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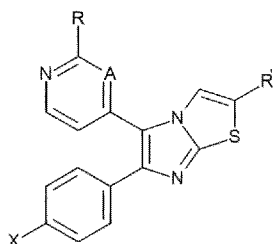
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(54) Title: CRYSTALLINE PHOSPHATE SALTS



(57) Abstract: The present invention is directed to crystalline phosphate salts of 5,6-diarylimidazo[2,1-b][1,3]thiazoles of Formula (I) or a solvate or hydrate thereof, wherein R = NH₂ or H; A = CH or N; R' = CH₂-1-Me-piperazin-4-yl or CH₂NMe₂; X = F, Cl, I or H which has enhanced solubility in water, and which shows high stability under conditions of high relative humidity. The present invention is also directed to a process of forming the crystalline phosphate salt and to its use in treating coccidiosis.



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Crystalline phosphate salts

The present invention relates to crystalline phosphate salts of 5,6-diarylimidazo[2,1-b][1,3]thiazoles and their use for treating coccidiosis.

Background

5 Coccidia are a subclass of microscopic, spore-forming, single-celled obligate intracellular parasites. As obligate intracellular parasites, they must live and reproduce within an animal cell. Coccidian parasites infect the intestinal tracts of animals and are the largest group of apicomplexan protozoa.

Infection with these parasites is known as coccidiosis. Coccidia can infect all mammals, some birds, some fish, some reptiles, and some amphibians. Most species of coccidia are species-specific in their
10 host. An exception is *Toxoplasma gondii*, which can infect all mammals, although it can only undergo sexual reproduction in cats. Depending on the species of coccidia, infection can cause fever, vomiting, diarrhea, muscle pain, and nervous system effects and changes to behavior, and may lead to death. Healthy adults may recover without medication—but those who are immunocompromised or young almost certainly require medication to prevent death. Humans generally become infected by eating under-
15 cooked meat but can contract infection with *T. gondii* by poor hygiene when handling cat waste.

The class of coccidia is divided into four orders, which are distinguished by the presence or absence of various asexual and sexual stages, namely Agamococcidiorida, Eucoccidiorida, Ixorheorida and Protococcidiorida. The order Eucoccidiorida is divided into two suborders. These two groups differ in their sexual development: syzygy for Adeleorina and independent gametes for Eimeriorina.

20 Infected animals spread spores called oocysts in their stool. The oocysts mature, called sporulation. When another animal passes over the location where the feces were deposited, they may pick up the spores, which they then ingest when grooming themselves.

Inside the host, the sporulated oocyst opens, and eight sporozoites are released. Each one finds a home in an intestinal cell and starts the process of reproduction. These offspring are called merozoites. When
25 the cell is stuffed full of merozoites, it bursts open, and each merozoite finds its own intestinal cell to continue the cycle.

As the infection continues, millions of intestinal cells may become infected. As they break open, they produce a bloody, watery diarrhea. This can cause dehydration and can lead to death in young or small pets.

30 Coccidiosis can be diagnosed by finding oocysts in fecal smears.

Coccidiosis is most commonly treated through the administration of coccidiostats, a group of medications that stop coccidia from reproducing. In dogs and cats, the most commonly administered coccidiostat is sulfa-based antibiotics. Once reproduction stops, the animal can usually recover on its own, a process that can take a few weeks, depending on the severity of the infection and the strength of the animal's
35 immune system.

In poultry, most species belong to the genus *Eimeria* and infect various sites in the intestine. The infectious process is rapid (4–7 days) and is characterized by parasite replication in host cells with extensive damage to the intestinal mucosa. Poultry coccidia are generally host-specific, and the different species parasitize specific parts of the intestine. However, in game birds, including quail, the coccidia may parasitize the entire intestinal tract. Coccidia are distributed worldwide in poultry, game birds reared in captivity, and wild birds.

Pathogenicity is influenced by host genetics, nutritional factors, concurrent diseases, age of the host, and species of the coccidium. *Eimeria necatrix* and *Eimeria tenella* are the most pathogenic in chickens, because schizogony occurs in the lamina propria and crypts of Lieberkühn of the small intestine and ceca, respectively, and causes extensive hemorrhage. *E. kofoidi* and *E. legionensis* are the most pathogenic in chukars, and *E. lefityae* is most pathogenic in bobwhite quail. Several *Eimeria* species are pathogenic in pheasants, particularly *E. phasiani* and *E. colchici*. Most species develop in epithelial cells lining the villi. Protective immunity usually develops in response to moderate and continuing infection. True age-immunity does not occur, but older birds are usually more resistant than young birds because of earlier exposure to infection.

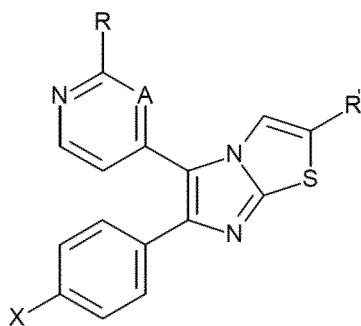
A. Scribner et al. (Bioorganic & Medicinal Chemistry Letters 18 (2008) 5263-5267) described the synthesis and biological activity of anticoccidial agents: 5,6-diarylimidazo[2,1-*b*][1,3]thiazoles. In this article, *in vivo* activity of various compounds of the 5,6-diarylimidazo[2,1-*b*][1,3]thiazoles family was determined by administering each compound (as a free base) orally in feed, and then ranking each for anticoccidial activity using a 7-day efficacy model. A quantitative measure of *Eimeria tenella*, *E. acervuline*, *E. mitis* and *E. maxima* oocysts shedding from infected birds provided an assessment of antiparasitic activity.

While the compounds disclosed by A. Scribner et al. have anticoccidial activity, they have the disadvantage of having a low solubility in water. Further, A. Scribner et al. is silent regarding the storage stability, in particular in view of humidity, of the synthesized 5,6-diarylimidazo[2,1-*b*][1,3]thiazoles.

In order to allow for the treatment of coccidiosis it is desirable to obtain 5,6-diarylimidazo[2,1-*b*][1,3]thiazoles having high solubility in water. It is also desirable to obtain 5,6-diarylimidazo[2,1-*b*][1,3]thiazoles having excellent storage stability, in particular in view of humidity. It is thus desirable to obtain 5,6-diarylimidazo[2,1-*b*][1,3]thiazoles which have an excellent solubility in water, and which can be stored for a long time. It is further desirable to obtain 5,6-diarylimidazo[2,1-*b*][1,3]thiazoles which can be stored under high humidity without taking up large amounts of water and/or without losing their crystalline structure, if they are provided in a crystalline form.

Summary of the invention

Surprisingly it was found that the objects can be met by providing a phosphate salt of a compound of Formula I



Formula I

or a solvate or hydrate thereof, wherein

$R = \text{NH}_2$ or H

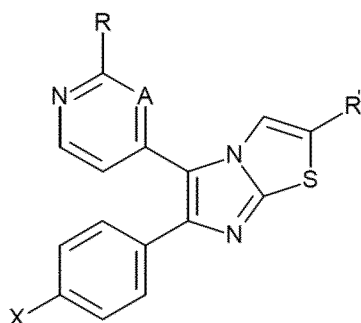
$A = \text{CH}$ or N

5 $R' = \text{CH}_2\text{-1-Me-piperazin-4-yl}$ or CH_2NMe_2

$X = \text{F}, \text{Cl}, \text{I}$ or H .

It was surprisingly found, that the phosphate salt according to the invention shows an increased solubility in water compared to the corresponding free base.

The present invention also is directed to a crystalline phosphate salt of a compound of Formula I



Formula I

or a solvate or hydrate thereof, wherein

$R = \text{NH}_2$ or H

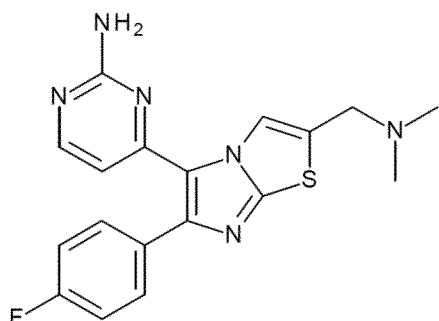
$A = \text{CH}$ or N

$R' = \text{CH}_2\text{-1-Me-piperazin-4-yl}$ or CH_2NMe_2

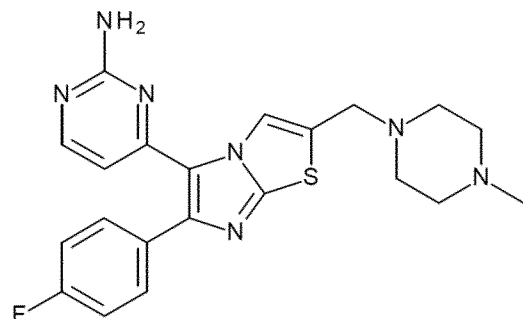
15 $X = \text{F}, \text{Cl}, \text{I}$ or H .

It was found that the crystalline form of the phosphate salt according to the invention displays a low hygroscopicity. Contrary to other crystal forms of salts like acetate, L-tartrate or citrate, the crystalline phosphate salt shows an excellent stability even at relative humidity values of 95%. It was observed that the crystalline structure remains intact and has a limited water uptake.

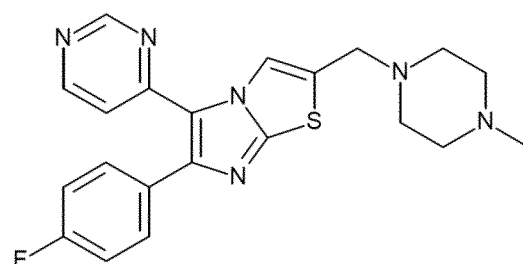
20 In one embodiment of the invention and/or embodiments thereof, the compound of Formula I is one of the following compounds of Formulae II to V:



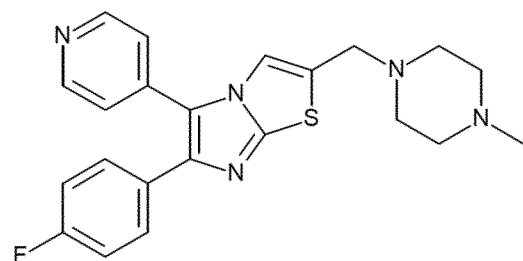
Formula II,



Formula III,



Formula IV,



Formula V.

5

In yet another embodiment of the invention and/or embodiments thereof, the phosphate salt is a monophosphate salt.

In yet another embodiment of the invention and/or embodiments thereof, the monophosphate salt is substantially anhydrous.

- 10 In another embodiment of the invention and/or embodiments thereof, the compound of general Formula I is the compound having the structure of Formula III as is present as monophosphate.

In another embodiment of the invention and/or embodiments thereof, the crystalline phosphate is substantially free of solvent and an XRPD of the monophosphate salt of compound of Formula III shows diffraction peaks at 9.9, 13.6, 13.8, 18.2, 19.5 and 19.8 °2θ (± 0.2 °2θ).

In another embodiment of the invention and/or embodiments thereof, the XRPD of the crystalline monophosphate salt of compound of Formula III further comprises peaks at 15.7, 22.0, 23.8, 24.5, 27.1 and 30.0 °2 θ ($\pm$ 0.2 °2 θ).

5 In yet another embodiment of the invention and/or embodiments thereof, the monophosphate salt of the compound of Formula III has a melting temperature of about 252 °C ($\pm$ 3 °C) as determined by the onset of the melting endotherm using DSC at a heating rate of 10 °C/min.

In another embodiment of the invention a monophosphate salt of the compound of Formula III is described by x-ray structure determination.

10 In yet another embodiment of the invention and/or embodiments thereof, the phosphate salts of the present invention are for use in treating coccidiosis in an animal.

In yet another embodiment of the invention and/or embodiments thereof, the animal is poultry.

In yet another embodiment of the invention and/or embodiments thereof, the poultry includes chickens, turkeys, geese and ducks.

15 In another embodiment of the invention and/or embodiments thereof, coccidiosis is caused by apicomplexan protozoan parasites of the genus *Eimeria*.

In some embodiment of the invention and/or embodiments thereof, the genus *Eimeria* comprises the species *E. tenella*, *E. acervulina*, *E. mitis* and *E. maxima*, *E. praecox*, *E. necatrix* and *E. brunetti*.

Another aspect of the present invention is a process of preparing a phosphate salt of the present invention comprising the steps:

- 20
- i) providing a compound of Formula I as free base;
 - ii) adding the free base of the compound of Formula I to a solvent to obtain a mixture;
 - iii) adding phosphoric acid to the mixture of step ii);

A further aspect of the present invention is a process of preparing a crystalline phosphate salt of the present invention comprising the steps:

- 25
- i) providing a compound of Formula I as free base;
 - ii) adding the free base of the compound of Formula I to a solvent to obtain a mixture;
 - iii) adding phosphoric acid to the mixture of step ii);
 - iv) allowing a phosphate salt of the compound of Formula I to crystallize;
 - v) collecting and drying the obtained solid.

30 In one embodiment of the invention and/or embodiments thereof, the process further comprises a step iii-a) of adding a solvent to the resulting mixture of step iii).

In another embodiment of the invention and/or embodiments thereof, the process further comprises a step iii-b) of seeding the resulting mixture of step iii) or step iii-a) with crystals of the corresponding phosphate salt of the invention.

5 In another embodiment of the invention and/or embodiments thereof, the molar ratio of phosphoric acid to the free base of the compound of Formula I is in the range of 0.5:1 to 1.5:1.

In yet another embodiment of the invention and/or embodiments thereof, in step iv) the mixture resulting from step iii), step iii-a) or step iii-b) is stirred at a temperature in the range of 10 to 70°C.

In yet another embodiment of the invention and/or embodiments thereof, the drying in step v) is carried out at a temperature in the range of 25 to 200°C.

10 In another embodiment of the invention and/or embodiments thereof, the solvent is selected from the group consisting of methanol, ethanol, *N,N*-dimethylacetamide or a mixture thereof.

A further aspect of the present invention is a method of treating coccidiosis comprising administering an effective amount of a phosphate salt of the present invention to an animal in need thereof.

In one embodiment of the invention, the animal is poultry.

15 In one further embodiment of the invention, the poultry includes chickens, turkeys, geese and ducks.

In another embodiment of the invention and/or embodiments thereof, coccidiosis is caused by Apicomplexan protozoan parasites of the genus *Eimeria*.

In yet another embodiment of the invention, the genus *Eimeria* comprises the species *E. tenella*, *E. acervulina*, *E. mitis* and *E. maxima*, *E. praecox*, *E. necatrix* and *E. brunetti*.

20 A further aspect of the present invention is a use of a phosphate salt of the present invention for the manufacture of a medicament for the treatment of coccidiosis in an animal in need thereof.

In one embodiment of the invention, the animal is poultry and coccidiosis is caused by apicomplexan protozoan parasites of the genus *Eimeria*.

Description of the Figures

25 **Figure 1:** XRPD of crystalline monophosphate of the compound of Formula III

Figure 2: CPMAS-NMR spectrum of the crystalline monophosphate salt of the compound of Formula III

Figure 3: DSC curve of the crystalline monophosphate salt of the compound of Formula III

30 **Figure 4:** a) XRPD of crystalline monophosphate salt of the compound of Formula III (solvent-free) as reference,
b) XRPD of crystalline monophosphate salt of the compound of Formula III after drying the methanol solvate of Example 2, corresponding to crystalline monophosphate (solvent-free).

35 **Figure 5:** a) XRPD of a monophosphate salt of the compound of Formula III crystallized from methanol/ethanol in Example 3, corresponding to a methanol solvate,

b) XRPD of the monophosphate salt of the compound of Formula III crystallized from methanol/ethanol, suspended at 60°C, corresponding to the solvent-free monophosphate salt.

Figure 6: **a)** XRPD of a monophosphate salt of the compound of Formula III crystallized from *N,N*-dimethylacetamide /methanol in Example 4,

b) XRPD of the monophosphate salt of the compound of Formula III crystallized from *N,N*-dimethylacetamide /methanol, suspended at 60°C.

Figure 7: XRPD of a crystalline acetate salt of the compound of Formula III:

a) using 120 µL acetic acid;

b) using 60 µL acetic acid.

Figure 8: XRPD of a crystalline L-tartrate salt of the compound of Formula III

Figure 9: XRPD of a crystalline citrate salt of the compound of Formula III:

a) using 17 mg, **b)** using 35 mg and **c)** using 53 mg citric acid monohydrate.

Figure 10: Adsorption/desorption curve of the crystalline phosphate salt of the compound of Formula III

Figure 11: XRPDs of the crystalline phosphate salt of the compound of Formula III:

a) before and **b)** after adsorption/desorption tests

Figure 12: Adsorption/desorption curve of crystalline acetate salt of the compound of Formula III

Figure 13: Adsorption/desorption curve of crystalline L-tartrate salt of the compound of Formula III

Figure 14: Adsorption/desorption curve of crystalline citrate salt of the compound of Formula III

Figure 15: Overlay of XRPD patterns of different batches of phosphate salt of the compound of Formula III

Figure 16: X-ray crystal structure of the crystalline phosphate salt of the compound of Formula III

Figure 17: ORTEP representation of the crystalline phosphate salt of the compound of Formula III hydrogen bonding network and ionic bond

Figure 18: Packing diagram for the crystalline phosphate salt of the compound of Formula III

Detailed Description of the Invention

For the avoidance of doubt, it is hereby stated that the information disclosed earlier in this specification under the heading "Background" is relevant to the invention and is to be read as part of the disclosure of the invention.

Throughout the description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification (which term encompasses both the description and the claims) is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

All the features disclosed in this specification (including any accompanying claims, abstract and drawings) and/or all of the steps of any process so disclosed may be combined in any combination (if not otherwise stated), except combinations where at least some of such features and/or steps are mutually exclusive. The invention is not restricted to the details of any foregoing embodiments. The invention extends to any

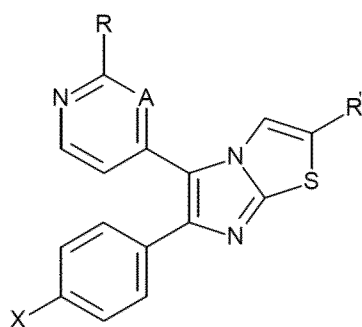
novel feature, or any novel combination of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel step, or any novel combination of the steps of any process so disclosed.

