

that the suppressive action on bladder contraction of the muscarinic receptor antagonist may cause adverse effects such as difficulty in urination, an increase in the amount of residual urine, and urinary retention, and it cannot be said that a satisfactory therapeutic effect is always achieved. Further, as a drug to overcome the problems of the

muscarinic receptor antagonist, a selective β_3 adrenergic receptor agonist was put on the market in 2011 in Japan. It is suggested that the selective β_3 adrenergic receptor agonist hardly affects the urination function while enhancing the urine collection function by a bladder relaxing action, and it exhibits the bladder relaxing action independent of contraction stimulation, and therefore is expected to work on a wide range of patients.

On the other hand, the risk of QT extension increases with an increase in the dose and it shows a heart rate increasing action by acting on the cardiac β receptor, and therefore, these are limiting factors for the dose.

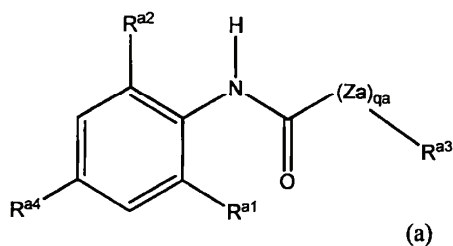
[0006]

From the above, in this field, there is a need in the art for a drug which has a bladder relaxing action independent of contraction stimulation and is free from fear of adverse effects, and a KCNQ2-5 channel activator is expected to be a drug which responds to this unmet medical need.

[0007]

A KCNQ activator having a monocyclic amide skeleton, for example, a compound represented by the general formula (a) was known in the art (see Patent Document 1).

[Chem. 1]



(wherein Za is O or S; qa is 0 or 1; R^{a1} and R^{a2} are each independently selected from the group consisting of halogen, cyano, amino, C_{1-6} -alkyl (alkenyl/alkynyl), and the like; R^{a3} is selected from the group consisting of C_{1-8} -alkyl (alkenyl/alkynyl), C_{3-8} -cycloalkyl

(cycloalkenyl), C₃₋₈-cycloalkyl (cycloalkenyl)-C₁₋₆-alkyl (alkenyl/alkynyl), aryl-C₁₋₆-alkyl (alkenyl/alkynyl), aryl-C₃₋₈-cycloalkyl (cycloalkenyl), and the like; and R^{a4} is selected from the group consisting of halogen, cyano, C₁₋₆-alkyl (alkenyl/alkynyl), C₃₋₈-cycloalkyl (cycloalkenyl), C₃₋₈-cycloalkyl (cycloalkenyl)-C₁₋₆-alkyl (alkenyl/alkynyl),
 5 and the like (the definitions of the groups were partially extracted). The compound I is not included in the general formula (a) of Patent Document 1. Further, Patent Document 1 does not describe or suggest a technique for achieving the compound I from the compound described in Patent Document 1.

[0008]

10 Further, in WO 2016/063990 (hereinafter sometimes abbreviated as Patent Document 2), the compound I is described as a KCNQ activator. However, Patent Document 2 does not describe that crystal polymorphism exists in the compound I.

CITED REFERENCES

15 PATENT DOCUMENTS

[0009]

Patent Document 1: International Publication number WO 2006/029623

Patent Document 2: International Publication number WO 2016/063990

NON-PATENT DOCUMENTS

20 [0010]

Non-Patent Document 1: Current Topics in Medicinal Chemistry, vol. 6, pp. 999-1023, 2006

Non-Patent Document 2: The Journal of Urology, vol. 172, pp. 2054-2058, 2004

25 Non-Patent Document 3: European Journal of Pharmacology, vol. 638, pp. 121-127, 2010

DISCLOSURE OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

30 [0011]

An object of the present invention is to provide a compound having a strong opening action with respect to KCNQ2-5 channels.

[0012]

Further, crystal polymorphism may exist in a crystalline compound. In the case where crystal polymorphism exists, solubility, dissolution rate, stability against heat, light, humidity, etc. or the like may differ, depending on the crystal form. Accordingly, in the production of a pharmaceutical product, it is a very important task to select a crystal form of a drug substance most suitable for a disease indication and a dosage form.

