

## Description

### Title of Invention: CRYSTAL OF OXAZEPINE DERIVATIVE OR CRYSTAL OF SOLVATE THEREOF

#### Technical Field

- [0001] The present invention relates to a crystal of an oxazepine derivative or a crystal of a solvate thereof, which is useful as a pharmaceutical product. Specifically, the invention relates to a crystal of an oxazepine derivative or a crystal of a solvate thereof, which has orexin type 2 receptor agonist activity and is useful for the prevention or treatment of narcolepsy, idiopathic hypersomnia, hypersomnia and the like.

#### Background Art

- [0002] Orexin is a neuropeptide produced by specific nerve cells localized in the brain lateral hypothalamic area. It is produced from prepro-orexin by prohormone converting enzymes, and there are two subtypes, orexin A and orexin B.

Here, in the present specification, unless otherwise specified, the term “orexin” is used as a meaning including orexin A and orexin B.

- [0003] Orexins bind to orexin receptors as endogenous ligands of orexin receptors, which are G protein-coupled receptors mainly expressed in the brain. Two subtypes of orexin receptors, a type 1 receptor (hereinafter sometimes abbreviated as OX1R) and a type 2 receptor (hereinafter sometimes abbreviated as OX2R), are known (Non-Patent Document 1).

Here, in the present specification, unless otherwise specified, the term “orexin receptor” is used as a meaning including OX1R and OX2R.

- [0004] As diseases associated with orexin type 1 or orexin type 2 receptor, in particular orexin type 2, for example, narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome and the like are known.

- [0005] For example, it has been suggested that narcolepsy is induced by a deficiency of orexin, based on the fact that a narcolepsy-like symptom, occurred in a transgenic mouse deficient in endogenous orexin by denaturing orexin-producing nerve cells, is improved by intraventricular administration of an orexin peptide (Non-Patent Document 2), and that a narcolepsy-like symptom is induced in a prepro-orexin deficient (KO) mouse, which is a precursor of orexin (Non-Patent Document 3).

- [0006] Furthermore, since it has been reported that hereditary narcolepsy can occur in dogs having a mutation of the OX2R (Non-Patent Document 4), and that a narcolepsy-like symptom is also induced in the OX2R KO mouse (Non-Patent Document 5), it is strongly suggested that stimulation of the orexin type 2 receptor is involved in the action of wakefulness maintenance.

[0007] In addition, narcolepsy type 1 and narcolepsy type 2 are known as diseases caused by abnormal action of orexin.

Here, in the present specification, unless otherwise specified, the term “narcolepsy” is used as a meaning including narcolepsy type 1 and narcolepsy type 2.

[0008] It has been reported that patients with narcolepsy type 1 show a low level of the concentration of orexin in the cerebrospinal fluid (Non-Patent Document 6). In addition, it has been suggested that patients with sleep apnea syndrome have a low level of the concentration of orexin A in the plasma (Non-Patent Document 7). Furthermore, it has been reported that drowsiness occurs in Parkinson's disease patients, and the cause thereof has been suggested to be the loss of orexin-producing nerve cells (Non-Patent Document 8).

[0009] From such a background, it has been suggested that OX2R agonists are promising therapeutic agents for narcolepsy and other sleep disorders exhibiting excessive sleepiness (Non-Patent Document 9).

[0010] Therefore, it is considered that compounds having OX2R agonist activity can be used as a prophylactic or therapeutic agent for narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome accompanying narcolepsy-like symptoms, hypersomnia syndrome accompanying hypersomnia during the day (for example, Parkinson's disease, dementia with Lewy bodies, Guillain-Barre syndrome, and Kleine-Levin syndrome).

[0011] In fact, it has been reported that compounds having OX2R agonist activity ameliorate the symptoms of narcolepsy (Patent Document 1). In addition, a clinical study of TAK-925 (intravenous administration), which has existing OX2R agonist activity, was conducted in healthy persons and patients with narcolepsy, and another compound, TAK-994 (oral administration), was reported to cause side effects in a clinical study, but the details are unknown.

(Citation List)

(Patent Document)

[0012] [Patent Document 1] WO 2021/048822 A1

**Non-Patent Document**

[0013] [Non-Patent Document 1] Cell, Vol. 92, 573-585, 1998

[Non-Patent Document 2] Proc. Natl. Acad. Sci. USA, Vol.101, 4649-4654, 2004

[Non-Patent Document 3] Cell, Vol. 98, 437-451, 1999

[Non-Patent Document 4] Cell, Vol. 98, 365-376, 1999

[Non-Patent Document 5] Neuron, Vol. 38, 715-730, 2003

[Non-Patent Document 6] THE LANCET, Vol. 355, 39-40, 2000

[Non-Patent Document 7] Respiration, Vol. 71, 575-579, 2004

[Non-Patent Document 8] Brain, Vol. 130, 1586-1595, 2007

[Non-Patent Document 9] CNS Drugs, Vol. 27, 83-90, 2013

### Summary of the Invention

[0014] (Problems to be Solved by the Invention)

An object of the invention is to provide a crystal of an oxazepine derivative or a crystal of a solvate thereof, which has excellent orexin type 2 receptor agonist activity and is useful for the prevention or treatment of, for example, narcolepsy, idiopathic hypersomnia, hypersomnia.

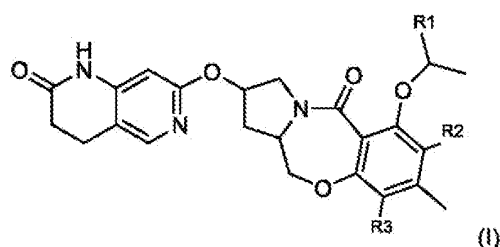
### Means for Solving the Problems

[0015] The present inventors have conducted intensive research for the above purpose, and as a result, have arrived at the following invention.

(1)

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

[Chem.1]



[in the formula (I), R<sup>1</sup> represents a methyl group or a methyl group substituted with 1 to 3 fluorine atoms; and R<sup>2</sup> and R<sup>3</sup> each independently represent a hydrogen atom or a fluorine atom],

or a crystal of a solvate of the compound represented by the formula (I).

(2)

The crystal according to [1], which is a crystal of (2S,11aR)-7-fluoro-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-6-(((R)-1,1,1-trifluoropropan-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one.

(3)

The crystal according to [2], in which the crystal has peaks at diffraction angles (2θ±0.5°) of 12.7°, 14.7°, 17.6°, 20.7°, and 21.1° in a powder X-ray diffraction spectrum.

(4)]

The crystal according to [2], in which the crystal has peaks at chemical shifts (±0.5 ppm) of 11.6, 14.7, 21.7, 30.8, 163.3, and 169.1 ppm in a solid-state NMR spectrum (<sup>13</sup>C).

(5)

The crystal according to [2], in which an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is  $166\pm 5^{\circ}\text{C}$ .

(6)

The crystal according to [1], which is a crystal of (2S,11aR)-7-fluoro-6-isopropoxy-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one

(7)]

The crystal according to [6], in which the crystal has peaks at diffraction angles ( $2\theta\pm 0.5^{\circ}$ ) of  $8.5^{\circ}$ ,  $12.7^{\circ}$ ,  $14.7^{\circ}$ , and  $17.7^{\circ}$  in a powder X-ray diffraction spectrum.

(8)

The crystal according to [6], in which the crystal has peaks at chemical shifts ( $\pm 0.5$  ppm) of 15.0, 22.2, 23.2, 30.7, and 149.8 ppm in a solid-state NMR spectrum ( $^{13}\text{C}$ ).

(9)]

The crystal according to [6], in which an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is  $222\pm 5^{\circ}\text{C}$ .

(10)

The crystal according to [6], in which the crystal has peaks at diffraction angles ( $2\theta\pm 0.5^{\circ}$ ) of  $5.3^{\circ}$ ,  $6.3^{\circ}$ , and  $13.4^{\circ}$  in a powder X-ray diffraction spectrum.

(11)

The crystal according to [6], in which an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is  $223\pm 5^{\circ}\text{C}$ .

(12)

The crystal according to [6], in which the crystal has peaks at diffraction angles ( $2\theta\pm 0.5^{\circ}$ ) of  $9.6^{\circ}$ ,  $13.3^{\circ}$ ,  $16.7^{\circ}$ ,  $18.7^{\circ}$ , and  $22.8^{\circ}$  in a powder X-ray diffraction spectrum.

(13)

The crystal according to [6], in which the crystal has peaks at chemical shifts ( $\pm 0.5$  ppm) of 15.7, 21.6, 162.4, 164.5, and 170.2 ppm in a solid-state NMR spectrum ( $^{13}\text{C}$ ).

(14)

The crystal according to [6], in which an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is  $223\pm 5^{\circ}\text{C}$ .

(15)

The crystal according to [6], in which the crystal has peaks at diffraction angles

(20±0.5°) of 3.8°, 12.0°, 21.1°, and 23.9° in a powder X-ray diffraction spectrum.

(16)

The crystal according to [6], in which the crystal has peaks at chemical shifts (±0.5 ppm) of 15.0, 23.0, 30.7, 144.4, and 150.2 ppm in a solid-state NMR spectrum (<sup>13</sup>C).

(17)

The crystal according to [6], in which an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is 214±5°C.

(18)

The crystal according to [6], in which the crystal has peaks at diffraction angles (20±0.5°) of 3.9°, 12.4°, and 20.1° in a powder X-ray diffraction spectrum.

(19)

The crystal according to [6], in which an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is 121±5°C.

(20)

The crystal according to [6], in which the crystal has peaks at diffraction angles (20±0.5°) of 11.5°, 11.9°, 19.7°, and 23.5° in a powder X-ray diffraction spectrum.

(21)

The crystal according to [1], which is a crystal of

(2S,11aR)-7-fluoro-6-(((R)-1-fluoropropan-2-yl)oxy)-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one.

(22)

The crystal according to [21], in which the crystal has peaks at diffraction angles (20±0.5°) of 13.4°, 18.8°, and 22.9° in a powder X-ray diffraction spectrum.

(23)

The crystal according to [21], in which an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is 220±5°C.

(24)

The crystal according to [1], which is a crystal of

(2S,11aR)-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-6-(((R)-1,1,1-trifluoropropan-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one.

(25)

The crystal according to [24], in which the crystal has peaks at diffraction angles (20±0.5°) of 12.7°, 14.7°, 17.7°, 20.8°, and 21.1° in a powder X-ray diffraction

spectrum.

(26)

The crystal according to [24], in which the crystal has peaks at chemical shifts ( $\pm 0.5$  ppm) of 10.8, 22.3, 31.2, 163.7, and 169.0 ppm in a solid-state NMR spectrum ( $^{13}\text{C}$ ).

(27)

The crystal according to [24], in which an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is  $216 \pm 5^\circ\text{C}$ .

(28)

The crystal according to [1], which is a crystal of

(2S,11aR)-9-fluoro-6-isopropoxy-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one

.

(29)

The crystal according to [28], in which the crystal has peaks at diffraction angles ( $2\theta \pm 0.5^\circ$ ) of  $15.5^\circ$ ,  $19.5^\circ$ , and  $21.8^\circ$  in a powder X-ray diffraction spectrum.

(30)

The crystal according to [28], in which an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is  $302 \pm 5^\circ\text{C}$ .

(31)

An orexin type 2 receptor agonist containing the crystal according to any one of [1] to [30].

(32)]

A pharmaceutical composition containing the crystal according to any one of [1] to [30].

(33)

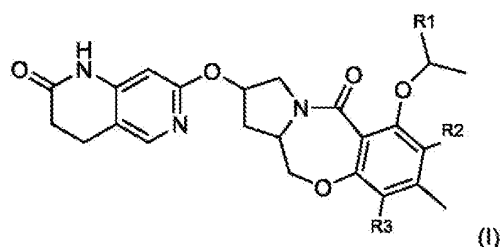
An agent containing the crystal according to any one of [1] to [30] for use for prophylactic or therapeutic treatment for narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome accompanying narcolepsy-like symptoms, hypersomnia accompanied by Parkinson's disease, hypersomnia accompanied by Guillain-Barre syndrome, hypersomnia accompanied by Kleine-Levin syndrome, or hypersomnia accompanied by dementia with Lewy bodies..

[0016] Further, the invention may be in the following forms.

(1)

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

[Chem.2]



(in the formula (I), R<sup>1</sup> represents a methyl group or a methyl group substituted with 1 to 3 fluorine atoms; and R<sup>2</sup> and R<sup>3</sup> each independently represent a hydrogen atom or a fluorine atom).

or a crystal of a solvate of the compound represented by the formula (I).

(2)

The crystal according to [1], which is a crystal of

(2S,11aR)-7-fluoro-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-6-(((R)-1,1,1-trifluoropropan-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one.

(3)

The crystal according to [2], in which the crystal has peaks at diffraction angles ( $2\theta \pm 0.5^\circ$ ) of  $12.7^\circ$ ,  $14.7^\circ$ ,  $17.6^\circ$ ,  $20.7^\circ$ , and  $21.1^\circ$  in a powder X-ray diffraction spectrum.

(4)

The crystal according to [2] or [3], in which the crystal has peaks at chemical shifts ( $\pm 0.5$  ppm) of 11.6, 14.7, 21.7, 30.8, 163.3, and 169.1 ppm in a solid-state NMR spectrum ( $^{13}\text{C}$ ).

(5)

The crystal according to any one of [2] to [4], in which an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is  $166 \pm 5^\circ\text{C}$ .

(6)

The crystal according to [1], which is a crystal of

(2S,11aR)-7-fluoro-6-isopropoxy-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one

.

(7)

The crystal according to [6], in which the crystal has peaks at diffraction angles ( $2\theta \pm 0.5^\circ$ ) of  $8.5^\circ$ ,  $12.7^\circ$ ,  $14.7^\circ$ , and  $17.7^\circ$  in a powder X-ray diffraction spectrum.

(8)

The crystal according to [6] or [7], in which the crystal has peaks at chemical shifts

( $\pm 0.5$  ppm) of 15.0, 22.2, 23.2, 30.7, and 149.8 ppm in a solid-state NMR spectrum ( $^{13}\text{C}$ ).

(9)

The crystal according to any one of [6] to [8], in which an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is  $222 \pm 5^\circ\text{C}$ .

(10)

The crystal according to [6], in which the crystal has peaks at diffraction angles ( $2\theta \pm 0.5^\circ$ ) of  $5.3^\circ$ ,  $6.3^\circ$ , and  $13.4^\circ$  in a powder X-ray diffraction spectrum.

(11)

The crystal according to [6] or [10], in which an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is  $223 \pm 5^\circ\text{C}$ .

(12)

The crystal according to [6], in which the crystal has peaks at diffraction angles ( $2\theta \pm 0.5^\circ$ ) of  $9.6^\circ$ ,  $13.3^\circ$ ,  $16.7^\circ$ ,  $18.7^\circ$ , and  $22.8^\circ$  in a powder X-ray diffraction spectrum.

(13)

The crystal according to [6] or [12], in which the crystal has peaks at chemical shifts ( $\pm 0.5$  ppm) of 15.7, 21.6, 162.4, 164.5, and 170.2 ppm in a solid-state NMR spectrum ( $^{13}\text{C}$ ).