- 5 In the context of the present invention, the term “active pharmaceutical ingredient” (API) is defined as a substance used in a finished pharmaceutical dosage form (medicament) intended to furnish pharmacological activity or to otherwise have a direct effect on the diagnosis, cure, mitigation, treatment of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings. As used herein, the active pharmaceutical ingredient can refer to its pharmaceutically acceptable salts, hydrates or solvates thereof as well as the free base/acid thereof.

“Crystalline” as used herein defines a solid material whose constituent atoms, molecules, or ions are arranged in an ordered pattern extending in all three spatial dimensions and thus exhibit a periodic arrangement over a great range. Due to the long-range order of the corresponding constituents, a crystal lattice may be formed which extends in all directions. In addition, a crystalline form may be characterized in that the X-ray powder diffractogram (XRPD) exhibits a pattern of distinct characteristic peaks. Contrary to a crystalline substance, the XRPD of an amorphous or non-crystalline substance shows a pattern which due to the absence of characteristic peaks shows a more or less elevated base line. Further, a crystalline substance may be characterized by having a distinct melting point.

20 When phosphate salt of a compound of Formula I is used, both the non-crystalline and the crystalline forms are intended. Likewise when phosphate salt of a compound of Formula II, III, IV or V is used, both the non-crystalline and the crystalline forms are intended.

- 25 It was found that a phosphate salt of 5,6-diarylimidazo[2,1-*b*][1,3]thiazoles, specifically a crystalline phosphate salt of a compound of Formula I



Formula I

or a solvate or hydrate thereof, wherein

R = NH₂ or H

- 30 A = CH or N

R' = CH₂-1-Me-piperazin-4-yl or CH₂NMe₂

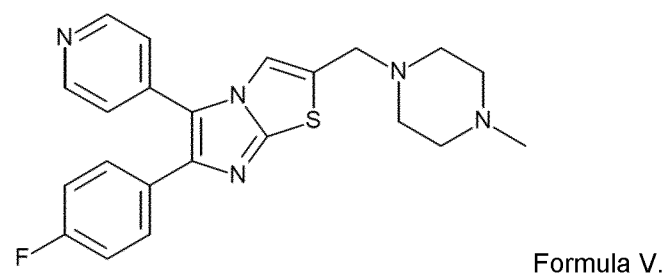
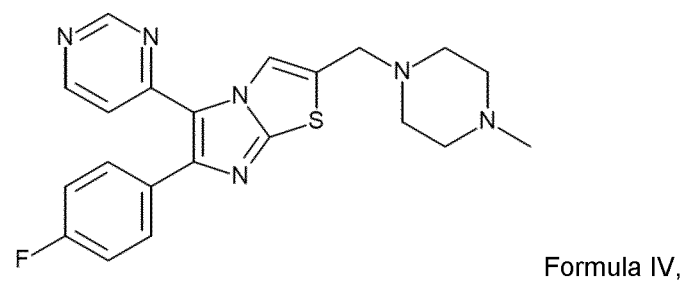
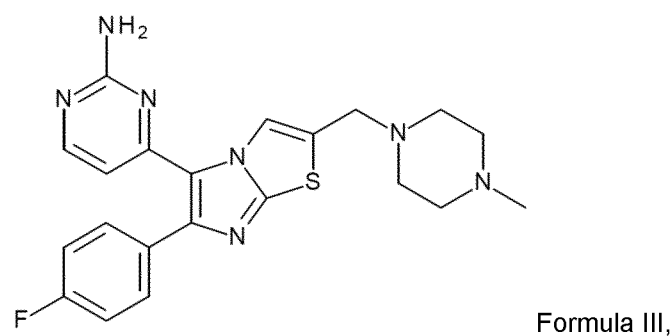
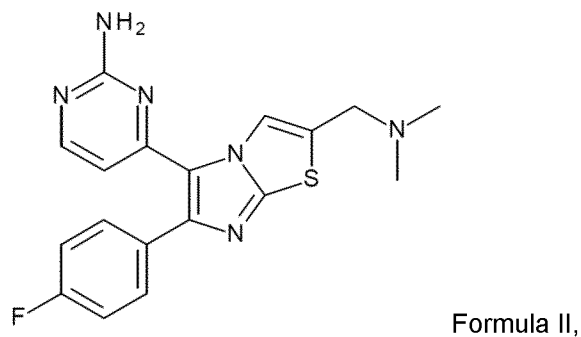
X = F, Cl, I or H, preferably F

has enhanced water solubility compared to the corresponding free base and the crystalline form also shows a high degree of stability under humid conditions, thus facilitating its storage. Specifically, the

- 35 solubility of the phosphate salts of the compounds of Formula I is greater than 50 mg/mL at 25°C in

water, while the solubility of the corresponding free bases is less than 10 mg/mL. Further, it has been surprisingly found out that the crystalline phosphate salt of the compounds of Formula III has a reduced hygroscopicity compared to other salts of the same compound (such as L-tartrate, citrate or acetate), enabling a storage at high relative humidity values without significant water uptake and without loss of the crystallinity.

In one embodiment of the invention, the compound of Formula I is one of the following compounds of Formulae II to V:

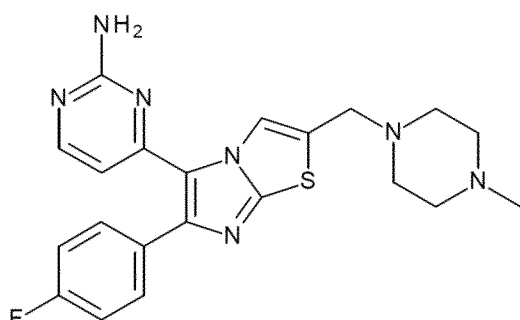


The phosphate salts of compounds of Formula I and/or the compounds of Formula II to V can be monophosphate, diphosphate or triphosphate salts. Preferably, the phosphate salts are monophosphate salts.

Further, the phosphate salts of the compounds of Formula I may contain amounts of water and/or other solvents. That is, the phosphate salts of the compounds of Formula I can be present in the form of hydrates or -more generally- solvates. Preferably, the solvate is a solvate of methanol, ethanol, *N,N*-dimethyl acetamide (DMAc), toluene or a mixture thereof.

Preferably, the phosphate salts of the compounds of Formula I are substantially free of solvent, in particular water (substantially anhydrous), as determined by thermogravimetric analysis (TGA). "Substantially free of solvent" means that a TGA analysis of a probe shows a weight reduction of preferably less than 10 wt.%, more preferably less than 5 wt.%, even more preferably less than 2 wt.% in the temperature range $T_s - 10^\circ\text{C} < T_s < T_s + 10^\circ\text{C}$, wherein T_s is the boiling point of the solvent. For example, a phosphate salt of a compound of Formula I is substantially anhydrous, if a TGA analysis shows in the range of 90-110°C (boiling point of water: 100°C) a weight reduction of the probe of 0-10 wt.%. Preferably, also the monophosphate salt of a compound of Formula I is substantially free of solvent, more preferably substantially anhydrous.

In another embodiment of the invention, the compound of general Formula I is preferably the compound having the structure of Formula III. In a preferred embodiment, the phosphate salt of the compound of general Formula I is a phosphate salt of the compound of Formula III,



Formula III,

wherein the phosphate salt is preferably a monophosphate and is substantially free of solvent. The crystalline phosphate salts of compounds of Formula I as provided by the present invention may be characterized by analytical methods well known in the field of the pharmaceutical industry for characterizing solids. Such methods comprise but are not limited to X-ray powder diffraction (XRPD), Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), particle size distribution (PSD), gravimetric moisture sorption (GMS) and X-ray crystallography. The crystalline phosphate salts of compounds of Formula I may be characterized by one of the aforementioned methods or by combining two or more of them. In particular, the crystalline phosphate salts of compounds of Formula I may be characterized by one of the following embodiments or by combining two or more of the following embodiments.

In a preferred embodiment the crystalline monophosphate salt of compound of Formula III can be characterized by an X-ray powder diffractogram comprising diffraction peaks at 9.9, 13.6, 13.8, 18.2, 19.5 and 19.8 °2 θ . These peaks may be regarded as particularly characteristic diffraction peaks for the

crystalline monophosphate salt of compound of Formula III. Preferably, the diffractogram comprises further peaks at 15.7, 22.0, 23.8, 24.5, 27.1 and 30.0 °2θ.

The crystalline monophosphate salt of compound of Formula III having an X-ray powder diffractogram comprising diffraction peaks as mentioned above is generally solvent free.

In a further embodiment, the crystalline monophosphate salt of compound of Formula III can be characterized by an X-ray powder diffractogram comprising following diffraction peaks and corresponding d-spacing (table 1):

Table 1: Diffraction peaks and d-spacing for mono-phosphate salt of compound of Formula III

Pos. [°2θ]	7.8	9.9	12.1	13.1	13.6	13.8	15.2	15.7	17.2
d-spacing [Å]	11.3	8.9	7.3	6.8	6.5	6.4	5.8	5.6	5.2

Pos. [°2θ]	17.6	18.2	19.5	19.8	20.3	21.0	21.4	22.0	23.8
d-spacing [Å]	5.1	4.9	4.6	4.5	4.4	4.2	4.2	4.0	3.7

Pos. [°2θ]	24.5	24.9	25.1	25.9	26.5	27.1	27.3	27.8	28.5
d-spacing [Å]	3.6	3.6	3.5	3.4	3.4	3.3	3.3	3.2	3.1

Pos. [°2θ]	28.9	29.3	30.0	30.7	31.8	32.5	33.5	34.0	34.9
d-spacing [Å]	3.1	3.0	3.0	2.9	2.8	2.8	2.7	2.6	2.6

Pos. [°2θ]	35.6	36.1	36.7	36.9	38.0	39.0	39.7
d-spacing [Å]	2.5	2.5	2.4	2.4	2.4	2.3	2.3

Alternatively, the crystalline monophosphate salt of compound of Formula III can preferably be characterized by having a powder X-ray diffractogram essentially the same as displayed in Figure 1 of the present invention.

In the present application, the XRPD is recorded as described in the experimental section below. Further, unless indicated otherwise, XRPD peaks are reported as °2θ values with a standard error of ± 0.2 °2θ.

In a further embodiment, the crystalline monophosphate salt of compound of Formula III can be preferably characterized by having a carbon-13 cross-polarization magic-angle spinning (CPMAS) nuclear magnetic resonance (NMR) spectrum comprising peaks at 44.34, 49.00, 52.00, 55.26, 57.64, 108.22, 113.39, 114.06, 120.39, 123.31, 126.98, 129.18, 148.69, 152.92, 155.39, 160.92, 162.39, 163.86 ppm.

Alternatively, the crystalline monophosphate salt of compound of Formula III can preferably be characterized by having a CPMAS-NMR spectrum essentially the same as displayed in Figure 2 of the present invention. In the present application the CPMAS-NMR spectrum is recorded as described in the experimental section below.

- 5 Alternatively, the crystalline monophosphate salt of compound of Formula III can preferably be characterized by x-ray crystallographic structure determination as displayed in Tables 3 to 10 and Figures 16 to 18.

10 In a further embodiment, the crystalline monophosphate salt of compound of Formula III can preferably have a melting point of about 252°C, as determined by the onset of the melting endotherm using DSC with a heating rate of 10°C/min. The endothermic peak is at about 256°C. Further, unless indicated otherwise, the melting point as measured by DSC has a standard error of ± 3 °C. In the present application the DSC is recorded as described in the experimental section below. A differential scanning calorimetric curve of the crystalline monophosphate salt of compound of Formula III is shown in Figure 3.

15 In yet a further embodiment, the anhydrous crystalline monophosphate salt of compound of Formula III can be characterized by showing a weight loss of about 2 wt.% or less based on the weight of crystalline monophosphate salt of compound of Formula III, when measured with thermogravimetric analysis.

In yet a further embodiment, the crystalline monophosphate salt of compound of Formula III can be characterized by an adsorption/desorption curve as shown in Figure 10 of the present invention.

20 In a further embodiment, the phosphate salts of compounds of Formula I of the present invention can be used for treating coccidiosis in an animal.

The term "treating", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. Preferably, the crystalline phosphate salt of the present invention reduces the number of oocysts in an animal, e.g. as described in A. Scribner et al. (Bioorganic & Medicinal Chemistry Letters 18 (2008) 5263-5267).

30 In an embodiment, the animal is selected from the group consisting of dogs, cats, cattle, poultry, sheep, goats, pigs and horses. Preferably, the animal is poultry.

In one embodiment of the invention, poultry includes chicken, turkeys, ducks, geese, quail, pheasants, emus and ostriches, preferably chickens, turkeys, geese and ducks.

35 The phosphate salts of compounds of Formula I of the present invention can be used to treat coccidiosis caused by any genus of the causative protozoa including *Eimeria*, *Isospora*, *Hammondia*, *Toxoplasma* and *Neospora*. The genus *Eimeria* preferably includes the species *Eimeria acervulina*, *Eimeria brunetti*, *Eimeria maxima*, *Eimeria mitis*, *Eimeria necatrix*, *Eimeria tenella*, *Eimeria meleagridis*, *Eimeria gallopavonis*, *Eimeria adenoeides*, *Eimeria dispersa*, *Eimeria praecox*. The genus *Isospora* preferably includes the species *I. canis*, *I. ohioensis*, *I. burrowsi*, *I. neorivolta*, *I. felis* and *I. rivolta*. The genus *Hammondia* preferably includes the species *H. heydorni*, *H. hammondi* and *H. pardalis*. The genus

40

Toxoplasma preferably includes the species *T. gondii*. The genus *Neospora* preferably includes the species *N. caninum*.

- 5 Preferably, the phosphate salts of the present invention can be used to treat coccidiosis caused by apicomplexan protozoan parasites of the genus *Eimeria*.

In a preferred embodiment, the phosphate salts of compounds of Formula I of the present invention can be used to treat coccidiosis caused by protozoa of the genus *Eimeria* comprising the species *Eimeria acervulina*, *Eimeria brunetti*, *Eimeria maxima*, *Eimeria mitis*, *Eimeria necatrix*, *Eimeria tenella*, *Eimeria*
10 *meleagritidis*, *Eimeria gallopavonis*, *Eimeria adenoeides*, *Eimeria dispersa*, *Eimeria praecox*.

In a preferred embodiment, the phosphate salts of compounds of Formula I of the present invention can be used to treat coccidiosis caused by protozoa of the genus *Eimeria* comprising the species *E. tenella*, *E. acervulina*, *E. mitis*, *E. maxima*, *Eimeria praecox*, *Eimeria necatrix*, *Eimeria brunetti*.

- 15 In a preferred embodiment, the phosphate salts of compounds of Formula I of the present invention can be used to treat coccidiosis caused by protozoa of the genus *Eimeria* comprising the species *Eimeria acervulina*, *Eimeria brunetti*, *Eimeria maxima*, *Eimeria mitis*, *Eimeria necatrix*, *Eimeria tenella*, *Eimeria meleagritidis*, *Eimeria gallopavonis*, *Eimeria adenoeides*, *Eimeria dispersa*, *Eimeria praecox* in poultry.
Preferably, the phosphate salts of compounds of Formula I of the present invention can be used to treat
20 coccidiosis caused by protozoa of the genus *Eimeria* comprising the species *E. tenella*, *E. acervulina*, *E. mitis*, *E. maxima*, *Eimeria praecox*, *Eimeria necatrix*, *Eimeria brunetti* in poultry.

- In a further preferred embodiment of the invention, the monophosphate salt of the compound of Formula III can be used to treat coccidiosis caused by protozoa of the genus *Eimeria* comprising the species
25 *Eimeria acervulina*, *Eimeria brunetti*, *Eimeria maxima*, *Eimeria mitis*, *Eimeria necatrix*, *Eimeria tenella*, *Eimeria meleagritidis*, *Eimeria gallopavonis*, *Eimeria adenoeides*, *Eimeria dispersa*, *Eimeria praecox*.

- In a further preferred embodiment of the invention, the monophosphate salt of the compound of Formula III can be used to treat coccidiosis caused by protozoa of the genus *Eimeria* comprising the species *E.*
30 *tenella*, *E. acervulina*, *E. mitis*, *E. maxima*, *Eimeria praecox*, *Eimeria necatrix*, *Eimeria brunetti*.

- In a further preferred embodiment of the invention, the monophosphate salt of the compound of Formula III can be used to treat coccidiosis caused by protozoa of the genus *Eimeria* comprising the species
35 *Eimeria acervulina*, *Eimeria brunetti*, *Eimeria maxima*, *Eimeria mitis*, *Eimeria necatrix*, *Eimeria tenella*, *Eimeria meleagritidis*, *Eimeria gallopavonis*, *Eimeria adenoeides*, *Eimeria dispersa*, *Eimeria praecox* in poultry.

- In a further preferred embodiment of the invention, the monophosphate salt of the compound of Formula III can be used to treat coccidiosis caused by protozoa of the genus *Eimeria* comprising the species *E.*
40 *tenella*, *E. acervulina*, *E. mitis*, *E. maxima*, *Eimeria praecox*, *Eimeria necatrix*, *Eimeria brunetti* in poultry.

Because coccidiosis is an intestinal disease, the phosphate salts of the present invention must be administered in a way that will allow them to reach the intestinal tract. Phosphate salts of the present invention may be administered according to standard methods known in the art, including by incorporating them into animal feed. The phosphate salts of the present invention may also be administered by other methods, such as by incorporating them into drinking water. In a preferred embodiment, the phosphate salt is administered in the feed. In a preferred embodiment, the phosphate salt is administered in drinking water.

The phosphate salts of the present invention can be evaluated by the in vitro and/or in vivo anti-coccidiosis test described in A. Scribner et al. (Bioorganic & Medicinal Chemistry Letters 18 (2008) 5263-5267).

A further aspect of the present invention is a method for treating coccidiosis in an animal comprising administering to the subject in need thereof an effective amount of a phosphate salt of the present invention and/or embodiments thereof.

In an embodiment, the animal is selected from the group consisting of dogs, cats, cattle, poultry, sheep, goats, pigs and horses. Preferably, the animal is poultry.

In one embodiment of the invention, poultry includes chicken, turkeys, ducks, geese, quail, pheasants, emus and ostriches, preferably chickens, turkeys, geese and ducks.

