

SPECIFICATION

TITLE OF THE INVENTION: CRYSTAL OF HETEROCYCLIC DERIVATIVE

TECHNICAL FIELD

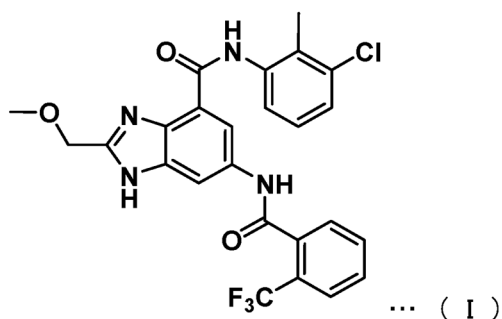
[0001] The present disclosure relates to crystals of a heterocyclic derivative.

BACKGROUND ART

[0002] Prostaglandins (PGs) are produced in large amounts at a site of inflammation and are involved in the development of inflammation. Among PGs, in particular, prostaglandin E2 (PGE2) induces fever, hyperalgesia, etc., as an inflammation-inducing substance in acute inflammation and chronic inflammation. PGE2 is known to be synthesized by PGE2 synthase (PGES), and PGES is responsible for the final stage of the synthesis pathway of PGE2, which is an inflammatory mediator. It has been found that there are three subtypes of PGES. Among them, like cyclooxygenase-2 (COX2), membrane-bound prostaglandin E synthase-1 (mPGES-1) is mainly induced during inflammation, and is deeply involved in PGE2 production in inflammatory lesions. Examples of active ingredients of therapeutic agents for inflammatory diseases focusing on such mechanisms include mPGES-1 inhibitors. mPGES-1 inhibitors inhibit only COX-2-dependent PGE2 production, and thus are considered to be able to reduce various side effects compared to NSAIDs and COX-2 inhibitors.

[0003] As an mPGES-1 inhibitor, PATENT DOCUMENT 1 describes N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-({[2-(trifluoromethyl)phenyl]carbonyl}amino)-1H-benzimidazole-4-carboxamide (hereinafter also referred to as “compound A”) represented by the following formula (I).

[Chem. 1]



CITATION LIST

[PATENT DOCUMENT]

[0004] [PATENT DOCUMENT 1] WO2013/024898 A1

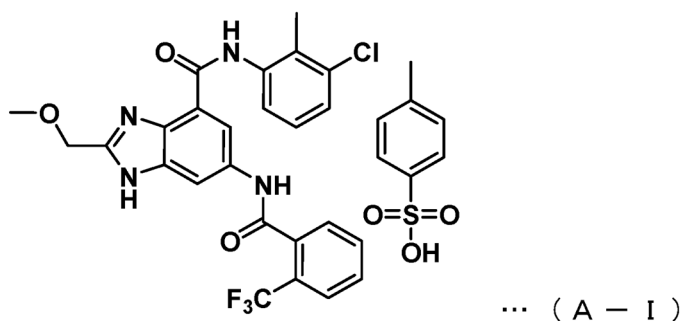
SUMMARY OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

[0005] As for compounds used as pharmaceutical products, it is known that the physical properties of the compounds that directly and significantly affect utilization as active ingredients of pharmaceutical products, such as storage stability and solubility, can vary depending on the form thereof (e.g., salts or solvates or crystals thereof).

[0006] An object of the present disclosure is to provide crystals of a heterocyclic derivative. An object of the present disclosure is to provide crystals of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate (hereinafter also referred to as “p-TsOH salt of the compound A”) represented by the following formula (A-I):

[Chem. 2]



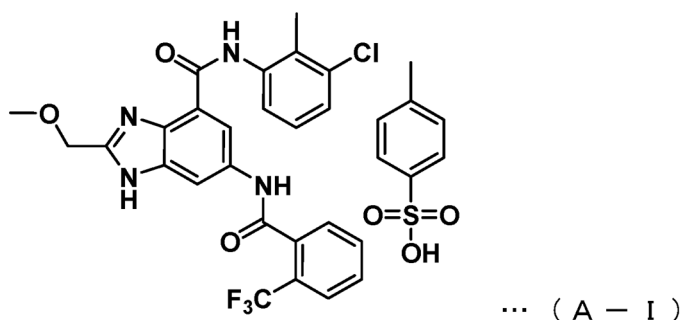
SOLUTION TO THE PROBLEMS

[0007] The present inventors have found new crystals of the p-TsOH salt of the compound A. Furthermore, the present inventors have found that the found crystals of the p-TsOH salt of the compound A are crystals having excellent physical properties that directly and significantly affect utilization as active ingredients of pharmaceutical products, such as storage stability or solubility.

[0008] The present disclosure is directed to, for example, <1> to <22> below.

<1> A Form-I crystal of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate represented by the following formula (A-I):

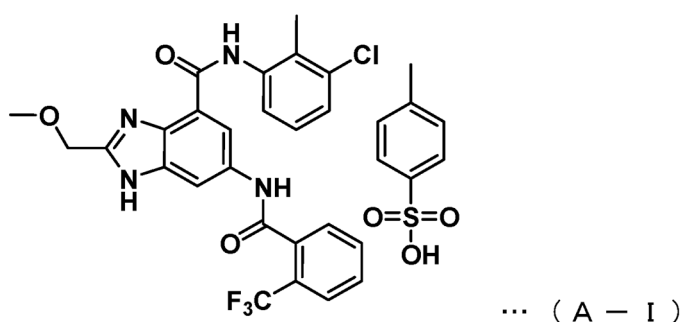
[Chem. 3]



the Form-I crystal having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 7.1° , 14.3° , 15.8° , and 18.3° in X-ray powder diffraction.

<2> A Form-I crystal of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-({[2-(trifluoromethyl)phenyl]carbonyl}amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate represented by the following formula (A-I):

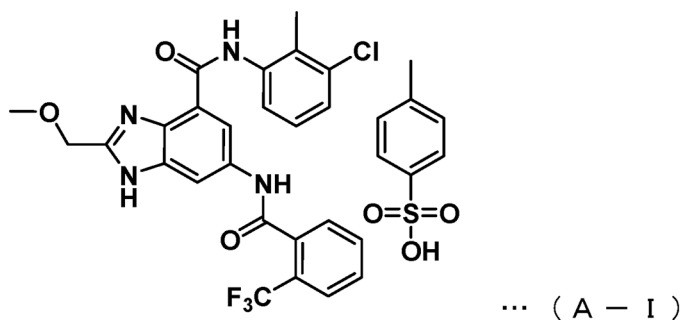
[Chem. 4]



the Form-I crystal having an endothermic peak at $265.8 \pm 3.0^\circ\text{C}$ in differential scanning calorimetry.

<3> A Form-III crystal of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-({[2-(trifluoromethyl)phenyl]carbonyl}amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate represented by the following formula (A-I):

[Chem. 5]

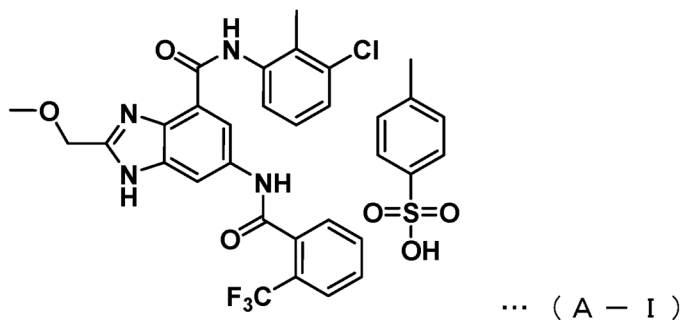


the Form-III crystal having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 6.3° , 15.0° , 16.4° ,

17.9°, and 22.7° in X-ray powder diffraction.

<4> A Form-III crystal of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate represented by the following formula (A-I):

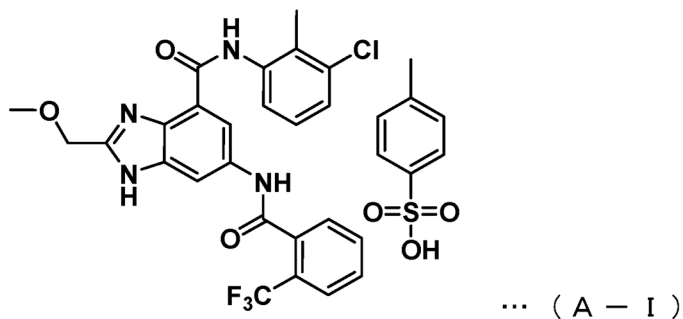
[Chem.6]



the Form-III crystal having an endothermic peak at $247.4 \pm 3.0^\circ\text{C}$ in differential thermal analysis.

<5> A Form-IV crystal of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate represented by the following formula (A-I):

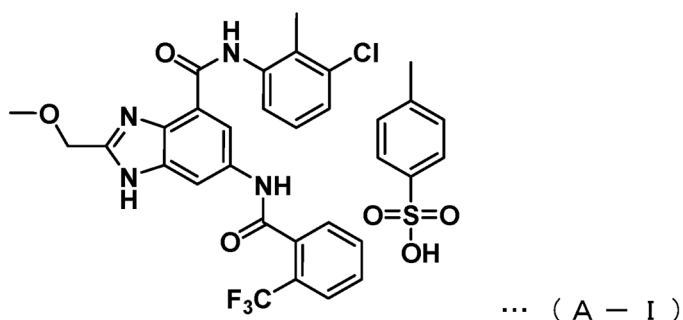
[Chem.7]



the Form-IV crystal having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 7.4° , 8.0° , 14.5° , 16.1° , and 20.6° in X-ray powder diffraction.

<6> A Form-IV crystal of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate represented by the following formula (A-I):

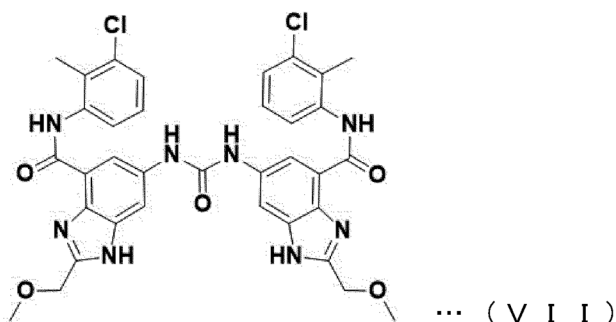
[Chem.8]



the Form-IV crystal having an endothermic peak at $212.5 \pm 3.0^\circ\text{C}$ in differential thermal analysis.

<7> A composition containing the crystal according to <1> or <2>, wherein a content of the crystal according to <1> or <2> is 95 mass% or more of the entire composition, and a content of a compound represented by following formula (VII):

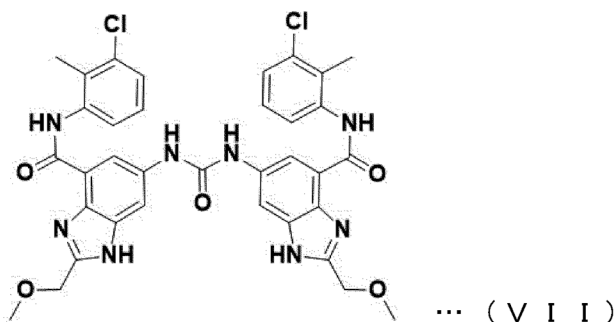
[Chem. 9]



is 100×10^{-4} mass% or less and preferably 50×10^{-4} mass% or less in terms of free form.

<8> A composition containing the crystal according to <1> or <2> and a compound represented by the following formula (VII):

[Chem. 10]

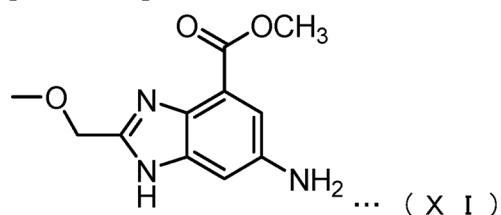


wherein a content of the crystal according to <1> or <2> is 95 mass% or more of the entire composition, and a content of the compound represented by the formula (VII) is 100×10^{-6} mass% or less and preferably 50×10^{-6} mass% or less in terms of free form.

