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(54) Title: SALTS OF IDELALISIB

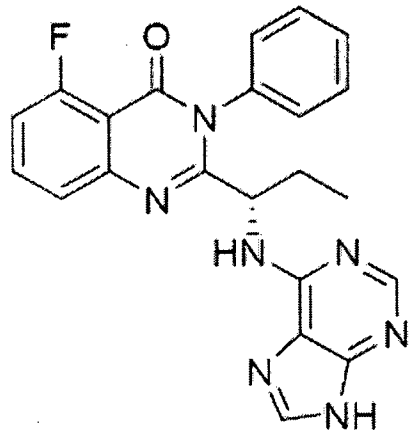
(57) Abstract: The present invention relates to salts of idelalisib, polymorphs of these salts, methods for their preparation, and pharmaceutical preparations comprising these salts.

Salts of idelalisib

The present invention relates to salts of idelalisib, polymorphs of these salts, methods for their preparation, and pharmaceutical preparations comprising these salts.

Idelalisib is a known active pharmaceutical ingredient which blocks the effect of an enzyme called PI3K-delta. This enzyme plays a role in the growth, migration and survival of white blood cells but is overactive in blood cancers, where it enables the survival of the cancer cells. By targeting this enzyme and blocking its effects, idelalisib causes death of the cancer cells, thereby delaying or stopping the progression of the cancer.

The chemical name of idelalisib is 5-fluoro-3-phenyl-2-[(1*S*)-1-(9*H*-purin-6-ylamino)propyl]quinazolin-4(3*H*)-one. Idelalisib has the following chemical structure:



Idelalisib, its manufacture and use is described in WO 2005/113556.

Polymorphic forms of the free base of idelalisib are disclosed in WO 2013/134288.

Idelalisib is a white to off-white solid practically insoluble in water at pH 7 and soluble in water at pH 1.2. The active substance has a chiral center assigned as 1*S* and is

manufactured as the pure enantiomer. The low solubility of idelalisib constitutes a problem in the formulation of pharmaceutical preparations and in bioavailability of the drug.

Therefore, there is still a need for further embodiments of idelalisib which show improved solubility and/or bioavailability. Furthermore, there is a need for embodiments of idelalisib which can be easily manufactured and which are stable under processing conditions, such as during manufacture of pharmaceutical formulations, and which are stable in a pharmaceutical formulation during storage.

It has now been found that the above and other problems can be solved by converting the free base of idelalisib into a salt of idelalisib. Therefore, the present invention relates to a salt of idelalisib.

It has furthermore been found that some salts of idelalisib after crystallization from a solvent are in the solvate form and it is difficult to transfer these salts into their desolvated form without observing a change of the polymorphic structure of the salt and in particular without transformation of a crystalline form into an amorphous form of the salts. On the other hand, solvates are often undesirable because of their solvent molecule content which can render them unacceptable for pharmaceutical applications. Therefore, there is a need for embodiments of salts of idelalisib which can be desolvated without losing crystallinity or which are not obtained as solvate. It is also an object of the present invention to solve these problems.

One advantage of the present invention is that a salt of idelalisib shows increased solubility compared to the free base of idelalisib.

Another advantage of the present invention is that a salt of idelalisib can exhibit high chemical and/or physical stability both, during processing of this salt and during storage. In this context physical stability includes the stability of a certain polymorphic form against conversion into another polymorphic form.

A further advantage of the present invention is that the salt of idelalisib can exhibit low hygroscopicity which makes such salt particularly suitable for the manufacture of pharmaceutical formulations.

The salt of idelalisib according to the invention may be crystalline, amorphous or partly crystalline.

In one embodiment of the present invention, the salt of idelalisib has a residual solvent content within pharmaceutically acceptable limits.

In the present application the term "residual solvent content within pharmaceutically acceptable limits" refers to a concentration limit (in ppm) of the corresponding solvent, which is regarded as pharmaceutically acceptable in the art.

Respective concentration limits for solvents can be found in Guidance for Industry, Q3C-Tables and List, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Bioligics Evaluation and Research (CBER), February 2012, ICH, Revision 2.

According to the above-mentioned guideline the solvents are categorized into three classes.

Class 1 relates to solvents that should be avoided in pharmaceutical products.

Solvent	**Concentration Limit (ppm)**	**Concern**
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethane	8	Toxic
1,1,1-Trichloroethane	1,500	Environmental hazard

Table 1: Class 1 solvents and their concentration limits

Class 2 relates to solvents that should be limited in pharmaceutical products because of their inherent toxicity.

Solvent	PDE (mg/day)	Concentration Limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3,880
Cumene	0.7	70
1,2-Dichloroethane	18.7	1,870
Dichloromethane	6.0	600
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1,090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethyleneglycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3,000
2-Methoxyethanol	0.5	50
Methylbutyl ketone	0.5	50
Methylcyclohexane	11.8	1,180
N-Methylpyrrolidone	5.3	530
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetrahydrofuran	7.2	720
Tetralin	1.0	100
Toluene	8.9	890
1,1,1-Trichloroethene	0.8	80
Xylene[1]	21.7	2,170

[1]Usually 60% m-xylene, 14% p-xylene, 9% o-xylene with 17% ethyl benzene

Table 2: Class 2 solvents and their concentration limits

Class 3 relates to solvents which should be limited by GMP or other quality-based requirements. These solvents should be present in an amount below 5000 ppm.

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethyl ketone
tert-Butylmethyl ether	Methylisobutyl ketone
Dimethyl sulfoxide	2-Methyl-1-propanol
Ethanol	Pentane
Ethyl acetate	1-Pentanol
Ethyl ether	1-Propanol
Ethyl formate	2-Propanol
Formic acid	Propyl acetate

Table 3: Class 3 solvents having a concentration limit of 5000 ppm.

In one embodiment the salt of idelalisib according to the invention may be a solvate, such as an ethanol, tetrahydrofuran, diethyl ether and/or acetone solvate and/or a hydrate. Thus, the term "solvate" includes hydrates.

In this case, the number of solvent molecule in the crystalline or amorphous structure of the salt is not limited and can be, for example, in the range of 0.1 to 2 mol per mol of idelalisib. Thus, solvates comprising for example 0.1 to 0.8 solvent molecules per idelalisib molecule are covered by the present invention.

In another embodiment, the salt of idelalisib may be desolvated.

In one embodiment, the salt of idelalisib is idelalisib hydrochloride. It has been found that idelalisib hydrochloride can be obtained in crystalline form from an ethanol-water mixture or from acetone and in part-crystalline form from tetrahydrofuran (THF). Preferably, the residual solvent content of the idelalisib hydrochloride is within pharmaceutically acceptable limits as defined above.

The idelalisib hydrochloride may be a solvate or desolvated. In one embodiment, the idelalisib hydrochloride is a solvate. In one embodiment, the idelalisib hydrochloride is a solvate in crystalline form. In another embodiment, the idelalisib hydrochloride is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in partly crystalline form. In another embodiment, the idelalisib hydrochloride is desolvated. In one embodiment, the idelalisib hydrochloride is desolvated and in crystalline form. In another embodiment, the idelalisib hydrochloride is desolvated and in amorphous form. In a further embodiment, the idelalisib hydrochloride is desolvated and in partly crystalline form.

In one embodiment, the crystalline idelalisib hydrochloride obtained from ethanol-water is the ethanol-H_2O solvate which for example contains about 0.3 equiv. EtOH. In another embodiment, the part-crystalline idelalisib hydrochloride obtained from THF is the THF solvate containing for example 0.1 to 0.25 equiv. THF.

It was found that crystalline idelalisib hydrochloride and in particular the ethanol-H_2O solvate can be stored at a temperature of 50°C without desolvation. Even at a temperature of above 80°C, desolvation occurs only slowly. Furthermore, no hygroscopicity was observed and even under high humidity the polymorph form did not change. Thus, idelalisib hydrochloride and in particular the ethanol-H_2O solvate thereof is particularly suitable for the manufacture of pharmaceutical formulations.

In a further embodiment, the present invention relates to a polymorph of crystalline idelalisib hydrochloride ethanol-H_2O solvate having an X-ray powder diffraction pattern comprising peaks at 6.9 ± 0.2, 8.8 ± 0.2, 11.5 ± 0.2, 13.5 ± 0.2, 13.7 ± 0.2 , 16.8 ± 0.2, 23.1 ± 0.2, 25.0 ± 0.2, and 26.2 ± 0.2 degrees 2-theta. Preferably, the X-ray powder diffraction pattern comprises peaks at 6.9 ± 0.2, 8.8 ± 0.2, 10.3 ± 0.2, 11.5 ± 0.2, 13.5 ± 0.2, 13.7 ± 0.2, 13.9 ± 0.2, 16.5 ± 0.2, 16.8 ± 0.2, 17.7 ± 0.2, 18.1 ± 0.2, 19.3 ± 0.2, 21.4 ± 0.2, 22.1 ± 0.2, 22.4 ± 0.2, 22.6 ± 0.2, 23.1 ± 0.2, 25.0 ± 0.2, 25.4 ± 0.2, 26.2 ± 0.2, 27.2 ± 0.2, 27.3 ± 0.2, 27.9 ± 0.2, 28.1 ± 0.2, 28.4 ± 0.2, 28.9 ± 0.2, 29.6 ± 0.2 and 29.7 ± 0.2 degrees 2-theta.

In a particularly preferred embodiment the idelalisib hydrochloride ethanol-H_2O solvate has an X-ray powder diffraction pattern substantially as shown in figure 1.

It was found that the above idelalisib hydrochloride solvate can be desolvated by preparing a slurry of the crystals in acetone. During desolvation, the crystalline idelalisib hydrochloride is transformed into a semi-crystalline form which turned out to be hygroscopic. Above 85 % rH (relative humidity) the amorphous solid becomes an oil which upon drying is transformed into amorphous idelalisib hydrochloride. The X-ray powder diffraction patterns of the semi-crystalline and the amorphous idelalisib hydrochloride are shown on figure 2.

In another embodiment, the crystalline idelalisib hydrochloride can be obtained from acetone. Preferably, the residual solvent content is within pharmaceutically acceptable limits.

In another embodiment, the crystalline idelalisib hydrochloride obtained from acetone is the acetone solvate which contains for example about 0.5 equiv. acetone.

In a further embodiment, the present invention relates to a polymorph of crystalline idelalisib hydrochloride acetone solvate having an X-ray powder diffraction pattern comprising peaks at 9.8 ± 0.2, 14.2 ± 0.2, 15.4 ± 0.2, 17.8 ± 0.2, 19.8 ± 0.2, 20.9 ± 0.2, 23.1 ± 0.2 and 24.1 ± 0.2 degrees 2-theta. Preferably, the X-ray powder diffraction pattern comprises peaks at 9.4 ± 0.2, 9.8 ± 0.2, 11.1 ± 0.2, 11.8 ± 0.2, 12.3 ± 0.2, 12.9 ± 0.2, 14.2 ± 0.2, 15.2 ± 0.2, 15.4 ± 0.2, 16.8 ± 0.2, 17.1 ± 0.2, 17.6 ± 0.2, 17.8 ± 0.2, 18.9 ± 0.2, 19.3 ± 0.2, 19.8 ± 0.2, 20.1 ± 0.2, 20.9 ± 0.2, 21.7 ± 0.2, 22.4 ± 0.2, 23.1 ± 0.2 and 24.1 ± 0.2 degrees 2-theta.

In a particularly preferred embodiment, the idelalisib hydrochloride acetone solvate has an X-ray powder diffraction pattern substantially as shown in figure 12.

It was found that the above idelalisib hydrochloride acetone solvate can be desolvated at 40-50°C under vacuum at 10-100 mbar without losing its crystallinity. This is an advantage over the above idelalisib hydrochloride ethanol-H_2O solvate which upon desolvation loses crystallinity.

In a further embodiment, the present invention relates to a desolvated polymorph of crystalline idelalisib hydrochloride having an X-ray powder diffraction pattern comprising peaks at 9.9 ± 0.2, 14.6 ± 0.2, 15.8 ± 0.2, 19.0 ± 0.2, 19.9 ± 0.2, 20.5 ± 0.2, 23.6 ± 0.2 and

24.2 ± 0.2 degrees 2-theta. Preferably, the X-ray powder diffraction pattern comprises peaks at 5.9 ± 0.2, 9.5 ± 0.2, 9.9 ± 0.2, 11.2 ± 0.2, 11.9 ± 0.2, 12.1 ± 0.2, 13.0 ± 0.2, 13.5 ± 0.2, 14.6 ± 0.2, 15.2 ± 0.2, 15.8 ± 0.2, 17.1 ± 0.2, 17.9 ± 0.2, 19.0 ± 0.2, 19.2 ± 0.2, 19.9 ± 0.2, 20.2 ± 0.2, 20.5 ± 0.2, 21.0 ± 0.2, 21.6 ± 0.2, 23.0 ± 0.2, 23.6 ± 0.2 and 24.2 ± 0.2 degrees 2-theta.

In a particularly preferred embodiment, the desolvated idelalisib hydrochloride has an X-ray powder diffraction pattern substantially as shown in figure 13. If this desolvated idelalisib hydrochloride is further subjected to thermal treatment (60°C), an amorphous idelalisib hydrochloride is formed.

In another embodiment, the salt of idelalisib according to the invention is the hydrogen sulfate salt of idelalisib. This salt can be obtained from ethanol in crystalline form and may be in form of the ethanol solvate. Preferably, the hydrogen sulfate salt of idelalisib has a residual solvent content which is within the pharmaceutical limits as defined above.

The hydrogen sulfate salt of idelalisib may be a solvate or desolvated. In one embodiment, the hydrogen sulfate salt of idelalisib is a solvate. In one embodiment, the hydrogen sulfate salt of idelalisib is a solvate in crystalline form. In another embodiment, the hydrogen sulfate salt of idelalisib is a solvate in amorphous form. In a further embodiment, the hydrogen sulfate salt of idelalisib is a solvate in partly crystalline form. In another embodiment, the hydrogen sulfate salt of idelalisib is desolvated. In one embodiment, the hydrogen sulfate salt of idelalisib is desolvated and in crystalline form. In another embodiment, the hydrogen sulfate salt of idelalisib is desolvated and in amorphous form. In a further embodiment, the hydrogen sulfate salt of idelalisib is desolvated and in partly crystalline form.

In a further embodiment, the present invention relates to a polymorphic form of the crystalline hydrogen sulfate salt of idelalisib as ethanol solvate. This polymorphic form has an X-ray powder diffraction pattern comprising peaks at 7.3 ± 0.2, 9.6 ± 0.2, 16.0 ± 0.2, 18.9 ± 0.2 and 23.9 ± 0.2 degrees 2-theta, preferably at 7.3 ± 0.2, 9.6 ± 0.2, 11.5 ± 0.2, 14.2 ± 0.2, 16.0 ± 0.2, 17.3 ± 0.2, 18.2 ± 0.2, 18.9 ± 0.2, 19.3 ± 0.2, 20.5 ± 0.2, 21.5 ± 0.2, 21.9 ± 0.2, 22.9 ± 0.2, 23.3 ± 0.2, 23.9 ± 0.2, 24.9 ± 0.2, 26.1 ± 0.2 and 26.3 ± 0.2 degrees 2-theta.

