Appeal decision

Appeal No. 2019-4288

Appellant Signal Pharmaceuticals LLC

Patent Attorney ISHIKAWA, Toru

The case of appeal against the examiner's decision of refusal of Japanese Patent Application No. 2016-549045, entitled "Solid forms of 2-(tert-butylamino)-4-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-pyrimidine-5-carboxamide, compositions thereof, and methods of their use" (international publication dated August 6, 2015, WO2015/116755, national publication dated February 9, 2017, National Publication of International Patent Application No. 2017-504632) has resulted in the following appeal decision:

Conclusion

The appeal of the case was groundless.

Reason

No. 1 History of the procedures

This application was submitted on January 29, 2015 as an international filing date (the claim of priority under the Paris Convention was received by the foreign receiving office on January 30, 2014 in the US, and July 16, 2014 in the US) to which written amendments were submitted on January 12 and March 6, 2018, reasons for refusal were notified on July 17, 2018, written amendments (two copies) were submitted on October 24, 2018, a supplemental statement of proceedings was submitted on October 25, 2018 (reception date), an examiner's decision of refusal was issued on November 27, 2018, an appeal against the examiner's decision of refusal was requested on April 3, 2019, and a supplemental statement of proceedings was submitted on April 3, 2019.

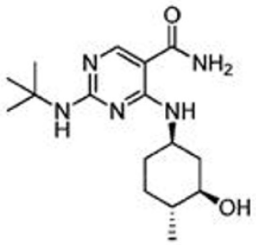
No. 2 Regarding the Invention

1. Recognition of the Invention

Inventions recited in Claims 1 to 36 of the present application are recognized to be as specified by the matters recited in Claims 1 to 36, which have been amended by

the procedures of amendment dated October 24, 2018, and the invention recited in Claim 2 (hereinafter referred to as "the Invention") is as follows:

"[Claim 2]
A Crystal Form B of Compound 1, or a tautomer thereof:
[Chemical 2]



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which has an X-ray powder diffraction pattern comprising peaks at 2θ values of approximately 9.80, 10.30, 14.62, 17.29, 18.23, 20.66, 21.74, and 30.55°."

No. 3 Reason for refusal stated in the examiner's decision

Outline of the reasons for refusal of the examiner's decision (Reason 1 in the notice of reasons for refusal dated July 17, 2018).

Inventions recited in the following claims of the present application could have been easily made by those who had ordinary skill in the art belonging to the Invention before the priority date, based on inventions disclosed in the following publications, Cited Documents 1 to 6, distributed in Japan or a foreign country prior to
the filing of the patent application, or inventions available to the public through electric telecommunication lines. Therefore, the present application cannot be allowed under the provisions of Article 29(2) of the Patent Act.

Note

Claims 1 to 36

1. Cited Document 1: International Publication No. WO 2012/145569
2. Cited Document 2: Mino R. Caira, Crystalline Polymorphism of Organic Compounds, Topics in Current Chemistry, 1998, No. 198, pp. 163-208
3. Cited Document 3: Noriaki Hirayama, Ed., "Organic compound crystal produced Handbook -Principles and Expertise-," MARUZEN, July 25, 2008, pp. 17-23, 37-40, 45-51, 57-65

4. Cited Document 4: Masakuni Matsuoka, "Advanced Crystallization Technology of Organic Materials Control of Size, Morphology, Polymorph and Purity," PHARM TECH JAPAN, May 1, 2003, vol. 19, No. 6, pp. 91-101
5. Cited Document 5: Teruzo Asahara and 4 others, Ed., "Solvents Handbook," KODANSHA, September 1, 1985, pp. 47-51
6. Cited Document 6: Isao Sugimoto and Yoshiteru Takahashi, "Solvates, Amorphous Solids and Pharmaceutical Preparations," Journal of the Society of Powder Technology, 1985, 22(2), pp. 85-97

Cited Documents 2 to 6 are documents indicating the technical knowledge at the time of the priority date of the present application.

No. 4 Judgment by the body

The body determines that, as stated in the reason for refusal stated in the examiner's decision, the Invention could have been easily made by those skilled in the art based on the invention disclosed in Publication 1 and the common general technical knowledge at the time of the priority date of the present application, and thus the Appellant should not be granted a patent for it under the provisions of Article 29(2) of the Patent Act.

The reasons are as stated below.

Publication 1: International Publication No. WO 2012/145569 (Cited Document 1, which is cited in the Examiner's decision)
Publication 2: Mino R. Caira, Crystalline Polymorphism of Organic Compounds, Topics in Current Chemistry, 1998, No. 198, pp. 163-208
Publication 3: Noriaki Hirayama, Ed.,″ Handbook of Organic Compound Crystal Production - Principle and Know-how -," MARUZEN, July 25, 2008, pp. 17-23, 37-40, 45-51, 57-65
Publication 4: Masakuni Matsuoka, "Advanced Crystallization Technology of Organic Materials Control of Size, Morphology, Polymorph and Purity," PHARM TECH JAPAN, May 1, 2003, vol. 19, No. 6, pp. 91-101
Publication 5: Teruzo Asahara and 4 others, Ed., "Solvents Handbook," KODANSHA, September 1, 1985, pp. 47-51
Publication 6: Cited Document 6: Isao Sugimoto and Yoshiteru Takahashi, "Solvates, Amorphous Solids and Pharmaceutical Preparations," Journal of the Society of Powder Technology, 1985, 22(2), pp. 85-97

Publication 7: Teisuke Okano, Ed., " Introduction to Modern Pharmaceutics (Revised 3rd Edition)," NANKODO,
Publication 8: C. G. WERMUTH, Ed., "The Practice of Medical Chemistry, 2nd Edition.," Translation supervisor: Hiroshi Nagase, TECHNOMIX INTERNATIONAL CORPORATION, September 25, 1991, pp. 452-453
Publication 9: Noriaki Hirayama, Ed.," Handbook of Organic Compound Crystal Production - Principle and Know-how -," MARUZEN, July 25, 2008, pp. 78-79
Publication 10: The Chemical Society of Japan, Ed., "The Fifth Series of Experimental Chemistry: Fundamental Techniques for Chemical Experiments," MARUZEN, February 28, 2015, pp. 24-25

Publications 2 to 10 are documents indicating the technical knowledge at the time of the priority date of the present application.