<9> The composition according to <7> or <8>, wherein a content of a compound

represented by the following formula (XI):

[Chem. 11]



is 100×10^{-4} mass% or less in terms of free form, and preferably the compound represented by the formula (XI) is not contained.

<10> A production method for the crystal according to <1> or <2>.

<11> A production method for the crystal according to <3> or <4>.

<12> The production method according to <11>, including a step of exposing N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate represented by the formula (A-I) to a temperature condition of 130°C or higher.

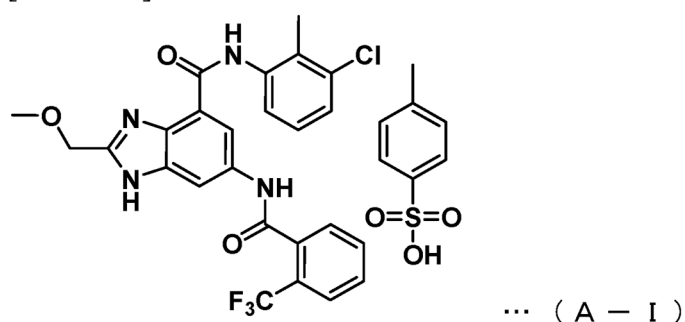
<13> A production method for the crystal according to <5> or <6>.

<14> The production method according to <13>, including a step of bringing N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate represented by the formula (A-I) into contact with acetonitrile and then exposing N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate to a temperature condition of 90°C or higher.

<15> A production method for the composition according to <7>, <8>, or <9>.

<16> A production method according to any one of <10> to <15>, including a step of obtaining N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate represented by the following formula (A-I):

[Chem. 12]



(i.e., a p-toluenesulfonate of a compound represented by the following formula (I):

[Chem. 13]



in accordance with a production method according to any one of [1] to [28].

<17> The crystal according to <1> or <2> produced by the production method according to <10> or <16>.

<18> The crystal according to <3> or <4> produced by the production method according to <11>, <12>, or <16>.

<19> The crystal according to <5> or <6> produced by the production method according to <13>, <14>, or <16>.

<20> The composition according to <7>, <8>, or <9> produced by the production method according to <15> or <16>.

<21> A pharmaceutical composition containing the crystal according to any one of <1> to <6> and <17> to <19> or the composition according to any one of <7> to <9> and <20> as an active ingredient.

<22> A membrane-bound prostaglandin E synthase-1 inhibitor containing the crystal according to any one of <1> to <6> and <17> to <19> or the composition according to any one of <7> to <9> and <20> as an active ingredient.

[0009] [1] to [28] in <16> are as follows.

[1] A production method for a p-toluenesulfonate of a compound (compound A) represented by the following formula (I):

[Chem. 14]

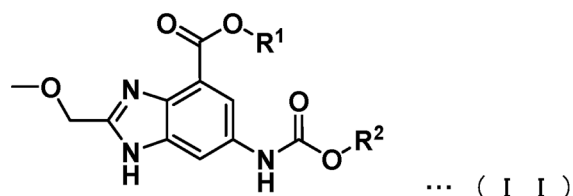


including a step of converting an N,N-dimethylacetamide solvate of the compound (compound

A) represented by the formula (I) into the p-toluenesulfonate of the compound (compound A) represented by the formula (I).

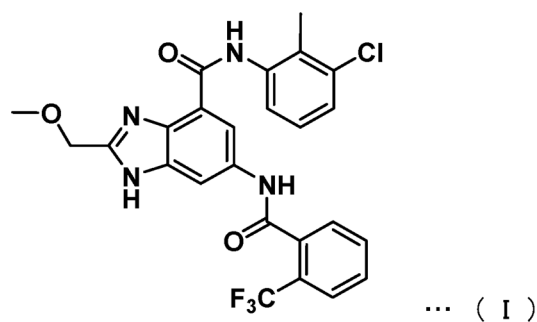
[2] The production method according to [1], further including a step of converting a compound represented by the following formula (II):

[Chem. 15]



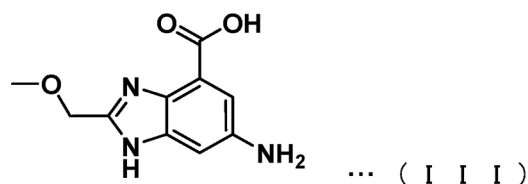
(wherein R¹ represents a protecting group for a carboxyl group or H, and R² represents a group that combines with -O-C(=O)- to form a protecting group for an aniline amino group) into an N,N-dimethylacetamide solvate of a compound represented by the following formula (I):

[Chem. 16]



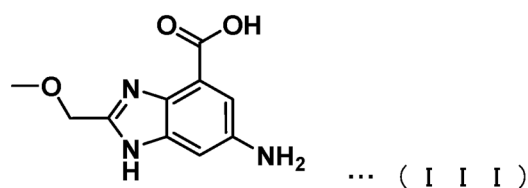
[3] The production method according to [2], wherein the step of converting the compound represented by the formula (II) into the compound represented by the formula (I) includes hydrolyzing the compound represented by the formula (II) in the presence of a base to obtain a compound represented by the following formula (III):

[Chem. 17]



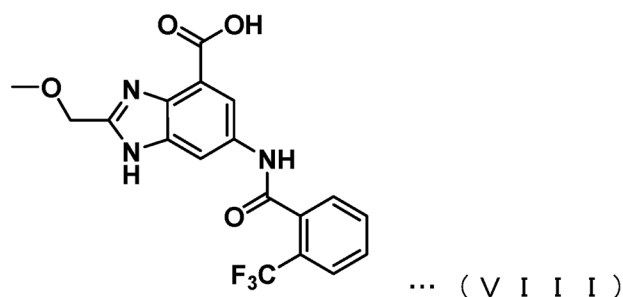
[4] The production method according to [2] or [3], wherein the step of converting the compound represented by the formula (II) into the compound represented by the formula (I) includes converting a compound represented by the following formula (III):

[Chem. 18]



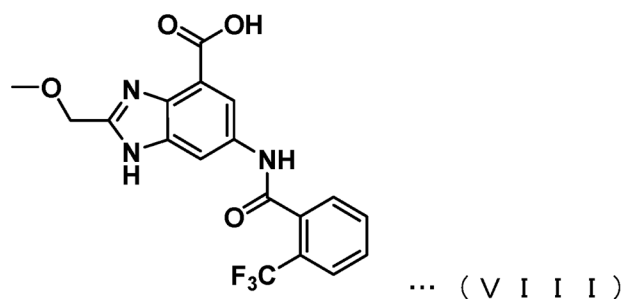
into a compound represented by the following formula (VIII):

[Chem. 19]



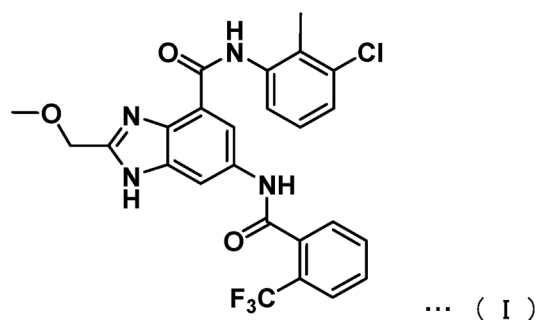
[5] The production method according to any one of [2] to [4], wherein the step of converting the compound represented by the formula (II) into the compound represented by the formula (I) includes converting a compound represented by the following formula (VIII):

[Chem. 20]



into an N,N-dimethylacetamide solvate of a compound represented by the following formula (I):

[Chem. 21]



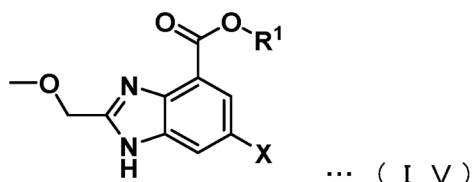
[6] The production method according to any one of [2] to [5], wherein R¹ and R² in the formula (II) each independently represent C₁-C₆ alkyl.

[7] The production method according to any one of [2] to [6], wherein R¹ and R² in

the formula (II) are each methyl.

[8] The production method according to any one of [1] to [7], further including a step of obtaining the compound represented by the formula (II), including bringing a compound represented by the following formula (IV):

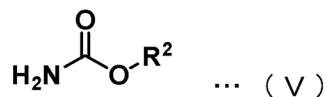
[Chem. 22]



(wherein R^1 is the same as R^1 in the formula (II), and X represents Cl, Br, I, or OTf)

or its protected product into contact with a compound represented by the following formula (V):

[Chem. 23]



(wherein R^2 is the same as R^2 in the formula (II))

to obtain the compound represented by the formula (II) or its protected product.

[9] The production method according to [8], wherein X in the formula (IV) is Cl, Br, I, or I.

[10] The production method according to [8] or [9], wherein X in the formula (IV) is Br.

[11] The production method according to any one of [8] to [10], wherein bringing the compound represented by the formula (IV) or its protected product into contact with the compound represented by the formula (V) in the step of obtaining the compound represented by the formula (II) is performed in the presence of a palladium catalyst.

[12] The production method according to [11], wherein the palladium catalyst is a palladium catalyst containing zero-valent palladium.

[13] The production method according to [11] or [12], wherein the palladium catalyst is tris(dibenzylideneacetone)dipalladium(0).

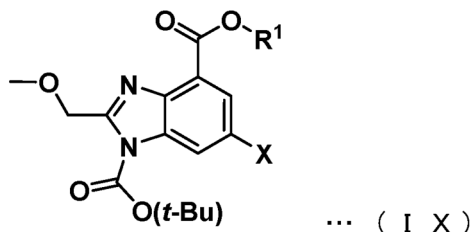
[14] The production method according to any one of [11] to [13], wherein bringing the compound represented by the formula (IV) or its protected product into contact with the compound represented by the formula (V) in the step of obtaining the compound represented by the formula (II) is performed in the presence of a ligand.

[15] The production method according to [14], wherein the ligand is 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl.

[16] The production method according to any one of [8] to [15], wherein the compound

represented by the formula (IV) or its protected product is a compound represented by the following formula (IX):

[Chem. 24]



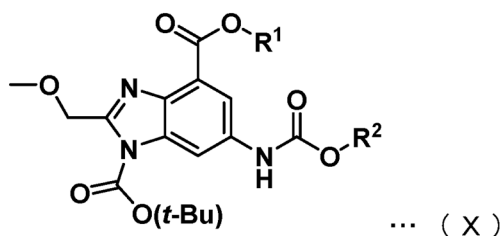
(wherein R^1 is the same as R^1 in the formula (II), and X is the same as X in the formula (IV)).

[17] The production method according to any one of [8] to [16], wherein the step of obtaining the compound represented by the formula (II), including bringing the compound represented by the formula (IV) or its protected product into contact with the compound represented by the formula (V), includes, in the following order,

converting the compound represented by the formula (IV) into the compound represented by the formula (IX),

bringing the compound represented by the formula (IX) into contact with the compound represented by the formula (V) to obtain a compound represented by the following formula (X):

[Chem. 25]

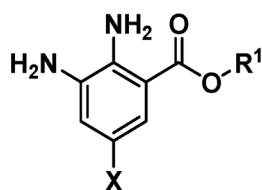


(wherein R^1 is the same as R^1 in the formula (II), and R^2 is the same as R^2 in the formula (V)), and

hydrolyzing the compound represented by the formula (X) in the presence of an acid to obtain the compound represented by the formula (II).

[18] The production method according to any one of [1] to [17], further including a step of bringing a compound represented by the following formula (VI):

[Chem. 26]



... (V I)

(wherein R¹ is the same as R¹ in the formula (II), and X is the same as X in the formula (IV)) into contact with methoxyacetic acid to obtain the compound represented by the formula (IV).

[19] The production method according to any one of [1] to [18], further including a step of purifying the N,N-dimethylacetamide solvate of the compound represented by the formula (I), by recrystallization.

