(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 July 2010 (01.07.2010)

PCT

(10) International Publication Number
WO 2010/072295 A1

(51) International Patent Classification:
C07D 403/14 (2006.01) *A61P 35/02* (2006.01)
A61K 31/506 (2006.01)

(21) International Application Number:
PCT/EP2009/008358

(22) International Filing Date:
24 November 2009 (24.11.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
08022253.2 22 December 2008 (22.12.2008) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

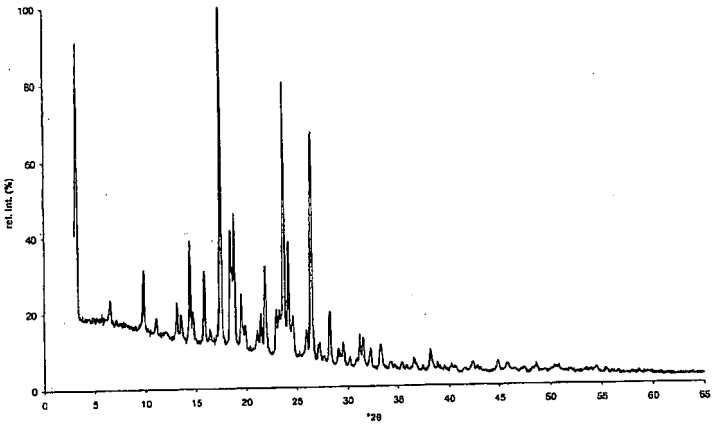
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) **Title**: NOVEL POLYMORPHIC FORMS OF 6-(1-METHYL-1H-PYRAZOL-4-YL)-2-{3-[5-(2-MORPHOLIN-4-YL-ETHOXY)-PYRIMIDIN-2-YL]-BENZYL}-2H-PYRIDAZIN-3-ONE DIHYDROGENPHOSPHATE AND PROCESSES OF MANUFACTURING THEREOF

Figure 1



(57) **Abstract**: The present invention relates to 6-(1-methyl-1 H-pyrazol-4-yl)-2-{3-[5-(2-morpholin- 4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate, its solvates and crystalline modifications thereof. The present invention further relates to processes of manufacturing these crystalline modifications as well as their use in the treatment and/or prophylaxis of physiological and/or pathophysiological conditions, which are caused, mediated and/or propagated by the inhibition, regulation and/or modulation of signal transduction of kinases, in particular by the inhibition of tyrosine kinases, e.g. pathophysiological conditions such as cancer.

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Novel Polymorphic Forms of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one Dihydrogenphosphate and Processes of Manufacturing thereof

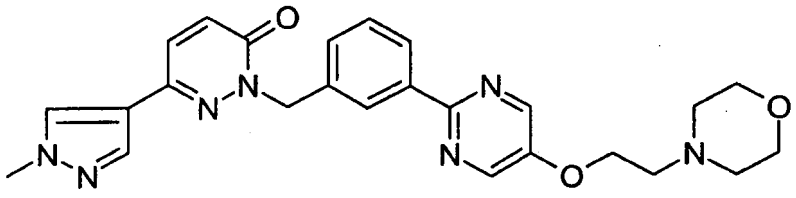
Description

Technical field

The present invention relates to 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate, its solvates and crystalline modifications thereof as well as their medical uses and processes of manufacturing.

Prior art

6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one (I)



(I)

was first described in international patent applications PCT/EP2008/003473, filed on 29 April 2008, and PCT/EP2008/005508, filed on 04 July 2008.

In PCT/EP2008/003473 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one is referred to as compound "A229". Example 38 of PCT/EP2008/003473 describes a first way of synthesizing 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one. p-Toluenesulfonate and phosphate are mentioned as possible salt forms. Besides, example 39 of PCT/EP2008/003473 describes an alternative way of synthesizing 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one. Example 1 of PCT/EP2008/005508 describes the same first way of synthesizing 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one and also mentions p-toluenesulfonate and

phosphate as possible salt forms. Example 2 of PCT/EP2008/005508 refers to sulfate, mesylate, besylate, tosylate, fumurate and maleate as additional salt forms.

Both prior art documents are silent about 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one as a dihydrogenphosphate salt and further do not mention polymorphic forms, crystal modifications or the like of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate.

Certain crystalline, i.e. morphological or polymorphic forms of pharmaceutical compounds may be of interest to those involved in the development of suitable pharmaceutical dosage forms. This is because if a certain polymorphic form is not held constant during clinical and stability studies, the exact dosage used or measured may not be comparable from one batch to the other. Once a pharmaceutical compound is produced for use, it is important to verify the morphological or polymorphic form delivered in each dosage form to assure that the production process delivers the same form and that the same amount of drug is included in each dosage. Therefore, it is imperative to assure that either a single morphological or polymorphic form or a known combination of morphological or polymorphic forms is present. In addition, certain morphological or polymorphic forms may exhibit enhanced thermodynamic stability and may be more suitable than other morphological or polymorphic forms for inclusion in pharmaceutical formulations.

The citation of any reference in this application is not an admission that the reference is relevant prior art to this application.

Description of the invention

The present invention has the object to provide novel salt forms of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one as well as novel polymorphic forms thereof.

The object of the present invention has surprisingly been solved in one aspect by providing 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate.

The object of the present invention has surprisingly been solved in another aspect by providing 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate solvate, preferably 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate.

It has been found that 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate is able to form solvates in crystalline modifications. Examples of such solvates include solvates from water, solvates from alcohols such as methanol, ethanol, propan-1-ol or propan-2-ol; solvates from organic esters such as ethyl acetate; solvates from nitriles such as acetonitrile; solvates from ketones such as acetone and butanone; solvates from ethers such as tetrahydrofuran (THF) and solvates from chlorinated hydrocarbons such as chloroform and solvates of hydrocarbons such as n-heptane or toluene. Preferred solvates are formed with polar solvents, preferably water, alcohols, organic esters, nitriles, ketones and ethers.

Preferably, 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate forms anhydrates and solvates with water, acetone, tetrahydrofuran, methanol, ethyl acetate or n-heptane in crystalline modifications that means the bound solvent together with 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate build the crystal structure. The molar ratio of the solvent to 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate could vary as known to skilled persons in the art. Preferably, the molar ratio is between 0,25:1 to 2,5:1, more preferably between 0,5:1 to 1:1, most preferably 1:1 (n-heptane solvate 1/15:1). It should be understood that the present anhydrates and solvates of the invention may contain unbound water that is to say water which is other than water of crystallization.

Hence, in a preferred embodiment, 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate solvate, preferably -(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate, is provided in its crystalline modifications.

The object of the present invention has surprisingly been solved in another aspect by providing 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate.

In a preferred embodiment, 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate is provided in its crystalline modification A1, which is characterized by XRD peaks comprising 3.2°, 6.5°, 9.8°, and 13.1° 2θ (all ± 0.1° 2θ, using Cu-Kα_1 radiation).

In a preferred embodiment, 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate is provided in its crystalline modification A1, which is characterized by XRD peaks comprising 18.4°, 18.8°, 23,7°, 24.2°, 26.4°, and 28.2° 2θ (all ± 0.1° 2θ, using Cu-Kα_1 radiation).

In a preferred embodiment, 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate is provided in its crystalline modification A1, which is characterized by XRD peaks comprising 14.4°, 15.8°, 17.5°, 19.5°, and 21.9° 2θ (all ± 0.1° 2θ, using Cu-Kα_1 radiation).

In a preferred embodiment, 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate is provided in its crystalline modification A1, which is characterized by the following XRD data:

Form A1:

Peak No.	d/Å	°2θ (Cu-Kα_1 radiation) ± 0.1°	Indexing (h, k, l)
1	27.45	3.2	(2, 0, 0)
2	13.62	6.5	(4, 0, 0)
3	9.02	9.8	(6, 0, 0)
4	6.75	13.1	(8, 0, 0)
5	6.15	14.4	(-2, 0, 2)
6	5.59	15.8	(-6, 0, 2)
7	5.07	17.5	(-8, 0, 2)

8	4.81	18.4	(9, 1, 0)
9	4.72	18.8	(-9, 1, 1)
10	4.55	19.5	(6, 0, 2)
11	4.06	21.9	(8, 0, 2)
12	3.75	23.7	(11, 1, 1)
13	3.68	24.2	(2, 2, 1)
14	3.37	26.4	(3, 1 3)
15	3.16	28.2	(-15, 1, 2)

The object of the present invention has surprisingly been solved in another aspect by providing 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate.

In a preferred embodiment, 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate is provided in its crystalline modification H1, which is characterized by XRD peaks comprising 3.1°, 9.4°, and 18.8° 2θ (all ± 0.1° 2θ, using Cu-Kα_1 radiation).

In a preferred embodiment, 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate is provided in its crystalline modification H1, which is characterized by XRD peaks comprising 19.1°, 22.8°, and 26.4° 2θ (all ± 0.1° 2θ, using Cu-Kα_1 radiation).

In a preferred embodiment, 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate is provided in its crystalline modification H1, which is characterized by XRD peaks comprising 14.4°, 15.0°, and 17.8° 2θ (all ± 0.1° 2θ, using Cu-Kα_1 radiation).

In a preferred embodiment, 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate is provided in its crystalline modification H1, which is characterized by XRD peaks comprising 14.7°, 18.6°, 23.2°, 23.8°, 26.8°, and 27.6° 2θ (all ± 0.1° 2θ, using Cu-Kα_1 radiation).

In a preferred embodiment, 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate is

provided in its crystalline modification H1, which is characterized by the following XRD data:

Form H1:

Peak No.	d/Å	°2θ (Cu-Kα$_1$ radiation) ± 0.1°	Indexing (h, k, l)
1	28.42	3.1	(1, 0, 0)
2	9.40	9.4	(3, 0, 0)
3	6.13	14.4	(0, 0, 2)
4	6.01	14.7	(2, 1, 1)
5	5.89	15.0	(1, 0, 2)
6	4.97	17.8	(3, 0, 2)
7	4.77	18.6	(4, 1, 1)
8	4.71	18.8	(6, 0, 0)
9	4.64	19.1	(5, 1, 0)
10	3.89	22.8	(2, 2, 0)
11	3.83	23.2	(-1, 2, 1)
12	3.73	23.8	(-2, 2, 1)
13	3.38	26.4	(0, 2, 2)
14	3.33	26.8	(-4, 1, 3)
15	3.22	27.6	(-3, 2, 2)

The object of the present invention has surprisingly been solved in another aspect by providing 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate in its crystalline modification NF3 (crystalline modification NF3 can be a hydrate or an anhydrate), which is characterized by XRD peaks comprising 15.3°, 16.7°, 21.6°, and 23.1° 2θ (all ± 0.1° 2θ, using Cu-Kα$_1$ radiation).

In a preferred embodiment, 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate is provided in its crystalline modification NF3, which is characterized by the following XRD data:

Form NF3:

Peak No.	d/Å	°2θ (Cu-Kα_1 radiation) ± 0.1°
1	27.30	3.2
2	13.62	6.5
3	9.02	9.8
4	6.71	13.2
5	6.11	14,5
6	5.79	15.3
7	5.57	15.9
9	5.32	16.7
9	5.05	17.5
10	4.81	18.4
11	4.58	19.4
12	4.12	21.6
13	4.04	22.0
14	3.84	23.1
15	3.75	23.7
16	3.69	24.1
17	3.37	26.4
18	3.16	28.3

The object of the present invention has surprisingly been solved in another aspect by providing 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate in its crystalline modification NF5, which is characterized by XRD peaks comprising 13.9°, 15.7°, 16.6°, 17.3°, 19.8°, and 22.1° 2θ (all ± 0.1° 2θ, using Cu-Kα_1 radiation).

In a preferred embodiment, 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate is provided in its crystalline modification NF5, which is characterized by the following XRD data:

Form NF5:

Peak No.	d/Å	°2θ (Cu-Kα_1 radiation) ± 0.1°
1	28.54	3.1
2	9.41	9.4
3	6.37	13.9
4	6.10	14.5
5	5.98	14.8
6	5.82	15.2
7	5.62	15.7
9	5.32	16.6
9	5.13	17.3
10	4.96	17.9
11	4.80	18.5
12	4.69	18.9
13	4.63	19.2
14	4.48	19.8
15	4.02	22.1
16	3.90	22.8
17	3.85	23.1
18	3.73	23.9
19	3.38	26.3
20	3.32	26.8
21	3.23	27.6

In the course of the present invention, the term "crystalline modification" is used as a synonym for terms "crystalline form", "polymorphic form", "polymorphic modification", "morphological form" and the like.

The crystalline modifications of the present invention, in particular crystalline modification A1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate, crystalline modification H1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate, crystalline modification NF3 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate (crystalline modification NF3 can be a hydrate or an anhydrate) and crystalline modification NF5 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate are surprisingly characterized by, among others, a reduced hygroscopicity, a better compressibility during the tableting process, a prolonged shelf life, a better thermodynamic stability, i.e. stability against heat and humidity, a better resistance to sunlight, i.e. UV-light, an increased bulk density, an improved solubility, bioavailability characteristics which are constant from one batch to the other, better flow and handling properties in the tableting process, an improved colour stability and better filtration properties in the production process. Therefore, by use of the crystalline modifications of the present invention, it is possible to obtain pharmaceutical formulations with improved homogeneity, stability, purity and uniformity from one batch to the other.

Furthermore, crystalline modification A1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate shows superior properties for drying purposes (no loss of hydrate water can occur) and exhibits a superior behavior in terms of physical stability over varying relative humidity (RH) conditions (physical stable form in the humidity range 0% up to at least 70% RH) as compared to crystalline modification H1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate and and crystalline modification NF5 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate. Furthermore, crystalline modification A1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate can be considered the thermodynamically more stable form in comparison with crystalline modification NF3 of

6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate, as shown by competitive slurry conversion experiments with binary mixtures of forms A1 and NF3 in several organic solvents at 25 °C and at 50 °C, respectively (see example 10).

In comparison, crystalline modification NF3 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate also shows superior properties for drying purposes (no loss of hydrate water can occur) and exhibits a superior behavior in terms of physical stability over varying relative humidity (RH) conditions (physical stable form in the humidity range 0% up to at least 70% RH) as compared to crystalline modification H1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate and crystalline modification NF5 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate. Furthermore, crystalline modification NF3 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate exhibits a lower kinetic solubility in a mixture of water:acetone (30:70, v:v, after 2 hours) in comparison with crystalline modification A1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate, which enables a higher yield from crystallization processes in this process-relevant solvent mixture (see example 14).

On the other hand, crystalline modification NF5 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate represents a more stable form at high water activity and hence is beneficial in aqueous dispersion systems compared to crystalline modification A1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate, as shown by a competitive slurry conversion experiment with a binary mixture of forms NF5 and A1 in DI water at 25 °C. (see example 11)

Furthermore, crystalline modification H1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate represents a stable form at high water activity and hence is beneficial in aqueous dispersion systems compared to crystalline modification NF5 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate, as shown by a competitive slurry con-

version experiment and with a binary mixture of forms NF5 and H1 in DI water at 25 °C, resulting in form H1 over time (see example 12). Also, crystalline modification H1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate is beneficial in aqueous dispersion systems compared to crystalline modification NF3 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate, as shown by a competitive slurry conversion experiment and with a binary mixture of forms H1 and NF3 in DI water at 25 °C, resulting in form H1 over time (see example 13).

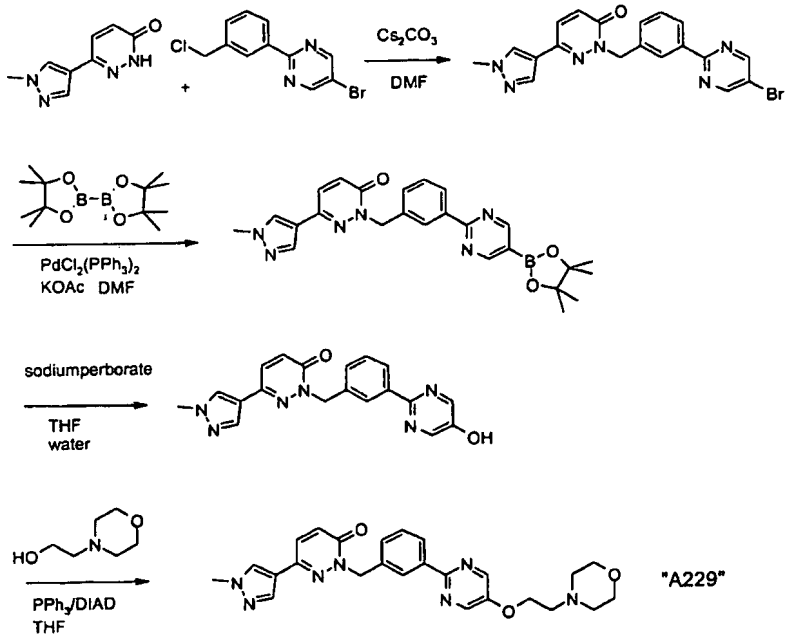
With regard to 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate as compared to 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one (free base), the dihydrogenphosphate salt shows a significantly superior stability in aqueous solution and an improved active pharmaceutical ingredient (API) stability in solution.

The crystalline modifications of the present invention can be characterized according to standard methods which can be found e.g. in Rolf Hilfiker, 'Polymorphism in the Pharmaceutical Industry', Wiley-VCH, Weinheim 2006, and references therein, e.g. X-Ray diffraction (XRD; chapter 6), IR and Raman spectroscopy (chapter 5), Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA) (chaper 3), Water Vapour Sorption Studies (chapter 9), or which can be found e.g. in H.G. Brittain (editor), Polymorphism in Pharmaceutical Solids, Vol. 95, Marcel Dekker Inc., New York 1999 (chapter 6: all there mentioned techniques).

6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate, 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate solvate, preferably 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate, preferably 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate in its crystalline modification, 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate in its crystalline modification NF5, 6-

(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate, 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate in its crystalline modification, 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate in its crystalline modification A1, 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate, 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate in its crystalline modification, 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate in its crystalline modification H1 and 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate in its crystalline modification NF3 are hereinafter referred to as "product(s) of the (present) invention".

6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one (free base) can be synthesized as described in PCT/EP2008/003473, example 38, and PCT/EP2008/005508, example 1, as follows:



A suspension of 7.68 g (43.6 mmol) of 6-(1-methyl-1H-pyrazol-4-yl)-2H-pyridazin-3-one in 90 ml DMF is reacted with 12.4 g (43.6 mmol) of 5-bromo-2-(3-chloromethyl-phenyl)-pyrimidine and 14.2 g (43.6 mmol) of caesium carbonate for 24 hours at room temperature under stirring. The reaction mixture is given to 400 ml water. The resulting precipitate of 2-[3-(5-bromopyrimidin-2-yl)-benzyl]-6-(1-methyl-1H-pyrazol-4-yl)-2H-pyridazin-3-one is sucked off, washed with water and dried in vacuo.

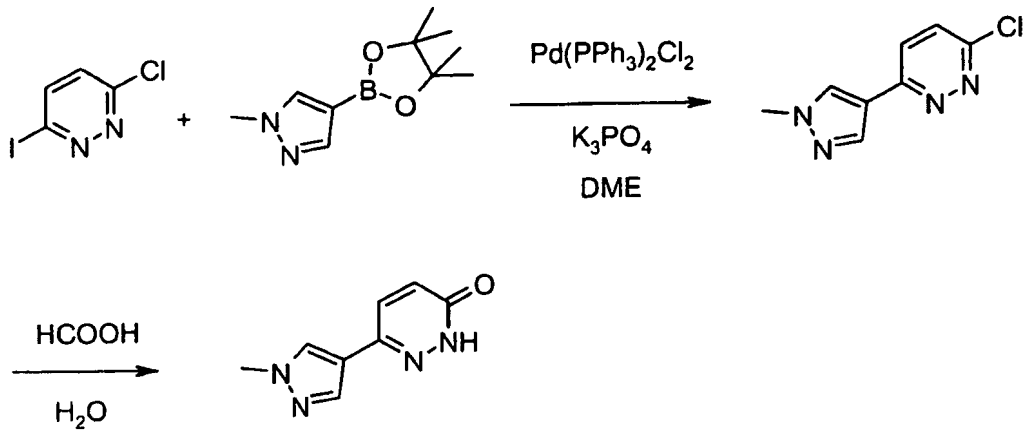
A suspension of 14.0 g (33.0 mmol) of 2-[3-(5-bromopyrimidin-2-yl)-benzyl]-6-(1-methyl-1H-pyrazol-4-yl)-2H-pyridazin-3-one in 65 ml DMF is reacted with 10.9 g (42.9 g) of bis(pinacolato)diboron and 9.72 g (99.0 mmol) of potassium acetate and heated up under nitrogen to 70° C. After 15 minutes of stirring at this temperature 695 mg (0.99 mmol) of bis(triphenylphosphin)-palladium(II)-chloride are added and the reaction mixture is stirred for 18 hours at 70°C under nitrogen. Subsequently, the reaction mixture is allowed to cool down to room temperature, water and dichloromethane are added, and the reaction mixture is filtrated over diatomite/kieselguhr before the organic phase is separated. The organic phase is then dried over sodium sulfate, concentrated and the residue is re-crystallized from 2-propanol to yield 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one.

To a suspension of 13.4 g (28.4 mmol) of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one in 55 ml THF and 55 ml water 8.50 g (85.1 mmol) of sodium perborate is given in portions under ice cooling. The reaction mixture is stirred for two hours at room temperature prior to being sucked off over diatomite/kieselguhr. The filtrate is concentrated in vacuo to approximately half of the original volume and titrated to pH 1 with 2N hydrochloric acid. The resulting precipitate of 2-[3-(5-hydroxy-pyrimidin-2-yl)-benzyl]-6-(1-methyl-1H-pyrazol-4-yl)-2H-pyridazin-3-one is sucked off, washed with water and dried in vacuo.

To a suspension of 360 mg (1.00 mmol) of 2-[3-(5-hydroxy-pyrimidin-2-yl)-benzyl]-6-(1-methyl-1H-pyrazol-4-yl)-2H-pyridazin-3-one in 2 ml THF 394 mg (1.50 mmol) of triphenylphosphine and 242 µl (2.00 mmol) of 4-(2-hydroxyethyl)morpholine are added one after the other. Under ice cooling 294 µl (1.50 mmol) of diisopropylazodicarboxylate are slowly added dropwise. The resulting solution is stirred for 18 hours at room temperature. The reaction mixture is then concentrated in vacuo and the oily residue is dissolved in 2-propanol. The resulting solid of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-

morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one resulted after some time is sucked off, washed with 2-propanol and tert-butylmethylether and dried in vacuo.

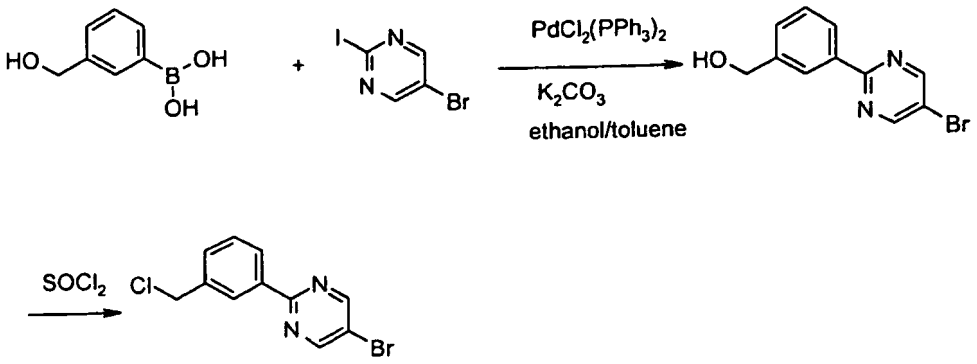
Starting product 6-(1-methyl-1H-pyrazol-4-yl)-2H-pyridazin-3-one can be synthesized as described in PCT/EP2008/003473 (pages 65 to 66) as follows:



A solution of 815 g (3.39 mol) of 3-chloro-6-iodo-pyridazine in 3.8 l of 1,2-dimethoxyethane is reacted with 705 g (3.39 mol) of 1-methyl-1H-pyrazol-4-boronic acid pinacolester and 1.44 kg tripotassiumphosphate trihydrate. The resulting suspension is heated up to 80° C under nitrogen and under stirring and 59.5 g (85 mmol) of bis(triphenylphosphine)-palladium(II)-chloride are added. The reaction mixture is stirred for 3 hours at 80° C. Subsequently, the reaction mixture is allowed to cool down to room temperature and 9 l water are added. The resulting precipitate of 3-chloro-6-(1-methyl-1H-pyrazol-4-yl)-pyridazine is sucked off, washed with water and dried in vacuo.

A suspension of 615 g (2.90 mol) of 3-chloro-6-(1-methyl-1H-pyrazol-4-yl)-pyridazine in a mixture of 1.86 l formic acid and 2.61 l water is heated up to 80° C under stirring and is continued to be stirred for 28 hours at this temperature. The reaction mixture is cooled down to room temperature, active coal (activated charcoal) is added, and the mixture is sucked off. The filtrate is titrated under ice cooling with 40% aqueous caustic soda solution to a pH of 7 and subsequently incubated for 16 hours at 6° C. The resulting precipitate of 6-(1-methyl-1H-pyrazol-4-yl)-2H-pyridazin-3-one is sucked off, washed with water and dried in vacuo.

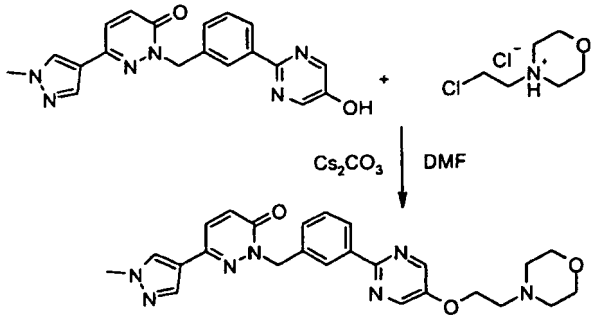
Starting product 5-bromo-2-(3-chloromethyl-phenyl)-pyrimidine can be synthesized as described in PCT/EP2008/003473, example 36, as follows:



A solution of 95.0 g (332 mmol) of 5-bromo-2-iodopyrimidine in 325 ml toluene kept under nitrogen is reacted with a solution of 70.0 g (660 mmol) of sodium carbonate in 325 ml water the mixture being heated up to 80° C. 2.3 g (3.3 mmol) of bis(triphenylphosphine)-palladium(II)-chloride are added to the reaction mixture and subsequently a solution of 50.0 g (329 mmol) of 3-(hydroxymethyl)-benzeneboronic acid in 650 ml ethanol are added dropwise. The reaction mixture is stirred for 18 hours at 80° C. The reaction mixture is cooled down to room temperature and filtrated. The filtrate is reacted with 1 l ethylacetate and 1 l water. The organic phase is separated, dried over sodiumsulfate and concentrated. The residue of [3-(5-bromopyrimidin-2-yl)-phenyl]-methanol is re-crystallized from 2-propanol.

To 159 ml (2.19 mol) of thionylchloride kept at 30° C 116 g (438 mmol) of [3-(5-bromopyrimidin-2-yl)-phenyl]-methanol are given in portions under stirring. The reaction mixture is stirred for 18 hours at room temperature. Subsequently, the reaction mixture is concentrated. The remainder is dissolved in toluene and again concentrated. The procedure is repeated three-times. The final remainder of 5-brom-2-(3-chloromethyl-phenyl)-pyrimidine is re-crystallized from toluene.

Alternatively, 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one (free base) can be synthesized as described in PCT/EP2008/003473, example 39, as follows:



"A229"

A suspension of 360 mg (1.00 mmol) of 2-[3-(5-hydroxy-pyrimidin-2-yl)-benzyl]-6-(1-methyl-1H-pyrazol-4-yl)-2H-pyridazin-3-one, 195 mg (1.05 mmol) of N-(2-chloroethyl)-morpholiniumchloride and 521 mg (1.60 mmol) of caesium carbonate in 2 ml DMF is heated up to 80° C under stirring and is continued to be stirred for 6 hours at this temperature. Subsequently, the reaction mixture is allowed to cool down and 50 ml water are added. The resulting precipitate of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one is sucked off, washed with water and dried in vacuo.

In another aspect of the invention, a pharmaceutical composition comprising a therapeutically effective amount of at least one product of the invention is provided.

In a preferred embodiment, the pharmaceutical composition further comprises at least one additional compound selected from the group consisting of physiologically acceptable excipients, auxiliaries, adjuvants, diluents, carriers and/or additional pharmaceutically active substances other than the products of the invention.

A further embodiment of the present invention is a process for the manufacture of said pharmaceutical compositions, characterized in that one or more products of the invention and one or more compounds selected from the group consisting of solid, liquid or semiliquid excipients, auxiliaries, adjuvants, diluents, carriers and pharmaceutically active substances other than the products of the invention, are converted in a suitable dosage form.

As used herein, the term "effective amount" refers to any amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, sys-

tem, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

In another aspect of the invention, a medicament comprising at least one product of the invention or a pharmaceutical composition as described herein is provided.

In a further aspect of the invention, a medicament as described herein for use in the treatment and/or prophylaxis of physiological and/or pathophysiological conditions, which are caused, mediated and/or propagated by the inhibition, regulation and/or modulation of signal transduction of kinases, in particular by the inhibition of tyrosine kinases, preferably Met-kinase, is provided. A corresponding use for the preparation of a medicament for the treatment and/or prophylaxis of the aforementioned conditions is intended to be comprised.

In a further aspect of the invention, a medicament as described herein for use in the treatment and/or prophylaxis of physiological and/or pathophysiological conditions selected from the group consisting of: "cancer, tumour, malignant tumours, benign tumours, solid tumours, sarcomas, carcinomas, hyperproliferative disorders, carcinoids, Ewing sarcomas, Kaposi sarcomas, brain tumours, tumours originating from the brain and/or the nervous system and/or the meninges, gliomas, glioblastomas, neuroblastomas, stomach cancer, kidney cancer, kidney cell carcinomas, prostate cancer, prostate carcinomas, connective tissue tumours, soft tissue sarcomas, pancreas tumours, liver tumours, head tumours, neck tumours, laryngeal cancer, oesophageal cancer, thyroid cancer, osteosarcomas, retinoblastomas, thymoma, testicular cancer, lung cancer, lung adenocarcinoma, small cell lung carcinoma, bronchial carcinomas, breast cancer, mamma carcinomas, intestinal cancer, colorectal tumours, colon carcinomas, rectum carcinomas, gynaecological tumours, ovary tumours/ovarian tumours, uterine cancer, cervical cancer, cervix carcinomas, cancer of body of uterus, corpus carcinomas, endometrial carcinomas, urinary bladder cancer, urogenital tract cancer, bladder cancer, skin cancer, epithelial tumours, squamous epithelial carcinoma, basaliomas, spinaliomas, melanomas, intraocular melanomas, leukaemias, monocyte leukaemia, chronic leukaemias, chronic myelotic leukaemia, chronic lymphatic leukemia, acute

leukaemias, acute myelotic leukaemia, acute lymphatic leukaemia and/or lymphomas" is provided. A corresponding use for the preparation of a medicament for the treatment and/or prophylaxis of the aforementioned conditions is intended to be comprised.

In another aspect of the invention, a medicament as described herein is provided, wherein in such medicament comprises at least one additional pharmacologically active substance (drug, ingredient).

In a preferred embodiment the at least one pharmacologically active substance is a substance as described herein.

In another aspect of the invention, a medicament as described herein is provided, wherein the medicament is applied before and/or during and/or after treatment with at least one additional pharmacologically active substance.

In a preferred embodiment the at least one pharmacologically active substance is a substance as described herein.

In a further aspect of the invention, a kit comprising a therapeutically effective amount of at least one product of the invention and/or at least one pharmaceutical composition as described herein and a therapeutically effective amount of at least one further pharmacologically active substance other than the products of the invention is provided.

Products of the invention may be used in combination with one or more other pharmacologically active substances (ingredients, drugs) in the treatment, prevention, suppression or amelioration of diseases or conditions for which products of the invention or the other substances have utility. Typically the combination of the drugs is safer or more effective than either drug alone, or the combination is safer or more effective than would it be expected based on the additive properties of the individual drugs. Such other drug(s) may be administered, by a route and in an amount commonly used contemporaneously or sequentially with a product of the invention. When a product of the invention is used contemporaneously with one or more other drugs, a combination product containing such other drug(s) and the product of the invention is preferred. However, combination therapy also includes therapies in which the product of the invention and one or more other drugs are administered on different overlapping schedules. It is contemplated that when used in combination with other active ingredients, the

product of the present invention or the other active ingredient or both may be used effectively in lower doses than when each is used alone. Accordingly, the pharmaceutical compositions of the present invention (pharmaceutical compositions as described herein) include those that contain one or more other active ingredients, in addition to a product of the invention.

Examples of other pharmacologically active substances (ingredients, drugs) that may be administered in combination with a product of the invention, and either administered separately or in the same pharmaceutical composition, include, but are not limited to the compounds classes and specific compounds listed in Table 1:

Table 1

Alkylating agents	Cyclophosphamide	Lomustine
	Busulfane	Procarbazine
	Ifosfamide	Altretamine
	Melphalane	Estramustinphosphate
	Hexamethylmelamine	Mechlorethamine
	Thiotepa	Streptozocine
	Chlorambucil	Temozolomide
	Dacarbazine	Semustine
	Carmustine	
Platinum agents	Cisplatin	Carboplatin
	Oxaliplatin	ZD-0473 (AnorMED)
	Spiroplatin	Lobaplatin (AeternaZentaris)
	Carboxyphthalatoplatinum	Satraplatin (Johnson Matthey)
	Tetraplatin	BBR-3464 (Hoffrnann-La Roche)
	Ormiplatin	SM-11355 (Sumitomo)
	Iproplatin	AP-5280 (Access)
Antimetabolites	Azacytidine	Tomudex
	Gemcitabine	Trimetrexate
	Capecitabine	Deoxycoformycine

	5-Fluoruracil	Fludarabine
	Floxuridine	Pentostatine
	2-Chlordesoxyadenosine	Raltitrexede
	6-Mercaptopurine	Hydroxyurea
	6-Thioguanine	Decitabine (SuperGen)
	Cytarabine	Clofarabine (Bioenvision)
	2-Fluordesoxycytidine	Irofulven (MGI Pharma)
	Methotrexate	DMDC (Hoffmann-La Roche)
	Idatrexate	Ethinylcytidine (Taiho)
Topoisomerase inhibitors	Amsacrine	Rubitecane (SuperGen)
	Epirubicine	Exatecanmesylate (Daiichi)
	Etoposide	Quinamed (ChemGenex)
	Teniposide or Mitoxantrone	Gimatecane (Sigma- Tau)
	Irinotecane (CPT-11)	Diflomotecane (Beaufour-Ipsen)
	7-Ethyl-10-hydroxycamptothecine	TAS-103 (Taiho)
	Topotecane	Elsamitrucine (Spectrum)
	Dexrazoxanet (TopoTarget)	J-107088 (Merck & Co)
	Pixantrone (Novuspharma)	BNP-1350 (BioNumerik)
	Rebeccamycin-Analogue (Exelixis)	CKD-602 (Chong Kun Dang)
	BBR-3576 (Novuspharrna)	KW-2170 (Kyowa Hakko)
Antitumor antibiotics	Dactinomycin (Actinomycin D)	Amonafide
	Doxorubicin (Adriamycin)	Azonafide
	Deoxyrubicin	Anthrapyrazole
	Valrubicin	Oxantrazole
	Daunorubicin (Daunomycin)	Losoxantrone
	Epirubicin	Bleomycinsulfate (Blenoxan)
	Therarubicin	Bleomycinacid
	Idarubicin	Bleomycin A
	Rubidazone	Bleomycin B
	Plicamycinp	Mitomycin C
		MEN-10755 (Menarini)

	Porfiromycin Cyanomorpholinodoxorubicin Mitoxantron (Novantron)	GPX-100 (Gem Pharmaceuticals)
Antimitotic agents	Paclitaxel Docetaxel Colchicin Vinblastine Vincristine Vinorelbine Vindesine Dolastatine 10 (NCI) Rhizoxine (Fujisawa) Mivobuline (Warner-Lambert) Cemadotine (BASF) RPR 109881A (Aventis) TXD 258 (Aventis) Epothilon B (Novartis) T 900607 (Tularik) T 138067 (Tularik) Cryptophycin 52 (Eli Lilly) Vinflunine (Fabre) Auristatine PE (Teikoku Hormone) BMS 247550 (BMS) BMS 184476 (BMS) BMS 188797 (BMS) Taxoprexine (Protarga)	SB 408075 (GlaxoSmith-Kline) E7010 (Abbott) PG-TXL (Cell Therapeutics) IDN 5109 (Bayer) A 105972 (Abbott) A 204197 (Abbott) LU 223651 (BASF) D 24851 (ASTA Medica) ER-86526 (Eisai) Combretastatine A4 (BMS) Isohomohalichondrin-B (PharmaMar) ZD 6126 (AstraZeneca) PEG-Paclitaxel (Enzon) AZ10992 (Asahi) IDN-5109 (Indena) AVLB (Prescient NeuroP-harma) Azaepothilon B (BMS) BNP- 7787 (BioNumerik) CA-4-Prodrug (OXiGENE) Dolastatin-10 (NrH) CA-4 (OXiGENE)
Aromatase inhibitors	Aminoglutethimide Letrozole Anastrazole Formestane	Exemestane Atamestane (BioMedicines) YM-511 (Yamanouchi)
Thymidylatesynt-	Pemetrexed (Eli Lilly)	Nolatrexed (Eximias)

hase inhibitors	ZD-9331 (BTG)	CoFactor™ (BioKeys)
DNA antagonists	Trabectedine (PharmaMar) Glufosfamide (Baxter International) Albumin + 32P (Isotope Solutions) Thymectacine (NewBiotics) Edotreotide (Novartis)	Mafosfamide (Baxter International) Apaziquone (Spectrum Pharmaceuticals) O6-Benzylguanine (Paligent)
Farnesyltransferase inhibitors	Arglabine (NuOncology Labs) Ionafarnibe (Schering-Plough) BAY-43-9006 (Bayer)	Tipifarnibe (Johnson & Johnson) Perillylalcohol (DOR BioPharma)
Pump inhibitors	CBT-1 (CBA Pharma) Tariquidar (Xenova) MS-209 (Schering AG)	Zosuquidar-Trihydrochloride (Eli Lilly) Biricodar-Dicitrate (Vertex)
Histoneacetyltransferase inhibitors	Tacedinaline (Pfizer) SAHA (Aton Pharma) MS-275 (Schering AG)	Pivaloyloxymethylbutyrate (Titan) Depsipeptide (Fujisawa)
Metalloproteinase inhibitors / Ribonucleosidereduktase inhibitors	Neovastat (Aeterna Laboratories) Marimastat (British Biotech) Galliummaltolate (Titan) Triapine (Vion)	CMT -3 (CollaGenex) BMS-275291 (Celltech) Tezacitabine (Aventis) Didox (Molecules for Health)
TNF-alpha agonists/ antagonists	Virulizine (Lorus Therapeutics) CDC-394 (Celgene)	Revimide (Celgene)
Endotheline-A re-	Atrasentane (Abbot)	YM-598 (Yamanouchi)

ceptor antagonists	ZD-4054 (AstraZeneca)	
Retinoic acid receptor agonists	Fenretinide (Johnson & Johnson) LGD-1550 (Ligand)	Alitretinoin (Ligand)
Immunomodulators	Interferon Oncophage (Antigenics) GMK (Progenics) Adenocarzinoma vaccine (Biomira) CTP-37 (AVI BioPharma) JRX-2 (Immuno-Rx) PEP-005 (Peplin Biotech) Synchrovax vaccine (CTL Immuno) Melanoma vaccine (CTL Immuno) p21-RAS vaccine (GemVax)	Dexosome therapy (Anosys) Pentrix (Australian Cancer Technology) JSF-154 (Tragen) Cancer vaccine (Intercell) Noreline (Biostar) BLP-25 (Biomira) MGV (Progenics) 13-Alethine (Dovetail) CLL-Thera (Vasogen)
Hormonal and anti-hormonal agents	Estrogens Conjugated Estrogens Ethinylestradiole Chlorotrianisen Idenestrole Hydroxyprogesteroncaproate Medroxyprogesterone Testosterone Testosteronpropionate Fluoxymesterone Methyltestosterone Diethylstilbestrole Megestrole Tamoxifen Toremofine	Prednisone Methylprednisolone Prednisolone Aminoglutethimide Leuprolide Goserelin Leuporelin Cetrorelix Bicalutamide Flutamide Octreotide Nilutamide Mitotane P-04 (Novogen) 2-Methoxyestradiol

	Dexamethasone	(EntreMed) Arzoxifen (Eli Lilly)
Photodynamic agents	Talaporfine (Light Sciences) Theralux (Theratechnologies) Motexafin Gadolinium (Pharmacyclics)	Pd-Bacteriopheophorbide (Yeda) Lutetium-Texaphyrine (Pharmacyclics) Hypericine
Tyrosinkinase inhibitors	Imatinib (Novartis) Leflunomid (Sugen/Pharmacia) ZDI839 (AstraZeneca) Erlotinib (Oncogene Science) Canertjnib (Pfizer) Squalamin (Genaera) SU5416 (Pharmacia) SU6668 (Pharmacia) ZD4190 (AstraZeneca) ZD6474 (AstraZeneca) Vatalanib (Novartis) PKI166 (Novartis) GW2016 (GlaxoSmithKline) EKB-509 (Wyeth) EKB-569 (Wyeth)	Kahalid F (PharmaMar) CEP- 701 (Cephalon) CEP-751 (Cephalon) MLN518 (Millenium) PKC412 (Novartis) Phenoxodiol O Trastuzumab (Genentech) C225 (ImClone) rhu-Mab (Genentech) MDX-H210 (Medarex) 2C4 (Genentech) MDX-447 (Medarex) ABX-EGF (Abgenix) IMC-1C11 (ImClone)
Different agents	SR-27897 (CCK-A inhibitor, Sanofi-Synthelabo) Tocladesine (cyclic-AMP agonist, Ribapharm) Alvocidib (CDK inhibitor, Aventis) CV-247 (COX-2-Inhibitor, Ivy Medical) P54 (COX-2 inhibitor, Phyto-	BCX-1777 (PNP inhibitor, BioCryst) Ranpirnase (Ribonuclease stimulans, Alfacell) Galarubicin (RNA synthesis inhibitor, Dong-A) Tirapazamin (reducing agent, SRI International) N-Acetylcystein (reducing

	pharm)	agent, Zambon)
	CapCell™ (CYP450 stimulans, Bavarian Nordic)	R-Flurbiprofen (NF-kappaB inhibitor, Encore)
	GCS-IOO (gal3 antagonist, GlycoGenesys)	3CPA (NF-kappaB inhibitor, Active Biotech)
	G17DT immunogen (Gastrin inhibitor, Aphton)	Seocalcitol (Vitamin-D receptor agonist, Leo)
	Efaproxiral (Oxygenator, Allos Therapeutics)	131-I-TM-601 (DNA antagonist, TransMolecular)
	PI-88 (Heparanase inhibitor, Progen)	Eflornithin (ODC inhibitor, ILEX Oncology)
	Tesmilifen (Histamine antagonist, YM BioSciences)	Minodronic acid (Osteoclasts inhibitor, Yamanouchi)
	Histamine (Histamine-H2 receptor agonist, Maxim)	Indisulam (p53 stimulans, Eisai)
	Tiazofurin (IMPDH inhibitor, Ribapharm)	Aplidin (PPT inhibitor, PharmaMar)
	Cilengitide (Integrine antagonist, Merck KGaA)	Rituximab (CD20 antibody, Genentech)
	SR-31747 (IL-1 antagonist, Sanofi-Synthelabo)	Gemtuzumab (CD33 antibody, Wyeth Ayerst)
	CCI-779 (mTOR kinase inhibitor, Wyeth)	PG2 (Hematopoesis enhancer, Pharmagenesis)
	Exisulind (PDE-V inhibitor, Cell Pathways)	Immunol™ (Triclosan oral irrigation, Endo)
	CP-461 (PDE-V inhibitor, Cell Pathways)	Triacetyluridine (Uridine prodrug, Wellstat)
	AG-2037 (GART inhibitor, Pfizer)	SN-4071 (sarcoma agent, Signature BioScience)
	WX-UK1 (Plasminogen activator inhibitor, Wilex)	TransMID-107™ (Immunotoxine, KS Biomedix)
	PBI-1402 (PMN stimulans, ProMetic LifeSciences)	PCK-3145 (Apoptosis enhancer, Procyon)
	Bortezomib (Proteasome inhibitor, Millennium)	Doranidazole (Apoptosis enhancer, Pola)

	SRL-172 (T-cell stimulans, SR Pharma) TLK-286 (Glutathione-S-transferase inhibitor, Telik) PT-100 (Growth factor agonist, Point Therapeutics) Midostaurin (PKC inhibitor, Novartis) Bryostatin-1 (PKC stimulans, GPC Biotech) CDA-II (Apoptosis enhancer, Everlife) SDX-101 (Apoptosis enhancer, Salmedix) Ceflatonin (Apoptosis enhancer, ChemGenex)	CHS-828 (cytotoxic agent, Leo) trans-Retinoic acid (Differentiator, NIH) MX6 (Apoptosis enhancer, MAXIA) Apomin (Apoptosis enhancer, ILEX Oncology) Urocidine (Apoptosis enhancer, Bioniche) Ro-31-7453 (Apoptosis enhancer, La Roche) Brostallicin (Apoptosis enhancer, Pharmacia)

In a preferred embodiment, a product of the invention is administered in combination with one or more known anti-tumor agents, such as the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxics, antiproliferative agents, prenyl proteintransferase inhibitors, HMG-CoA-reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, angiogenesis inhibitors.

The products of the invention are in particular well suited for administration in combination with radiotherapy. The synergistic effects of VEGF inhibition in combination with radiotherapy are known to the skilled artisan (WO 00/61186).

The term "estrogen receptor modulators" in the course of the present invention refers to compounds that interfere with or inhibit the binding of estrogen to estrogen receptor – independently from the mode of action. Non-limiting examples of estrogen receptor modulators are tamoxifen, raloxifen, idoxifen, LY353381, LY 117081, toremifen, fulvestrant, 4-[7-(2,2-Dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]phenyl-2,2-dimethyl-propanoate, 4,4'-Dihydroxybenzophenon-2,4-dinitrophenylhydrazone and SH646.

The term "androgen receptor modulators" in the course of the present invention refers to compounds that interfere with or inhibit the binding of androgens to androgen receptor – independently from the mode of action. Non-limiting examples of androgen receptor modulators are finasteride and other 5alpha-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole and abirateron acetate.

The term "retinoid receptor modulators" in the course of the present invention refers to compounds that interfere with or inhibit the binding of retinoids to retinoid receptor – independently from the mode of action. Non-limiting examples of retinoid receptor modulators are bexaroten, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, alpha-difluoromethylornithine, ILX23-7553, trans-N-(4'-Hydroxyphenyl)retinamide and N-4-carboxyphenylretinamide.

The term "cytotoxics" in the course of the present invention refers to compounds that primarily trigger cell death through direct action on cell function(s) or which interfere with or inhibit cell myosis, such as alkylating agents, tumor necrosis factors, intercalating agents, microtubule inhibitors and topoisomerase inhibitors. Non-limiting examples of cytotoxics are tirapazimin, sertenef, cachectine, ifosfamide, tasonermine, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcit, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustin, improsulfan-tosylate, trofosfamide, nimustine, dibrospidium-chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-amindichloro(2-methylpyridine)platin, benzylguanine, glufosfamide, GPX100, (trans,trans,trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platin(II)]bis-[diamine(chloro)platin(II)]-tetrachloride, diarizidinylspermine, arsenium trioxide, 1-(11-Dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantren, mitoxantron, pirarubicin, pinafide, valrubicine, amrubicine, antineoplaston, 3'-desamino-3'-morpholino-13-desoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755 and 4-desmethoxy-3-desamino-3-aziridinyl-4-methylsulfonyl-daunorubicin (WO 00/50032).

Non-limiting examples of microtubule inhibitors are paclitaxel, vindesine-sulfate, 3',4'-dideshydro-4'-desoxy-8'-norvincaleukoblastine, docetaxol, rhizoxine, dolastatine, mivobuline-isethionate, auristatine, cemadotine, RPR109881, BMS184476, vinflunine, cryptophycine, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl)-benzenesulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258 and BMS188797.

Non-limiting examples of topoisomerase inhibitors are topotecane, hycaptamine, irinotecane, rubitecane, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusine, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H)propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo-[de]-pyrano-[3',4':b,7]indolizino[1,2b]quiinoline-10,13(9H,15H)-dione, lurtotecane, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecine, BNP1350, BNPI1100, BN80915, BN80942, etoposide-phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-desoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a,5aB,8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydroxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexohydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylendioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]phenanthridinium, 6,9-bis[(2-aminoethyl)amino]-benzo[g]isoquinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]-acridine-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxane-then-4-ylmethyl]formamide, N-(2-(dimethyl-amino)-ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)-ethyl]amino]-3-hydroxy-7H-indeno[2,1-c]quinolin-7-one and dimesna.

Non-limiting examples of antiproliferative agents are antisense RNA- and antisense-DNA oligonucleotides, such as G3139, ODN698, RVASKRAS, GEM231 and INX3001, as well as antimetabolites scuh as enocitabine, carmofur, tegafur, pentostatine, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabinocfosfate, fosteabine sodiumhydrate, raltitrexed, paltitrexide, emitefur, tiazofurine, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-desoxy-2'-methylidencytidine, 2'-fluoromethylen-2'-desoxycytidine, N-[5-(2,3-dihydrobenzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-desoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidine, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazine-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutaminic acid, aminopterine, 5-fluorouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diaza-tetracyclo-(7.4.1.0.0)-tetradeca-2,4,6-trien-9-ylacetic acid ester, swainsonine, lometrexole, dexrazoxane, methioninase, 2'-cyan-2'-desoxy-N4-palmitoyl-1-B-D-arabinofuranosylcytosine and 3-aminopyridine-2-carboxaldehyde-thiosemicarbazone.

"Antiproliferative agents" also comprises monoclonal antibodies against growth factors that have not been listed under "angiogenesis inhibitors", such as trastuzumab, as well as tumor suppressor genes, such as p53.

The pharmaceutical compositions of the present invention (as described herein) may be administered by any means that achieve their intended purpose. For example, administration may be by oral, parenteral, topical, enteral, intravenous, intramuscular, inhalant, nasal, intraarticular, intraspinal, transtracheal, transocular, subcutaneous, intraperitoneal, transdermal, or buccal routes. Alternatively, or concurrently, administration may be by the oral route. The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired. Parenteral administration is preferred. Oral administration is especially preferred.

Suitable dosage forms include, but are not limited to capsules, tablets, pellets, dragees, semi-solids, powders, granules, suppositories, ointments, creams, lotions, inhalants, injections, cataplasms, gels, tapes, eye drops, solution, syrups, aerosols, suspension, emulsion, which can be produced according to methods known in the art, for example as described below:

tablets: mixing of active ingredient/s and auxiliaries, compression of said mixture into tablets (direct compression), optionally granulation of part of mixture before compression.

capsules: mixing of active ingredient/s and auxiliaries to obtain a flowable powder, optionally granulating powder, filling powders/granulate into opened capsules, capping of capsules.

semi-solids (ointments, gels, creams): dissolving/dispersing active ingredient/s in an aqueous or fatty carrier; subsequent mixing of aqueous/fatty phase with complementary fatty/ aqueous phase, homogenization (creams only).

suppositories (rectal and vaginal): dissolving/dispersing active ingredient/s in carrier material liquified by heat (rectal: carrier material normally a wax; vaginal: carrier normally a heated solution of a gelling agent), casting said mixture into suppository forms, annealing and withdrawal suppositories from the forms.

aerosols: dispersing/dissolving active agent/s in a propellant, bottling said mixture into an atomizer.

In general, non-chemical routes for the production of pharmaceutical compositions and/or pharmaceutical preparations comprise processing steps on suitable mechanical means known in the art that transfer one or more products of the invention into a dosage form suitable for administration to a patient in need of such a treatment. Usually, the transfer of one or more products of the invention into such a dosage form comprises the addition of one or more compounds, selected from the group consisting of carriers, excipients, auxiliaries and pharmaceutical active ingredients other than the products of the invention. Suitable processing steps include, but are not limited to combining, milling, mixing, granulating, dissolving, dispersing, homogenizing, casting and/or compressing the respective active and non-active ingredients. Mechanical means for performing said processing steps are known in the art, for example from Ullmann's Encyclopedia of Industrial Chemistry, 5th Edition. In this respect, active ingredients are preferably at least one product of the invention and one or more additional compounds other than the products of the invention, which show valuable pharmaceutical properties, preferably those pharmaceutical active agents other than the products of the invention, which are disclosed herein.

Particularly suitable for oral use are tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops, suitable for rectal use are suppositories, suitable for parenteral use are solutions, preferably oil-based or aqueous solutions, furthermore suspensions, emulsions or implants, and suitable for topical use are ointments, creams or powders. The products of the invention may also be lyophilised and the resultant lyophilisates used, for example, for the preparation of injection preparations. The preparations indicated may be sterilised and/or comprise assistants, such as lubricants, preservatives, stabilisers and/or wetting agents, emulsifiers, salts for modifying the osmotic pressure, buffer substances, dyes, flavours and/or a plurality of further active ingredients, for example one or more vitamins.

Suitable excipients are organic or inorganic substances, which are suitable for enteral (for example oral), parenteral or topical administration and do not react with the products of the invention, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatine, carbohydrates, such as lactose, sucrose, mannitol, sorbitol or starch (maize starch, wheat starch, rice starch, potato starch), cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, magnesium stearate, talc, gelatine, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, polyvinyl pyrrolidone and/or vaseline.

If desired, disintegrating agents may be added such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries include, without limitation, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings, which, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices or to provide a dosage form affording the advantage of prolonged action, the tablet, dragee or pill can comprise an inner dosage and an outer dosage component me latter being in the form of an envelope over the former. The two components can be separated by an enteric layer, which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, acetyl alcohol, solutions of suitable cellulose preparations such as acetyl-cellulose phthalate, cellulose acetate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

Suitable carrier substances are organic or inorganic substances which are suitable for enteral (e.g. oral) or parenteral administration or topical application and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc and petroleum jelly. In particular, tablets, coated tablets, capsules, syrups, suspensions, drops or suppositories are used for enteral administration, solutions, preferably oily or aqueous solutions, furthermore suspensions, emulsions or implants, are used for parenteral administration, and ointments, creams or powders are used for topical application. The products of the invention can also be lyophilized and the lyophilizates obtained can be used, for example, for the production of injection preparations.

