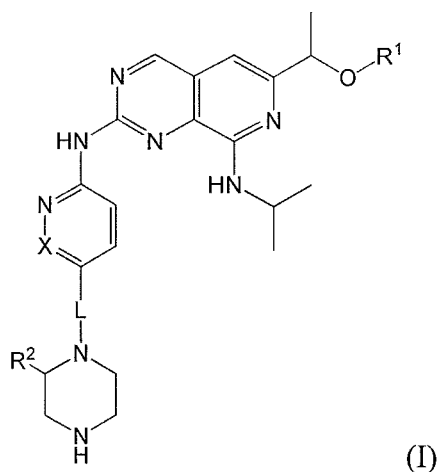


Thus, the present invention relates to a crystal of a compound represented by formula (I) or a solvate thereof.

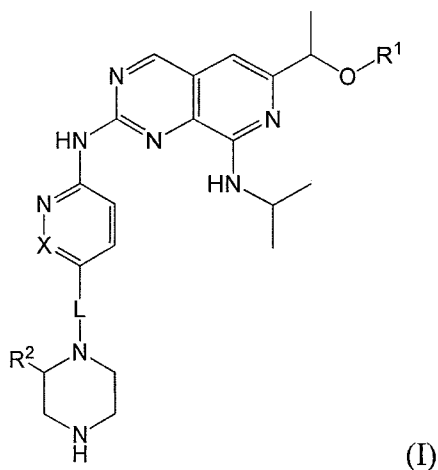


[0014]

In the formula, R^1 represents a hydrogen atom or a C_{1-3} alkyl group, R^2 represents a hydrogen atom or an oxo group (in the case of a oxo group, R^2 is bound to the piperazine ring via a double bond), L represents a single bond or a C_{1-3} alkylene group, and X represents CH or N.

[0014a]

The present invention provides a crystal of a compound represented by formula (I):



wherein R^1 represents a hydrogen atom or a C_{1-3} alkyl group, R^2 represents a hydrogen atom or an oxo group, L represents a single bond or a C_{1-3} alkylene group, and X represents CH or N;

or a solvate thereof.

[0014b]

The present invention provides a pharmaceutical composition comprising a crystal as described herein and a pharmaceutically acceptable carrier.

[0014c]

The present invention also provides a pharmaceutical composition having a CDK4/6 inhibitory activity, comprising a crystal as described herein as an active ingredient.

[0014d]

The present invention provides a use of a pharmaceutical composition comprising a crystal as described herein and a pharmaceutically acceptable carrier in the manufacture of a medicament for prophylaxis or treatment of rheumatoid arthritis, arteriosclerosis, pulmonary fibrosis, cerebral infarction and/or cancer.

EFFECT OF THE INVENTION

[0015]

The present invention provides a crystal of a pyrido[3,4-d]pyrimidine derivative or a solvate thereof that exhibits excellent CDK4/6 inhibitory activity and is useful as a prophylactic or therapeutic drug of, e.g., rheumatoid arthritis, arteriosclerosis, pulmonary fibrosis, cerebral infarction and/or cancer.

The crystal according to the present invention can be used as an active pharmaceutical ingredient in the manufacture of a pharmaceutical product.

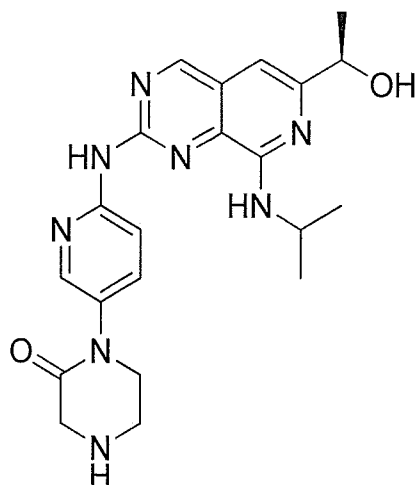
BRIEF DESCRIPTION OF DRAWINGS

[0016]

[FIG.1] Figure 1 is a powder X-ray diffraction spectrum of Crystal D of 1-(6-((6-((1R)-1-hydroxyethyl)-8-(isopropylamino)pyrido[3,4-d]pyrimidine-2-yl)amino)-3-pyridyl)piperazine-2-one.

