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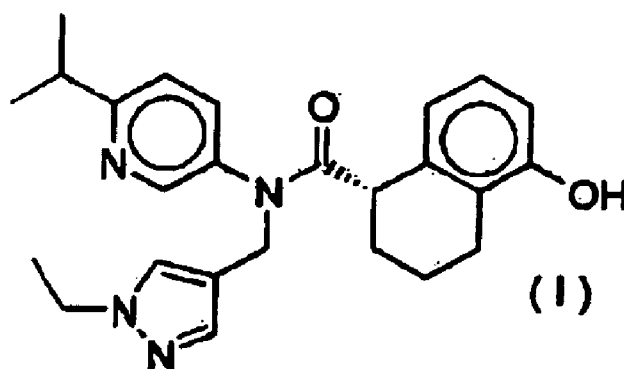
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(54) **Title:** NOVEL CRYSTAL OF TETRAHYDRONAPHTHALENE COMPOUND



(57) **Abstract:** An isolated crystal of (1S) - (-)-N- [(1-ethyl-1H-pyrazol-4-yl)methyl] -5-hydroxy-N- (6-isopropylpyridin-3-yl, 2, 3, 4- tetrahydronaphthalene-1-carboxamide showing peaks at diffraction angles 2θ of at least about $4.6^\circ \pm 0.2^\circ$, $10.9^\circ \pm 0.2^\circ$, $13.2^\circ \pm 0.2^\circ$ and $16.6^\circ \pm 0.2^\circ$, in powder X-ray diffraction spectrum is provided. Since the crystal is stable under conditions of less than 60°C and does not transform into other crystals, it is useful as a bulk drug of pharmaceutical products as compared to previously-identified other crystals.

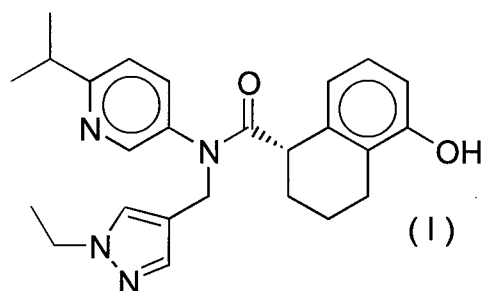
DESCRIPTION

Title of Invention

NOVEL CRYSTAL OF TETRAHYDRONAPHTHALENE COMPOUND

Technical Field

5 The present invention relates to a novel, isolated crystal form of (1S)-(-)-N-[(1-ethyl-1H-pyrazol-4-yl)methyl]-5-hydroxy-N-(6-isopropylpyridin-3-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide represented by the following formula (I)



10

a production method thereof and a pharmaceutical use thereof.

Background Art

N-[(1-Ethyl-1H-pyrazol-4-yl)methyl]-5-hydroxy-N-(6-isopropylpyridin-3-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide is a known compound (patent documents 1 and 2).
 15 The S isomer (1S)-(-)-N-[(1-ethyl-1H-pyrazol-4-yl)methyl]-5-hydroxy-N-(6-isopropylpyridin-3-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide has a superior C5a
 20 receptor antagonistic action, and is useful as a prophylactic and/or therapeutic drug for the diseases caused by binding of C5a to a C5a receptor, for example, autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus and the like; sepsis; adult respiratory distress syndrome; chronic
 25 obstructive pulmonary disease; allergic diseases such as asthma and the like; atherosclerosis; cardiac infarction; cerebral infarction; psoriasis; Alzheimer's disease; serious organ injury (e.g., pneumonia, nephritis, hepatitis, pancreatitis and the like) due to leukocyte activation caused

by ischemia reperfusion, trauma, burn, surgical invasion and the like; moreover, since C5a has a strong inflammation inducing action, the S isomer is useful as an anti-inflammatory drug, and further, as a prophylactic and/or
5 therapeutic drug for infectious diseases caused by bacteria or virus that invades via a C5a receptor. Patent document 2 describes two free crystal forms of (1S)-(-)-N-[(1-ethyl-1H-pyrazol-4-yl)methyl]-5-hydroxy-N-(6-isopropylpyridin-3-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide.

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Document List

patent documents

patent document 1: WO2002/22556

patent document 2: WO2006/82975

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Summary of Invention

Problems to be Solved by the Invention

One object of the present invention is to provide a crystal that is uniform, pure, and more stable. In particular,
20 it is an object of the present invention to provide a novel crystal of (1S)-(-)-N-[(1-ethyl-1H-pyrazol-4-yl)methyl]-5-hydroxy-N-(6-isopropylpyridin-3-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide in an isolated and/or purified form. Another object is to provide a production
25 method capable of providing the crystal in an industrial scale safely and efficiently.

Generally, compounds showing crystalline polymorphism sometimes show different properties for each crystal. Particularly, solubility, dissolution rate, stability,
30 absorbability and the like may vary among crystals for pharmaceutical products. That is, even when a single compound is used, expression of efficacy and side effects varies due to the different crystal forms, which may produce an unexpected situation. When a crystalline substance is used as an active

ingredient of a medicament, therefore, the crystal is desired to be uniform, pure, and more stable.

To secure consistent efficacy expression and side effect expression, it is desired to obtain a uniform and stable
5 crystal of a compound for pharmaceutical applications. It is also desired to provide a production method capable of constantly providing the crystal in an industrial scale safely and efficiently.

10 Means of Solving the Problems

After the research and development of the compound, a novel crystal of N-[(1-ethyl-1H-pyrazol-4-yl)methyl]-5-hydroxy-N-(6-isopropylpyridin-3-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide was isolated. The novel
15 crystal has been clarified to be more stable than the conventionally-known crystals. Furthermore, it has been found that the novel crystal can be selectively produced as uniform crystal by crystallization using water or an organic solvent having a carbon number of two or more at a solvent temperature
20 within the range of from not less than the melting point of the solvent to less than 60°C.

In one embodiment of the present invention, there is provided an isolated crystal of (1S)-(-)-N-[(1-ethyl-1H-pyrazol-4-yl)methyl]-5-hydroxy-N-(6-isopropylpyridin-3-yl)-
25 1,2,3,4-tetrahydronaphthalene-1-carboxamide, wherein the crystal has peaks at diffraction angles 2θ of at least about $4.6^\circ \pm 0.2^\circ$, $10.9^\circ \pm 0.2^\circ$, $13.2^\circ \pm 0.2^\circ$ and $16.6^\circ \pm 0.2^\circ$ in a powder X-ray diffraction spectrum.

