.1$ ,  $12.8\pm 0.1$ ,  $15.9\pm 0.1$ ,  $19.2\pm 0.1$ ,  
5  $19.5\pm 0.1$ ,  $20.1\pm 0.1$ ,  $21.5\pm 0.1$ ,  $21.7\pm 0.1$ ,  $22.2\pm 0.1$ ,  $23.2\pm 0.1$ ,  $23.4\pm 0.1$ ,  $24.0\pm 0.1$  and  $25.4\pm 0.1$ .

In another particular embodiment of the present invention the *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate has an XRPD pattern comprising peaks at  $2\theta$  of  $7.3\pm 0.1$ ,  $8.7\pm 0.1$ ,  $8.9\pm 0.1$ ,  $10.0\pm 0.1$ ,  $10.6\pm 0.1$ ,  $11.7\pm 0.1$ ,  $12.1\pm 0.1$ ,  
10  $12.8\pm 0.1$ ,  $13.6\pm 0.1$ ,  $14.2\pm 0.1$ ,  $15.1\pm 0.1$ ,  $15.9\pm 0.1$ ,  $16.8\pm 0.1$ ,  $17.7\pm 0.1$ ,  $19.2\pm 0.1$ ,  $19.5\pm 0.1$ ,  $20.1\pm 0.1$ ,  $21.5\pm 0.1$ ,  $21.1\pm 0.1$ ,  $21.7\pm 0.1$ ,  $22.2\pm 0.1$ ,  $23.2\pm 0.1$ ,  $23.4\pm 0.1$ ,  $24.0\pm 0.1$ ,  $25.4\pm 0.1$ ,  $26.3\pm 0.1$ ,  $27.3\pm 0.1$ ,  $28.7\pm 0.1$ ,  $30.3\pm 0.1$ ,  $31.3\pm 0.1$ ,  $33.7\pm 0.1$ ,  $35.7\pm 0.1$  and  $37.7\pm 0.1$ .

In another particular embodiment of the present invention the *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate has an XRPD pattern substantially as shown in Figure 5.

In a particular embodiment of the present invention the addition salt is *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate type A polymorph, or pharmaceutically acceptable solvates thereof.

In another particular embodiment of the present invention, the *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate type A polymorph has an XRPD pattern with at least one peak at  $2\theta$  of  $7.6\pm 0.1$ .

In another particular embodiment of the present invention, the *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate type A polymorph has an XRPD pattern with at least one peak at  $2\theta$  of  $7.6\pm 0.1$ , and does not have a peak at  $2\theta$  of  $9.9\pm 0.1$ .

In another particular embodiment of the present invention the *N*-[4-(4-[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate type A polymorph has an XRPD pattern with at least two peaks at  $2\theta$  of  $7.5\pm 0.1$  and  $7.6\pm 0.1$ , and does not have peaks at  $2\theta$  of  $9.9\pm 0.1$  and  $20.0\pm 0.1$ .

In another particular embodiment of the present invention the *N*-[4-(4-[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate type A polymorph has an XRPD pattern comprising peaks at  $2\theta$  of  $7.5\pm 0.1$ ,  $7.6\pm 0.1$ ,  $12.7\pm 0.1$ ,  $15.8\pm 0.1$ ,  $18.5\pm 0.1$ ,  $19.0\pm 0.1$ ,  $19.5\pm 0.1$ ,  $22.0\pm 0.1$ ,  $22.4\pm 0.1$  and  $24.1\pm 0.1$ .

In another particular embodiment of the present invention the *N*-[4-(4-[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate type A polymorph has an XRPD pattern comprising peaks at  $2\theta$  of  $7.5\pm 0.1$ ,  $7.6\pm 0.1$ ,  $8.9\pm 0.1$ ,  $9.2\pm 0.1$ ,  $10.5\pm 0.1$ ,  $11.6\pm 0.1$ ,  $12.7\pm 0.1$ ,  $15.1\pm 0.1$ ,  $15.8\pm 0.1$ ,  $16.6\pm 0.1$ ,  $17.6\pm 0.1$ ,  $18.5\pm 0.1$ ,  $19.0\pm 0.1$ ,  $19.5\pm 0.1$ ,  $22.0\pm 0.1$ ,  $22.4\pm 0.1$ ,  $23.5\pm 0.1$ ,  $24.1\pm 0.1$ ,  $25.3\pm 0.1$ ,  $26.3\pm 0.1$ ,  $27.0\pm 0.1$ ,  $28.6\pm 0.1$  and  $30.8\pm 0.1$ .

In another particular embodiment of the present invention the *N*-[4-(4-[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate type A polymorph has an XRPD pattern substantially as shown in Figure 9.

In a particular embodiment of the present invention the addition salt is *N*-[4-(4-[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate type B polymorph, or pharmaceutically acceptable solvates thereof.

In another particular embodiment of the present invention, the *N*-[4-(4-[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate type B polymorph has an XRPD pattern with at least one peak at  $2\theta$  of  $9.9\pm 0.1$ .

In another particular embodiment of the present invention, the *N*-[4-(4-((1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate type B polymorph has an XRPD pattern with at least one peak at  $2\theta$  of  $9.9\pm 0.1$ , and does not have a peak at  $2\theta$  of  $7.6\pm 0.1$ .

5

In another particular embodiment of the present invention the *N*-[4-(4-((1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate type B polymorph has an XRPD pattern with at least two peaks at  $2\theta$  of  $9.9\pm 0.1$  and  $20.0\pm 0.1$ , and does not have peaks at  $2\theta$  of  $7.5\pm 0.1$  and  $7.6\pm 0.1$ .

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In another particular embodiment of the present invention the *N*-[4-(4-((1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate type B polymorph has an XRPD pattern comprising peaks at  $2\theta$  of  $8.5\pm 0.1$ ,  $9.9\pm 0.1$ ,  $12.7\pm 0.1$ ,  $16.7\pm 0.1$ ,  $17.7\pm 0.1$ ,  $19.5\pm 0.1$ ,  $20.0\pm 0.1$ ,  $21.7\pm 0.1$ ,  $23.3\pm 0.1$  and  $27.2\pm 0.1$ .

15

In another particular embodiment of the present invention the *N*-[4-(4-((1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate type B polymorph has an XRPD pattern comprising peaks at  $2\theta$  of  $8.5\pm 0.1$ ,  $9.9\pm 0.1$ ,  $11.1\pm 0.1$ ,  $12.7\pm 0.1$ ,  $13.5\pm 0.1$ ,  $14.0\pm 0.1$ ,  $14.3\pm 0.1$ ,  $16.7\pm 0.1$ ,  $17.7\pm 0.1$ ,  $19.5\pm 0.1$ ,  $20.0\pm 0.1$ ,  $21.7\pm 0.1$ ,  $22.1\pm 0.1$ ,  $22.5\pm 0.1$ ,  $23.3\pm 0.1$ ,  $24.1\pm 0.1$ ,  $25.5\pm 0.1$ ,  $25.8\pm 0.1$ ,  $26.6\pm 0.1$ ,  $27.2\pm 0.1$  and  $28.1\pm 0.1$ .

20

In another particular embodiment of the present invention the *N*-[4-(4-((1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate type B polymorph has an XRPD pattern substantially as shown in Figure 10.

25

In a particular embodiment of the present invention the addition salt is *N*-[4-(4-((1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide benzenesulfonate, or pharmaceutically acceptable solvates thereof.

30

Preferably *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide

benzenesulfonate contains 1 molar equivalent of *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide per molar equivalent of the benzenesulfonic acid.

Typically, benzenesulfonic acid (CAS RN 98-11-3) is a solid at 20°C with the molecular formula C<sub>6</sub>H<sub>6</sub>O<sub>3</sub>S (molecular weight of 158.18 g/mol). Salts of benzenesulfonic acid are known as benzenesulfonates, besilates (International Nonproprietary Name or INN) or besylates (United States Adopted Name or USAN).

In another particular embodiment of the present invention the *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide benzenesulfonate has an XRPD pattern with at least one peak at 2θ selected of 19.5±0.1.

In another particular embodiment of the present invention the *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide benzenesulfonate has an XRPD pattern comprising peaks at 2θ of 6.7±0.1, 8.5±0.1, 12.9±0.1, 13.7±0.1, 16.6±0.1, 19.5±0.1, 20.3±0.1, 20.7±0.1, 21.9±0.1, 22.8±0.1, 23.5±0.1, 24.9±0.1, 26.4±0.1 and 27.6±0.1.

In another particular embodiment of the present invention the *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide benzenesulfonate has an XRPD pattern comprising peaks at 2θ of 6.7±0.1, 8.5±0.1, 10.5±0.1, 12.5±0.1, 12.9±0.1, 13.7±0.1, 14.6±0.1, 15.5±0.1, 16.6±0.1, 17.0±0.1, 18.7±0.1, 19.5±0.1, 20.3±0.1, 20.7±0.1, 21.9±0.1, 22.8±0.1, 23.5±0.1, 24.9±0.1, 26.4±0.1, 27.6±0.1, 26.8±0.1, 29.3±0.1, 29.7±0.1, 31.0±0.1 and 31.6±0.1.

In another particular embodiment of the present invention the *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide benzenesulfonate has an XRPD pattern substantially as shown in Figure 12.

The invention also encompasses pharmaceutical compositions comprising a therapeutically effective amount of a salt as hereinabove defined and a pharmaceutically acceptable carrier.

5

### General synthetic procedures

The salts of the invention can be prepared using the methods and procedures described herein, or using similar methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of  
10 reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

15 Processes for preparing salts of the invention are provided as further embodiments of the invention and are illustrated by the procedures below.

The salt of the invention can be synthesized from *N*-[4-(4-[[*(1S)*-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7H-pyrrolo[2,3-*d*]pyrimidin-  
20 5-yl)-1H-indol-6-yl]sulfamide and methanesulfonic acid, ethanesulfonic acid or benzenesulfonic acid, which are commercially available from, for example, Scharlau or Sigma-Aldrich.

Suitable solvents for carrying out the reaction can be selected by a skilled chemist and  
25 may depend on the specific salt to be formed. Mixtures of appropriate solvents may be used, optionally containing water. For example, the appropriate solvents may be selected from methanol, ethanol, isopropanol, dichloromethane, tetrahydrofuran, acetone, acetonitrile, water or a mixture thereof.

30 Upon completion of any of the foregoing reactions, the salt can be isolated from the reaction mixture by any conventional means such as precipitation, concentration, centrifugation and the like.

A salt of the invention typically contains between about 0.60 and 1.20 molar equivalents of  
35 *N*-[4-(4-[[*(1S)*-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-

yl)ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide per molar equivalent of the acid, more typically 0.85 and 1.15 molar equivalents of *N*-[4-(4-[[[(1S)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide per molar equivalent of the acid, even  
5 more typically about 1 molar equivalent of *N*-[4-(4-[[[(1S)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide per molar equivalent of the acid.

The molar ratios described in the methods of the invention can be readily determined by  
10 various methods available to those skilled in the art. For example, such molar ratios can be readily determined by <sup>1</sup>H-NMR. Alternatively, elemental analysis and HPLC methods can be used to determine the molar ratio.

## 15 EXAMPLES

**General.** Reagents, starting materials, and solvents were purchased from commercial suppliers and used as received.

Crystallization tests of salts *N*-[4-(4-[[[(1S)-1-(5-methyl-4-oxo-3-phenyl-3,4-  
20 dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide with a broad range of pharmaceutically acceptable acids in a range of different pharmaceutically acceptable solvents (isopropanol, ethyl acetate, *tert*-butyl methyl ether and methyl isobutyl ketone) have been undertaken.

