

DESCRIPTION

[Title of Invention]

NOVEL CRYSTALLINE POLYMORPHS OF PYRIDINE DERIVATIVE
5 AND METHOD FOR PRODUCING THE SAME

[Technical Field]

[0001]

The present invention relates to crystals of a novel
pyridine derivative, which are useful as therapeutic or
10 prophylactic agents for gout, hyperuricemia, and the
like, and to a method for producing the crystals.

[Background Art]

[0002]

15 Uric acid is the final product resulting from purine
degradation in the liver. The primary route through
which uric acid in the body is excreted is the kidney,
and about two-thirds of it is excreted in the urine, with
the remainder excreted in the stool. Blood uric acid
20 levels are maintained in healthy individuals, but, when
an excessive production of uric acid or a decreased
excretion of uric acid occurs, this causes hyperuricemia.

[0003]

Hyperuricemia, in which blood uric acid levels
25 become elevated, is a factor that causes gout and urinary
calculus, and furthermore it is said to contribute to
nephropathy and arteriosclerosis. In addition, there
have recently been an increasing number of reports
describing that the higher the blood uric acid level, the
30 higher the incidence rates of lifestyle-related diseases
such as metabolic syndrome and hypertension, chronic
kidney disease, and the like, and hyperuricemia is being
recognized to be a risk factor for these diseases. Thus,
an improvement in hyperuricemia is expected to lead to
35 improvements in various diseases (NPL 1).

[0004]

Recently, the gene (SLC22A12) encoding a human renal

urate transporter has been identified. The transporter (urate transporter 1, URAT1) encoded by this gene is a twelve-span transmembrane molecule belonging to the OAT family. Its mRNA is specifically expressed in the
5 kidney, and further, its localization on the luminal side of the proximal renal tubule has been observed in human kidney tissue sections. URAT1-mediated uric acid uptake has been shown by experiments using the *Xenopus* oocyte expression system. Furthermore, it has been reported
10 that probenecid or benzbromarone, which inhibits URAT1, is useful as a therapeutic or prophylactic agent for hyperuricemia, gout, and the like (NPL 2).

[Citation List]

15 [Non Patent Literature]

[0005]

[NPL 1]

The Guideline Revising Committee of Japanese Society of Gout and Nucleic Acid Metabolism, ed., *Guideline for
20 the management of hyperuricemia and gout*, second edition, Medical Review (2010).

[NPL 2]

Enomoto A. et al., *Nature* 417, 447-452 (2002).

25 [Summary of Invention]

[Technical Problems]

[0006]

It is an object of the present invention to provide crystals of a novel compound, which are useful as
30 therapeutic or prophylactic agents for gout, hyperuricemia, and the like. It is also an object of the present invention to provide a method by which crystals that are chemically stable and suitable as pharmaceutical crude drugs can be produced with high reproducibility.

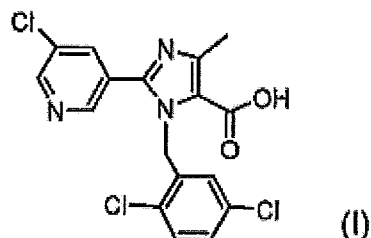
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[Solution to Problem]

[0007]

As a result of diligent studies with the above objects, the present inventors have found that the compound represented by the following formula (I):

[Chem. 1]



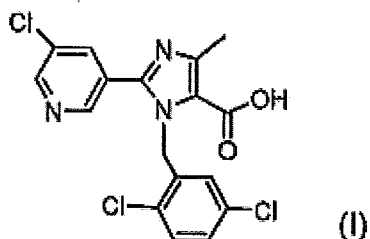
is capable of crystallization and possesses at least two crystalline polymorphs. They have also found that it is possible to selectively produce the crystalline polymorphs according to the crystallization method.

[0008]

That is, the present invention provides the following.

[1] A crystal of 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid represented by the following formula (I).

[Chem. 2]



[2] The crystal according to [1], wherein the crystal has a crystal form A.

[3] The crystal according to [2], wherein the crystal has characteristic peaks at diffraction angles of $2\theta = 13.4^\circ, 15.2^\circ, 20.0^\circ, 20.8^\circ, 24.0^\circ, 26.6^\circ, 30.1^\circ, 30.7^\circ, 31.3^\circ$, and 33.0° in its X-ray powder diffraction spectrum.

[4] The crystal according to [2], wherein its X-ray powder diffraction spectrum has a pattern shown in Figure 1.

[5] The crystal according to [2], wherein the crystal

has characteristic peaks at chemical shifts of 125.8 ppm, 134.8 ppm, 136.7 ppm and 150.1 ppm in its solid-state NMR spectrum (^{13}C).

5 [6] The crystal according to [2], wherein its solid-state NMR spectrum (^{13}C) has a pattern shown in Figure 3.

[7] The crystal according to [2], wherein the crystal has characteristic peaks at wave numbers of 1313 cm^{-1} , 1324 cm^{-1} , and 1391 cm^{-1} in its infrared absorption spectrum (KBr method).

10 [8] The crystal according to [2], wherein its infrared absorption spectrum (KBr method) has a pattern shown in Figure 5.

[9] The crystal according to any one of [2] to [8], wherein its endothermic peak in
15 thermogravimetry/differential thermal analysis is at 234°C .

[10] The crystal according to [1], wherein the crystal has a crystal form B.

20 [11] The crystal according to [10], wherein the crystal has characteristic peaks at diffraction angles of $2\theta = 10.8^{\circ}$, 12.0° , 13.8° , 16.0° , 19.3° , 21.0° , 22.4° , 23.7° , 26.6° , and 31.2° in its X-ray powder diffraction spectrum.

[12] The crystal according to [10], wherein its X-ray powder diffraction spectrum has a pattern shown in Figure
25 2.

[13] The crystal according to [10], wherein the crystal has characteristic peaks at chemical shifts of 16.4 ppm (double peak), 120.5 ppm, and 135.6 ppm in its solid-state NMR spectrum (^{13}C).