In one embodiment of the method for treating coccidiosis of the present invention, coccidiosis can be caused by any genus of the causative protozoa including *Eimeria*, *Isospora*, *Hammondia*, *Toxoplasma* and *Neospora*. The genus *Eimeria* preferably includes the species *Eimeria acervulina*, *Eimeria brunetti*, *Eimeria maxima*, *Eimeria mitis*, *Eimeria necatrix*, *Eimeria tenella*, *Eimeria meleagriditis*, *Eimeria gallopavonis*, *Eimeria adenoeides*, *Eimeria dispersa*, *Eimeria praecox*. The genus *Isospora* preferably includes the species *I. canis*, *I. ohioensis*, *I. burrowsi*, *I. neorivolta*, *I. felis* and *I. rivolta*. The genus *Hammondia* preferably includes the species *H. heydorni*, *H. hammondi* and *H. pardalis*. The genus *Toxoplasma* preferably includes the species *T. gondii*. The genus *Neospora* preferably includes the species *N. caninum*.

Preferably, in the method for treating coccidiosis of the present invention coccidiosis can be caused by Apicomplexan protozoan parasites of the genus *Eimeria*.

In a preferred embodiment of the method for treating coccidiosis of the present invention, coccidiosis can be caused by protozoa of the genus *Eimeria* comprising the species *Eimeria acervulina*, *Eimeria brunetti*, *Eimeria maxima*, *Eimeria mitis*, *Eimeria necatrix*, *Eimeria tenella*, *Eimeria meleagriditis*, *Eimeria gallopavonis*, *Eimeria adenoeides*, *Eimeria dispersa*, *Eimeria praecox*.

In a preferred embodiment of the method for treating coccidiosis of the present invention, coccidiosis can be caused by protozoa of the genus *Eimeria* comprising the species *E. tenella*, *E. acervulina*, *E. mitis*, *E. maxima*, *Eimeria praecox*, *Eimeria necatrix*, *Eimeria brunetti*.

5 In a further preferred embodiment of the method for treating coccidiosis of the present invention, an effective amount of the monophosphate salt of the compound of Formula III is administered to an animal in need thereof and coccidiosis is caused by protozoa of the genus *Eimeria* comprising the species *Eimeria acervulina*, *Eimeria brunetti*, *Eimeria maxima*, *Eimeria mitis*, *Eimeria necatrix*, *Eimeria tenella*, *Eimeria meleagritidis*, *Eimeria gallopavonis*, *Eimeria adenoeides*, *Eimeria dispersa*, *Eimeria praecox*.

10 In a further preferred embodiment of the method for treating coccidiosis of the present invention, an effective amount of the monophosphate salt of the compound of Formula III is administered to an animal in need thereof and coccidiosis is caused by protozoa of the genus *Eimeria* comprising the species *E. tenella*, *E. acervulina*, *E. mitis*, *E. maxima*, *Eimeria praecox*, *Eimeria necatrix*, *Eimeria brunetti*.

15 In a further preferred embodiment of the method for treating coccidiosis of the present invention, an effective amount of the monophosphate salt of the compound of Formula III is administered to an animal in need thereof and coccidiosis is caused by protozoa of the genus *Eimeria* comprising the species *Eimeria acervulina*, *Eimeria brunetti*, *Eimeria maxima*, *Eimeria mitis*, *Eimeria necatrix*, *Eimeria tenella*,
20 *Eimeria meleagritidis*, *Eimeria gallopavonis*, *Eimeria adenoeides*, *Eimeria dispersa*, *Eimeria praecox* in poultry.

In a further preferred embodiment of the method for treating coccidiosis of the present invention, an effective amount of the monophosphate salt of the compound of Formula III is administered to an animal
25 in need thereof and coccidiosis is caused by protozoa of the genus *Eimeria* comprising the species *E. tenella*, *E. acervulina*, *E. mitis*, *E. maxima*, *Eimeria praecox*, *Eimeria necatrix*, *Eimeria brunetti* in poultry.

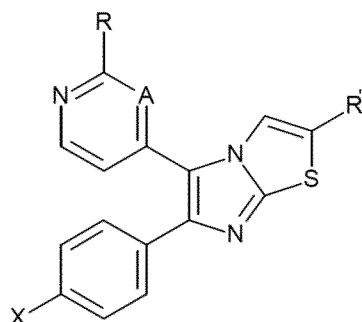
In a further preferred embodiment of the method for treating coccidiosis of the present invention, an effective amount of the monophosphate salt of the compound of Formula III is administered to an animal
30 in need thereof and coccidiosis is caused by protozoa of the genus *Eimeria* comprising the species *Eimeria acervulina*, *Eimeria brunetti*, *Eimeria maxima*, *Eimeria mitis*, *Eimeria necatrix*, *Eimeria tenella*, *Eimeria meleagritidis*, *Eimeria gallopavonis*, *Eimeria adenoeides*, *Eimeria dispersa*, *Eimeria preacox* in poultry.

35 In a further preferred embodiment of the method for treating coccidiosis of the present invention, an effective amount of the monophosphate salt of the compound of Formula III is administered to an animal in need thereof and coccidiosis is caused by protozoa of the genus *Eimeria* comprising the species *E. tenella*, *E. acervulina*, *E. mitis*, *E. praecoxmaxima*, *Eimeria preacox*, *Eimeria necatrix*, *Eimeria brunetti* in poultry.

40

A further aspect of the present invention is a process of preparing a phosphate salt of the present invention comprising the steps:

- i) providing a compound of Formula I



Formula I

or a solvate or hydrate thereof, wherein

R = NH₂ or H

A = CH or N

R' = CH₂-1-Me-piperazin-4-yl or CH₂NMe₂

X = F, Cl, I or H

as free base;

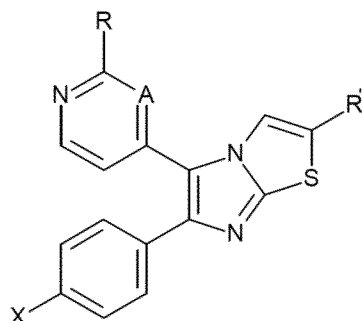
- ii) adding the free base of the compound of Formula I to a solvent to obtain a mixture;

- iii) adding phosphoric acid to the mixture of step ii);

Optionally the phosphate salt is precipitated.

A further aspect of the present invention is a process of preparing a crystalline phosphate salt of the present invention comprising the steps:

- i) providing a compound of Formula I



Formula I

or a solvate or hydrate thereof, wherein

R = NH₂ or H

A = CH or N

R' = CH₂-1-Me-piperazin-4-yl or CH₂NMe₂

X = F, Cl, I or H

as free base;

- ii) adding the free base of the compound of Formula I to a solvent to obtain a mixture;

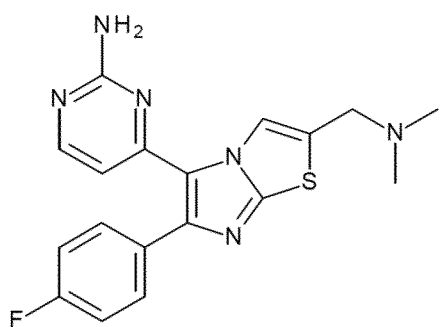
- iii) adding phosphoric acid to the mixture of step ii);

- iv) allowing a phosphate salt of the compound of Formula I to crystallize;

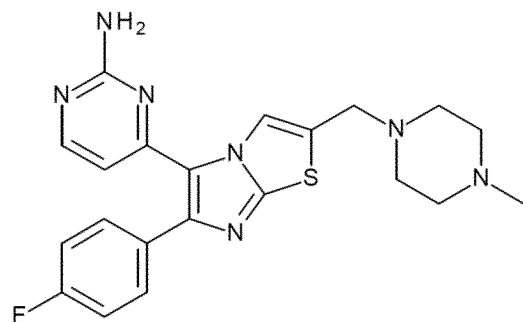
v) collecting and drying the obtained solid.

In step i) a compound of Formula I as free base is provided. In an embodiment, the free base of the compound of Formula I is present as a solvate or more specifically as a hydrate. In a further embodiment, the free base of the compound of Formula I is substantially free of solvent. Further, the free base of the compound of Formula I can be amorphous or crystalline.

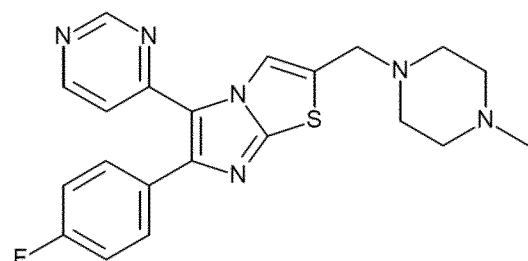
5 In one embodiment of step i), the compound of general Formula I is one of the following compounds of Formulae II to V:



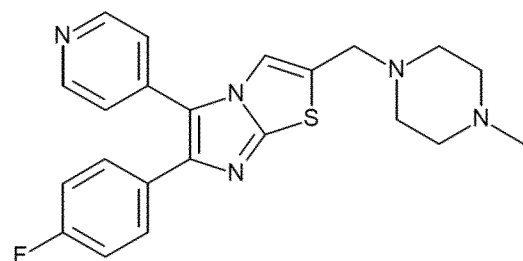
Formula II,



Formula III,



Formula IV,



Formula V.

Preferably, the compound of general Formula I is the compound of Formula III.

15 In step ii), the free base of the compound of Formula I is added to a solvent. A solvent is regarded as a substance, preferably a substance being liquid at 25°C at 1013 mbar, which is able to at least partially dissolve a solute, wherein in the present case the compound of Formula I (free base) is the solute.

In a preferred embodiment of the invention the solvent has a boiling point at 1013 mbar between 50°C and 200°C, preferably between 60°C and 170°C.

Preferably, the solvent is a polar protic or polar aprotic solvent. Non-limiting examples of suitable polar solvents are nitromethane, acetonitrile, *N,N*-dimethyl acetamide (DMAc), *N,N*-dimethyl formamide, tetrahydrofuran (THF), acetone, ethyl acetate, an alcohol, such as methanol, ethanol, 1-propanol, 2-propanol, 2-methyl-1-propanol, 2-methyl-2-propanol, 2,2-dimethyl-1-propanol, 1-butanol, 2-butanol, 2-methyl-1-butanol, 2-methyl-2-butanol, 3-methyl-1-butanol, 3-methyl-2-butanol, 1-pentanol and 1-hexanol, or a mixture thereof. More preferably, the solvent is selected from an alcohol, DMAc or a mixture thereof.

A preferred alcohol is ethanol or methanol.

In one embodiment, the solvent can be a mixture of two of the above-mentioned solvents. Preferably, the solvent is a mixture of two alcohols, or an alcohol and a second solvent as mentioned above being not an alcohol. Mixtures of two alcohols are for example methanol and ethanol, methanol and 1-propanol, methanol and 2-propanol, methanol and 2-methyl-1-butanol, ethanol and 1-propanol, ethanol and 2-propanol, ethanol and 2-methyl-2-propanol, ethanol and 2,2-dimethyl-1-propanol, ethanol and 3-methyl-2-butanol, 2-propanol and 2-methyl-1-propanol, 2-propanol and 2,2-dimethyl-1-propanol, 2-propanol and 3-methyl-1-butanol. Mixtures of an alcohol and a second solvent as mentioned above being not an alcohol are for example methanol and DMAc, methanol and acetonitrile, methanol and *N,N*-dimethyl formamide, ethanol and THF, ethanol and acetone, ethanol and ethyl acetate. More preferably, the solvent is a mixture of ethanol and methanol, or methanol and DMAc.

In one embodiment, the first alcohol, such as ethanol, is mixed with the second alcohol, such as methanol, in a ratio (v/v) from 25:1 to 1:25, such as 20:1, 15:1, 10:1, 8:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1, 1:1.5, 1:2, preferably from 10:1 to 1:10, such as 8:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1, 1:1.5, 1:2, 1:3, 1:4, 1:6, more preferably from 4:1 to 1:4, such as 4:1, 3:1, 2:1, 1.5:1, 1.25:1, 1:1, 1:1.25, 1:1.5, 1:2, 1:3. In one embodiment, the alcohol, such as methanol, is mixed with the second solvent as mentioned above being not an alcohol, such as DMAc, in a ratio (v/v) from 25:1 to 1:25, such as 20:1, 15:1, 10:1, 8:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1, 1:1.5, 1:2, preferably from 10:1 to 1:10, such as 8:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1, 1:1.5, 1:2, 1:3, 1:4, 1:6, more preferably from 4:1 to 1:4, such as 3:1, 3:1, 2:1, 1.5:1, 1:1, 1:1.5, 1:2, 1:3, 1:4. Preferably, in step ii) the solvent is a single solvent and not a mixture.

Preferably, the ratio (w/v) of compound of Formula I (free base) to solvent is from 1:100 to 1:10, for example 1:95, 1:90, 1:80, 1:70, 1:60, 1:50, 1:45, 1:40, 1:30, 1:20, 1:8, more preferably from 1:75 to 1:15, such as 1:70, 1:60, 1:50, 1:45, 1:40, 1:30, 1:20.

In one embodiment, the compound of Formula I is added to the solvent under mechanical movement such as stirring or shaking, preferably stirring.

In a further embodiment, step ii) can be carried out at a temperature from 5°C to 80°C, i.e. the solvent has a temperature from 5°C to 80°C when the compound of step i) is added thereto. Preferably, the solvent

has a temperature from 10°C to 60°C, more preferably 20°C to 40°C. A most preferred temperature is 25°C (room temperature).

In one embodiment, the mixture resulting from the addition of the free base of the compound of Formula I to a solvent in step ii) is a suspension or a solution, preferably a suspension.

"Suspension" as used herein means a heterogeneous mixture in which the solute particles do not dissolve but get suspended throughout the bulk of the solvent. The particles are visible to the naked eye, and are generally larger than 1 µm, and will settle over time if left undisturbed. This distinguishes a suspension from a colloid, in which the suspended particles are smaller and do not settle. However, as used herein, the term suspension also encompasses colloids.

"Solution" as use herein means a homogeneous mixture composed of two or more substances, which is liquid above -10°C. In such a mixture, a solute is a substance dissolved in another substance, known as a solvent. The solution assumes the phase of the solvent when the solvent is the larger fraction of the mixture, as is commonly the case.

Preferably, the concentration of the free base of the compound of Formula I in the solvent in the mixture resulting from step ii) is from 0.01M to 1M, more preferably from 0.05M to 0.5M.

In step iii), phosphoric acid is added to the mixture resulting from step ii). As used herein, "phosphoric acid" is synonymous with ortho phosphoric acid having the chemical formula H_3PO_4 .

In one embodiment, phosphoric acid can be added to the mixture of step ii) as 80-90% aqueous solution, preferably 85%, which is generally commercially available. In a further embodiment, a solution of phosphoric acid in an organic solvent is prepared prior to step iii). Preferably, an 80-90% aqueous solution, preferably 85%, of phosphoric acid is dissolved in an organic solvent. Preferably, the solvent is a polar protic or polar aprotic solvent. Non-limiting examples of suitable polar solvents are nitromethane, acetonitrile, *N,N*-dimethyl acetamide (DMAc), *N,N*-dimethyl formamide, tetrahydrofuran (THF), acetone, ethyl acetate, an alcohol, such as methanol, ethanol, 1-propanol, 2-propanol, 2-methyl-1-propanol, 2-methyl-2-propanol, 2,2-dimethyl-1-propanol, 1-butanol, 2-butanol, 2-methyl-1-butanol, 2-methyl-2-butanol, 3-methyl-1-butanol, 3-methyl-2-butanol, 1-pentanol and 1-hexanol. More preferably, the solvent is selected from an alcohol, preferably ethanol or methanol, and DMAc.

The concentration of phosphoric acid in the organic solvent is not limited but is preferably from 0.1M to 3M (i.e. 0.1 mol/l to 3 mol/l).

In one embodiment, the solvent in which phosphoric acid is dissolved and the solvent of step ii) are the same or different, preferably the same.

In one embodiment of the invention, the phosphoric acid can be added to the to the mixture of step ii) in a molar ratio (mol phosphoric acid: mol free base of compound of Formula I) from 0.5:1 to 1.5:1, preferably from 0.6:1 to 1.3:1, more preferably from 0.7:1 to 1.15:1.

Preferably, the addition of phosphoric acid to the mixture in step iii) can be carried out at a temperature from 5°C to 80°C, i.e. the mixture resulting from step ii) has a temperature from 5°C to 80°C when phosphoric acid is added thereto. Preferably, the mixture resulting from step ii) has a temperature from

10°C to 60°C, more preferably 20°C to 40°C. A most preferred temperature is 25°C (room temperature). In one preferred embodiment, steps ii) and iii) are carried out at the same temperature.

In one embodiment, a solution is obtained following addition of phosphoric acid to the mixture of step ii).

In a further embodiment, a suspension is obtained following addition of phosphoric acid to the mixture of
5 step ii).

In one embodiment of the process of the present invention, the process can comprise an additional step iii-a) of adding a solvent to the mixture resulting from step iii). Preferably, the solvent is a polar protic or polar aprotic solvent. Non-limiting examples of suitable polar solvents are nitromethane, acetonitrile, *N,N*-
10 dimethyl acetamide (DMAc), *N,N*-dimethyl formamide, tetrahydrofuran (THF), acetone, ethyl acetate, an alcohol, such as methanol, ethanol, 1-propanol, 2-propanol, 2-methyl-1-propanol, 2-methyl-2-propanol, 2,2-dimethyl-1-propanol, 1-butanol, 2-butanol, 2-methyl-1-butanol, 2-methyl-2-butanol, 3-methyl-1-butanol, 3-methyl-2-butanol, 1-pentanol and 1-hexanol, or a mixture thereof. More preferably, the solvent is selected from an alcohol, DMAc or a mixture thereof. A preferred alcohol is ethanol or methanol. Even
15 more preferably, the solvent is selected from DMAc, ethanol and methanol.

Preferably, step iii-a) can be carried out when the mixture resulting from step iii) is a suspension. In that case, the solvent in step iii-a) is added in an amount sufficient just to transform the suspension into a solution. In a further embodiment, the ratio of the solvent added in step i) to the solvent added in step iii-a) is preferably from 20:1 to 1:2, such as 18:1, 16:1, 15:1, 13:1, 12:1, 10:1, 8:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1,
20 1:1.5, more preferably from 10:1 to 1:1, such as 8:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1.