25 A number of solids which were semi-crystalline or displayed hints of crystallinity were obtained during the salt screen from isopropanol and ethyl acetate. No crystalline solids were obtained from methyl isobutyl ketone, *tert*-butyl methyl ether (with the exception of L-aspartic acid) or from further treatment of the gums obtained.

30 Surprisingly, only the salts from methanesulfonic acid, ethanesulfonic acid and benzenesulfonic acid had the required properties for dry powder inhalation.

Particularly good methods to prepare the addition salts of the invention are illustrated in the following examples.

35



X-Ray Powder Diffraction (XRPD) patterns were collected on a Bruker D8 diffractometer using Cu K $\alpha$  radiation ( $\lambda = 1.54056 \text{ \AA}$ , 40 kV, 40 mA),  $\theta - 2\theta$  goniometer, and divergence of V4 and receiving slits, a Ge monochromator and a Lynxeye detector. The instrument is performance checked using a certified Corundum standard (NIST 1976). The software used for data collection was Diffrac Commander v3.0 and the data were analysed and presented using Diffrac.EVA v4.0.

Samples were run under ambient conditions as flat plate specimens using powder as received. The sample was gently packed into a cavity cut into polished, zero-background (510) silicon wafer. The sample was rotated in its own plane during analysis. The details of the data collection were:

- Angular range: 5 to 40  $^{\circ}2\theta$
- Step size: 0.02  $^{\circ}2\theta$
- Collection time: 0.5 s/step

XRPD angle values may vary in the range  $\pm 1$  on the last decimal place. The measured relative intensities vs. the strongest peak are given as very strong (vs) above 50%, as strong (s) between 25 and 50%, as medium (m) between 10 and 25%, as weak (w) between 5 and 10% and as very weak (vw) under 5% relative peak height. It will be appreciated by a person skilled in the art that the XRPD intensities may vary between different samples and different sample preparations for a variety of reasons including preferred orientation. It will also be appreciated by a person skilled in the art that smaller shifts in the measured Angle may occur for a variety of reasons including variation of sample surface level in the diffractometer.

The differential scanning calorimetry (DSC) thermograms were obtained using a Mettler Toledo Instrument DSC1 STARe System equipped with a 34 position auto-sampler. Data were analysed and presented using STARe Software v12.10b. The calibration for energy and temperature was carried out using certified indium and zinc. Typically 0.5 – 3 mg of each sample, in a pin-holed aluminium pan, was heated at 10  $^{\circ}\text{C}/\text{min}$  from 25  $^{\circ}\text{C}$  to 300  $^{\circ}\text{C}$  (some runs up to 400 $^{\circ}\text{C}$ ). A purge of dry nitrogen at 50 ml/min was maintained over the sample. DSC values may vary in the range  $\pm 2$  on the last decimal place.

<sup>1</sup>H Nuclear Magnetic Resonance Spectra were recorded on a Varian Mercury plus operating at a frequency of 400 MHz for the <sup>1</sup>H spectra. Samples were dissolved in the specified deuterated solvent. Tetramethylsilane was used as reference.

- 5 Thermo-Gravimetric analysis (TGA) isotherms were collected on a Mettler Toledo TGA/SDTA 851e system, equipped with a 34 position autosampler. Data were analysed and presented using STARe Software v12.10b The instrument was temperature calibrated using certified Aluminium and Zinc and loss on drying was calibrated using and standard of Calcium Oxalate Monohydrate. Typically 1 – 10 mg of each sample was loaded onto a  
10 pre-tared aluminium DSC pan and heated at 10 °C/min from room temperature to 400°C. A nitrogen purge at 60 ml/min was maintained over the sample.

Gravimetric Vapour Sorption (GVS; also known as Dynamic Vapour Sorption or DVS) isotherms were obtained using a IGASORP moisture sorption analyser, controlled by DVS  
15 software IGASORP v6.20.43. The sample temperature was maintained at 25°C by the instrument controls. The humidity was controlled by mixing streams of dry and wet nitrogen. The relative humidity (RH) was measured by a calibrated Rotronic probe (dynamic range of 1.0 – 100 %RH), located near the sample. The weight change (mass relaxation) of the sample as a function of %RH was constantly monitored by the  
20 microbalance (accuracy ±0.005 mg). The microbalance was calibrated with weights of 20 and 200 mg and the relative humidity was calibrated with 10%, 50% and 80% RH standards and at 25°C and 40°C.

Typically 5 – 20 mg of sample were placed in a tared mesh stainless steel basket under ambient conditions. The sample was loaded and unloaded at 40 %RH and 25 °C (typical  
25 room conditions). A moisture sorption isotherm was performed as outlined below (4 scans giving 2 complete cycles). The standard isotherm was performed at 25°C at 10% RH intervals over a 0 – 90% RH range.

30 **Example 1: Preparation of *N*-[4-(4-[[*(1S)*]-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide methanesulfonate**

400 mg of *N*-[4-(4-[[*(1S)*]-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide were dissolved  
35 in 12 mL of isopropanol at 50°C. 1.1 equivalents of methanesulfonic acid

(methanesulfonic acid dissolved in tetrahydrofuran, 1M) were then added dropwise as a neat liquid. The sample was stirred (500 rpm) at 50°C for 1 hour. The sample was then slowly cooled to 5°C at 0.1°C/min and held at 5°C overnight. The solid formed was matured (50°C/5°C, cycles of 8h) for a week. The sample was filtered and then dried in a vacuum oven at 50°C for 2 days.

The <sup>1</sup>H-NMR spectra of the sample obtained confirmed the 1:1 stoichiometry of the solid.

Figure 1 illustrates the XRPD diffractogram of *N*-[4-(4-[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide methanesulfonate. The sample exhibits a good crystallinity.

The summary of the XRPD angles and relative intensities are given in Table 1 below.

Table 1

Diffraction Angle (2-Theta °)	Relative Intensity
8.1	s
8.7	vw
9.6	s
10.1	m
10.4	w
11.2	m
12.1	m
12.2	m
13.1	s
13.5	m
15.3	m
15.9	s
16.0	m
16.6	s
16.7	m
17.5	s
17.7	m
18.4	m
19.1	vs

Diffraction Angle (2-Theta °)	Relative Intensity
19.6	m
20.6	m
20.8	m
21.8	m
22.3	vs
22.8	s
23.2	m
23.5	s
24.1	s
24.6	s
25.5	m
26.0	m
26.7	w
28.2	w
28.7	w
30.1	w
30.6	vw
31.9	vw
32.4	w
33.0	vw
39.8	vw

Figure 2 illustrates the DSC thermogram of *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide methanesulfonate. The sample exhibits a characteristic high endotherm at onset 195.6°C (±0.2°C) followed by melting and decomposition. This behaviour confirms high stability of the sample until more than 185°C.

Figure 3 illustrates the GVS isotherm of *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide methanesulfonate. Mass change was approx. 2% from 0-80% RH.

Figure 4 corresponds to the <sup>1</sup>H-NMR spectrum of the methanesulfonate salt. It clearly shows a stoichiometry ratio of 1:1 free base / methanesulfonic acid, as inferred from the comparison between the integral values of the protons corresponding to the methyl group of methanesulfonate and a methyl group of *N*-[4-(4-[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide.

**Example 2: Preparation of *N*-[4-(4-[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-**

**10 dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate**

400 mg of *N*-[4-(4-[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide were dissolved in 12 mL of isopropanol at 50°C. 1.1 equivalents of ethanesulfonic acid (ethanesulfonic acid dissolved in tetrahydrofuran, 1M) were then added dropwise as a neat liquid. The sample was stirred (500 rpm) at 50°C for 1 hour. The sample was then slowly cooled to 5°C at 0.1°C/min and then warmed up to 50°C at the same speed. These cycles of 8h were repeated for 4 days. The solid formed was filtered and then dried in a vacuum oven at 50°C for 2 days.

The <sup>1</sup>H-NMR spectra of the sample obtained confirmed the 1:1 stoichiometry of the solid with no residual solvents.

Figure 5 illustrates the XRPD diffractogram of *N*-[4-(4-[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate. The sample exhibits a good crystallinity.

The summary of the XRPD angles and relative intensities are given in Table 2 below.

30 Table 2

Diffraction Angle (2-Theta °)	Relative Intensity (%)
7.3	vs
8.7	vs
8.9	s
10.0	s

Diffraction Angle (2-Theta °)	Relative Intensity (%)
10.6	m
11.7	m
12.1	m
12.8	s
13.6	w
14.2	w
15.1	w
15.9	s
16.8	m
17.7	m
19.2	s
19.5	vs
20.1	s
21.5	s
21.1	m
21.7	vs
22.2	s
23.2	s
23.4	s
24.0	s
25.4	s
26.3	m
27.3	m
28.7	w
30.3	w
31.3	vw
33.7	w
35.7	vw
37.7	vw

Figure 6 illustrates the DSC thermogram of *N*-[4-(4-[[1*S*]-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide ethanesulfonate. The sample exhibits a characteristic high endotherm

at onset 107.9°C ( $\pm 0.2^\circ\text{C}$ ) and 180.0°C ( $\pm 0.2^\circ\text{C}$ ). This confirms the high stability of the sample until more than 100°C.

Figure 7 illustrates the GVS isotherm of *N*-[4-(4-[[*(1S)*]-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate. Mass change was approx. 3.5% from 0-80% RH. This water sorption was reversible and no hydrates were formed during the GVS process.

Figure 8 corresponds to the  $^1\text{H}$ -NMR spectrum of the ethanesulfonate salt. It clearly shows a stoichiometry ratio of **1:1** free base / ethanesulfonic acid, as inferred from the comparison between the integral values of the protons corresponding to the  $\text{CH}_3$ - group of ethanesulfonate and a methyl group of *N*-[4-(4-[[*(1S)*]-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide.

15

**Example 3: Preparation of *N*-[4-(4-[[*(1S)*]-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate type A polymorph**

20 A mixture of 0.8 kg of *N*-[4-(4-[[*(1S)*]-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide and 18.2 kg of isopropanol were heated at 50°C. Then a solution of 0.153 kg of ethanesulfonic acid in 1.0 kg of tetrahydrofuran was added during 1 h approx. The mixture was stirred at 50°C for 15 minutes, and after that, slowly cooled to 20-25°C. The solid formed was filtered and then dried in a vacuum oven, first at 50°C, and after that at 70°C. This crude product is dissolved in a boiling mixture of 10.2 Kg of isopropanol and 10.3 Kg of methanol, and then, slowly cooled to 0-5°C. The solid formed was filtered and then dried in a vacuum oven, first at 50°C, and after that at 70°C. Around 0.6-0.7 kg of the desired product were obtained.

30 The  $^1\text{H}$  NMR spectra of the sample obtained confirmed the 1:1 stoichiometry of the solid with no residual solvents.

Figure 9 illustrates the XRPD diffractogram of *N*-[4-(4-[[*(1S)*]-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-

indol-6-yl]sulfamide ethanesulfonate type A polymorph. The sample exhibits a good crystallinity.

The summary of the XRPD angles and relative intensities are given in Table 3 below.

5

Table 3

Diffraction Angle (2-Theta °)	Relative Intensity (%)
7.5	vs
7.6	vs
8.9	w
9.2	w
10.5	vw
11.6	w
12.7	m
15.1	vw
15.8	m
16.6	w
17.6	w
18.5	m
19.0	m
19.5	s
22.0	m
22.4	s
23.5	w
24.1	m
25.3	w
26.3	vw
27.0	vw
28.6	vw
30.8	vw

10 **Example 4: Preparation of *N*-[4-(4-[[*(1S)*]-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino}-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate type B polymorph**



Method 1: 0.5 g of the product obtained above (polymorph A) are stirred in 1.5 mL of Methanol for 5 days, and then filtered. After drying in a vacuum oven at 50°C, polymorph B is obtained.

