Appeal decision

Appeal No. 2019-1601

Appellant	KBP Biosciences Co., Ltd.
Patent Attorney	MURAYAMA, Yasuhiko
Patent Attorney	JITSUHIRO, Shinya
Patent Attorney	ABE, Tatsuhiko

The case of appeal against the examiner's decision of refusal of Japanese Patent Application No. 2017-131078, entitled "Crystal Form of Compound Used as Mineralocorticoid Receptor Antagonist and Preparation" (the application published on September 21, 2017, Japanese Unexamined Patent Application Publication No. 2017-165787) has resulted in the following appeal decision:

Conclusion

The appeal of the case was groundless.

Reason

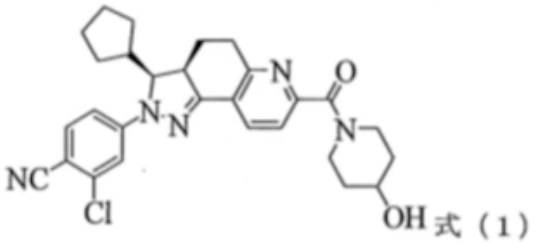
No. 1 History of the procedures

The present application is a divisional application filed on July 4, 2017 from Japanese Patent Application No. 2015-548180 filed on December 23, 2013 (claim of priority under the Paris Convention was received by the foreign receiving office on December 22, 2012, China (CN)) as an international patent application date, under the provisions of Article 44(1) of the Patent Act. A notice of reasons for refusal was issued on March 2, 2018, and despite submission of a written opinion on August 13, 2018, the examiner's decision of refusal was issued on September 27, 2018. Against this decision, a request for a trial against an examiner's decision of refusal was filed on February 5, 2019.

No. 2 The Invention

The inventions recited in Claims 1 to 9 of the present application are specified by the matters stated in Claims 1 to 9 of the scope of claims. The invention stated in

Claim 1 (hereinafter, referred to as "the Invention") is identified as follows:
"[Claim 1]
A crystal form of a compound represented by formula (1), 2-chloro-4-[(3S,3aR)-3-cyclopentyl-7-(4-hydroxypiperidin-1-carbonyl)-3,3a,4,5-tetrahydro-2H-pyrazolo[3,4-f]quinolin-2-yl]benzonitrile,
Formula (1):
[Chemical 1]



式（1）　　Formula (1)

having the following characteristic peaks in an X-ray powder diffraction pattern at diffraction angle of 2θ when measured using Cu-Ka radiation:

Crystal Form I: 9.8°±0.2°, 12.9°±0.2°, 14.8°±0.2°, 15.4°±0.2°, 16.9°±0.2°, 17.4°±0.2°, 19.4°±0.2°, 19.8°±0.2°, 22.6°±0.2°, 26.2°±0.2°;

Crystal Form II: 4.5°±0.2°, 9.0°±0.2°, 12.2°±0.2°, 14.0°±0.2°, 14.6°±0.2°, 18.0°±0.2°, 18.7°±0.2°, 19.9°±0.2°, 21.2°±0.2°, 24.6°±0.2°."

In the above statement of Claim 1, Crystal Form I and Crystal Form II are not explicitly stated as alternatives, but they have different peaks in an X-ray powder diffraction pattern. Referring to the Detailed Description of the Invention, Crystal Form I and Crystal Form II are described as those different from each other and independently produced and identified. Thus, the above statement of Claim 1 can be recognized to mean that the crystal form of a compound is represented by formula (1) and is one having Crystal Form I or Crystal Form II.

No. 3 Reasons in the examiner's decision

The reasons in the examiner's decision are based on Reason 1 stated in the notice of reasons for rejection dated March 2, 2018 and are roughly as follows: The inventions recited in Claims 1 to 9 of the present application could have been easily invented by a person skilled in the art based on the invention disclosed in Cited Document 1 distributed before the Present Application and the technical matters described in Cited

Document 2. Therefore, the Appellant should not be granted a patent for the Invention under the provisions of Article 29(2) of the Patent Act.

No. 4 Judgment by the body

As stated in the reasons in the examiner's decision, the body determines that the Appellant should not be granted a patent for the Invention under the provisions of Article 29(2) of the Patent Act, because the Invention could have been easily invented by a person skilled in the art based on the invention disclosed in Cited Document 1 and the well-known technical matters at the time of the priority date of the present application.

The reasons are as follows:

1 Cited Documents

(1) Cited Document 1: International Publication No. WO 2012/022121.

(2) Cited Document 2: I Noriaki Hirayama, Ed., "Handbook of Organic Compound Crystal Production - Principle and Know-how -," MARUZEN Co., Ltd., July 25, 2008, pp. 17-23, 37-40, 45-51, 57-65

(3) Cited Document 3: Kazuhide Ashizawa, "Evaluation of Physical Properties of Molecular State of Pharmaceutical Crystals (12) Optimization of Salt and Crystal Form and Crystallization Technology," PHARM TECH JAPAN, Jiho Inc., September 1, 2002, vol. 18, No. 10, pp. 1629-1644

(4) Cited Document 4: Stephen Byrn, Ralph Pfeiffer, Michael Ganey, Charles Hoiberg, Guirag Poochikian, "Review Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations," Pharmaceutical Research, 1995, Vol. 12, No. 7, pp. 945-954

(5) Cited Document 5: The Chemical Society of Japan, Ed., "4th Edition Experimental Chemistry Course 1 Basic Operation I," 2nd Printing, Maruzen Co., Ltd.," April 5, 1996, pp. 184-186

(6) Cited Document 6: Saburo Nagakura, Hiroo Inokuchi, Hiroshi Ezawa, Hiizu Iwamura, Fumitaka Sato, and Ryogo Kubo, Ed., "Iwanami Dictionary of Physics and Chemistry, 5th Edition," 5th edition, 8th printing, December 20, 2004, Iwanami Shoten, Publishers., pp. 504

(7) Cited Document 7: Akira Ogata, Taro Komoda, and Nobuyoshi Ninobu, "Chemical Experiment Operation Method," 36th Corrected Edition, June 20, 1977, Nankodo Co., Ltd., pp. 55-59. 526-533

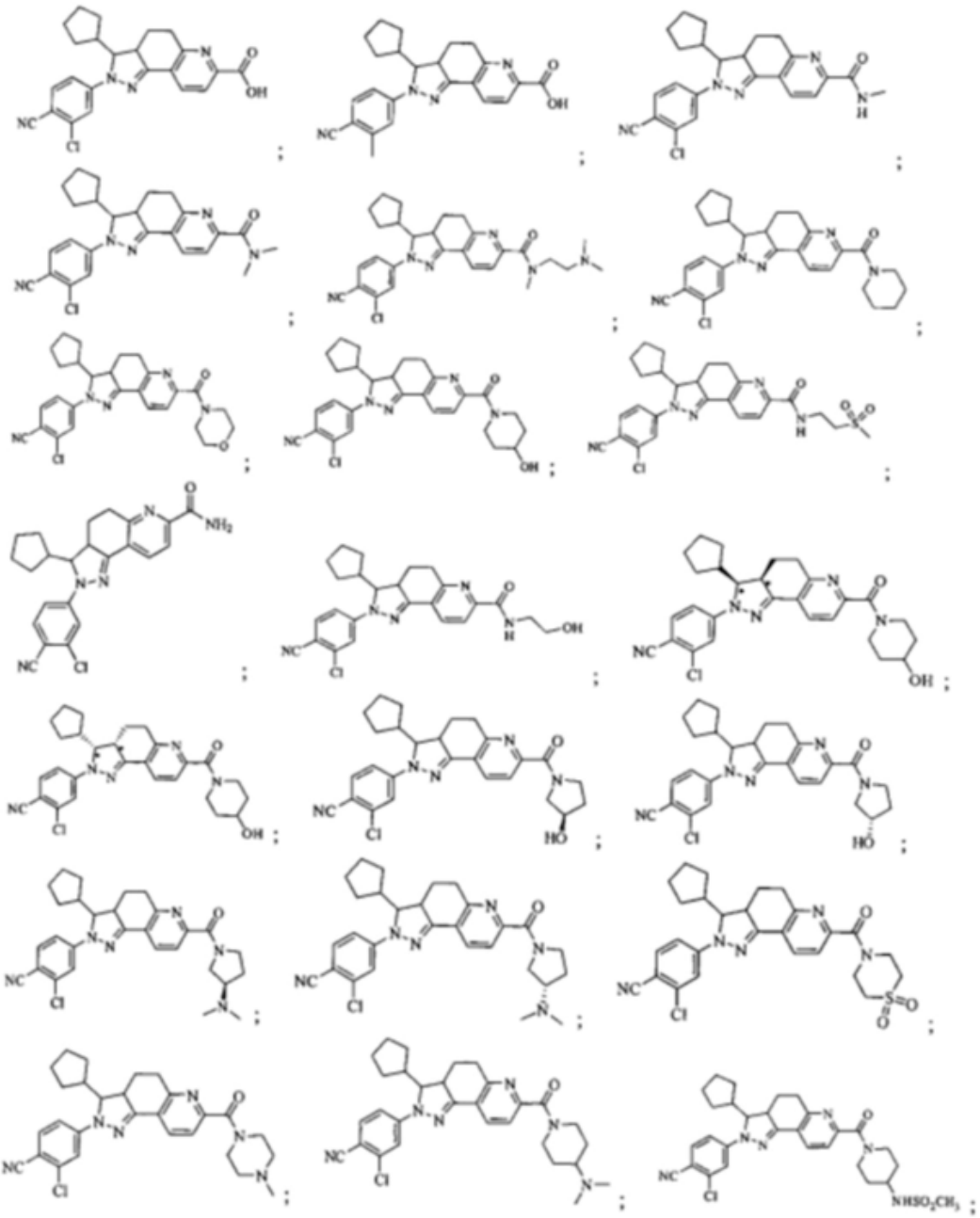
(8) Cited Document 8: The Chemical Society of Japan, "Chemistry Handbook, Applied Chemistry, 6th Edition," Maruzen Co., Ltd., January 30, 2003, pp. 178
(9) Cited Document 9: Japanese Unexamined Patent Application Publication No. H6-192228
(10) Cited Document 10: Japanese Unexamined Patent Application Publication No. H7-53581
(11) Cited Document 11: Japanese Patent Publication No. 52-45716
(12) Cited Document 12: Japanese Unexamined Patent Application Publication No. S61-263985
(13) Cited Document 13: Japanese Unexamined Patent Application Publication No. H4-235188

In addition to Cited Document 2, Cited Documents 3 to 13 are cited to indicate the well-known technical matters at the time of the priority date for the Invention. Among them, Cited Documents 9 to 13 respectively correspond to Cited Documents 4 to 8, which were cited in addition to Cited Document 2 in the decision of refusal to indicate the common technical knowledge at the time of the priority date of the present application,

2 Matters described in Cited Documents
(1) Cited Document 1

Since the descriptions in Cited Document 1 are in Chinese, the body represents them in Japanese as the translated descriptions with reference to the corresponding National Publication of International Patent Application No. 2013-534226.

(1a) "12. A compound selected from the group consisting of:



or a pharmaceutically acceptable salt or an isomer thereof (pages 58 to 60, Claim 12 of the scope of claims).

(1b) "TECHNICAL FIELD

The present invention generally belongs to a pharmaceutical field, and specifically relates to fused-ring compounds as an antagonist of the mineralocorticoid receptor, pharmaceutically acceptable salts thereof and isomers thereof; a preparation method for these compounds; pharmaceutical agents containing these compounds; and use of these compounds, pharmaceutically acceptable salts thereof, or isomers thereof in

manufacture of the pharmaceutical agents for treating and/or preventing kidney injury, cardiovascular disease such as hypertension, and/or endocrine disease.

BACKGROUND ART

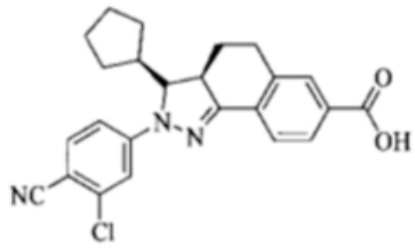
Kidney injury disorders, including primary nephropathy and secondary nephropathy such as diabetic nephropathy and renal inadequacy, are clinically manifested as heavy proteinuria, which, if not treated timely, would result in kidney failure. There are many inducing causes for kidney injury, including common diseases such as diabetes and hypertension which can result in kidney injury. For example, 15%-25% of patients having Type I diabetes and 30%-40% of patients having Type II diabetes have diabetic nephropathy, which has become the primary etiology in the end-stage nephropathy (accounting for 40%). At present there is no effective therapeutic medicine for treating kidney injury.

Aldosterone is a mineralocorticoid synthesized in the adrenal cortex and distributes in several tissues including the kidney, colon, epithelial cells of the sweat glands, blood vessels, brain, and cardiac muscle. It activates a mineralocorticoid receptor by combining with its receptor, so as to promote sodium retention and potassium secretion and has important effects on electrolyte balance and the change in structure and function of endothelial cell on arterial wall, vascular smooth muscle cell, fibroblast, and tunica adventitia of artery and the matrix on its medium.

The extra high level of aldosterone results in abnormal activation of the mineralocorticoid receptor. This causes electrolyte imbalance and injury and filtration of blood vessels of the kidney, resulting in kidney injury, hypertension, etc.

Drugs block the combination of aldosterone and the mineralocorticoid receptor by competitively combining with the mineralocorticoid receptor, so at to inhibit the toxic effect mediated by aldosterone and reduce kidney injury. There are two commercially available drugs in the market: Spironolactone and Eplerenone, which are indicated for treating hypertension, heart failure, renal syndrome, etc. These two drugs belong to steroid class compounds, have poor selectivity over other steroid hormone receptors, and are liable to cause hyperkaliemia and other major side effects. Furthermore, these two drugs have complicated structures and therefore are difficult to synthesize. In addition, these two drugs have poor physical/chemical properties that limit their clinical use.

A non-steroid compound (as shown in formula V) mentioned in China Patent Application CN200780043333.0 has entered clinical stage I trials, has a better performance than the listed drugs in terms of preclinical pharmaceutical effect and safety, and has effects in reducing proteinuria and reducing kidney injury.



(V)

However, the compound has poor cellular activity and sub-optimal physical chemical properties. In order to improve the clinical efficacy and safe clinical administration, there is need to develop a novel non-steroid class compound that has good activity, is synthetically feasible, and has good physical and chemical properties.

SUMMARY OF THE INVENTION

An object of the present invention is to provide a new non-steroid class compound that has good activity, and a preparation method thereof.

Another object of the present invention is to provide a new non-steroid class compound that is easy to synthesize, and a preparation method thereof.

Another object of the present invention is to provide a new non-steroid class compound that has a good activity and is easy to synthesize, and a preparation method thereof.

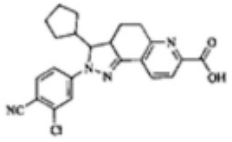
Another object of the present invention is to provide a new compound useful for replacing the currently available drugs for treating and/or preventing kidney injury.

Another object of the present invention is to provide the above compound for treating and/or preventing diseases.

Another object of the present invention is to provide the above compound for treating and/or preventing kidney injury, cardiovascular disease such as hypertension, and/or endocrine disease.

Another object of the present invention is to provide the use of the above compound in the medicine for treating and/or preventing kidney injury, cardiovascular disease such as hypertension, and/or endocrine disease." (page 1, line 2 to page 2, line 16)

(1c) "In another embodiment, the present invention provides compounds, or pharmaceutically acceptable salts or isomers thereof, which are represented by the following formula:

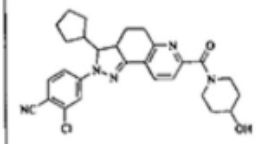
Ex.	構　造	化合物名
1		2-(3-クロロ-4-シアノフェニル)-3-シクロペンチル-3,3a,4,5-テトラヒドロ-2H-ピラゾロ[3,4-f]キノリン-7-カルボン酸

構造 Structure

化合物名　　Compound name

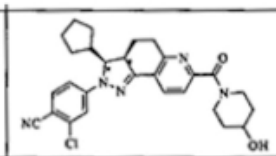
２－（３－クロロ－４－シアノフェニル）－３シクロペンチル－３，３ａ，４，５－テトラヒドロ－２Ｈ－ピラゾロ［３，４－ｆ］キノリン－７カルボン酸 2-(3-chloro-4-cyanophenyl)-3-cyclopentyl-3,3a,4,5- tetrahydro-2H-pyrazolo[3,4-f]quinoline-7-carboxylic acid

...