In one embodiment, the crystal has peaks at diffraction
30 angles 2θ of at least about $10.5^\circ \pm 0.2^\circ$ and $14.0^\circ \pm 0.2^\circ$ in a powder X-ray diffraction spectrum.

The crystal may have endothermic peaks at 143-149°C (extrapolated onset temperature) and 171-177°C (extrapolated onset temperature) in a differential scanning calorimetry

measurement.

Also, the crystal may have a physicochemical property of the following A and/or B where A is having a powder X-ray diffraction pattern of peaks shown in Fig. 1, and B is having
5 a differential scanning calorimetry curve shown in Fig 2.

In one embodiment of the present invention, there is provided a method of producing the aforementioned crystal, where a solvent temperature is set to fall within the range of from not less than a melting point of water or an organic
10 solvent having a carbon number of two or more to less than 60°C, a crystal of (1S)-(-)-N-[(1-ethyl-1H-pyrazol-4-yl)methyl]-5-hydroxy-N-(6-isopropylpyridin-3-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide dissolved in the water or the organic solvent is formed, and the crystal is recovered.

15 In another embodiment of the present invention, there is provided a medicament including the aforementioned crystal, wherein the crystal has a purity of at least 95%.

In another embodiment, there is provided a pharmaceutical composition including the aforementioned crystal and a
20 pharmaceutically acceptable additive.

In another embodiment, there is provided a method of treating a disease caused by binding of C5a to a C5a receptor, where an effective amount of the aforementioned crystal is administered to a subject in need thereof.

25 In another embodiment, there is provided a method of treating a disease caused by binding of C5a to a C5a receptor, where the disease caused by binding of C5a to a C5a receptor is one of an autoimmune disease, sepsis, adult respiratory distress syndrome, chronic obstructive pulmonary disease, an
30 allergic disease, atherosclerosis, cardiac infarction, cerebral infarction, psoriasis, Alzheimer's disease, and serious organ injury due to leukocyte activation caused by ischemia reperfusion, trauma, burn or surgical invasion.

In another embodiment, there is provided a method of

treating inflammation, where an effective amount of an anti-inflammatory agent comprising the aforementioned crystal is administered to a subject in need thereof.

In another embodiment, there is provided a method of
5 treating an infectious disease, where an effective amount of a C5a receptor antagonist comprising the aforementioned crystal is administered to a subject in need thereof.

In another embodiment, there is provided a method of treating an infectious disease, where the infectious disease is
10 caused by bacteria or virus that invades via a C5a receptor.

In another embodiment, there is provided a method of treating rheumatoid arthritis, where an effective amount of the aforementioned crystal is administered to a subject in need thereof.

15 In another embodiment, there is provided a prophylactic and/or therapeutic drug for a disease caused by binding of C5a to a C5a receptor, comprising the aforementioned crystal.

In another embodiment, there is provided a prophylactic and/or therapeutic drug for a disease caused by binding of C5a
20 to a C5a receptor, where the disease caused by binding of C5a to a C5a receptor is one of an autoimmune disease, sepsis, adult respiratory distress syndrome, chronic obstructive pulmonary disease, an allergic disease, atherosclerosis, cardiac infarction, cerebral infarction, psoriasis, Alzheimer's
25 disease, and serious organ injury due to leukocyte activation caused by ischemia reperfusion, trauma, burn or surgical invasion.

In another embodiment, there is provided an anti-inflammatory agent, comprising the aforementioned crystal.

30 In another embodiment, there is provided a prophylactic and/or therapeutic drug for an infectious disease, comprising the aforementioned crystal.

In another embodiment, there is provided a prophylactic and/or therapeutic drug for an infectious disease, where the

infectious disease is caused by bacteria or virus that invades via a C5a receptor.

In another embodiment, there is provided a prophylactic and/or therapeutic drug for rheumatoid arthritis, comprising
5 the aforementioned crystal.

In another embodiment, there is provided a C5a receptor antagonist, comprising the aforementioned crystal.

Effect of the Invention

10 The crystal of the present invention is stable under conditions of less than 60°C, and has properties preferable as a bulk drug of pharmaceutical products. In addition, the production method of the present invention can provide the crystal of the present invention in an industrial scale safely
15 and constantly.

The above summary highlights certain aspects of the invention. Additional objects, aspects and embodiments of the invention are found in the detailed description of the invention.

20

Brief Description of Drawings

A more complete appreciation of the invention and many of the attendant advantages thereof will be readily obtained as the same becomes better understood by reference to the
25 following Figures in conjunction with the detailed description below.

Fig. 1 shows a powder X-ray diffraction pattern of the crystal of the present invention.

Fig. 2 shows the results of differential scanning
30 calorimetry (DSC) of the crystal of the present invention.

Fig. 3 shows powder X-ray diffraction patterns before and after preservation of the crystal (Form I crystal) described in Example 3 of patent document 2 under conditions of 40°C/75%RH for 6 months, wherein the vertical axis shows

intensity (CPS).

Fig. 4 shows powder X-ray diffraction patterns before and 1 day, 3 days and 8 days after preservation of the crystal (Form II crystal) described in Example 22 of patent document 2 under conditions of 40°C/75%RH for 8 days, and powder X-ray diffraction pattern of the crystal (Form I crystal) described in Example 3 of patent document 2, wherein the vertical axis shows intensity (CPS).

Fig. 5 shows powder X-ray diffraction patterns before and 10 after preservation of the crystal of the present invention under conditions of 40°C/75%RH for 6 months, wherein the vertical axis shows intensity (CPS).

(Detailed Description of the Invention)

15 Description of Embodiments

Unless specifically defined, all technical and scientific terms used herein have the same meaning as commonly understood by a skilled artisan in pharmaceutical and medical sciences.

All methods and materials similar or equivalent to those 20 described herein can be used in the practice or testing of the present invention, with suitable methods and materials being described herein.