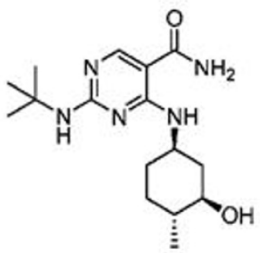
1 Described matters in Cited Publications
(1) Publication 1

Publication 1, which is a publication distributed before the priority date of the application and cited in the reason for refusal stated in the examiner's decision, includes the following descriptions:

The descriptions are represented by translation.

(1a) "[0001] Provided herein are certain diaminocarboxamide and diaminocarbonitrile pyrimidine compounds, compositions comprising an effective amount of such compounds, and methods for treating or preventing liver fibrotic disorders or a condition treatable or preventable by inhibition of a JNK pathway, comprising administering an effective amount of such diaminocarboxamide and diaminocarbonitrile pyrimidine compounds to a subject in need thereof." (page 1, lines 4 to 9)

(1b) "Example 32: 2-(tert-butylamino)-4-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-pyrimidine-5-carboxamide



[00394] A. (R)-tert-Butyl 4-methylcyclohex-3-enylcarbamate and (S)-tert-butyl 4-methylcyclohex-3-enylcarbamate

...

[00395] B. tert-Butyl (lR,3R,4R)-3-hydroxy-4-methylcyclohexylcarbamate, tert-butyl (lR,3S,4S)-3-hydroxy-4-methylcyclohexylcarbamate, tert-butyl (lS,3R,4R)-3-hydroxy-4-methylcyclohexylcarbamate, tert-butyl (lS,3S,4S)-3- hydroxy-4-methylcyclohexylcarbamate

...

[00402] C. (lR,2R,5R)-5-Amino-2-methylcyclohexanol hydrochloride

...

[00403] D. 5-Bromo-N-tert-butyl-4-(methylthio)pyrimidin-2-amine

...

[00404] E. 2-(tert-Butylamino)-4-(methylthio)pyrimidine-5-carbonitrile

...

[00405] F. 2-(tert-Butylamino)-4-(methylthio)pyrimidine-5-carboxamide

...

[00406] G. 2-(tert-Butylamino)-4-(methylsulfinyl)pyrimidine-5-carboxamide

...

[00407] H. 2-(tert-Butylamino)-4-((lR,3R,4R)-3-hydroxy-4-methylcyclohexyl-amino)pyrimidine-5-carboxamide. To a stirring suspension of 2-(tert-butylamino)-4-(methylsulfinyl)pyrimidine-5-carboxamide (0.092 g, 0.359 mmol) and (lR,2R,5R)-5-amino-2-methylcyclohexanol hydrochloride (0.065 g, 0.395 mmol) in DMF (2 mL), N-ethyl-N-isopropylpropan-2-amine (0.157 mL, 0.897 mmol) was added, and reaction proceeded overnight under heating at 90°C. The crude reaction mixture was concentrated under reduced pressure, and then ice-cold water (20 mL) was added to the residue. The resulting mixture was vigorously stirred for 1 h and then the product was filtered, washed with water, and dried under vacuum to afford 2-(tert-butylamino)-4-((lR,3R,4R)-3-hydroxy-4-methylcyclohexylamino)pyrimidine-5-carboxamide (0.074 g, 0.230 mmol, 64.1% yield). 1H NMR (400 MHz, DMSO-d6) δ ppm 8.94 (br. s., 1 H), 8.34 (s, 1 H), 6.69 (br. s., 1 H), 4.59 (d, J=5.47 Hz, 1 H), 3.87 (br. s., 1 H), 2.92 - 3.01 (m, 1 H), 2.14 (d, J=10.15 Hz, 1 H), 1.91 (d, J=11.71 Hz, 1 H), 1.67 (dd, J=13.28, 3.12 Hz, 1H), 1.07 - 1.24 (m, 3 H), 0.91 - 0.99 (m, 4 H). MS (ESI) m/z 322.3 [M+l]+."

(Underlines are added by the body, the same shall apply hereinafter.) (page 148, line 9 to page 153, line 10)

(2) Publication 2

Publication 2, which is a publication distributed before the priority date of the application and cited in the reason for refusal stated in the examiner's decision, includes the following descriptions:

The descriptions are represented by translation.

(2a) "2

Crystal Polymorphism – Theoretical Principles and Practical Implications

2.1

Background – The Role of Polymorphism in the Production of Materials

Many of the inconsistencies encountered in product performance in the chemical, chemical engineering, pharmaceutical, food, and related industries can be attributed to polymorphism. An important example is inconsistent behavior of drug substances upon dissolution, which may have a direct influence on bioavailability. This arises because different polymorphic forms of the same drug may have solubilities which differ by an order of magnitude." (page 165, lines 3 to 12)

(3) Publication 3

Publication 3, which is a publication distributed before the priority date of the application and cited in the reason for refusal stated in the examiner's decision, includes the following descriptions:

(3a) "Method for crystallizing pharmaceutical products

4.1 Introduction

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, and the like. 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 determines 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, and the like, 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. ... Of solvates, hydrates are of particular importance. ...

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 crystalline 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[1), 2)] to guarantee the quality of the pharmaceutical products[3)]. This chapter outlines crystallization from the viewpoint of quality design of such pharmaceutical products." (page 57, line 1 to page 58, the last line).

(3b) "4.2 Crystal polymorphs

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 polymorphism must be determined by repeating trial and error. Therefore, although polymorphism 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 crystal polymorphism[4, 5].

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[4]. The choice of a solvent often allows control of the crystal polymorphism 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.

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

溶媒　　solvent

結晶形　　crystal form

（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）加温溶解し結晶が折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

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
Ｎ、Ｎ-ジメチルホルムアミド	N,N-dimethylformamide
微少	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℃　20℃　40℃　60℃
	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℃　70℃　120℃
	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
溶媒 solvent
結晶形 crystal form
（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、結晶が折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
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
ジクロロメタンーメタノール混合溶媒（4:1） Dichloromethane-methanol mixed solvent (4:1)
クロロホルムーメタノール混合溶媒（4:1） Chloroform-methanol mixed solvent (4:1)
クロロホルムーＮ、Ｎージメチルホルムアミド混合溶媒（4:1） Chloroform-N,N-dimethylformamide mixed solvent (4:1)
温度 Temperature
乾燥温度 Drying temperature

非晶質	Amorphous
出典	Source

...
" (page 59, line 1 to page 60, line 8 from the bottom)

(4) Publication 4

Publication 4, which is a publication distributed before the priority date of the application and cited in the reason for refusal stated in the examiner's decision, includes the following descriptions:

(4a) "5. Polymorphic control

(1) Crystal polymorph

Many organic crystals are known to likely cause polymorphism. Statistical results regarding molecular structures that cause polymorphism have been reported[15)]. Generally, polymorphs have different crystal structures, and thus have different fundamental physical properties, such as melting point, density, heat of fusion, and solubility. Especially in the case of pharmaceutical products, strict control is indispensable because of different levels of in vivo efficacy among different polymorphs.