[FIG.2] Figure 2 is a powder X-ray diffraction spectrum of Crystal A of 1-(6-((6-((1R)-1-hydroxyethyl)-8-(isopropylamino)pyrido[3,4-d]pyrimidine-2-yl)amino)-3-pyridyl)piperazine-2-one.

[Chemical formula 13]



(a)

[0084]

Trifluoroacetic acid (0.15 ml) was added to a solution of Compound (a)-10 (9.2 mg, 0.15 mmol) in dichloromethane (0.35 ml) at room temperature, and the solution was stirred for one hour. After the solution was evaporated to dryness, tetrahydrofuran (0.15 ml) and methanol (0.15 ml) was added, and then aqueous 4M lithium hydroxide solution (0.018 ml) was added. The solution after the reaction was neutralized with formic acid, the resultant was purified by silica gel column chromatography to give a titled compound.

¹H-NMR (DMSO) δ : 10.16 (1H,s), 9.26 (1H,s), 8.31 (1H,m), 8.29 (1H,s), 7.81 (1H,m), 7.00 (1H,s), 6.42 (1H,m), 5.18 (1H,d), 4.63 (1H,m), 4.27 (1H,m), 3.65 (2H,m), 3.41 (2H,s), 3.05 (2H,m), 1.39 (3H,d), 1.30 (6H,m)

[0085]

<Production of Crystal D of Compound (a)>

The solution of Compound (a) purified by the silica gel column chromatography was concentrated until crystals were precipitated. Crystal D of Compound (a) was thereby prepared.

[0086]

<Evaluation of Crystal D of Compound (a)>

Fig. 1 illustrates the X-ray diffraction spectrum of the resulting crystal. Peaks were observed at 6.3°, 6.6°, 11.6°, 16.9°, and 20.0° (diffraction angle 2 θ).

The heat flow curve by differential scanning calorimetry (DSC) had an endothermic peak at 277°C.

Fig. 10 illustrates the IR absorption spectrum (KBr) of the crystal. Absorption Peaks were observed at 703 cm⁻¹, 896 cm⁻¹ and 3418 cm⁻¹ (wave number).

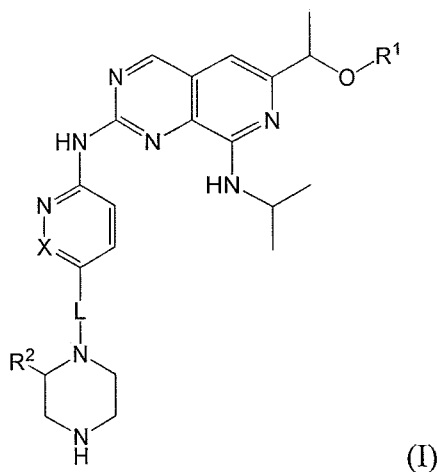
[0087]

Figs. 17-1 and 17-2 illustrate solid ¹³C-NMR spectra of the crystal. Fig.17-1 exhibits 6500Hz mode and Fig.17-2 exhibits 14000Hz mode. Peaks were observed at 136.0ppm,

CLAIMS

[Claim 1]

A crystal of a compound represented by formula (I):



- 5 wherein R¹ represents a hydrogen atom or a C₁₋₃ alkyl group, R² represents a hydrogen atom or an oxo group, L represents a single bond or a C₁₋₃ alkylene group, and X represents CH or N;
 or a solvate thereof.

10 [Claim 2]

 The crystal according to claim 1, wherein the compound is 1-(6-((6-((1R)-1-hydroxyethyl)-8-(isopropylamino)pyrido[3,4-d]pyrimidine-2-yl)amino)-3-pyridyl)piperazine-2-one.

15 [Claim 3]

 The crystal according to claim 2, which exhibits peaks at diffraction angles 2θ = 6.3°, 6.6°, 11.6°, 16.9° and 20.0° on a powder X-ray diffraction spectrum.

[Claim 4]

- 20 The crystal according to claim 3, which exhibits an extrapolated onset temperature for an endothermic peak of 277°C according to differential scanning calorimetry.

[Claim 5]

- 25 The crystal according to claim 3, which exhibits distinctive absorption peaks with wave numbers of 703 cm⁻¹, 896 cm⁻¹ and 3418 cm⁻¹ on an infrared absorption spectrum (KBr method).