MEANS FOR SOLVING THE PROBLEMS

[0013]

The present inventors found that other than the crystal form (M crystal) of the compound I produced in Example 25(5) of the above-mentioned Patent Document 2, other crystal forms exist in the compound I. Therefore, when they made intensive studies of the crystal polymorphism of the compound I, A crystal and W crystal were identified as novel crystal forms of the compound I, and further, a crystal of a hydrate (H crystal) of the compound I was identified (these novel crystal forms are sometimes abbreviated as “crystal form of the present invention”).

[0014]

That is, the present invention relates to:

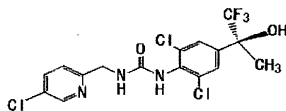
(1) a crystal of 1-[(5-chloro-2-pyridinyl)methyl]-3-{2,6-dichloro-4-[(2S)-1,1,1-trifluoro-2-hydroxy-2-propanyl]phenyl}urea, having at least peaks of about 15.3, 16.9, 17.4, 19.3, and 19.6 °2θ in a powder X-ray diffraction spectrum;

(2) the crystal of 1-[(5-chloro-2-pyridinyl)methyl]-3-{2,6-dichloro-4-[(2S)-1,1,1-trifluoro-2-hydroxy-2-propanyl]phenyl}urea according to the above (1), having no peaks of about 7.0 and 9.2 °2θ in a powder X-ray diffraction spectrum;

(3) the crystal of 1-[(5-chloro-2-pyridinyl)methyl]-3-{2,6-dichloro-4-[(2S)-1,1,1-trifluoro-2-hydroxy-2-propanyl]phenyl}urea according to the above (1) or (2), having peaks of about 11.3, 11.6, 11.9, 12.8, 13.9, 15.3, 16.4, 16.9, 17.4, 18.1, 19.3, 19.6, 20.5, 21.1, 22.2, 22.8, 23.5, 23.8, 24.3, and 24.7 °2θ in a powder X-ray diffraction spectrum;

(4) the crystal of 1-[(5-chloro-2-pyridinyl)methyl]-3-{2,6-dichloro-4-[(2S)-1,1,1-trifluoro-2-hydroxy-2-propanyl]phenyl}urea according to any one of the above (1) to (3), characterized by a powder X-ray diffraction spectrum chart shown in FIG. 3;

(5) a crystal of 1-[(5-chloro-2-pyridinyl)methyl]-3-{2,6-dichloro-4-[(2S)-1,1,1-trifluoro-2-hydroxy-2-propanyl]phenyl}urea, having an endothermic peak with an onset temperature of about 166°C or a peak temperature of about 167°C in differential scanning calorimetry;



[0018]

In the present invention, two types of anhydrous crystals: A crystal and W crystal, and a crystal of a hydrate: H crystal were identified, as novel crystal forms of the compound I. Differences among the crystal forms are distinguished by particularly powder X-ray diffraction spectra or/and differential scanning calorimetry (DSC).

[0019]

The A crystal of the compound I is characterized by physicochemical data of at least one of the following (a) and (b). Preferably, it is characterized by physicochemical data of both (a) and (b). These characteristics are (a) a powder X-ray diffraction spectrum chart shown in the following FIG. 3, diffraction angles (2θ) shown in the following Table 2, or having at least peaks of about 15.3, 16.9, 17.4, 19.3, and 19.6 $^{\circ}2\theta$ (further preferably, having no peaks of about 7.0 and/or 9.2 $^{\circ}2\theta$) in a powder X-ray diffraction spectrum; and (b) a DSC chart shown in the following FIG. 4 or having an endothermic peak with an onset temperature of about 166 $^{\circ}\text{C}$ and/or a peak temperature of about 167 $^{\circ}\text{C}$ in DSC.

[0020]

The W crystal of the compound I is characterized by physicochemical data of at least one of the following (c) and (d). Preferably, it is characterized by physicochemical data of both (c) and (d). These characteristics are (c) a powder X-ray diffraction spectrum chart shown in the following FIG. 5 or diffraction angles (2θ) shown in the following Table 3 (further preferably, having no peaks of about 7.0 and/or 9.2 $^{\circ}2\theta$); and (d) a DSC chart shown in the following FIG. 6 or having an endothermic peak with an onset temperature of about 89 $^{\circ}\text{C}$ and/or a peak temperature of about 94 $^{\circ}\text{C}$ in DSC.