30 [14] The crystal according to [10], wherein its solid-state NMR spectrum (^{13}C) has a pattern shown in Figure 4.

[15] The crystal according to [10], wherein the crystal has characteristic peaks at wave numbers of 1329 cm^{-1} , 1382 cm^{-1} , and 1401 cm^{-1} in its infrared absorption
35 spectrum (KBr method).

[16] The crystal according to [10], wherein its infrared

absorption spectrum (KBr method) has a pattern shown in Figure 6.

[17] The crystal according to any one of [10] to [16], wherein its endothermic peak in

5 thermogravimetry/differential thermal analysis is at 236°C.

[18] A method for producing the crystal of 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid, comprising the steps of:

10 suspending an alkyl ester of 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid in a solvent and performing hydrolysis by adding an aqueous solution of a base thereto; and neutralizing the reaction product.

15 [19] The method for producing the crystal according to [18], further comprising the step of stirring the neutralized product while cooling.

[20] The method for producing the crystal according to [18] or [19], wherein the solvent is a single organic solvent selected from methanol, ethanol, 2-propanol, 1-butanol, and tetrahydrofuran, or a mixture solvent of the organic solvent and water, or a mixture of two or more organic solvents selected from methanol, ethanol, 2-propanol, and 1-butanol, or a mixture solvent of the mixture of the organic solvents and water.

25 [21] The method for producing the crystal according to [20], wherein the solvent is a single organic solvent selected from methanol, ethanol, 2-propanol, and 1-butanol, or a mixture solvent of the single organic solvent and water.

30 [22] The method for producing the crystal according to [21], wherein the solvent is ethanol.

[23] The method for producing the crystal according to [18] or [19], wherein the solvent is a mixture solvent of tetrahydrofuran and ethanol.

35 [24] A pharmaceutical composition comprising the crystal according to any one of [1] to [17] and a

pharmaceutically acceptable carrier.

[25] A URAT1 inhibitor comprising the crystal according to any one of [1] to [17] as an active ingredient.

5 [26] A therapeutic or prophylactic agent for one or more diseases selected from the group consisting of gout, hyperuricemia, hypertension, renal disease, diabetes, arteriosclerosis, and Lesch-Nyhan syndrome, comprising the crystal according to any one of [1] to [17] as an active ingredient.

10

[Advantageous Effects of Invention]

[0009]

15 The present invention provides crystals of a novel pyridine derivative, which are useful as therapeutic or prophylactic agents for gout, hyperuricemia, and the like, and a method for producing the crystals. These crystals can be used as crude drugs for producing medicaments.

20

[Brief Description of Drawings]

[0010]

[Figure 1] Figure 1 is a X-ray powder diffraction spectrum of crystal form A.

25

[Figure 2] Figure 2 is a X-ray powder diffraction spectrum of crystal form B.

[Figure 3] Figure 3 is a solid-state NMR spectrum of crystal form A.

[Figure 4] Figure 4 is a solid-state NMR spectrum of crystal form B.

30

[Figure 5] Figure 5 is an infrared absorption spectrum of crystal form A.

[Figure 6] Figure 6 is an infrared absorption spectrum of crystal form B.

[Description of Embodiments]

35

[0011]

The crystals of the present invention are characterized by X-ray powder diffraction spectra, solid-

state NMR spectra, infrared absorption spectra, and/or thermogravimetry/differential thermal analysis (TG/DTA) and the like. The X-ray powder diffraction (XRD) spectra, solid-state NMR spectra, and infrared absorption spectra of these crystals exhibit characteristic patterns, and each crystal has specific diffraction angle 2θ values. In addition, each of these crystals also exhibits its own characteristic thermal behavior in thermogravimetry/differential thermal analysis (TG/DTA).

10 **[0012]**

The crystal form A of the present invention has characteristic peaks at diffraction angles of $2\theta = 13.4^\circ$, 15.2° , 20.0° , 20.8° , 24.0° , 26.6° , 30.1° , 30.7° , 31.3° , and 33.0° in its X-ray powder diffraction spectrum. In addition, the crystal form A of the present invention has a pattern shown in Figure 1 in its X-ray powder diffraction spectrum.

The crystal form A of the present invention has peaks at chemical shifts of 125.8 ppm, 134.8 ppm, 136.7 ppm and 150.1 in its ^{13}C solid-state NMR spectrum. In addition, the crystal form A of the present invention has a pattern shown in Figure 3 in its ^{13}C solid-state NMR spectrum.

The crystal form A of the present invention has absorption peaks at wave numbers of 1313 cm^{-1} , 1324 cm^{-1} , and 1391 cm^{-1} in its infrared absorption spectrum (KBr method). In addition, the crystal form A of the present invention has a pattern shown in Figure 5 in its infrared absorption spectrum (KBr method).

30 The crystal form A of the present invention has an endothermic peak at 234°C in the thermogravimetry/differential thermal analysis (TG/DTA). The crystal form A is an anhydrous crystal.

[0013]

35 The crystal form B of the present invention has characteristic peaks at diffraction angles of $2\theta = 10.8^\circ$,

12.0°, 13.8°, 16.0°, 19.3°, 21.0°, 22.4°, 23.7°, 26.6°, and 31.2° in its X-ray powder diffraction spectrum. In addition, the crystal form B of the present invention has a pattern shown in Figure 2 in its X-ray powder
5 diffraction spectrum.

The crystal form B of the present invention has peaks at chemical shifts of 16.4 ppm (double peak), 120.5 ppm, and 135.6 in its ¹³C solid-state NMR spectrum. In addition, the crystal form B of the present invention has a pattern shown in Figure 4 in its ¹³C solid-state NMR
10 spectrum.

The crystal form B of the present invention has absorption peaks at wave numbers of 1329 cm⁻¹, 1382 cm⁻¹, and 1401 cm⁻¹ in its infrared absorption spectrum (KBr method). In addition, the crystal form B of the present invention has a pattern shown in Figure 6 in its infrared
15 absorption spectrum (KBr method).