The preparations indicated can be sterilized and/or can contain excipients such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for affecting the osmotic pressure, buffer substances, colorants, flavourings and/or aromatizers.

They can, if desired, also contain one or more further active compounds, e.g. one or more vitamins.

Other pharmaceutical preparations, which can be used orally include push-fit capsules made of gelatine, as well as soft, sealed capsules made of gelatine and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules, which may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils, or liquid paraffin. In addition, stabilizers may be added.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatine.

Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts and alkaline solutions. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400 (the compounds are soluble in PEG-400).

Aqueous injection suspensions may contain substances, which increase the viscosity of the suspension, including, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran, optionally, the suspension may also contain stabilizers.

For administration as an inhalation spray, it is possible to use sprays in which the active ingredient is either dissolved or suspended in a propellant gas or propellant gas mixture (for example CO_2 or chlorofluorocarbons). The active ingredient is advantageously used here in micronized form, in which case one or more additional physiologically acceptable solvents may be present, for example ethanol. Inhalation solutions can be administered with the aid of conventional inhalers.

Possible pharmaceutical preparations, which can be used rectally include, for example, suppositories, which consist of a combination of one or more of the active compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, or paraffin hydrocarbons. In addition, it is also possible to use gelatine rectal capsules, which consist of a combination of the active compounds with a base. Possible base materials include, for example, liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

For use in medicine, the products of the present invention will be in the form of pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the products of the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the products of the invention include acid addition salts which may, for example be formed by mixing a solution of the product of the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the products of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic bases, e.g. quaternary ammonium salts.

The pharmaceutical preparations can be employed as medicaments in human and veterinary medicine. As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function. Said therapeutic effective amount of one or more of the products of the invention is known to the skilled artisan or can be easily determined by standard methods known in the art.

The products of the invention and the additional pharmacologically active substances are generally administered analogously to commercial preparations. Usually,

suitable doses that are therapeutically effective lie in the range between 0.0005 mg and 1000 mg, preferably between 0.005 mg and 500 mg and especially between 0.5 mg and 100 mg per dose unit. The daily dose is preferably between about 0.001 mg/kg and 10 mg/kg of body weight.

Those of skill will readily appreciate that dose levels can vary as a function of the specific compound, the severity of the symptoms and the susceptibility of the subject to side effects. Some of the specific compounds are more potent than others. Preferred dosages for a given compound are readily determinable by those of skill in the art by a variety of means. A preferred means is to measure the physiological potency of a given compound.

For the purpose of the present invention, all mammalian species are regarded as being comprised. In a preferred embodiment, such mammals are selected from the group consisting of "primate, human, rodent, equine, bovine, canine, feline, domestic animals, cattle, livestock, pets, cow, sheep, pig, goat, horse, pony, donkey, hinny, mule, hare, rabbit, cat, dog, guinea pig, hamster, rat, mouse". More preferably, such mammals are humans. Animal models are of interest for experimental investigations, providing a model for treatment of human diseases.

The specific dose for the individual patient depends, however, on the multitude of factors, for example on the efficacy of the specific compounds employed, on the age, body weight, general state of health, the sex, the kind of diet, on the time and route of administration, on the excretion rate, the kind of administration and the dosage form to be administered, the pharmaceutical combination and severity of the particular disorder to which the therapy relates. The specific therapeutic effective dose for the individual patient can readily be determined by routine experimentation, for example by the doctor or physician, which advises or attends the therapeutic treatment.

In the case of many disorders, the susceptibility of a particular cell to treatment with the subject compounds may be determined by in vitro testing. Typically a culture of the cell is combined with a subject compound at varying concentrations for a period of time sufficient to allow the active agents to show a relevant reaction, usually between about one hour and one week. For in vitro testing, cultured cells from a biopsy sample may be used.

The object of the present invention has surprisingly been solved in another aspect by providing a process for manufacturing crystalline modification A1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate comprising the steps:

(a) dissolving or dispersing 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one (free base) or one or more salts thereof in a solvent or a solvent mixture, preferably 2-propanole or chloroform, optionally under stirring,

(b) converting 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one (free base) or one or more salts thereof into the corresponding dihydrogenphosphate salt by addition of aqueous or ethanolic phosphoric acid solution, optionally under stirring,

(c) stirring the resulting dispersion of step (b) at room temperature for one or more hours or days, preferably for 1 or 2 hours,

(d) recovering precipitated 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate by filtration, optionally subsequent washing with a solvent or a solvent mixture, and optionally subsequent drying, preferably in vacuo, optionally at elevated temperature T, preferably 30° C to 95° C, more preferably 70° C.

In the course of the present invention, the terms "elevated temperature" and "elevated temperature T or T_x" (with x = 1, 2, 3 etc.)" refer to an individual specific temperature for a given process step or sub-step that is independent from any other "elevated temperature" and that can be any temperature within the temperature range from "above room temperature" to "boiling temperature" of a given solvent or solvent mixture and/or "melting temperature" of a given solid, educt, intermediate or product or mixture thereof, whatever applies.

In the course of the present invention, the term "one or more salts of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one (free base)" refers to any and all salts, preferably pharmaceutically acceptable salts, of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one (free base), which include, but are not limited to, acetate,

adipate, alginate, arginate, aspartate, benzoate, benzolsulphonate (besylate), bisulphate, bisulphite, bromide, butyrate, bampforat, campforsulphonate, caprylate, chloride, chlorobenzoate, citrate, cyclopentanpropionate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulphate, ethansulphonate, fumarate, galacterate, galacturonate, glucoheptanoate, gluconate, glutamate, glycerophosphate, hemisuccinate, hemisulphate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulphonate, iodide, isothionate, isobutyrate, lactate, lactobionate, malate, maleate, malonate, mandelate, metaphosphate, methansulphonate, methylbenzoate, monohydrogenphosphate, 2-naphthalinsulphonate, nicotinate, nitrate, oxalate, oleate, pamoate, pectinate, persulphate, phenylacetate, 3-phenylpropionate, phosphate, phosphonate, and phthalate.

In the course of the present invention, the term "a solvent or a solvent mixture" refers to any and all solvents, preferably organic solvents and water, more preferably pharmaceutically acceptable organic solvents and water, which include, but are not limited to, methanol, ethanol, 2-propanol, n-btanol, iso-butanol, acetone, methylethylketone, ethylacetate, 1,4-dioxane, diethylether, MTBE, THF, acetonitrile, dichloromethane, chloroform, DMF, cyclohexane, cyclopentane, n-hexane, n-heptane, n-pentane, toluene, o-xylene, p-xylene, DMSO, pyridine, acetic acid, anisole, butylacetate, cumene, ehylformate, formic acid, iso-butylacetate, iso-propylacetate, methylacetate, 3-methyl-1-butanol, methylisobutylketone, 2-methyl-1-propanol, 1-pentanol, propylacetate, ethylenglycole, and 1-methyl-2-pyrrolidone, as well as any and all mixtures of two or more such solvents, preferably binary mixtures, more preferably binary mixtures of water and a pharmaceutically acceptable organic solvent.

The object of the present invention has surprisingly been solved in another aspect by providing a process for manufacturing crystalline modification A1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate comprising the steps:

(a) dispersing 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one (free base) or one or more salts thereof in a solvent or a solvent mixture, preferably in water, and addition of aqueous phosphoric acid solution, optionally under stirring,

(b) heating the resulting dispersion of step (a) up to elevated temperature T1, preferably 30° C to 95° C, more preferably 50°°C, optionally under stirring, and cooling down the resulting solution, preferably to 0° C to 40° C, more preferably to 20°°C, optionally under stirring, before diluting it with a solvent or a solvent mixture, preferably acetone, optionally under stirring,

(c) stirring the resulting dispersion of step (b) at 0° C to 40° C, preferably 10° C, until crystallization is complete and/or incubating it at room temperature for one or more hours or days, optionally under stirring,

(d) recovering precipitated 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate by filtration, optionally cooling down the resulting dispersion of step (c) to 0° C to 20° C, preferably 5° C, prior to filtration optionally under stirring, optionally subsequent washing with a solvent or a solvent mixture, preferably acetone, and optionally subsequent drying, preferably in vacuo, optionally at elevated temperature T2, preferably 30° C to 95° C, more preferably 70° C,

(e) optionally, boiling the resulting dried crystals of step (d) in a solvent or a solvent mixture, preferably ethanol, as dispersion for one or more minutes, preferably 30 minutes, and recovering them by filtration from the hot dispersion.

The object of the present invention has surprisingly been solved in another aspect by providing a process for manufacturing crystalline modification A1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate comprising the steps:

(a) dispersing 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one (free base) or one or more salts thereof in a solvent mixture, preferably in water:acetone mixtures, and addition of aqueous phosphoric acid solution, optionally under stirring,

(b) heating the resulting dispersion of step (a) up to elevated temperature T1, preferably 30° C to 95° C, more preferably 55°C, optionally under stirring, and cooling down the resulting solution, preferably to 0° C to 50° C, optionally under stirring, with a defined cooling rate, preferably 0.1-1 K/min, more preferably 0.1-0.3 K/min, optionally under stirring, until crystallization sets in,

(c) further cooling the resulting dispersion of step (b) preferably to -20° C to 0° C, more preferably to -10°C, optionally under stirring, with a defined cooling rate, preferably 0.1-1 K/min, more preferably 0.1-0.3 K/min, optionally under stirring,

(d) stirring the resulting dispersion of step (c) at -20° C to 40° C, preferably -10° C, until crystallization is complete,

(e) recovering crystallized 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate by filtration, optionally subsequent washing with a solvent or a solvent mixture, preferably acetone, and optionally subsequent drying, preferably in vacuo, optionally at elevated temperature T2, preferably 30° C to 95° C, more preferably 70° C.

The object of the present invention has surprisingly been solved in another aspect by providing a process for manufacturing crystalline modification H1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate comprising the steps:

(a) spreading 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate crystalline modification A1 onto a surface, preferably a bordered surface of a container, more preferably of a Petri dish, and subsequently incubating it in a sealed desiccator over water or aqueous salt solutions with defined relative humidity (RH), preferably 80-100% RH, more preferably 90-100% RH, for one or more days or weeks.

The object of the present invention has surprisingly been solved in another aspect by providing a process for manufacturing crystalline modification H1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate comprising the steps:

(a) dispersing 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate crystalline modification A1 in a mixture of two or more solvents, preferably a binary mixture of water and an organic solvent, where preferably the organic solvent is selected from the group consisting of: "methanol, ethanol, 2-propanol,

acetone, TFH and acetonitrile", optionally under stirring, and stirring the resulting dispersion at elevated temperature T1, preferably 30° C to 95° C, more preferably 50° C, for one or more days or weeks,

(b) recovering precipitated 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate by filtration, optionally subsequent washing with a solvent or a solvent mixture, and optionally subsequent drying, preferably in vacuo, optionally at elevated temperature T2, preferably 30° C to 95° C, more preferably 70° C.

The object of the present invention has surprisingly been solved in another aspect by providing a process for manufacturing crystalline modification NF3 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate comprising the steps:

(a) dispersing or dissolving 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate crystalline modification A1 in a mixture of two or more solvents, preferably a binary mixture, where preferably the solvents are selected from the group consisting of: "water, methanol, ethanol, 2-propanol, acetone, TFH, acetonitrile and 1,4-dioxane", optionally under stirring, and subsequently evaporating the mixture of two or more solvents at room temperature or elevated temperature T1, preferably 30° C to 95° C, more preferably 50° C. until crystallization occurs,

(b) recovering precipitated 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate by filtration, optionally subsequent washing with a solvent or a solvent mixture, and optionally subsequent drying, preferably in vacuo, optionally at elevated temperature T2, preferably 30° C to 95° C, more preferably 70° C.

The object of the present invention has surprisingly been solved in another aspect by providing a process for manufacturing crystalline modification NF5 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate comprising the steps:

(a) dissolving 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate crystalline modification A1 into a binary solvent mixture, preferably water:methanol, most preferably in a ratio of 1:1 (v:v), and quickly evaporating the solvent mixture at elevated temperature, preferably 40-80 °C, most preferably 60 °C, under vacuum until a precipitate is obtained,

(b) optionally further spreading the precipitate obtained from step (a) as a powder onto a surface, preferably a bordered surface of a container, more preferably of a Petri dish, and subsequently incubating it in a sealed desiccator over water or aqueous salt solutions with defined relative humidity (RH), preferably 80-100% RH, more preferably 90-100% RH, for one or more days or weeks.

The object of the present invention has surprisingly been solved in another aspect by providing a process for manufacturing crystalline modification NF5 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate comprising the step:

(a) spreading 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate crystalline form NF3 as a powder onto a surface, preferably a bordered surface of a container, more preferably of a Petri dish, and subsequently incubating it in a sealed desiccator over water or aqueous salt solutions with defined relative humidity (RH), preferably 80-100% RH, more preferably 90-100% RH, for one or more days or weeks.

Brief description of the drawings

Figure 1 depicts the powder X-ray diffractogram of crystalline modification A1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate.

Figure 2 depicts single crystal X-Ray Structure data of crystalline modification A1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate viewed along b-axis.

Figure 3 depicts the FT-IR spectrum of crystalline modification A1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate.

Figure 4 depicts the FT-Raman spectrum of crystalline modification A1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate.

Figure 5 depicts the DSC scan profile (Perkin-Elmer Diamond DSC, 5 K/min, nitrogen purge gas 50 mL/min) of crystalline modification A1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate.

Figure 6 depicts the TGA scan profile (Perkin-Elmer Pyris TGA1, 5 K/min, nitrogen purge gas 50 mL/min) of crystalline modification A1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate.

Figure 7 depicts the Water Vapour Sorption Isotherm (25 °C) (SMS DVS 1) of crystalline modification A1, type a, of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate.

Figure 8 depicts the Water Vapour Sorption Isotherm (25 °C) (SMS DVS 1) of crystalline modification A1, type b, of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate.

Figure 9 depicts the powder X-ray diffractogram of crystalline modification H1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate.

Figure 10 depicts single crystal X-Ray Structure data of crystalline modification H1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate.

Figure 11 depicts the FT-IR spectrum of crystalline modification H1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate.

Figure 12 depicts the DSC scan profile (Perkin-Elmer Diamond DSC, 5 K/min, nitrogen purge gas 50 mL/min) of crystalline modification H1 of 6-(1-methyl-1H-pyrazol-

4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate.

Figure 13 depicts the TGA scan profile (Perkin-Elmer Pyris TGA1, 5 K/min, nitrogen purge gas 50 mL/min) of crystalline modification H1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate.

Figure 14 depicts the Water Vapour Sorption Isotherm (25 °C) (SMS DVS Intrinsic) of crystalline modification H1 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate.

Figure 15 depicts the powder X-ray diffractogram of crystalline modification NF3 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate.

Figure 16 depicts the FT-IR spectrum of crystalline modification NF3 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate.

Figure 17 depicts the FT-Raman spectrum of crystalline modification NF3 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate.

Figure 18 depicts the DSC scan profile (Perkin-Elmer Diamond DSC, 5 K/min, nitrogen purge gas 50 mL/min) of crystalline modification NF3 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate.

Figure 19 depicts the TGA scan profile (Perkin-Elmer Pyris TGA1, 5 K/min, nitrogen purge gas 50 mL/min) of crystalline modification NF3 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate.

Figure 20 depicts the Water Vapour Sorption Isotherm (25 °C) (SMS DVS Intrinsic) of crystalline modification NF3 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate.

Figure 21 depicts the powder X-ray diffractogram of crystalline modification NF5 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate.

Figure 22 depicts the DSC scan profile (Perkin-Elmer Diamond DSC, 5 K/min, nitrogen purge gas 50 mL/min) of crystalline modification NF5 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate.

Figure 23 depicts the TGA scan profile (Perkin-Elmer Pyris TGA1, 5 K/min, nitrogen purge gas 50 mL/min) of crystalline modification NF5 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate.

Figure 24 depicts the Water Vapour Sorption Isotherm (25 °C) (SMS DVS Intrinsic) of crystalline modification NF5 of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate.

Even without further details, it is assumed that a person skilled in the art will be able to utilise the above description in the broadest scope. The preferred embodiments should therefore merely be regarded as descriptive disclosure, which is absolutely not limiting in any way.

The contents of all cited references are hereby incorporated by reference in their entirety. The invention is explained in more detail by means of the following examples without, however, being restricted thereto.

Examples

Example 1:

Production of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate in its crystalline modification A1

Method 1

Approx. 118 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one (free base) were dissolved in approx. 7 mL warm 2-propanole. After addition of approx. 0.017 mL aqueous phosphoric acid solution (85%), precipitation occurred. The dispersion was agitated for 2 hours at room temperature, and subsequently filtered. The resulting crystals were dried under vacuum at 70 °C.

^{1}H-NMR (d_6-DMSO): δ [ppm] = 2.50 (m, 4H + DMSO), 2.75 (t, 2H), 3.57 (t, 4H), 3.87 (s, 3H), 4.30 (t, 2H), 5.34 (s, 2H), 7.05 (d, 1H), 7.44 (m, 2H), 7.80 (d, 1H), 7.89 (s, 1H), 8.21 (m, 2H), 8.28 (m, 1H), 8.65 (s, 2H).

Ion Chromatography: 19.3 wt% Phosphate (equivalent to molar acid:base ratio of 1.14)

Method 2

Approx. 500 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one (free base) were dissolved in approx. 10 mL chloroform. After addition of approx. 2.1 mL ethanolic phosphoric acid solution (0.5 mmol/L), the dispersion was agitated for 1 h at room temperature. The resulting precipitate was filtered and the harvested crystals were dried under vacuum at 70 °C.

^{1}H-NMR (d_6-DMSO): δ [ppm] = 2.55 (m, 4H), 2.80 (t, 2H), 3.60 (m, 4H), 3.88 (s, 3H), 4.33 (t, 2H), 5.35 (s, 2H), 7.07 (d, 1H), 7.46 (m, 2H), 7.82 (d, 1H), 7.90 (s, 1H), 8.23 (m, 2H), 8.30 (m, 1H), 8.65 (s, 2H).

Ion Chromatography: 14.9 wt% Phosphate (equivalent to molar acid:base ratio of 0.88)

Method 3

Approx. 354 g of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one (free base) were dispersed in approx. 450 mL DI water at 23 °C. After addition of approx. 57.3 mL aqueous phosphoric acid solution (85%), the dispersion was heated to 50 °C, resulting in a clear solution. The solution was cooled down to 20 °C, and diluted with approx. 1.2 L acetone, resulting in crystallisation. The dispersion was agitated at 10 °C until the crystallisation was completed. The dispersion was left at room temperature for several days and subsequently cooled down to 5 °C and filtered. The resulting crystals were washed with acetone and dried under vacuum at 70 °C. The dried crystals were subsequently boiled in ethanol as dispersion for 30 minutes, and filtrated from the hot dispersion.

^{1}H-NMR (d_6-DMSO): δ [ppm] = 2.50 (m, 4H + DMSO), 2.74 (t, 2H), 3.58 (m, 4H), 3.87 (s, 3H), 4.32 (t, 2H), 5.34 (s, 2H), 7.05 (d, 1H), 7.45 (m, 2H), 7.82 (d, 1H), 7.89 (s, 1H), 8.22 (m, 2H), 8.28 (m, 1H), 8.65 (s, 2H).

Ion Chromatography: 19.5 wt% Phosphate (equivalent to molar acid:base ratio of 1.15)

Method 4

Approx. 1.1 kg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one (free base) were dispersed in approx. 1.37 L DI water at 23 °C. After addition of approx. 240 mL aqueous phosphoric acid solution (85%), the dispersion was heated to 50 °C, resulting in a clear solution. The solution was cooled down to 20 °C, and slowly diluted with approx. 1 L acetone under agitation, resulting in beginning crystallisation. Another approx. 3 L acetone were slowly added, resulting in a white dispersion, which was agitated at room temperature over night. The dispersion was filtered, and resulting crystals were washed with Acetone and dried under vacuum at 70 °C.

^{1}H-NMR (d_6-DMSO): δ [ppm] = 2.50 (m, 4H + DMSO), 2.74 (t, 2H), 3.57 (m, 4H), 3.87 (s, 3H), 4.30 (t, 2H), 5.34 (s, 2H), 7.05 (d, 1H), 7.45 (m, 2H), 7.82 (d, 1H), 7.89 (s, 1H), 8.22 (m, 2H), 8.28 (m, 1H), 8.64 (s, 2H).

Ion Chromatography: 16.8 wt% Phosphate (equivalent to molar acid:base ratio of 0.99)

Method 5

Approx. 100 g of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one (free base) were dispersed in approx. 171.4 g DI water at 23 °C. After addition of approx. 36.55 g aqueous phosphoric acid solution (85%), the solution was filtered. The resulting filtrate was diluted with approx. 331.05 g acetone, resulting in a dispersion. The dispersion was heated to 55 °C, resulting in a clear solution. The solution was cooled down to -10 °C with a defined cooling rate of 0.3 K/min, resulting in a dispersion, which was post-slurried at -10 °C for one hour. The dispersion was filtered, and resulting crystals were washed with acetone and dried under vacuum at 70 °C.

^{1}H NMR (500 MHz, DMSO) δ = 8.64 (s, 2H), 8.31 – 8.26 (m, 1H), 8.25 – 8.19 (m, 2H), 7.89 (s, 1H), 7.81 (d, *J*=9.6, 1H), 7.53 – 7.38 (m, 2H), 7.05 (d, *J*=9.6, 1H), 5.33 (s, 2H), 4.31 (t, *J*=5.6, 2H), 3.87 (s, 3H), 3.65 – 3.52 (m, 4H), 2.75 (t, *J*=5.6, 2H), 2.50 (m, 4H)

Ion Chromatography: 17.7 wt% Phosphate (equivalent to molar acid:base ratio of 1.04)

Method 6

Approx. 15.2 kg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one (free base) were dispersed in approx. 31 kg DI water at T<30 °C. After addition of approx. 5.5 kg aqueous phosphoric acid solution (85%), the solution was slurried for 30 minutes, and subsequently filtered. The resulting filtrate was diluted at 25 °C with approx. 55.8 kg acetone, resulting in a dispersion. The dispersion was heated to 62 °C, resulting in a clear solution. The solution was cooled down to 50 °C (thermostate jacket temperature) with a defined cooling rate of 0.1 K/min, and slurried for approx. 6.5 hours, until a turbid dispersion was resulting. The dispersion was further cooled down to -10 °C (thermostate jacket temperature) with a defined cooling rate of 0.1 K/min, and post-slurried for approx. 1 hour at this temperature. The dispersion was filtered, and resulting crystals were washed with acetone and dried under vacuum at 70 °C.

^{1}H NMR (500 MHz, DMSO) δ = 8.65 (s, 2H), 8.35 – 8.26 (m, 1H), 8.25 – 8.19 (m, 2H), 7.89 (s, 1H), 7.81 (d, *J*=9.6, 1H), 7.53 – 7.38 (m, 2H), 7.06 (d, *J*=9.6, 1H), 5.34 (s, 2H), 4.33 (t, *J*=5.5, 2H), 3.87 (s, 3H), 3.69 – 3.52 (m, 4H), 2.82 (t, *J*=5.4, 2H), 2.64 – 2.53 (m, 4H).

Ion Chromatography: 17.1 wt% Phosphate (equivalent to molar acid:base ratio of 1.01)

Example 2:

Production of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate in its crystalline modification H1

Method 1

Approx. 400 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate in its crystalline modification A1 were spread onto a Petri dish and stored in a closed desiccator over pure DI water (100% relative humidity atmosphere) for 2 weeks.

^{1}H-NMR (d_6-DMSO): δ [ppm] = 2.50 (m, 4H + DMSO), 2.74 (t, 2H), 3.57 (m, 4H), 3.87 (s, 3H), 4.30 (t, 2H), 5.34 (s, 2H), 7.05 (d, 1H), 7.45 (m, 2H), 7.82 (d, 1H), 7.89 (s, 1H), 8.22 (m, 2H), 8.29 (m, 1H), 8.65 (s, 2H).

Ion Chromatography: 17.1 wt% Phosphate (equivalent to molar acid:base ratio of 1.08 based on phosphate salt with observed water content as specified below).

Karl-Fischer-Titration: 6.5 wt% water.

Method 2

Approx. 45 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate in its crystalline modification A1 were dispersed in approx. 0.2 mL of a binary mixture DI water/ethanol (1:1, v/v), and shaken as slurry at 50 °C at 1000 rpm for 7 days. The dispersion was then filtered and resulting crystals were dried at ambient conditions on the filter.

Method 3

Approx. 45 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate in its crystalline modification A1 were dispersed in approx. 0.2 mL of a binary mixture DI water/methanol (1:1, v/v), and shaken as slurry at 50 °C at 1000 rpm for 7 days. The dispersion was then filtered and resulting crystals were dried at ambient conditions on the filter.

Method 4

Approx. 50 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate in its crystalline modification A1 were dispersed in approx. 0.2 mL of a binary mixture DI water/2-propanole (1:1, v/v), and shaken as slurry at 50 °C at 1000 rpm for 7 days. The dispersion was then filtered and resulting crystals were dried at ambient conditions on the filter.

Method 5

Approx. 30 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate in its crystalline modification A1 were dispersed in approx. 0.2 mL of a binary mixture DI water/acetone (1:1, v/v), and shaken as slurry at 50 °C at 1000 rpm for 7 days. The dispersion was then filtered and resulting crystals were dried at ambient conditions on the filter.

Method 6

Approx. 65 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate in its crystalline modification A1 were dispersed in approx. 0.2 mL of a binary mixture DI water/THF (1:1, v/v), and shaken as slurry at 50 °C at 1000 rpm for 7 days. The dispersion was then filtered and resulting crystals were dried at ambient conditions on the filter.

Method 7

Approx. 50 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate in its crystalline modification A1 were dispersed in approx. 0.15 mL of a binary mixture DI water/acetonitrile (1:1, v/v), and shaken as slurry at 50 °C at 1000 rpm for 7 days. The dispersion was then filtered and resulting crystals were dried at ambient conditions on the filter.

Example 3:

Production of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate in its crystalline modification NF3

Method 1

Approx. 30 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate in its crystalline modification A1 were dissolved in approx. 3 ml of a binary mixture DI water/ethanol (1:1, v/v). Crystallization occured on evaporation of the solvent at ambient conditions. The crystals were isolated by filtration and dried at ambient conditions on the filter.

Method 2

Approx. 155 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate in its crystalline modification A1 werde dissolved in approx. 15 ml of a binary mixture DI water/1,4-dioxane (1:1, v/v). Crystallization occured on evaporation of the solvent at 50 °C. The crystals were isolated by filtration and dried at ambient conditions on the filter.

^{1}H NMR (500 MHz, DMSO) d = 8.63 (s, 2H), 8.31 – 8.26 (m, 1H), 8.25 – 8.18 (m, 2H), 7.89 (s, 1H), 7.80 (d, *J*=9.6, 1H), 7.55 – 7.40 (m, 2H), 7.05 (d, *J*=9.6, 1H), 5.34 (s, 2H), 4.31 (t, *J*=5.6, 2H), 3.87 (s, 3H), 3.80 – 3.30 (m, 4H) 2.74 (t, *J*=5.5, 2H), 2.50 (m, 4H)

Ion Chromatography: 16.0 wt% Phosphate (equivalent to molar acid:base ratio of 0.94).

Example 4:

Production of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate in its crystalline modification NF5

Method 1

Approx. 100 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate in its crystalline modification A1 were dissolved in approx. 1 ml of a binary mixture DI water/methanol (1:1, v:v). The solution was heated to 60 °C, and simultaneously evacuated for fast solvent evaporation. The resulting precipitate was spread as a powder onto a Petri dish, and subsequently incubated in a sealed desiccator over saturated salt solution of KNO_3 (94% RH) for several days.

^{1}H NMR (500 MHz, DMSO) d = 8.64 (s, 2H), 8.31 – 8.25 (m, 1H), 8.25 – 8.19 (m, 2H), 7.88 (s, 1H), 7.80 (d, *J*=9.6, 1H), 7.52 – 7.38 (m, 2H), 7.04 (d, *J*=9.6, 1H), 5.33 (s, 2H), 4.30 (t, *J*=5.6, 2H), 3.87 (s, 3H), 3.66 – 3.50 (m, 4H), 2.73 (t, *J*=5.6, 2H), 2.50 (m, 4H)

Ion Chromatography: 14.8 wt% Phosphate (equivalent to molar acid:base ratio of 0.94 based on phosphate salt with observed water content as specified below).

Karl-Fischer-Titration: 7.3 wt% water.

Method 2:

Approx. 100 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate in its crystalline modification NF3 were spread as a powder onto a a Petri dish, and subsequently incubated in a sealed desiccator over saturated salt solution of KNO_3 (94% RH) for several days.

Example 5:

Structural and physico-chemical characterization of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogen-phosphate anhydrate in its crystalline modification A1

A Powder X-Ray Diffraction (XRD) pattern of crystalline modification A1 was obtained by standard techniques as described in European Pharmacopeia, 6th Edition, chapter 2.9.33. Crystalline modification A1 is characterized by the X-ray powder diffractogram (Cu-$K\alpha_1$ radiation, λ = 1.5406 Å, Stoe StadiP 611 KL diffractometer.) depicted in **Figure 1.**

Crystalline modification A1 is characterized by the following XRD data:

Powder X-ray diffractogram peak list:

Peak No.	**d/Å**	**°2θ (Cu-$K\alpha_1$ radiation) ± 0.1°**	**Indexing (h, k, l)**
1	27.45	3.2	(2, 0, 0)
2	13.62	6.5	(4, 0, 0)
3	9.02	9.8	(6, 0, 0)
4	6.75	13.1	(8, 0, 0)
5	6.15	14.4	(-2, 0, 2)
6	5.59	15.8	(-6, 0, 2)
7	5.07	17.5	(-8, 0, 2)
8	4.81	18.4	(9, 1, 0)
9	4.72	18.8	(-9, 1, 1)
10	4.55	19.5	(6, 0, 2)
11	4.06	21.9	(8, 0, 2)
12	3.75	23.7	(11, 1, 1)
13	3.68	24.2	(2, 2, 1)

14	3.37	26.4	(3, 1 3)
15	3.16	28.2	(-15, 1, 2)

Single crystal X-Ray Structure data were obtained on crystalline modification A1 as well (XCalibur diffractometer from Oxford Diffraction equipped with graphite monochromator and CCD Detector using Mo K_α radiation at 301 K). The single crystal structure of crystalline modification A1 viewed along b-axis is depicted in **Figure 2**.

Crystalline modification A1 crystallizes in the monoclinic space group *C2/c* with the lattice parameters a = 55.1 Å, b = 7.9 Å, c = 12.2 Å, and β = 102.2° (with $\alpha = \gamma = 90°$). From the single crystal structure it is obvious that crystalline modification A1 represents an anhydrous form.

Crystalline modification A1 was further characterized by IR- and Raman-spectroscopy. FT-Raman and FT-IR spectra were obtained by standard techniques as described in the European Pharmacopeia, 6th Edition, chapter 2.02.24 and 2.02.48. For measurement of the FT-IR and FT-Raman-spectra a Bruker Vector 22 and a Bruker RFS 100 spectrometer were used. FT-IR spectra were base-line corrected using Bruker OPUS software. FT-Raman spectra were vector normalized using the same software.

An FT-IR spectrum was obtained using a KBr pellet as sample preparation technique. The FT-IR spectrum is depicted in **Figure 3** and the band positions are given below.

Crystalline modification A1 IR band positions $\pm$2 cm^{-1} (relative intensity*)

2949 cm^{-1} (w), 2885 cm^{-1} (w), 2368 cm^{-1} (w, broad), 1661 cm^{-1} (s), 1603 cm^{-1} (s), 1549 cm^{-1} (m), 1446 cm^{-1} (s), 1429 cm^{-1} (s), 1283 cm^{-1} (s), 1261 cm^{-1} (m), 1226 cm^{-1} (m), 1132 cm^{-1} (s), 1068 cm^{-1} (s), 945 cm^{-1} (s), 854 cm^{-1} (s), 713 cm^{-1} (m)

*"s" = strong (transmittance $\leq$ 50 %), "m" = medium (50 % < transmittance $\leq$ 70 %), "w" = weak (transmittance > 70 %)

An FT-Raman spectrum is depicted in **Figure 4** and the band positions are given below.

Crystalline modification A1 Raman band positions ±2 cm^{-1} (relative intensity*):

3061 cm^{-1} (w), 2951 cm^{-1} (w), 1604 cm^{-1} (s), 1579 cm^{-1} (s), 1568 cm^{-1} (m), 1515 cm^{-1} (w), 1446 cm^{-1} (m), 1430 cm^{-1} (m), 1327 cm^{-1} (m), 1161 cm^{-1} (w), 1001 cm^{-1} (m), 802 cm^{-1} (w), 793 cm^{-1} (w)

*"s" = strong (relative Raman intensity $\geq$ 0.04), "m" = medium (0.04 > relative Raman intensity $\geq$ 0.02), "w" = weak (relative Raman intensity < 0.02)

Crystalline modification A1 is a crystalline anhydrous form, which is further characterized by the following physical properties:

- Thermal behavior shows a melting peak at approx. 207 °C, with a very small mass loss up to the melting temperature. DSC profile (Perkin-Elmer Diamond DSC, 5 K/min, nitrogen purge gas 50 mL/min) and TGA profile (Perkin-Elmer Pyris TGA1, 5 K/min, nitrogen purge gas 50 mL/min) are displayed in **Figure 5** and **6**, respectively.
- Water Vapor Sorption behavior shows small water uptake levels upon adsorption in the range 0-70% relative humidity (RH) (crystalline modification A, type a) and 0-90% RH (crystalline modification A, type b), respectively. Pronounced water uptake levels are observed above 70% RH (crystalline modification A type a) and above 90% RH (crystalline modification A type b), respectively, which results in formation of dihydrate crystalline modification H1 (water uptake levels of approx. 6 wt%) at elevated relative humidity (RH). Water Vapor Sorption isotherms [Water Vapour Sorption Isotherm (25 °C) (SMS DVS 1)] of crystalline modification A1 (types a and b) are displayed in **Figure 7** and **8**, respectively.

Example 6:

Structural and physico-chemical characterization of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogen-phosphate dihydrate in its crystalline modification H1

A Powder X-Ray Diffraction (XRD) pattern of crystalline modification H1 was obtained by standard techniques as described in European Pharmacopeia, 6th Edition, chapter 2.9.33. Crystalline modification H1 is characterized by the X-ray powder diffractogram (Cu-Kα_1 radiation, λ = 1.5406 Å, Stoe StadiP 611 KL diffractometer.) depicted in **Figure 9**.

Crystalline modification H1 is characterized by the following XRD data:

Powder X-ray diffractogram peak list:

Peak No.	**d/Å**	**°2θ (Cu-Kα_1 radiation) ± 0.1°**	**Indexing (h, k, l)**
1	28.42	3.1	(1, 0, 0)
2	9.40	9.4	(3, 0, 0)
3	6.13	14.4	(0, 0, 2)
4	6.01	14.7	(2, 1, 1)
5	5.89	15.0	(1, 0, 2)
6	4.97	17.8	(3, 0, 2)
7	4.77	18.6	(4, 1, 1)
8	4.71	18.8	(6, 0, 0)
9	4.64	19.1	(5, 1, 0)
10	3.89	22.8	(2, 2, 0)
11	3.83	23.2	(-1, 2, 1)
12	3.73	23.8	(-2, 2, 1)
13	3.38	26.4	(0, 2, 2)
14	3.33	26.8	(-4, 1, 3)
15	3.22	27.6	(-3, 2, 2)

Single crystal X-Ray Structure data were obtained on crystalline modification H1 as well (XCalibur diffractometer from Oxford Diffraction equipped with graphite mono-

chromator and CCD Detector using Mo K_α radiation at 301 K). The single crystal structure of crystalline modification H1 is depicted in **Figure 10**.

Crystalline modification H1 crystallizes in the monoclinic space group $P2_1/C$ with the lattice parameters a = 28.2 Å, b = 8.1 Å, c = 12.3 Å, and β = 94.1° (with $\alpha = \gamma = 90°$). From the single crystal structure it is obvious that crystalline modification H1 represents a stoichiometric dihydrate.

Crystalline modification H1 was further characterized by IR-spectroscopy. FT-IR spectra were obtained by standard techniques as described in the European Pharmacopeia, 6th Edition, chapter 2.02.24 and 2.02.48. For measurement of the FT-IR spectra a Bruker Vector 22 spectrometer was used. FT-IR spectra were base-line corrected using Bruker OPUS software.

An FT-IR spectrum was obtained using a KBr pellet as sample preparation technique. The FT-IR spectrum is depicted in **Figure 11** and the band positions are given below.

Crystalline modification H1 IR band positions ±2 cm^{-1} (relative intensity*)

2984 cm^{-1} (s), 2944 cm^{-1} (s), 2451 cm^{-1} (m, broad), 1661 cm^{-1} (s), 1603 cm^{-1} (s), 1548 cm^{-1} (s), 1446 cm^{-1} (s), 1430 cm^{-1} (s), 1277 cm^{-1} (s), 1260 cm^{-1} (s), 1226 cm^{-1} (s), 1124 cm^{-1} (s), 1040 cm^{-1} (s), 940 cm^{-1} (s), 852 cm^{-1} (s), 713 cm^{-1} (s)

*"s" = strong (transmittance ≤ 50 %), "m" = medium (50 % < transmittance ≤ 70 %), "w" = weak (transmittance > 70 %)

FT-Raman spectroscopy of crystalline modification H1 shows an identical spectrum to crystalline modification A1, since dehydration of hydrate water occurs as a consequence of the laser excitation.

Crystalline modification H1 is a crystalline dihydrate form, which is further characterized by the following physical properties:

- Thermal behavior shows dehydration of hydrate water from approx. 30-120 °C upon heating, with subsequent melting of the anhydrous form at approx. 208 °C. DSC profile (Perkin-Elmer Diamond DSC, 5 K/min, nitrogen purge gas 50 mL/min)

and TGA profile (Perkin-Elmer Pyris TGA1, 5 K/min, nitrogen purge gas 50 mL/min) are displayed in **Figure 12** and **13**, respectively.

- Water Vapor Sorption behavior shows loss of hydrate water <40% relative humidity (RH), with re-conversion to dihydrate crystalline modification H1 upon adsorption >70% RH. Water Vapor Sorption isotherm (25 °C) of Form H1 is displayed below. Water Vapor Sorption isotherm [Water Vapour Sorption Isotherm (25 °C) (SMS DVS Intrinsic)] of crystalline modification H1 is displayed in **Figure 14**.

Example 7:

Structural and physico-chemical characterization of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogen-phosphate in its crystalline modification NF3

A Powder X-Ray Diffraction (XRD) pattern of crystalline modification NF3 was obtained by standard techniques as described in European Pharmacopeia, 6th Edition, chapter 2.9.33. Crystalline modification NF3 is characterized by the X-ray powder diffractogram (Cu-$K\alpha_1$ radiation, λ = 1.5406 Å, Stoe StadiP 611 KL diffractometer.) depicted in **Figure 15**.

Crystalline modification NF3 is characterized by the following XRD data:

Powder X-ray diffractogram peak list:

Peak No.	**d/Å**	**°2θ (Cu-$K\alpha_1$ radiation) ± 0.1°**
1	27.30	3.2
2	13.62	6.5
3	9.02	9.8
4	6.71	13.2
5	6.11	14,5
6	5.79	15.3
7	5.57	15.9
9	5.32	16.7

9	5.05	17.5
10	4.81	18.4
11	4.58	19.4
12	4.12	21.6
13	4.04	22.0
14	3.84	23.1
15	3.75	23.7
16	3.69	24.1
17	3.37	26.4
18	3.16	28.3

Crystalline modification NF3 was further characterized by IR- and Raman-spectroscopy. FT-Raman and FT-IR spectra were obtained by standard techniques as described in the European Pharmacopeia, 6th Edition, chapter 2.02.24 and 2.02.48. For measurement of the FT-IR and FT-Raman-spectra a Bruker Vector 22 and a Bruker RFS 100 spectrometer were used. FT-IR spectra were base-line corrected using Bruker OPUS software. FT-Raman spectra were vector normalized using the same software.

An FT-IR spectrum was obtained using a KBr pellet as sample preparation technique. The FT-IR spectrum is depicted in **Figure 16** and the band positions are given below.

Crystalline modification NF3 IR band positions ± 2 cm^{-1} (relative intensity*)

2949 cm^{-1} (m), 2873 cm^{-1} (w), 2365 cm^{-1} (w, broad), 1661 cm^{-1} (s), 1602 cm^{-1} (s), 1549 cm^{-1} (m), 1445 cm^{-1} (s), 1430 cm^{-1} (s), 1280 cm^{-1} (s), 1262 cm^{-1} (m), 1226 cm^{-1} (m), 1132 cm^{-1} (s), 1072 cm^{-1} (s), 944 cm^{-1} (s), 851 cm^{-1} (s), 713 cm^{-1} (m)

*"s" = strong (transmittance $\leq$ 50 %), "m" = medium (50 % < transmittance $\leq$ 70 %), "w" = weak (transmittance > 70 %)

An FT-Raman spectrum is depicted in **Figure 17** and the band positions are given below.

Crystalline modification NF3 Raman band positions ±2 cm^{-1} (relative intensity*):

3061 cm^{-1} (m), 2952 cm^{-1} (m), 1604 cm^{-1} (s), 1581 cm^{-1} (s), 1568 cm^{-1} (s), 1515 cm^{-1} (m), 1446 cm^{-1} (s), 1430 cm^{-1} (s), 1327 cm^{-1} (s), 1167 cm^{-1} (m), 1001 cm^{-1} (s), 802 cm^{-1} (w), 793 cm^{-1} (w)

*"s" = strong (relative Raman intensity ≥ 0.04), "m" = medium (0.04 > relative Raman intensity ≥ 0.02), "w" = weak (relative Raman intensity < 0.02)

Crystalline modification NF3 is a crystalline form, most likely an anhydrate form, which is further characterized by the following physical properties:

- Thermal behavior shows two exothermic events at approx. 100-130 °C and 180-190 °C, followed by a melting peak at approx. 208 °C, with a small mass loss of approx. 1.5 wt% up to the melting temperature. DSC profile (Perkin-Elmer Diamond DSC, 5 K/min, nitrogen purge gas 50 mL/min) and TGA profile (Perkin-Elmer Pyris TGA1, 5 K/min, nitrogen purge gas 50 mL/min) are displayed in **Figure 18** and **19**, respectively.
- Water Vapor Sorption behavior shows small water uptake levels upon adsorption in the range 0-70% relative humidity (RH). Pronounced water uptake levels are observed above 70% RH, which results in formation of crystalline hydrate modification NF5 (water uptake levels of approx. 5-6 wt%) at elevated relative humidity (RH). A Water Vapor Sorption isotherm [Water Vapour Sorption Isotherm (25 °C) (SMS DVS Intrinsic)] of crystalline modification NF3 is displayed in **Figure 20**.

Example 8:

Structural and physico-chemical characterization of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate in its crystalline modification NF5

A Powder X-Ray Diffraction (XRD) pattern of crystalline modification NF5 was obtained by standard techniques as described in European Pharmacopeia, 6th Edition, chapter 2.9.33. Crystalline modification NF5 is characterized by the X-ray powder diffractogram

(Cu-Kα_1 radiation, λ = 1.5406 Å, Stoe StadiP 611 KL diffractometer.) depicted in **Figure 21**.

Crystalline modification NF5 is characterized by the following XRD data:

Powder X-ray diffractogram peak list:

Peak No.	**d/Å**	**°2θ (Cu-Kα_1 radiation) ± 0.1°**
1	28.54	3.1
2	9.41	9.4
3	6.37	13.9
4	6.10	14.5
5	5.98	14.8
6	5.82	15.2
7	5.62	15.7
9	5.32	16.6
9	5.13	17.3
10	4.96	17.9
11	4.80	18.5
12	4.69	18.9
13	4.63	19.2
14	4.48	19.8
15	4.02	22.1
16	3.90	22.8
17	3.85	23.1
18	3.73	23.9
19	3.38	26.3
20	3.32	26.8
21	3.23	27.6

Crystalline modification NF5 is a crystalline hydrate form, which is further characterized by the following physical properties:

- Thermal behavior shows dehydration of hydrate water from approx. 30-100 °C upon heating, with subsequent melting of the anhydrous form at approx. 210 °C. DSC profile (Perkin-Elmer Diamond DSC, 5 K/min, nitrogen purge gas 50 mL/min) and TGA profile (Perkin-Elmer Pyris TGA1, 5 K/min, nitrogen purge gas 50 mL/min) are displayed in **Figure 22** and **23**, respectively.
- Water Vapor Sorption behavior shows loss of hydrate water <40% relative humidity (RH), with re-conversion to hydrate crystalline modification NF5 upon adsorption >70% RH. Water Vapor Sorption isotherm (25 °C) of Form NF5 is displayed below. Water Vapor Sorption isotherm [Water Vapour Sorption Isotherm (25 °C) (SMS DVS Intrinsic)] of crystalline modification NF5 is displayed in **Figure 24**.

Example 9:

Solubility determination of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate

For solubility determination 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one (free base) and its dihydrogenphosphate salt are weighted into a GC-Vial, 300µL of the solvent medium are added to result in a maximal possible concentration of 10mg/mL. The mixture is stirred at 1000 rpm on a magnetic stirring plate at ambient temperature. At the sampling point 100µL of the respective solution/suspension are transferred to a 500 µL Eppendorff cap and are centrifuged for 5 min at 14000 rpm. The centrifugate is analysed by HPLC (dilution may be necessary before analysis).

Table 1 shows the solubility of the free base of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one and its corresponding dihydrogenphosphate salt in water, measured after 1 and 2 hours.

Table 1

	Sample Point 1h		Sample Point 2h	
	Solubility [mg/ml]	**pH value**	**Solubility [mg/ml]**	**pH value**
free base	0,167	n.d.	0,156	n.d.
dihydrogenphosphate	9,863	3,91	> 10	3,97

The results clearly demonstrate the significantly higher solubility of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate in aqueous solutions compared to its free base.

Example 10:

Competitive slurry conversion experiments of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate crystalline modifications A1 and NF3 in organic solvents.

Approximately 10 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate crystalline modification A1 and 10 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate crystalline modification NF3 were mixed as powder blend, and dispersed in 1 mL organic solvent in 4 mL glass vials with PTFE sealed caps. PTFE-coated stirring rods were inserted into the dispersions prior to sealing the vials. Dispersions were agitated in closed vials for 5 days, using a magnetic stirrer, at 25 °C and 50 °C, respectively. Solid-state residues were filtered, and analyed by XRD to monitor morphic form after solvent slurrying.

The results of the competitive slurry conversion experiments are compiled in **Table 2**.

Table 2

Slurry in	Mixtures A1+NF3 (approx. 1:1, wt/wt)	
	Residue 25 °C, 5 d	Residue 50 °C, 5 d
Acetone	A1	A1
Ethanol	A1	A1
1,4-Dioxane	A1	A1
THF	A1 + very small fraction NF3	A1

At both temperatures, crystalline modification A1 is obtained as only or preferred form at the end of the slurry experiments starting from binary 1:1 mixtures of forms A1 and NF3, clearly demonstrating that A1 can be considered as more stable form.

Example 11:

A competitive slurry conversion experiment of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate crystalline modifications A1 and NF5 in water.

Approximately 20 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate crystalline modification A1 and 20 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate crystalline modification NF5 were mixed as powder blend, and dispersed in 0.3 mL water in a 4 mL glass vial with a PTFE sealed cap. A PTFE-coated stirring rod was inserted into the dispersion prior to sealing the vial. The dispersion was agitated in closed vial for 12 days, using a magnetic stirrer, at 25 °C. The solid-state residue was filtered, and analyzed by XRD to monitor morphic form after solvent slurrying.

The result of the competitive slurry conversion experiment is compiled in **Table 3**.

Table 3

Slurry in	Mixtures A1+NF5 (approx. 1:1, wt/wt) Residue 25 °C, 12 d
Water	NF5 + very small fractions of A1

The experiments shows that prolonged aqueous slurrying of modifications A1 and NF5 at 25 °C results in hydrate form NF5 as preferred form, clearly showing that NF5 is the more stable form in an aqueous dispersion system.

Example 12:

A competitive slurry conversion experiment of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate crystalline modifications H1 and NF5 in water.

Approximately 20 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate crystalline modification H1 and 20 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate crystalline modification NF5 were mixed as powder blend, and dispersed in 0.3 mL water in a 4 mL glass vial with a PTFE sealed cap. A PTFE-coated stirring rod was inserted into the dispersion prior to sealing the vial. The dispersion was agitated in closed vial for 12 days, using a magnetic stirrer, at 25 °C. The solid-state residue was filtered, and analyed by XRD to monitor morphic form after solvent slurrying.

The result of the competitive slurry conversion experiment is compiled in **Table 4**.

Table 4

Slurry in	Mixtures H1+NF5 (approx. 1:1, wt/wt) Residue 25 °C, 12 d
Water	H1

The experiments shows that prolonged aqueous slurrying of modifications H1 and NF5 at 25 °C results in dihydrate form H1 as preferred form, clearly showing that H1 is a stable form in an aqueous dispersion system.

Example 13:

A competitive slurry conversion experiment of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate crystalline modifications H1 and NF3 in water.

Approximately 10 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate crystalline modification H1 and 10 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate crystalline modification NF3 were mixed as powder blend, and dispersed in 0.2 mL water in a 4 mL glass vial with a PTFE sealed cap. A PTFE-coated stirring rod was inserted into the dispersion prior to sealing the vial. The dispersion was agitated in closed vial for 5 days, using a magnetic stirrer, at 25 °C. The solid-state residue was filtered, and analyed by XRD to monitor morphic form after solvent slurrying.

The result of the competitive slurry conversion experiment is compiled in **Table 5**.

Table 5

Slurry in	**Mixtures H1+NF3 (approx. 1:1, wt/wt) Residue 25 °C, 5 d**
Water	H1

The experiments shows that prolonged aqueous slurrying of modifications H1 and NF3 at 25 °C results in dihydrate form H1 as preferred form, clearly showing that H1 is a more stable form in an aqueous dispersion system.

Example 14:

Kinetic solubility determinations of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate crystalline forms A1 (anhydrate) and NF3 in a mixture of water:acetone 30:70 (v:v) after 2 hours.

Approximately 70 mg of 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate crystalline modification A1 were dispersed in 1 mL of a binary mixture water:acetone (30:70, v:v) in a 5 mL Whtamn Uniprep Syringeless Filter vial. The dispersion was agitated at RT for 2 hours at 450 rpm. After filtration of the dispersion after 2 hours, the filtrate is analysed by HPLC (dilution may be necessary before analysis). The solid-state residue is analysed by Powder X-Ray Diffraction (PXRD).

The results of the kinetic solubility determination in water:acetone is compiled in **Table 6**.

Table 6

Form	Solubility water:acetone (30:70, v:v) after 2h [mg/mL]	SS Residue
A1	18.2	H1
NF3	10.6	H1+NF5

Both anhydrous forms undergo conversion to dihydrate form H1 (in mixture with hydrate form NF5 in case of form NF3). The corresponding solubility levels clearly show that form NF3 exhibits a lower solubility level after 2 hours than form A1.

Claims

1. 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate.

2. 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate solvate, preferably 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate.

3. The compound of claim 2 in its crystalline modifications.

4. 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate.

5. The compound of claim 4 in its crystalline modification A1, which is characterized by XRD peaks comprising 3.2°, 6.5°, 9.8°, and 13.1° 2θ (all ± 0.1° 2θ, using Cu-$K\alpha_1$ radiation).

6. The compound of claim 4 in its crystalline modification A1, which is characterized by XRD peaks comprising 18.4°, 18.8°, 23,7°, 24.2°, 26.4°, and 28.2° 2θ (all ± 0.1° 2θ, using Cu-$K\alpha_1$ radiation).

7. The compound of claim 4 in its crystalline modification A1, which is characterized by XRD peaks comprising 14.4°, 15.8°, 17.5°, 19.5°, and 21.9° 2θ (all ± 0.1° 2θ, using Cu-$K\alpha_1$ radiation).

8. The compound of any of claims 4 to 7 in its crystalline modification A1, which is characterized by the following XRD data:

Form A1:

Peak No.	d/Å	°2θ (Cu-Kα$_1$ radiation) ± 0.1°
1	27.45	3.2
2	13.62	6.5
3	9.02	9.8
4	6.75	13.1
5	6.15	14.4
6	5.59	15.8
7	5.07	17.5
8	4.81	18.4
9	4.72	18.8
10	4.55	19.5
11	4.06	21.9
12	3.75	23.7
13	3.68	24.2
14	3.37	26.4
15	3.16	28.2

9. 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate.

10. The compound of claim 9 in its crystalline modification H1, which is characterized by XRD peaks comprising 3.1°, 9.4°, and 18.8° 2θ (all ± 0.1° 2θ, using Cu-Kα$_1$ radiation).

11. The compound of claim 9 in its crystalline modification H1, which is characterized by XRD peaks comprising 19.1°, 22.8°, and 26.4° 2θ (all ± 0.1° 2θ, using Cu-$K\alpha_1$ radiation).

12. The compound of claim 9 in its crystalline modification H1, which is characterized by XRD peaks comprising 14.4°, 15.0°, and 17.8° 2θ (all ± 0.1° 2θ, using Cu-$K\alpha_1$ radiation).

13. The compound of claim 9 in its crystalline modification H1, which is characterized by XRD peaks comprising 14.7°, 18.6°, 23.2°, 23.8°, 26.8°, and 27.6° 2θ (all ± 0.1° 2θ, using Cu-$K\alpha_1$ radiation).

14. The compound of any of claims 9 to 13 in its crystalline modification H1, which is characterized by the following XRD data:

Form H1:

Peak No.	d/Å	°2θ (Cu-$K\alpha_1$ radiation) ± 0.1°
1	28.42	3.1
2	9.40	9.4
3	6.13	14.4
4	6.01	14.7
5	5.89	15.0
6	4.97	17.8
7	4.77	18.6
8	4.71	18.8
9	4.64	19.1
10	3.89	22.8
11	3.83	23.2

12	3.73	23.8
13	3.38	26.4
14	3.33	26.8
15	3.22	27.6

15. 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate in its crystalline modification NF3, which is characterized by XRD peaks comprising 15.3°, 16.7°, 21.6°, and 23.1° 2θ (all ± 0.1° 2θ, using Cu-$K\alpha_1$ radiation).