In one embodiment, the hydrogen sulfate salt of idelalisib as ethanol solvate in crystalline form has an X-ray powder diffraction pattern substantially as shown in figure 3.

Upon drying this solvate, the crystals desolvate and the hydrogen sulfate salt of idelalisib is obtained in amorphous form. The X-ray diffraction pattern of amorphous hydrogen sulfate salt of idelalisib is shown on figure 4.

In one embodiment, the hydrogen sulfate salt of idelalisib is a solvent-free anhydrate. In another embodiment, the hydrogen sulfate salt of idelalisib is a hydrate which is, however, free of any solvent molecules other than water.

In a further embodiment, the present invention relates to a polymorphic form of the crystalline hydrogen sulfate salt of idelalisib as anhydrate. This polymorphic form has an X-ray powder diffraction pattern comprising peaks at 9.7 ± 0.2, 20.2 ± 0.2, 21.0 ± 0.2 and 26.5 ± 0.2 degrees 2-theta, preferably at 4.8 ± 0.2, 9.7 ± 0.2, 13.8 ± 0.2, 17.6 ± 0.2, 20. 2 ± 0.2, 21.0 ± 0.2, 24.6 ± 0.2, 25.3 ± 0.2 and 26.5 ± 0.2 degrees 2-theta.

In one embodiment, the hydrogen sulfate salt of idelalisib as anhydrate in crystalline form has an X-ray powder diffraction pattern substantially as shown in figure 5.

In a further embodiment, the present invention relates to a polymorphic form of the crystalline hydrogen sulfate salt of idelalisib as hydrate. This polymorphic form has an X-ray powder diffraction pattern comprising peaks at 8.4 ± 0.2, 12.0 ± 0.2, 18.8 ± 0.2, 20.7 ± 0.2 and 26.7 ± 0.2 degrees 2-theta, preferably at 8.4 ± 0.2, 12.0 ± 0.2, 12.4 ± 0.2, 15.4 ± 0.2, 16.8 ± 0.2, 17.7 ± 0.2, 18.8 ± 0.2, 20.7 ± 0.2, 22.5 ± 0.2, 23.5 ± 0.2, 24.3 ± 0.2, 25.3 ± 0.2 and 26.7 ± 0.2 degrees 2-theta.

In one embodiment, the hydrogen sulfate salt of idelalisib as hydrate in crystalline form has an X-ray powder diffraction pattern substantially as shown in figure 6.
In another embodiment, the salt of idelalisib according to the invention can be the nitric acid salt of idelalisib. This salt can be obtained in crystalline form from THF/water. This crystalline form can be present as THF solvate. It was found that crystalline nitric acid salt of idelalisib can be present as THF-H_2O solvate comprising for example about 0.3 mol THF per mol of idelalisib. These crystals are stable up to a temperature of 120°C and exhibit very low hygroscopicity. Therefore, this salt is particularly suitable for the manufacture of

pharmaceutical formulations. Preferably, the nitric acid salt of idelalisib has a residual solvent content which is within pharmaceutically acceptable limits as defined above.

The nitric acid salt of idelalisib may be a solvate or desolvated. In one embodiment, the nitric acid salt of idelalisib is solvated. In one embodiment, the nitric acid salt of idelalisib is a solvate in crystalline form. In another embodiment, the nitric acid salt of idelalisib is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in partly crystalline form. In another embodiment, the nitric acid salt of idelalisib is desolvated. In one embodiment, the nitric acid salt of idelalisib is desolvated and in crystalline form. In another embodiment, the nitric acid salt of idelalisib is desolvated and in amorphous form. In a further embodiment, the nitric acid salt of idelalisib is desolvated and in partly crystalline form.

The invention furthermore relates to a polymorphic form of the above crystalline nitric acid salt of idelalisib as THF-H_2O solvate having an X-ray powder diffraction pattern comprising peaks at 4.2 ± 0.2, 11.1 ± 0.2, 15.2 ± 0.2, 19.4 ± 0.2 and 26.5 ± 0.2 degrees 2-theta, preferably at 4.2 ± 0.2, 11.1 ± 0.2, 14.6 ± 0.2, 15.2 ± 0.2, 16.4 ± 0.2, 16.9 ± 0.2, 18.4 ± 0.2, 19.4 ± 0.2, 22.0 ± 0.2, 22.4 ± 0.2, 26.5 ± 0.2 and 28.2 ± 0.2 degrees 2-theta.

In one embodiment, the polymorphic form of crystalline nitric acid salt of idelalisib as THF-H_2O solvate has an X-ray powder diffraction pattern substantially as shown in figure 7.
In a further embodiment, the salt of idelalisib according to the invention is idelalisib hydrobromide. The idelalisib hydrobromide can be obtained in crystalline form from ethanol. In one embodiment, the crystalline idelalisib hydrobromide is an ethanol solvate comprising for example about 0.125 mol ethanol per mol of idelalisib. Preferably, the idelalisib hydrobromide has a residual solvent content which is within pharmaceutically acceptable limits as defined above.

The idelalisib hydrobromide may be a solvate or desolvated. In one embodiment, the idelalisib hydrobromide is a solvate. In one embodiment, the idelalisib hydrobromide is a solvate in crystalline form. In another embodiment, the idelalisib hydrobromide is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in partly crystalline form. In another embodiment, the idelalisib hydrobromide is desolvated. In one embodiment, the idelalisib hydrobromide is desolvated and in crystalline form. In another

embodiment, the idelalisib hydrobromide is desolvated and in amorphous form. In a further embodiment, the idelalisib hydrobromide is desolvated and in partly crystalline form.

Crystalline idelalisib hydrobromide in the form of a solvate as described above shows low hygroscopicity and is therefore particularly suitable for the manufacture of pharmaceutical formulations.

The present invention furthermore relates to a polymorphic form of crystalline idelalisib hydrobromide as a solvate as described above having an X-ray powder diffraction pattern comprising peaks at 5.9 ± 0.2, 9.6 ± 0.2, 15.0 ± 0.2, 19.2 ± 0.2 and 23.6 ± 0.2 degrees 2-theta, preferably at 5.9 ± 0.2, 9.6 ± 0.2, 12.7 ± 0.2, 15.0 ± 0.2, 18.3 ± 0.2, 19.2 ± 0.2, 20.1 ± 0.2, 20.3 ± 0.2, 21.6 ± 0.2, 22.7 ± 0.2, 22.9 ± 0.2, 23.6 ± 0.2, 24.6 ± 0.2, 25.6 ± 0.2, 26.5 ± 0.2, 27.7 ± 0.2, 28.3 ± 0.2, 28.7 ± 0.2 and 30.1 ± 0.2 degrees 2-theta.

In one embodiment, the crystalline idelalisib hydrobromide as the above solvate has an X-ray powder diffraction pattern substantially as shown in figure 8.

In a further embodiment the hydrobromide salt is in the form of an ethanol-water-ethyl ether solvate. This solvate of the hydrobromide form has an X-ray powder diffraction pattern defined by peaks at 6.8 ± 0.2, 12.1 ± 0.2, 14.3 ± 0.2, 16.3 ± 0.2, 16.9 ± 0.2 and 21.6 ± 0.2 degrees 2-theta. Preferably, this form of the hydrobromide salt of idelalisib is defined by the following peaks at 6.8 ± 0.2, 10.3 ± 0.2, 12.1 ± 0.2, 14.1 ± 0.2, 14.3 ± 0.2, 15.6 ± 0.2, 16.1 ± 0.2, 16.3 ± 0.2, 16.9 ± 0.2, 17.5 ± 0.2, 20.0 ± 0.2, 21.1 ± 0.2, 21.6 ± 0.2, 22.1 ± 0.2, 22.3 ± 0.2, 22.9 ± 0.2, 23.7 ± 0.2, 23.8 ± 0.2, 24.2 ± 0.2, 24.6 ± 0.2, 25.1 ± 0.2, 25.9 ± 0.2, 26.1 ± 0.2, 27.0 ± 0.2, 27.5 ± 0.2, 27.8 ± 0.2, 28.2 ± 0.2, 28.4 ± 0.2, 28.8 ± 0.2, 29.6 ± 0.2 and 29.9 ± 0.2 degree 2-theta.

In a further embodiment, the idelalisib hydrobromide salt is a tetrahydrofuran solvate. This solvate may be at least partially crystalline and has for example an X-ray powder diffraction pattern substantially as shown in figure 9.

In a further embodiment, the salt of idelalisib according to the invention is the phosphoric acid salt of idelalisib. This salt can be obtained from ethanol or THF by evaporating the solvent. Dispersing the solid residue in diethyl ether/acetone results in amorphous

phosphoric acid salt of idelalisib. The X-ray powder diffraction pattern of this amorphous salt is shown in figure 10.

Preferably, the phosphoric acid salt of idelalisib has a residual solvent content which is within the pharmaceutically acceptable limits as defined above.

The phosphoric acid salt of idelalisib may be a solvate or desolvated. In one embodiment, the phosphoric acid salt of idelalisib is a solvate. In one embodiment, the phosphoric acid salt of idelalisib is a solvate in crystalline form. In another embodiment, the phosphoric acid salt of idelalisib is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in partly crystalline form. In another embodiment, the phosphoric acid salt of idelalisib is desolvated. In one embodiment, the phosphoric acid salt of idelalisib is desolvated and in crystalline form. In another embodiment, the phosphoric acid salt of idelalisib is desolvated and in amorphous form. In a further embodiment, the phosphoric acid salt of idelalisib is desolvated and in partly crystalline form.
In another embodiment, the salt of idelalisib according to the invention is an organic acid salt of idelalisib. In a preferred embodiment, the organic acid is a dicarboxylic acid or a tricarboxylic acid, such as oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, phthalic acid, isophthalic acid, terephthalic acid, maleic acid, fumaric acid, citric acid, isocitric acid, malic acid and tartaric acid.

Preferably, the organic acid salt of idelalisib being a dicarboxylic acid or a tricarboxylic acid, such as oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, phthalic acid, isophthalic acid, terephthalic acid, maleic acid, fumaric acid, citric acid, isocitric acid, malic acid and tartaric acid, has a residual solvent content which is within the pharmaceutical acceptable limits as defined above.

The oxalic acid salt of idelalisib may be a solvate or desolvated. In one embodiment, the oxalic acid salt of idelalisib is a solvate. In one embodiment, the oxalic acid salt of idelalisib is a solvate in crystalline form. In another embodiment, the oxalic acid salt of idelalisib is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in partly crystalline form. In another embodiment, the oxalic acid salt of idelalisib is desolvated. In one embodiment, the oxalic acid salt of idelalisib is desolvated and in crystalline form. In another embodiment, the oxalic acid salt of idelalisib is desolvated and in amorphous form.

In a further embodiment, the oxalic acid salt of idelalisib is desolvated and in partly crystalline form.

The malonic acid salt of idelalisib may be a solvate or desolvated. In one embodiment, the malonic acid salt of idelalisib is a solvate. In one embodiment, the malonic acid salt of idelalisib is a solvate in crystalline form. In another embodiment, the malonic acid salt of idelalisib is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in partly crystalline form. In another embodiment, the malonic acid salt of idelalisib is desolvated. In one embodiment, the malonic acid salt of idelalisib is desolvated and in crystalline form. In another embodiment, the malonic acid salt of idelalisib is desolvated and in amorphous form. In a further embodiment, the malonic acid salt of idelalisib is desolvated and in partly crystalline form.

The succinic acid salt of idelalisib may be a solvate or desolvated. In one embodiment, the succinic acid salt of idelalisib is a solvate. In one embodiment, the succinic acid salt of idelalisib is a solvate in crystalline form. In another embodiment, the succinic acid salt of idelalisib is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in partly crystalline form. In another embodiment, the succinic acid salt of idelalisib is desolvated. In one embodiment, the succinic acid salt of idelalisib is desolvated and in crystalline form. In another embodiment, the succinic acid salt of idelalisib is desolvated and in amorphous form. In a further embodiment, the succinic acid salt of idelalisib is desolvated and in partly crystalline form.

The glutaric acid salt of idelalisib may be a solvate or desolvated. In one embodiment, the glutaric acid salt of idelalisib is a solvate. In one embodiment, the glutaric acid salt of idelalisib is a solvate in crystalline form. In another embodiment, the succinic glutaric salt of idelalisib is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in partly crystalline form. In another embodiment, the glutaric acid salt of idelalisib is desolvated. In one embodiment, the glutaric acid salt of idelalisib is desolvated and in crystalline form. In another embodiment, the glutaric acid salt of idelalisib is desolvated and in amorphous form. In a further embodiment, the glutaric acid salt of idelalisib is desolvated and in partly crystalline form.

The adipic acid salt of idelalisib may be a solvate or desolvated. In one embodiment, the adipic acid salt of idelalisib is a solvate. In one embodiment, the adipic acid salt of idelalisib

is a solvate in crystalline form. In another embodiment, the adipic acid salt of idelalisib is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in partly crystalline form. In another embodiment, the adipic acid salt of idelalisib is desolvated. In one embodiment, the adipic acid salt of idelalisib is desolvated and in crystalline form. In another embodiment, the adipic acid salt of idelalisib is desolvated and in amorphous form. In a further embodiment, the adipic acid salt of idelalisib is desolvated and in partly crystalline form.

The pimelic acid salt of idelalisib may be a solvate or desolvated. In one embodiment, the pimelic acid salt of idelalisib is a solvate. In one embodiment, the pimelic acid salt of idelalisib is a solvate in crystalline form. In another embodiment, the pimelic acid salt of idelalisib is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in partly crystalline form. In another embodiment, the pimelic acid salt of idelalisib is desolvated. In one embodiment, the pimelic acid salt of idelalisib is desolvated and in crystalline form. In another embodiment, the pimelic acid salt of idelalisib is desolvated and in amorphous form. In a further embodiment, the pimelic acid salt of idelalisib is desolvated and in partly crystalline form.

The phthalic acid salt of idelalisib may be a solvate or desolvated. In one embodiment, the phthalic acid salt of idelalisib is a solvate. In one embodiment, the phthalic acid salt of idelalisib is a solvate in crystalline form. In another embodiment, the phthalic acid salt of idelalisib is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in partly crystalline form. In another embodiment, the phthalic acid salt of idelalisib is desolvated. In one embodiment, the phthalic acid salt of idelalisib is desolvated and in crystalline form. In another embodiment, the phthalic acid salt of idelalisib is desolvated and in amorphous form. In a further embodiment, the phthalic acid salt of idelalisib is desolvated and in partly crystalline form.

The isophthalic acid salt of idelalisib may be a solvate or desolvated. In one embodiment, the isophthalic acid salt of idelalisib is a solvate. In one embodiment, the isophthalic acid salt of idelalisib is a solvate in crystalline form. In another embodiment, the isophthalic acid salt of idelalisib is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in partly crystalline form. In another embodiment, the isophthalic acid salt of idelalisib is desolvated. In one embodiment, the isophthalic acid salt of idelalisib is desolvated and in crystalline form. In another embodiment, the isophthalic acid salt of

idelalisib is desolvated and in amorphous form. In a further embodiment, the isophthalic acid salt of idelalisib is desolvated and in partly crystalline form.