The crystal of the present invention can be produced by 1) synthesizing the compound according to a method, for 25 example, described in patent document 2, while setting the temperature of the reaction solution to not less than the melting point of the solvent and less than 60°C, 2) crystallizing the compound, and 3) recovering the crystal. The method of the crystallization is not limited, and methods such 30 as cooling of the reaction mixture, standing after concentration of the reaction mixture, continuance of stirring, adding seed crystal and the like can be used. In addition, the compound N-[(1-ethyl-1H-pyrazol-4-yl)methyl]-5-hydroxy-N-(6-isopropylpyridin-3-yl)-1,2,3,4-tetrahydronaphthalene-1-

carboxamide does not need to be completely dissolved in a solvent, and the crystal can also be produced, for example, by adding a solvent to a free Form I crystal described in Example 3 of patent document 2 to give a suspension, and continuously
5 stirring the suspension at a solvent temperature of not less than the melting point of the solvent and less than 60°C.

While the range of the solvent temperature for obtaining the crystal is not particularly limited as long as it is from not less than the melting point of the solvent to less than
10 60°C, in case of water, preferably it is from not less than 5°C to less than 60°C and more preferably it is from not less than 10°C to less than 60°C, in case of an organic solvent, preferably it is from not less than -20°C to less than 60°C and more preferably it is from not less than 10°C to less than 60°C
15 in general.

While the solvent usable for the production of the crystal is not particularly limited as long as it is water or an organic solvent having a carbon number of two or more, use of a solvent acceptable for the production of a pharmaceutical
20 product is desirable. The organic solvent having a carbon number of two or more means that the molecule constituting the solvent has a carbon number of two or more. Examples thereof include ethanol, acetic acid, acetonitrile, acetone, dimethylformamide, 1-propanol, 2-propanol, 1-butanol, 2-
25 butanol, 2-methyl-2-propanol, 2-methyl-1-propanol, ethyl acetate, 1-pentanol, 2-pentanol, 3-pentanol, 3-methyl-1-butanol, methyl isobutyl ketone, hexane, toluene, anisole, heptane and tetrahydrofuran. Here, preferred examples thereof include ethanol, acetone, 1-propanol, 2-propanol, 2-butanol, 2-
30 methyl-2-propanol, ethyl acetate, 3-methyl-1-butanol, toluene, anisole, heptane and tetrahydrofuran. Furthermore, a mixed solvent thereof, for example, a mixed solvent of water and ethanol, a mixed solvent of ethanol and heptane and the like can also be used.

The thus-obtained crystal of the present invention shows peaks at diffraction angles 2θ of about $4.6^\circ \pm 0.2^\circ$, $10.9^\circ \pm 0.2^\circ$, $13.2^\circ \pm 0.2^\circ$ and $16.6^\circ \pm 0.2^\circ$, and further, at diffraction angles 2θ of about $10.5^\circ \pm 0.2^\circ$ and $14.0^\circ \pm 0.2^\circ$, in powder X-ray diffraction spectrum. These peaks are not observed in the crystals described in Example 3 (Form I crystal) and Example 22 (Form II crystal) of patent document 2. In addition, the crystal of the present invention shows endothermic peaks at $145\text{--}152^\circ\text{C}$ (extrapolated onset temperature) and $171\text{--}177^\circ\text{C}$ (extrapolated onset temperature) in differential scanning calorimetry measurement. While the measurement conditions of the powder X-ray diffraction and differential scanning calorimetry are not particularly limited, the measurements are preferably performed under the measurement conditions described in the present specification.

Generally, in the technical field of crystals, peaks at diffraction angles 2θ in powder X-ray diffraction spectrum may vary, irrespective of the crystal forms, depending on the temperature and relative humidity during sample analysis and changes in the amount of water and the like contained in the sample, and therefore, $\pm 0.2^\circ$ variation of peak values at 2θ does not prevent identification of the crystal of the present invention. Therefore, the present invention includes not only crystals with peak values of complete match but also those showing peak values with a difference of $\pm 0.2^\circ$.

Some of the terms used in the present specification are defined below.

The "prophylactic drug" means a drug to be administered to a healthy subject before onset of a disease, which is, for example, a drug administered for the purpose of preventing the onset of the disease.

The "therapeutic drug" means a drug to be administered to a subject (patient) diagnosed by a physician to have developed a disease, which is, for example, a drug administered for the

purpose of alleviation of disease or symptom, or recovery of health. When the drug is to be administered to a patient, even if the administration purpose is prevention of aggravation of a disease or symptom, or prevention of a fit, the drug is a
5 therapeutic drug.

The "substances that bind to a C5a receptor" means C5a, a decomposition product of C5a (e.g., C5a desArg wherein the carboxy terminal arginine of C5a has been deleted), and known or unknown substances, which are other than C5a, having affinity
10 for C5a receptor.

The "C5a receptor antagonist" is a substance that inhibits binding of a C5a receptor with a "substance that binds with a C5a receptor".

The "C5a receptor antagonistic action" means an action
15 that inhibits a reaction that causes some physiological changes (e.g., increase of intracellular Ca^{2+} , and the like) by binding of a "substance that binds with a C5a receptor" via the C5a receptor with a cell that expresses the C5a receptor.

The crystal of the present invention could be used in a
20 purified and/or isolated form. Within an embodiment of the present invention, the term "pure" or "purified" means at least 50% pure based on the total mass of the target crystal found within an isolated crystal mixture. Also, within the embodiment of the present invention, "pure" or "purified" further embraces
25 the following ranges: at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% and at least 98%, at least 99%, at least 99.5%.

The compound in the crystal form of the present invention shows a C5a receptor antagonistic action, and is useful as a
30 drug for the prophylaxis or treatment of diseases caused by binding of C5a with a C5a receptor, for example, autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus and the like; sepsis; adult respiratory distress syndrome; chronic obstructive pulmonary disease; allergic

diseases such as asthma and the like; atherosclerosis; myocardial infarction; cerebral infarction; psoriasis; Alzheimer's disease; serious organ injury due to leukocyte activation caused by ischemia reperfusion, trauma, burn, 5 surgical invasion and the like (e.g., pneumonia, nephritis, hepatitis, pancreatitis and the like) and the like. Here, preferred examples of autoimmune diseases include rheumatoid arthritis. Since C5a has a strong inflammation-inducing action, the compound in the crystal form of the present invention is 10 useful as an anti-inflammatory agent, and further, a drug for the prophylaxis and/or treatment of infectious diseases caused by bacteria or virus that invades via a C5a receptor.