(14)

The crystal according to any one of [6], [12], and [13], in which an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is  $223 \pm 5^\circ\text{C}$ .

(15)

The crystal according to [6], in which the crystal has peaks at diffraction angles ( $2\theta \pm 0.5^\circ$ ) of  $3.8^\circ$ ,  $12.0^\circ$ ,  $21.1^\circ$ , and  $23.9^\circ$  in a powder X-ray diffraction spectrum.

(16)

The crystal according to [6] or [15], in which the crystal has peaks at chemical shifts ( $\pm 0.5$  ppm) of 15.0, 23.0, 30.7, 144.4, and 150.2 ppm in a solid-state NMR spectrum ( $^{13}\text{C}$ ).

(17)

The crystal according to any one of [6], [15], and [16], in which an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is  $214 \pm 5^\circ\text{C}$ .

(18)

The crystal according to [6], in which the crystal has peaks at diffraction angles

(20±0.5°) of 3.9°, 12.4°, and 20.1° in a powder X-ray diffraction spectrum.

(19)

The crystal according to [6] or [18], in which an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is 121±5°C.

(20)

The crystal according to [6], in which the crystal has peaks at diffraction angles (20±0.5°) of 11.5°, 11.9°, 19.7°, and 23.5° in a powder X-ray diffraction spectrum.

(21)

The crystal according to [1], which is a crystal of

(2S,11aR)-7-fluoro-6-(((R)-1-fluoropropan-2-yl)oxy)-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one.

(22)

The crystal according to [21], in which the crystal has peaks at diffraction angles (20±0.5°) of 13.4°, 18.8°, and 22.9° in a powder X-ray diffraction spectrum.

(23)

The crystal according to [21] or [22], in which an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is 220±5°C.

(24)

The crystal according to [1], which is a crystal of

(2S,11aR)-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-6-(((R)-1,1,1-trifluoropropan-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one.

(25)

The crystal according to [24], in which the crystal has peaks at diffraction angles (20±0.5°) of 12.7°, 14.7°, 17.7°, 20.8°, and 21.1° in a powder X-ray diffraction spectrum.

(26)

The crystal according to [24] or [25], in which the crystal has peaks at chemical shifts (±0.5 ppm) of 10.8, 22.3, 31.2, 163.7, and 169.0 ppm in a solid-state NMR spectrum (<sup>13</sup>C).

(27)

The crystal according to any one of [24] to [25], in which an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is 216±5°C.

(28)

The crystal according to [1], which is a crystal of  
(2S,11aR)-9-fluoro-6-isopropoxy-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one

(29)

The crystal according to [27], in which the crystal has peaks at diffraction angles ( $2\theta \pm 0.5^\circ$ ) of  $15.5^\circ$ ,  $19.5^\circ$ , and  $21.8^\circ$  in a powder X-ray diffraction spectrum.

(30)

The crystal according to [28] or [29], in which an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is  $302 \pm 5^\circ\text{C}$ .

(31)

An orexin type 2 receptor agonist containing the crystal according to any one of [1] to [30].

(32)

A pharmaceutical composition containing the crystal according to any one of [1] to [30].

(33)

An agent containing the crystal according to any one of [1] to [31] for use for prophylactic or therapeutic treatment of narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome accompanying narcolepsy-like symptoms, hypersomnia accompanied by Parkinson's disease, hypersomnia accompanied by Guillain-Barre syndrome, hypersomnia accompanied by Kleine-Levin syndrome, or hypersomnia accompanied by dementia with Lewy bodies.

(Advantageous Effects of Invention)

[0017] According to the invention, crystals of an oxazepine derivative or crystals of a solvate thereof, which have excellent orexin type 2 receptor agonist activity and are useful for the prevention or treatment of, for example, narcolepsy, idiopathic hypersomnia, hypersomnia, are provided. In addition, the crystals of the invention can be used as a drug substance for producing a pharmaceutical product.

### Brief Description of Drawings

[0018] [Fig.1]Fig. 1 is a powder X-ray diffraction spectrum of a crystal of Compound I.  
[Fig.2]Fig. 2 is a  $^{13}\text{C}$  solid-state NMR spectrum of a crystal of Compound I.  
[Fig.3]Fig. 3 is a powder X-ray diffraction spectrum of crystal form A of Compound II.  
[Fig.4]Fig. 4 is a  $^{13}\text{C}$  solid-state NMR spectrum of crystal form A of Compound II.  
[Fig.5]Fig. 5 is a powder X-ray diffraction spectrum of crystal form B of Compound II.

[Fig.15] Fig. 15 is a powder X-ray diffraction spectrum of a crystal of Compound V.

(2S,11aR)-7-fluoro-6-isopropoxy-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthy

ridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one

(Compound III)

(2S,11aR)-7-fluoro-6-(((R)-1-fluoropropan-2-yl)oxy)-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one

(Compound IV)

(2S,11aR)-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-6-(((R)-1,1,1-trifluoropropan-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one

(Compound V)

(2S,11aR)-9-fluoro-6-isopropoxy-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one

[0023] The above-mentioned various compounds can be produced with reference to Examples and the like described later. In addition, as is clear from Examples and the like described later, the compound has an orexin type 2 receptor agonist activity, and is useful for various diseases such as narcolepsy.

[0024] (Crystal of Compound I)

The crystal of Compound I of the invention is a crystal of

(2S,11aR)-7-fluoro-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-6-(((R)-1,1,1-trifluoropropan-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one.

[0025] The crystal of Compound I of the invention is characterized by, for example, a powder X-ray diffraction spectrum. Specifically, it has characteristic peaks at diffraction angles ( $2\theta$ ) of  $12.7^\circ$ ,  $14.7^\circ$ ,  $17.6^\circ$ ,  $20.7^\circ$ , and  $21.1^\circ$ . In another embodiment, it has characteristic peaks at  $12.7^\circ$ ,  $14.7^\circ$ ,  $17.6^\circ$ ,  $19.3^\circ$ ,  $20.2^\circ$ ,  $20.7^\circ$ ,  $21.1^\circ$ ,  $21.9^\circ$ ,  $24.8^\circ$ , and  $28.0^\circ$ .

[0026] The crystal of Compound I of the invention is characterized by, for example, a solid-state NMR spectrum ( $^{13}\text{C}$ ). Specifically, it has characteristic peaks at chemical shifts of 11.6, 14.7, 21.7, 30.8, 163.3, and 169.1 ppm. In another embodiment, it has characteristic peaks at chemical shifts of 11.6, 14.7, 21.7, 30.0, 30.8, 114.4, 117.9, 120.2, 130.5, 138.6, 146.1, 148.1, 149.6, 150.3, 163.3, and 169.1 ppm.

[0027] The crystal of Compound I of the invention is characterized by, for example, an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis. Specifically, the extrapolated onset temperature of the endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis, preferably in thermogravimetry-differential thermal analysis, is  $166\pm 5^\circ\text{C}$ .

[0028] (Crystal of Compound II)

The crystal of Compound II of the invention is a crystal of (2S,11aR)-7-fluoro-6-isopropoxy-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one.

- [0029] The above-mentioned crystal of Compound II of the invention includes six forms, and therefore, for convenience, they are referred to as crystal form A, crystal form B, crystal form C, crystal form D, crystal form E and crystal form F, respectively. Hereinafter, each form will be described in detail.
- [0030] Crystal form A of Compound II of the invention is characterized by, for example, a powder X-ray diffraction spectrum. Specifically, it has characteristic peaks at diffraction angles ( $2\theta$ ) of  $8.5^\circ$ ,  $12.7^\circ$ ,  $14.7^\circ$ , and  $17.7^\circ$ . In another embodiment, it has characteristic peaks at  $8.5^\circ$ ,  $12.7^\circ$ ,  $14.7^\circ$ ,  $17.7^\circ$ ,  $19.3^\circ$ ,  $20.2^\circ$ ,  $20.7^\circ$ ,  $21.2^\circ$ , and  $22.0^\circ$ .
- [0031] Crystal form A of Compound II of the invention is characterized by, for example, a solid-state NMR spectrum ( $^{13}\text{C}$ ). Specifically, it has characteristic peaks at chemical shifts of 15.0, 22.2, 23.2, 30.7, and 149.8 ppm. In another embodiment, it has characteristic peaks at chemical shifts of 15.0, 22.2, 23.2, 30.7, 31.4, 114.7, 117.6, 122.5, 129.3, 142.5, 145.8, 149.8, 151.9, 162.7, 164.1, and 169.6 ppm.
- [0032] Crystal form A of Compound II of the invention is characterized by, for example, an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis. Specifically, the extrapolated onset temperature of the endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis, preferably in thermogravimetry-differential thermal analysis, is  $222\pm 5^\circ\text{C}$ .
- [0033] Crystal form B of Compound II of the invention is characterized by, for example, a powder X-ray diffraction spectrum. Specifically, it has characteristic peaks at diffraction angles ( $2\theta$ ) of  $5.3^\circ$ ,  $6.3^\circ$ , and  $13.4^\circ$ . In another embodiment, it has characteristic peaks at  $5.3^\circ$ ,  $6.3^\circ$ ,  $9.3^\circ$ ,  $10.6^\circ$ ,  $10.9^\circ$ ,  $13.4^\circ$ ,  $19.1^\circ$ ,  $19.4^\circ$ , and  $20.5^\circ$ .
- [0034] Crystal form B of Compound II of the invention is characterized by, for example, an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis. Specifically, the extrapolated onset temperature of the endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis, preferably in thermogravimetry-differential thermal analysis, is  $223\pm 5^\circ\text{C}$ .
- [0035] Crystal form C of Compound II of the invention is characterized by, for example, a powder X-ray diffraction spectrum. Specifically, it has characteristic peaks at diffraction angles ( $2\theta$ ) of  $9.6^\circ$ ,  $13.3^\circ$ ,  $16.7^\circ$ ,  $18.7^\circ$ , and  $22.8^\circ$ . In another embodiment, it has characteristic peaks at  $9.6^\circ$ ,  $11.2^\circ$ ,  $12.0^\circ$ ,  $13.3^\circ$ ,  $16.7^\circ$ ,  $18.7^\circ$ ,  $20.7^\circ$ ,  $22.8^\circ$ , and  $25.3^\circ$ .
- [0036] Crystal form C of Compound II of the invention is characterized by, for example, a solid-state NMR spectrum ( $^{13}\text{C}$ ). Specifically, it has characteristic peaks at chemical

shifts of 15.7, 21.6, 162.4, 164.5, and 170.2 ppm. In another embodiment, it has characteristic peaks at chemical shifts of 15.7, 21.6, 23.5, 24.4, 30.6, 33.3, 114.5, 115.2, 117.0, 122.5, 128.1, 128.9, 142.5, 144.2, 148.6, 150.4, 152.4, 162.4, 164.5, and 170.2 ppm.

- [0037] Crystal form C of Compound II of the invention is characterized by, for example, an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis. Specifically, the extrapolated onset temperature of the endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis, preferably in thermogravimetry-differential thermal analysis, is  $223\pm 5^{\circ}\text{C}$ .
- [0038] Crystal form D of Compound II of the invention is characterized by, for example, a powder X-ray diffraction spectrum. Specifically, it has characteristic peaks at diffraction angles ( $2\theta$ ) of  $3.8^{\circ}$ ,  $12.0^{\circ}$ ,  $21.1^{\circ}$ , and  $23.9^{\circ}$ . In another embodiment, it has characteristic peaks at  $3.8^{\circ}$ ,  $7.6^{\circ}$ ,  $12.0^{\circ}$ ,  $13.1^{\circ}$ ,  $16.4^{\circ}$ ,  $17.4^{\circ}$ ,  $18.9^{\circ}$ ,  $19.9^{\circ}$ ,  $21.1^{\circ}$ , and  $23.9^{\circ}$ .
- [0039] Crystal form D of Compound II of the invention is characterized by, for example, a solid-state NMR spectrum ( $^{13}\text{C}$ ). Specifically, it has characteristic peaks at chemical shifts of 15.0, 23.0, 30.7, 144.4, and 150.2 ppm. In another embodiment, it has characteristic peaks at chemical shifts of 13.4, 15.0, 20.1, 21.8, 23.0, 30.1, 114.7, 119.3, 126.8, 130.6, 144.4, 147.6, 150.2, 152.6, 154.8, 161.7, 163.3, 170.2, and 173.4 ppm.
- [0040] Crystal form D of Compound II of the invention is characterized by, for example, an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis. Specifically, the extrapolated onset temperature of the endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis, preferably in thermogravimetry-differential thermal analysis, is  $214\pm 5^{\circ}\text{C}$ .
- [0041] Crystal form E of Compound II of the invention is characterized by, for example, a powder X-ray diffraction spectrum. Specifically, it has characteristic peaks at diffraction angles ( $2\theta$ ) of  $3.9^{\circ}$ ,  $12.4^{\circ}$ , and  $20.1^{\circ}$ . In another embodiment, it has characteristic peaks at  $3.9^{\circ}$ ,  $12.4^{\circ}$ ,  $13.1^{\circ}$ ,  $14.8^{\circ}$ ,  $16.7^{\circ}$ ,  $17.6^{\circ}$ , and  $20.1^{\circ}$ .
- [0042] Crystal form E of Compound II of the invention is characterized by, for example, an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis. Specifically, the extrapolated onset temperature of the endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis, preferably in thermogravimetry-differential thermal analysis, is  $121\pm 5^{\circ}\text{C}$ .
- [0043] Crystal form F of Compound II of the invention is characterized by, for example, a powder X-ray diffraction spectrum. Specifically, it has characteristic peaks at diffraction angles ( $2\theta$ ) of  $11.5^{\circ}$ ,  $11.9^{\circ}$ ,  $19.7^{\circ}$ , and  $23.5^{\circ}$ . In another embodiment, it has characteristic peaks at  $11.5^{\circ}$ ,  $11.9^{\circ}$ ,  $17.0^{\circ}$ ,  $17.8^{\circ}$ ,  $19.7^{\circ}$ ,  $22.8^{\circ}$ ,  $23.5^{\circ}$ ,  $24.7^{\circ}$ , and  $26.6^{\circ}$ .
- [0044] (Crystal of Compound III)

The crystal of Compound III of the invention is a crystal of (2S,11aR)-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-6-(((R)-1,1,1-trifluoropropan-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one.