16. The compound of claim 15 in its crystalline modification NF3, which is characterized by the following XRD data:

Form NF3:

Peak No.	**d/Å**	**°2θ (Cu-$K\alpha_1$ radiation) ± 0.1°**
1	27.30	3.2
2	13.62	6.5
3	9.02	9.8
4	6.71	13.2
5	6.11	14.5
6	5.79	15.3
7	5.57	15.9
9	5.32	16.7
9	5.05	17.5
10	4.81	18.4
11	4.58	19.4
12	4.12	21.6
13	4.04	22.0
14	3.84	23.1

15	3.75	23.7
16	3.69	24.1
17	3.37	26.4
ä18	3.16	28.3

17. 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate.

18. The compound of claim 17 in its crystalline modification NF5, which is characterized by XRD peaks comprising 13.9°, 15.7°, 16.6°, 17.3°, 19.8°, and 22.1° 2θ (all ± 0.1° 2θ, using Cu-Kα_1 radiation).

19. The compound of any of claims 17 to 18 in its crystalline modification NF5, which is characterized by the following XRD data:

Form NF5:

Peak No.	**d/Å**	**°2θ (Cu-Kα_1 radiation) ± 0.1°**
1	28.54	3.1
2	9.41	9.4
3	6.37	13.9
4	6.10	14.5
5	5.98	14.8
6	5.82	15.2
7	5.62	15.7
9	5.32	16.6
9	5.13	17.3
10	4.96	17.9
11	4.80	18.5
12	4.69	18.9

13	4.63	19.2
14	4.48	19.8
15	4.02	22.1
16	3.90	22.8
17	3.85	23.1
18	3.73	23.9
19	3.38	26.3
20	3.32	26.8
21	3.23	27.6

20. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound according to any of claims 1 to 19.

21. The pharmaceutical composition as claimed in claim 9 further comprising at least one additional compound selected from the group consisting of physiologically acceptable excipients, auxiliaries, adjuvants, diluents, carriers and/or additional pharmaceutically active substances other than the compounds according to any of claims 1 to 19.

22. Medicament comprising at least one compound according to any of claims 1 to 19 or a pharmaceutical composition according to any of claims 20 to 21.

23. Medicament according to claim 22 for use in the treatment and/or prophylaxis of physiological and/or pathophysiological conditions, which are caused, mediated and/or propagated by the inhibition, regulation and/or modulation of signal transduction of kinases, in particular by the inhibition of tyrosine kinases, preferably Met-kinase.

24. Medicament according to claim 22 for use in the treatment and/or prophylaxis of physiological and/or pathophysiological conditions selected from the group consisting of: "cancer, tumour, malignant tumours, benign tumours, solid tumours, sarco-

mas, carcinomas, hyperproliferative disorders, carcinoids, Ewing sarcomas, Kaposi sarcomas, brain tumours, tumours originating from the brain and/or the nervous system and/or the meninges, gliomas, glioblastomas, neuroblastomas, stomach cancer, kidney cancer, kidney cell carcinomas, prostate cancer, prostate carcinomas, connective tissue tumours, soft tissue sarcomas, pancreas tumours, liver tumours, head tumours, neck tumours, laryngeal cancer, oesophageal cancer, thyroid cancer, osteosarcomas, retinoblastomas, thymoma, testicular cancer, lung cancer, lung adenocarcinoma, small cell lung carcinoma, bronchial carcinomas, breast cancer, mamma carcinomas, intestinal cancer, colorectal tumours, colon carcinomas, rectum carcinomas, gynaecological tumours, ovary tumours/ovarian tumours, uterine cancer, cervical cancer, cervix carcinomas, cancer of body of uterus, corpus carcinomas, endometrial carcinomas, urinary bladder cancer, urogenital tract cancer, bladder cancer, skin cancer, epithelial tumours, squamous epithelial carcinoma, basaliomas, spinaliomas, melanomas, intraocular melanomas, leukaemias, monocyte leukaemia, chronic leukaemias, chronic myelotic leukaemia, chronic lymphatic leukemia, acute leukaemias, acute myelotic leukaemia, acute lymphatic leukaemia and/or lymphomas".

25. The medicament as claimed in any of claims 22 to 24, wherein in such medicament comprises at least one additional pharmacologically active substance.

26. The medicament as claimed in any of claims 22 to 24, wherein the medicament is applied before and/or during and/or after treatment with at least one additional pharmacologically active substance.

27. Kit comprising a therapeutically effective amount of at least one compound according to any of claims 1 to 19 and/or at least one pharmaceutical composition as claimed in any of claims 20 to 21 and a therapeutically effective amount of at least one further pharmacologically active substance other than the compounds as claimed in any of claims 1 to 19.

28. Process for manufacturing crystalline modification A1 according to any of claims 5 to 8 comprising the steps:

(a) dissolving or dispersing 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one (free base) or one or more salts thereof in a solvent or a solvent mixture, preferably 2-propanole or chloroform, optionally under stirring,

(b) converting 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one (free base) or one or more salts thereof into the corresponding dihydrogenphosphate salt by addition of aqueous or ethanolic phosphoric acid solution, optionally under stirring,

(c) stirring the resulting dispersion of step (b) at room temperature for one or more hours or days, preferably for 1 or 2 hours,

(d) recovering precipitated 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate by filtration, optionally subsequent washing with a solvent or a solvent mixture, and optionally subsequent drying, preferably in vacuo, optionally at elevated temperature T, preferably 30° C to 95° C, more preferably 70° C.

29. Process for manufacturing crystalline modification A1 according to any of claims 5 to 8 comprising the steps:

(a) dispersing 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one (free base) or one or more salts thereof in a solvent or a solvent mixture, preferably in water, and addition of aqueous phosphoric acid solution, optionally under stirring,

(b) heating the resulting dispersion of step (a) up to elevated temperature T1, preferably 30° C to 95° C, more preferably 50°°C, optionally under stirring, and cooling down the resulting solution, preferably to 0° C to 40° C, more preferably to 20°°C, optionally under stirring, before diluting it with a solvent or a solvent mixture, preferably acetone, optionally under stirring,

(c) stirring the resulting dispersion of step (b) at 0° C to 40° C, preferably 10° C, until crystallization is complete and/or incubating it at room temperature for one or more hours or days, optionally under stirring,

(d) recovering precipitated 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhy-

drate by filtration, optionally cooling down the resulting dispersion of step (c) to 0° C to 20° C, preferably 5° C, prior to filtration optionally under stirring, optionally subsequent washing with a solvent or a solvent mixture, preferably acetone, and optionally subsequent drying, preferably in vacuo, optionally at elevated temperature T2, preferably 30° C to 95° C, more preferably 70° C,

(e) optionally, boiling the resulting dried crystals of step (d) in a solvent or a solvent mixture, preferably ethanol, as dispersion for one or more minutes, preferably 30 minutes, and recovering them by filtration from the hot dispersion.

30. Process for manufacturing crystalline modification A1 according to any of claims 5 to 8 comprising the steps:

(a) dispersing 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one (free base) or one or more salts thereof in a solvent mixture, preferably in water:acetone mixtures, and addition of aqueous phosphoric acid solution, optionally under stirring,

(b) heating the resulting dispersion of step (a) up to elevated temperature T1, preferably 30° C to 95° C, more preferably 55°C, optionally under stirring, and cooling down the resulting solution, preferably to 0° C to 50° C, optionally under stirring, with a defined cooling rate, preferably 0.1-1 K/min, more preferably 0.1-0.3 K/min, optionally under stirring, until crystallization sets in,

(c) further cooling the resulting dispersion of step (b) preferably to -20° C to 0° C, more preferably to -10°C, optionally under stirring, with a defined cooling rate, preferably 0.1-1 K/min, more preferably 0.1-0.3 K/min, optionally under stirring,

(d) stirring the resulting dispersion of step (c) at -20° C to 40° C, preferably -10° C, until crystallization is complete,

(e) recovering crystallised 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate by filtration, optionally subsequent washing with a solvent or a solvent mixture, preferably acetone, and optionally subsequent drying, preferably in vacuo, optionally at elevated temperature T2, preferably 30° C to 95° C, more preferably 70° C,

31. Process for manufacturing crystalline modification H1 according to any of claims 10 to 14 comprising the steps:

(a) spreading 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate crystalline modification A1 onto a surface, preferably a bordered surface of a container, more preferably of a Petri dish, and subsequently incubating it in a sealed desiccator over water or aqueous solvent mixtures for one or more days or weeks.

32. Process for manufacturing crystalline modification H1 according to any of claims 10 to 14 comprising the steps:

(a) dispersing 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate crystalline modification A1 in a mixture of two or more solvents, preferably a binary mixture, where preferably the solvents are selected from the group consisting of: "water, methanol, ethanol, 2-propanol, acetone, TFH and acetonitrile", optionally under stirring, and stirring the resulting dispersion at elevated temperature T1, preferably 30° C to 95° C, more preferably 50° C, for one or more days or weeks,

(b) recovering precipitated 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate dihydrate by filtration, optionally subsequent washing with a solvent or a solvent mixture, and optionally subsequent drying, preferably in vacuo, optionally at elevated temperature T2, preferably 30° C to 95° C, more preferably 70° C.

33. Process for manufacturing crystalline modification NF3 according to any of claims 15 to 16, comprising the steps:

(a) dispersing or dissolving 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate crystalline modification A1 in a mixture of two or more solvents, preferably a binary mixture, where preferably the solvents are selected from the group consisting of: "water, methanol, ethanol, 2-propanol, acetone, TFH, acetonitrile and 1,4-dioxane", optionally under stirring, and subsequently evaporating the

mixture of two or more solvents at room temperature or elevated temperature T1, preferably 30° C to 95° C, more preferably 50° C. until crystallization occurs,

(b) recovering precipitated 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate hydrate by filtration, optionally subsequent washing with a solvent or a solvent mixture, and optionally subsequent drying, preferably in vacuo, optionally at elevated temperature T2, preferably 30° C to 95° C, more preferably 70° C.

34. Process for manufacturing crystalline modification NF5 according to any of claims 18 to 19, comprising the steps:

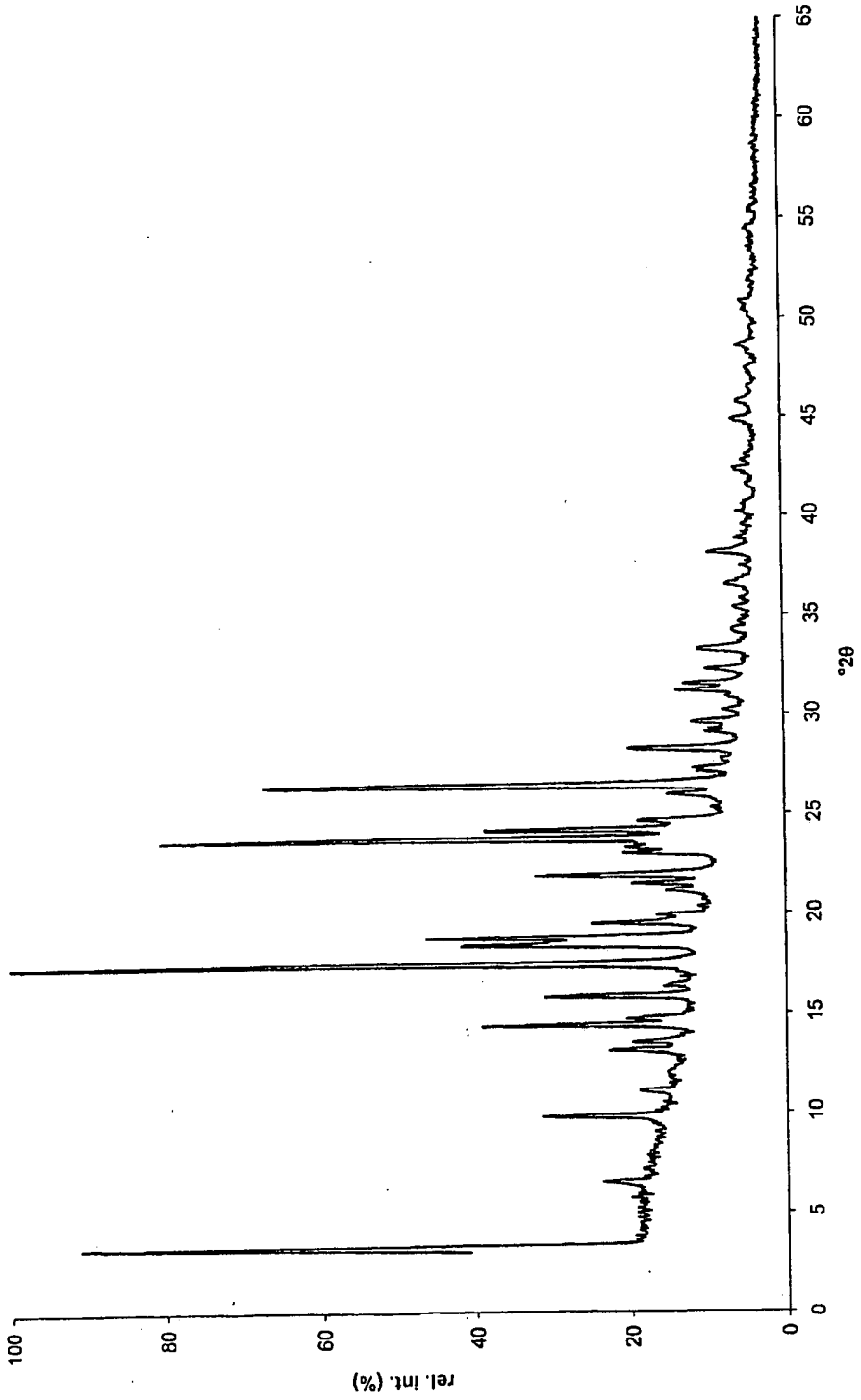
(a) dissolving 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate anhydrate crystalline modification A1 into a binary solvent mixture, preferably water:methanol, most preferably in a ratio of 1:1 (v:v), and quickly evaporating the solvent mixture at elevated temperature, preferably 40-80 °C, most preferably 60 °C, under vacuum until a precipitate is obtained

(b) optionally further spreading the precipitate obtained from step (a) as a powder onto a surface, preferably a bordered surface of a container, more preferably of a Petri dish, and subsequently incubating it in a sealed desiccator over water or aqueous salt solutions with defined relative humidity (RH), preferably 80-100% RH, more preferably 90-100% RH, for one or more days or weeks.

35. Process for manufacturing crystalline modification NF5 according to any of claims 18 to 19, comprising the step:

(a) spreading 6-(1-methyl-1H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-benzyl}-2H-pyridazin-3-one dihydrogenphosphate crystalline form NF3 as a powder onto a surface, preferably a bordered surface of a container, more preferably of a Petri dish, and subsequently incubating it in a sealed desiccator over water or aqueous salt solutions with defined relative humidity (RH), preferably 80-100% RH, more preferably 90-100% RH, for one or more days or weeks.

Figure 1



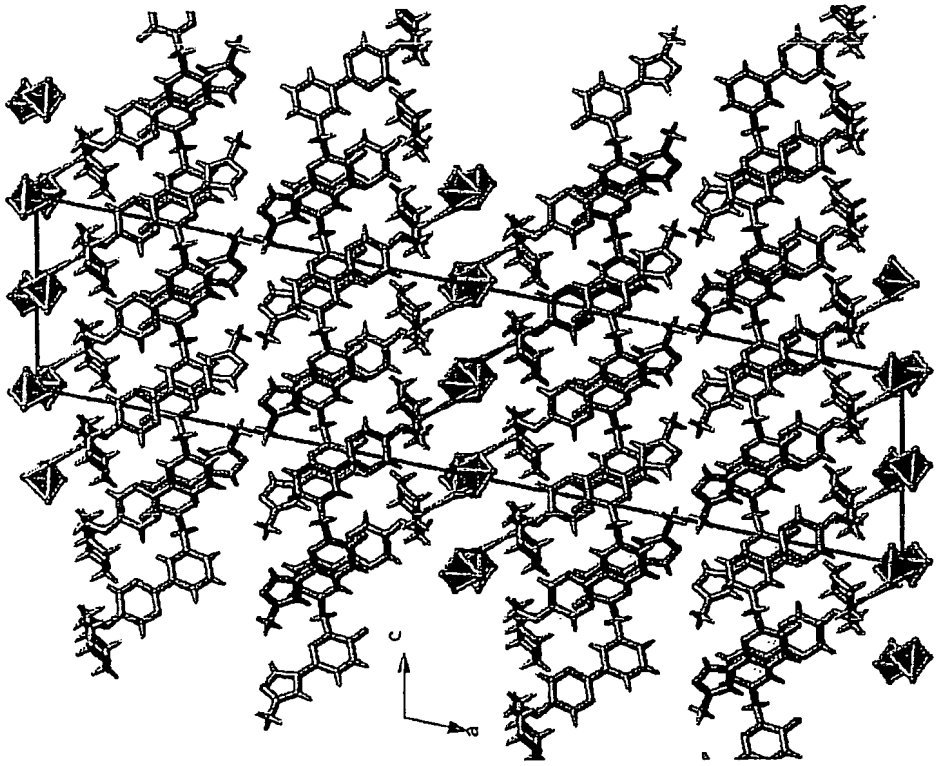


Figure 2

Figure 3

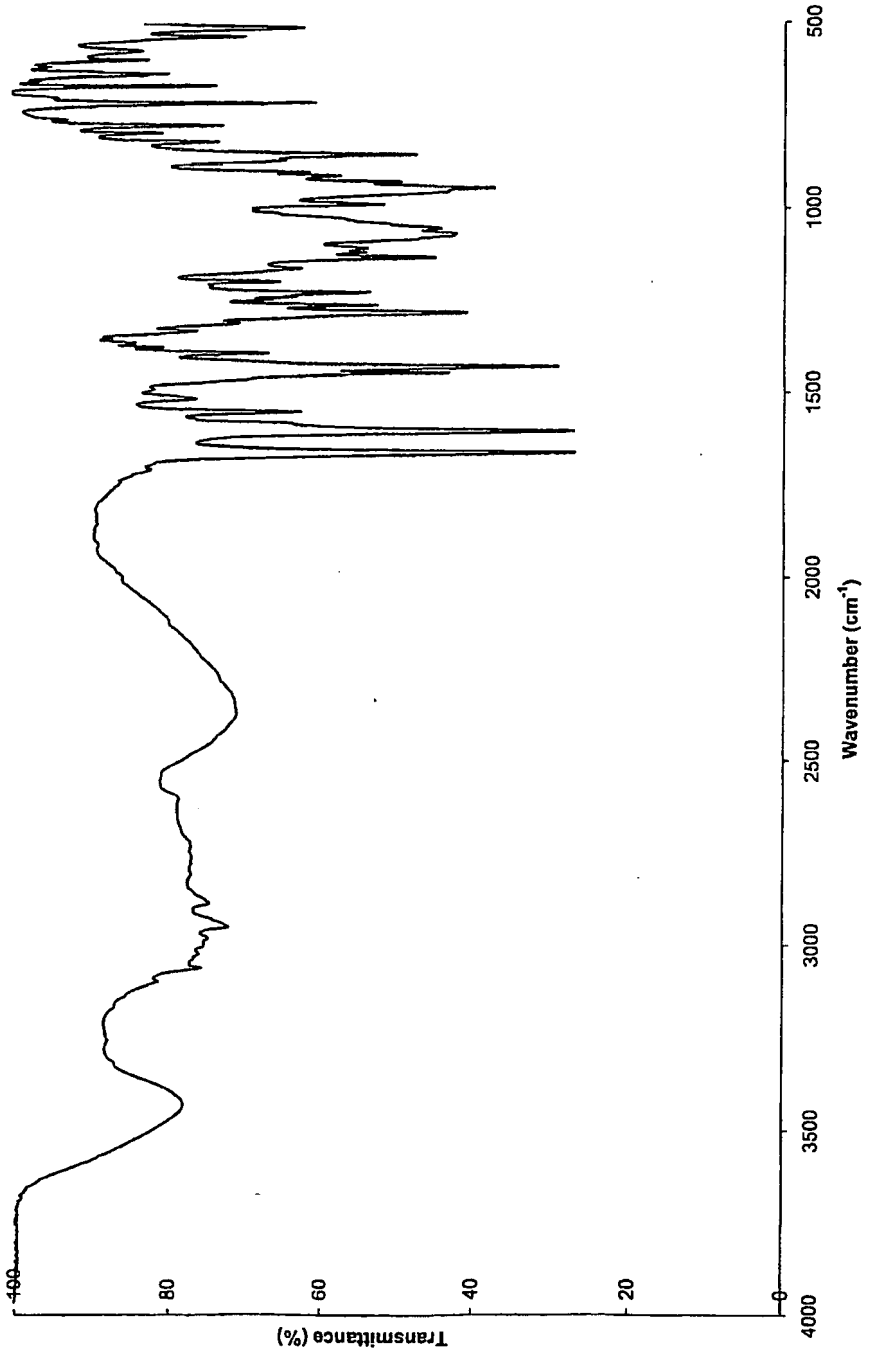

Transmittance (%)
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
500
Wavenumber (cm-1)

Figure 4

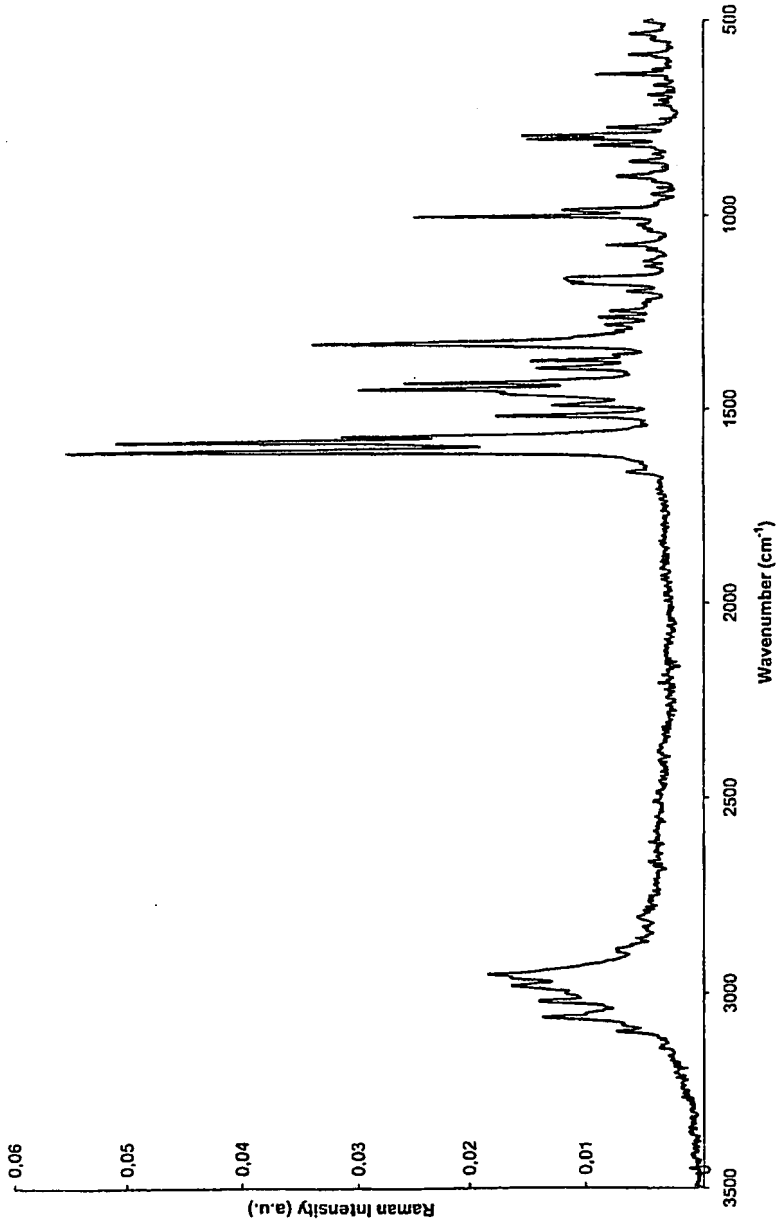
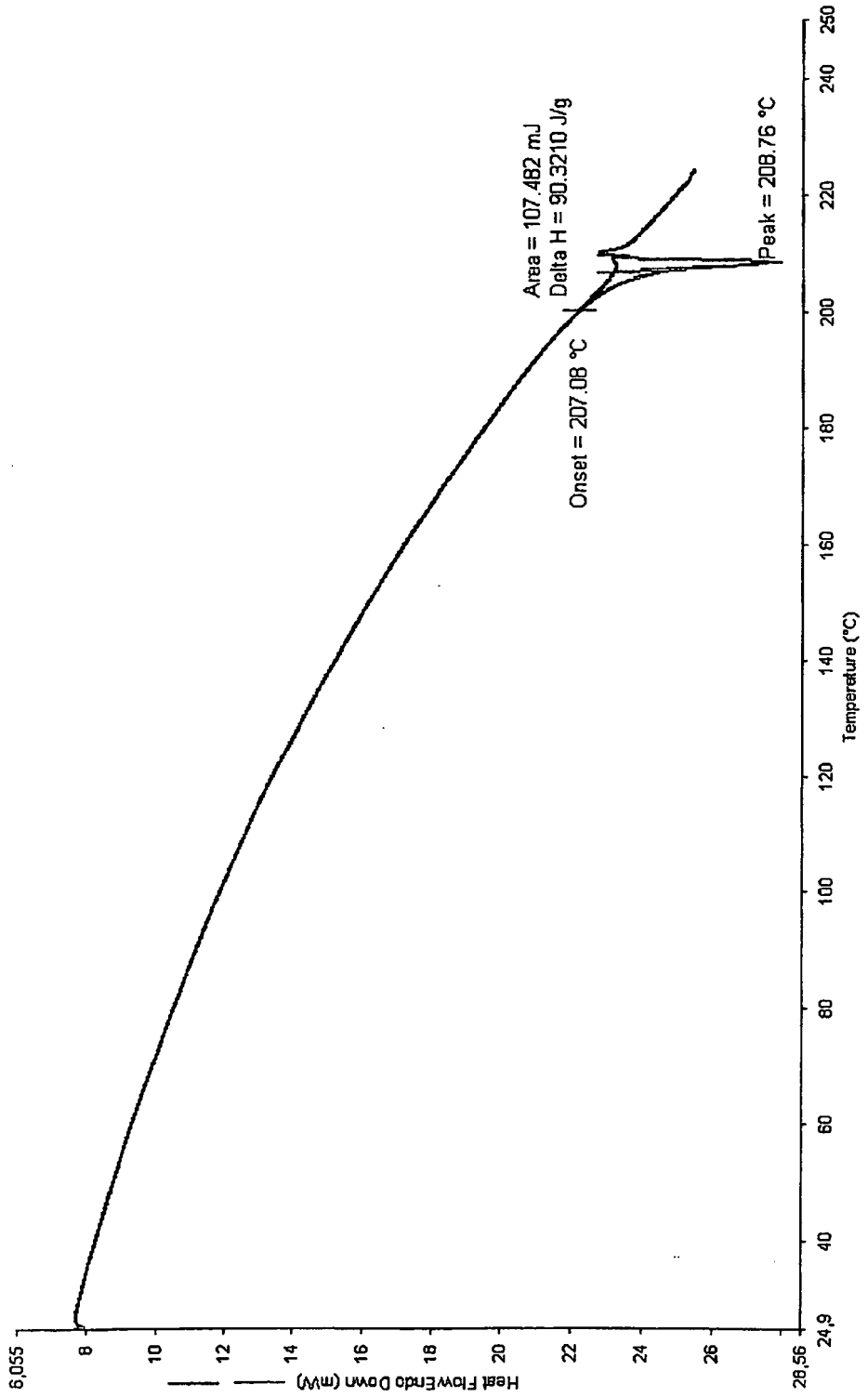

Raman Intensity (a.u.)
0,06
0,05
0,04
0,03
0,02
0,01
0
3500
3000
2500
2000
1500
1000
500
Wavenumber (cm-1)

Figure 5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Delta H = 90.3210 J/g
Onset = 207.08 °C
Peak = 208.76 °C
Heat FlowEndo Down (mW)
Temperature (°C)
6,055
8
10
12
14
16
18
20
22
24
26
28,56
24,9
40
60
80
100
120
140
160
180
200
220
240
250

Figure 6

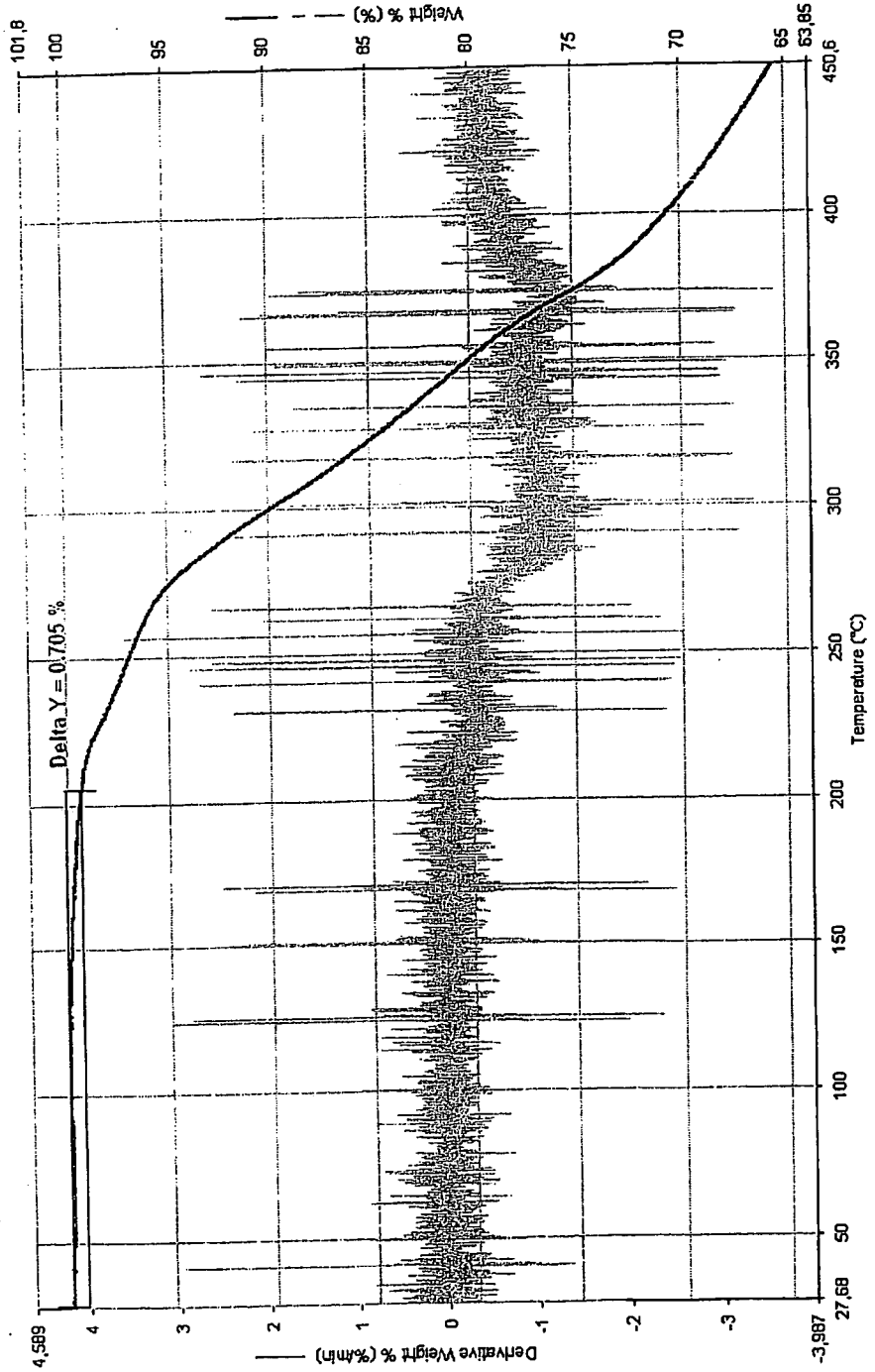

Weight % (%)
Derivative Weight % (%/min)
Temperature (°C)
Delta Y = 0.705 %
101,8
100
95
90
85
80
75
70
65
63,85
450,6
400
350
300
250
200
150
100
50
27,68
4,589
4
3
2
1
0
-1
-2
-3
-3,987

Figure 7

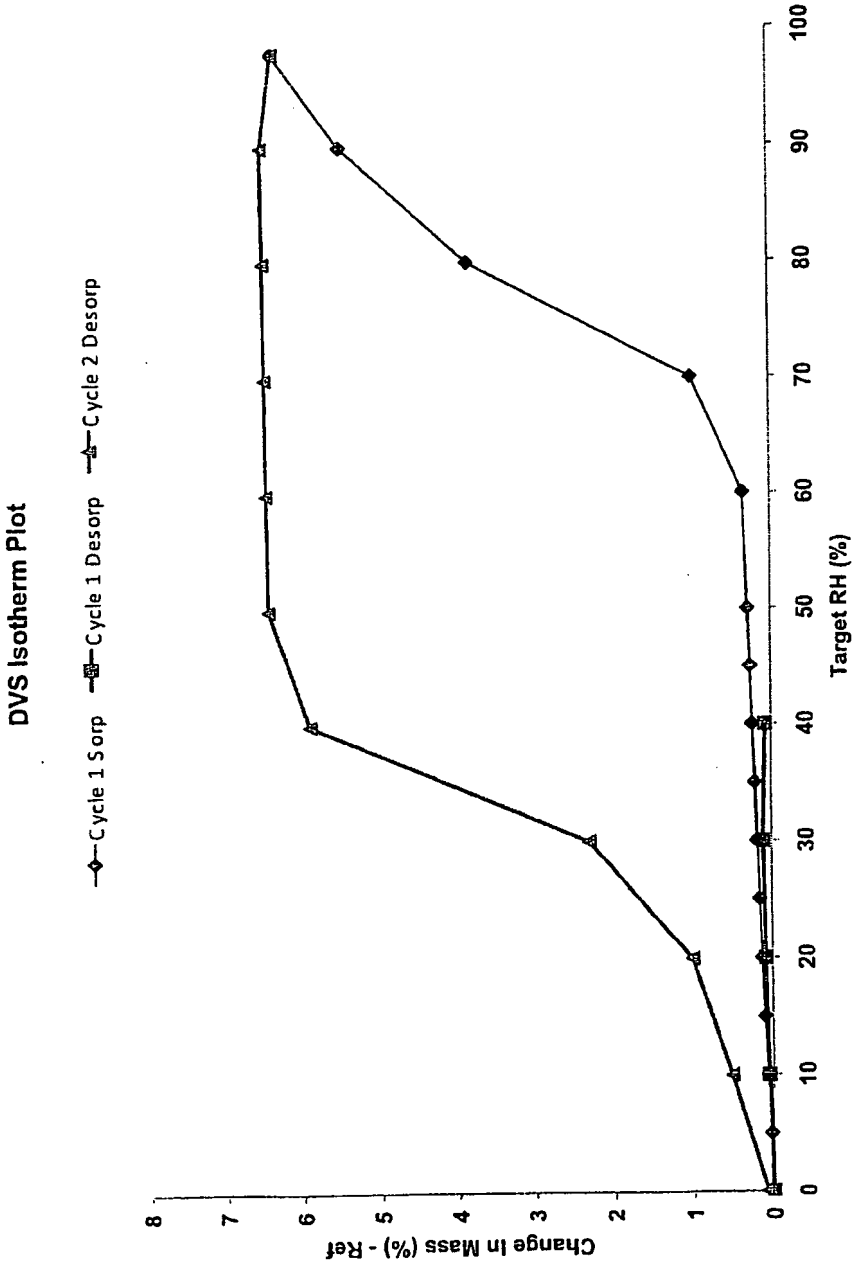

DVS Isotherm Plot
Cycle 1 Sorp
Cycle 1 Desorp
Cycle 2 Desorp
Change in Mass (%) - Ref
Target RH (%)
0
1
2
3
4
5
6
7
8
0
10
20
30
40
50
60
70
80
90
100

Figure 8

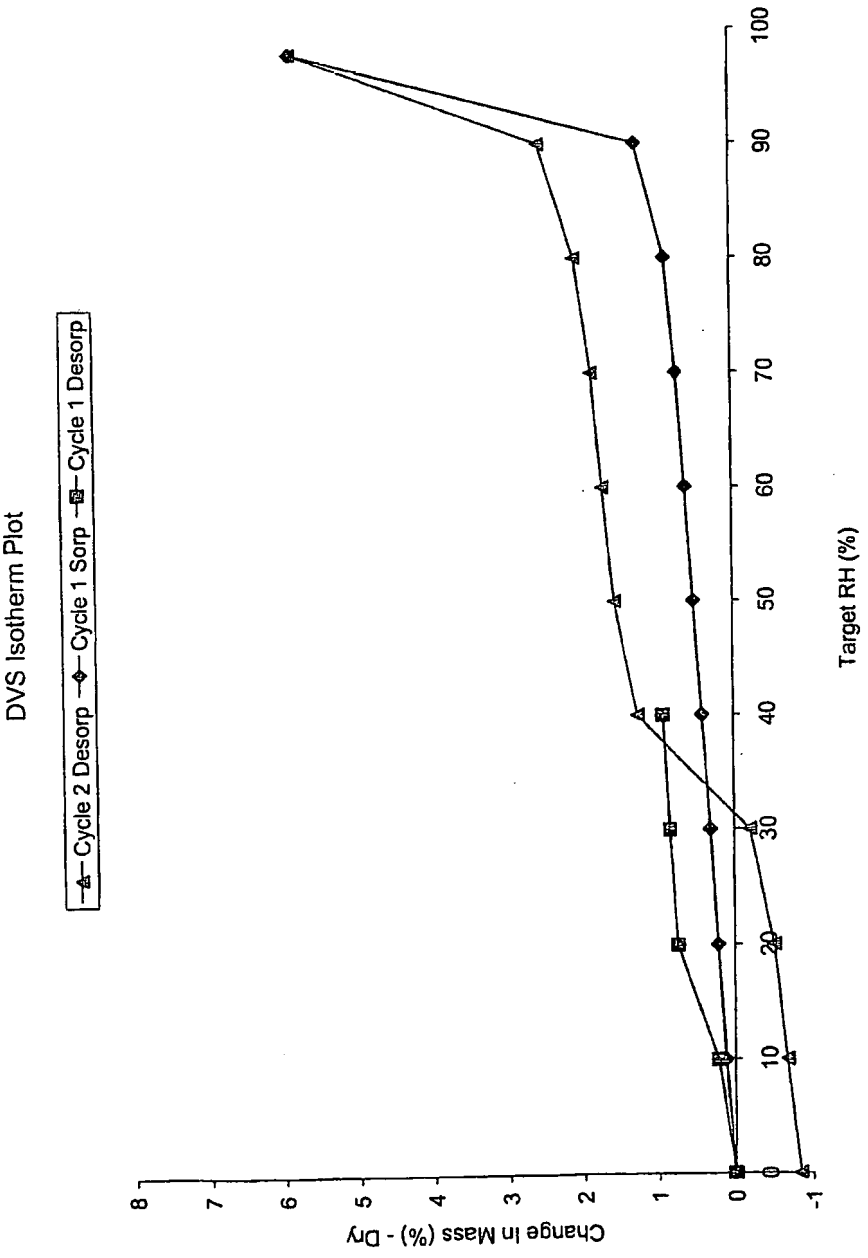
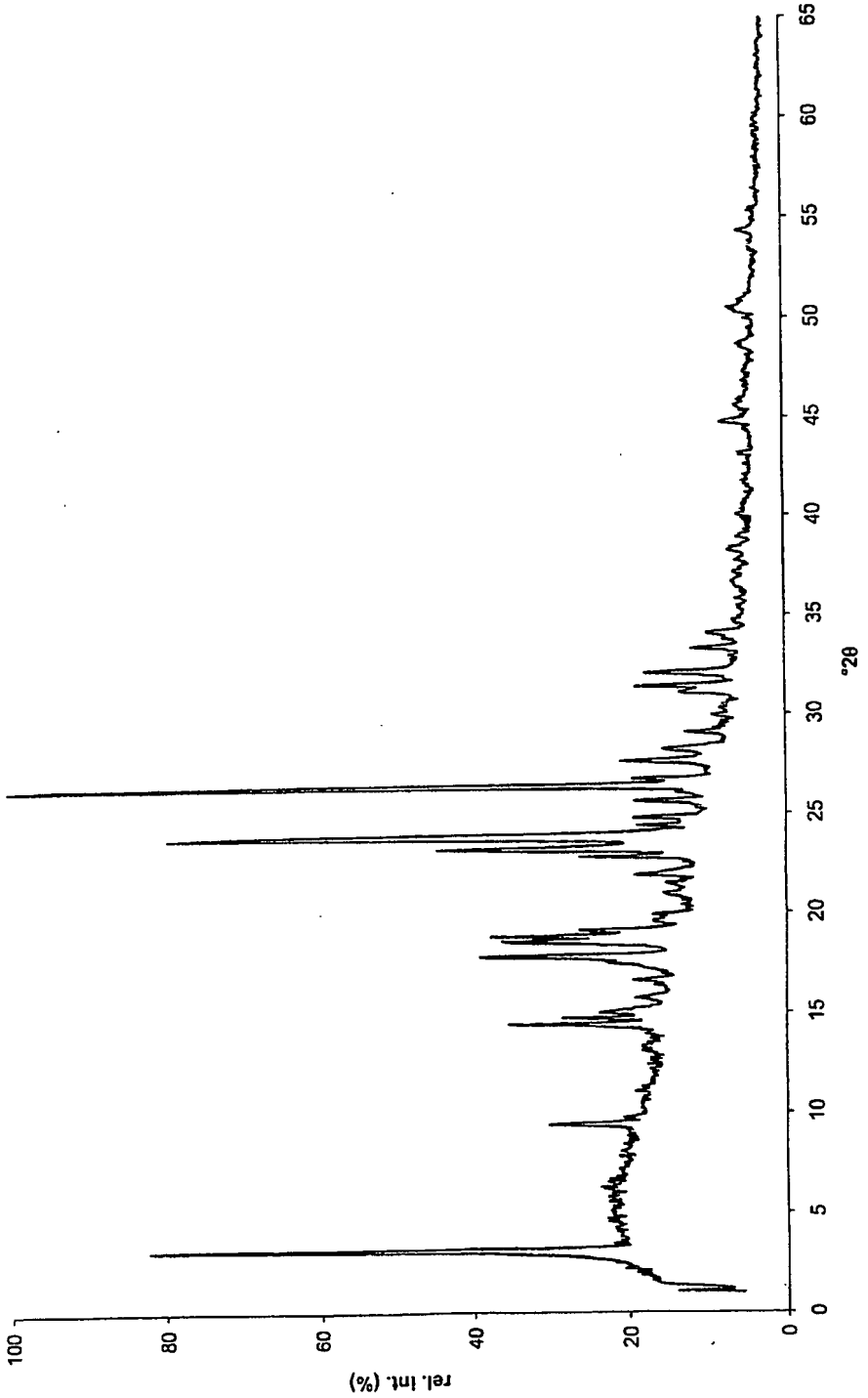

DVS Isotherm Plot
Cycle 2 Desorp
Cycle 1 Sorp
Cycle 1 Desorp
Change in Mass (%) - Dry
Target RH (%)
8
7
6
5
4
3
2
1
0
-1
0
10
20
30
40
50
60
70
80
90
100

Figure 9



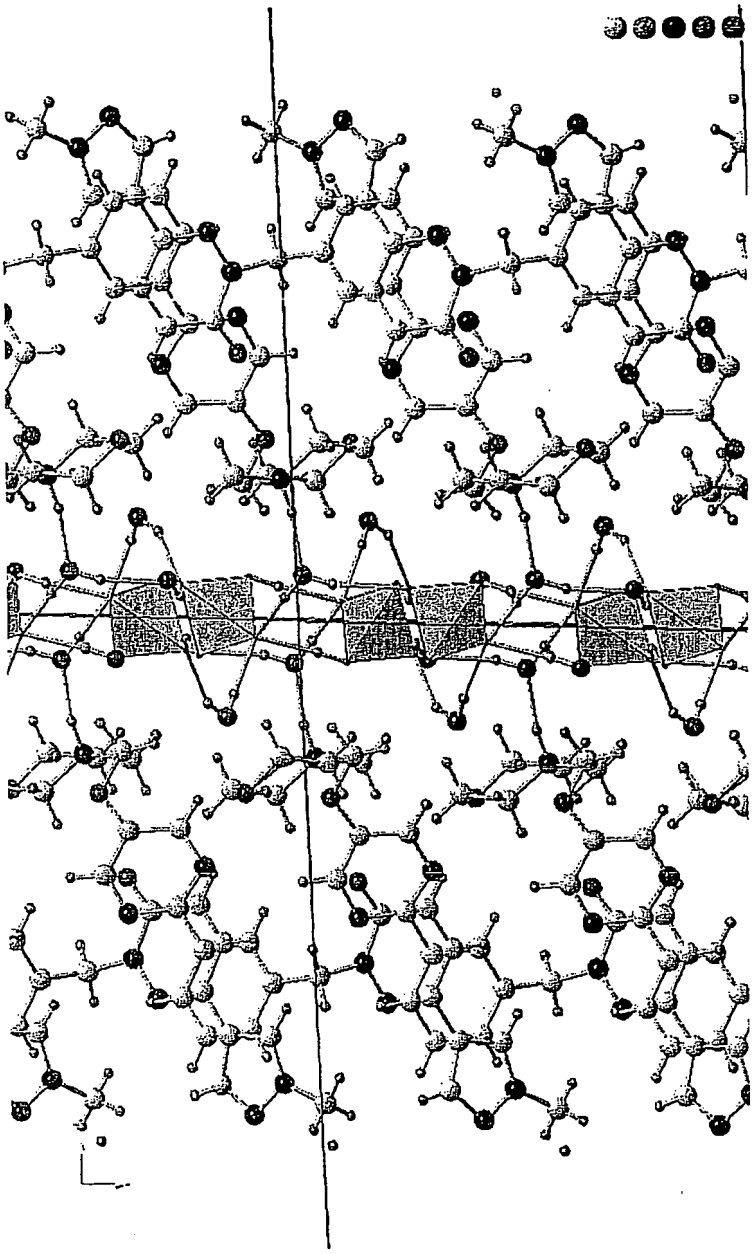


Figure 10

Figure 11

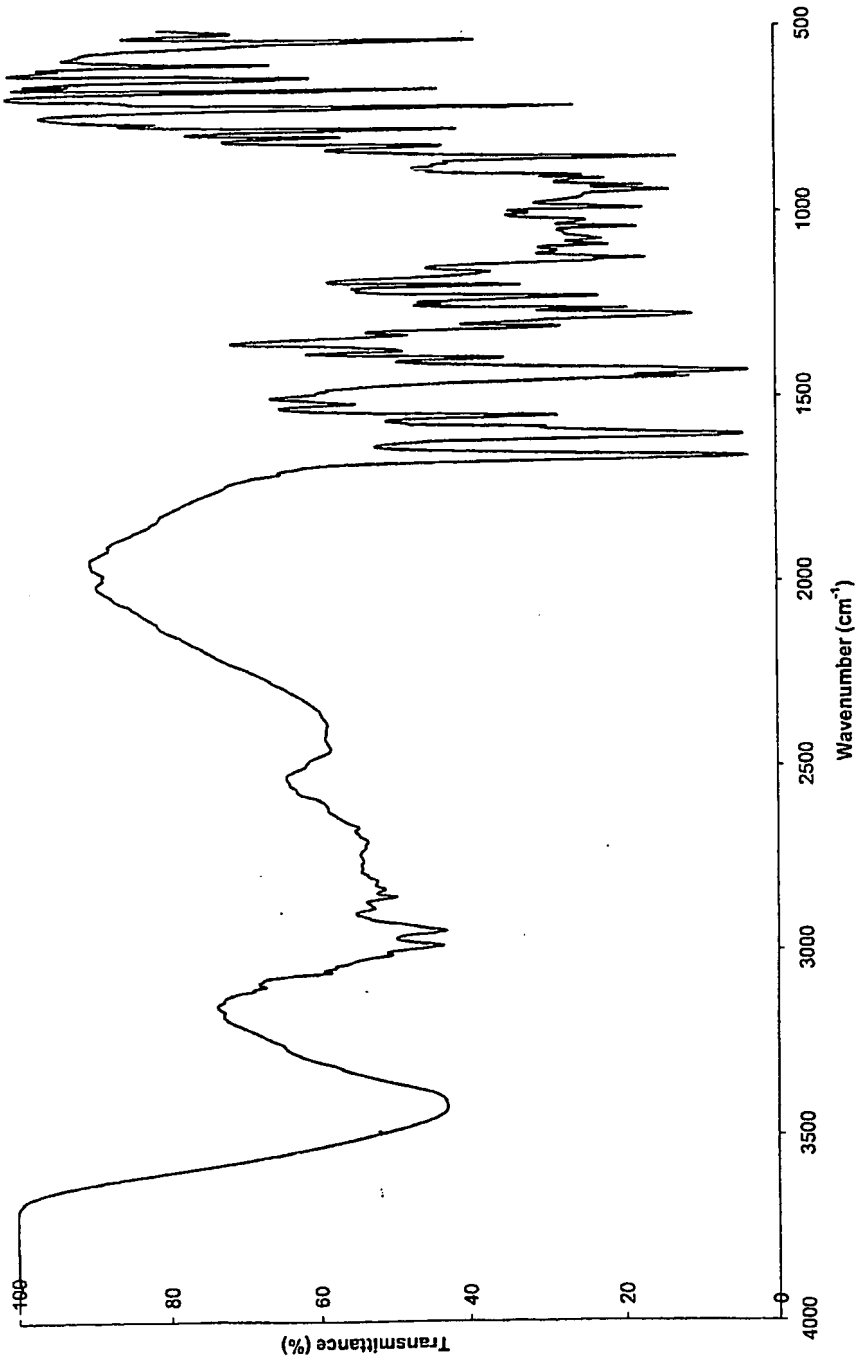

Transmittance (%)
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
500
Wavenumber (cm-1)

Figure 12

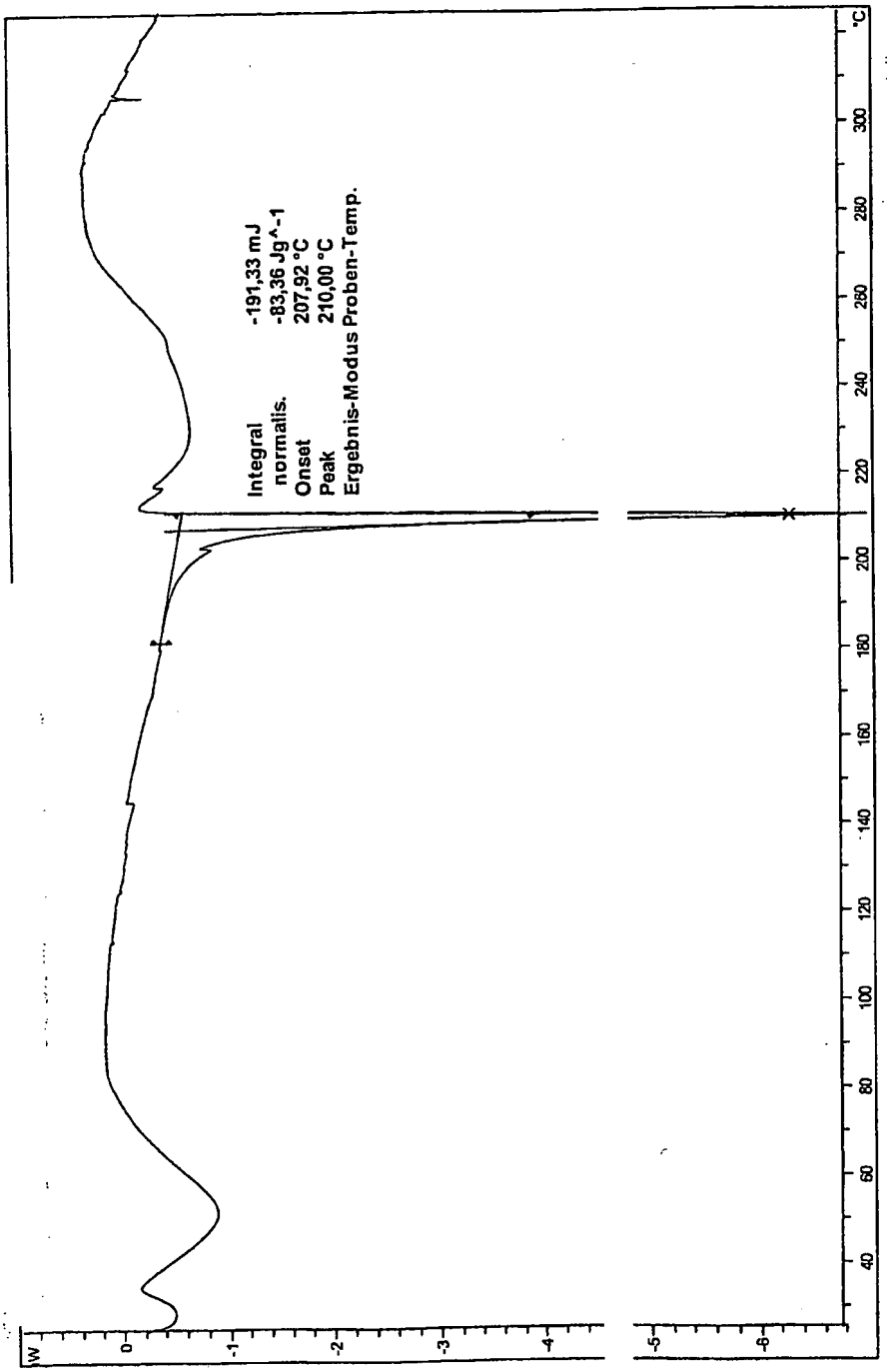

Integral -191,33 mJ
normalis. -83,36 Jg^-1
Onset 207,92 °C
Peak 210,00 °C
Ergebnis-Modus Proben-Temp.
W
°C

