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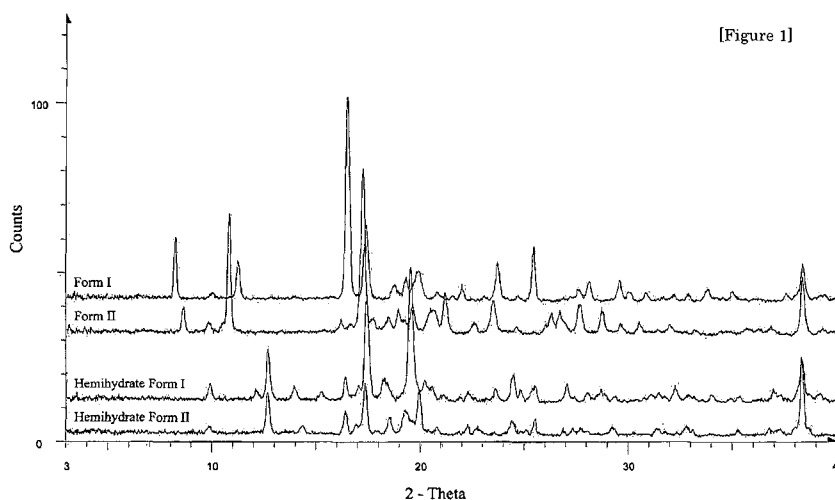
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(54) Title: A HYDRATE OF A CYCLOHEXANAMINE DERIVATIVE



[Figure 1]

(57) Abstract: This invention provides a cyclohexanamine derivative which is useful as a medicine. It was found that a hydrate of a cyclohexanamine derivative is useful as an active pharmaceutical ingredient.

[Document's name] Description

[Title] A hydrate of a cyclohexanamine derivative

[Field of the Invention]

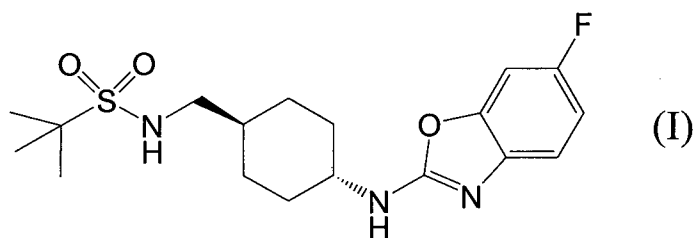
[0001]

This invention relates to a hydrate of a cyclohexanamine derivative and a pharmaceutical composition comprising them. Furthermore, it relates to a process for the preparation of the hydrate.

[Background Art]

[0002]

Patent Document 1 discloses that a compound of formula (I):



has NPY Y5 receptor specific antagonistic activity and it is useful as an anorectic or anti-obesity composition. The Patent Document 1 discloses that the compound of formula (I) is an anhydride.

[Prior Art Document]

[Patent Document]

[0003]

[Patent Document 1] WO2009/054434

[Disclosure of Invention]

[Problems to be solved by the Invention]

[0004]

When the anhydride of the compound of formula (I) in Patent Document 1 was tried to grind, it could not be ground because the ground powder contracted and aggregated in a grinding room. For example, when A-O JET MILL manufactured by Seishin Enterprise Co., Ltd., Spiral 50 AS manufactured by Hosokawa Micron Corporation or the like were used for grind, the anhydride of the compound of formula (I) in Patent Document 1 could not be ground. When the grind is impossible, it is difficult to keep the content homogeneity of an active ingredient in a formulation and develop the formulation as a medicine. That is, a compound of formula (I) which is useful as an active pharmaceutical ingredient was required.

[Means for Solving the Problem]

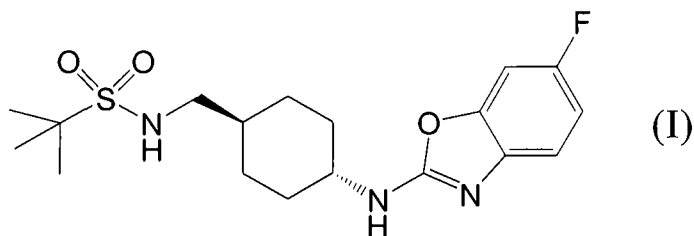
[0005]

The inventors found that hydrates of a compound of formula (I), especially 0.5 hydrates can be ground through their intensive studies to find a grindable form of a compound of formula (I). That is, these inventors found that the hydrates of a compound of formula (I), especially the 0.5 hydrates, are useful as an active pharmaceutical ingredient. Furthermore, these inventors found that there are two crystal forms of Form I and Form II for 0.5 hydrates of the compound of formula (I) and Form I crystals are more thermodynamically stable compared with Form II crystals.

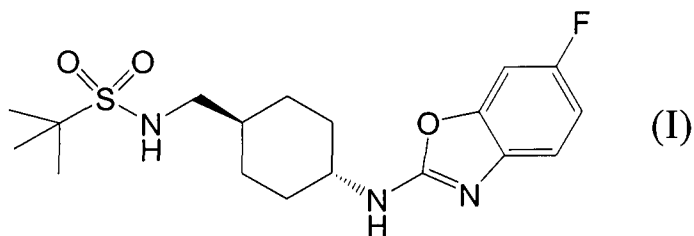
[0006]

This invention includes the followings.

(1) A hydrate of a compound of formula (I):



(2) A 0.5 hydrate of a compound of formula (I):



(3) The hydrate of (2) having peaks at diffraction angles (2θ): $13.9^\circ \pm 0.2^\circ$ and $15.2^\circ \pm 0.2^\circ$ in a X ray powder diffraction spectrum.

(4) The hydrate of (2) having peaks at diffraction angles (2θ): $12.7^\circ \pm 0.2^\circ$, $13.9^\circ \pm 0.2^\circ$, $15.2^\circ \pm 0.2^\circ$, $17.4^\circ \pm 0.2^\circ$ and $19.5^\circ \pm 0.2^\circ$ in a X ray powder diffraction spectrum.

(5) The hydrate of (3) or (4) not having peaks at diffraction angles (2θ): $8.2^\circ \pm 0.2^\circ$, $8.6^\circ \pm 0.2^\circ$, $10.8^\circ \pm 0.2^\circ$, $11.2^\circ \pm 0.2^\circ$, $14.3^\circ \pm 0.2^\circ$ and $19.9^\circ \pm 0.2^\circ$ in a X ray powder diffraction spectrum.

(6) The hydrate of (2) having one or more chemical shift(s) of $147.9 \text{ ppm} \pm 0.2 \text{ ppm}$, $138.1 \text{ ppm} \pm 0.2 \text{ ppm}$, $61.9 \text{ ppm} \pm 0.2 \text{ ppm}$ and $48.7 \text{ ppm} \pm 0.2 \text{ ppm}$ in a solid state ^{13}C -NMR spectrum.

(7) The hydrate of (2) having chemical shifts which are substantially similar to 147.9 ppm $\pm$ 0.2 ppm, 138.1 ppm $\pm$ 0.2 ppm, 61.9 ppm $\pm$ 0.2 ppm and 48.7 ppm $\pm$ 0.2 ppm in a solid state ^{13}C -NMR spectrum.

(8) The hydrate of (2) characterized by one or more spectrum (spectra) and/or a curve selected from the following (a) to (c):

(a) a X ray powder diffraction spectrum substantially corresponding to Figure 2;

(b) a solid state ^{13}C -NMR spectrum substantially corresponding to hemihydrate I in Figure 6; and

(c) a differential scanning calorimetry curve substantially corresponding to Figure 7.

(9) The hydrate of (2) having peaks at diffraction angles (2θ): $14.3^\circ \pm 0.2^\circ$ and $19.9^\circ \pm 0.2^\circ$ in a X ray powder diffraction spectrum.

(10) The hydrate of (2) having peaks at diffraction angles (2θ): $12.6^\circ \pm 0.2^\circ$, $14.3^\circ \pm 0.2^\circ$, $17.3^\circ \pm 0.2^\circ$ and $19.9^\circ \pm 0.2^\circ$ in a X ray powder diffraction spectrum.

(11) The hydrate of (9) or (10) not having peaks at diffraction angles (2θ): $8.2^\circ \pm 0.2^\circ$, $8.6^\circ \pm 0.2^\circ$, $10.8^\circ \pm 0.2^\circ$, $11.2^\circ \pm 0.2^\circ$, $13.9^\circ \pm 0.2^\circ$ and $15.2^\circ \pm 0.2^\circ$ in a X ray powder diffraction spectrum.

(12) The hydrate of (2) having one or more combination(s) of chemical shifts of 147.8 ppm $\pm$ 0.2 ppm and 147.2 ppm $\pm$ 0.2 ppm, 137.9 ppm $\pm$ 0.2 ppm and 137.3 ppm $\pm$ 0.2 ppm, and 50.2 ppm $\pm$ 0.2 ppm and 48.7 ppm $\pm$ 0.2 ppm in a solid state ^{13}C -NMR spectrum.

(13) The hydrate of (2) having one or more chemical shift(s) of 147.8 ppm $\pm$ 0.2 ppm, 147.2 ppm $\pm$ 0.2 ppm, 137.9 ppm $\pm$ 0.2 ppm, 137.3 ppm $\pm$ 0.2 ppm, 61.6 ppm $\pm$ 0.2 ppm, 50.2 ppm $\pm$ 0.2 ppm and 48.7 ppm $\pm$ 0.2 ppm in a solid state ^{13}C -NMR spectrum.

(14) The hydrate of (2) having chemical shifts substantially similar to 147.8 ppm $\pm$ 0.2 ppm, 147.2 ppm $\pm$ 0.2 ppm, 137.9 ppm $\pm$ 0.2 ppm, 137.3 ppm $\pm$ 0.2 ppm, 61.6 ppm $\pm$ 0.2 ppm, 50.2 ppm $\pm$ 0.2 ppm and 48.7 ppm $\pm$ 0.2 ppm in a solid state ^{13}C -NMR spectrum.

(15) The hydrate of (2) characterized by one or more spectrum (spectra) selected from the following (a) and (b):

(a) a X ray powder diffraction spectrum substantially corresponding to Figure 2; and

(b) a solid state ^{13}C -NMR spectrum substantially corresponding to hemihydrate II in Figure 6.

(16) A pharmaceutical composition comprising the hydrate of any one of (1) to (15).

(17) The pharmaceutical composition of (16) having NPY Y5 receptor antagonistic activity.

(18) The pharmaceutical composition of (16) for the prevention or treatment of obesity

or an obesity-related disorder, or the weight management for obesity.

(19) The pharmaceutical composition of (18), wherein the obesity-related disorder is overeating; hypertension; impaired glucose tolerance; type II diabetes; metabolic syndrome; abnormal lipid metabolism; arteriosclerosis; hyperuricemia; gout; fatty liver; endometrial, breast, prostate or colon cancer; osteoarthritis; lumbago; obstructive sleep apnea syndrome; coronary artery disease; cerebral infarction; menstrual disorder; the Prader-Willi Syndrome; Frohlich's syndrome; or pickwickian syndrome.

(20) A method for the prevention or treatment of a NPY Y5 related disease, comprising a step of administering the hydrate of any one of (1) to (15).

(21) A method for the prevention or treatment of obesity or an obesity-related disorder, or the weight management for obesity, comprising a step of administering the hydrate of any one of (1) to (15).

(22) A method for inducing or accelerating weight loss, or maintaining or managing body weight, comprising a step of administering the hydrate of any one of (1) to (15).

(23) Use of the hydrate of any one of (1) to (15) for the manufacture of an agent for the prevention or treatment of a NPY Y5 related disease.

(24) Use of the hydrate of any one of (1) to (15) for the manufacture of a pharmaceutical composition for the prevention or treatment of obesity or an obesity-related disorder, or the weight management for obesity.

(25) Use of the hydrate of any one of (1) to (15) for the manufacture of a pharmaceutical composition for inducing or accelerating weight loss, or maintaining or managing body weight.

(26) The hydrate of any one of (1) to (15) for the prevention or treatment of a NPY Y5 related disease.

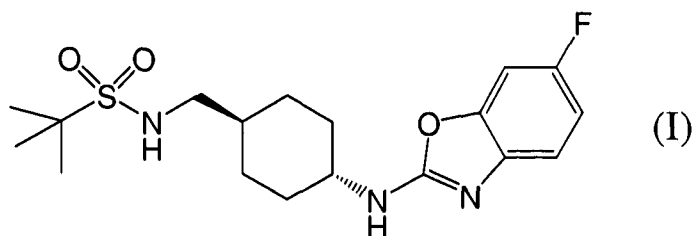
(27) The hydrate of any one of (1) to (15) for the prevention or treatment of obesity or an obesity-related disorder, or the weight management for obesity.

(28) The hydrate of any one of (1) to (15) for inducing or accelerating weight loss, or maintaining or managing body weight.

[0007]

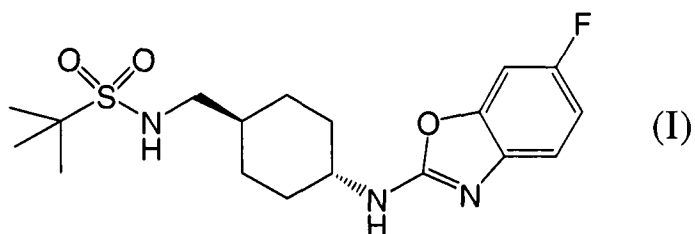
Additionally, this invention also includes the followings.

(29) A process for the preparation of the hydrate of the compound of formula (I):



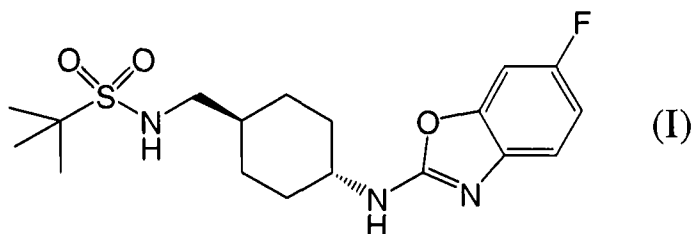
of any one of (1) to (15), characterized by crystallizing the compound of formula (I) from an aqueous organic solvent.