- [0045] The crystal of Compound III of the invention is characterized by, for example, a powder X-ray diffraction spectrum. Specifically, it has characteristic peaks at diffraction angles ( $2\theta$ ) of  $13.4^\circ$ ,  $18.8^\circ$ , and  $22.9^\circ$ . In another embodiment, it has characteristic peaks at  $9.8^\circ$ ,  $12.0^\circ$ ,  $13.4^\circ$ ,  $15.8^\circ$ ,  $16.8^\circ$ ,  $18.8^\circ$ ,  $22.9^\circ$ , and  $23.3^\circ$ .
- [0046] The crystal of Compound III of the present invention is characterized by, for example, an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis. Specifically, the extrapolated onset temperature of the endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis, preferably in thermogravimetry-differential thermal analysis, is  $220\pm 5^\circ\text{C}$ .
- [0047] (Crystal of Compound IV)  
The crystal of Compound IV of the invention is a crystal of (2S,11aR)-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-6-(((R)-1,1,1-trifluoropropan-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one.
- [0048] The crystal of Compound IV of the invention is characterized by, for example, a powder X-ray diffraction spectrum. Specifically, it has characteristic peaks at diffraction angles ( $2\theta$ ) of  $12.7^\circ$ ,  $14.7^\circ$ ,  $17.7^\circ$ ,  $20.8^\circ$ , and  $21.1^\circ$ . In another embodiment, it has characteristic peaks at  $10.3^\circ$ ,  $12.7^\circ$ ,  $14.7^\circ$ ,  $15.3^\circ$ ,  $17.7^\circ$ ,  $19.4^\circ$ ,  $20.8^\circ$ ,  $21.1^\circ$ ,  $22.1^\circ$ , and  $24.9^\circ$ .
- [0049] The crystal of Compound IV of the invention is characterized by, for example, a solid-state NMR spectrum ( $^{13}\text{C}$ ). Specifically, it has characteristic peaks at chemical shifts of 10.8, 22.3, 31.2, 163.7, and 169.0 ppm. In another embodiment, it has characteristic peaks at chemical shifts of 10.8, 21.8, 22.3, 29.6, 31.2, 114.2, 115.4, 115.9, 144.1, 145.7, 149.2, 152.8, 156.5, 163.7, and 169.0 ppm.
- [0050] The crystal of Compound IV of the invention is characterized by, for example, an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis. Specifically, the extrapolated onset temperature of the endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis, preferably in thermogravimetry-differential thermal analysis, is  $216\pm 5^\circ\text{C}$ .
- [0051] (Crystal of Compound V)  
The crystal of Compound V of the invention is a crystal of (2S,11aR)-9-fluoro-6-isopropoxy-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one

- [0052] The crystal of Compound V of the invention is characterized by, for example, a powder X-ray diffraction spectrum. Specifically, it has characteristic peaks at diffraction angles ( $2\theta$ ) of  $15.5^\circ$ ,  $19.5^\circ$ , and  $21.8^\circ$ . In another embodiment, it has characteristic peaks at  $9.8^\circ$ ,  $11.9^\circ$ ,  $15.5^\circ$ ,  $16.7^\circ$ ,  $17.7^\circ$ ,  $19.0^\circ$ ,  $19.5^\circ$ ,  $21.1^\circ$ , and  $21.8^\circ$ .
- [0053] The crystal of Compound V of the present invention is characterized by, for example, an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis. Specifically, the extrapolated onset temperature of the endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis, preferably in thermogravimetry-differential thermal analysis, is  $302\pm 5^\circ\text{C}$ .
- [0054] Here, the above-mentioned "characteristic peak" means an inherent peak which characterizes each pattern of the entire spectrum in the powder X-ray diffraction spectrum or solid-state NMR spectrum ( $^{13}\text{C}$ ) of each crystal form. The crystal form of the invention also includes a crystal form that has peaks other than the above-mentioned characteristic peaks.
- [0055] Since the position and the relative intensity of the diffraction angle  $2\theta$  in the powder X-ray diffraction spectrum may slightly vary depending on the measurement conditions, the identity of the crystal form should be determined by appropriately referring to the pattern of the entire spectrum even in a case where  $2\theta$  is slightly different, and the crystal form within the range of such an error is also included in the invention. For example,  $\pm 0.5^\circ$  and preferably  $\pm 0.2^\circ$  are considered as the error of  $2\theta$ . That is, the crystal form specified by the above-described diffraction angle includes a crystal form that coincides within a range of  $\pm 0.5^\circ$  or  $\pm 0.2^\circ$ .
- [0056] In determining the identity of crystal forms using powder X-ray diffractometry, even if the number of peaks is small, it may be possible to determine the crystal forms to be the same crystal form when a plurality of peaks that coincide with each other are confirmed with an error within  $\pm 0.5^\circ$  or  $\pm 0.2^\circ$ . Especially, when an analysis is performed using a substance containing a mixture, such as a tablet, because peaks of other components, such as excipients, contained in the tablet or the like are also mixed with respect to the case where a drug substance powder is used as an analysis sample, and as a result, peaks that cannot be distinguished may be generated due to overlapping of peaks of a plurality of components.
- [0057] In addition, a crystal form within a range of an error derived from measurement conditions (for example, an apparatus) of a powder X-ray diffraction spectrum is also included in the invention.
- [0058] With respect to the value of the analysis result of the powder X-ray diffraction spectrum, the difference between the actual measured value of a standard of a crystal form, for example, each crystal form obtained by the method described in Examples of

the present application, and the numerical value of each analysis result described in the application is also allowed as a measurement error. That is, a crystal form in which the diffraction angles coincide with each other within the error range calculated by such a method is also included in the crystal form of the invention.

When a substance containing a mixture, such as a tablet, is used for analysis, the peak intensity tends to be smaller than when a drug substance powder is used as an analysis sample. Therefore, when the identity of the crystal form in the mixture is analyzed by the powder X-ray diffractometry, the measurement time may be extended, and it is also useful to increase the number of integrations.

[0059] In addition, in general, the chemical shift in the solid-state NMR spectrum ( $^{13}\text{C}$ ) also causes an error. The error is, for example, within a range of  $\pm 0.5$  ppm, and preferably  $\pm 0.25$  ppm. That is, the crystal forms specified by the above chemical shifts include those which are identical with each other within a range of  $\pm 0.25$  ppm to  $\pm 0.5$  ppm. In addition, the peak intensity may change, or the peak may appear or disappear depending on the difference in the rotational frequency or the measuring instrument at the time of measurement. In the determination of the identity of crystal forms using a solid-state NMR spectrum ( $^{13}\text{C}$ ), even when the number of peaks is small, in a case where a plurality of peaks that coincide with each other with errors within  $\pm 0.25$  ppm (in some cases, within  $\pm 0.5$  ppm) are confirmed, the crystals may be determined to be the same crystals. Especially, when an analysis is performed using a substance containing a mixture, such as a tablet, because peaks of multiple components, such as excipients, contained in the tablet or the like are also mixed with respect to the case where a drug substance powder is used as an analysis sample, and as a result, peaks that cannot be distinguished may be generated due to overlapping of peaks of a plurality of components.

[0060] When a substance containing a mixture, such as a tablet, is used for analysis, the peak intensity tends to be smaller than when a drug substance powder is used as an analysis sample. Therefore, when the identity of the crystal form in the mixture is analyzed by solid-state NMR, the measurement time may be extended, and it is also useful to increase the number of integrations.

[0061] Furthermore, with respect to the values of the analysis results of any of powder X-ray diffraction spectrum, thermogravimetry-differential thermal analysis, differential thermal analysis, and solid-state NMR spectrum ( $^{13}\text{C}$ ), the difference between the actual measured value of a standard of a crystal, for example, each crystal obtained by the method described in Examples of the application, and the numerical value of each analysis result described in the application is also allowed as a measurement error. That is, crystals having the same diffraction angles, chemical shifts, endothermic and exothermic peaks within the error range calculated by the above method are also

included in the crystals of the invention.

[0062] <Pharmaceutical Composition, Prophylactic, and Therapeutic Agent of the Present Invention>

Since the above-described compound according to the invention has orexin type 2 receptor agonist activity, the crystal of the invention is useful for the treatment or prevention of a disease mediated by orexin type 2 receptor agonist activity. Specifically, for example, the crystal of the invention is useful for the treatment or prevention of narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome accompanying narcolepsy-like symptoms, hypersomnia accompanied by Parkinson's disease, hypersomnia accompanied by Guillain-Barre syndrome, hypersomnia accompanied by Kleine-Levin syndrome, and hypersomnia accompanied by dementia with Lewy bodies, and is particularly useful for the treatment or prevention of narcolepsy.

Here, the above-mentioned “prevention” means to prevent the onset or the disease in an individual who has not yet suffered from the onset or the disease, and the above-mentioned “treatment” means to cure, suppress, or improve the disease or the symptom in an individual who has already suffered from the onset or the disease.

[0063] In addition, the compound according to the invention and the crystal of the invention preferably have selectivity for the orexin type 2 receptor agonist activity. For example, the compound of the invention and the crystal of the invention preferably have a significantly high orexin type 2 receptor agonist activity compared with an orexin type 1 receptor agonist activity.

[0064] A therapeutic agent or a prophylactic containing the crystal of the invention as an active ingredient can be prepared into a pharmaceutical composition using a carrier, a base, an excipient, and other additives that are usually used for formulation. Such carriers, bases, and excipients may be either solid or liquid, and specific examples thereof include lactose, magnesium stearate starch, talc, gelatin, agar, pectin, gum arabic, olive oil, sesame oil, cocoa butter, ethylene glycol, medium-chain fatty acid triglyceride, and other commonly used substances.

[0065] In addition, the administration of the pharmaceutical composition of the invention may be in any form of oral administration by tablets, pills, capsules, soft capsules, granules, powders, solutions, or the like, or parenteral administration by injections such as intravenous injection and intramuscular injection, suppositories, transdermal administration, nasal administration, or the like.

[0066] In addition, the crystal of the invention may be in the form of an orexin type 2 receptor agonist containing these as active ingredients. The expression “agonist” includes forms usually used in this field, that is, activators, agonists, stimulants and the like.

[0067] The therapeutically effective amount of the active ingredient in the therapeutic agent, the prophylactic, the agonist, or the pharmaceutical composition of the invention varies depending on the administration route, age and sex of the patient, and severity of the diseases, but is usually about 1 to 1,500 mg/day, and the number of administrations is usually 1 to 3 times/day or 1 to 3 times/week. It is preferable to prepare a preparation so as to satisfy such conditions.

However, since the dose varies depending on various conditions, a dose smaller than the above-mentioned dose may be sufficient in some cases, and a dose exceeding the above-mentioned range may be necessary in some cases.

### Examples

[0068] Hereinafter, the invention will be specifically described with reference to Examples. However, the following Examples do not limit the invention. For example, the synthesis method, purification method and crystallization method of the compound exemplified in the following Examples are merely examples of the method for obtaining the crystal of the invention, and the crystal of the invention is not limited to the crystal obtained only by the synthesis method, purification method and crystallization method disclosed below.

[0069] The structures of the compounds according to the crystals of Examples and the novel compounds isolated during the synthesis were confirmed by <sup>1</sup>H-NMR spectra or mass spectrometry using LC/MS (liquid chromatography/mass spectrometer).

[0070] The <sup>1</sup>H-NMR spectrum was measured using JEOL JNM-ECZ400S (400 MHz), and the observed chemical shift (δ: ppm) and coupling constant (J: Hz) are shown. When CDCl<sub>3</sub> was used as a solvent, a tetramethylsilane peak (0.00 ppm) or a chloroform peak (7.26 ppm) was used as a standard peak, and when DMSO-d<sub>6</sub> was used as a solvent, a dimethylsulfoxide peak (2.50 ppm) was used as a standard peak.

[0071] Regarding the results of LCMS, the measurement was performed using the following apparatus and under the following analytical conditions, and the observed value of [M+H]<sup>+</sup> (molecular weight actual measurement value: that is, actual measurement value obtained by adding a proton (H<sup>+</sup>) to the molecular mass (M) of the compound) and the retention time Rt (min) are shown.

[0072] Mass spectrometer: Agilent Technologies LC/MS 6130  
HPLC: LC-1260  
Column: Phenomenex Gemini C1 3 μm, 4.6 mm × 30 mm  
UV: PDA detection (254 nm)  
Column temperature: 40°C  
Detection voltage: 70 V

[0073] (Gradient Condition (Volume Ratio))  
Solvent:

A: H<sub>2</sub>O/acetonitrile = 95/5, 0.05% TFA

B: H<sub>2</sub>O/acetonitrile = 5/95, 0.05% TFA

Flow rate: 1.0 mL/min

Gradient:

0 min, solvent B: 2%, solvent A: 98%

0 to 0.3 min, solvent B: 2% → 10%, solvent A: 98% → 90%

0.3 to 1.5 min, solvent B: 10% → 100%, solvent A: 90% → 0%

1.5 to 3.5 min, solvent B: 100%, solvent A: 0%

3.5 to 3.51 min, solvent B: 100% → 2%, solvent A: 0% → 98%

3.51 min to 4.5 min, solvent B: 2%, solvent A: 98%

[0074] The powder X-ray diffraction (XRD) spectrum of the crystal according to Examples 2-6 and 9-10 was measured under the following conditions.

Apparatus: MiniFlex600-C manufactured by Rigaku Corporation

Radiation source: Cu · K $\alpha$

Wavelength: 1.541862 (10<sup>-10</sup> m)

Tube voltage-Tube current: 40 kV-15 mA

Detector: high-speed one dimensional detector D/tex Ultra2

Scan range: 3 to 40°

Step condition: 0.01°

Measurement speed: 10° per minute

DS: 1/4°

IHS: 10 mm

Incident/Receiving Soller slit: 2.5°, K $\beta$  filter (Ni)

For Example 7, analyses were performed in transmission mode (the sample is placed between Kapton (Registered Trademark) and Polypropylene foils), on the angular range  $2\theta = 2 - 50^\circ$ , with a step size of 0.026° and a time per step of 20.4s, unless stated otherwise. It is worth noting that Kapton (Registered Trademark) exhibits a low intensity signal in the shape of a large hump around  $2\theta = 5.5^\circ$ .

[0075] The thermogravimetric differential thermal analysis (TG-DTA) of the crystal according to Examples was measured under the following conditions. The melting point and other described temperatures of each crystal were obtained by an extrapolation method from endothermic and exothermic peaks in differential thermal analysis (DTA) (extrapolated onset temperature).

Apparatus: Thermo plus EVO2 TG-DTA8122 manufactured by Rigaku Corporation

Temperature increase rate: 10°C per minute

Atmosphere: air

Sample pan: aluminum

Reference: aluminum oxide

Measurement temperature range: 25 to 300°C

Only the crystal of Compound V in the invention described below was measured at a measurement temperature range of 25 to 350°C. The other crystals were measured under the above-described conditions.

[0076] The solid-state NMR spectrum ( $^{13}\text{C}$ ) of the crystal according to Examples was measured under the following conditions.

Apparatus: AvanceIII 500 manufactured by Bruker BioSpin K.K. (MAS rotor: 3.2 mm $\Phi$ )

Measurement nucleus:  $^{13}\text{C}$

Observation frequency: 125.8 MHz

Measurement mode: VCAP/MAS

MAS rotation speed: 10 kHz

Contact time: 2 milliseconds

Pulse repetition time: 5 seconds

Set temperature: 25°C

External standard substance: Glycine ( $\alpha$ -type crystal) (measured by setting the carbonyl peak of glycine in the  $\alpha$ -type crystal to 176.03 ppm)

[0077] In the examples, the following abbreviations may be used.