[0021]

The H crystal which is a crystal of a hydrate of the compound I is characterized by physicochemical data of at least one of the following (e) and (f). Preferably, it is characterized by physicochemical data of both (e) and (f). These characteristics are (e) a powder X-ray diffraction spectrum chart shown in the following FIG. 7, diffraction angles (2θ) shown in the following Table 4, or having at least peaks of about 13.0, 14.5, 18.3, 19.0, and 21.7 $^{\circ}2\theta$ (further preferably, having no peaks of about 7.0 and/or 9.2 $^{\circ}2\theta$) in a powder

X-ray diffraction spectrum; and (f) a DSC chart shown in the following FIG. 8 or having an endothermic peak with an onset temperature of about 32°C and/or a peak temperature of about 48°C in DSC.

[0022]

5 On the other hand, the M crystal of the compound I described in the above-mentioned Patent Document 2 is characterized by physicochemical data of (g) a powder X-ray diffraction spectrum chart shown in FIG. 1 or diffraction angles (2θ) shown in the following Table 1 and/or (h) a DSC chart (onset temperature: about 90°C, peak temperature: about 100°C) shown in FIG. 2.

10 [0023]

In the present invention, the respective crystal forms of the compound I are specified by the physicochemical data described in this specification, however, the respective spectrum data can slightly vary due to their nature, and therefore should not be strictly construed.

15 [0024]

For example, in the powder X-ray diffraction spectrum data, the diffraction angle (2θ) or the overall pattern is important for determination of the identity of the crystals due to their nature, and the relative intensity can slightly vary depending on the crystal growth direction, the grain size, and the measurement conditions.

20 [0025]

Further, also in the DSC data, the overall pattern is important for determination of the identity of the crystals and can slightly vary depending on the measurement conditions.

[0026]

25 Therefore, those showing a powder X-ray diffraction spectrum pattern or a DSC pattern which is similar as a whole to that of the crystal form of the present invention are included in the crystal form of the present invention.

[0027]

30 In this specification, the description of the diffraction angle (2θ (°)) in the powder X-ray diffraction spectrum pattern and the onset temperature (°C) and the peak temperature (°C) of the endothermic peak in the DSC analysis means that they include error ranges generally allowed in the data measurement methods, and means that they are approximately the diffraction angle, and the onset temperature and the peak

The A crystal of the compound I can be produced, for example, from the compound I produced in the same manner as in Example 25(5) of Patent Document 2 by, for example, the following method.

[0033]

5 The compound I is dissolved in a solvent (for example, ethanol) or a mixed solvent (for example, a mixed solvent of ethanol and water), followed by cooling, whereby the A crystal of the compound I can be obtained.

[0034]

10 The H crystal which is the crystal of a hydrate of the compound I can be produced, for example, from the compound I produced in the same manner as in Example 25(5) of Patent Document 2 or the compound I produced in the same manner as in the below-mentioned Example 10 by, for example, the following method.

[0035]

15 The compound I is added to a solvent (for example, water) or a mixed solvent (for example, a mixed solvent of acetone and water), followed by stirring at 25 to 40°C for 1 week or more, whereby the H crystal which is the crystal of a hydrate of the compound I can be obtained.

[0036]

20 Alternatively, the compound I is dissolved in a mixed solvent of acetone and water, followed by cooling, whereby the H crystal which is the crystal of a hydrate of the compound I can be obtained.

[0037]

25 The W crystal of the compound I can be produced, for example, from the compound I produced in the same manner as in Example 25(5) of Patent Document 2 or the below-mentioned Example 10 by, for example, the following method.

[0038]

30 The compound I is dissolved in a solvent (for example, methanol) or a mixed solvent (for example, a mixed solvent of methanol and water) at 40 to 60°C, followed by

recombinant botulinum toxins (senrebotase, etc.), (5) opioid μ receptor agonists (TRK-130, etc.), (6) $\alpha 4\beta 2$ -nicotinic acetylcholine receptor antagonists (dexmecamylamine, etc.), (7) C-fiber inhibitors (besipirdine, etc.), (8) TRPV1 antagonists (XEN-D0501, etc.), (9) EP1 antagonists (KEA-0447, etc.), (10) central nervous drugs (REC-1819, etc.), (11) $\alpha 1$ -adrenergic receptor antagonists (for example, tamsulosin, silodosin, naftopidil, urapidil, etc.), (12) 5α -reductase inhibitors (dutasteride, finasteride, etc.), (13) phosphodiesterase-5 inhibitors (sildenafil, tadalafil, and vardenafil), (14) vasopressin V2 receptor agonists (desmopressin), and the like.