The crystal B of the present invention has an endothermic peak at 236°C in thermogravimetry/differential thermal analysis (TG/DTA). The crystal form B is an anhydrous crystal.
20

[0014]

As used herein, "characteristic peaks" mean peaks which are mainly observed in the X-ray powder diffraction spectrum, ¹³C solid-state NMR spectrum, and infrared
25 absorption spectrum (KBr method) of each crystal polymorph, as well as unique peaks. The crystals of the present invention identified by the peaks of these spectra also include peaks other than those observed as the characteristic peaks described above.
30

[0015]

The position and the relative intensity of diffraction angle 2θ in X-ray powder diffraction spectrum may vary somewhat depending on the measurement
35 conditions, and therefore, in the case where 2θ is slightly different, the identity of a crystal form should

be recognized by appropriately referring to the pattern of the entire spectrum. Crystals within the range of such errors are also included in the present invention. The errors in 2θ are, for example, in the range of $\pm 0.5^\circ$,
5 and typically in the range of $\pm 0.2^\circ$. In other words, the crystals identified by the above diffraction angles also include those with diffraction angles which coincide in the range of $\pm 0.5^\circ$ or $\pm 0.2^\circ$.

Generally, errors can arise also in chemical shifts in ^{13}C solid-state NMR spectra. Such errors are in the
10 range, for example, of ± 0.5 ppm, typically ± 0.25 ppm. In other words, the crystals identified by the above chemical shifts also include those with chemical shifts which coincide in the range of ± 0.25 ppm or ± 0.5 ppm.

15 Generally, errors can arise also in absorption peaks in infrared absorption spectrum (KBr method). Such errors are in the range, for example, of $\pm 5\text{ cm}^{-1}$, typically $\pm 2\text{ cm}^{-1}$. In other words, the crystals identified by the above wave numbers also include those
20 with wave numbers which coincide in the range of $\pm 2\text{ cm}^{-1}$ or $\pm 5\text{ cm}^{-1}$.

[0016]

Errors in endothermic peaks in the thermogravimetry/differential thermal analysis (TG/DTA)
25 are, for example, in the range of $\pm 5^\circ\text{C}$, typically in the range of $\pm 2^\circ\text{C}$. In other words, the crystals identified by the above endothermic peaks also include those with endothermic peaks which coincide in the range of $\pm 5^\circ$ or $\pm 2^\circ$.

30 **[0017]**

A crystal of 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid can be produced by a method comprising the steps of:
suspending an alkyl ester of 2-(5-chloropyridin-3-yl)-1-
35 (2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic

acid in a solvent and performing hydrolysis by adding an aqueous solution of a base thereto ; and neutralizing the reaction product.

5 In addition, the method for producing a crystal of the present invention can further comprise the step of stirring the neutralized product while cooling.

[0018]

10 The crystals of the present invention are obtained by suspending an alkyl ester of 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid in a reaction-inert solvent, including one or more organic solvents selected from methanol, ethanol, 2-propanol, 1-butanol, and tetrahydrofuran, or a mixture solvent of the organic solvent(s) and water, and adding
15 an aqueous solution of a base thereto. The solvent for use in the production of crystal form A includes a single organic solvent selected from methanol, ethanol, 2-propanol, 1-butanol, and tetrahydrofuran, or a mixture solvent of the organic solvent and water, or a mixture of
20 two or more organic solvents selected from methanol, ethanol, 2-propanol, and 1-butanol, or a mixture solvent of the mixture of the organic solvents and water. Preferably, the solvent is a single organic solvent selected from methanol, ethanol, 2-propanol, and 1-
25 butanol, or a mixture solvent of the single organic solvent and water, and more preferably, it is ethanol. When two or more solvents are mixed, the mixing ratio can be appropriately adjusted by a person skilled in the art.

[0019]

30 The solvent for use in the production of crystal form B includes a mixture solvent of tetrahydrofuran and ethanol. The mixing ratio of tetrahydrofuran and ethanol can be appropriately adjusted by a person skilled in the art, but 1:1 is preferred.

35 **[0020]**

As the alkyl ester of 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic

acid, C1-C6 alkyl esters are preferred, and ethyl ester is more preferred. As used herein, alkyl esters refer to straight-chain or branched-chain saturated aliphatic hydrocarbon esters. Specific examples of the C1-C6 alkyl esters can include methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, isopentyl ester, hexyl ester, and the like.

[0021]

The hydrolysis reaction of the alkyl ester of 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid to 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid proceeds by suspending the alkyl ester of 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid in the above solvent, and by adding a base in an amount equivalent to or a slight excess of the alkyl ester of 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid to the suspension. Preferred bases can include sodium hydroxide, potassium hydroxide, or lithium hydroxide. This reaction proceeds at 0°C to 100°C, but it is preferably carried out at room temperature to 60°C.

[0022]

After the hydrolysis reaction, neutralization is carried out by reacting the base used with an equivalent or a slight excess of an acid. Preferred acids include hydrochloric acid. The neutralization reaction proceeds at 0°C to 100°C, but it is preferably carried out at 0°C to 60°C.

[0023]

Then, the neutralized reaction product is stirred while cooling, after which precipitates are collected by filtration and dried to give crystals. Although the stirring conditions and the time that elapses before filtering off the precipitates are not particularly

limited, it is preferred that they are set by combining them variously depending on the purpose, since those conditions may affect the yield, chemical purity, particle diameter, particle size distribution of the crystals and the like. For the collection by filtration, a common method, for example, natural filtration, pressure filtration, vacuum filtration, or centrifugation, can be used. For the drying, a common method, for example, natural drying, vacuum drying, heat drying, or vacuum heat drying, can be used.