(30) A process for the preparation of the 0.5 hydrate of the compound of formula (I):



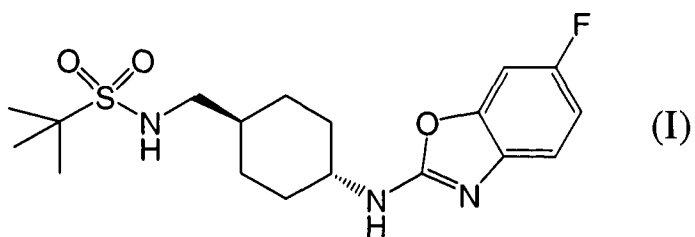
of any one of (3) to (8), characterized by crystallizing the compound of formula (I) from aqueous acetone.

(31) A process for the preparation of the 0.5 hydrate of the compound of formula (I):



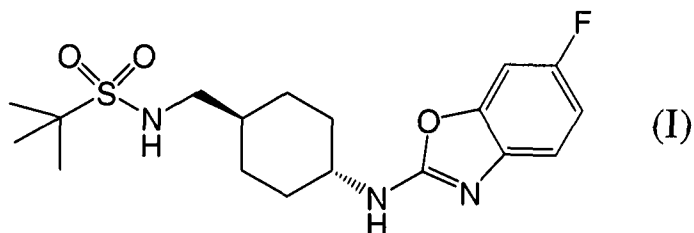
of any one of (9) to (15), characterized by crystallizing the compound of formula (I) from aqueous isopropyl alcohol.

(32) A compound of formula (I):



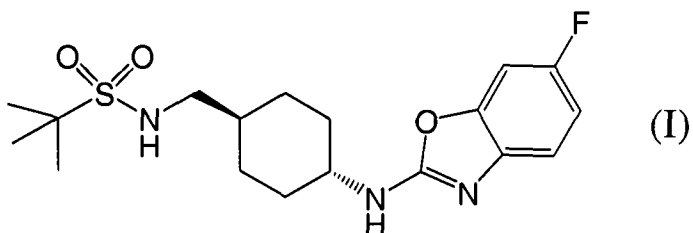
or hydrate thereof wherein X₅₀ is 1.5 to 5.0 μm.

(33) A compound of formula (I):



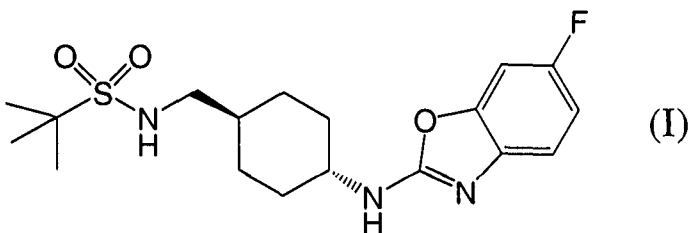
or hydrate thereof wherein X50 is 2.0 to 5.0 μm .

(34) A compound of formula (I):



or hydrate thereof wherein X90 is 1.5 to 30.0 μm .

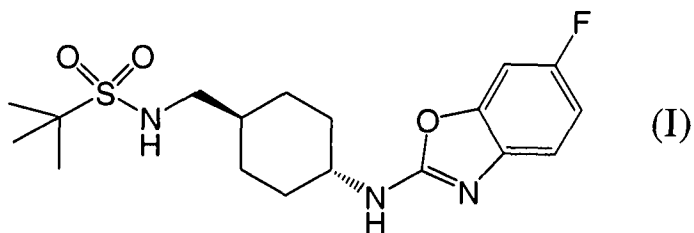
(35) A compound of formula (I):



or hydrate thereof wherein X90 is 2.0 to 10.0 μm .

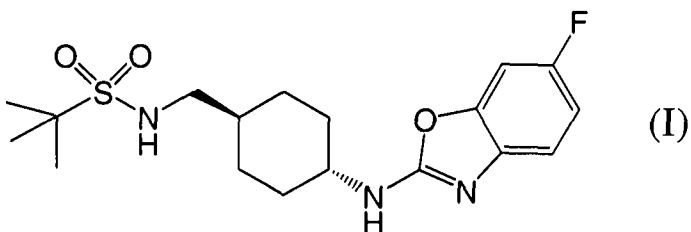
(36) A pharmaceutical composition comprising the compound or hydrate thereof of any one of (32) to (35).

(37) A ground product of a compound of formula (I):



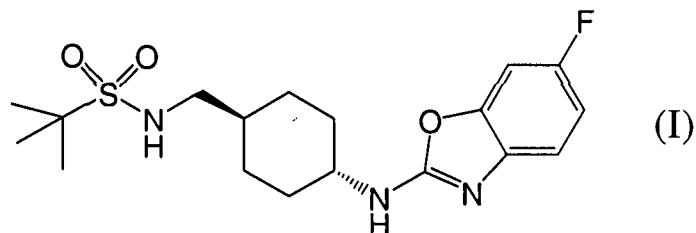
or hydrate thereof wherein X50 is 1.5 to 5.0 μm .

(38) A ground product of a compound of formula (I):



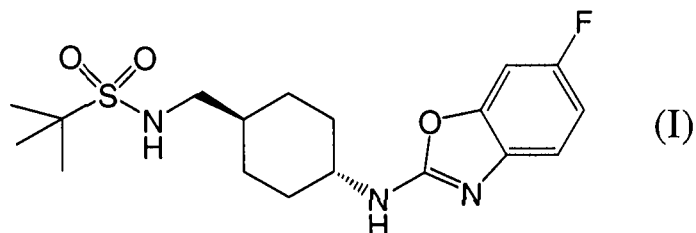
or hydrate thereof wherein X50 is 2.0 to 5.0 μm .

(39) A ground product of a compound of formula (I):



or hydrate thereof wherein X90 is 1.5 to 30.0 μm .

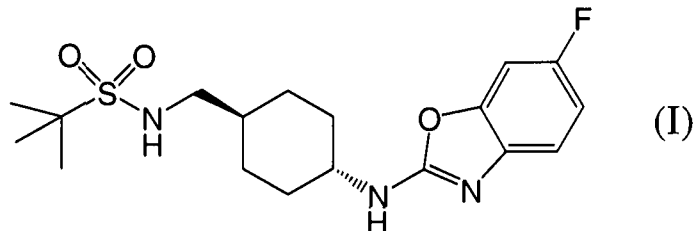
(40) A ground product of a compound of formula (I):



or hydrate thereof wherein X90 is 2.0 to 10.0 μm .

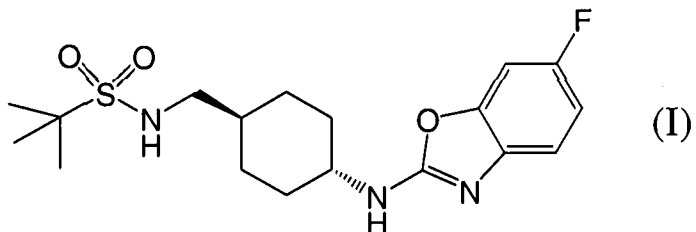
(41) A pharmaceutical composition comprising the ground product of any one of (37) to (40).

(42) A powder of a compound of formula (I):



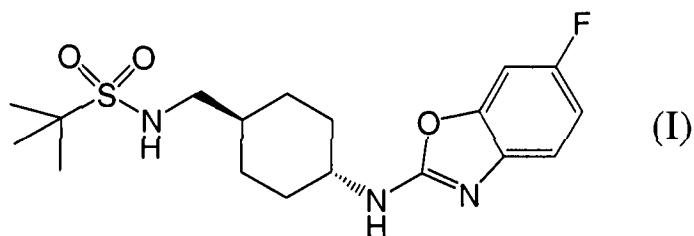
or hydrate thereof wherein X50 is 1.5 to 5.0 μm .

(43) A powder of a compound of formula (I):



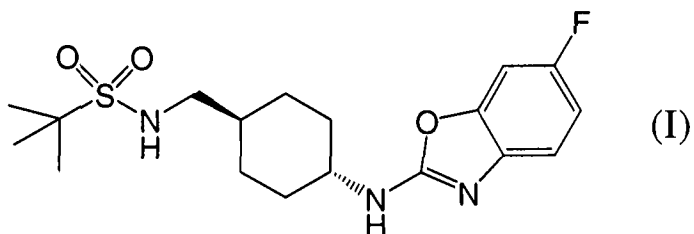
or hydrate thereof wherein X50 is 2.0 to 5.0 μm .

(44) A powder of a compound of formula (I):



or hydrate thereof wherein X90 is 1.5 to 30.0 μm .

(45) A powder of a compound of formula (I):



or hydrate thereof wherein X90 is 2.0 to 10.0 μm .

(46) A pharmaceutical composition comprising the powder of any one of (42) or (45).

[Effect of the Invention]

[0008]

A hydrate of this invention is useful as an active pharmaceutical ingredient of a compound of formula (I). That is, pharmaceutical compositions comprising a hydrate of this invention are very useful as a medicine for prevention or treatment of obesity or obesity-related disorders. Furthermore, the pharmaceutical compositions are very useful for the weight management for obesity.

[Brief Description of the Drawings]

[0009]

[Figure 1] X ray powder diffraction spectra of Form I crystal (Form I) and Form II crystal (Form II) of an anhydride of a compound of formula (I), and Form I crystal (Hemihydrate Form I) and Form II crystal (Hemihydrate Form II) of the 0.5 hydrate. The horizontal axis shows 2θ ($^\circ$) and vertical axis shows intensity (Count).

[Figure 2] A X ray powder diffraction spectrum of Form I crystal of a 0.5 hydrate of a compound of formula (I). The horizontal axis shows 2θ ($^\circ$) and vertical axis shows intensity (Count).

[Figure 3] A X ray powder diffraction spectrum of Form II crystal of a 0.5 hydrate of a compound of formula (I). The horizontal axis shows 2θ ($^\circ$) and vertical axis shows intensity (Count).

[Figure 4] A X ray powder diffraction spectrum of Form I crystal of an anhydride of a compound of formula (I). The horizontal axis shows 2θ ($^\circ$) and vertical axis shows

intensity (Count).

[Figure 5] A X ray powder diffraction spectrum of Form II crystal of an anhydride of a compound of formula (I). The horizontal axis shows 2θ ($^{\circ}$) and vertical axis shows intensity (Count).

[Figure 6] Solid state ^{13}C -NMR spectra of Form I crystal (Form I) and Form II crystal (Form II) of an anhydride of a compound of formula (I), and Form I crystal (Hemihydrate Form I) and Form II crystal (Hemihydrate Form II) of the 0.5 hydrate. The horizontal axis shows ppm and vertical axis shows peak intensity.

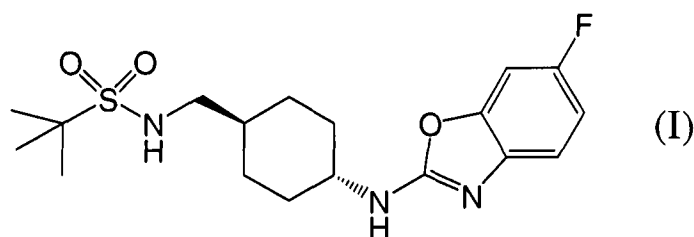
[Figure 7] A differential scanning calorimetry curve of Form I crystal of a 0.5 hydrate of a compound of formula (I). The horizontal axis shows a temperature and vertical axis shows heat capacity.

[Figure 8] A differential scanning calorimetry curve of Form I crystal of an anhydride of a compound of formula (I). The horizontal axis shows a temperature and vertical axis shows heat capacity.

[Figure 9] A differential scanning calorimetry curve of Form II crystal of an anhydride of a compound of formula (I). The horizontal axis shows a temperature and vertical axis shows heat capacity.

[Mode for Carrying Out the Invention]

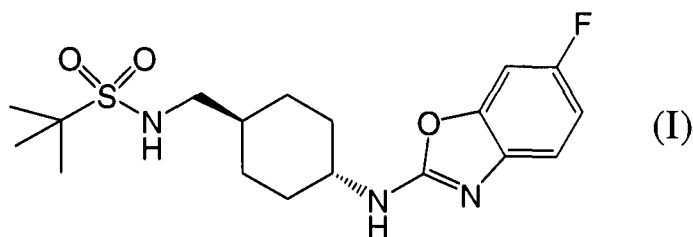
A compound of formula (I):



is a NPY Y5 receptor specific antagonist described in Patent Document 1 and a pharmaceutical composition comprising the compound is very useful for the prevention or treatment of obesity or an obesity-related disorder. An anhydride of a compound of formula (I) can be prepared according to a method described in Patent Document 1.

[0010]

A hydrate of a compound of formula (I):



can be prepared by crystallizing of a compound of formula (I) from an aqueous organic solvent.

For example, a compound of formula (I) can be dissolved in an organic solvent at 40 to 90 °C, and water can be added thereof after the solvent is cooled to room temperature. Alternatively, a compound of formula (I) can be dissolved in an organic solvent at 40 to 90 °C, and the organic solvent dissolving the compound of formula (I) can be added dropwise to water. As just described, a hydrate of a compound of formula (I) can be prepared by crystallizing a compound of formula (I) from an aqueous organic solvent (e.g., aqueous acetone, aqueous alcohol, aqueous tetrahydrofuran, aqueous dimethylformamide or the like).

A hydrate of a compound of formula (I) means the thing wherein arbitrary number of water molecules are hydrated to a compound of formula (I) as crystallization water and it exists as a solid crystal. For example, it is 0.5 hydrate, 1 hydrate, 1.5 hydrate, 2 hydrate or the like. It can be measured by elemental analysis or the like how many water molecules are hydrated.

As a hydrate of a compound of formula (I), a 0.5 hydrate of a compound of formula (I) is preferable.

There are Form I and Form II as a 0.5 hydrate of a compound of formula (I). Form I crystal is a stable form compared with Form II crystal. Both Form I and Form II hydrates can be easily ground.

For example, Form I crystal of a 0.5 hydrate of a compound of formula (I) can be prepared by crystallizing a compound of formula (I) from aqueous acetone according to a method in Example in this description or the like. Then, Form II crystal of a 0.5 hydrate of a compound of formula (I) can be prepared by crystallizing a compound of formula (I) from aqueous isopropyl alcohol.