8		2-クロロ-4-(3-シクロペンチル-7-(4-ヒドロキシピペリジン-1-カルボニル)-3,3a,4,5-テトラヒドロ-2H-ピラゾロ[3,4-f]キノリン-2-イル)ベンゾニトリル

２－クロロ－４－（３－シクロペンチル－７－（４－ヒドロキシピペリジン－１－カルボニル）－３，３ａ，４，５－テトラヒドロ－２Ｈ－ピラゾロ［３，４－ｆ］キノリン－２－イル）ベンゾニトリル 2-chloro-4-(3-cyclopentyl-7-(4-hydroxylpipendine-1-carbonyl)-3,3a,4,5-tetrahydro-2H-pyrazolo[3,4-f]quinolin-2-yl)benzonitrile

...

12		2-クロロ-4-[(3S,3aR)-3-シクロペンチル-7-(4-ヒドロキシピペリジン-1-カルボニル)-3,3a,4,5-テトラヒドロ-2H-ピラゾロ[3,4-f]キノリン-2-イル]ベンゾニトリル

２－クロロ－４－［（３Ｓ，３ａＲ）－３－シクロペンチル－７－（４－ヒドロキシピペリジン－１－カルボニル）－３，３ａ，４，５－テトラヒドロ－２Ｈ－ピラゾロ［３，４－ｆ］キノリン－２－イル］ベンゾニトリル　2-chloro-4-[(3S,3aR)-3-cyclopentyl-7-(4-hydroxypiperidin-1-carbonyl)-3,3a,4,5-tetrahydro-2H-pyrazolo[3,4-f]quinolin-2-yl]benzonitrile

... " (page 15, lines 3 to 4 and tables in pages 15 to 18)

(1d) "The advantageous effects of the present compound will be further illustrated by the following in-vitro pharmacological assay; however, it should not be construed that the present compound has only the following advantageous effects.

Experimental Example The In-Vitro Pharmacological Activity of the Present Compound

Samples: Compounds 1-11 according to the present invention, lab-made; their chemical names, and structural formulae are shown hereinbefore; Compound of formula V (optically active), lab-made; its structural formula is shown hereinbefore.

Mineralocorticoid receptor (MR) Antagonism Test

Experimental method:

Each of samples; i.e., Compounds 1-23 and the Compound of formula V, was weighed accurately. DMSO was added to dissolve the sample. Each of the mixtures was mixed homogenously to formulate into 1000 μM mother liquor. Then each of the mother liquors was diluted with DMSO gradually to 200 μM, 40 μM, 8 μM, 1.6 μM, 0.3 μM, 0.06 μM, and 0.01 μM.

Dual-luciferase detection: 1 μL pBind-MR (100 ng/μL), 1 μL pG5luc (100 ng/μL), 2.5 μL DMEM, and 0.5 μL Fugene were taken and mixed homogenously. The mixture was incubated at room temperature for 15 min to produce a transfection liquor. To each of wells were added 100 μL 3×10^5 cells/mL HEK293 cell suspensions. After homogeneous mixing each of the cell suspensions with the transfection liquor, the mixtures were incubated at 37°C under 5% CO_2 in an incubator for 24 hr.

Each of 1 μL of samples in various concentrations was placed in an incubation well. After 30 min, 1 μL agonist (10% aldosterone in DMSO) was added. The mixtures were incubated at 37°C under 5% CO_2 in an incubator for 24 hr.

Firefly renilla luciferase signal pathway was measured by the dual-luciferase reporter gene test system.

The above assay was relegated to Shanghai ChemPartner Co. Ltd.

IC_{50} values of the compounds to be measured (samples) for the mineralocorticoid receptor (i.e., the concentration of the compound to be measured at which 50% activation induced by the mineralocorticoid receptor agonist was blocked, in comparison with the activation in the absence of the antagonist) were measured in this assay.

Results and conclusion:

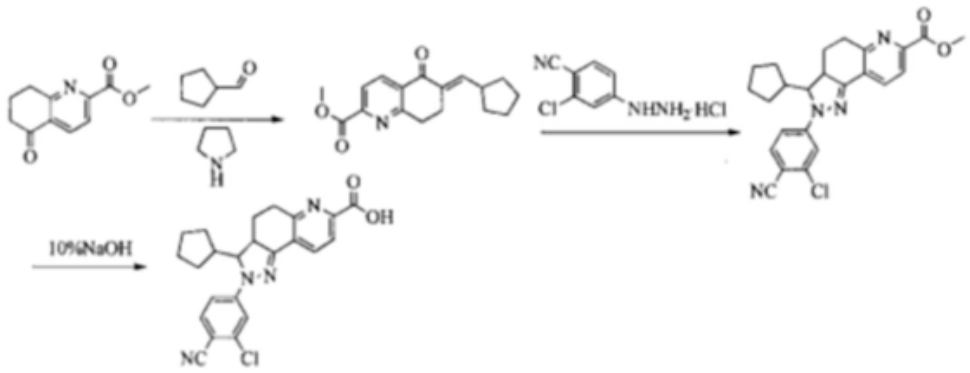
TABLE 1 The antagonistic action of the present compound against the mineralocorticoid receptor (MR)

試　料	IC_{50} (nM)
化合物　1	39.7
化合物　2	11.4
化合物　3	16.3
化合物　4	14.0
化合物　5	15.6
化合物　6	28.5
化合物　7	11.3
化合物　8	6.16
化合物　9	4.31
化合物１０	8.67
化合物１１	10.2
化合物１２	4.06
化合物１４	6.93
化合物１５	9.62
化合物１６	6.17
化合物１７	11.4
化合物１８	10.7
化合物１９	7.93
化合物２０	3.68
化合物２１	5.53
化合物２２	10.9
化合物２３	12.8
式Ｖの化合物	85.7

試料	Sample
化合物	Compound
式Ｖの化合物	Compound of formula V

The present compounds 1-23 had good antagonistic actions against the mineralocorticoid receptor, which were better than that of the positive control (compound of formula V). ... " (page 27, line 12 to page 28, line 3 from the bottom)

(1e) "Example 1 Preparation of 2-(3-chloro-4-cyanophenyl)-3-cyclopentyl-3,3a,4,5-tetrahydro-2H-pyrazolo[3,4-f]quinoline-7-carboxylic acid (Compound 1)



(1) Preparation of methyl 6-(cyclopentylmethylene)-5-oxo-5,6,7,8-tetrahydroquinoline-2-carboxylate

...

(2) Preparation of methyl 2-(3-chloro-4-cyanophenyl)-3-cyclopentyl-3,3a,4,5-tetrahydro-2H-pyrazolo[3,4-f]quinoline-7-carboxylate

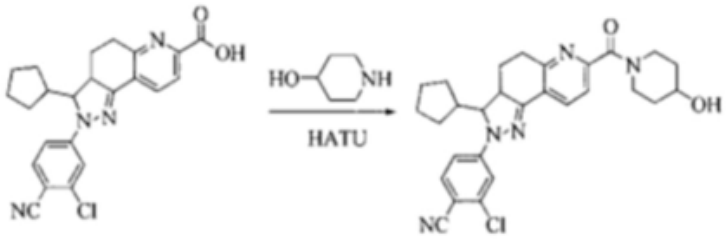
...

(3) Preparation of 2-(3-chloro-4-cyanophenyl)-3-cyclopentyl-3,3a,4,5-tetrahydro-2H-pyrazolo[3,4-f]quinoline-7-carboxylic acid

... filtered to obtain a crude yellow solid, which was then washed with ethanol and ether to obtain a solid (0.496 g) at 59.0% yield. ...

...

Example 8 Preparation of 2-chloro-4-(3-cyclopentyl-7-(4-hydroxylpiperidine-1-carbonyl)-3,3a,4,5-tetrahydro-2H-pyrazolo[3,4-f]quinolin-2-yl)benzonitrile (Compound 8)



In a dried reaction flask, the crude 2-(3-chloro-4-cyanophenyl)-3-cyclopentyl-3,3a,4,5-tetrahydro-2H-pyrazolo[3,4-f]quinoline-7-carboxylic acid (Compound 1) ... concentrated at reduced pressure to produce a crude yellow solid, which was washed with ether and ethyl acetate to produce a purified product (0.217 g) at 47.8% yield.

...

Example 12 Preparation of 2-chloro-4-[(3S,3aR)-3-cyclopentyl-7-(4-

hydroxylpiperidine-1-carbonyl)-3,3a,4,5-tetrahydro-2H-pyrazolo[3,4-f]quinolin-2-yl]benzonitrile (Compound 12)

Chiral resolution of the racemic mixture of Compound 8 produced (3S,3aR)-2-chloro-4-(-3-cyclopentyl-7-(4-hydroxylpiperidine-1-carbonyl)-3,3a,4,5-tetrahydro-2H-pyrazolo[3,4-f]quinolin-2-yl)benzonitrile. The ee value was 96.9%. The optical rotation $[\alpha]^{d}_{20}$ was −1220.0° to −1250.0° (c = 1, CH_2Cl_2).

The specific resolution conditions for supercritical fluid chromatography were ChiralPak AD-H, 300×50 mm, 50% methanol/supercritical carbon dioxide, 130 mL/min. Retention Time t_R = 13.2 min." (page 29, line 6 to page 36, line 19)

(2) Cited Document 2

(2a) " Most pharmaceutical products are organic compounds chemically synthesized or derived from natural products, and they are often prepared as crystalline powders by crystallization in the final step of production.

Crystals show various structures, shapes, sizes, and aggregation states, depending on the crystallization conditions. These solid or powder physical properties have an important influence on a pharmaceutical product's biological effectiveness, stability, formulation, etc. For example, polymorphs with different crystal structures and crystals with different crystal habits generally have different dissolution rates, resulting in different levels of biological effectiveness among pharmaceutical products. These differences are particularly noticeable when solid state pharmaceutical products, such as powders, tablets, granules, and capsules, are orally administered. One of the factors that determine the concentration of a pharmaceutical product that reaches the site of action is the effect of absorption from the site of administration, because the orally administered pharmaceutical product is greatly affected by absorption in the digestive tract, due to the solubility of the main drug released from the preparation.

The crystal polymorphs have different densities, melting points, lattice energies, etc., and consequently differences in physical or chemical stability of crystals against stress, such as heat, humidity, and light. For these reasons, depending on storage conditions, a metastable-to-stable crystal transition may occur to change the biological effectiveness of a pharmaceutical product. From the viewpoint of stability, therefore, a crystal form stable at room temperature is generally selected. However, the solubility of the metastable form may be significantly superior to that of the stable form. Thus, the metastable form may be daringly selected as the basic form for development, and a formulation with excellent biological efficacy may be designed.

A solvate crystal in which a solvent is incorporated into a crystal is called a

pseudo-polymorph, to distinguish it from a crystal polymorph in a strict sense. ...

Since pharmaceutical products act directly on the human body, each of them is strongly demanded to have a certain quality so that it surely exhibits an expected drug efficacy and safety in addition to being effective in treating and preventing diseases. Therefore, the decision trees regarding the handling of crystal polymorphs and solvates are presented in the guidelines of ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use).

Crystallization of pharmaceutical products is usually attained by various combinations of methods, such as those of cooling a solution, evaporating a solvent, adding a low-solubility solvent, and forming a salt, with other methods, such as one of adding a seed crystal with stirring. Various factors, such as solvent properties, supersaturation, and temperature, which are involved in these crystallization conditions, determine the properties of crystals. Therefore, it is important to clarify the correlation between the crystallization conditions and various properties of the precipitated crystals to guarantee the quality of the pharmaceutical products. This chapter outlines crystallization from the viewpoint of quality design of such pharmaceutical products." (page 57, line 3 to page 58, last line).

(2b) "4.2.1 Search for crystal polymorphs

Crystal polymorphism in which multiple crystalline phases are present is a phenomenon often observed in pharmaceutical products. However, the correlation between crystal structure and crystallization conditions has not yet been clarified. At present, the presence or absence of crystal polymorph must be determined by repeating trial and error. Therefore, although a crystal polymorph is often found accidentally, there are some reports that search is performed by a relatively simple method by appropriately combining each factor that seems to have an important influence on the search for a crystal polymorph.

Table 4.1 is one of the examples and summarizes the precipitation conditions of Furosemide widely used as an antihypertensive agent or a diuretic, and the precipitation behavior of each crystal form. The choice of a solvent often allows control of the crystal polymorph in pharmaceutical products. Again, 18 different solvents including water were used in the study. By combining various cooling methods and solvent evaporation methods with these solvents, conditions involving different temperatures and supersaturations were generated. As a result, even though only two types of polymorphs, type I and type II, have conventionally been reported, an additional type of polymorph (type III) as well as two solvents respectively containing N,N-

dimethylformamide and 1,4-dioxane (type IV and type V) are found. In the process of (1) in Table 4.1 in which heating, dissolving, and slow cooling are carried out, type I tends to precipitate from a low-boiling point solvent, such as methanol or ethanol, and type II tends to precipitate from a higher-boiling point solvent, such as butanol. The same tendency is observed in the process of (3) in which heating and dissolving in an organic solvent and addition of water are carried out, as well as in the process of (4) in which heating and dissolving in N,N-dimethylformamide and adding another solvent are carried out." (page 59, line 2 to page 60, last line)

(2c) "

表 4.1 結晶多形の検索事例

方法	溶媒	結晶形
(1) 加温溶解し室温で放置，徐冷する	アセトン	(I)
	メタノール	(I)
	エタノール	(I)
	メチルエチルケトン	(I)
	2-プロパノール	(I)+(II)微少
	1-プロパノール	(I)+(II)微少
	2-ブタノール	(II)
	1-ブタノール	(II)
	1-ペンタノール	(II)
	1,4-ジオキサン	(V)
(2) 加温溶解し急冷する	2-プロパノール	(I)+(II)微少
(3) 加温溶解し結晶が析出し始めるまで水を添加する	アセトン	(I)
	メタノール	(I)+(II)微少
	エタノール	(I)+(II)微少
	2-プロパノール	(II)+(I)微少
	1,4-ジオキサン	(V)
	N,N-ジメチルホルムアミド	(IV)

表４.１　結晶多形の検索事例　　Table 4.1　　Examples of search for crystal polymorphs

方法　Method

（１）加温溶解し室温で放置、徐冷する　　(1) Dissolve by heating, leave at room temperature, and slowly cool

（２）加温溶解し急冷する　　(2) Melt by heating and quench

（３）加温溶解し結晶が析出し始めるまで水を添加する　　(3) Add water until dissolved by heating and crystals start to precipitate

溶媒 Solvent

アセトン　　Acetone

メタノール	Methanol
エタノール	Ethanol
メチルエチルケトン	Methyl ethyl ketone
２－プロパノール	2-propanol
１－プロパノール	1-propanol
２－ブタノール	2-butanol
１－ブタノール	1-butanol
１－ペンタノール	1-pentanol
１，４－ジオキサン	1,4-dioxane
２－プロパノール	2-propanol
アセトン	Acetone
メタノール	Methanol
エタノール	Ethanol
２－プロパノール	2-propanol
１，４－ジオキサン	1,4-dioxane
Ｎ，Ｎ－ジメチルホルムアミド	N,N-dimethylformamide
結晶形　Crystal form	
（Ｉ）＋（ＩＩ）微少	(I) + (II) Minute
（ＩＩ）＋（Ｉ）微少	(II) + (I) Minute

表 4.1 つづき

方法	溶媒	結晶形
(4) *N,N*-ジメチルホルムアミド(DMF)またはシクロヘキサノンに加温溶解し，結晶が析出し始めるまで溶媒を添加する	DMF+ジクロロメタン	(I)
	DMF+クロロホルム	(I)
	DMF+ベンゼン	(I)+(II)
	DMF+トルエン	(I)+(II)
	DMF+キシレン	(IV)
	シクロヘキサノン+クロロホルム	(I)
(5) 飽和溶液を冷水にかくはんしつつ添加する	アセトン	(I)
	メタノール	(I)
(6) 飽和溶液を室温で放置し，溶媒を蒸発乾固する	アセトン	(I)+(III)
	メタノール	(I)+(II)
(7) 種々の温度で減圧下，溶媒を除去する		温度 0°C 20°C 40°C 60°C
	アセトン	(III) (III) (III) (III)
	メタノール	— (III) (III) (III)
	エタノール	— (III) (III) (III)
	2-プロパノール	— (III) (III) (III)
	1-プロパノール	— — (III) (II)+(III)
	2-ブタノール	— — — (II)
	1-ブタノール	— — — (II)
(8) 3種の温度条件下で噴霧乾燥する		乾燥温度 30°C 70°C 120°C
	ジクロロメタン-メタノール混合溶媒(4:1)	非晶質 非晶質 非晶質
	クロロホルム-メタノール混合溶媒(4:1)	非晶質 非晶質 非晶質
	クロロホルム-*N,N*-ジメチルホルムアミド混合溶媒(4:1)	(IV) (I)+(IV) (I)