The type of precipitated polymorph depends on the conditions of deposition, including the type of solvent, temperature, cooling rate, and the like." (page 98, right column, lines 7 to 16)

(5) Publication 5

Publication 5, which is a publication distributed before the priority date of the application and cited in the reason for refusal stated in the examiner's decision, includes the following descriptions:

(5a) "3.2 Recrystallization

An important factor in achieving the purpose of recrystallization is to use a suitable solvent together with its technical procedure. The suitable solvent selection is of course made in a small amount of preliminary experiments, but there are some rules or rules of thumb to find the optimal solvent as soon as possible.

3.2.1 How to select a solvent

...

3.2.2 Precautions for solvent selection

...

3.2.3 Types and characteristics of recrystallization solvent

Commonly used recrystallization solvents are listed in Tables 3.3 and 3.4. Table 3.3 presents the most commonly used solvents, and, if these are not successful, use of any of slightly more specific ones listed in Table 3.4 is recommended. Note that the solvent names in Table 3.3 are not in strict order, but non-polar solvents and polar solvents are arranged in that order from the upper part to the lower part. Table 3.5 (p.51) shows commonly used mixed solvents.

...

表 3.3 最も一般的に使用される再結晶溶媒

溶媒名	融点(℃)	(沸点℃)	水との混和性
石油エーテル	—	30~70	−
石油ベンジン	—	50~90	−
リグロイン	—	75~120	−
ヘキサン	−95.3	68.7	−
シクロヘキサン	6.54	80.72	−
ベンゼン	5.53	80.10	−
四塩化炭素	−22.95	76.75	−
ジエチルエーテル	−116.3	34.6	−
ジイソプロピルエーテル	−85.89	68.47	−
クロロホルム	−63.55	61.15	−
酢酸エチル	−83.8	77.11	−
アセトン	−94.7	56.12	+
エタノール	−114.5	78.32	+
メタノール	−97.49	64.51	+

表 3．3　最も一般的に使用される再結晶溶媒　　Table 3.3 Most commonly used recrystallization solvents

溶媒名	Solvent name
融点 Melting point	
沸点 Boiling point	
水との混和性	Miscibility with water
石油エーテル	Oil ether
石油ベンジン	Petroleum benzine
リグロイン	Ligroin
ヘキサン	Hexane
シクロヘキサン	Cyclohexane
ベンゼン	Benzene
四塩化炭素	Carbon tetrachloride
ジエチルエーテル	Diethyl ether
ジイソプロピルエーテル	Diisopropyl ether
クロロホルム	Chloroform

酢酸エチル　　Ethyl acetate
アセトン　　acetone
エタノール　　Ethanol
メタノール　　Methanol

表 3.4　有用な再結晶溶媒（表 3.3 にあげたものは除く）

溶媒名	融点 (℃)	沸点 (℃)	水との混和性
炭化水素類			
ペンタン	−129.7	36.1	−
ヘプタン	−90.6	98.4	−
メチルシクロヘキサン	−126.6	100.93	−
オクタン	−56.8	125.67	−
α-ピネン	−64	156.0	−
デカリン	*cis*:−42.98 *trans*:−30.38	*cis*:195.82 *trans*:187.31	−
トルエン	−94.99	110.63	−
キシレン	−	137~140 (*o*, *m*, *p* の混合物)	−
クメン	−93.0†	152.39	−
p-シメン	−67.94	177.10	−
ハロゲン化炭化水素類			
ジクロロメタン	−95.14	39.75	−
1,2-ジクロロエタン	−35.4	83.48	−
トリクロロエチレン	−86.4	87.19	−
テトラクロロエチレン	−22.35	121.20	−
1,2-ジブロモエタン	10.06	131.41	−
1,1,2,2-テトラクロロエタン	−42.5	146.3	−
クロロベンゼン	−45.58	131.69	−
ブロモベンゼン	−30.6†	156.06	−
o-ジクロロベンゼン	−17.01	180.48	−
エーテル類			
テトラヒドロフラン	−108.5	66	+
ジプロピルエーテル	−122	90.5	−
ジオキサン	11.80	101.32	+
ジイソプチルエーテル		122~124	−
ジブチルエーテル	−98	142.4	−
アニソール	−37.3	153.75	−
ジイソペンチルエーテル	>−75	172	−
フェネトール	−28.6	172	−
ジフェニルエーテル	28	258.3	−
エーテルアルコール類			
2-メトキシエタノール	−85.1†	124.6	+
2-エトキシエタノール	−70†	135.6	+
ジエチレングリコールモノエチルエーテル	<−76	202.0	+
エステル類			
ギ酸エチル	−79.4	54.15	−
酢酸メチル	−98.05	57.80	一部+
酢酸イソプロピル	−73.4	89	−
酢酸イソブチル	−98.85	118.0	−
酢酸イソペンチル	−78.5	142.0	−
安息香酸メチル	−12.5	199.6	−
フタル酸ジブチル	−35	339	−
ケトン類			
メチルエチルケトン	−86.69	79.64	一部+
シクロヘキサノン	−45	155.65	−
アルコール類			
2-プロパノール	−89.5	82.40	+
アリルアルコール	−129	96.9	+
1-プロパノール	−126.2	97.2	+
イソブチルアルコール	−108	107.9	一部+
1-ブタノール	−89.8	117.7	一部+
イソペンチルアルコール	−117.2	130.8	−
シクロヘキサノール	25.15	161	−
1,2-プロパンジオール	−59.5	187.3	+
1,2-エタンジオール	−12.6	197.85	+
ベンジルアルコール	−15.3	205.45	−
グリセリン	18.18	290.0 (分解)	+
フェノール	40.90	181.75	一部+
クレゾール	−	195~205 (*o*, *m*, *p* の混合物)	−
酸類			
ギ酸	8.27	100.56	+
酢酸	16.66	118.1	+
アミン類			
アニリン	−6†	184.7	−
ピリジン	−42†	115.3	+
ピコリン			+
2,6-ルチジン	−6.16	144.05	一部+
コリジン			一部+
キノリン	−15.6	237.10	
ニトロ化合物類			
ニトロメタン	−28.5	101.2	−
ニトロベンゼン	5.76	210.9	−
シアノ化合物類			
アセトニトリル	−43.84	81.60	+
プロピオニトリル	−92.78	97.35	一部+
酸アミド類			
N, *N*-ジメチルホルムアミド	−60.43	153.0	+
N, *N*-ジメチルアセトアミド	−20	166.1	+
ヘキサメチルリン酸トリアミド	7.20	233	+
酸無水物			
無水酢酸	−73.1	140.0	反応する
硫黄化合物類			
二硫化炭素	−111.57	46.23	−
ジメチルスルホキシド	18.54	189.0	+
スルホラン	28.45	287.3	+