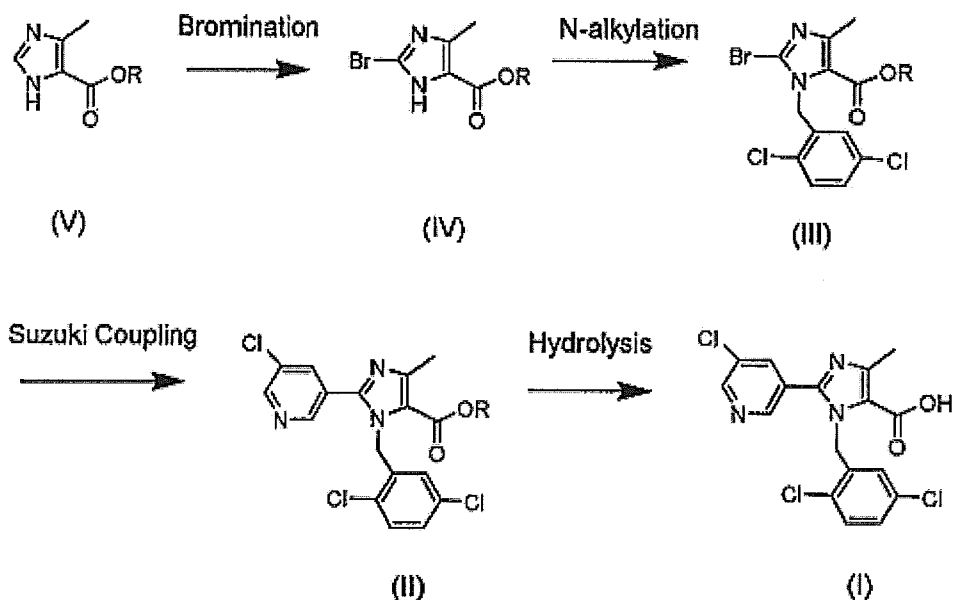
[0024]

Synthesis of an alkyl ester of 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid can be performed as shown in Scheme A below, although the synthesis may be performed by any other methods. That is, after the imidazole derivative (V) is brominated to give the compound (IV), N-alkylation is carried out by a reaction using a base and a halide compound, or by a Mitsunobu reaction using an alcohol, to give the compound (III). The alkyl ester (II) of 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid is obtained by a Suzuki coupling reaction of the compound (III) and a boronate derivative. 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid (I) can be obtained by hydrolyzing the ester group of the compound (II).

[0025]

[Chem. 3]

Scheme A



[0026]

5 (In the scheme, R is an alkyl group). Suitable reagents for the bromination of the compound (V) to (IV) in Scheme A include bromine, N-bromosuccinimide (NBS), etc. Solvents in this reaction include, but are not particularly limited to, for example, ethers such as tetrahydrofuran (THF), 1,4-dioxane, 1,2-dimethoxyethane, or 1,2-diethoxyethane, halogenated solvents such as dichloromethane or carbon tetrachloride, acetonitrile, mixed solvents thereof, or the like. This reaction proceeds at 0°C to 100°C, but it is preferably carried out at room temperature to 50°C.

[0027]

20 The N-alkylation of the compound (IV) to the compound (III) proceeds in a reaction using a base and a halide compound, or by a Mitsunobu reaction using an alcohol. When a base and a halide compound are used, the base includes potassium carbonate, cesium carbonate, triethylamine, diisopropylethylamine, sodium hydride, etc., among which the preferred base is potassium

carbonate, cesium carbonate, triethylamine, or diisopropylethylamine. The halide compound includes chloride, bromide, or iodide, among which the preferred halide compound is a chloride or bromide. The
5 temperature for the reaction in the presence of a base and a halide compound is preferably from room temperature to 150°C, and more preferably from 50°C to 120°C. Solvents in this reaction include, but are not particularly limited to, for example, ethers such as
10 tetrahydrofuran (THF), 1,4-dioxane, 1,2-dimethoxyethane, or 1,2-diethoxyethane, amides such as dimethylformamide or N-methylpyrrolidone, dimethyl sulfoxide (DMSO), toluene, xylene, mixed solvents thereof, or the like. The N-alkylation of the compound (IV) to the compound
15 (III) also proceeds by a Mitsunobu reaction using an alcohol. As for conditions for the Mitsunobu reaction, a phosphine compound, a condensation agent, an alcohol, and the compound (IV) are reacted in an inert solvent to give the compound (III). The phosphine includes
20 tributylphosphine, triphenylphosphine, tricyclohexylphosphine, etc., but preferably triphenylphosphine. A preferred condensation agent is diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD). The reaction temperature for
25 this Mitsunobu reaction may be anywhere from 0°C to 100°C, but the preferred reaction temperature is from room temperature to 80°C. The solvent in the Mitsunobu reaction includes, but is not particularly limited to, for example, ethers such as tetrahydrofuran (THF), 1,4-dioxane, 1,2-dimethoxyethane, or 1,2-diethoxyethane,
30 amides such as dimethylformamide or N-methylpyrrolidone, halogenated solvents such as dichloromethane, toluene, xylene, mixed solvents thereof, or the like.

[0028]

35 The Suzuki coupling reaction of the compound (III) to the compound (II) proceeds by heating the compound

(III), a boronate derivative, a palladium catalyst, and a base in a reaction-inert solvent. Preferably, this reaction is carried out under an inert gas atmosphere. Preferred examples of the boronate derivative include boronic acid and boronic acid pinacol ester. As the palladium catalyst, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) ($\text{PdCl}_2(\text{dppf})$), tetrakis(triphenylphosphine)palladium ($\text{Pd}(\text{PPh}_3)_4$), or the like is preferably used. As the base, potassium carbonate, cesium carbonate, or potassium phosphate is mentioned as being preferred. Although the solvent in this reaction is not particularly limited, it is preferable to use, for example, ethers such as tetrahydrofuran (THF), 1,4-dioxane, 1,2-dimethoxyethane, or 1,2-diethoxyethane, amides such as dimethylformamide or N-methylpyrrolidone, alcohols such as ethanol, 2-propanol, or butanol, toluene, xylene, water, or mixed solvents thereof. This reaction proceeds at 50°C to 150°C, but it is preferably carried out at 80°C to 120°C.