- 5 Method 2: 10 g of *N*-[4-(4-[[*(1S)*]-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide were dissolved at 50°C in a mixture of 150 mL of isopropanol, 150 mL of methanol and 3 mL of water. Then 1.91 g of ethanesulfonic acid were added dropwise. The mixture was slowly cooled to 0-5°C. The solid formed was filtered and then dried in a vacuum oven,  
10 first at 50°C, and after that at 70°C. Around 9.2 g of esylate were obtained. 8.7 g of this crude product is stirred in 43.5 mL of methanol, and heated at reflux during 30 minutes. The mixture was slowly cooled to 0-5°C, and the solid filtered and then dried in a vacuum oven at 50°C. 7.7 g of polymorph B were obtained.

- The <sup>1</sup>H NMR spectra of the sample obtained confirmed the 1:1 stoichiometry of the solid  
15 with no residual solvents.

- Figure 10 illustrates the XRPD diffractogram of *N*-[4-(4-[[*(1S)*]-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate type B polymorph. The sample exhibits a good  
20 crystallinity.

The summary of the XRPD angles and relative intensities are given in Table 4 below.

Table 4

Diffraction Angle (2-Theta °)	Relative Intensity (%)
8.5	vs
9.9	s
11.1	m
12.7	s
13.5	m
14.0	m
14.3	w
16.7	s
17.7	m

Diffraction Angle (2-Theta °)	Relative Intensity (%)
19.5	s
20.0	s
21.7	m
22.1	m
22.5	m
23.3	s
24.1	m
25.5	w
25.8	m
26.6	m
27.2	m
28.1	m

**Example 5: Preparation of *N*-[4-(4-[[*(1S)*-1-(5-methyl-4-oxo-3-phenyl-3,4-**

**5 dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino}-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide benzenesulfonate**

400 mg of *N*-[4-(4-[[*(1S)*-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino}-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide were dissolved  
 10 in 12 mL of isopropanol at 50°C. 1.1 equivalents of benzenesulfonic acid (benzenesulfonic acid dissolved in tetrahydrofuran, 1M) were then added dropwise as a neat liquid. The sample was stirred (500 rpm) at 50°C for 1 hour. The sample was then slowly cooled to 5°C at 0.1°C/min and then warmed up to 50°C at the same speed. These cycles of 8h were repeated for 4 days. The solid formed was filtered and then dried in a vacuum oven  
 15 at 50°C for 2 days.

The <sup>1</sup>H-NMR spectra of the sample obtained confirmed the 1:1 stoichiometry of the solid.

Figure 12 illustrates the XRPD diffractogram of *N*-[4-(4-[[*(1S)*-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino}-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-  
 20 indol-6-yl]sulfamide benzenesulfonate. The sample exhibits a good crystallinity.

The summary of the XRPD angles and relative intensities are given in Table 5 below.

Table 5

Diffraction Angle (2-Theta °)	Relative Intensity (%)
6.7	vs
8.5	s
10.5	m
12.5	m
12.9	s
13.7	vs
14.6	m
15.5	m
16.6	s
17.0	m
18.7	m
19.5	vs
20.3	vs
20.7	vs
21.9	s
22.8	s
23.5	s
24.9	vs
26.4	s
27.6	s
26.8	m
29.3	m
29.7	w
31.0	m
31.6	m

Figure 13 illustrates the DSC thermogram of *N*-[4-(4-[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide benzenesulfonate. The sample exhibits a characteristic high endotherm at onset 170.6°C (±0.2°C). This confirms the high stability of the sample until more than 160°C.

Figure 14 illustrates the GVS isotherm of *N*-[4-(4-[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide benzenesulfonate. Mass change was approx. 5% from 0-80% RH.

5

Figure 15 corresponds to the <sup>1</sup>H-NMR spectrum of the benzenesulfonate salt. It clearly shows a stoichiometry ratio of **1:1** free base / benzenesulfonic acid, as inferred from the comparison between the integral values of the protons corresponding to benzene group of benzenesulfonate and a methyl group of *N*-[4-(4-[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide.

10

As it can be seen from the above results, the salts of the present invention displayed good thermal behaviour, are not hygroscopic, had a relatively high melting point and showed appropriate XRPD pattern before and after GVS determination (no change in form or crystallinity).

15

### Pharmaceutical compositions

The pharmaceutical formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient(s) into association with the carrier. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

25

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Formulations generally comprise a powder mix for inhalation of the salt of the invention and a suitable powder base (carrier substance) such as starch or a pharmaceutically acceptable sugar, such as lactose or glucose. Use of lactose is preferred. The powder base may include additional components such as preservatives, stabilizing agents, absorption enhancers or aerodynamic modifier.

30

Each capsule or cartridge may generally contain between 0.1 µg and 9000 µg of each therapeutically active ingredient. Alternatively, the active ingredient (s) may be presented without excipients.

- 5 Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi-dose delivery, the formulation can be pre-metered or metered in use. Dry powder inhalers are thus classified into three groups: (a) single dose, (b) multiple unit dose and (c) multi dose devices. Preferably, the formulation is administered by a multi-dose device.

10

Multi-dose inhalers do not contain pre-measured quantities of the powder formulation. They consist of a relatively large container and a dose measuring principle that has to be operated by the patient. The container bears multiple doses that are isolated individually from the bulk of powder by volumetric displacement. Various dose measuring principles exist, including rotatable membranes (e. g. EP0069715) or disks (e. g. GB 2041763; EP 15 0424790; DE 4239402 and EP 0674533), rotatable cylinders (e. g. EP 0166294; GB 2165159 and WO 92/09322) and rotatable frustums (e. g. WO 92/00771), all having cavities which have to be filled with powder from the container. Other multi dose devices have measuring plungers with a local or circumferential recess to displace a certain 20 volume of powder from the container to a delivery chamber or an air conduit (e. g. EP 0505321, WO 92/04068 and WO 92/04928), or measuring slides such as the Genuair® devise (formerly known as Novolizer SD2FL) which is described in the following patent applications: WO 97/000703, WO 03/000325 and WO2006/008027.

- 25 Formulation Example 1 (Formulation for inhalation with a DPI)

Ingredient	Amount
<i>N</i> -[4-(4-[[1 <i>S</i> ]-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1- <i>f</i> ][1,2,4]triazin-2-yl)ethyl]amino)-7 <i>H</i> -pyrrolo[2,3- <i>d</i> ]pyrimidin-5-yl)-1 <i>H</i> -indol-6-yl]sulfamide methanesulfonate (micronized)	15 mg
Lactose	3000 mg

Formulation Example 2 (Formulation for inhalation with a DPI)

Ingredient	Amount
<i>N</i> -[4-(4-[[[(1 <i>S</i> )-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1- <i>f</i> ][1,2,4]triazin-2-yl)ethyl]amino]-7 <i>H</i> -pyrrolo[2,3- <i>d</i> ]pyrimidin-5-yl)-1 <i>H</i> -indol-6-yl]sulfamide ethanesulfonate (micronized)	15 mg
Lactose	3000 mg

## Formulation Example 3 (Formulation for inhalation with a DPI)

Ingredient	Amount
<i>N</i> -[4-(4-[[[(1 <i>S</i> )-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1- <i>f</i> ][1,2,4]triazin-2-yl)ethyl]amino]-7 <i>H</i> -pyrrolo[2,3- <i>d</i> ]pyrimidin-5-yl)-1 <i>H</i> -indol-6-yl]sulfamide ethanesulfonate type A polymorph (micronized)	15 mg
Lactose	3000 mg

## Formulation Example 4 (Formulation for inhalation with a DPI)

Ingredient	Amount
<i>N</i> -[4-(4-[[[(1 <i>S</i> )-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1- <i>f</i> ][1,2,4]triazin-2-yl)ethyl]amino]-7 <i>H</i> -pyrrolo[2,3- <i>d</i> ]pyrimidin-5-yl)-1 <i>H</i> -indol-6-yl]sulfamide ethanesulfonate type B polymorph (micronized)	15 mg
Lactose	3000 mg

5

## Formulation Example 5 (Formulation for inhalation with a DPI)

Ingredient	Amount
<i>N</i> -[4-(4-[[[(1 <i>S</i> )-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1- <i>f</i> ][1,2,4]triazin-2-yl)ethyl]amino]-7 <i>H</i> -pyrrolo[2,3- <i>d</i> ]pyrimidin-5-yl)-1 <i>H</i> -indol-6-yl]sulfamide benzenesulfonate (micronized)	15 mg

Lactose	3000 mg
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### Additional therapeutic agents

The salts of the invention may also be combined with a therapeutically effective amount of one or more other therapeutic agents useful in the treatment or prevention of pathological conditions or diseases susceptible to amelioration by inhibition of Phosphoinositide 3-Kinase (PI3K).

The combinations of the invention can optionally comprise a therapeutically effective amount one or more additional active substances which are known to be useful in the treatment of respiratory diseases, such as: (a) corticosteroids and glucocorticoids; (b) antihistamines; (c) chemokine receptor antagonists; (d) chemoattractant receptor homologous molecule expressed on TH<sub>2</sub> cells (CRTH<sub>2</sub>) antagonist; (e) leukotriene receptor antagonists; (f) Janus kinase (JAK) inhibitors; (g) Spleen tyrosine kinase (Syk) inhibitors; (h) Phosphodiesterase (PDE) IV inhibitors; (i) p38 Mitogen-Activated Protein Kinase (p38 MAPK) Inhibitors; (j) Anticholinergic agents; (k) Beta adrenergic agonists; (l) MABA (molecules with dual activity: beta-adrenergic agonists and muscarinic receptor antagonist; (m) Protein Kinase Inhibitors (PKC) inhibitors; (n) 5-lipoxygenase-activating protein (FLAP) inhibitors; (o) 5-lipoxygenase (5-LO) inhibitors; (p) Cysteinyl leukotriene (CysLT) receptor antagonists; (q) CYSLTR2 antagonists; (r) BLT1 antagonists; (s) BLT2 antagonists; (t) thromboxane A<sub>2</sub> antagonists; (u) DP1 receptor antagonists; (v) DP1 receptor agonists; (w) IP receptor agonists; (x) Anti-IgE; (y) IL5 antibody; (z) leukotriene formation inhibitors; (aa) decongestants; (bb) mucolytics; (cc) antitussives; (dd) analgesics; and (ee) expectorants.

The amount of each active which is required to achieve a therapeutic effect will, of course, vary with the particular active, the route of administration, the subject under treatment, and the particular disorder or disease being treated.

The active ingredients may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity. Preferably, the active ingredients are administered once or twice a day.

Examples of suitable corticosteroids and glucocorticoids that can be combined with salt compound of the present invention are prednisolone, methylprednisolone, dexamethasone, dexamethasone cipeclate, naflocort, deflazacort, halopredone acetate, budesonide, beclomethasone dipropionate, hydrocortisone, triamcinolone acetonide, 5 fluocinolone acetonide, fluocinonide, clocortolone pivalate, methylprednisolone aceponate, dexamethasone palmitoate, tipredane, hydrocortisone aceponate, prednicarbate, alclometasone dipropionate, halometasone, methylprednisolone suleptanate, mometasone furoate, rimexolone, prednisolone farnesylate, ciclesonide, butixocort propionate, deprodone propionate, fluticasone propionate, fluticasone furoate, 10 halobetasol propionate, loteprednol etabonate, betamethasone butyrate propionate, flunisolide, prednisone, dexamethasone sodium phosphate, triamcinolone, betamethasone 17-valerate, betamethasone, betamethasone dipropionate, hydrocortisone acetate, hydrocortisone sodium succinate, prednisolone sodium phosphate or hydrocortisone probutate.