[Claim 6]

The crystal according to claim 3, which exhibits distinctive peaks at 136.0ppm, 111.2ppm, 105.1ppm, 101.8ppm, 52.7ppm, 49.6ppm, 42.9ppm, 23.8ppm and 18.5ppm on a solid NMR spectrum (^{13}C).

5 [Claim 7]

The crystal according to claim 3, which exhibits distinctive peaks at 248.6ppm, 245.7ppm, 229.2ppm, 214.5ppm, 174.3ppm, 86.5ppm, 54.7ppm and -12.4ppm on a solid NMR spectrum (^{15}N).

10 [Claim 8]

The crystal according to claim 2, which exhibits peaks at diffraction angles $2\theta = 5.3^\circ$, 7.3° , 10.3° , 15.1° and 17.4° on a powder X-ray diffraction spectrum.

[Claim 9]

15 The crystal according to claim 8, which exhibits an extrapolated onset temperature for an endothermic peak of 277°C according to differential scanning calorimetry.

[Claim 10]

20 The crystal according to claim 8, which exhibits distinctive absorption peaks with wave numbers of 874 cm^{-1} , 1330 cm^{-1} and 3314 cm^{-1} on an infrared absorption spectrum (KBr method).

[Claim 11]

25 The crystal according to claim 8, which exhibits distinctive peaks at 154.7ppm, 138.8ppm, 133.6ppm, 113.2ppm, 101.6ppm, 100.4ppm, 67.4ppm, 51.8ppm, 26.6ppm and 23.3ppm on a solid NMR spectrum (^{13}C).

[Claim 12]

30 The crystal according to claim 8, which exhibits distinctive peaks at 243.6ppm, 86.7ppm, 56.7ppm and -12.4 ppm on a solid NMR spectrum (^{15}N).

[Claim 13]

The crystal according to claim 2, which exhibits peaks at diffraction angles $2\theta = 5.3^\circ$, 6.0° , 6.7° , 10.4° and 20.8° on a powder X-ray diffraction spectrum.

35

[Claim 14]

The crystal according to claim 13, which exhibits an extrapolated onset temperature for an endothermic peak of 271°C according to differential scanning calorimetry.

[Claim 15]

5 The crystal according to claim 2, which exhibits peaks at diffraction angles $2\theta = 6.0^\circ$, 10.0° , 13.7° , 20.3° and 23.0° on a powder X-ray diffraction spectrum.

[Claim 16]

10 The crystal according to claim 15, which exhibits an extrapolated onset temperature for an endothermic peak of 100°C and 278°C according to differential scanning calorimetry.

[Claim 17]

15 The crystal according to claim 15, which exhibits distinctive absorption peaks with wave numbers of 840 cm^{-1} , 904 cm^{-1} , 955 cm^{-1} , 1490 cm^{-1} and 3281 cm^{-1} on an infrared absorption spectrum (KBr method).

[Claim 18]

20 The crystal according to claim 2, which exhibits peaks at diffraction angles $2\theta = 5.2^\circ$, 7.2° , 9.5° , 14.5° , 16.5° , 20.9° , 25.0° and 27.9° on a powder X-ray diffraction spectrum.

[Claim 19]

 The crystal according to claim 18, which exhibits an extrapolated onset temperature for an endothermic peak of 272°C according to differential scanning calorimetry.

25 [Claim 20]

 The crystal according to claim 18, which exhibits distinctive absorption peaks with wave numbers of 1081 cm^{-1} and 1260 cm^{-1} on an infrared absorption spectrum (KBr method).

[Claim 21]

30 The crystal according to claim 1, which is a crystal of the compound represented by formula (I), wherein the compound is 1-(6-(((1R)-1-methoxyethyl)-8-(isopropylamino)pyrido[3,4-d]pyrimidine-2-yl)amino)-3-pyridazyl)piperazine.

[Claim 22]

35 The crystal according to claim 21, which exhibits peaks at diffraction angles $2\theta = 5.2^\circ$, 7.6° , 8.4° , 10.5° , 15.2° , 16.9° , 20.1° , 21.0° , 23.3° and 26.6° on a powder X-ray diffraction

spectrum.

[Claim 23]

The crystal according to claim 22, which exhibits an extrapolated onset temperature for an endothermic peak of 225°C according to differential scanning calorimetry.