[0029]

The crystals of the present invention can also be obtained by suspending the 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid obtained by the above reaction in a suitable solvent and stirring the suspension. Such a solvent includes methanol, ethanol, 2-propanol, 1-butanol, acetone, methyl ethyl ketone, methyl isobutyl ketone, acetic acid, t-butyl methyl ether, tetrahydrofuran, ethyl acetate, dimethyl sulfoxide, dichloromethane, N,N-dimethylformamide, acetonitrile, toluene, anisole, and water. Although each of the crystal forms of the present invention is distinguishable from the other crystal form by its characteristic X-ray powder diffraction spectrum or thermogravimetry/differential thermal analysis (TG/DTA), this does not refer to a contamination rate of the other crystal form. When a particular crystal form is to be obtained exclusively, at least, such a degree of

contamination that cannot be detected by these measurement methods is accepted. In addition, it is also not intended to mean that, when each particular crystal form is used as a crude drug to be formulated as a medicament, inclusion of the other crystal form is not accepted.

[0030]

Each of the crystal forms of the present invention can be used as an active ingredient of a medicament. Further, they can be used not only as a single crystal form, but also as a mixture of two or more crystal forms.

In the present invention, obtaining 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid as a crystal provides advantages in terms of handling during production, reproducibility, stability, storage stability, and the like, compared to the compound which is not crystalline.

A pharmaceutical composition can be made using a crystal of the present invention and a pharmaceutically acceptable carrier.

[0031]

A pharmaceutical preparation containing a crystal of the present invention is prepared with additives commonly used to formulate pharmaceutical preparations. Those additives include, in the case of a solid pharmaceutical preparation, an excipient such as lactose, sucrose, glucose, cornstarch, potato starch, crystalline cellulose, light anhydrous silicic acid, synthetic aluminum silicate, magnesium aluminometasilicate, and calcium hydrogenphosphate; a binder such as crystalline cellulose, carboxymethyl cellulose, hydroxypropylcellulose, sodium carboxymethylcellulose, and polyvinylpyrrolidone; a disintegrant such as starch, sodium carboxymethylcellulose, calcium carboxymethylcellulose, croscarmellose sodium, and sodium carboxymethyl starch; a lubricant such as talc and stearates; a coating agent such as

hydroxymethylpropylcellulose,
hydroxypropylmethylcellulose phthalate, and
ethylcellulose; a coloring agent; in the case of a
semisolid pharmaceutical preparation, a substrate such as
5 white petrolatum; in the case of liquid pharmaceutical
preparation, a solvent such as ethanol; a solubilizing
agent such as ethanol; a preservative such as
paraoxybenzoate; an isotonization agent such as glucose;
a buffering agent such as citrates; an antioxidant such
10 as L-ascorbic acid; a chelating agent such as EDTA; and a
suspending agent/an emulsifier such as polysorbate 80;
and the like.

[0032]

The crystals of the present invention can be used in
15 any dosage form such as solid pharmaceutical preparation,
semi-solid pharmaceutical preparation, and liquid
pharmaceutical preparation, and in any pharmaceutical
preparation for application including oral and parenteral
preparations (injections, transdermal preparations,
20 ophthalmic solutions, suppositories, nasal preparations,
inhalants, and the like).

[0033]

A pharmaceutical composition containing a crystal of
the present invention as an active ingredient can be used
25 as a URAT1 inhibitor, or a therapeutic or prophylactic
agent for URAT1-associated diseases, such as gout,
hyperuricemia, hypertension, renal disease (such as
interstitial nephritis), diabetes, arteriosclerosis, or
Lesch-Nyhan syndrome. Here, "preventing" refers to
30 obviating contraction or development of a disease in an
individual who has not yet contracted or developed it,
and "treating" refers to curing, suppressing, or
ameliorating a disease or symptom in an individual who
has already contracted or developed it.

35

[Examples]

[0034]

[Measurement Method]

The X-ray powder diffraction of the crystals of the present invention was measured under the following conditions.

5 Apparatus: D8 DISCOVER With GADDS produced by Bruker AXS
CS source: Cu-K α , Wave length: 1.541838 (10^{-10} m), 40 kV-
40 mA,
Incident-side flat-plate graphite monochromator,
Collimator ϕ 300 μ m, Two-dimensional PSPC detector,
10 Scanning 3 to 40°

[Measurement Method]

The solid-state NMR spectra of the crystals of the present invention were measured under the following conditions.

15 Apparatus: DSX300WB produced by Bruker
Measurement temperature: room temperature
Measured nucleus: ^{13}C
Pulse repetition time: 5 seconds
Pulse mode: CP/MAS measurement

20 [Measurement Method]

The infrared absorption spectra of the crystals of the present invention were measured according to the potassium bromide disk method, which is an infrared spectrum measurement method described in general test
25 methods of the Japanese Pharmacopoeia, under the following conditions.

Apparatus: AVATAR320 produced by Thermo Fisher Scientific.
Measurement range: 4000 to 400 cm^{-1}
30 Resolution: 4 cm^{-1}
Integration: 64 times

[0035]

The thermogravimetry/differential thermal analysis (TG/DTA) of the crystals of the present invention was
35 measured under the following conditions.