[出典：Y. Matsuda, E. Tatsumi, *Int. J. Pharm.*, 60, 11 (1990)]

表４.１　つづき　Table 4.1 Continued

方法　Method

（４）Ｎ，Ｎ－ジメチルホルムアミド（ＤＭＦ）またはシクロヘキサノンに加温溶解し、結晶が析出し始めるまで溶媒を添加する　(4) Dissolve in N,N-dimethylformamide (DMF) or cyclohexanone by heating and add a solvent until crystals start to precipitate

（５）飽和溶液を冷水にかくはんしつつ添加する　(5) Add a saturated solution to cold water with stirring

（６）飽和溶液を室温で放置し、溶媒を蒸発乾固する　(6) Leave the saturated solution at room temperature and evaporate the solvent to dryness

（７）種々の温度で減圧下、溶媒を除去する　(7) Remove the solvent under reduced pressure at various temperatures

（８）３種の温度条件下で噴霧乾燥する　(8) Spray drying under three temperature conditions

溶媒　Solvent	
ＤＭＦ＋ジクロロメタン	DMF + dichloromethane
ＤＭＦ＋クロロホルム	DMF + chloroform
ＤＭＦ＋ベンゼン	DMF + benzene
ＤＭＦ＋トルエン	DMF + toluene
ＤＭＦ＋キシレン	DMF + xylene
シクロヘキサノン＋クロロホルム	Cyclohexanone + chloroform
アセトン	Acetone
メタノール	Methanol
エタノール	Ethanol
２－プロパノール	2-propanol
１－プロパノール	1-propanol
２－ブタノール	2-butanol
１－ブタノール	1-butanol
ジクロロメタン－メタノール混合溶媒（４：１）	Dichloromethane-methanol mixed solvent (4:1)
クロロホルム－メタノール混合溶媒（４：１）	Chloroform-methanol mixed solvent (4:1)
クロロホルム－Ｎ，Ｎ－ジメチルホルムアミド混合溶媒（４：１）	Chloroform-N,N-dimethylformamide mixed solvent (4:1)
結晶形	Crystal form
温度　Temperature	
乾燥温度	Drying temperature
非晶質	Non-crystalline
出典　Source	

" (pages 59 to 60, Table 4.1)

(3) Cited Document 3

(3a) "For advancing the drug development quickly and efficiently, an important key is the selection of polymorph as well as the selection of salt form, which is the basic form of a drug substance to be developed." (page 1629, left column, lines 2 to 4).

(3b) "2. Crystallization conditions

Many drug substances are often produced in the crystalline state in the final process, such as purification in the synthetic process. This may be based on the idea that a drug substance of constant quality may be produced stably because of three-dimensional regular arrangement of crystalline atoms and molecules and may also be based on the idea that, in comparison with liquids, crystals are superior in chemical stability and are far more convenient in handling, such as weighing and processing of formulations. In this way, although the drug substance crystals are more homogeneous in quality than the solutions, it is necessary to optimize the crystallization conditions in order to control the existence form of the solid for attaining consistent and stable production. Crystals are often prepared by crystallization from a solution in a crystallization process. Various crystal forms, shapes, sizes, agglutination, etc. are often observed, depending on the crystallization conditions.

The basis for controlling crystal polymorph in the crystallization operation is information on the solubility of each crystal in the solvent used for crystallization. Generally, in the case of pharmaceutical products, many cooling crystallizations utilize the difference in solubility depending on the temperature as shown in FIG. 2, and are based on creation of a temperature-solubility curve." (page 1630, right column, line 7 to last line)

(3c) "(1) Solvent used for crystallization

As mentioned earlier, as a solvent used for crystallization in an API process, it is ideally recommended to use a highly safe Class 3 solvent described in ICH's "Guideline for residual solvents in non-crystal form." The solvents classified in the ICH's guideline as Class 3, Class 2, Class 1, and other solvents are shown in the ICH guidelines. ...

表２　ICHのガイドライン，クラス３の溶媒
GMPまたはその他の品質基準により規制されるべき溶媒

酢酸	酢酸エチル	メチルイソブチルケトン
アセトン	ジエチルエーテル	2-メチル-1-プロパノール
アニソール	ギ酸エチル	ペンタン
1-ブタノール	ギ酸	1-ペンタノール
2-ブタノール	ヘプタン	1-プロパノール
酢酸n-ブチル	酢酸イソブチル	2-プロパノール
t-ブチルメチルエーテル	酢酸イソプロピル	酢酸プロピル
クメン	酢酸メチル	N-メチルピロリドン
ジメチルスルホキシド	3-メチル-1-ブタノール	
エタノール	メチルエチルケトン	

表２　ＩＣＨのガイドライン、クラス３の溶媒　　Table 2 ICH guidelines, Class 3 solvents

ＧＭＰまたはその他の品質基準により規制されるべき溶媒　　Solvents to be regulated by GMP or other quality standards

酢酸　Acetic acid	
アセトン	Acetone
アニソール	Anisole
１－ブタノール	1-Butanol
２－ブタノール	2-Butanol
酢酸ｎ－ブチル	N-Butyl acetate
ｔ-ブチルメチルエーテル	t-Butyl methyl ether
クメン	Cumene
ジメチルスルホキシド	Dimethyl sulfoxide
エタノール	Ethanol
酢酸エチル	Ethyl acetate
ジエチルエーテル	Diethyl ether
ギ酸エチル	Ethyl formate
ギ酸　Formic acid	
ヘプタン	Heptane
酢酸イソブチル	Isobutyl acetate
酢酸イソプロピル	Isopropyl acetate
酢酸メチル	Methyl acetate
３－メチル－１－ブタノール	3-Methyl-1-butanol

メチルエチルケトン	Methyl ethyl ketone
メチルイソブチルケトン	Methyl isobutyl ketone
２－メチル－１－プロパノール	2-Methyl-1-propanol
ペンタン	Pentane
１－ペンタノール	1-Pentanol
１－プロパノール	1-Propanol
２－プロパノール	2-Propanol
酢酸プロピル	Propyl acetate
Ｎ－メチルピロリドン	N-methylpyrrolidone

"(page 1631, right column, line 5 from the bottom to page 1632, left column, line 1 and Table 2)

(3d) "(2) Solution state and crystallization operation diagram

The basic principle of crystallization is to utilize the difference in solubility due to temperature as shown in FIG. 2 above. The crystallization process is divided into two stages: the first stage is the nucleation process in which solute molecules form an aggregate; and the second stage is crystal growth from the nucleus in which the solute molecules are regularly stacked one after another and are in equilibrium with the solution to complete the crystal growth." (page 1633, left column, line 7 from the bottom to last line)

(3e) "(3) Crystallization method

As shown in the crystallization operation diagram, a drug can be crystallized from a solution by preparing a saturated solution and slowly changing the solution to a supersaturated state to obtain the desired crystal. In many cases, the supersaturated solution can be left standing to obtain relatively large crystals by standing. In industrial crystallization, stirring and vibration precipitate a large number of microcrystals and crystalline production is controlled by addition of seed crystals. The basic principle of crystallization is crystallization from a supersaturated solution. Many attempts have been made as to the method of crystallization, depending on the desired use of the crystal and the purpose thereof. For example, if a single crystal for crystal structure analysis is desired, a method is selected so that a homogeneous and relatively large crystal can be obtained by standing. If the purpose is industrial crystallization, the goal is to obtain a polycrystalline body with controlled particle size and constant quality at high yield. Since crystallization occurs in the supersaturated

region, the solution must be supersaturated. Five different methods for supersaturating a solution will be described below. Since each of them has its own characteristics, it is necessary to select a method that suits the purpose.
[1] (Note added by the appeal decision: The original text is a circled number, but it is indicated by the number in square brackets. Hereinafter all the circled numbers in the descriptions in the cited document are represented in the same way.) Crystallization method to control temperature change
...
[2] Crystallization method by solvent evaporation
..
[3] Crystallization method by steam diffusion
..
[4] Reaction crystallization method
..
[5] Pressure crystallization method by pressurization" (page 1634, left column, line 4 from the bottom to page 1635, left column, line 9)

(3f) "6. Evaluation of physical properties of candidate compounds for development

Before deciding a candidate compound for development, it is necessary to evaluate the salt and crystal form while evaluating the physical properties of the compound in consideration of evaluating the physical properties of the surrounding compounds.

In particular, in the case of solid orally administered preparations, it is considered necessary to evaluate the salt and crystal form and physical properties when selecting a candidate compound for development at the final stage of the search. As reported by Hashida et al., chemical stability, oral absorption, physical stability (crystallinity and hydration), etc. may be definitely prioritized as evaluation items for physical properties. The evaluation items for the physical properties of a candidate compound for development include the following:
[1] Evaluation of crystallinity

Crystals are important basic physical properties that affect chemical stability, solubility, oral absorbability, and physical stability (crystallinity and hydration) as well as the manufacture of APIs and formulations. Thus, evaluation methods such as X-ray diffraction, thermal analysis, infrared absorption spectrum, and automatic moisture adsorption/desorption measurement can be appropriately used as needed. Based on this, preliminarily, the crystal polymorph, crystallinity, and phase transition between

crystal forms are evaluated, and the salt form and crystal form are searched using various solvents to predict the eligibility as a candidate compound for development.

[2] Evaluation of chemical stability

The stability of a pharmaceutical product is one of the important physical properties for guaranteeing the quality of the product. In addition to evaluating the crystallinity of a compound, the stability thereof to heat, humidity, and light in the solid state is evaluated. Specifically, it is important to predict the eligibility of the compound as a candidate compound for development in a short period of time under harsher test conditions than the conditions of the stability test that is usually performed. In addition, the basic properties of the compound are grasped by evaluating the chemical stability of the compound in aqueous solutions or various kinds of solvents or solutions with different pH values to preliminarily predict the eligibility of the compound as a candidate compound for development.

[3] Evaluation of solubility

Solubility of a drug is an important physical property that affects oral absorption and drug efficacy. It is important to evaluate the solubility of the drug in consideration of gastrointestinal absorption while considering the results of crystallinity and chemical stability. By considering this together with the evaluation result of crystallinity, a value close to true solubility is predicted to preliminarily predict the eligibility of the drug as a candidate compound for development. For evaluating the solubility, standard aqueous solutions, such as JP1 solution and JP2 solution of the Japanese Pharmacopoeia, and various buffer solutions prepared in consideration of the characteristics of the drug can be used with consideration given to absorption. Furthermore, at this stage, it is expected that the amount of drug substance cannot be secured sufficiently. Therefore, it may be necessary to contrive an evaluation with a small amount.

[4] Physical stability

Evaluating the physical stability of a drug substance crystal, specifically the crystallinity and hydration degrees thereof, is very important, as is the evaluation of crystallinity. The hydration degree, such as the hydration number, of a hydrate often varies in the process of allowing water molecules to be incorporated into the crystal structure in the process of water adsorption or recrystallization. In the search for salt and crystal forms using various solvents, the phase transition between crystal forms is evaluated. At the same time, it is important to predict the eligibility of a compound as a candidate compound for development, in addition to understanding the mechanochemical stability, such as amorphization caused by heating and grinding.

[5] Evaluation of moisture absorbency

Moisture absorbency is an important basic property that affects manufacturing processes, packaging, storage conditions, and chemical and physical stability.

[6] Evaluation of compatibility with formulation additives

...

[7] Evaluation considering salt form" (page 1642, left column, line 1 to the same page, right column, line 7 from the bottom)

(4) Cited Document 4

Since the descriptions in Cited Document 4 are in English, the body represents them in translation.

(4a) "CRYSTAL POLYMORPHS

The flow chart/decision tree for polymorphs is shown in FIG. 1. It outlines investigations of the formation of polymorphs, the analytical tests available for identifying polymorphs, studies of the physical properties of polymorphs, and the controls needed to ensure the integrity of drug substance containing either a single morphic form or a mixture." (page 946, right column, lines 12 to 18)

(4b) "

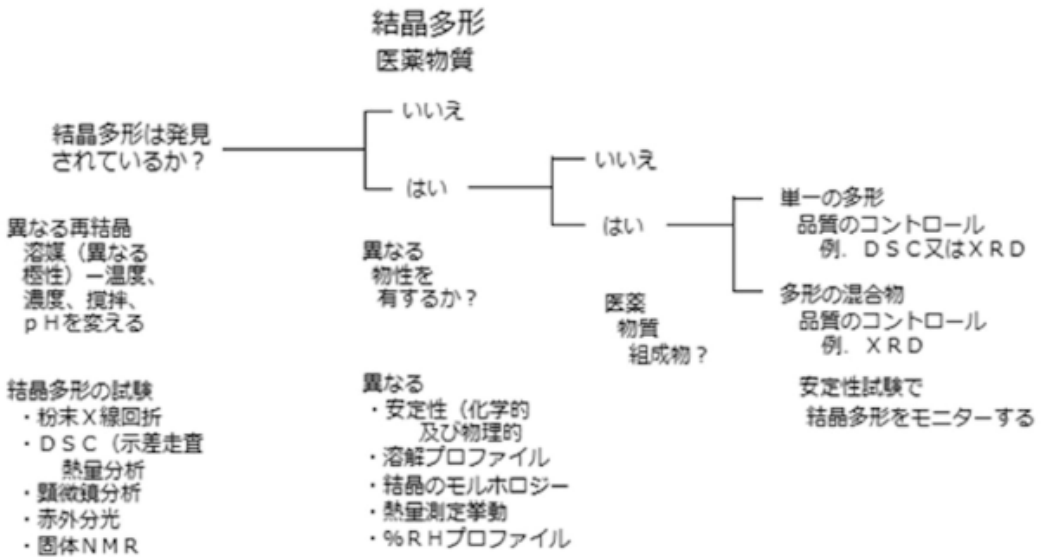


図１．結晶多形のためのフローチャート／決定ツリー

結晶多形　　Crystal polymorph

医薬物質　Drug substance
結晶多形は発見されているか？　Crystal polymorphs discovered?
いいえ　No
はい　Yes
異なる再結晶溶媒（異なる極性）－温度、濃度、攪拌、ｐＨを変える　Different recrystallizing solvents (different polarity) - vary temperature, concentration, agitation, pH
結晶多形の試験　Tests for crystal polymorphs
・粉末Ｘ線回析　- X-ray power diffraction
・ＤＳＣ（示差走査　熱量分析）　- DSC (differential scanning calorimetry)
・顕微鏡分析　- Microscopy
・赤外分光　- IR
・固体ＮＭＲ　- Sold state NMR
異なる物性を有するか？　Different physical properties?
異なる　Different
・安定性（化学的及び物理的）　- Stability (chemical & physical)
・溶解プロファイル　- Solubility profile
・結晶のモルホロジー　- Morphology of crystals
・熱量測定挙動　- Calorimetric behavior
・％ＲＨプロファイル　- %RH profile
医薬　Drug
物質　Substance
組成物？　Composition?
単一の多形　Single polymorph
品質のコントロール　Qualitative Control
例．ＤＳＣ又はＸＲＤ　e.g., DCS or XRD
多形の混合物　Mixture of polymorphs
例．ＸＲＤ　e.g., XRD
安定性試験で結晶多形をモニターする　Monitor polymorph in stability studies
図１.結晶多形のためのフローチャート／決定ツリー　FIG. 1. Flow chart/decision tree for crystal polymorphs.

" (page 946, FIG. 1)

(4c) "A. formation of crystal polymorphs - Have crystal polymorphs been discovered?