$^1\text{H}$ -NMR: proton nuclear magnetic resonance

LCMS: liquid chromatograph mass spectrometer

XRD: powder X-ray diffraction

MS: mass spectrum

Rt: retention time

min: minutes

s: singlet

d: doublet

t: triplet

q: quartet

dd: double doublet

dt: double triplet

m: multiplet

J: coupling constant

Hz: hertz

M: molar concentration

DMF: N,N-dimethylformamide

THF: tetrahydrofuran

DIAD: diisopropyl azodicarboxylate

WSC-HCl: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

HOBt: 1-hydroxybenzotriazole

Selectfluor: 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane  
bis(tetrafluoroborate)

Boc: tert-butoxycarbonyl

TFA: trifluoroacetic acid

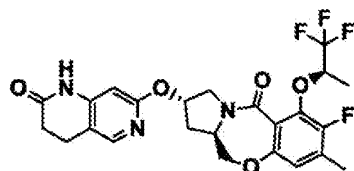
TBDPS: tert-butyldiphenylsilyl

CDCl<sub>3</sub>: deuterated chloroform

DMSO-d<sub>6</sub>: deuterated dimethylsulfoxide

[0078] <Example 1: Production of crystals of  
(2S,11aR)-7-fluoro-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-  
6-(((R)-1,1,1-trifluoropropan-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[  
2,1-c][1,4]oxazepin-5-one (Compound I)>

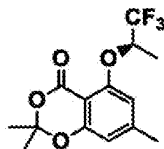
[0079] [Chem.4]



[0080] [Step 1]

(R)-2,2,7-trimethyl-5-(((1,1,1-trifluoropropan-2-yl)oxy))-4H-benzo[d][1,3]dioxin-4-one

[0081] [Chem.5]



[0082] (S)-1,1,1-trifluoro-2-propanol (10.0 g, 87.7 mmol) and pyridine (7.43 mL, 92.0 mmol) were dissolved in dichloromethane (65.8 mL), and trifluoromethanesulfonic anhydride (14.4 mL, 87.7 mmol) was added thereto at 0°C. The reaction liquid was warmed to room temperature and stirred overnight. The reaction liquid was filtered, and the filtrate was added to a mixture of 5-hydroxy-2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-4-one [CAS No. 1646145-58-5] (7.30 g, 35.1 mmol), potassium carbonate (14.5 g, 105 mmol), and DMF (65.8 mL), and the mixture was stirred at 60°C for 3 days. The reaction liquid was cooled to room temperature, a saturated aqueous solution of sodium hydrogen carbonate was added thereto, and the mixture was extracted with heptane/ethyl acetate (1/1). The organic layer was washed twice with saturated brine, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by amino silica gel column chromatography (heptane/ethyl acetate), thereby obtaining the title compound

(6.10 g).

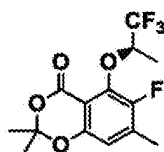
[0083] <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 6.52 (1H, s), 6.50 (1H, s), 4.75-4.66 (1H, m), 2.35 (3H, s), 1.70 (3H, s), 1.69 (3H, s), 1.59 (3H, d, J = 6.4 Hz)

LCMS: 305.1 [M+H]<sup>+</sup> (R<sub>t</sub> = 2.346 min)

[0084] [Step 2]

(R)-6-fluoro-2,2,7-trimethyl-5-((1,1,1-trifluoropropan-2-yl)oxy)-4H-benzo[d][1,3]dioxin-4-one

[0085] [Chem.6]



[0086] The compound (400 mg, 1.31 mmol) obtained in Step 1 was dissolved in acetonitrile (6.57 mL), and Selectfluor (931 mg, 2.63 mmol) was added thereto at 0°C. The reaction liquid was heated to 40°C and stirred for 2 days. A saturated aqueous solution of sodium hydrogen carbonate was added to the reaction liquid, and the mixture was extracted with ethyl acetate. The organic layer was washed twice with saturated brine, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (heptane/ethyl acetate), thereby obtaining the title compound (258 mg).

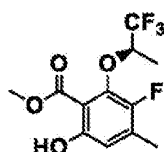
[0087] <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 6.60 (1H, d, J = 5.5 Hz), 4.72-4.62 (1H, m), 2.32 (3H, d, J = 2.3 Hz), 1.69 (6H, d, J = 7.8 Hz), 1.62 (3H, d, J = 6.4 Hz)

LCMS: 323.1 [M+H]<sup>+</sup> (R<sub>t</sub> = 2.387 min)

[0088] [Step 3] methyl

(R)-3-fluoro-6-hydroxy-4-methyl-2-((1,1,1-trifluoropropan-2-yl)oxy)benzoate

[0089] [Chem.7]



[0090] The compound (258 mg, 0.80 mmol) obtained in Step 2 was dissolved in methanol (2.67 mL), and potassium carbonate (332 mg, 2.40 mmol) was added thereto, followed by stirring at room temperature for 1 hour. Water was added to the reaction liquid, and the mixture was extracted with ethyl acetate. The organic layer was washed twice with saturated brine, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by amino silica gel column chromatography (heptane/ethyl acetate), thereby obtaining the title compound (177 mg).

[0091] <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 11.01 (1H, s), 6.60 (1H, d, J = 5.9 Hz), 4.62-4.52 (1H, m), 3.95

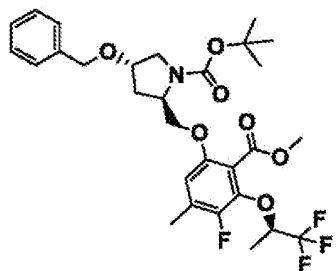
(3H, s), 2.28 (3H, d, J = 2.3 Hz), 1.54 (3H, d, J = 6.4 Hz)

LCMS: 297.0 [M+H]<sup>+</sup> (Rt = 2.352 min)

[0092] [Step 4] tert-butyl

(2R,4S)-4-(benzyloxy)-2-((4-fluoro-2-(methoxycarbonyl)-5-methyl-3-(((R)-1,1,1-trifluoropropan-2-yl)oxy)phenoxy)methyl)pyrrolidine-1-carboxylate

[0093] [Chem.8]



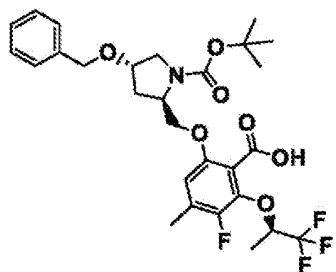
[0094] The compound (2.25 g, 7.59 mmol) obtained in Step 3, tert-butyl (2R,4S)-4-(benzyloxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate [CAS No. 1800019-47-9] (2.80 g, 9.11 mmol), and triphenylphosphine (2.99 g, 11.4 mmol) were dissolved in THF (25.3 mL), and DIAD (2.21 mL, 11.4 mmol) was added thereto at 0°C. The reaction liquid was heated to 40°C and stirred for 3 days. The reaction liquid was cooled to room temperature, water was added, and the solvent was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed twice with saturated brine, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by amino silica gel column chromatography (heptane/ethyl acetate), thereby obtaining the title compound (4.16 g).

[0095] LCMS: 486.2 [M+H-Boc]<sup>+</sup> (Rt = 2.637 min)

[0096] [Step 5]

6-(((2R,4S)-4-(benzyloxy)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl)methoxy)-3-fluoro-4-methyl-2-(((R)-1,1,1-trifluoropropan-2-yl)oxy)benzoic acid

[0097] [Chem.9]



[0098] The compound (4.16 g, 7.10 mmol) obtained in Step 4 was dissolved in a mixed

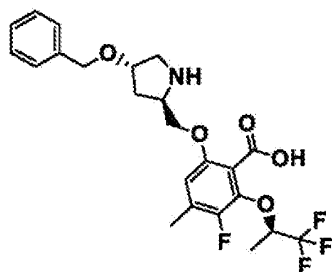
solvent of methanol (21.3 mL), THF (7.10 mL), and water (14.2 mL), potassium hydroxide (1.99 g, 35.5 mmol) was added thereto, followed by stirring at 85°C for 2 days. The reaction liquid was cooled to room temperature, 2 M aqueous hydrochloric acid solution (17.0 mL) was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed twice with saturated brine, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure to obtain the title compound (4.11 g).

[0099] LCMS: 472.2 [M+H-Boc]<sup>+</sup> (R<sub>t</sub> = 2.492 min)

[0100] [Step 6]

6-(((2R,4S)-4-(benzyloxy)pyrrolidin-2-yl)methoxy)-3-fluoro-4-methyl-2-(((R)-1,1,1-trifluoropropan-2-yl)oxy)benzoic acid

[0101] [Chem.10]



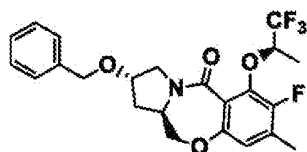
[0102] The compound (4.11 g, 7.20 mmol) obtained in Step 5 was dissolved in 1,4-dioxane (21.6 mL), a 4 M hydrochloric acid/1,4-dioxane solution (7.20 mL, 28.8 mmol) was added thereto, and the mixture was stirred at 50°C for 2 hours. The reaction liquid was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate and concentrated under reduced pressure. The obtained residue was dissolved in ethyl acetate again and concentrated under reduced pressure to obtain the title compound (3.62 g).

LCMS: 472.2 [M+H]<sup>+</sup> (R<sub>t</sub> = 1.935 min)

[0103] [Step 7]

(2S,11aR)-2-(benzyloxy)-7-fluoro-8-methyl-6-(((R)-1,1,1-trifluoropropan-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one

[0104] [Chem.11]



[0105] The compound (3.62 g, 7.67 mmol) obtained in Step 6 and N,N-diisopropylethylamine (6.14 mL, 10.7 mmol) were dissolved in DMF (47.5 mL), WSC-HCl (2.05 g, 10.7 mmol) and HOBt (1.64 g, 10.7 mmol) were added thereto, and

the mixture was stirred at 40°C overnight. The reaction liquid was cooled to room temperature, a saturated aqueous solution of sodium hydrogen carbonate was added thereto, and the mixture was extracted with heptane/ethyl acetate (1/2). The organic layer was washed twice with saturated brine, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (heptane/ethyl acetate), thereby obtaining the title compound (1.97 g).

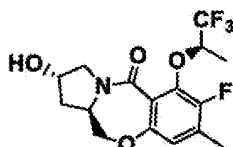
[0106] <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.37-7.28 (5H, m), 6.67 (1H, d, J = 5.9 Hz), 4.67-4.58 (2H, m), 4.47 (1H, d, J = 11.9 Hz), 4.30-4.25 (1H, m), 4.15-4.10 (1H, m), 4.01-3.90 (3H, m), 3.83 (1H, dd, J = 12.8, 5.0 Hz), 2.27-2.22 (4H, m), 1.86 (1H, dt, J = 13.3, 5.0 Hz), 1.59-1.57 (3H, m)

LCMS: 454.2 [M+H]<sup>+</sup> (Rt = 2.403 min)

[0107] [Step 8]

(2S,11aR)-7-fluoro-2-hydroxy-8-methyl-6-(((R)-1,1,1-trifluoropropan-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one

[0108] [Chem.12]

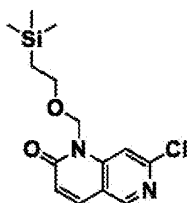


[0109] The compound (1.97 g, 4.34 mmol) obtained in Step 7 was dissolved in ethyl acetate (21.7 mL), 20% palladium hydroxide-activated carbon (197 mg) was added thereto, and the mixture was stirred at room temperature for 1 hour in a hydrogen atmosphere at normal pressure. The reaction liquid was filtered through Celite (registered trademark), and the filtrate was concentrated under reduced pressure to obtain the title compound (1.57 g).

[0110] LCMS: 364.1 [M+H]<sup>+</sup> (Rt = 2.056 min)

[0111] [Step 9] 7-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1,6-naphthyridin-2(1H)-one

[0112] [Chem.13]



[0113] 7-Chloro-1,6-naphthyridin-2(1H)-one [CAS No. 1345091-18-0] (1.00 g, 5.54 mmol) was dissolved in THF (27.7 mL), 1.5 M lithium bis(trimethylsilyl)amide/THF solution (4.60 mL, 6.92 mmol) was added thereto, and the mixture was stirred at room temperature for 30 minutes. Thereafter, 2-(trimethylsilyl)ethoxymethyl chloride (1.17 mL,

6.64 mmol) was added thereto, and the mixture was stirred at room temperature for 1 hour. Saturated brine was added to the reaction liquid, and the solvent was concentrated under reduced pressure. Saturated brine was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed twice with saturated brine, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (heptane/ethyl acetate), thereby obtaining the title compound (1.37 g).

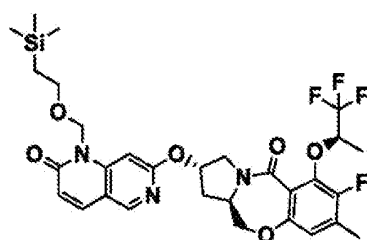
[0114]  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 8.55 (1H, s), 7.71 (1H, d,  $J = 9.6$  Hz), 7.48 (1H, s), 6.69 (1H, d,  $J = 9.6$  Hz), 5.66 (2H, s), 3.67 (2H, t,  $J = 8.2$  Hz), 0.97-0.93 (2H, m), -0.02 (9H, s)

LCMS: 311.1  $[\text{M}+\text{H}]^+$  ( $R_t = 2.413$  min)

[0115] [Step 10]

(2S,11aR)-7-fluoro-8-methyl-2-((2-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-1,2-dihydro-1,6-naphthyridin-7-yl)oxy)-6-(((R)-1,1,1-trifluoropropan-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one

[0116] [Chem.14]



[0117] The compound (1.57 g, 4.31 mmol) obtained in Step 8 was dissolved in DMF (13.1 mL), and 50% sodium hydride (0.33 g, 6.90 mmol) was added thereto at  $0^\circ\text{C}$ . The reaction liquid was warmed to room temperature and stirred for 1 hour. The reaction liquid was cooled to  $0^\circ\text{C}$ , and the compound (1.74 g, 5.61 mmol) obtained in Step 9 was added thereto. The reaction liquid was warmed to room temperature and stirred for 3 days. A saturated aqueous solution of sodium hydrogen carbonate was added to the reaction liquid, and the mixture was extracted with heptane/ethyl acetate (1/4). The organic layer was washed twice with saturated brine, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (heptane/ethyl acetate), thereby obtaining the title compound (1.60 g).

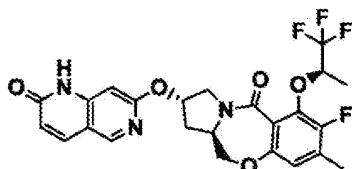
[0118]  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 8.32 (1H, s), 7.64 (1H, d,  $J = 9.6$  Hz), 6.75 (1H, s), 6.70 (1H, d,  $J = 5.9$  Hz), 6.50 (1H, d,  $J = 9.6$  Hz), 5.75-5.70 (1H, m), 5.68 (1H, d,  $J = 10.5$  Hz), 5.50 (1H, d,  $J = 10.5$  Hz), 4.64-4.58 (1H, m), 4.25-4.00 (0H, m), 3.64 (2H, dd,  $J = 8.9, 7.5$  Hz), 2.46-2.40 (1H, m), 2.28 (3H, d,  $J = 1.8$  Hz), 2.09 (1H, td,  $J = 9.5, 4.4$  Hz), 1.60-1.58 (3H, m), 0.94-0.86 (2H, m), -0.05 (9H, s)

LCMS: 638.3  $[\text{M}+\text{H}]^+$  ( $R_t = 2.586$  min)

[0119] [Step 11]

(2S,11aR)-7-fluoro-8-methyl-2-((2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl)oxy)-6-(((R)-1,1,1-trifluoropropan-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one

[0120] [Chem.15]



[0121] The compound (1.60 g, 2.51 mmol) obtained in Step 10 was dissolved in 1,4-dioxane (25.1 mL), a 4 M hydrochloric acid aqueous solution (12.6 mL, 50.3 mmol) was added thereto, and the mixture was stirred at room temperature for 4 days. The reaction liquid was concentrated under reduced pressure, a 2 M sodium carbonate aqueous solution was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed twice with saturated brine, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol), thereby obtaining the title compound (1.19 g).