Apparatus: TG8120 produced by Rigaku

Heating rate: 10°C/minute, Atmosphere: nitrogen, Sample pan: aluminum, Reference: alumina, Sampling: 1.0 second, Measured temperature range: 20 to 300°C

[0036]

5 [Example 1]

Production of crystal form A of 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid

10 Ethyl 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylate (5.0 g, 11.7 mmol) was suspended in ethanol (32.5 mL), and 2 M aqueous sodium hydroxide solution (11.7 mL, 23.5 mmol) was added thereto. Then, the suspension was stirred at 60°C for one hour and dissolution was confirmed. After
15 the reaction, the reaction product was passed through a filter and washed with water (5.0 mL), followed by neutralization by adding 2 M hydrochloric acid (11.7 mL, 4.4 mmol) over 1 hour or more at 60°C. After crystals were precipitated, stirring was carried out at 60°C for 30
20 minutes, at room temperature for 30 minutes, and at 0°C for 30 minutes, after which the crystals were collected by filtration. The resultant crystals were washed with a mixture solvent of water (90 mL) and ethanol (10 mL) and vacuum dried overnight at 50°C to give crystals of 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid. The XRD of the resultant
25 crystals is shown in Figure 1. Peaks were observed at diffraction angles of $2\theta = 13.4^\circ, 15.2^\circ, 20.0^\circ, 20.8^\circ, 24.0^\circ, 26.6^\circ, 30.1^\circ, 30.7^\circ, 31.3^\circ, \text{ and } 33.0^\circ$. The solid-state NMR spectrum of the resultant crystals is shown in
30 Figure 3 and the infrared absorption spectrum in Figure 5. In addition, the endothermic peak in thermogravimetry/differential thermal analysis (TG/DTA) was observed at 234°C.

35 $^1\text{H-NMR (DMSO-d}_6\text{)}\delta$: 13.13 (1H, s), 8.70 (1H, brs), 8.55 (1H, brs),

8.02 (1H, brs), 7.50 (1H, d, J=8.0Hz),
7.38 (1H, dd, J=8.4, 2.4Hz), 6.60 (1H, brs), 5.60 (2H, s),
2.49 (3H, s).

[0037]

5 [Example 2]

Production of crystal form B of 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid

10 Ethyl 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylate (1.0 g, 2.35 mmol) was suspended in a mixture solvent of tetrahydrofuran (6.5 mL) and ethanol (6.5 mL), and 2 M aqueous sodium hydroxide solution (2.35 mL, 4.7 mmol) was added thereto. Then, the suspension was stirred at 50°C
15 for one hour and dissolution was confirmed. After the reaction, the reaction product was passed through a filter and washed with water (10 mL), followed by cooling to room temperature and neutralization by adding 2 M hydrochloric acid (2.35 mL, 4.7 mmol). After crystals
20 were precipitated, the mixture was cooled to 0°C and stirred for 30 minutes, after which the crystals were collected by filtration. The resultant crystals were washed with a mixture solvent of water (4.5 mL) and ethanol (0.5 mL) and vacuum dried overnight at 45°C to
25 give crystals of 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid (917 mg). The XRD of the resultant crystals is shown in Figure 2. Peaks were observed at diffraction angles of 2θ = 10.8°, 12.0°, 13.8°, 16.0°, 19.3°, 21.0°, 22.4°, 23.7°,
30 26.6°, and 31.2°. The solid-state NMR spectrum of the resultant crystals is shown in Figure 4 and the infrared absorption spectrum in Figure 6. In addition, the endothermic peak in thermogravimetry/differential thermal analysis (TG/DTA) was observed at 236°C.
35 ¹H-NMR (DMSO-d₆) δ: 13.13 (1H, s), 8.70 (1H, brs), 8.55 (1H, brs), 8.02 (1H, brs), 7.50 (1H, d, J=8.0Hz),

7.38 (1H, dd, J=8.4, 2.4 Hz), 6.60 (1H, brs), 5.61 (2H, s),
2.49 (3H, s).

[0038]

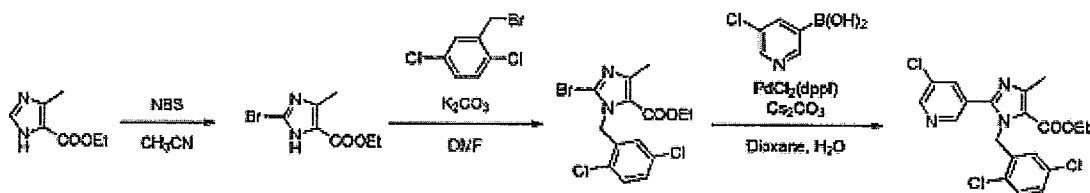
[Reference Example 1]

5 Production of ethyl 2-(5-chloropyridin-3-yl)-1-(2,5-
dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylate

Ethyl 2-(5-chloropyridin-3-yl)-1-(2,5-
dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylate used
in Examples 1 and 2 was produced according to the
10 following method.

[0039]

[Chem. 4]



[0040]

15 (1) Ethyl 4-methyl-1H-imidazole-5-carboxylate (7.5 g,
48.7 mmol) was dissolved in acetonitrile (120 mL), N-
bromosuccinimide (10.4 g, 58.4 mmol) was added thereto,
and the mixture was stirred at room temperature for 3
hours. After the reaction, saturated aqueous sodium
20 hydrogen carbonate was added and the mixture was
extracted twice with ethyl acetate. After washing the
organic layer with saturated aqueous sodium chloride, it
was dried over anhydrous sodium sulfate. After
concentrating the organic layer, the residue was purified
25 by column chromatography to obtain ethyl 2-bromo-4-
methyl-1H-imidazole-5-carboxylate (3.6 g):

$^1\text{H-NMR}$ (CDCl_3) δ : 4.35 (2H, q, J=7.1 Hz), 2.51 (3H, s),
1.37 (3H, t, J=7.1 Hz).

[0041]

30 (2) Ethyl 2-bromo-4-methyl-1H-imidazole-5-carboxylate
(2.75 g, 11.81 mmol) described in (1) was dissolved in
DMF (20 mL), potassium carbonate (3.26 g, 23.62 mmol) and
2,5-dichlorobenzyl bromide (3.4 g, 14.17 mmol) were added

thereto, and the mixture was stirred at 90°C for 3 hours. After the reaction, water was added and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and subsequently dried over sodium sulfate. After concentrating the organic layer, the residue was purified by column chromatography to obtain ethyl 2-bromo-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylate (1.72 g):

¹H-NMR (CDCl₃) δ: 7.34 (1H, d, J=8.8Hz), 7.20 (1H, dd, J=8.8, 2.4Hz), 6.40 (1H, d, J=2.4Hz), 5.60 (2H, s), 4.25 (2H, q, J=7.2Hz), 2.56 (3H, s), 1.27 (3H, t, J=7.1Hz).