In one embodiment, the solvent in step iii-a) can be added to the mixture resulting from step iii) at a temperature from 5°C to 80°C, i.e. the mixture resulting from step iii) has a temperature from 5°C to 80°C when the solvent in step iii-a) is added thereto. Preferably, the mixture resulting from step iii) has a temperature from 10°C to 60°C, more preferably 20°C to 40°C. A most preferred temperature is 25°C
25 (room temperature). In one preferred embodiment, steps ii), iii) and iii-a) are carried out at the same temperature, preferably from 10°C to 30°C, more preferably at 25°C.

In a further embodiment of the process of the invention, the process can comprise an additional step iii-b) of seeding the mixture resulting from step iii) or step iii-a) with crystals of the corresponding, desired
30 phosphate salt. The desired phosphate salt can be generally obtained also without the seeding step iii-b), but seeding the mixture resulting from step iii) or iii-a) may accelerate crystallization. Preferably, the amount of seedings crystals ranges from 0.1 wt.% to 5.0 wt.% based on the amount of the free base provided in step i). The seeding crystals are crystalline phosphate salts of the same compound of Formula I that is provided in step i) as free base. For example, if in step i) the free base of the compound
35 of Formula III is provided, then in optional step iii-b) the corresponding crystalline phosphate salt according to the invention is used as seeding crystal. Moreover, the seeding crystal corresponds to the product to be obtained by the process of the present invention.

In step iv), a phosphate salt of the compound of Formula I is allowed to crystallize in the mixture resulting from step iii), step iii-a) or step iii-b). During this step the phosphate salt of the compound of Formula I
40 which is formed in step ii) by the addition of phosphoric acid is crystallized, optionally after addition of seedings crystals in step iii-b), under suitable conditions.

In one embodiment, in step iv) the mixture resulting from step iii), step iii-a) or step iii-b) is treated by mechanical movement such as stirring or shaking, preferably stirring. In a further, less preferred embodiment, in step iv) the mixture resulting from step iii), step iii-a) or step iii-b) is left without mechanical treatment, preferably at a temperature from 0°C to 100°C for a period of time from 30 min to 24 hours.

In one embodiment, in step iv) the mixture resulting from step iii), step iii-a) or step iii-b) is stirred for a period of time from 30 min to 24 hours, more preferably from 1 to 18 hours, even more preferably from 2 to 12 hours.

In one embodiment of step iv), stirring can be preferably carried out at a temperature from 0°C to 100°C, more preferably from 20°C to 70°C.

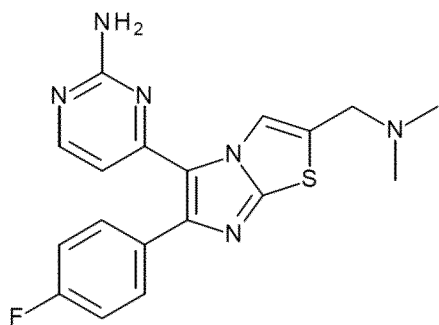
In step v) the crystalline phosphate salt of the compound of Formula I resulting from step iv) is collected and dried. Collecting the crystalline phosphate salt can preferably comprise filtering off the product from step iv). Filtering off the precipitate can for example be carried out with a suction device, a funnel with sieve bottom or filter paper.

Further, the filtered product can preferably be washed, preferably with the solvent which was used in step ii).

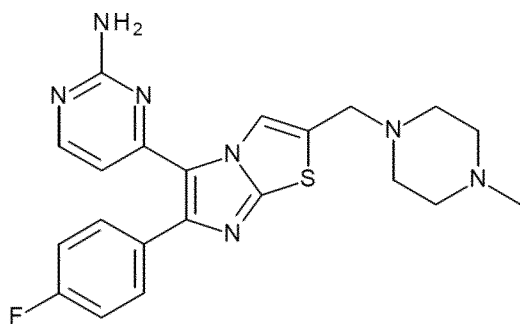
Further, the product can preferably be dried. Drying can preferably be carried out at a pressure from 1 to 1013 mbar (standard pressure). Drying can be carried out under atmospheric pressure, such as, from about 870 to about 1085 mbar, or from about 985 to about 1013 mbar. Drying can also be carried out under reduced pressure, such as from 1 to 600 mbar, 5 to 400 mbar. Further, drying can be carried out at a temperature from 100°C to 200°C, preferably from 20°C to 150°C, more preferably from 20°C to 75°C, even more preferably at 25°C (room temperature).

In one embodiment of the process of the present invention, the process comprises the steps:

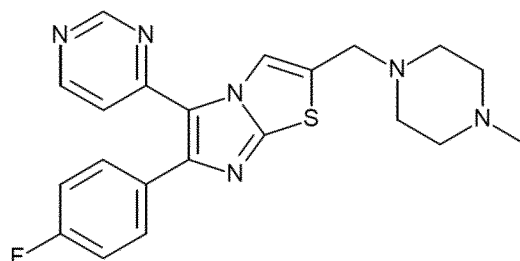
i) providing one of the following compounds of Formulae II to V:



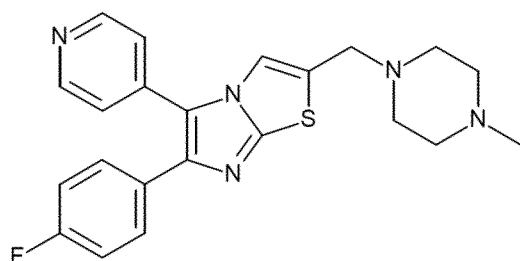
Formula II,



Formula III,



Formula IV,



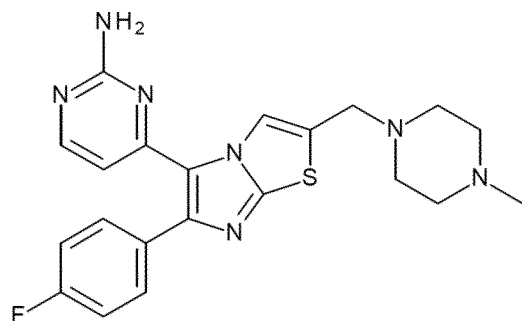
Formula V

as free base,

- 5 ii) adding the free base of step i) to a solvent, preferably methanol, ethanol, DMAc or a mixture thereof at a temperature from 10°C to 30°C, more preferably 25 °C, thus obtaining a mixture having a concentration of the free base of step i) in the solvent from 0.05 to 0.5M,
- iii) adding to the resulting mixture of step ii) at a temperature from 10°C to 30°C a solution of 85% phosphoric acid in an organic solvent, preferably an alcohol, more preferably ethanol or methanol,
- 10 wherein the phosphoric acid has a concentration in the organic solvent from 0.1M to 1.5M, wherein the molar ratio of phosphoric acid to the free base of the compound of Formula II-V is in the range of from 0.5:1 to 1.3:1, preferably from 0.7:1 to 1.15:1,
- iii-a) optionally adding to the resulting mixture from step iii) a solvent, wherein the solvent is preferably the same as used in step i), wherein the ratio of the solvent added in step i) to the solvent added in step
- 15 iii-a) is preferably 10:1 to 1:1, such as 8:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1,
- iii-b) optionally, seeding crystals are added to the mixture resulting from step iii) or step iii-a) to accelerate crystallization of the desired phosphate salt, wherein the amount of seedings crystals ranges from 0.1 wt.% to 5.0 wt.% based on the amount of the free base provided in step i),
- iv) the mixture resulting from step iii), iii-a) or iii-b) is stirred at a temperature from 20°C to 70°C for a
- 20 period of time from 2 to 12h,
- v) the phosphate salt crystals of the compound of one of the compounds of Formulae II to V is collected by filtration and is then dried at a temperature from 20°C to 150°C at a pressure from 600 to 1085 mbar, or at atmospheric pressure.

In a further embodiment of the process of the present invention, the process comprises the steps:

- i) providing a compound of Formula III



as free base,

- ii) adding the free base of step i) to a solvent, preferably methanol, ethanol or DMAc at a temperature from 10°C to 30°C, more preferably 25 °C, thus obtaining a mixture having a concentration of the free base of step i) in the solvent from 0.05 to 0.5M,
- iii) adding to the resulting mixture of step ii) at a temperature from 10°C to 30°C a solution of 85% phosphoric acid in an organic solvent, preferably an alcohol or DMAc, more preferably ethanol or methanol, wherein the phosphoric acid has a concentration in the organic solvent from 0.1M to 1.5M, the molar ratio of phosphoric acid to the free base of the compound of Formula III is in the range of 0.7 : 1 to 1.15 : 1,
- iii-a) optionally adding to the resulting mixture from step iii) a solvent, wherein the solvent is preferably the same as used in step i), wherein the ratio of the solvent added in step i) to the solvent added in step iii-a) is preferably 10:1 to 1:1, such as 8:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1,
- iii-b) optionally, seeding crystals are added to the mixture resulting from step iii) or step iii-a) to accelerate crystallization of the desired phosphate salt, wherein the amount of seedings crystals ranges from 0.1 wt.% to 5.0 wt.% based on the amount of the free base provided in step i),
- iv) the mixture resulting from step iii), iii-a) or iii-b) is stirred at a temperature from 20°C to 70°C for a period of time from 2 to 12 hours,
- v) the phosphate salt crystals of the compound of Formula III is collected by filtration and is then dried at a temperature from 20°C to 150°C at a pressure from 600 to 1085 mbar, or at atmospheric pressure.

In a preferred embodiment of the process of forming a crystalline phosphate salt of the compound of Formula III:

- in step ii) the free base of the compound of Formula III is added to ethanol, methanol or DMAc, wherein the concentration of the free base of the compound of Formula III in the solvent is from 0.05M to 0.3M,
- in step iii) phosphoric acid is added to the mixture resulting from step ii) at a molar ratio of phosphoric acid to the free base of the compound of Formula III being in the range of 0.7 : 1 to 1.15 : 1, wherein phosphoric acid can be added as 85% aqueous solution or as a 0.1M to 1.5M solution of 85% phosphoric acid in an organic solvent, preferably methanol, ethanol or DMAc, wherein the solvent in which phosphoric acid is dissolved is preferably the same as in step ii),
- optional step iii-a) is preferably carried out in case the solvent in step i) is ethanol or methanol, and comprises adding a solvent to the resulting mixture from step iii), wherein the ratio of the solvent added in step i) to the solvent added in step iii-a) is preferably 3:1 to 1:1, more preferably 2:1, 1.5:1 or 1:1,

- in step iii-b) seeding crystals of the phosphate salt of the compound of Formula III are added to the mixture resulting from step iii) or step iii-a), wherein the amount of seedings crystals ranges from 0.1 wt.% to 5.0 wt.% based on the amount of the free base provided in step i),

wherein step iii-b) is optional in case the solvent in step ii) is ethanol or DMAc,

5 - in step iv) the mixture resulting from iii), iii-a) or iii-b) are stirred:

- in case the solvent in at least steps ii) and iii-a) is ethanol or methanol, the mixture resulting from step iii), step iii-a) or step iii-b) is stirred at a temperature from 10°C to 30°C or from 40°C to 70°C for a period of time of 2 to 12 hours,

10 - in case the solvent in step ii) and step iii-a) is DMAc, the mixture resulting from step iii), step iii-a) or step iii-b) is stirred at a temperature from 10°C to 30°C for a period of time of 2 to 12 hours,

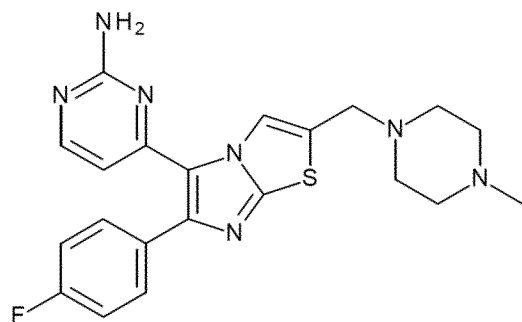
- in case the solvent in step ii) is DMAc and in step iii-a) is ethanol or methanol, the mixture resulting from step iii-a) is stirred at a temperature from 40°C to 70°C for a period of time of 2 to 12 hours, preferably from 2 to 5 hours,

15 - in step v) the phosphate salt crystals of the compound of Formula III is collected by filtration and is then dried at a temperature from 20°C to 80°C at a pressure from 600 to 1085 mbar, or at atmospheric pressure.

In one embodiment of the process of the invention, the solvent in step ii), step iii) or step iii-a) can comprise methanol. The presence of methanol can lead to the formation of a crystalline methanol solvate of the monophosphate salt of a compound of Formula I, preferably of the compound of Formula III, as shown for example in **Figure 5a**). Preferably, the methanol solvate is transformed into the solvent-free crystalline monophosphate salt of the compound of Formula III by drying the methanol solvate in step v) at a temperature from 20°C to 80°C at a pressure from about 600 to 1085 mbar, more preferably from 20°C to 50°C, or by heating the suspension resulting from step iv) at a temperature from 50°C to 80°C for a period of time from 2 to 12 hours. Further preferably, instead of heating the suspension resulting from step iv), the methanol solvate can be isolated, such as by filtration, and resuspended in a solvent, such as one of the solvent described above for step ii), before heating the suspension at a temperature from 50°C to 150°C, preferably 50°C to 100°C, for a period of time from 2 to 12 hours, preferably from 2 to 6 hours. Next, hereunder specific embodiments of the process of the invention will be described.

25 In an embodiment, the process of forming a crystalline monophosphate salt of the compound of Formula III according to the present invention comprises the steps:

30 i) providing a compound of Formula III



Formula III

as free base,

ii) adding the free base of step i) to ethanol at a temperature from 10°C to 30°C, more preferably 25 °C, thus obtaining a mixture having a concentration of the free base of step i) in the solvent from 0.05 to 0.5M,

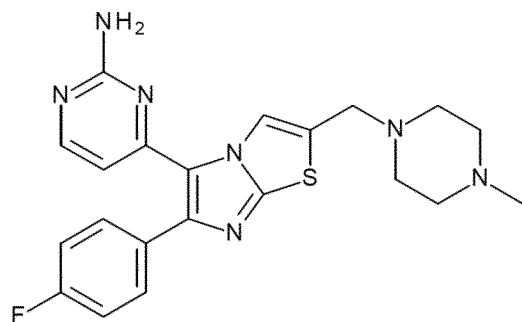
iii) adding to the resulting mixture of step ii) at a temperature from 10°C to 30°C a solution of 85% phosphoric acid in ethanol, wherein the phosphoric acid has a concentration in the organic solvent from 0.1M to 1.5M, the molar ratio of phosphoric acid to the free base of the compound of Formula III is in the range of 0.5 : 1 to 1.15 : 1,

iv) the mixture resulting from step iii) is stirred at a temperature from 10°C to 30°C for a period of time from 2 to 24 hours, preferably from 2 to 12 hours,

v) the monophosphate salt crystals of the compound of Formula III are collected by filtration and are then dried at a temperature from 20°C to 30°C a pressure from 600 to at 1085 mbar, or at atmospheric pressure.

In another embodiment, the process of forming a crystalline monophosphate salt of the compound of Formula III according to the present invention comprises the steps:

i) providing a compound of Formula III



Formula III

as free base,

ii) adding the free base of step i) to ethanol at a temperature from 10°C to 30°C, more preferably 25 °C, thus obtaining a mixture having a concentration of the free base of step i) in the solvent from 0.05 to 0.5M,

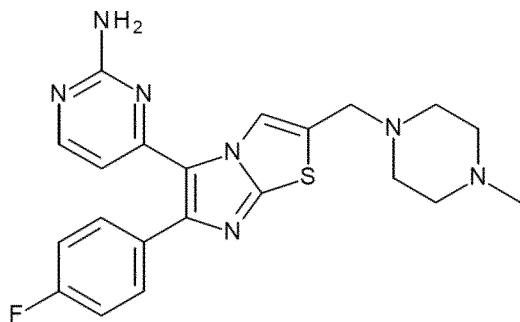
iii) adding to the resulting mixture of step ii) at a temperature from 40°C to 70°C a solution of 85% phosphoric acid in ethanol, wherein the phosphoric acid has a concentration in the organic solvent from 0.1M to 1.5M, the molar ratio of phosphoric acid to the free base of the compound of Formula III is in the range of 0.5 : 1 to 1.15 : 1,

iv) the mixture resulting from step iii) is stirred at a temperature from 40°C to 70°C for a period of time from 1h to 12h, preferably from 2 to 6 hours,

v) the monophosphate salt crystals of the compound of Formula III are collected by filtration and are then dried at a temperature from 20°C to 30°C at a pressure from 600 to 1085 mbar, or at atmospheric pressure.

In another embodiment, the process of forming a crystalline monophosphate salt of the compound of Formula III according to the present invention comprises the steps:

i) providing a compound of Formula III



Formula III

as free base,

ii) adding the free base of step i) to methanol at a temperature from 10°C to 30°C, more preferably 25 °C, thus obtaining a mixture having a concentration of the free base of step i) in the solvent from 0.05 to 0.5M,

iii) adding to the resulting mixture of step ii) at a temperature from 10°C to 30°C a solution of 85% phosphoric acid in methanol, wherein the phosphoric acid has a concentration in the organic solvent from 0.1M to 1.5M, the molar ratio of phosphoric acid to the free base of the compound of Formula III is in the range of 0.5 : 1 to 1.15 : 1,

iii-a) adding to the resulting mixture from step iii) methanol, wherein the ratio of the solvent added in step i) to the solvent added in step iii-a) is preferably 10:1 to 1:1, such as 8:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1, more preferably 4:1 to 1:1,

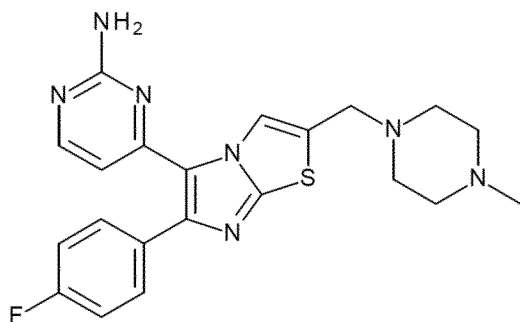
iii-b) adding seeding crystals to the mixture resulting from step iii-a) to accelerate crystallization of the desired phosphate salt, wherein the amount of seedings crystals ranges from 0.1 wt.% to 5.0 wt.% based on the amount of the free base provided in step i),

iv) the mixture resulting from step iii-b) is stirred at a temperature from 10°C to 30°C for a period of time from 1 to 24 hours, preferably from 2 to 12 hours,

v) the methanol solvate monophosphate salt crystals of the compound of Formula III are collected by filtration and are then dried at a temperature from 20°C to 30°C at a pressure from 600 to 1085 mbar, or at atmospheric pressure, thus obtaining crystalline solvent-free monophosphate of the compound of Formula III.

