

suspending an alkyl ester of 4-methyl-2-[4-(2-methylpropoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid in a solvent and performing hydrolysis by adding an aqueous solution of a base thereto and

neutralizing the reaction product;

[35] The method of production according to [34], further comprising the step of adding water to the neutralized product and stirring it;

[36] A method for producing the crystal form B of 4-methyl-2-[4-(2-methylpropoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid, comprising the step of suspending the crystal form A of 4-methyl-2-[4-(2-methylpropoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid in a solvent;

[37] The method of production according to [36], further comprising the step of heating the suspension;

[38] The method for producing the crystal according to [36] or [37], wherein the solvent is selected from the group consisting of ethers, ketones, esters, alcohols, water, and a mixture solvent thereof; and

[39] A method for producing the crystal form C of 4-methyl-2-[4-(2-methylpropoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid, comprising crystallization from a N,N-dimethylformamide solution thereof.

[39a] A therapeutic or prophylactic agent comprising the compound as disclosed herein or the crystal as disclosed herein as an active ingredient for use in the treatment or prevention of one or more diseases selected from the group consisting of gout, hyperuricemia, tumor lysis syndrome, urinary calculi, hypertension, dyslipidemia, diabetes, cardiovascular diseases, kidney diseases, respiratory diseases, inflammatory bowel diseases and autoimmune diseases.

[Advantageous Effects of Invention]

The present invention provides crystals of an azole
benzene derivative, which are useful as therapeutic or
prophylactic agents for diseases associated with xanthine
5 oxidase such as gout, hyperuricemia, tumor lysis
syndrome, urinary calculi, hypertension, dyslipidemia,
diabetes, cardiovascular diseases such as
arteriosclerosis or heart failure, kidney diseases such
as diabetic nephropathy, respiratory diseases such as
10 chronic obstructive pulmonary diseases, inflammatory

CLAIMS

[Claim 1]

A crystal of 4-methyl-2-[4-(2-methylpropoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid.

5 [Claim 2]

The crystal according to claim 1, wherein the crystal has characteristic peaks at diffraction angles of $2\theta (\pm 0.5^\circ) = 8.6^\circ, 10.2^\circ, 13.3^\circ, 14.4^\circ, 18.5^\circ, 19.9^\circ, 21.8^\circ, 25.1^\circ, 25.6^\circ, 26.6^\circ, 27.1^\circ$ and 29.5° in its powder X-ray diffraction spectrum (crystal form A).

[Claim 3]

10 The crystal according to claim 1, wherein its powder X-ray diffraction spectrum has a pattern shown in Fig. 1 (crystal form A).

[Claim 4]

The crystal according to claim 1, wherein the crystal has characteristic peaks at chemical shifts (± 0.5 ppm) of 116.3 ppm, 117.6 ppm, 120.0 ppm, 123.6 ppm, 125.9 ppm,
15 127.4 ppm, 143.7 ppm, 151.8 ppm, 161.1 ppm, 162.3 ppm and 165.5 ppm in its solid-state ^{13}C NMR spectrum (crystal form A).

[Claim 5]

The crystal according to claim 1, wherein its solid-state ^{13}C NMR spectrum has a pattern shown in Fig. 5 (crystal form A).

20 [Claim 6]

The crystal according to claim 1, wherein the crystal has characteristic peaks at wave numbers ($\pm 5\text{cm}^{-1}$) of $745\text{ cm}^{-1}, 822\text{ cm}^{-1}, 889\text{ cm}^{-1}, 975\text{ cm}^{-1}, 997\text{ cm}^{-1}, 1611\text{ cm}^{-1}$ and 1705 cm^{-1} in its infrared absorption spectrum (KBr method) (crystal form A).

[Claim 7]

25 The crystal according to claim 1, wherein its infrared absorption spectrum (KBr method) has a pattern shown in Fig. 8 (crystal form A).

[Claim 8]

The crystal according to claim 1, wherein its exothermic peak in thermogravimetry/differential thermal analysis is at $222^{\circ}\text{C} \pm 2^{\circ}\text{C}$ (crystal form A).

[Claim 9]

5 The crystal according to claim 1, wherein the crystal has characteristic peaks at diffraction angles of $2\theta (\pm 0.5^{\circ}) = 10.1^{\circ}, 12.6^{\circ}, 13.1^{\circ}, 14.0^{\circ}, 18.6^{\circ}, 24.2^{\circ}, 25.2^{\circ}, 25.7^{\circ}, 27.2^{\circ}$ and 30.5° in its powder X-ray diffraction spectrum (crystal form B).

[Claim 10]

10 The crystal according to claim 1, wherein its powder X-ray diffraction spectrum has a pattern shown in Fig. 2 (crystal form B).

[Claim 11]

15 The crystal according to claim 1, wherein the crystal has characteristic peaks at chemical shifts ($\pm 0.5\text{ppm}$) of 115.4 ppm, 118.0 ppm, 119.8 ppm, 123.2 ppm, 126.4 ppm, 129.1 ppm, 142.7 ppm, 151.2 ppm, 160.9 ppm and 166.6 ppm in its solid-state ^{13}C NMR spectrum (crystal form B).

[Claim 12]

 The crystal according to claim 1, wherein its solid-state ^{13}C NMR spectrum has a pattern shown in Fig. 6 (crystal form B).

[Claim 13]

20 The crystal according to claim 1, wherein the crystal has characteristic peaks at wave numbers ($\pm 5\text{cm}^{-1}$) of $744\text{ cm}^{-1}, 810\text{ cm}^{-1}, 972\text{ cm}^{-1}, 997\text{ cm}^{-1}, 1005\text{ cm}^{-1}, 1611\text{ cm}^{-1}$ and 1710 cm^{-1} in its infrared absorption spectrum (KBr method) (crystal form B).