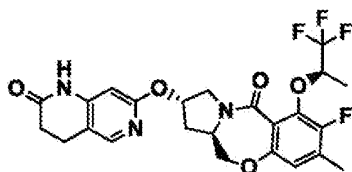
[0122] <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 10.43 (1H, s), 8.37 (1H, s), 7.73 (1H, d, J = 9.6 Hz), 6.70 (1H, d, J = 5.9 Hz), 6.50 (1H, d, J = 9.6 Hz), 6.47 (1H, s), 5.74-5.69 (1H, m), 4.64-4.58 (1H, m), 4.25-4.18 (1H, m), 4.15-4.06 (3H, m), 4.01 (1H, dd, J = 13.3, 5.0 Hz), 2.44-2.38 (1H, m), 2.28 (3H, d, J = 2.3 Hz), 2.08 (1H, dt, J = 14.0, 5.4 Hz), 1.58 (3H, d, J = 6.9 Hz)

LCMS: 508.2 [M+H]<sup>+</sup> (R<sub>t</sub> = 2.103 min)

[0123] [Step 12]

(2S,11aR)-7-fluoro-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-6-(((R)-1,1,1-trifluoropropan-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one (Compound I)

[0124] [Chem.16]



[0125] The compound (1.19 g, 2.34 mmol) obtained in Step 11 was dissolved in a mixed solvent of dichloromethane (11.7 mL) and methanol (11.7 mL), 20% palladium hydroxide-activated carbon (237 mg) was added thereto, and the mixture was stirred at

room temperature for 3 days in a hydrogen atmosphere at normal pressure. The reaction liquid was filtered through Celite (registered trademark), and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol), thereby obtaining a crude product (0.85 g) of the title compound.

[0126]  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 7.86 (1H, s), 7.46 (1H, s), 6.69 (1H, d,  $J = 5.9$  Hz), 6.03 (1H, s), 5.65-5.60 (1H, m), 4.63-4.56 (1H, m), 4.23-4.15 (1H, m), 4.08-3.83 (4H, m), 2.94-2.90 (2H, m), 2.68-2.64 (2H, m), 2.40-2.37 (1H, m), 2.27 (3H, d,  $J = 1.8$  Hz), 2.06-2.00 (1H, m), 1.59 (3H, d,  $J = 6.4$  Hz)

LCMS: 510.2  $[\text{M}+\text{H}]^+$  ( $R_t = 1.962$  min)

[0127] [Step 13] Preparation of crystals of  
(2S,11aR)-7-fluoro-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-6-(((R)-1,1,1-trifluoropropan-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one (Compound I)

[0128] Ethyl acetate (50.0 mL) was added to the crude product (848 mg) of the compound obtained in Step 12 to dissolve the compound, and the mixture was concentrated under reduced pressure. Diethyl ether (8.48 mL) was added to the obtained amorphous crude product to dissolve the compound, and the mixture was allowed to stand overnight. The precipitated solid was filtered, washed with diethyl ether, and dried to obtain crystals (703 mg) of the title compound.

[0129] The XRD spectrum of the obtained crystal is shown in Fig. 1. Peaks were observed at diffraction angles  $2\theta = 8.5^\circ, 10.3^\circ, 11.3^\circ, 12.7^\circ, 14.7^\circ, 15.3^\circ, 17.6^\circ, 18.8^\circ, 19.3^\circ, 20.2^\circ, 20.7^\circ, 21.1^\circ, 21.9^\circ, 23.0^\circ, 23.7^\circ, 24.2^\circ, 24.8^\circ, 27.3^\circ, 28.0^\circ, 28.9^\circ, 29.7^\circ$ , and  $31.7^\circ$ . In Fig. 1, the horizontal axis represents the value of the diffraction angle  $2\theta$ , and the vertical axis represents the intensity of diffraction X rays (the same applies to the following figures).

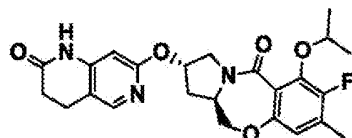
[0130] The melting point (extrapolated onset temperature of endothermic peak in TG-DTA) of the obtained crystal was  $165.6^\circ\text{C}$ .

[0131] The  $^{13}\text{C}$  solid-state NMR spectrum of the obtained crystal is shown in Fig. 2. Peaks were observed at chemical shifts of 11.6 ppm, 14.7 ppm, 21.7 ppm, 30.0 ppm, 30.8 ppm, 49.4 ppm, 52.9 ppm, 71.0 ppm, 73.7 ppm, 78.1 ppm, 95.3 ppm, 114.4 ppm, 117.9 ppm, 120.2 ppm, 130.5 ppm, 138.6 ppm, 146.1 ppm, 148.1 ppm, 149.6 ppm, 150.3 ppm, 163.3 ppm, and 169.1 ppm.

[0132] <Example 2: Production of crystals (Crystal form A) of  
(2S,11aR)-7-fluoro-6-isopropoxy-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one (Compound II)>

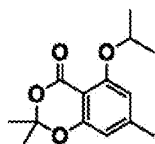
[0133]

[Chem.17]



[0134] [Step 1] 5-isopropoxy-2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-4-one

[0135] [Chem.18]



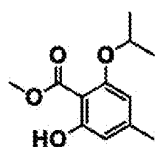
[0136] 5-Hydroxy-2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-4-one [CAS No. 1646145-58-5] (10.0 g, 48.0 mmol) was dissolved in DMF (80.0 mL), 2-iodopropane (6.68 mL, 67.2 mmol) and potassium carbonate (9.96 g, 72.0 mmol) were added thereto, and the mixture was stirred at 50°C overnight. The reaction liquid was cooled to room temperature, saturated brine was added thereto, and the mixture was extracted with heptane/ethyl acetate (1/1). The organic layer was washed twice with saturated brine, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (heptane/ethyl acetate), thereby obtaining the title compound (12.0 g).

[0137] <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 6.43 (1H, s), 6.33 (1H, s), 4.67-4.58 (1H, m), 2.32 (3H, s), 1.68 (6H, s), 1.42 (6H, d, J = 5.9 Hz)

LCMS: 251.1 [M+H]<sup>+</sup> (Rt = 2.278 min)

[0138] [Step 2] methyl 2-hydroxy-6-isopropoxy-4-methylbenzoate

[0139] [Chem.19]



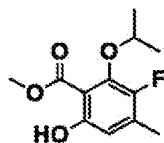
[0140] The compound (12.0 g, 47.9 mmol) obtained in Step 1 was dissolved in methanol (95.9 mL), and potassium carbonate (19.9 g, 144 mmol) was added thereto, followed by stirring at room temperature for 2 hours. The reaction liquid was concentrated under reduced pressure, saturated brine was added to the residue, and the mixture was extracted with heptane/ethyl acetate (1/3). The organic layer was washed twice with saturated brine, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure to obtain the title compound (10.1 g).

[0141] <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 11.44 (1H, s), 6.40 (1H, s), 6.24 (1H, s), 4.58-4.49 (1H, m), 3.91 (3H, s), 2.28 (3H, s), 1.35 (6H, d, J = 5.9 Hz)

LCMS: 225.1 [M+H]<sup>+</sup> (Rt = 2.315 min)

[0142] [Step 3] methyl 3-fluoro-6-hydroxy-2-isopropoxy-4-methylbenzoate

[0143] [Chem.20]



[0144] The compound (4.73 g, 21.2 mmol) obtained in Step 2 was dissolved in acetonitrile (42.2 mL), and Selectfluor (11.2 g, 31.6 mmol) was added thereto at 0°C, followed by stirring at 0°C for 6 hours. A saturated aqueous solution of sodium hydrogen carbonate was added to the reaction liquid, the solvent was concentrated under reduced pressure, and the residue was extracted with heptane/ethyl acetate (1/1). The organic layer was washed twice with a saturated aqueous solution of sodium hydrogen carbonate, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by amino silica gel column chromatography (heptane/ethyl acetate), thereby obtaining the title compound (2.73 g).

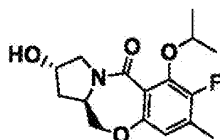
[0145] <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 10.93 (1H, s), 6.53 (1H, d, J = 5.9 Hz), 4.46-4.37 (1H, m), 3.96 (3H, s), 2.26 (3H, d, J = 2.3 Hz), 1.32-1.30 (6H, m)

LCMS: 243.1 [M+H]<sup>+</sup> (Rt = 2.332 min)

[0146] [Step 4]

(2S,11aR)-7-fluoro-2-hydroxy-6-isopropoxy-8-methyl-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one

[0147] [Chem.21]



[0148] The compound (16.3 g, 67.3 mmol) obtained in Step 3 and tert-butyl (2R,4S)-4-(benzyloxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate [CAS No. 1800019-47-9] (24.8 g, 80.7 mmol) were used as raw materials, and the same operations as in Step 4 to Step 8 of Example 1 were performed to obtain the title compound (15.7 g).

[0149] <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 6.61 (1H, d, J = 5.9 Hz), 4.61 (1H, dd, J = 8.7, 4.1 Hz), 4.53-4.47 (1H, m), 4.16-4.12 (1H, m), 4.07-4.00 (1H, m), 3.97-3.92 (1H, m), 3.88-3.79 (2H, m), 2.26 (3H, s), 2.19-2.13 (1H, m), 1.97 (1H, d, J = 3.7 Hz), 1.86 (1H, dt, J = 13.1, 5.4 Hz), 1.35 (3H, d, J = 5.9 Hz), 1.28 (3H, d, J = 6.4 Hz)

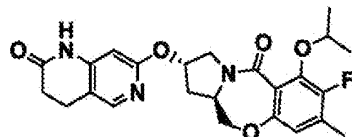
LCMS: 310.2 [M+H]<sup>+</sup> (Rt = 1.971 min)

[0150] [Step 5]

(2S,11aR)-7-fluoro-6-isopropoxy-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyri

din-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one  
(Compound II)

[0151] [Chem.22]



[0152] The compound (10.0 g, 32.3 mmol) obtained in Step 4 and the compound (13.1 g, 42.0 mmol) obtained in Step 9 of Example 1 were used as raw materials, and the same operations as in Step 10 to Step 12 of Example 1 were performed to obtain a crude product (6.06 g) of the title compound.

[0153]  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 7.92 (1H, s), 7.86 (1H, s), 6.62 (1H, d,  $J = 5.5$  Hz), 6.01 (1H, s), 5.64-5.59 (1H, m), 4.50-4.44 (1H, m), 4.19-3.97 (5H, m), 2.94-2.90 (2H, m), 2.67-2.63 (2H, m), 2.38-2.32 (1H, m), 2.26 (3H, s), 2.09-2.03 (1H, m), 1.36 (3H, d,  $J = 6.4$  Hz), 1.26 (3H, d,  $J = 5.9$  Hz)

LCMS: 456.2  $[\text{M}+\text{H}]^+$  ( $R_t = 1.947$  min)

[0154] [Step 6] Preparation of crystals (Crystal form A) of  
(2S,11aR)-7-fluoro-6-isopropoxy-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one  
(Compound II)

[0155] Ethyl acetate (6.05 mL) was added to the crude product (1.21 g) of the compound obtained in Step 5 to dissolve the compound, and the mixture was concentrated under reduced pressure. Diethyl ether (6.05 mL) was added to the obtained amorphous crude product to dissolve the compound, and the mixture was allowed to stand for 1 hour. The precipitated solid was filtered, washed with diethyl ether, and dried to obtain crystals (1.02 g) of the title compound.

In the above production, when an ether-based solvent such as diethyl ether or tert-butyl methyl ether is used as the solvent in the crystallization process, the crystal form A of Compound II is efficiently precipitated.

[0156] The XRD spectrum of the obtained crystal is shown in Fig. 3. Peaks were observed at diffraction angles  $2\theta = 8.5^\circ, 11.4^\circ, 12.7^\circ, 14.7^\circ, 17.7^\circ, 18.1^\circ, 18.8^\circ, 19.3^\circ, 20.2^\circ, 20.7^\circ, 21.2^\circ, 22.0^\circ, 23.1^\circ, 23.8^\circ, 24.1^\circ, 24.4^\circ, 24.9^\circ, 28.1^\circ, 29.0^\circ$ , and  $29.3^\circ$ .

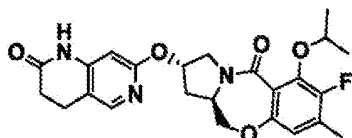
[0157] The melting point (extrapolated onset temperature of endothermic peak in TG-DTA) of the obtained crystal was  $222^\circ\text{C}$ .

[0158] The  $^{13}\text{C}$  solid-state NMR spectrum of the obtained crystal is shown in Fig. 4. Peaks were observed at chemical shifts of 15.0 ppm, 22.2 ppm, 23.2 ppm, 30.7 ppm, 31.4 ppm, 49.9 ppm, 52.7 ppm, 70.8 ppm, 76.9 ppm, 77.9 ppm, 96.1 ppm, 114.7 ppm, 117.6 ppm, 122.5 ppm, 129.3 ppm, 142.5 ppm, 145.8 ppm, 149.8 ppm, 151.9 ppm,

162.7 ppm, 164.1 ppm, and 169.6 ppm.

[0159] <Example 3: Production of crystals (Crystal form B) of (2S,11aR)-7-fluoro-6-isopropoxy-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one (Compound II)>

[0160] [Chem.23]



[0161] Water (1.00 mL) was added to the crude product (10.3 mg) of the compound obtained in Step 5 of Example 2 to form a slurry, and the slurry was stirred at room temperature for 18 days. The solid was filtered and dried to obtain crystals of the title compound.

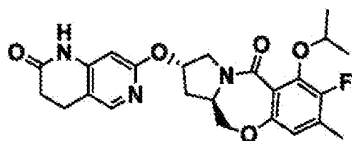
[0162] The XRD spectrum of the obtained crystal is shown in Fig. 5. Peaks were observed at diffraction angles  $2\theta = 5.3^\circ, 6.3^\circ, 7.7^\circ, 9.3^\circ, 10.6^\circ, 10.9^\circ, 11.2^\circ, 12.1^\circ, 13.2^\circ, 13.4^\circ, 13.7^\circ, 14.1^\circ, 14.4^\circ, 16.6^\circ, 17.6^\circ, 18.5^\circ, 19.1^\circ, 19.4^\circ, 20.2^\circ, 20.5^\circ, 20.7^\circ, 20.9^\circ, 21.1^\circ, 21.3^\circ, 21.7^\circ, 23.0^\circ, \text{ and } 23.3^\circ$ .

[0163] In the TG-DTA spectrum of the obtained crystal, an endothermic peak accompanied by weight loss was confirmed from  $115^\circ\text{C}$  and an exothermic peak was confirmed from  $149^\circ\text{C}$ . The melting point (extrapolated onset temperature of endothermic peak not accompanied by weight change) was  $223^\circ\text{C}$ .