The terephthalic acid salt of idelalisib may be a solvate or desolvated. In one embodiment, the terephthalic acid salt of idelalisib is a solvate. In one embodiment, the terephthalic acid salt of idelalisib is a solvate in crystalline form. In another embodiment, the terephthalic acid salt of idelalisib is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in partly crystalline form. In another embodiment, the terephthalic acid salt of idelalisib is desolvated. In one embodiment, the terephthalic acid salt of idelalisib is desolvated and in crystalline form. In another embodiment, the terephthalic acid salt of idelalisib is desolvated and in amorphous form. In a further embodiment, the terephthalic acid salt of idelalisib is desolvated and in partly crystalline form.

The maleic acid salt of idelalisib may be a solvate or desolvated. In one embodiment, the maleic acid salt of idelalisib is a solvate. In one embodiment, the maleic acid salt of idelalisib is a solvate in crystalline form. In another embodiment, the maleic acid salt of idelalisib is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in partly crystalline form. In another embodiment, the maleic acid salt of idelalisib is desolvated. In one embodiment, the maleic acid salt of idelalisib is desolvated and in crystalline form. In another embodiment, the maleic acid salt of idelalisib is desolvated and in amorphous form. In a further embodiment, the maleic acid salt of idelalisib is desolvated and in partly crystalline form.

The fumaric acid salt of idelalisib may be a solvate or desolvated. In one embodiment, the fumaric acid salt of idelalisib is a solvate. In one embodiment, the fumaric acid salt of idelalisib is a solvate in crystalline form. In another embodiment, the fumaric acid salt of idelalisib is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in partly crystalline form. In another embodiment, the fumaric acid salt of idelalisib is desolvated. In one embodiment, the fumaric acid salt of idelalisib is desolvated and in crystalline form. In another embodiment, the fumaric acid salt of idelalisib is desolvated and in amorphous form. In a further embodiment, the fumaric acid salt of idelalisib is desolvated and in partly crystalline form.

The citric acid salt of idelalisib may be a solvate or desolvated. In one embodiment, the citric acid salt of idelalisib is a solvate. In one embodiment, the citric acid salt of idelalisib is

a solvate in crystalline form. In another embodiment, the citric acid salt of idelalisib is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in the partly crystalline form. In another embodiment, the citric acid salt of idelalisib is desolvated. In one embodiment, the citric acid salt of idelalisib is desolvated and in crystalline form. In another embodiment, the citric acid salt of idelalisib is desolvated and in amorphous form. In a further embodiment, the citric acid salt of idelalisib is desolvated and in partly crystalline form.

The isocitric acid salt of idelalisib may be a solvate or desolvated. In one embodiment, the isocitric acid salt of idelalisib is a solvate. In one embodiment, the isocitric acid salt of idelalisib is a solvate in crystalline form. In another embodiment, the isocitric acid salt of idelalisib is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in partly crystalline form. In another embodiment, the isocitric acid salt of idelalisib is desolvated. In one embodiment, the isocitric acid salt of idelalisib is desolvated and in crystalline form. In another embodiment, the isocitric acid salt of idelalisib is desolvated and in amorphous form. In a further embodiment, the isocitric acid salt of idelalisib is desolvated and in partly crystalline form.

The malic acid salt of idelalisib may be a solvate or desolvated. In one embodiment, the malic acid salt of idelalisib is a solvate. In one embodiment, the malic acid salt of idelalisib is a solvate in crystalline form. In another embodiment, the malic acid salt of idelalisib is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in partly crystalline form. In another embodiment, the malic acid salt of idelalisib is desolvated. In one embodiment, the malic acid salt of idelalisib is desolvated and in crystalline form. In another embodiment, the malic acid salt of idelalisib is desolvated and in amorphous form. In a further embodiment, the malic acid salt of idelalisib is desolvated and in partly crystalline form.

The tartaric acid salt of idelalisib may be a solvate or desolvated. In one embodiment, the tartaric acid salt of idelalisib is a solvate. In one embodiment, the tartaric acid salt of idelalisib is a solvate in crystalline form. In another embodiment, the tartaric acid salt of idelalisib is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in partly crystalline form. In another embodiment, the tartaric acid salt of idelalisib is desolvated. In one embodiment, the tartaric acid salt of idelalisib is desolvated and in crystalline form. In another embodiment, the tartaric acid salt of idelalisib is desolvated and

in amorphous form. In a further embodiment, the tartaric acid salt of idelalisib is desolvated and in partly crystalline form.

In one embodiment, the salt of idelalisib according to the invention is the citric acid salt of idelalisib. This salt can be obtained in amorphous form from ethanol by evaporation and subsequent dispersion of the semi-solid residue in diethyl ether.

In a further embodiment, the salt of idelalisib according to the invention is the maleic acid salt of idelalisib. This salt can be obtained in crystalline form from ethanol by evaporation and subsequent dispersion of the oily residue in ethanol/diethyl ether.

Crystalline maleic acid salt of idelalisib can be in the form of a solvate, such as a hydrate, a diethyl ether solvate and/or an ethanol solvate.

The present invention furthermore relates to a polymorphic form of the crystalline maleic acid salt of idelalisib which has an X-ray powder diffraction pattern comprising peaks at 11.7 ± 0.2, 18.2 ± 0.2, 21.0 ± 0.2, 24.0 ± 0.2 and 24.6 ± 0.2 degrees 2-theta, preferably at 10.3 ± 0.2, 11.7 ± 0.2, 12.5 ± 0.2, 13.1 ± 0.2, 14.5 ± 0.2, 15.0 ± 0.2, 16.1 ± 0.2, 17.8 ± 0.2, 18.2 ± 0.2, 19.6 ± 0.2, 20.2 ± 0.2, 21.0 ± 0.2, 24.0 ± 0.2, 24.6 ± 0.2, 26.1 ± 0.2, 26.5 ± 0.2, 26.7 ± 0.2, 27.8 ± 0.2, 28.1 ± 0.2, 28.4 ± 0.2 and 30.7 ± 0.2 degrees 2-theta.

In one embodiment, the polymorphic form of crystalline maleic acid salt of idelalisib has an X-ray powder diffraction pattern of substantially as shown in figure 11.

In a further embodiment, the salt of idelalisib according to the invention is a sulfonic acid salt of idelalisib. Suitable sulfonic acids are, for example, methane sulfonic acid, benzene sulfonic acid and toluene sulfonic acid.

Preferably, the sulfonic acid salt of idelalisib, such as methane sulfonic acid, benzene sulfonic acid and toluene sulfonic acid idelalisib salt, has a residual solvent content which is within the pharmaceutically acceptable limits as defined above.

The methane sulfonic acid salt of idelalisib may be a solvate or desolvated. In one embodiment, the methane sulfonic acid salt of idelalisib is a solvate. In one embodiment, the methane sulfonic acid salt of idelalisib is a solvate in crystalline form. In another

embodiment, the methane sulfonic acid salt of idelalisib is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in partly crystalline form. In another embodiment, the methane sulfonic acid salt of idelalisib is desolvated. In one embodiment, the methane sulfonic acid salt of idelalisib is desolvated and in crystalline form. In another embodiment, the methane sulfonic acid salt of idelalisib is desolvated and in amorphous form. In a further embodiment, the methane sulfonic acid salt of idelalisib is desolvated and in partly crystalline form.

The benzene sulfonic acid salt of idelalisib may be a solvate or desolvated. In one embodiment, the benzene sulfonic acid salt of idelalisib is a solvate. In one embodiment, the benzene sulfonic acid salt of idelalisib is a solvate in crystalline form. In another embodiment, the benzene sulfonic acid salt of idelalisib is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in partly crystalline form. In another embodiment, the benzene sulfonic acid salt of idelalisib is desolvated. In one embodiment, the benzene sulfonic acid salt of idelalisib is desolvated and in crystalline form. In another embodiment, the benzene sulfonic acid salt of idelalisib is desolvated and in amorphous form. In a further embodiment, the benzene sulfonic acid salt of idelalisib is desolvated and in partly crystalline form.

The toluene sulfonic acid salt of idelalisib may be a solvate or desolvated. In one embodiment, the toluene sulfonic acid salt of idelalisib is a solvate. In one embodiment, the toluene sulfonic acid salt of idelalisib is a solvate in crystalline form. In another embodiment, the toluene sulfonic acid salt of idelalisib is a solvate in amorphous form. In a further embodiment, the idelalisib is a solvate in the partly crystalline form. In another embodiment, the toluene sulfonic acid salt of idelalisib is desolvated. In one embodiment, the toluene sulfonic acid salt of idelalisib is desolvated and in crystalline form. In another embodiment, the toluene sulfonic acid salt of idelalisib is desolvated and in amorphous form. In a further embodiment, the toluene sulfonic acid salt of idelalisib is desolvated and in partly crystalline form.

In a further embodiment, the salt of idelalisib according to the invention is idelalisib mesylate. Crystalline idelalisib mesylate can be obtained from ethanol and acetone. The crystalline idelalisib mesylate can be present as acetone solvate which transforms into its amorphous form upon drying.

The acetone solvate of the idelalisib mesylate is preferably characterized by peaks at 11.5 ± 0.2, 16.5 ± 0.2, 16.8 ± 0.2, 18.5 ± 0.2, 20.5 ± 0.2 and 21.0 ± 0.2 degree 2-theta, preferably at 11.5 ± 0.2, 13.1 ± 0.2, 16.5 ± 0.2, 16.8 ± 0.2, 18.5 ± 0.2, 18.9 ± 0.2, 20.1 ± 0.2, 20.5 ± 0.2, 21.0 ± 0.2, 22.2 ± 0.2, 22.5 ± 0.2, 23.0 ± 0.2, 23.6 ± 0.2, 24.5 ± 0.2, 24.9 ± 0.2, 26.1 ± 0.2, 26.3 ± 0.2, 27.6 ± 0.2, 29.4 ± 0.2, 29.7 ± 0.2, 30.0 ± 0.2, 31.0 ± 0.2 degrees 2-theta.

The peaks of the non-solvated mesylate are very similar, but in non-solvated mesylate, the peaks at 23.6 ± 0.2 and at 26.3 ± 0.2 degrees 2-theta cannot be found. Instead, characteristic peaks at 9.2 ± 0.2 and 13.4 ± 0.2 degrees 2-theta can be found, which are not present at all (or only with very low intensity) in the acetone solvate.

Amorphous idelalisib mesylate is highly hygroscopic.

In a further embodiment, the salt of idelalisib according to the invention is idelalisib tosylate. Crystalline idelalisib tosylate can be obtained from ethanol or acetone. Upon evaporation, an oily residue is obtained which as a dispersion in THF crystallizes. Crystalline idelalisib tosylate can be present as THF solvate comprising for example about 0.7 mol THF per mol idelalisib. Alternatively, crystalline idelalisib tosylate can be obtained from THF.

The THF solvate of the tosylate salt of idelalisib can be characterized e.g. by peaks at 9.0 ± 0.2, 10.3 ± 0.2, 16.2 ± 0.2, 16.7 ± 0.2 and 20.3 ± 0.2 degrees 2-theta, preferably at 5.7 ± 0.2, 9.0 ± 0.2, 10.3 ± 0.2, 11.4 ± 0.2, 14.3 ± 0.2, 16.2 ± 0.2, 16.7 ± 0.2, 17.4 ± 0.2, 18.1 ± 0.2, 18.3 ± 0.2, 18.6 ± 0.2, 19.2 ± 0.2, 20.3 ± 0.2, 20.7 ± 0.2, 21.7 ± 0.2, 22.4 ± 0.2, 23.0 ± 0.2, 24.4 ± 0.2, 24.7 ± 0.2, 25.8 ± 0.2, 26.0 ± 0.2, 26.5 ± 0.2, 27.0 ± 0.2, 28.8 ± 0.2, 29.5 ± 0.2 and 30.1 degrees 2-theta.

In a further embodiment, the salt of idelalisib according to the invention is idelalisib besylate. This salt can be obtained from ethanol by evaporation and dispersion of the oily residue in diethyl ether as amorphous solid.

The X-ray powder diffraction patterns of the salts of idelalisib according to the invention were measured in Bragg-Brentano-Geometry using a BrukerAXS Advance-D8 with measurement parameters as shown in the following table.

Table: conditions of measurement were as follows

on vertical goniometer	435 mm measurement circle diameter	reflection, theta /2theta,
on 9 position sample stage	with sample rotation	30 rpm
	Start angle: 2°	End Angle: 55°
Measurement time:	11 min.	Step size 0.016° 2Theta
Radiation:	Cu Kα1(1.5406A)/	Tube (Siemens FLCu2K),
		power 34kV/40mA
Monochromator:		None
Detector:	position sensitive VANTEC-1	3° capture angle (2theta)
	Anti scatter slit	6.17 mm
	Detector slit	10.39 mm
	primary beam stop	(<2° 2theta)
		4° soller slit,
	Second β filter	Ni filter 0.1 mm (0.5%)
Software	Diffrac^{Plus} EVA (Bruker-AXS, Karlsruhe)	release 2007

The invention furthermore relates to a pharmaceutical formulation comprising a salt of idelalisib as described above. Such pharmaceutical formulation may comprise one or more pharmaceutically acceptable excipients known to the skilled person. The pharmaceutical formulation may be for oral administration, such as a tablet or capsule.

The present invention furthermore relates to the above described salt of idelalisib for use in the treatment of cancer. In one embodiment, the cancer is a hematologic malignancy. The cancer may be selected from the group consisting of acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), chronic myeloid leukemia (CML), multiple myeloma (MM), non-Hodgkin's lymphoma (iNHL), refractory iNHL, non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), follicular lymphoma, Waldestrom's macroglobulinemia (WM), T-cell lymphoma, B-celllymphoma, and diffuse large B-celllymphoma (DLBCL).

In the attached figures,

Figure 1 shows the XRPD pattern of crystalline idelalisib hydrochloride, ethanol-H_2O solvate,

Figure 2 shows the XRPD pattern of semi-crystalline and amorphous idelalisib hydrochloride,

Figure 3 shows the XRPD pattern of crystalline hydrogen sulfate salt of idelalisib as ethanol solvate,

Figure 4 shows the XRPD pattern of amorphous hydrogen sulfate salt of idelalisib,

Figure 5 shows the XRPD pattern of crystalline hydrogen sulfate salt of idelalisib as anhydrate,

Figure 6 shows the XRPD pattern of crystalline hydrogen sulfate salt of idelalisib as hydrate,

Figure 7 shows the XRPD pattern of crystalline nitric acid salt of idelalisib,

Figure 8 shows the XRPD pattern of crystalline idelalisib hydrobromide, ethanol solvate,

Figure 9 shows the XRPD pattern of crystalline idelalisib hydrobromide, tetrahydrofuran solvate,

Figure 10 shows the XRPD pattern of amorphous phosphoric acid salt of idelalisib,

Figure 11 shows the XRPD pattern of crystalline maleic acid salt of idelalisib,

Figure 12 shows the XRPD pattern of crystalline idelalisib hydrochloride acetone solvate, and

Figure 13 shows the XRPD pattern of crystalline desolvated idelalisib hydrochloride.

The invention will now be explained in more detail by the following examples which are not intended to be construed as limiting.