15

Examples of suitable anti-histamines that can be combined with the salts of the invention are methapyrilene, mequitazine, azelastine hydrochloride, acrivastine, emedastine difumarate, emedastine fumarate, loratadine, cyproheptadine hydrochloride, diphenhydramine hydrochloride, doxepin hydrochloride, promethazine hydrochloride, 20 levocabastine hydrochloride, desloratadine, cinnarizine, setastine hydrochloride, mizolastine, ebastine, cetirizine hydrochloride, epinastine hydrochloride, olopatadine hydrochloride, bepotastine besilate, triprolidine hydrochloride, rupatadine fumarate, fexofenadine hydrochloride, levocetirizine dihydrochloride, ketotifen, azatadine maleate, dimethindene maleate, clemastine fumarate, alcaftadine, bilastine, vapitadine 25 hydrochloride, AZD-1744, GSK-1004723D, GSK-835726 or SUN-1334H.

Examples of suitable chemokine receptor antagonists that can be combined with the salts of the invention are maraviroc or enfuvirtide.

30 Examples of suitable CRTH<sub>2</sub> antagonist that can be combined with the salts of the present invention are ramatroban, AMG-009, OC-000459, AZD-1981, ACT-129968 or QAV-680.

Examples of suitable leukotriene antagonist that can be combined with the salts of the present invention are CYSLTR1 antagonists, such as montelukast, pranlukast or 35 zafirlukast; or CYSLTR2 antagonists, such as pranlukast, zafirlukast or tipilukast.



Examples of suitable JAK inhibitors that can be combined with the salt of the present invention are tofacitinib, ruxolitinib, baricitinib, decernotinib, filgotinib, peficitinib, INCB-039110, INCB-047986, ABT-494, INCB-047986 or AC-410.

5

Examples of suitable Syk kinase inhibitors that can be combined with the salts of the present invention are fosfatinib (from Rigel), R-348 (from Rigel), R-343 (from Rigel), R-112 (from Rigel), piceatannol, 2-(2-Aminoethylamino)-4-[3-(trifluoromethyl)phenylamino]pyrimidine-5-carboxamide, R-091 (from Rigel), 6-[5-Fluoro-2-(3,4,5-trimethoxyphenylamino)pyrimidin-4-ylamino]-2,2-dimethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-3-one benzenesulfonate (R-406 from Rigel), 1-(2,4,6-Trihydroxyphenyl)-2-(4-methoxyphenyl)ethan-1-one, N-[4-[6-(Cyclobutylamino)-9H-purin-2-ylamino]phenyl]-N-methylacetamide (QAB-205 from Novartis), CI-1002 (from Pfizer), VRT-750018 (from Vertex), PRT-062607, 2-[7-(3,4-Dimethoxyphenyl)imidazo[1,2-c]pyrimidin-5-ylamino]pyridine-3-carboxamide dihydrochloride (BAY-61-3606 from Bayer) or AVE-0950 (from Sanofi-Aventis).

Examples of suitable PDE4 inhibitors that can be combined with salt compounds of the present invention are benafentrine dimaleate, etazolate, denbufylline, rolipram, 20 cipamfylline, zardaverine, arofylline, filaminast, tipelukast, tofimizast, piclamilast, tolafentrine, mesopram, drotaverine hydrochloride, lirimilast, roflumilast, cilomilast, oglemilast, apremilast, tetomilast, filaminast, (R)-(+)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine (CDP-840), N-(3,5-Dichloro-4-pyridinyl)-2-[1-(4-fluorobenzyl)-5-hydroxy-1H-indol-3-yl]-2-oxoacetamide (GSK-842470), 9-(2-25 Fluorobenzyl)-N6-methyl-2-(trifluoromethyl)adenine (NCS-613), N-(3,5-Dichloro-4-pyridinyl)-8-methoxyquinoline-5-carboxamide (D-4418), 3-[3-(Cyclopentyloxy)-4-methoxybenzyl]-6-(ethylamino)-8-isopropyl-3H-purine hydrochloride (V-11294A), 6-[3-(N,N-Dimethylcarbamoyl)phenylsulfonyl]-4-(3-methoxyphenylamino)-8-methylquinoline-3-carboxamide hydrochloride (GSK-256066), 4-[6,7-Diethoxy-2,3-30 bis(hydroxymethyl)naphthalen-1-yl]-1-(2-methoxyethyl)pyridin-2(1H)-one (T-440), (-)-trans-2-[3'-[3-(N-Cyclopropylcarbamoyl)-4-oxo-1,4-dihydro-1,8-naphthyridin-1-yl]-3-fluorobiphenyl-4-yl]cyclopropanecarboxylic acid (MK-0873), CDC-801, UK-500001, BLX-914, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one, *cis* [4-cyano-4-(3-cyclopropylmethoxy-4-

difluoromethoxyphenyl)cyclohexan-1-ol, CDC-801 or 5(S)-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3(S)-(3-methylbenzyl)piperidin-2-one (IPL-455903).

5 Example of suitable p38 MAPK inhibitor that can be combined with salt compounds of the present invention is ARRY-797.

Examples of suitable M3 antagonists (anticholinergics) that can be combined with salt compounds of the present invention are tiotropium, umeclidinium, acridinium, glycopyrrolate or ipratropium.

10

Examples of suitable beta adrenergic agonists ( $\beta$ 2-agonists) that can be combined with the PI3K inhibitors of the present invention are salmeterol, formoterol, arformoterol, indacaterol, vilanterol, abediterol or olodaterol.

15 Examples of suitable MABA compounds that can be combined with salt compounds of the present invention are batefenterol, LAS190792, LAS191351 or TEI-3252.

Example of suitable PKC inhibitor that can be combined with salt compounds of the present invention is NVP-AEB071.

20

Examples of suitable FLAP inhibitors that can be combined with salt compounds of the present invention are MK886 or BAY X 1005.

25 Example of suitable 5-LO inhibitor that can be combined with salt compounds of the present invention is WY-50295T.

Example of suitable CysLT receptor antagonists that can be combined with salt compounds of the present invention is montelukast.

30 Example of suitable thromboxane A2 antagonists that can be combined with salt compounds of the present invention is ramatroban.

Example of suitable DP1 receptor antagonists that can be combined with salt compounds of the present invention is laropiprant.

35

Example of suitable DP1 receptor agonists that can be combined with salt compounds of the present invention is BW-245C.

5 Example of suitable IP receptor agonists that can be combined with salt compounds of the present invention is RO-1138452.

Example of suitable Anti-IgE that can be combined with salt compounds of the present invention is omalizumab.

10 Example of suitable IL5 antibody that can be combined with salt compounds of the present invention is mepolizumab.

15 Examples of suitable decongestants that can be combined with salt compounds of the present invention are ephedrine, levo-methamphetamine, naphazoline, oxymetazoline, phenylephrine, phenylpropanolamine, propylhexedrine, pseudoephedrine, synephrine or tetrahydrozoline.

20 Examples of suitable mucolytics that can be combined with salt compounds of the present invention are acetylcysteine, ambroxol, bromhexine, carbocisteine, domiodol, eprazinone, erdosteine, letosteine, neltenequine, sobrerol, stepronin or tiopronin.

Example of suitable antitussives that can be combined with salt compounds of the present invention is dextromethorphan.

25 Examples of suitable analgesics that can be combined with salt compounds of the present invention are aspirin, paracetamol, rofecoxid, celecoxib, morphine, codeine, oxycodone, hydrocodone, dihydromorphine or flupirtine.

30 And examples of suitable expectorants that can be combined with salt compounds of the present invention are antimony pentasulfide, guaiacolsulfonate, guaifenesin, potassium iodide or tyloxapol.

35 **Treatment of a pathological conditions or diseases associated with phosphoinositide 3-kinase (PI3K) activity**

The salts of the invention, pharmaceutical compositions and the combinations of the invention may be used in the treatment of a pathological condition or disease susceptible to amelioration by inhibition of Phosphoinositide 3-Kinase (PI3K), typically respiratory diseases. The respiratory disease is preferably one selected from asthma, Chronic  
5 Obstructive Pulmonary Disease (COPD), cystic fibrosis, bronchiectasis, cough, idiopathic pulmonary fibrosis and sarcoidosis. Asthma or chronic obstructive pulmonary disease are more preferred.

10 The active compound in the combination and the other therapeutic agent(s) as defined above, may be administered together in the same pharmaceutical composition or in different compositions intended for separate, simultaneous, concomitant or sequential administration by the same or a different route.

15 It is contemplated that all active agents would be administered at the same time, or very close in time. Alternatively, one or two actives could be taken in the morning and the other(s) later in the day. Or in another scenario, one or two actives could be taken twice daily and the other(s) once daily, either at the same time as one of the twice-a-day dosing occurred, or separately. Preferably at least two, and more preferably all, of the actives would be taken together at the same time. Preferably, at least two, and more preferably all  
20 actives would be administered as an admixture.

The active substance compositions according to the invention are preferably administered in the form of compositions for inhalation delivered with the help of inhalers, especially dry powder inhalers, however, any other form or parenteral or oral application is possible.  
25 Here, the application of inhaled compositions embodies the preferred application form, especially in the therapy of chronic obstructive pulmonary disease or for the treatment of asthma.

30

## CLAIMS

1. A pharmaceutically acceptable crystalline addition salt of *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-  
5 d]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide with sulfonic acid derivatives selected from methanesulfonic acid, ethanesulfonic acid and benzenesulfonic acid, or any pharmaceutically acceptable solvates thereof.
2. A salt according to claim 1 which is *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-  
10 dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide methanesulfonate, or pharmaceutically acceptable solvates thereof.
3. A salt according to claim 1 which is *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-  
15 dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide ethanesulfonate, or pharmaceutically acceptable solvates thereof.
4. A salt according to claim 1 which is *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-  
20 dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide benzenesulfonate, or pharmaceutically acceptable solvates thereof.
5. A pharmaceutical composition comprising a therapeutically effective amount of a salt as defined in any one of claims 1 to 4 and a pharmaceutically acceptable carrier.
6. A pharmaceutical composition according to claim 5, which is formulated for  
25 administration by inhalation as a dry powder.
7. A pharmaceutical composition according to claim 5 or 6, wherein the composition further comprises a therapeutically effective amount of one or more other therapeutic  
30 agents.
8. A pharmaceutical composition according to claim 7 wherein the other therapeutic agent is selected from:
- (a) corticosteroids and glucocorticoids;
  - (b) antihistamines;
  - 35 (c) chemokine receptor antagonists;

- (d) chemoattractant receptor homologous molecule expressed on TH<sub>2</sub> cells  
(CRTH<sub>2</sub>) antagonist;
- (e) leukotriene receptor antagonists;
- (f) Janus kinase (JAK) inhibitors;
- 5 (g) Spleen tyrosine kinase (Syk) inhibitors;
- (h) Phosphodiesterase (PDE) IV inhibitors;
- (i) p38 Mitogen-Activated Protein Kinase (p38 MAPK) Inhibitors;
- (j) Anticholinergic agents;
- (k) Beta adrenergic agonists;
- 10 (l) MABA (molecules with dual activity: beta-adrenergic agonists and muscarinic  
receptor antagonist;
- (m) Protein Kinase Inhibitors (PKC) inhibitors;
- (n) 5-lipoxygenase-activating protein (FLAP) inhibitors;
- (o) 5-lipoxygenase (5-LO) inhibitors;
- 15 (p) Cysteinyl leukotriene (CysLT) receptor antagonists;
- (q) Cysteinyl leukotriene Receptor 2 (CYSLTR2) antagonists;
- (r) BLT1 antagonists;
- (s) BLT2 antagonists;
- (t) thromboxane A<sub>2</sub> antagonists;
- 20 (u) DP1 receptor antagonists;
- (v) DP1 receptor agonists;
- (w) IP receptor agonists;
- (x) Anti-IgE;
- (y) IL5 antibody;
- 25 (z) leukotriene formation inhibitors;
- (aa) decongestants;
- (bb) mucolytics;
- (cc) antitussives;
- (dd) analgesics; and
- 30 (ee) expectorants.