On the other hand, there are Form I and Form II also for an anhydride of a compound of formula (I). Form I crystal is a stable form compared with Form II crystal. These Form I and Form II anhydrides are difficult to be ground.

Form I crystal, which is one form of a 0.5 hydrate of a compound of formula (I), has characteristic peaks at $13.9^{\circ} \pm 0.2^{\circ}$ and $15.2^{\circ} \pm 0.2^{\circ}$ (2 θ) in a X ray powder

diffraction. Furthermore, strong intensity peaks include $12.7^{\circ} \pm 0.2^{\circ}$, $17.4^{\circ} \pm 0.2^{\circ}$ and $19.5^{\circ} \pm 0.2^{\circ}$ (2 θ). Form I crystal of a 0.5 hydrate does not have peaks at $8.2^{\circ} \pm 0.2^{\circ}$ and $11.2^{\circ} \pm 0.2^{\circ}$ (2 θ), which are characteristic for Form I crystal of an anhydride and peaks at $8.6^{\circ} \pm 0.2^{\circ}$ and $10.8^{\circ} \pm 0.2^{\circ}$ (2 θ), which are characteristic for Form II crystal of an anhydride. Additionally, it does not have peaks at $14.3^{\circ} \pm 0.2^{\circ}$ and $19.9^{\circ} \pm 0.2^{\circ}$ (2 θ), which are characteristic for Form II crystal of a 0.5 hydrate.

Form I crystal of a 0.5 hydrate of a compound of formula (I) has one or more chemical shift(s) of $147.9 \text{ ppm} \pm 0.2 \text{ ppm}$, $138.1 \text{ ppm} \pm 0.2 \text{ ppm}$, $61.9 \text{ ppm} \pm 0.2 \text{ ppm}$ and $48.7 \text{ ppm} \pm 0.2 \text{ ppm}$ in a solid state ^{13}C -NMR spectrum. Preferably, it has 2 and more, or 3 and more shifts of them.

Form I crystal of a 0.5 hydrate of a compound of formula (I) has chemical shifts which are substantially similar to $147.9 \text{ ppm} \pm 0.2 \text{ ppm}$, $138.1 \text{ ppm} \pm 0.2 \text{ ppm}$, $61.9 \text{ ppm} \pm 0.2 \text{ ppm}$ and $48.7 \text{ ppm} \pm 0.2 \text{ ppm}$ in a solid state ^{13}C -NMR spectrum. Since the external standards are employed for the solid state NMR unlike a solution NMR, chemical shifts may wholly shift. Therefore, a crystal having substantially similar chemical shifts even if chemical shifts wholly shifted can be called Form I crystal of a 0.5 hydrate of a compound of formula (I).

Alternatively, Form I crystal of a 0.5 hydrate of a compound of formula (I) is characterized by one or more spectrum (spectra) and/or a curve selected from the following (a) to (c):

- (a) a X ray powder diffraction spectrum substantially corresponding to Figure 2;
 - (b) a solid state ^{13}C -NMR spectrum substantially corresponding to hemihydrate I in Figure 6; and
 - (c) a differential scanning calorimetry curve substantially corresponding to Figure 7.
- [0011]

Form II crystal, which is one form of a 0.5 hydrate of a compound of formula (I), has characteristic peaks at $14.3^{\circ} \pm 0.2^{\circ}$ and $19.9^{\circ} \pm 0.2^{\circ}$ (2 θ) in a X ray powder diffraction. Furthermore, strong intensity peaks include $12.6^{\circ} \pm 0.2^{\circ}$ and $17.3^{\circ} \pm 0.2^{\circ}$ (2 θ). Form II crystal of a 0.5 hydrate does not have peaks at $8.2^{\circ} \pm 0.2^{\circ}$ and $11.2^{\circ} \pm 0.2^{\circ}$ (2 θ), which are characteristic for Form I crystal of an anhydride and peaks at $8.6^{\circ} \pm 0.2^{\circ}$ and $10.8^{\circ} \pm 0.2^{\circ}$ (2 θ), which are characteristic for Form II crystal of an anhydride. Additionally, it does not have peaks at $13.9^{\circ} \pm 0.2^{\circ}$ and $15.2^{\circ} \pm 0.2^{\circ}$ (2 θ), which are characteristic for Form I crystal of a 0.5 hydrate.

Form II crystal of a 0.5 hydrate of a compound of formula (I) has one or more chemical shift(s) of $147.8 \text{ ppm} \pm 0.2 \text{ ppm}$, $147.2 \text{ ppm} \pm 0.2 \text{ ppm}$, $137.9 \text{ ppm} \pm 0.2 \text{ ppm}$,

137.3 ppm $\pm$ 0.2 ppm, 61.6 ppm $\pm$ 0.2 ppm, 50.2 ppm $\pm$ 0.2 ppm and 48.7 ppm $\pm$ 0.2 ppm in a solid state ^{13}C -NMR spectrum. Preferably, it has 2 and more, or 3 and more shifts of them. Especially, it has one or more combination of chemical shifts of 147.8 ppm $\pm$ 0.2 ppm and 147.2 ppm $\pm$ 0.2 ppm, 137.9 ppm $\pm$ 0.2 ppm and 137.3 ppm $\pm$ 0.2 ppm, and 50.2 ppm $\pm$ 0.2 ppm and 48.7 ppm $\pm$ 0.2 ppm. Preferably, it has 2 and more, or 3 and more combinations of them. That is, as shown in Figure 6, it has characteristics that each of many carbons shows 2 kinds of chemical shifts.

Furthermore, Form II crystal of a 0.5 hydrate of a compound of formula (I) has chemical shifts which are substantially similar to 147.8 ppm $\pm$ 0.2 ppm, 147.2 ppm $\pm$ 0.2 ppm, 137.9 ppm $\pm$ 0.2 ppm, 137.3 ppm $\pm$ 0.2 ppm, 61.6 ppm $\pm$ 0.2 ppm, 50.2 ppm $\pm$ 0.2 ppm and 48.7 ppm $\pm$ 0.2 ppm in a solid state ^{13}C -NMR spectrum. Since the external standards are employed for the solid state NMR unlike a solution NMR, chemical shifts may wholly shift. Therefore, a crystal having substantially similar chemical shifts even if chemical shifts wholly shifted can be called Form II crystal of a 0.5 hydrate of a compound of formula (I).

Alternatively, Form II crystal of a 0.5 hydrate of a compound of formula (I) is characterized by one or more spectrum (spectra) selected from the following (a) and (b): (a) a X ray powder diffraction spectrum substantially corresponding to Figure 3; and (b) a solid state ^{13}C -NMR spectrum substantially corresponding to hemihydrate II in Figure 6.

Unless otherwise noted, numerical values described and claimed herein are approximate. Variation within the values may be attributed to equipment calibration, equipment errors, purity of the materials, crystal size, sample size and other factors.

[0012]

"Crystal" used in this description means a material that has an ordered, long range molecular structure. The degree of crystallinity of a crystal form can be determined by many techniques including, for example, X ray powder diffraction, moisture sorption, differential scanning calorimetry, solution calorimetry and dissolution properties.

"Hydrate" of a compound of formula (I) means "crystal" that a compound of formula (I) and water molecule are crystallized together. It includes a crystalline compound in which water is contained within the crystalline structure and a crystalline compound in which water is part of the crystalline structure.

[0013]

X ray powder diffraction (XRPD)

X ray powder diffraction (XRPD) is acknowledged to be one of the most sensitive methods to determine the crystallinity of solids. Crystals yield explicit diffraction maxima that arise at specific angles consistent with the lattice interplanar spacings, as predicted by Bragg's law. On the contrary, amorphous materials do not possess long-range order and they show a featureless broad XRPD pattern..

[0014]

A 0.5 hydrate of a compound of formula (I) can be characterized by a X ray powder diffraction pattern or the characteristic peaks. A 0.5 hydrate of a compound of formula (I) can be distinguished from the other crystal forms (e.g., anhydrous or the like) disclosed herein by the presence of characteristic diffraction peaks. Characteristic diffraction peaks used in this description are peaks selected from the observed diffraction pattern. When distinguishing multiple crystals, a peak which is shown for the crystal and not shown for the other crystal becomes a more preferable characteristic peak than the size of a peak when the crystal is specified. The crystals can be characterized by one or two peak(s) if it is such characteristic peak(s). If the chart obtained by measuring is compared and these characteristic peaks correspond, it can be said that the X ray powder diffraction spectrum substantially corresponds.

[0015]

Since an error in the range of $\pm 0.2^\circ$ may occur in diffraction angles (2θ) in a X ray powder diffraction, in general, the value of the diffraction angle of a X ray powder diffraction should be understood as including values in a range of around $\pm 0.2^\circ$. Therefore, this invention includes not only crystals whose diffraction angles of the peaks in a X ray powder diffraction perfectly match, but also crystals whose diffraction angles of the peaks match within an error of around $\pm 0.2^\circ$.

[0016]

In general, it is known that the relative or absolute intensities of various peaks shown in the Tables and Figures below may vary due to a number of factors such as orientation effects of crystals in the X-ray beam or the purity of the material being analyzed or the degree of crystallinity of the sample. The peak positions may also shift for variations in sample height. Furthermore, measurements using a different wavelength will result in different shifts according to the Bragg equation ($n\lambda=2d \sin \theta$). Such further XRPD patterns obtained by using a different wavelength are within the scope of this invention.

[0017]

Solid state ^{13}C -NMR (Nuclear magnetic resonance)

Solid state ^{13}C -NMR (Newclear magnetic resonance) is useful to identify a crystal form because (i) the number of spectra corresponds to carbon number of the compound, (ii) range of chemical shift is wide compared with ^1H -NMR, (iii) signals are sharp compared with ^1H -NMR, (iv) chemical shift does not change even if an additive is include, or the like. It is expected that the observed chemical shifts slightly change according to a used specific spectrometer or a sample preparation technique of an analyst. The error span in a solid state ^{13}C -NMR spectrum is approximately ± 0.2 ppm.

[0018]

DSC (differential scanning calorimetry)

DSC, one of the main measuring methods for thermal analysis, is a method of measuring the thermal properties of the substance as an aggregate of an atom(s) and a molecule(s).

A differential scanning calorimetry curve can be obtained by measuring temperatures of a pharmaceutical active ingredient or change of heat capacity over time by DSC, and plotting the obtained data to temperatures or times. From a differential scanning calorimetry curve, the information about the onset temperature, melting endothermic maximum and enthalpy of a medical activity ingredient can be obtained.

As to DSC, it is known that the observed temperature can depend on rate of temperature change, the sample preparations techniques or the specific devices. The error span in the onset temperature obtained from a differential scanning calorimetry curve is approximately ± 2 °C. In identity certification of a crystal, overall pattern is important and may change somewhat depending on a measurement condition.

[0019]

A pharmaceutical composition comprising a hydrate of this invention is very useful as a medicine for treatment or prevention of obesity or obesity-related disorders. Furthermore, the pharmaceutical composition is very useful for the weight management for obesity.

[0020]

The "obesity-related disorders" are associated with, caused by, or result from obesity. Examples of obesity-related disorder are overeating, hypertension, impaired glucose tolerance, type II diabetes, metabolic syndrome, abnormal lipid metabolism, dyslipidemia, arteriosclerosis, hyperuricemia, gout, fatty liver, endometrial, breast, prostate or colon cancer, osteoarthritis, lumbago, obstructive sleep apnea syndrome,

coronary artery disease (coronary heart disease), cerebral infarction, menstrual disorder, the Prader-Willi Syndrome, Frohlich's syndrome, pickwickian syndrome and the like. The pharmaceutical compositions of the present invention are also useful for reducing the risk of secondary outcomes of obesity, such as reducing the risk of left ventricular hypertrophy or the like. They are also useful to treat Alzheimer's disease.

[0021]

A hydrate of this invention can be administered to a human patient or can be administered in pharmaceutical compositions in which the hydrate of this invention is mixed with suitable carriers or excipient(s). Techniques for formulation and administration of a medicine can be used by combination of or appropriate selection from pharmaceutical formulations or techniques which are known by people skilled in the art.

[0022]

Suitable routes of administration of a hydrate of this invention and a pharmaceutical composition thereof may include, without limitation, oral, rectal, transmucosal, or intestinal administration or intramuscular, subcutaneous, intramedullary, intrathecal, direct intraventricular, intravenous, intravitreal, intraperitoneal, intranasal, or intraocular injections. The preferred routes of administration are oral.

[0023]

A pharmaceutical composition of this invention may be manufactured by processes well known in the art, for example, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

[0024]

For oral administration, a pharmaceutical composition of this invention can be formulated by combining a hydrate of this invention with pharmaceutically acceptable carriers well known in the art. Such carriers enable a hydrate of this invention to be formulated as tablets, pills, lozenges, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like. Pharmaceutical preparations for oral use can be made using a solid excipient, grinding the resulting mixture, and processing the mixture of granules, after adding other suitable auxiliaries if desired, to obtain tablets or dragee cores.

[0025]

Useful excipients are, in particular, fillers such as sugars, including lactose,

sucrose, mannitol, or sorbitol, cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch and the like, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethylcellulose, and/or sodium carboxymethylcellulose. If desired, disintegrating agents such as agar, alginic acid or the like may be added. A salt such as sodium alginate or the like may also be used.

[0026]

The pharmaceutical compositions also may include suitable solid, gel phase carriers or excipients. Examples of such carriers or excipients include calcium carbonate, calcium phosphate, various sugar, starches, cellulose derivatives, gelatin, polymers such as polyethylene glycols and the like.

[0027]

For any hydrate of this invention or pharmaceutical compositions thereof used in the methods of the invention, the therapeutically effective amount can be estimated initially from cell culture assays. Then, the dosage can be formulated for use in animal models so as to achieve a circulating concentration range that includes the IC₅₀ as determined in cell culture (i.e., the concentration of the hydrate of this invention or pharmaceutical compositions thereof which achieves a half-maximal inhibition of the PK activity). Such information can then be used to more accurately determine useful doses in humans.

[0028]

Therapeutic efficacy of a hydrate of this invention or a pharmaceutical composition thereof can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, for example, an assay for biological tests described in Patent Document 1. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage may vary depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition.