When the compound in the crystal form of the present invention is used as the aforementioned prophylactic and/or 15 therapeutic drug, it is generally administered systemically or topically and orally or parenterally in an effective amount. The dose to patients varies depending on the age, body weight, sex, general health conditions, treatment effect, diet, administration time, administration method, clearance rate, 20 combination of drugs, the condition of the disease under treatment and the like. It is generally desirably in the range of from 0.1 mg to 500 mg per dose for an adult by oral administration once to several times a day, or in the range of from 0.01 mg to 200 mg per dose for an adult by parenteral 25 administration (preferably intravenous administration) once to several times a day. The dose is more desirably increased or decreased as appropriate according to the condition of patients.

The compound in the crystal form of the present invention can be used orally or parenterally, for example, by inhalation, 30 rectal administration, topical administration and the like as a pharmaceutical composition or preparation (e.g., powder, granule, tablet, pill, capsule, syrup, elixir, suspension, solution and the like), wherein at least one compound in the crystal form of the present invention can be used alone or used upon admixing

with a pharmaceutically acceptable carrier (excipient, binder, disintegrant, corrigent, corrective, emulsifier, diluent and/or dissolution aids and the like).

A pharmaceutical composition can be prepared according to
5 a general method. In the present specification, by the parenteral is meant subcutaneous injection, intravenous injection, intramuscular injection, intraperitoneal injection, drip and the like. A composition for injection, such as sterile suspension for injection and oil suspension can be prepared
10 using a suitable dispersing agent, wetting agent, or suspending agent according to a method known in the art.

A solid composition for oral administration is exemplified by tablet, pill, capsule, powder, granule and the like. In the above-mentioned solid composition, one or more active compounds
15 can be admixed with at least one additive.

In addition, the above-mentioned composition can contain further additives such as lubricant, preservative, antioxidant, disintegrant, stabilizer, dissolution aids, binder, thickener, sweetener, flavor, perfume and the like.

20 Where necessary, the tablet and pill may be coated with a film of a gastric soluble or enteric material, or may be coated with two or more layers.

The liquid composition for oral administration comprises pharmaceutically acceptable solution, emulsion, syrup, elixir
25 and the like, and may contain a generally used inactive diluent. This composition may contain, besides the inactive diluent, auxiliaries such as wetting agent, suspending agent, and the like, sweetening agent, flavor, perfume and preservative. Other compositions for oral administration are, for example, spray
30 agent containing one or more active substances and formulated by a method known *per se*.

The composition for injection for parenteral administration may comprise sterile aqueous or non-aqueous solution, suspension and emulsion. The above-mentioned

composition may further contain auxiliaries such as preservative, wetting agent, emulsifier, dispersing agent, stabilizer and dissolution aids. These can be sterilized by, for example, filtration through a bacteria-retaining filter, addition of
5 microbicide or irradiation.

The composition for injection can be also used by producing a sterile solid composition and dissolving, for example, the lyophilized product in sterile water or sterile solvent for injection before use.

10 Other composition for parenteral administration include external solution, ointment, liniment, suppository and the like, containing one or more active substances and formulated by a conventional method.

The suppository for rectal administration can be produced
15 by admixing the drug and a suitable non-irritant vehicle, such as a substance which is solid at ambient temperature but shows liquid properties at the temperature of intestinal tract and which melts in the rectum to release the drug.

20 EXAMPLES

The present invention is more specifically explained below by referring to non-limiting Examples and Experimental Examples, which are not to be construed to improperly limit the invention.

25

Example 1: Production method of the crystal of the present invention (1)

To (1S)-(-)-N-[(1-ethyl-1H-pyrazol-4-yl)methyl]-5-hydroxy-N-(6-isopropylpyridin-3-yl)-1,2,3,4-
30 tetrahydronaphthalene-1-carboxamide (20.0 g) synthesized according to the method described in Example 3 of patent document 2 were added ethanol (40.0 ml) and water (12.0 ml), and the mixture was heated to 45°C for dissolution. The solution was filtered, washed with a solution prepared from

ethanol (15.0 ml) and water (5.0 ml), cooled to 15°C, and added with a seed crystal (0.02 g). Water (12.6 ml) was added dropwise, and the mixture was stirred for 8 min to allow crystallization of a white solid. The solid was confirmed and
5 the mixture was stirred at 15°C for 2 hr. After warming to 20°C, the mixture was stirred for 1 hr, cooled to 12°C, and stirred for 1 hr. At 10°C, water (81.4 ml) was added dropwise over 0.5 hr, and the mixture was stirred at the same temperature for 1.5 hr. The suspension was filtered, and the
10 solid was washed with a solution prepared from ethanol (10.0 ml) and water (20.0 ml), and dried under reduced pressure at 45°C for 16 hr to give a white solid (19.6 g) as crystals (purity 99.97%, optical purity 100%ee).

The obtained crystals were subjected to powder X-ray
15 diffraction (XRD) analyses under the following conditions.

apparatus: RINT-TTR III (Rigaku Corporation)

conditions:

X-ray vacuum tube: Cu

electric current: 300 mA

20 electric voltage: 50 kV

scanning speed: 2°/min

scanning range: $2\theta=2 - 40^\circ$

The powder X-ray diffraction pattern is shown in Fig. 1, and peaks with relative intensity of not less than 15 when the
25 peak intensity at a diffraction angle 2θ of 16.6° is 100, and the relative intensities thereof are shown in Table 1.

Table 1

2 θ (°)	relative intensity
4.6	73
10.5	15
10.9	26
13.2	21
14.0	17
16.3	67
16.6	100
17.3	59
18.1	27
18.7	40
20.2	53
21.1	43
22.5	59
24.3	17
24.6	33
25.3	25
25.6	32
26.0	21
28.8	15

The characteristic peaks of the crystals obtained in Example 1 at diffraction angles 2 θ were 4.6°, 10.5°, 10.9°, 13.2°, 14.0° and 16.6° (respectively $\pm 0.2^\circ$). These characteristic peaks were not observed in Form I crystal and Form II crystal, and therefore, the crystal obtained in Example 1 is a novel crystal of (1S)-(-)-N-[(1-ethyl-1H-pyrazol-4-yl)methyl]-5-hydroxy-N-(6-isopropylpyridin-3-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide.

Next, the crystal (1.59 mg) obtained in Example 1 was placed on a differential scanning calorimeter DSC-1 (manufactured by METTLER-TOLEDO), and measured at a scanning rise rate of 5°C/min (25 to 300°C, dried nitrogen 50.0 mL/min,

aluminum cell container). As a result, the first melting peak was found at 145°C (extrapolated onset temperature), and the maximum peak in the first melting peak was found at 148°C. In addition, after observation of the first melting peak, an
5 exothermic peak associated with transformation to Form I crystal was observed, and further, a melting peak of Form I crystal was observed at 176°C (extrapolated onset temperature). The differential scanning calorimetry (DSC) curve is shown in Fig. 2.