Example 1

Idelalisib hydrochloride EtOH-H_2O

A screw capped sample tube, equipped with magnetic stirrer bar, was charged with 5-fluoro-3-phenyl-2-((1S)-l-((9-(tetrahydro-2H-pyran-2-yi)-9H-purin-6-yl)amino)propyl)-quinazolin-4(3H)-one (2.06 g, 0.0050 mol), absolute ethanol (2.23 g, 2.82 mL, 0.0483 mol), and water (1.41 mL, 0.0782 mol). 10N hydrochloric acid (HCl 32%) was added in portions with a Pasteur pipette (1.07 g, 0.91 mL, 0.0101 mol).

The clear to slightly turbid mixture was agitated overnight at about 21°C but no suspension of solid hydrochloride was obtained by the procedure. The mixture remained slightly turbid.

Additional absolute ethanol was added, (3.95 g, 5.00 mL 0.0858 mol) and the sample was stirred over weekend. A total amount of EtOH, 10.82 mL, 8.58 g was added, but the small amount of semisolid oily layer, which settled after ethanol addition, did not crystallize and thus could not be filtered off.

Finally the amount of dry ethanol was raised by additional 5.00 mL and stirring for 72 h completed crystallization to a filterable suspension. The filtered wet solid (2.02 g) was air dried to constant weight after 6h (1.603 g, 66%).

The XRPD pattern of the obtained idelalisib hydrochloride was measured and is shown in figure 1. A sample of the air-dried idelalisib hydrochloride (0.5173 g) was slurried at room temperature in acetone (4.0 g, 5 mL) for 48 hours and then undissolved fraction of solid was filtered off. The wet solid from the slurry (0.502 g) was dried on air for 5 days to constant weight. The XRPD pattern of the thus obtained solid is shown in figure 2 (lower pattern) indicating that the crystalline idelalisib hydrochloride was present as ethanol-H_2O solvate which was desolvated in acetone and thereby transformed into a part-crystalline idelalisib hydrochloride.

The sample material of the part-crystalline idelalisib hydrochloride was found highly hygroscopic. At 90 % rH material had a 10 % weight gain which rose to 15 % at 95 % rH. In the following drying toward 0 % rH, the absorbed water was removed completely and a completely amorphous phase of idelalisib hydrochloride was obtained. The XRPD pattern of this amorphous phase is shown in figure 2 (upper pattern).

Example 2

Preparation of Idelalisib hydrogen sulfate ethanol solvate without seeding (Form I)

A 1000 mL 3-necked round-bottom flask (tare 118.50 g) was charged with 5-fluoro-3-phenyl-2-((1S)-1-((9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-yl)amino)propyl)quinazolin-4(3H)-one (gros 143.435 g, net 24.90, 0.0699 mol) and absolute ethanol (gros 266.2, net 122.80, 155.44 mL, 2.6656 mol, 44.43 equiv.).
In a 50 mL Schott Bottle (tare 65.10 g) a ~25% aqueous solution of H_2SO_4 was prepared from ice-water (gros 85.5 g, net 20.40 g, 20.4 mL) and sulfuric acid (H_2SO_4 conc. 96 %, gros 92.9 g, net 7.40 g ,4.0 mL ,0.0754 mol,1.25 equiv.).

This diluted acid (1.2 equiv.) was charged to the suspension by a dropping funnel within 15 min.

The mixture was agitated at about 21°C. Shortly after about 50 % of the acid was introduced, a cake was formed on the bottom of the flask. This cake was dissolved largely after full amount of acid was introduced with stirring. Then a slurry of fine particles was formed from the turbid mixture. To fasten the dissolution of the initial cake the mixture was warmed to about 40°C for 15 min. The mixture was stirred overnight until it was turned into a homogenous thick (pulpy) suspension of white solid.

The suspension was transferred to a Buchner filter Funnel (tare 91.4000 g) solid was filtered from EtOH by vacuum.

Residual material was rinsed from flask to the funnel with filtrate (Mother liquor), subsequently the solid was rinsed and washed with Ethanol (28.06 g ,0.6090 mol) The filter cake was sucked to dryness on the filter (gros,121.8000 g, net,30.4000 g). The wet solid was dried on the filter with a stream of air (gros 117.10 g, net 25.70 g) to a get dry solid (74.2%).

The crystalline form of solvated Idelalisib hydrogen sulfate was detected (ethanol solvate). The XRPD pattern of this crystalline form is shown in figure 3.

Example 3

Preparation of amorphous Idelalisib hydrogen sulfate (Form II)

The solid obtained in example 2 was dried under vacuum (11 mbar) in a drying cabinet at 50°C leaving 16.7 g (52.4 %) of solvent free but widely amorphous product after 120 h of drying. The XRPD pattern of this amorphous form is shown in figure 4.

Example 4

Preparation of Idelalisib hydrogen sulfate anhydrate (Form III)

The mother liquor from the crystallization in example 1 was transferred to rotavapor and the solvent evaporated at 50°C / 15 mbar until an oily layer remained. This oily layer was placed in a storage cabinet for crystallization. From the oily layer after 14 weeks standing

at room temperature a crystalline mass had separated. The crystal cake was slurried for short with cold isopropanol, filtered, and dried.
These crystals were free from ethanol and free from water. The XRPD pattern of this crystalline form is shown in figure 5.

Example 5

Preparation of seeding material for the hydrogen sulfate salt of Idelalisib (Ethanol solvate, Form I).

A 18 mL screw capped sample tube was equipped with a magnetic stirrer bar rod (tare 17.9861 g) and charged with 5-fluoro-3-phenyl-2-((1S)-1-((9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-yl)amino)propyl)quinazolin-4(3H)-one (gros 18.4883 g, net,0.5022 g, 0.0012 mol). Then some amount of dry ethanol was added (gros 23.5057 g, net 5.0174 g, 6.37 mL, 0.1092 mol) and the mixture stirred and vortexed to achieve homogenous suspension. From water (tare15.6874 g, gros 15.949,net 0.2616 g) and sulfuric acid (gros 16.0078, net 0.0588 g) a mixture of aqueous H_2SO_4 was prepared in a separate vial and introduced to the suspension.
No solid was observed from tan colored solution and the tube was allowed to stand for 72 h at room temperature, when a small solid residual had formed.
The tube was stirred for additional 16 h (overnight), and the solid was filtered from the mixture through Buchner filter funnel (tare 52.1329, gros 52.8369 g, net 0.7040 wet), sucked to dryness, then allowed to dry on air at room temperature (gros 52.6783 g, net 0.5454, LOD: 0.1586 g, 22.53%).

Example 6

Preparation of Idelalisib hydrogen sulfate Ethanol Solvate with seeding (Form I)

A 1000 mL 3-necked roundbottom flask (tare 301.30 g) was charged with 5-fluoro-3-phenyl-2-((1S)-1-((9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-yl)amino)propyl)quinazolin-4(3H)-one (gros 326.40 g, net 25.10, 0.0604 mol, 1.007 equiv.) and ethanol (gros 452.70 g, net 126.30 g,159.9 mL, 2.74 mol 2.6656 mol, 45.69 equiv.).

In a 50 mL Schott Bottle (tare 48.90 g) a ~20% aqueous solution of H_2SO_4 was prepared from ice-water (20.1 g, 1.1154 mol, 18.60 equiv.) and sulfuric acid (H_2SO_4 conc. 98-96 %, gros 75.30 g, 3.42 mL, 6.30 g, 0.0642 mol,1.07055 equiv.).
This diluted acid (1.05 equiv.) was charged to the suspension by a dropping funnel within 5 to 10 min.
The mixture was agitated vigorously at about 21°C until all initially formed lumps had been redissolved again. To the turbid mixture seeds of Idelalisib sulfate (form I - ethanol solvate, 0.005 equiv., 0.0003 mol) obtained in example 5 were added. The suspension was stirred overnight until it was turned into a slurry of white solid.
The pulpy suspension was transferred to a Buchner filter funnel (tare 188.90 g) solid was filtered from EtOH by vacuum and residual material was rinsed from flask to the funnel with filtrate (mother liquor). Subsequently the solid was rinsed and washed with ethanol (28.06 g, 0.6090 mol). The filter cake was sucked to dryness on the filter (gros, 225.10 g, net, 36.20 g). The wet solid was dried on the filter with a stream of air overnight (gros 220.80 g, net 31.90 g), air dry solid. A sample (1.00 g) was analyzed.
The crystalline form I of solvated Idelalisib sulfate was detected (ethanol solvate).

After sampling the remainder of the batch (27.47 g) was transferred to a beaker (tare 95.576 g) and placed in a drying cabinet and dried under vacuum (9 mbar) at 50°C for 24 hours (gros 118.376 g, net 22.80 g, 83.0% recovery) to leave a completely desolvated amorphous solid (loss on drying - 4.674 g).

Example 7

Preparation of Idelalisib hydrogen sulfate hydrate (Form IV)

The mother liquor from the batch obtained in example 6 was evaporated on a Rotavapor, and the oily reminder was allowed to stand for several weeks in a cabinet for crystallization. A small amount of semi-crystalline layer was found. The fine crystals formed were filtered from oily suspension on a glass sinter filter. A hydrated Form of the sulfate was detected containing no other solvent (Form IV). The XRPD pattern of this crystalline form is shown in figure 6.

Example 8

Preparation of seeding material for the maleate salt of Idelalisib

A 18 mL screw capped sample tube was equipped with a magnetic stirrer bar rod (tare 18.6852 g) and charged with 5-fluoro-3-phenyl-2-((1S)-1-((9-(tetrahydro- 2H-pyran-2-yl)-9H-purin-6-yl)amino)propyl)quinazolin-4(3H)-one (gros 19.1975 g, net 0.5123 g, 0.0012 mol). Then some amount of dry ethanol was added (gros 24.2273 g, net 5.0298 g, 6.37 mL, 0.1092 mol) and the mixture stirred and vortexed to achieve homogenous suspension. Maleinic acid was charged as a solid (gros 24.3710 g, net 0.144 g, 0.0013 mol).
The mixture was agitated at about 21°C and vortexed until all solids had been dissolved. Diethyl ether was added in small aliquots to the tan solution (gros 30.041 g, net 5.670 g). This solution was stirred over weekend when a white suspension was formed, and crystalline solid settled.
The suspension was transferred to Buchner funnel (tare 53.592 g) and solid was filtered, sucked to dryness and washed with diethyl ether (5mL) The solid (gros 53.936 g, net 0.344 g, 48.6% o.th) was air dried on the filter for 17 h in a good vented hood at room temperature.

Example 9

Preparation of maleate salt of Idelalisib through seeding process

A 1000 mL 3N-RBF equipped with paddel stirrer, reflux condensor, dropping funnel (100 mL) was immersed into heating bath. 9 parts of 10 parts of dry ethanol, exactly measured (total 215.52 g, 273 mL, 4.68 mole) were added to the flask, (about 950 g of Ethanol might be necessary to dissolve free base of Idelalisib at room temperature).
The flask with ethanol was warmed to 60°C, at which temperature 5-fluoro-3-phenyl-2-((1S)-1-((9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-yl)amino)propyl)quinazolin-4(3H)-one (45.54 g, 0.1096 mol) was charged in aliquots through a powder funnel placed on one neck of the flask. With remaining part from 10 parts the powder funnel was rinsed. The flask was kept for 1 h at the selected temperature while stirring and additional ethanol was added (35.92 g) to rinse solids from the walls of the flask under reduced stirrer speed. In the meantime a solution of maleic acid (19.12 g, 0.1647 mol, 1.5 equiv.) in dry ethanol (58.70 g, 74.32 mL, 1.2744 mol) was prepared under room temperature conditions.

The maleic acid solution (77.82 g, 24.6%) in dry ethanol was charged to the dropping funnel and then the solution was added dropwise (10 mL/min.) to the warm suspension while the mixture was agitated at about 58 °C (IT). Shortly, after 2/3 (1 equiv.) of the maleic acid solution had been added, nearly all of the base was dissolved, the flask with ethanol was kept at 60 °C for 1 h while remaining amount of maleic acid was added. After that the heating was stopped and the temperature allowed coming to room temperature overnight. Seeds from example 8 were used to initialize the crystallization process. The mixture is stirred for at least 17 h while reaching room temperature. The solids were collected on the filter on a Buchner funnel (tare 382.68 g) by vacuum filtration and the residual amounts of solid from flask rinsed with filtrate to filter and washed with little cold ethanol (28.78 g). All solid was sucked to dryness (gros 450.52 g, net 58.28) leaving a slightly wet solid with light smell of ethanol.
(Filtrate 1,158.40 g).
The solid was further dried to constant weight on the filter in a stream of air (air sucked through the powder bed under ambient conditions overnight), leaving air dried maleate salt of (S)-2-(1-(9H-purin-6-ylamino)propyl)-5-fluoro-3-phenylquinazolin-4(3H)-one (56.12 g, 96.3% from theory). The XRPD pattern of this crystalline form is shown in figure 11.

Example 10

The nitiric acid salt of idelalisib, idelalisib hydrobromide ethanol and THF (tetrahydrofuran) solvates, idelalisib hydrochloride acetone solvate, the phosphoric acid salt of idelalisib, the citric acid salt of idelalisib, idelalisib mesylate, idelalisib tosylate and idelalisib besylate and solvates thereof were prepared similar to the method described in example 1 using ethanol, THF and acetone as solvent, respectively.

The XRPD pattern of crystalline idelalisib hydrobromide ethanol solvate is shown in figure 8. The XRPD pattern of low crystalline idelalisib hydrobromide THF solvate is shown in figure 9. Desolvation of this THF solvate results in an amorphous product.

The XRPD pattern of crystalline idelalisib hydrochloride acetone solvate is shown in figure 12. This salt can be desolvated upon drying at 40-50°C under vacuum at 10-100 mbar yielding desolvated idelalisib hydrochloride, the XRPD pattern of which is shown in figure 13.

Example 11

The solubilities of various salts of idelalisib in buffers and selected media were measured. The results are summarized in the following tables 4 and 5:

Table 4

		free base	hydrochloride EtOH-H_2O	hydrobromide EtOH	hydrogen-sulfate Form I
water demin. (pH dep.)	15 min.	0.098	7.632	8.648	8.820
	60 min.	0.081	17.065	12.102	8.772
20mM NaOAc pH 4.5	15 min.	0.092	0.399	0.423	5.867
	60 min.	0.100	3.274	1.094	5.982
0,01m HCl pH ~2.2	15 min.	0.947	17.855	12.460	9.945
	60 min.	1.051	31.904	13.837	9.814
50mM KH_2PO_4 pH 6.8	15 min.	0.086	0.353	0.339	4.961
	60 min.	0.088	1.605	1.484	5.292
0.1 % TPGS (FaSSIF) *	15 min.	0.141	0.715	1.633	6.082
	60 min.	0.107	3.812	3.481	6.268
2.0% TPGS (FeSSIF) *	15 min.	1.056	10.284	9.623	11.400
	60 min.	1.172	14.036	11.168	11.612

TPGS: d-alpha tocopheryl polyethylene glycol 1000 succinate
FaSSIF Fasted State Simulated intestinal Fluid
FeSSIF Fed State Simulated Intestinal Fluid

Table 5

		free base	mesylate	tosylate	maleate
water demin. (pH dep.)	15 min.	0.098	63.941	4.051	1.934
	60 min.	0.081	62.606	8.607	2.095
20mM NaAc pH 4.5	15 min.	0.092	37.700	1.088	0.411
	60 min.	0.100	40.065	2.889	0.475
0,01m HCl pH ~2.2	15 min.	0.947	62.096	4.998	2.445
	60 min.	1.051	63.513	10.301	2.655
50mM KH_2PO_4 pH 6.8	15 min.	0.086	27.524	1.560	0.355
	60 min.	0.088	22.953	3.457	0.393
0.1 % TPGS (FaSSIF) *	15 min.	0.141	33.818	2.503	0.662
	60 min.	0.107	25.815	5.729	1.121
2.0% TPGS (FeSSIF) *	15 min.	1.056	41.337	7.625	6.798
	60 min.	1.172	29.433	15.719	6.984

TPGS: d-alpha tocopheryl polyethylene glycol 1000 succinate
FaSSIF Fasted State Simulated intestinal Fluid
FeSSIF Fed State Simulated Intestinal Fluid

Example 12

The hygroscopicity, the residual solvent content, the solubility in water and the chemical stability at room temperature and 60 % rH (relative humidity) and at 40°C and 75 % rH were measured for various salts of idelalisib. The results are summarized in tables 6 and 7 below.