[0029]

It is also an aspect of this invention that a hydrate of this invention or a pharmaceutical composition thereof might be combined with other medical agents for the treatment of the diseases and disorders. For example, a hydrate of this invention or the pharmaceutical composition can be used in combination of the other anti-obesity agent(s).

[0030]

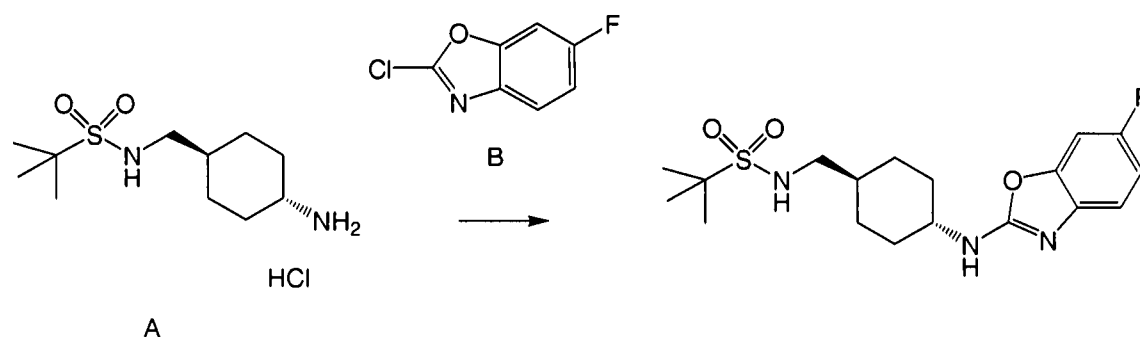
This invention is further explained by the following Examples and Reference Examples, which are not intended to limit the scope of this invention. With respect to numbers (e.g., amounts, temperature etc.), some errors and deviations should be accounted for.

[Example 1]

[0031]

A process for the preparation of Form I crystal of a 0.5 hydrate

Step 1



Compound A (737.4 g, 2.59 mol) are suspended in N, N-dimethylformamide (3.69 L). Triethylamine (2.17 L, 15.54 mol) and potassium iodide (128.9 g, 0.78 mol) were added thereto. To the mixture with stirring under ice cooling, added dropwise Compound B (457.4 g, 2.67 mol) dissolved in N,N-dimethylformamide (1.48 L). After adding dropwise, the mixture was stirred under ice cooling for 1 hour, at room temperature for 1 hour, and at 40 °C for 2 hours. Then, the mixture was cooled to room temperature by water cooling. To the mixture, water (5.16 L) was added dropwise and suspended. After stirring at room temperature for 3 hours, the precipitated crystal was filtered and washed with water (5.16 L) to give a compound of formula (I) as a crude crystal (903.4 g).

Step 2

The obtained crude crystal of a compound of formula (I) (10.0g) was dissolved in acetone (160 ml) at 70 °C and insoluble substance was removed by filtration with filter paper. The filter paper was washed with acetone (20 ml) and the solution was mixed with the previous obtained filtrate. The acetone solution was stirred at room temperature and pure water (60 ml) was added dropwise thereto. After adding dropwise, the mixture was stirred at room temperature for 150 minutes. Then, the mixture was stirred under ice cooling for 120 minutes and the suspension was filtrated. The obtained crystal was washed with cooled 50 % acetone aqueous solution (30 ml)

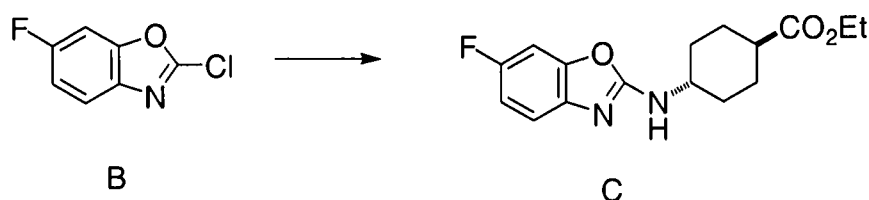
and pure water (30 ml), and dried at 50°C under reduced pressure to give Form I crystal of a 0.5 hydrate of a compound of formula (I) (8.49 g).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 0.93-1.06 (m, 2H), 1.21-1.49 (m, 3H), 1.27 (s, 9H), 1.77-1.87 (m, 2H), 1.98-2.10 (m, 2H), 2.89 (t, 2H, $J = 6.3$ Hz), 3.38-3.54 (m, 1H), 6.87 (t, 1H, $J = 5.7$ Hz), 6.90-6.98 (m, 1H), 7.20 (dd, 1H, $J = 8.7, 5.1$ Hz), 7.33 (dd, 1H, $J = 8.4, 2.4$ Hz), 7.88 (d, 1H, $J = 7.8$ Hz). Anal. Calcd for $\text{C}_{18}\text{H}_{26}\text{FN}_3\text{O}_3\text{S} \cdot 0.5\text{H}_2\text{O}$: C, 55.08; H, 6.93; F, 4.84; N, 10.71; S, 8.17. Found: C, 55.22; H, 7.05; F, 4.68; N, 10.79; S, 7.78.

[Reference Example 1]

[0032]

Step 1

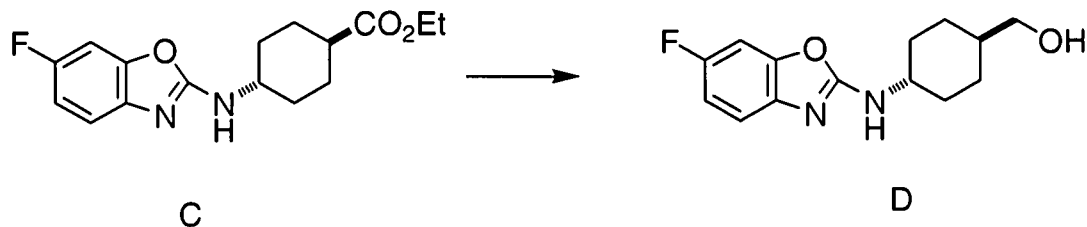


To N, N-dimethylformamide (10mL), were added trans-4-amino-cyclohexane carboxylic acid ethylester (2.08 g, 10 mmol) and triethylamine (5.0 mL, 36 mmol). During stirring under cooling to 5 °C or less, Compound B (2.23 g, 13 mmol) (Reference: EP572893) in N,N-dimethylformamide (4 mL) solution was added dropwise in the suspension. The mixture was stirred at room temperature for 2 hours. To the reaction solution, were added ethyl acetate (25 mL) and 5 %-aqueous solution of citric acid brine (25 mL). The organic layer was separated and water layer was extracted with ethyl acetate (25 mL) again. The organic layer was mixed, and washed with 5 %-brine, dried over anhydrous magnesium sulfate. The solvent was removed and the obtained residue was purified by silica gel column chromatography (n-hexane—ethyl acetate 100:0→50:50(v/v)) to give Compound C (3.04 g, yield 98 %) as colorless solid.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.26 (t, $J = 7.10$ Hz, 3H), 1.27-1.38 (m, 2H), 1.58-1.68 (m, 2H), 2.04-2.13 (m, 2H), 2.23-2.34 (m, 2H), 3.63-3.79 (m, 1H), 4.14 (q, $J = 7.10$ Hz, 2H), 5.31 (s, 1H), 6.86-6.93 (m, 1H), 7.00 (dd, $J = 8.24, 2.53$ Hz, 1H), 7.23 (dd, $J = 8.24, 4.82$ Hz, 1H). MS: $[\text{M} + \text{H}]^+$ m/z 307.1

[0033]

Step 2



Compound C (1.23 g, 4.0 mmol) was dissolved in tetrahydrofuran-methanol (6.0 mL-5.0 mL). During stirring at 70 °C, LiBH_4 (2.0 M-tetrahydrofuran solution, 4.0 mL, 8.0 mmol) was added dropwise to the solution for 2 hours and stirred at 70 °C for 1 hour. Furthermore, methanol (1.2 mL) and tetrahydrofuran (1.2 mL) was added thereto. LiBH_4 (2.0 M-tetrahydrofuran solution, 4.0 mL, 8.0 mmol) was added dropwise to the mixture for 2 hours and stirred at 70 °C for 1 hour. The reaction solution was cooled to 5°C. 2N-hydrochloric acid (32 mL), 2N-sodium hydroxide solution (24 mL), and 5 %-sodium hydrogen carbonate aqueous solution (12 mL) were added sequentially and extracted with ethyl acetate (15 mL). The water layer was extracted with ethyl acetate (15 mL). The organic layer was mixed and washed with saturated saline (7.5mL) and dried over anhydrous sodium sulphate. After removing the solvent, the obtained residue was washed n-hexane and isopropyl ether to give Compound D (0.95 g, yield 91 %) as light brown solid.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 0.91-1.06 (m, 2H), 1.19-1.40 (m, 3H), 1.79 (d, $J = 11.66$ Hz, 2H), 2.00-2.08 (m, 2H), 3.20-3.26 (m, 2H), 3.43-3.52 (m, 1H), 4.41-4.49 (m, 1H), 6.92-6.97 (m, 1H), 7.19 (dd, $J = 8.49, 4.82$ Hz, 1H), 7.32 (dd, $J = 8.49, 2.53$ Hz, 1H), 7.87 (d, $J = 8.11$ Hz, 1H).

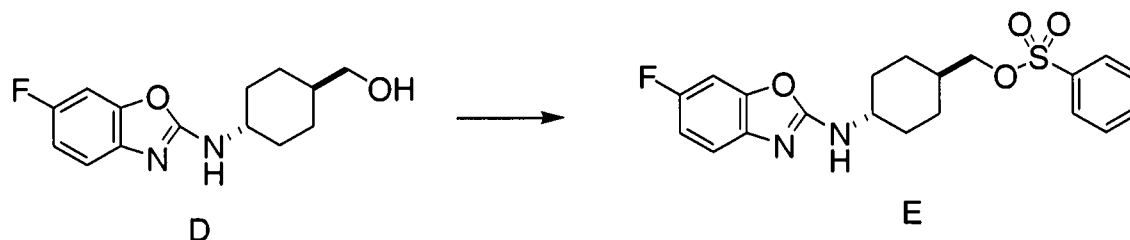
MS: $[\text{M} + \text{H}]^+$ m/z 265.0

[Example 2]

[0034]

A process for the preparation of Form II crystal of a 0.5 hydrate

Step 1

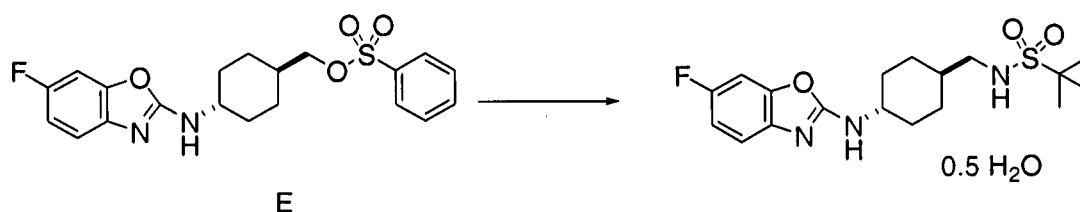


To Compound D (5 g, 18.9 mmol) and dimethylamino pyridine (6.93 g, 56.8 mmol),

was added N-methylpyrrolidone (40 ml). Benzenesulfonyl chloride (3.62 ml, 28.4 mmol) was added dropwise at room temperature and stirred at room temperature for 270 minutes. After keeping static at 4 °C for 14 hours, ethyl acetate (40 ml) and 10% aqueous solution of citric acid (40 ml) were added and stirred vigorously, and the organic layer was separated. The organic layer was washed with 5% sodium bicarbonate aqueous solution (40 ml) and pure water (40 ml). The organic layer was separated and the solution was concentrated under reduced pressure until about 10 ml of ethyl acetate remained. Under room temperature, n-heptane (20 ml) and seed crystals were added, and the obtained crystal was filtrated to give a crude crystal. To the crude crystal, was added ethyl acetate (12 ml) and dissolved at 40 °C. To the mixture was added n-heptane (14 ml). The obtained crystal was filtered and dried at 50 °C under reduced pressure to give Compound E (5.23 g, yield 68.4 %).

[0035]

Step 2



To Compound E (250 mg, 0.73 mmol), potassium carbonate (513 mg, 3.71 mmol) and t-butylsulfonamide (170 mg, 1.23 mmol), was added isopropyl alcohol (1 ml). The mixture was heated at 80 °C and stirred for 8 hours. After keeping static at room temperature about 12 hours, isopropyl alcohol (1.75 ml) and pure water (1.25 ml) were added thereto and heated at 80 °C again. After confirming that the solution became homogeneous, it was cooled to 15 °C. The precipitated crystal was filtrated and dried under reduced pressure at 50 °C to give Form II crystal of a 0.5 hydrate of a compound of formula (I) (173 mg, yield 73 %).

[Reference Example 2]

[0036]

Experiment 1 Affinity for mouse NPY Y5 receptor

cDNA sequence encoding a mouse NPY Y5 receptor (Biochim. Biophys. Acta 1328:83-89, 1997) was cloned in a vector (pME18S, Takebe et al. Mol. Cell. Biol. 8, 8957). The obtained expression vector was transfected into CHO cells as a host by using Lipofect AMINE reagent (Trademark, Gico BRL Co., Ltd.) according to the

instruction manual. The cells that stably express NPY Y5 receptor were obtained.

The membranes prepared from the CHO cells expressing mouse NPY Y5 receptor, 0.5 hydrate of a compound of formula (I) and 30,000 cpm [¹²⁵I] peptide YY (60 pM of final concentration: GE healthcare) were incubated in the assay buffer (20 mM HEPES-Hanks buffer containing 0.1% bovine serum albumin, pH 7.4) at 25 °C for 2 hours, and then the membrane was filtered from the mixture through a glass filter (GF/C) presoaked with 1 % polyethyleneimine. After washing with 50 mM Tris-HCl buffer (pH 7.4), radioactivity retained on the filters was quantified with a gamma counter. Nonspecific binding was defined as the amount of radioactivity bound to the membranes after incubation in the presence of 200 nM of peptide YY. The 50 % inhibitory concentration of the test compound against the specific peptide YY binding (IC₅₀ value) was calculated (Inui, A. et al. Endocrinology 131, 2090 - 2096 (1992)).