Figure 13

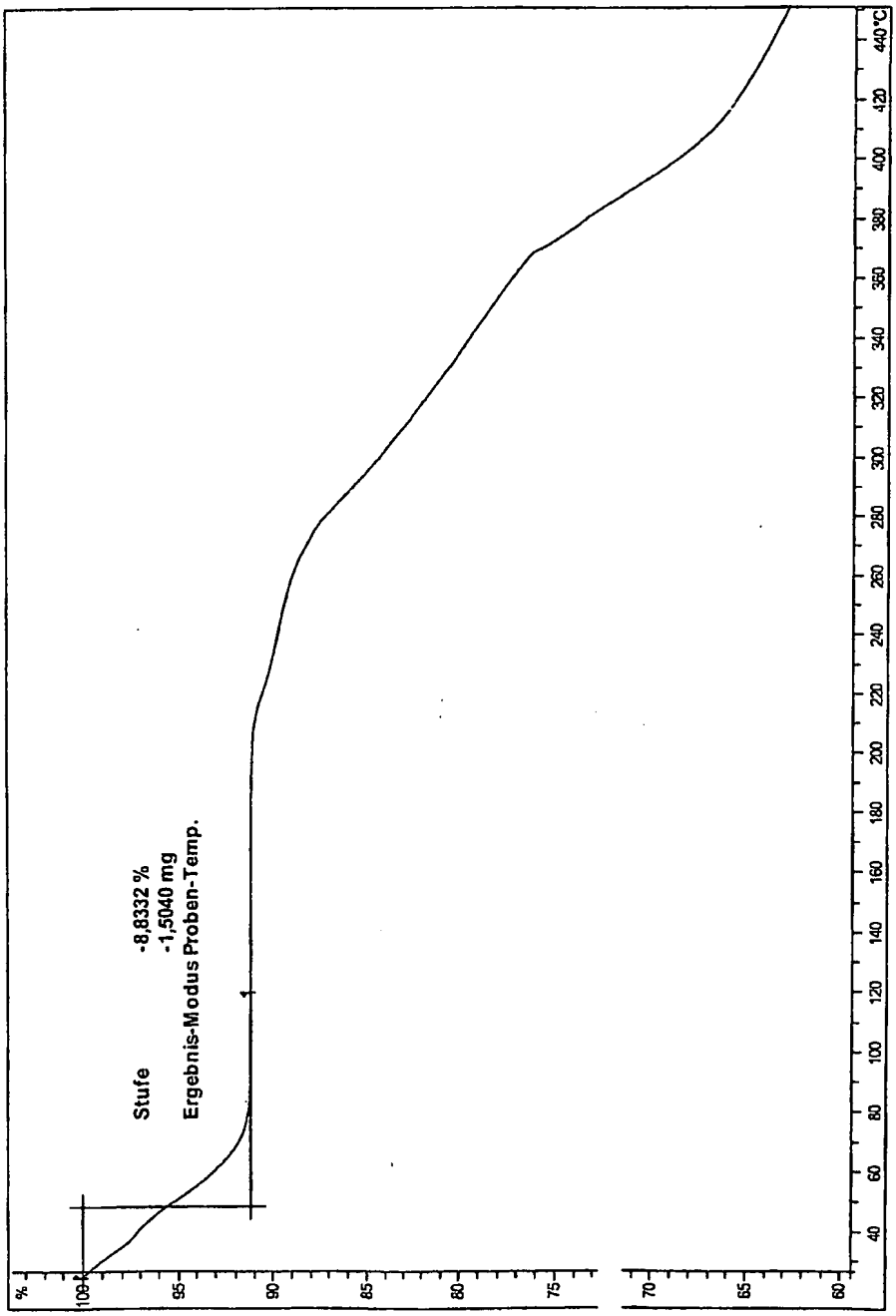


Figure 14

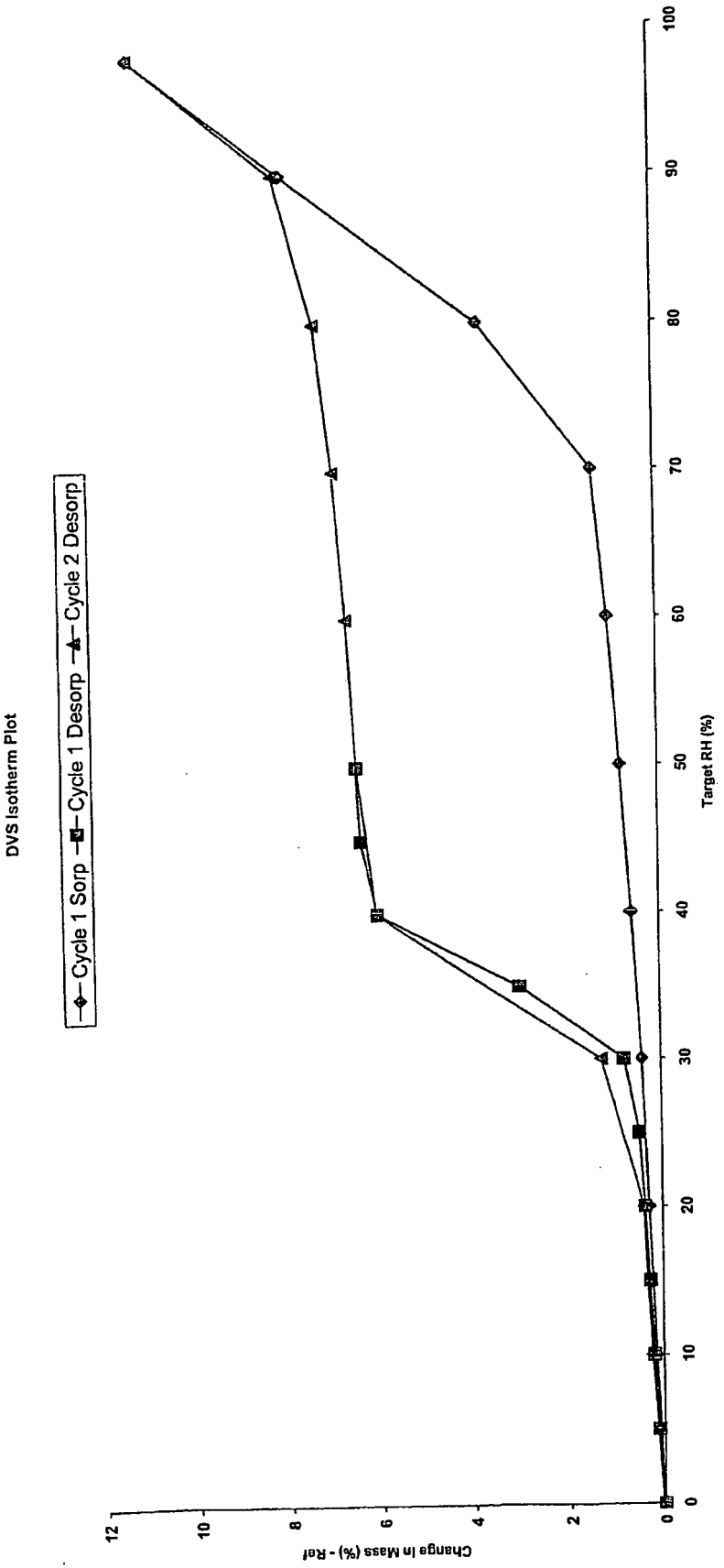
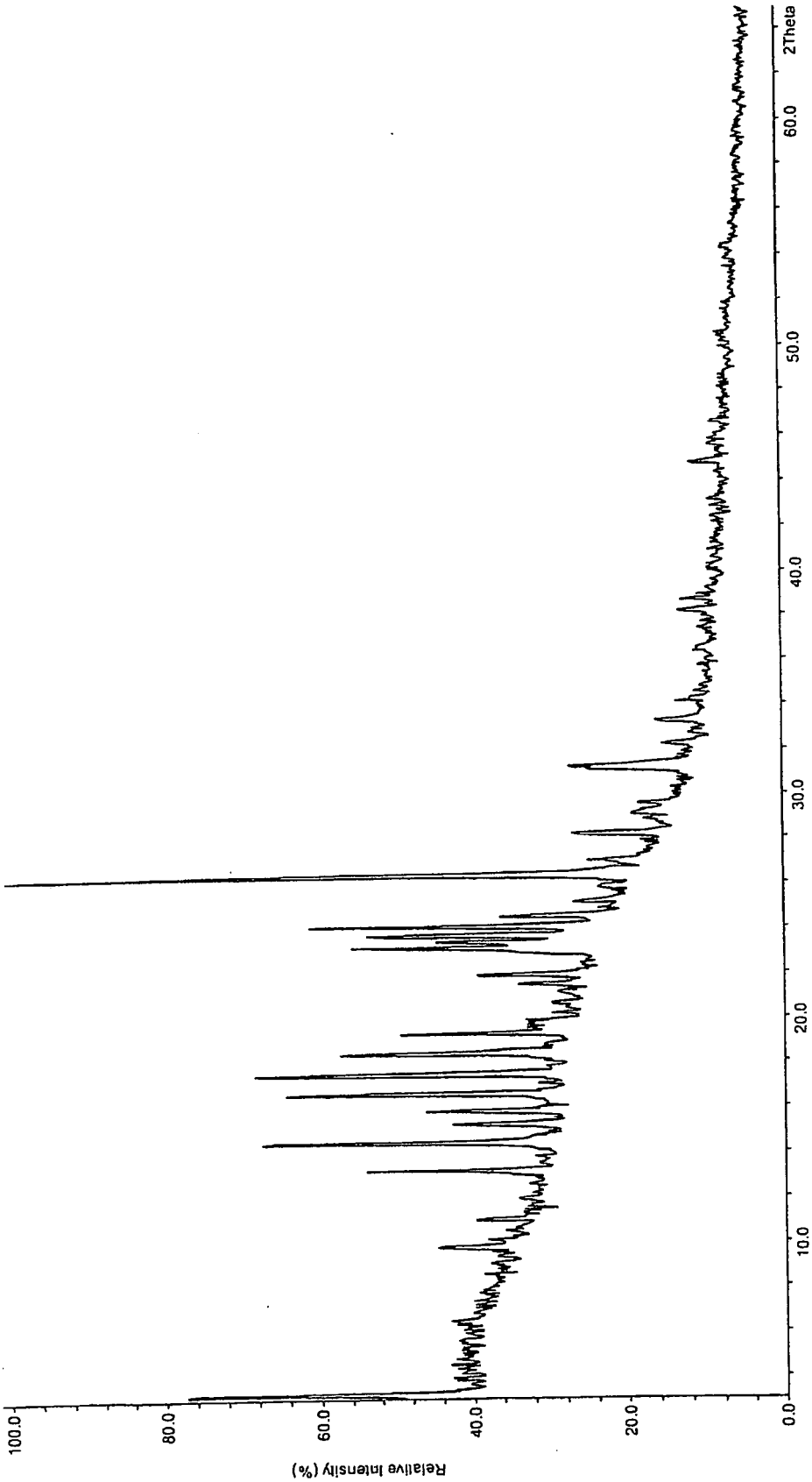

DVS Isotherm Plot
Cycle 1 Sorp
Cycle 1 Desorp
Cycle 2 Desorp
Change in Mass (%) - Ref
Target RH (%)
0
2
4
6
8
10
12
0
10
20
30
40
50
60
70
80
90
100

Figure 15


Relative Intensity (%)
100.0
80.0
60.0
40.0
20.0
0.0
10.0
20.0
30.0
40.0
50.0
60.0
2Theta

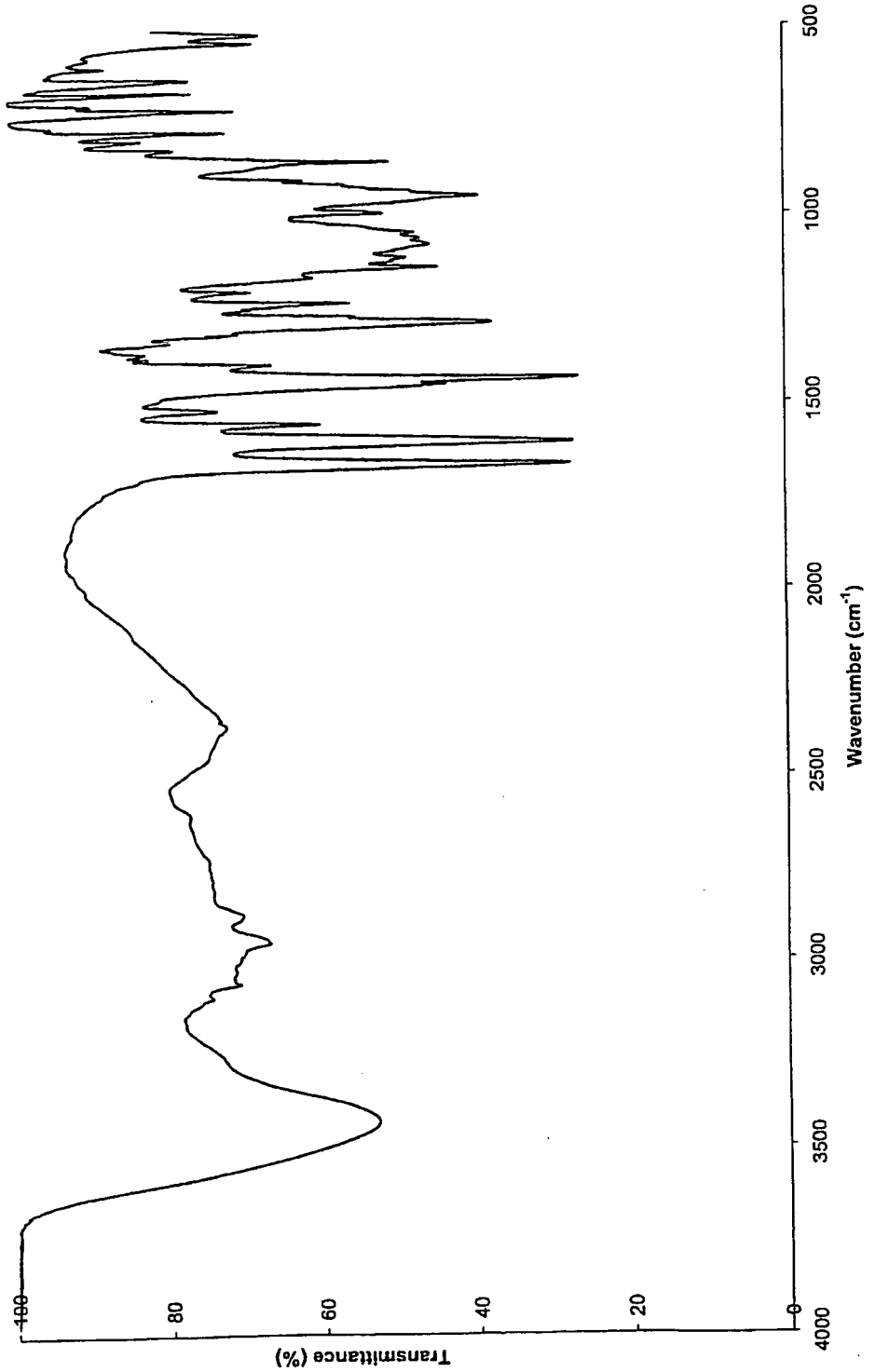

Transmittance (%)
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
500
Wavenumber (cm-1)

Figure 16

Figure 17

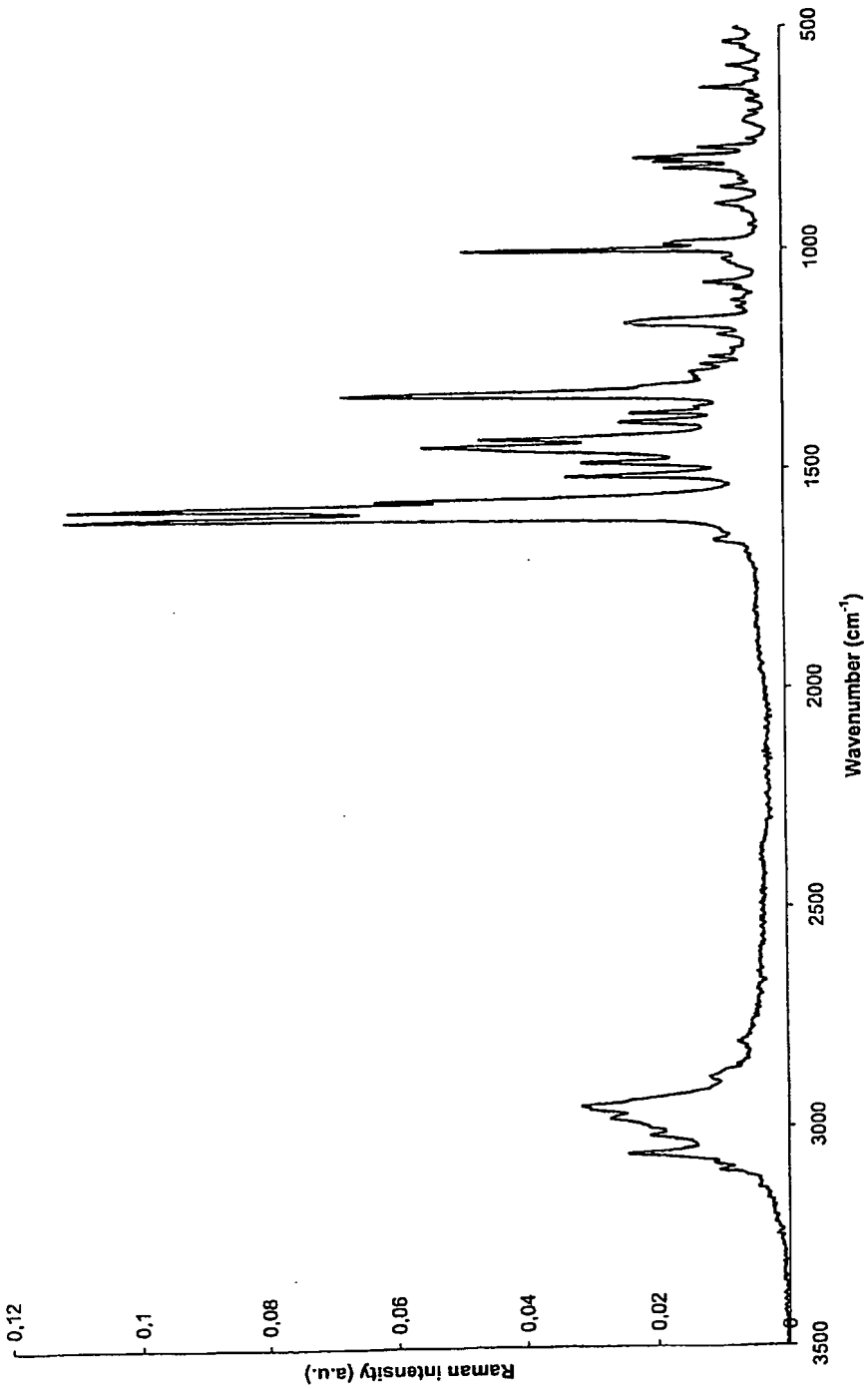

Raman intensity (a.u.)
0,12
0,1
0,08
0,06
0,04
0,02
0
3500
3000
2500
2000
1500
1000
500
Wavenumber (cm-1)

Figure 18

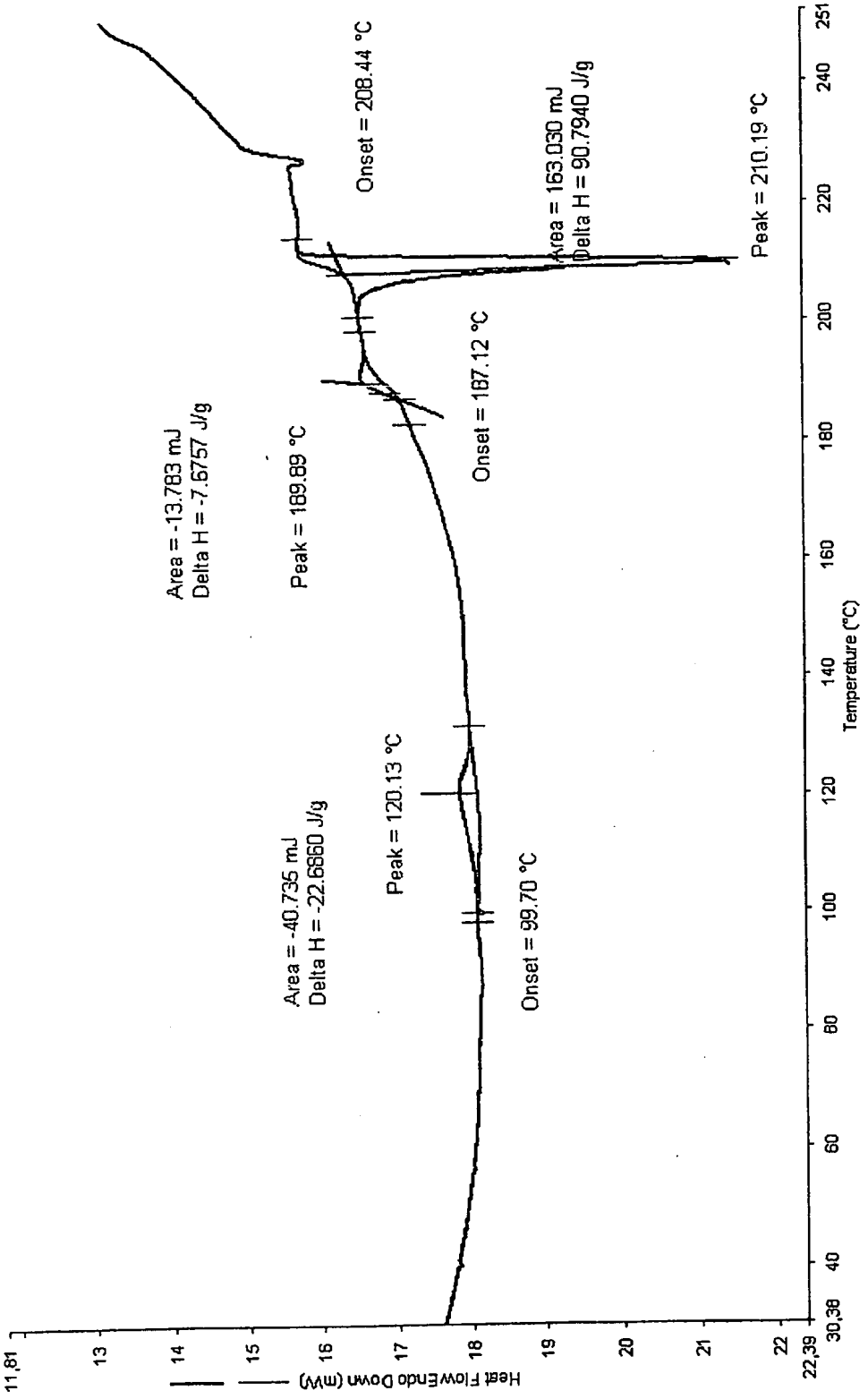

Area = -13.783 mJ
Delta H = -7.6757 J/g
Peak = 189.89 °C
Onset = 208.44 °C
Area = 163.030 mJ
Delta H = 90.7940 J/g
Peak = 210.19 °C
Onset = 187.12 °C
Area = -40.735 mJ
Delta H = -22.6860 J/g
Peak = 120.13 °C
Onset = 99.70 °C
Heat Flow Endo Down (mW)
Temperature (°C)
11,81
13
14
15
16
17
18
19
20
21
22
22,39
30,38
40
60
80
100
120
140
160
180
200
220
240

Figure 19

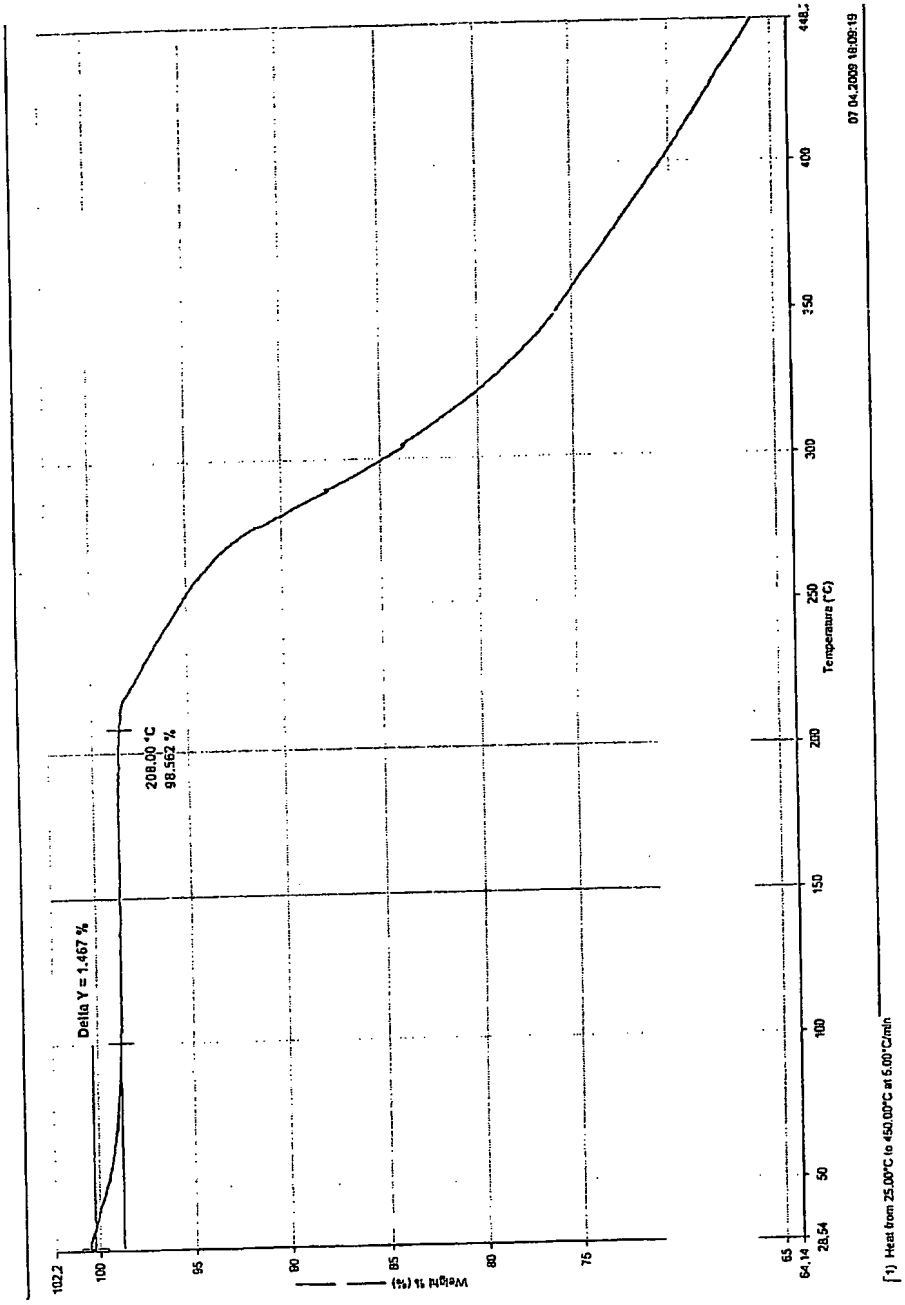

Delta Y = 1.467 %
208.00 °C
98.562 %
Weight % (%)
Temperature (°C)
07.04.2009 18:09:19
(1) Heat from 25.00°C to 450.00°C at 5.00°C/min

Figure 20

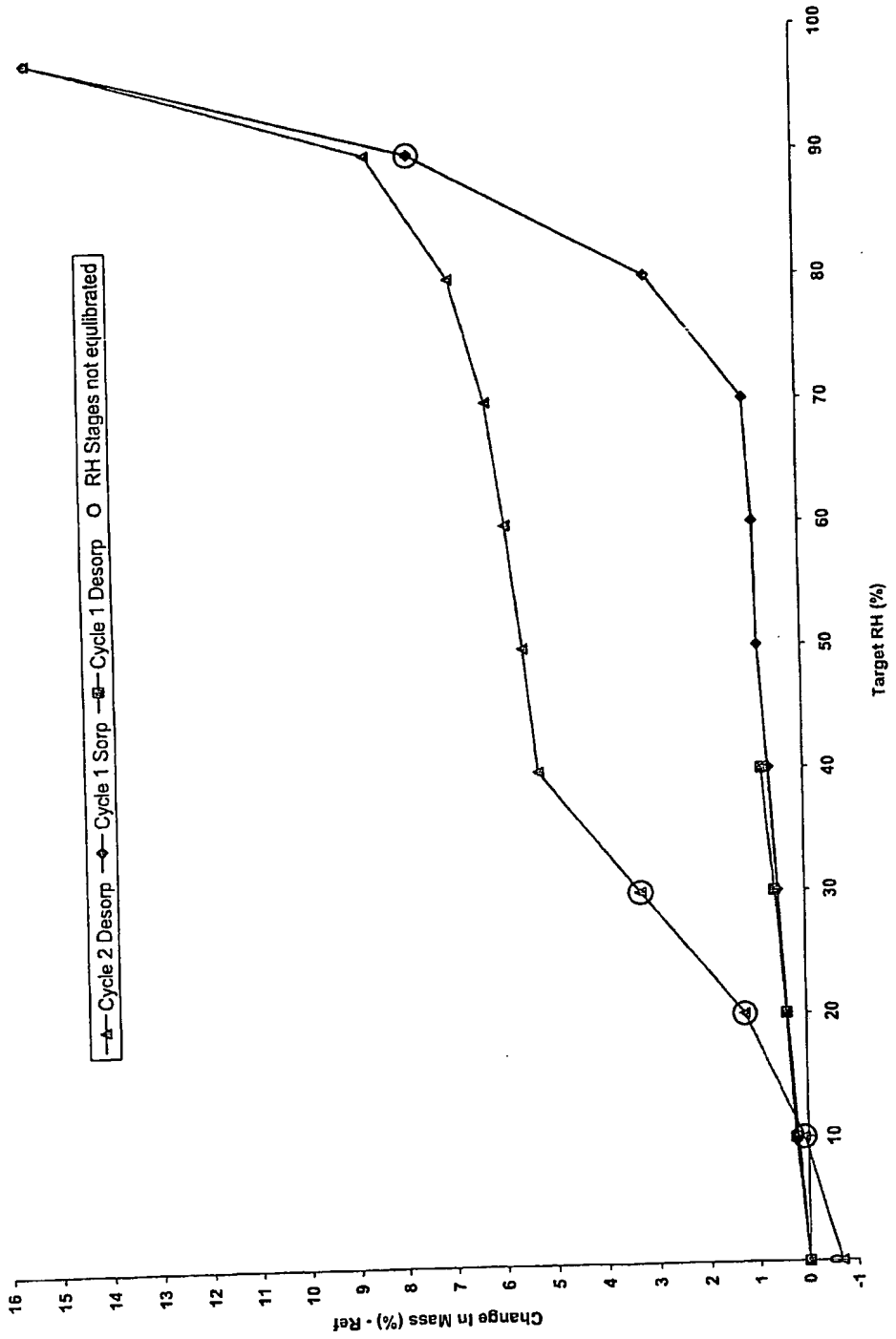

Cycle 2 Desorp
Cycle 1 Sorp
Cycle 1 Desorp
RH Stages not equilibrated
Change In Mass (%) - Ref
Target RH (%)
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
100
90
80
70
60
50
40
30
20
10

Figure 21

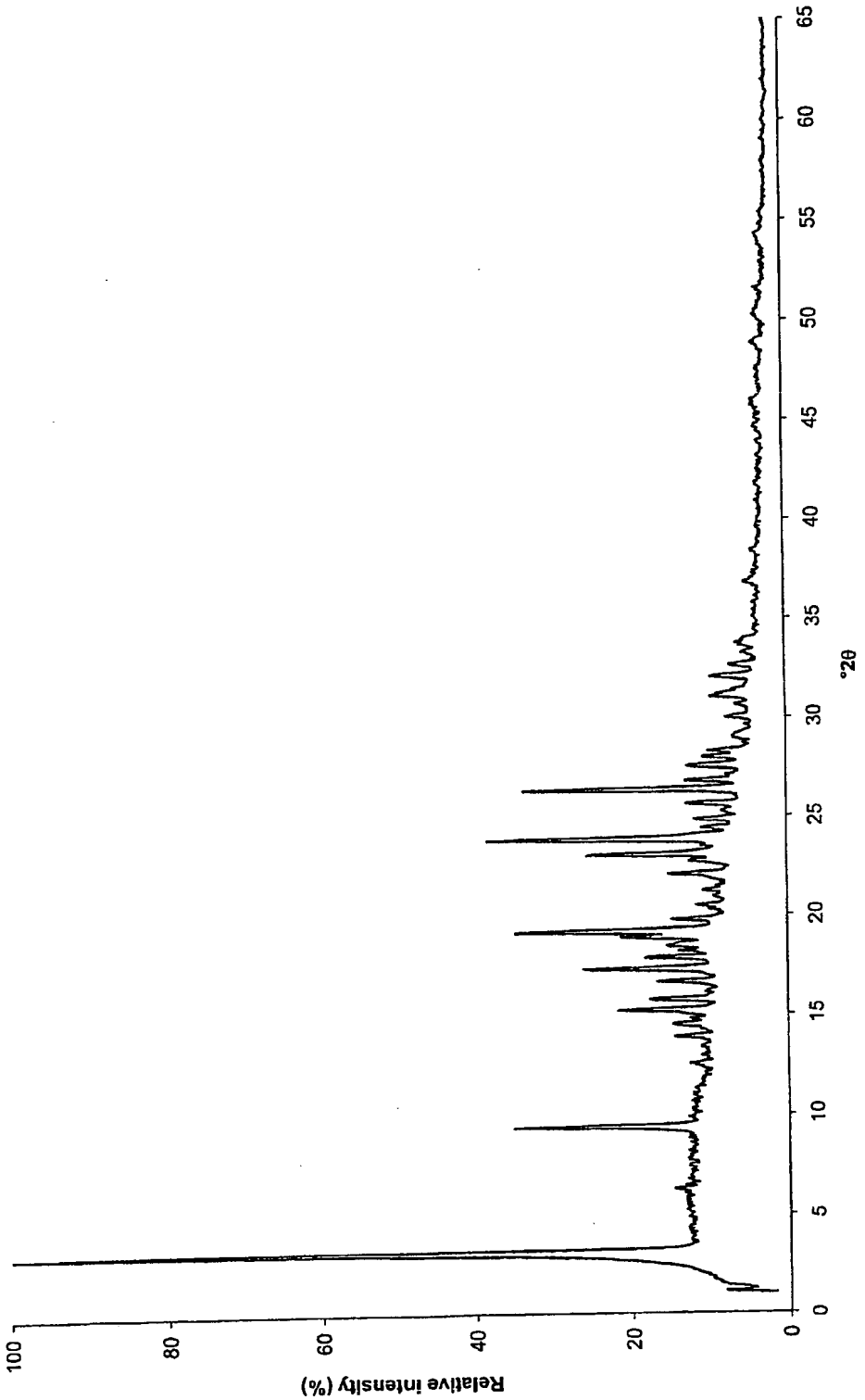

Relative intensity (%)
100
80
60
40
20
0
0
5
10
15
20
25
30
35
40
45
50
55
60
65
°2θ

Figure 22

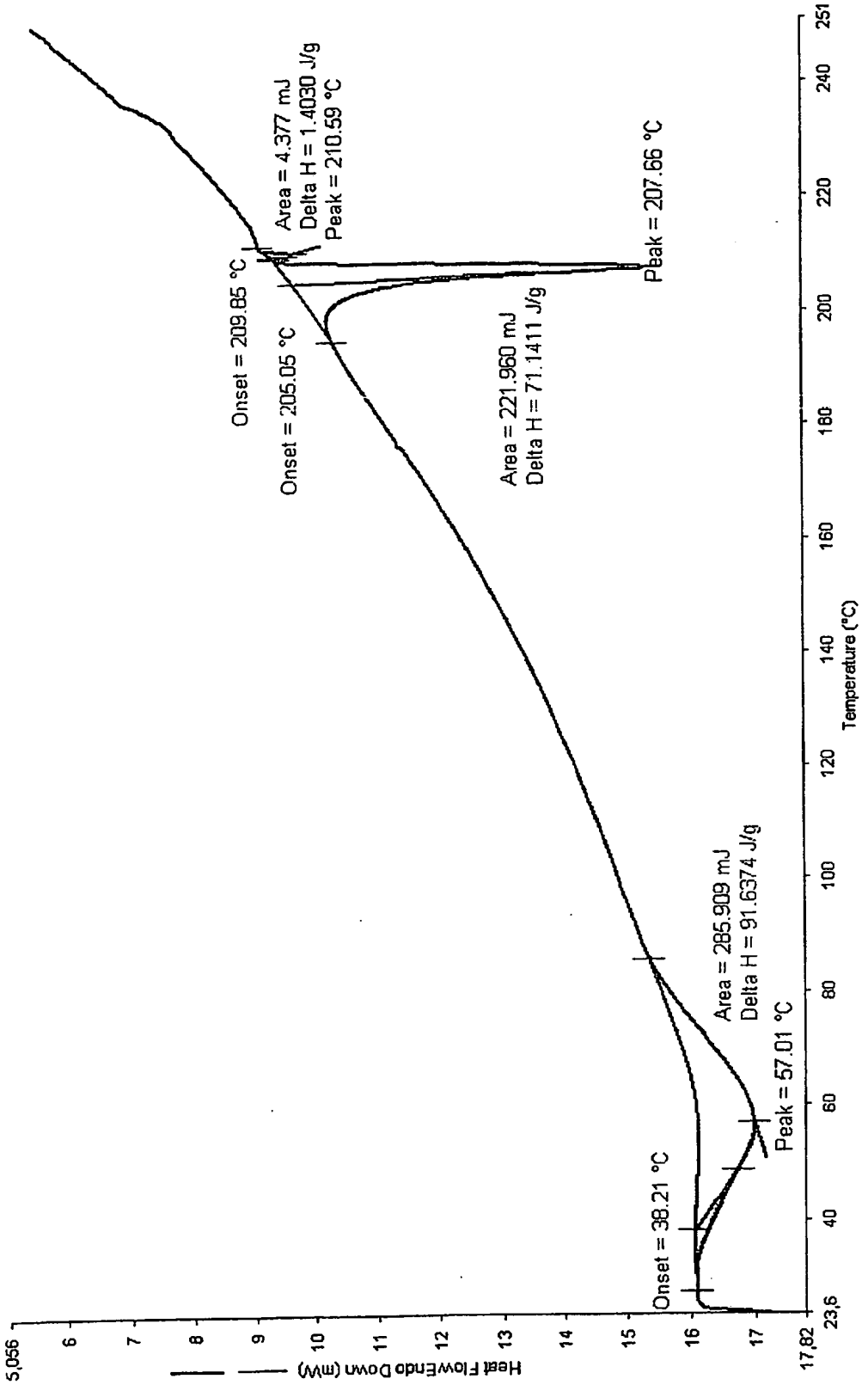

Onset = 209.85 °C
Area = 4.377 mJ
Delta H = 1.4030 J/g
Peak = 210.59 °C
Onset = 205.05 °C
Area = 221.960 mJ
Delta H = 71.1411 J/g
Peak = 207.66 °C
Area = 285.909 mJ
Delta H = 91.6374 J/g
Onset = 38.21 °C
Peak = 57.01 °C
Heat FlowEndo Down (mW)
Temperature (°C)
5,056
17,82
23,6
251

Figure 23

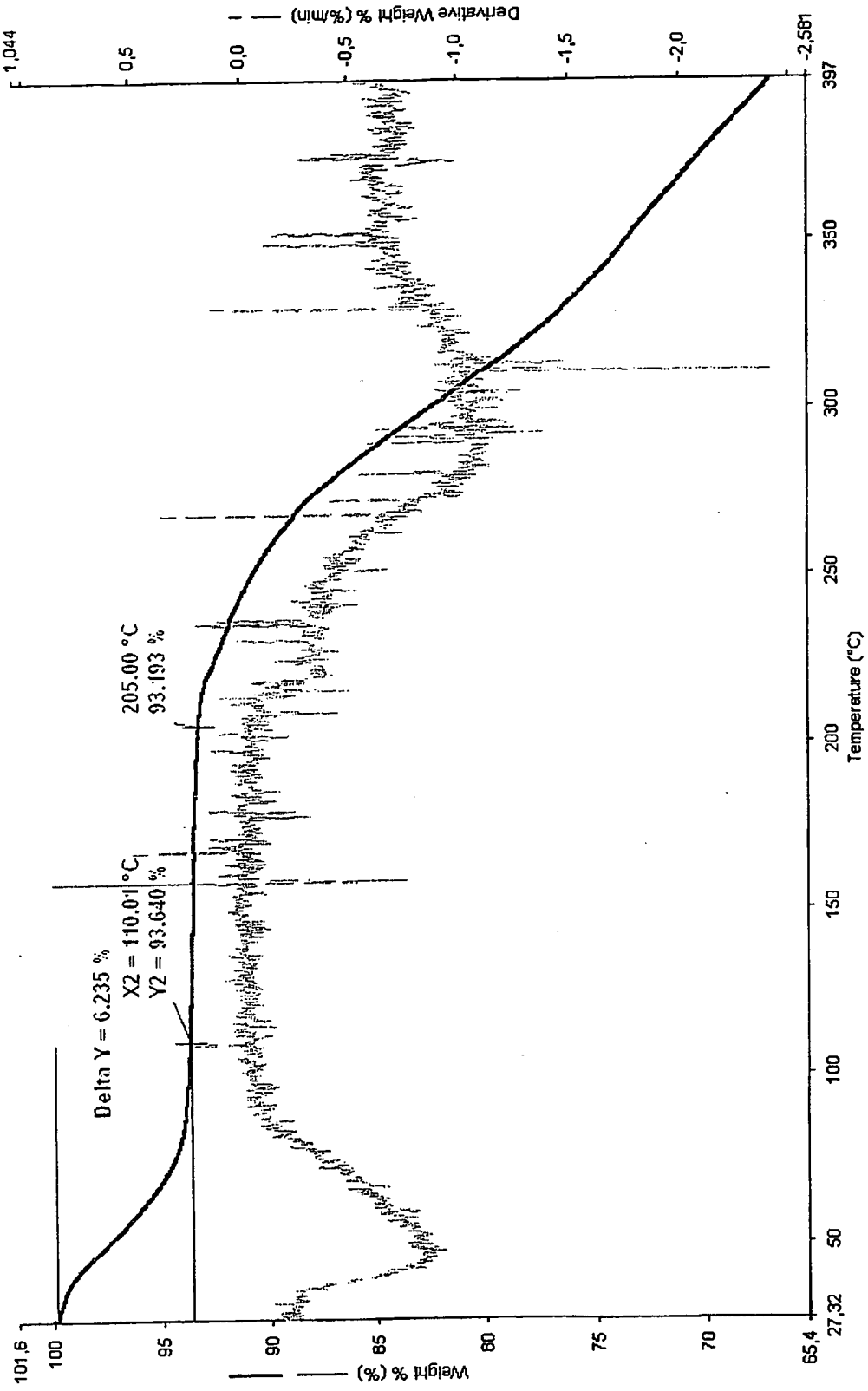
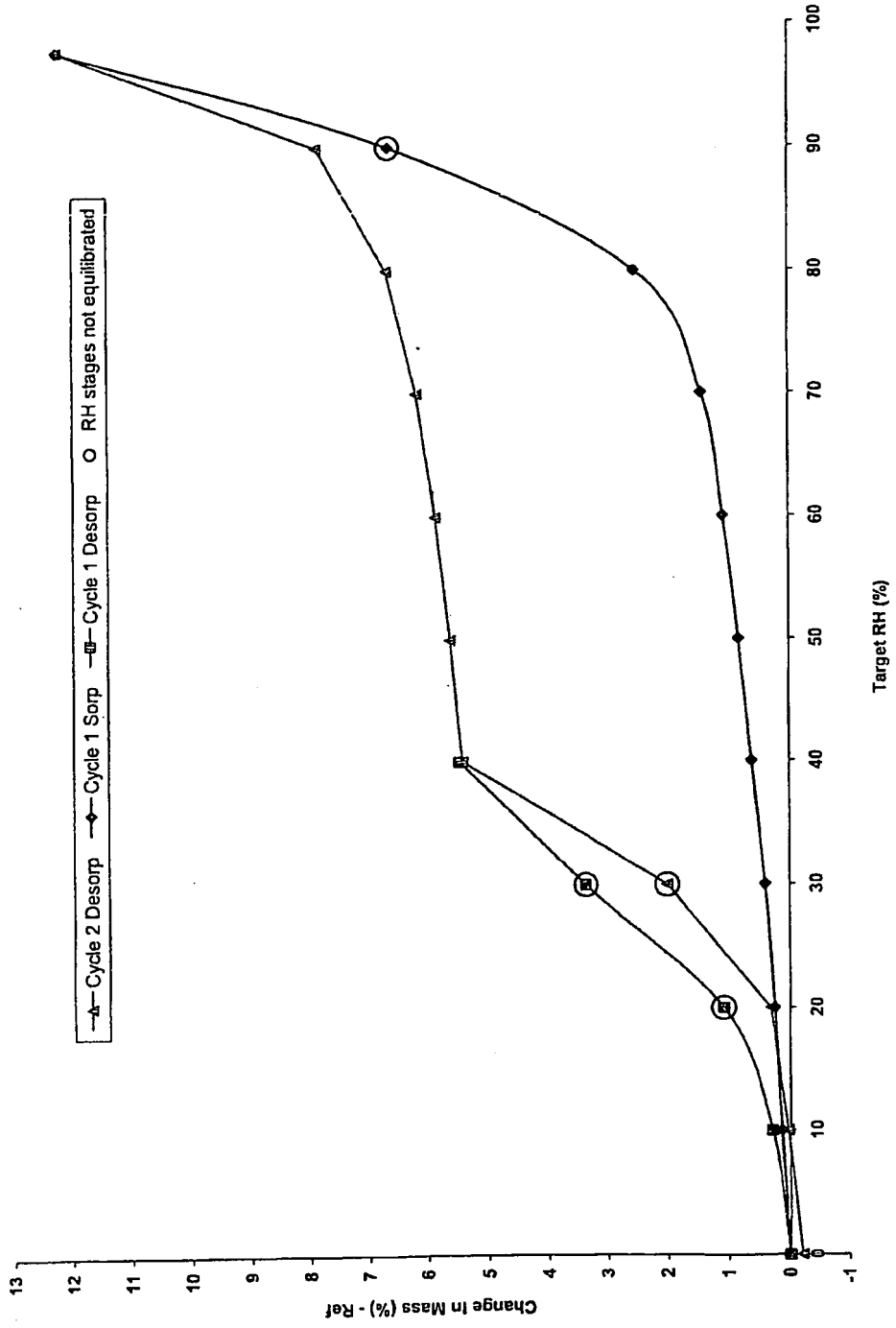

Derivative Weight % (%/min)
1,044
0,5
0,0
-0,5
-1,0
-1,5
-2,0
-2,581
397
350
300
250
200
150
100
50
27,32
Temperature (°C)
205.00 °C
93.193 %
Delta Y = 6.235 %
X2 = 110.01 °C
Y2 = 93.640 %
Weight % (%)
101,6
100
95
90
85
80
75
70
65,4

Figure 24


Cycle 2 Desorp
Cycle 1 Sorp
Cycle 1 Desorp
RH stages not equilibrated
Change In Mass (%) - Ref
Target RH (%)
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
100
90
80
70
60
50
40
30
20
10
0

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/008358

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/14 A61K31/506 A61P35/02

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 A61K 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 practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2009/007074 A (MERCK PATENT GMBH [DE]; SCHADT OLIVER [DE]; DORSCH DIETER [DE]; STIEBE) 15 January 2009 (2009-01-15) cited in the application examples A,C	1
A	WO 2007/065518 A (MERCK PATENT GMBH [DE]; DORSCH DIETER [DE]; SCHADT OLIVER [DE]; BLAUKA) 14 June 2007 (2007-06-14)	

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 February 2010	15/02/2010
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Skulj, Primoz

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/008358

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009007074 A	15-01-2009	AR 066543 A1	26-08-2009
		AR 067505 A1	14-10-2009
		DE 102007032507 A1	02-04-2009
		WO 2009006959 A1	15-01-2009
WO 2007065518 A	14-06-2007	AR 057214 A1	21-11-2007
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		EA 200801428 A1	30-10-2008
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		EP 1960370 A1	27-08-2008
		JP 2009518323 T	07-05-2009
		KR 20080077664 A	25-08-2008
		US 2008293719 A1	27-11-2008
		ZA 200805877 A	29-07-2009

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 102264729 A
(43)申请公布日 2011.11.30

(21)申请号 200980151790.0

(22)申请日 2009.11.24

(30)优先权数据
08022253.2 2008.12.22 EP

(85)PCT申请进入国家阶段日
2011.06.22

(86)PCT申请的申请数据
PCT/EP2009/008358 2009.11.24

(87)PCT申请的公布数据
WO2010/072295 EN 2010.07.01

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(51)Int.Cl.
C07D 403/14(2006.01)
A61K 31/506(2006.01)
A61P 35/02(2006.01)

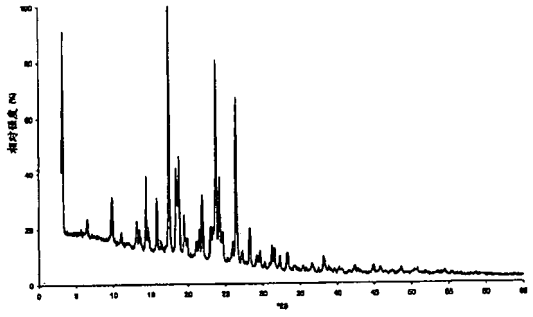
权利要求书 7 页 说明书 46 页 附图 24 页

(54)发明名称

6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐的新多晶型物及其制备方法

(57)摘要

本发明涉及6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐、它的溶剂合物和其结晶变型。本发明还涉及制备这些结晶变型的方法以及它们在治疗和/或预防生理学和/或病理生理学病症中的用途，所述生理学和/或病理生理学病症是通过抑制、调控和/或调节激酶信号转导、特别是通过抑制酪氨酸激酶而被引起、介导和/或传播的，例如病理生理学病症，如癌症。



CN 102264729 A

1. 6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐。

2. 6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐溶剂合物，优选6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐水合物。

3. 权利要求2的化合物，为其结晶变型。

4. 6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐无水物。

5. 权利要求4的化合物，为其结晶变型A1，特征是XRD峰包括3.2°、6.5°、9.8°和13.1° 2θ（全部±0.1° 2θ，使用Cu-Kα$_1$放射源）。

6. 权利要求4的化合物，为其结晶变型A1，特征是XRD峰包括18.4°、18.8°、23.7°、24.2°、26.4°和28.2° 2θ（全部±0.1° 2θ，使用Cu-Kα$_1$放射源）。

7. 权利要求4的化合物，为其结晶变型A1，特征是XRD峰包括14.4°、15.8°、17.5°、19.5°和21.9° 2θ（全部±0.1° 2θ，使用Cu-Kα$_1$放射源）。

8. 权利要求4至7中任意一项的化合物，为其结晶变型A1，特征是下面的XRD数据：

晶形A1：

峰编号	d/Å	°2θ (Cu-Kα$_1$放射源) ±0.1°
1	27.45	3.2
2	13.62	6.5
3	9.02	9.8
4	6.75	13.1
5	6.15	14.4
6	5.59	15.8
7	5.07	17.5
8	4.81	18.4
9	4.72	18.8
10	4.55	19.5
11	4.06	21.9
12	3.75	23.7
13	3.68	24.2
14	3.37	26.4
15	3.16	28.2

9.6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐二水合物。

10. 权利要求9的化合物，为其结晶变型H1，特征是XRD峰包括3.1°、9.4°和18.8° 2θ（全部±0.1° 2θ，使用Cu-Kα$_1$放射源）。

11. 权利要求9的化合物，为其结晶变型H1，特征是XRD峰包括19.1°、22.8°和26.4° 2θ（全部±0.1° 2θ，使用Cu-Kα$_1$放射源）。

12. 权利要求9的化合物，为其结晶变型H1，特征是XRD峰包括14.4°、15.0°和17.8° 2θ（全部±0.1° 2θ，使用Cu-Kα$_1$放射源）。

13. 权利要求9的化合物，为其结晶变型H1，特征是XRD峰包括14.7°、18.6°、23.2°、23.8°、26.8°和27.6° 2θ（全部±0.1° 2θ，使用Cu-Kα$_1$放射源）。

14. 权利要求9至13中任意一项的化合物，为其结晶变型H1，特征是下面的XRD数据：

晶形H1：

峰编号	d/Å	°2θ (Cu-Kα$_1$放射源) ±0.1°
1	28.42	3.1
2	9.40	9.4
3	6.13	14.4
4	6.01	14.7
5	5.89	15.0
6	4.97	17.8
7	4.77	18.6
8	4.71	18.8
9	4.64	19.1
10	3.89	22.8
11	3.83	23.2
12	3.73	23.8
13	3.38	26.4
14	3.33	26.8
15	3.22	27.6

15.6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐，为其结晶变型NF3，特征是XRD峰包括15.3°、16.7°、21.6°和23.1° 2θ（全部±0.1° 2θ，使用Cu-Kα$_1$放射源）。

16. 权利要求15的化合物，为其结晶变型NF3，特征是下面的XRD数据：

晶形 NF3：

峰编号	d/Å	°2θ (Cu-Kα$_1$ 放射源) ± 0.1°
1	27.30	3.2
2	13.62	6.5
3	9.02	9.8
4	6.71	13.2
5	6.11	14.5
6	5.79	15.3
7	5.57	15.9
9	5.32	16.7
9	5.05	17.5
10	4.81	18.4
11	4.58	19.4
12	4.12	21.6
13	4.04	22.0
14	3.84	23.1
15	3.75	23.7
16	3.69	24.1
17	3.37	26.4
ä18	3.16	28.3

17. 6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐水合物。

18. 权利要求 17 的化合物，为其结晶变型 NF5，特征是 XRD 峰包括 13.9°、15.7°、16.6°、17.3°、19.8° 和 22.1° 2θ（全部 ±0.1° 2θ，使用 Cu-Kα$_1$ 放射源）。

19. 权利要求 17 至 18 中任意一项的化合物，为其结晶变型 NF5，特征是下面的 XRD 数据：

晶形 NF5：

峰编号	d/Å	°2θ (Cu-Kα$_1$ 放射源) ± 0.1°
1	28.54	3.1
2	9.41	9.4
3	6.37	13.9
4	6.10	14.5
5	5.98	14.8
6	5.82	15.2
7	5.62	15.7
9	5.32	16.6
9	5.13	17.3
10	4.96	17.9
11	4.80	18.5
12	4.69	18.9
13	4.63	19.2
14	4.48	19.8
15	4.02	22.1
16	3.90	22.8
17	3.85	23.1
18	3.73	23.9
19	3.38	26.3
20	3.32	26.8
21	3.23	27.6