The first step in the crystal polymorphs decision tree is to crystallize the substance from a number of different solvents in order to attempt to answer the question. Are crystal polymorphs possible? Solvents should include those used in the final crystallization steps and those used during formulation and processing and may also include water, methanol, ethanol, propanol, isopropanol, acetone acetonitrile, ethyl acetate, hexane and mixtures if appropriate. New crystal forms can often be obtained by cooling hot saturated solutions or partially evaporating clear saturated solutions. The solids produced are analyzed using X-ray diffraction and at least one of the other methods. In these analyses, care must be taken to show that the method of sample preparation (i.e., drying, grinding) has not affected the solid form. If the analyses show that the solids obtained are identical (e.g. have the same X-ray diffraction patterns and IR spectra) then the answer to the question 'Are crystal polymorphs possible?' is 'No,' and further research is not needed." (page 946, right column, line 19 to page 947, left column, line 1)

(5) Cited Document 5

(5a) "a. Recrystallization

The basic operations for purifying substances include distillation and recrystallization. Recrystallization is performed by dissolving a solute in a solvent under heating to obtain a saturated solution. When this solution is cooled, the solubility of the solute lowers, and the excess solute precipitates (forms crystals). On the other hand, impurities do not reach the saturated solution and remain in the solution as they are. This is shown by the solubility curve in FIGS. 4 and 12. When a saturated solution of solute A at a temperature of T_1 is cooled to T_2 with respect to 100 g of a solvent, $(S_1-S_2)/g$ is precipitated. On the other hand, impurity B dissolves in S_3/g even at T_2. Thus, one containing S_3/g or less of impurity B in solute A can be removed by recrystallization.

(i) Sample purity The purity of a sample to be recrystallized, especially an organic substance, is first confirmed by thin layer chromatography. At that time, the relationship between the polarity of a developing agent used and the Rf value on a thin layer is useful for selecting the solvent for recrystallization, and also shows the approximate polarity of the impurities. It is desirable that the purity of the substance to be purified is high. If the purity is too low, it is advisable to perform distillation, column chromatography, and decolorization with activated carbon to remove some contaminants in advance. Of course, whether or not purification is possible is related

to the shape of the solubility curve, from the viewpoint of the principle of recrystallization. Therefore, even when there are many impurities, pure crystals are often obtained.

(ii) Selecting recrystallization solvent There is no given rule, and selection is conducted basically by trial and error. Accordingly, it is recommended to check solubility to the solvent and crystalline nature using samples of about 20 mg in test tubes. If it is a known compound, it is recommended to check recrystallization solvent and solubility with compound dictionaries, etc. With respect to unknown compounds, it is recommended to refer to data of known compounds of homologues. However, since early times, there is an empirical rule that a homologue dissolves a homologue well, and good selection can be made based on this. Namely, considerations are whether or not the compound to be refined is hydrogen-bonding, whether the compound has any polar group or hydrophobic group, whether or not it is ionic, etc. Normally, if hydrogen-bonding nature and polarity are taken into consideration, it would be sufficient to select from the following 6 solvents.

Hexane < benzene < ethyl acetate < acetone < ethanol < water (in the order of polarity from low to high).

If any solvent with an intermediate polarity is necessary, either mix two solvents or refer to Table 4.5. On this occasion, polarity values (permittivity ε, solubility parameter δ, polarity values $E\tau$; the larger the value of ε, δ, or $E\tau$, the higher the polarity), the boiling point, and the melting point may be used as criteria for selection. Reactive solvents and solvents having a high boiling point should be avoided if possible. There are many examples in which desorption or substitution occurred during recrystallization of organic substances with such solvents.

(iii) Heat dissolution Dissolution is carried out by shaking up used conical flasks in a water bath, and in the case of any crystal that is difficult to dissolve, crystals shall be milled and heat dissolved for one hour in reflux stirring with magnetic stirrers. Dissolution by ultrasonic wave may be tried.

(iv) Crystallization Deposition rate, size, and shape of crystals differ depending on cooling speed, solvent, concentration, etc. In some cases, crystal composition may differ. Generally speaking, substances having low melting point or large molecular weight are difficult to crystallize. If it is difficult to crystallize, [1] carry out cooling gradually (leave in hot-water bath); [2] add seed crystals; [3] rub the tube wall with a glass bar to create seeds; [4] leave in a refrigerator for several days to several months; [5] use mixed solvent to reduce solubility; and [6] wait for natural evaporation. If cooled down quickly, in many cases, no crystals are formed, the sample becomes an

oily substance, and refining cannot be carried out. Although it is not described in the article, it is not a rare occurrence that crystals for X-ray structural analysis happen to be obtained from NMR sample tubes left alone.

(v) Confirmation of purity For checking the purity of a substance, various instrumental analyses such as chromatography, various spectrum analyses, and elemental assay are currently employed, but melting point measurement is a method that can be carried out easily and should not be neglected. If the substance is not pure, the melting point becomes lower than the value in literature and is unclear. It should be noted that liquid crystal state might be observed in some cases when the melting point is measured" (page 184, line 20 to page 186, last line).

(5b) "

表 4・5 溶媒の物理的性質と極性値

溶媒	化学式	融点/°C	沸点/°C	誘電率 (ε)*1	E_T*1	溶解度パラメーター (δ)
1) プロトン性極性溶媒						
水	H_2O	0	100	78.5	63.1	23.4
メタノール	CH_3OH	−96	64.65	32.6	55.5	14.2
エタノール	C_2H_5OH	−114.5	78.3	24.3	51.9	12.9
1-プロパノール	1-C_3H_7OH	−126.5	97.15	19.7	50.7	11.9
2-プロパノール	2-C_3H_7OH	−89.5	82.4	18.3	48.6	11.5
1-ブタノール	1-C_4H_9OH	−89.5	117.5	17.7	50.2	11.4
酢酸	CH_3COOH	16.6	117.8	6.19	51.9	10.1
2) 非プロトン性極性溶媒						
アセトニトリル	CH_3CN	−45.72	81.6	37.5	44.3	11.8
ジメチルスルホキシド	CH_3SOCH_3	18.45	189	48.9	45.0	13
ジメチルホルムアミド	$HCON(CH_3)_2$	−61	153.0	36.71	43.8	12.0
アセトン	CH_3COCH_3	−94.82	56.3	20.5	42.2	9.8
酢酸エチル	$CH_3COOC_2H_5$	−83.6	76.82	6.03	38.1	9.04
3) 塩基性溶媒						
ピリジン	C_5H_5N	−42	115.5	12.3	40.0	10.8
α-ピコリン	α-$CH_3C_5H_4N$	−69.9	129	9.94	38.3	—
4) ハロゲン化炭化水素						
クロロホルム	$CHCl_3$	−63.5	61.2	4.70	39.1	9.24
ジクロロメタン	CH_2Cl_2	−96.8	40	8.9	41.1	9.88
四塩化炭素	CCl_4	−22.9	76.68	2.23	32.5	8.58
5) 無極性溶媒						
ベンゼン	C_6H_6	5.49	80.13	2.27	34.5	9.15
シクロヘキサン	C_6H_{12}	6.5	80.8	2.02	—	8.2
ヘキサン	C_6H_{14}	−95.3	68.8	1.90	30.9	7.24

*1 25°C.

表 4・5 溶媒の物理的性質と極性値 Table 4·5 Physical characteristics and

polarity values of solvents

溶媒　Solvent	
化学式	Chemical formula
融点　Melting point	
沸点　Boiling point	
誘電率	Permittivity
溶解度パラメーター	Solubility parameter
プロトン性極性溶媒	Protonic polar solvent
水　　Water	
メタノール	Methanol
エタノール	Ethanol
１－プロパノール	1-Propanol
２－プロパノール	2-Propanol
１－ブタノール	1-Butanol
酢酸　Acetic acid	
非プロトン性極性溶媒	Aprotic polar solvent
アセトニトリル	Acetonitrile
ジメチルスルホキシド	Dimethyl sulfoxide
ジメチルホルムアミド	Dimethyl formamide
アセトン	Acetone
酢酸エチル	Ethyl acetate
塩基性溶媒	Basic solvent
ピリジン	Pyridine
α－ピコリン	α-Picoline
ハロゲン化炭化水素	Halogenated hydrocarbon
クロロホルム	Chloroform
ジクロロメタン	Dichloromethane
四塩化炭素	Carbon tetrachloride
無極性溶媒	Non-polar solvent
ベンゼン	Benzene
シクロヘキサン	Cyclohexane
ヘキサン	Hexane

" (page 186, Table 4·5)

(6) Cited Document 6

(6a) "Recrystallization [1] It refers to the operation of dissolving a crystalline substance in a solvent and precipitating it as crystals again by an appropriate method. Adaptable methods for this purpose include cooling a high-temperature saturated solution by utilizing the difference in solubility depending on the temperature, evaporating a solvent to concentrate it, adding another suitable solvent to the solution to reduce the solubility, and so on. In many cases, any of these methods allows coexisting impurities to remain in the solution and is thus often used as a purification method." (page 504, right column, lines 43 to 51)

(7) Cited Document 7

(7a) "Organic solvent

...

Ethanol (bp 78.4°, miscible with water)

In general, ethanol hardly dissolves inorganic substances but easily dissolves organic substances, and thus ethanol is often used to separate organic compounds from inorganic compounds. ...

...

Ethanol is extremely valuable as a solvent in that it mixes with water in an arbitrary proportion. This property of ethanol makes it particularly convenient to use as a solvent during recrystallization. ...

...

Propanol (bp 97°, miscible with water),

Isopropanol (bp 82°, miscible with water)

...

Butanol (bp 117°, soluble in water at a ratio of 1:12) (page 55, line 16 to page 59, line 3 from the bottom)

(7b) "Fractional crystallization (fractionally crystallize out)

Recrystallization is used in separation and purification of a mixture of two or more substances and utilizes the properties of substances such that, since the solubility of each substance in a solvent is different, one substance precipitates and the other substance remains in the mother liquor when the solvent is used appropriately.

Therefore, even when the crystallization rates of the two substances from the same solvent are significantly different, the two substances can be separated by the method of fractional crystallization." (page 526, lies 16 to 22)

(7c) "Method of cooling and crystallizing a saturated solution

This method is a general recrystallization method, and when it is usually said to 'recrystallize,' this method or the method described below is applied.

Recrystallization is performed by heating a solvent to which a solute is added to the boiling point, dissolving the solute in it as much as it dissolves, straining it at the time of heating, and cooling the filtrate to precipitate crystals....

Method of choosing a solvent [1] ...

[2] ...

[3] ...

[4] ... This pre-test is performed on various solvents, and the one with the largest difference in solubility of a substance between being cooled and being heated is adopted. However, no matter how large the difference in solubility of the substance between being cooled and being heated, a solvent in which it is difficult to separate crystals from the mother liquor or a solvent in which the precipitation rate of crystals is too fast involves troublesome operations. Therefore, it is better to choose another one even with a slightly unsatisfactory solubility. Once the solvent is determined, it goes to the next step of true recrystallization operation.

Method of dissolving a substance (see "Method of choosing a solvent" above) Matters to be aware of when dissolving a substance depend on the properties of the substance and a solvent. Thus, in general, the solvent should not be used in excessive amount. When the substance is solidified into a large mass, even if a solvent is added and heated, it does not immediately become a saturated solution at the temperature of heating. Therefore, the substance is first ground as finely as possible (p. 77) and added with the minimum required amount of the solvent. Even if the liquid begins to boil by heating, it will continue to be in such a state for a while. The solvent is added only when the substance is not completely dissolved. When a volatile solvent, such as carbon disulfide, petroleum ether, ether, acetone, ethanol, benzene, or chloroform, is used, the substance is placed in an Erlenmeyer flask, which is subsequently attached with a reflux condenser, and then heated on a water bath.

Unlike the substance solved in in a test tube as mentioned in the above "Method of choosing a solvent," some substances do not promptly dissolve in large amount in a solvent. Also, some substances that have been sufficiently powdered in advance may be formed into nodules and hardly decrease in size even after passing time. In such a case, a cooling device is temporarily removed while care is taken not to catch fire. The substance can be quickly dissolved by continuously heating after crushing the lumps with a glass rod (p. 18). If all of the substance is dissolved in this way and only

foreign matter and filter paper fibers are suspended in the liquid, it is filtered at warm temperature. (p. 382) ...

...

A clear filtrate is obtained and then cooled to precipitate crystals. The method of cooling differs depending on whether a large crystal is formed or a small crystal is formed (see, p. 519). When the "filtrate" cools during filtration and crystals appear in it, the crystals are dissolved again by heating. When making large crystals, a container is loosely "plugged" and placed in a bath at a suitable temperature, followed by being cooled very slowly together with the bath. When making small crystals, the "filtrate" is cooled rapidly by an appropriate method. In any case, even if the solution is cooled to a certain temperature, not all crystals that can be precipitated under the conditions are immediately precipitated. Thus, the solution should be left standing for a while to wait for the precipitation to complete. In this way, the crystals produced at room temperature are separated. Further cooling of the "filtrate" may still result in a large number of crystals." (page 527, line 26 to page 529, line 17)

(7d) "Method of concentrating and crystallizing a solution

Evaporating and concentrating a solution of a substance to precipitate crystals therefrom is less preferable than 'Method of cooling and crystallizing a saturated solution' (p. 527) from the viewpoint of purifying the substance. However, the amount of crystals produced is small just by cooling the solution. Therefore, it is usually the case that crystals are produced by appropriately concentrating. Concentration and crystallization are carried out in the following cases:

[1] When the solvent is used to excess If a solvent is accidentally used to excess, as a matter of course, it takes much time to dissolve a substance in a solvent in an amount sufficient to make it a saturated solution. Thus, it is common that a slightly excessive amount of the solvent is added to the extent that the substance is easily dissolved, followed by being concentrated appropriately to produce crystals.

[2] When a substance cannot be heated and melted If a substance cannot be heated because of being easily decomposed by heat, the substance is first saturated with a solvent at room temperature and filtered, and then a part of the solvent is distilled off at low pressure and low temperature.

[3] When there is no big difference in the solubility of a substance between being cooled and being heated ...

...

A crystal container for evaporating and crystallizing a part of a solvent differs

depending on the properties of a substance and whether the solvent is evaporated at room temperature or during heating. When evaporating at room temperature, a wide-mouthed shallow 'dish' is used.

...

When a solvent is flammable or expensive, such as ether or acetone, the solvent is prevented from evaporating on a water bath and recovered by distillation. In this case, an Erlenmeyer flask is used as a container. Crystals that dry and stick to the part surrounding the liquid in the flask during distillation are sometimes dropped into the liquid by shaking the flask to dissolve them in the liquid. Alternatively, breath from the mouth is blown on the outer wall of the flask where the crystals are stuck (p. 211).

The second crystal is obtained by leaving the mother liquor obtained by straining the first crystal as it is or by evaporating or distilling and concentrating it to an appropriate concentration. In practice, the method of cooling and precipitating and the method of concentrating and precipitating are often performed together." (page 531, line 17 to page 532, line 5 from the bottom)

(7e) " Method of adding another liquid to a solution to crystallize

In addition to the method of cooling a solution or evaporating or distilling off a solvent to lead to a supersaturated state, there is also a method of mixing another liquid with a solution to reduce the solubility of a solute to precipitate crystals.

The main combinations of solvents used for this are as follows:

...

The most commonly used solvents in this method are water and ethanol. Since these two are mixed at an arbitrary ratio, a substance that dissolves in one and does not dissolve in the other will crystallize well if these two solvents are used properly." (page 533, lines 15 to 26)

(8) Cited Document 8

(8a) "4.3.3 Crystallization

a. Crystallization and its role

Crystallization is a technique for reliably producing crystals with the desired characteristics with good reproducibility. Crystallization is widely used in the production of chemical substances in general, and is important not only for separation and purification but also for the production of functional solids (crystals). Examples of the production include the production of foods such as sugars and amino acids, the production of electronic materials such as α-iron (α-Fe) and maghemite (γ-Fe_2O_3) as

recording media, the production of nanoparticles, and the production of non-crystal form (drug substances), 90% of which are crystalline, and their intermediates. Any of these highly requires control of crystal properties.

According to a 1998 survey (Crystallization Technology Special Study Group, Society of Chemical Engineers), crystallization from solutions accounts for 80% of the crystallization performed in Japan. In addition, 75% is performed by the batch method. The next most common is crystallization from the melt. Excellent techniques for large-scale purified crystallization, such as the KCP method (Kureha Engineering), have been developed.

b. Crystal characteristics

The main characteristics of crystals are crystal habit, particle size, particle size distribution, purity, polymorph, and crystallinity. Crystals that differ in these characteristics differ in solubility, dissolution rate, stability, specific volume, operability (? property, dust explosiveness, tableting property, metricity, etc. In the case of non-crystal form, it is very important to control the crystal properties especially because of the difference in bioavailability.