As a result, IC₅₀ value of a 0.5 hydrate of a compound of formula (I) was 0.47 nM. That is, a 0.5 hydrate of a compound of formula (I) showed affinity to mouse NPY Y5 receptor.

[Example 3]

[0037]

Measurement of X ray powder diffraction patterns

X ray powder diffractions of an anhydride of a compound of formula (I) and hydrates obtained from Examples were measured according to a measurement method of a X ray powder diffraction described as general test procedures in Japanese Pharmacopoeia. Measurement conditions are shown below.

(Device)

D-8 DISCOVER manufactured by Bruker Corporation.

(Operations procedures)

Samples were measured under the following conditions.

Measurement method: Reflection method

Type of a light source: Cu tube

Used wavelengths: CuK α radiation

Tube currents: 40 mA

Tube voltage: 40 Kv

Sample plates: Aluminum

X-ray incident angle: 3° and 12°

[0038]

The result shown in Table 1 to 4 and Figure 1 to 5. In Figure 1, Form I means

Form I crystal of an anhydride of a compound of formula (I). Form II means Form II crystal of an anhydride of a compound of formula (I). Hemihydrate Form I means Form I crystal of a 0.5 hydrate of a compound of formula (I). Hemihydrate Form II means Form II crystal of a 0.5 hydrate of a compound of formula (I). In addition, the aluminum plates are employed as sample folders. In Figure 1 to 5, the peak at which the 2-Theta value appears near 38° is a peak of aluminum.

The following Tables 1 to 4 was considered and the characteristic peaks which can distinguish each crystal were examined.

Table 1 X ray powder diffraction peaks of Form I crystal of a 0.5 hydrate of a compound of formula (I)

[Table 1]

Diffraction angles	Intensity	Diffraction angles	Intensity	Diffraction angles	Intensity
2 θ (°)	Count	2 θ (°)	Count	2 θ (°)	Count
9.877	7.13	20.213	8.24	28.065	4.45
12.098	5.41	20.552	6.26	29.377	3.37
12.674	17.3	21.916	2.94	31.474	4.46
13.934	6.01	22.31	4.89	32.267	6.56
15.222	4.68	23.605	5.65	34.05	3.78
16.381	9.32	24.459	9.75	34.954	2.63
17.427	31.6	24.824	5.25	35.351	3.35
18.237	8.09	25.503	6.62	36.983	5.49
19.535	41.7	27.071	7.12	39.199	4.14

In the above X ray powder diffraction peaks, peaks of diffraction angles (2 θ): 13.934 and 15.222 are especially characteristic as Form I crystal of a 0.5 hydrate of a compound of formula (I). Furthermore, the strong intensity peaks include 12.674, 17.427 and 19.535.

Table 2 X ray powder diffraction peaks of Form II crystal of a 0.5 hydrate of a compound of formula (I)

[Table 2]

Diffraction angles	Intensity	Diffraction angles	Intensity	Diffraction angles	Intensity
$2\theta(^{\circ})$	Count	$2\theta(^{\circ})$	Count	$2\theta(^{\circ})$	Count
9.86	4.46	19.931	14.5	29.258	4.34
12.639	14.4	20.818	4.25	31.425	3.72
14.318	4.67	22.282	4.98	32.837	4.57
16.383	9.1	22.725	4	35.301	3.57
16.924	5.19	24.402	6.18	36.803	3.88
17.334	17.3	25.518	6.57	37.306	3.43
18.512	7.17	26.916	3.98		
19.258	9.34	27.379	3.91		

In the above X ray powder diffraction peaks, peaks of diffraction angles (2θ): 14.318 and 19.931 are especially characteristic as Form II crystal of a 0.5 hydrate of a compound of formula (I). Furthermore, the strong intensity peaks include 12.639 and 17.334.

(Reference Example)

Table 3 X ray powder diffraction peaks of Form I crystal of an anhydride of a compound of formula (I)

[Table 3]

Diffraction angles	Intensity
2 θ (°)	Count
8.198	20.6
11.223	13.7
16.499	62.1
17.377	24.3
18.737	6.5
19.303	8.74
19.906	10.6
20.829	4.32
21.552	3.2

Diffraction angles	Intensity
2 θ (°)	Count
22.014	6.54
23.09	3.16
23.71	12.8
24.681	3.37
25.441	17.8
27.634	5
28.128	6.94
29.59	7.72
30.043	4.32

Diffraction angles	Intensity
2 θ (°)	Count
30.872	3.92
32.221	3.37
32.905	3.86
33.818	4.99
35.011	4.32
37.576	3.84
39.419	3.45

In the above X ray powder diffraction peaks, peaks of diffraction angles (2 θ): 8.198 and 11.223 are especially characteristic as Form I crystal of an anhydride of a compound of formula (I).

Table 4 X ray powder diffraction peaks of Form II crystal of an anhydride of a compound of formula (I)

[Table 4]

Diffraction angles	Intensity	Diffraction angles	Intensity	Diffraction angles	Intensity
2 θ (°)	Count	2 θ (°)	Count	2 θ (°)	Count
8.583	9.37	19.62	10.6	27.682	10.6
9.812	5.53	20.587	8.8	28.752	9.66
10.791	37.6	21.193	14	29.636	5.06
16.191	6.44	22.612	4.87	30.549	5.39
17.245	50.8	23.488	11.6	32.016	4.65
17.725	6.72	24.618	4.19	33.201	3.19
18.473	6.97	26.304	7.88	36.831	4.18
18.952	9.14	26.715	8.78	39.309	3.61

In the above X ray powder diffraction peaks, peaks of diffraction angles (2 θ): 8.583 and 10.791 are especially characteristic as Form II crystal of an anhydride of a compound of formula (I).

[Example 4]

[0039]

Measurement of solid state ^{13}C -NMR spectrum

Solid state ^{13}C -NMR spectrum of an anhydride of a compound of formula (I) and hydrates obtained from each Example were measured by Varian 600MHz NMR Systems (^1H frequency: 599.8MHz) spectrometer with 3.2 mm ϕ probes according to CP/MS method (the cross polarization magic-angle spinning method). Measurement conditions are shown below.

Spectral width: 43103.4 Hz

Acquisition Time: 0.04 s

Recycle Delay: 10 s

Contact Time: 3 ms to 5 ms

External standard: Adamantane (Methine carbon: 38.52 ppm)

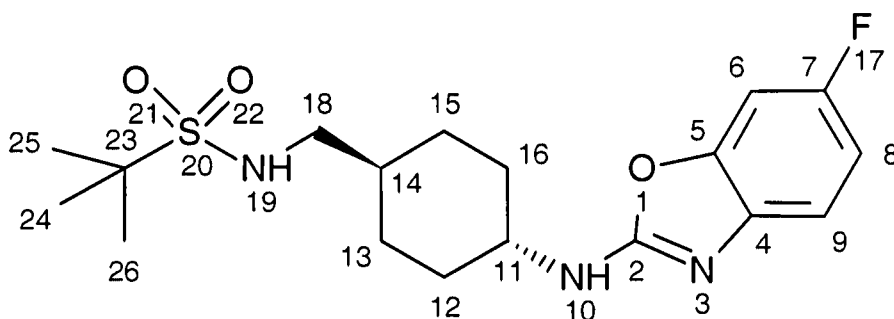
Measured temperature: 10 °C

Speed: 20000 rps

Probe: 3.2 mm T3 HX Probe

[0040]

The results are shown in Table 5 and Figure 6. In Table 5 and Figure 6, Form I means Form I crystal of an anhydride of a compound of formula (I). Form II means Form II crystal of an anhydride of a compound of formula (I). Hemihydrate Form I means Form I crystal of a 0.5 hydrate of a compound of formula (I). Hemihydrate Form II means Form II crystal of a 0.5 hydrate of a compound of formula (I).



[Table 5]

	Form I	Form II	Hemihydrate I	Hemihydrate II
Attribution	δ	δ	δ	δ
C-2	162.2	163.1	162.6	162.4
				161.3
C-4	139.0	140.0	138.1	137.9
				137.3
C-5	149.5	148.6	147.9	147.8
				147.2
C-6	99.4	98.8	97.3	97.3
C-7	158.8	158.0	158.7	158.4
	($^1J_{CF}=254\text{Hz}$)	($^1J_{CF}=254\text{Hz}$)	($^1J_{CF}=254\text{Hz}$)	($^1J_{CF}=254\text{Hz}$)
C-8	110.4	110.3	112.3	112.0
C-9	115.7	115.3	116.5	116.2
				115.4
C-11	53.2	54.1	54.1	53.3
C-12,16	34.8	35.2	33.9	34.4
C-12,16	34.1	34.9	33.3	33.9
				33.3
				32.9
C-13,15	30.9	29.9	28.5	30.4
C-13,15	30.4	29.5		28.5
C-14	40.5	41.4	41.1	40.9
				40.6
C-18	51.3	50.2	48.7	50.2
				48.7
C-23	59.7	60.3	61.9	61.6
C-24,25,26	25.5	25.1	25.1	25.1
				24.7

Note) These data are effective to measurement on the measurement conditions of Example 4.

In the above solid state ^{13}C -NMR spectra, the especially characteristic peaks as Form I crystal of a 0.5 hydrate of a compound of formula (I) are 147.9

ppm, 138.1 ppm, 61.9 ppm and 48.7 ppm. The especially characteristic peaks as Form II crystal of a 0.5 hydrate of a compound of formula (I) are 147.8 ppm, 147.2 ppm, 137.9 ppm, 137.3 ppm, 61.6 ppm, 50.2 ppm and 48.7 ppm. Unlike other crystals, Form II crystal of a 0.5 hydrate of a compound of formula (I) have a feature that many carbons are observed as two kinds of signals.

As a reference, the especially characteristic peaks as Form I crystal of an anhydride of a compound of formula (I) are 149.5 ppm, 139.0 ppm, 59.7 ppm and 51.3 ppm. The especially characteristic peaks as Form II crystal of an anhydride of a compound of formula (I) are 148.6 ppm, 140.0 ppm, 60.3 ppm and 50.2 ppm.

[Example 5]

[0041]

Measurement of DSC data

DSC for an anhydride of a compound of formula (I) and hydrates obtained from each Example were measured. The measurement carried out under the following conditions after 3 mg of samples were weighted on aluminum pan and sample sealed.

(Measurement condition)

Device: TA Instrument DSC Q1000

Measured temperature range: 0 °C-melting point +20 °C

Rates of temperature increase: 10 °C/min

Atmosphere: N₂ 50mL/min

[0042]

The result are shown in Figure 7 to 9. Figure 7 shows a differential scanning calorimetry curve of Form I crystal of a 0.5 hydrate of a compound of formula (I). The horizontal axis represents temperature and vertical axis represents heat capacity. Water molecules are eliminated and observed absorption of heat around 134.68°C. Melting is started around 200.57 °C and the melting endothermic maximum is around 201.78 °C.

Figure 8 shows a differential scanning calorimetry curve of Form I crystal of an anhydride of a compound of formula (I). The horizontal axis represents temperature and vertical axis represents heat capacity. Melting is started around 200.82 °C and the melting endothermic maximum is around 201.47 °C.

Figure 9 shows a differential scanning calorimetry curve of Form II crystal of an anhydride a compound of formula (I). The horizontal axis represents temperature and vertical axis represents heat capacity. Melting is started

around 200.56 °C and the melting endothermic maximum is around 202.65 °C.

Thus, it is the feature of the differential scanning calorimetry curve of a 0.5 hydrate of a compound of formula (I) that absorption of heat accompanying elimination of water molecules is observed around 134.68 °C. In addition, such absorption of heat is not observed for anhydride of a compound of formula (I).

[Example 6]

[0043]

As to the grind

An anhydride of a compound of formula (I) and hydrates obtained from each Example were ground under the following conditions and measured the yields.

(Device)

A-O JET MILL manufactured by Seishin Enterprise Co., Ltd.

(Grinding conditions)

Supplied pressure 0.35 Pa

Grinding pressure 0.25 Pa

Fider (Device to send samples) 20 g/h

[0044]

As a result, although the sample was supplied, an anhydride of a compound of formula (I) hardly appeared in the collected bag. Because internal adhering was observed, the grinding was stopped. Therefore, the yield was 0 %. On the other hand, a 0.5 hydrate of a compound of formula (I) was ground without internal adhering and the yield after the grinding was 94.5 %.

[Reference Example 3]

[0045]

Regarding an anhydride of a compound of formula (I) obtained by a similar method of Step 1 of Example 1, data of the particle size distribution were obtained by a laser diffraction particle size distribution analyzer, HELOS Particle Size Analysis manufactured by Sympatec (hereinafter referred to as a particle size distribution analyzer). As a result, X50 is 20.5 μm and X90 is 69.5 μm . X50 means 50% undersize cumulative diameter and X90 means 90% undersize cumulative diameter. When total volume of powder is 100% and a cumulative curve was drawn, particle diameters of points for 50% and 90% in the cumulative curve are 50% undersize cumulative diameter and 90% undersize cumulative diameter (μm), respectively. X50 and X90 described below have same meanings.

[0046]

The anyhydride of a compound of formula (I) could not be ground by A-O JET MILL manufactured by Seishin Enterprise Co., Ltd., Spiral 50 AS manufactured by Hosokawa Micron Corporation or the like.

[Example 7]

[0047]

Regarding a 0.5 hydride of a compound of formula (I) obtained by a similar method of Example 1, data of the particle size distribution were obtained by a particle size distribution analyzer. As a result, X50 is 102 μm and X90 is 262 μm .

The 0.5 hydride of a compound of formula (I) was ground under the following conditions and data of the particle size distribution were obtained by a particle size distribution analyzer. As a result, X50 is 3.57 μm and X90 is 26.0 μm .

(Device)

A-O JET MILL manufactured by Seishin Enterprise Co., Ltd.