20. 药物组合物，其包含治疗有效量的至少一种权利要求 1 至 19 中任意一项所述的化合物。

21. 权利要求 9 中要求保护的药物组合物，其进一步包含至少一种另外的化合物，其选自生理可接受的赋形剂、辅剂、助剂、稀释剂、载体和 / 或另外的权利要求 1 至 19 中任意一项所述的化合物以外的药学活性物质。

22. 药剂，其包含至少一种权利要求 1 至 19 中任意一项所述的化合物或权利要求 20 至 21 中任意一项所述的药物组合物。

23. 根据权利要求 22 所述的药剂，其用于治疗和 / 或预防生理学和 / 或病理生理学病症，所述生理学和 / 或病理生理学病症是通过抑制、调控和 / 或调节激酶信号转导、特别是通过抑制酪氨酸激酶、优选 Met 激酶而被引起、介导和 / 或传播的。

24. 根据权利要求 22 所述的药剂，其用于治疗和 / 或预防生理学和 / 或病理病理学病

症，所述生理学和 / 或病理生理学病症选自：“癌症、肿瘤、恶性肿瘤、良性肿瘤、实体肿瘤、肉瘤、癌、过度增殖性障碍、类癌、尤因肉瘤、卡波西肉瘤、脑肿瘤、起源于脑和 / 或神经系统和 / 或脑脊膜的肿瘤、神经胶质瘤、成胶质细胞瘤、成神经细胞瘤、胃癌、肾癌、肾细胞癌、前列腺癌症、前列腺癌、结缔组织肿瘤、软组织肉瘤、胰腺肿瘤、肝肿瘤、头肿瘤、颈肿瘤、喉癌、食管癌、甲状腺癌、骨肉瘤、视网膜母细胞瘤、胸腺瘤、睾丸癌、肺癌、肺腺癌、小细胞肺癌、支气管癌、乳腺癌、乳房癌、肠癌、结肠直肠肿瘤、结肠癌、直肠癌、妇科肿瘤、卵巢肿瘤 / 卵巢的肿瘤、子宫癌、子宫颈的癌症、宫颈癌、子宫体的癌症、子宫体癌、子宫内膜癌、膀胱癌、泌尿生殖道癌、膀胱癌症、皮肤癌、上皮肿瘤、鳞状上皮癌、基底细胞癌、棘细胞癌、黑素瘤、眼内黑素瘤、白血病、单核细胞白血病、慢性白血病、慢性髓性白血病、慢性淋巴性白血病、急性白血病、急性髓性白血病、急性淋巴性白血病和 / 或淋巴瘤”。

25. 权利要求 22 至 24 中任意一项所要求保护的药剂，其中在所述药剂中包含至少一种另外的药理学活性物质。

26. 权利要求 22 至 24 中任意一项所要求保护的药剂，其中所述药剂在用至少一种另外的药理学活性物质进行治疗之前和 / 或期间和 / 或之后应用。

27. 药盒，其包含治疗有效量的至少一种权利要求 1 至 19 中任意一项所述的化合物和 / 或至少一种权利要求 20 至 21 中任意一项所要求保护的药物组合物和治疗有效量的至少一种另外的权利要求 1 至 19 中任意一项所要求保护的化合物以外的药理学活性物质。

28. 制备权利要求 5 至 8 中任意一项所述的结晶变型 A1 的方法，其包括以下步骤：

(a) 将 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮（游离碱）或其一种或多种盐溶解或分散在溶剂或溶剂混合物、优选 2- 丙醇或氯仿中，任选在搅拌下进行，

(b) 通过加入磷酸的水溶液或乙醇溶液将 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮（游离碱）或其一种或多种盐转化成相应的磷酸二氢盐，任选在搅拌下进行，

(c) 将步骤 (b) 得到的分散物于室温搅拌一个或多个小时或者一天或多天，优选 1 或 2 小时，

(d) 通过过滤回收沉淀的 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物，任选随后用溶剂或溶剂混合物洗涤，和任选随后干燥，优选在真空中干燥，任选于升高的温度 T、优选 30℃至 95℃、更优选 70℃干燥。

29. 制备权利要求 5 至 8 中任意一项所述的结晶变型 A1 的方法，其包括以下步骤：

(a) 将 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮（游离碱）或其一种或多种盐分散在溶剂或溶剂混合物、优选水中，和加入磷酸水溶液，任选在搅拌下进行，

(b) 将步骤 (a) 得到的分散物加热至升高的温度 T1，优选 30℃至 95℃，更优选 50℃，任选在搅拌下进行，和冷却得到的溶液，优选冷却至 0℃至 40℃，更优选冷却至 20℃，任选在搅拌下进行，然后将其用溶剂或溶剂混合物、优选丙酮稀释，任选在搅拌下进行，

(c) 将步骤 (b) 得到的分散物于 0℃至 40℃、优选 10℃进行搅拌，直至结晶完全，和 / 或将其于室温孵育一个或多个小时或者一天或多天，任选在搅拌下进行，

(d) 通过过滤回收沉淀的6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐无水物，任选将步骤(c)得到的分散物冷却至0℃至20℃、优选5℃，然后过滤，任选在搅拌下进行，任选随后用溶剂或溶剂混合物、优选丙酮洗涤，和任选随后干燥，优选在真空中干燥，任选于升高的温度T2、优选30℃至95℃、更优选70℃干燥，

(e) 任选地，将分散物形式的在溶剂或溶剂混合物、优选乙醇中的步骤(d)得到的干燥的晶体沸腾一分钟或多分钟、优选30分钟，和通过过滤从热分散物中回收它们。

30. 制备权利要求5至8中任意一项所述的结晶变型A1的方法，其包括以下步骤：

(a) 将6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮(游离碱)或其一种或多种盐分散在溶剂混合物、优选水：丙酮混合物中，和加入磷酸水溶液，任选在搅拌下进行，

(b) 将步骤(a)得到的分散物加热至升高的温度T1、优选30℃至95℃、更优选55℃，任选在搅拌下进行，和将所得的溶液冷却，优选冷却至0℃至50℃，任选在搅拌下进行，该冷却以既定的冷却速度、优选0.1-1K/min、更优选0.1-0.3K/min进行，任选在搅拌下进行，直至结晶开始，

(c) 进一步冷却步骤(b)得到的分散物，优选冷却至-20℃至0℃，更优选冷却至-10℃，任选在搅拌下进行，该冷却以既定的冷却速度、优选0.1-1K/min、更优选0.1-0.3K/min进行，任选在搅拌下进行，

(d) 将步骤(c)得到的分散物于-20℃至40℃、优选-10℃进行搅拌，直至结晶完全，

(e) 通过过滤回收结晶的6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐无水物，任选随后用溶剂或溶剂混合物、优选丙酮洗涤，和任选随后干燥，优选在真空中干燥，任选于升高的温度T2、优选30℃至95℃、更优选70℃干燥。

31. 制备权利要求10至14中任意一项所述的结晶变型H1的方法，其包括以下步骤：

(a) 将6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐无水物的结晶变型A1铺展在一个表面、优选容器的一个有边的表面、更优选培养皿的一个有边的表面上，和随后将其在密封的干燥器中在水或含水溶剂混合物上孵育一天或多天或者一周或多周。

32. 制备权利要求10至14中任意一项所述的结晶变型H1的方法，其包括以下步骤：

(a) 将6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐无水物的结晶变型A1分散在两种或更多种溶剂的混合物、优选二元混合物中，其中所述有机溶剂优选选自："水、甲醇、乙醇、2-丙醇、丙酮、TFH和乙腈"，任选在搅拌下进行，和将得到的分散物于升高的温度T1、优选30℃至95℃、更优选50℃搅拌一天或多天或者一周或多周，

(b) 通过过滤回收沉淀的6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐二水合物，任选随后用溶剂或溶剂混合物洗涤，和任选随后干燥，优选在真空中干燥，任选于升高的温度T2、优选30℃至95℃、更优选70℃干燥。

33. 制备权利要求15至16中任意一项所述的结晶变型NF3的方法，其包括以下步骤：

(a) 将 6-(1- 甲 基 -1H- 吡 唑 -4- 基)-2-{3-[5-(2- 吗 啉 -4- 基 - 乙 氧 基)- 嘧 啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 分散或溶解在两种或更多种溶剂的混合物、优选二元混合物中，其中所述溶剂优选选自："水、甲醇、乙醇、2- 丙醇、丙酮、TFH、乙腈和 1,4- 二噁烷"，任选在搅拌下进行，和随后于室温或升高的温度 T1、优选 30℃至 95℃、更优选 50℃蒸发所述两种或更多种溶剂的混合物，直至出现结晶，

(b) 通过过滤回收沉淀的 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐水合物，任选随后用溶剂或溶剂混合物洗涤，和任选随后干燥，优选在真空中干燥，任选于升高的温度 T2、优选 30℃至 95℃、更优选 70℃干燥。

34. 制备权利要求 18 至 19 中任意一项所述的结晶变型 NF5 的方法，其包括以下步骤：

(a) 将 6-(1- 甲 基 -1H- 吡 唑 -4- 基)-2-{3-[5-(2- 吗 啉 -4- 基 - 乙 氧 基)- 嘧 啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 溶解在二元溶剂混合物、优选水 : 甲醇、最优选比例为 1 : 1(v : v) 的水 : 甲醇中，和于升高的温度、优选 40-80℃、最优选 60℃在真空下快速蒸发溶剂混合物，直至获得沉淀物，

(b) 任选地，进一步将粉末形式的从步骤 (a) 获得的沉淀物铺展在一个表面、优选容器的一个有边的表面、更优选培养皿的一个有边的表面上，和随后将其在密封的干燥器中以既定的相对湿度 (RH)、优选 80-100％ RH、更优选 90-100％ RH 在水或盐的水溶液上孵育一天或多天或者一周或多周。

35. 制备权利要求 18 至 19 中任意一项所述的结晶变型 NF5 的方法，其包括以下步骤：

(a) 将粉末形式的 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐的晶形 NF3 铺展在一个表面、优选容器的一个有边的表面、更优选培养皿的一个有边的表面上，和随后将其在密封的干燥器中以既定的相对湿度 (RH)、优选 80-100％ RH、更优选 90-100％ RH 在水或盐的水溶液上孵育一天或多天或者一周或多周。

6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐的新多晶型物及其制备方法

[0001] 说明书

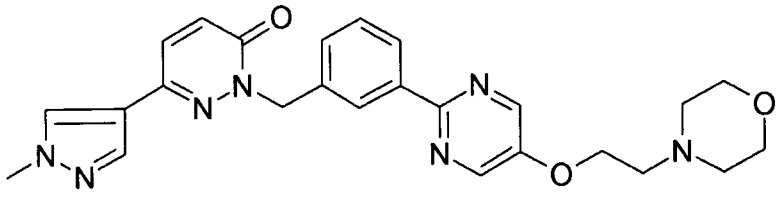
技术领域

[0002] 本发明涉及6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐、它的溶剂合物及其结晶变型(crystalline modification),以及它们的医学用途和制备方法。

现有技术

[0003] 6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮(I)

[0004]



(I)

[0005] 在2008年4月29日提交的国际专利申请PCT/EP2008/003473和2008年7月4日提交的国际专利申请PCT/EP2008/005508中首次被描述。

[0006] 在PCT/EP2008/003473中,6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮被称为化合物"A229"。PCT/EP2008/003473的实施例38描述了合成6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮的第一个方法。对甲苯磺酸盐和磷酸盐作为可能的盐形式被提及。此外,PCT/EP2008/003473的实施例39还描述了合成6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮的一个可供选择的方法。PCT/EP2008/005508的实施例1描述了与合成6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮的第一个方法相同的方法,并且作为可能的盐形式也提及了对甲苯磺酸盐和磷酸盐。PCT/EP2008/005508的实施例2作为另外的盐形式提及了硫酸盐、甲磺酸盐、苯磺酸盐、甲苯磺酸盐、富马酸盐和马来酸盐。

[0007] 这两篇现有技术文献均没有记载磷酸二氢盐形式的6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮,也没有提及6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐的多晶型物、结晶变型等。

[0008] 对于开发合适的药物剂型中所涉及的药用化合物而言,药用化合物的某些晶形、

即形态学形式或多晶型物可能是重要的。这是因为如果某种多晶型物在临床和稳定性研究中无法保持恒定，则所使用或所测量的精确剂量从一批到另一批可能不具有可比性。一旦一种药用化合物被生产待用，验证其在每种剂型中被递送的形态学形式或多晶型物是重要的，以确保生产方法产生相同的形式，并且在每个剂量中包含相同的药物量。因此，必须确保存在单一的形态学形式或多晶型物或者存在形态学形式或多晶型物的已知组合。此外，某些形态学形式或多晶型物可以显示出增强的热力学稳定性，并且可能比其它形态学形式或多晶型物更合适被包含在药物制剂中。

[0009] 本申请中对任何参考文献的引用不是承认该参考文献对于本申请而言是相关的现有技术。

发明内容

[0010] 本发明的目的是提供6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮的新的盐形式以及其新的多晶型物。

[0011] 本发明的目的在一方面已经通过提供6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐而令人惊奇地得到解决。

[0012] 本发明的目的在另一方面已经通过提供6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐溶剂合物、优选6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐水合物而令人惊奇地得到解决。

[0013] 已经发现6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐能在结晶变型中形成溶剂合物。这类溶剂合物的实例包括：在水中形成的溶剂合物；在醇如甲醇、乙醇、1-丙醇或2-丙醇中形成的溶剂合物；在有机酯如乙酸乙酯中形成的溶剂合物；在腈如乙腈中形成的溶剂合物；在酮如丙酮和丁酮中形成的溶剂合物；在醚如四氢呋喃(THF)中形成的溶剂合物；在氯代烃如氯仿中形成的溶剂合物；烃如正庚烷或甲苯的溶剂合物。优选的溶剂合物是与极性溶剂、优选水、醇、有机酯、腈、酮和醚形成的。

[0014] 优选地，6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐在结晶变型中形成无水物和与水、丙酮、四氢呋喃、甲醇、乙酸乙酯或正庚烷的溶剂合物，意指结合的溶剂与6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐一起构成晶体结构。溶剂与6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐的摩尔比能如本领域技术人员所知的那样变化。所述摩尔比优选在0.25 ： 1至2.5 ： 1之间，更优选在0.5 ： 1至1 ： 1之间，最优选为1 ： 1(正庚烷溶剂合物1/15 ： 1)。应当理解的是，本发明的无水物和溶剂合物可以含有非结合水，即不是结晶水的水。

[0015] 因此，在一个优选的实施方案中，6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐溶剂合物、优选6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄

基}-2H-哒嗪-3-酮磷酸二氢盐水合物以其结晶变型的形式被提供。

[0016] 本发明的目的在另一方面已经通过提供6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐无水物而令人惊奇地得到解决。

[0017] 在一个优选的实施方案中,6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐无水物以其结晶变型A1的形式被提供,所述结晶变型A1的特征是XRD峰包括3.2°、6.5°、9.8°和13.1° 2θ(全部±0.1° 2θ,使用Cu-Kα$_1$放射源)。

[0018] 在一个优选的实施方案中,6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐无水物以其结晶变型A1的形式被提供,所述结晶变型A1的特征是XRD峰包括18.4°、18.8°、23.7°、24.2°、26.4°和28.2° 2θ(全部±0.1° 2θ,使用Cu-Kα$_1$放射源)。

[0019] 在一个优选的实施方案中,6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐无水物以其结晶变型A1的形式被提供,所述结晶变型A1的特征是XRD峰包括14.4°、15.8°、17.5°、19.5°和21.9° 2θ(全部±0.1° 2θ,使用Cu-Kα$_1$放射源)。

[0020] 在一个优选的实施方案中,6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐无水物以其结晶变型A1的形式被提供,所述结晶变型A1的特征是以下XRD数据:

[0021] 晶形A1:

[0022]

峰编号	d/Å	°2θ (Cu-Kα1 放射源) ± 0.1°	指标化 (h, k, l)
1	27.45	3.2	(2, 0, 0)
2	13.62	6.5	(4, 0, 0)
3	9.02	9.8	(6, 0, 0)
4	6.75	13.1	(8, 0, 0)
5	6.15	14.4	(-2, 0, 2)
6	5.59	15.8	(-6, 0, 2)
7	5.07	17.5	(-8, 0, 2)
8	4.81	18.4	(9, 1, 0)
9	4.72	18.8	(-9, 1, 1)
10	4.55	19.5	(6, 0, 2)
11	4.06	21.9	(8, 0, 2)
12	3.75	23.7	(11, 1, 1)
13	3.68	24.2	(2, 2, 1)
14	3.37	26.4	(3, 1 3)
15	3.16	28.2	(-15, 1, 2)

[0023] 本发明的目的在另一方面已经通过提供6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐二水合物而令人惊奇地得到解决。

[0024] 在一个优选的实施方案中,6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐二水合物以其结晶变型H1的形式被提供,所述结晶变型H1的特征是XRD峰包括3.1°、9.4°和18.8° 2θ(全部±0.1° 2θ,使用Cu-Kα1放射源)。

[0025] 在一个优选的实施方案中,6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐二水合物以其结晶变型H1的形式被提供,所述结晶变型H1的特征是XRD峰包括19.1°、22.8°和26.4° 2θ(全部±0.1° 2θ,使用Cu-Kα1放射源)。

[0026] 在一个优选的实施方案中,6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐二水合物以其结晶变型H1的形式被提供,所述结晶变型H1的特征是XRD峰包括14.4°、15.0°和17.8° 2θ(全部±0.1° 2θ,使用Cu-Kα1放射源)。

[0027] 在一个优选的实施方案中,6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐二水合物以其结晶变型H1的形式被提供,所述结晶变型H1的特征是XRD峰包括14.7°、18.6°、23.2°、

23.8°、26.8° 和 27.6° 2θ（全部 ±0.1° 2θ，使用 Cu-Kα1 放射源）。

[0028] 在一个优选的实施方案中，6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐二水合物以其结晶变型 H1 的形式被提供，所述结晶变型 H1 的特征是以下 XRD 数据：

[0029] 晶形 H1：

[0030]

峰编号	d/Å	°2θ (Cu-Kα1 放射源) ± 0.1°	指标化 (h, k, l)
1	28.42	3.1	(1, 0, 0)
2	9.40	9.4	(3, 0, 0)
3	6.13	14.4	(0, 0, 2)
4	6.01	14.7	(2, 1, 1)
5	5.89	15.0	(1, 0, 2)
6	4.97	17.8	(3, 0, 2)
7	4.77	18.6	(4, 1, 1)
8	4.71	18.8	(6, 0, 0)
9	4.64	19.1	(5, 1, 0)
10	3.89	22.8	(2, 2, 0)
11	3.83	23.2	(-1, 2, 1)
12	3.73	23.8	(-2, 2, 1)
13	3.38	26.4	(0, 2, 2)
14	3.33	26.8	(-4, 1, 3)
15	3.22	27.6	(-3, 2, 2)

[0031]

[0032] 本发明的目的在另一方面已经通过以其结晶变型 NF3 的形式提供 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐（结晶变型 NF3 可以是水合物或无水物）而令人惊奇地得到解决，所述结晶变型 NF3 的特征是 XRD 峰包括 15.3°、16.7°、21.6° 和 23.1° 2θ（全部 ±0.1° 2θ，使用 Cu-Kα1 放射源）。

[0033] 在一个优选的实施方案中，6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐以其结晶变型 NF3 的形式被提供，所述结晶变型 NF3 的特征是以下 XRD 数据：

[0034] 晶形 NF3：

[0035]

峰编号	d/Å	°2θ (Cu-Kα$_1$ 放射源) ± 0.1°
1	27.30	3.2
2	13.62	6.5
3	9.02	9.8
4	6.71	13.2
5	6.11	14,5
6	5.79	15.3
7	5.57	15.9
9	5.32	16.7
9	5.05	17.5
10	4.81	18.4
11	4.58	19.4
12	4.12	21.6
13	4.04	22.0
14	3.84	23.1
15	3.75	23.7
16	3.69	24.1
17	3.37	26.4
18	3.16	28.3

[0036]

[0037] 本发明的目的在另一方面已经通过以结晶变型 NF5 的形式提供 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐水合物而令人惊奇地得到解决，所述结晶变型 NF5 的特征是 XRD 峰包括 13.9°、15.7°、16.6°、17.3°、19.8° 和 22.1° 2θ（全部 ±0.1° 2θ，使用 Cu-Kα$_1$ 放射源）。

[0038] 在一个优选的实施方案中，6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐水合物以其结晶变型 NF5 的形式被提供，所述结晶变型 NF5 的特征是以下 XRD 数据：

[0039] 晶形 NF5：

[0040]

峰编号	d/Å	°2θ (Cu-Kα$_1$ 放射源) ± 0.1°
1	28.54	3.1
2	9.41	9.4
3	6.37	13.9
4	6.10	14.5
5	5.98	14.8
6	5.82	15.2
7	5.62	15.7
9	5.32	16.6
9	5.13	17.3
10	4.96	17.9
11	4.80	18.5
12	4.69	18.9
13	4.63	19.2
14	4.48	19.8
15	4.02	22.1
16	3.90	22.8
17	3.85	23.1
18	3.73	23.9
19	3.38	26.3
20	3.32	26.8
21	3.23	27.6

[0041]

[0042] 在本发明中，术语“结晶变型”被用作术语“晶形”、“多晶型物”、“多晶型变型”、“形态学形式”等的同义词。

[0043] 本发明的结晶变型、特别是6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐无水物的结晶变型A1、6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐二水合物的结晶变型H1、6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐的结晶变型NF3(结晶变型NF3可以是水合物或无水物)和6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐水合物的结晶变型NF5令人惊奇地尤其具有以下特征：降低的吸湿性、在压片过

程中更好的可压性、延长的贮藏期、更好的热力学稳定性（即对抗热和湿度的稳定性）、对光（即紫外线）更好的耐受性、增加的堆积密度、改善的溶解性、从一批到另一批保持恒定的生物利用度特性、在压片过程中更好的流动和处理性质、改善的颜色稳定性和在生产过程中更好的过滤性质。因此，通过使用本发明的结晶变型，获得具有改善的均一性、稳定性、纯度和批间均匀度的药物制剂是可能的。

[0044] 此外，与 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐二水合物的结晶变型 H1 和 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐水合物的结晶变型 NF5 相比，6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 就干燥目的而言表现出更优越的性质（不会出现水合水的损失）并且在不同相对湿度 (RH) 条件下的物理稳定性方面表现出更优越的性质（在从 0％到至少 70％ RH 的湿度范围内为物理稳定形式）。此外，与 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐的结晶变型 NF3 相比，6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 会被认为是热力学更稳定的形式，如通过对晶形 A1 和 NF3 的二元混合物在多种有机溶剂中分别于 25℃和 50℃进行的竞争性浆液转化实验所示（参见实施例 10）。

[0045] 相比之下，与 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐二水合物的结晶变型 H1 和 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐水合物的结晶变型 NF5 相比，6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐的结晶变型 NF3 也就干燥目的而言表现出更优越的性质（不会出现水合水的损失）并且在不同相对湿度 (RH) 条件下的物理稳定性方面表现出更优越的性质（在从 0％到至少 70％ RH 的湿度范围内为物理稳定形式）。此外，与 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 相比，6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐的结晶变型 NF3 在水：丙酮 (30 ： 70，v ： v，2 小时后）的混合物中表现出更低的动力学溶解性，这使得结晶方法能在该与方法相关的溶剂混合物中具有更高的收率（参见实施例 14）。

[0046] 另一方面，与 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 相比，6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐水合物的结晶变型 NF5 在高水活度下是更稳定的形式，因此在水性分散体系中是有利的，如通过对晶形 NF5 和 A1 的二元混合物在 DI 水中于 25℃进行的竞争性浆液转化实验所示（参见实施例 11）。

[0047] 此外，与 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐水合物的结晶变型 NF5 相比，6-(1- 甲

基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐二水合物的结晶变型 H1 在高水活度下是更稳定的形式，因此在水性分散体系中是有利的，如通过对晶形 NF5 和 H1 的二元混合物在 DI 水中于 25℃进行的竞争性浆液转化实验所示，随着时间的推移得到晶形 H1（参见实施例 12）。此外，与 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐的结晶变型 NF3 相比，6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐二水合物的结晶变型 H1 在水性分散体系中是有利的，如通过对晶形 H1 和 NF3 的二元混合物在 DI 水中于 25℃进行的竞争性浆液转化实验所示，随着时间的推移得到晶形 H1（参见实施例 13）。

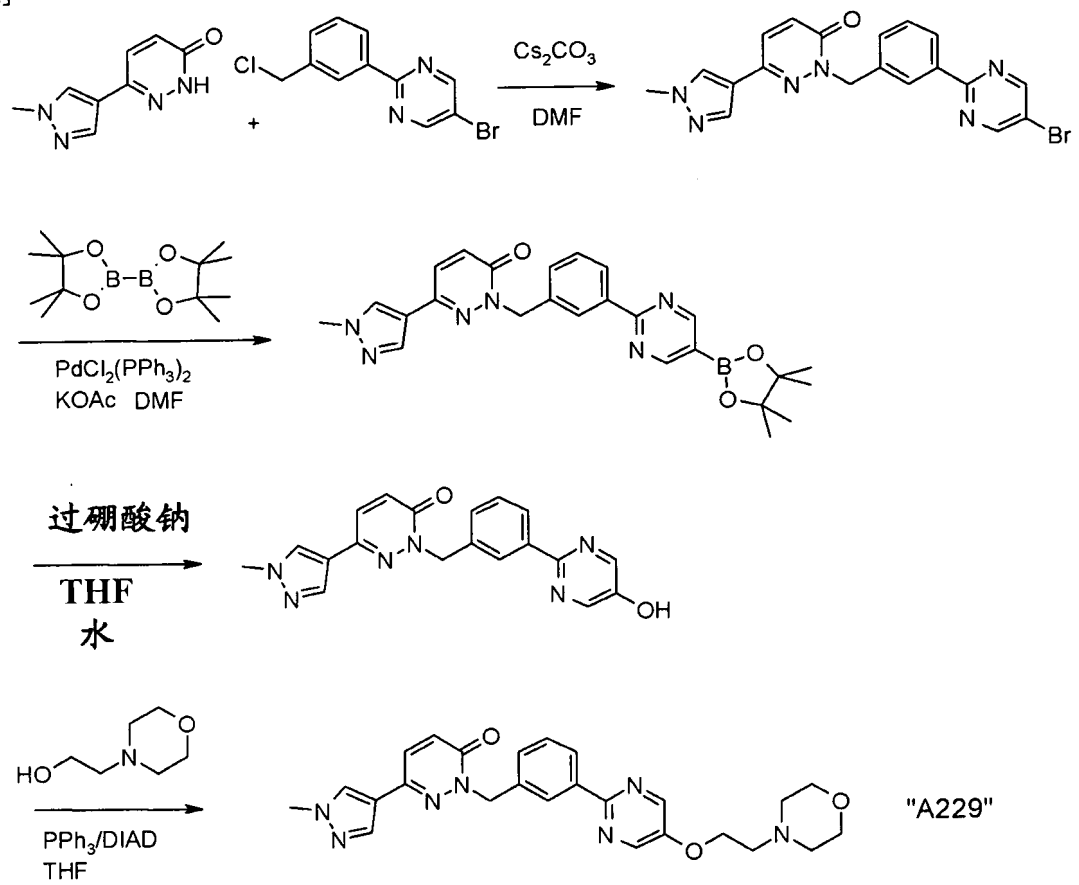
[0048] 对于 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐，与 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮（游离碱）相比，磷酸二氢盐在水性溶液中表现出显著更优的稳定性，在溶液中表现出升高的活性药物成分 (API) 稳定性。

[0049] 本发明的结晶变型可以根据标准方法表征，所述标准方法可以在例如 Rolf Hilfiker，'Polymorphism in the Pharmaceutical Industry'，Wiley-VCH，Weinheim 2006 和其中的参考文献中找到，例如 X 射线衍射 (XRD；第 6 章)、IR 和拉曼光谱（第 5 章)、差示扫描量热法 (DSC) 和热解重量分析法 (TGA)（第 3 章)、水蒸气吸附研究（第 9 章)，或者所述标准方法可以在例如 H. G. Brittain（编辑)，Polymorphism in Pharmaceutical Solids，Vol. 95，Marcel Dekker Inc.，纽约 1999（第 6 章：所有提及的技术）中找到。

[0050] 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐、6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐溶剂合物、优选 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐水合物、优选 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐水合物的结晶变型、6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐水合物的结晶变型 NF5、6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物、6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型、6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1、6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐二水合物、6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐二水合物的结晶变型、6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐二水合物的结晶变型 H1 和 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐的结晶变型 NF3 在下文被称为“本发明的产品”。

[0051] 6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮（游离碱）可以如PCT/EP2008/003473的实施例8和PCT/EP2008/005508的实施例1中所述的那样如下合成：

[0052]



[0053] 将7.68g(43.6mmol)6-(1-甲基-1H-吡唑-4-基)-2H-哒嗪-3-酮在90mlDMF中的混悬液与12.4g(43.6mmol)5-溴-2-(3-氯甲基-苯基)-吡啶和14.2g(43.6mmol)碳酸铯于室温在搅拌下反应24小时。将反应混合物加入到400ml水中。抽滤出所得的2-[3-(5-溴嘧啶-2-基)-苄基]-6-(1-甲基-1H-吡唑-4-基)-2H-哒嗪-3-酮沉淀物，用水洗涤并在真空中干燥。

[0054] 将14.0g(33.0mmol)2-[3-(5-溴嘧啶-2-基)-苄基]-6-(1-甲基-1H-吡唑-4-基)-2H-哒嗪-3-酮在65ml DMF中的混悬液与10.9g(42.9g)双（频哪醇合）二硼(bis(pinacolato)diboron)和9.72g(99.0mmol)乙酸钾反应并在氮气下加热至70℃。在该温度下搅拌15分钟后，加入695mg(0.99mmol)氯化双（三苯膦）-钯(II)并将反应混合物于70℃在氮气下搅拌18小时。随后，使反应混合物冷却至室温，加入水和二氯甲烷，将反应混合物在硅藻土上过滤，然后分离有机相。然后将有机相用硫酸钠干燥，浓缩，将残余物用2-丙醇重结晶，得到6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮。

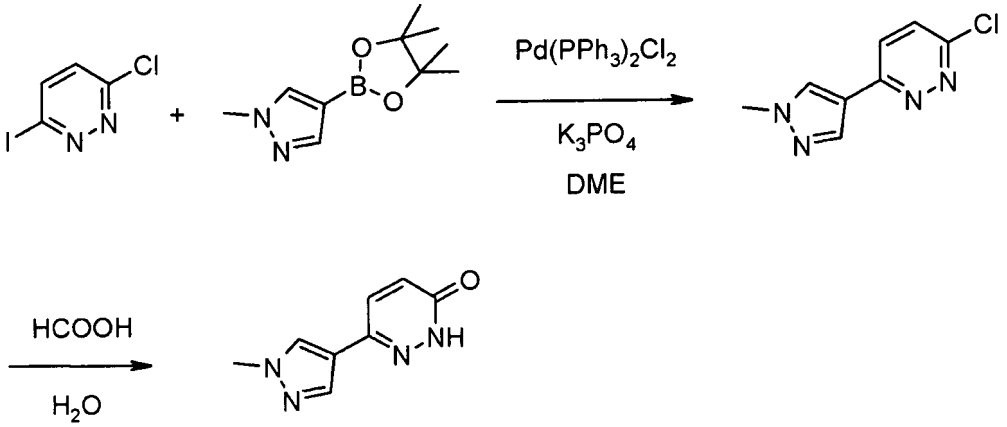
[0055] 在冰冷却下，向13.4g(28.4mmol)6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(4,4,5,5-四甲基-[1,3,2]二氧杂硼杂环戊烷-2-基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮在55ml THF和55ml水中的混悬液中分份加入8.50g(85.1mmol)过硼酸钠。将反应混合物于

室温搅拌 2 小时，然后在硅藻土上抽滤。将滤液在真空中浓缩至约初始体积的一半，用 2N 盐酸滴定至 pH 1。抽滤出所得的 2-[3-(5- 羟基 - 嘧啶 -2- 基)- 苄基]-6-(1- 甲基 -1H- 吡唑 -4- 基)-2H- 哒嗪 -3- 酮沉淀物，用水洗涤并在真空中干燥。

[0056] 向 360mg(1.00mmol)2-[3-(5- 羟基 - 嘧啶 -2- 基)- 苄基]-6-(1- 甲基 -1H- 吡唑 -4- 基)-2H- 哒嗪 -3- 酮在 2ml THF 中的混悬液中相继加入 394mg(1.50mmol) 三苯膦和 242μl(2.00mmol)4-(2- 羟基乙基) 吗啉。在冰冷却下缓慢滴加 294μl(1.50mmol) 偶氮二甲酸二异丙酯。将所得的溶液于室温搅拌 18 小时。然后将反应混合物在真空中浓缩并将油状残余物溶解在 2- 丙醇中。一段时间后抽滤出所得的 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮固体，用 2- 丙醇和甲基叔丁基醚洗涤并在真空中干燥。

[0057] 起始产品 6-(1- 甲基 -1H- 吡唑 -4- 基)-2H- 哒嗪 -3- 酮可以如 PCT/EP2008/003473(65-66 页) 中所述的那样如下合成：

[0058]

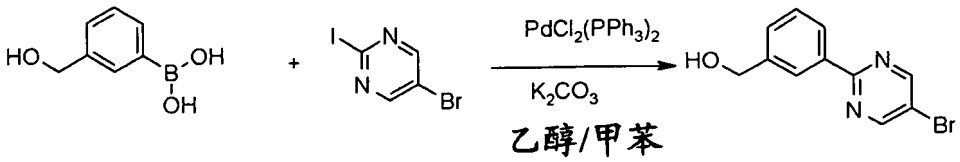


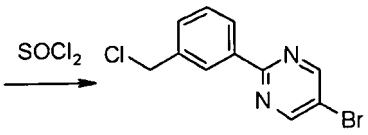
[0059] 将 815g(3.39mol)3- 氯 -6- 碘 - 哒嗪在 3.8L 1,2- 二甲氧基乙烷中的溶液与 705g(3.39mol)1- 甲基 -1H- 吡唑 -4- 硼酸频哪醇酯和 1.44kg 磷酸三钾三水合物反应。将所得的混悬液在氮气和搅拌下加热至 80℃并加入 59.5g(85mmol) 氯化双 (三苯膦)- 钯 (II)。将反应混合物于 80℃搅拌 3 小时。随后，使反应混合物冷却至室温并加入 9L 水。抽滤出所得的 3- 氯 -6-(1- 甲基 -1H- 吡唑 -4- 基)- 哒嗪沉淀物，用水洗涤并在真空中干燥。

[0060] 将 615g(2.90mol)3- 氯 -6-(1- 甲基 -1H- 吡唑 -4- 基)- 哒嗪在 1.86L 甲酸和 2.61L 水的混合物中的混悬液在搅拌下加热至 80℃并于该温度下继续搅拌 28 小时。将反应混合物冷却至室温，加入活性炭 (活性碳)，抽滤混合物。将滤液用 40％苛性钠水溶液在冰冷却下滴定至 pH 7 并随后于 6℃孵育 16 小时。抽滤出所得的 6-(1- 甲基 -1H- 吡唑 -4- 基)-2H- 哒嗪 -3- 酮沉淀物，用水洗涤并在真空中干燥。

[0061] 起始产品 5- 溴 -2-(3- 氯甲基 - 苯基)- 吡啶可以如 PCT/EP2008/003473 的实施例 36 中所述的那样如下合成：

[0062]



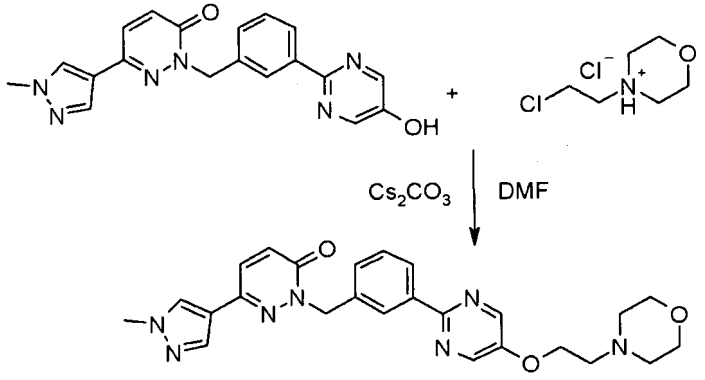


[0063] 将保持在氮气下的 95.0g(332mmol)5- 溴 -2- 碘吡啶在 325ml 甲苯中的溶液与 70.0g(660mmol) 碳酸钠在 325ml 水中的溶液反应，将混合物加热至 80℃。向反应混合物中加入 2.3g(3.3mmol) 氯化双（三苯膦）- 钯 (II)，随后滴加 50.0g(329mmol)3-（羟基甲基）- 苯硼酸在 650ml 乙醇中的溶液。将反应混合物于 80℃搅拌 18 小时。将反应混合物冷却至室温并过滤。将滤液与 1L 乙酸乙酯和 1L 水反应。分离有机相，用硫酸钠干燥并浓缩。将 [3-(5- 溴嘧啶 -2- 基）- 苯基]- 甲醇的残余物用 2- 丙醇重结晶。

[0064] 在搅拌下，向保持在 30℃的 159ml(2.19mol) 亚硫酰氯中分份加入 116g(438mmol) [3-(5- 溴嘧啶 -2- 基）- 苯基]- 甲醇。将反应混合物于室温搅拌 18 小时。随后，将反应混合物浓缩。将剩余物溶解在甲苯中并再次浓缩。将该操作重复三遍。将最终的 5- 溴 -2-(3- 氯甲基 - 苯基）- 吡啶剩余物用甲苯重结晶。

[0065] 作为替代选择，6-(1- 甲基 -1H- 吡唑 -4- 基）-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基）- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮（游离碱）可以如 PCT/EP2008/003473 的实施例 39 中所述的那样如下合成：

[0066]



"A229"

[0067] 将 360mg(1.00mmol)2-[3-(5- 羟基 - 嘧啶 -2- 基）- 苄基]-6-(1- 甲基 -1H- 吡唑 -4- 基）-2H- 哒嗪 -3- 酮、195mg(1.05mmol) 氯化 N-(2- 氯乙基）- 吗啉鎓和 521mg(1.60mmol) 碳酸铯在 2ml DMF 中的混悬液在搅拌下加热至 80℃并于该温度继续搅拌 6 小时。随后，使反应混合物冷却并加入 50ml 水。抽滤出所得的 6-(1- 甲基 -1H- 吡唑 -4- 基）-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基）- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮沉淀物，用水洗涤并在真空中干燥。

[0068] 在本发明的另一方面，提供了包含治疗有效量的至少一种本发明的产品的药物组合物。

[0069] 在一个优选的实施方案中，所述药物组合物进一步包含至少一种另外的化合物，其选自生理上可接受的赋形剂、辅剂 (auxiliary)、佐剂 (adjuvant)、稀释剂、载体和 / 或本发明的产品以外的另外的药学活性物质。

[0070] 本发明的另一个实施方案是制备所述药物组合物的方法，其特征在于将一种或多种本发明的产品和一种或多种另外的化合物转化成合适的剂型，所述另外的化合物选自固体、液体或半液体的赋形剂、辅剂、佐剂、稀释剂、载体和 / 或除本发明的产品以外的另外的药学活性物质。

[0071] 本文所用的术语“有效量”是指任何将引起例如研究者或临床医师所寻求的组织、系统、动物或人的生物学或医学反应的药物或药用物质的量。此外，术语“治疗有效量”意指与相应的未接受该量的个体相比任何导致疾病、障碍或副作用的改进的治疗、治愈、预防或改善或者疾病或障碍的进展速度减小的量。该术语在其范围内还包括对增强正常生理功能有效的量。

[0072] 在本发明的另一方面，提供了包含至少一种本发明的产品或本文所述的药学组合物的药剂。

[0073] 在本发明的另外一个方面，提供了本文所述的药剂，其用于治疗和 / 或预防生理学和 / 或病理生理学病症，所述生理学和 / 或病理生理学病症是通过抑制、调控和 / 或调节激酶信号转导、特别是通过抑制酪氨酸激酶、优选 Met 激酶而被引起、介导和 / 或传播的。相应的在制备用于治疗和 / 或预防上述病症的药剂中的用途也包括在本发明的范围内。

[0074] 在本发明的另外一个方面，提供了本文所述的药剂，其用于治疗和 / 或预防生理学和 / 或病理生理学病症，所述生理学和 / 或病理生理学病症选自 :“癌症 (cancer)、肿瘤、恶性肿瘤、良性肿瘤、实体肿瘤、肉瘤、癌 (carcimoma)、过度增殖性障碍、类癌、尤因肉瘤、卡波西肉瘤、脑肿瘤、起源于脑和 / 或神经系统和 / 或脑脊膜的肿瘤、神经胶质瘤、成胶质细胞瘤、成神经细胞瘤、胃癌、肾癌、肾细胞癌、前列腺癌症、前列腺癌、结缔组织肿瘤、软组织肉瘤、胰腺肿瘤、肝肿瘤、头肿瘤、颈肿瘤、喉癌、食管癌、甲状腺癌、骨肉瘤、视网膜母细胞瘤、胸腺瘤、睾丸癌、肺癌、肺腺癌、小细胞肺癌、支气管癌、乳腺癌 (breast cancer)、乳房癌 (mamma carcinoma)、肠癌、结肠直肠肿瘤、结肠癌、直肠癌、妇科肿瘤、卵巢肿瘤 / 卵巢的肿瘤、子宫癌、子宫颈的癌症、宫颈癌、子宫体的癌症、子宫体癌、子宫内膜癌、膀胱癌、泌尿生殖道癌、膀胱癌症、皮肤癌、上皮肿瘤、鳞状上皮癌、基底细胞癌、棘细胞癌 (spinalioma)、黑素瘤、眼内黑素瘤、白血病、单核细胞白血病、慢性白血病、慢性髓性白血病 (chronic myelotic leukaemia)、慢性淋巴性白血病、急性白血病、急性髓性白血病、急性淋巴性白血病和 / 或淋巴瘤”。相应的在制备用于治疗和 / 或预防上述病症的药剂中的用途也包括在本发明的范围内。

[0075] 在本发明的另一方面，提供了本文所述的药剂，其中所述药剂包含至少一种另外的药理学活性物质 (药物，成分)。

[0076] 在一个优选的实施方案中，所述的至少一种药理学活性物质是本文所述的物质。

[0077] 在本发明的另一方面，提供了本文所述的药剂，其中所述药剂在用至少一种另外的药理学活性物质进行治疗之前和 / 或期间和 / 或之后被应用。

[0078] 在一个优选的实施方案中，所述的至少一种药理学活性物质是本文所述的物质。

[0079] 在本发明的另外一个方面，提供了一种药盒，其包含治疗有效量的至少一种本发

明的产品和 / 或至少一种本文所述的药物组合物和治疗有效量的至少一种另外的本发明的产品以外的药理学活性物质。

[0080] 本发明的产品可以与一种或多种其它药理学活性物质（成份，药物）组合使用用于治疗、预防、抑制或改善本发明的产品或所述其它物质对其具有功效的疾病或病症。通常，药物的组合比组合中的任意一种药物单独使用更安全或更有效，或者药物的组合比基于各药物的相加性质所预期的更安全或更有效。所述的其它一种或多种药物可以通过通常使用的途径、以通常使用的量与本发明的产品同时或相继施用。当本发明的产品与一种或多种其它药物同时使用时，含有所述一种或多种其它药物和本发明的产品的组合产品是优选的。然而，组合治疗也包括其中本发明的产品和一种或多种其它药物以不同的交错方案被施用的治疗。预期当与其它活性成份组合使用时，本发明的产品或其它活性成份或两者可以以比各自单独使用时的剂量更低的剂量被有效地使用。因此，本发明的药物组合物（本文所述的药物组合物）包括除本发明的产品以外还含有一种或多种其它活性成分的那些。

[0081] 可以与本发明的产品组合施用（分别施用或在相同药物组合物中施用）的药理学活性物质（成份，药物）的实例包括但不限于表 1 中所列出的化合物种类和具体化合物：

[0082]

表1		
烷化剂	环磷酰胺	洛莫司汀
	白消安	丙卡巴肼
	异环磷酰胺	六甲三聚氰胺
	白消安	磷酸雌莫司汀
	六甲密胺	氮芥
	噻替哌	链佐星
	苯丁酸氮芥	替莫唑胺

[0083]

	达卡巴嗪 卡莫司汀	司莫司汀
铂剂	顺铂 奥沙利铂 螺铂 Carboxyphthalatoplatinum 四铂 Ormiplatin 异丙铂	卡铂 ZD-0473 (AnorMED) 洛铂 (AeternaZentaris) 沙铂 (Johnson Matthey) BBR-3464 (Hoffrnann-La Roche) SM-11355 (Sumitomo) AP-5280 (Access)
抗代谢物	氮胞苷 吉西他滨 卡培他滨 5-氟尿嘧啶 氟尿苷 2-氯脱氧腺苷 6-巯嘌呤 6-巯鸟嘌呤 阿糖胞苷 2-氟脱氧胞苷 甲氨蝶呤 Idatrexate	拓优得 三甲曲沙 脱氧考福霉素 氟达拉滨 喷司他丁 雷替曲塞 羟基脲 地西他滨(SuperGen) 氯法拉滨(Bioenvision) 伊罗夫文(MGI Pharma) DMDC(Hoffmann-La Roche) 乙炔基胞苷(Taiho)
拓扑异构酶抑制剂	安吖啶 表柔比星 依托泊苷 替尼泊苷或米托蒽醌 伊立替康(CPT-11)	卢比替康(SuperGen) 甲磺酸依沙替康(Daiichi) Quinamed (ChemGenex) 吉马替康(Sigma- Tau) 二氟替康(Beaufour-Ipsen)

[0084]

	7-乙基-10-羟基喜树碱	TAS-103(Taiho)
	拓扑替康	依沙芦星(Spectrum)
	Dexrazoxanet (TopoTarget)	J-107088(Merck & Co)
	Pixantrone (Novuspharrna)	BNP-1350(BioNumerik)
	瑞必克霉素-类似物(Exelixis)	CKD-602(Chong Kun Dang)
	BBR-3576 (Novuspharrna)	KW-2170(Kyowa Hakko)
抗肿瘤抗生素	更生霉素(放线菌素D)	氨萘非特
	多柔比星(阿霉素)	Azonafide
	Deoxyrubicin	蒽吡唑(Anthrapyrazole)
	戊柔比星	必散特隆
	柔红霉素(道诺霉素)	洛索蒽醌
	表柔比星	硫酸博来霉素(Blenoxan)
	Therarubicin	Bleomycinacid
	伊达比星	博来霉素 A
	佐柔比星	博来霉素 B
	Plicamycinp	丝裂霉素 C
	泊非霉素	MEN-10755 (Menarini)
	氰基吗啉代多柔比星	GPX-100 (Gem
	米托蒽醌(Novantron)	Pharmaceuticals)
抗有丝分裂剂	紫杉醇	SB 408075 (GlaxoSmithKline)
	多西他赛	E7010 (Abbott)
	秋水仙碱	PG-TXL (Cell Therapeutics)
	长春碱	IDN 5109 (Bayer)
	长春新碱	A 105972 (Abbott)
	长春烯碱	A 204197 (Abbott)
	长春地辛	LU 223651 (BASF)
	多拉司他汀 10 (NCI)	D 24851 (ASTA Medica)
	根霉素(Fujisawa)	ER-86526 (Eisai)
		考布他汀A4 (BMS)

[0085]

	米伏布林 (Warner-Lambert) 西马多丁(BASF) RPR 109881A (Aventis) TXD 258 (Aventis) 埃坡霉素B (Novartis) T 900607 (Tularik) T 138067 (Tularik) Cryptophycin 52 (Eli Lilly) 长春氟宁 (Fabre) Auristatine PE (Teikoku Hormone) BMS 247550 (BMS) BMS 184476 (BMS) BMS 188797 (BMS) Taxoprexine (Protarga)	Isohomohalichondrin-B (PharmaMar) ZD6126 (AstraZeneca) PEG-紫杉醇(Enzon) AZ10992 (Asahi) !DN-5109 (Indena) AVLB (Prescient NeuroPharma) Azaepothilon B (BMS) BNP- 7787 (BioNumerik) CA-4-前体药物(OXiGENE) 多拉司他汀-10 (NrH) CA-4 (OXiGENE)
芳香酶抑制剂	氨鲁米特 来曲唑 阿那曲唑 福美坦	依西美坦 阿他美坦(BioMedicines) YM-511(Yamanouchi)
胸苷酸合酶抑制剂	培美曲塞(Eli Lilly) ZD-9331(BTG)	诺拉曲塞(Eximias) CoFactor™ (BioKeys)
DNA拮抗剂	曲贝替定(PharmaMar) 葡磷酰胺(Baxter International) 白蛋白+32P(Isotope Solutions) Thymectacine(NewBiotics)	马磷酰胺(Baxter International) Apaziquone (Spectrum Pharmaceuticals) O6-苄基鸟嘌呤 (Paligent)

[0086]

	Edotreotide(Novartis)	
法尼基转移酶抑制剂	Arglabine (NuOncology Labs) lonafarnibe (Schering-Plough) BAY-43-9006 (Bayer)	Tipifarnibe (Johnson & Johnson) 紫苏子醇(DOR BioPharma)
泵抑制剂	CBT-1 (CBA Pharma) 他立喹达(Xenova) MS-209 (Schering AG)	三盐酸佐舒喹达(Eli Lilly) 二柠檬酸比立考达(Vertex)
组蛋白乙酰基转移酶抑制剂	他地那兰 (Pfizer) SAHA (Aton Pharma) MS-275 (Schering AG)	丁酸新戊酰氧基甲酯(Titan) 缩肽(Fujisawa)
金属蛋白酶抑制剂 / 核糖核苷还原酶抑制剂	新伐司他 (Aeterna Laboratories) 马立马司他 (British Biotech) Galliummaltolate (Titan) Triapine(Vion)	CMT -3 (CollaGenex) BMS-275291 (Celltech) Tezacitabine (Aventis) Didox (Molecules for Health)
TNF-α激动剂/拮抗剂	维鲁利秦(Lorus Therapeutics) CDC-394 (Celgene)	Revimide (Celgene)
内皮素-A受体 拮抗剂	阿曲生坦 (Abbot) ZD-4054 (AstraZeneca)	YM-598 (Yamanouchi)
视黄酸受体	芬维A胺(Johnson&Johnson)	阿利维A酸(Ligand)

[0087]

激动剂	LGD-1550 (Ligand)	
免疫调节剂	干扰素	Dexosome治疗(Anosys)
	Oncophage(Antigenics)	Pentrix (Australian Cancer
	GMK(Progenics)	Technology)
	腺癌疫苗(Biomira)	JSF-154 (Tragen)
	CTP-37(AVI BioPharma)	癌疫苗(Intercell)
	JRX-2(Immuno-Rx)	Noreline(Biostar)
	PEP-005(Peplin Biotech)	BLP-25(Biomira)
	Synchrovax疫苗(CTL	MGV(Progenics)
	Immuno)	13-Alethine(Dovetail)
	黑素瘤疫苗(CTL Immuno)	CLL-Thera(Vasogen)
	p21-RAS 疫苗(GemVax)	
激素和抗激素药	雌激素	泼尼松
	轭合雌激素	甲泼尼龙
	乙炔雌二醇	泼尼松龙
	氯烯雌醚	氨鲁米特
	Idenestrole	亮丙立德
	己酸羟孕酮	戈舍瑞林
	甲羟孕酮	Leuporelin
	睾酮	西曲瑞克
	丙酸睾酮	比卡鲁胺
	氟甲睾酮	氟他胺
	甲睾酮	奥曲肽
	己烯雌酚	尼鲁米特
	甲地孕酮	米托坦
	他莫昔芬	P-04 (Novogen)
	Toremofine	2-甲氧基雌二醇(EntreMed)
	地塞米松	阿佐昔芬(Eli Lilly)

[0088]

光动力活性剂	他拉泊芬(Light Sciences) Theralux (Theratechnologies) 莫特沙芬钆(Pharmacyclics)	Pd- Bacteriopheophorbide (Yeda) Lutetium-Texaphyrine (Pharmacyclics) 金丝桃素
酪氨酸激酶抑制剂	伊马替尼(Novartis) 来氟米特 (Sugen/Pharmacia) ZDl839 (AstraZeneca) 厄洛替尼(Oncogene Science) Canertjnib (Pfizer) 角鲨胺(Genaera) SU5416 (Pharmacia) SU6668 (Pharmacia) ZD4190 (AstraZeneca) ZD6474 (AstraZeneca) 伐他拉尼(Novartis) PKI166 (Novartis) GW2016 (GlaxoSmithKline) EKB-509 (Wyeth) EKB-569 (Wyeth)	Kahalid F (PharmaMar) CEP- 701 (Cephalon) CEP-751 (Cephalon) MLN518 (Millenium) PKC412 (Novartis) 苯妥帝尔O (Phenoxodiol O) 曲妥单抗(Genentech) C225 (ImClone) rhu-Mab (Genentech) MDX-H210 (Medarex) 2C4 (Genentech) MDX-447 (Medarex) ABX-EGF (Abgenix) IMC-1C11 (ImClone)
不同的活性剂	SR-27897(CCK-A抑制剂, Sanofi-Synthelabo) 托拉地新(环-AMP 激动剂, Ribapharm) Alvocidib (CDK抑制剂, Aventis) CV-247 (COX-2-抑制剂, Ivy	BCX-1777 (PNP抑制剂, BioCryst) 豹蛙酶(核糖核酸酶刺激物, Alfacell) 加柔比星(RNA合成抑制剂, Dong-A) 替拉扎明(还原剂, SRI

[0089]