Since the endothermic peak accompanied by weight loss was confirmed, the present crystal is presumed to be a crystal of a solvate such as a hydrate.

[0164] <Example 4: Production of crystals (Crystal form C) of (2S,11aR)-7-fluoro-6-isopropoxy-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one (Compound II)>

[0165] [Chem.24]



[0166] The crude product (38.3 g) of the compound obtained in Step 5 of Example 2 was dissolved in dichloromethane (80.0 mL), 2-propanol (160 mL) was added thereto, and dichloromethane was distilled off under reduced pressure. Thereafter, the reaction liquid was heated to  $60^\circ\text{C}$  and stirred as it was for 13 hours. The suspension containing the precipitated solid was cooled to room temperature. The solid was filtered, washed

with 2-propanol (80.0 mL), and dried, thereby obtaining crystals (25.0 g) of the title compound.

In the above production, for example, when a solvent other than an ether-based solvent (for example, an ester-based solvent such as ethyl acetate or isopropyl acetate, an alcohol-based solvent such as ethanol or 2-propanol, acetone or the like) is used as the solvent in the crystallization process, the crystal form C of Compound II is efficiently precipitated.

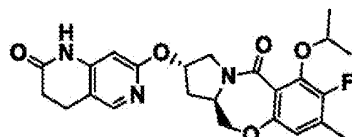
[0167] The XRD spectrum of the obtained crystal is shown in Fig. 6. Peaks were observed at diffraction angles  $2\theta = 7.5^\circ, 9.6^\circ, 11.2^\circ, 12.0^\circ, 12.4^\circ, 13.3^\circ, 15.7^\circ, 16.7^\circ, 18.1^\circ, 18.7^\circ, 19.4^\circ, 20.7^\circ, 22.8^\circ, 25.0^\circ, 25.3^\circ, 25.5^\circ, 26.9^\circ, 29.0^\circ, \text{ and } 29.8^\circ$ .

[0168] The melting point (extrapolated onset temperature of endothermic peak in TG-DTA) of the obtained crystal was  $223^\circ\text{C}$ .

[0169] The  $^{13}\text{C}$  solid-state NMR spectrum of the obtained crystal is shown in Fig. 7. Peaks were observed at chemical shifts of 15.7 ppm, 21.6 ppm, 23.5 ppm, 24.4 ppm, 30.6 ppm, 33.3 ppm, 48.5 ppm, 49.7 ppm, 54.5 ppm, 72.6 ppm, 73.9 ppm, 77.1 ppm, 94.4 ppm, 114.5 ppm, 115.2 ppm, 117.0 ppm, 122.5 ppm, 128.1 ppm, 128.9 ppm, 142.5 ppm, 144.2 ppm, 148.6 ppm, 150.4 ppm, 152.4 ppm, 162.4 ppm, 164.5 ppm, and 170.2 ppm.

[0170] <Example 5: Production of crystals (Crystal form D) of (2S,11aR)-7-fluoro-6-isopropoxy-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one (Compound II)>

[0171] [Chem.25]



[0172] Ethyl acetate (10.0 mL) was added to the crystals (2.00 g) obtained in Example 3 and dissolved, and the solvent was concentrated under reduced pressure. Ethyl acetate (10.0 mL) was added to the obtained amorphous crude product to dissolve it, and the mixture was concentrated under reduced pressure until the amount of the solvent in the reaction liquid became less than half. The reaction liquid was cooled to  $-10^\circ\text{C}$  and stirred as it was for 2 hours. The precipitated solid was filtered and dried to obtain crystals of the title compound.

[0173] The XRD spectrum of the obtained crystal is shown in Fig. 8. Peaks were observed at diffraction angles  $2\theta = 3.8^\circ, 7.6^\circ, 11.4^\circ, 12.0^\circ, 12.4^\circ, 13.1^\circ, 13.5^\circ, 14.0^\circ, 14.7^\circ, 15.1^\circ, 16.4^\circ, 17.4^\circ, 18.0^\circ, 18.9^\circ, 19.9^\circ, 20.7^\circ, 21.1^\circ, 23.9^\circ, 26.5^\circ, 27.3^\circ, \text{ and } 28.1^\circ$ .

[0174] In the TG-DTA spectrum of the obtained crystal, an endothermic peak accompanied

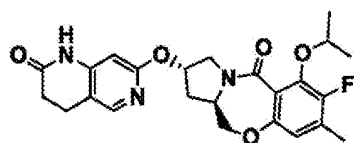
by weight loss was confirmed from 126°C and an exothermic peak was confirmed from 163°C. The melting point (extrapolated onset temperature of endothermic peak not accompanied by weight change) was 214°C.

Since the endothermic peak accompanied by weight loss was confirmed, the present crystal is presumed to be a crystal of a solvate such as a hydrate.

[0175] The <sup>13</sup>C solid-state NMR spectrum of the obtained crystal is shown in Fig. 9. Peaks were observed at chemical shifts of 13.4 ppm, 15.0 ppm, 20.1 ppm, 21.8 ppm, 23.0 ppm, 30.7 ppm, 49.8 ppm, 54.7 ppm, 70.5 ppm, 77.4 ppm, 79.1 ppm, 95.4 ppm, 114.7 ppm, 119.3 ppm, 126.8 ppm, 130.6 ppm, 144.4 ppm, 147.6 ppm, 150.2 ppm, 152.6 ppm, 154.8 ppm, 161.7 ppm, 163.3 ppm, 170.2 ppm, and 173.7 ppm.

[0176] <Example 6: Production of crystals (Crystal form E) of (2S,11aR)-7-fluoro-6-isopropoxy-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one (Compound II)>

[0177] [Chem.26]



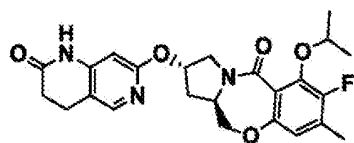
[0178] The crude product (400 mg) of the compound obtained in Step 5 of Example 2 was dissolved in Toluene (2.00 mL). Since a solid precipitated immediately after the dissolution, the reaction liquid was heated to 70°C and stirred as it was for 2 hours. The suspension containing the precipitated solid was cooled to room temperature. The solid was filtered, washed with toluene (0.80 mL), and dried, thereby obtaining crystals of the title compound (363 mg).

[0179] The XRD spectrum of the obtained crystal is shown in Fig. 10. Peaks were observed at diffraction angles  $2\theta = 3.9^\circ, 11.3^\circ, 11.6^\circ, 12.4^\circ, 13.1^\circ, 14.8^\circ, 15.3^\circ, 15.6^\circ, 16.7^\circ, 17.2^\circ, 17.6^\circ, 18.0^\circ, 19.2^\circ, 19.6^\circ, 20.1^\circ, 21.3^\circ, 22.7^\circ, 23.7^\circ, 25.5^\circ, 26.5^\circ, \text{ and } 28.1^\circ$ .

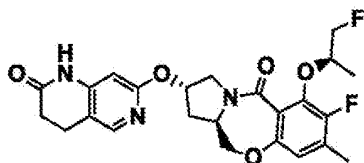
[0180] The melting point (extrapolated onset temperature of endothermic peak in TG-DTA) of the obtained crystal was 121°C.

[0181] <Example 7: Production of crystals (Crystal form F) of (2S,11aR)-7-fluoro-6-isopropoxy-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one (Compound II)>

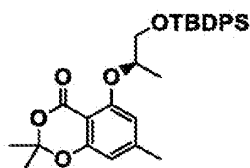
[0182] [Chem.27]



- [0183] The crude product (48 mg) of the compound obtained in Step 5 of Example 2 was dissolved in toluene (35 mL) at 50°C. The homogeneous solution was then cooled down to room temperature in 2.5h; kept at room temperature for seven days, then kept at 4°C for eight days, finally at -26°C for 15 days. An alternative method consisted in placing the sample directly at 0°C for 5min under stirring, then keeping it for 24h at 4°C, finally for 12 days at -26°C. The suspension was centrifuged, the liquid phase removed and the solid phase extracted and analyzed by X-Ray diffraction.
- [0184] The XRD spectrum of the obtained crystal is shown in Fig. 11. Peaks were observed at diffraction angles  $2\theta = 3.8^\circ, 11.5^\circ, 11.9^\circ, 12.7^\circ, 13.6^\circ, 14.8^\circ, 15.2^\circ, 16.1^\circ, 16.5^\circ, 17.0^\circ, 17.5^\circ, 17.8^\circ, 18.7^\circ, 19.0^\circ, 19.7^\circ, 20.6^\circ, 20.9^\circ, 22.2^\circ, 22.8^\circ, 23.1^\circ, 23.5^\circ, 23.9^\circ, 24.7^\circ, 25.0^\circ, 25.5^\circ, 25.8^\circ, 26.1^\circ, 26.6^\circ, 27.2^\circ, 27.5^\circ, 28.0^\circ, 28.6^\circ, 28.9^\circ, 29.2^\circ, 29.8^\circ, 30.9^\circ, 31.2^\circ, 31.4^\circ, 32.0^\circ, 32.5^\circ, 33.2^\circ, 33.9^\circ, 34.5^\circ, 35.2^\circ, 35.8^\circ, 35.9^\circ, 36.4^\circ, 36.6^\circ, 36.8^\circ, 37.2^\circ, 37.7^\circ, 38.8^\circ, \text{ and } 39.6^\circ$ .
- [0185] <Example 7: Production of crystals of  
(2S,11aR)-7-fluoro-6-(((R)-1-fluoropropan-2-yl)oxy)-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one (Compound III)>
- [0186] [Chem.28]



- [0187] [Step 1]  
(R)-5-((1-(((tert-butyldiphenylsilyl)oxy)propan-2-yl)oxy)-2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-4-one
- [0188] [Chem.29]



- [0189] 5-Hydroxy-2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-4-one [CAS No. 1646145-58-5] (400 mg, 1.92 mmol), (S)-1-(((tert-butyldiphenylsilyl)oxy)propan-2-ol [CAS No. 1240285-01-1] (725 mg, 2.31 mmol), and triphenylphosphine (655 mg, 2.50 mmol) were dissolved in THF (5.77 mL), DIAD (0.49 mL, 2.50 mmol) was added thereto, and the mixture was stirred at room temperature for 1 hour. A saturated aqueous solution of sodium hydrogen carbonate was added to the reaction liquid, and the mixture was extracted with ethyl acetate. The organic layer was washed twice with saturated brine,

dried with anhydrous magnesium sulfate, and concentrated under reduced pressure.

The residue was purified by silica gel column chromatography (heptane/ethyl acetate), thereby obtaining the title compound (1.03 g).

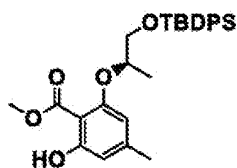
[0190]  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 7.68-7.64 (4H, m), 7.44-7.35 (6H, m), 6.47 (1H, s), 6.32 (1H, s), 4.66-4.58 (1H, m), 3.95 (1H, dd,  $J = 10.3, 6.2$  Hz), 3.73 (1H, dd,  $J = 10.3, 5.7$  Hz), 2.27 (3H, s), 1.65 (6H, d,  $J = 14.2$ , Hz), 1.41 (3H, d,  $J = 5.9$ , Hz), 1.01 (9H, s)

LCMS: 505.3  $[\text{M}+\text{H}]^+$  ( $R_t = 2.880$  min)

[0191] [Step 2] methyl

(R)-2-((1-((tert-butyldiphenylsilyl)oxy)propan-2-yl)oxy)-6-hydroxy-4-methylbenzoate

[0192] [Chem.30]



[0193] The compound (1.03 g, 2.05 mmol) obtained in Step 1 was dissolved in methanol (6.82 mL), and potassium carbonate (848 mg, 6.14 mmol) was added thereto, followed by stirring at room temperature for 2 hours. Water was added to the reaction liquid, and the mixture was extracted with ethyl acetate. The organic layer was washed twice with saturated brine, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure to obtain the title compound (939 mg).

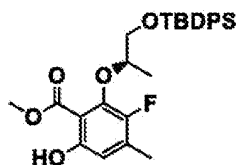
[0194]  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 11.45 (1H, s), 7.65-7.64 (4H, m), 7.44-7.34 (6H, m), 6.39 (1H, s), 6.24 (1H, s), 4.53-4.50 (1H, m), 3.85 (1H, dd,  $J = 10.3, 5.1$  Hz), 3.80 (3H, s), 3.71 (1H, dd,  $J = 10.5, 5.3$  Hz), 2.23 (3H, s), 1.35 (3H, d,  $J = 5.9$  Hz), 1.03 (9H, s)

LCMS: 479.2  $[\text{M}+\text{H}]^+$  ( $R_t = 2.900$  min)

[0195] [Step 3] methyl

(R)-2-((1-((tert-butyldiphenylsilyl)oxy)propan-2-yl)oxy)-3-fluoro-6-hydroxy-4-methylbenzoate

[0196] [Chem.31]



[0197] The compound (1.62 g, 3.39 mmol) obtained in Step 2 was dissolved in acetonitrile (11.3 mL), and Selectfluor (1.80 g, 5.09 mmol) was added thereto at  $0^\circ\text{C}$ . The reaction liquid was warmed to room temperature and stirred overnight. A saturated aqueous solution of sodium hydrogen carbonate was added to the reaction liquid, and the mixture was extracted three times with ethyl acetate. The organic layer was collected,

washed with saturated brine, dried with sodium sulfate, and concentrated under reduced pressure. The residue was purified by amino silica gel column chromatography (heptane/ethyl acetate), thereby obtaining the title compound (832 mg).

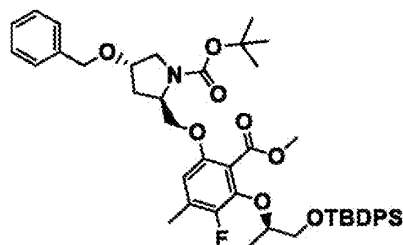
[0198]  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 10.94 (1H, s), 7.61-7.57 (4H, m), 7.43-7.32 (6H, m), 6.50 (1H, d,  $J = 5.9$  Hz), 4.41-4.34 (1H, m), 3.87 (1H, dd,  $J = 10.5, 5.0$  Hz), 3.77 (3H, s), 3.65 (1H, dd,  $J = 10.3, 5.7$  Hz), 2.24 (3H, d,  $J = 2.3$  Hz), 1.31 (3H, d,  $J = 6.4$  Hz), 0.98 (9H, s)

LCMS: 497.3  $[\text{M}+\text{H}]^+$  ( $R_t = 2.928$  min)

[0199] [Step 4] tert-butyl

(2R,4S)-4-(benzyloxy)-2-((3-(((R)-1-((tert-butyldiphenylsilyl)oxy)propan-2-yl)oxy)-4-fluoro-2-(methoxycarbonyl)-5-methylphenoxy)methyl)pyrrolidine-1-carboxylate

[0200] [Chem.32]



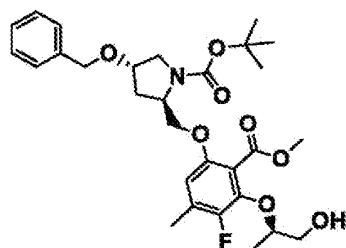
[0201] The compound (832 mg, 1.68 mmol) obtained in Step 3 and tert-butyl (2R,4S)-4-(benzyloxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate [CAS No. 1800019-47-9] (618 mg, 2.01 mmol) were used as raw materials, and the same operation as in Step 4 of Example 1 was performed to obtain the title compound (1.21 g).