(i) Crystal habit ...

(ii) Particle size, particle size distribution, ...

(iii) Purity There are two mechanisms for the uptake of impurities into crystals: uptake of mother liquor into the crystals or adhesion to the crystal surface; and incorporation into the crystal structure. The former is caused by coarseness of crystal growth, aggregation, etc., and may be solved by adjusting the crystallization rate, washing, etc. The latter requires fundamental changes such as solvent changes and polymorphic selection. Crystal solvents (solvents incorporated into the crystal structure) can also be considered to be impurities.

(iv) Polymorph Polymorphs have the same compound but different crystal structures. Solvated crystals are called pseudo-polymorphs depending on the presence or absence of the crystal solvent. Polymorphic crystals cannot be judged from their appearance alone. It is necessary to identify by powder or single crystal X-ray diffraction, infrared absorption (IR), differential scanning calorimetry (DSC), etc. Polymorphs are affected by solvent type, temperature, cooling rate, supersaturation, stirring rate, impurities, etc. In many cases, different solvents cause different precipitated polymorphs. For important solvents, including mixed solvents, it is necessary to check what kind of crystals are precipitated. The choice of solvent can cause different results: one in which the desired crystal polymorph is only selectively obtained and the other in which crystal polymorphs (semi-stable crystals) once

precipitated are transferred to other polymorphs (stable crystals) over time; i.e., so-called solvent-mediated transition occurs. The cause of solvent-mediated transition is the difference in solubility between metastable crystals and stable crystals. Which polymorph is deposited is said to follow Ostwald's Step Rule (the law that the transition of states progresses sequentially via the closest energetic state). Usually, the crystal with the higher solubility is precipitated first. However, there are cases where Ostwald's Step Rule is not followed. Control of polymorphism may require kinetic studies as well as equilibrium theory (Ostwald's Step Law).

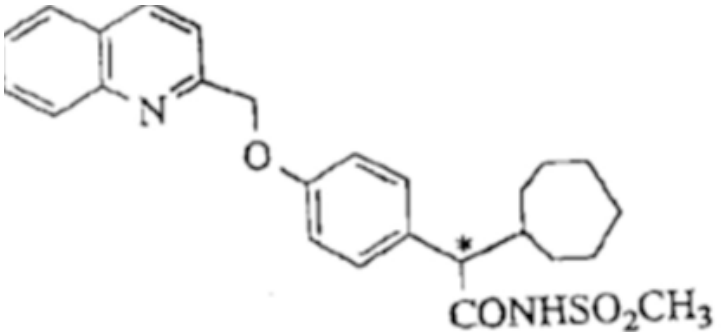
c. Crystallization operation

In many cases, the crystallization operations performed include cooling crystallization, concentrated crystallization, reaction crystallization, and poor solvent crystallization." (page 178, left column, line 5 to right column, line 26)

(9) Cited Document 9

(9a) "[Claim 1] (R)-(-)-2-cycloheptyl-N-methylsulfonyl-[4-(2-quinolinyl-methoxy)-phenyl]-acetamide of the following formula in crystalline state.

[Chemical 1]



[Claim 2] A process for preparing the compound having an activity for crystallization according to Claim 1, which process comprises suspending non-crystalline (R)-(-)-2-cycloheptyl-N-methylsulfonyl-[4-(2-quinolinyl-methoxy)-phenyl]-acetamide in an inert organic solvent in the presence of water at elevated temperature until conversion to the crystal form of the compound has occurred; separating off the resulting crystals of the crystalline modification by customary methods; and, to remove any solvent residues which may be present, drying the crystals to constant weight at temperatures of +20 to +70°C."

(9b) "[0001]

[Industrial Application Field] The invention relates to a crystal form of the (R)-(-)-2-

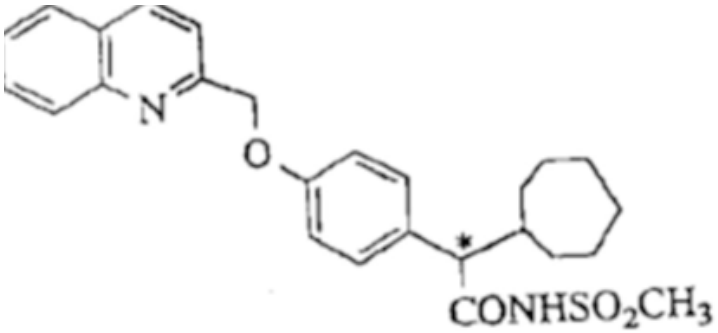
cycloheptyl-N-methylsulfonyl-[4-(2-quinolinyl-methoxy)-phenyl]-acetamide, and a process for its preparation and its use in medicaments.

[0002]

[Conventional Art] An inhibitor of leukotriene synthesis represented by the following formula (I):

[0003]

[Chemical 2]



[0004] (R)-(-)-2-cycloheptyl-N-methylsulfonyl-[4-(2-quinolinyl-methoxy)-phenyl]-acetamide, and its preparation and its use in medicaments, are already described in EP 344,519.

[0005] According to the preparation process described therein, the compound of the formula (I) is obtained in the form of a non-crystalline powder. A solvate-free, crystalline modification is hitherto unknown.

[0006] However, it has become evident that the compound (I) in the non-crystalline state has crucial disadvantages, in particular in the preparation of solid medicaments. Thus, medicaments which contain the compound of the formula (I) in the amorphous form exhibit very unsatisfactory storage stability, for example. This physical instability which preferentially arises when the preparations are stored over a relatively long period of time at temperatures above 30°C impairs the absorption efficacy and the safety of these preparations."

(9c) "[0007]

[Problem to be Solved by the Invention] It is therefore of great importance to make available a stable form of the compound of the formula (I), which does not possess the abovementioned disadvantages, for preparing medicaments.

[0008]

[Means for Solving the Problem] A novel crystal form of the compound ((R)-(-)-2-cycloheptyl-N-methylsulfonyl-[4-(2-quinolinyl-methoxy)-phenyl]-acetamide has now been found, and the novel crystal form is distinguished from the known non-crystalline

form in increased physical stability and reduced sensitivity to pressure, and is therefore considerably more suitable for the preparation of various medicament forms than the non-crystalline form.

(10) Cited Document 10

(10a) "[Claim 1] A method for producing a crystalline L-ascorbic acid-2-phosphate ester magnesium salt, comprising crystallizing a L-ascorbic acid-2-phosphate ester magnesium salt under an aqueous medium.

(10b) "[0001]

[Industrial Application Field] The present invention relates to a method for producing a crystal of a L-ascorbic acid-2-phosphate ester magnesium salt (hereinafter, referred to as "crystalline L-ascorbic acid-2-phosphate ester magnesium salt") useful in pharmaceutical products, cosmetics, food, and animal feed.

[0002]

[Prior Art and Problems] Since the currently commercially available L-ascorbic acid-2-phosphate ester magnesium salt is non-crystalline, it tends to absorb moisture during storage and tends to cause agglomeration of the powder. Moreover, the chemical stability of the L-ascorbic acid-2-phosphate ester magnesium salt itself is not sufficient, and it is often affected when the drug is blended with other drugs. Further, there is often a problem in that it causes troubles in formulation due to occurrence of caking or insufficient fluidity, and there is likely to be a variation in quality, which becomes a hindrance in practical use. Accordingly, it is desired to provide a stable crystal, crystalline L-ascorbic acid-2-phosphate ester magnesium salt. Examples of methods for crystallization of L-ascorbic acid-2-phosphate ester magnesium salt include: a method in which methanol is added to an aqueous solution of an L-ascorbic acid-2-phosphate ester magnesium salt, and the resulting precipitate is recrystallized from water-methanol [Chemical and Pharmaceutical Bulletin (Chem. Pharm. Bull.), 17, 381 (1969) and Chemical and Pharmaceutical Bulletin (Chem. Pharm. Bull.), 30, 1024 (19982)]; and a method in which alcohols, acetone, etc. is added to an aqueous solution containing L-ascorbic acid-2-phosphate ester magnesium salt to obtain the crystals (Japanese Unexamined Patent Application Publication No. S59-51293). However, these methods are not sufficient in terms of crystal purity, stability, and easiness of crystallization."

(10c) "[0023]

[Examples] Hereinafter, the present invention will be described in more detail with

reference to Examples, but the present invention is not limited thereto.

Example 1

One liter of water was added to 20 g of amorphous L-ascorbic acid-2-phosphate ester magnesium salt to make 2W/V% and dissolved and heated to 50 to 60°C. The resulting solution was filtered and the filtrate was then concentrated under reduced pressure to give 80 ml of solution. The concentration of L-ascorbic acid-2-phosphate ester magnesium salt in the obtained solution [total weight (g) of precipitated APMg and APMg dissolved in water / volume of water (ml)] × 100 (%) was 25 W/V%. Subsequently, the mixture was cooled to room temperature and crystals were then precipitated to give desired crystals. As a result of confirming the obtained crystals by the DSC chart, it was found that the crystals were all crystalline L-ascorbic acid-2-phosphate ester magnesium salt.

...

[0028] Test Example 1

The residual rate of the crystalline L-ascorbic acid-2-phosphate ester magnesium salt obtained in Example 1 was measured at 60°C in a sealed vessel and compared with an amorphous L-ascorbic acid-2-phosphate ester magnesium salt [Phospitan C, manufactured by Showa Denko K. K.] to evaluate its stability. The results are shown in Table 1.

[0029]

[Table 1]

６０℃下の安定性（残存率 %）

	2週	1カ月	2カ月	3カ月	6カ月
本発明での結晶	99.9	99.1	98.4	97.6	95.3
非晶質	99.0	96.5	93.9	90.5	78.5

６０℃下の安定性（残存率%）	Stability at 60°C (residual rate%)
２週 2 weeks	
１ヵ月	1 month
２ヵ月	2 months
３ヵ月	3 months
６ヵ月	6 months
本発明での結晶	Crystals in the present invention
非晶質	Amorphous

[0030] As is evident from Table 1, the crystals according to the invention have excellent stability."

(11) Cited Document 11

(11a) "Claims

1 A method for producing an ampicillin sodium salt type I crystal, the method comprising:

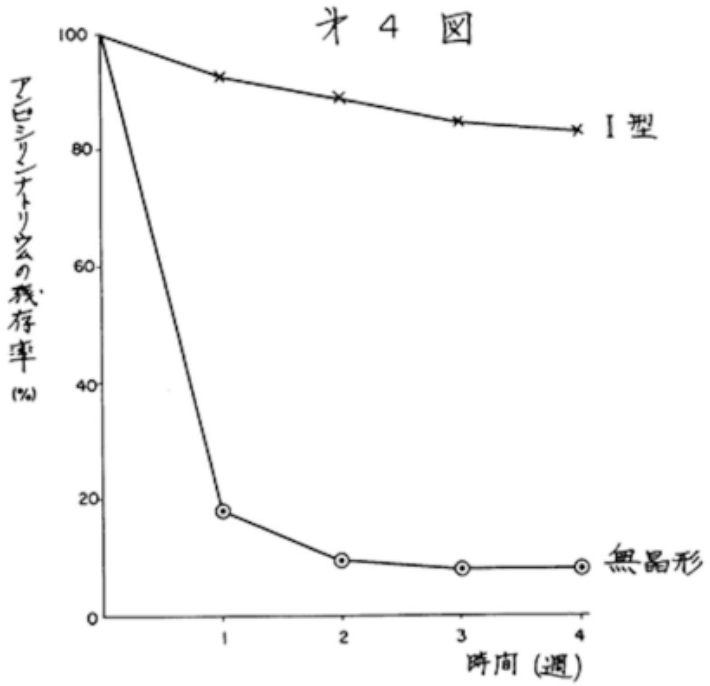
allowing sodium hydroxide or sodium salt to act on ampicillin or a salt or silyl derivative thereof to produce and crystalize out ampicillin sodium salt from the hydrous solvent system." (page 4, column 8, lines 8 to last lines)

(11b) "The present invention relates to a method for producing an ampicillin sodium salt.

Ampicillin, one of the semi-synthetic penicillins, is widely used because of its effectiveness against various infections caused by Gram-positive and Gram-negative bacteria. Currently, ampicillin is generally used in free form and sodium salt. Of these, the forms of free ampicillin include crystalline anhydrate (Japanese Patent Publication No. S41-8349) and trihydrate (US Patent No. 3,157,640). These are known to be more stable than their amorphous versions. However, the crystallinity and stability of sodium salts have not been fully studied." (page 1, column 1, line 11 to page 1, column 2, line 2)

(11c) "According to the method of the present invention, the ampicillin sodium salt can be obtained in a stable crystal form (referred to as type I). Compared with the amorphous one obtained by freeze-drying an aqueous solution of ampicillin sodium salt, for example, this type I crystal has a remarkably excellent residual rate and moisture absorption level when stored under the conditions of, for example, a relative humidity of 52.4% at 40°C as shown in FIGS. 4 and 5 (the residual rate is based on the cup method test using Sarcina lutea, ATCC-9314)." (page 2, column 3, lines 31 to 40)

(11d) "



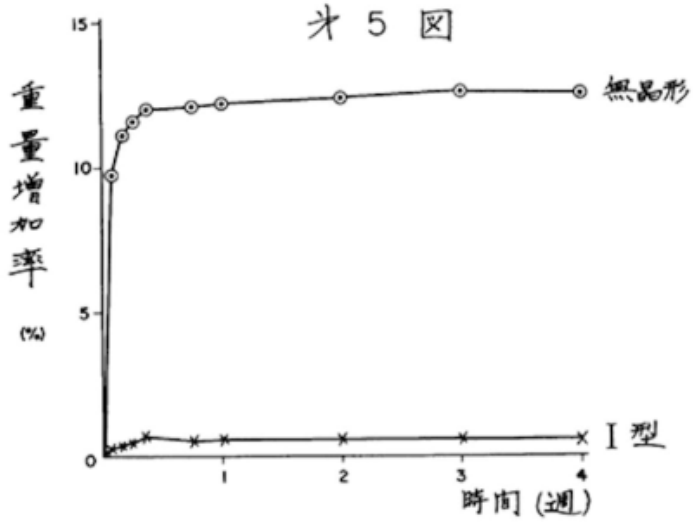
第４図
アンピシリンナトリウムの残存率
Ⅰ型　Type I
無晶形
時間（週）

FIG. 4
Residual rate of ampicillin sodium

Amorphous
Time (weeks)

" (page 7, FIG. 4)

(11e) "



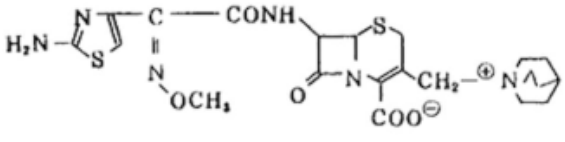
第５図
重量増加率
無晶形
Ｉ型
時間（週）

FIG. 5
Weight increase rate
Amorphous
Type I
Time (weeks)

" (page 7, FIG. 5)

(12) Cited Document 12
(12a) "2. Claims
1. A crystalline anhydrate, 0.5 hydrate, monohydrate, or trihydrate of a cephalosporin derivative, wherein the derivative is (6R,7R)-7-[(Z)-2-(2-aminothiazole-4-yl)-2-methoxyiminoacetamide]-3-(1-quinuclidiniummethyl)-3-cephem-4-carboxyrate or (6R,7R)-7-[(Z)-2-(5-amino-1-thia-2,4-diazol-3-yl)-2-methoxyiminoacetamide]-3-1-quinuclidiniummethyl)-3-cephem-4-carboxyrate.
2. A process for producing a crystalline anhydrate, 0.5 hydrate, monohydrate, or trihydrate of a cephalosporin derivative, the process comprising: dissolving the derivative, wherein an amorphous product of a cephalosporin derivative, which is (6R,7R)-7-[(Z)-2-(2-aminothiazole-4-yl)-2-methoxyiminoacetamide]-3-(1-quinuclidiniummethyl)-3-cephem-4-carboxyrate or (6R,7R)-7-[(Z)-2-(5-amino-1-thia-2,4-diazol-4-yl)-2-methoxyiminoacetamide]-3-1-quinuclidiniummethyl)-3-cephem-4-carboxyrate, is dissolved in an aqueous organic solvent and subjecting a resulting solution to addition of an organic solvent or cooling, and then optionally drying." (page 1, left column line 4 to page 1, right column, line 12)