[20] The production method according to [19], wherein recrystallization of the N,N-dimethylacetamide solvate of the compound represented by the formula (I) is performed using a mixed solvent of N,N-dimethylacetamide and water.

[21] The production method according to [19] or [20], wherein recrystallization of the N,N-dimethylacetamide solvate of the compound represented by the formula (I) is performed using a mixed solvent of N,N-dimethylacetamide and water in which a content of N,N-dimethylacetamide is 75 vol% or more.

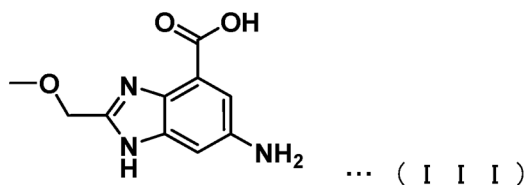
[22] The production method according to [1] to [21], including a step of purifying the p-toluenesulfonate of the compound represented by the formula (I) by bringing the p-toluenesulfonate into contact with activated carbon after the step of converting the N,N-dimethylacetamide solvate of the compound represented by the formula (I) into the p-toluenesulfonate of the compound represented by the formula (I), and a step of recrystallizing the p-toluenesulfonate of the compound represented by the formula (I) after being brought into contact with the activated carbon, to obtain a Form-I crystal of the p-toluenesulfonate of the compound represented by the formula (I).

[23] The production method according to [22], wherein a mass of the activated carbon to be brought into contact with the p-toluenesulfonate of the compound represented by the formula (I) is 0.04 times or more a mass of the p-toluenesulfonate of the compound represented by the formula (I).

[24] A production method for a p-toluenesulfonate of a compound (compound A) represented by the following formula (I):

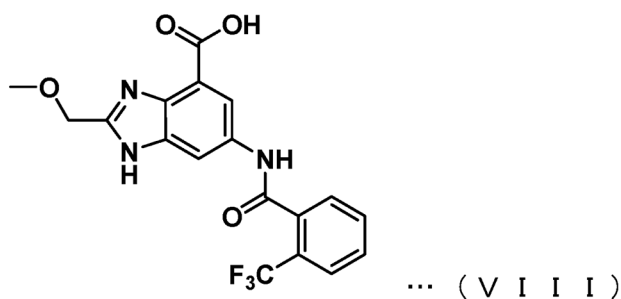
hydrolyzing the compound represented by the formula (II) in the presence of a base to obtain a compound represented by the following formula (III):

[Chem. 31]



converting the compound represented by the formula (III) into a compound represented by the following formula (VIII):

[Chem. 32]

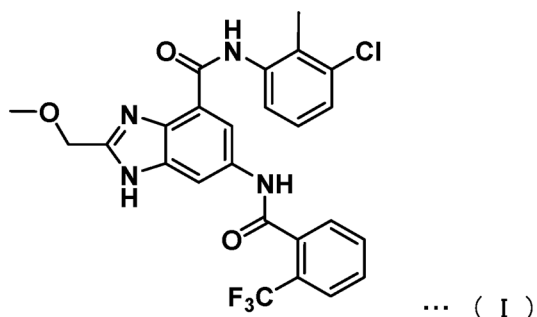


converting the compound represented by the formula (VIII) into the N,N-dimethylacetamide solvate of the compound (compound A) represented by the formula (I); and

a step of converting the N,N-dimethylacetamide solvate of the compound (compound A) represented by the formula (I) into a p-toluenesulfonate of the compound (compound A) represented by the formula (I).

[25] A production method for a p-toluenesulfonate of a compound (compound A) represented by the following formula (I):

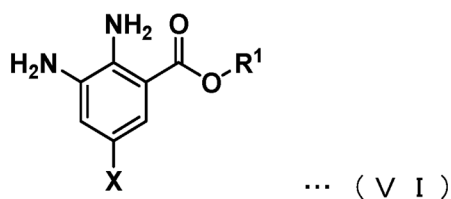
[Chem. 33]



including, in the following order:

a step of bringing a compound represented by the following formula (VI):

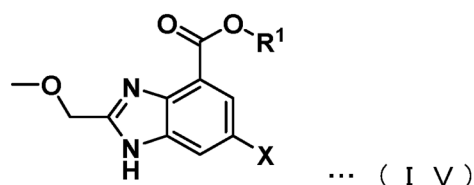
[Chem. 34]



(wherein R¹ represents a protecting group for a carboxyl group or H, and X represents Cl, Br, I, or OTf)

into contact with methoxyacetic acid to obtain a compound represented by the following formula (IV):

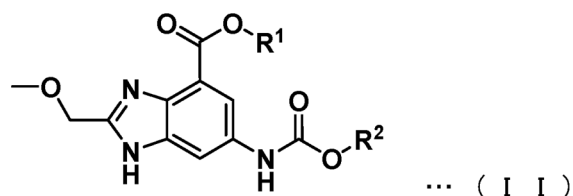
[Chem. 35]



(wherein R¹ and X are the same as R¹ and X in the formula (VI), respectively);

a step of converting the compound represented by the formula (IV) into a compound represented by the following formula (II):

[Chem. 36]

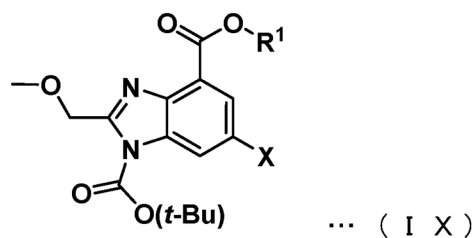


(wherein R¹ is the same as R¹ in the formula (VI), and R² represents a group that combines with -O-C(=O)- to form a protecting group for an aniline amino group),

including, in the following order,

converting the compound represented by the formula (IV) into a compound represented by the following formula (IX):

[Chem. 37]

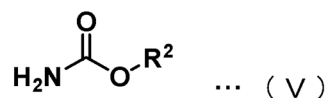


(wherein R¹ and X are the same as R¹ and X in the formula (VI), respectively),

bringing the compound represented by the formula (IX) into contact with a

compound represented by the following formula (V):

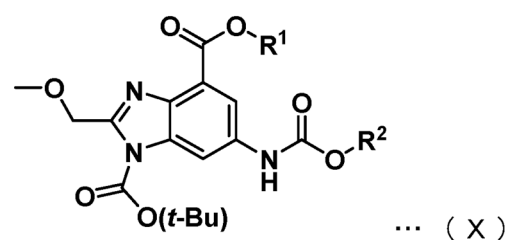
[Chem. 38]



(wherein R^2 is the same as R^2 in the formula (II))

to obtain a compound represented by the following formula (X):

[Chem. 39]



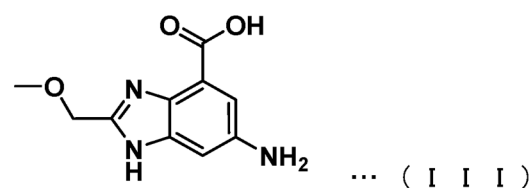
(wherein R^1 is the same as R^1 in the formula (VI), and R^2 is the same as R^2 in the formula (II)),
and

hydrolyzing the compound represented by the formula (X) in the presence of
an acid to obtain the compound represented by the formula (II);

a step of converting the compound represented by the formula (II) into an N,N-
dimethylacetamide solvate of the compound (compound A) represented by the formula (I),
including

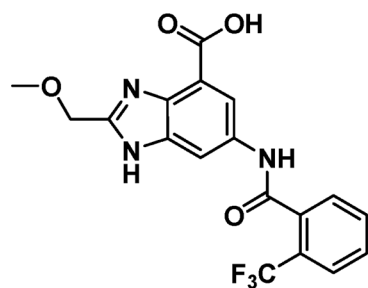
hydrolyzing the compound represented by the formula (II) in the presence of a
base to obtain a compound represented by the following formula (III):

[Chem. 40]



converting the compound represented by the formula (III) into a compound
represented by the following formula (VIII):

[Chem. 41]



... (V I I I)

, and

converting the compound represented by the formula (VIII) into the N,N-dimethylacetamide solvate of the compound (compound A) represented by the formula (I);

a step of converting the N,N-dimethylacetamide solvate of the compound (compound A) represented by the formula (I) into a p-toluenesulfonate of the compound (compound A) represented by the formula (I);

a step of purifying the N,N-dimethylacetamide solvate of the compound (compound A) represented by the formula (I) by recrystallization;

a step of purifying the p-toluenesulfonate of the compound (compound A) represented by the formula (I) by bringing the p-toluenesulfonate into contact with activated carbon; and

recrystallizing the p-toluenesulfonate of the compound (compound A) represented by the formula (I) after being brought into contact with the activated carbon, to obtain a Form-I crystal of the p-toluenesulfonate of the compound (compound A) represented by the formula (I).

[26] The production method according to [24] or [25], wherein R¹ and R² are each C₁-C₆ alkyl and preferably methyl, and X is Cl, Br, or I and preferably Br.

[27] The production method according to [25], wherein
R¹ and R² are each C₁-C₆ alkyl and preferably methyl,
X is Cl, Br, or I and preferably Br,

bringing the compound represented by the formula (IV) or its protected product into contact with the compound represented by the formula (V) is performed in the presence of a palladium catalyst,

recrystallization of the N,N-dimethylacetamide solvate of the compound represented by the formula (I) is performed using a mixed solvent of N,N-dimethylacetamide and water, and is preferably performed using a mixed solvent of N,N-dimethylacetamide and water in which a content of N,N-dimethylacetamide is 75 vol% or more, and

a mass of the activated carbon to be brought into contact with the p-toluenesulfonate of the compound represented by the formula (I) is 0.04 times or more and preferably 0.08 times or more a mass of the p-toluenesulfonate of the compound represented by

the formula (I).

[28] The production method according to any one of [24] to [27], wherein bringing the compound represented by the formula (IV) or its protected product into contact with the compound represented by the formula (V) is performed in the presence of a ligand and a palladium catalyst containing zero-valent palladium, and is preferably performed in the presence of tris(dibenzylideneacetone)dipalladium(0) and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl.

ADVANTAGEOUS EFFECTS OF THE INVENTION

[0010] According to the present disclosure, it is possible to provide new crystals of the p-TsOH salt of the compound A and pharmaceutical compositions and membrane-bound prostaglandin E synthase-1 inhibitors containing the crystals. In addition, according to the present disclosure, it is possible to provide production methods for the crystals of the p-TsOH salt of the compound A.

[0011] According to one embodiment of the present disclosure, it is possible to provide a Form-I crystal of the p-TsOH salt of the compound A. The Form-I crystal of the p-TsOH salt of the compound A is a crystal of the p-TsOH salt of the compound A having high stability. According to one embodiment of the present disclosure, it is possible to provide a Form-I crystal of the p-TsOH salt of the compound A having excellent storage stability, and a pharmaceutical composition and a membrane-bound prostaglandin E synthase-1 inhibitor containing the Form-I crystal.

[0012] According to one embodiment of the present disclosure, it is possible to provide a Form-III crystal of the p-TsOH salt of the compound A. The Form-III crystal of the p-TsOH salt of the compound A is a crystal of the p-TsOH salt of the compound A having high solubility. According to one embodiment of the present disclosure, it is possible to provide a Form-III crystal of the p-TsOH salt of the compound A having excellent solubility and absorbability (e.g., bioavailability) in a body, and a pharmaceutical composition and a membrane-bound prostaglandin E synthase-1 inhibitor containing the Form-III crystal.

[0013] According to one embodiment of the present disclosure, it is possible to provide a Form-IV crystal of the p-TsOH salt of the compound A and a pharmaceutical composition and a membrane-bound prostaglandin E synthase-1 inhibitor containing the Form-IV crystal.

[0014] According to one embodiment of the present disclosure, it is possible to provide a crystal of the p-TsOH salt of the compound A having excellent stability. According to one embodiment of the present disclosure, it is possible to provide a crystal of the p-TsOH salt of the compound A having excellent solubility. Such crystals of the p-TsOH salt of the compound A

having excellent physical properties are suitable for use as active ingredients in a pharmaceutical composition and a membrane-bound prostaglandin E synthase-1 inhibitor.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] [FIG. 1] FIG. 1 shows the results of X-ray powder diffraction of a Form-I crystal of the p-TsOH salt of the compound A in Example 1.