10

Experimental Example 1: Stability test of crystal (1)

Three kinds of crystals of Form I crystal, Form II crystal, and the crystal obtained according to the method described in above-mentioned Example 1 were each placed in
15 sample bottles, and open-preserved at 40°C/75%RH. As a result, the crystal forms of Form I crystal and the crystals obtained according to the method described in the above-mentioned Example 1 did not change even after lapse of 6 months. However, Form II crystal transformed into Form I crystal 8 days later
20 (see Figs. 3 - 5).

The results reveal that the crystal of the present invention obtained by the method described in the above-mentioned Example 1 does not transform into a different crystal even after preservation for 6 months under the
25 conditions of 40°C/75%RH, and is superior in stability during long-term preservation as compared to Form II crystal.

Experimental Example 2 and Example 2: Stability test of crystal (2) and production method of the crystal of the 30 present invention (2)

Water (6 ml) was added to Form I crystal (1 g), and the mixture was stirred at room temperature. After stirring for 20 hr, a part of the suspension was collected and centrifuged. The wet crystal was subjected to powder X-ray measurement

under similar conditions as in Example 1.

Based on the comparison of X-ray diffraction patterns, Form I crystal was partially transformed into the crystal obtained by the method described in Example 1. The compound in
5 the crystal form of the present invention can be used as an active ingredient of a medicament. Generally, a medicament is formulated into a preparation and distributed in the market, and water is mostly used during the formulation step. Therefore, when Form I crystal is used as an active ingredient,
10 partial crystal transformation may take place during the formulation step, which may lead to inconsistent expression of efficacy and side effects, thus possibly causing an unexpected situation. On the other hand, when the crystal of the present invention is used as an active ingredient, such a problem can
15 be suppressed, and a more uniform preparation can be obtained.

Experimental Example 3 and Example 3: Stability test of crystal (3) and production method of the crystal of the present invention (3)

20 The crystals obtained according to the method described in the above-mentioned Example 1 and Form I crystal were added to a solvent, and the mixture was stirred in a suspension state. Thereafter, a part of the suspension was collected, and the crystal in the suspension was subjected to powder X-ray
25 measurement under similar conditions as in Example 1. The weight of the crystal added to the solvent, the solvent used, the temperature of the solvent and the stirring time are as shown in Table 2. The results are shown in Table 4.

Table 2

solvent	crystal amount	tempera- ture	stirring time
Ethanol 4 ml	1.5 g each	50°C	1.5 hr
Ethanol 4 ml	3.5 g each	70°C	1.5 hr
Ethanol 3 ml + water 1 ml	2.5 g each	50°C	1.5 hr
Ethanol 1.5 ml + water 0.5 ml	2.0 g each	60°C	1.5 hr
Ethanol 1 ml + water 3 ml	0.5 g each	50°C	1.5 hr
Ethanol 1 ml + water 3 ml	2.0 g each	60°C	1.5 hr
Ethanol 0.5 ml + water 1.5 ml	0.5 g each	65°C	1.5 hr
Ethanol 4 ml	0.8 g each	10°C	1.5 hr
Ethanol 3 ml + water 1 ml	0.8 g each	10°C	1.5 hr
Ethanol 1 ml + water 3 ml	0.5 g each	10°C	1.5 hr
water 2 ml	0.25 g each	r.t.	1.5 hr
Acetone 1 ml	0.25 g each	r.t.	1.5 hr
Methanol 1.5 ml	0.25 g each	r.t.	1.5 hr
Formic acid 1 ml + water 1 ml	0.5 g each	r.t.	1.5 hr
Anisole 1.5 ml	0.25 g each	r.t.	1.5 hr
2-Butanol 2 ml	0.25 g each	r.t.	1.5 hr
3-Methyl-1-butanol 2 ml	0.25 g each	r.t.	1.5 hr
Heptane 3 ml	0.25 g each	50°C	6.5 hr
Toluene 2 ml	0.25 g each	50°C	1 hr
2-Methyl-2-propanol 2 ml	0.25 g each	50°C	1 hr
Ethanol 0.5 ml + heptane 0.5 ml	0.25 g each	50°C	1 hr
1-Propanol 1 ml + heptane 1 ml	0.25 g each	50°C	1 hr
2-Propanol 1 ml + heptane 1 ml	0.25 g each	50°C	1 hr
2-Butanol 1 ml + heptane 1 ml	0.25 g each	50°C	1 hr
2-Methyl-2-propanol 1 ml + heptane 1 ml	0.25 g each	50°C	1 hr
3-Methyl-1-butanol 1 ml + heptane 1 ml	0.25 g each	50°C	1 hr
Tetrahydrofuran 1 ml + heptane 1 ml	0.25 g each	50°C	1 hr
Ethyl acetate 1 ml + heptane 1 ml	0.25 g each	50°C	1 hr

(In the Table 2, "r. t." means room temperature.)

In addition, while maintaining the mixed solvent shown in
 5 Table 3 at 70°C, the crystals obtained according to the method

described in the above-mentioned Example 1 and Form I crystal (250 mg each) were added to the mixed solvent, and the mixture was stirred for 5 min in a suspension state. 40 to 60 μ l of the suspension was collected, and the crystal in the

5 suspension was subjected to powder X-ray measurement under similar conditions as in Example 1. Furthermore, after the temperature of the remaining suspension was confirmed to have reached 60°C, the crystals (5 to 10 mg) obtained according to the method described in the above-mentioned Example 1 were

10 further added and the mixture was stirred for 10 min while maintaining the temperature of the suspension at 60°C. 40 to 60 μ l of the suspension was collected, and the crystal in the suspension was subjected to powder X-ray measurement under similar conditions as in Example 1. Furthermore, the crystals

15 (ca 20 mg) obtained according to the method described in the above-mentioned Example 1 were further added to the remaining suspension and the mixture was stirred for 1 hr while maintaining the temperature of the suspension at 60°C and at room temperature overnight. Thereafter, the crystal in the

20 suspension was subjected to powder X-ray measurement under similar conditions as in Example 1. The results were shown in Table 4.