(12b) "<Background of the Invention>
A cephalosporin derivative having a 2-(2-aminothiazole-4-yl)-2-methoxyimino acetamide group at the 7-position is known as an antibiotic having strong antibacterial activity.
For example, (6R,7R)-7-[(Z)-2-(2-aminothiazole-4-yl)-2-methoxyiminoacetamide]-3-(1-quinuclidiniummethyl)-3-cephem-4-carboxyrate represented by the formula



has a cephalosporin derivative having a betaine structure and having strong antibacterial activity against various Gram-positive and Gram-negative bacteria (Japanese Unexamined Patent Application Publication No. S59-219292).
These cephalosporin derivatives are usually chemically unstable, because the β-lactam ring contained in the molecule is easily hydrolyzed." (page 2, left upper column, line 14 to page 2, right upper column, line 4 from the bottom)

(12c) "Therefore, when such a cephalosporin derivative is used as a medicine, it is very important to use it in a stable form.
<Disclosure of the Invention>

An object of the invention is to provide a stabilized crystalline compound of (6R,7R)-7-[(Z)-2-(2-aminothiazole-4-yl)-2-methoxyiminoacetamide]-3-(1-quinuclidiniummethyl)-3-cephem-4-carboxyrate or a derivative thereof." (page 2, right upper column to line 3 from the bottom to page 2 left lower column, line 8)

(12d) "(2) The trihydrate, monohydrate, 0.5 hydrate, and anhydrate were sealed in brown vials, stored at 85°C, and analyzed by high-speed liquid chromatography. The results are shown in the table below. (Residual rate, %)

試料 ＼ 経時	１０日後	２４日後
無定形物	0	0
３水和物	９７.０	８６.８
１水和物	９６.１	８５.５
０.５水和物	９８.３	８６.３
無水物	９７.５	８６.０

試料　Sample
経時　Lapse of time

１０日後	10 days later
２４日後	24 days later
無定形物	Amorphous product
３水和物	Trihydrate
１水和物	Monohydrate
０．５水和物	0.5 hydrate
無水物	Anhydride

" (page 8, right upper column, line 4 from the bottom to left lower column, table)

(13) Cited Document 13

(13a) "[Claim 1] A crystalline (+)-(5R,6S)-6-[(R)-1-hydroxyethyl]-3-(3-pyridyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid pivaloyloxymethyl ester having a diffraction pattern which shows main peaks at spacing of 12.8, 8.8, 5.6, 4.44, 4.36, and 4.2Å according to powder X-ray diffraction.

[Claim 2] A process for producing a crystalline (+)-(5R,6S)-6-[(R)-1-hydroxyethyl]-3-(3-pyridyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid pivaloyloxymethyl which comprises dissolving (+)-(5R,6S)-6-[(R)-1-hydroxyethyl]-3-(3-pyridyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid pivaloyloxymethyl ester in a good solvent, adding thereto a poor solvent which is miscible with the good solvent, stirring the mixture and then cooling to a temperature of not higher than 30°C to obtain crystalline (+)-(5R,6S)-6-[(R)-1-hydroxyethyl]-3-(3-pyridyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid pivaloyloxymethyl having a diffraction pattern which shows main peaks at spacing of 12.8, 8.8, 5.6, 4.44, 4.36, and 4.2Å according to powder X-ray diffraction."

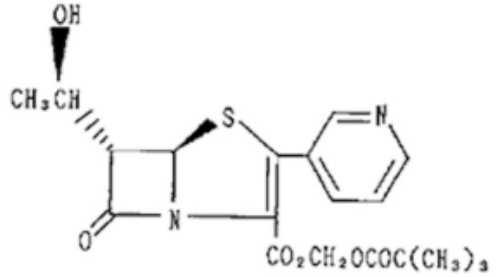
(13b) [0001]

[Industrial Application Field] The present invention relates to a crystalline penem compound which is useful as an antibacterial compound for medical use, and to its production and use.

[0002]

Japanese Unexamined Patent Application Publication No. S62-263138 discloses certain 2-pyridyl-penem compounds. Among them, (+)-(5R,6S)-6-[(R)-1-hydroxyethyl]-3-(3-pyridyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid pivaloyloxymethyl ester of the formula:

[Chemical 1]



is a particularly useful penem compound which manifests excellent antibacterial

activities against not only gram-negative bacteria but also gram-positive bacteria by oral administration, and its practical use has been studied. However, in spite of its excellent antibacterial activities, the penem compound has been obtained only in an amorphous form. This amorphous solid has a disadvantage that it has insufficient stability and decolors when it is stored for a long period of time under normal conditions, which results in decrease in the content of an active component upon production of its preparations. Further, there is another disadvantage that a complicated purification step is required to obtain a substantially pure amorphous solid. Under these circumstances, the present inventors have intensively studied to obtain the penem compound having excellent antibacterial activities in a form having good storage stability to improve the above disadvantages. As a result, it has been found that the penem compound can be obtained as a stable crystal form, the purification can be easily conducted by crystallization, and further the crystalline penem compound can be obtained from a water-ethanol system which is beneficial as medicines from the viewpoint of a residual solvent in crystals."

(13c) "[0010] Example 1

An amorphous powder of (+)-(5R,6S)-6-[(R)-1-hydroxyethyl]-3-(3-pyridyl)-7-oxo-4-thia-1-azabicyclo-[3.2.0]hept-2-ene-carboxylic acid pivaloyloxymethyl ester (19.5 g) obtained in the above Reference Example was dissolved in ethanol (98 ml). This solution was heated to 31°C, followed by the addition of water which had been heated to 32°C. To the mixture was added an activated charcoal (Shirasagi P, manufactured by Takeda Pharmaceutical Company Limited., 0.98 g) and the mixture was stirred for 10 minutes. Then, the activated charcoal was removed and washed with a mixed solvent of ethanol (20 ml) and water (29 ml). The filtrate was stirred at 25 to 30°C for one hour, cooled to 10°C, and further stirred for one hour. The crystals deposited were filtered off, washed in turn with a mixed solvent of ethanol (20 ml) and water (39 ml) and further water (120 ml), and then dried under reduced pressure at 35°C for 5 hours to obtain crystals (16.6 g) of the ester as white powder. Melting point: 95 to 96°C

...

[0014] Experimental Example

The crystalline powder of the ester produced according to the process of the present invention and the amorphous powder produced in the Reference Example were stored at a dark place in a sealed container at a temperature of 60°C, and the residual rate was measured. The results are shown in Table 1 below.

粉末の種類	保存条件	残存率
無晶形粉末	６０℃　１４日間	３７．７％
実施例１の結晶形粉末	６０℃　１９日間	９８．７％
実施例２の結晶形粉末	６０℃　１４日間	９８．９％

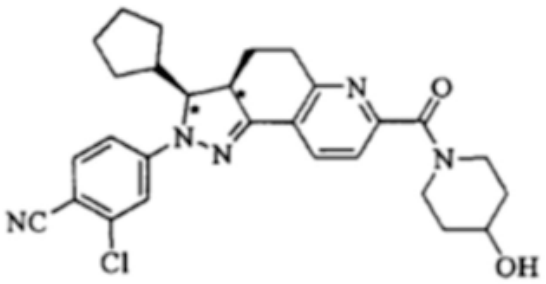
粉末の種類	Powder type
保存条件	Storing Conditions
残存率	Residual Rate
無晶形粉末	Amorphous Powder
実施例１の結晶形粉末	Crystalline Powder of Example 1
実施例２の結晶形粉末	Crystalline Powder of Example 2
１４日間	14 days
１９日間	19 days

"

3 Invention described in the Cited Document

Cited Document 1 is a patent document relating to non-steroidal fused ring compounds used as mineralocorticoid receptor antagonists (the above (1b)).

In Cited Document 1, 26 specific compounds are listed in Claim 12 for the above compounds, and the following compound is shown at the twelfth of them (the above (1a)).



This compound is referred to as "Compound 12" and is stated as one having the compound name of "2-chloro-4-[(3S,3aR)-3-cyclopentyl-7-(4-hydroxypiperidin-1-carbonyl)-3,3a,4,5-tetrahydro-2H-pyrazolo[3,4-f]quinolin-2-yl]benzonitrile" (the above (1c)).

Then, Cited Document 1 describes that Compound 12 was sequentially synthesized by the procedures of Examples 1, 8, and 12. Specifically, it is described that Compound 12 was prepared by synthesizing 2-chloro-4-(3-cyclopentyl-7-(4-hydroxypipendine-1-carbonyl)-3,3a,4,5-tetrahydro-2H-pyrazolo[3,4-f]quinolin-2-

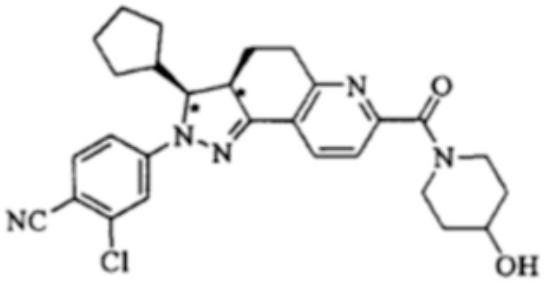
yl)benzonitrile (Compound 8) as a racemic mixture by the procedures of Examples 1 and 8, and carrying out chiral resolution of the racemic mixture by the procedures of Example 12 with specific resolution conditions for supercritical fluid chromatography (ChiralPak AD-H, 300×50 mm, 50% methanol/supercritical carbon dioxide, 130 mL/min) with a retention time of t_R = 13.2 minutes to give Compound 12.

In addition, Cited Document 1 describes that a mineralocorticoid receptor antagonism test was carried out using a solution prepared by dissolving Compound 12 in DMSO to a predetermined concentration and as a result, compared with the prior art compound of formula V showing an IC_{50} value of 85.7 nM (the above (1b)), Compound 12 showed a good antagonistic effect as an IC_{50} value of 4.06 nM (the above (1d)).

Therefore, it can be said that Cited Document 1 describes the following invention (hereinafter, referred to as "Cited Invention" ["Cited Invention"]).

Cited Invention:

"A compound 12: 2-chloro-4-[(3S,3aR)-3-cyclopentyl-7-(4-hydroxypiperidin-1-carbonyl)-3,3a,4,5-tetrahydro-2H-pyrazolo[3,4-f]quinolin-2-yl]benzonitrile, represented by the following formula:



"

4. Comparison / judgment

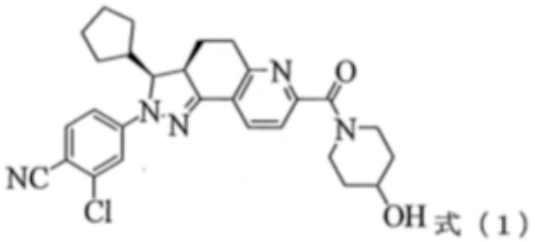
(1) Comparison

The comparison between the Invention and the Cited Invention shows that the compounds of the two inventions have the same chemical structural formula and compound name and thus Compound 12 of the Cited Invention corresponds to the compound represented by formula (1) of the Invention.

From the above, the corresponding feature and the different feature between the two inventions are as follows:

Corresponding Feature:

The two inventions are identical to each other in that each of them is "a compound 2-chloro-4-[(3S,3aR)-3-cyclopentyl-7-(4-hydroxypiperidin-1-carbonyl)-3,3a,4,5-tetrahydro-2H-pyrazolo[3,4-f]quinolin-2-yl]benzonitrile represented by formula (1):



式（1）　　Formula (1)"

Different Feature:

Regarding the compound represented by formula (1), the Invention is specified as one having "a crystal form having the following characteristic peaks in an X-ray powder diffraction pattern at diffraction angle of 2θ when measured using Cu-Ka radiation: Crystal Form I: 9.8°±0.2°, 12.9°±0.2°, 14.8°±0.2°, 15.4°±0.2°, 16.9°±0.2°, 17.4°±0.2°, 19.4°±0.2°, 19.8°±0.2°, 22.6°±0.2°, 26.2°±0.2°;
Crystal Form II: 4.5°±0.2°, 9.0°±0.2°, 12.2°±0.2°, 14.0°±0.2°, 14.6°±0.2°, 18.0°±0.2°, 18.7°±0.2°, 19.9°±0.2°, 21.2°±0.2°, 24.6°±0.2°."
In Cited Invention, on the other hand, such a specified matter is not applied to Compound 12.

(2) Examination on Different Feature
A　Regarding motivation for obtaining crystal polymorphs

(A) In general, at the time of the priority date of the present application, because of superiority of crystalline substances in terms of stability, purity, ease of handling, etc. for pharmaceutical compounds, a person skilled in the art had a strong motivation for crystallizing the compounds.　It is therefore recognized that examining the crystallization conditions of pharmaceutical compounds and investigating crystal polymorphs had been commonly performed by a person skilled in the art.

Some of the references presented are textbooks and reviews, such as Cited Documents 2 to 4 and 8.　It was well known that the crystals actually obtained may differ depending on their crystallization conditions (the above (2a) to (2c), (3a) to (3f), (4a) to (4c), (8a)).

Furthermore, the patent documents, such as Cited Documents 9 to 13, describe

the following matters, respectively.

Specifically, Cited Document 9 is a document relating to the crystalline (R)-(-)-2-cycloheptyl-N-methylsulfonyl-[4-(2-quinolinyl-methoxy)-phenyl]-acetamide and describes that non-crystalline compounds have significant drawbacks in the production of solid chemicals and crystalline compounds have better physical stability than non-crystalline compounds (the above (9a) to (9c)).

Cited Document 10 is a document on a method for producing crystalline L-ascorbic acid-2-phosphate ester magnesium salt and describes that a stable crystalline L-ascorbic acid-2-phosphate ester magnesium salt is desirable, because amorphous L-ascorbic acid-2-phosphate ester magnesium salt easily absorbs moisture during storage (the above (10a) to (10c)).

Cited Document 11 is a document on a method for producing an ampicillin sodium salt type I crystal and describes that type I crystals have remarkably excellent residual rates and moisture absorption levels when stored under the conditions of, for example, a relative humidity of 52.4°C at 40°C, compared with amorphous crystals (the above (11a), (11c) to (11e)); and crystalline anhydrate and trihydrate, which are the forms of free ampicillin, are also more stable than amorphous ampicillin (the above (11b)).

Cited Document 12 is a document on a crystalline anhydrate, 0.5 hydrate, monohydrate, or trihydrate of a cephalosporin derivative and describes that cephalosporin derivatives are susceptible to hydrolysis and are chemically unstable; the amorphous product has a residual rate of 0 after 10 days at 85°C, whereas each of the crystalline anhydride, 0.5 hydrate, monohydrate, and trihydrate has a stable residual rate of 96.1% or more (the above (12a) to (12d)).

Cited Document 13 is a document on crystals of a penem compound and a method for producing the same and describes that the amorphous solid of the penem compound has insufficient stability and has a problem of a lowered content of the active ingredient at the time of formulation; and the crystalline powder of the penem compound has good storage stability (the above (13a) to (13c)).

(B) Compound 12 of the Cited Invention is a pharmaceutical compound having a pharmacological action as a mineralocorticoid receptor antagonist and useful for producing a pharmaceutical agent for treating and/or preventing renal diseases, cardiovascular diseases such as hypertension, and endocrine diseases.

Cited Document 1 does not specify that Compound 12 was obtained as a solid or crystal, but describes that Compound 8 before the chiral division of the racemic mixture

was obtained as a solid (the above (1e), Example 8). Further, according to the general technical common sense at the time of the priority date of the present application, most of pharmaceutical compounds could be produced in a crystalline state (the above (3b)). Thus, it is considered that a person skilled in the art could obtain Compound 12, which is one of the enantiomers prepared by chiral division of the racemic mixture, as a solid or crystal.

For Compound 12 of the Cited Invention, therefore, it can be acknowledged that a person skilled in the art could have sufficient motivation to examine crystallization conditions, investigate crystal polymorphs, and analyze the obtained crystals.

B Regarding the matter of adopting a specific process and the matter of specifying a crystal by the peak of the diffraction angle 2θ of an X-ray powder diffraction pattern

(A) For Compound 12 of the Cited Invention, it is recognized that a person skilled in the art could ordinarily follow the motivation of the above A and make trial and error about the crystallization conditions to obtain crystals with desired properties, followed by analyzing the resulting crystals by an X-ray powder diffraction pattern, etc.