9. A combination comprising a salt as defined in any one of claims 1 to 4 and one or more other therapeutic agents, as defined in claim 8.

10. A salt as defined in any one of claims 1 to 4, a pharmaceutical composition as defined in any one of claims 5 to 8 or a combination as defined in claim 9 for use in the treatment of a pathological condition or disease susceptible to amelioration by inhibition of Phosphoinositide 3-Kinase (PI3K).

5

11. A salt, pharmaceutical composition or combination for use as defined in claim 10, wherein the pathological condition or disease are respiratory disease, preferably, asthma, Chronic Obstructive Pulmonary Disease (COPD), cystic fibrosis, bronchiectasis, cough, idiopathic pulmonary fibrosis and sarcoidosis.

10

12. A salt, pharmaceutical composition or combination for use as defined in claim 11, wherein the pathological condition or disease is asthma or Chronic Obstructive Pulmonary Disease (COPD).

15

13. Use of a salt as defined in any one of claims 1 to 4, a pharmaceutical composition as defined in any one of claims 5 to 8 or a combination as defined in claim 9 for the manufacture of a medicament for the treatment of a pathological condition or disease as defined in any one of claims 10 to 12.

20

14. A method of treatment of a subject afflicted with a pathological condition or disease as defined in any one of claims 10 to 12, which comprises administering to said subject an effective amount of a salt as defined in any one of claims 1 to 4, a pharmaceutical composition as defined in any one of claims 5 to 8 or a combination as defined in claim 9.

Figure 1

XRPD diffractogram of *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino}-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide methanesulfonate

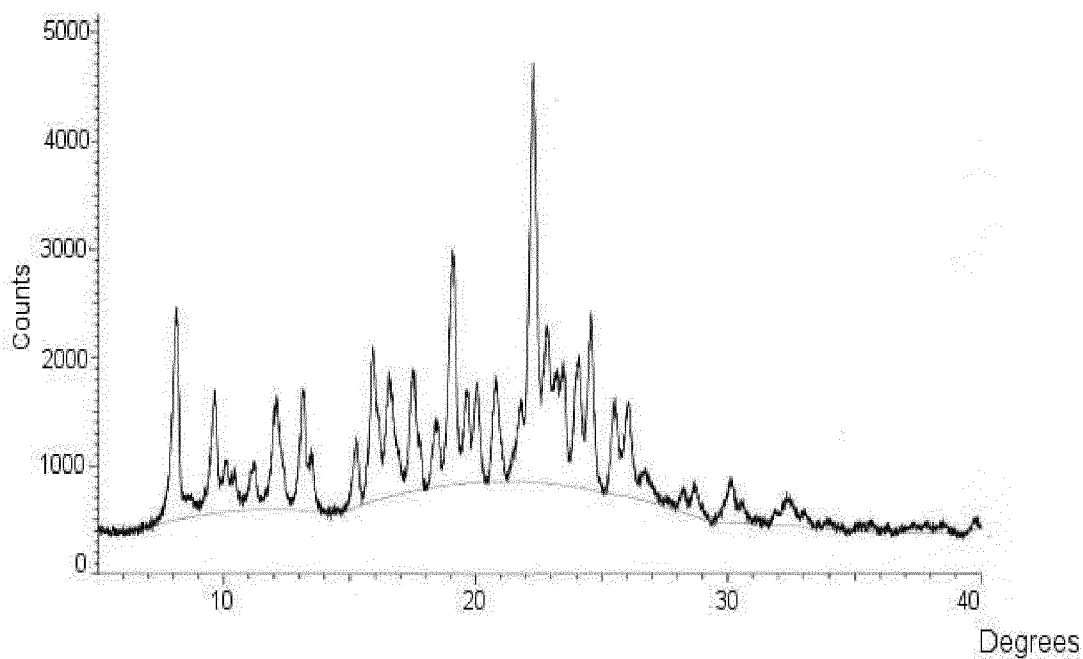




Figure 2

DSC thermogram of *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino}-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide methanesulfonate

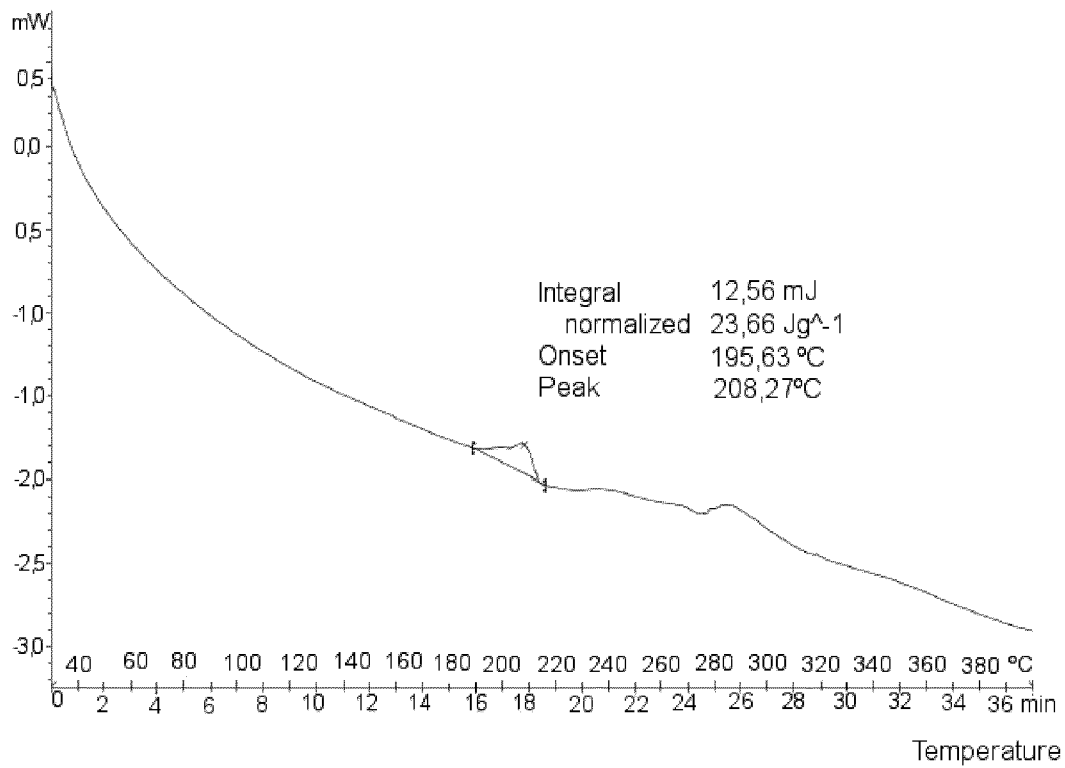


Figure 3

GVS isotherm of *N*-[4-(4-[[1*S*]-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino}-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide methanesulfonate

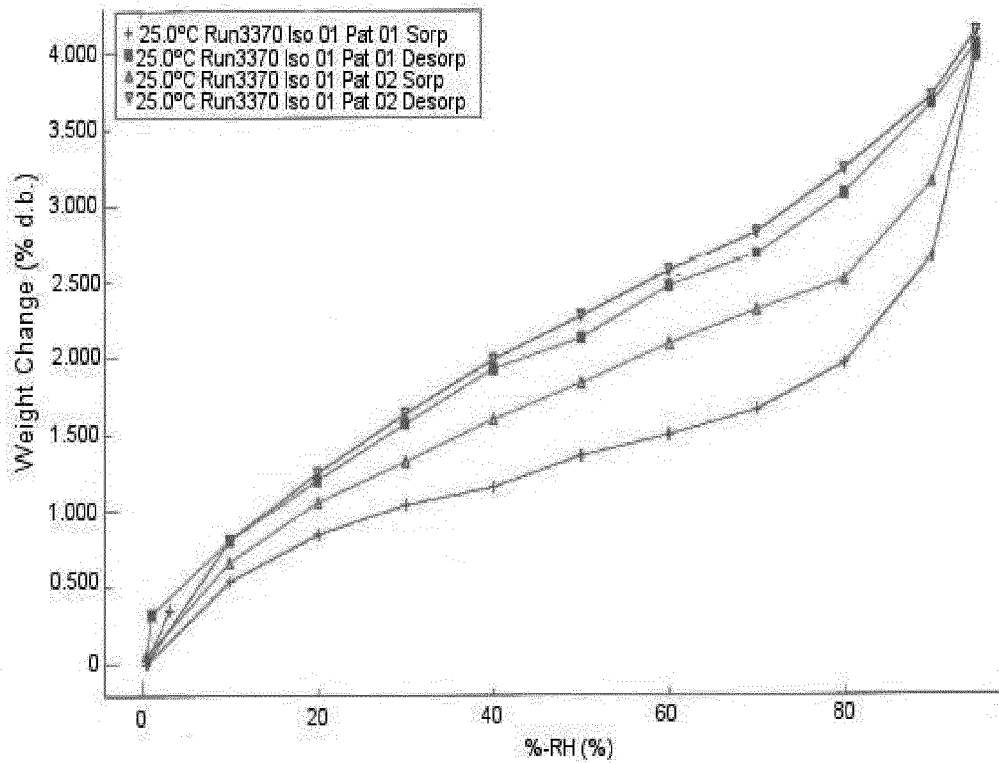


Figure 4

<sup>1</sup>H-NMR spectrum (400MHz, DMSO-*d*<sub>6</sub>) of *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide ethanesulfonate