	Medical)	International)
	P54 (COX-2抑制剂, Phytopharm)	N-乙酰半胱氨酸(还原剂, Zambon)
	CapCell™ (CYP450 刺激物, Bavarian Nordic)	R-氟比洛芬(NF-κB抑制剂, Encore)
	GCS-IOO (gal3 ant激动剂, GlycoGenesys)	3CPA (NF-κB抑制剂, Active Biotech)
	G17DT免疫原(Gastrin抑制剂, Aphton)	西奥骨化醇(维生素-D受体激动剂, Leo)
	乙法昔罗(Oxygenator, AIIos Therapeutics)	131-I-TM-601 (DNA拮抗剂, TransMolecular)
	PI-88 (类肝素酶(Heparanase)抑制剂, Progen)	依氟鸟氨酸(ODC抑制剂, ILEX肿瘤学)
	替米利芬(Histamine ant激动剂, YM BioSciences)	米诺膦酸(破骨细胞抑制剂, Yamanouchi)
	组胺(组胺-H2受体激动剂, Maxim)	Indisulam (p53刺激物, Eisai)
	噻唑呋林(IMPDH抑制剂, Ribapharm)	Aplidin (PPT抑制剂, PharmaMar)
	西仑吉肽(整联蛋白拮抗剂, Merck KGaA)	利妥昔单抗(CD20抗体, Genentech)
	SR-31747 (IL-1拮抗剂, Sanofi-Synthelabo)	吉姆单抗(CD33抗体, Wyeth Ayerst)
	CCI-779 (mTOR激酶抑制剂, Wyeth)	PG2 (造血促进剂, Pharmagenesis)
	依昔舒林(PDE-V抑制剂, Cell Pathways)	Immunol™ (三氯生漱口剂, Endo)
	CP-461 (PDE-V抑制剂, Cell Pathways)	三乙酰基尿苷(尿苷前体药物, WellStat)
		SN-4071 (肉瘤药, Signature BioScience)

[0090]

	AG-2037 (GART抑制剂, Pfizer) WX-UK1 (纤溶酶原激活物抑制剂, Wilex) PBI-1402 (PMN刺激物, ProMetic LifeSciences) 硼替佐米(蛋白酶体抑制剂, Millennium) SRL-172(T-细胞刺激物, SR Pharma) TLK-286(谷胱甘肽-S-转移酶抑制剂, Telik) PT-100(生长因子激动剂, Point Therapeutics) 米哚妥林(PKC抑制剂, Novartis) 苔藓抑素-1 (PKC刺激物, GPC Biotech) CDA-II (细胞凋亡促进剂, Everlife) SDX-101 (细胞凋亡促进剂, Salmedix) Ceflatonin (细胞凋亡促进剂, ChemGenex)	TransMID-107™ (免疫毒素, KS Biomedix) PCK-3145 (细胞凋亡促进剂, Procyon) Doranidazole (细胞凋亡促进剂, Pola) CHS-828 (细胞毒性剂, Leo) 反式-视黄酸(分化剂, NIH) MX6 (细胞凋亡促进剂, MAXIA) Apomin (细胞凋亡促进剂, ILEX Oncology) Urocidine (细胞凋亡促进剂, Bioniche) Ro-31-7453 (细胞凋亡促进剂, La Roche) Brostallicin (细胞凋亡促进剂, Pharmacia)

[0091] 在一个优选的实施方案中，本发明的产品与一种或多种已知的抗肿瘤剂组合施用，例如下列抗肿瘤剂：雌激素受体调节剂、雄激素受体调节剂、类视色素 (retinoid) 受体调节剂、细胞毒素、抗增殖剂剂、异戊二烯基蛋白转移酶 (prenyl proteintransferase) 抑制剂、HMG-CoA- 还原酶抑制剂、HIV 蛋白酶抑制剂、逆转录酶抑制剂、血管生成抑制剂。

[0092] 本发明的产品特别是非常适合与放射疗法组合施用。VEGF 抑制与放射疗法组合的协同作用对本领域技术人员而言是已知的 (WO 00/61186)。

[0093] 在本发明中，术语“雌激素受体调节剂”是指干扰或抑制雌激素与雌激素受体结合的化合物—与作用方式无关。雌激素受体调节剂的非限制性实例有他莫西芬、雷洛昔芬、艾多昔芬、LY353381、LY 117081、托瑞米芬、氟维司群、4-[7-(2,2- 二甲基 -1- 氧代丙氧基 -4- 甲基 -2-[4-[2-(1- 哌啶基) 乙氧基] 苯基]-2H-1- 苯并吡喃 -3- 基] 苯基 -2,2- 二

甲基 - 丙酸酯 / 盐、4,4′ - 二羟基二苯甲酮 -2,4- 二硝基苯基腙和 SH646。

[0094] 在本发明中，术语“雄激素受体调节剂”是指干扰或抑制雄激素与雄激素受体结合的化合物—与作用方式无关。雄激素受体调节剂的非限制性实例有非那雄胺和其它 5α - 还原酶抑制剂、尼鲁米特、氟他胺、比卡鲁胺、利阿唑和乙酸阿比特龙。

[0095] 在本发明中，术语“类视色素受体调节剂”是指干扰或抑制类视色素与类视色素受体结合的化合物—与作用方式无关。类视色素受体调节剂的非限制性实例有贝沙罗汀、维甲酸、13- 顺式 - 视黄酸、9- 顺式 - 视黄酸、α - 二氟甲基鸟氨酸、ILX23-7553、反式 -N-(4′ - 羟基苯基）维甲酰胺和 N-4- 羧基苯基维甲酰胺。

[0096] 在本发明中，术语“细胞毒素”是指通过直接作用于细胞功能主要引起细胞死亡的化合物或者干扰或抑制细胞减数分裂的化合物，例如烷化剂、肿瘤坏死因子、嵌入剂、微管抑制剂和拓扑异构酶抑制剂。细胞毒素的非限制性实例有替拉扎明 (tirapazimin)、sertenef、恶液质素、异环磷酰胺、他索纳明、氯尼达明、卡铂、六甲三聚氰胺、泼尼莫司汀、二溴卫矛醇、雷莫司汀、福莫司汀、奈达铂、奥沙利铂、替莫唑胺、庚铂 (heptaplatin)、雌莫司汀、甲苯磺酸英丙舒凡、曲磷胺、尼莫司汀、二溴螺氯铵、嘌嘧替派、洛铂、沙铂、甲基丝裂霉素、顺铂、伊罗夫文、右异环磷酰胺、顺式 - 氨基二氯 (2- 甲基吡啶）铂 (cis-amin dichloro(2-methylpyridine)platin)、苄基鸟嘌呤、葡磷酰胺、GPX100、（反式，反式，反式）- 双 - μ -（己烷 -1,6- 二胺）- μ -[二胺 - 铂 (II)] 双 -[二胺（氯）铂 (II)]- 四氯化物、二氮丙啶基精胺 (diarizidinylspermine)、三氧化砷、1-(11- 十二烷基氨基 -10- 羟基十一烷基）-3,7- 二甲基黄嘌呤、佐柔比星、伊达比星、柔红霉素、比生群、米托蒽醌、吡柔比星、吡萘非特、戊柔比星、氨柔比星、抗瘤酮、3′ - 去氨基 -3′ - 吗啉代 -13- 去氧代 -10- 羟基洋红霉素、安那霉素、加柔比星、依利奈法德、MEN10755 和 4- 去甲氧基 -3- 去氨基 -3- 氮丙啶基 -4- 甲基磺酰基 - 柔红霉素 (WO 00/50032)。

[0097] 微管抑制剂的非限制性实例有紫杉醇、硫酸长春地辛、3′，4′ - 二脱氢 -4′ - 脱氧 -8′ - 去甲长春碱、多西他赛、根霉素、多拉司他汀、米伏布林 - 羟乙基磺酸盐、auristatine、西马多丁、RPR109881、BMS184476、长春氟宁、cryptophycine、2,3,4,5,6- 五氟 -N-(3- 氟 -4- 甲氧基苯基）- 苯磺酰胺、去水长春碱、N,N- 二甲基 -L- 缬氨酰基 -L- 缬氨酰基 -N- 甲基 -L- 缬氨酰基 -L- 脯氨酰基 -L- 脯氨酸 - 叔 - 丁基酰胺、TDX258 和 BMS188797。

[0098] 拓扑异构酶抑制剂的非限制性实例有拓扑替康、hycaptamine、伊立替康、鲁比特康、6- 乙氧基丙酰基 -3′，4′ -O- 外 - 亚苄基 - 教酒菌素 (chartreusine)、9- 甲氧基 -N,N- 二甲基 -5- 硝基吡唑并 [3,4,5-kl] 吖啶 -2-(6H) 丙胺、1- 氨基 -9- 乙基 -5- 氟 -2,3- 二氢 -9- 羟基 -4- 甲基 -1H,12H- 苯并 -[de]- 吡喃并 -[3′，4′ :b,7] 中氮茚并 [1,2b] 喹啉 -10,13(9H,15H)- 二酮、勒托替康、7-[2-(N- 异丙基氨基）乙基]-(20S) 喜树碱、BNP1350、BNPI1100、BN80915、BN80942、磷酸依托泊苷、替尼泊苷、索布佐生、2′ - 二甲氨基 -2′ - 脱氧 - 依托泊苷、GL331、N-[2-（二甲氨基）乙基]-9- 羟基 -5,6- 二甲基 -6H- 吡啶并 [4,3-b] 咔唑 -1- 甲酰胺、asulacrine、(5a,5aB,8aa,9b)-9-[2-[N-[2-（二甲氨基）乙基]-N- 甲基氨基] 乙基]-5-[4- 羟基 -3,5- 二甲氧基苯基]-5,5a,6,8,8a,9- 六氢呋喃并 (3′，4′ :6,7) 萘并 (2,3-d)-1,3- 二氧杂环戊烯 -6- 酮、2,3-（亚甲二氧基）-5- 甲基 -7- 羟基 -8- 甲氧基苯并 [c] 菲啶鎓、6,9- 双 [(2- 氨基乙基）氨基]- 苯并 [g] 异喹啉 -5,10- 二酮、5-(3- 氨基丙基氨基）-7,10- 二羟基 -2-(2- 羟基乙基氨基甲基）-6H- 吡唑

并[4,5,1-de]-吖啶-6-酮、N-[1-[2(二乙基氨基)乙基氨基]-7-甲氧基-9-氧代-9H-噻嗯烷-then-4-基甲基]甲酰胺、N-(2-(二甲基-氨基)-乙基)吖啶-4-甲酰胺、6-[[2-(二甲氨基)-乙基]氨基]-3-羟基-7H-茚并[2,1-c]喹啉-7-酮和地美司钠。

[0099] 抗增殖剂的非限制性实例有反义RNA-和反义DNA-寡核苷酸如G3139、ODN698、RVASKRAS、GEM231和INX3001以及抗代谢物如依诺他滨、卡莫氟、替加氟、喷司他丁、脱氧氟尿苷、三甲曲沙、氟达拉滨、卡培他滨、加洛他滨、阿糖胞苷十八烷基磷酸钠(cytarabine ocfosfate)、fosteabine钠水合物、雷替曲塞、paltitrexide、乙嘧替氟、噻唑呋林、地西他滨、诺拉曲塞、培美曲塞、奈拉滨、2′-脱氧-2′-亚甲基胞苷、2′-氟亚甲基-2′-脱氧胞苷、N-[5-(2,3-二氢苯并呋喃基)磺酰基]-N′-(3,4-二氯苯基)脲、N6-[4-脱氧-4-[N2-[2(E),4(E)-四癸二烯酰基]甘氨酰基氨基]-L-甘油-B-L-甘露-庚吡喃糖苷基(heptopyranosyl)]腺嘌呤、aplidine、海鞘素、曲沙他滨、4-[2-氨基-4-氧代-4,6,7,8-四氢-3H-嘧啶并[5,4-b][1,4]噻嗪-6-基-(S)-乙基]-2,5-噻吩酰基-L-谷氨酸、氨基蝶呤、5-氟尿嘧啶、阿拉诺新、11-乙酰基-8-(氨甲酰基氧基甲基)-4-甲酰基-6-甲氧基-14-氧杂-1,11-二氮杂-四环-(7.4.1.0.0)-十四-2,4,6-三烯-9-基乙酸酯、八氢吲嗪三醇、洛美曲索、右雷佐生、蛋氨酸酶(methioninase)、2′-氰基-2′-脱氧-N4-棕榈酰基-1-B-D-阿糖呋喃糖基胞嘧啶和3-氨基吡啶-2-甲醛-缩氨基硫脲。

[0100] “抗增殖剂”还包括没有被列举在“血管生成抑制剂”下的对抗生长因子的单克隆抗体如曲妥单抗以及肿瘤抑制基因如p53。

[0101] (本文所述的)本发明的药物组合物可以通过任何实现其预期目的的方法被施用。例如,施用可以通过口服、胃肠外、局部、肠内、静脉内、肌内、吸入、鼻、关节内、脊柱内、经气管、经眼、皮下、腹膜内、经皮或口含途径进行。作为替代选择地或并行地,施用可以通过口服途径进行。所施用的剂量将取决于接受者的年龄、健康状况和体重,如果有并行治疗,还取决于并行治疗的种类、治疗的频率,以及所需效果的性质。优选胃肠外施用。尤其优选口服施用。

[0102] 合适的剂型包括但不限于胶囊剂、片剂、小丸、糖锭剂(dragee)、半固体制剂、散剂、颗粒剂、栓剂、软膏剂、乳膏剂、洗剂、吸入剂、注射剂、泥罨剂、凝胶剂、带剂(tape)、滴眼剂、溶液剂、糖浆剂、气雾剂、混悬剂、乳剂,其可以根据本领域已知的方法制备,例如如下所述制备:

[0103] 片剂:将活性成分与辅剂混合,将所述混合物压制成片剂(直接压片法),在压片前任选将部分混合物制粒。

[0104] 胶囊剂:将活性成分与辅剂混合以得到可流动的粉末,任选将粉末制粒,将粉末/颗粒填充入打开的胶囊中,将胶囊盖上帽。

[0105] 半固体制剂(软膏剂、凝胶剂、乳膏剂):将活性成分溶解/分散在水性或脂肪性载体中;随后将水相/脂肪相与互补的脂肪相/水相混合,均化(只对乳膏剂)。

[0106] 栓剂(直肠栓剂和阴道栓剂):将活性成分溶解/分散在通过加热被液化的载体材料中(直肠栓剂:载体材料通常是蜡;阴道栓剂:载体材料通常是加热的胶凝剂的溶液),将所述混合物投入栓剂模具中,退火并将栓剂从模具中取出。

[0107] 气雾剂:将活性剂分散/溶解在抛射剂中,将所述混合物装入喷雾器中。

[0108] 一般而言,用于制备药物组合物和/或药物制剂的非化学途径包括在本领域已知

的合适的机械工具上进行的处理步骤，所述处理步骤将一种或多种本发明的产品转化成适合对需要这类治疗的患者施用的剂型。通常，将一种或多种本发明的产品转化成这类剂型包括加入一种或多种选自以下的化合物：载体、赋形剂、辅剂和本发明的产品以外的药学活性成分。合适的处理步骤包括但不限于结合、碾磨、混合、制粒、溶解、分散、均化、模铸和/或压缩各活性和非活性成分。用于进行所述处理步骤的机械工具是本领域已知的，例如从 Ullmann′ s Encyclopedia of Industrial Chemistry，第五版知道。在这一方面，活性成分优选是至少一种本发明的产品和一种或多种另外的本发明的产品以外的显示出有价值的药学性质的化合物、优选本文所公开的本发明的产品以外的那些药学活性剂。

[0109] 特别适合口服使用的是片剂、丸剂、包衣片剂、胶囊剂、散剂、颗粒剂、糖浆剂、汁液(juice)或滴剂，适合直肠使用的是栓剂，适合胃肠外使用的是溶液剂，优选基于油的溶液或水溶液，此外还有混悬剂、乳剂或植入剂，适合局部使用的是软膏剂、乳膏剂或散剂。本发明的产品也可以被冻干，生成的冻干物用于例如制备注射制剂。所给出的制剂可以被灭菌和/或包含辅助剂(assistant)，如润滑剂、防腐剂、稳定剂和/或润湿剂、乳化剂、用于改变渗透压的盐、缓冲物质、染料、矫味剂和/或众多另外的活性成分，例如一种或多种维生素。

[0110] 合适的赋形剂是有机或无机物质，这些物质适合肠内（例如口服）、胃肠外或局部施用并且不与本发明的产品发生反应，例如水、植物油、苄醇、烷撑二醇、聚乙二醇、甘油三乙酸酯、明胶、碳水化合物如乳糖、蔗糖、甘露醇、山梨醇或淀粉（玉米淀粉、小麦淀粉、米淀粉、马铃薯淀粉）、纤维素制品和/或磷酸钙盐例如磷酸三钙或磷酸氢钙、硬脂酸镁、滑石粉、明胶、西黄蓍胶、甲基纤维素、羟丙基甲基纤维素、羧甲基纤维素钠、聚乙烯吡咯烷酮和/或凡士林。

[0111] 如果需要，可以加入崩解剂，如上面提到的淀粉以及羧甲基淀粉、交联聚乙烯吡咯烷酮、琼脂或者海藻酸或其盐如藻酸钠。辅剂包括不限于流动调节剂和润滑剂，例如二氧化硅、滑石粉、硬脂酸或其盐如硬脂酸镁或硬脂酸钙和/或聚乙二醇。糖锭剂心具有合适的包衣，如果需要，所述包衣可以耐胃液的。就该目的而言，可以使用浓糖溶液，该浓糖溶液可任选含有阿拉伯胶、滑石粉、聚乙烯吡咯烷酮、聚乙二醇和/或二氧化钛、涂膜溶液(lacquer solution)和合适的有机溶剂或溶剂混合物。为了制备耐胃液的包衣或者提供具有长效优势的剂型，片剂、糖锭剂或丸剂可以包含内剂量组份和外剂量组份，后者以外壳的形式包裹前者。这两种组份可通过肠溶层被分开，肠溶层用于抵抗在胃中的崩解并且使内组份完整无损地通过胃进入十二指肠或者被延迟释放。多种材料可以用于这类肠溶层或包衣，这类材料包括许多聚合酸和聚合酸与诸如虫胶、acetyl alcohol、合适的纤维素制品的溶液如邻苯二甲酸乙酰纤维素、乙酸纤维素或羟丙基甲基纤维素邻苯二甲酸酯。可以向片剂或糖锭剂的包衣中加入染料或色素，例如用于识别或为了标示出活性化合物剂量的组合。

[0112] 合适的载体物质是有机或无机物质，这些物质适合肠内（例如口服）或胃肠外或局部施用并且不与新化合物发生反应，例如水、植物油、苄醇、聚乙二醇、明胶、碳水化合物如乳糖或淀粉、硬脂酸镁、滑石粉和矿脂。特定地，片剂、包衣片剂、胶囊剂、糖浆剂、混悬剂、滴剂或栓剂被用于肠内施用，溶液剂、优选油性或水性溶液剂、还有混悬剂、乳剂或植入剂被用于胃肠外施用，软膏剂、乳膏剂或散剂被用于局部应用。本发明的产品也可以被冻干，得到的冻干物可以被用于例如制备注射制剂。

[0113] 所给出的制剂可以被灭菌和/或可以含有赋形剂如润滑剂、防腐剂、稳定剂和/或

润湿剂、乳化剂、用于影响渗透压的盐、缓冲物质、着色剂、矫味剂和 / 或芳香剂。如果需要，它们也可以含有一种或多种另外的活性化合物，例如一种或多种维生素。

[0114] 其它可以口服使用的药物制剂包括由明胶制成的推入契合式 (push-fit) 胶囊以及由明胶和增塑剂如甘油或山梨醇制成的软密封胶囊。推入契合式胶囊可以含有颗粒形式的活性化合物，其可以与填充剂如乳糖、粘合剂如淀粉和 / 或润滑剂如滑石粉或硬脂酸镁以及任选的稳定剂混合。在软胶囊中，活性化合物优选溶解或混悬于合适的液体如脂肪油或液体石蜡中。此外，可以加入稳定剂。

[0115] 本发明的新组合物可以并入其中的用于口服施用的液体形式包括水性溶液、适当矫味的糖浆剂、水性或油性混悬液和具有可食用的油如棉子油、芝麻油、椰子油或花生油的经矫味的乳剂以及酏剂和类似的药物介质。用于水性混悬液的合适的分散剂或助悬剂包括合成的和天然的树胶如西黄蓍胶、阿拉伯胶、藻酸盐、右旋糖酐、羧甲基纤维素钠、甲基纤维素、聚乙烯吡咯烷酮或明胶。

[0116] 用于胃肠外施用的合适的制剂包括水溶形式的活性化合物的水性溶液，例如，水溶性盐和碱溶液。此外，可以施用活性化合物的混悬剂如适宜的油性注射混悬剂。合适的亲脂性溶剂或介质包括脂肪油例如芝麻油或者合成的脂肪酸酯例如油酸乙酯或甘油三酯或聚乙二醇 -400(化合物可溶于 PEG-400)。

[0117] 水注射混悬剂可以含有增加混悬剂的粘度的物质，包括例如羧甲基纤维素钠、山梨醇和 / 或右旋糖酐，所述混悬剂还可以任选含有稳定剂。

[0118] 对于吸入喷雾剂形式的施用，使用其中活性成分溶解或混悬于抛射气体或抛射气体混合物 (例如 CO_2 或含氯氟烃) 中的喷雾剂是可能的。在此活性成分以微粉化形式被有利地使用，在这种情况下可以存在一种或多种另外的生理可接受的溶剂，例如乙醇。吸入溶液可以借助常规吸入器被施用。

[0119] 可以直肠使用的可能的药物制剂包括例如栓剂，其由一种或多种活性化合物与栓剂基质的组合组成。合适的栓剂基质有例如天然或合成的甘油三酯或石蜡烃。此外，也可以使用明胶直肠胶囊，其由活性化合物与基质的组合组成。可能的基质材料包括例如液体甘油三酯、聚乙二醇或石蜡烃。

[0120] 对于医学上的使用，本发明的产品将是药学上可接受的盐形式。然而，其它盐可用于制备本发明的产品或它们的药学上可接受的盐。本发明的产品的合适的药学上可接受的盐包括酸加成盐，其可以例如通过将本发明的产品与药学上可接受的酸的溶液混合来形成，所述药学上接受的酸如盐酸、硫酸、甲磺酸、富马酸、马来酸、琥珀酸、乙酸、苯甲酸、草酸、柠檬酸、酒石酸、碳酸或磷酸。此外，在本发明的产品携带酸性基团的情况下，其合适的药学上可接受的盐可以包括碱金属盐，例如钠或钾盐；碱土金属盐，例如钙或镁盐；以及与合适的有机碱形成的盐，例如季铵盐。

[0121] 药物制剂可以在人和兽医学中用作药剂。本文所用的术语“有效量”意指将引起例如研究者或临床医师所寻求的组织、系统、动物或人的生物学或医学反应的药物或药用物质的量。此外，术语“治疗有效量”意指与相应的未接受该量的个体相比任何导致疾病、障碍或副作用的改进的治疗、治愈、预防或改善或者疾病或障碍的进展速度减小的量。该术语在其范围内还包括对增强正常生理功能有效的量。所述的一种或多种本发明的产品的治疗有效量对本领域技术人员而言是已知的或者可以通过本领域已知的标准方法容易地确定。

[0122] 本发明的产品和另外的药理学活性物质一般与商品化的制剂类似地被施用。通常，治疗有效的合适的剂量位于 0.0005mg 至 1000mg、优选 0.005mg 至 500mg、尤其是 0.5mg 至 100mg/ 剂量单位的范围内。日剂量优选在约 0.001mg/kg 体重至 10mg/kg 体重之间。

[0123] 本领域技术人员能容易地理解的是，剂量水平可以根据具体化合物、症状的严重程度以及个体对副作用的易感性而变化。一些特定的化合物比其它化合物的更有效。本领域技术人员利用多种方法可容易地确定给定化合物的优选剂量。一个优选的方法是测定给定化合物的生理效力。

[0124] 对于本发明的目的而言，包括所有哺乳动物种类。在一个优选的实施方案中，所述哺乳动物选自“灵长类动物、人、啮齿类动物、马科动物、牛科动物、犬科动物、猫科动物、家畜、牛、牲畜、宠物、奶牛、绵羊、猪、山羊、马、矮种马 (pony)、驴、驴骡、马骡、野兔、家兔、猫、狗、豚鼠、仓鼠、大鼠、小鼠”。更优选地，所述哺乳动物是人。对于实验研究而言动物模型是重要的，提供了治疗人疾病的模型。

[0125] 然而，各患者个体的特定剂量取决于众多因素，例如所使用的具体化合物的效力、年龄、体重、总体健康状况、性别、饮食种类、施用的时间和途径、排泄速度、施用的种类和施用的剂型、药物组合和与治疗有关的特定障碍的严重程度。各患者的特定治疗有效量可以通过常规实验容易地确定，例如由建议和负责治疗的医生或内科医生确定。

[0126] 在许多障碍的情况下，特定细胞对用主题化合物进行的治疗的易感性可以通过体外试验来确定。通常，将细胞培养物与不同浓度的主题化合物组合一段时间，该段时间足以使活性剂显示出相关的反应，通常约 1 小时至一周。对于体外试验，可以使用活检样品的培养细胞。

[0127] 本发明的目的在另一方面已经通过提供制备 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 的方法而令人惊奇地得到解决，所述方法包括以下步骤：

[0128] (a) 将 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮 (游离碱) 或其一种或多种盐溶解或分散在溶剂或溶剂混合物、优选 2- 丙醇或氯仿中，任选在搅拌下进行，

[0129] (b) 通过加入磷酸的水溶液或乙醇溶液将 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮 (游离碱) 或其一种或多种盐转化成相应的磷酸二氢盐，任选在搅拌下进行，

[0130] (c) 将步骤 (b) 得到的分散物于室温搅拌一个或多个小时或者一天或多天，优选 1 或 2 小时，

[0131] (d) 通过过滤回收沉淀的 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物，任选随后用溶剂或溶剂混合物洗涤，和任选随后干燥，优选在真空中干燥，任选于升高的温度 T、优选 30℃至 95℃、更优选 70℃干燥。

[0132] 在本发明中，无论如何使用，术语“升高的温度”和“升高的温度 T 或 T_x”(其中 x = 1、2、3 等)”是指对于给定的方法步骤或分步骤的各特定温度，其独立于任意其它“升高的温度”并且可以是从“高于室温”至给定的溶剂或溶剂混合物的“沸腾温度”和 / 或给定的固体、离析物、中间体或产物或其混合物的“熔化温度”范围内的任意温度。

[0133] 在本发明中，术语“6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮（游离碱）的一种或多种盐”是指 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮（游离碱）的任何和所有盐，优选药学上可接受的盐，其包括但不限于乙酸盐、己二酸盐、藻酸盐、精氨酸盐、天冬氨酸盐、苯甲酸盐、苯基磺酸盐（苯磺酸盐）、硫酸氢盐、亚硫酸氢盐、溴化物、丁酸盐、樟脑酸盐 (bampforat)、樟脑磺酸盐 (campforsulphonate)、辛酸盐、氯化物、氯苯甲酸盐、柠檬酸盐、环戊烷丙酸盐、二葡糖酸盐 (digluconate)、磷酸二氢盐、二硝基苯甲酸盐、十二烷基硫酸盐、乙磺酸盐、富马酸盐、半乳糖二酸盐 (galacterate)、半乳糖醛酸盐、葡庚糖酸盐、葡糖酸盐、谷氨酸盐、甘油磷酸盐、半琥珀酸盐、半硫酸盐、庚酸盐、己酸盐、马尿酸盐、盐酸盐、氢溴酸盐、氢碘酸盐、2- 羟基乙磺酸盐、碘化物、羟乙基磺酸盐、异丁酸盐、乳酸盐、乳糖酸盐、苹果酸盐、马来酸盐、丙二酸盐、扁桃酸盐、偏磷酸盐、甲磺酸盐、甲基苯甲酸盐、磷酸一氢盐、2- 萘磺酸盐、烟酸盐、硝酸盐、草酸盐、油酸盐、双羟萘酸盐、果胶酯酸盐、过硫酸盐、苯基乙酸盐、3- 苯基丙酸盐、磷酸盐、膦酸盐和邻苯二甲酸盐。

[0134] 在本发明中，术语“溶剂或溶剂混合物”是指任何和所有溶剂，优选有机溶剂和水，更优选药学上可接受的有机溶剂和水，其包括但不限于甲醇、乙醇、2- 丙醇、正丁醇，异丁醇、丙酮、甲基乙基酮、乙酸乙酯、1,4- 二噁烷、乙醚、MTBE、THF、乙腈、二氯甲烷、氯仿、DMF、环己烷、环戊烷、正己烷、正庚烷、正戊烷、甲苯、邻二甲苯、对二甲苯、DMSO、吡啶、乙酸、苯甲醚、乙酸丁酯、异丙基苯、甲酸乙酯、甲酸、乙酸异丁酯、乙酸异丙酯、乙酸甲酯、3- 甲基 -1- 丁醇、甲基异丁基酮、2- 甲基 -1- 丙醇、1- 戊醇、乙酸丙酯、乙二醇和 1- 甲基 -2- 吡咯烷酮，以及任何和所有两种或更多种这类溶剂的混合物，优选二元混合物，更优选水和药学上可接受的有机溶剂的二元混合物。

[0135] 本发明的目的在另一方面已经通过提供制备 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 的方法而令人惊奇地得到解决，所述方法包括以下步骤：

[0136] (a) 将 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮（游离碱）或其一种或多种盐分散在溶剂或溶剂混合物、优选水中，和加入磷酸水溶液，任选在搅拌下进行，

[0137] (b) 将步骤 (a) 得到的分散物加热至升高的温度 T1，优选 30℃至 95℃，更优选 50℃，任选在搅拌下进行，和冷却得到的溶液，优选冷却至 0℃至 40℃，更优选冷却至 20℃，任选在搅拌下进行，然后将其用溶剂或溶剂混合物、优选丙酮稀释，任选在搅拌下进行，

[0138] (c) 将步骤 (b) 得到的分散物于 0℃至 40℃、优选 10℃进行搅拌，直至结晶完全，和 / 或将其于室温孵育一个或多个小时或者一天或多天，任选在搅拌下进行，

[0139] (d) 通过过滤回收沉淀的 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物，任选将步骤 (c) 得到的分散物冷却至 0℃至 20℃、优选 5℃，然后过滤，任选在搅拌下进行，任选随后用溶剂或溶剂混合物、优选丙酮洗涤，和任选随后干燥，优选在真空中干燥，任选于升高的温度 T2、优选 30℃至 95℃、更优选 70℃干燥，

[0140] (e) 任选地，将分散物形式的在溶剂或溶剂混合物、优选乙醇中的步骤 (d) 得到的干燥的晶体沸腾一分钟或多分钟、优选 30 分钟，和通过过滤从热分散物中回收它们。

[0141] 本发明的目的在另一方面已经通过提供制备6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐无水物的结晶变型A1的方法而令人惊奇地得到解决，所述方法包括以下步骤：

[0142] (a)将6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮(游离碱)或其一种或多种盐分散在溶剂混合物、优选水：丙酮混合物中，和加入磷酸水溶液，任选在搅拌下进行，

[0143] (b)将步骤(a)得到的分散物加热至升高的温度T1、优选30℃至95℃、更优选55℃，任选在搅拌下进行，和将所得的溶液冷却，优选冷却至0℃至50℃，任选在搅拌下进行，该冷却以既定的冷却速度、优选0.1-1K/min、更优选0.1-0.3K/min进行，任选在搅拌下进行，直至结晶开始，

[0144] (c)进一步冷却步骤(b)得到的分散物，优选冷却至-20℃至0℃，更优选冷却至-10℃，任选在搅拌下进行，该冷却以既定的冷却速度、优选0.1-1K/min、更优选0.1-0.3K/min进行，任选在搅拌下进行，

[0145] (d)将步骤(c)得到的分散物于-20℃至40℃、优选-10℃进行搅拌，直至结晶完全，

[0146] (e)通过过滤回收结晶的6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐无水物，任选随后用溶剂或溶剂混合物、优选丙酮洗涤，和任选随后干燥，优选在真空中干燥，任选于升高的温度T2、优选30℃至95℃、更优选70℃干燥。

[0147] 本发明的目的在另一方面已经通过提供制备6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐二水合物的结晶变型H1的方法而令人惊奇地得到解决，所述方法包括以下步骤：

[0148] (a)将6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐无水物的结晶变型A1铺展在一个表面、优选容器的一个有边的表面、更优选培养皿的一个有边的表面上，和随后将其在密封的干燥器中以既定的相对湿度(RH)、优选80-100％ RH、更优选90-100％ RH在水或盐的水溶液上孵育一天或多天或者一周或多周。

[0149] 本发明的目的在另一方面已经通过提供制备6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐二水合物的结晶变型H1的方法而令人惊奇地得到解决，所述方法包括以下步骤：

[0150] (a)将6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐无水物的结晶变型A1分散在两种或更多种溶剂的混合物、优选水和有机溶剂的二元混合物中，其中所述有机溶剂优选选自：“甲醇、乙醇、2-丙醇、丙酮、TFH和乙腈”，任选在搅拌下进行，和将得到的分散物于升高的温度T1、优选30℃至95℃、更优选50℃搅拌一天或多天或者一周或多周，

[0151] (b)通过过滤回收沉淀的6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐二水合物，任选随后用溶剂或溶剂混合物洗涤，和任选随后干燥，优选在真空中干燥，任选于升高的温度T2、优选30℃至95℃、更优选70℃干燥。

[0152] 本发明的目的在另一方面已经通过提供制备6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐的结晶变型NF3的方法而令人惊奇地得到解决，所述方法包括以下步骤：

[0153] (a)将6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐无水物的结晶变型A1分散或溶解在两种或更多种溶剂的混合物、优选二元混合物中，其中所述溶剂优选选自："水、甲醇、乙醇、2-丙醇、丙酮、TFH、乙腈和1,4-二噁烷"，任选在搅拌下进行，和随后于室温或升高的温度T1、优选30℃至95℃、更优选50℃蒸发所述两种或更多种溶剂的混合物，直至出现结晶，

[0154] (b)通过过滤回收沉淀的6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐水合物，任选随后用溶剂或溶剂混合物洗涤，和任选随后干燥，优选在真空中干燥，任选于升高的温度T2、优选30℃至95℃、更优选70℃干燥。

[0155] 本发明的目的在另一方面已经通过提供制备6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐水合物的结晶变型NF5的方法而令人惊奇地得到解决，所述方法包括以下步骤：

[0156] (a)将6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐无水物的结晶变型A1溶解在二元溶剂混合物、优选水：甲醇、最优选比例为1：1(v：v)的水：甲醇中，和于升高的温度、优选40-80℃、最优选60℃在真空下快速蒸发溶剂混合物，直至获得沉淀物，

[0157] (b)任选地，进一步将粉末形式的从步骤(a)获得的沉淀物铺展在一个表面、优选容器的一个有边的表面、更优选培养皿的一个有边的表面上，和随后将其在密封的干燥器中以既定的相对湿度(RH)、优选80-100％ RH、更优选90-100％ RH在水或盐的水溶液上孵育一天或多天或者一周或多周。

[0158] 本发明的目的在另一方面已经通过提供制备6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐水合物的结晶变型NF5的方法而令人惊奇地得到解决，所述方法包括以下步骤：

[0159] (a)将粉末形式的6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐的晶形NF3铺展在一个表面、优选容器的一个有边的表面、更优选培养皿的一个有边的表面上，和随后将其在密封的干燥器中以既定的相对湿度(RH)、优选80-100％ RH、更优选90-100％ RH在水或盐的水溶液上孵育一天或多天或者一周或多周。

[0160] 附图简要说明

[0161] 图1描述了6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐无水物的结晶变型A1的粉末X-射线衍射图。

[0162] 图2描述了沿b轴观察的6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐无水物的结晶变型A1的单晶X-射线结构数据。

[0163] 图3描述了6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧

啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 的 FT-IR 光谱。

[0164] 图 4 描述了 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 的 FT- 拉曼光谱。

[0165] 图 5 描述了 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 的 DSC 扫描图 (Perkin-Elmer Diamond DSC,5K/min, 氮气流量 50mL/min)。

[0166] 图 6 描述了 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 的 TGA 扫描图 (Perkin-Elmer Pyris TGA1,5K/min, 氮气流量 50mL/min)。

[0167] 图 7 描述了 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1,a 型的水蒸气吸附等温线 (25℃)(SMS DVS 1)。

[0168] 图 8 描述了 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1,b 型的水蒸气吸附等温线 (25℃)(SMS DVS 1)。

[0169] 图 9 描述了 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐二水合物的结晶变型 H1 的粉末 X- 射线衍射图。

[0170] 图 10 描述了 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐二水合物的结晶变型 H1 的单晶 X- 射线结构数据。

[0171] 图 11 描述了 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐二水合物的结晶变型 H1 的 FT-IR 光谱。

[0172] 图 12 描述了 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐二水合物的结晶变型 H1 的 DSC 扫描图 (Perkin-Elmer Diamond DSC,5K/min, 氮气流量 50mL/min)。

[0173] 图 13 描述了 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐二水合物的结晶变型 H1 的 TGA 扫描图 (Perkin-Elmer Pyris TGA1,5K/min, 氮气流量 50mL/min)。

[0174] 图 14 描述了 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐二水合物的结晶变型 H1 的水蒸气吸附等温线 (25℃)(SMS DVS Intrinsic)。

[0175] 图 15 描述了 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐的结晶变型 NF3 的粉末 X- 射线衍射图。

[0176] 图 16 描述了 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐的结晶变型 NF3 的 FT-IR 光谱。

[0177] 图 17 描述了 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐的结晶变型 NF3 的 FT- 拉曼光谱。

[0178] 图 18 描述了 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧

啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐的结晶变型NF3的DSC扫描图(Perkin-Elmer Diamond DSC,5K/min,氮气流量50mL/min)。

[0179] 图19描述了6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐的结晶变型NF3的TGA扫描图(Perkin-Elmer Pyris TGA1,5K/min,氮气流量50mL/min)。

[0180] 图20描述了6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐的结晶变型NF3的水蒸气吸附等温线(25℃)(SMS DVS Intrinsic)。

[0181] 图21描述了6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐水合物的结晶变型NF5的粉末X-射线衍射图。

[0182] 图22描述了6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐水合物的结晶变型NF5的DSC扫描图(Perkin-Elmer Diamond DSC,5K/min,氮气流量50mL/min)。

[0183] 图23描述了6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐水合物的结晶变型NF5的TGA扫描图(Perkin-Elmer Pyris TGA1,5K/min,氮气流量50mL/min)。

[0184] 图24描述了6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐水合物的结晶变型NF5的水蒸气吸附等温线(25℃)(SMS DVS Intrinsic)。

[0185] 即使没有更进一步的细节,本领域技术人员也将能在最宽的范围内利用上面描述的内容。因此,优选的实施方案应当仅视为描述性的披露,绝对不以任何方式限制本发明。

[0186] 所有引用的参考文献的内容在此整体引入作为参考。利用下面的实施例更详细地说明了本发明,然而这些实施例并不限制本发明。

实施例

[0187] 实施例1:

[0188] 6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐无水物的结晶变型A1的制备

[0189] 方法1

[0190] 将约118mg 6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮(游离碱)溶解于约7mL温热的2-丙醇中。加入约0.017mL磷酸水溶液(85%)后,出现沉淀。将分散物于室温搅动2小时,随后过滤。将得到的晶体于70℃在真空下干燥。

[0191] ^{1}H-NMR(d_6-DMSO):δ[ppm] = 2.50(m,4H+DMSO),2.75(t,2H),3.57(t,4H),3.87(s,3H),4.30(t,2H),5.34(s,2H),7.05(d,1H),7.44(m,2H),7.80(d,1H),7.89(s,1H),8.21(m,2H),8.28(m,1H),8.65(s,2H).

[0192] 离子色谱法:19.3重量%磷酸根(相当于酸:碱摩尔比为1.14)。

[0193] 方法2

[0194] 将约500mg 6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮（游离碱）溶解于约10mL氯仿中。加入约2.1mL磷酸乙醇溶液(0.5mmol/L)后，将分散物于室温搅动1h。将得到的沉淀物过滤，将收获的晶体于70℃在真空下干燥。

[0195] ^{1}H-NMR(d_6-DMSO)：δ[ppm] = 2.55(m,4H)，2.80(t,2H)，3.60(m,4H)，3.88(s,3H)，4.33(t,2H)，5.35(s,2H)，7.07(d,1H)，7.46(m,2H)，7.82(d,1H)，7.90(s,1H)，8.23(m,2H)，8.30(m,1H)，8.65(s,2H).

[0196] 离子色谱法：14.9重量%磷酸根（相当于酸：碱摩尔比为0.88）。

[0197] 方法3

[0198] 将约354g 6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮（游离碱）于23℃分散于约450mL DI水中。加入约57.3mL磷酸水溶液(85%)后，将分散物加热至50℃，得到澄清的溶液。将溶液冷却至20℃，用约1.2L丙酮稀释，导致结晶。将分散物于10℃搅动，直至结晶完全。将分散物置于室温几天，随后冷却至5℃并过滤。将得到的晶体用丙酮洗涤并于70℃在真空下干燥。随后将干燥的晶体在乙醇中以分散物的形式沸腾30分钟，从热分散物中过滤出晶体。

[0199] ^{1}H-NMR(d_6-DMSO)：δ[ppm] = 2.50(m,4H+DMSO)，2.74(t,2H)，3.58(m,4H)，3.87(s,3H)，4.32(t,2H)，5.34(s,2H)，7.05(d,1H)，7.45(m,2H)，7.82(d,1H)，7.89(s,1H)，8.22(m,2H)，8.28(m,1H)，8.65(s,2H).

[0200] 离子色谱法：19.5重量%磷酸根（相当于酸：碱摩尔比为1.15）。

[0201] 方法4

[0202] 将约1.1kg 6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮（游离碱）于23℃分散于约1.37L DI水中。加入约240mL磷酸水溶液(85%)后，将分散物加热至50℃，得到澄清的溶液。将溶液冷却至20℃，在搅动下缓慢用约1L丙酮稀释，导致开始结晶。缓慢加入另外约3L丙酮，得到白色的分散物，将其于室温搅动过夜。将分散物过滤，将得到的晶体用丙酮洗涤并于70℃在真空下干燥。

[0203] ^{1}H-NMR(d_6-DMSO)：δ[ppm] = 2.50(m,4H+DMSO)，2.74(t,2H)，3.57(m,4H)，3.87(s,3H)，4.30(t,2H)，5.34(s,2H)，7.05(d,1H)，7.45(m,2H)，7.82(d,1H)，7.89(s,1H)，8.22(m,2H)，8.28(m,1H)，8.64(s,2H).

[0204] 离子色谱法：16.8重量%磷酸根（相当于酸：碱摩尔比为0.99）。

[0205] 方法5

[0206] 将约100g 6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮（游离碱）于23℃分散于约171.4g DI水中。加入约36.55g磷酸水溶液(85%)后，将溶液过滤。将得到的滤液用约331.05g丙酮稀释，得到分散物。将分散物加热至55℃，得到澄清的溶液。将溶液以0.3K/min的既定冷却速度冷却至-10℃，得到分散物，将其于-10℃后成浆1小时。将分散物过滤，将得到的晶体用丙酮洗涤并于70℃在真空下干燥。

[0207] ^{1}H NMR(500MHz，DMSO) δ = 8.64(s,2H)，8.31-8.26(m,1H)，8.25-8.19(m,2H)，7.89(s,1H)，7.81(d，J = 9.6,1H)，7.53-7.38(m,2H)，7.05(d，J = 9.6,1H)，5.33(s,2H)，

4.31(t, J = 5.6,2H),3.87(s,3H),3.65-3.52(m,4H),2.75(t, J = 5.6,2H),2.50(m,4H)

[0208] 离子色谱法:17.7 重量%磷酸根(相当于酸:碱摩尔比为 1.04)。

[0209] 方法 6

[0210] 将约 15.2kg 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮(游离碱)于 T < 30℃分散于约 31kg DI 水中。加入约 5.5kg 磷酸水溶液 (85%) 后,将溶液成浆 30 分钟,随后过滤。将得到的滤液于 25℃用约 55.8kg 丙酮稀释,得到分散物。将分散物加热至 62℃,得到澄清的溶液。将溶液以 0.1K/min 的既定冷却速度冷却至 50℃(恒温夹套温度),并成浆约 6.5 小时,直至得到浑浊的分散物。将分散物以 0.1K/min 的既定冷却速度进一步冷却至 -10℃(恒温夹套温度),并于该温度后成浆约 1 小时。将分散物过滤,将得到的晶体用丙酮洗涤并于 70℃在真空下干燥。

[0211] ^{1}H NMR(500MHz, DMSO) δ = 8.65(s,2H),8.35-8.26(m,1H),8.25-8.19(m,2H),7.89(s,1H),7.81(d, J = 9.6,1H),7.53-7.38(m,2H),7.06(d, J = 9.6,1H),5.34(s,2H),4.33(t, J = 5.5,2H),3.87(s,3H),3.69-3.52(m,4H),2.82(t, J = 5.4,2H),2.64-2.53(m,4H).

[0212] 离子色谱法:17.1 重量%磷酸根(相当于酸:碱摩尔比为 1.01)。

[0213] 实施例 2:

[0214] 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐二水合物的结晶变型 H1 的制备

[0215] 方法 1

[0216] 将约 400mg 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 铺展在培养皿上,并在封闭的干燥器中贮存在纯 DI 水上 (100% 相对湿度气氛)2 周。

[0217] ^{1}H-NMR(d_6-DMSO):δ [ppm] = 2.50(m,4H+DMSO),2.74(t,2H),3.57(m,4H),3.87(s,3H),4.30(t,2H),5.34(s,2H),7.05(d,1H),7.45(m,2H),7.82(d,1H),7.89(s,1H),8.22(m,2H),8.29(m,1H),8.65(s,2H).

[0218] 离子色谱法:17.1 重量%磷酸根(相当于酸:碱摩尔比为 1.08,基于具有下面所给出的实测水含量的磷酸盐)。

[0219] Karl-Fischer- 滴定法:6.5 重量%水。

[0220] 方法 2

[0221] 将约 45mg 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 分散于约 0.2mL DI 水 / 乙醇 (1 : 1,v/v) 的二元混合物中,于 50℃以浆液形式在 1000rpm 下振摇 7 天。然后将分散物过滤,将得到的晶体于环境条件在过滤器上干燥。

[0222] 方法 3

[0223] 将约 45mg 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 分散于约 0.2mL DI 水 / 甲醇 (1 : 1,v/v) 的二元混合物中,于 50℃以浆液形式在 1000rpm 下振摇 7 天。然后将分散物过滤,将得到的晶体于环境条件在过滤器上干燥。

[0224] 方法 4

[0225] 将约 50mg 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 分散于约 0.2mL DI 水 /2- 丙醇 (1 ： 1,v/v) 的二元混合物中，于 50℃以浆液形式在 1000rpm 下振摇 7 天。然后将分散物过滤，将得到的晶体于环境条件在过滤器上干燥。

[0226] 方法 5

[0227] 将约 30mg 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 分散于约 0.2mL DI 水 / 丙酮 (1 ： 1,v/v) 的二元混合物中，于 50℃以浆液形式在 1000rpm 下振摇 7 天。然后将分散物过滤，将得到的晶体于环境条件在过滤器上干燥。

[0228] 方法 6

[0229] 将约 65mg 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 分散于约 0.2mL DI 水 /THF(1 ： 1,v/v) 的二元混合物中，于 50℃以浆液形式在 1000rpm 下振摇 7 天。然后将分散物过滤，将得到的晶体于环境条件在过滤器上干燥。

[0230] 方法 7

[0231] 将约 50mg 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 分散于约 0.15mL DI 水 / 乙腈 (1 ： 1,v/v) 的二元混合物中，于 50℃以浆液形式在 1000rpm 下振摇 7 天。然后将分散物过滤，将得到的晶体于环境条件在过滤器上干燥。

[0232] 实施例 3 ：

[0233] 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐的结晶变型 NF3 的制备

[0234] 方法 1

[0235] 将约 30mg 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 溶解于约 3ml DI 水 / 乙醇 (1 ： 1,v/v) 的二元混合物中。通过于环境条件蒸发溶剂出现结晶。将晶体通过过滤分离并于环境条件在过滤器上干燥。

[0236] 方法 2

[0237] 将约 155mg 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 溶解于约 15ml DI 水 /1,4- 二噁烷 (1 ： 1, v/v) 的二元混合物中。通过于 50℃蒸发溶剂出现结晶。将晶体通过过滤分离并于环境条件在过滤器上干燥。

[0238] ^{1}H NMR(500MHz, DMSO)d = 8.63(s,2H),8.31-8.26(m,1H),8.25-8.18(m,2H),7.89(s,1H),7.80(d, J = 9.6,1H),7.55-7.40(m,2H),7.05(d, J = 9.6,1H),5.34(s,2H),4.31(t, J = 5.6,2H),3.87(s,3H),3.80-3.30(m,4H)2.74(t, J = 5.5,2H),2.50(m,4H)

[0239] 离子色谱法 :16.0 重量 % 磷酸根 (相当于酸 ： 碱摩尔比为 0.94)。

[0240] 实施例 4 ：

[0241] 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧

啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐水合物的结晶变型 NF5 的制备

[0242] 方法 1

[0243] 将约 100mg 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 溶解于约 1ml DI 水 / 甲醇 (1 ： 1,v ： v) 的二元混合物中。将溶液加热至 60℃,同时抽真空以快速蒸发溶剂。将粉末形式的得到的沉淀物铺展在培养皿上,随后在密封的干燥器中在 KNO_3 的饱和盐溶液上 (94% RH) 孵育几天。

[0244] ^1H NMR(500MHz, DMSO)d = 8.64(s,2H),8.31-8.25(m,1H),8.25-8.19(m,2H),7.88(s,1H),7.80(d, J = 9.6,1H),7.52-7.38(m,2H),7.04(d, J = 9.6,1H),5.33(s,2H),4.30(t, J = 5.6,2H),3.87(s,3H),3.66-3.50(m,4H),2.73(t, J = 5.6,2H),2.50(m,4H)

[0245] 离子色谱法 :14.8 重量 % 磷酸根 (相当于酸 ： 碱摩尔比为 0.94,基于具有下面所给出的实测水含量的磷酸盐)。

[0246] Karl-Fischer- 滴定法 :7.3 重量 % 水。

[0247] 方法 2 :

[0248] 将约 100mg 粉末形式的 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐的结晶变型 NF3 铺展在培养皿上,随后在密封的干燥器中在 KNO_3 的饱和盐溶液上 (94% RH) 孵育几天。

[0249] 实施例 5 :

[0250] 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 的结构和物理化学表征

[0251] 结晶变型 A1 的粉末 X- 射线衍射 (XRD) 图是通过欧洲药典第 6 版第 2.9.33 章中所述的标准技术获得的。结晶变型 A1 以图 1 中所描绘的 X- 射线粉末衍射图 (Cu-K α_1 放射源,$\boldsymbol{\lambda = 1.5406\ \text{Å}}$, Stoe StadiP611KL 衍射仪) 为特征。

[0252] 结晶变型 A1 以下面的 XRD 数据为特征 ：

[0253] 粉末 X- 射线衍射图峰列表 ：

[0254]

峰编号	d/Å	°2θ (Cu-Kα$_1$ 放射源) ± 0.1°	指标化 (h, k, l)
1	27.45	3.2	(2, 0, 0)
2	13.62	6.5	(4, 0, 0)
3	9.02	9.8	(6, 0, 0)
4	6.75	13.1	(8, 0, 0)
5	6.15	14.4	(-2, 0, 2)
6	5.59	15.8	(-6, 0, 2)
7	5.07	17.5	(-8, 0, 2)
8	4.81	18.4	(9, 1, 0)
9	4.72	18.8	(-9, 1, 1)
10	4.55	19.5	(6, 0, 2)
11	4.06	21.9	(8, 0, 2)
12	3.75	23.7	(11, 1, 1)
13	3.68	24.2	(2, 2, 1)
14	3.37	26.4	(3, 1 3)
15	3.16	28.2	(-15, 1, 2)

[0255] 还获取了结晶变型 A1 的单晶 X- 射线结构数据 (XCalibur 衍射仪来自 Oxford Diffraction，配备有石墨单色器和 CCD 检测器，于 301K 使用 MoK。放射源）。沿 b- 轴观察的结晶变型 A1 的单晶结构如图 2 所示。

[0256] 结晶变型 A1 以单斜晶空间群 C2/c 结晶，其晶胞参数 $a = 55.1$ Å, $b = 7.9$ Å, $c = 12.2$ Å, $\beta = 102.2°$ ($\alpha = \gamma = 90°$)。从单晶结构明显可见结晶变型 A1 是一种无水晶形。

[0257] 进一步用 IR- 和拉曼 - 光谱表征了结晶变型 A1。FT- 拉曼和 FT-IR 光谱是通过欧洲药典第 6 版第 2.02.24 和 2.02.48 章中所述的标准技术获得的。为了测定 FT-IR 和 FT- 拉曼 - 光谱，使用了 Bruker Vector 22 和 Bruker RFS100 光谱仪。使用 Bruker OPUS 软件对 FT-IR 光谱进行了基线校正。使用相同的软件对 FT- 拉曼光谱进行了矢量归一化。

[0258] FT-IR 光谱是使用 KBr 压片作为样品制备技术获得的。所述 FT-IR 光谱如图 3 中所示，谱带位置在下面给出。

[0259] 结晶变型 A1IR 谱带位置 ±2cm^{-1}（相对强度 * ）

[0260] 2949cm^{-1}(w)，2885cm^{-1}(w)，2368cm^{-1}(w，宽)，1661cm^{-1}(s)，1603cm^{-1}(s)，1549cm^{-1}(m)，1446cm^{-1}(s)，1429cm^{-1}(s)，1283cm^{-1}(s)，1261cm^{-1}(m)，1226cm^{-1}(m)，

1132cm^{-1}(s),1068cm^{-1}(s),945cm^{-1}(s),854cm^{-1}(s),713cm^{-1}(m)

[0261] *“s”=强(透射率≤50%),“m”=中等(50%<透射率≤70%),“w”=弱(透射率>70%)

[0262] 所述FT-拉曼光谱如图4中所示,谱带位置在下面给出。

[0263] 结晶变型A1拉曼谱带位置±2cm^{-1}(相对强度*):

[0264] 3061cm^{-1}(w),2951cm^{-1}(w),1604cm^{-1}(s),1579cm^{-1}(s),1568cm^{-1}(m),1515cm^{-1}(w),1446cm^{-1}(m),1430cm^{-1}(m),1327cm^{-1}(m),1161cm^{-1}(w),1001cm^{-1}(m),802cm^{-1}(w),793cm^{-1}(w)

[0265] *“s”=强(相对拉曼强度≥0.04),“m”=中等(0.04>相对拉曼强度≥0.02),“w”=弱(相对拉曼强度<0.02)