[FIG. 2] FIG. 2 shows the results of thermophysical property measurement by differential scanning calorimetry (DSC) of the Form-I crystal of the p-TsOH salt of the compound A in Example 1.

[FIG. 3] FIG. 3 shows the results of thermophysical property measurement by differential thermal analysis (DTA) and thermogravimetric analysis (TGA) of the Form-I crystal of the p-TsOH salt of the compound A in Example 1.

[FIG. 4] FIG. 4 shows the results of X-ray powder diffraction of an amorphous substance of the p-TsOH salt of the compound A in Preparation Example 1.

[FIG. 5] FIG. 5 is an enlarged view showing the results of X-ray powder diffraction of the amorphous substance of the p-TsOH salt of the compound A in Preparation Example 1.

[FIG. 6] FIG. 6 shows the results of X-ray powder diffraction of a Form-III crystal of the p-TsOH salt of the compound A in Example 2.

[FIG. 7] FIG. 7 shows the results of thermophysical property measurement by differential thermal analysis (DTA) and thermogravimetric analysis (TGA) of the Form-III crystal of the p-TsOH salt of the compound A in Example 2.

[FIG. 8] FIG. 8 shows the results of X-ray powder diffraction of an intermediate product in the production of a Form-IV crystal of the p-TsOH salt of the compound A in Example 3.

[FIG. 9] FIG. 9 shows the results of thermophysical property measurement by differential thermal analysis (DTA) and thermogravimetric analysis (TGA) of the intermediate product in the production of the Form-IV crystal of the p-TsOH salt of the compound A in Example 3.

[FIG. 10] FIG. 10 shows the results of X-ray powder diffraction of the Form-IV crystal of the p-TsOH salt of the compound A in Example 3.

[FIG. 11] FIG. 11 shows the results of thermophysical property measurement by differential thermal analysis (DTA) and thermogravimetric analysis (TGA) of the Form-IV crystal of the p-TsOH salt of the compound A in Example 3.

[FIG. 12] FIG. 12 shows the results of X-ray powder diffraction of an

intermediate product in the production of a Form-V crystal of the p-TsOH salt of the compound A in Comparative Example 1.

[FIG. 13] FIG. 13 shows the results of thermophysical property measurement by differential thermal analysis (DTA) and thermogravimetric analysis (TGA) of the intermediate product in the production of the Form-V crystal of the p-TsOH salt of the compound A in Comparative Example 1.

[FIG. 14] FIG. 14 shows the results of X-ray powder diffraction of the Form-V crystal of the p-TsOH salt of the compound A in Comparative Example 1.

[FIG. 15] FIG. 15 shows the results of thermophysical property measurement by differential thermal analysis (DTA) and thermogravimetric analysis (TGA) of the Form-V crystal of the p-TsOH salt of the compound A in Comparative Example 1.

[FIG. 16] FIG. 16 shows the results of X-ray powder diffraction of an intermediate product in the production of a Form-VI crystal of the p-TsOH salt of the compound A in Comparative Example 2.

[FIG. 17] FIG. 17 shows the results of X-ray powder diffraction of the Form-VI crystal of the p-TsOH salt of the compound A in Comparative Example 2.

[FIG. 18] FIG. 18 shows the results of thermophysical property measurement by differential thermal analysis (DTA) and thermogravimetric analysis (TGA) of the Form-VI crystal of the p-TsOH salt of the compound A in Comparative Example 2.

[FIG. 19] FIG. 19 shows the results of X-ray powder diffraction of an intermediate product in the production of a Form-VII crystal of the p-TsOH salt of the compound A in Comparative Example 3.

[FIG. 20] FIG. 20 shows the results of X-ray powder diffraction of the Form-VII crystal of the p-TsOH salt of the compound A in Comparative Example 3.

[FIG. 21] FIG. 21 shows the results of thermophysical property measurement by differential thermal analysis (DTA) and thermogravimetric analysis (TGA) of the Form-VII crystal of the p-TsOH salt of the compound A in Comparative Example 3.

[FIG. 22] FIG. 22 shows the results of X-ray powder diffraction after 3, 4, 7, and 8 days from the start of stirring at 20°C in Example 9.

[FIG. 23] FIG. 23 shows the results of X-ray powder diffraction after 3 and 4 days from the start of stirring at 55°C in Example 9.

[FIG. 24] FIG. 24 shows the results of X-ray powder diffraction of a Form-I crystal of the p-TsOH salt of the compound A subjected to various treatments in Example 12.

[FIG. 25] FIG. 25 shows the results of X-ray powder diffraction of a Form-II crystal of the p-TsOH salt of the compound A in Comparative Example 4.

[FIG. 26] FIG. 26 shows the results of thermophysical property measurement by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) of the Form-II crystal of the p-TsOH salt of the compound A in Comparative Example 4.

[FIG. 27] FIG. 27 shows the results of X-ray powder diffraction when the Form-II crystal of the p-TsOH salt of the compound A was heated and cooled in Example 14.

[FIG. 28] FIG. 28 shows the results of X-ray powder diffraction for evaluating the stability of a Form-I crystal of the p-TsOH salt of the compound A in various solvents in Example 16.

[FIG. 29] FIG. 29 shows the results of X-ray powder diffraction of a Form-I crystal of the p-TsOH salt of the compound A in Reference Example 1.

[FIG. 30] FIG. 30 shows the results of thermophysical property measurement by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) of the Form-I crystal of the p-TsOH salt of the compound A in Reference Example 1.

DETAILED DESCRIPTION

[0016] Hereinafter, embodiments for carrying out the present disclosure will be described, but the present disclosure is not limited to the following embodiments.

[0017] In the present disclosure, unless otherwise specified, the term “compound” includes any form of the compound, including the free form of the compound, salts thereof, and solvates thereof, etc. Meanwhile, the terms “hydrochloride of the compound”, “N,N-dimethylacetamide solvate of the compound”, “p-toluenesulfonate of the compound”, etc., refer to the stated salt or solvate of the compound and do not include the compound in other forms. More specifically, for example, “converting a compound represented by structural formula (1) into a compound represented by structural formula (2)” means converting the compound represented by structural formula (1) in any form into the compound represented by structural formula (2) in any form. For example, the phrase “hydrolyzing the compound represented by structural formula (1) to obtain an N,N-dimethylacetamide solvate of the compound represented by structural formula (2)” means hydrolyzing the compound represented by structural formula (1) in any form to obtain the compound represented by structural formula (2) in the form of an N,N-dimethylacetamide solvate. For example, the phrase “bringing a hydrochloride of the compound represented by structural formula (1) into contact with a compound represented by structural formula (3) to obtain a p-toluenesulfonate of the compound represented by structural formula (2)” means bringing the compound represented by structural formula (1) in the form of a hydrochloride into contact with the compound represented by structural formula (3) in any form to obtain the compound represented by structural formula (2) in the form of a p-toluenesulfonate.

In the present disclosure, the “N,N-dimethylacetamide solvate of the compound” refers to a solvate obtained by solvating the compound with N,N-dimethylacetamide. The p-toluenesulfonate of the compound according to the present disclosure may be, for example, a salt in which the ratio between the number of molecules of the compound and the number of molecules of p-toluenesulfonic acid is 1:1. The N,N-dimethylacetamide solvate of the compound according to the present disclosure may be, for example, a solvate in which the ratio between the number of molecules of the compound and the number of molecules of the N,N-dimethylacetamide solvate is 1:1.

[0018] The chemical reactions in the present disclosure may be quenched by methods commonly used by those skilled in the art, and the products may be collected by methods commonly used by those skilled in the art, such as distillation under reduced pressure, filtration, or extraction. The products by the chemical reactions in the present disclosure may also be purified by methods commonly used by those skilled in the art, such as recrystallization or column chromatography. From the viewpoint of mass production, in one preferred embodiment, purification may be performed by recrystallization. The reactions in each step in the present disclosure may be tracked by methods commonly used by those skilled in the art, such as chromatography including reversed-phase liquid chromatography (HPLC), and the products may be analyzed by methods commonly used by those skilled in the art, such as HPLC, nuclear magnetic resonance (NMR), mass spectrometry, X-ray crystallography, and DSC.

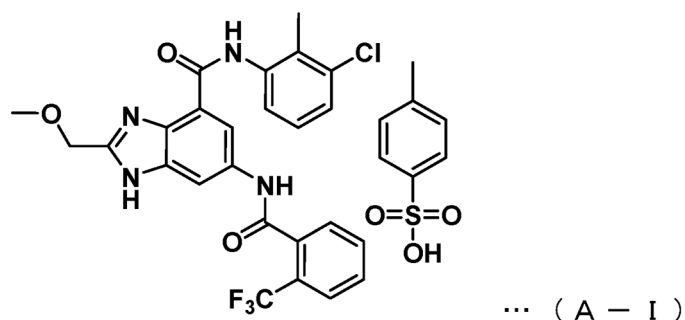
[0019] In the present disclosure, 4-methylbenzenesulfonate is sometimes referred to as p-toluenesulfonic acid, para-toluenesulfonic acid, tosic acid, or p-TsOH.

[0020] In the present disclosure, “having a diffraction peak at a diffraction angle ($2\theta \pm X^\circ$) of Y° ” means having a diffraction peak at a diffraction angle (2θ) of $Y \pm X^\circ$. For example, “having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 14.5° ” means having a diffraction peak in a range where the diffraction angle (2θ) is 14.3° or more and 14.7° or less. In the present disclosure, a diffraction angle and a diffraction pattern of X-ray powder diffraction mean a diffraction angle and a diffraction pattern obtained by irradiation with copper K α rays (CuK α).

[0021] <Form-I crystal of p-TsOH salt of compound A>

A first aspect of the present disclosure is directed to a Form-I crystal of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-({[2-(trifluoromethyl)phenyl]carbonyl}amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate represented by the following formula (A-I):

[Chem. 42]



That is, the first aspect of the present disclosure is directed to a Form-I crystal of the p-TsOH salt of the compound A. In one embodiment, the first aspect of the present disclosure may be a Form-I crystal of the p-TsOH salt of the compound A produced by a production method according to a fifth aspect of the present disclosure described later.

[0022] The Form-I crystal of the p-TsOH salt of the compound A according to one embodiment of the first aspect of the present disclosure has diffraction peaks at diffraction angles (2θ), diffraction angles ($2\theta \pm 0.1^\circ$), diffraction angles ($2\theta \pm 0.2^\circ$), diffraction angles ($2\theta \pm 0.3^\circ$), diffraction angles ($2\theta \pm 0.4^\circ$), or diffraction angles ($2\theta \pm 0.5^\circ$) of 7.1° , 14.3° , 15.8° , and 18.3° in X-ray powder diffraction. In one preferred embodiment of the first aspect of the present disclosure, the Form-I crystal of the p-TsOH salt of the compound A has diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 7.1° , 14.3° , 15.8° , and 18.3° in X-ray powder diffraction. In one embodiment of the present disclosure, the Form-I crystal of the p-TsOH salt of the compound A may have diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 7.1° , 14.3° , 15.8° , 18.3° , and 22.0° in X-ray powder diffraction. In one embodiment of the present disclosure, the Form-I crystal of the p-TsOH salt of the compound A may have diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 7.1° , 8.5° , 14.3° , 15.8° , 18.3° , 18.8° , 19.6° , 20.1° , 22.0° , and 25.8° in X-ray powder diffraction. In one embodiment of the present disclosure, the Form-I crystal of the p-TsOH salt of the compound A may have diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 7.1° , 8.5° , 11.8° , 14.3° , 14.7° , 15.8° , 16.4° , 17.4° , 18.3° , 18.8° , 19.6° , 20.1° , 22.0° , 23.5° , 24.4° , 25.3° , 25.8° , 27.3° , 28.8° , and 29.0° in X-ray powder diffraction.