[Claim 24]

The crystal according to claim 22, which exhibits distinctive absorption peaks with wave numbers of 1369 cm⁻¹, 1424 cm⁻¹, 1508 cm⁻¹, 1545 cm⁻¹ and 1566 cm⁻¹ on an infrared absorption spectrum (KBr method).

[Claim 25]

The crystal according to claim 22, which exhibits distinctive peaks at 163.4ppm, 157.6ppm, 155.5ppm, 117.8ppm, 82.2ppm, 56.1ppm and 42.3ppm on a solid NMR spectrum (¹³C).

[Claim 26]

The crystal according to claim 22, which exhibits distinctive peaks at 311.7ppm, 232.4ppm, 168.5ppm, 79.5ppm, 53.3ppm, 32.9ppm and -4.3ppm on a solid NMR spectrum (¹⁵N).

[Claim 27]

The crystal according to claim 21, which exhibits peaks at diffraction angles 2θ = 5.2°, 6.6°, 8.1°, 15.2°, 15.9°, 16.2°, 18.8°, 20.5°, 20.8° and 21.7°, on a powder X-ray diffraction spectrum.

[Claim 28]

The crystal according to claim 27, which exhibits an extrapolated onset temperature for an endothermic peak of 221°C according to differential scanning calorimetry.

[Claim 29]

The crystal according to claim 21, which exhibits peaks at diffraction angles 2θ = 5.2°, 7.6°, 8.4°, 10.0°, 10.5°, 11.9°, 15.2°, 17.0°, 20.9° and 21.2°, on a powder X-ray diffraction spectrum.

[Claim 30]

The crystal according to claim 29, which exhibits an extrapolated onset temperature for an endothermic peak of 223°C according to differential scanning calorimetry.

[Claim 31]

5 The crystal according to claim 29, which exhibits distinctive absorption peaks with wave numbers of 1369 cm⁻¹, 1424 cm⁻¹, 1507cm⁻¹, 1546cm⁻¹ and 1566 cm⁻¹ on an infrared absorption spectrum (KBr method).

[Claim 32]

10 The crystal according to claim 1, which is a crystal of the compound represented by formula (I), wherein the compound is (R)-N8-isopropyl-6-(1-methoxyethyl)-N2-(5-(piperazine-1-ylmethyl)pyridin-2-yl)pyrido[3,4-d]pyrimidine-2,8-diamine.

[Claim 33]

15 The crystal according to claim 32, which exhibits peaks at diffraction angles 2θ = 4.8°, 7.6°, 8.2°, 9.7°, 15.3°, 16.6°, 19.1°, 19.8°, 22.4° and 26.2° on a powder X-ray diffraction spectrum.

[Claim 34]

20 The crystal according to claim 33 which exhibits an extrapolated onset temperature for an endothermic peak of 182°C according to differential scanning calorimetry.

[Claim 35]

25 The crystal according to claim 33, which exhibits distinctive absorption peaks with wave numbers of 1115 cm⁻¹, 1446 cm⁻¹, 1508 cm⁻¹, 1560 cm⁻¹ and 1601 cm⁻¹ on an infrared absorption spectrum (KBr method).

[Claim 36]

30 The crystal according to claim 33, which exhibits distinctive peaks at 161.3ppm, 150.8ppm, 138.9ppm, 128.1ppm, 109.8ppm, 82.7ppm, 47.6ppm, 42.5ppm, 41.5ppm, 24.5ppm and 21.7ppm on a solid NMR spectrum (¹³C).

[Claim 37]

35 The crystal according to claim 33, which exhibits distinctive peaks at 242.8ppm, 233.8ppm, 219.0ppm, 171.7ppm, 86.9ppm, 54.9ppm, 11.3ppm and -5.5ppm on a solid NMR spectrum (¹⁵N).

[Claim 38]

A pharmaceutical composition comprising a crystal according to any one of claims 1 to 37 and a pharmaceutically acceptable carrier.

5

[Claim 39]

A pharmaceutical composition having a CDK4/6 inhibitory activity, comprising a crystal according to any one of claims 1 to 37 as an active ingredient.

10

[Claim 40]

Use of a pharmaceutical composition comprising a crystal according to any one of claims 1 to 37 and a pharmaceutically acceptable carrier in the manufacture of a medicament for prophylaxis or treatment of rheumatoid arthritis, arteriosclerosis, pulmonary fibrosis, cerebral infarction and/or cancer.