Example 13

The particle size distribution (volume) of various salts of idelalisib were measured by laser diffraction using the following measurement parameters:

Measurement parameters

Analysis Model:	Fraunhofer
Dispersant:	Silicone oil
Obscuration:	10 - 20%
Stirrer speed:	2000 rpm
Stirring duration:	5 min prior to first measurement cycle
Sonication:	no
Background time:	10 sec
Measurement time:	10 sec
Measurement cycles:	3

The results are summarized in Table 8 below.

Table 6

Form	Crystallinity	Hygroscopicity [weight gain at 75% rH]	Residual solvent content [ppm]		Solubility in water [mg/ mL] 15 min. / 60 min.	Chemical Stability RT (60% rh)	Chemical Stability 40°C (75% rH)
Hydrochloride EtOH-H_2O	crystalline	0.2% (0.5%)	Ethanol:	60610	7 / 17	99.54 / 99.51 (99.56) stable	99.51 / 99.51 (99.56) stable
Hydrochloride Acetone	crystalline	n.d.	Acetone:	75000	n.d.	n.d.	n.d.
Hydrochloride desolvated	crystalline	5% (15% at 95%rH)	Acetone:	350	n.d.	99.64 / 99.66 (99.65) stable	99.63 / 99.62 (99.65) stable
Hydrochloride amorphous	amorphous	n.d.	Acetone:	n.d.	n.d.	n.d.	n.d.
Hydrogensulfate Form I	crystalline	n.d.	Ethanol:	10000	n.d.	99.82 / 99.81 (99.90) stable	99.52 / 99.52 (99.90) stable
Hydrogensulfate Form II	amorphous	n.d.	Ethanol:	10	8/8	99.90 / 99.85 (99.54) stable	99.56 / 99.56 (99.54) stable
Hydrobromide Acetone	Low crystalline	10%	THF	90000	n.d.	n.d.	n.d.
Hydrobromide amorphous	amorphous	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Hydrobromide Ethanol	crystalline	None 0.2%	Ethanol:	16580	9 / 12	n.d.	n.d.
Mesylate	crystalline	n.d.	Acetone:	4800	64 /63	99.75 / 99.59 (99.87) stable	93.49 / 90.64 (99.87) instable (decomposed)

Table 6 (continued)

Form	Crystallinity	Hygroscopicity [weight gain at 75% rH]	Residual solvent content [ppm]		Solubility in water [mg/ mL] 15 min. / 60 min.	Chemical Stability RT (60% rh)	Chemical Stability 40°C (75% rH)	R-Enantiomer content
Mesylate	crystalline	n.d.	Acetone:	1000	n.d.	99.89 / 99.81 (99.90) stable	92.14 / 90.88 (99.90) instable (decomposed)	0.1
Tosylate	n.d.	n.d.	THF		4 / 9	n.d.	n.d.	n.d.
Maleate	crystalline	n.d.	Ethanol:	2000	2 / 2	99.06 / 99.02 (99.80) stable *	98.76 / 98.78 (99.80) stable *	0.12
Nitrate	crystalline	None 0.2%	THF:	42000	n.d.	n.d.	n.d.	n.d.
Phosphate	amorphous	n.d.	IPA	80000	n.d.	n.d.	n.d.	n.d.
Citrate	amorphous	n.d.	EtOH/ Diethyl ether	119200	n.d.	n.d.	n.d.	n.d.

Table 7

Salt / Base Form	State (stable/instable Form at RT)	Hygroscopicity [weight gain at 75% - 80% rH (95%rh)]	Residual solvent content [ppm]	
free Base	crystalline	0.2 % (0.3%)	Ethanol:	50
Hydrochloride EtOH-H_2O	crystalline	0.2 % (0.5%)	Ethanol:	60610
Hydrochloride Acetone	crystalline (instable)	-	Acetone:	75000
Hydrochloride desolvate	crystalline	5% (15%)	Acetone:	350
Hydrochloride amorphous	widely amorphous	n.d.	Acetone:	n.d.
Hydrogensulfate Form I	crystalline (instable)	n.d.	Ethanol:	10000
Hydrogensulfate Form II	completely amorphous	n.d.	Ethanol:	10
Hydrobromide Acetone	low crystalline, (instable) widely amorphous	10%	THF	90000
Hydrobromide amorphous	amorphous (dry from DVS)	-	THF	n.d.
Hydrobromide Ethanol	crystalline	0.2 % (0.5%)	Ethanol:	16580
Mesylate	crystalline (instable)	5% (25%)	Acetone:	4364
Mesylate	Amorphous (dry after DVS)	-	Acetone:	n.d.
Tosylate	crystalline	0.1% (5%)	THF	48325
Tosylate	widely amorphous (dry from DVS)	n.d.	THF	n.d.
Besylate	amorphous (instable)	n.d.	Diethylether Ethanol	17000 25060
Maleate (1:1)	crystalline (stable)	0.3% (0.7% at 95% rH)	Ethanol:	2000
Nitrate	crystaline	None (0.2% at 95% rH)	THF	42000
Phosphate	amorphous	n.d.	IPA	80000
Citrate (1:1)	amorphous	n.d.	EtOH/ Diethyl ether	119200

Table 8

	D((0.1) [µm]	D(0.5) [µm]	D(0.9) [µm]
free base	2.5	10	40
Maleate (A)	3.1	38	73
HCl EtOH-H_2O	2.1	9	36
Mesylate	2.4	62	143
Sulfate (A)	1.4	7.5	76 (aggregates)
Sulfate (B)	10	58	109
Maleate (B)	5.6	25	47
HCl (acetone solvate)	1.1	9	25

Claims

1. Salt of idelalisib.

2. Salt according to claim 1 being crystalline.

3. Salt according to claim 1 being amorphous.

4. Salt according to any of the preceding claims having a residual solvent content within pharmaceutically acceptable limits.

5. Salt according to any of the preceding claims being a solvate.

6. Salt according to claim 5, wherein the solvate is an ethanol, tetrahydrofuran, diethyl ether or acetone solvate, each of the above optionally in combination with water or a hydrate.

7. Salt according to any of claims 1 to 4 being a desolvate.

8. Salt according to any of claims 1 to 7 being an organic acid salt of idelalisib.

9. Salt according to claim 8 wherein the organic acid is a dicarboxylic acid or a tricarboxylic acid.

10. Salt according to claim 9 being the maleic acid salt of idelalisib.

11. Salt according to claim 10 being crystalline and having an X-ray powder diffraction pattern comprising peaks at 11.7 ± 0.2, 18.2 ± 0.2, 21.0 ± 0.2, 24.0 ± 0.2 and 24.6 ± 0.2 degrees 2-theta.

12. Salt according to claim 11 having an X-ray powder diffraction pattern substantially as shown in figure 11.

13. Salt according to claim 9 being the citric acid salt of idelalisib.

14. Salt according to claim 8 being a sulfonic acid salt of idelalisib.

15. Salt according to claim 14 being idelalisib mesylate.

16. Salt according to claim 14 being idelalisib tosylate.

17. Salt according to claim 14 being idelalisib besylate.

18. Salt according to any of claims 1 to 6 being idelalisib hydrochloride, ethanol-H_2O solvate.

19. Salt according to claim 18 being crystalline and having an X-ray powder diffraction pattern comprising peaks at 6.9 ± 0.2, 8.8 ± 0.2, 11.5 ± 0.2, 13.5 ± 0.2, 13.7 ± 0.2, 16.8 ± 0.2, 23.1 ± 0.2, 25.0 ± 0.2, and 26.2 ± 0.2 degrees 2-theta.

20. Salt according to claim 19 having an X-ray powder diffraction pattern substantially as shown in figure 1.

21. Salt according to any of claims 1 to 7 being the hydrogen sulfate salt of idelalisib.

22. Salt according to claim21 being the hydrogen sulfate salt of idelalisib, ethanol solvate.

23. Salt according to claim 22 being crystalline and having an X-ray powder diffraction pattern comprising peaks at 7.3 ± 0.2, 9.6 ± 0.2, 16.0 ± 0.2, 18.9 ± 0.2 and 23.9 ± 0.2 degrees 2-theta.

24. Salt according to claim 23 having an X-ray powder diffraction pattern substantially as shown in figure 3a.

25. Salt according to claim 21, being the hydrogen sulfate salt of idelalisib, hydrate or anhydrate.

26. Salt according to claim 25 being crystalline, an anhydrate and having an X-ray powder diffraction pattern comprising peaks at 9.7 ± 0.2, 20.2 ± 0.2, 21.0 ± 0.2 and 26.5 ± 0.2 degrees 2-theta.

27. Salt according to claim 26, having an X-ray powder diffraction pattern substantially as shown in figure 5.

28. Salt according to claim 25, being crystalline, a hydrate and having an X-ray powder diffraction pattern comprising peaks at 8.4 ± 0.2, 12.0 ± 0.2, 18.8 ± 0.2, 20.7 ± 0.2 and 26.7 ± 0.2 degrees 2-theta.

29. Salt according to claim 28, having an X-ray powder diffraction pattern substantially as shown in figure 6.

30. Salt according to any of claims 1 to 7 being the nitric acid salt of idelalisib.

31. Salt according to claim30 being the nitric acid salt of idelalisib as THF-H_2O solvate.

32. Salt according to claim 31 being crystalline and having an X-ray powder diffraction pattern comprising peaks at 4.2 ± 0.2, 11.1 ± 0.2, 15.2 ± 0.2, 19.4 ± 0.2 and 26.5 ± 0.2 degrees 2-theta.

33. Salt according to claim 32 having an X-ray powder diffraction pattern substantially as shown in figure 7.

34. Salt according to any of claims 1 to 7 being idelalisib hydrobromide.

35. Salt according to claim34 being idelalisib hydrobromide, ethanol solvate.

36. Salt according to claim 35 being crystalline and having an X-ray powder diffraction pattern comprising peaks at 5.9 ± 0.2, 9.6 ± 0.2, 15.0 ± 0.2, 19.2 ± 0.2 and 23.6 ± 0.2 degrees 2-theta.

37. Salt according to claim 36 having an X-ray powder diffraction pattern substantially as shown in figure 8.

38. Salt according to claim 34 being idelalisib hydrobromide, tetrahydrofuran solvate.

39. Salt according to claim 38 being at least partially crystalline having an X-ray powder diffraction pattern substantially as shown in figure 9.

40. Salt according to any of claims 1 to 7 being the phosphoric acid salt of idelalisib.

41. Salt according to any of claims 1 to 6 being idelalisib hydrochloride, acetone solvate.

42. Salt according to claim 41 being crystalline and having an X-ray powder diffraction pattern comprising peaks at 9.8 ± 0.2, 14.2 ± 0.2, 15.4 ± 0.2, 17.8 ± 0.2, 19.8 ± 0.2, 23.1 ± 0.2 and 24.1 ± 0.2 degrees 2-theta.

43. Salt according to claim 42, having an X-ray powder diffraction pattern substantially as shown in figure 12.

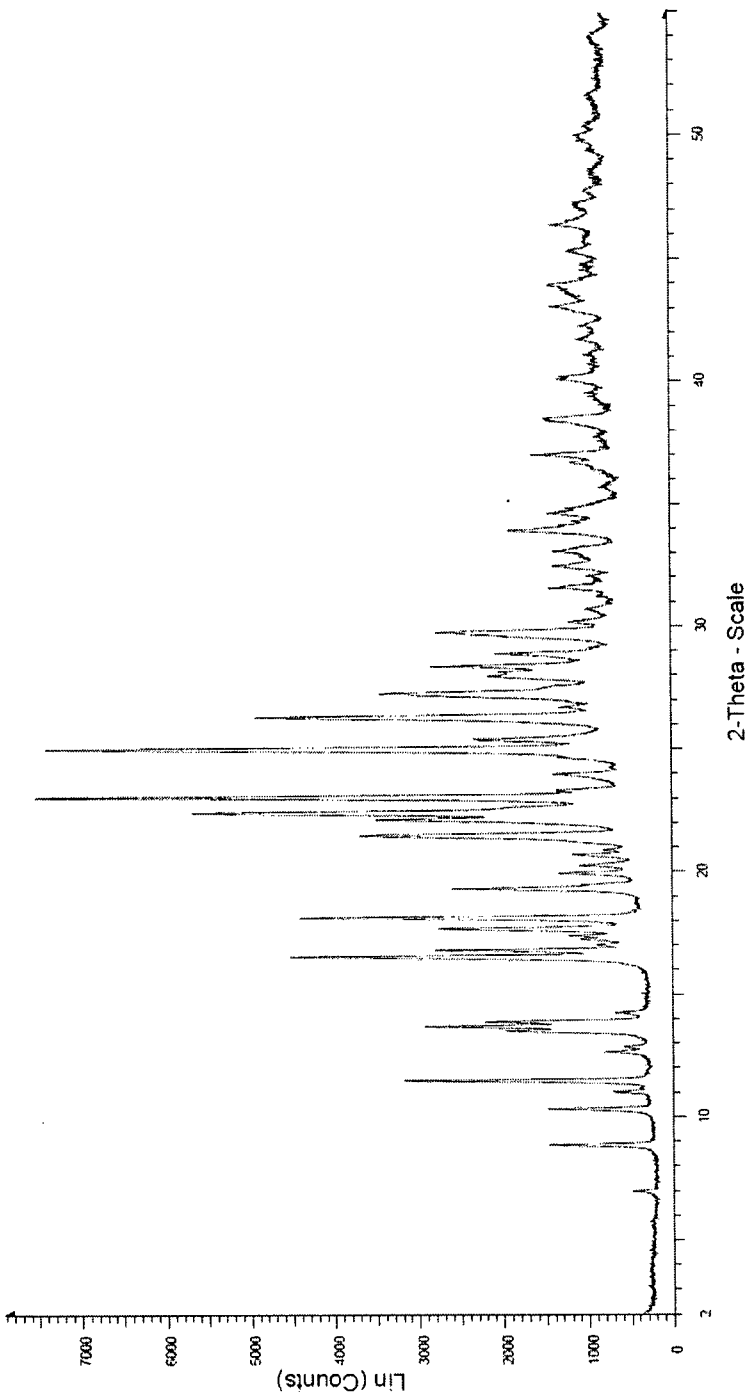
44. Salt according to claim 7 being idelalisib hydrochloride, desolvate.