In another embodiment, the process of forming a crystalline monophosphate salt of the compound of Formula III according to the present invention comprises the steps:

i) providing a compound of Formula III



Formula III

as free base,

ii) adding the free base of step i) to methanol at a temperature from 10°C to 30°C, more preferably 25 °C, thus obtaining a mixture having a concentration of the free base of step i) in the solvent from 0.05 to 0.5M,

iii) adding to the resulting mixture of step ii) at a temperature from 10°C to 30°C a solution of 85% phosphoric acid in methanol, wherein the phosphoric acid has a concentration in the organic solvent from 0.1M to 1.5M, the molar ratio of phosphoric acid to the free base of the compound of Formula III is in the range of 0.5 : 1 to 1.15 : 1,

iii-a) adding to the resulting mixture from step iii) ethanol, wherein the ratio of the solvent added in step i) to the solvent added in step iii-a) is preferably 10:1 to 1:1, such as 8:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1:1, more preferably 4:1 to 1:1,

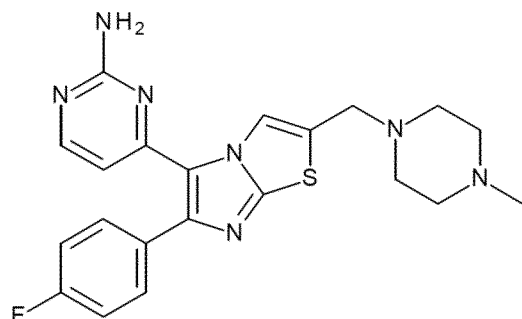
iii-b) adding seeding crystals to the mixture resulting from step iii-a) to accelerate crystallization of the desired phosphate salt, wherein the amount of seedings crystals ranges from 0.1 wt.% to 5.0 wt.% based on the amount of the free base provided in step i),

iv) the mixture resulting from step iii-b) is stirred at a temperature from 10°C to 30°C for a period of time from 1 to 24 hours, preferably from 2 to 12 hours, then the suspension of monophosphate salt solvate crystals of the compound of Formula III is heated at a temperature from 50°C to 70°C for a period of time from 1 to 24 hours, preferably from 2 to 12 hours,

v) the monophosphate salt crystals of the compound of Formula III are collected by filtration and are then dried at a temperature from 20°C to 30°C at a pressure from 600 to 1085 mbar, or at atmospheric pressure.

In another embodiment, the process of forming a crystalline monophosphate salt of the compound of Formula III according to the present invention comprises the steps:

i) providing a compound of Formula III



Formula III

as free base,

ii) adding the free base of step i) to DMAc at a temperature from 10°C to 30°C, more preferably 25 °C, thus obtaining a mixture having a concentration of the free base of step i) in the solvent from 0.05 to 0.5M,

iii) adding to the resulting mixture of step ii) at a temperature from 10°C to 30°C a solution of 85% phosphoric acid in methanol, wherein the phosphoric acid has a concentration in the organic solvent from 0.1M to 1.5M, the molar ratio of phosphoric acid to the free base of the compound of Formula III is in the range of 0.5 : 1 to 1.15 : 1,

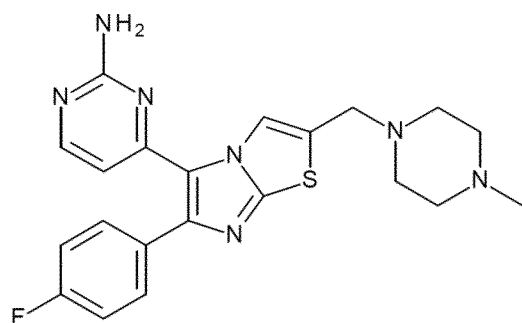
iv) the mixture resulting from step iii) is stirred at a temperature from 10°C to 30°C for a period of time from 1 to 24 hours, preferably from 2 to 12 hours, then the suspension of monophosphate salt

solvate crystals of the compound of Formula III is heated at a temperature from 50°C to 70°C for a period of time from 1 to 24 hours, preferably from 2 to 6 hours,

v) the monophosphate salt crystals of the compound of Formula III are collected by filtration and are then dried at a temperature from 20°C to 30°C at a pressure from 600 to 1085 mbar, or at atmospheric pressure.

In another embodiment, the process of forming a crystalline monophosphate salt of the compound of Formula III according to the present invention comprises the steps:

i) providing a compound of Formula III



Formula III

as free base,

ii) adding the free base of step i) to DMAc at a temperature from 10°C to 30°C, more preferably 25 °C, thus obtaining a mixture having a concentration of the free base of step i) in the solvent from 0.05 to 0.5M,

iii) adding to the resulting mixture of step ii) at a temperature from 10°C to 30°C a solution of 85% phosphoric acid in DMAc, wherein the phosphoric acid has a concentration in the organic solvent from 0.1M to 1.5M, the molar ratio of phosphoric acid to the free base of the compound of Formula III is in the range of 0.5 : 1 to 1.15 : 1,

iii-b) adding seeding crystals to the mixture resulting from step iii) to accelerate crystallization of the desired phosphate salt, wherein the amount of seedings crystals ranges from 0.1 wt.% to 5.0 wt.% based on the amount of the free base provided in step i),

iv) the mixture resulting from step iii-b) is stirred at a temperature from 10°C to 30°C for a period of time from 0.5 to 24 hours, preferably from 1 to 6 hours,

v) the monophosphate salt crystals of the compound of Formula III are collected by filtration and are then dried at a temperature from 20°C to 30°C a pressure from 600 to at 1085 mbar, or at atmospheric pressure.

The invention will now be further described by the following, non-limiting, examples.

EXAMPLES

The crystalline monophosphate salt of the compound of Formula III was characterized by X-ray powder diffraction (XRPD), carbon-13 solid state NMR (CPMAS), Differential Scanning Calorimetry (DSC), Ultra Performance Liquid Chromatography (UPLC), Particle Size Distribution (PSD) and X-ray crystallography (X-Ray). Additionally, adsorption/desorption tests were carried out.

X-ray powder diffraction (XRPD)

The X-ray powder diffraction pattern of the crystalline monophosphate salt of the compound of Formula III was generated on Bruker D8 Advance Diffraction System. A PW3373/00 ceramic Cu LEF X-ray tube K- α radiation was used as the source. A typical precision of the 2θ values is in the range of about $\pm 0.2^\circ 2\theta$. Thus a diffraction peak that appears at $5.0^\circ 2\theta$ can appear between 4.8 and $5.2^\circ 2\theta$ on most X-ray diffractometers under standard conditions.

Solid State NMR (CPMAS)

In addition to the X-ray powder diffraction patterns described above, the crystalline monophosphate salt of the compound of Formula III was characterized based on its solid-state carbon-13 nuclear magnetic resonance (NMR) spectrum. The carbon-13 spectrum was recorded on a Bruker AV400 NMR spectrometer operating at a carrier frequency of 400.14 MHz, using a Bruker 4 mm H/F/X BB triple resonance CPMAS probe. The spectrum was collected utilizing proton/carbon-13 variable-amplitude cross-polarization (VACP) at 80 kHz, with a contact time of 3 ms. Other experimental parameters used for data acquisition were a proton 90-degree pulse of 100 kHz, SPINAL64 decoupling at 100 kHz, a pulse delay of 4.5 s, and signal averaging for 10600 scans. The magic-angle spinning (MAS) rate was set to 13 kHz. A Lorentzian line broadening of 30 Hz was applied to the spectrum before Fourier Transformation. Chemical shifts are reported on the TMS scale using the carbonyl carbon of glycine (176.70 ppm.) as a secondary reference.

X-ray crystallography

All diffraction measurements were made at approximately 100 K on a Bruker Apex II diffractometer.

Differential Scanning Calorimetry (DSC)

DSC data were acquired using TA Instruments DSC Q2000. A sample with a weight between 1 and 6 mg was weighed into an open pan. This pan was placed in the sample position in the calorimeter cell. An empty pan was placed in the reference position. The calorimeter cell was closed, and a flow of nitrogen was passed through the cell. The heating program was set to heat the sample at a heating rate of $10^\circ\text{C}/\text{min}$ to a temperature of 300°C . When the run was completed, the data were analyzed using the DSC analysis program in the system software. The observed endo- and exotherms were integrated between baseline temperature points that are above and below the temperature range over which the endotherm was observed. The data reported are the onset temperature, peak temperature and enthalpy.

Ultra-Performance Liquid Chromatography (UPLC)

The phosphoric acid content in the phosphate salt of the compound of Formula III was determined by UPLC by comparison with the corresponding free base. The parameters of the chromatographic method used to assess the content of phosphoric acid are described below:

Chromatographic Column:	Cortecs C18 2.1 μm , 2.1x150mm
Mobile Phase A:	0.1% Formic acid in water
Mobile Phase B:	Acetonitrile
Flow Rate:	0.3 mL/min
Column Temp:	40°C

Wavelength: 363 nm

Injection Volume: 1 µL

Run Time: 15 min

Gradient:

Time (min)	%A	%B
0	90	10
2	90	10
10	5	95
12	5	95
13	90	10
15	90	10

5

Adsorption/Desorption

Hygroscopicity was assessed using a dynamic vapor sorption analyzer VTI-SA by TA-Instruments. The relative humidity (RH) was varied from 5% to 95% and back to 5% in 10% intervals at 25°C. The data is reported as % weight change as a function of RH%.

10

Particle Size Distribution (PSD)

Instrument: Malvern Mastersizer 3000 with Hydro Medium Volume automated dispersion unit

Method parameters

Measurement Details

15	Accessory Name	Hydro MV
	Background Measurement Time	10.00 s
	Sample Measurement Time	10.00 s
	Obscuration lower limit (%)	2
	Obscuration higher limit (%)	15
20	Number of measurements	3
	Analysis	
	Particle Type	Non-spherical
	Particle Refractive Index	1.600
	Particle Absorption Index	0.100
25	Dispersant Name	Isopar G
	Dispersant Refractive Index	1.420
	Sonication time	60s at 100%
	Stirring speed	2000 rpm
	Scattering Model	Fraunhofer
30	Analysis Model	General Purpose

Sample Preparation for PSD

Approximately 20-50 mg of API was added to 1 mL of Isopar G containing 1% (wt/vol) lecithin. The vial was capped and shaken for ~ 30 s. The sample was added to the Hydro MV sample reservoir dropwise

using a pipette until the obscuration exceeded 2%. The sample was sonicated for 60 seconds. The measurement was initiated 3 minutes after the end of the sonication to allow the air bubbles level to decrease until no peak above 1000 microns was visible.

5 Example 1: Crystallization of a monophosphate salt of the compound of Formula III from ethanol

a) At 25°C (room temperature)

100 mg (0.22 mmol) of the free base of compound of Formula III was weighed in a vial. 1 mL ethanol was added to the free base, followed by 10 µL (0.15 mmol) of 85% phosphoric acid. The suspension was stirred at room temperature for 12 hours (overnight). The suspension was then filtered and subsequently
10 air dried, thus obtaining a crystalline phosphate salt. UPLC analysis using the free base as standard demonstrated that the product was a monophosphate salt having a free base content of 80 wt.%, close to the theoretical free base content of 81 wt% in a monophosphate salt.

The X-ray powder diffractogram of the crystalline monophosphate salt of the compound of Formula III is shown in **Figure 1**.

15 The solid-state C-13 CP MAS NMR spectrum of the crystalline monophosphate salt of the compound of Formula III is shown in **Figure 2**.

A typical DSC curve of the crystalline monophosphate salt of the compound of Formula III is shown in **Figure 3**. The DSC curve is characterized by a melting point of about 252°C, as determined by the onset of the melting endotherm. The endothermic peak is reached at about 255°C. The DSC curve also shows
20 that the crystalline monophosphate salt of the compound of Formula III is anhydrous through the absence of endotherm around 100°C.

The structure of the crystalline monophosphate salt of the compound of Formula III determined by X-ray crystallography is shown in **Figure 16 to 18** and atom coordinates and other descriptive data are shown in **Tables 3 to 10** (Example 9).

b) At 25°C (room temperature)

100 mg (0.22 mmol) of the free base of compound of Formula III was weighed in a vial. 1 mL ethanol was added to the free base, followed by 20 µL (0.29 mmol) of 85% phosphoric acid. The suspension was stirred at room temperature for 12 hours (overnight). The suspension was then filtered and subsequently
30 air dried, thus obtaining a crystalline phosphate salt. UPLC analysis using the free base as standard demonstrated that the product was a monophosphate salt having a free base content of 80 wt.%, close to the theoretical free base content of 81 wt% in a monophosphate salt.

The XRPD pattern was consistent with **Figure 1**.

35 c) At 60°C

50 mg (0.11 mmol) of the free base of compound of Formula III were dispensed in an amber vial, 1 mL ethanol was added thereto, and the suspension was placed at 60°C. After the suspension of the free base in ethanol reached 60 °C, 230 µL of a 0.1M phosphoric acid solution in ethanol was added to the vial. The sample was suspended for 2 hours, then part of the suspension was centrifuged, the
40 supernatant was returned to the vial and the wet cake was analyzed by XRPD. The XRPD pattern was consistent with **Figure 1**.

d) At 60°C

50 mg (0.11 mmol) of the free base of compound of Formula III were dispensed in an amber vial, 1 mL ethanol was added thereto, and the suspension was placed at 60°C. After the suspension of the free base in ethanol reached 60 °C, 100 µL of 1.34M phosphoric acid solution in ethanol was added to the vial. The sample was suspended for 2 hours, then part of the suspension was centrifuged, the supernatant was returned to the vial and the wet cake was analyzed by XRPD. The XRPD pattern was consistent with **Figure 1**.

Example 2: Crystallization of a monophosphate salt of the compound of Formula III from methanol

200.6 mg (0.44 mmol) of the free base of compound of Formula III was suspended in 4 mL methanol and stirred. 1 mL of a phosphoric acid solution in methanol (163 µL of 85% phosphoric acid in 5 mL methanol) was added in 0.2 mL increments. The solids almost completely dissolved. Additional 4 mL of MeOH were added and the solution was seeded with crystals of the monophosphate salt of the compound of Formula III (from Example 1). Nucleation started almost immediately.

The suspension was stirred for 12 hours at 25°C, then filtered, obtaining a crystalline methanol solvate of the phosphate salt of the compound of Formula III that transformed to the phosphate salt of the compound of Formula III (having an XRPD as in Figure 1) upon drying under air, see **Figure 4b**).

Example 3: Crystallization of a monophosphate salt of the compound of Formula III from methanol/ethanol 5:4 (v:v)

199.7 mg (0.44 mmol) of the free base of compound of Formula III was suspended in 4 mL methanol and stirred. 1 mL of a phosphoric acid solution in methanol (163 µL of 85% phosphoric acid in 5 mL methanol) was added in 0.2 mL increments. The solids almost completely dissolved. 4 mL of ethanol was added, and the solution was seeded with crystals of monophosphate salt of the compound of Formula III (from Example 1). Nucleation started after approximately 30 sec. The suspension was stirred at 25°C for 12 hours (overnight).

The suspension contained a crystalline solvate of the phosphate salt of the compounds of Formula III as shown in **Figure 5a**), which converted to the phosphate salt of the compound of Formula III (having an XRPD as in Figure 1) after the suspension was equilibrated at 60°C overnight (see **Figure 5b**)).

Example 4: Crystallization of a monophosphate salt of the compound of Formula III from dimethyl acetamide/methanol 4:1 (v:v)

200 mg (0.44 mmol) of the free base of compound of Formula III was suspended in 4 mL *N,N*-dimethyl acetamide (DMAc) and stirred. 1 mL of a phosphoric acid solution in methanol (163 µL of 85% phosphoric acid in 5 mL methanol) was added in 0.2 mL increments. The suspension that formed contained a crystalline solvate of the phosphate of the compound of Formula III as shown in **Figure 6a**). Aliquots from the resulting suspension were equilibrated 60 °C for 3 hours, then centrifuged and the supernatant decanted. XRPD analysis showed that the solid has converted to the phosphate salt of the compound of Formula III having an XRPD as in Figure 1, as shown in **Figure 6b**).

Example 5: Crystallization of a monophosphate salt of the compound of Formula III from DMAc

100 mg (0.22 mmol) of the free base of compound of Formula III was placed in 8 mL vial. 3 mL DMAc were added followed by 0.5 mL 0.5M of a phosphoric acid solution in DMAc (0.5 M). A clear solution formed. Under stirring, the solution was then seeded with the monophosphate salt from Example 1. After 2 hours, the suspension was filtered, and the product analyzed by XRPD, showing to be the phosphate salt according to Figure 1.

Example 6 (Comparative): Formation of acetate, L-tartrate and citrate salts of compound of Formula III

100 mg (0.22 mmol) of the free base of compound of Formula III was placed in 6 vials and suspended with 1 mL ethanol. Then, in the first two vials 60 μ L (1 mmol) and 120 μ L (2 mmol) of acetic acid were added. In the third vial 38mg (0.25 mmol) L-tartaric acid was added. In the last three vials 17 mg (0.09 mmol), 35 mg (0.17 mmol) and 53 mg (0.25 mmol) citric acid monohydrate, respectively, were added. The suspensions were stirred at room temperature for 12 hours. The suspensions were then filtered and subsequently air dried, thus obtaining crystalline acetates [Figures 7a) and b)], L-tartrate (Figure 8) and citrates [Figures 9a)-c)], respectively, of the compound of Formula III.

Example 7: Adsorption/desorption tests

The monophosphate salt of compound of Formula III as obtained in Examples 1-5 as well as the acetate, L-tartrate and citrate salts of Example 6 (Comparative) were tested in adsorption/desorption tests. In these tests, the monophosphate salt of compound of Formula III absorbed 1.1 wt.% at 75% relative humidity (RH). The water uptake at 85%RH was 3.8 wt.% and 10.6 wt.% at 95%RH. The adsorption/desorption curve of the monophosphate salt of compound of Formula III is shown in Figure 10. After completion of the adsorption and desorption experiment an XRPD of the probe was taken, showing no difference from the XRPD taken before the adsorption/desorption test, as shown in Figures 11a) and b). Hence, water absorption and desorption left the crystalline structure of the phosphate salt of compound of Formula III unchanged.