(Grinding conditions)

Supplied pressure 0.35 Pa

Grinding pressure 0.25 Pa

Fider (Device to send samples) 20 g/h

[0048]

As a result, 0.5 hydrate of a compound of formula (I) was ground without internal adhering and the yield after the grinding was 92.0 %.

[Example 8]

[0049]

Regarding a 0.5 hydride of a compound of formula (I) obtained by a similar method of Example 1, data of the particle size distribution were obtained by a particle size distribution analyzer. As a result, X50 is 83.8 μm and X90 is 267 μm .

The 0.5 hydride of a compound of formula (I) was ground under the following conditions and data of the particle size distribution were obtained by a particle size distribution analyzer. As a result, X50 is 1.78 μm and X90 is 3.95 μm .

(Device)

Hosokawa/Alpine Spiral 50 AS manufactured by Hosokawa Micron Corporation

(Grinding conditions)

Supplied pressure 0.30 Pa

Grinding pressure 0.20 Pa

Fider (Device to send samples) 10rpm

[0050]

As a result, 0.5 hydrate of a compound of formula (I) was ground without internal adhering and the yield after the grinding was 96.5 %.

[0051]

Formulation Example

The following Formulation Examples are only exemplified and not intended to limit the scope of this invention.

Formulation Example 1: Tablets

Hydrates of a compound of formula (I)	15mg
Starch	15 mg
Lactose	15 mg
Crystalline cellulose	19 mg
Polyvinyl alcohol	3 mg
Distilled water	30 ml
Calcium stearate	3 mg

All of the above ingredients except for calcium stearate are uniformly mixed. Then the mixture is crushed, granulated and dried to obtain a suitable size of granules. Next, calcium stearate is added to the granules. Finally, tableting is performed under a compression force.

[0052]

Formulation Example 2: Capsules

Hydrates of a compound of formula (I)	10mg
Magnesium stearate	10 mg
Lactose	80 mg

The above ingredients are mixed uniformly to obtain powders or fine granules, and then the obtained mixture is filled into capsules.

[0053]

Formulation Example 3: Granules

Hydrates of a compound of formula (I)	30g
Lactose	265 g
Magnesium stearate	5 g

After the above ingredients are mixed uniformly, the mixture is compressed, crushed, granulated and sieved to obtain a suitable size of granules.

[Industrial Applicability]

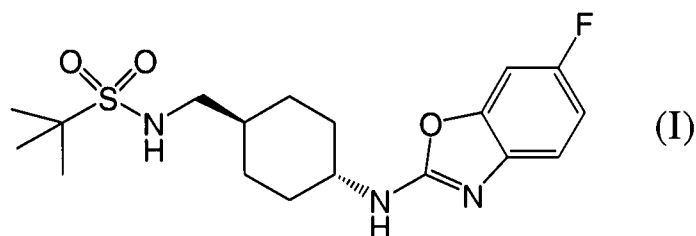
[0054]

A hydrate of a compound of formula (I) which is this invention is important as an active pharmaceutical ingredient. Furthermore, pharmaceutical compositions comprising the hydrate of a compound of formula (I) are very useful as a medicine for prevention or treatment of obesity or obesity-related disorders. Furthermore, the pharmaceutical compositions are very useful for the weight management for obesity.

[Document's name] Claims

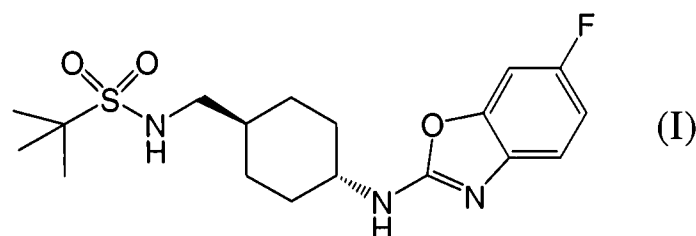
[Claim 1]

A hydrate of a compound of formula (I):



[Claim 2]

A 0.5 hydrate of a compound of formula (I):



[Claim 3]

The hydrate of Claim 2 having peaks at diffraction angles (2θ): $13.9^\circ \pm 0.2^\circ$ and $15.2^\circ \pm 0.2^\circ$ in a X ray powder diffraction spectrum.

[Claim 4]

The hydrate of Claim 2 having peaks at diffraction angles (2θ): $12.7^\circ \pm 0.2^\circ$, $13.9^\circ \pm 0.2^\circ$, $15.2^\circ \pm 0.2^\circ$, $17.4^\circ \pm 0.2^\circ$ and $19.5^\circ \pm 0.2^\circ$ in a X ray powder diffraction spectrum.

[Claim 5]

The hydrate of claim 3 or 4 not having peaks at diffraction angles (2θ): $8.2^\circ \pm 0.2^\circ$, $8.6^\circ \pm 0.2^\circ$, $10.8^\circ \pm 0.2^\circ$, $11.2^\circ \pm 0.2^\circ$, $14.3^\circ \pm 0.2^\circ$ and $19.9^\circ \pm 0.2^\circ$ in a X ray powder diffraction spectrum.

[Claim 6]

The hydrate of claim 2 having one or more chemical shift(s) of $147.9 \text{ ppm} \pm 0.2 \text{ ppm}$, $138.1 \text{ ppm} \pm 0.2 \text{ ppm}$, $61.9 \text{ ppm} \pm 0.2 \text{ ppm}$ and $48.7 \text{ ppm} \pm 0.2 \text{ ppm}$ in a solid state ^{13}C -NMR spectrum.

[Claim 7]

The hydrate of claim 2 having chemical shifts which are substantially similar to $147.9 \text{ ppm} \pm 0.2 \text{ ppm}$, $138.1 \text{ ppm} \pm 0.2 \text{ ppm}$, $61.9 \text{ ppm} \pm 0.2 \text{ ppm}$ and $48.7 \text{ ppm} \pm 0.2 \text{ ppm}$ in a solid state ^{13}C -NMR spectrum.

[Claim 8]

The hydrate of claim 2 characterized by one or more spectrum (spectra) and/or a curve selected from the following (a) to (c):

- (a) a X ray powder diffraction spectrum substantially corresponding to Figure 2;
- (b) a solid state ^{13}C -NMR spectrum substantially corresponding to hemihydrate I in Figure 6; and
- (c) a differential scanning calorimetry curve substantially corresponding to Figure 7.

[Claim 9]

The hydrate of claim 2 having peaks at diffraction angles (2θ): $14.3^\circ \pm 0.2^\circ$ and $19.9^\circ \pm 0.2^\circ$ in a X ray powder diffraction spectrum.

[Claim 10]

The hydrate of claim 8 having peaks at diffraction angles (2θ): $12.6^\circ \pm 0.2^\circ$, $14.3^\circ \pm 0.2^\circ$, $17.3^\circ \pm 0.2^\circ$ and $19.9^\circ \pm 0.2^\circ$ in a X ray powder diffraction spectrum.

[Claim 11]

The hydrate of claim 9 or 10 not having peaks at diffraction angles (2θ): $8.2^\circ \pm 0.2^\circ$, $8.6^\circ \pm 0.2^\circ$, $10.8^\circ \pm 0.2^\circ$, $11.2^\circ \pm 0.2^\circ$, $13.9^\circ \pm 0.2^\circ$ and $15.2^\circ \pm 0.2^\circ$ in a X ray powder diffraction spectrum.

[Claim 12]

The hydrate of claim 2 having one or more combination(s) of chemical shifts of $147.8 \text{ ppm} \pm 0.2 \text{ ppm}$ and $147.2 \text{ ppm} \pm 0.2 \text{ ppm}$, $137.9 \text{ ppm} \pm 0.2 \text{ ppm}$ and $137.3 \text{ ppm} \pm 0.2 \text{ ppm}$, and $50.2 \text{ ppm} \pm 0.2 \text{ ppm}$ and $48.7 \text{ ppm} \pm 0.2 \text{ ppm}$ in a solid state ^{13}C -NMR spectrum.

[Claim 13]

The hydrate of claim 2 having one or more chemical shift(s) of $147.8 \text{ ppm} \pm 0.2 \text{ ppm}$, $147.2 \text{ ppm} \pm 0.2 \text{ ppm}$, $137.9 \text{ ppm} \pm 0.2 \text{ ppm}$, $137.3 \text{ ppm} \pm 0.2 \text{ ppm}$, $61.6 \text{ ppm} \pm 0.2 \text{ ppm}$, $50.2 \text{ ppm} \pm 0.2 \text{ ppm}$ and $48.7 \text{ ppm} \pm 0.2 \text{ ppm}$ in a solid state ^{13}C -NMR spectrum.

[Claim 14]

A hydrate of claim 2 having chemical shifts substantially similar to $147.8 \text{ ppm} \pm 0.2 \text{ ppm}$, $147.2 \text{ ppm} \pm 0.2 \text{ ppm}$, $137.9 \text{ ppm} \pm 0.2 \text{ ppm}$, $137.3 \text{ ppm} \pm 0.2 \text{ ppm}$, $61.6 \text{ ppm} \pm 0.2 \text{ ppm}$, $50.2 \text{ ppm} \pm 0.2 \text{ ppm}$ and $48.7 \text{ ppm} \pm 0.2 \text{ ppm}$ in a solid state ^{13}C -NMR spectrum.

[Claim 15]

The hydrate of claim 2 characterized by one or more spectrum (spectra) selected

from the following (a) and (b):

(a) a X ray powder diffraction spectrum substantially corresponding to Figure 3;
and

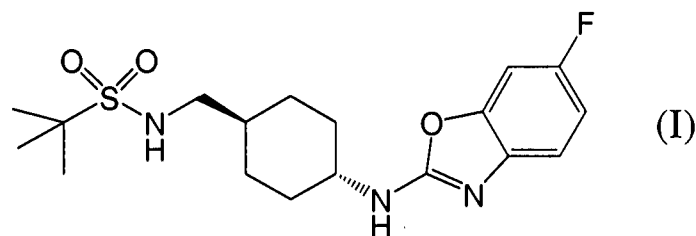
(b) a solid state ^{13}C -NMR spectrum substantially corresponding to hemihydrate II in Figure 6.

[Claim 16]

A pharmaceutical composition comprising the hydrate of any one of claims 1 to 15.

[Claim 17]

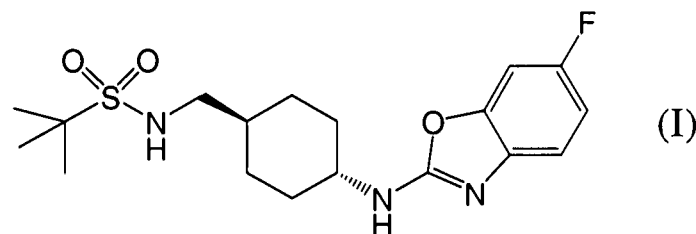
A process for the preparation of the hydrate of the compound of formula (I):



of any one of claims 1 to 16, characterized by crystallizing the compound of formula (I) from an aqueous organic solvent.

[Claim 18]

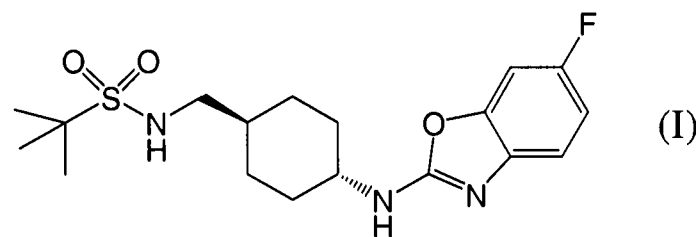
A compound of formula (I):



or hydrate thereof wherein X50 is 1.5 to 5.0 μm .

[Claim 19]

A compound of formula (I):



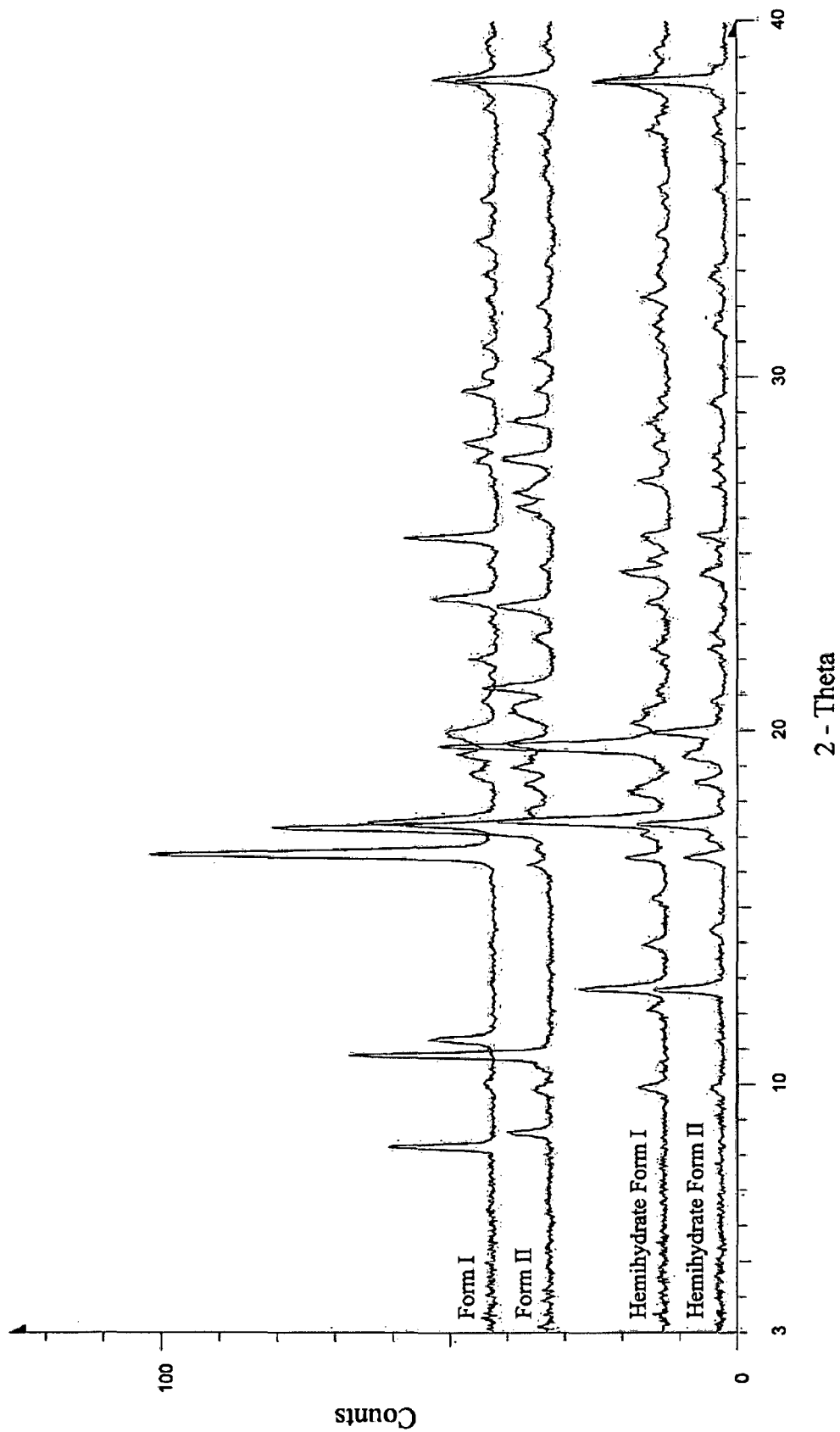
or hydrate thereof wherein X90 is 1.5 to 30.0 μm .