[0266] 结晶变型A1是一种无水晶形,其进一步被以下物理性质表征:

[0267] -热行为显示熔化峰在约207℃,升至熔化温度有非常小的质量损失。DSC图(Perkin-Elmer Diamond DSC,5K/min,氮气流量50mL/min)和TGA图(Perkin-Elmer Pyris TGA1,5K/min,氮气流量50mL/min)分别在图5和图6中给出。

[0268] -水蒸气吸附行为显示分别在范围为0-70%的相对湿度(RH)(结晶变型A,a型)和0-90%的RH(结晶变型A,b型)中吸附后有小的水摄取水平。在高于70% RH(结晶变型A,a型)和高于90% RH(结晶变型A,b型)下分别观察到显著的水摄取水平,这导致在升高的相对湿度(RH)下形成二水合物结晶变型H1(水摄取水平为约6重量%)。结晶变型A1(a型和b型)的水蒸气吸附等温线[水蒸气吸附等温线(25℃)(SMS DVS 1)]分别在图7和图8中给出。

[0269] 实施例6:

[0270] 6-(1-甲基-1H-吡唑-4-基)-2-{3-[5-(2-吗啉-4-基-乙氧基)-嘧啶-2-基]-苄基}-2H-哒嗪-3-酮磷酸二氢盐二水合物的结晶变型H1的结构和物理化学表征

[0271] 结晶变型H1的粉末X-射线衍射(XRD)图是通过欧洲药典第6版第2.9.33章中所述的标准技术获得的。结晶变型H1以图9中所示的X-射线粉末衍射图(Cu-Kα_1放射源,$\lambda = 1.5406$ Å,Stoe StadiP611 KL衍射仪)为特征。

[0272] 结晶变型H1以下面的XRD数据为特征:

[0273] 粉末X-射线衍射图峰列表:

[0274]

峰编号	d/Å	°2θ (Cu-Kα$_1$ 放射源) ± 0.1°	指标化 (h, k, l)
1	28.42	3.1	(1, 0, 0)
2	9.40	9.4	(3, 0, 0)
3	6.13	14.4	(0, 0, 2)
4	6.01	14.7	(2, 1, 1)
5	5.89	15.0	(1, 0, 2)
6	4.97	17.8	(3, 0, 2)
7	4.77	18.6	(4, 1, 1)
8	4.71	18.8	(6, 0, 0)
9	4.64	19.1	(5, 1, 0)
10	3.89	22.8	(2, 2, 0)
11	3.83	23.2	(-1, 2, 1)
12	3.73	23.8	(-2, 2, 1)
13	3.38	26.4	(0, 2, 2)
14	3.33	26.8	(-4, 1, 3)
15	3.22	27.6	(-3, 2, 2)

[0275]

[0276] 还获取了结晶变型 H1 的单晶 X- 射线结构数据 (XCalibur 衍射仪来自 Oxford Diffraction，配备有石墨单色器和 CCD 检测器，于 301K 使用 MoK$_\alpha$ 放射源)。结晶变型 H1 的单晶结构如图 10 中所示。结晶变型 H1 以单斜晶空间群 $P2_1/C$ 结晶，其晶胞参数 $a = 28.2$ Å, $b = 8.1$ Å, $c = 12.3$ Å 和 $\beta = 94.1°$ ($\alpha = \gamma = 90°$)。从单晶结构明显可见结晶变型 H1 是化学计量的二水合物。

[0277] 进一步用 IR- 光谱表征了结晶变型 H1。FT-IR 光谱是通过欧洲药典第 6 版第 2.02.24 和 2.02.48 章中所述的标准技术获得的。为了测定 FT-IR 光谱，使用了 Bruker Vector 22 光谱仪。使用 Bruker OPUS 软件对 FT-IR 光谱进行了基线校正。

[0278] FT-IR 光谱是使用 KBr 压片作为样品制备技术获得的。所述 FT-IR 光谱如图 11 中所示，谱带位置在下面给出。

[0279] 结晶变型 H1IR 谱带位置 ±2cm^{-1} (相对强度 *)

[0280] 2984cm^{-1}(s)，2944cm^{-1}(s)，2451cm^{-1}(m，宽)，1661cm^{-1}(s)，1603cm^{-1}(s)，1548cm^{-1}(s)，1446cm^{-1}(s)，1430cm^{-1}(s)，1277cm^{-1}(s)，1260cm^{-1}(s)，1226cm^{-1}(s)，1124cm^{-1}(s)，1040cm^{-1}(s)，940cm^{-1}(s)，852cm^{-1}(s)，713cm^{-1}(s) *“s”= 强 (透射率≤ 50%)，

“m”＝中等（50%＜透射率≤ 70%），“w”＝弱（透射率＞ 70%）

[0281] 结晶变型 H1 的 FT- 拉曼光谱显示与结晶变型 A1 相同的光谱，因为作为激光激发的结果，出现水合水的失去。

[0282] 结晶变型 H1 是一种二水合物晶形，其进一步被以下物理性质表征：

[0283] - 热行为显示经加热从约 30-120℃失去水合水，随后无水形式在约 208℃熔化。DSC 图 (Perkin-Elmer Diamond DSC，5K/min，氮气流量 50mL/min) 和 TGA 图 (Perkin-Elmer Pyris TGA1，5K/min，氮气流量 50mL/min) 分别在图 12 和图 13 中给出。

[0284] - 水蒸气吸附行为显示在＜ 40%的相对湿度 (RH) 下失去水合水，在＞ 70% RH 下进行吸附后重新转化为二水合物结晶变型 H1。晶型 H1 的水蒸气吸附等温线 (25℃) 在下面给出。结晶变型 H1 的水蒸气吸附等温线 [水蒸气吸附等温线 (25℃) (SMS DVS Intrinsic)] 在图 14 中给出。

[0285] 实施例 7：

[0286] 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐的结晶变型 NF3 的结构和物理化学表征

[0287] 结晶变型 NF3 的粉末 X- 射线衍射 (XRD) 图是通过欧洲药典第 6 版第 2.9.33 章中所述的标准技术获得的。结晶变型 NF3 以图 15 中所示的 X- 射线粉末衍射图 (Cu-K α_1 放射源，$\lambda = 1.5406$ Å，Stoe StadiP611 KL 衍射仪）为特征。

[0288] 结晶变型 NF3 以下面的 XRD 数据为特征：

[0289] 粉末 X- 射线衍射图峰列表：

[0290]

峰编号	d/Å	°2θ (Cu-Kα$_1$ 放射源) ± 0.1°
1	27.30	3.2
2	13.62	6.5
3	9.02	9.8
4	6.71	13.2
5	6.11	14,5
6	5.79	15.3
7	5.57	15.9
9	5.32	16.7
9	5.05	17.5
10	4.81	18.4
11	4.58	19.4

[0291]

12	4.12	21.6
13	4.04	22.0
14	3.84	23.1
15	3.75	23.7
16	3.69	24.1
17	3.37	26.4
18	3.16	28.3

[0292] 进一步用 IR- 和拉曼 - 光谱表征了结晶变型 NF3。FT- 拉曼和 FT-IR 光谱是通过欧洲药典第 6 版第 2.02.24 和 2.02.48 章中所述的标准技术获得的。为了测定 FT-IR 和 FT- 拉曼 - 光谱，使用了 Bruker Vector 22 和 Bruker RFS100 光谱仪。使用 Bruker OPUS 软件对 FT-IR 光谱进行了基线校正。使用相同的软件对 FT- 拉曼光谱进行了矢量归一化。

[0293] FT-IR 光谱是使用 KBr 压片作为样品制备技术获得的。所述 FT-IR 光谱如图 16 中所示，谱带位置在下面给出。

[0294] 结晶变型 NF3IR 谱带位置 ±2cm^{-1}（相对强度＊）

[0295] 2949cm^{-1}(m)，2873cm^{-1}(w)，2365cm^{-1}(w，宽)，1661cm^{-1}(s)，1602cm^{-1}(s)，1549cm^{-1}(m)，1445cm^{-1}(s)，1430cm^{-1}(s)，1280cm^{-1}(s)，1262cm^{-1}(m)，1226cm^{-1}(m)，1132cm^{-1}(s)，1072cm^{-1}(s)，944cm^{-1}(s)，851cm^{-1}(s)，713cm^{-1}(m)

[0296] ＊“s”＝强（透射率≤ 50%），“m”＝中等 (50%＜透射率≤ 70%)，“w”＝弱（透射率＞ 70%）

[0297] 所述 FT- 拉曼光谱如图 17 中所示，谱带位置在下面给出。

[0298] 结晶变型 NF3 拉曼谱带位置 ±2cm^{-1}（相对强度＊）：

[0299] 3061cm^{-1}(m)，2952cm^{-1}(m)，1604cm^{-1}(s)，1581cm^{-1}(s)，1568cm^{-1}(s)，1515cm^{-1}(m)，1446cm^{-1}(s)，1430cm^{-1}(s)，1327cm^{-1}(s)，1167cm^{-1}(m)，1001cm^{-1}(s)，802cm^{-1}(w)，793cm^{-1}(w)

[0300] ＊“s”＝强（相对拉曼强度≥ 0.04)，“m”＝中等 (0.04 ＞相对拉曼强度≥ 0.02)，“w”＝弱（相对拉曼强度＜ 0.02)

[0301] 结晶变型 NF3 是一种晶形，最可能是一种无水晶形，其进一步被以下物理性质表征：

[0302] - 热行为显示两个放热事件分别在约 100-130℃和 180-190℃，随后是熔化峰在约 208℃，升至熔化温度有约 1.5 重量%的小的质量损失。DSC 图 (Perkin-Elmer Diamond DSC，5K/min，氮气流量 50mL/min) 和 TGA 图 (Perkin-Elmer Pyris TGA1，5K/min，氮气流量 50mL/min) 分别在图 18 和图 19 中给出。

[0303] - 水蒸气吸附行为显示在范围为 0-70% 的相对湿度 (RH) 中吸附后有小的水摄取水平。在高于 70% RH 下观察到显著的水摄取水平，这导致在升高的相对湿度 (RH) 下形成水合物结晶变型 NF5（水摄取水平为约 5-6 重量%）。结晶变型 NF3 的水蒸气吸附等温线 [水蒸气吸附等温线 (25℃)(SMS DVS Intrinsic)] 在图 20 中给出。

[0304] 实施例 8：

[0305] 6-(1- 甲 基 -1H- 吡 唑 -4- 基)-2-{3-[5-(2- 吗 啉 -4- 基 - 乙 氧 基)- 嘧 啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐水合物的结晶变型 NF5 的结构和物理化学表征

[0306] 结晶变型 NF5 的粉末 X- 射线衍射 (XRD) 图是通过欧洲药典第 6 版第 2.9.33 章中所述的标准技术获得的。结晶变型 NF5 以图 21 中所示的 X- 射线粉末衍射图 (Cu-K α 1 放射源,$\lambda = 1.5406$ Å, Stoe StadiP611 KL 衍射仪) 为特征。

[0307] 结晶变型 NF5 以下面的 XRD 数据为特征 :

[0308] 粉末 X- 射线衍射图峰列表 :

[0309]

峰编号	d/Å	°2θ (Cu-Kα1 放射源) ± 0.1°
1	28.54	3.1
2	9.41	9.4
3	6.37	13.9
4	6.10	14.5
5	5.98	14.8
6	5.82	15.2
7	5.62	15.7
9	5.32	16.6
9	5.13	17.3
10	4.96	17.9
11	4.80	18.5
12	4.69	18.9
13	4.63	19.2
14	4.48	19.8
15	4.02	22.1
16	3.90	22.8
17	3.85	23.1
18	3.73	23.9
19	3.38	26.3
20	3.32	26.8
21	3.23	27.6

[0310]

[0311] 结晶变型 NF5 是一种水合物晶形，其进一步被以下物理性质表征：

[0312] -热行为显示经加热从约 30-100℃失去水合水，随后无水形式在约 210℃熔化。DSC 图 (Perkin-Elmer Diamond DSC，5K/min，氮气流量 50mL/min) 和 TGA 图 (Perkin-Elmer Pyris TGA1，5K/min，氮气流量 50mL/min) 分别在图 22 和图 23 中给出。

[0313] -水蒸气吸附行为显示在＜ 40％的相对湿度 (RH) 下失去水合水，在＞ 70％ RH 下进行吸附后重新转化为水合物结晶变型 NF5。晶型 NF5 的水蒸气吸附等温线 (25℃) 在下面给出。结晶变型 NF5 的水蒸气吸附等温线 [水蒸气吸附等温线 (25℃) (SMS DVS Intrinsic)] 在图 24 中给出。

[0314] 实施例 9：

[0315] 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐的溶解度测定

[0316] 为了进行溶解度测定，将 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮 (游离碱) 和它的磷酸二氢盐称重到 GC- 管瓶中，加入 300μL 溶剂媒介物，得到 10mg/mL 的最大可能浓度。将混合物于环境温度在 1000rpm 下在磁力搅拌盘上搅拌。在取样点将 100μL 各溶液 / 混悬液转移至一个 500μL Eppendorff 管并在 14000rpm 下离心 5min。将离心物通过 HPLC 进行分析 (在分析前进行稀释可能是必需的)。

[0317] 表 1 给出了 1 小时和 2 小时后测得的 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮的游离碱和它的相应的磷酸二氢盐在水中的溶解度。

[0318] 表 1

[0319]

	取样点 1h		取样点 2h	
	溶解度 [mg/ml]	pH值	溶解度 [mg/ml]	pH值
游离碱	0,167	n.d.	0,156	n.d.
磷酸二氢盐	9,863	3,91	＞ 10	3,97

[0320] 结果清楚地证明，与它的游离碱相比，6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐在水性溶液中具有显著更高的溶解度。

[0321] 实施例 10：

[0322] 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐的结晶变型 A1 和 NF3 在有机溶剂中的竞争性浆液转化实验

[0323] 将约 10mg 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 和 10mg6-(1- 甲

基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐的结晶变型 NF3 混合成粉末共混物，在具有 PTFE 密封帽的 4mL 玻璃管瓶中分散于 1mL 有机溶剂中。将 PTFE 包被的搅拌棒插入分散物中，然后密封管瓶。将分散物分别于 25℃和 50℃在封闭的管瓶中使用磁力搅拌器搅动 5 天。将固态残余物过滤，通过 XRD 进行分析以监测在溶剂成浆后的形态形式。

[0324] 竞争性浆液转化实验的结果汇编在表 2 中。

[0325] 表 2

[0326]

成浆溶剂	混合物 A1+NF3 (约 1:1，重量/重量)	
	残余物 25°C，5 d	残余物 50°C，5 d
丙酮	A1	A1
乙醇	A1	A1
1,4-二噁烷	A1	A1
THF	A1 +非常小部分的 NF3	A1

[0327] 在两个温度下，在从晶形 A1 和 NF3 的二元 1 ： 1 混合物开始的成浆实验结束时，结晶变型 A1 作为唯一的或优选的晶形被获得，清楚地证明 A1 能被视为更稳定的晶形。

[0328] 实施例 11 ：

[0329] 6-(1- 甲 基 -1H- 吡 唑 -4- 基)-2-{3-[5-(2- 吗 啉 -4- 基 - 乙 氧 基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐的结晶变型 A1 和 NF5 在水中的竞争性浆液转化实验

[0330] 将约 20mg 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 和 20mg6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐水合物的结晶变型 NF5 混合成粉末共混物，在具有 PTFE 密封帽的 4mL 玻璃管瓶中分散于 0.3mL 水中。将 PTFE 包被的搅拌棒插入分散物，然后密封管瓶。将分散物于 25℃在封闭的管瓶中使用磁力搅拌器搅动 12 天。将固态残余物过滤，通过 XRD 进行分析以监测在溶剂成浆后的形态形式。

[0331] 竞争性浆液转化实验的结果汇编在表 3 中。

[0332] 表 3

[0333]

成浆溶剂	混合物 A1+NF5 (约 1:1，重量/重量)
	残余物 25°C，12 d
水	NF5 + 非常小部分的 A1

[0334] 实验显示于 25℃变型 A1 和 NF5 的延长的水性成浆作为优选的晶形导致水合物晶形 NF5，清楚地显示 NF5 在水性分散体系中是更稳定的晶形。

[0335] 实施例 12：

[0336] 6-(1- 甲 基 -1H- 吡 唑 -4- 基)-2-{3-[5-(2- 吗 啉 -4- 基 - 乙 氧 基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐的结晶变型 H1 和 NF5 在水中的竞争性浆液转化实验

[0337] 将约 20mg 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐二水合物的结晶变型 H1 和 20mg6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐水合物的结晶变型 NF5 混合成粉末共混物，在具有 PTFE 密封帽的 4mL 玻璃管瓶中分散于 0.3mL 水中。将 PTFE 包被的搅拌棒插入分散物，然后密封管瓶。将分散物于 25℃在封闭的管瓶中使用磁力搅拌器搅动 12 天。将固态残余物过滤，通过 XRD 进行分析以监测在溶剂成浆后的形态形式。

[0338] 竞争性浆液转化实验的结果汇编在表 4 中。

[0339] 表 4

[0340]

成浆溶剂	混合物 H1+NF5 (约 1:1，重量/重量) 残余物 25°C，12 d
水	H1

[0341] 实验显示于 25℃变型 H1 和 NF5 的延长的水性成浆作为优选的晶形导致二水合物晶形 H1，清楚地显示 H1 在水性分散体系中是更稳定的晶形。

[0342] 实施例 13：

[0343] 6-(1- 甲 基 -1H- 吡 唑 -4- 基)-2-{3-[5-(2- 吗 啉 -4- 基 - 乙 氧 基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐的结晶变型 H1 和 NF3 在水中的竞争性浆液转化实验

[0344] 将约 10mg 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐二水合物的结晶变型 H1 和 10mg6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐的结晶变型 NF3 混合成粉末共混物，在具有 PTFE 密封帽的 4mL 玻璃管瓶中分散于 0.2mL 水中。将 PTFE 包被的搅拌棒插入分散物，然后密封管瓶。将分散物于 25℃在封闭的管瓶中使用磁力搅拌器搅动 5 天。将固态残余物过滤，通过 XRD 进行分析以监测在溶剂成浆后的形态形式。

[0345] 竞争性浆液转化实验的结果汇编在表 5 中。

[0346] 表 5

[0347]

成浆溶剂	混合物 H1+NF3 (约 1:1，重量/重量) 残余物 25°C，5 d
水	H1

[0348] 实验显示于 25℃变型 H1 和 NF3 的延长的水性成浆作为优选的晶形导致二水合物晶形 H1，清楚地显示 H1 在水性分散体系中是更稳定的晶形。

[0349] 实施例 14：

[0350] 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐的晶形 A1(无水物) 和 NF3 在水：丙酮 30 ： 70(v ： v) 的混合物中 2 小时后的动力学溶解度测定

[0351] 将约 70mg 6-(1- 甲基 -1H- 吡唑 -4- 基)-2-{3-[5-(2- 吗啉 -4- 基 - 乙氧基)- 嘧啶 -2- 基]- 苄基 }-2H- 哒嗪 -3- 酮磷酸二氢盐无水物的结晶变型 A1 在 5mLWhtamn Uniprep 非注射样滤器管瓶中分散于 1mL 水：丙酮 (30 ： 70,v ： v) 的二元混合物中。将分散物于室温在 450rpm 下搅动 2 小时。2 小时后过滤分散物后，将滤液通过 HPLC 进行分析 (在分析前稀释可能是必需的)。将固态残余物通过粉末 X- 射线衍射 (PXRD) 进行分析。

[0352] 在水中：丙酮中的动力学溶解度测定的结果汇编在表 6 中。

[0353] 表 6

[0354]

晶形	2 小时后的溶解度 水:丙酮(30:70, v:v) [mg/mL]	SS 残余物
A1	18.2	H1
NF3	10.6	H1+NF5

[0355] 两种无水晶形经历了向二水合物晶形 H1 的转化 (在晶形 NF3 的情况下，为与水合物晶形 NF5 的混合物形式)。相应的溶解度水平清楚地显示晶形 NF3 比晶形 A1 在 2 小时后表现出更低的溶解度水平。

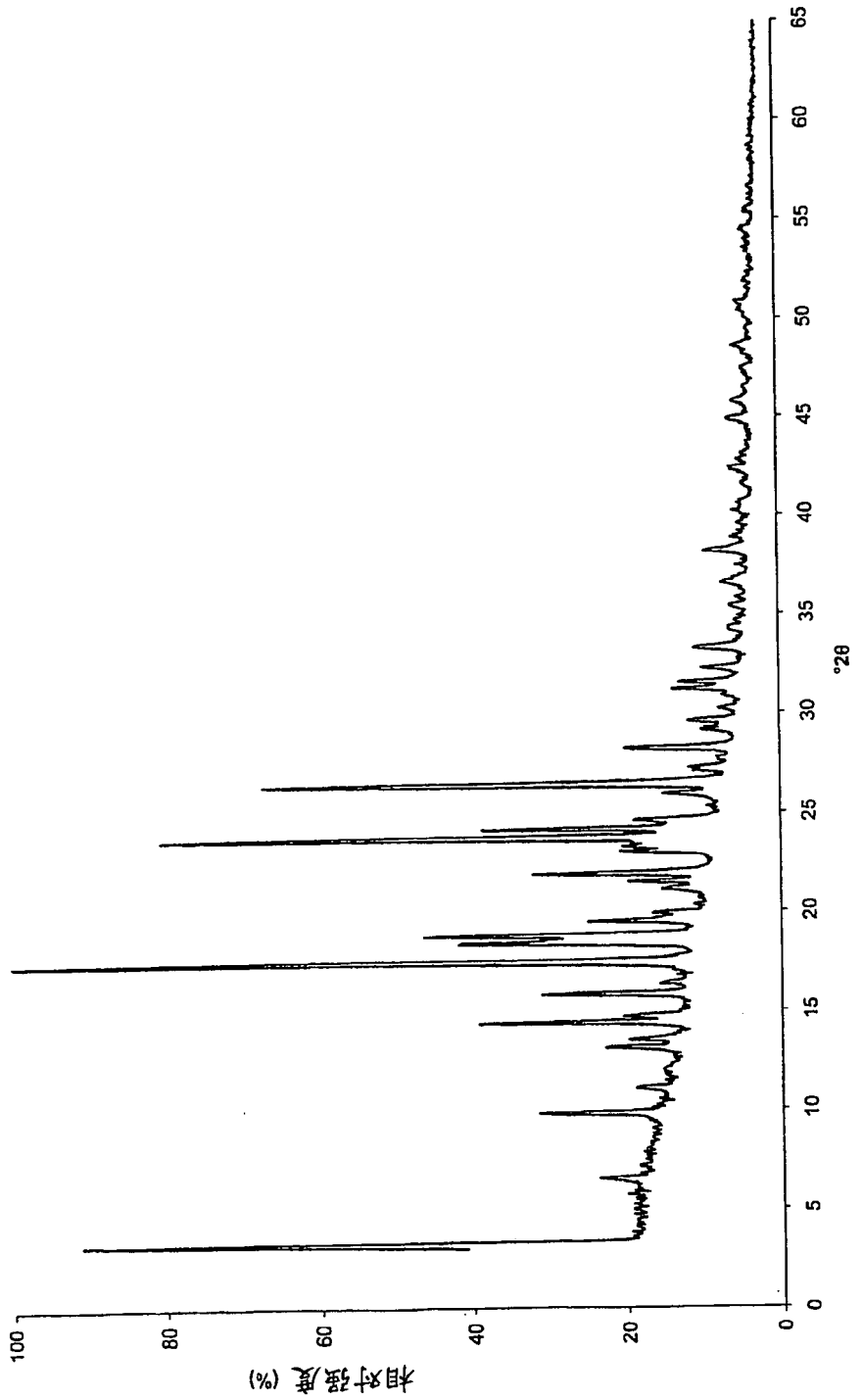


图 1

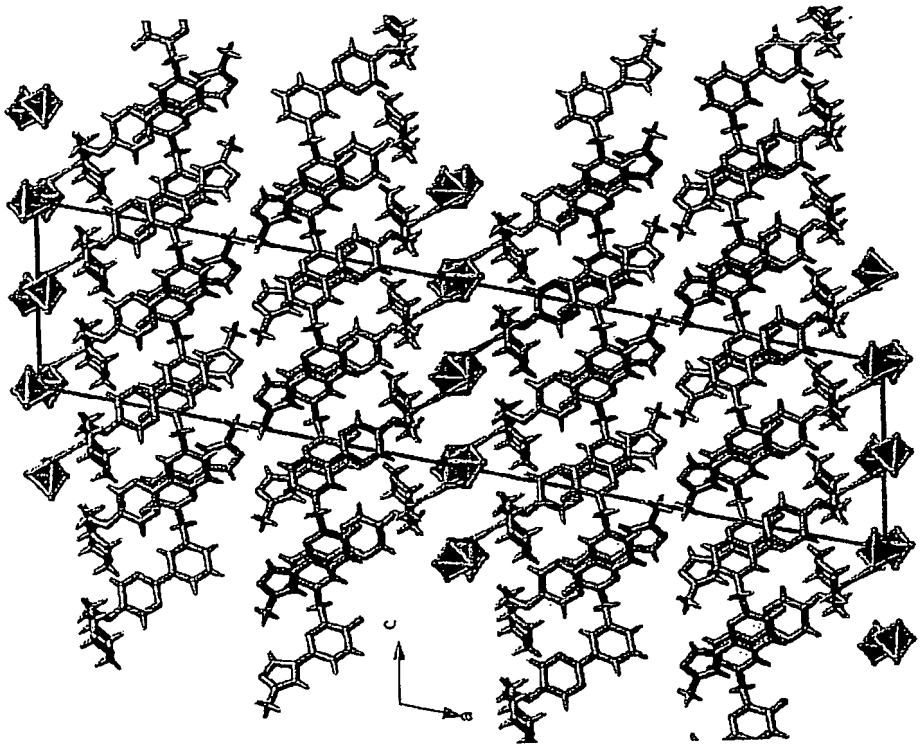


图 2

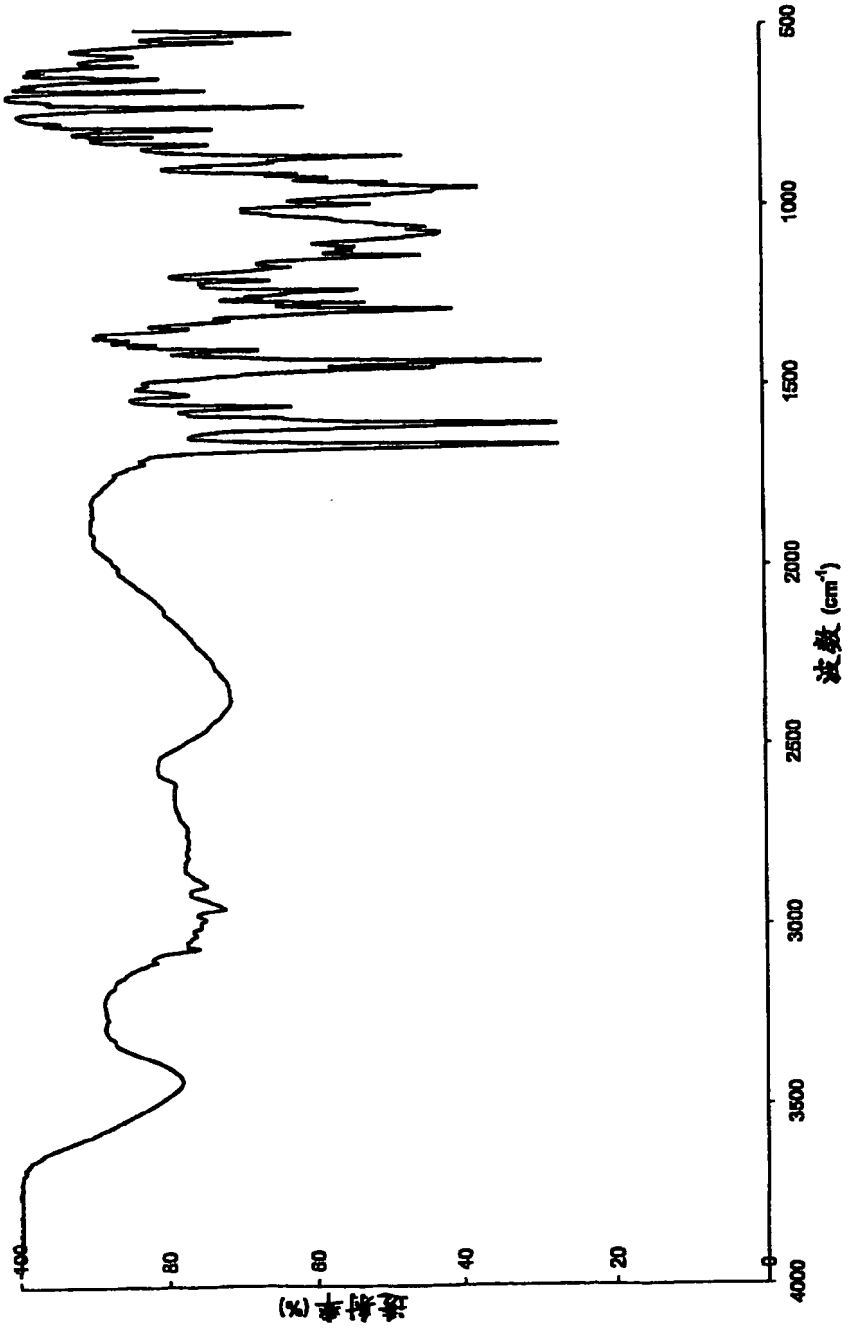

500
1000
1500
2000
2500
3000
3500
4000
波数 (cm⁻¹)
100
80
60
40
20
0
透射率(%)

图 3

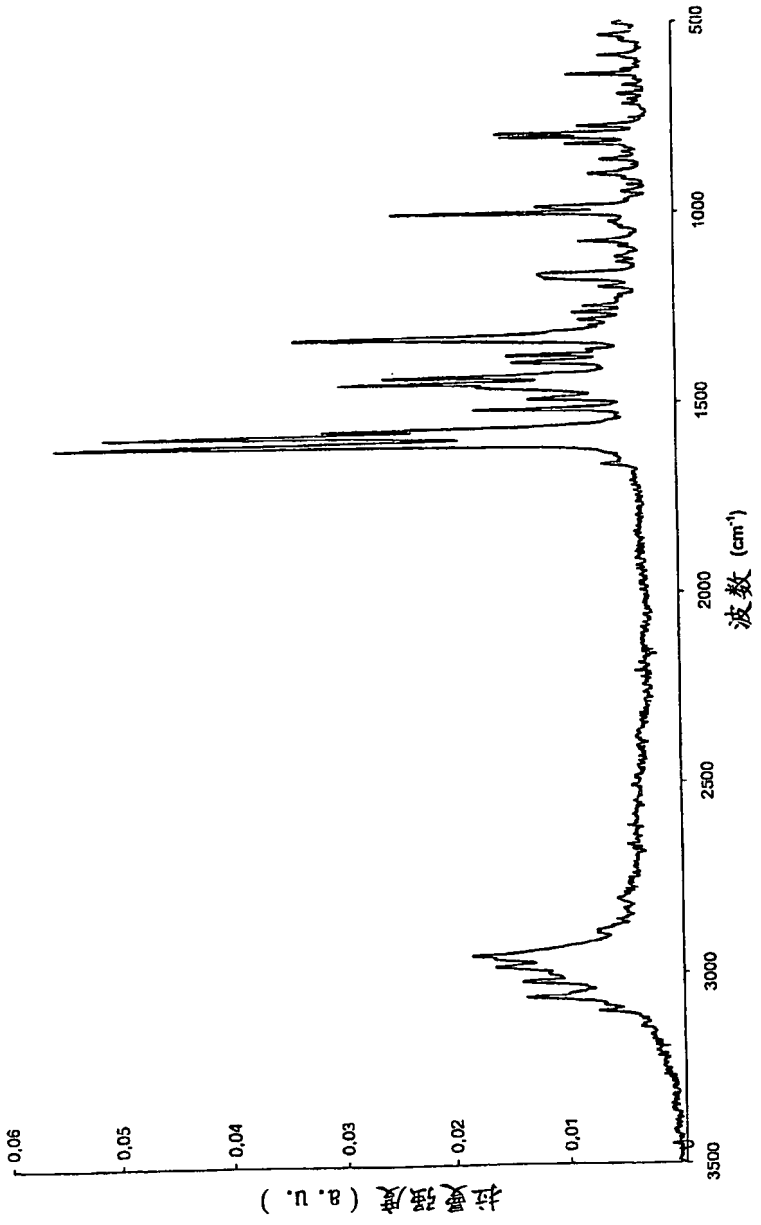

拉曼强度 (a. u.)
0.06
0.05
0.04
0.03
0.02
0.01
3500
3000
2500
2000
1500
1000
500
波数 (cm-1)

图 4

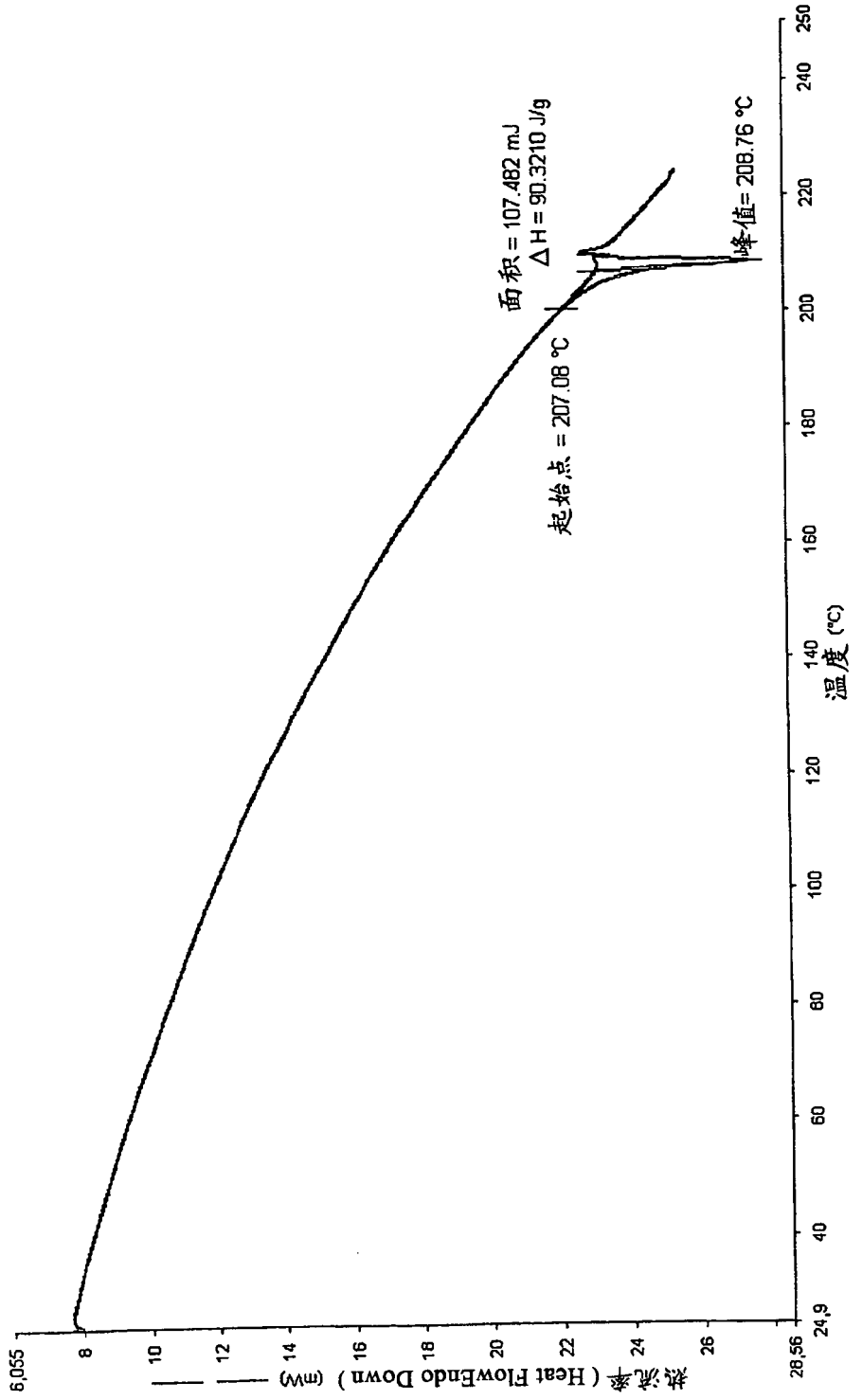

面积 = 107.482 mJ
ΔH = 90.3210 J/g
起始点 = 207.08 ℃
峰值= 208.76 ℃
热流率 (Heat FlowEndo Down) (mW)
温度 (℃)
6,055
8
10
12
14
16
18
20
22
24
26
28,56
24,9
40
60
80
100
120
140
160
180
200
220
240
250

图 5

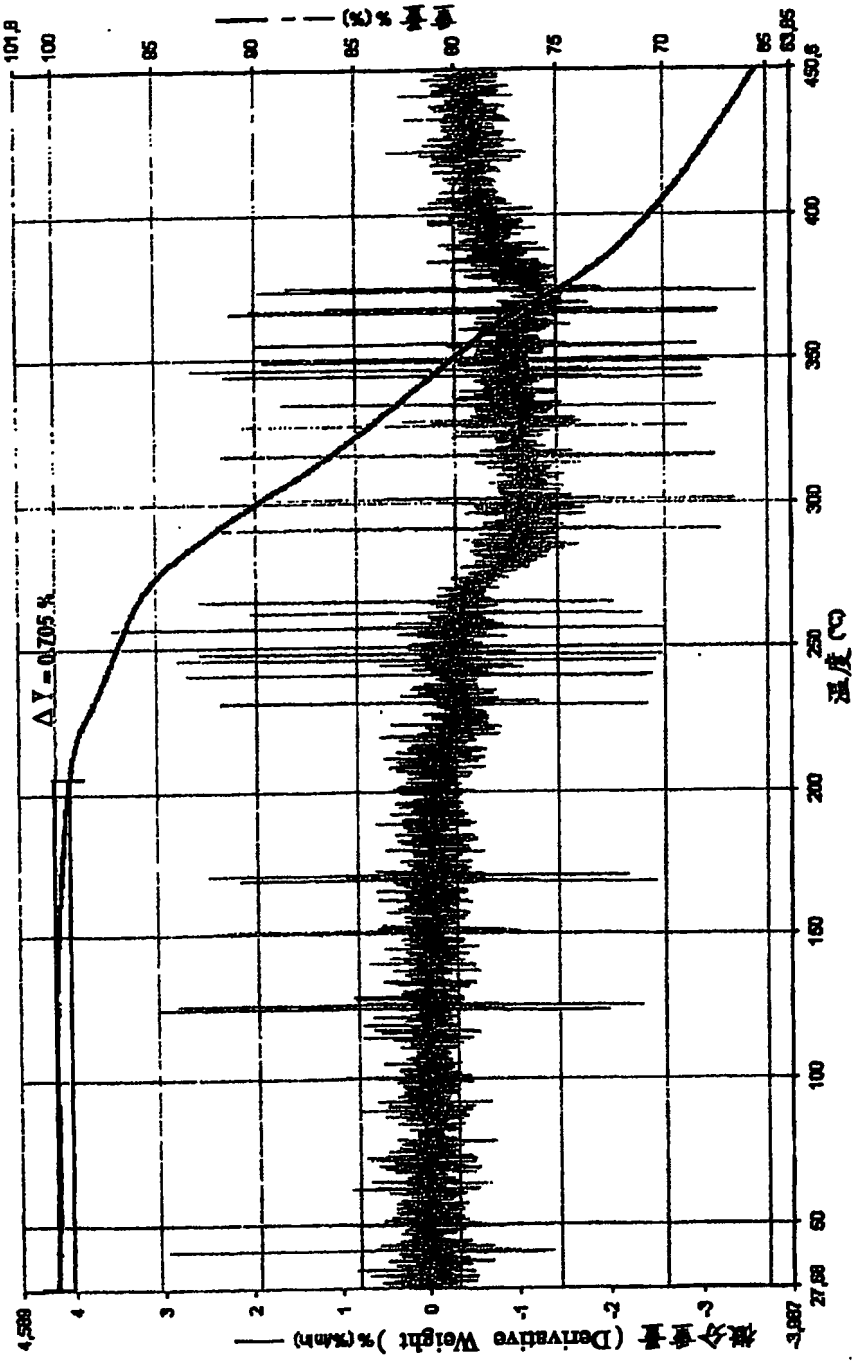

重量 %(%)
101.8
100
95
90
85
80
75
70
65
63.85
450.6
400
350
300
250
200
150
100
50
27.88
温度 (C)
ΔY = 0.705 %
4.588
4
3
2
1
0
-1
-2
-3
-3.887
微分重量 (Derivative Weight) %(%/min)

图 6

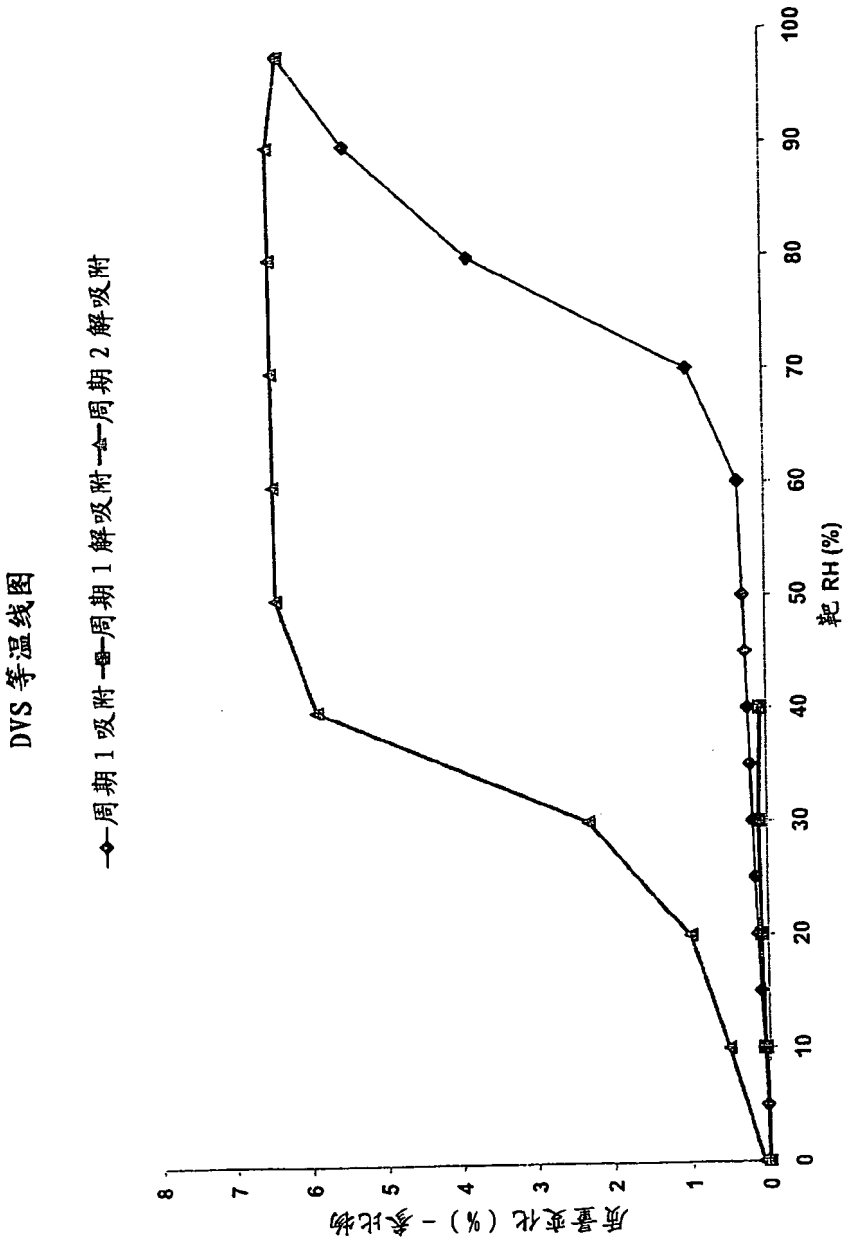

DVS 等温线图
—◆—周期 1 吸附 —■—周期 1 解吸附 —▲—周期 2 解吸附
质量变化（%）- 参比物
0
1
2
3
4
5
6
7
8
0
10
20
30
40
50
60
70
80
90
100
靶 RH (%)

图 7

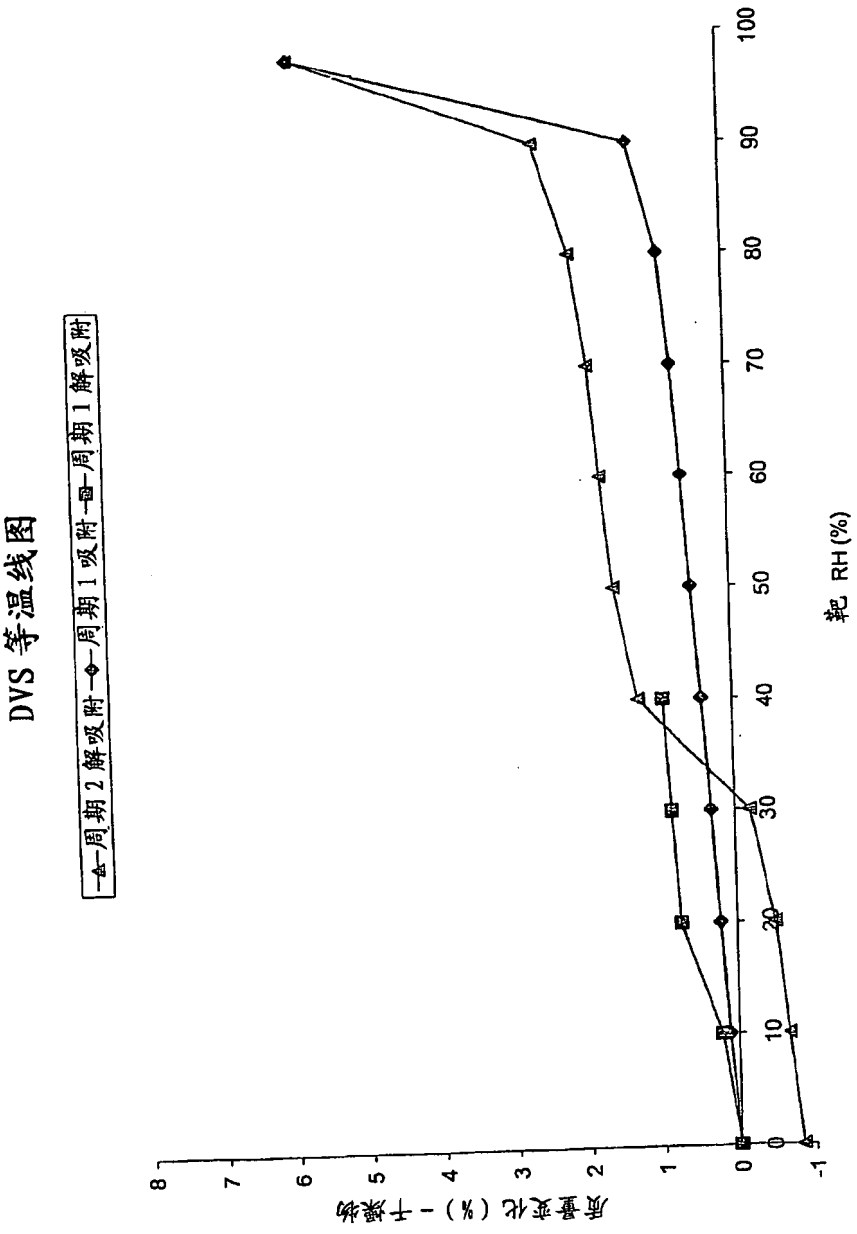

DVS 等温线图
—▲—周期 2 解吸附—◆—周期 1 吸附—■—周期 1 解吸附
质量变化 (%) - 干燥物
RH (%)
8
7
6
5
4
3
2
1
0
-1
100
90
80
70
60
50
40
30
20
10
0

图 8

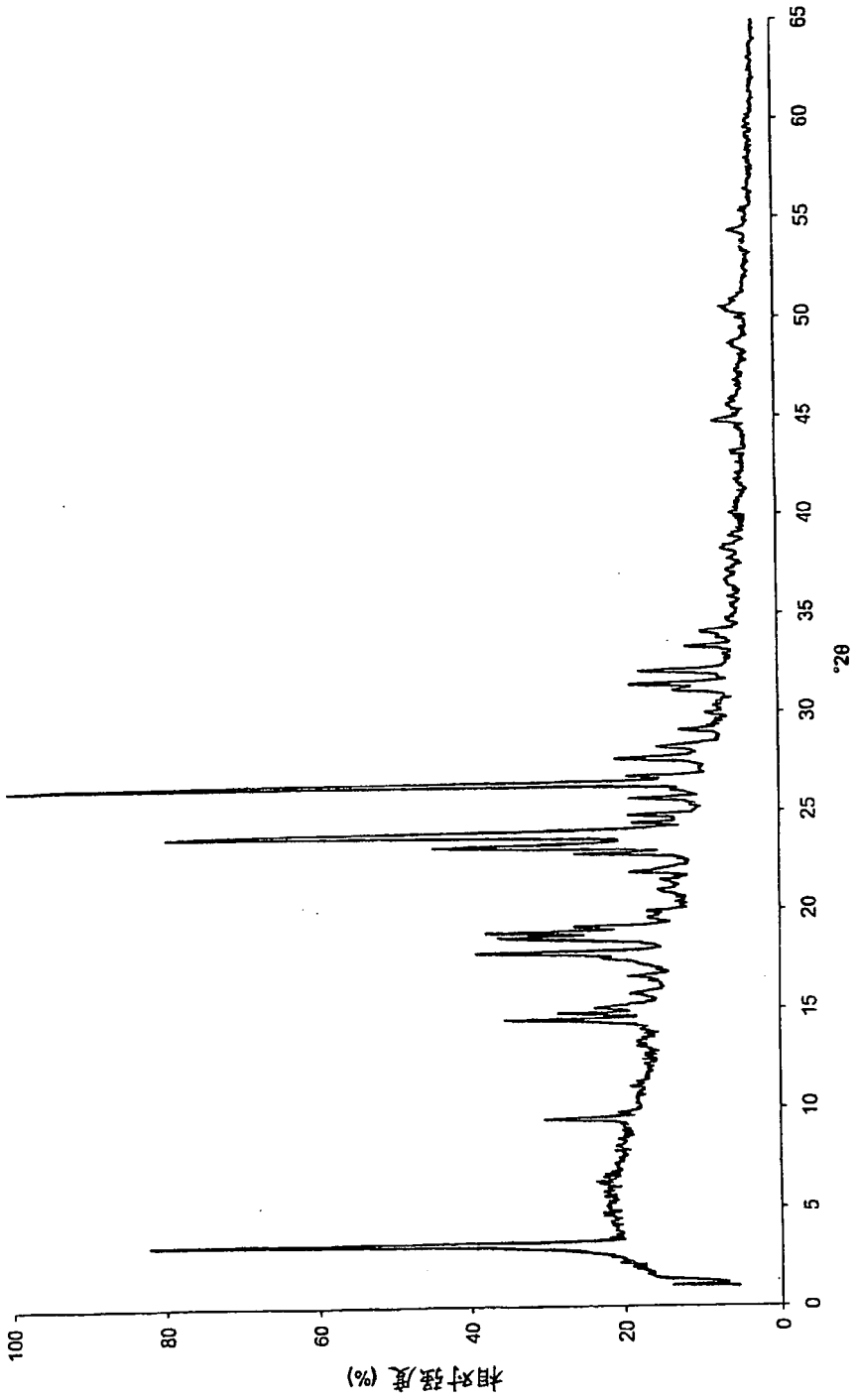


图 9

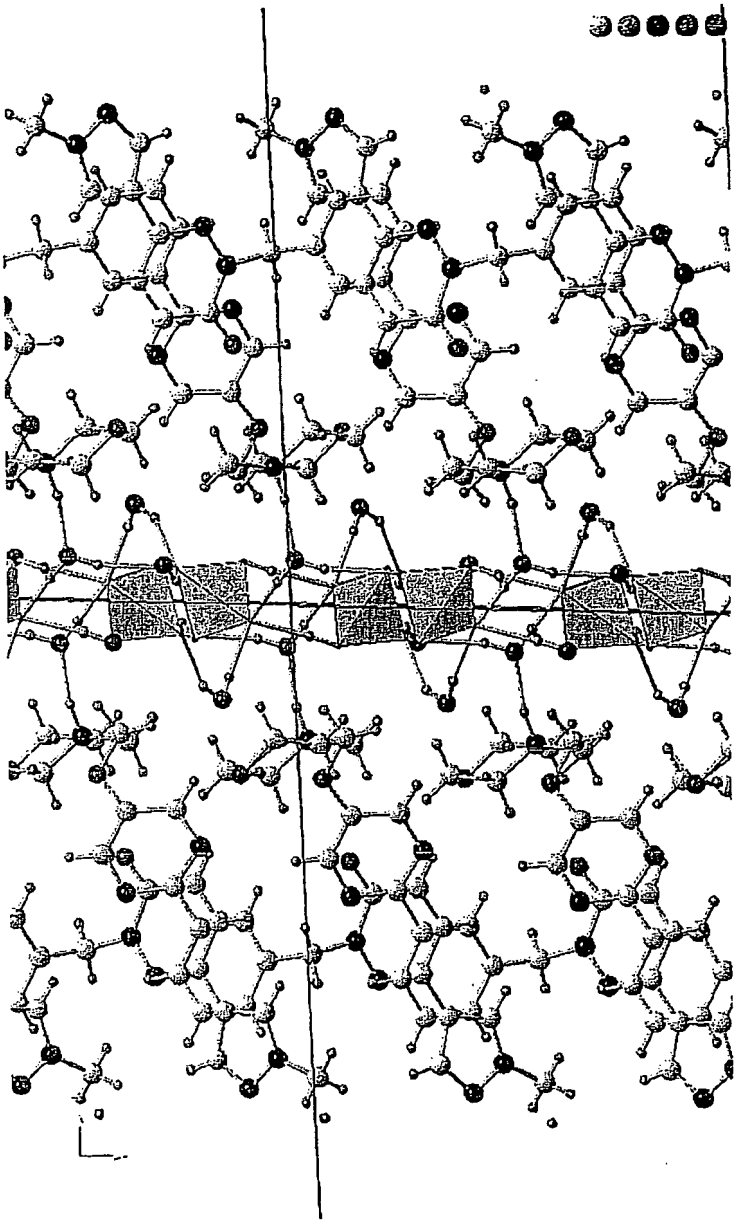


图 10

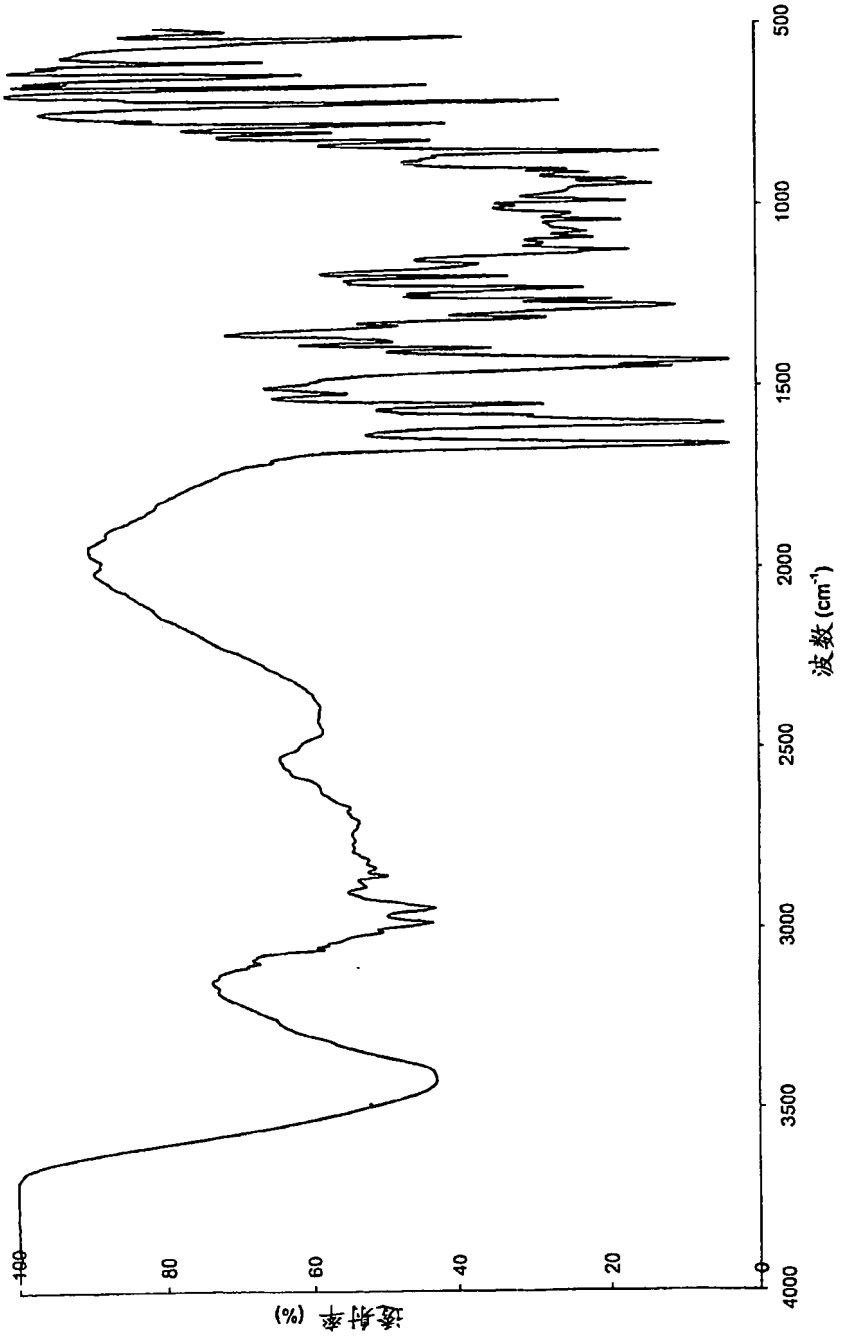

500
1000
1500
2000
2500
3000
3500
4000
波数 (cm-1)
0
20
40
60
80
100
透射率 (%)