† 凝固点

総論編　　General statement

表 3．4　有用な再結晶溶媒（表 3．3 にあげたものは除く）　Table 3.4 Useful recrystallization solvents (excluding those listed in Table 3.3)

溶媒名　　Solvent name

融点　　Melting point

沸点	Boiling point
水との混和性	Miscibility with water
炭化水素類	Hydrocarbons
ペンタン	Pentane
ヘプタン	Heptane
メチルシクロヘキサン	Methylcyclohexane
オダタン	Odatan
αーピネン	α-pinene
デカリン	Decalin
トルエン	toluene
キシレン	Xylene
クメン	Cumene
ρーシメン	ρ-simene
ハロゲン化炭化水素類	Halogenated hydrocarbons
ジクロロメタン	Dichloromethane
1、2ージクロロエタン	1,2-dichloroethane
トリクロロエチレン	Trichlorethylene
テトラクロロエチレン	Tetrachlorethylene
1、2ージプロモエタン	1,2-dipromoethane
1、1、2、3ーテトラクロロエタン	1,1,2,3-tetrachloroethane
クロロベンゼン	Chlorobenzene
プロモベンゼン	Promobenzene
oージクロロベンゼン	o-Dichlorobenzene
エーテル類	Ethers
テトラヒドロフラン	Tetrahydrofuran
ジプロピルエーテル	Dipropyl ether
ジオキサン	Dioxane
ジイソプチルエーテル	Diisobutyl ether
ジプチルエーテル	Dibutyl ether
アニソール	Anisole
ジイソペンチルエーテル	Diisopentyl ether
フェネトール	Phenetole
ジフェニルエーテル	Diphenyl ether
エーテルアルコール類	Ether alcohols
2ーメトキシエタノール	2-methoxyethanol
2ーエトキシエタノール	2-ethoxyethanol

ジエチレングリコールモノエチルエーテル	Diethylene glycol monoethyl ether
エステル類	Esters
ギ酸エチル	Ethyl formate
酢酸メチル	Methyl acetate
酢酸イソプロピル	Isopropyl acetate
酢酸イソブチル	Isobutyl acetate
酢酸イソペンチル	Isopentyl acetate
安息香酸メチル	Methyl benzoate
凝固点	Freezing point
（o、m、ρの混合物）	(A mixture of o, m, and ρ)
一部＋	Part +
フタル酸ジブチル	Dibutyl phthalate
ケトン類	Ketones
メチルエチルケトン	Methyl ethyl ketone
シクロヘキサノン	Cyclohexanone
アルコール類	Alcohol
2－プロパノール	2-Propanol
アリルアルコール	Allyl alcohol
1－プロパノール	1-Propanol
イソブチルアルコール	Isobutyl alcohol
1－ブタノール	1-butanol
イソペンチルアルコール	Isopentyl alcohol
シクロヘキサノール	Cyclohexanol
1、2－プロパンジオール	1,2-propanediol
1、2－エタンジオール	1,2-ethanediol
ベンジルアルコール	Benzyl alcohol
グリセリン	Glycerin
フェノール	Phenol
クレゾール	Cresol
酸類	Acids
ギ酸	Formic acid
酢酸	Acetic acid
アミン類	Amines
アニリン	Aniline
ピリジン	Pyridine
ピコリン	Picoline

2、6ールチジン	2,6-lutidine
コリジン	Collidine
キノリン	Quinoline
ニトロ化合物類	Nitro compounds
ニトロメタン	Nitromethane
ニトロベンゼン	Nitrobenzene
シアノ化合物類	Cyano compounds
アセトニトリル	Acetonitrile
プロピオニトリル	Propionitrile
酸アミド類	Acid amides
Ｎ、Ｎージメチルホルムアミド	N,N-dimethylformamide
Ｎ、Ｎージメチルアセトアミド	N,N-dimethylacetamide
ヘキサメチルリン酸トリアミド	Hexamethylphosphoric triamide
酸無水物	Acid anhydride
無水酢酸	Acetic anhydride
硫黄化合物類	Sulfur compounds
二硫化炭素	Carbon disulfide
ジメチルスルホキシド	Dimethyl sulfoxide
スルホラン	Sulfolane
（分解）	(Decomposition)
反応する	React

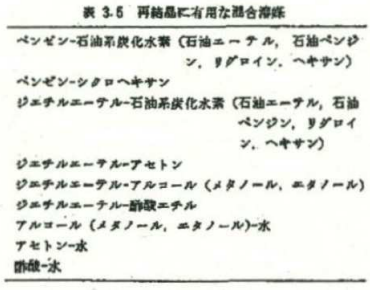


表 3.5 再結晶に有用な混合溶媒

ベンゼン-石油系炭化水素（石油エーテル，石油ベンジン，リグロイン，ヘキサン）
ベンゼン-シクロヘキサン
ジエチルエーテル-石油系炭化水素（石油エーテル，石油ベンジン，リグロイン，ヘキサン）
ジエチルエーテル-アセトン
ジエチルエーテル-アルコール（メタノール，エタノール）
ジエチルエーテル-酢酸エチル
アルコール（メタノール，エタノール）-水
アセトン-水
酢酸-水