[Claim 20]

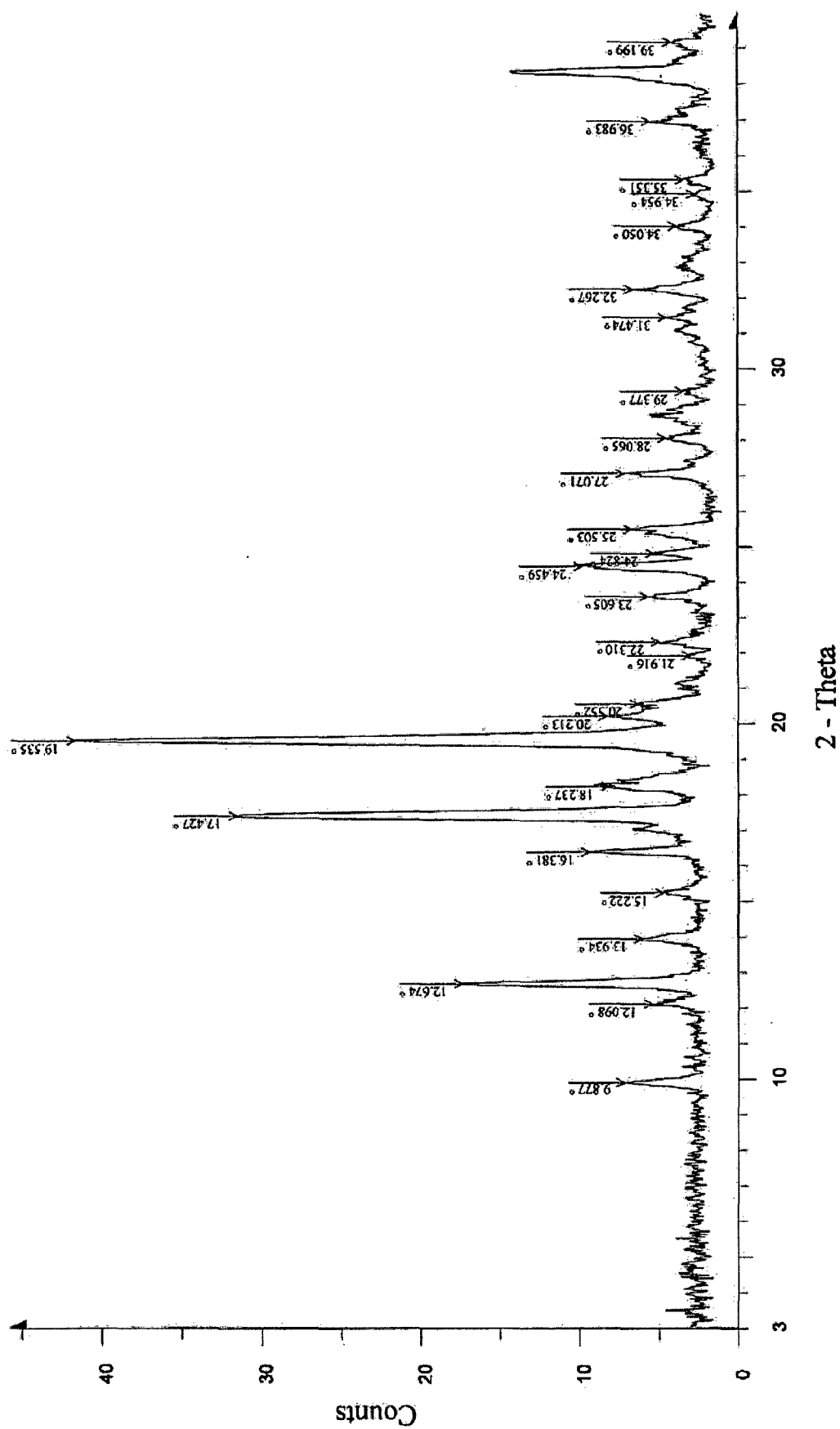
A pharmaceutical composition comprising the compound or hydrate thereof of Claim 18 or 19.

[Document's name] Figures

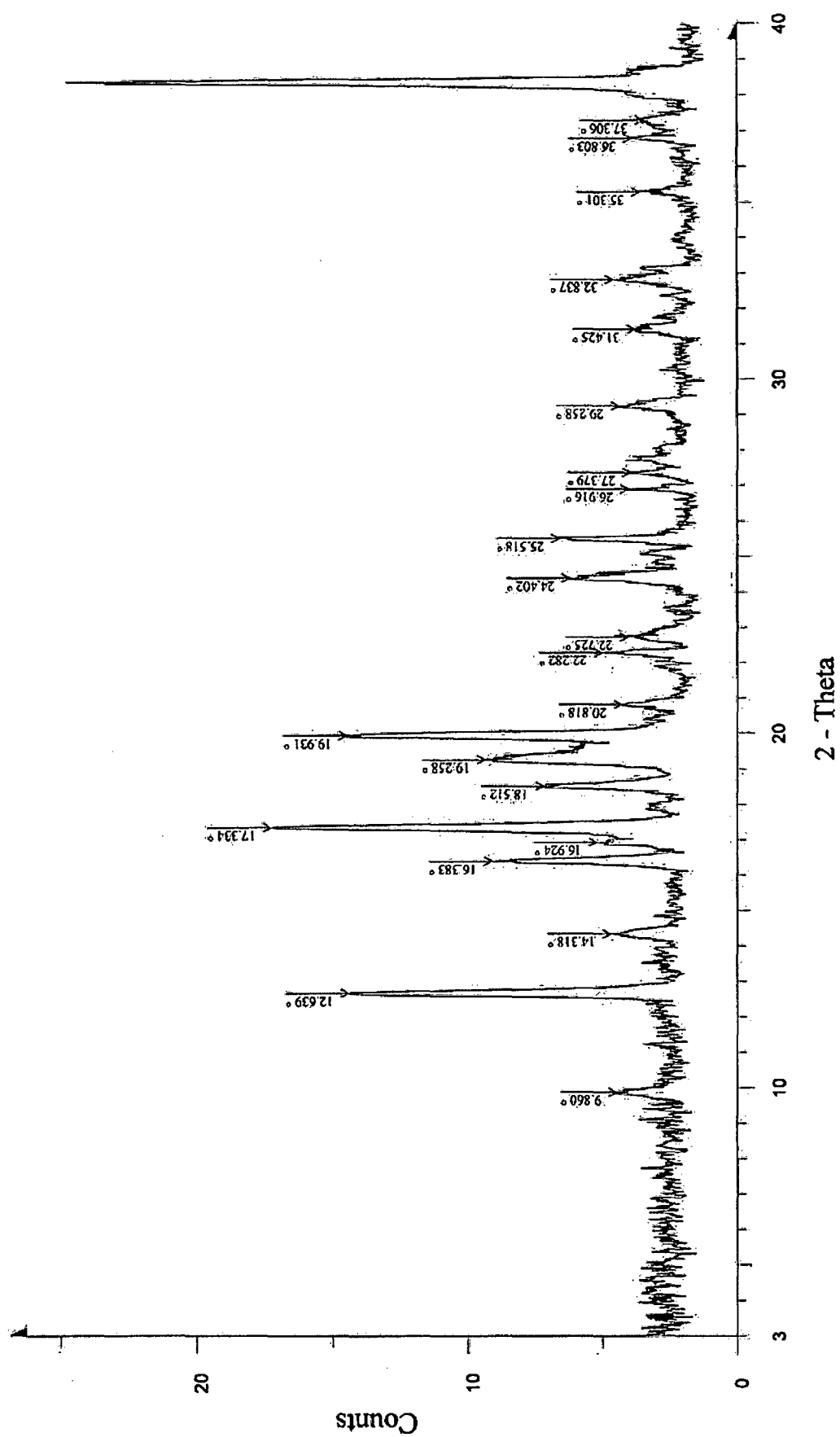
[Figure 1]



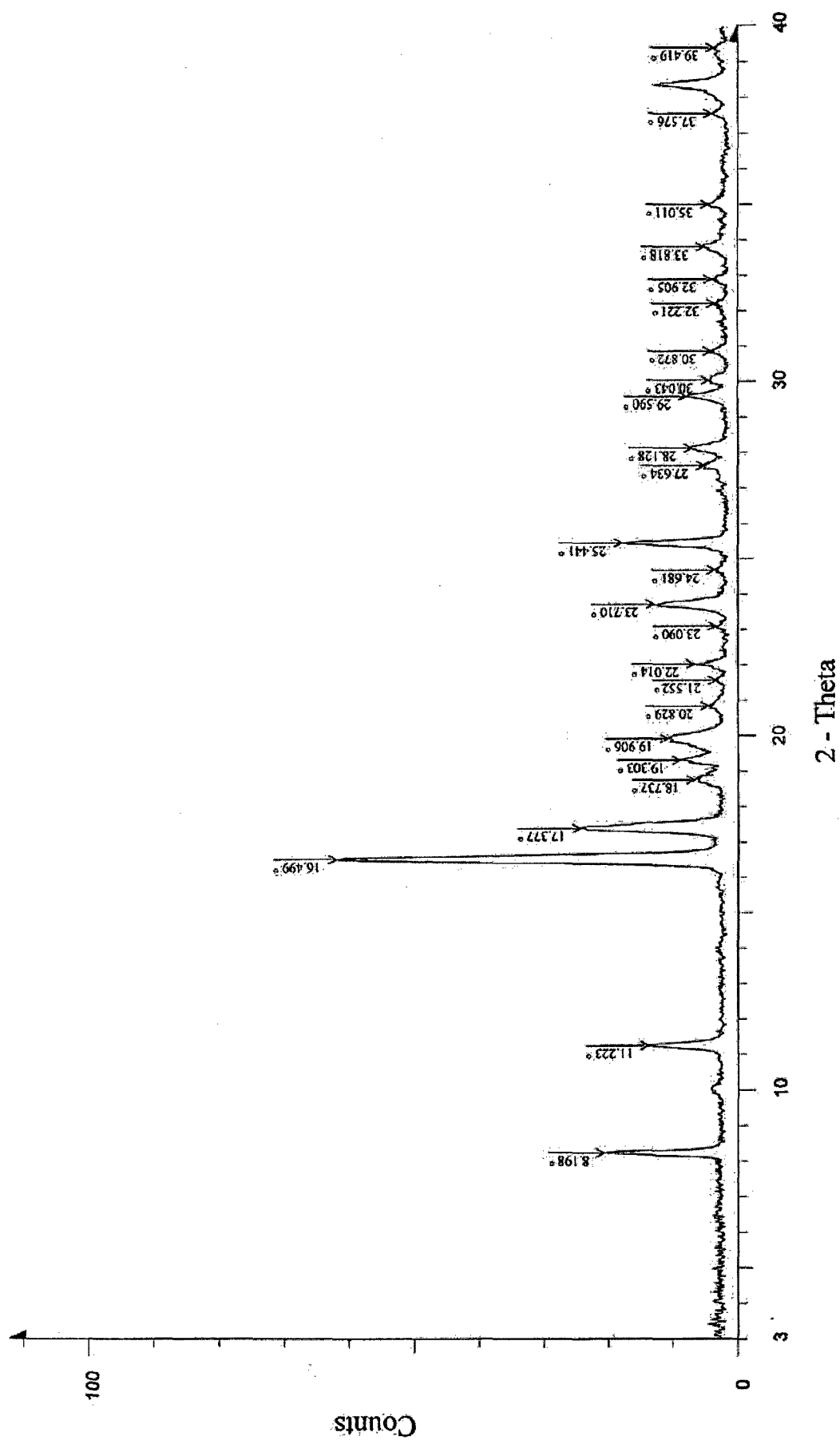
[Figure 2]