Table 3

Ethanol 0.5 ml + heptane 0.5 ml
2-butanol 0.5 ml + heptane 0.5 ml
3-methyl-1-butanol 10.5 ml + heptane 0.5 ml
ethyl acetate 0.5 ml + heptane 0.5 ml

Table 4

	10°C	r. t.	50°C	60°C	65°C	70°C
water	-	O	-	-	-	-
ethanol	O	-	O	-	-	x (Form I)
75% aqueous ethanol	O	-	O	x (Form I)	-	-
25% aqueous ethanol	O	-	O	x (Form I)	x (Form I)	-
acetone	-	O	-	-	-	-
methanol	-	x (Form II)	-	-	-	-
50% aqueous formic acid	-	x (Form II)	-	-	-	-
anisole	-	O	-	-	-	-
2-butanol	-	O	-	-	-	-
3-methyl-1-butanol	-	O	-	-	-	-
heptane	-	-	O	-	-	-
toluene	-	-	O	-	-	-
2-methyl-2-propanol	-	-	O	-	-	-
ethanol/haptane	-	O	O	x (Form I)	-	x (Form I)
1-propanol/heptane	-	-	O	-	-	-
2-propanol/heptane	-	-	O	-	-	-
2-butanol/heptane	-	O	O	x (Form I)	-	x (Form I)
2-methyl-2-propanol/heptane	-	-	O	-	-	-
3-methyl-1-butanol/heptane	-	O	O	x (Form I)	-	x (Form I)
tetrahydrofuran/heptane	-	-	O	-	-	-
Ethyl acetate/heptane	-	O	O	x (Form I)	-	x (Form I)

In the Table 4, "r. t." means room temperature, "O" means that crystal having the same powder X-ray diffraction peaks as the crystals obtained according to the method described in the above-mentioned Example 1 was obtained, "x (Form I)" means that crystal having the same powder X-ray diffraction peaks as Form I crystal was obtained, "x (Form II)" means that crystal having the same powder X-ray diffraction peaks as Form II crystal was obtained, and "-" means that the test was not performed.

These results clearly reveal that when the compound is crystallized using a solvent having a carbon number of 1 such as methanol, formic acid and the like, only Form II crystal is obtained; when it is crystallized using water or an organic solvent having a carbon number of two or more under conditions of not less than 60°C, only Form I crystal is obtained; and when it is crystallized using water or an organic solvent having a carbon number of two or more under conditions of not less than the melting point of the solvent and less than 60°C, only the crystal of the present invention is selectively obtained. Generally, the solubility of a solid becomes high as the temperature of the solvent increases. To obtain crystals in a high yield, therefore, crystallization is preferably performed at a low solvent temperature. In addition, when production worker comes into contact with a high temperature solvent, the worker may be injured (e.g., burn etc.). To ensure safety of production workers, the solvent temperature is preferably low. For production of pure Form I crystal alone, which is free of other crystals, the solvent temperature needs to be not less than 60°C. For production of the crystal of the present invention in an isolated and/or purified form, a lower temperature solvent can be used. Thus, the crystal of the present invention can be produced more safely and efficiently as compared to Form I crystal. Moreover, since the crystal of the present invention is more stable around room temperature as compared to Form I crystal and does not transform into other crystals during the formulation step and the like, it is easy to handle and has advantageous properties as a bulk pharmaceutical product.

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Industrial Applicability

Since the crystal of the present invention is stable under conditions of less than 60°C and does not transform into other crystals, it is useful as a bulk drug of pharmaceutical

products as compared to other previously-identified crystals. In addition, the production method of the present invention can selectively produce the crystal of the present invention safely, efficiently and selectively.

5 The above written description of the invention provides a manner and process of making and using it such that any person skilled in this art is enabled to make and use the same, this enablement being provided in particular for the subject matter of the appended claims, which make up a part of the original
10 description. As used herein, the phrases "selected from the group consisting of," "chosen from," and the like include mixtures of the specified materials. Where a numerical limit or range is stated herein, the endpoints are included. Also, all values and subranges within a numerical limit or range are
15 specifically included as if explicitly written out.

 This application is based on US provisional application 61/437,949, the contents of which are incorporated in full herein.

Claims

1. An isolated crystal of (1S)-(-)-N-[(1-ethyl-1H-pyrazol-4-yl)methyl]-5-hydroxy-N-(6-isopropylpyridin-3-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide, wherein the crystal has peaks at diffraction angles 2θ of at least about $4.6^{\circ}\pm 0.2^{\circ}$, $10.9^{\circ}\pm 0.2^{\circ}$, $13.2^{\circ}\pm 0.2^{\circ}$ and $16.6^{\circ}\pm 0.2^{\circ}$ in a powder X-ray diffraction spectrum.
2. The crystal of claim 1, wherein the crystal has peaks at diffraction angles 2θ of at least about $10.5^{\circ}\pm 0.2^{\circ}$ and $14.0^{\circ}\pm 0.2^{\circ}$ in a powder X-ray diffraction spectrum.
3. The crystal of claim 1 or 2, wherein the crystal has endothermic peaks at $143-149^{\circ}\text{C}$ (extrapolated onset temperature) and $171-177^{\circ}\text{C}$ (extrapolated onset temperature) in a differential scanning calorimetry measurement.
4. The crystal of any one of claims 1 to 3, wherein the crystal has a physicochemical property of the following A and/or B:
A: having a powder X-ray diffraction pattern of peaks shown in Fig. 1,
B: having a differential scanning calorimetry curve shown in Fig 2.
5. A method of producing the crystal of any one of claims 1 to 4, comprising:
 setting a solvent temperature to fall within the range of from not less than a melting point of water or an organic solvent having a carbon number of two or more to less than 60°C ;
 forming a crystal of (1S)-(-)-N-[(1-ethyl-1H-pyrazol-4-yl)methyl]-5-hydroxy-N-(6-isopropylpyridin-3-yl)-1,2,3,4-

tetrahydronaphthalene-1-carboxamide dissolved in the water or the organic solvent; and

recovering the crystal of claim 1.

5 6. A medicament comprising the crystal of any one of claim 1 to 4, wherein the crystal has a purity of at least 95%.

7. A pharmaceutical composition comprising the crystal of any one of claims 1 to 4 and a pharmaceutically acceptable
10 additive.

8. A method of treating a disease caused by binding of C5a to a C5a receptor, comprising:
administering to a subject in need thereof an effective
15 amount of the crystal of any one of claims 1 to 4.