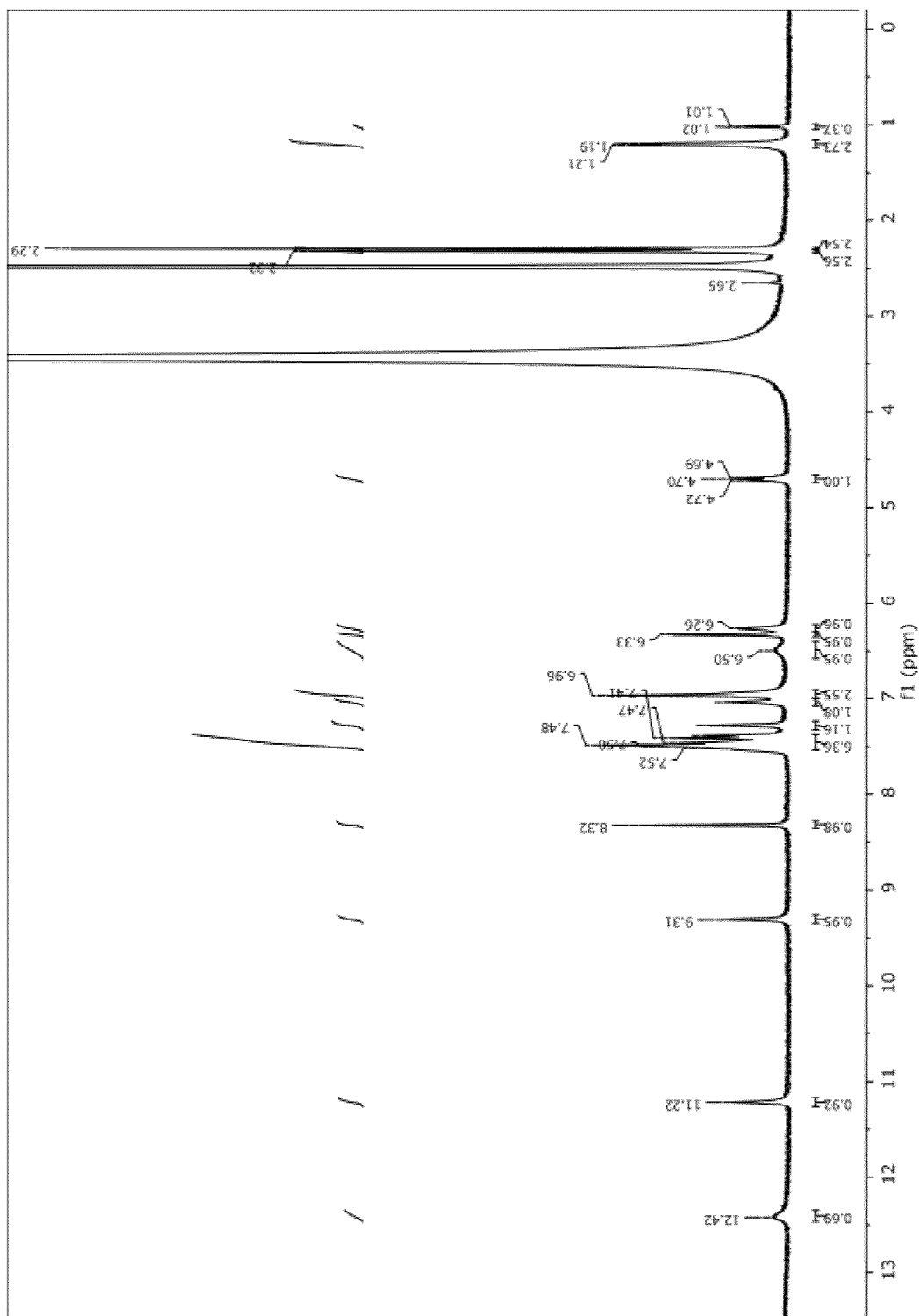


Figure 5

XRPD diffractogram of *N*-[4-(4-[[*(1S)*-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino}-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide ethanesulfonate

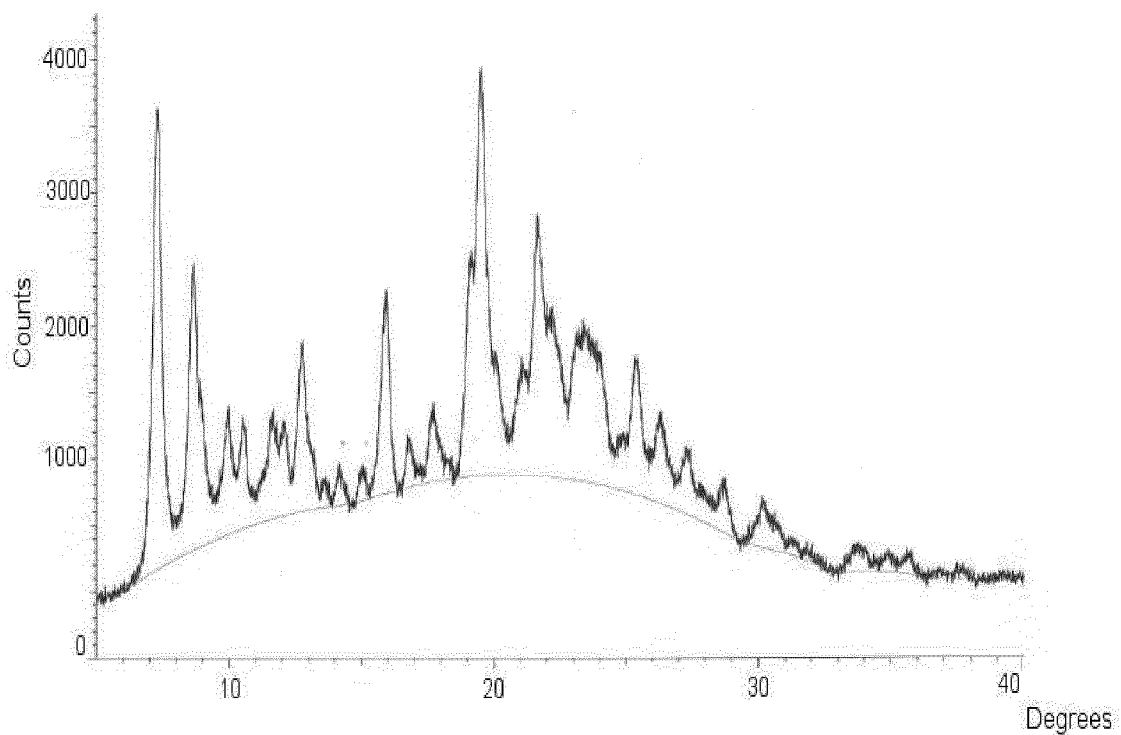


Figure 6

DSC thermogram of *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino}-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate

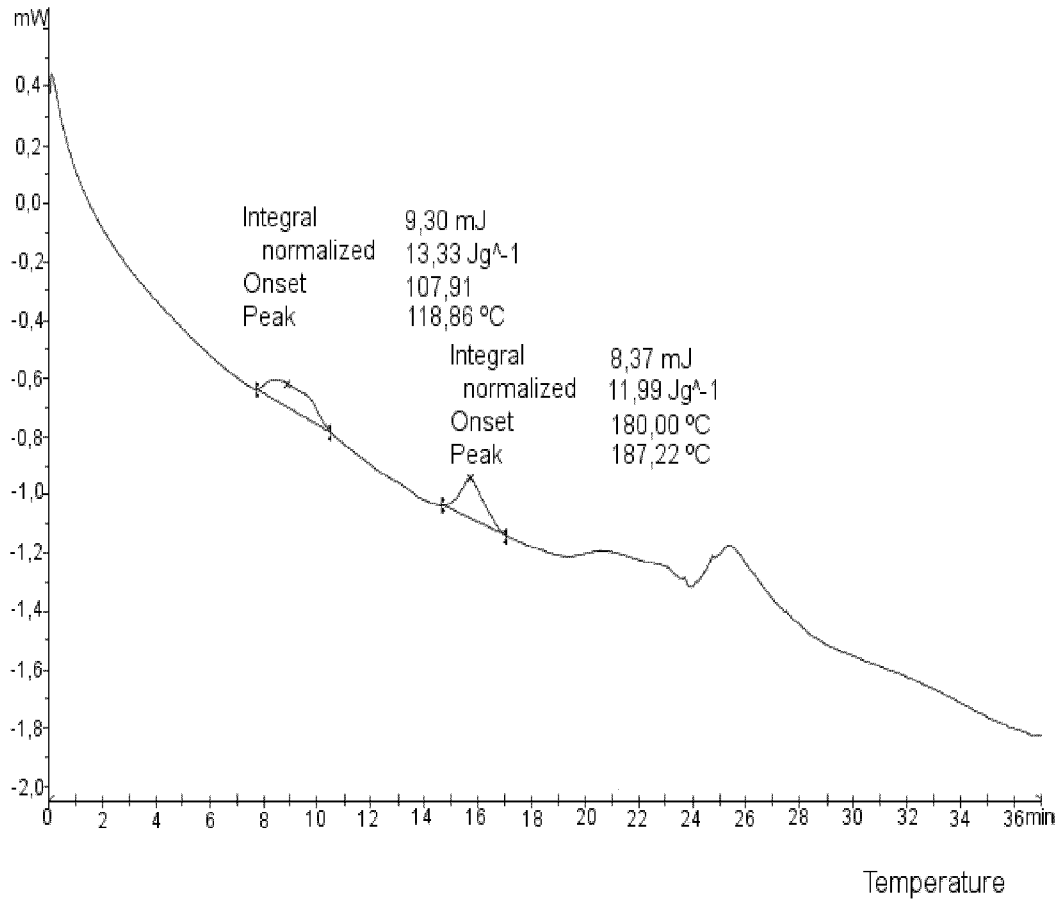


Figure 7

GVS isotherm of *N*-[4-(4-[[*(1S)*]-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino}-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide ethanesulfonate

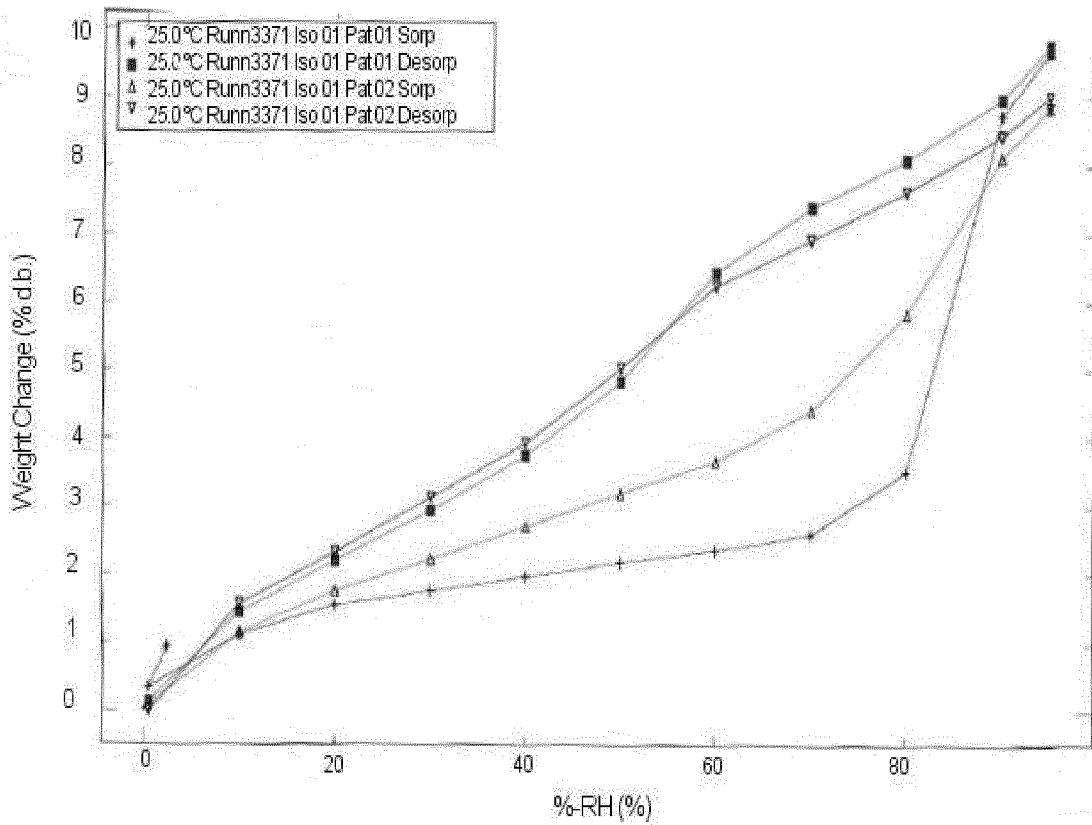


Figure 8

<sup>1</sup>H-NMR spectrum (400MHz, DMSO-d<sub>6</sub>) of *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide ethanesulfonate