45. Salt according to claim 44, being crystalline and having an X-ray powder diffraction pattern comprising peaks at 9.9 ± 0.2, 14.6 ± 0.2, 15.8 ± 0.2, 19.0 ± 0.2, 19.9 ± 0.2, 20.5 ± 0.2, 23.6 ± 0.2 and 24.2 ± 0.2 degrees 2-theta.

46. Salt according to claim 45, having an X-ray powder diffraction pattern substantially as shown in figure 13.

47. Pharmaceutical formulation comprising a salt of idelalisib according to any of claims 1 to 46.

48. Salt of idelalisib according to any of claims 1 to 46 for use in the treatment of cancer.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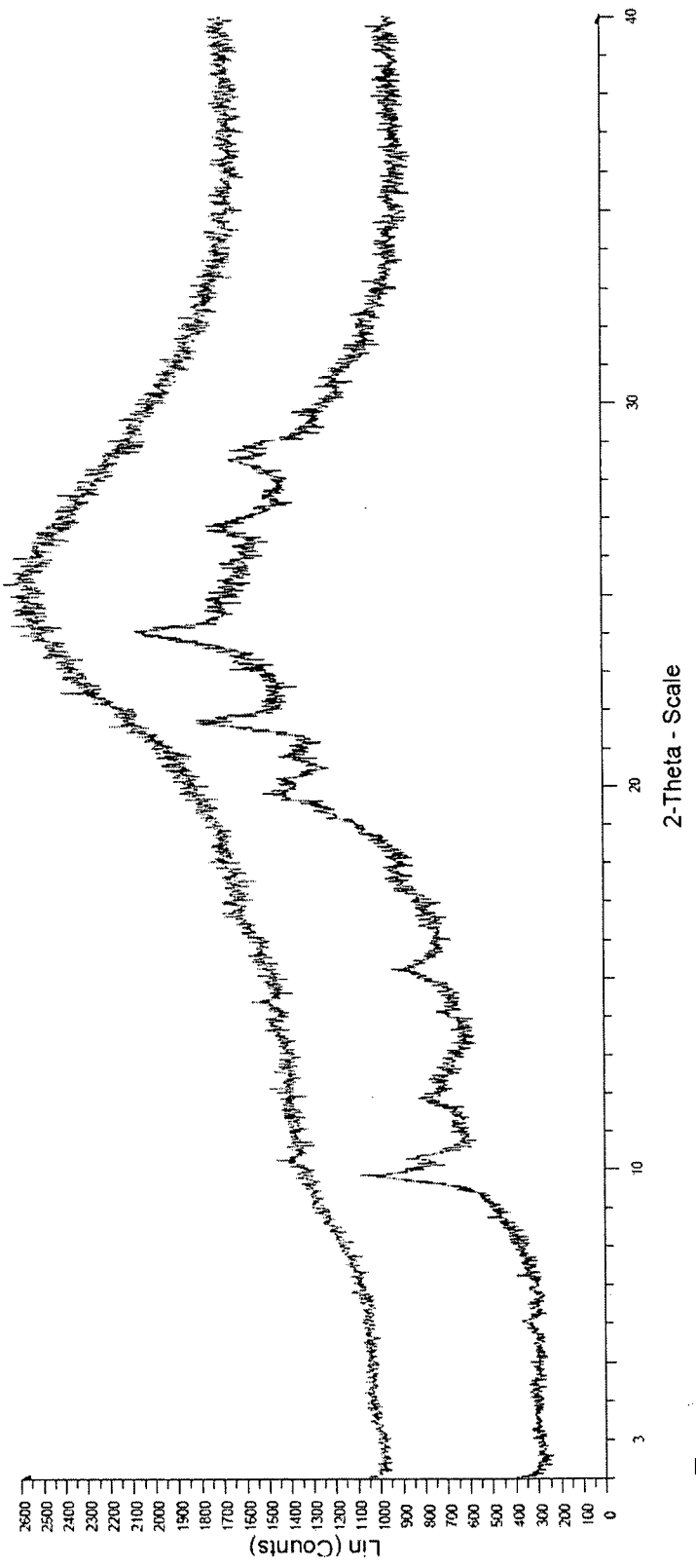
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Figure 2

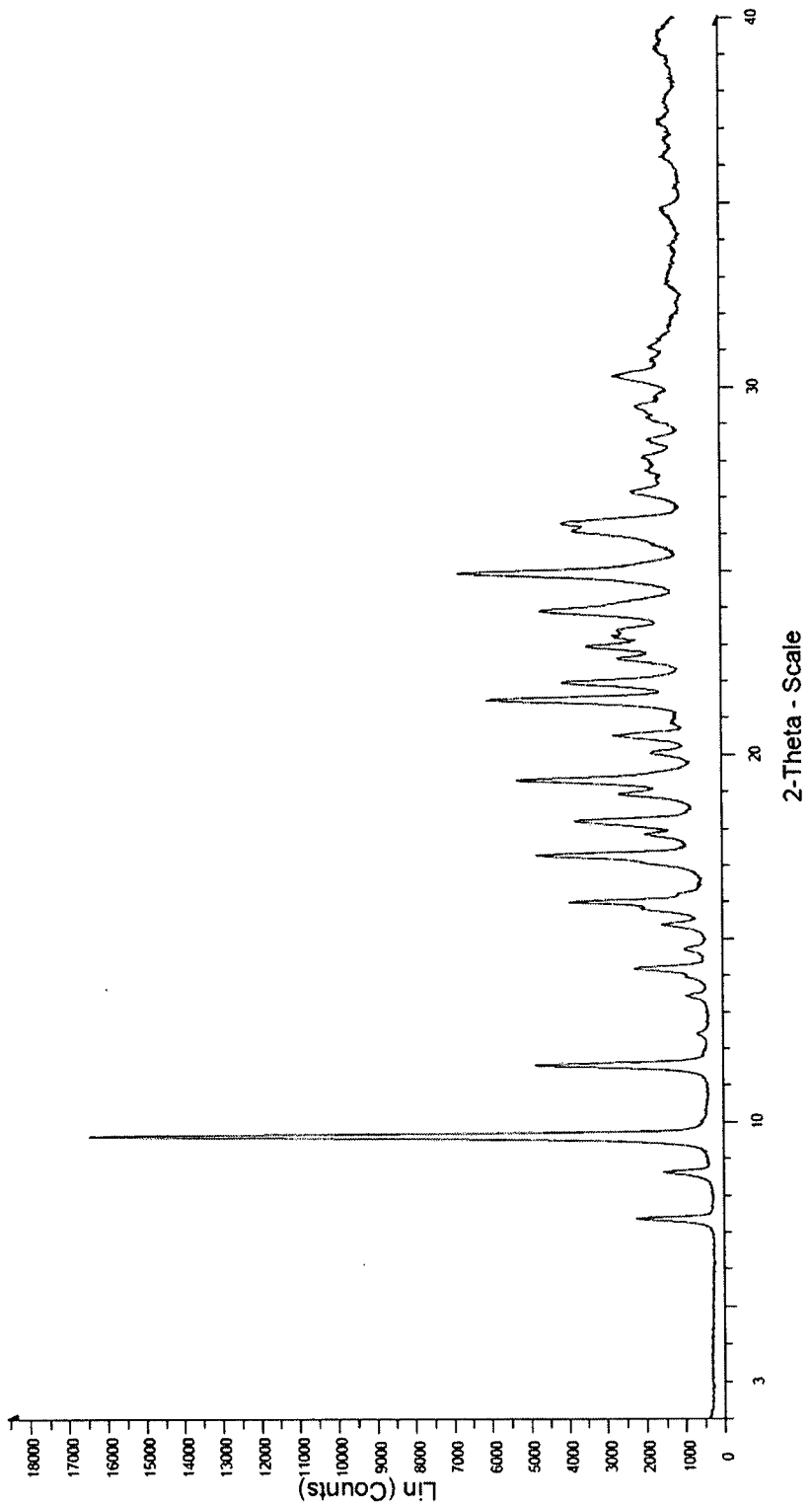
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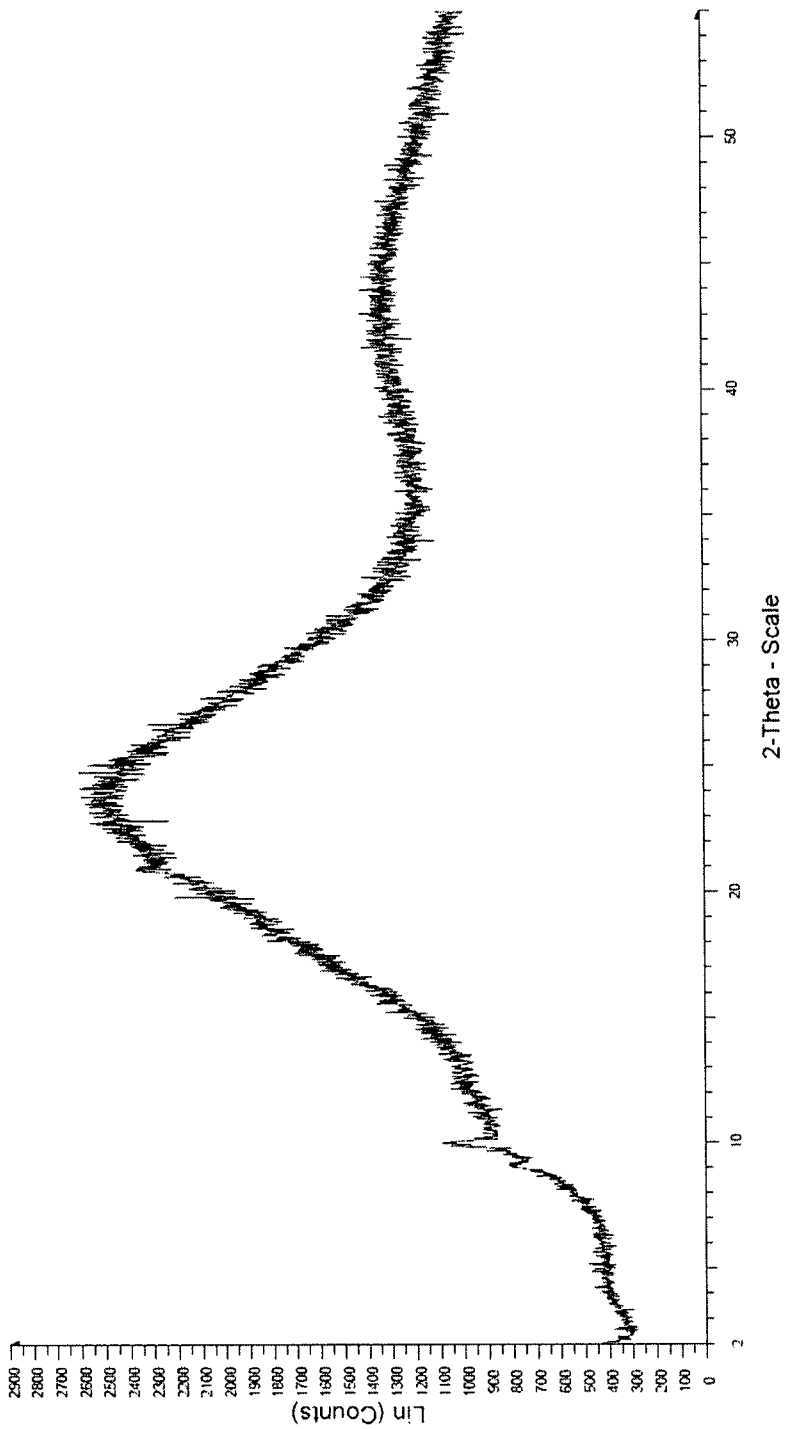
Figure 3