表 3．5　再結晶に有用な混合溶媒　Table 3.5 Mixed solvent useful for recrystallization

ベンゼンー石油系炭化水素（石油エーテル、石油ベンジン、リグロイン、ヘキサン）	Benzene-petroleum hydrocarbons (petroleum ether, petroleum benzine, ligroine, hexane)
ベンゼンーシクロヘキサン	Benzene-cyclohexane

ジエチルエーテル一石油系炭化水素（石油エーテル、石油ベンジン、リグロイン、ヘキサン） Diethyl ether-petroleum hydrocarbons (petroleum ether, petroleum benzine, ligroin, hexane)
ジエチルエーテル一アセトン Diethyl ether-acetone
ジエチルエーテル一アルコール（メタノール、エタノール） Diethyl ether-alcohol (methanol, ethanol)
ジエチルエーテル一酢酸エチル Diethyl ether-ethyl acetate
アルコール（メタノール、エタノール）一水 Alcohol (methanol, ethanol)-water
アセトン一水 Acetone-water
酢酸一水 Acetic acid-water

" (page 47, right column, line 20 to page 51, left column, upper table)

(6) Publication 6

Publication 6, which is a publication distributed before the priority date of the application and cited in the reason for refusal stated in the examiner's decision, includes the following descriptions:

(6a) "5. Amorphous solid

...

The usefulness of this amorphous solid was introduced relatively recently in the field of pharmaceutical preparations. Mullins and Macek published in 1960 the properties of the antimicrobial agent novobiocin in two forms (crystalline and amorphous solid).

...

Thus, although the study of formulation of amorphous solids is relatively recent, the number of reports is very small. Since amorphous solids have higher potential energy than substances in a crystalline state, amorphous solids are difficult to prepare. In addition, amorphous solids are easily transformed into stable forms. Therefore, research in this field seems to be delayed. In the case of the above novobiocin, an amorphous novobiocin (acid) is obtained by acidifying an aqueous solution of Na salt, but it is said to be easily transformed into a stable crystal form, particularly at high temperature." (page 89, right column, line 20 to page 90, right column, line 16).

(7) Publication 7

Publication 7, which is a publication distributed before the priority date of the application, includes the following descriptions:

(7a) "1. 2. 3 Chemical structure and solubility

...

ix. Of the polymorphs, the metastable form (low melting point) is more soluble than the stable form (high melting point) (e.g., indomethacin). *

x. Amorphous substances that are similar drugs are more soluble than crystals (e.g., novobiocin) **." (page 26, lines 10 to 27)

(7b) "Polymorphism: A phenomenon such that the same compound has more than one different crystal structure and crystal form is called polymorphism. Polymorphic crystals differ in X-ray diffraction image, melting point, refractive index, solubility, and so on. Many compounds are polymorphic. Also, in pharmaceutical products, many compounds have been reported as being polymorphic, including aspirin, indomethacin, cocoa butter, glyceride, fatty acid, sulfonamides, cephaloridine, barbitals, chloramphenicol palmitate, steroid hormones (prednisolone, estrone, etc.), and riboflavin.[3)] Five crystal forms of progesterone are known.

The fact that different crystal polymorphs have different solubilities is pharmaceutically important. In many cases, the solubility (or dissolution rate) of crystals limits absorption in the digestive tract, and the higher the solubility, the faster the absorption. Of polymorphs, less stable crystals (meta-stable forms) have lower melting points and higher solubility than stable forms. According to Ostwald, when crystals precipitate from solution, the metastable form crystallizes first (law of successive transformation). The transition of the crystal form occurs due to the recrystallization solvent, the crystallization speed (cooling temperature), the storage temperature condition, pulverization, and the like. For example, the crystal forms of aspirin recrystallized from 95% ethanol and those reconstituted from n-hexane are different, but the latter dissolves in water much faster." (page 111, lines 3 to 18)

(7c) "c) Crystal form

As already described, many drugs exhibit crystal polymorphism*, and, among polymorphs the metastable form is more soluble than the stable form.

Chloramphenicol palmitate crystals have at least two different polymorphs A and B2, and type B is more soluble. When the suspension is orally administered, the Cmax of B type is reported to be 7 times higher than that of A type. In addition, Indomethacin has three polymorphic forms. Of these, both α and γ types are

practically used. When used as a suppository, the dissolution rate of α-type is superior to that of γ-type ... the blood concentration of α-type suppository is also higher ... .
...

Among crystal polymorphs, the metastable form with higher solubility is more thermodynamically unstable than the stable form, and the former transforms into the latter over time. It is therefore necessary to keep in mind that the bioavailability of the drug is reduced during storage when the drug is prepared using the metastable form.

Drugs in amorphous form do not have to overcome the crystal lattice energy during dissolution, so they are more easily dissolved than those in crystalline form. Insulin-zinc complexes include crystalline and amorphous ones, and the latter absorbs more quickly ...." (page 256, line 3 from the bottom, to page 257, line 8 from the bottom)

(8) Publication 8

Publication 8, which is a publication distributed before the priority date of the application, includes the following descriptions:

(8a) "IV. Mesomorphic crystalline [translator's note 5]

Certain substances are known to have multiple crystalline states when crystallized. Factors that determine the crystal state include the physical properties of the crystallization solvent, the temperature at which crystallization occurs, the presence or absence of impurities, and the like. Such properties are called crystalline polymorphism or simply polymorphism. Among the possible crystalline states, there are metastable crystals. This change can be divided into two types: enantiotropy, which is reversible transition and monotropy, which is irreversible transition. The former is the case where each state of the polymorphism is literally convertible to each other. The former is the case where the respective polymorphic states are literally interconvertible. The latter is a phenomenon that changes from a thermodynamically unstable state to a more stable state, and this type of metastasis is common. Examples of a method for distinguishing each crystal form when a drug shows different crystal forms include melting point measurement, solubility measurement, differential scanning calorimetry, thermogravimetric analysis, infrared spectroscopy, X-ray diffraction analysis, and morphological observation by a scanning electron microscope.