图 11

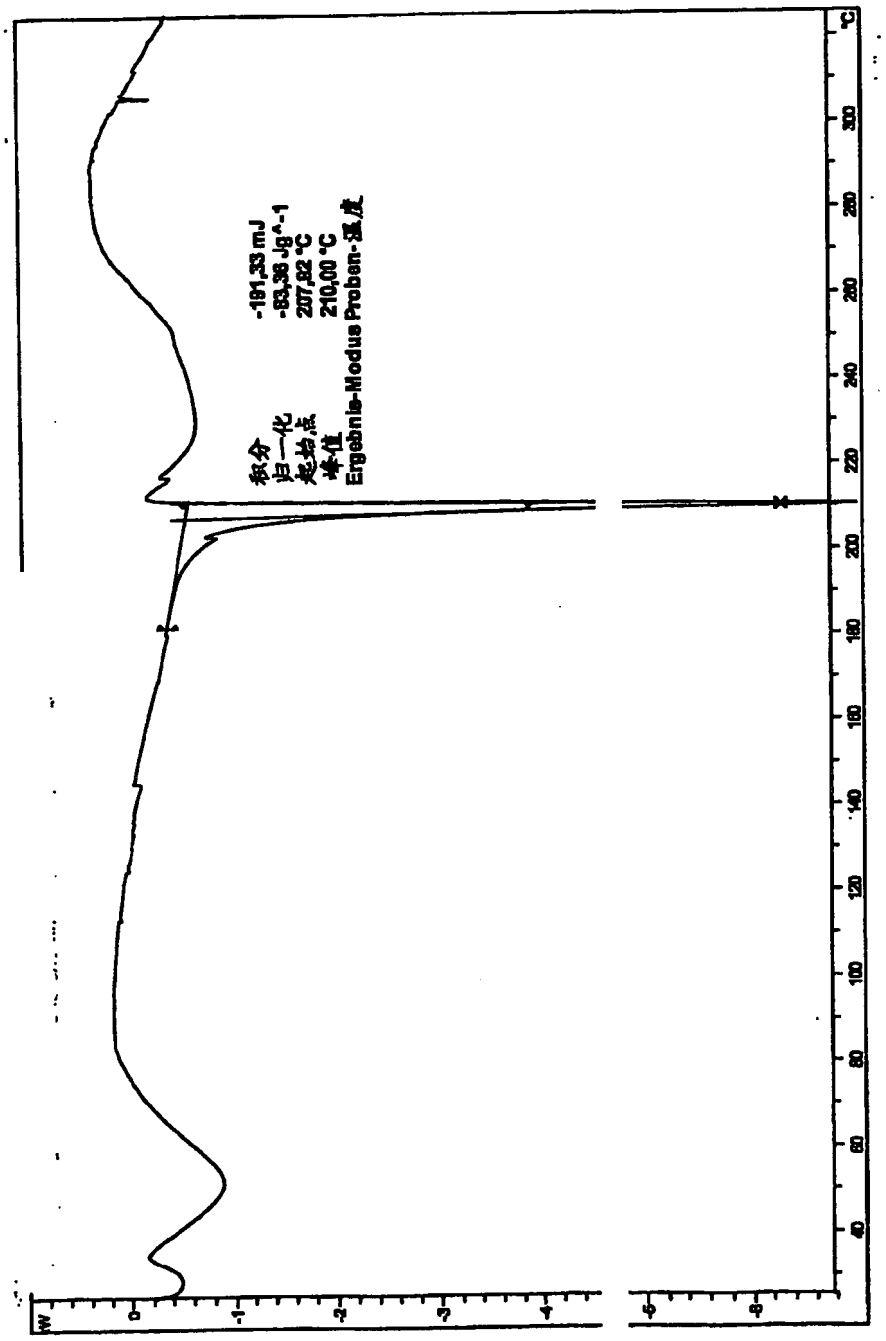

-191,33 mJ
-83,38 Jg^-1
207,82 °C
210,00 °C
积分
归一化
起始点
峰值
Ergebnis-Modus Proben-
°C
mW

图 12

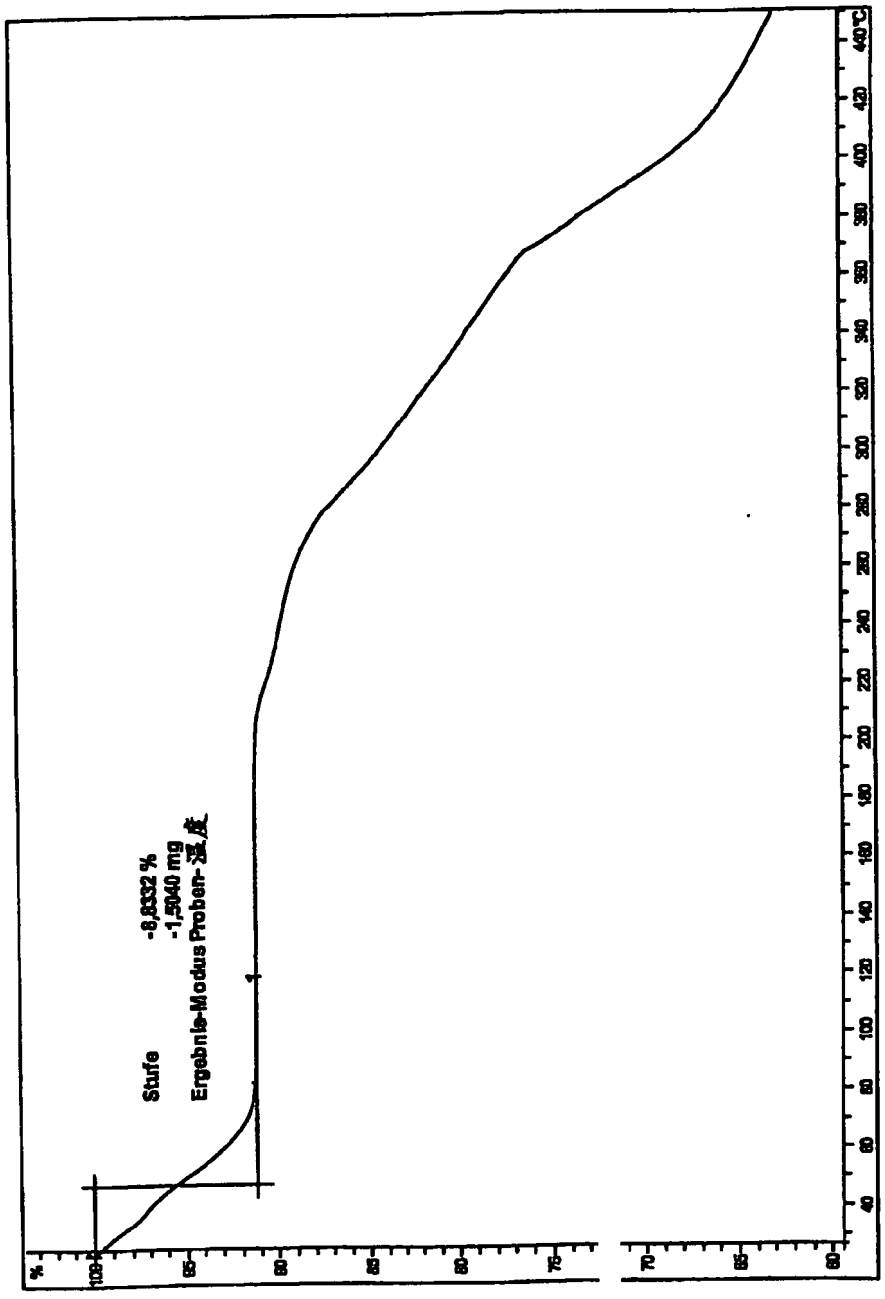


图 13

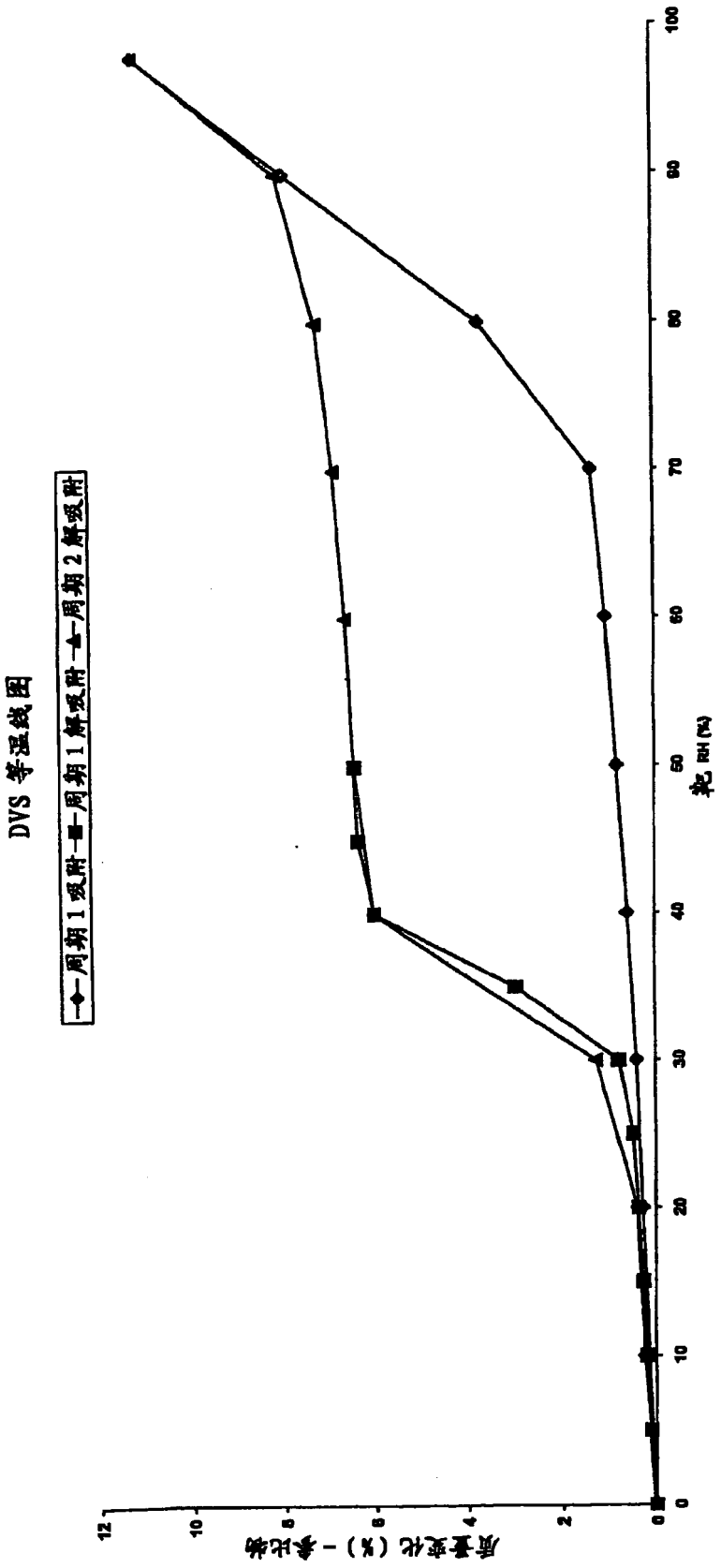

DVS 等温线图
—◆—周期 1 吸附—■—周期 1 解吸附—▲—周期 2 解吸附
质量变化 (%) - 参比物
RH (%)
0
2
4
6
8
10
12
0
10
20
30
40
50
60
70
80
90
100

图 14

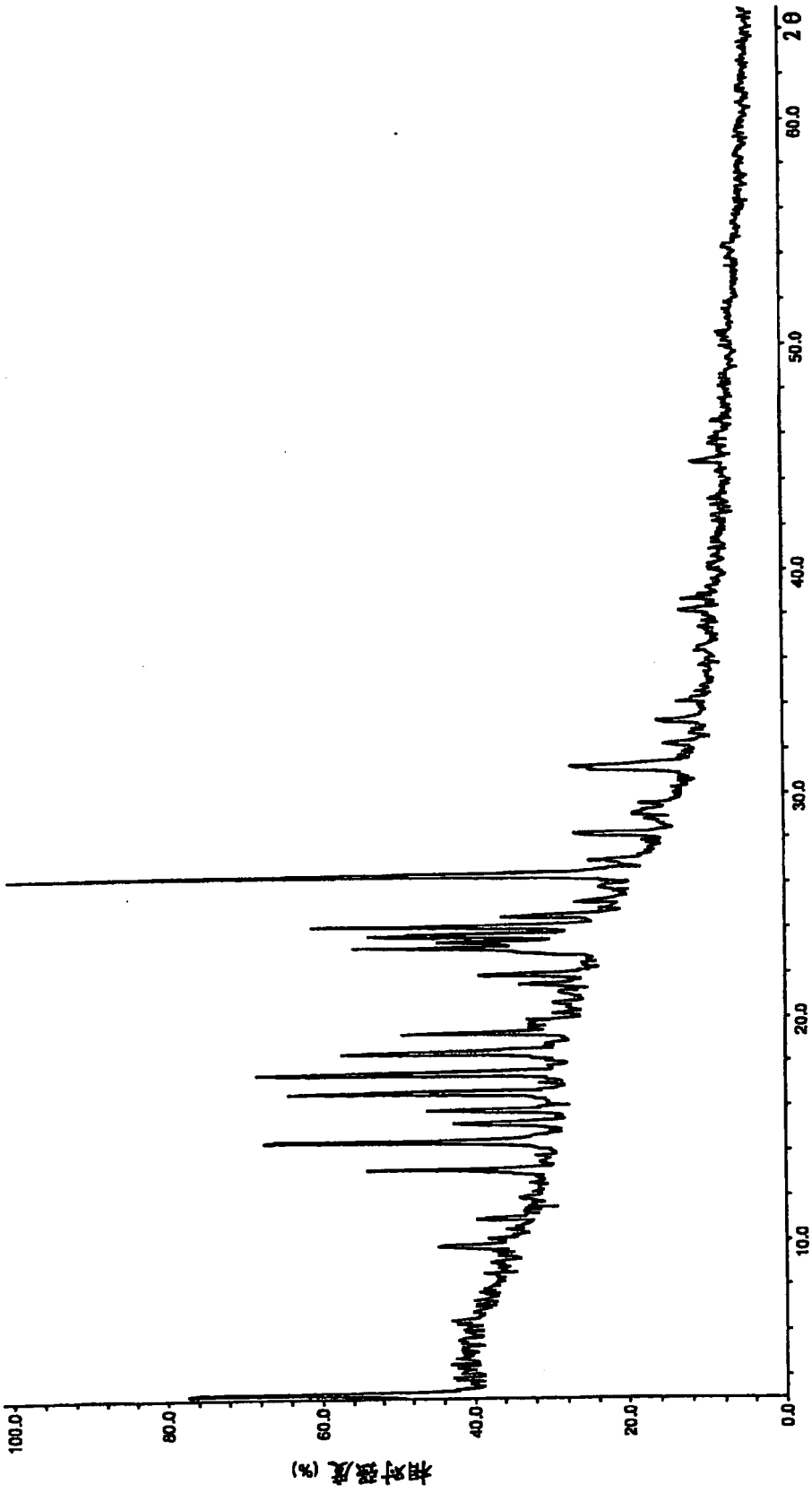


图 15

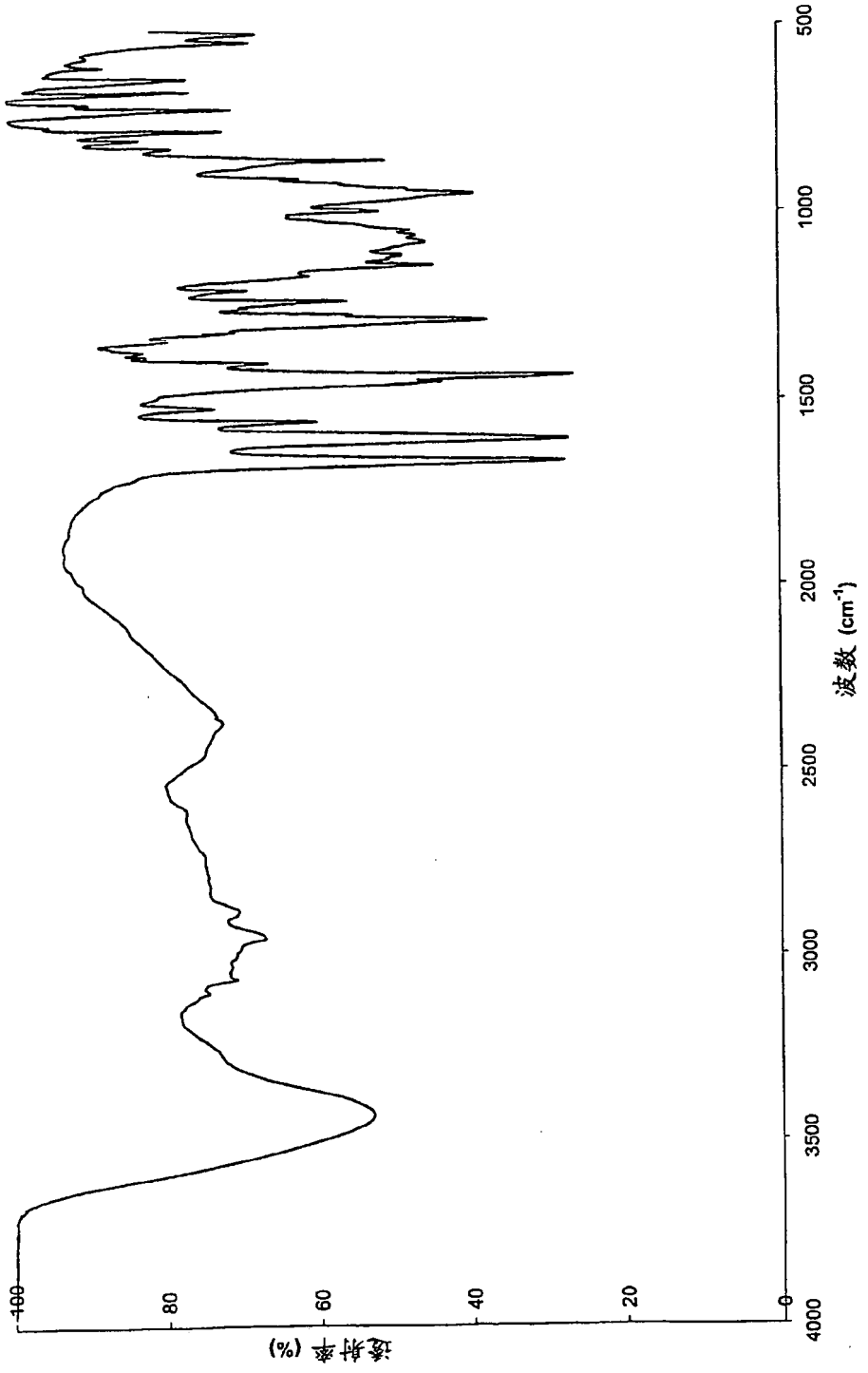

500
1000
1500
2000
2500
3000
3500
4000
波数 (cm-1)
0
20
40
60
80
100
透射率 (%)

图 16

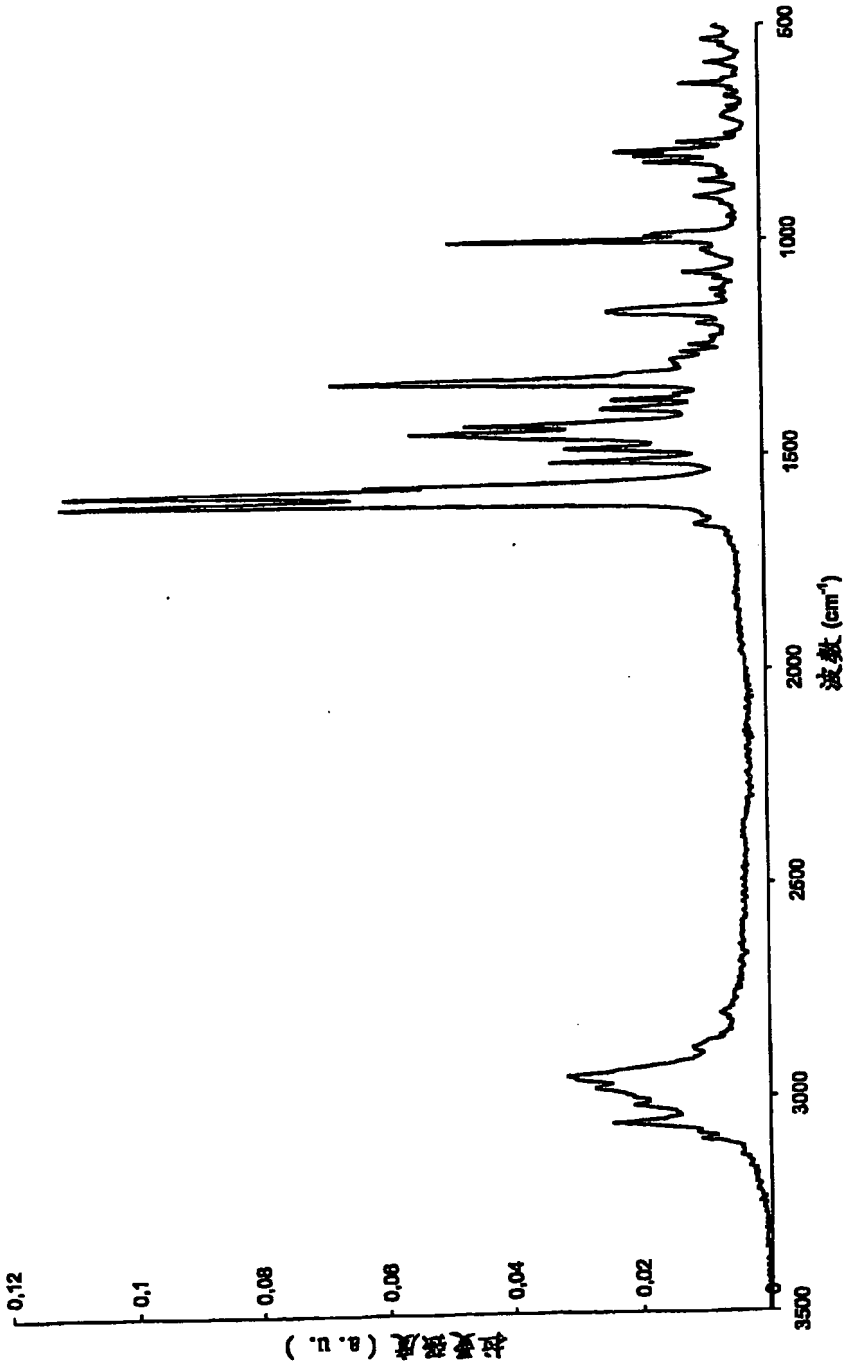

0,12
0,1
0,08
0,06
0,04
0,02
0
3500
3000
2500
2000
1500
1000
500
波数 (cm-1)
拉曼强度 (a. u.)

图 17

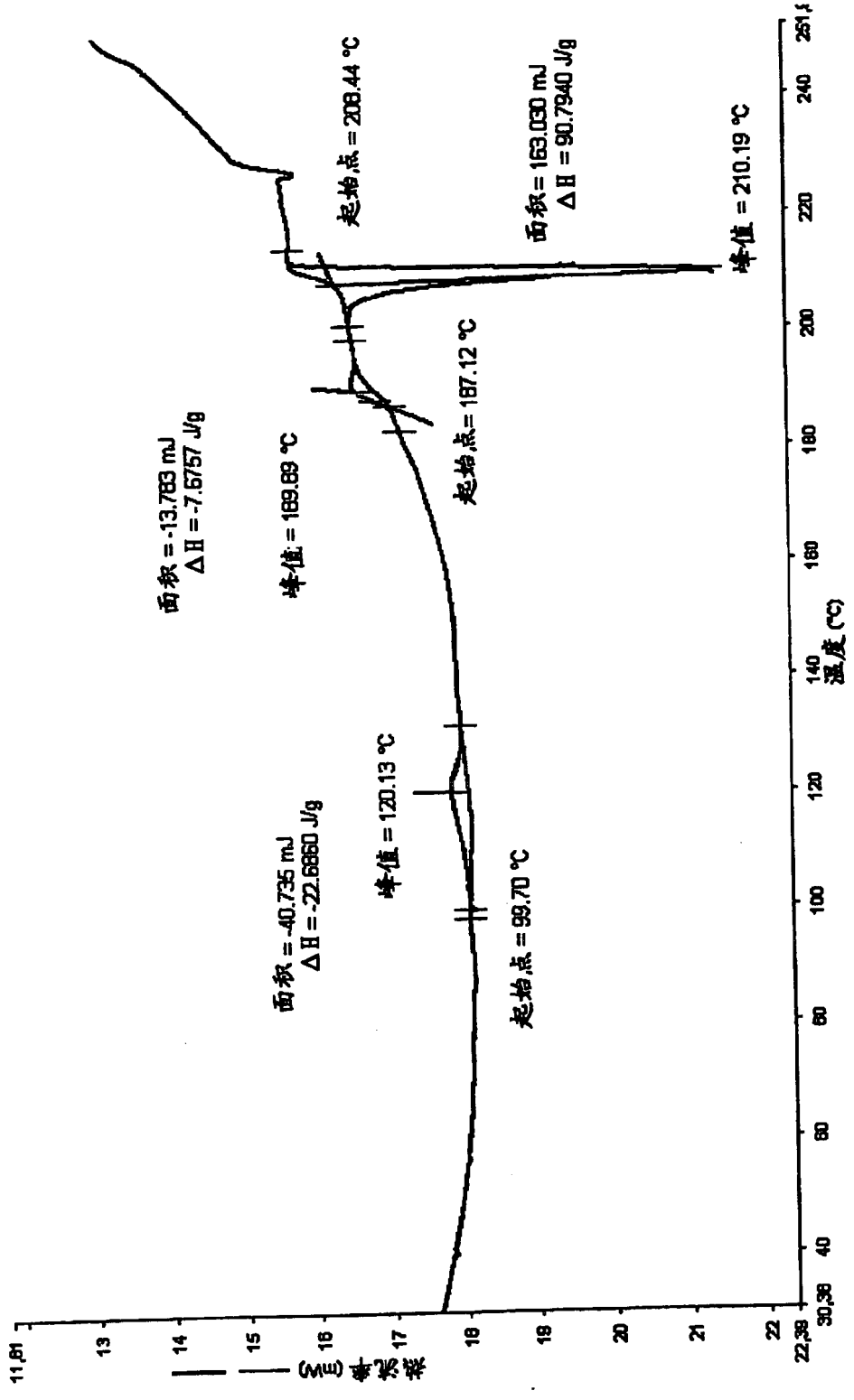

面积 = -13.783 mJ
ΔH = -7.6757 J/g
峰值 = 189.69 ℃
起始点 = 208.44 ℃
面积 = 163.030 mJ
ΔH = 90.7940 J/g
峰值 = 210.19 ℃
起始点 = 187.12 ℃
面积 = -40.735 mJ
ΔH = -22.6860 J/g
峰值 = 120.13 ℃
起始点 = 99.70 ℃
温度 (℃)

图 18

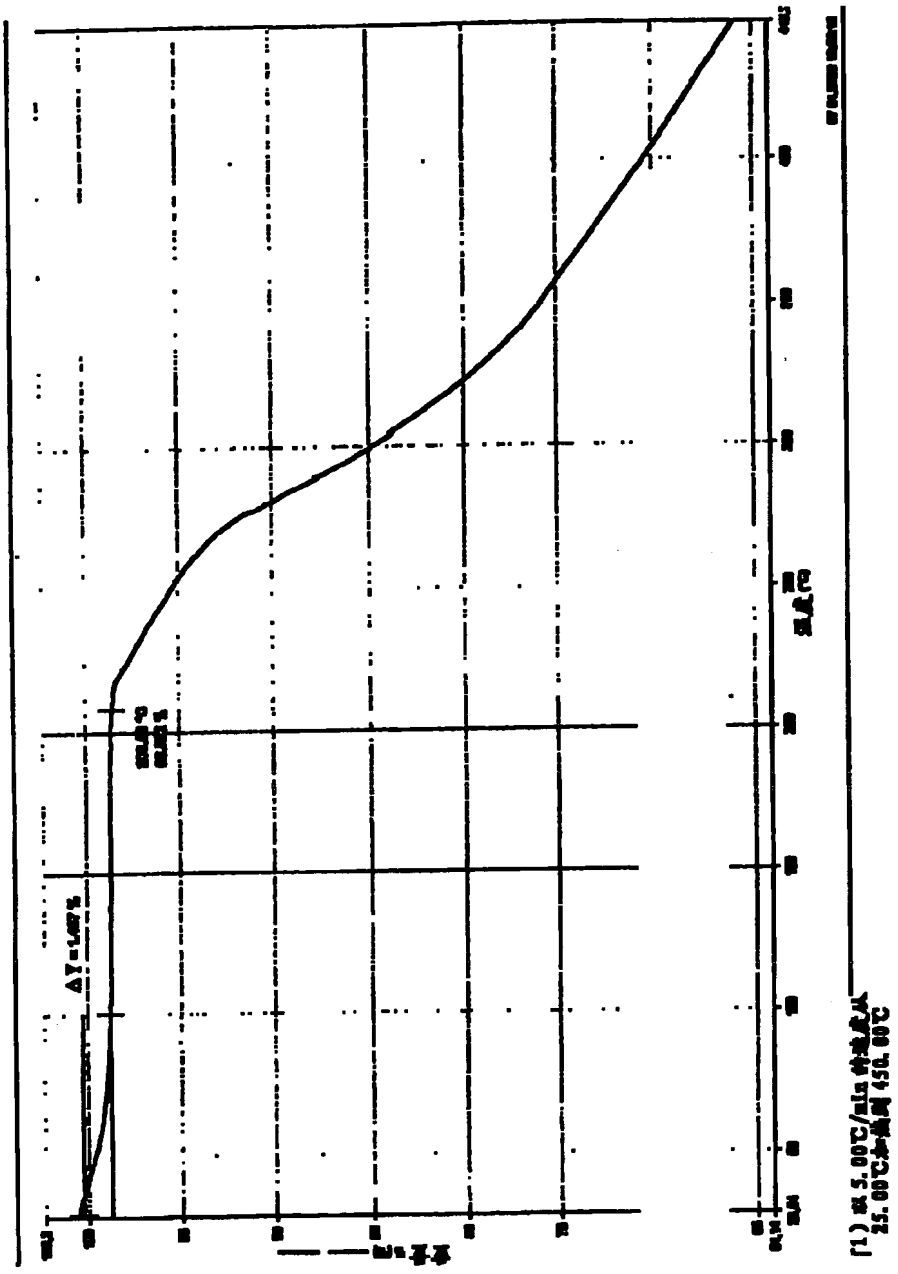


图 19

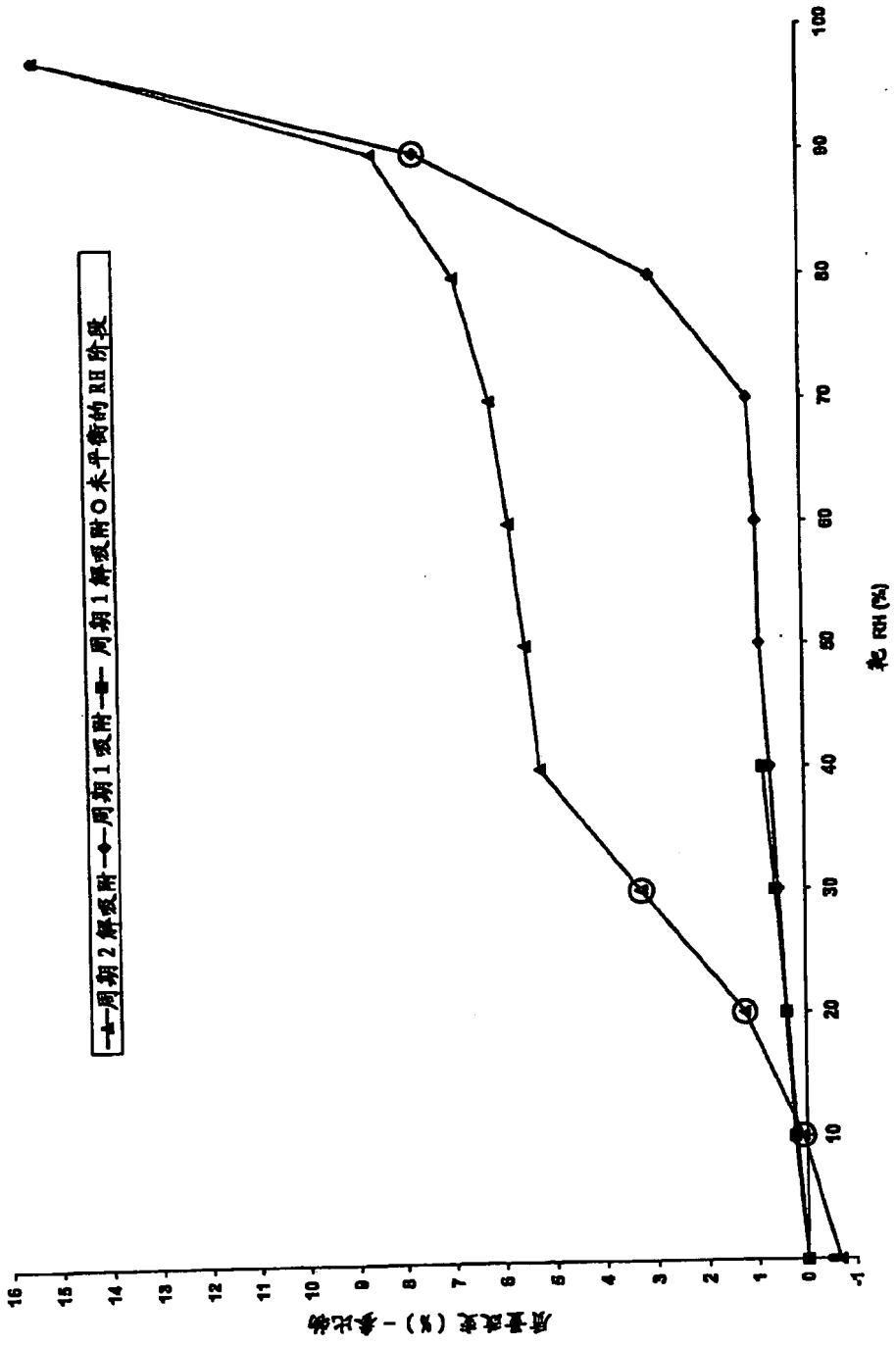


图 20

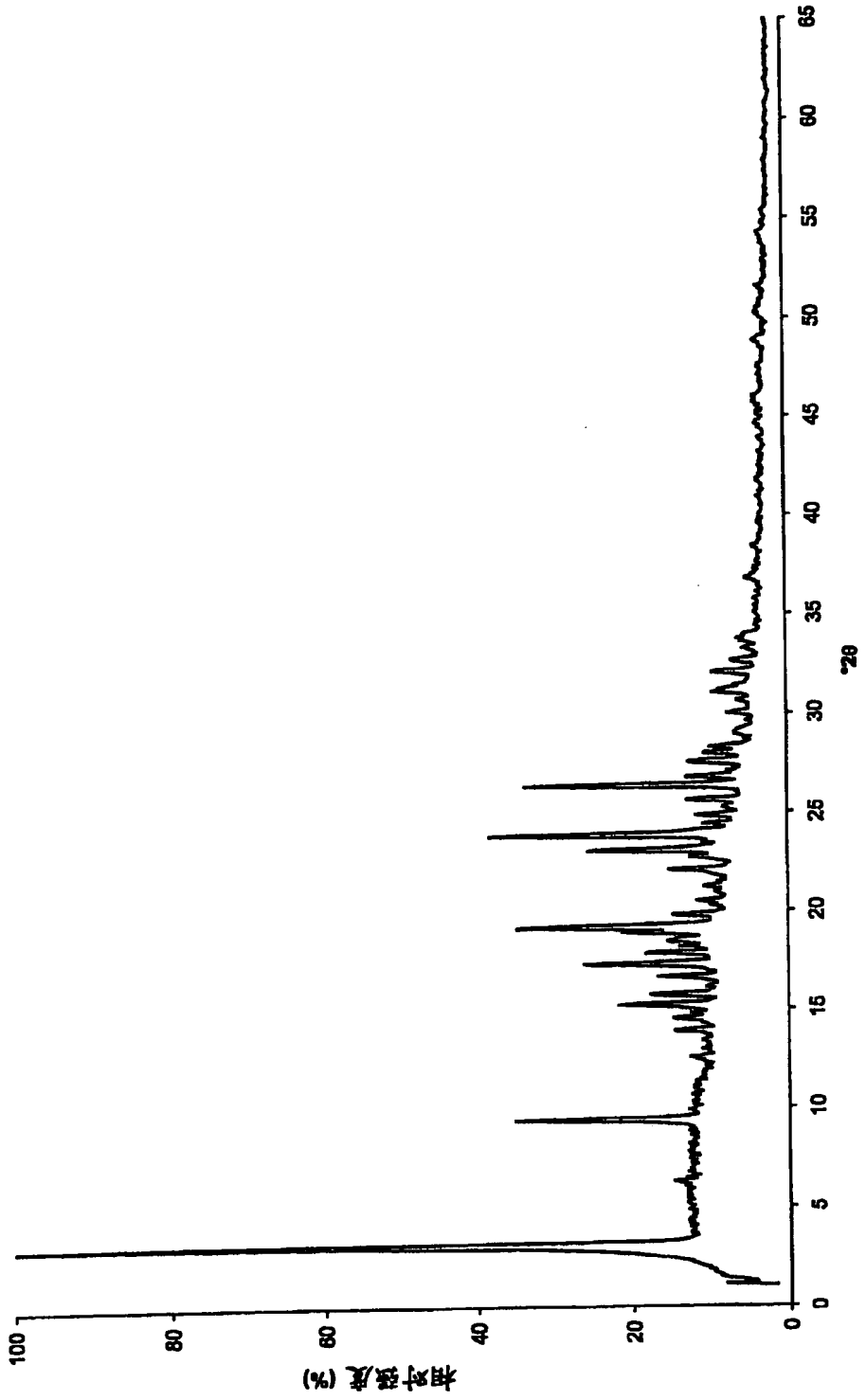


图 21

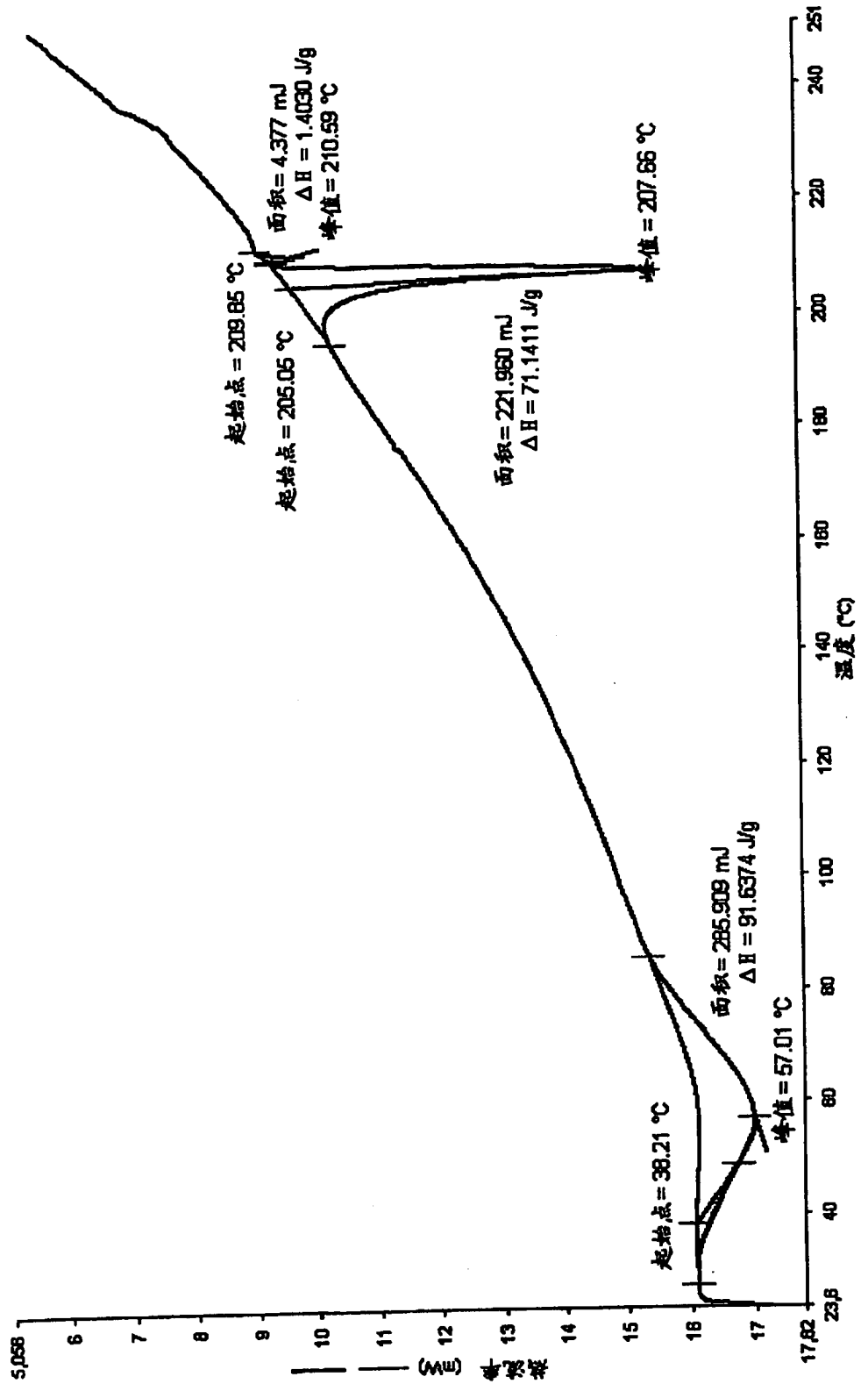

起始点 = 209.85 °C
面积= 4.377 mJ
ΔH = 1.4030 J/g
峰值 = 210.59 °C
起始点 = 205.05 °C
面积= 221.960 mJ
ΔH = 71.1411 J/g
峰值 = 207.66 °C
面积= 285.909 mJ
ΔH = 91.6374 J/g
起始点 = 38.21 °C
峰值 = 57.01 °C
温度 (°C)

图 22

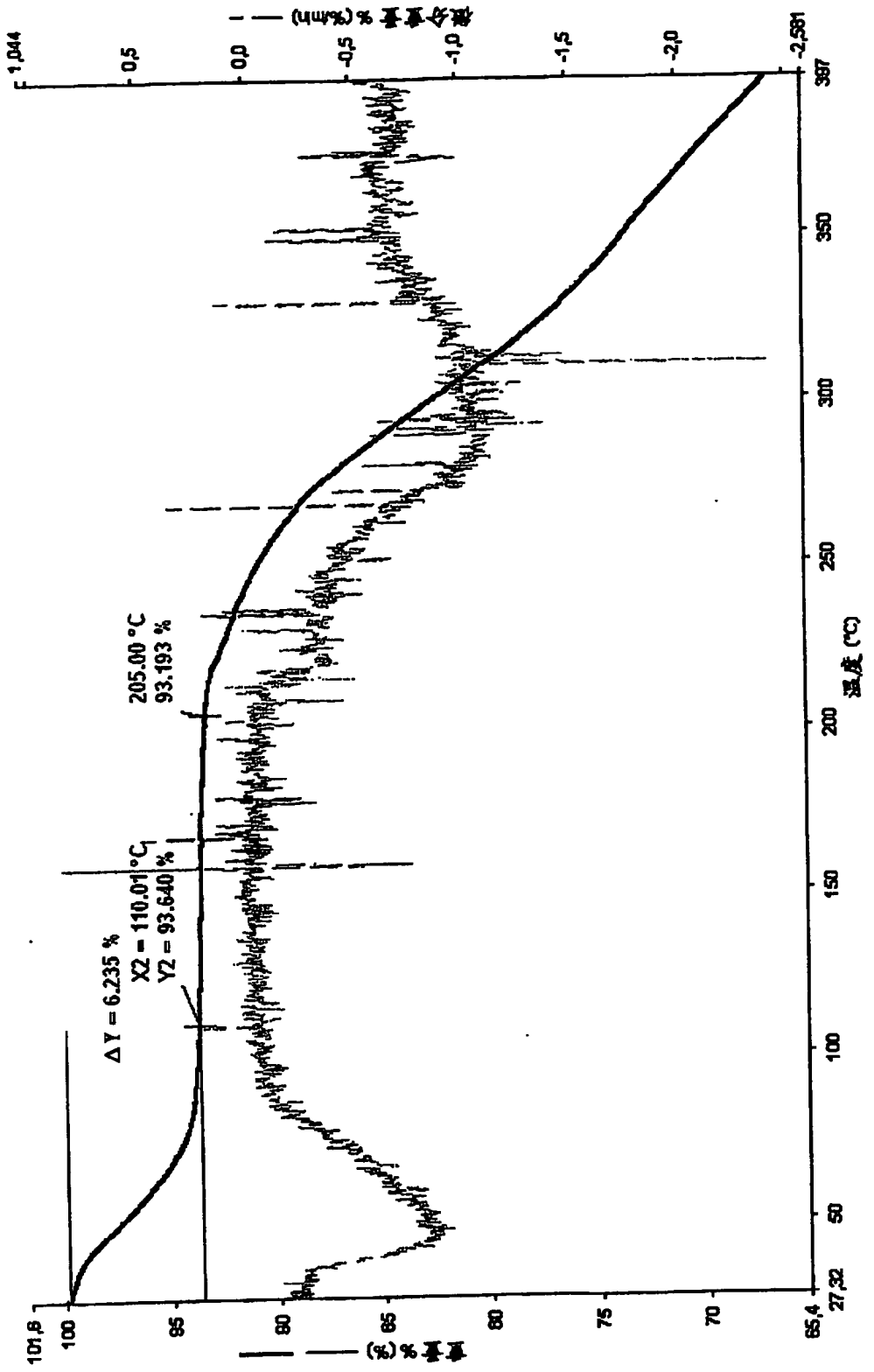


图 23

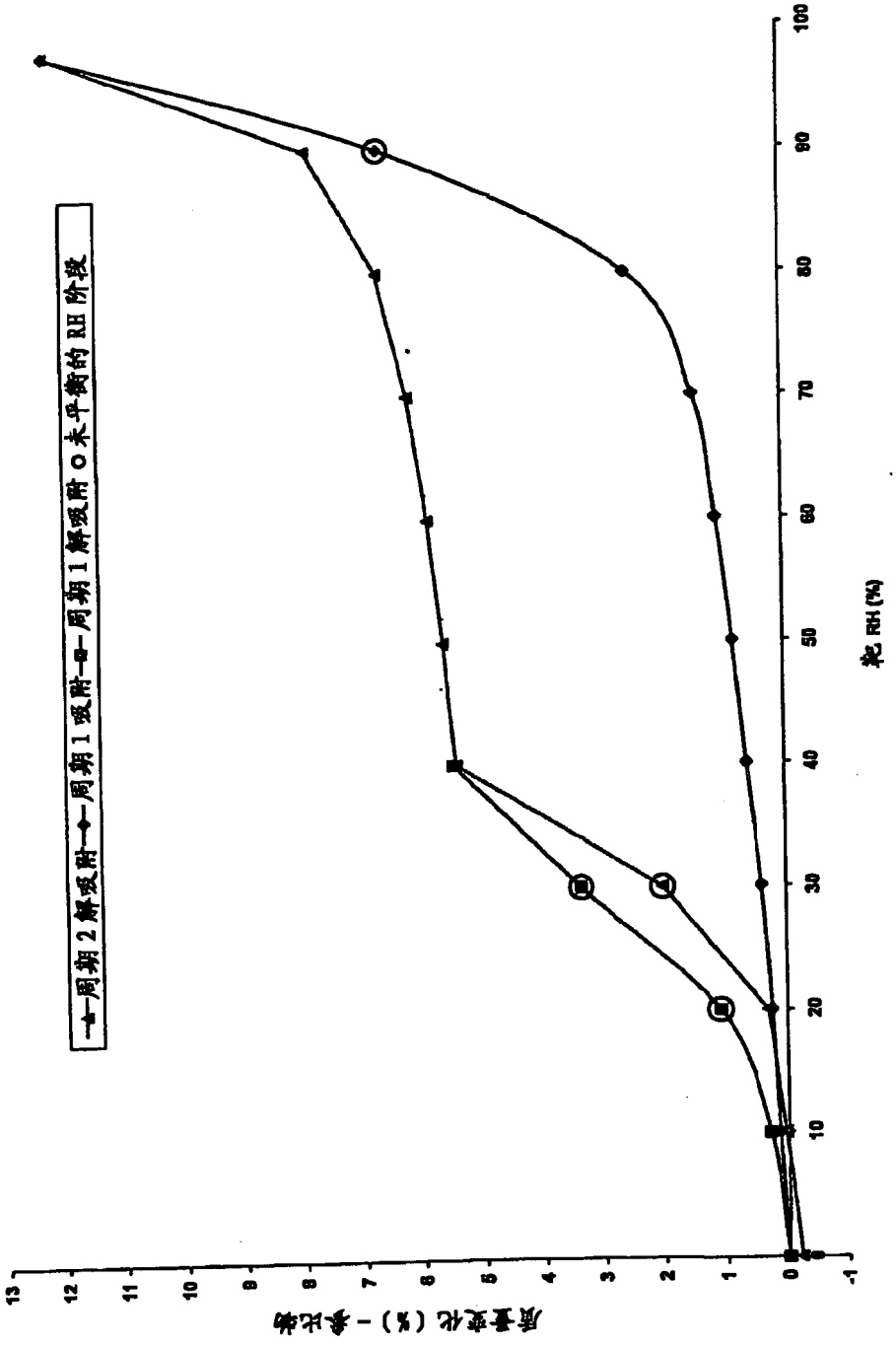


图 24

ABSTRACT

The present invention relates to 6-(1-methyl-1 H-pyrazol-4-yl)-2-{3-[5-(2-morpholin-4-yl-ethoxy)-pyrimidin-2-yl]-be nzyl}-2H- pyridazin-3-one dihydrogenphosphate, its solvates and crystalline modifications thereof. The present invention further relates to processes of manufacturing these crystalline modifications as well as their use in the treatment and/or prophylaxis of physiological and/or pathophysiological conditions, which are caused, mediated and/or propagated by the inhibition, regulation and/or modulation of signal transduction of kinases, in particular by the inhibition of tyrosine kinases, e.g. pathophysiological conditions such as cancer.