[0042]

(3) Ethyl 2-bromo-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylate (100 mg, 0.26 mmol), 5-chloropyridin-3-ylboronic acid (30 mg, 0.51 mmol), PdCl₂(dppf) (28 mg, 0.038 mmol), and cesium carbonate (166 mg, 0.51 mmol) were dissolved in a mixed solvent of 1,4-dioxane (0.71 mL) and water (0.14 mL), and the resultant solution was stirred at 95°C over night under a nitrogen atmosphere. After the reaction, water was added and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and subsequently dried over sodium sulfate. After concentrating the organic layer, the residue was purified by column chromatography to obtain ethyl 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylate (35 mg):

¹H-NMR (CDCl₃) δ: 8.62 (1H, d, J=2.0Hz), 8.46 (1H, d, J=2.0), 7.89 (1H, t, J=2.4Hz), 7.37 (1H, d, J=8.4Hz), 7.25 (1H, dd, J=9.2, 2.6Hz), 6.65 (1H, d, J=2.0), 5.55 (2H, s), 4.27 (2H, q, J=6.8Hz), 2.64 (3H, s), 1.28 (3H, t, J=6.8Hz).

[0043]

[Reference Example 2]

Production of 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid

Ethyl 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylate (35 mg, 0.0824 mmol) was dissolved in a mixture solvent of tetrahydrofuran (1 mL) and ethanol (0.5 mL), and 2 M aqueous sodium hydroxide solution (0.2 mL, 0.4 mmol) was added thereto. Then, the resultant solution was stirred at 50°C for three hours. After the reaction, 2 M hydrochloric acid (0.2 mL, 0.4 mmol) was added for neutralization, and the neutralized product was concentrated. The residue was purified by conventional methods to give 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid (22 mg).

¹H-NMR (DMSO-d₆) δ: 8.71 (1H, d, J=2.4 Hz), 8.56 (1H, d, J=2.0 Hz), 8.02 (1H, t, J=2.0 Hz), 7.50 (1H, d, J=8.3 Hz), 7.38 (1H, dd, J=8.8, 2.4 Hz), 6.62 (1H, d, J=2.4 Hz), 5.61 (2H, s), 2.50 (3H, s).

[0044]

[Reference Example 3]

Test for inhibition of uric acid transport using human URAT1-expressing cells

2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid was dissolved in DMSO (produced by Sigma) to a concentration of 20 mM and the concentration was subsequently adjusted to a value desired for use. Full-length cDNA of human URAT1 (hURAT1) (produced by OriGene Technologies, Inc., NCBI Reference Sequence: NM 144585) was subcloned into an expression vector, pCMV6-Kan/Neo (produced by OriGene Technologies, Inc.), and hURAT1 gene was transfected into human embryonic kidney-derived cells (HEK 293 cells) by liposome method using Lipofectamine 2000 (produced by Invitrogen Corporation), whereupon HEK 293 cells expressing human URAT1 gene were selected on the basis of Geneticin resistance. By a method similar to the following method, functional expression of human URAT1 gene was confirmed by using transport of ¹⁴C -labeled uric

acid into the cells as an index.

The HEK 293 cells expressing human URAT1 were seeded in a 24-well cell culture dish to a density of 3×10^5 cells/mL/well and were cultured in Dulbecco's modified Eagle's medium (D-MEM medium) containing 10% fetal bovine serum at 37°C for 2 days. Thereafter, the following test for inhibition of uric acid transport was performed.

[0045]

After the medium was removed by aspiration from each well, the medium was replaced with a solution obtained by substituting NaCl in Hank's Balanced Salt Solution (HBSS) with Na gluconate (hereinafter, HBSS/Na-gluconate) and the cells were preincubated at 37°C for about 10 minutes. HBSS/Na-gluconate was removed by aspiration and a ^{14}C -uric acid solution that was warmed at 37°C in advance containing various concentrations of the compound and a radioactive ligand (^{14}C -labeled uric acid; final concentration 25 μM) was added and an uptake reaction was carried out by incubating at 37°C for 5 min. After the reaction, ^{14}C -labeled uric acid solution was removed by aspiration and the cells were washed three times with ice-cold HBSS. The HEK 293 cells expressing human URAT1 were lysed in 0.2 mol/L aqueous NaOH (hereafter, the cell sample) and sampled from the well. The cell sample and a liquid scintillation liquid, ULTIMA GOLD (produced by PerkinElmer, Inc.) were mixed and the radioactivity was measured by a liquid scintillation counter (Beckman Coulter, Inc.).

The uric acid transport rate of the Example compound at each concentration (% of control uptake) was calculated relative to the radioactivity (radioactivity in human URAT1 expressing HEK 293 cells without addition of the compound (DMSO addition)) showing URAT1-specific uric acid transport as 100%, and the concentration (IC_{50}) of the compound at which the uric acid transport rate is inhibited by 50% was determined. IC_{50} was found to be 0.2

μM or less.

[0046]

[Reference Example 4]

Drug efficacy evaluation test for Cebus apella

5 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid (3 mg/kg to 30 mg/kg) dispersed in a 0.5% methylcellulose solution was administered to Cebus apella from the nasal cavity to the stomach using a disposable catheter and a syringe barrel.