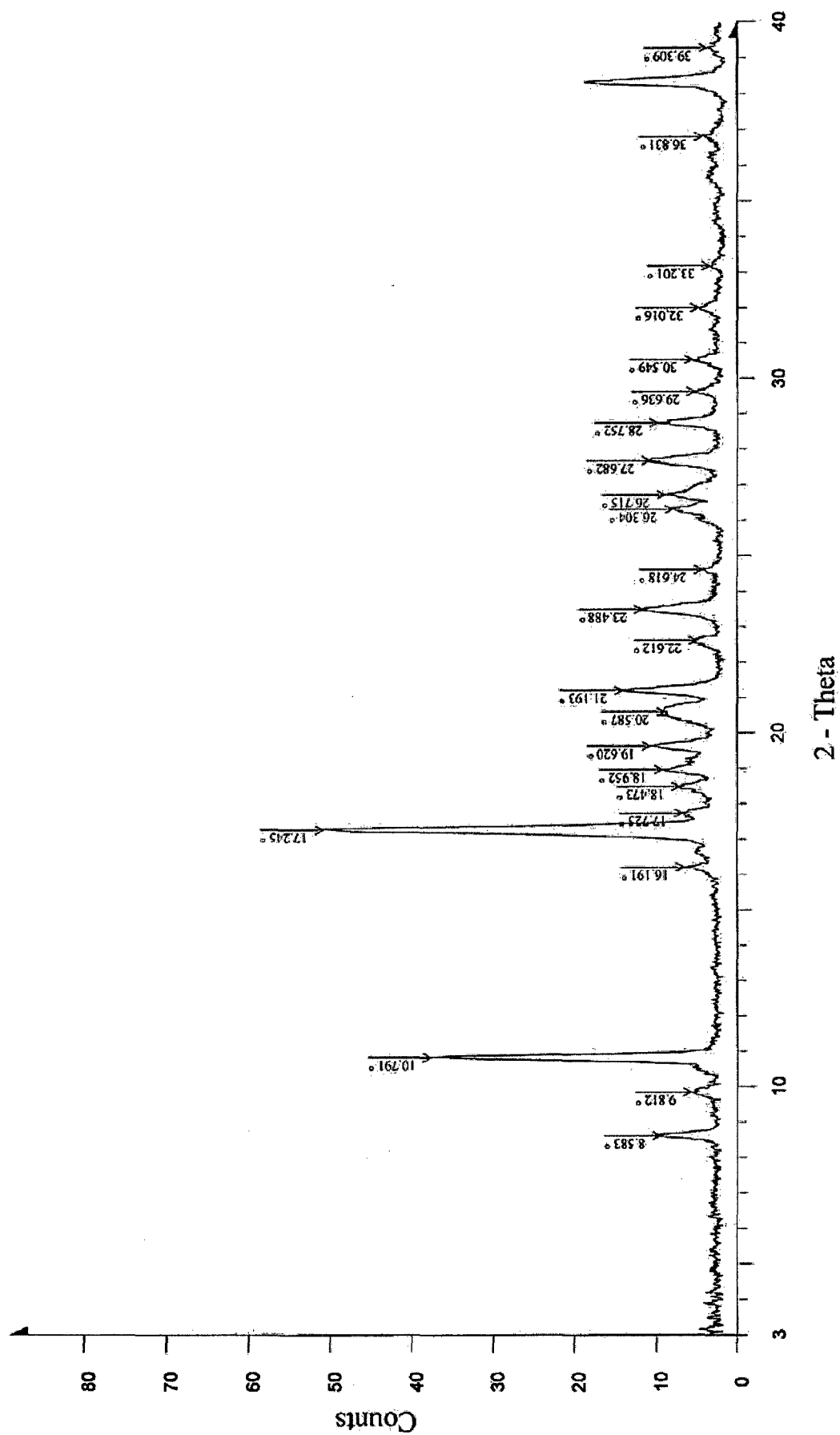
[Figure 3]



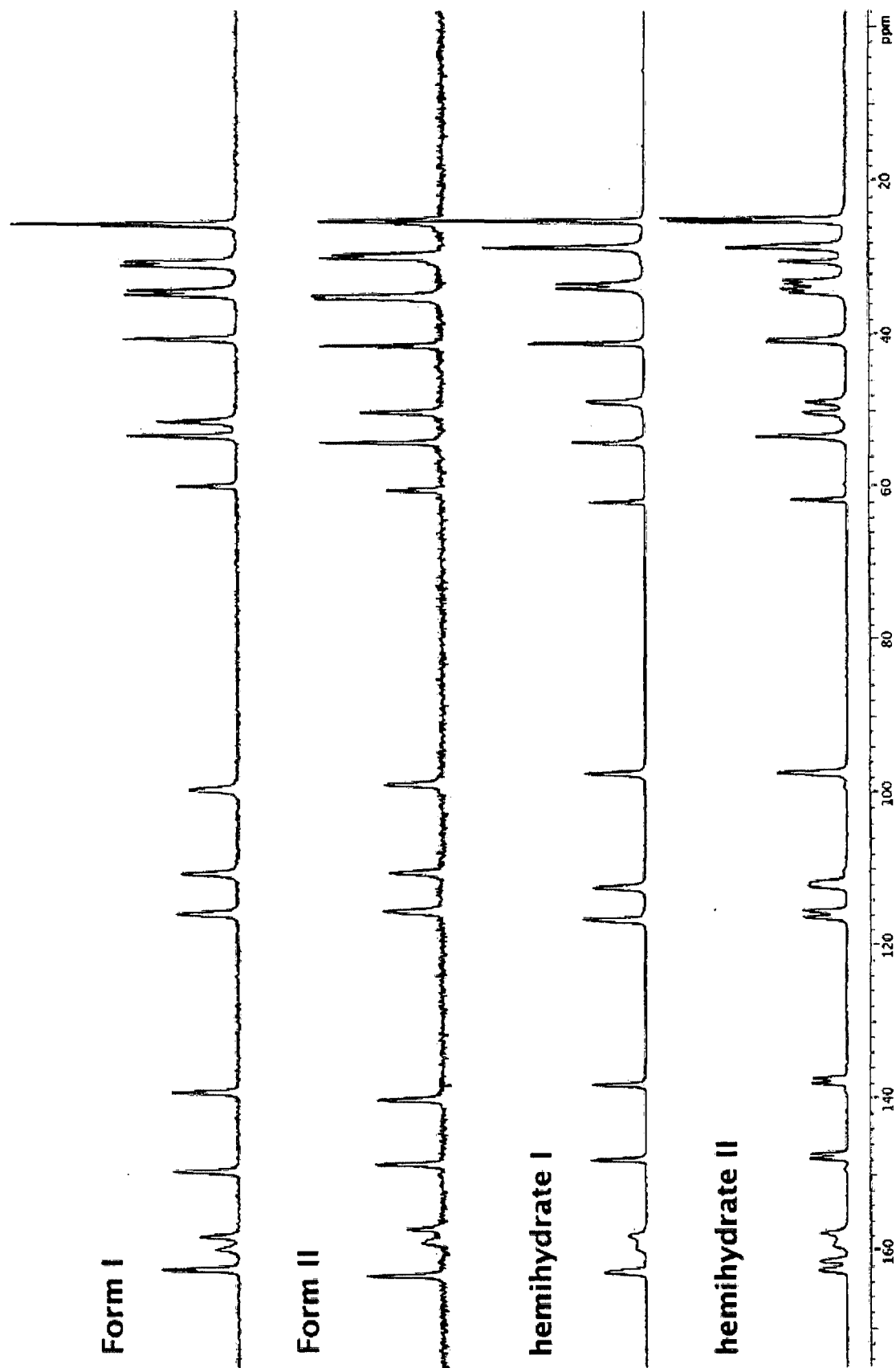
[Figure 4]



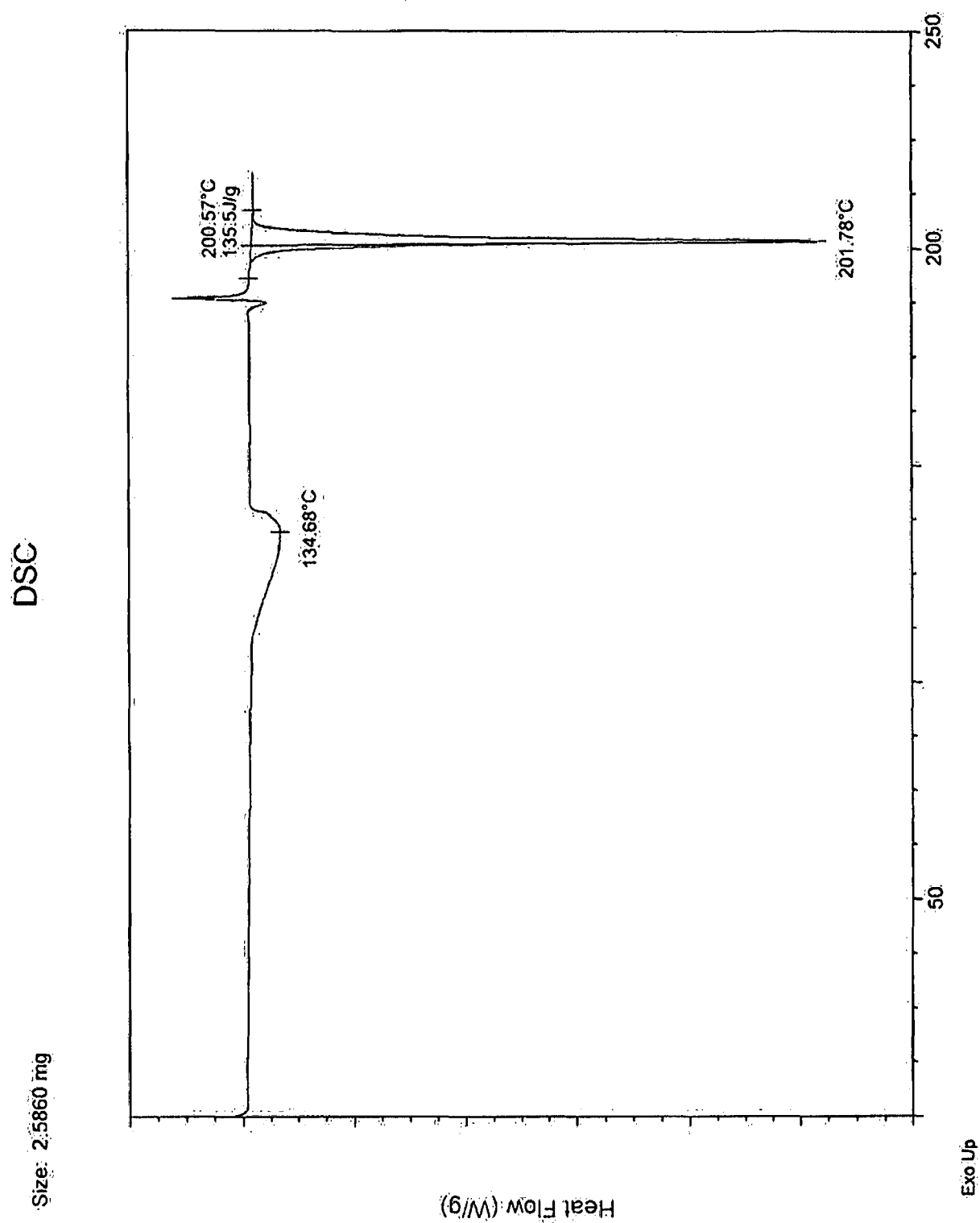
[Figure 5]



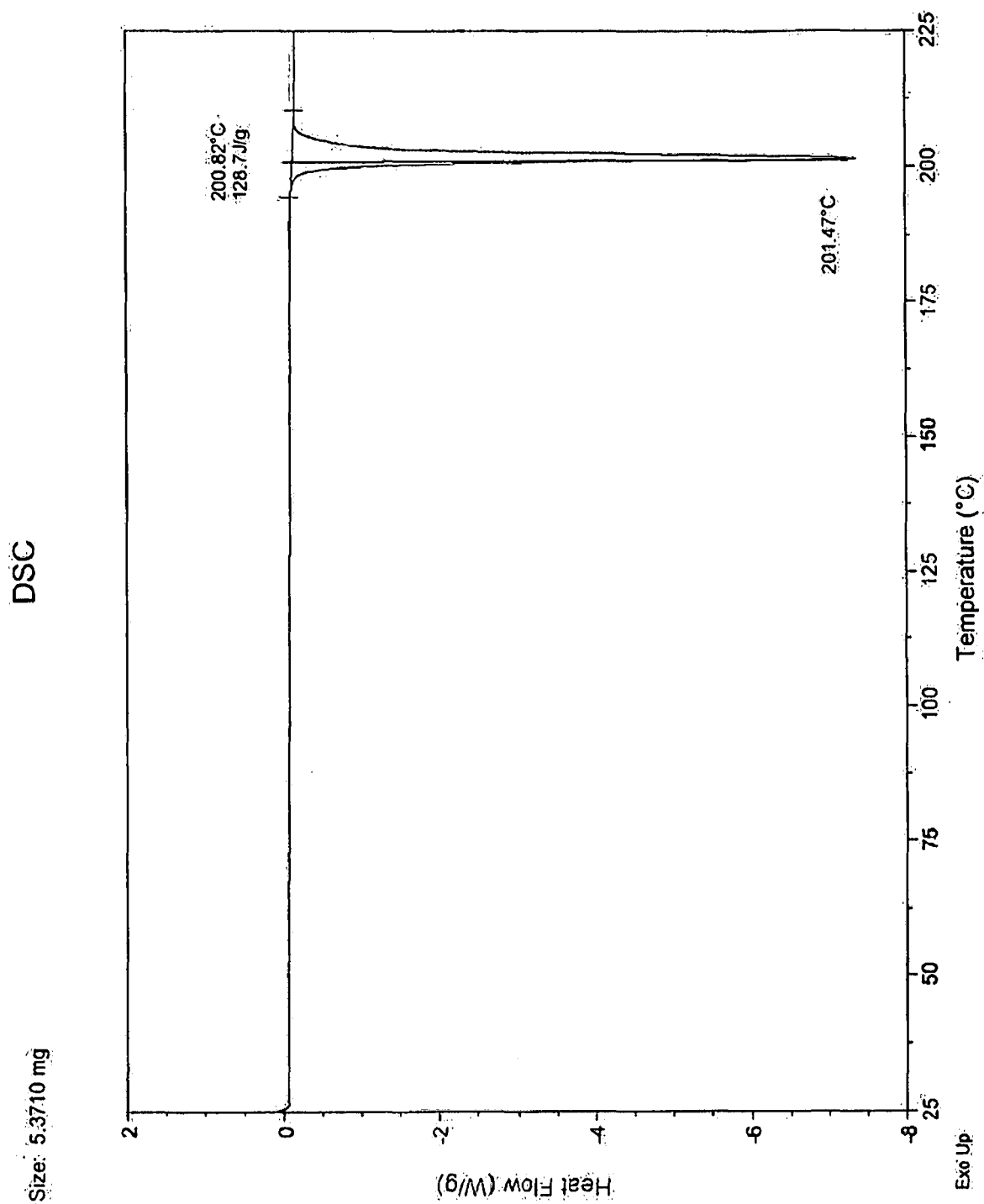
[Figure 6]



[Figure 7]



[Figure 8]



[Figure 9]