[0050]

10 The dose of the other drug can be appropriately selected based on the clinically used dose. Further, the combining ratio of the compound I to the other drug can be appropriately selected according to the age and body weight of an administration target, an administration method, an administration period, a target disease, symptoms, a combination thereof, etc. For example, the other drug may be used in an amount of
15 0.01 to 100 parts by mass with respect to 1 part by mass of the compound I. As the other drug, any two or more drugs may be combined at an appropriate ratio and administered. Further, in the other drug, not only drugs which have been found so far, but also drugs which will be found in future are also included.

[0051]

20 In order to use the compound I or the concomitant drug of the compound I and the other drug for the above-mentioned purpose, it is generally formulated into an appropriate pharmaceutical composition together with a pharmaceutically acceptable carrier and then administered systemically or topically in the form of an oral or parenteral preparation.

25 [0052]

The compound I is administered to a mammal (preferably, a human, more preferably, a patient) in a pharmaceutically effective amount.

[0053]

30 The dose of the compound I is dependent on the age, body weight, symptoms, a desired therapeutic effect, an administration route, a treatment period, etc., and therefore inevitably varies. In general, the compound I is orally administered at a dose ranging from 0.1 mg to 1000 mg once to several times a day per patient, or parenterally administered at a dose ranging from 0.01 mg to 100 mg once to several times a day per

concentrated under reduced pressure. The resulting residue was dissolved in tetrahydrofuran (3.6 mL), and (5-chloropyridin-2-yl)methanamine hydrochloride (186 mg) (CAS Registry Number: 871826-13-0) and triethylamine (241 μ L) were added thereto, followed by stirring at room temperature for 1 hour. To the reaction mixture, water was added, and extraction was performed with ethyl acetate. The organic layer was sequentially washed with water and a saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. To the resulting residue, methanol (3.6 mL) and trifluoroacetic acid (1 mL) were added, followed by stirring at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, and thereafter, a saturated aqueous sodium hydrogen carbonate solution was added thereto, and extraction was performed with ethyl acetate. The organic layer was sequentially washed with water and a saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 60:40 $\rightarrow$ 10:90), whereby the title compound having the following physical property values was obtained (243 mg). In Examples of the present invention, production is performed by the same production method as in Example 25(5) of Patent Document 2.

TLC: R_f 0.22 (hexane:ethyl acetate = 1:1);
¹H-NMR (DMSO-d₆): δ 1.69, 4.36, 6.93, 7.06, 7.38, 7.64, 7.94, 8.37, 8.55.

[0072]

The powder X-ray diffraction spectrum chart and the DSC chart of the crystal measured under the following conditions are shown in FIG. 1 and FIG. 2, respectively.

(1) Powder X-Ray Diffraction Spectrum

Device: SmartLab, manufactured by Rigaku Corporation
 Target: Cu
 Voltage: 45 kV
 Current: 200 mA
 Scanning rate: 5 $^{\circ}$ /min

[0073]

The results of diffraction angles (2 θ) ($^{\circ}$) and relative intensities (%) obtained by powder X-ray diffraction spectrometry using a Cu-K α ray are shown in Table 1.

[Table 1]

Current: 200 mA

Scanning rate: 20 °/min

Temperature raising rate: 2 °C/min (room temperature to 150°C)

[0098]

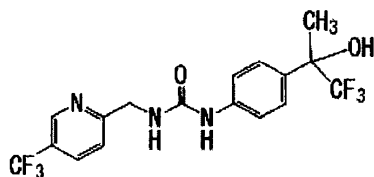
- 5 At around 40 to 50°C, an endothermic peak accompanying dehydration, and a change in pattern in the X-ray diffraction spectrum chart accompanying a change in crystal structure were observed.

[0099]

Comparative Example 1

- 10 1-[4-(1,1,1-trifluoro-2-hydroxy-2-propanyl)phenyl]-3-{{5-(trifluoromethyl)-2-pyridinyl}methyl}urea

[Chem. 4]



- 15 The title compound having the following physical property values was obtained by performing the same procedure as in Comparative Example 1 of Patent Document 2.