10 Blood samples were taken before administration and 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, and 24 hours after administration; and urine samples were collected for the time intervals of immediately after to 4 hours after administration, from 4 hours to 8 hours

15 after administration, from 8 hours to 16 hours after administration, and from 16 hours to 24 hours after administration. Concentrations of uric acid and creatinine in the blood and urine samples collected were measured by an automatic analyzer (JEOL Ltd.). Uric acid

20 and creatine were measured using L-type Wako UA·F (Wako Pure Chemicals Industries, Ltd.) and L-type Creatine F (Wako Pure Chemicals Industries, Ltd.), respectively. Uric acid clearance was calculated from the uric acid concentrations in blood and urine and, similarly,

25 creatinine clearance was calculated from the creatinine concentrations. From these values, the uric acid excretion rate was determined according to the following equation:

Uric acid excretion rate (%) = (uric acid
30 clearance/creatinine clearance) × 100

In the present test, excellent activity to promote uric acid excretion was confirmed for 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid.

35

[Industrial Applicability]

[0047]

The crystals of 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid of the present invention are used as medicaments.

Furthermore, these crystals can be used as a crude drug
5 for producing medicaments.

CLAIMS

[Claim 1]

A crystal of 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid.

[Claim 2]

The crystal according to claim 1, wherein the crystal is form A crystal having characteristic peaks at diffraction angles of $2\theta = 13.4^\circ, 15.2^\circ, 20.0^\circ, 20.8^\circ, 24.0^\circ, 26.6^\circ, 30.1^\circ, 30.7^\circ, 31.3^\circ, \text{ and } 33.0^\circ$ in its X-ray powder diffraction spectrum.

[Claim 3]

The crystal according to claim 1, wherein the crystal is form A crystal having an X-ray powder diffraction spectrum pattern shown in Figure 1.

[Claim 4]

The crystal according to claim 1, wherein the crystal is form A crystal having characteristic peaks at chemical shifts of 125.8 ppm, 134.8 ppm, 136.7 ppm and 150.1 ppm in its solid-state ^{13}C -NMR spectrum.

[Claim 5]

The crystal according to claim 1, wherein the crystal is form A crystal having a solid-state ^{13}C -NMR spectrum pattern shown in Figure 3.

[Claim 6]

The crystal according to claim 1, wherein the crystal is form A crystal having a characteristic peaks at wave numbers of $1313\text{ cm}^{-1}, 1324\text{ cm}^{-1}, \text{ and } 1391\text{ cm}^{-1}$ in its infrared absorption spectrum according to the potassium bromide disk method.

[Claim 7]

The crystal according to claim 1, wherein the crystal is form A crystal having an infrared absorption spectrum pattern shown in Figure 5 according to the potassium bromide disk method.

[Claim 8]

The crystal according to any one of claims 2 to 7, wherein its endothermic peak in thermogravimetry/differential

thermal analysis is at 234°C.

[Claim 9]

The crystal according to claim 1, wherein the crystal is form B crystal having characteristic peaks at diffraction angles of $2\theta = 10.8^\circ, 12.0^\circ, 13.8^\circ, 16.0^\circ, 19.3^\circ, 21.0^\circ, 22.4^\circ, 23.7^\circ, 26.6^\circ$, and 31.2° in its X-ray powder diffraction spectrum.

[Claim 10]

The crystal according to claim 1, wherein the crystal is form B crystal having an X-ray powder diffraction spectrum shown in Figure 2.

[Claim 11]

The crystal according to claim 1, wherein the crystal is form B crystal having characteristic peaks at chemical shifts of 16.4 ppm (double peak), 120.5 ppm, and 135.6 ppm in its solid-state ^{13}C -NMR spectrum.

[Claim 12]

The crystal according to claim 1, wherein the crystal is form B crystal having an solid-state ^{13}C -NMR spectrum pattern shown in Figure 4.

[Claim 13]

The crystal according to claim 1, wherein the crystal is form B crystal having characteristic peaks at wave numbers of 1329 cm^{-1} , 1382 cm^{-1} , and 1401 cm^{-1} in its infrared absorption spectrum according to the potassium bromide disk method.

[Claim 14]

The crystal according to claim 1, wherein the crystal is form B crystal having an infrared absorption spectrum pattern shown in Figure 6 according to the potassium bromide disk method.

[Claim 15]

The crystal according to any one of claims 9 to 14, wherein its endothermic peak in thermogravimetry/differential thermal analysis is at 236°C.

[Claim 16]

A method for producing a crystal of 2-(5-chloropyridin-3-

yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid, comprising the steps of:

suspending an alkyl ester of 2-(5-chloropyridin-3-yl)-1-(2,5-dichlorobenzyl)-4-methyl-1H-imidazole-5-carboxylic acid in a solvent and performing hydrolysis by adding an aqueous solution of a base thereto; and

neutralizing the reaction product.

[Claim 17]

The method for producing a crystal according to claim 16, further comprising the step of stirring the neutralized product while cooling.

[Claim 18]

The method for producing a crystal according to claim 16 or 17, wherein the solvent is a single organic solvent selected from methanol, ethanol, 2-propanol, 1-butanol, and tetrahydrofuran, or a mixture solvent of the organic solvent and water, or a mixture of two or more organic solvents selected from methanol, ethanol, 2-propanol, and 1-butanol, or a mixture solvent of the mixture of the organic solvents and water.

[Claim 19]

The method for producing a crystal according to claim 18, wherein the solvent is a single organic solvent selected from methanol, ethanol, 2-propanol, and 1-butanol, or a mixture solvent of the single organic solvent and water.

[Claim 20]

The method for producing a crystal according to claim 18, wherein the solvent is ethanol.

[Claim 21]

The method for producing a crystal according to claim 16 or 17, wherein the solvent is a mixture solvent of tetrahydrofuran and ethanol.

[Claim 22]

A pharmaceutical composition comprising the crystal according to any one of claims 1 to 15 and a pharmaceutically acceptable carrier.

[Claim 23]

A URAT1 inhibitor comprising the crystal according to any

one of claims 1 to 15 as an active ingredient.

[Claim 24]

A therapeutic or prophylactic agent for one or more diseases selected from the group consisting of gout, hyperuricemia, hypertension, renal disease, diabetes, arteriosclerosis, and Lesch-Nyhan syndrome, comprising the crystal according to any one of claims 1 to 15 as an active ingredient.