As a general theory, a metastable substance is characterized in that its solubility and dissolution rate are higher than those in the stable state. In extreme cases, the difference in dissolution rate between the two states may be more than four times[21, 22,] and a commonly observed phenomenon is one in which the solubility increases up to 50

to 100%[23]. Riboflavin is mentioned here as an example. This drug has three polymorphs and their respective solubilities are 60 mg/L, 810 mg/L, and 1200 mg/L, which widely differ from one another. Further, if the metastable crystal is allowed to come into contact with the solvent, the crystal may gradually change to the most stable state, and the solubility may decrease accordingly. For example, novobiocin, which is an acidic amorphous solid (amorphous or amorphous solid), is susceptible to transformation into crystals with very low solubility[25]. This makes it difficult to administer novobiocin as a suspension. Spray drying may allow a drug to be made as a highly soluble amorphous solid by spray drying. In this case, a pure drug may be sprayed, and in fact, additives are often added to obtain a homogeneously dispersed drug[26].

The transition, the phenomenon that one crystalline state changes to another state, can occur even in an industrial manufacturing process. For example, crystals of chloroquine diphosphate monohydrate may be changed to be anhydrous when stored at high temperatures. This dehydration reaction also tends to occur when the drug is crushed. Furthermore, if chloroquine diphosphate anhydride is stored in a high humidity state, it may be transferred to other hydrates. In addition, when the bulk powder of a drug is compressed, its crystal form may be changed[27]. In the case of chloramphenicol stearate, it is known that crushing crystal A (form A) in the presence of colloidal silica changes it to crystal B (form B)[28]. As is clear from the above cases, here, emphasis should be placed on the particular importance of standardizing a process during the manufacture of a solid drug and at the same time perform more precise inspection of the crystalline state of the solid drug as part of quality control." (page 452, line 12 from the bottom to page 453, line 20)

(9) Publication 9

The above "Publication 9", which is a publication distributed before the priority date of the application, includes the following descriptions:

(9a) "4.5 Example of crystallization of pharmaceutical products

4.5.1 General crystallization conditions

In the development of pharmaceutical products, crystalline polymorphs are searched under various conditions in the initial stage to select the crystal form that will be the basic form of development in consideration of the results of formulation studies. After that, it is necessary to study scale-up for industrialization and make preparations so that production in the factory can be stably performed. Therefore, it is very important to study the crystalline state, including the presence or absence of

polymorphism in the initial stage of development, in order to efficiently proceed with the development of pharmaceutical products. ... Here, general conditions for crystallizing pharmaceutical products are shown, and a practical example of crystallizing pharmaceutical products is described.

A commonly used crystallization solvent is ... acetone... .

For crystallization, the following method is used.

(1) The sample is added to a solvent on a warmed water bath to form a saturated solution, subjected to hot filtration (here, the word "ろ" in "ろ過し(filtrate)" in Japanese is "さんずい" + "戸" in the original text). Then, after removal of the residual sample, the saturated solution is gradually cooled to around room temperature.

...

(3) To a solution prepared by dissolving the sample in an appropriate solvent, a solvent in which the sample is difficult to dissolve is added.

(4) The solution prepared by dissolving the sample in the appropriate solvent is desolvated using an evaporator or the like.

... " (page 78, line 14 to page 79, line 9).

(10) Publication 10

The above "Publication 10", which is a publication distributed before the priority date of the application, includes the following descriptions:

(10a) "(i) Recrystallization: Distillation and recrystallization are the basic operations for purifying substances. ... In the recrystallization method, a solute is dissolved in a solvent under heating to prepare a saturated solution, and then the solution is cooled to reduce the solubility of the solute to precipitate (crystallize) the saturated solute, whereas the impurities do not reach the saturated solution and stay in the solution as they are. ... The impurities ... can be removed by recrystallization.

(1) Sample purity

The purity of a sample to be recrystallized, especially an organic compound, should first be confirmed by thin layer chromatography. At this time, the relationship between the polarity of a developing agent used and the Rf value on the thin layer is useful for selecting a solvent for recrystallization, and the Rf value shows the approximate polarity of impurities. It is desirable that the substance to be purified has high purity. If the purity is too low, it is generally preferable to remove impurities to some extent by performing any of pretreatments, such as distillation, purification by column chromatography, and decolorization with activated carbon. Of course, the possibility of purification is related to the solubility curve from the principle of

recrystallization. Pure crystals are often obtained even in the presence of many impurities.

(2) Solvent and dissolution

Since there is no fixed rule for selecting a solvent for dissolution and recrystallization, it is basically selected by trial and error. Therefore, it is advisable to check in advance the solubility and crystallinity of the sample in a solvent in a sample tube using a sample of a few mg. If it is a known compound, its data may be referred to in a compound dictionary[1)]. Since there has been an empirical rule that homologues melt well, it is possible to make a good choice by selecting on the basis of this when no data are at hand. That is, what to consider is whether the compound to be purified is hydrogen-bonding or non-hydrogen-bonding, the presence or absence of a polar group or a hydrophobic group, whether it is ionic, or the like. Generally, considering the hydrogen bonding property and the polarity, it will be sufficient to select from the following six kinds of solvents.

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

If a solvent with an intermediate polarity is desired, two different solvents may be mixed, or reference may be made to Table 1.4. At that time, the polarity value (dielectric constant ε, solubility parameter δ, polarity value ET, dipole efficiency d.p.; the larger the numerical value, the greater the polarity), the boiling point, and the melting point may be used as a selection criteria. Reactive solvents and solvents with high boiling points should be avoided if possible. In such a solvent, desorption or substitution may occur during heating of the sample.

... " (page 24, line 6 to page 25, line 9)

2 Regarding the invention described in Publication 1

According to Description (1a), Publication 1 is a document on diaminocarboxamide compounds that treat or prevent liver fibrotic disorders or a condition treatable or preventable by inhibition of a JNK pathway. As an invention disclosed in Publication 1, Description (1b) describes an example in which 2-(tert-butylamino)-4-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-pyrimidine-5-carboxamide was synthesized with a specific manufacturing method and the product was then filtered, washed with water, and dried under vacuum.

Then, Publication 1 can be said to describe

"a vacuum dried product of 2-(tert-butylamino)-4-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-pyrimidine-5-carboxamide"
(hereinafter it is referred to as the "Cited Invention" and the compound thereof is referred to as the "Cited Invention compound").

3 Comparison / Judgment
(1) Comparison

The Invention and the Cited Invention are compared.

The cited Invention compound, "2-(tert-butylamino)-4-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-pyrimidine-5-carboxamide," is a compound having the same chemical structure as "Compound 1" of the Invention, corresponding to "Compound 1 or its tautomer."

It is a vacuum dried product obtained by filtering the product, washing it with water, and drying it under vacuum, and thus can be obtained as a solid.