(B) On the other hand, the method for obtaining crystals of Crystal Form I of the compound represented by formula (1) of the Invention, which is disclosed in the present specification, includes recrystallization from an ethanol solution as stated below.

Specifically, the present specification describes that the compound represented by formula (1) is recrystallized in ethanol to obtain Crystal Form I as follows:

"[0042]

16. Crystal Forms I, II, and III and the amorphous form of the compound represented by formula (1) can be converted with each other under certain conditions. The present invention also provides the conversion among Crystal Form I, Crystal Form II, Crystal Form III, and the amorphous form.

[0043]

The amorphous form can be recrystallized in anhydrous ethanol to produce Crystal Form I;

...

Crystal Form II can be recrystallized in anhydrous ethanol to produce Crystal Form I;

...

Crystal Form III can be recrystallized in anhydrous ethanol to produce Crystal Form I."

Furthermore, in the examples of the present specification, a specific production method for obtaining Crystal Form I of the compound represented by formula (1) and the results of an X-ray powder diffraction pattern of the obtained crystals are described as follows:

"[0080]

Example 2

Preparation of Crystal Form I of 2-chloro-4-[(3S,3aR)-3-cyclopentyl-7-(4-hydroxypiperidin-1-carbonyl)-3,3a,4,5-tetrahydro-2H-pyrazolo[3,4-f]quinolin-2-yl]benzonitrile (1)

One gram of the compound represented by formula (1) as prepared in Example 1 was added in anhydrous ethanol (3 mL). The mixture was heated to 80°C until the solution became clear. Then the mixture was slowly cooled to room temperature. A large amount of solid was precipitated, filtered, and washed with anhydrous ethanol for three times. The resulting solid was placed at 60°C in a vacuum drier for 12 hours to produce Crystal Form I. The X-ray powder diffraction (XRD) spectrum of Crystal Form I is shown in FIG. 1, and its main parameters are as follows:

[0081]

[Table 1]

２Θ角度 単位：度（°）	d値 単位：Å	強度 単位：%
3.423	25.79197	2.2
4.571	19.31406	2.9
5.664	15.58973	3.1
8.343	10.58992	4.1
9.703	9.10809	47.6
10.764	8.21218	18.1
11.137	7.93840	16.5
12.122	7.29549	30.8
12.785	6.91833	48.9
14.690	6.02527	77.8
15.331	5.77476	39.2
16.834	5.26232	56.3
17.310	5.11893	100.0
17.987	4.92761	19.5
19.342	4.58548	71.7
19.639	4.51659	97.6
20.769	4.27346	11.5
21.191	4.18935	12.5
22.439	3.95900	40.0
23.159	3.83756	9.0
24.498	3.63081	21.9
26.103	3.41101	52.4
27.586	3.23093	20.4
29.564	3.01911	20.6
30.956	2.88642	12.0
31.954	2.79856	4.2
33.085	2.70537	4.9
33.516	2.67160	8.5
35.260	2.54333	4.0
35.946	2.49634	8.2
36.464	2.46209	9.4
37.729	2.38237	4.2
39.509	2.27904	6.2
40.615	2.21951	6.2
41.018	2.19865	6.8
42.503	2.12517	5.0
42.828	2.10982	6.0
44.139	2.05012	4.3

２Θ角度	2θ angle
d値	d value
強度	Strength
単位：度	Unit: degree
単位	Unit

"

The crystals obtained in Example 2 satisfy the matter specifying the invention, which is "having the following characteristic peaks in an X-ray powder diffraction pattern at diffraction angle of 2θ ... Crystal Form I: 9.8°±0.2°, 12.9°±0.2°, 14.8°±0.2°, 15.4°±0.2°, 16.9°±0.2°, 17.4°±0.2°, 19.4°±0.2°, 19.8°±0.2°, 22.6°±0.2°, 26.2°±0.2°," of

the Invention. In the method for producing Crystal Form I of the compound represented by formula (1) described in the above Example 2, in short, the compound represented by formula (1) is dissolved in ethanol and cooled to precipitate crystals. This is an aspect of the method for producing Crystal Form I described in the above paragraph [0043]. Here, since the crystallization is from a solution, it does not matter whether the starting material is amorphous or crystalline.

(C) As described in Cited Documents 2 to 8, such an operation is a very common method of crystallization of a compound by cooling the solution in which the compound is dissolved (the above (2b) to (2c), (3b) to (3e), (4c), (5a) to (5b), (6a), (7a) to (7c), (8a)). As for the selection of the solvent, it is recognized that a common solvent usually selected by a person skilled in the art for crystallization of the compound, such as ethanol, is used (the above (2c), (3c), (4c), (5a) to (5b), (7a)).

Then, Crystal Form I of the compound represented by formula (1) of the Invention could be obtained by a crystallization operation from a solution usually performed by a person skilled in the art in the Cited Invention. Therefore, it is recognized that it could be obtained by trial and error to the extent that a person skilled in the art would usually make.

Furthermore, the use of the measured value of the peak of the diffraction angle 2θ of an X-ray powder diffraction pattern to identify the crystal form had been a common practice in the technical field of crystals of pharmaceutical compounds, as described in Cited Documents 3, 4, and 8 (the above (3f), (4b) to (4c), and (8a)).

C Accordingly, in the Cited Invention, a person skilled in the art could easily conceive of examining the crystallization conditions of Compound 12 to investigate crystal polymorphs and analyzing the resulting crystals to make the crystals having "a crystal form having the following characteristic peaks in an X-ray powder diffraction pattern at diffraction angle of 2θ when measured using Cu-Ka radiation:
Crystal Form I: 9.8°±0.2°, 12.9°±0.2°, 14.8°±0.2°, 15.4°±0.2°, 16.9°±0.2°, 17.4°±0.2°, 19.4°±0.2°, 19.8°±0.2°, 22.6°±0.2°, 26.2°±0.2°" for the Different Feature.

(3) Effects of the Invention
A Descriptions in the present specification
(A) The present specification describes as follows:
"[0008]

The study on the crystal form is very important in drug development. Different

crystal forms of a compound will result in differences in properties such as the stability and the solubility. Therefore, the present inventors have conducted extensive research on the crystal form of the compound represented by formula (1)."

(B) The stability of the compound represented by formula (1) is described as follows:
"[0092]
Experimental Example 1:

Stability for Crystal Form I of the present compound

Sample:

Crystal Form I of the compound represented by formula (1): Crystal Form I was prepared according to Example 2.

Test conditions for investigating the influencing factors:

High temperature tests:

(i) Crystal Form I of the compound represented by formula (1) was laid on a dry and clean watch glass, and kept at 60°C for 10 days. Samples were taken respectively on Day 5 and Day 10. The contents of the relevant substance and the compound represented by formula (1) in the sample were measured, and compared with the contents of those in the sample taken on Day 0;

(ii) Crystal Form I of the compound represented by formula (1) was packaged and sealed with a low-density polyethylene bag for pharmaceutical use in the inner layer and with a polyester/aluminum/polyethylene composite film for pharmaceutical package in the outer layer, and kept at 60°C for 10 days. Samples were taken respectively on Day 5 and Day 10. The contents of the relevant substance and the compound represented by formula (1) in the sample were measured, and compared with the contents of those in the sample taken on Day 0.
[0093]

High humidity test: Crystal Form I of the compound represented by formula (1) was laid on a dry and clean watch glass, and kept at 25°C under a relative humidity (RH) of 90%±5% for 10 days. Samples were taken respectively on Day 5 and Day 10. The contents of the relevant substance and the compound represented by formula (1) in the sample were measured, and compared with the contents of those in the sample taken on Day 0.

Photostability test: Crystal Form I of the compound represented by formula (1) was laid on a dry and clean watch glass, and kept at an illuminance of 4500 Lx±500 Lx in a photostability test box for 10 days. Samples were taken respectively on Day 5 and Day 10. The contents of the relevant substance and the compound represented by

formula (1) in the sample were measured, and compared with the contents of those in the sample taken on Day 0.

Content: The content of the compound represented by formula (1) was measured by using an external standard method in accordance with the High Performance Liquid Chromatography in Chinese Pharmacopoeia, Appendix V D, Edition 2010.

Relevant substance: The content of the relevant substance was measured by using an area normalization method in accordance with the High Performance Liquid Chromatography in Chinese Pharmacopoeia, Appendix V D, Edition 2010.

[0094]

Test results: Test results are shown in Table 1.

[0095]

[Table 4]

表１　式（１）で示される化合物の結晶形Ｉの影響因子試験の検討結果

実験条件	日数	式（１）で示される化合物の含有量（%）	関連物質（%）
６０℃－(i)	０	９９．５	０．５４
	５	９８．９	０．８２
	１０	９８．１	０．９７
６０℃－(ii)	５	９９．７	０．５８
	１０	９９．０	０．６０
ＲＨ９０％±５％	５	９９．１	０．５６
	１０	９９．０	０．５６
４５００Ｌｘ±５００Ｌｘ	５	９８．１	１．２
	１０	９７．０	２．０

表１　式（１）で示される化合物の結晶形Ｉの影響因子試験の検討結果

TABLE 1　The investigation results of the influencing factor tests for Crystal Form I of the compound represented by formula (1)

実験条件　Experimental conditions

日数　Day

式（１）で示される化合物の含有量　Content of compound represented by formula (1)

関連物質　Relevant substance

[0096]

The present inventors investigated the stability of Crystal Form I of the compound represented by formula (1). It could be clear from the investigation results that the contents of the relevant substance and the compound represented by formula (1)

substantially did not change at a high temperature, at a high humidity, and under an illumination condition. Crystal Form I was superior to the amorphous form in the stability, which showed that Crystal Form I of the compound represented by formula (1) had a relatively high stability that was suitable for drug preparation, storage, and transport and was favorable for ensuring efficacy and safety in drug use."

B Effects of the Invention

Then, it is recognized that the effects of the Invention are as follows: the compound represented by formula (1) recited in Claim 1 can be provided as crystals of Crystal Form I; and Crystal Form I of the compound represented by formula (1) has stability so that the content of the compound represented by formula (1) and the content of the related substance hardly change even under any of the conditions of after leaving for 10 days in an open or closed system at 60°C, after leaving for 10 days at 25°C and RH 90%±5%, and after leaving for 10 days at an illuminance of 4500Lx±500Lx, thereby allowing it to be convenient for drug preparation, storage, and transportation and to guarantee efficacy and safety in the use of non-crystal form.

C Studies on the effects

However, the above effects of the Invention cannot be said to be special effects, as stated below.

(A) First, as stated in the above (2), a person skilled in the art could easily obtain Crystal Form I of the compound represented by formula (1). Therefore, it cannot be said that capability of providing Crystal Form I of the compound represented by formula (1) is a specific effect.

(B) Next, regarding stability as well, as described in Cited Documents 2 to 4 and 8 to 13, it is common technical knowledge for a person skilled in the art that a compound in a crystalline state is more stable than a compound in an amorphous state. Further, it can be said that it is common technical knowledge that when there are a plurality of crystal forms, the stability differs for each crystal form (the above (2a), (3b) and (3f), (4b), (8a), (9a) to (9c), (10a) to (10c), (11a) to (11e), (12a) to (12d), and (13a) to (13c)).

Table 1 of Assay 1 in the present specification shown in the above A represents the evaluation of the stability for the present compound after leaving for 10 days in an open or closed system at 60°C, after leaving for 10 days at 25°C and RH 90%±5%, and after leaving for 10 days at an illuminance of 4500Lx±500Lx. In light of the above

common general knowledge, such a degree of stability could not be recognized to be exceptionally remarkable beyond the expectations of a person skilled in the art, as compared with the storage stability normally required for pharmaceutical compounds.

Therefore, from the descriptions in the present specification, it cannot be recognized that the stability of Crystal Form I of the compound represented by formula (1) is remarkable beyond the range that can be predicted from ordinary crystals.

(4) Appellant's allegation

A In the appeal brief, the Appellant represents the results of a newly conducted comparative experiment and makes the following allegations:

(A) Stability

Fourth, in response to the above points made by the examiner, the Applicant strongly asserts again that in particular, the "compound represented by the formula (1)" in the predetermined crystal form of "Crystal Form I" and the same in "Crystal Form II," which are defined in the Invention, have exceptionally superior effects in terms of stability compared to the same compound in "amorphous form" described in Cited Document 1.

This point is fully supported by Assay 1 (for Crystal Form I) in [0092] to [0096] and Assay 2 (for Crystal Form II) in [0097] to [0101] of the original specification of the application. Here, this point will be examined in detail below for asserting that "Different Feature 1" pointed out by the examiner could not be easily achieved by a person skilled in the art.

Please see the table below, which represents the results of the comparative test conducted on the stability of "Crystal Form I", "Crystal Form II," and "amorphous (non-crystalline)" of the same "compound represented by formula (1)." The data in "assay conditions" of "Crystal Form I" and "Crystal Form II" completely correspond to those in Table 1 (paragraph [0095]) and Table 2 (paragraph [0100]) in the original specification of the application.

[Table 1]

式（１）で示される化合物の結晶形I、結晶形II及び非晶質の影響因子試験の検討結果

実験条件	日数	結晶形Ｉの含有量(%)	結晶形 IIの含有量(%)	非晶質の含有量(%)
60℃-(i)	0	９９．５	９６．２	９７．７
	5	９８．９	－	－
	１０	９８．１	９６．２	９７．１
60℃-(ii)	5	９９．７	－	－
	１０	９９．０	９７．１	９８．３
RH90%±5%	5	９９．１	－	－
	１０	９９．０	９６．９	９７．４
4500Lx±500Lx	5	９８．１	－	８７．２
	１０	９７．０	９５．５	８３．０
０日目に対する変化のパーセンテージ（%）				
60℃-(i)	１０	↓１．４	０．０	↓０．６
60℃-(ii)	１０	↓０．５	↑０．９	↑０．６
RH90%±5%	１０	↓０．５	↑０．７	↓０．３
4500Lx±500Lx	5	↓１．４	－	↓１０．５
	１０	↓２．５	↓０．７	↓１４．７

式（１）で示される化合物の結晶形Ｉ、結晶形ＩＩ及び非晶質の影響因子試験の検討結果　The investigation results of the influencing factor tests for Crystal Form I, Crystal Form II, and amorphous of the compound represented by formula (1)

実験条件　Experimental conditions

日数　Day

結晶形Ｉの含有量　Content of Crystal Form I

結晶形ＩＩの含有量　Content of Crystal Form II

非晶質の含有量　Content of Amorphous

０日目に対する変化のパーセンテージ　Percentage of Change at Day 0

As can be seen from the results in this table, it is clear that the amorphous (non-crystalline) form (the compound described in Cited Document 1) is less sensitive to high temperatures and humidity but very sensitive and significantly unstable under light irradiation conditions.

Then, the results are as follows when compared by the amounts of related substances (%):

[Table 2]

式（１）で示される化合物の結晶形I、結晶形II及び非晶質の影響因子試験の検討結果

実験条件	日数	結晶形Ｉの関連物質	結晶形 II の関連物質	非晶質の関連物質
	0	0．54	2．6	1．7
60℃-(i)	5	0．82	−	−
	10	0．97	2．8	2．9
60℃-(ii)	5	0．58	−	−
	10	0．60	2．7	2．1
RH90%±5%	5	0．56	−	−
	10	0．56	2．6	3．0
4500Lx±500Lx	5	1．2	−	8．9
	10	2．0	2．8	13．6
０日目に対する変化のパーセンテージ（%）				
60℃-(i)	10	↑0．43	↑0．2	↑1．2
60℃-(ii)	10	↑0．06	↑0．1	↑0．4
RH90%±5%	10	↑0．02	0．0	↑1．3
4500Lx±500Lx	5	↑0．66	−	↑7．2
	10	↑1．46	↑0．2	↑11．9

式（１）で示される化合物の結晶形Ｉ、結晶形ＩＩ及び非晶質の影響因子試験の検討結果　The investigation results of the influencing factor tests for Crystal Form I, Crystal Form II, and amorphous of the compound represented by formula (1)

実験条件　Experimental Conditions

日数　Day

結晶形Ｉの関連物質　Crystal Form I Relevant Substance

結晶形ＩＩの関連物質　Crystal Form II Relevant Substance

非晶質の関連物質　Non-crystalline Relevant Substance

０日目に対する変化のパーセンテージ　Percentage of change at day 0

As can be seen from the results in this table, it is clear that the content of amorphous form (non-crystalline) does not change significantly under hot and humid conditions when compared to Crystal Forms I and II, but significantly changes under hot and humid conditions when compared to the amount of Relevant substance.