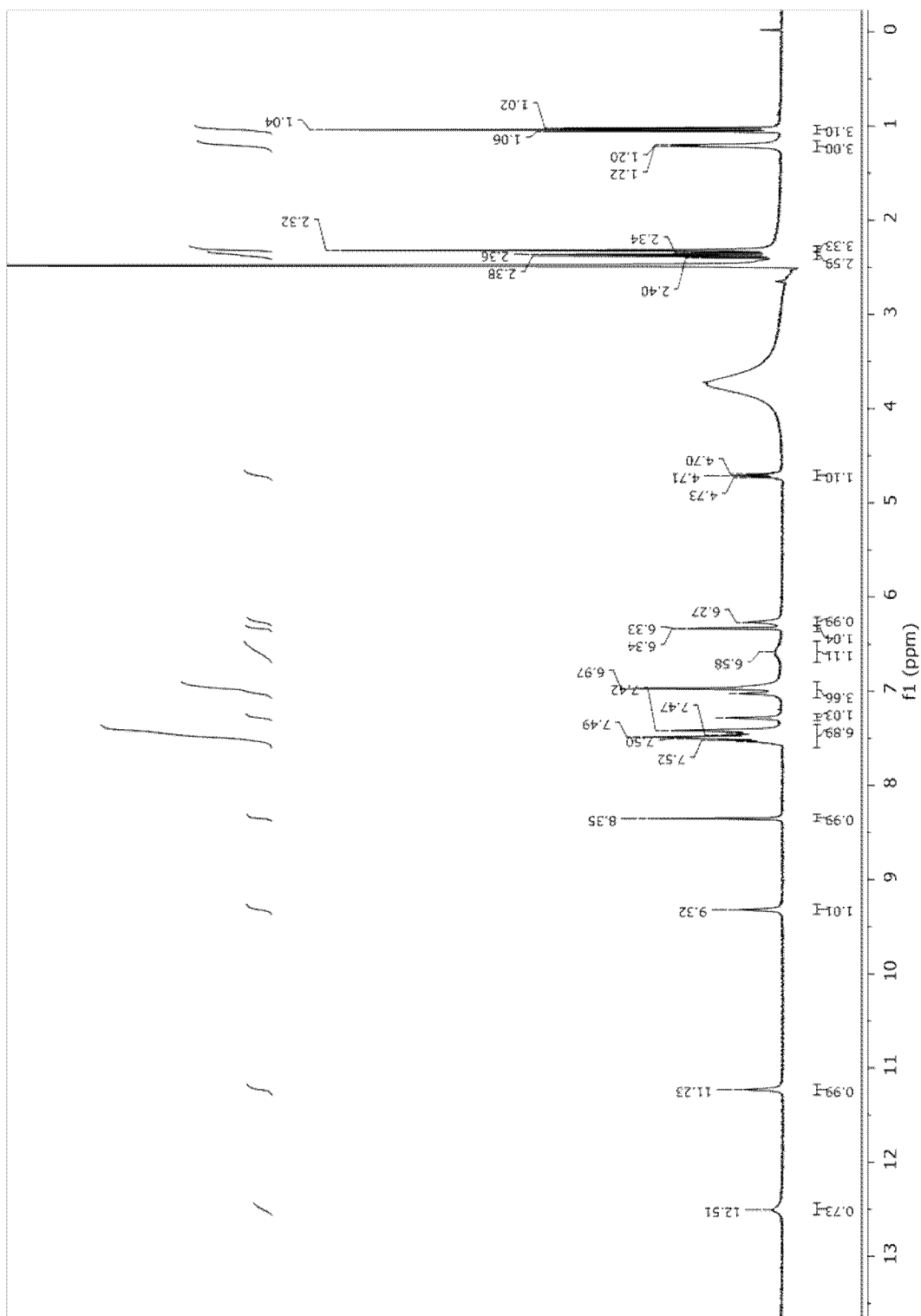


Figure 9

XRPD diffractogram of *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide ethanesulfonate type A polymorph.

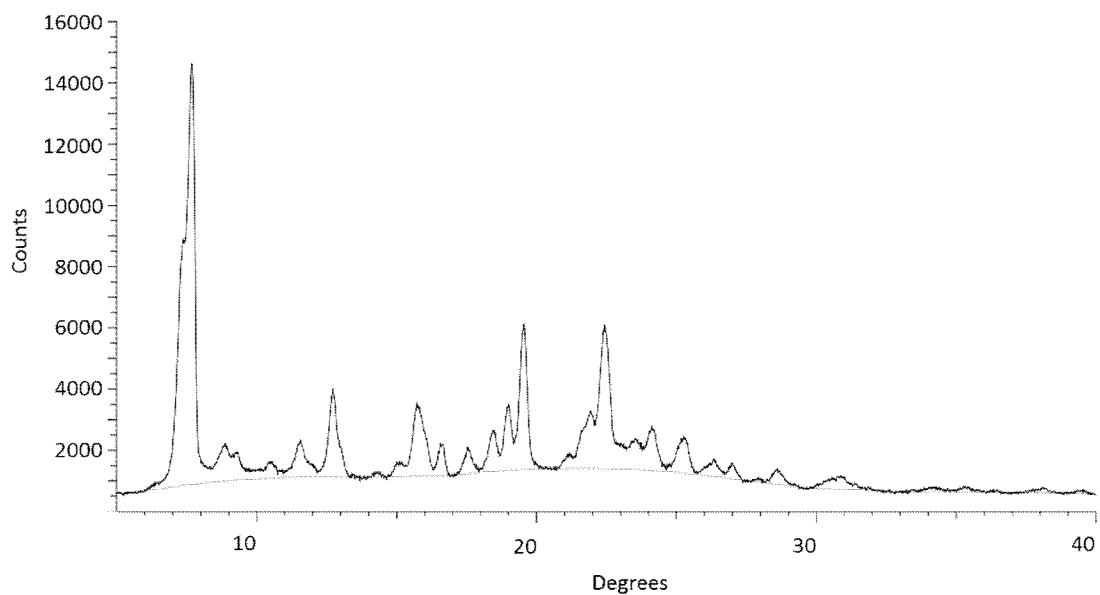




Figure 10

XRPD diffractogram of *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide ethanesulfonate type B polymorph.

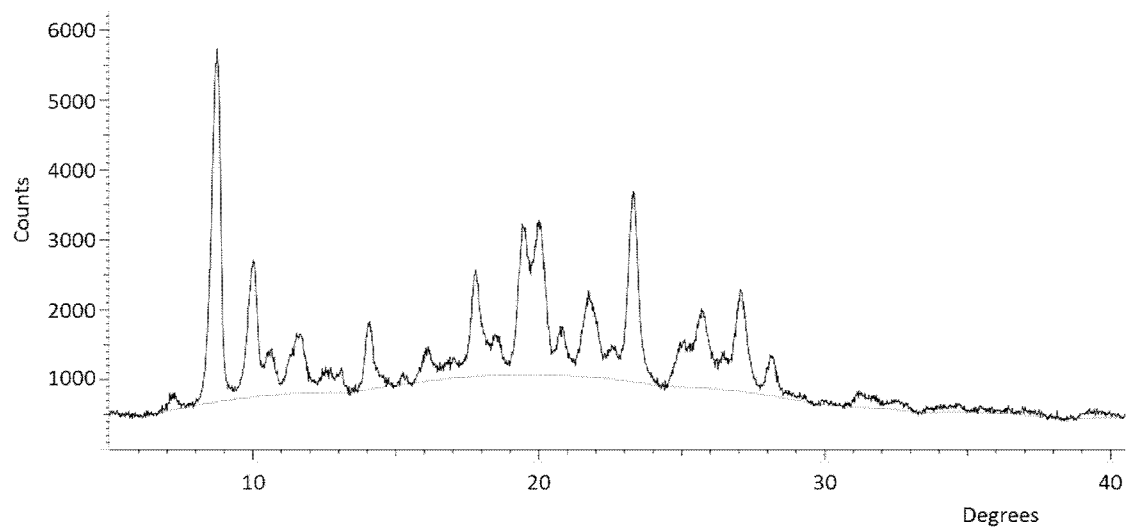


Figure 11

XRPD pattern of samples of the type A and type B polymorphs of *N*-[4-(4-[[*(1S)*-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino)-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide ethanesulfonate.

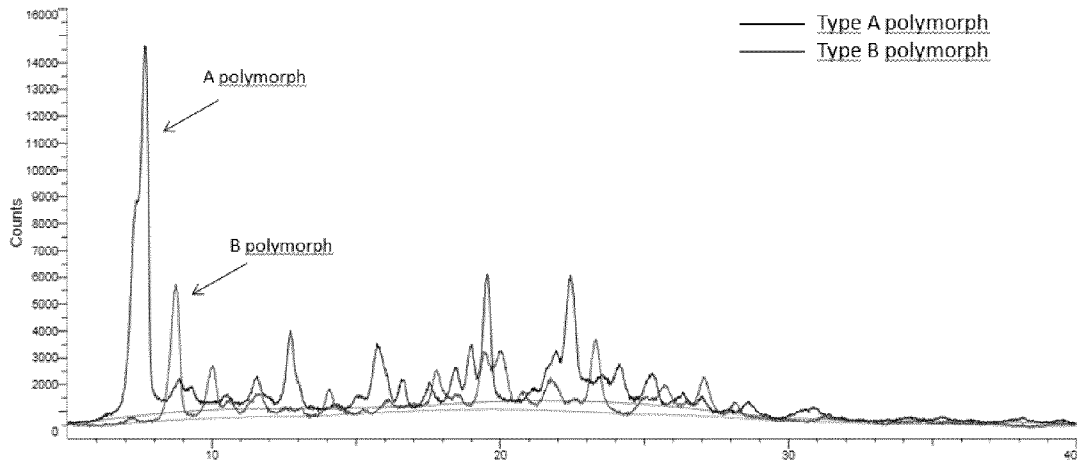


Figure 12

XRPD diffractogram of *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino}-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide benzenesulfonate

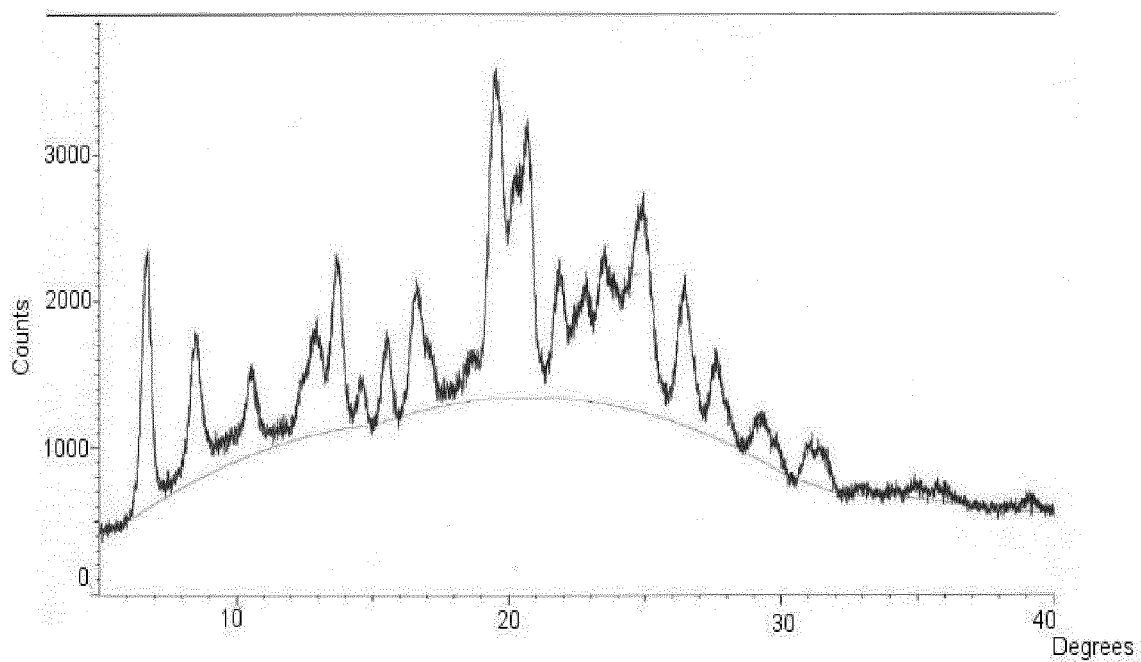


Figure 13

DSC thermogram of *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino}-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide benzenesulfonate