The acetate salt of compound of Formula III (obtained using 120 μ L acetic acid) lost 4.7 wt.% at 5%RH, which was regained at 45%RH. The sample absorbed greater than 40 wt.% water at 95%RH. The adsorption/desorption curve of the acetate salt of compound of Formula III is shown in Figure 12. The sample recovered from the hygroscopicity experiment was an amorphous glassy solid, indicating that the sample had deliquesced.

The L-tartrate salt of compound of Formula III absorbed 5 wt.% water at 65%RH and 37 wt.% at 95%RH. The adsorption/desorption curve of the L-tartrate salt of compound of Formula III is shown in Figure 13.

The XRPD analysis of the solid recovered at the end of the experiment showed that the sample was amorphous and thus that the sample had deliquesced at high relative humidity.

The citrate salt of compound of Formula III (obtained using 35 mg citric acid) lost 2.7 wt.% at 5%RH, which was regained at 25%RH. The sample absorbed 6.3 wt.% water up to 75%RH, and 29 wt.% water at 95%RH. The adsorption/desorption curve of the citrate salt of compound of Formula III is shown in Figure 14. The sample recovered from the hygroscopicity experiment was amorphous, indicating that the sample had deliquesced.

The adsorption/desorption tests show a surprising reduced hygroscopicity of the monophosphate salt of the compound of Formula III of the present invention compared to other crystalline salts of the same compound. Due to its particularly reduced hygroscopicity, the monophosphate salt of the compound of Formula III is stable even under conditions of high humidity, thus maintaining its crystalline structure unchanged.

Example 8: Crystallization of a monophosphate salt of the compound of Formula III from ethanol under different conditions

A slurry of 10 g of compound of Formula III in 50 – 200 mL ethanol was stirred between ambient temperature and 60°C (column B). 1.6 mL H₃PO₄ (85%) was dissolved in 22 mL or 45 mL ethanol and added to the slurry during less than 1 to 50 minutes under stirring. Stirring was continued between ambient temperature and 60°C (column F) for 4 hours or overnight (column G). For some entries stirring was continued at ambient temperature overnight (columns H and I). The mixture was filtered and the solid was washed with ethanol (1 x 50 mL and 1 x 25 mL). The washed solid was dried under reduced pressure at 40°C leading to batches 1 – 11.

According to figure 15 all XRPD correspond to the reference XRPD in **Figure 1**. All conditions lead to the same polymorph of the crystalline mono-phosphate salt of compound of Formula III.

However, different PSD is obtained depending on variation of the parameters studied (columns K – M).

Details for volumes, times, temperatures and PSD are given in the **Table 2**.

Table 2: Crystallization conditions for mono-phosphate of the compound of Formula III

Entry	A Ethanol [mL]	B Temp [°C]	C H ₃ PO ₄ 85% [mL]	D Ethanol [mL]	E Duration of H ₃ PO ₄ addition [min]	F Temp [°C]	G Stirring time [h]	H Temp [°C]	i Stirring time [h]	j Batch number	K PSD D10 (µm)	L PSD D50 (µm)	M PSD D90 (µm)
1	200	ambient	1.6	45	10	ambient	overnight	/	/	1	1.4	4.8	26.4
2	200	60	1.6	45	12	60	4	ambient	overnight	2	2.4	13.9	29.7
3	100	60	1.6	45	11	60	4	ambient	overnight	3	3.2	17.6	33.6
4	100	40	1.6	45	11	40	4	ambient	overnight	4	1.5	7.0	14.8
5	100	40	1.6	22	8	40	4	ambient	overnight	5	1.7	7.7	16.1
6	100	40	1.6	22	< 1	40	overnight	/	/	6	9.4	17.4	26.7
7	100	40	1.6	22	8	ambient	overnight	/	/	7	0.9	3.5	21.0
8	75	40	1.6	45	30	40	4	ambient	overnight	8	2.3	11.5	23.7
9	50	60	1.6	45	50	60	4	ambient	overnight	9	1.5	7.5	17.8
10*	120	/	/	/	/	60	4	ambient	overnight	10	1.4	8.3	26.0
11	200	ambient	1.6	45	26	ambient	overnight	/	/	11	1.0	39.6	143.0

*Entry 10: 6 x 1 g of different batches of the monophosphate salt of the compound of Formula III were combined and used.

Example 9: Crystal structure of a monophosphate salt of the compound of Formula III

The crystal was grown via cooling to room temperature of a refluxing saturated solution of the monophosphate salt of compound of Formula III in ethanol.

The refinement was complete at an excellent level ($R = 2.9\%$) and the molecular geometry shows no unusual quantities. The compound has crystallized in the centrosymmetric space group P-1 as an anhydrous monophosphate salt with one molecule in the asymmetric unit. The molecules form a hydrogen-bonded network with hydrogen-bonding between the phosphate and various nitrogen within the molecule. A proton is transferred from O2 to N19 to form the salt. An ORTEP representation of the crystalline mono-phosphate salt of compound of Formula III is shown in **Figure 16**. Images of the hydrogen-bonding network with the ionic bond and the packed unit cell are shown in **Figures 17 and 18**, respectively. No major voids in the lattice are apparent.

Table 3: Crystal structure data and structure refinement for example 9

Identification code	mdo032
Empirical formula	C ₂₁ H ₂₅ N ₇ O ₄ FPS
Formula weight	521.51
Temperature	100(2) K
Radiation	CuK α ($\lambda = 1.54178$)
Crystal system	triclinic
Space group	P-1
Unit Cell Dimensions	$a = 7.528(6) \text{ \AA}$ $\alpha = 79.24(3)^\circ$
	$b = 9.275(6) \text{ \AA}$ $\beta = 84.813(12)^\circ$
	$c = 17.230(7) \text{ \AA}$ $\gamma = 79.24(3)^\circ$
Volume	1140.8(13) ($\text{\AA}^3$)
Z	2
Density	1.518 (g/cm ³)
Absorption coefficient	2.398 mm ⁻¹
F(000)	544.0
Crystal size	0.18 × 0.16 × 0.12 mm ³
2 θ range for data collection	10.014° to 141.296°
Index ranges	-9 ≤ h ≤ 9, -11 ≤ k ≤ 11, -20 ≤ l ≤ 20
Reflections collected	26260
Independent reflections	4240 [$R_{\text{int}} = 0.0245$, $R_{\text{sigma}} = 0.0139$]
Completeness to $\Theta=67.679^\circ$	0.992
Absorption correction	multi-scan
Max. and min. transmission	0.7534 and 0.7057
Refinement Method	Full-matrix least-squares on F^2
Data/restraints/parameters	4240/0/319
Goodness-of-fit on F^2	1.030
Final R indexes [$ I \geq 2\sigma(I)$]	$R_1 = 0.0291$, $wR_2 = 0.0742$
Final R indexes [all data]	$R_1 = 0.0292$, $wR_2 = 0.0743$
Largest diff. peak/hole	0.29/-0.37 e $\text{\AA}^{-3}$

Table 4: Fractional Atomic Coordinates (×104) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for mdo032

Atom	x	y	z	U(eq)
C1	11823(2)	695.7(16)	-845.6(9)	19.1(3)
C2	10458(2)	1952.1(17)	-1112.1(8)	18.9(3)

C3	9600.5(19)	2902.6(16)	-585.4(8)	14.8(3)
C4	10076.5(18)	2584.8(15)	204.6(8)	12.8(3)
C5	11430.4(19)	1267.0(15)	455.2(8)	15.4(3)
C6	12333.3(19)	325.8(16)	-72.6(9)	18.1(3)
C7	9044.4(18)	3621.4(15)	732.9(8)	12.3(3)
C9	6747.7(18)	5296.0(15)	1083.1(8)	12.9(3)
C11	5716.7(18)	6767.8(15)	2162.2(8)	13.7(3)
C12	7307.1(18)	5719.0(15)	2311.0(8)	12.9(3)
C14	9454.9(18)	3843.4(14)	1468.1(8)	11.7(3)
C15	4889.6(18)	7963.5(15)	2653.6(8)	14.8(3)
C17	2314.5(19)	6959.2(15)	3242.8(8)	14.1(3)
C18	254.5(19)	7336.2(15)	3436.6(8)	14.5(3)
C19	-2268.1(19)	9010.5(16)	4114.5(8)	17.1(3)
C20	323.6(19)	9963.1(15)	3435.0(8)	15.7(3)
C21	2371.6(19)	9530.9(15)	3249.1(9)	15.8(3)
C22	11114.5(18)	3445.9(14)	1921.4(8)	11.6(3)
C24	12351.5(18)	3249.0(14)	3118.9(8)	11.7(3)
C26	14332.7(18)	2947.5(15)	2040.6(8)	13.1(3)
C27	12892.3(18)	3139.5(15)	1559.9(8)	13.5(3)
F1	12674.7(14)	-236.8(10)	-1365.3(5)	29.8(2)
N8	7347.7(15)	4533.3(13)	500.1(7)	13.8(2)
N13	7897.8(15)	4902.7(12)	1695.7(7)	11.7(2)
N16	2882.9(15)	8287.2(12)	2790.2(7)	13.0(2)
N19	-267.0(15)	8615.0(13)	3892.8(6)	12.3(2)
N23	10844.6(15)	3507.1(12)	2696.1(7)	11.9(2)
N24	12084.3(15)	3256.9(13)	3898.2(7)	15.1(2)
N25	14102.7(15)	3001.8(12)	2815.5(7)	12.4(2)
O1	2976.1(12)	7151.0(11)	6402.7(6)	14.9(2)
O2	1231.6(13)	7490.2(12)	5233.2(6)	18.0(2)
O3	4768.3(13)	6870.5(10)	5098.5(6)	14.3(2)
O4	3106.2(14)	4897.6(11)	5777.0(6)	18.7(2)
P1	3054.6(4)	6644.8(4)	5582.2(2)	10.95(9)
S10	4844.7(4)	6741.8(4)	1255.4(2)	14.61(9)

Table 5 Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for mdo032

Atom	U11	U22	U33	U23	U13	U12
C1	23.0(7)	17.1(7)	20.0(7)	-9.7(6)	9.7(6)	-9.0(6)
C2	26.3(8)	20.4(7)	11.8(7)	-3.1(6)	2.4(6)	-9.9(6)
C3	16.5(7)	14.3(6)	14.3(7)	-1.1(5)	-0.4(5)	-6.3(5)
C4	12.5(6)	13.4(6)	14.1(6)	-2.8(5)	0.5(5)	-6.0(5)
C5	15.8(7)	15.2(7)	15.8(7)	-2.6(5)	-1.8(5)	-4.7(5)
C6	15.6(7)	14.1(7)	24.1(7)	-4.1(6)	1.4(6)	-3.0(5)
C7	11.7(6)	11.7(6)	13.1(6)	-0.7(5)	-1.0(5)	-3.0(5)
C9	10.2(6)	13.1(6)	14.1(6)	-0.2(5)	-2.1(5)	-1.5(5)
C11	13.6(6)	13.2(6)	13.9(6)	-1.4(5)	1.0(5)	-3.9(5)
C12	13.3(6)	13.0(6)	12.5(6)	-2.9(5)	1.3(5)	-3.7(5)
C14	11.0(6)	10.0(6)	13.3(6)	-2.2(5)	0.5(5)	-1.2(5)
C15	12.6(6)	13.1(6)	18.6(7)	-4.3(5)	0.9(5)	-2.4(5)
C17	16.9(7)	10.3(6)	15.2(6)	-2.7(5)	1.3(5)	-3.8(5)

C18	18.0(7)	14.3(6)	13.5(6)	-4.8(5)	0.6(5)	-6.5(5)
C19	13.0(7)	21.0(7)	17.5(7)	-3.8(6)	1.2(5)	-4.4(5)
C20	15.0(7)	11.1(6)	19.5(7)	-2.0(5)	2.8(5)	-2.3(5)
C21	15.3(7)	11.3(6)	21.3(7)	-5.2(5)	3.1(5)	-3.8(5)
C22	13.8(6)	7.6(6)	13.6(6)	-1.6(5)	-2.1(5)	-2.5(5)
C24	13.1(6)	8.0(6)	14.2(6)	-1.6(5)	-1.6(5)	-2.7(5)
C26	12.3(6)	10.9(6)	16.0(7)	-3.0(5)	1.1(5)	-2.6(5)
C27	14.2(6)	13.5(6)	12.8(6)	-3.5(5)	0.1(5)	-2.7(5)
F1	38.9(6)	25.1(5)	25.2(5)	-14.5(4)	13.3(4)	-5.4(4)
N8	12.2(5)	14.9(6)	13.6(6)	-1.9(4)	-1.7(4)	-2.1(4)
N13	10.9(5)	11.9(5)	11.6(5)	-2.1(4)	-0.8(4)	-1.7(4)
N16	12.8(6)	10.3(5)	15.3(6)	-2.5(4)	1.9(4)	-2.2(4)
N19	11.7(5)	13.4(5)	11.7(5)	-2.4(4)	-0.1(4)	-3.1(4)
N23	11.6(5)	11.0(5)	12.6(5)	-1.9(4)	-1.3(4)	-1.8(4)
N24	10.6(5)	23.1(6)	11.8(6)	-3.3(5)	-1.4(4)	-4.2(5)
N25	11.7(5)	11.9(5)	13.9(6)	-2.6(4)	-1.4(4)	-2.7(4)
O1	9.3(4)	21.3(5)	14.6(5)	-7.7(4)	-1.4(4)	-0.8(4)
O2	12.0(5)	27.4(5)	12.4(5)	-2.4(4)	-1.9(4)	-1.4(4)
O3	12.8(5)	14.4(5)	15.9(5)	-3.8(4)	1.9(4)	-3.7(4)
O4	21.9(5)	15.6(5)	18.6(5)	-6.0(4)	9.6(4)	-6.2(4)
P1	9.26(17)	12.86(17)	10.62(17)	-3.02(12)	-0.37(12)	-1.84(12)
S10	11.38(16)	14.71(17)	15.37(17)	-2.10(13)	-2.15(12)	1.22(12)

Table 6: Bond Lengths for mdo032

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C1	C2	1.376(2)	C15	N16	1.468(2)
C1	C6	1.376(2)	C17	C18	1.520(2)
C1	F1	1.3642(17)	C17	N16	1.4698(18)
C2	C3	1.385(2)	C18	N19	1.4938(18)
C3	C4	1.397(2)	C19	N19	1.488(2)
C4	C5	1.400(2)	C20	C21	1.510(2)
C4	C7	1.474(2)	C20	N19	1.4957(19)
C5	C6	1.389(2)	C21	N16	1.4702(19)
C7	C14	1.394(2)	C22	C27	1.407(2)
C7	N8	1.3848(19)	C22	N23	1.3414(18)
C9	N8	1.3162(19)	C24	N23	1.3487(19)
C9	N13	1.3622(18)	C24	N24	1.3408(18)
C9	S10	1.7383(16)	C24	N25	1.352(2)
C11	C12	1.345(2)	C26	C27	1.379(2)
C11	C15	1.495(2)	C26	N25	1.3395(18)
C11	S10	1.7551(15)	O1	P1	1.5624(11)
C12	N13	1.3914(18)	O2	P1	1.5096(14)
C14	C22	1.462(2)	O3	P1	1.5105(13)
C14	N13	1.4004(18)	O4	P1	1.5833(14)

Table 7 Bond Angles for mdo032

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
------	------	------	---------	------	------	------	---------

C6	C1	C2	122.62(14)	C27	C22	C14	122.23(13)
F1	C1	C2	118.60(14)	N23	C22	C14	115.94(12)
F1	C1	C6	118.76(14)	N23	C22	C27	121.62(12)
C1	C2	C3	118.58(14)	N23	C24	N25	125.03(13)
C2	C3	C4	121.07(13)	N24	C24	N23	117.25(12)
C3	C4	C5	118.33(13)	N24	C24	N25	117.71(12)
C3	C4	C7	117.57(12)	N25	C26	C27	123.24(13)
C5	C4	C7	124.01(13)	C26	C27	C22	116.36(13)
C6	C5	C4	121.08(13)	C9	N8	C7	104.22(11)
C1	C6	C5	118.27(14)	C9	N13	C12	114.49(12)
C14	C7	C4	130.91(12)	C9	N13	C14	106.58(12)
N8	C7	C4	117.75(12)	C12	N13	C14	138.61(12)
N8	C7	C14	111.32(12)	C15	N16	C17	111.18(11)
N8	C9	N13	113.60(12)	C15	N16	C21	106.54(10)
N8	C9	S10	135.28(11)	C17	N16	C21	109.35(11)
N13	C9	S10	111.10(11)	C18	N19	C20	110.06(11)
C12	C11	C15	124.32(13)	C19	N19	C18	112.43(11)
C12	C11	S10	112.62(11)	C19	N19	C20	110.98(11)
C15	C11	S10	122.62(11)	C22	N23	C24	117.27(12)
C11	C12	N13	112.12(12)	C26	N25	C24	116.40(11)
C7	C14	C22	135.10(12)	O1	P1	O4	105.34(6)
C7	C14	N13	104.15(12)	O2	P1	O1	104.64(6)
N13	C14	C22	119.72(12)	O2	P1	O3	116.88(7)
N16	C15	C11	115.96(11)	O2	P1	O4	108.50(7)
N16	C17	C18	110.93(11)	O3	P1	O1	111.16(6)
N19	C18	C17	110.12(11)	O3	P1	O4	109.62(6)
N19	C20	C21	109.34(11)	C9	S10	C11	89.65(7)
N16	C21	C20	111.64(11)				

Table 8: Hydrogen Bonds for mdo032

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A°
N24	H24A	O2 ¹	0.88	2.18	2.963(2)	148.4
N24	H24B	O3 ²	0.88	2.15	3.023(2)	169.7
O1	H1	N25 ²	0.84	1.84	2.641(2)	158.1
O4	H4	O3 ¹	0.84	1.76	2.5812(17)	167.0

Table 9: Torsion Angles for mdo032

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C1	C2	C3	C4	-1.3(2)	C18	C17	N16	C21	58.28(14)
C2	C1	C6	C5	-0.2(2)	C20	C21	N16	C15	-179.51(11)
C2	C3	C4	C5	-0.8(2)	C20	C21	N16	C17	-59.27(15)
C2	C3	C4	C7	-177.57(12)	C21	C20	N19	C18	-57.08(14)
C3	C4	C5	C6	2.5(2)	C21	C20	N19	C19	177.82(11)
C3	C4	C7	C14	-162.02(14)	C22	C14	N13	C9	166.72(12)
C3	C4	C7	N8	19.77(18)	C22	C14	N13	C12	-6.1(2)

C4	C5	C6	C1	-2.0(2)	C27	C22	N23	C24	-0.57(18)
C4	C7	C14	C22	15.9(3)	C27	C26	N25	C24	0.46(19)
C4	C7	C14	N13	-176.29(13)	F1	C1	C2	C3	-179.67(12)
C4	C7	N8	C9	178.76(11)	F1	C1	C6	C5	-178.71(12)
C5	C4	C7	C14	21.4(2)	N8	C7	C14	C22	-165.76(14)
C5	C4	C7	N8	-156.80(13)	N8	C7	C14	N13	2.01(14)
C6	C1	C2	C3	1.8(2)	N8	C9	N13	C12	178.70(11)
C7	C4	C5	C6	179.02(12)	N8	C9	N13	C14	3.88(15)
C7	C14	C22	C27	22.5(2)	N8	C9	S10	C11	-177.29(15)
C7	C14	C22	N23	-162.61(14)	N13	C9	N8	C7	-2.54(15)
C7	C14	N13	C9	-3.37(14)	N13	C9	S10	C11	0.64(10)
C7	C14	N13	C12	-176.23(15)	N13	C14	C22	C27	-143.86(13)
C11	C12	N13	C9	-1.42(16)	N13	C14	C22	N23	31.06(17)
C11	C12	N13	C14	171.06(14)	N16	C17	C18	N19	-57.94(15)
C11	C15	N16	C17	63.52(16)	N19	C20	C21	N16	58.83(15)
C11	C15	N16	C21	-177.42(11)	N23	C22	C27	C26	-1.71(19)
C12	C11	C15	N16	-139.82(14)	N23	C24	N25	C26	-3.09(19)
C12	C11	S10	C9	-1.46(11)	N24	C24	N23	C22	-177.69(11)
C14	C7	N8	C9	0.21(15)	N24	C24	N25	C26	177.75(12)
C14	C22	C27	C26	172.92(12)	N25	C24	N23	C22	3.14(19)
C14	C22	N23	C24	-175.52(11)	N25	C26	C27	C22	1.8(2)
C15	C11	C12	N13	-170.57(12)	S10	C9	N8	C7	175.34(12)
C15	C11	S10	C9	171.14(12)	S10	C9	N13	C12	0.29(14)
C17	C18	N19	C19	-178.73(11)	S10	C9	N13	C14	-174.53(9)
C17	C18	N19	C20	57.00(14)	S10	C11	C12	N13	1.89(15)
C18	C17	N16	C15	175.65(11)	S10	C11	C15	N16	48.46(16)

Table 10: Hydrogen Atom Coordinates ($\text{\AA} \times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for mdo032.