[0023] The Form-I crystal of the p-TsOH salt of the compound A according to one embodiment of the first aspect of the present disclosure has an endothermic peak at $265.8 \pm 3.0^\circ\text{C}$ in differential scanning calorimetry. The Form-I crystal of the p-TsOH salt of the compound A according to one embodiment of the first aspect of the present disclosure has diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 7.1° , 14.3° , 15.8° , and 18.4° in X-ray powder diffraction, and has an endothermic peak at $265.8 \pm 3.0^\circ\text{C}$ in differential scanning calorimetry. In addition, the Form-I crystal of the p-TsOH salt of the compound A according to one embodiment of the first

aspect of the present disclosure has an endothermic peak at $263.0 \pm 3.0^{\circ}\text{C}$ in differential thermal analysis. In addition, the Form-I crystal of the p-TsOH salt of the compound A according to one embodiment of the first aspect of the present disclosure can stably exist for 7 days or longer even under the conditions of a temperature of 40°C and a relative humidity of 75%.

[0024] The Form-I crystal of the p-TsOH salt of the compound A according to one embodiment of the first aspect of the present disclosure is a crystal having excellent stability. In the present disclosure, a crystal having excellent stability means, for example, that the crystal has excellent storage stability, also means, for example, that the crystal is stable against processing in formulation, and also means, for example, that the crystal is in the most stable form out of a plurality of crystal forms of the same compound.

[0025] The crystal of the p-TsOH salt of the compound A having excellent storage stability means that, when the crystal is allowed to stand or when the crystal is exposed to stimulus such as heating stimulus, light stimulus, or humidifying stimulus, the p-TsOH salt of the compound A contained in the crystal does not significantly decompose and the crystal form thereof does not significantly change. An example in which such significant change is not observed is that the percentage of the crystal of the p-TsOH salt of the compound A in the same crystal form as that before exposure to the stimulus in a substance derived from the p-TsOH salt of the compound A contained in the crystal after exposure to the stimulus is 80% or more, 85% or more, 90% or more, 95% or more, 97% or more, 98% or more, 99% or more, 99.5% or more, 99.6% or more, or 99.65% or more. Another example in which such significant change is not observed is that the rate of decrease in the percentage of the crystal of the p-TsOH salt of the compound A in the same crystal form as the crystal of the crystal of the p-TsOH salt of the compound A in this crystal before and after exposure to the stimulus is 10% or less, 5% or less, 3% or less, 1% or less, 0.5% or less, 0.4% or less, 0.3% or less, 0.2% or less, 0.01% or less, or 0.005% or less. In these cases, the percentage (%) may be, for example, the percentage (%) of the peak area (e.g., peak area of absorbance at a wavelength of 230 nm) in HPLC, or may be a mass percentage, or may be the percentage of the peak area in HPLC in one preferred embodiment.

[0026] The crystal of the p-TsOH salt of the compound A being stable against processing in formulation means that, when the crystal is subjected to processing in formulation, such as when the crystal is mixed with an excipient, when the crystal is pulverized, when the crystal is exposed to water, or when the crystal is tableted, the p-TsOH salt of the compound A contained in the crystal does not significantly decompose and the crystal form thereof does not significantly change. An example in which such significant change is not observed is that the percentage of the crystal of the p-TsOH salt of the compound A in the same crystal form as that

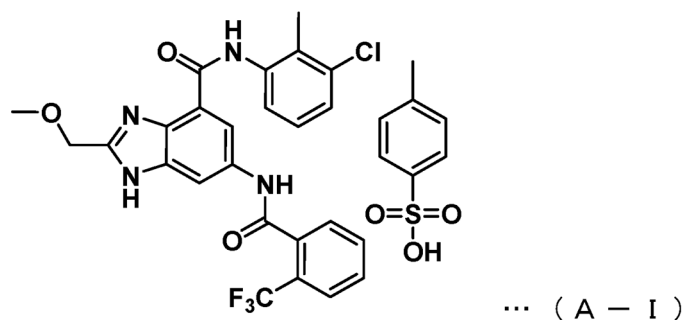
before the processing in a substance derived from the p-TsOH salt of the compound A contained in the crystal after the processing is 80% or more, 85% or more, 90% or more, 95% or more, 97% or more, 98% or more, 99% or more, 99.5% or more, 99.6% or more, or 99.65% or more. Another example in which such significant change is not observed is that the rate of decrease in the percentage of the crystal of the p-TsOH salt of the compound A in the same crystal form as the crystal of the crystal of the p-TsOH salt of the compound A in this crystal before and after the processing is 10% or less, 5% or less, 3% or less, 1% or less, 0.5% or less, 0.4% or less, 0.3% or less, 0.2% or less, 0.01% or less, or 0.005% or less. In these cases, the percentage may be, for example, the percentage (%) of the peak area (e.g., peak area of absorbance at a wavelength of 230 nm) in HPLC, or may be a mass percentage, or may be the percentage (%) of the peak area in HPLC in one preferred embodiment.

[0027] The crystal of the p-TsOH salt of the compound A being in the most stable form out of a plurality of crystal forms of the same compound may mean, for example, when a plurality of crystals of the p-TsOH salt of the compound A are tested for storage stability or stability against formulation processing described above, exhibiting most excellent stability among the tested crystals of the p-TsOH salt of the compound A. The crystal of the p-TsOH salt of the compound A being in the most stable form out of a plurality of crystal forms of the same compound may mean, for example, when a plurality of crystals of the p-TsOH salt of the compound A are caused to be present in equal amounts in one mixed solution and incubated, being in the crystal form that is finally present in the largest quantity in the mixture.

[0028] <Form-III crystal of p-TsOH salt of compound A>

A second aspect of the present disclosure is directed to a Form-III crystal of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate represented by the following formula (A-I):

[Chem. 43]



That is, the second aspect of the present disclosure is directed to a Form-III crystal of the p-TsOH salt of the compound A. In one embodiment, the second aspect of the present disclosure

may be a Form-III crystal of the p-TsOH salt of the compound A produced by a production method according to a sixth aspect of the present disclosure described later.

[0029] The Form-III crystal of the p-TsOH salt of the compound A according to one embodiment of the second aspect of the present disclosure has diffraction peaks at diffraction angles (2θ), diffraction angles ($2\theta \pm 0.1^\circ$), diffraction angles ($2\theta \pm 0.2^\circ$), diffraction angles ($2\theta \pm 0.3^\circ$), diffraction angles ($2\theta \pm 0.4^\circ$), or diffraction angles ($2\theta \pm 0.5^\circ$) of 6.3° , 15.0° , 16.4° , 17.9° , and 22.7° in X-ray powder diffraction. In one preferred embodiment of the second aspect of the present disclosure, the Form-III crystal of the p-TsOH salt of the compound A has diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 6.3° , 15.0° , 16.4° , 17.9° , and 22.7° in X-ray powder diffraction.

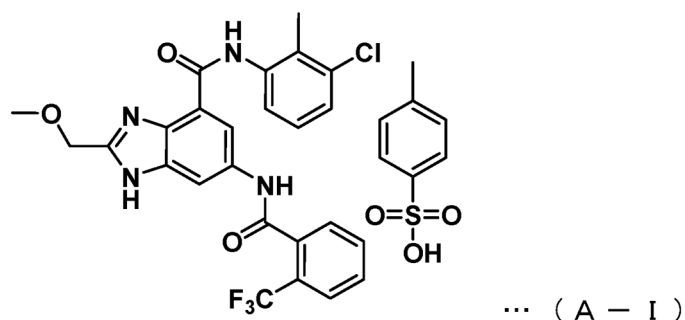
[0030] The Form-III crystal of the p-TsOH salt of the compound A according to one embodiment of the second aspect of the present disclosure has an endothermic peak at $247.4 \pm 3.0^\circ\text{C}$ in differential thermal analysis. The Form-III crystal of the p-TsOH salt of the compound A according to one embodiment of the second aspect of the present disclosure has diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 6.3° , 15.0° , 16.4° , 17.9° , and 22.7° in X-ray powder diffraction, and has an endothermic peak at $247.4 \pm 3.0^\circ\text{C}$ in differential thermal analysis. In addition, the Form-III crystal of the p-TsOH salt of the compound A according to one embodiment of the second aspect of the present disclosure can stably exist for 7 days or longer even under the conditions of a temperature of 40°C and a relative humidity of 75%.

[0031] The Form-III crystal of the p-TsOH salt of the compound A according to one embodiment of the second aspect of the present disclosure has excellent solubility. While not wishing to be bound by any theory, the Form-III crystal of the p-TsOH salt of the compound A has relatively lower stability than the Form-I crystal which is in the most stable form, and thus is considered to require less energy for dissolution thereof and have higher solubility.

[0032] <Form-IV crystal of p-TsOH salt of compound A>

A third aspect of the present disclosure is directed to a Form-IV crystal of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-({[2-(trifluoromethyl)phenyl]carbonyl}amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate represented by the following formula (A-I):

[Chem. 44]



That is, the third aspect of the present disclosure is directed to a Form-IV crystal of the p-TsOH salt of the compound A. In one embodiment, the third aspect of the present disclosure may be a Form-IV crystal of the p-TsOH salt of the compound A produced by a production method according to a seventh aspect of the present disclosure described later.

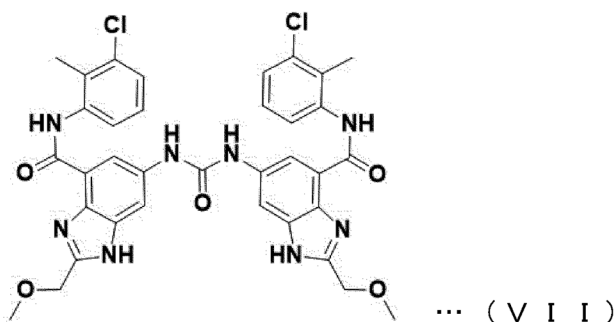
[0033] The Form-IV crystal of the p-TsOH salt of the compound A according to one embodiment of the third aspect of the present disclosure has diffraction peaks at diffraction angles (2θ), diffraction angles ($2\theta \pm 0.1^\circ$), diffraction angles ($2\theta \pm 0.2^\circ$), diffraction angles ($2\theta \pm 0.3^\circ$), diffraction angles ($2\theta \pm 0.4^\circ$), or diffraction angles ($2\theta \pm 0.5^\circ$) of 7.4° , 8.0° , 14.5° , 16.1° , and 20.6° in X-ray powder diffraction. In one preferred embodiment of the third aspect of the present disclosure, the Form-IV crystal of the p-TsOH salt of the compound A has diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 7.4° , 8.0° , 14.5° , 16.1° , and 20.6° in X-ray powder diffraction.

[0034] The Form-IV crystal of the p-TsOH salt of the compound A according to one embodiment of the third aspect of the present disclosure has an endothermic peak at $212.5 \pm 3.0^\circ\text{C}$ in differential thermal analysis. The Form-IV crystal of the p-TsOH salt of the compound A according to one embodiment of the third aspect of the present disclosure has diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 7.4° , 8.0° , 14.5° , 16.1° , and 20.6° in X-ray powder diffraction, and has an endothermic peak at $212.5 \pm 3.0^\circ\text{C}$ in differential thermal analysis.

[0035] <Composition>

A fourth aspect of the present disclosure is a composition containing the Form-I crystal of the p-TsOH salt of the compound A according to the first aspect of the present disclosure, wherein the content of the Form-I crystal of the p-TsOH salt of the compound A is 95 mass% or more of the entire composition, and the content of a compound (hereinafter also referred to as “compound B”) represented by the following formula (VII):

[Chem. 45]



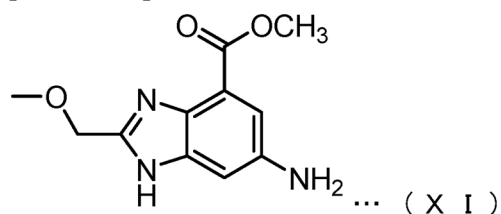
is a predetermined upper limit or less. Another embodiment of the fourth aspect of the present disclosure is a composition containing the Form-I crystal of the p-TsOH salt of the compound A according to the first aspect of the present disclosure and the compound B, wherein the content of the Form-I crystal of the p-TsOH salt of the compound A is 95 mass% or more of the entire composition, and the content of the compound B is a predetermined upper limit or less. The composition according to the fourth aspect of the present disclosure means a composition composed of one or more components contained in any material used in the process of preparing the Form-I crystal of the p-TsOH salt of the compound A and a product by a one-step or multi-step reaction therebetween.