9. The method of claim 8, wherein the disease caused by binding of C5a to a C5a receptor is one selected from the group consisting of an autoimmune disease, sepsis, adult
20 respiratory distress syndrome, chronic obstructive pulmonary disease, an allergic disease, atherosclerosis, cardiac infarction, cerebral infarction, psoriasis, Alzheimer's disease, and serious organ injury due to leukocyte activation caused by ischemia reperfusion, trauma, burn or surgical invasion.

25

10. A method of treating inflammation, comprising:
administering to a subject in need thereof an effective amount of an anti-inflammatory agent comprising the crystal of any one of claims 1 to 4.

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11. A method of treating an infectious disease, comprising:
administering to a subject in need thereof an effective amount of a C5a receptor antagonist comprising the crystal of any one of claims 1 to 4.

12. The method of claim 11, wherein the infectious disease is caused by bacteria or virus that invades via a C5a receptor.
- 5 13. A method of treating rheumatoid arthritis, comprising:
administering to a subject in need thereof an effective amount of the crystal of any one of claims 1 to 4.
- 10 14. A prophylactic and/or therapeutic drug for a disease caused by binding of C5a to a C5a receptor, comprising the crystal of any one of claims 1 to 4 as an active ingredient.
- 15 15. The prophylactic and/or therapeutic drug of claim 14, wherein the disease caused by binding of C5a to a C5a receptor is one selected from the group consisting of an autoimmune disease, sepsis, adult respiratory distress syndrome, chronic obstructive pulmonary disease, an allergic disease, atherosclerosis, cardiac infarction, cerebral infarction, psoriasis, Alzheimer's disease, and serious organ injury due
20 to leukocyte activation caused by ischemia reperfusion, trauma, burn or surgical invasion.
16. An anti-inflammatory agent comprising the crystal of any one of claims 1 to 4 as an active ingredient.
- 25 17. A prophylactic and/or therapeutic drug for an infectious disease comprising the crystal of any one of claims 1 to 4 as an active ingredient.
- 30 18. The prophylactic and/or therapeutic drug of claim 17, wherein the infectious disease is caused by bacteria or virus that invades via a C5a receptor.
19. A prophylactic and/or therapeutic drug for rheumatoid

arthritis, comprising the crystal of any one of claims 1 to 4 as an active ingredient.