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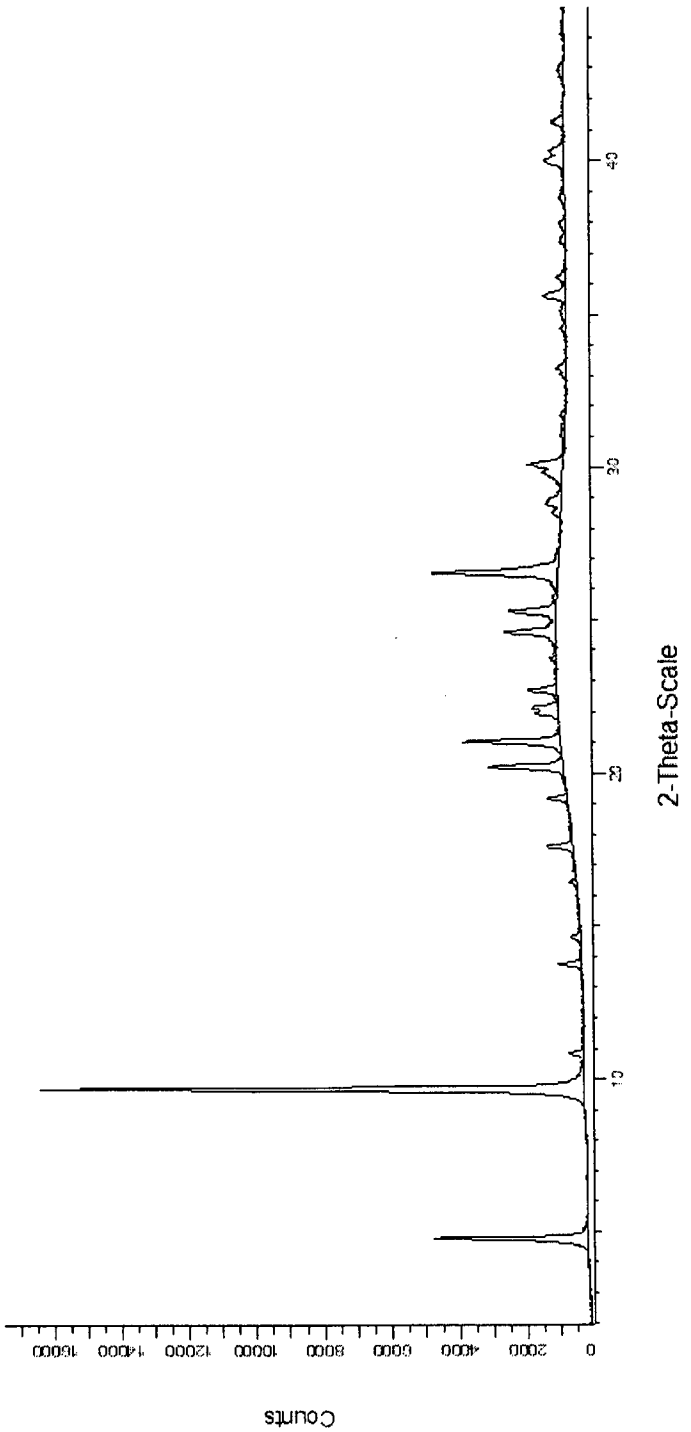
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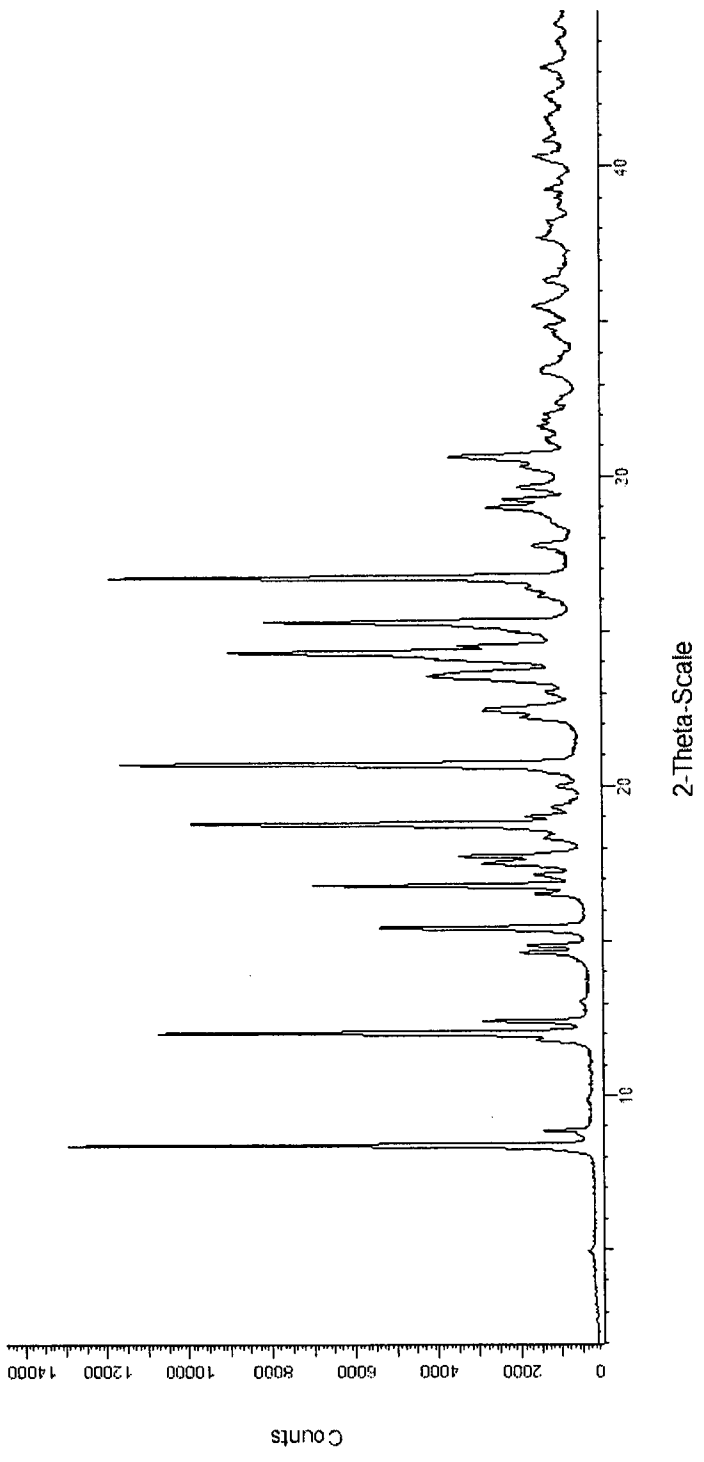
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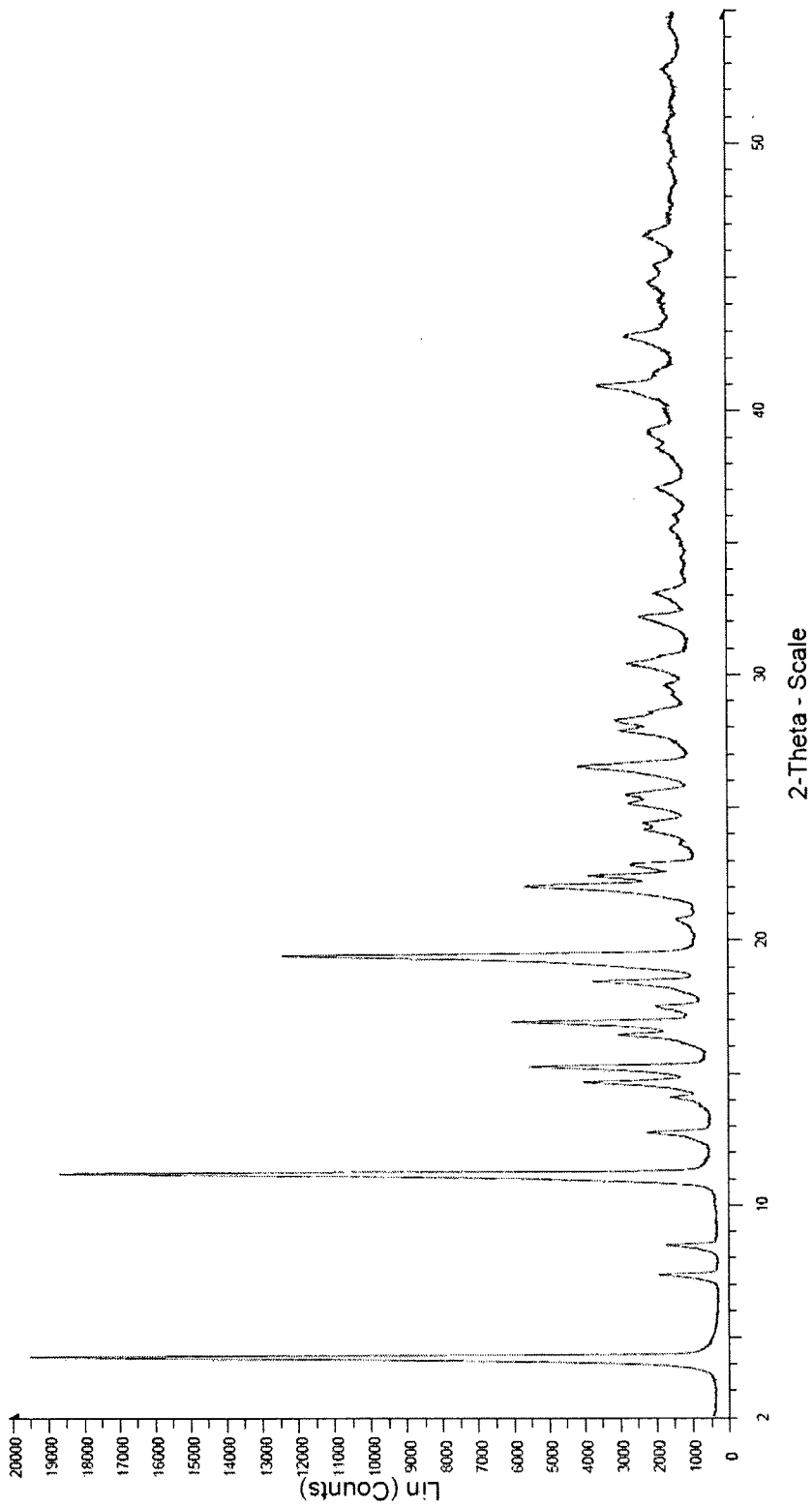
Figure 6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2-Theta - Scale

Figure 7

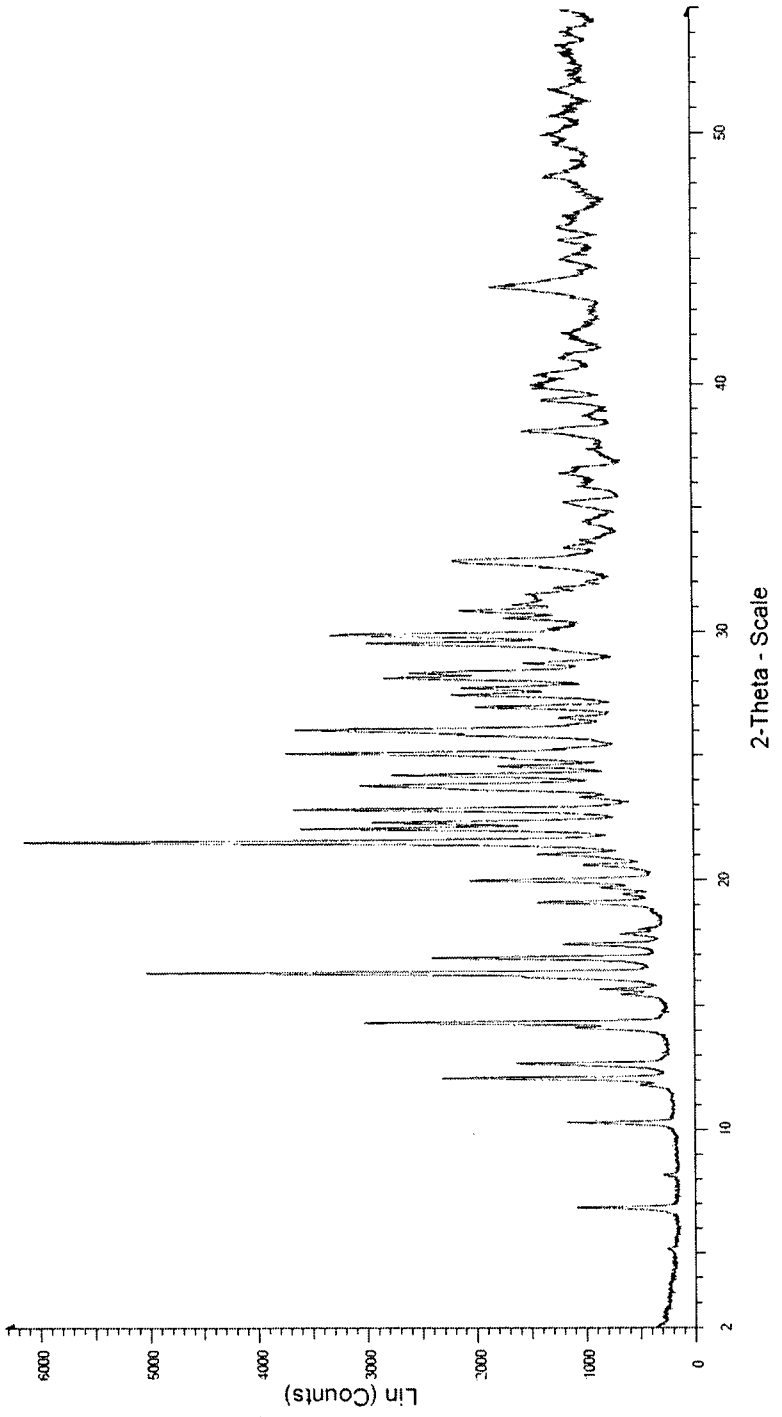
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Figure 8