TLC: R_f 0.25 (hexane:ethyl acetate = 1:1);

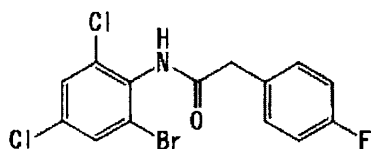
¹H-NMR (DMSO-d₆): δ 1.63, 4.49, 6.42, 6.86, 7.41, 7.57, 8.18, 8.90.

- 20 [0100]

Comparative Example 2

N-(2-bromo-4,6-dichlorophenyl)-2-(4-fluorophenyl)acetamide (Example 1g of Patent Document 1)

[Chem. 5]



The title compound (1.28 g) having the following physical property values was obtained by performing the same procedure as in Comparative Example 2 of Patent Document 2.

- 5 TLC: R_f 0.43 (hexane:ethyl acetate = 1:1);
¹H-NMR (CD₃OD): δ 3.72, 7.02-7.08, 7.38-7.43, 7.58, 7.69.

[0101]

The effects of the compound I can be demonstrated by the following experiments, but is not limited thereto.

10 [0102]

(1) Biological Example 1: Opening Action with respect to KCNQ2/3 Channel by Depolarization Stimulation

- Human KCNQ2/3 expression cells (CHO-DHFR- cells) were seeded in each well of a 384-well plate (collagen-coated, black, clear bottom) at 0.5×10^4 cells/50 μ L per well and cultured in a MEM ALPHA medium (containing 10 vol% inactivated (56°C, 30 min) fetal bovine serum, 100 IU/mL penicillin, 100 μ g/mL streptomycin, and 2 mM L-glutamine) at 37°C in 5% CO₂ for 18 to 24 hours. After the medium in the plate was removed, incubation (room temperature, 60 minutes, shading) was performed in a loading buffer (prepared by the method described in the manual of FluxOR Thallium Detection Kit (Invitrogen, F10016, F10017)). A KCNQ2/3 channel opening action (thallium influx into cells) by depolarization stimulation (5 mM potassium and 0.5 mM thallium) was measured by FLIPR TETRA (Molecular Devices). The compound I was treated 5 minutes before the depolarization stimulation, and the reaction induced by the depolarization stimulation was measured over time for 180 seconds. The channel opening action of the compound I was evaluated based on the change amount of the fluorescence intensity from the time before the depolarization stimulation to the time after the elapse of 180 seconds, and the concentration (EC₅₀) satisfying 50% of the fluorescence intensity change of a maximum reaction (in the

treatment at 10 μ M) of retigabine under the conditions of this experiment was calculated.

[0103]

As a result, the opening action (EC₅₀ value) of the compound I with respect to the KCNQ2/3 channel was 0.6 μ M. On the other hand, the EC₅₀ value of Comparative Example 1 was >10 μ M, and the EC₅₀ value of Comparative Example 2 was 0.2 μ M.

[0104]

Further, in the above-mentioned method, by using human KCNQ4 or human KCNQ5 expression cells in place of the human KCNQ2/3 expression cells and appropriately changing the above-mentioned conditions based on the ordinary knowledge of those skilled in the art, the opening action with respect to the human KCNQ4 channel or the human KCNQ5 channel can be measured.

[0105]

(2) Biological Example 2: Relaxing Action on Bladder

Extracted from Rat

Female Jcl:Wistar rats (CLEA Japan, Inc., body weight at use: 170 to 200 g) were anesthetized by intraperitoneal administration of about 40 mg/kg of pentobarbital (Somnopentyl, Schering Plough Animal Health Corporation), and killed by bloodletting. The bladder was extracted by abdominal incision and immediately thereafter immersed in ice-cooled Krebs buffer (Krebs Ringer bicarbonate buffer (Sigma-Aldrich Co. LLC) supplemented with sodium hydrogen carbonate (final concentration: 15 mM) and calcium chloride (final concentration: 2.5 mM)) saturated with a mixed gas (95% O₂, 5% CO₂).

[0106]

The bladder body extracted from each rat was cut into an oblong strip shape (about 10 × 3 mm), whereby a specimen was prepared on ice. Immediately thereafter, the specimen was suspended in a Magnus tube filled with Krebs buffer (37°C) bubbled with the mixed gas while applying a tension load of 500 mg thereto. Incidentally, the specimen was prepared within 24 hours after extracting the tissue.

[0107]

The change in tension of the specimen was recorded in data collection system (NR-1000, KEYENCE CORPORATION) through a Magnus system equipped with an