Atom	x	y	z	U(eq)
H2	10111.63	2162.87	-1646.05	23
H3	8673.49	3785.05	-764.05	18
H5	11736.62	1012.29	994.95	18
H6	13278.39	-550.36	95.87	22
H12	7952.1	5554.56	2781.29	15
H15A	5461.24	7654.91	3173.54	18
H15B	5216.96	8912.68	2394.34	18
H17A	2981.75	6611.49	3739.55	17
H17B	2641.2	6125.5	2931.18	17
H18A	-417.24	7620.56	2940.91	17
H18B	-94.41	6435.19	3752.01	17
H19A	-2965.02	9463.84	3638.4	26
H19B	-2512.2	9735.58	4481.63	26

H19C	-2645.23	8092.69	4369.53	26
H20A	22.89	10793.37	3748.76	19
H20B	-340.22	10324.23	2937.73	19
H21A	2760.84	10423.07	2945.03	19
H21B	3027.38	9218.92	3749.22	19
H26	15548.26	2767.86	1810.74	16
H27	13089.46	3068.62	1014.46	16
H19	416.07	8287.99	4392.49	15
H24A	10960.55	3425.9	4113.48	18
H24B	13032.64	3093.12	4194.51	18
H1	4048.67	6975.33	6558.46	22
H4	3866.11	4436.47	5463.98	28

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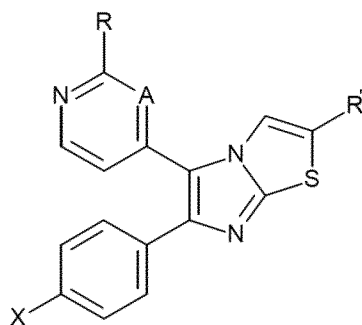
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Claims

1. A phosphate salt of a compound of Formula I



Formula I

or a solvate or hydrate thereof, wherein

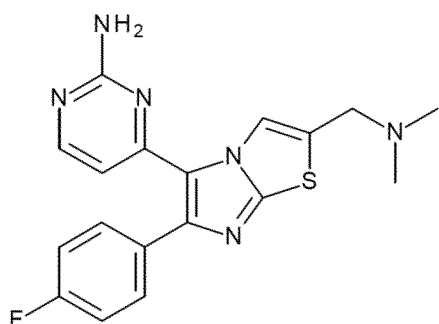
R = NH₂ or H

A = CH or N

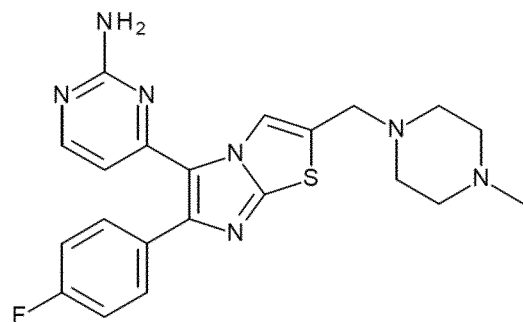
R' = CH₂-1-Me-piperazin-4-yl or CH₂NMe₂

X = F, Cl, I or H.

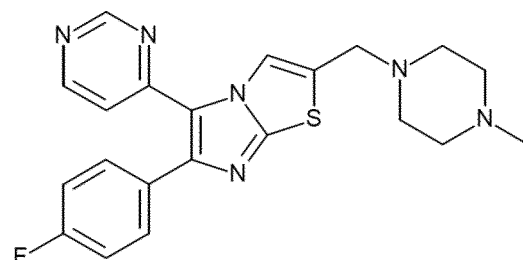
2. The phosphate salt according to claim 1, wherein the compound of Formula I is one of the following compounds of Formulae II to V



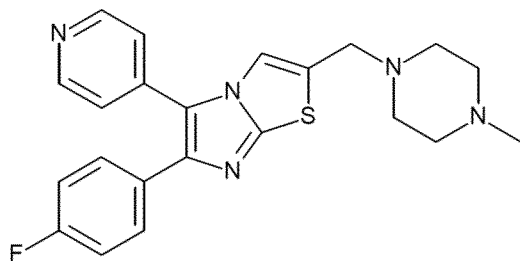
Formula II,



Formula III,



Formula IV,



Formula V.

3. The phosphate salt according to claim 1 or 2, wherein the phosphate salt is a monophosphate salt, preferably, the monophosphate salt is substantially anhydrous.
4. The phosphate salt according to any one claim 1-3, wherein the compound of Formula I is having the structure of Formula III.
5. The phosphate salt according to any one claim 1-4 wherein the phosphate salt is crystalline.
6. The phosphate salt according to claim 5, wherein the phosphate is substantially free of solvent and wherein an XRPD of the crystalline monophosphate salt of the compound of Formula III shows diffraction peaks at 9.9, 13.6, 13.8, 18.2, 19.5 and 19.8 °2θ (± 0.2 °2θ).
7. The phosphate salt according to claim 5 or 6, wherein the XRPD further comprises peaks at 15.7, 22.0, 23.8, 24.5, 27.1 and 30.0 °2θ (± 0.2 °2θ).
8. The phosphate salt according to any one of claims 5 to 7 having a melting temperature of about 252 °C, as determined by the onset of the melting endotherm using DSC at a heating rate of 10 °C/min.
9. The phosphate salt according to any one of claims 5 to 8 wherein the structure of the crystalline monophosphate salt of the compound of Formula III determined by X-ray crystallography is as shown in Figure 16 to 18.
- 5 10. The phosphate salt according to any one of claims 5 to 9 wherein the structure of the crystalline monophosphate salt of the compound of Formula III is defined by the atom coordinates and other descriptive data are as shown in Table 4
- 10 11. The phosphate salt according to any one of claims 5 to 10 wherein the structure of the crystalline monophosphate salt of the compound of Formula III is defined by the anisotropic displacement parameters as shown in table 5.

12. The phosphate salt according to any one of claims 5 to 11 wherein the structure of the crystalline monophosphate salt of the compound of Formula III is defined by bond length, bond angles, hydrogen bonds, torsion angles as shown in table 6-9.
- 5 13. The phosphate salt according to any one of claims 5 to 12 wherein the structure of the crystalline monophosphate salt of the compound of Formula III is defined by the hydrogen atom coordinates as shown in table 10.
14. The phosphate salt according to any one of claims 1 to 13 for use in treating coccidiosis in an animal.
15. The phosphate salt for use according to according to claim 14, wherein the animal is poultry, preferably wherein the poultry includes chickens, turkeys, geese and ducks.
16. The phosphate salt for use according to anyone of claims 14 to 15, wherein coccidiosis is caused by Apicomplexan protozoan parasites of the genus *Eimeria*, preferably wherein the genus *Eimeria* comprises the species *E. tenella*, *E. acervulina*, *E. mitis*, *E. maxima*, *E. praecox*, *E. necatrix* and *E. brunetti*.
17. Process of preparing a salt according to any one of claims 1 to 13 comprising the steps:
- i) providing a compound of Formula I as free base;
 - ii) adding the free base of the compound of Formula I to a solvent to obtain a mixture;
 - iii) adding to the mixture of step ii) phosphoric acid;
 - iv) allowing a phosphate of the compound of Formula I to crystallize;
 - v) collecting and drying the obtained crystals.
18. The process of claim 17, further comprising a step iii-a) of adding a solvent to the resulting mixture of step iii).
19. The process of claim 17 or 18, further comprising a step iii-b) of seeding the resulting mixture of step iii) or step iii-a) with crystals of the corresponding phosphate salt of anyone of claims 1 to 8.
20. The process of any one of claims 17 to 19, wherein the molar ratio of phosphoric acid to the free base of the compound of Formula I is in the range of 0.5:1 to 1.5:1.
21. The process of any one of claims 17 to 20, wherein in step iv) the mixture resulting from step iii), step iii-a) or step iii-b) is stirred at a temperature in the range of 10 to 70°C.
22. The process of any one of claims 17 to 21, wherein the drying in step v) is carried out at a temperature in the range of 25 to 200°C.

23. The process of any one of claims 17 to 22, wherein the solvent is selected from the group consisting of methanol, ethanol, *N,N*-dimethylacetamide and a mixture thereof.