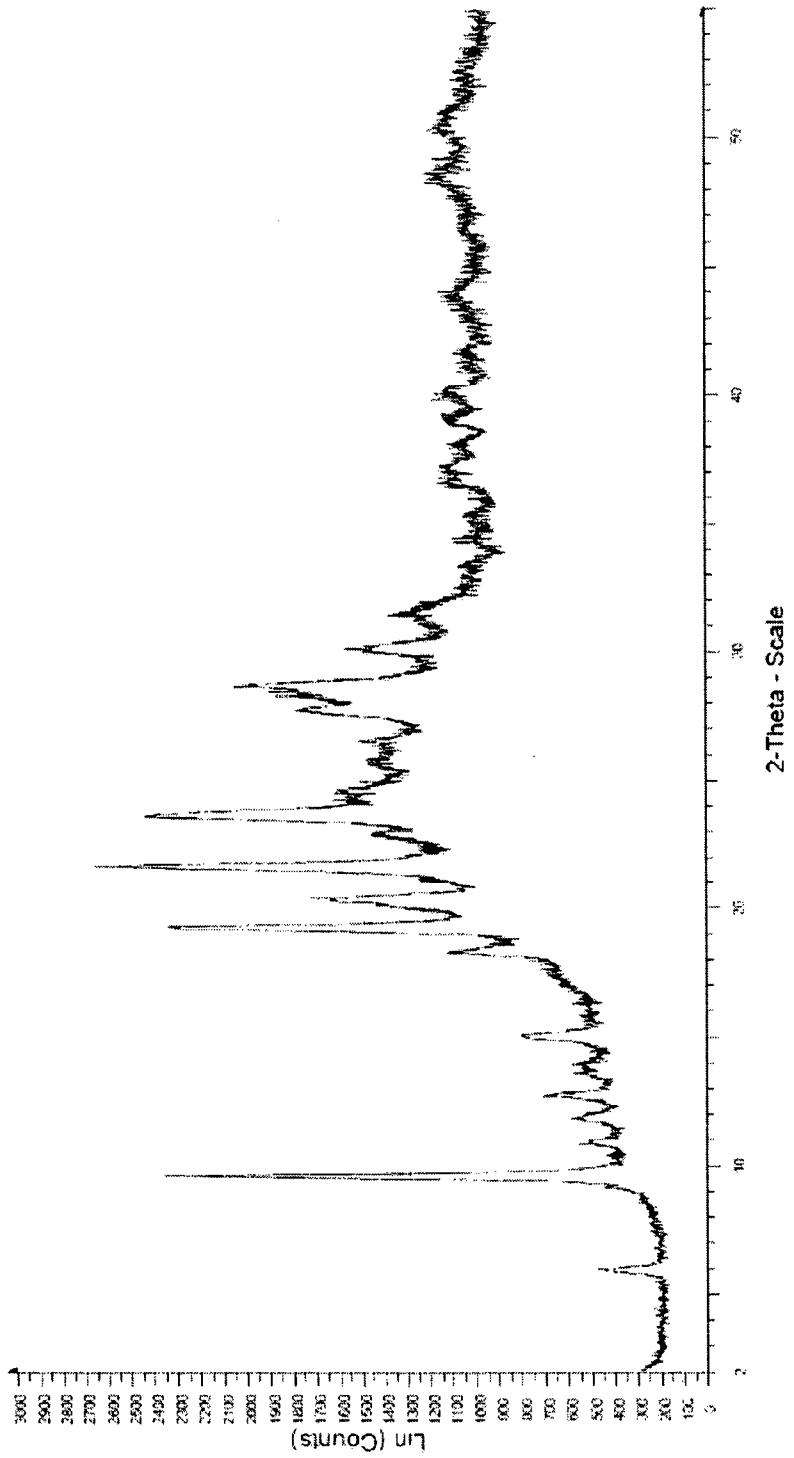


Figure 9

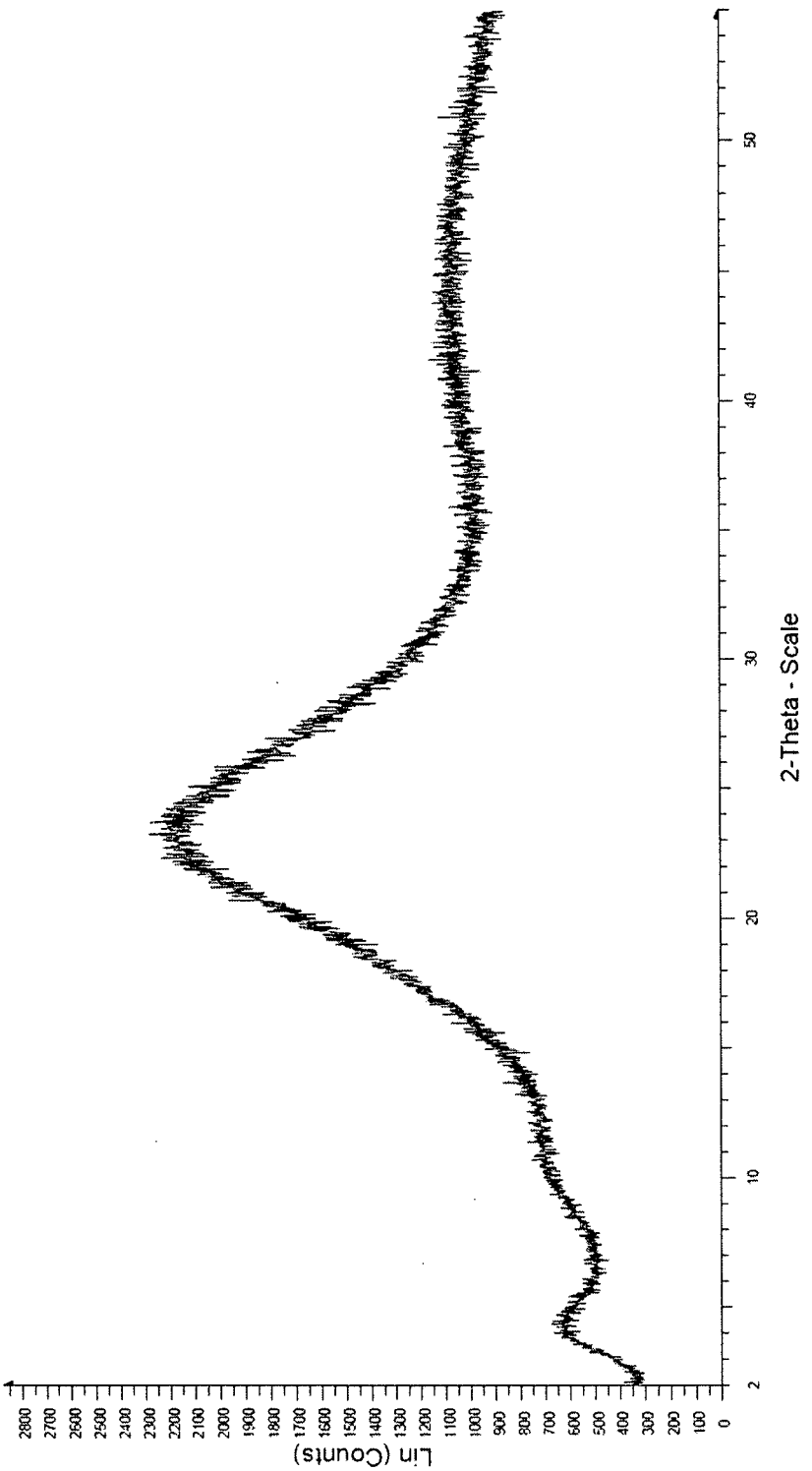
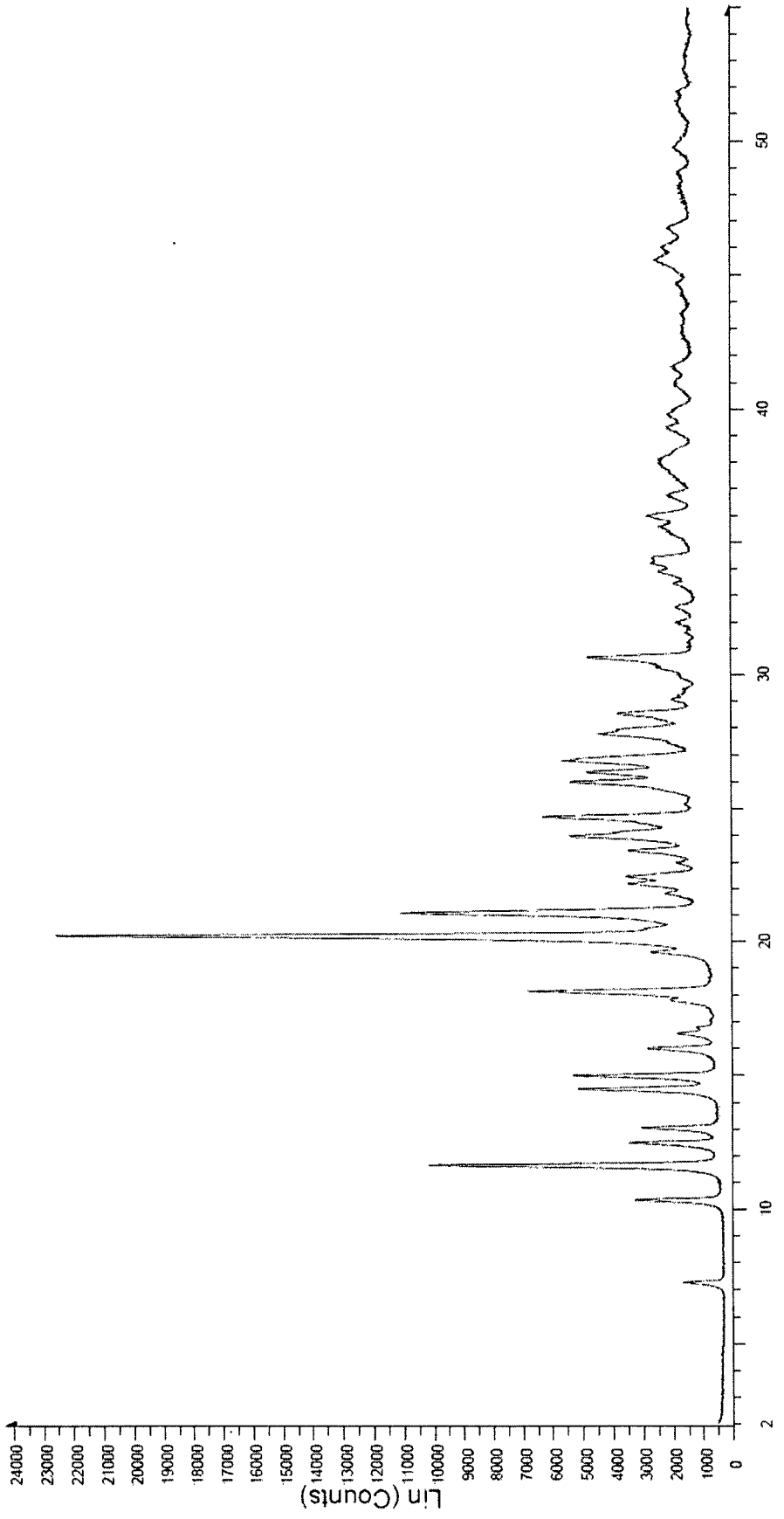

Lin (Counts)
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900
2000
2100
2200
2300
2400
2500
2600
2700
2800
2-Theta - Scale
2
10
20
30
40
50

Figure 10


Lin (Counts)
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23000
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
2
10
20
30
40
50
2-Theta scale

Figure 11

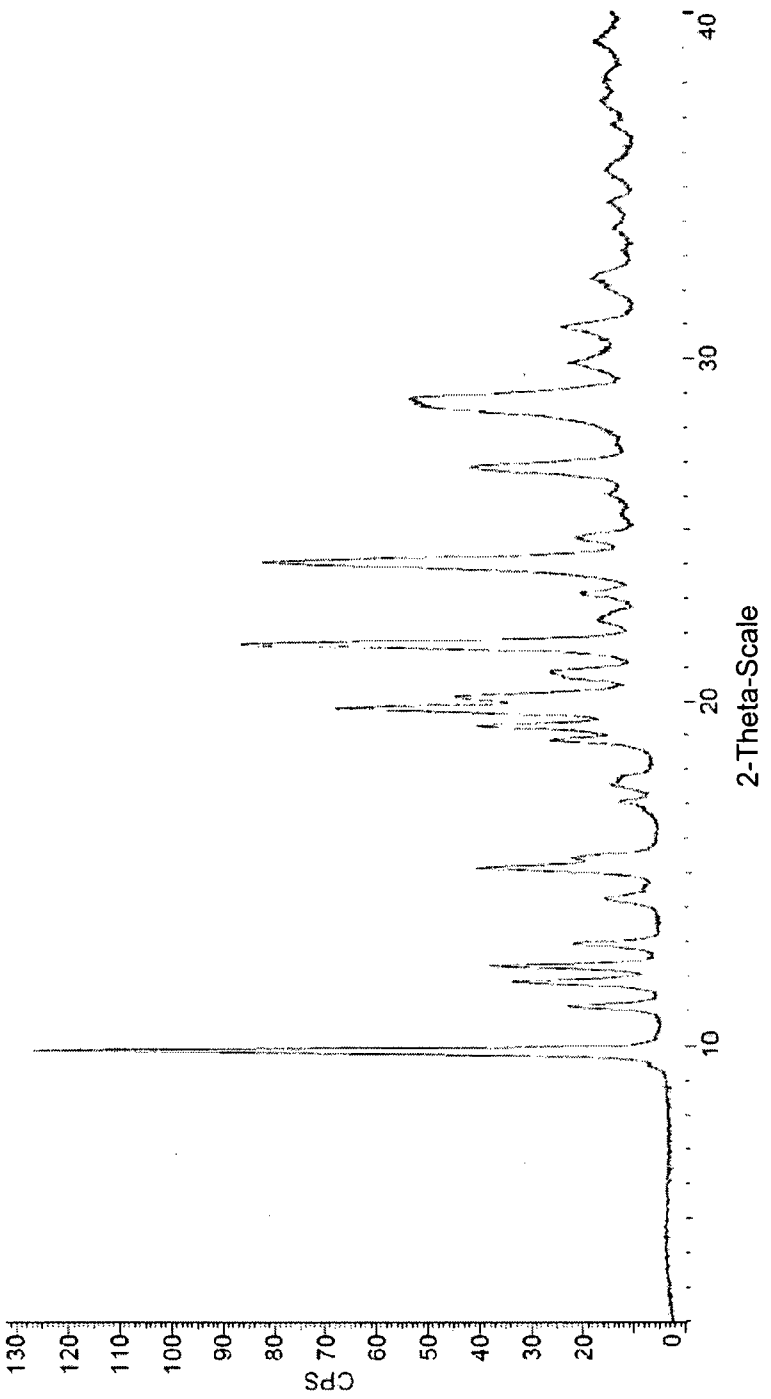
CPS
130
120
110
100
90
80
70
60
50
40
30
20
0
10
20
30
40
2-Theta-Scale

Figure 12

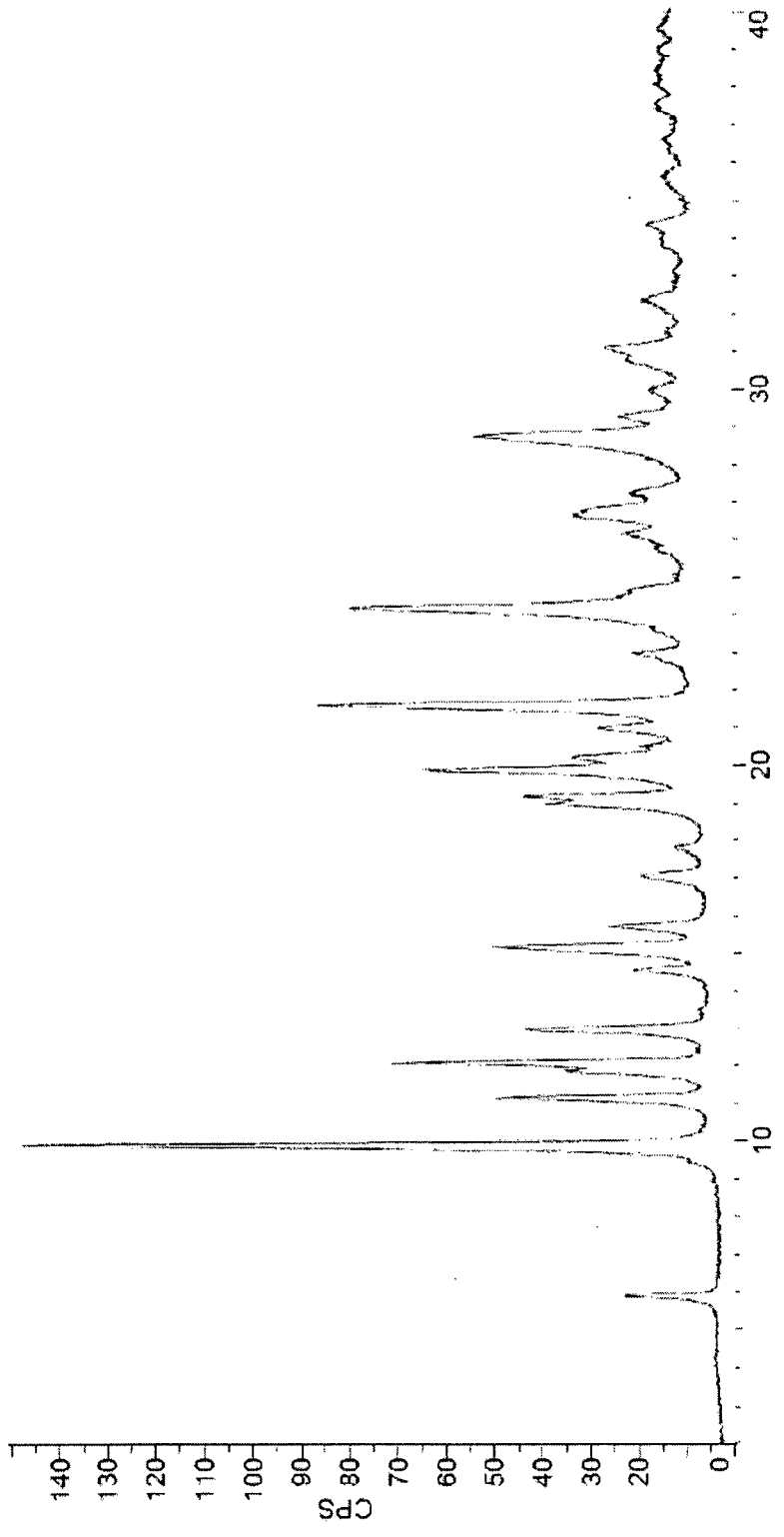
CPS
0
20
30
40
50
60
70
80
90
100
110
120
130
140
10
20
30
40
2-Theta-Scale

Figure 13

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/002484

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D473/34 A61K31/52 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/134288 A1 (GILEAD CALISTOGA LLC [US]) 12 September 2013 (2013-09-12) cited in the application Whole documents specially p. 4, l. 26-27, p. 7, l. 11-12 and p. 27, l. 20-21 and example 12	1-48
X,P	WO 2015/095605 A1 (GILEAD CALISTOGA LLC [US]) 25 June 2015 (2015-06-25) the whole document	1,2,4-7, 44-48

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 February 2016	23/02/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sahagún Krause, H

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2015/002484

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO 2015095605 A1	25-06-2015