[0036] The compound B may be involved in mutagenicity and may arise in the process of producing the Form-I crystal of the p-TsOH salt of the compound A. In a composition according to one embodiment of the present disclosure, the amount of the compound B is reduced, so that the risk of mutagenicity when this composition is used in the production of a pharmaceutical product can be reduced, and the burden of controlling the contamination amount of the compound B, which is required to be controlled in the order of ppm, can be reduced in the production of the Form-I crystal of the p-TsOH salt of the compound A.

[0037] The content of the compound B in the composition according to one embodiment of the fourth aspect of the present disclosure may be, for example, 1000×10^{-4} mass%, 600×10^{-4} mass%, 300×10^{-4} mass%, 100×10^{-4} mass%, 50×10^{-4} mass%, or 20×10^{-4} mass% of the entire composition in terms of free form. As a specific example, the content of the compound B may be 100×10^{-4} mass% or less in terms of free form. In addition, the content of the p-toluenesulfonate of the compound A in the composition according to one embodiment of the fourth aspect of the present disclosure may be 95 mass% or more, 96 mass% or more, 97 mass% or more, 98 mass% or more, or 99 mass% or more of the entire composition.

[0038] In the composition according to one embodiment of the fourth aspect of the present disclosure, the content of a compound (hereinafter also referred to as “compound C”) represented by the following formula (XI):

[Chem. 46]



is a predetermined upper limit or less in terms of free form, and the predetermined upper limit is, for example, 1000×10^{-4} mass%, 600×10^{-4} mass%, 300×10^{-4} mass%, 100×10^{-4} mass%, 50×10^{-4} mass%, or 20×10^{-4} mass%. As a specific example, the content of the compound C may be 50×10^{-4} mass% or less in terms of free form. The composition according to one preferred embodiment of the fourth aspect of the present disclosure does not contain the compound C.

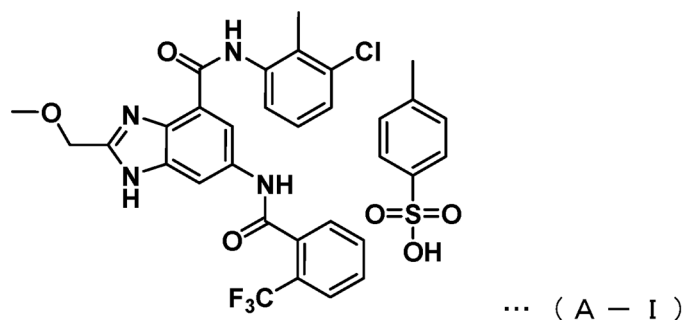
[0039] The compound C is a synthetic intermediate in the case where the compound A is produced by the production method described in PATENT DOCUMENT 1, and it has been clarified that there is a high possibility that the compound C has mutagenicity (genotoxicity), by evaluation using multiple In Silico test software programs capable of predicting mutagenicity (genotoxicity). Therefore, in the composition according to one embodiment of the fourth aspect of the present disclosure, if the content of the compound C is the predetermined upper limit or less or the compound C is not contained, the risk of mutagenicity in a pharmaceutical product for which the composition according to one embodiment of the fourth aspect of the present disclosure is used for production can be reduced, and the burden of controlling the contamination amount of the compound C, which is required to be controlled in the order of ppm, can be reduced in the production of the Form-I crystal of the p-TsOH salt of the compound A.

[0040] <Production method for Form-I crystal of p-TsOH salt of compound A or composition containing the same>

The fifth aspect of the present disclosure is a production method for a Form-I crystal of the p-TsOH salt of the compound A or a composition containing the same. In one embodiment, the fifth aspect of the present disclosure may be a production method for the Form-I crystal of the p-TsOH salt of the compound A according to one embodiment of the first aspect of the present disclosure or the composition according to one embodiment of the fourth aspect of the present disclosure.

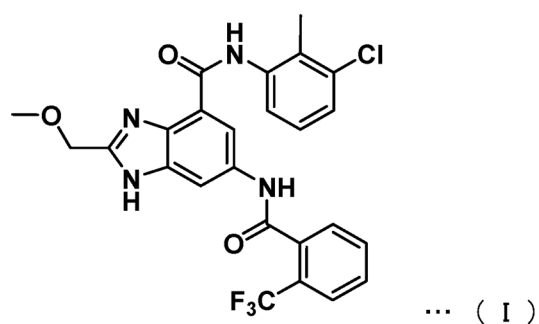
[0041] In one embodiment, the production method according to the fifth aspect of the present disclosure includes a step of obtaining N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-({[2-(trifluoromethyl)phenyl]carbonyl}amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate represented by the following formula (A-I):

[Chem. 47]



(i.e., a p-toluenesulfonate of a compound represented by the following formula (I):

[Chem. 48]



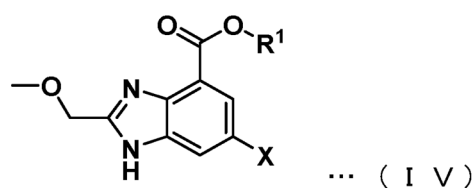
).

One embodiment of such a production method will be described below.

[0042] <First step>

A first step is a step of obtaining a compound represented by the following formula (IV):

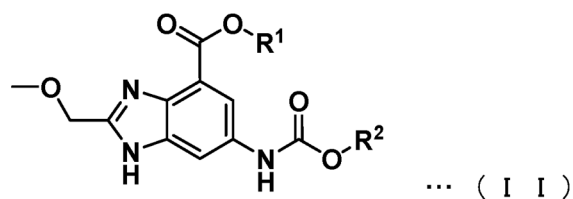
[Chem. 49]



(wherein R¹ represents a protecting group for a carboxyl group or H, and X represents Cl, Br, I, or OTf).

[0043] R¹ in the above formula (IV) is a protecting group for a carboxyl group or H, and preferably a protecting group for a carboxyl group. In the present disclosure, the protecting group for a carboxyl group is not particularly limited as long as the protecting group for a carboxyl group is a group that is not removed in a second/third step described later and that can be removed in a fourth step described later without breaking at least bonds other than urethane bonds in a compound represented by the following formula (II):

[Chem. 50]



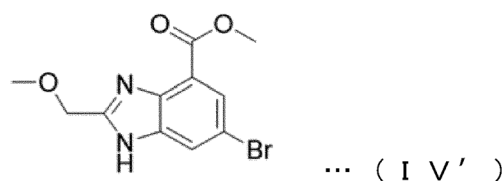
(wherein R^1 is the same as R^1 in the above formula (VI), and R^2 combines with $-O-C(=O)-$ to form a protecting group for an aniline amino group)

to obtain a compound in which R^1 in the above formula (II) is H. R^1 in the above formula (IV) may be, for example, alkyl, cycloalkyl, alkenyl, alkoxymethyl, or a benzyl protecting group, may be C_1 - C_6 alkyl, C_4 - C_6 cycloalkyl, C_1 - C_6 alkenyl, C_1 - C_6 alkoxymethyl (C_1 - C_6 alkoxyated methyl), benzyl, phenethyl, or para-methoxybenzyl in one embodiment, may be C_1 - C_6 alkyl in one preferred embodiment, may be methyl, ethyl, propyl, isopropyl, butyl, tertiary-butyl, pentyl, hexyl, cyclopentyl, cyclohexyl, vinyl, allyl, methoxymethyl, benzyl, or para-methoxybenzyl in another preferred embodiment, may be methyl or ethyl in a more preferred embodiment, and may be methyl in a most preferred embodiment.

[0044] X in the above formula (IV) is Cl, Br, I, or OTf ($O-SO_2-CF_3$), may be Cl, Br, or I in one preferred embodiment, may be Cl or Br in a more preferred embodiment, and may be Br in a most preferred embodiment.

[0045] In a most preferred embodiment, the compound represented by the above formula (IV) may be methyl 6-bromo-2-(methoxymethyl)-1H-benzimidazole-4-carboxylate represented by the following formula (IV'):

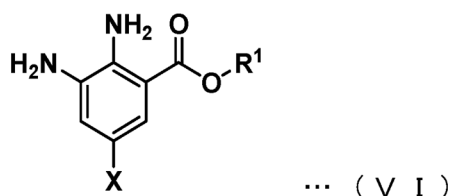
[Chem. 51]



The form of the above formula (IV') obtained in the first step is not particularly limited, and may be the free form in one embodiment.

[0046] In one embodiment, the first step may be a step of bringing a compound represented by the following formula (VI):

[Chem. 52]



(wherein R¹ and X are the same as R¹ and X in formula (IV))

into contact with methoxyacetic acid to obtain the compound represented by the above formula (IV).

[0047] The temperature at which the compound represented by the above formula (VI) is brought into contact with methoxyacetic acid is not particularly limited as long as this temperature is a temperature at which the imidazole ring of the compound represented by the above formula (IV) is formed, and may be 50°C to 150°C, 60°C to 120°C, 70°C to 105°C, or 80°C to 95°C, for example. When the compound represented by the above formula (VI) is brought into contact with methoxyacetic acid, the contact may be achieved in a solvent, or may be achieved by dissolving the compound represented by the above formula (VI) in methoxyacetic acid without using a solvent. In one preferred embodiment, from the viewpoint of causing the reaction with high efficiency, the contact may be achieved by dissolving the compound represented by the above formula (VI) in methoxyacetic acid without using a solvent. When a solvent is used, the solvent may be an organic solvent in which the compound represented by the above formula (VI) and methoxyacetic acid are dissolved and whose boiling point is equal to or lower than the above temperature range, and, for example, N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), etc., are suitable for use as the solvent.

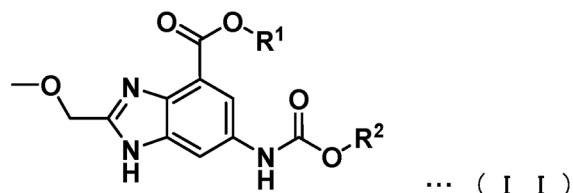
[0048] The reaction time in the contact between the compound represented by the above formula (VI) and methoxyacetic acid is not particularly limited as long as the reaction time is a time that allows the compound represented by the above formula (IV) to be obtained, and may be 5 hours to 20 hours, for example. In addition, during this time, a reaction vessel may be purged with an inert gas such as nitrogen or argon.

[0049] The equivalent relationship between the compound represented by the above formula (VI) and methoxyacetic acid in the contact therebetween is not particularly limited as long as the compound represented by the above formula (IV) can be obtained at a high yield (e.g., a yield of 75% or more) relative to the compound represented by the above formula (VI), which is a raw material. In one embodiment, the equivalent of methoxyacetic acid may be, for example, 1 to 100, 2 to 50, or 4 to 25 equivalents per equivalent of the compound represented by the above formula (VI), and may be 10 equivalents as a specific example.

[0050] <Second/third step>

A second/third step is a step of obtaining a compound represented by the following formula (II):

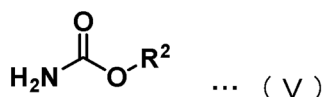
[Chem. 53]



(wherein R^1 is the same as R^1 in the above formula (VI), and R^2 represents a group that combines with $-O-C(=O)-$ to form a protecting group for an aniline amino group).

The second/third step includes bringing the compound represented by the above formula (IV) or its protected product into contact with a compound represented by the following formula (V):

[Chem. 54]



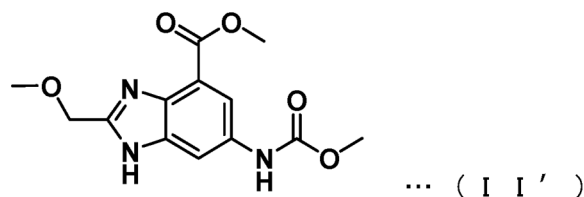
(wherein R^2 is the same as R^2 in the above formula (II))

to obtain the compound represented by the above formula (II) or its protected product.