20. A C5a receptor antagonist comprising the crystal of any
5 one of claims 1 to 4 as an active ingredient.

Fig. 1

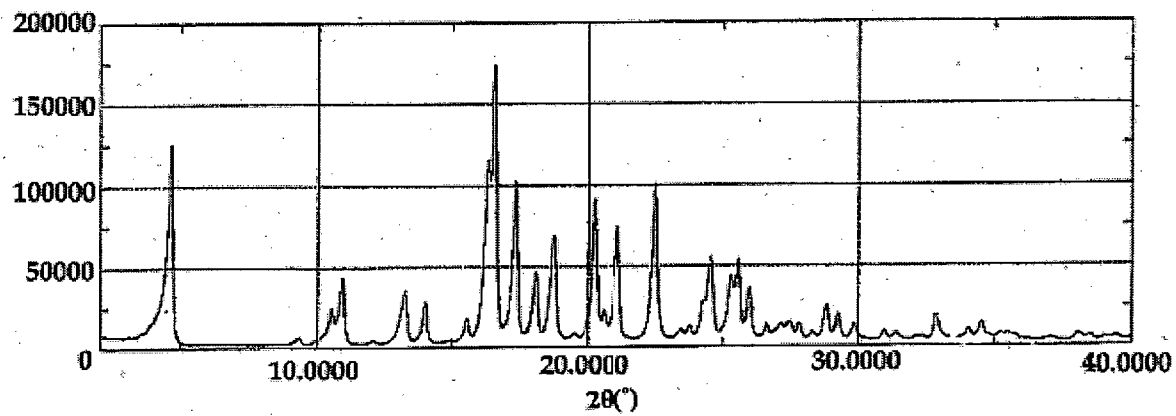


Fig. 2

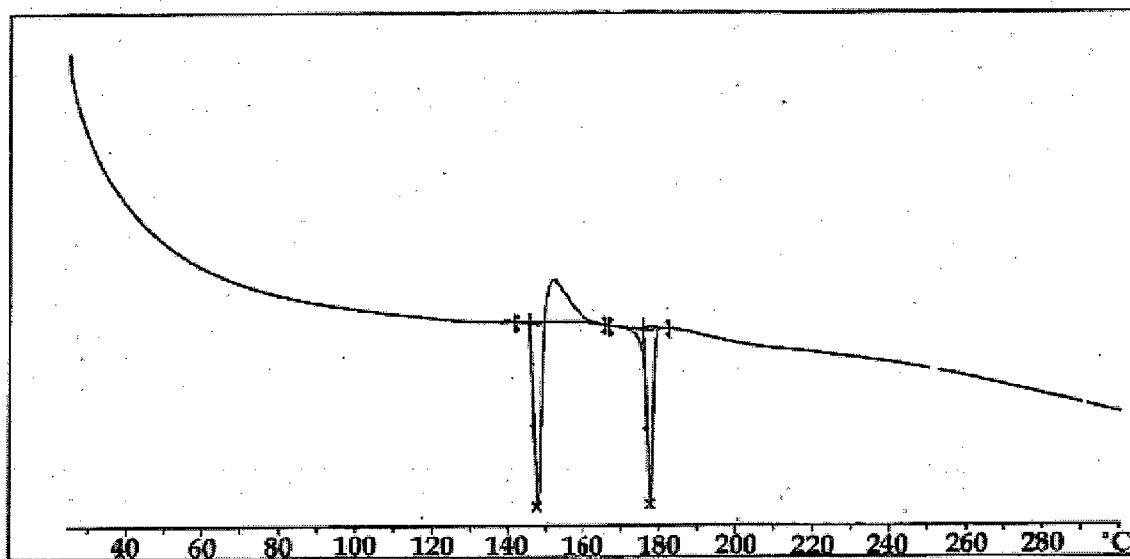


Fig. 3

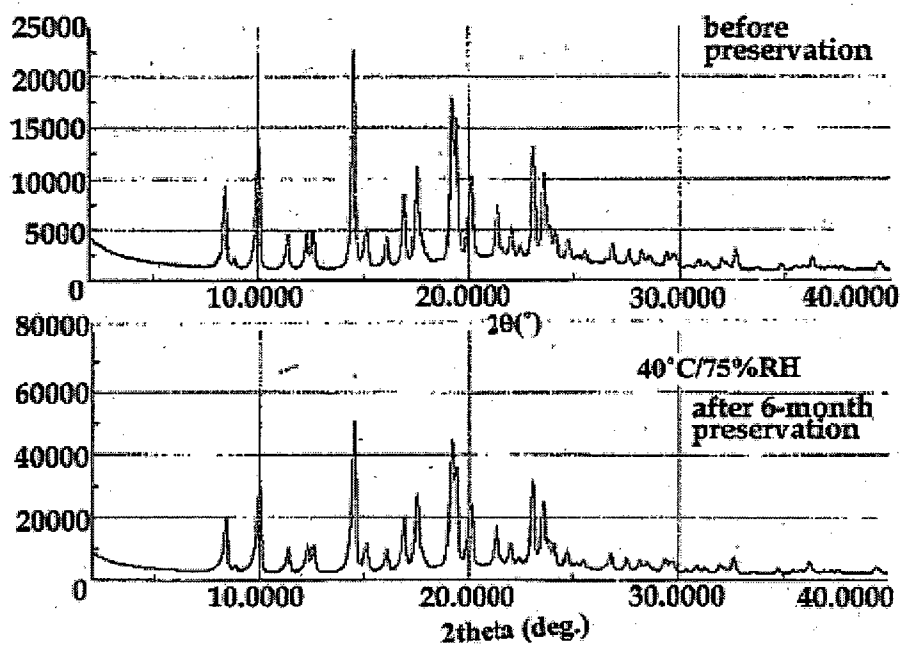


Fig. 4

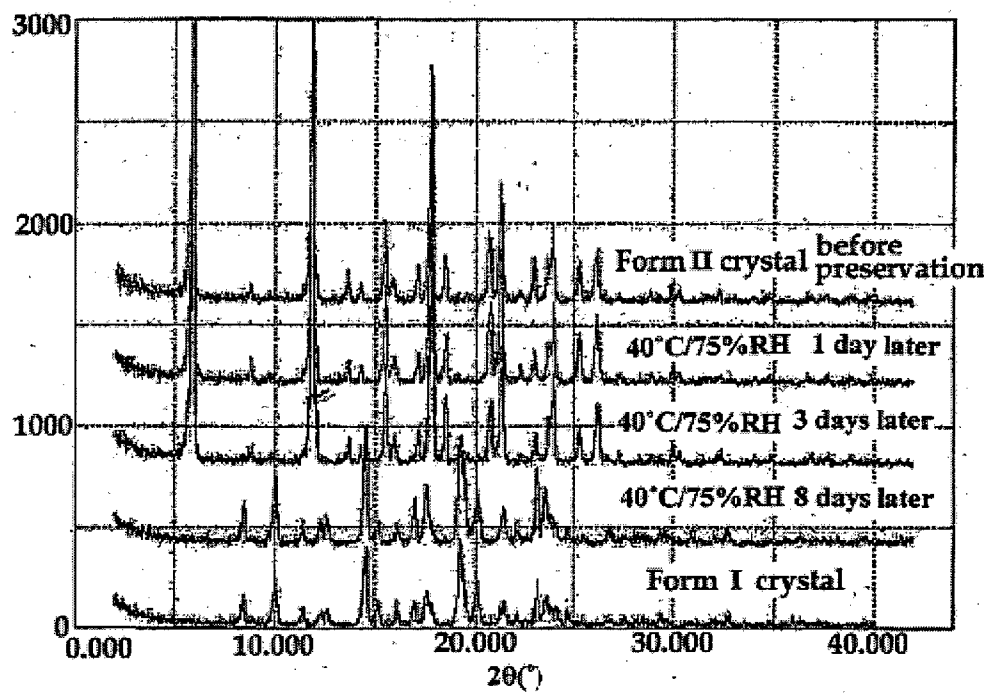
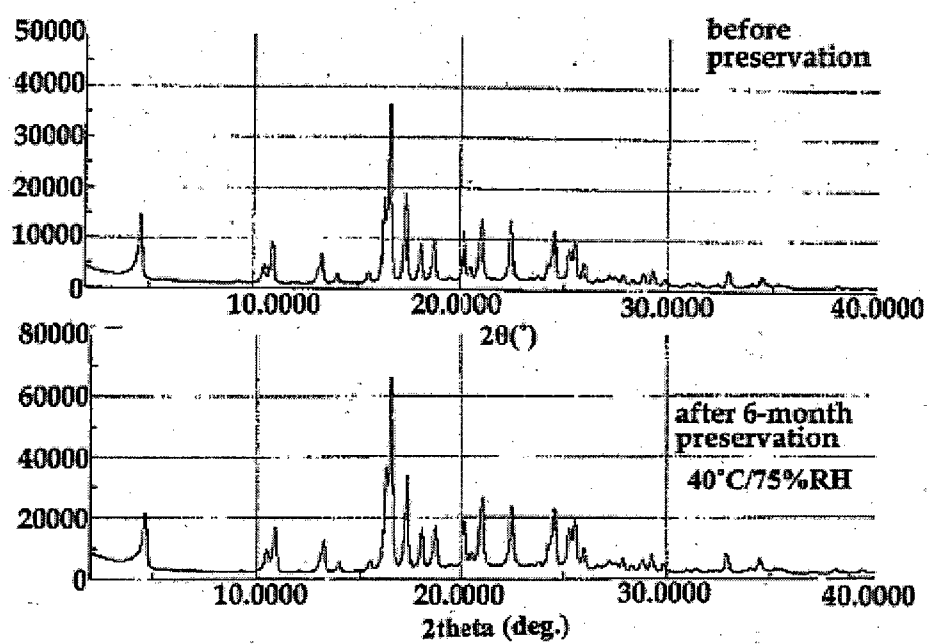


Fig. 5



INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2012/052575

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/12 A61K31/4439 A61P31/00 A61P29/00 A61P37/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 852 431 A1 (MITSUBISHI PHARMA CORP [JP] MITSUBISHI TANABE PHARMA CORP [JP]) 7 November 2007 (2007-11-07) cited in the application claims 8, 16 -----	1-20



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search

24 April 2012

Date of mailing of the international search report

08/05/2012

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/JP2012/052575

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1852431	A1	07-11-2007	CA 2596993 A1 10-08-2006
			CN 101119986 A 06-02-2008
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