LCMS: 686.4  $[\text{M}+\text{H-Boc}]^+$  ( $R_t = 3.296$  min)

[0202] [Step 5] tert-butyl

(2R,4S)-4-(benzyloxy)-2-((4-fluoro-3-(((R)-1-hydroxypropan-2-yl)oxy)-2-(methoxycarbonyl)-5-methylphenoxy)methyl)pyrrolidine-1-carboxylate

[0203] [Chem.33]



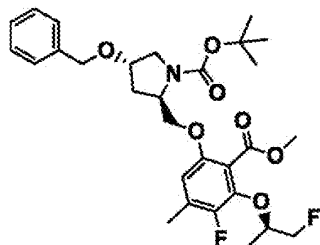
[0204] The compound (1.21 g, 1.54 mmol) obtained in Step 4 was dissolved in THF (5.13 mL), a 1 M tetrabutylammonium fluoride/THF solution (2.31 mL, 2.31 mmol) was added thereto at  $0^\circ\text{C}$ , followed by stirring at  $0^\circ\text{C}$  for 3 hours. A saturated aqueous

solution of ammonium chloride was added to the reaction liquid, and the mixture was extracted three times with ethyl acetate. The organic layer was collected, washed with saturated brine, dried with sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (heptane/ethyl acetate), thereby obtaining the title compound (818 mg).

[0205]  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 7.35-7.26 (5H, m), 6.46-6.38 (1H, m), 4.51-4.46 (3H, m), 4.25-3.55 (11H, m), 3.39-3.41 (1H, m), 2.24-2.18 (5H, m), 1.47-1.45 (9H, m), 1.32 (3H, d,  $J = 6.4$  Hz)

[0206] [Step 6] tert-butyl  
(2R,4S)-4-(benzyloxy)-2-((4-fluoro-3-(((R)-1-fluoropropan-2-yl)oxy)-2-(methoxycarbonyl)-5-methylphenoxy)methyl)pyrrolidine-1-carboxylate

[0207] [Chem.34]

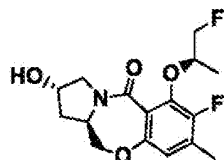


[0208] The compound (400 mg, 0.73 mmol) obtained in Step 5 was dissolved in dichloromethane (7.31 mL), and bis(2-methoxyethyl)aminosulfur trifluoride (0.26 mL, 1.46 mmol) was added thereto, followed by stirring at room temperature overnight. A saturated aqueous solution of sodium hydrogen carbonate was added to the reaction liquid, and the mixture was extracted with ethyl acetate. The organic layer was washed twice with saturated brine, dried with sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (heptane/ethyl acetate), thereby obtaining the title compound (150 mg).

[0209]  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 7.32-7.29 (5H, m), 6.49-6.42 (1H, m), 4.59-4.46 (4H, m), 4.40 (1H, d,  $J = 4.1$  Hz), 4.25-3.96 (4H, m), 3.85 (3H, s), 3.84-3.34 (2H, m), 2.23-2.18 (5H, m), 1.47-1.45 (9H, m), 1.32 (3H, d,  $J = 6.4$  Hz)

[0210] [Step 7]  
(2S,11aR)-7-fluoro-6-(((R)-1-fluoropropan-2-yl)oxy)-2-hydroxy-8-methyl-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one

[0211] [Chem.35]



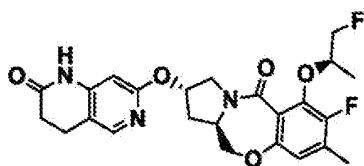
[0212] The compound (150 mg, 0.27 mmol) obtained in Step 6 was used as a raw material, and the same operations as in Step 5 to Step 8 of Example 1 were performed to obtain the title compound (115 mg).

LCMS: 328.2 [M+H]<sup>+</sup> (R<sub>t</sub> = 1.937 min)

[0213] [Step 8]

(2S,11aR)-7-fluoro-6-(((R)-1-fluoropropan-2-yl)oxy)-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one (Compound III)

[0214] [Chem.36]



[0215] The compound (115 mg, 0.35 mmol) obtained in Step 7 and the compound (141 mg, 0.45 mmol) obtained in Step 9 of Example 1 were used as raw materials, and the same operations as in Step 10 to Step 12 of Example 1 were performed to obtain a crude product of the title compound.

[0216] <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.86 (1H, s), 7.78 (1H, s), 6.65 (1H, d, J = 5.9 Hz), 6.06 (1H, s), 5.64-5.60 (1H, m), 4.64-4.32 (3H, m), 4.18-4.16 (1H, m), 4.05-3.97 (4H, m), 2.93-2.90 (2H, m), 2.70-2.63 (2H, m), 2.38-2.32 (1H, m), 2.27 (3H, d, J = 1.8 Hz), 2.08-2.02 (1H, m), 1.40-1.38 (3H, m)

LCMS: 474.2 [M+H]<sup>+</sup> (R<sub>t</sub> = 1.901 min)

[0217] [Step 9] Preparation of crystals of

(2S,11aR)-7-fluoro-6-(((R)-1-fluoropropan-2-yl)oxy)-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one (Compound III)

[0218] Ethyl acetate (2.00 mL) was added to the crude product obtained in Step 8 for dissolution, and concentrated under reduced pressure. The obtained solid was collected and dried to obtain crystals (46.3 mg) of the title compound.

[0219] The XRD spectrum of the obtained crystal is shown in Fig. 11. Peaks were observed at diffraction angles 2θ = 9.8°, 11.4°, 12.0°, 12.4°, 13.4°, 15.8°, 16.8°, 18.1°, 18.8°, 20.7°, 22.7°, 22.9°, 23.3°, 25.0°, 25.4°, 27.0°, 27.7°, and 29.1°.

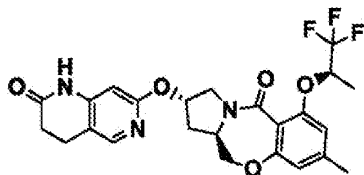
[0220] The melting point (extrapolated onset temperature of endothermic peak in TG-DTA) of the obtained crystal was 220°C.

[0221] <Example 8: Production of crystals of

(2S,11aR)-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-6-(((R)-1,1,1-trifluoropropan-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]

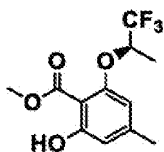
]oxazepin-5-one (Compound IV)>

[0222] [Chem.37]



[0223] [Step 1] methyl (R)-2-hydroxy-4-methyl-6-((1,1,1-trifluoropropan-2-yl)oxy)benzoate

[0224] [Chem.38]



[0225] The compound (8.21 g, 27.0 mmol) obtained in Step 1 of Example 1 was dissolved in methanol (54.0 mL), and potassium carbonate (11.2 g, 81.0 mmol) was added thereto, followed by stirring at room temperature for 3 hours. Water was added to the reaction liquid, the solvent was concentrated under reduced pressure, and the residue was extracted with heptane/ethyl acetate (1/1). The organic layer was washed twice with saturated brine, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure to obtain the title compound (7.37 g).

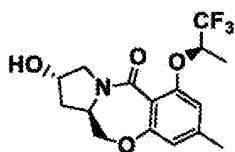
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 11.45 (1H, s), 6.51 (1H, s), 6.23 (1H, s), 4.71-4.62 (1H, m), 3.92 (3H, s), 2.30 (3H, s), 1.52 (3H, d, J = 6.4 Hz)

LCMS: 279.1 [M+H]<sup>+</sup> (R<sub>t</sub> = 2.344 min)

[0226] [Step 2]

(2S,11aR)-2-hydroxy-8-methyl-6-(((R)-1,1,1-trifluoropropan-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one

[0227] [Chem.39]



[0228] The compound (7.70 g, 27.7 mmol) obtained in Step 1 and tert-butyl (2R,4S)-4-(benzyloxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate [CAS No. 1800019-47-9] (10.2 g, 33.2 mmol) were used as raw materials, and the same operations as in Step 4 to Step 8 of Example 1 were performed to obtain the title compound (5.60 g).

[0229] <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 6.70 (1H, s), 6.62 (1H, s), 4.72-4.63 (1H, m), 4.63-4.57 (1H, m), 4.15 (1H, dd, J = 9.1, 4.1 Hz), 4.10-3.95 (2H, m), 3.88-3.79 (2H, m), 2.32 (3H, s),

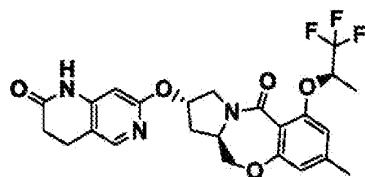
2.20-2.13 (1H, m), 1.94 (1H, s), 1.86 (1H, dt,  $J = 13.4, 5.3$  Hz), 1.59-1.57 (3H, m)

LCMS: 346.1  $[M+H]^+$  ( $R_t = 1.996$  min)

[0230] [Step 3]

(2S,11aR)-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-6-(((R)-1,1,1-trifluoropropan-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one (Compound IV)

[0231] [Chem.40]



[0232] The compound (5.60 g, 16.2 mmol) obtained in Step 2 and the compound (5.55 g, 17.8 mmol) obtained in Step 9 of Example 1 were used as raw materials, and the same operations as in Step 10 to Step 12 of Example 1 were performed to obtain a crude product (3.66 g) of the title compound.

[0233]  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 7.90 (1H, s), 7.85 (1H, s), 6.70 (1H, s), 6.63 (1H, s), 6.08 (1H, s), 5.64-5.59 (1H, m), 4.72-4.62 (1H, m), 4.19-4.18 (1H, m), 4.11-4.07 (2H, m), 4.05-3.97 (2H, m), 2.93-2.89 (2H, m), 2.67-2.63 (2H, m), 2.38-2.33 (4H, m), 2.10-2.04 (1H, m), 1.57 (3H, d,  $J = 6.9$  Hz)

LCMS: 492.2  $[M+H]^+$  ( $R_t = 1.940$  min)

[0234] [Step 4] Preparation of crystals of

(2S,11aR)-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-6-(((R)-1,1,1-trifluoropropan-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one (Compound IV)

[0235] A mixed solvent of dichloromethane (8.00 mL) and methanol (2.00 mL) was added to the crude product (3.66 g) of the compound obtained in Step 3 to dissolve the compound, and the mixture was concentrated under reduced pressure. Ethyl acetate (18.3 mL) was added to the obtained amorphous crude product to dissolve the compound, and the mixture was concentrated under reduced pressure until the amount of the solvent in the reaction liquid became less than 1/4. Since a solid precipitated immediately, the reaction liquid was allowed to stand at room temperature as it was. The obtained solid was filtered, washed with ethyl acetate (18.3 mL), and dried, thereby obtaining crystals (3.00 g) of the title compound.

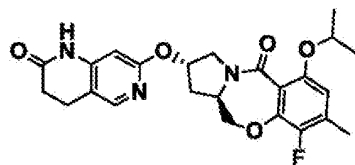
[0236] The XRD spectrum of the obtained crystal is shown in Fig. 12. Peaks were observed at diffraction angles  $2\theta = 8.5^\circ, 10.3^\circ, 11.3^\circ, 12.7^\circ, 14.7^\circ, 15.3^\circ, 17.7^\circ, 18.0^\circ, 19.4^\circ, 20.3^\circ, 20.8^\circ, 21.1^\circ, 21.8^\circ, 22.1^\circ, 23.0^\circ, 23.8^\circ, 24.2^\circ, 24.4^\circ, 24.9^\circ, 27.5^\circ, 28.1^\circ, 28.9^\circ$ , and  $29.9^\circ$ .

[0237] The melting point (extrapolated onset temperature of endothermic peak in TG-DTA) of the obtained crystal was 216°C.

[0238] The  $^{13}\text{C}$  solid-state NMR spectrum of the obtained crystal is shown in Fig. 13. Peaks were observed at chemical shifts of 10.8 ppm, 21.8 ppm, 22.3 ppm, 29.6 ppm, 31.2 ppm, 49.7 ppm, 52.8 ppm, 71.0 ppm, 77.9 ppm, 96.3 ppm, 109.9 ppm, 114.2 ppm, 115.4 ppm, 115.9 ppm, 144.1 ppm, 145.7 ppm, 149.2 ppm, 152.8 ppm, 156.5 ppm, 163.7 ppm, and 169.0 ppm.

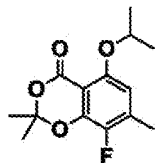
[0239] <Example 9: Production of crystals of (2S,11aR)-9-fluoro-6-isopropoxy-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one (Compound V)>

[0240] [Chem.41]



[0241] [Step 1] 8-fluoro-5-isopropoxy-2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-4-one

[0242] [Chem.42]



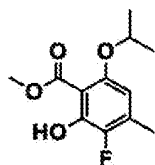
[0243] The compound (5.05 g, 20.2 mmol) obtained in Step 1 of Example 2 was dissolved in acetonitrile (60.7 mL), and Selectfluor (12.9 g, 36.4 mmol) was added thereto. The reaction liquid was heated to 40°C and stirred overnight. The reaction liquid was filtered through Celite (registered trademark), and a saturated aqueous solution of sodium hydrogen carbonate was added to the filtrate. The solvent was concentrated under reduced pressure, and the residue was extracted with ethyl acetate. The organic layer was washed twice with saturated brine, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (heptane/ethyl acetate), thereby obtaining the title compound (290 mg).

LCMS: 269.1  $[\text{M}+\text{H}]^+$  ( $R_t = 2.331$  min)

[0244] [Step 2] methyl 3-fluoro-2-hydroxy-6-isopropoxy-4-methylbenzoate

[0245]

[Chem.43]



[0246] The compound (290 mg, 1.08 mmol) obtained in Step 1 was used as a raw material, and the same operation as in Step 3 of Example 1 was performed to obtain the title compound (246 mg).

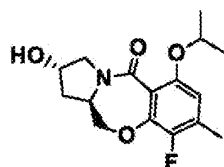
[0247] <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 11.49 (1H, s), 6.21 (1H, d, J = 5.5 Hz), 4.51-4.42 (1H, m), 3.93 (3H, s), 2.28 (3H, d, J = 2.3 Hz), 1.33 (6H, d, J = 5.9 Hz)

LCMS: 243.1 [M+H]<sup>+</sup> (R<sub>t</sub> = 2.300 min)

[Step 3]

(2S,11aR)-9-fluoro-2-hydroxy-6-isopropoxy-8-methyl-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one

[0248] [Chem.44]



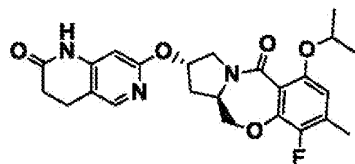
[0249] The compound (246 mg, 1.01 mmol) obtained in Step 2 and tert-butyl (2R,4S)-4-(benzyloxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate [CAS No. 1800019-47-9] (374 mg, 1.22 mmol) were used as raw materials, and the same operations as in Step 4 to Step 8 of Example 1 were performed to obtain the title compound (236 mg).