[0051] R^2 in the above formula (II) represents a group that combines with $-O-C(=O)-$ to form a protecting group for an aniline amino group. The protecting group for an aniline amino group in this case is not particularly limited as long as this protecting group is a protecting group that is not removed in the process of removing R^1 in the above formula (II) to convert R^1 to H in the fourth step described later. R^2 forming such a protecting group for an aniline amino group may be, for example, alkyl, cycloalkyl, alkenyl, or a hydrocarbon group having one or more aromatic rings, may be C_1 - C_6 alkyl, C_4 - C_6 cycloalkyl, C_1 - C_6 alkenyl, benzyl, phenethyl, para-methoxybenzyl, or 9-fluorenylmethyl in one embodiment, may be C_1 - C_6 alkyl in one preferred embodiment, may be methyl, ethyl, propyl, isopropyl, butyl, tertiary-butyl, pentyl, hexyl, cyclopentyl, cyclohexyl, vinyl, allyl, benzyl, phenethyl, or 9-fluorenylmethyl in another preferred embodiment, may be methyl or ethyl in a more preferred embodiment, and may be methyl in a most preferred embodiment.

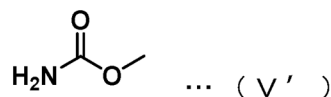
[0052] In a most preferred embodiment, the compound represented by the above formula (II) may be methyl 6-[(methoxycarbonyl)amino]-2-(methoxymethyl)-1H-benzimidazole-4-carboxylate represented by the following formula (II'):

[Chem. 55]



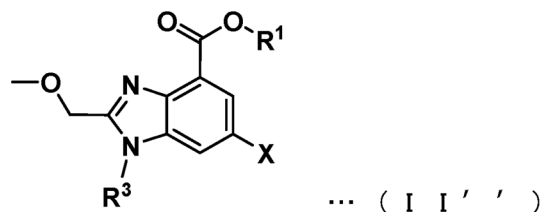
The form of the compound represented by the above formula (II') and obtained in the second/third step is not particularly limited, and in one embodiment, this form may be the form of a salt of an acid used in deprotection of a secondary amino group at 1-position described later, or may be the form of a hydrochloride, for example. In the above most preferred embodiment, the compound represented by the above formula (V) is methyl carbamate represented by the following formula (V'):

[Chem. 56]



[0053] The protected product of the compound represented by the above formula (II) means a compound represented by the following formula (II''):

[Chem. 57]



(wherein R¹ and X are the same as R¹ and X in the above formula (VI), and R³ represents a protecting group for an amino group, and represents, for example, a tertiary-butoxycarbonyl (Boc) group, an allyloxycarbonyl (Alloc) group, a 9-fluorenylmethyloxycarbonyl (Fmoc) group, a trimethylsilyl (TMS) group, or a benzyl group).

[0054] The second/third step includes bringing the compound represented by the above formula (IV) or its protected product into contact with the compound represented by the above formula (V) to obtain the compound represented by the above formula (II) or its protected product. While not wishing to be bound by any theory, a functional group represented by X in the compound represented by the above formula (IV) or its protected product is substituted with the nitrogen atom in the terminal amide of the compound represented by the above formula (V), by Buchwald-Hartwig cross-coupling, to obtain the compound represented by the above formula (II) or its protected product.

[0055] The temperature at which the compound represented by the above formula (IV) or its protected product is brought into contact with the compound represented by the above

formula (V) is not particularly limited as long as the compound represented by the above formula (II) or its protected product can be obtained, and may be 60°C to 120°C, 70°C to 110°C, 80 to 105°C, or 88°C to 97°C, for example. At this time, a solvent used for bringing the compound represented by the above formula (IV) or its protected product into contact with the compound represented by the above formula (V) is not particularly limited as long as the solvent is a solvent whose boiling point is equal to or higher than the above temperature range or that is capable of heating reflux in the above temperature range, and is a solvent that is not reactive with any of the compound represented by the above formula (IV), its protected product, and the compound represented by the above formula (V) in the reaction system. For example, toluene or 1,4-dioxane is suitable for use as the solvent, and the solvent may be toluene in one preferred embodiment. In addition, the time for bringing the compound represented by the above formula (IV) or its protected product into contact with the compound represented by the above formula (V) is not particularly limited, and may be 10 minutes to 168 hours, for example. During this time, the reaction vessel may be purged with an inert gas such as nitrogen or argon.

[0056] The equivalent relationship when bringing the compound represented by the above formula (IV) or its protected product into contact with the compound represented by the above formula (V) is not particularly limited as long as the compound represented by the above formula (II) or its protected product can be obtained at a high yield (e.g., a yield of 85% or more) relative to the compound represented by the above formula (IV) or its protected product which is a starting material. For example, the equivalent of the compound represented by the above formula (V) may be 1 to 5, 1.2 to 4, or 1.5 to 3 equivalents per equivalent of the compound represented by the above formula (IV) or its protected product, and may be 2 equivalents as a specific example.

[0057] In one embodiment, bringing the compound represented by the above formula (IV) or its protected product into contact with the compound represented by the above formula (V) is performed in the presence of a palladium catalyst. The palladium catalyst is not particularly limited as long as the compound represented by the above formula (II) or its protected product can be obtained by bringing the compound represented by the above formula (IV) or its protected product into contact with the compound represented by the above formula (V), and the palladium catalyst may be, for example, a palladium catalyst containing zero-valent palladium (Pd(0)) or a palladium catalyst containing divalent palladium (Pd(2)), and may be a palladium catalyst containing zero-valent palladium (Pd(0)) in one embodiment. Specific examples of the palladium catalyst include tris(dibenzylideneacetone)dipalladium(0) (Pd₂(dba)₃), bis(dibenzylideneacetone)palladium(0) (Pd(dba)₂), palladium(2) acetate, and palladium(2) chloride, and the palladium catalyst may be tris(dibenzylideneacetone)dipalladium(0) in one

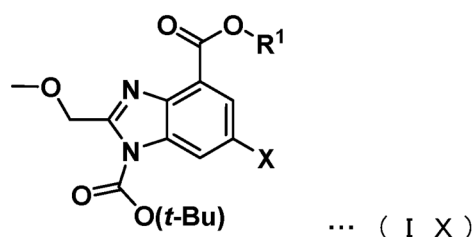
preferred embodiment. The equivalent of the palladium catalyst in bringing the compound represented by the above formula (IV) or its protected product into contact with the compound represented by the above formula (V) may be, for example, 0.0005 to 0.2, 0.001 to 0.1, or 0.003 to 0.05 equivalents per equivalent of the compound represented by the above formula (IV) or its protected product.

[0058] In one embodiment, bringing the compound represented by the above formula (IV) or its protected product into contact with the compound represented by the above formula (V) is performed in the presence of a ligand in addition to the palladium catalyst. The ligand is not particularly limited as long as the compound represented by the above formula (II) or its protected product can be obtained by bringing the compound represented by the above formula (IV) or its protected product into contact with the compound represented by the above formula (V), examples of the ligand include 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos), 1,1'-bis(diphenylphosphino)ferrocene (DPPF), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), and 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos), and the ligand may be, for example, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos) in one preferred embodiment. The equivalent of the ligand in bringing the compound represented by the above formula (IV) or its protected product into contact with the compound represented by the above formula (V) may be, for example, 0.005 to 0.08, 0.008 to 0.05, or 0.01 to 0.04 equivalents per equivalent of the compound represented by the above formula (IV) or its protected product.

[0059] In one embodiment, bringing the compound represented by the above formula (IV) or its protected product into contact with the compound represented by the above formula (V) is performed in the presence of a base in addition to the palladium catalyst and the ligand. The base is not particularly limited as long as the compound represented by the above formula (II) or its protected product can be obtained by bringing the compound represented by the above formula (IV) or its protected product into contact with the compound represented by the above formula (V), and the base may be potassium carbonate, cesium carbonate, potassium hydroxide, sodium tertiary butoxide, or sodium methoxide, for example. The equivalent of the base in bringing the compound represented by the above formula (IV) or its protected product into contact with the compound represented by the above formula (V) may be, for example, 1.5 to 20, 2.0 to 10, or 3.0 to 7.0 equivalents per equivalent of the compound represented by the above formula (IV) or its protected product.

[0060] In one embodiment, the second/third step includes, in the following order, converting the compound represented by the above formula (IV) into a compound represented by the following formula (IX):

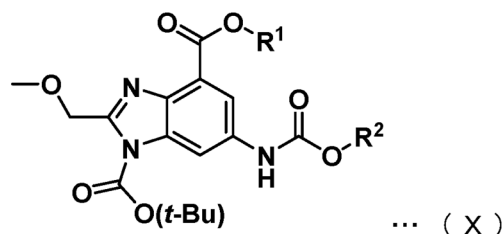
[Chem. 58]



(wherein R^1 is the same as R^1 in the above formula (II), and X is the same as X in the above formula (IV)),

bringing the compound represented by the above formula (IX) into contact with the compound represented by the above formula (V) to obtain a compound represented by the following formula (X):

[Chem. 59]



(wherein R^1 is the same as R^1 in the above formula (II), and R^2 is the same as R^2 in the above formula (V)), and

hydrolyzing the compound represented by the above formula (X) in the presence of an acid to obtain the compound represented by the above formula (II).

[0061] In this case, converting the compound represented by the above formula (IV) into the compound represented by the above formula (IX) can be performed by a method commonly used by those skilled in the art, and may be performed by bringing, for example, about 1.1 to 3 equivalents of di-tert-butyl dicarbonate ((Boc)₂O) into contact with, for example, 1 equivalent of the compound represented by the above formula (IV) and dissolved in an organic solvent such as toluene, at a temperature condition of room temperature to about 60°C. In this case, about 1.2 to 5 equivalents of a base (e.g., potassium carbonate) may be further present in the system.

[0062] In one embodiment, converting the compound represented by the above formula (IV) into the compound represented by the above formula (IX) and bringing the compound represented by the above formula (IX) into contact with the compound represented by the above formula (V) to obtain the compound represented by the above formula (X) in the second/third step may be performed in one reaction vessel (one pot). A specific example may be the case where, after the compound represented by the above formula (IV) is brought into contact with di-tert-butyl dicarbonate in an organic solvent such as toluene in which a base may be dissolved, the

compound represented by the above formula (V), a palladium catalyst, a ligand, and a base are added to the reaction vessel, and the reaction solution is heated to obtain the compound represented by the above formula (X).

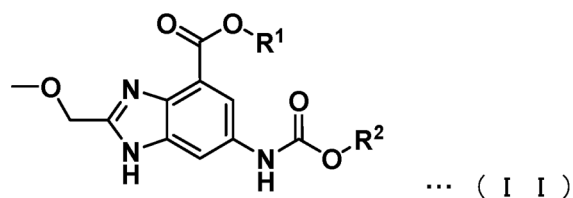
[0063] Hydrolyzing the compound represented by the above formula (X) in the presence of an acid to obtain the compound represented by the above formula (II) can be performed by a method commonly used by those skilled in the art, and can be performed, for example, by bringing an excess amount of an acid such as concentrated hydrochloric acid or trifluoroacetic acid into contact with the above formula (X) in isopropanol (2-propanol), methanol, or acetonitrile. In this case, the reaction solution may be heated to about 50 to 60°C if necessary.

[0064] In one embodiment, hydrolyzing the compound represented by the above formula (X) in the presence of an acid to obtain the compound represented by the above formula (II) may be performed without purification after bringing the compound represented by the above formula (IX) into contact with the compound represented by the above formula (V) to obtain the compound represented by the above formula (X). In this case, this can be performed by filtering the reaction solution obtained after bringing the compound represented by the above formula (IX) into contact with the compound represented by the above formula (V) to obtain the compound represented by the above formula (X), to remove the base such as potassium carbonate, etc., as insoluble material, reducing or drying the solvent by removing the solvent under reduced pressure if necessary, then adding the solvent used for hydrolysis in the presence of an acid, and the acid, and performing incubation.