Fig. 1

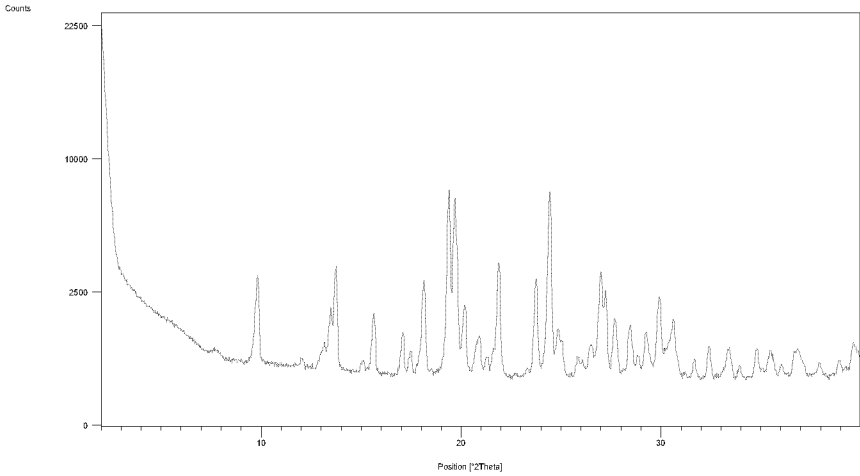


Fig. 2

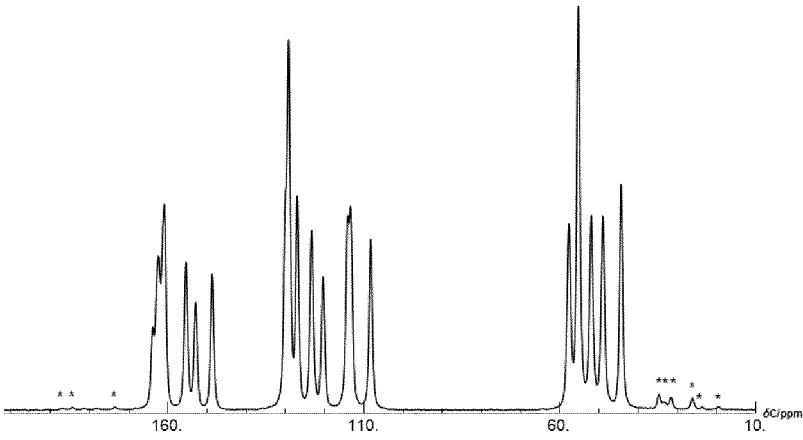


Fig. 3

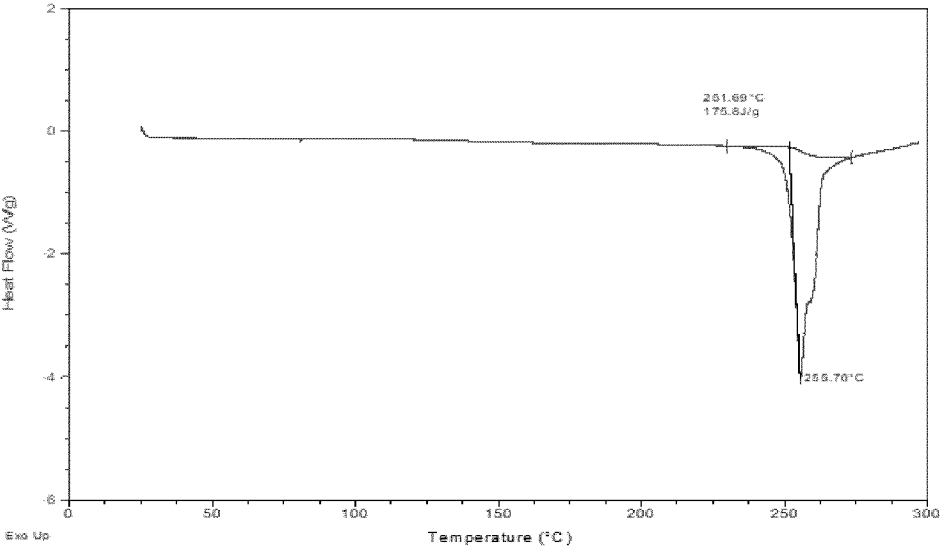


Fig. 4

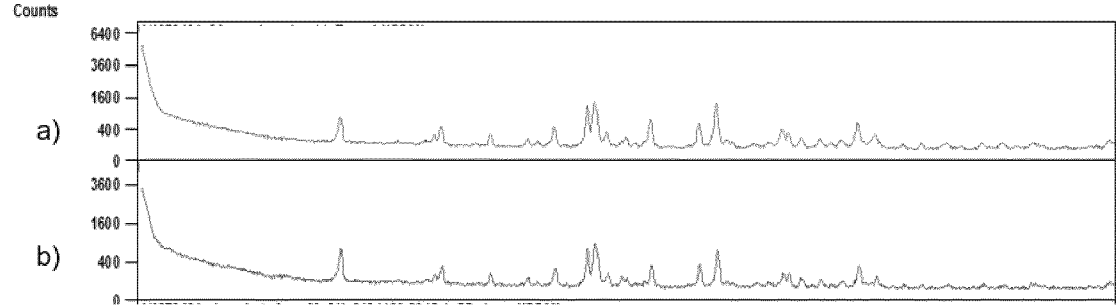


Fig. 5

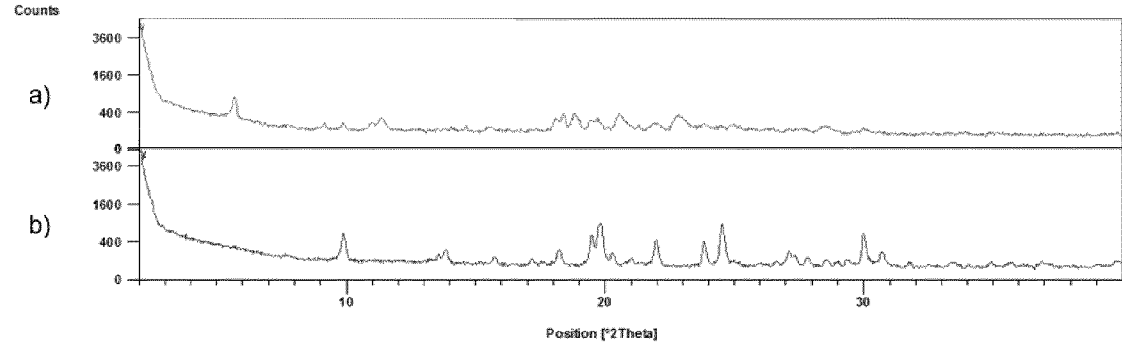


Fig. 6

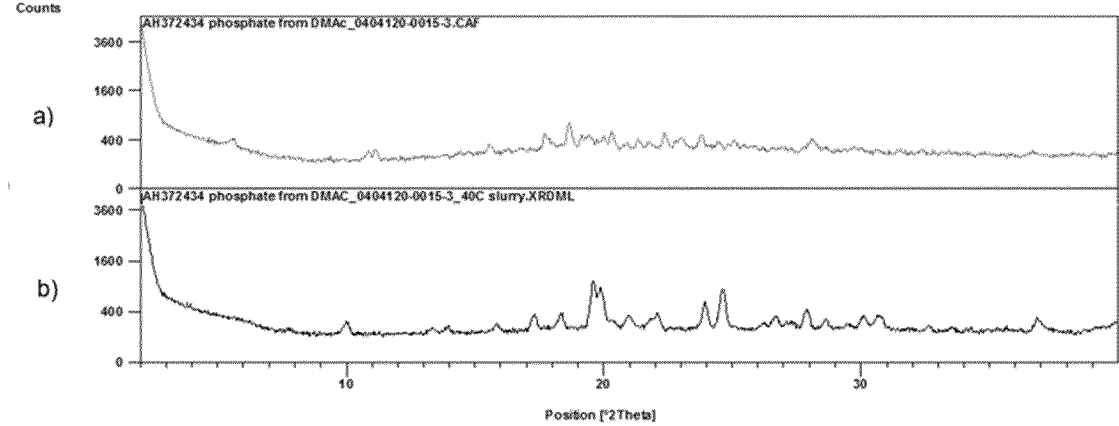


Fig. 7

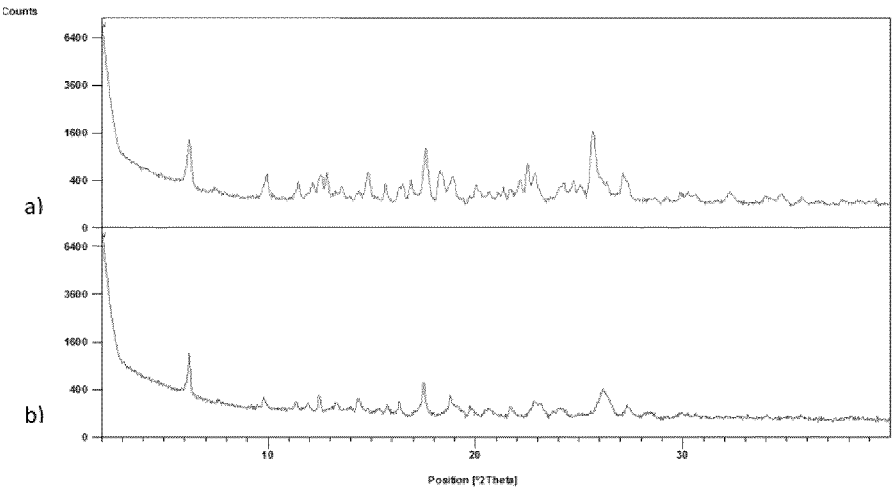


Fig. 8

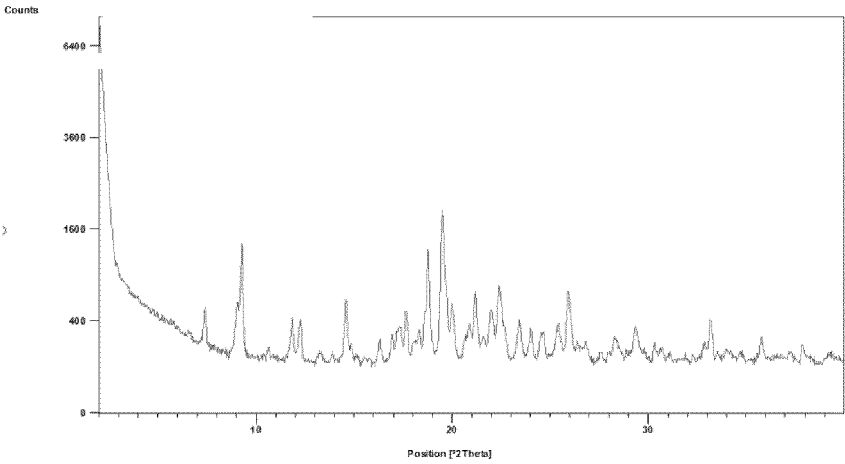


Fig. 9

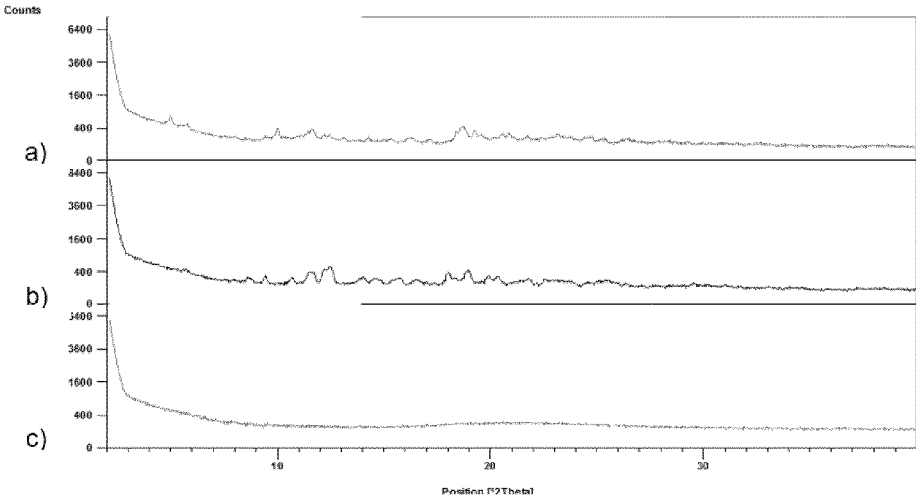


Fig. 10

Adsorption/Desorption Isotherm

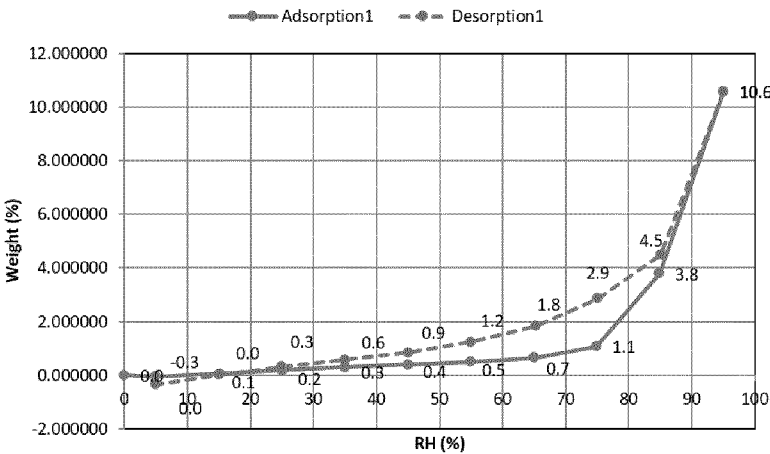


Fig. 11

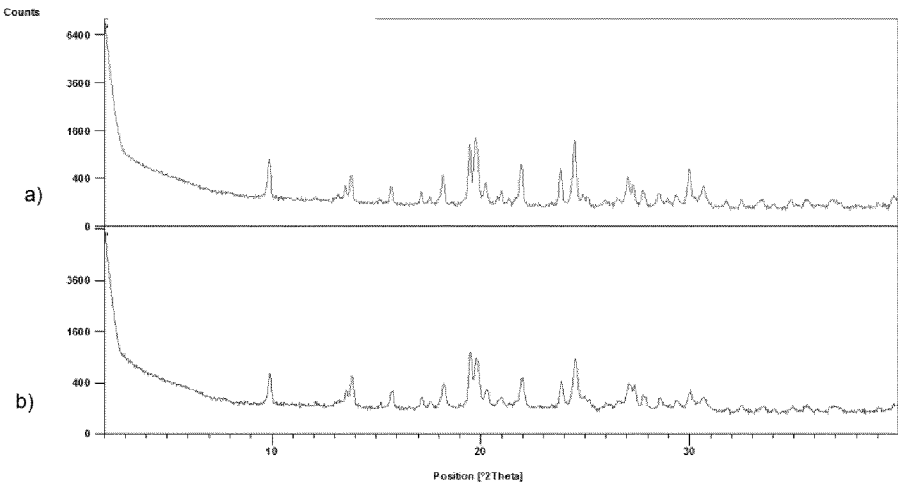


Fig. 12

Adsorption/Desorption Isotherm

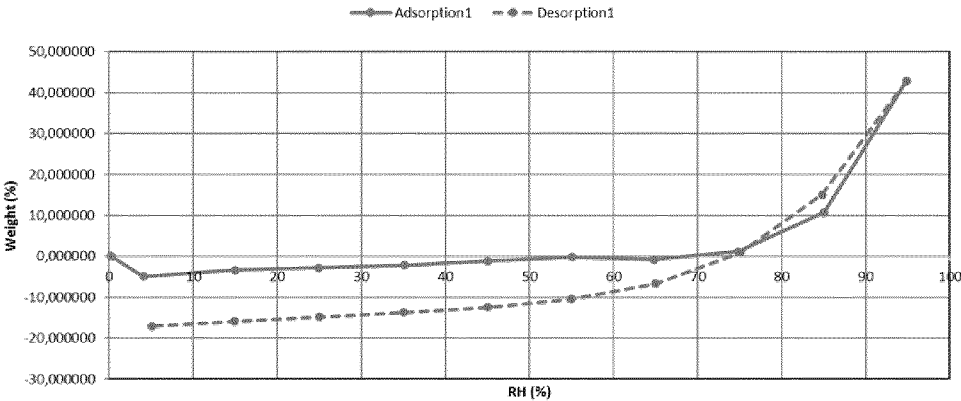


Fig. 13

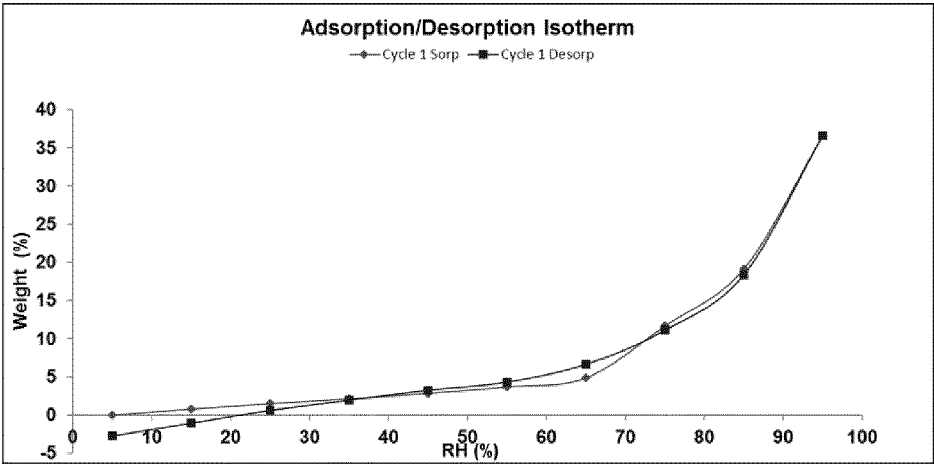


Fig. 14

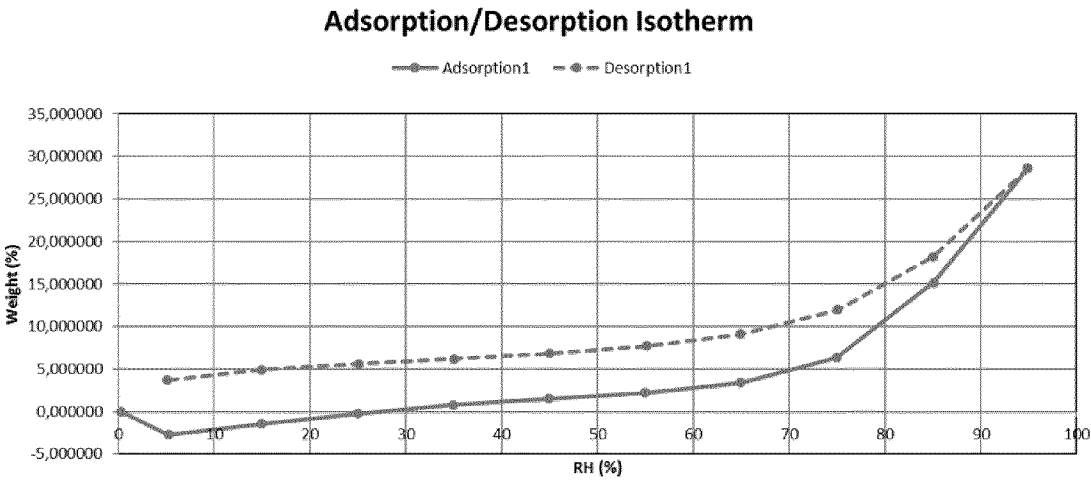


Fig.15

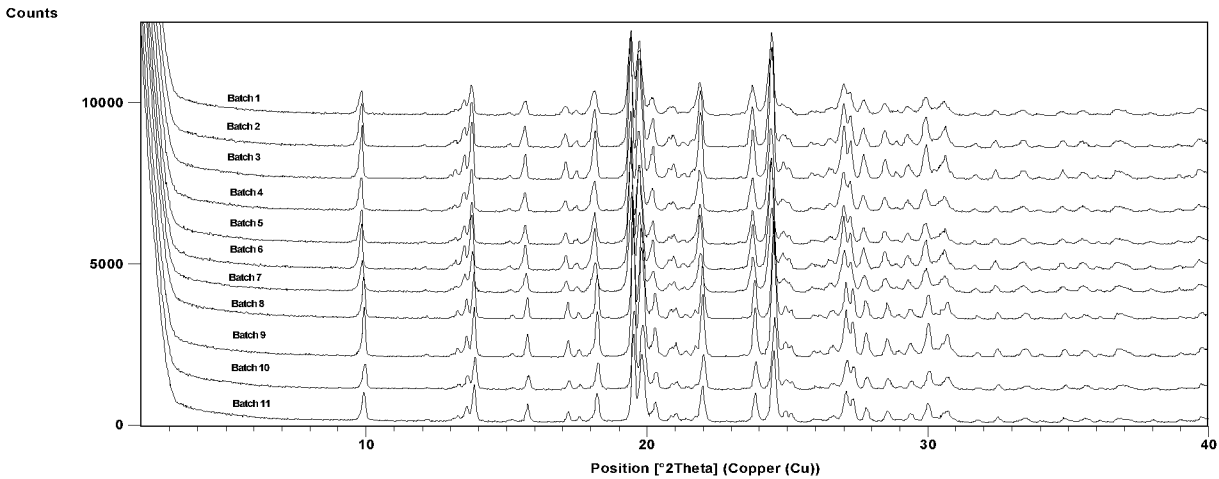


Fig. 16

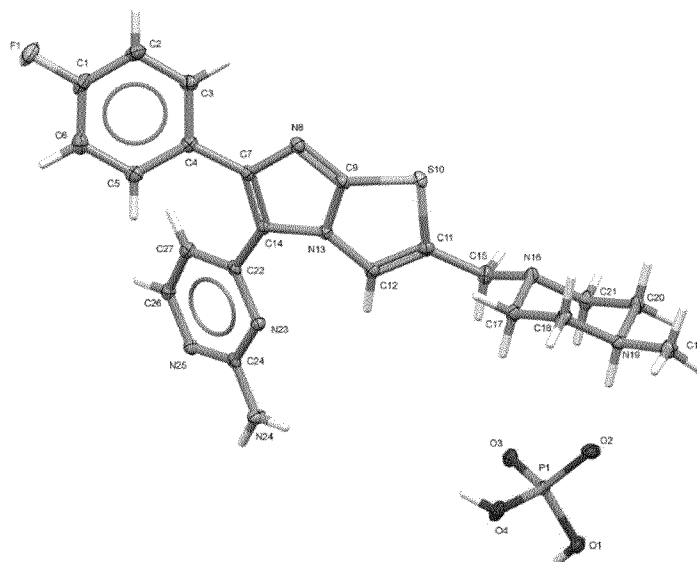


Fig. 17

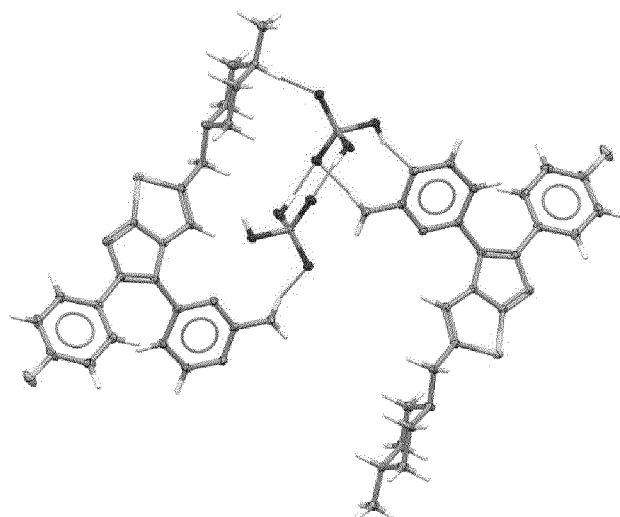
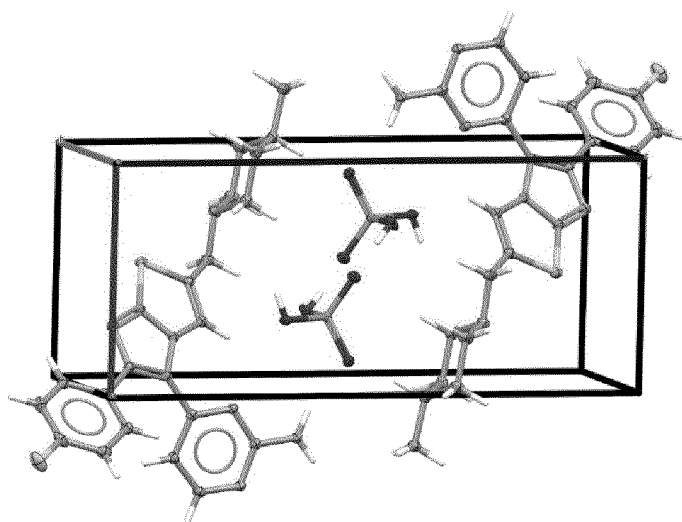


Fig.18



INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2019/086350

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D513/04 A61P33/02 A61K31/496 A61K31/506
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 A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCRIBNER A ET AL: "Synthesis and biological activity of anticoccidial agents: 5,6-Diarylimidazo[2,1-b][1,3]thiazoles", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 18, no. 19, October 2008 (2008-10), pages 5263-5267, XP025433914, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2008.08.063 [retrieved on 2008-08-22] cited in the application	1-5, 14-23
A	table 1 ----- -/--	6-13



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

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

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

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Date of the actual completion of the international search

4 March 2020

Date of mailing of the international search report

12/03/2020

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2019/086350

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SERAJUDDIN ET AL: "Salt formation to improve drug solubility", ADVANCED DRUG DELIVERY REVIEWS, ELSEVIER, AMSTERDAM, NL, vol. 59, no. 7, 24 August 2007 (2007-08-24), pages 603-616, XP022211982, ISSN: 0169-409X, DOI: 10.1016/J.ADDR.2007.05.010 the whole document -----	1-23