Then the Invention and the Cited Invention are identical in that
each of them is "Compound 1 or its tautomer solid",
and are different in the following feature.

Different Feature:

In the present invention, Compound 1 is identified as a "Crystal Form B having an X-ray powder diffraction pattern comprising peaks at 2θ values of approximately 9.80, 10.30, 14.62, 17.29, 18.23, 20.66, 21.74, and 30.55°" and a crystal form characterized by an X-ray containing a specific 2θ peak pair. Whereas it is specified to be a crystal form characterized by a powder diffraction pattern, it is not so identified in Cited Invention.

(2) Judgment on the Different Feature

A Examination on making Compound 1 a crystal having an X-ray powder diffraction pattern containing a specific set of 2θ peaks

(A) Well known matters of pharmaceutical compounds at the time of the priority date of this application are as follows: crystalline powder is often obtained by crystallization in the final step of production; crystal polymorphism is a phenomenon often observed in pharmaceutical products; and strict control is essential because the crystalline polymorphs have important effects on the biological efficacy, solubility, stability, and

formulation of pharmaceutical products (Description (2a), Description (3a), Description (3b), Description (4a), Description (7b), and Description (8a)).

In addition, since a crystalline substance is excellent in terms of stability, purity, ease of handling, and the like, there is a strong motivation for crystallizing a substance. Thus, it is recognized that those skilled in the art would examine the conditions under which a pharmaceutical compound can be obtained in crystals. It is also well known that the crystals obtained may differ depending on the crystallization conditions (Descriptions (7a) to (7c) and Description (8a)).

Then, those skilled in the art could recognize sufficient motivation for Compound 1 to study the conditions under which crystals are obtained and to analyze the obtained crystals.

(B) Then, the crystal comprising the above "Crystal Form B having an X-ray powder diffraction pattern comprising peaks at 2θ values at approximately 9.80, 10.30, 14.62, 17.29, 18.23, 20.66, 21.74, and 30.55°" of the Invention is recognized as a crystal described as Form B in the specification of the Invention as described in the following paragraphs [0332] to [0335]:

"[0332]

(Form B)

In certain embodiments, provided herein is Form B.

[0333]

In one embodiment, Form B is a solid form of Compound 1. In another embodiment, Form B is crystalline. In one embodiment, Form B is a solvated form of Compound 1. In one embodiment, Form B is an acetone solvated form of Compound 1. In one embodiment, Form B is an acetone hemi-solvated form of Compound 1.

[0334]

In certain embodiments, Form B provided herein is obtained by equilibration experiments, evaporation experiments, and anti-solvent recrystallization experiments (see Table 1, Table 2 and Table 3). In certain embodiments, Form B is obtained from certain solvent systems including acetone, MEK, DCM, THF, THF/H2O (about 1:1), and IPA with heptane as an anti-solvent.

[0335]

In certain embodiments, a solid form provided herein, e.g., Form B, is substantially crystalline, as indicated by, e.g., X-ray powder diffraction measurements. In one embodiment, Form B has an X-ray powder diffraction pattern substantially as shown in FIG. 10. In one embodiment, Form B has one or more characteristic X-ray powder

diffraction peaks at 2θ values of approximately 9.80, 10.30, 12.23, 14.62, 16.70, 17.29, 18.23, 18.59, 19.61, 20.19, 20.66, 20.94, 21.74, 23.03, 23.84, 24.32, 24.58, 25.88, 26.27, 26.86, 27.52, 28.35, 28.62, 29.63, 30.55, 30.87, 31.44, 32.12, 33.71, 33.95, 34.96, 35.94, 36.14, 36.56, 37.22, and 38.76° as depicted in FIG. 10. In a specific embodiment, Form B has one, two, three, four, five, six, seven, or eight characteristic X-ray powder diffraction peaks at 2θ values of approximately 9.80, 10.30, 14.62, 17.29, 18.23, 20.66, 21.74, and 30.55°. In another embodiment, Form B has one, two, three, or four characteristic X-ray powder diffraction peaks at 2θ values of approximately 9.80, 17.29, 18.23, and 21.74°. In another embodiment, Form B has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, or thirty-six characteristic X-ray powder diffraction peaks as set forth in Table 9." (Underlines are added by the body, the same shall apply hereinafter.)

Then, as a method of preparing Form B of Compound 1 recited in the Invention, various methods are described in the following paragraphs [0489] and [0504] to [0507].

"[0489]

Table 5. Summary of Physical Characterization of Compound 1 Crystalline Forms.

[Table 8]

...

Form	Description	Representative conditions ...
...		
B	Solvate	Recrystallization from slurry or acetone (or DCM, THF)

..."

"[0504]

(Form B)

Form B was obtained from recrystallization or slurry experiments of Form A in acetone, CH2Cl2, or THF. Form B had a crystalline XRPD pattern as shown in FIG. 10. TGA and DSC thermograms of Form B obtained from acetone are shown in FIG. 11 and FIG. 12, respectively. The TGA weight loss of 8.5 wt% corresponded to small broad DSC peak around 147°C and can be attributed to loss of solvent in Form B. The major DSC peak with onset temperature of 223°C corresponded to the melt/decomposition of Form A. The 1H-NMR spectrum was obtained for the Form B sample and showed approximately 0.5 molar equivalents of acetone (see FIG. 13). The theoretical acetone content of a hemi-solvate of Compound 1 is 8.3 wt%, matching

the TGA weight loss observed. These observations suggest that Form B is an acetone hemi-solvate of Compound 1. Form transfer experiment showed that heating Form B above the desolvation temperature resulted in Form A. Slurry of Form B in water also resulted in Form A.

[0505]

A list of X-Ray Diffraction Peaks for Form B is provided below in Table 9.

[0506]

Table 9. X-Ray Diffraction Peaks for Form B

[Table 12]

...

[0507]

FIG. 13 provides a 1H NMR (DMSO-d6) of Form B as follows:"

As a method for making a solid form of Compound 1, various methods are described in the following paragraphs [0312] to [0314].

"[0312]

In certain embodiments, provided herein are methods for making a solid form of Compound 1, comprising 1) dissolving Form A in a solvent to yield a solution; 2) filtering the solution if Form A does not dissolve completely; and 3) evaporating the solution under certain air pressure (e.g., about 1 atm) at a certain temperature (e.g., about 25°C or about 50°C) to yield a solid. ... In certain embodiments, the methods for making a solid form of Compound 1 are evaporation experiments.