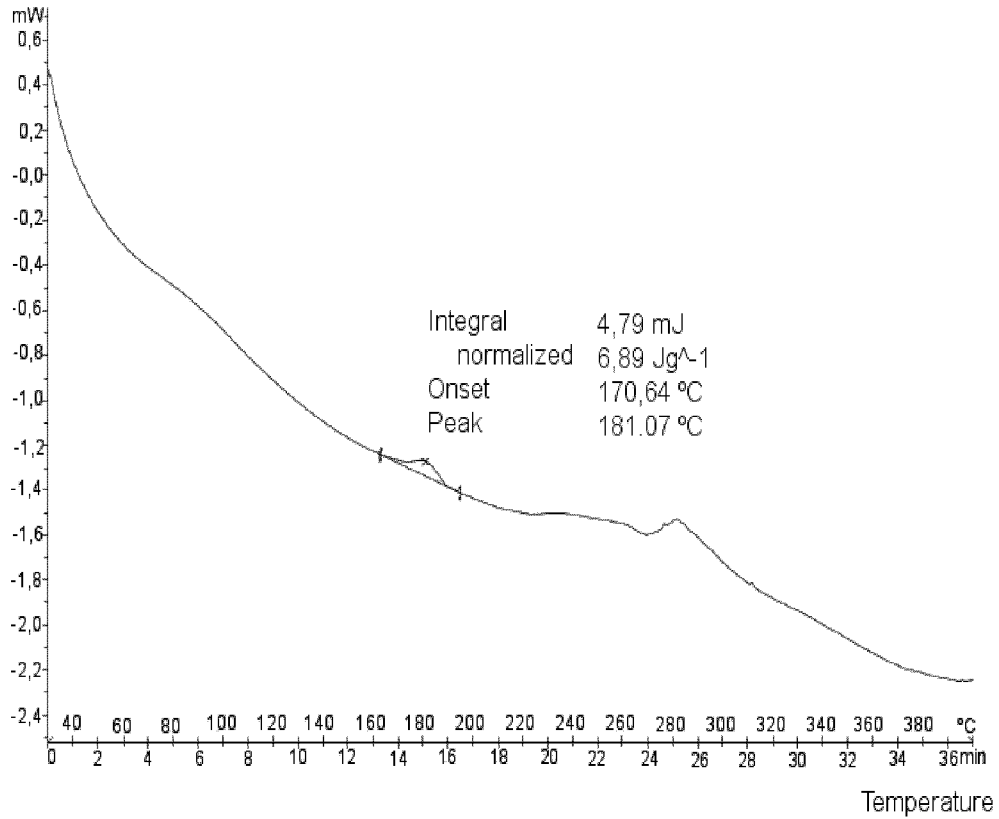


Figure 14

GVS isotherm of *N*-[4-(4-[[[(1*S*)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)ethyl]amino}-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-indol-6-yl]sulfamide benzenesulfonate

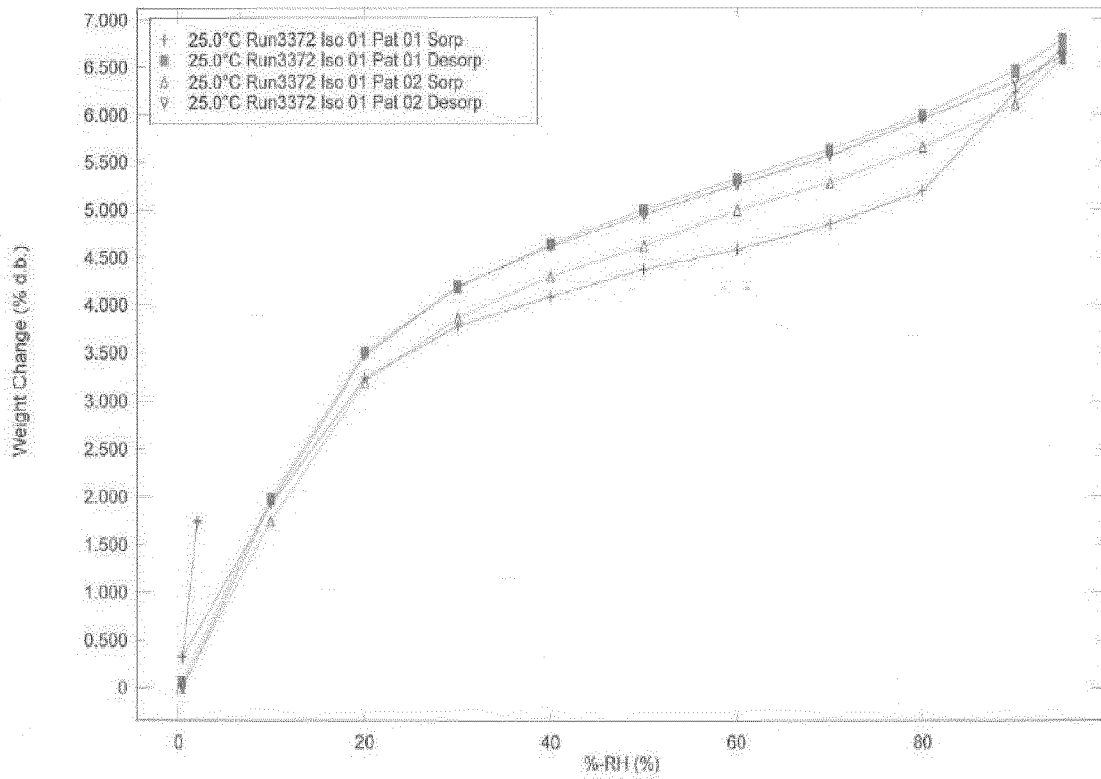
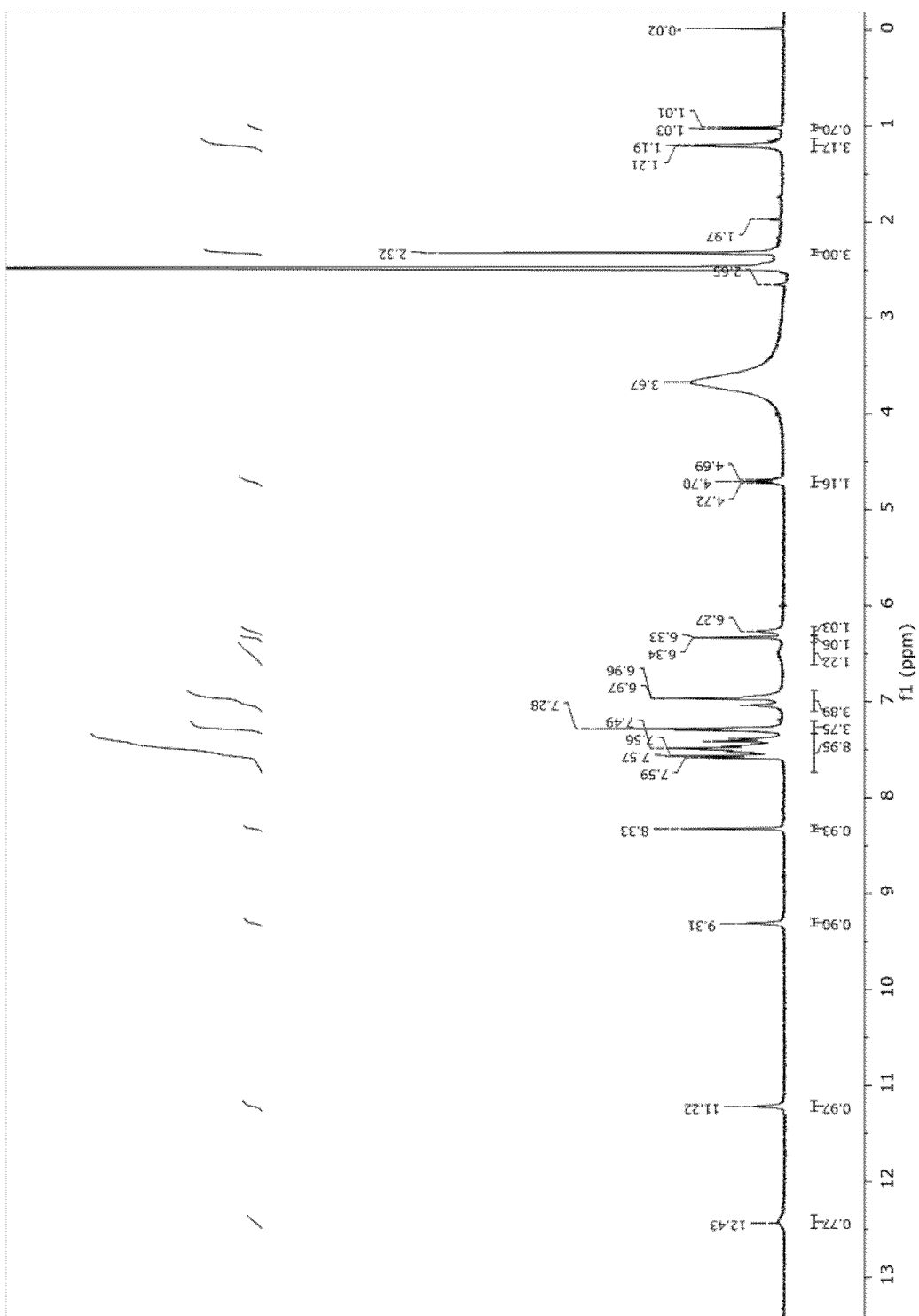


Figure 15

<sup>1</sup>H-NMR spectrum (400MHz, DMSO-d<sub>6</sub>) of *N*-[4-(4-[[[(1S)-1-(5-methyl-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)ethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1H-indol-6-yl]sulfamide benzenesulfonate



**INTERNATIONAL SEARCH REPORT**

International application No  
PCT/EP2016/076594

A. CLASSIFICATION OF SUBJECT MATTER  
 INV. C07D519/00 A61K31/519 A61P11/00 A61P11/06 A61P11/14  
 ADD.  
 According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED  
 Minimum documentation searched (classification system followed by classification symbols)  
 C07D  
 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/060432 A1 (ALMIRALL SA [ES]) 24 April 2014 (2014-04-24) cited in the application page 349; claims 1,19-20; example 184 -----	1-14

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

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- "E" earlier application or patent but published on or after the international filing date
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- "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
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- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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Date of the actual completion of the international search

23 November 2016

Date of mailing of the international search report

07/12/2016

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Authorized officer

Gettins, Marc

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2016/076594

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014060432	A1	24-04-2014	
		AR 093036 A1	13-05-2015
		AU 2013333938 A1	09-04-2015
		CA 2883426 A1	24-04-2014
		CL 2015000956 A1	19-06-2015
		CN 104854108 A	19-08-2015
		CR 20150175 A	11-05-2015
		DO P2015000077 A	30-04-2015
		EA 201500426 A1	30-10-2015
		EP 2909207 A1	26-08-2015
		HK 1211027 A1	13-05-2016
		JP 2015533181 A	19-11-2015
		KR 20150068953 A	22-06-2015
		MD 20150048 A2	31-10-2015
		PE 06372015 A1	08-05-2015
		PH 12015500813 A1	08-06-2015
		SG 11201502032V A	28-05-2015
		TN 2015000112 A1	29-06-2016
		TW 201429975 A	01-08-2014
		US 2015291595 A1	15-10-2015
		UY 35086 A	30-05-2014
		WO 2014060432 A1	24-04-2014

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