[Claim 14]

25 The crystal according to claim 1, wherein its infrared absorption spectrum (KBr method) has a pattern shown in Fig. 9 (crystal form B).

[Claim 15]

The crystal according to claim 1, wherein its exothermic peak in thermogravimetry/differential thermal analysis is at $225^{\circ}\text{C}\pm 2^{\circ}\text{C}$ and it is an anhydrous crystal (crystal form B).

5 [Claim 16]

The crystal according to claim 1, wherein the crystal has characteristic peaks at diffraction angles of $2\theta (\pm 0.5^{\circ}) = 7.2^{\circ}, 12.5^{\circ}, 13.0^{\circ}, 14.7^{\circ}, 19.2^{\circ}, 20.0^{\circ}, 21.4^{\circ}, 21.7^{\circ}, 24.7^{\circ}$ and 26.0 in its powder X-ray diffraction spectrum (crystal form C).

[Claim 17]

10 The crystal according to claim 1, wherein its powder X-ray diffraction spectrum has a pattern shown in Fig. 3 (crystal form C).

[Claim 18]

The crystal according to claim 1, wherein the crystal has characteristic peaks at chemical shifts ($\pm 0.5\text{ppm}$) of 116.1 ppm, 119.6 ppm, 123.1 ppm, 126.1 ppm, 127.1 ppm,
15 130.0 ppm, 143.6 ppm, 150.3 ppm, 158.3 ppm, 160.7 ppm, 163.9 ppm, 165.5 ppm and 167.0ppm in its solid-state ^{13}C NMR spectrum (crystal form C).

[Claim 19]

The crystal according to claim 1, wherein its solid-state ^{13}C NMR spectrum has a pattern shown in Fig. 7 (crystal form C).

20 [Claim 20]

The crystal according to claim 1, wherein the crystal has characteristic peaks at wave numbers ($\pm 5\text{cm}^{-1}$) of $745\text{ cm}^{-1}, 751\text{ cm}^{-1}, 809\text{ cm}^{-1}, 820\text{ cm}^{-1}, 971\text{ cm}^{-1}, 1006\text{ cm}^{-1}, 1613\text{ cm}^{-1}, 1682\text{ cm}^{-1}$ and 1710 cm^{-1} in its infrared absorption spectrum (KBr method) (crystal form C).

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[Claim 21]

The crystal according to claim 1, wherein its infrared absorption spectrum (KBr method) has a pattern shown in Fig. 10 (crystal form C).

[Claim 22]

5 The crystal according to claim 1, wherein its endothermic peak is at 88°C and exothermic peak is at 225°C±2°C in thermogravimetry/differential thermal analysis (crystal form C).

[Claim 23]

10 Sodium 4-methyl-2-[4-(2-methylpropoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5-carboxylate.

[Claim 24]

A crystal of the compound according to claim 23.

[Claim 25]

15 The crystal according to claim 24, wherein the crystal has characteristic peaks at diffraction angles of $2\theta (\pm 0.5^\circ) = 7.2^\circ, 10.9^\circ, 13.3^\circ, 15.9^\circ, 18.2^\circ, 20.8^\circ, 22.1^\circ, 25.2^\circ, 26.1^\circ$ and 29.1° in its powder X-ray diffraction spectrum.

[Claim 26]

The crystal according to claim 24, wherein its powder X-ray diffraction spectrum has a pattern shown in Fig. 4.

20 [Claim 27]

The crystal according to claim 24, wherein its exothermic peak in thermogravimetry/differential thermal analysis is at 281°C±2°C.

[Claim 28]

25 A pharmaceutical composition comprising the compound according to claim 23 or the crystal according to any one of claims 1 to 22 and 24 to 27 and a pharmaceutically acceptable carrier.

[Claim 29]

A xanthine oxidase inhibitor comprising the compound according to claim 23 or the crystal according to any one of claims 1 to 22 and 24 to 27 as an active ingredient.

[Claim 30]

5 A therapeutic or prophylactic agent comprising the compound according to claim 23 or the crystal according to any one of claims 1 to 22 and 24 to 27 as an active ingredient for use in the treatment or prevention of one or more diseases selected from the group consisting of gout, hyperuricemia, tumor lysis syndrome, urinary calculi, hypertension, dyslipidemia, diabetes, cardiovascular diseases, kidney diseases,
10 respiratory diseases, inflammatory bowel diseases and autoimmune diseases.

[Claim 31]

A method for producing the crystal form A of 4-methyl-2-[4-(2-methylpropoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid according to any one of claims 2 to 8, comprising the steps of:

15 suspending an alkyl ester of 4-methyl-2-[4-(2-methylpropoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid in a solvent and performing hydrolysis by adding an aqueous solution of a base thereto; and
neutralizing the reaction product.

[Claim 32]

20 The method for production according to claim 31 further comprising the step of adding water to the neutralized product and stirring it.

[Claim 33]

A method for producing the crystal form B of 4-methyl-2-[4-(2-methylpropoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid
25 according to any one of claims 9 to 15, comprising the step of suspending the crystal

form A of 4-methyl-2-[4-(2-methylpropoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid in a solvent.

[Claim 34]

The method of production according to claim 33, further comprising the step of
5 heating the suspension.

[Claim 35]

The method for producing the crystal according to claim 33 or claim 34, wherein the solvent is selected from the group consisting of ethers, ketones, esters, alcohols, water, and a mixture solvent thereof.

10 [Claim 36]

A method for producing the crystal form C of 4-methyl-2-[4-(2-methylpropoxy)-3-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-1,3-thiazole-5-carboxylic acid according to any one of claims 16 to 22, comprising crystallization from an N,N-dimethylformamide solution thereof.

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