More importantly, the table shows that the content of the amorphous form (non-crystalline) is reduced to about 10 to 15% under light irradiation conditions (Table 1 above) and thus does not meet the requirements for medicinal use, whereas the contents of Crystal Forms I and II are very stable under all experimental conditions.

In more detail, it can be seen that the content change of the non-Crystal Form is 7.5 times that of Crystal Form I after 5 days of observation. After 10 days of observation, the changes in the content of the non-crystal form were also found to be 5.88 times and 21 times those of Crystal Forms I and II, respectively. Light exposure is unavoidable during the processes of preparing and packaging non-crystal form.

Therefore, it is calculated that light exposure to the drug for 10 days reduces the content of the compound of formula (1) in the non-crystal form by 14.7%, while increasing the content of other substances contained in the non-crystal form by 11.9%.

As revealed by these results, the compound of formula (1) in the amorphous (non-crystalline) form described in Cited Document 1 cannot be used as non-crystal form. On the other hand, when the "compound represented by formula (1)" in each of the predetermined crystal form "Crystal Form I" and "Crystal Form II" specified in the Invention is exposed to light for 10 days, the active ingredients and other substances in non-crystal form change little. Therefore, it is clear that the improved stability of Crystal forms I and II produces unexpectedly superior effects compared to the non-crystal form described in Cited Document 1.

Support for this point is described in paragraphs [0096] and [0101] of the original specification in combination as follows:
The present inventors investigated the stability of Crystal Form I of the compound represented by formula (1). It could be clear from the investigation results that the contents of the relevant substance and the compound represented by formula (1) in Crystal Forms I and II of the compound represented by formula (1) substantially did not change at a high temperature, at a high humidity, and under an illumination condition. Crystal Forms I and II were superior to the amorphous form (the invention disclosed in Cited Document 1) in stability, which showed that Crystal Forms I and II of the compound represented by formula (1) had a relatively high stability that was suitable for drug preparation, storage, and transport and was favorable for ensuring efficacy and safety in use of the drug.

From the above, the compound represented by the formula (I) having Crystal Forms I and II according to the Invention has an effect of extra stability with respect to the amorphous form of the same compound described in Cited Document 1. In general, selecting a specific crystal form from those of non-crystalline requires undue trial and error, even for a person skilled in the art.

A person skilled in the art could not be easily motivated to obtain the crystal form having specific peaks defined in the Invention even if compounds in the non-crystal form had been known. As is clear from the above Tables 1 and 2, a person skilled in the art would take excessive trial and error to select a crystal form having a high stability effect from a wide variety of crystal forms.

(B) Bioavailability

Fifth, it can be asserted that comparing the "compound represented by the

formula (1)" in the predetermined crystal forms "Crystal Form I" and "Crystal Form II" specified in the Invention with the amorphous (non-crystalline) form described in Cited Document 1, the "compound represented by the formula (1)" has good oral bioavailability.

As stated above, the "compound represented by the formula (1)" in the predetermined crystal forms "Crystal Form I" and "Crystal Form II" specified in the Invention is more stable than the compound in the amorphous (non-crystalline) form described in Cited Document 1. Therefore, a person skilled in the art would predict a decrease in oral bioavailability of the former.

Surprisingly, however, the Applicant tested the bioavailability of the "compound of formula (I)" in Crystal Form I, Crystal Form II, and amorphous form (non-crystalline) according to the following procedures and found that the compound according to the Invention has better oral bioavailability than the compounds listed in Cited Document 1.

[Experimental procedure]

Each of the compounds represented by formula (I) in Crystal Form I, Crystal Form II, and amorphous form was suspended in a 0.5%-MC aqueous solution to give a final concentration of 0.1 mg/mL. Then, the suspension prepared above was intragastrically administered to SD rats at a dose of 1.0 mg/kg, and administered immediately before administration and after 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 10 hours, and 24 hours.

In addition, the above compounds were independently dissolved in a solution containing 5% DMSO and 95% 6% HP-β-CD aqueous solution. Then, 2 mg/kg was intravenously administered to SD rats. Blood was collected from each rat immediately before administration and 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, and 24 hours after administration.

Rats were kept immobile during blood collection and the tail was then heated in a water bath for 10 minutes. Subsequently, about 100 μL of blood sample was taken from the tail vein into an anticoagulant tube with sodium heparin. Blood samples were centrifuged at 8000 rpm for 6 minutes at 4°C to give plasma. The plasma should be prepared within 30 minutes after the blood collection. The plasma was stored at −80°C for the next analysis.

For sample analysis, 50 μL of plasma was placed in a centrifuge tube and mixed with 100 μL of water and 400 μL of MTBE (internal standard) aqueous solution (50 ng/mL). The tube was vortexed and then centrifuged at 4000 rpm for 10 minutes. Subsequently, 300 μL of the supernatant was transferred to another centrifuge tube, and

the tube was then blown off by a nitrogen stream. The material remaining in the test tube was redissolved in 200 μL of 1: 1 methanol: aqueous solution. Next, 20 μL of the obtained solution was injected into LC-MS/MS.

The concentration of the solute was output from Analyst 1.6.1 (AB SCIEX). As needed, means, standard errors, coefficients of variation, and other parameters were calculated in Microsoft Excel. Pharmacokinetic parameters were calculated by Pharsight Phoenix 6.1 using non-compartmental analysis.

[Results]

When the "compound represented by formula (1)" in the non-crystal form was intravenously administered to SD rats at a dose of 2 mg/kg, AUCinf was found to be 3126 h*ng/mL. When the "compound represented by formula (1)" in Crystal Form I, Crystal Form II or non-crystalline is intragastrically administered to SD rats at a dose of 1 mg/kg, AUCinf was 949 h*ng/mL for Crystal Form I type, 860 h*ng/mL for Crystal Form II, and 692 h*ng/mL for non-crystalline. The bioavailability was 60.7% for Crystal Form I, 55.0% for Crystal Form II, and 44.3% for non-crystalline.

[Table 3]

	AUC_{inf}	バイオアベイラビリティ
式（1）の化合物 [a]	3126 h*ng/mL	
結晶形Ｉ [b]	949 h*ng/mL	60.7%=949/(3126/2)
結晶形ＩＩ [b]	860 h*ng/mL	55.0%=860/(3126/2)
無定形（非晶質） [b]	692 h*ng/mL	44.3%=692/(3126/2)

[a] ２ｍｇ／ｋｇの用量での静脈内投与

[b] １ｍｇ／ｋｇの用量での胃内投与

バイオアベイラビリティ	Bioavailability
式（１）の化合物	Compound of Formula (1)
結晶形Ｉ	Crystal Form I
結晶形ＩＩ	Crystal Form II
無定形（非晶質）	Amorphous Form (Non-Crystalline)
２ｍｇ／ｋｇの用量での静脈内投与	Intravenous administration at a dose of 2 mg/kg
１ｍｇ／ｋｇの用量での胃内投与	Intragastric administration at a dose of 1 mg/kg

As is evident from the above experimental data, the "compounds represented by formula (1)" in Crystal Form I and Crystal Form II specified in the Invention were absorbed in rats far more than the same compounds in amorphous form (non-

crystalline) described in Cited Document 1. It is clear that these results were unexpected.

The original specification of the application clearly describes that the "compound represented by formula (1)" in the crystal form has good stability and biological activity (bioavailability). The "compounds represented by formula (1)" in Crystal Form I and Crystal form II specified in the Invention are much more stable than the same compounds in the amorphous form (non-crystalline) described in Cited Document 1 and have good bioavailability. Therefore, the Applicant considers that the Invention has an inventive step over Cited Documents 1 and 2.

There may be a positive correlation between drug absorption and drug biological activity (bioavailability) and a negative correlation between stability and drug dissolution. In general, drug dissolution must precede the absorption process. The simplest model that properly describes this process is shown in the scheme below.

Solid drug- (Step 1: Degradation) –> Dissolved drug- (Step 2: Absorption) –> Drug in circulation

Step 1 is often the rate-determining step in the overall absorption process, as the rate of dissolution of the drug is generally slow. As a result, onset, intensity, and duration of pharmacological activity, and thus bioavailability, are affected by changes in dissolution rate.

Therefore, it is common for the crystal form to be more difficult to dissolve than the non-crystal form, even assuming that the crystal form is more stable than the corresponding non-crystal form. It was common technical knowledge in the art that the crystalline form had lower bioavailability (or the biological activity of the drug) than the corresponding non-crystal form. That is, it was a well-known technical matter that it cannot be expected to improve both stability and bioavailability at the same time.

On the other hand, the Invention has found the "compounds represented by formula (1)" in Crystal Form I and Crystal form II with not only unexpectedly improved stability but also high bioavailability compared to the non-crystal form. Therefore, the Applicant considers that the Invention has an inventive step over Cited Documents 1 and 2.

Furthermore, the Applicant considers that the data shown in Example 3 described in paragraphs [0102] to [0110], in particular Tables 6 and 7 of the original specification of the application, exhibit improved pharmacokinetic activity of the "compounds represented by formula (1)" in Crystal Form I and Crystal form II as defined in the Invention. The Applicant considers that this underlies the inventive step over the same compound in the amorphous form described in Cited Document 1.

In other words, the original specification of the Application actually describes the unexpected and beneficial effects of the "compounds represented by formula (1)" in Crystal Form I and Crystal Form II specified in the Invention and properly supports the inventive step of the Invention. The data from the additional experiments stated above are provided solely for the purpose of further supporting the inventive step of the Invention.

B Appellant's allegations will be sequentially considered.

(A) Stability

As stated in the above (3) B (b), it is common technical knowledge of a person skilled in the art that compounds in the crystalline state are more stable than compounds in the amorphous state. It is also common technical knowledge that when there are multiple crystal forms, the stability differs for each crystal form.

Then, stability is, of course, a matter of concern for a person skilled in the art to explore new crystals. "In addition to evaluating the crystallinity of a compound, the stability thereof to heat, humidity, and light in the solid state is evaluated." (the above (3f)) as described in the section of "[2] Evaluation of chemical stability" in "6. Evaluation of physical properties of candidate compounds for development" of Cited Document 3, for example, it is also common technical knowledge that stability under high temperature conditions, high humidity conditions, and light irradiation conditions is also included in the above matter of stability. For example, Cited Document 10 carried out the assay at 60°C for up to 6 months to evaluate the residual rate (the above (10c)), Cited Document 11 carried out the assay at 40°C under a relative humidity of 52.4°C for up to 4 weeks to evaluate the residual rate (the above (11c) and (11d)), Cited Document 12 carried out the assay at 85°C up to 24 days to evaluate the residual rate (the above (12d)), and Cited Document 13 carried out the assay at 60°C up to 14 days or 19 days to evaluate the residual rate (the above (13c)).

In addition, the behavior with respect to humidity can be also said to be a matter of concern for a person skilled in the art to explore new crystals as described in the section of "[5] Evaluation of moisture absorbency" of "6. Evaluation of physical properties of candidate compounds for development" in Cited Document 3 as "Moisture absorbency is an important basic property that affects ... chemical and physical stability" (the above (3f)) and in FIG. 1 of Cited Document 4 as "% profile" (the above (4b)).

Then, even if the compound in Crystal Form I represented by the formula (1) of the Invention shows stability under high temperature conditions, high humidity conditions, and light irradiation conditions as represented in [Table 1] and [Table 2] of

the above A (a), compared to the non-crystalline compound, it cannot be said to be exceptionally remarkable beyond the expectations of a person skilled in the art.

(B) Bioavailability

Cited Document 2 describes that the solid-state physics of a pharmaceutical compound has an important effect on bioavailability as well as stability; depending on the storage conditions, a crystal transition from the metastable form to the stable form occurs; there are differences in bioavailability due to differences in solubility among crystal forms; for that reason, a stable crystal form is often selected; on the other hand, the metastable form may have excellent solubility; for this reason, the metastable type may be selected; and it is therefore strongly required to maintain a certain quality and ensure stability so that the expected medicinal effect can be obtained (the above (2a)).

Furthermore, in Cited Document 3, the section of "6. Evaluation of physical properties of candidate compounds for development" describes that crystals are important physical properties that affect solubility, oral absorbability (bioavailability), etc., in addition to chemical stability; and the section of "[3] Evaluation of solubility" describes that " It is important to evaluate the solubility of the drug in consideration of gastrointestinal absorption while considering the results of crystallinity and chemical stability" (the above (3f)). In Cited Document 4, FIG. 1 describes "Solubility Profile." In Cited Document 8, the section of "b. Crystal characteristics" describes that "In the case of non-crystal form, it is very important to control the crystal properties, especially because of the difference in bioavailability." (the above (8a)). Therefore, when a person skilled in the art searches for a new crystal of a pharmaceutical compound, it can be said that bioavailability is a matter of course to be paid attention to while considering stability. For example, Cited Document 9 describes that since a compound in the non-crystalline state shows inadequate storage stability and has the drawback of impairing absorption efficiency, the inventors have found a stable crystal form to overcome the drawback (the above (9c)).

In addition, the Appellant considers as well-known technical matters that common technical knowledge is that crystals are generally less soluble than non-crystalline and thus their bioavailability is also low; and improvements in both stability and bioavailability at the same time cannot be expected. It is also known that stable crystals may have better solubility than non-crystalline crystals. Specifically, the following matters are described in Documents A to C (in this order, equivalent to Cited Documents 9 to 11 cited in the decision of refusal to indicate the well-known technical matters at the time of the priority date for the Invention) with respect to the solubility of

crystals of the pharmaceutical compounds.

Document A (International Publication No. WO 2012/043700) describes that the non-crystalline dry powder of a sodium salt of 6-fluoro-3-hydroxy-2-pyrazinecarboxamide, which is prepared with the expectation of improved solubility, is unexpectedly poorly soluble (see [0004]); and crystals of 6-fluoro-3-hydroxy-2-pyrazinecarboxamide are more soluble in water and more stable than non-crystalline (see [0010], [0012], [0070], and [0075]).

Document B (National Publication of International Patent Application No. 2011-503127) describes that an object is to increase the solubility of non-crystalline diphenylazetidinone (see [0002]); compared to the non-crystalline compound of formula II, the crystalline hydrate of formula I has a significantly increased solubility (see [0252]); and, in general, it is advantageous that the crystalline hydrate of formula I has significantly higher solubility than non-crystalline compound II, because crystalline compounds are thermodynamically stable and therefore have a lower solubility than non-crystalline compounds (see [0256] to [0257]).

Document C (International Publication No. WO 2006/101082) describes that crystals of 5-[2-amino-4-(2-furyl)pyrimidin-5-yl]-1-methylpyridin-2(1H)-one are provided (see [0008]); and C-type crystals and hydrate crystals have better solubility than non-crystalline compounds (see [0082] to [0083] and FIG. 17).

Therefore, from the description of the above documents A to C, even if there is common technical knowledge or well-known technical matters alleged by the Appellant, they are not always valid for all crystals and non-crystalline solids. It can be said that this was known as of the priority date of the present application. In the first place, in [0104], etc., the present specification only describes that Crystal Form I of the compound represented by formula (1) of the Invention is evaluated for its medicinal activity in the body using a test animal. The present specification does not specifically describe not only the results of bioavailability tests but also the superiority of Crystal Form I in bioavailability over non-crystalline.

Then, even if Crystal Form I of the compound represented by the formula (1) of the Invention shows bioavailability as described in [Table 3] of the above A (a) presented in the appeal brief as compared with that of non-crystalline compound, it cannot be said that it is exceptionally remarkable beyond the expectation of a person skilled in the art.

(5) Summary

Therefore, the Invention could have been invented with ease by a person skilled

in the art based on the invention disclosed in Cited Document 1 distributed before the priority date of the present application and the present application. Therefore, the Appellant should not be granted a patent for the invention in accordance with the provisions of Article 29(2) of the Patent Act.

No. 5 Closing

As described above, since the Invention cannot be granted a patent, the Present Application should be rejected without considering the rest.

Therefore, the appeal decision shall be made as described in the conclusion.

June 19, 2020

Chief administrative judge: SASAKI, Hidetsugu

Administrative judge: TOMINAGA, Tamotsu

Administrative judge: SEKI, Mihogi