[0250] LCMS: 310.2 [M+H]<sup>+</sup> (R<sub>t</sub> = 1.970 min)

[0251] [Step 4]

(2S,11aR)-9-fluoro-6-isopropoxy-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one (Compound V)

[0252] [Chem.45]



[0253] The compound (236 mg, 0.76 mmol) obtained in Step 3 and the compound (308 mg, 0.99 mmol) obtained in Step 9 of Example 1 were used as raw materials, and the same

operations as in Step 10 to Step 12 of Example 1 were performed to obtain a crude product of the title compound.

[0254] <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.87 (1H, s), 7.61 (1H, s), 6.60 (1H, d, J = 5.5 Hz), 6.03 (1H, s), 5.65-5.60 (1H, m), 4.48-4.39 (1H, m), 4.26-4.23 (1H, m), 4.15-3.96 (4H, m), 2.92 (2H, t, J = 7.5 Hz), 2.68-2.64 (2H, m), 2.38-2.31 (1H, m), 2.28 (3H, d, J = 1.8 Hz), 2.13-2.11 (1H, m), 1.35 (3H, d, J = 5.9 Hz), 1.29 (3H, d, J = 6.4 Hz)

LCMS: 456.2 [M+H]<sup>+</sup> (R<sub>t</sub> = 1.920 min)

[0255] [Step 5] Preparation of crystals of

(2S,11aR)-9-fluoro-6-isopropoxy-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one (Compound V)

[0256] Ethyl acetate (2.16 mL) was added to the crude product obtained in Step 4 for dissolution, and concentrated under reduced pressure. Ethyl acetate (2.16 mL) was added to the precipitated solid to form a slurry, and the slurry was allowed to stand at room temperature as it was. The solid was filtered, washed with ethyl acetate, and dried, thereby obtaining crystals (147 mg) of the title compound.

[0257] The XRD spectrum of the obtained crystal is shown in Fig. 14. Peaks were observed at diffraction angles 2θ = 9.8°, 11.5°, 11.9°, 13.9°, 14.6°, 15.5°, 16.7°, 17.3°, 17.7°, 18.5°, 19.0°, 19.5°, 20.2°, 20.8°, 21.1°, 21.8°, 22.6°, 23.1°, 23.4°, 23.9°, 24.5°, 25.6°, and 29.6°.

[0258] The melting point (extrapolated onset temperature of endothermic peak in TG-DTA) of the obtained crystal was 302°C.

[0259] <Example 10: Evaluation of OX1R and OX2R Agonist Activity>

OX1R and OX2R agonist activity evaluation was performed on the compounds I to V.

[0260] (Preparation of cells Forcibly Expressing OX1R or OX2R)

In order to obtain cell clones stably expressing human orexin type 1 receptor (hOX1R, NP\_001516.2) or human orexin type 2 receptor (hOX2R, NP\_001371201.1), cDNA of hOX1R or hOX2R was respectively inserted into a pcDNA5/FRT plasmid vector (Invitrogen) to prepare plasmid DNA for hOX1R or hOX2R expression (pcDNA5/FRT/hOX1R or pcDNA5/FRT/hOX2R), respectively. This plasmid DNA was introduced into Flp-In 293 cells (Invitrogen) with Lipofectamine2000 (Thermo Fisher Scientific), and hOX1R-expressing clonal cells and hOX2R-expressing clonal cells were obtained by a limiting dilution method using Hygromycin drug resistance as a selection marker.

[0261] (Agonist Activity Evaluation)

Flp-In 293 cells in which human orexin type 1 receptor (hOX1R) or human orexin type 2 receptor (hOX2R) was forcibly expressed were seeded in each well on a 384

well black plate (BD Falcon) at 5000 cells/25  $\mu$ L using Glutamax-supplemented DMEM (Thermo Fisher Scientific) supplemented with 10% FBS (Corning) and 1% Penicillin-Streptomycin (Thermo Fisher Scientific), and cultured for 24 hours (37°C, 5% CO<sub>2</sub>). Thereafter, 25  $\mu$ L of assay buffer A (20 mM HEPES (Thermo Fisher Scientific), 5 mM Probenecid (Sigma-Aldrich), Hank's balanced salt solution (FUJIFILM Wako Pure Chemical Corporation)) containing Calcium 5 Dye (Molecular Devices) was added, and the mixture was incubated for 60 minutes (37°C, 5% CO<sub>2</sub>). Next, in order to evaluate a change in intracellular calcium ion concentration, measurement of fluorescence intensity was started using FLIPR Tetra (Molecular Devices), and 10 seconds later, 12.5  $\mu$ L of Orexin A (R & D Systems, Cat #1455) or a test compound was added.

Fluorescence intensity was measured from the start of measurement to 170 seconds later. Orexin A and the test compound were dissolved in DMSO and diluted with assay buffer B (20 mM HEPES, Hank's balanced salt solution, 0.05% BSA (Sigma-Aldrich), 2.5 mM Probenecid) so that the final concentration of DMSO was 0.5%. The difference between the minimum value of fluorescence intensity before the addition of the test compound and the maximum value of fluorescence intensity after the addition of the test compound was used as a signal of change in intracellular calcium ion concentration. The 50% agonist concentration (EC<sub>50</sub> value) of the test compound was calculated using XLFit ver. 5.5 (IDBS Software), where the signal in the vehicle control (0.5% DMSO) well was defined as 0%, and the average value of the signal in the wells to which Orexin A was added at a final concentration of 5 nM was defined as 100%. The calculation formula is as follows.

[0262] (Fitting method)

$$y = (A + ((B - A)/(1 + (10^{((C - x)*D)}))))$$

(fitting formula: 4 parameter logistic model (xlfrit 208))

- x = log conc (M) of compounds
- y = % of control
- A = min (0%), B = max (100%), C = -log(EC<sub>50</sub>), D = slope

[0263] (OX2R Agonist Activity Evaluation Result)

The agonist activity of the orexin type 2 receptor according to this evaluation is shown in the table. The activity was evaluated in the following range.

\*: 10 nM < EC<sub>50</sub>

\*\*: 1 nM < EC<sub>50</sub> ≤ 10 nM

\*\*\*: 0.1 nM < EC<sub>50</sub> ≤ 1 nM

\*\*\*\*: EC<sub>50</sub> ≤ 0.1 nM

When the activity of Orexin A was evaluated a plurality of times in this evaluation system, the activity values (EC<sub>50</sub> value) were 0.02 nM to 0.05 nM. As is clear from

Table 1, the compounds I to V of the invention exhibited good orexin type 2 receptor agonist activity.

[0264] [Table 1]

| Compound number | EC <sub>80</sub> |
|-----------------|------------------|
| Compound I      | ****             |
| Compound II     | ****             |
| Compound III    | ****             |
| Compound IV     | ***              |
| Compound V      | ***              |

### Industrial Applicability

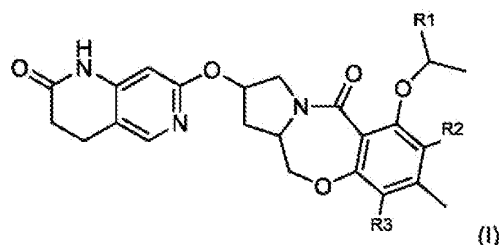
[0265] The crystals of the present invention can be used as a drug substance for producing a pharmaceutical product.

## Claims

[Claim 1]

1. A crystal of a compound represented by the following formula (I):

[Chem.1]



[wherein R<sup>1</sup> represents a methyl group or a methyl group substituted with 1 to 3 fluorine atoms; and R<sup>2</sup> and R<sup>3</sup> each independently represent a hydrogen atom or a fluorine atom],

or a crystal of a solvate of the compound represented by the formula (I).

[Claim 2]

2. The crystal according to claim 1, which is a crystal of (2S,11aR)-7-fluoro-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-6-(((R)-1,1,1-trifluoropropan-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one.

[Claim 3]

3. The crystal according to claim 2, wherein the crystal has peaks at diffraction angles ( $2\theta \pm 0.5^\circ$ ) of  $12.7^\circ$ ,  $14.7^\circ$ ,  $17.6^\circ$ ,  $20.7^\circ$ , and  $21.1^\circ$  in a powder X-ray diffraction spectrum.

[Claim 4]

4. The crystal according to claim 2 or 3, wherein the crystal has peaks at chemical shifts ( $\pm 0.5$  ppm) of 11.6, 14.7, 21.7, 30.8, 163.3, and 169.1 ppm in a solid-state NMR spectrum ( $^{13}\text{C}$ ).

[Claim 5]

5. The crystal according to any one of claims 2 to 4, wherein an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is  $166 \pm 5^\circ\text{C}$ .

[Claim 6]

6. The crystal according to claim 1, which is a crystal of (2S,11aR)-7-fluoro-6-isopropoxy-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one.

[Claim 7]

7. The crystal according to claim 6, wherein the crystal has peaks at diffraction angles ( $2\theta \pm 0.5^\circ$ ) of  $8.5^\circ$ ,  $12.7^\circ$ ,  $14.7^\circ$ , and  $17.7^\circ$  in a powder X-ray diffraction spectrum.

[Claim 8]

8. The crystal according to claim 6 or 7, wherein the crystal has peaks at chemical shifts ( $\pm 0.5$  ppm) of 15.0, 22.2, 23.2, 30.7, and 149.8 ppm

- in a solid-state NMR spectrum ( $^{13}\text{C}$ ).
- [Claim 9] 9. The crystal according to any one of claims 6 to 8, wherein an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is  $222\pm 5^\circ\text{C}$ .
- [Claim 10] 10. The crystal according to claim 6, wherein the crystal has peaks at diffraction angles ( $2\theta\pm 0.5^\circ$ ) of  $5.3^\circ$ ,  $6.3^\circ$ , and  $13.4^\circ$  in a powder X-ray diffraction spectrum.
- [Claim 11] 11. The crystal according to claim 6 or 10, wherein an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is  $223\pm 5^\circ\text{C}$ .
- [Claim 12] 12. The crystal according to claim 6, wherein the crystal has peaks at diffraction angles ( $2\theta\pm 0.5^\circ$ ) of  $9.6^\circ$ ,  $13.3^\circ$ ,  $16.7^\circ$ ,  $18.7^\circ$ , and  $22.8^\circ$  in a powder X-ray diffraction spectrum.
- [Claim 13] 13. The crystal according to claim 6 or 12, wherein the crystal has peaks at chemical shifts ( $\pm 0.5$  ppm) of 15.7, 21.6, 162.4, 164.5, and 170.2 ppm in a solid-state NMR spectrum ( $^{13}\text{C}$ ).
- [Claim 14] 14. The crystal according to any one of claims 6, 12, and 13, wherein an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is  $223\pm 5^\circ\text{C}$ .
- [Claim 15] 15. The crystal according to claim 6, wherein the crystal has peaks at diffraction angles ( $2\theta\pm 0.5^\circ$ ) of  $3.8^\circ$ ,  $12.0^\circ$ ,  $21.1^\circ$ , and  $23.9^\circ$  in a powder X-ray diffraction spectrum.
- [Claim 16] 16. The crystal according to claim 6 or 15, wherein the crystal has peaks at chemical shifts ( $\pm 0.5$  ppm) of 15.0, 23.0, 30.7, 144.4, and 150.2 ppm in a solid-state NMR spectrum ( $^{13}\text{C}$ ).
- [Claim 17] 17. The crystal according to any one of claims 6, 15, and 16, wherein an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is  $214\pm 5^\circ\text{C}$ .
- [Claim 18] 18. The crystal according to claim 6, wherein the crystal has peaks at diffraction angles ( $2\theta\pm 0.5^\circ$ ) of  $3.9^\circ$ ,  $12.4^\circ$ , and  $20.1^\circ$  in a powder X-ray diffraction spectrum.
- [Claim 19] 19. The crystal according to claim 6 or 18, wherein an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is  $121\pm 5^\circ\text{C}$ .
- [Claim 20] 20. The crystal according to claim 6, wherein the crystal has peaks at

- diffraction angles ( $2\theta \pm 0.5^\circ$ ) of  $11.5^\circ$ ,  $11.9^\circ$ ,  $19.7^\circ$ , and  $23.5^\circ$  in a powder X-ray diffraction spectrum.
- [Claim 21] 21. The crystal according to claim 1, which is a crystal of (2S,11aR)-7-fluoro-6-(((R)-1-fluoropropan-2-yl)oxy)-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one.
- [Claim 22] 22. The crystal according to claim 21, wherein the crystal has peaks at diffraction angles ( $2\theta \pm 0.5^\circ$ ) of  $13.4^\circ$ ,  $18.8^\circ$ , and  $22.9^\circ$  in a powder X-ray diffraction spectrum.
- [Claim 23] 23. The crystal according to claim 21 or 22, wherein an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is  $220 \pm 5^\circ\text{C}$ .
- [Claim 24] 24. The crystal according to claim 1, which is a crystal of (2S,11aR)-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-6-(((R)-1,1,1-trifluoropropan-2-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one.
- [Claim 25] 25. The crystal according to claim 24, wherein the crystal has peaks at diffraction angles ( $2\theta \pm 0.5^\circ$ ) of  $12.7^\circ$ ,  $14.7^\circ$ ,  $17.7^\circ$ ,  $20.8^\circ$ , and  $21.1^\circ$  in a powder X-ray diffraction spectrum.
- [Claim 26] 26. The crystal according to claim 24 or 25, wherein the crystal has peaks at chemical shifts ( $\pm 0.5$  ppm) of 10.8, 22.3, 31.2, 163.7, and 169.0 ppm in a solid-state NMR spectrum ( $^{13}\text{C}$ ).
- [Claim 27] 27. The crystal according to any one of claims 24 to 26, wherein an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is  $216 \pm 5^\circ\text{C}$ .
- [Claim 28] 28. The crystal according to claim 1, which is a crystal of (2S,11aR)-9-fluoro-6-isopropoxy-8-methyl-2-((2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)oxy)-2,3,11,11a-tetrahydro-1H,5H-benzo[f]pyrrolo[2,1-c][1,4]oxazepin-5-one.
- [Claim 29] 29. The crystal according to claim 28, wherein the crystal has peaks at diffraction angles ( $2\theta \pm 0.5^\circ$ ) of  $15.5^\circ$ ,  $19.5^\circ$ , and  $21.8^\circ$  in a powder X-ray diffraction spectrum.
- [Claim 30] 30. The crystal according to claim 28 or 29, wherein an extrapolated onset temperature of an endothermic peak in thermogravimetry-differential thermal analysis or differential thermal analysis is  $302 \pm 5^\circ\text{C}$ .
- [Claim 31] 31. An orexin type 2 receptor agonist comprising the crystal according to any one of claims 1 to 30.

- [Claim 32] 32. A pharmaceutical composition comprising the crystal according to any one of claims 1 to 30.
- [Claim 33] 33. A crystal according to any one of claims 1 to 30 for use for prophylaxis or therapeutic treatment for narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome accompanying narcolepsy-like symptoms, hypersomnia accompanied by Parkinson's disease, hypersomnia accompanied by Guillain-Barre syndrome, hypersomnia accompanied by Kleine-Levin syndrome, or hypersomnia accompanied by dementia with Lewy bodies.