[0313]

In certain embodiments, provided herein are methods for making a solid form of Compound 1, comprising 1) obtaining a saturated solution of Form A in a solvent at a first temperature (e.g., about 60°C); 2) stirring the solution at the first temperature for a period of time (e.g., 10 minutes); 3) filtering the solution; 4) cooling the solution slowly to a second temperature (e.g., about −5°C to about 15°C); and 5) isolating solids from the solution and optionally drying. ... In certain embodiments, the methods for making a solid form of Compound 1 are cooling recrystallization experiments.

[0314]

In certain embodiments, provided herein are methods for making a solid form of Compound 1, comprising 1) obtaining a saturated solution of Form A in a solvent at a first temperature (e.g., about 60°C); 2) stirring the solution at the first temperature for a period of time (e.g., 10 minutes); 3) filtering the solution; 4) cooling the solution slowly to a second temperature (e.g., about −5°C to about 15°C); and 5) isolating solids from

the solution and optionally drying. ... In certain embodiments, the methods for making a solid form of Compound 1 are cooling recrystallization experiments."

Here, in Table 5, which is a table summarizing the physical characterization of the crystalline morphology of Compound 1, Form B is described as being recrystallized from acetone as a typical condition. In paragraph [0504], it is also described that Form B is obtained from recrystallization of acetone.

Furthermore, as acetone is one of the most commonly used recrystallization solvents in Descriptions (5a), (9a), and (10a) of Publication 5, the method of preparing Form B (Crystal Form B) of the above Compound 1 is a very common crystallization by recrystallization from a solvent. As the recrystallization method, the well-known methods (Description (9a)), such as evaporation, cooling, and anti-solvent methods, are used as described above.

(C) Therefore, it is recognized that the crystal of Crystal Form B of Compound 1 recited in the Invention is obtained by a recrystallization operation which is usually performed by those skilled in the art in the Cited Invention.

Then, the difference in that a crystal has an X-ray powder diffraction pattern containing a specific set of 2θ peaks merely presents the X-ray diffraction results by a recrystallization operation that could be usually performed by those skilled in the art in the Cited Invention.

According to the above statement, in Cited Invention 1, those skilled in the art could easily conceive of making an attempt to obtain the crystals of Compound 1 and, at this time, considering crystallization conditions and analyzing the obtained crystals to achieve the configuration of the Invention relating to the difference.

(D) Examination on Appellant's allegation

The Appellant submitted the supplemental statement of proceedings (received on October 25, 2018) and alleges in the written opinion dated October 24, 2018, page 2, line 21 to page 3, line 29 that there is no guarantee of discovery of preparing a crystal form and an amorphous form and there is no predictability thereof.

However, as stated above, under the strong motivation to obtain stable crystals from the solid of Compound 1, which is supposed to be used as a medicine of the Invention, it is possible for those skilled in the art to obtain Crystal Form B of the

Invention by a recrystallization operation, which has been usually performed by those skilled in the art, by selecting acetone, which is a very general solvent, and using a well-known recrystallization method.

Therefore, the Appellant's allegation cannot be accepted.

B Examination on the effects of the Invention

(A) Regarding the effects of the Invention, in the Specification of the Invention, paragraph [0002] describes "Provided herein are methods of making and solid forms of 2-(tert-butylamino)-4-((1R,3R,4R)-3-hydroxy-4-methylcyclohexylamino)-pyrimidine-5-carboxamide, compositions thereof, methods of their use for the treatment of a disease, disorder, or condition, and the solid forms for use in such methods." and paragraph [0332] describes "[0332]

(Form B)

In certain embodiments, provided herein is Form B." It is therefore described that Crystal Form B is provided along with other crystal forms.

The stability and solubility of crystals differ from crystal to crystal. It is common general technical knowledge that the crystal form has higher thermal stability than the amorphous form (Description (2a) Description (3a), Description (4a) Description (6a), Descriptions (7a) to (7c), Description (8a), Description (9a)). The physical properties and analytical results of the Invention, along with other crystal forms of Compound 1, mean that the Invention has no remarkable effect that exceeds the prediction of those skilled in the art.

Even in that respect, it cannot be said that Crystal Form B of the Invention, which shows no particularly remarkable property compared to other crystal forms, exerts no remarkable effect.

(B) Examination on Appellant's allegation

In the written opinion dated October 24, 2018, page 3, lines 30 to 39, and the written demand for trial, page 5, line 26 to page 6, line 23, the Appellant alleges that Crystal Forms A to I including Crystal Form B of the Invention have high thermal stability, for example, melting points of 100°C or higher than the glass transition point of the amorphous form, and show a remarkable effect that exceeds the prediction of those skilled in the art, compared with reference examples represented in the supplemental statement of proceedings dated April 4, 2019 (alleges about 34°C or higher in the case of bis(2-ethylhexyl) phthalate).

However, it is natural that the thermal stability differs for each compound and

for each crystal form. Conversely, therefore, even in the case of the reference example, it can be said that the crystal form still has higher thermal stability than the amorphous form.

Then, as stated above, considering that it was common general technical knowledge for those skilled in the art that the crystal form has higher thermal stability than the amorphous form, it cannot be recognized that the Invention has a remarkable effect on the thermal stability compared to the amorphous form.

Therefore, the Appellant's allegation cannot be accepted.

4 Summary

As stated above, the Invention could have been easily made by those skilled in the art based on the invention disclosed in Publication 1 and the common general technical knowledge in any of Publications 2 to 10 at the time of the priority date of the present application, and thus Appellant should not be granted a patent for it under the provisions of Article 29(2) of the Patent Act.

No. 5 Closing

As stated above, the Invention could have been easily made by those who had ordinary skill in the art belonging to the Invention before the priority date based on the invention disclosed in Publication 1 distributed in Japan before the priority date of the present application and the common general technical knowledge at the time of the priority date of the present application, and thus Appellant should not be granted a patent for it under the provisions of Article 29(2) of the Patent Act.

Therefore, the application shall be rejected even without examining the inventions associated with the other claims.

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

February 3, 2020

Chief administrative judge: MURAKAMI, Kimitaka
Administrative judge: SERA, Satoki
Administrative judge: KUSHIBIKI, Satoko