[0065] <Fourth step>

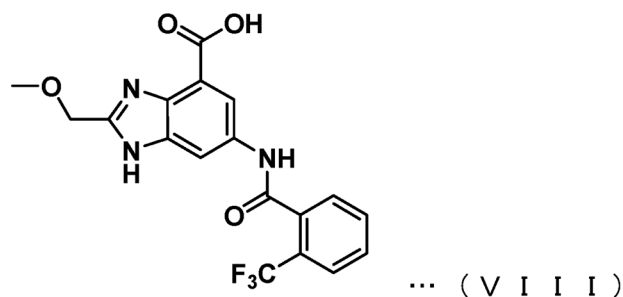
The fourth step is a step of converting a compound represented by the following formula (II):

[Chem. 60]



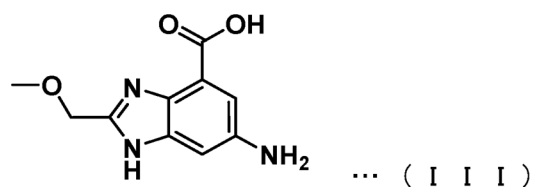
(wherein R^1 represents a protecting group for a carboxyl group or H, and R^2 represents a group that combines with $-O-C(=O)-$ to form a protecting group for an aniline amino group) into a compound represented by the following formula (VIII):

[Chem. 61]



[0066] In one embodiment, the step of converting the compound represented by the above formula (II) into the compound represented by the above formula (VIII) includes converting the compound represented by the above formula (II) into a compound represented by the following formula (III):

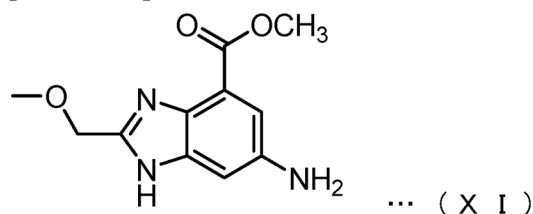
[Chem. 62]



In one preferred embodiment, the step of converting the compound represented by the above formula (II) into the compound represented by the above formula (VIII) includes hydrolyzing the compound represented by the above formula (II) in the presence of a base to obtain the compound represented by the above formula (III).

[0067] Converting the compound represented by the above formula (II) into the compound represented by the above formula (III) can be performed by a method commonly used by those skilled in the art. According to the method including such a step, it is possible to avoid isolation of a compound (compound C) whose mutagenicity is a concern and which is represented by the following formula (XI):

[Chem. 63]



as a powder, so that the risk of mutagenicity due to scattering or the like of the compound C isolated as a powder can be avoided, and the cost in terms of time and money for worker protection and environmental countermeasures (containment) can be reduced. In one embodiment, the step of converting the compound represented by the above formula (II) into the compound represented by the above formula (VIII) includes converting the compound

represented by the above formula (II) into the compound represented by the above formula (III), and the compound represented by the formula (III) is obtained as a solution thereof. In one embodiment, the step of converting the compound represented by the above formula (II) into the compound represented by the above formula (VIII) includes hydrolyzing the compound represented by the above formula (II) in the presence of a base to obtain the compound represented by the above formula (III) as a solution thereof. In one embodiment, the step of converting the compound represented by the above formula (II) into the compound represented by the above formula (VIII) does not include isolating the compound represented by the above formula (III) as a powder. In one embodiment, the step of converting the compound represented by the above formula (II) into the compound represented by the above formula (VIII) does not include handling the compound represented by the above formula (III) in a state other than a solution thereof.

[0068] Hydrolyzing the compound represented by the above formula (II) by a base can be performed under conditions commonly employed by those skilled in the art, and an example thereof is to add the compound represented by the above formula (II) or its salt (e.g., hydrochloride) to a sodium hydroxide solution having a concentration of about 5 to 30 mass% or 10 to 25 mass%, and stir the mixture at a temperature condition of about 40 to 70°C or 50 to 60°C. The reaction time is not particularly limited, may be, for example, 10 minutes to 72 hours, 1 to 24 hours, or 2 to 12 hours, and may be 6 hours as an example.

[0069] In one embodiment of the present disclosure, the step of converting the compound represented by the above formula (II) into the compound represented by the above formula (VIII) includes converting the compound represented by the above formula (III) into the compound represented by the above formula (VIII) after converting the compound represented by the above formula (II) into the compound represented by the above formula (III). Converting the compound represented by the above formula (III) into the compound represented by the above formula (VIII) can be performed by a method commonly used by those skilled in the art, and may be performed, for example, by a method of bringing an acid halide such as an acid chloride or acid bromide of 2-(trifluoromethyl)benzoic acid into contact with the compound represented by the above formula (VIII) to amidate the aniline amino group in the compound represented by the above formula (VIII), or may be performed by a method of bringing 2-(trifluoromethyl)benzoic acid into contact with the compound represented by the above formula (VIII) in the presence of a condensing agent such as HATU (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate) to amidate the aniline amino group in the compound represented by the above formula (VIII). Among them, from the viewpoint of avoiding a reduction in yield due to byproducts being produced due to the

involvement of the carboxyl group of the compound represented by the above formula (VIII) in the amide formation, it is preferable that converting the compound represented by the above formula (III) into the compound represented by the above formula (VIII) is performed by the method of bringing an acid halide such as an acid chloride or acid bromide of 2-(trifluoromethyl)benzoic acid into contact with the compound represented by the above formula (VIII) to amidate the aniline amino group in the compound represented by the above formula (VIII), and this may be performed, for example, by bringing the compound represented by the above formula (VIII) into contact with 2-(trifluoromethyl)benzoyl chloride.

[0070] In the above case, a solvent normally selected by those skilled in the art may be used as a solvent in bringing an acid halide of 2-(trifluoromethyl)benzoic acid into contact with the compound represented by the above formula (VIII), and the solvent may be, for example, acetonitrile or a mixed solvent of acetonitrile and water. The temperature in the reaction is not particularly limited as long as the temperature is a temperature at which the compound represented by the above formula (VIII) is formed, and may be, for example, -10°C to 20°C, -10°C to 10°C, or -5°C to 5°C, and the reaction time is also not particularly limited as long as the reaction time is a time for which the compound represented by the above formula (VIII) is formed, and may be, for example, 1 minute to 3 hours, 5 minutes to 1 hour, or 10 minutes to 30 minutes. In addition, from the viewpoint of increasing the yield by decomposing compounds obtained by reaction of multiple molecules of the acid halide of 2-(trifluoromethyl)benzoic acid which is a byproduct, the reaction solution may be further incubated, for example, at a temperature of 50 to 80°C or 60 to 70°C, for example, for 5 minutes to 12 hours, 15 minutes to 6 hours, or 30 minutes to 4 hours after the reaction under the above conditions. In addition, the equivalent relationship between the acid halide of 2-(trifluoromethyl)benzoic acid and the compound represented by the above formula (VIII) is not particularly limited as long as the compound represented by the above formula (III) is obtained at a high yield (e.g., a yield of 80% or more) relative to the compound represented by the above formula (VIII). For example, the equivalent of the acid halide of 2-(trifluoromethyl)benzoic acid may be 0.90 to 1.50, 0.95 to 1.30, 0.97 to 1.10, or 0.99 to 1.01 equivalents per equivalent of the compound represented by the above formula (VIII). In addition, in the reaction system, a compound having a carboxyl group, such as acetic acid, may be further present in about 1 equivalent (e.g., 0.7 to 1.5 or 0.9 to 1.1 equivalents) relative to the compound represented by the above formula (VIII).

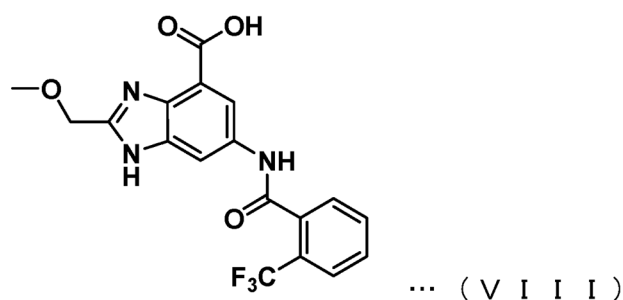
[0071] In one embodiment, converting the compound represented by the above formula (II) into the compound represented by the above formula (III) and converting the compound represented by the above formula (III) into the compound represented by the above formula (VIII) may be performed in one reaction vessel (one pot). In this case, for example, after the

compound represented by the above formula (II) is converted into the compound represented by the above formula (III), acetonitrile, water, acetic acid, and an acid halide of 2-(trifluoromethyl)benzoic acid may be further added to the reaction solution.

[0072] <Fifth step>

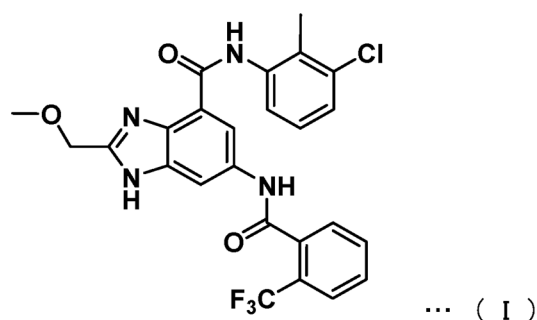
A fifth step is a step of converting a compound represented by the following formula (VIII):

[Chem. 64]



into an N,N-dimethylacetamide solvate of a compound (compound A) represented by the following formula (I):

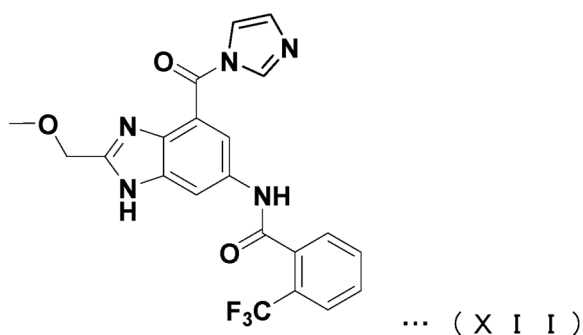
[Chem. 65]



In one embodiment, the fifth step includes converting the compound represented by the above formula (VIII) into the compound represented by the above formula (I), and bringing the compound represented by the above formula (I) into contact with N,N-dimethylacetamide to obtain the N,N-dimethylacetamide solvate of the compound represented by the above formula (I).

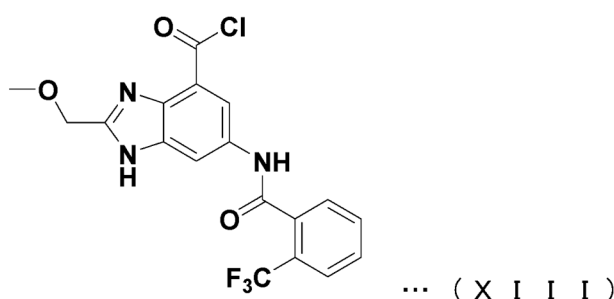
[0073] Converting the compound represented by the above formula (VIII) into the compound represented by the above formula (I) can be performed by a method commonly used by those skilled in the art, and can be performed, for example, by bringing a compound obtained by bringing the compound represented by the above formula (VIII) into contact with 1,1'-carbonyldiimidazole (CDI) or the like and represented by the following formula (XII):

[Chem. 66]



or an acid halide derivative such as a compound obtained by bringing the compound represented by the above formula (VIII) into contact with thionyl chloride or the like and represented by the following formula (XIII):

[Chem. 67]



into contact with 3-chloro-2-methylaniline. For example, this can be performed by bringing the compound represented by the above formula (VIII) into contact with 3-chloro-2-methylaniline in the presence of a condensing agent such as HATU or DMTMM (4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride), and in one preferred embodiment, this can be performed by bringing the compound obtained by bringing the compound represented by the above formula (VIII) into contact with CDI and represented by the above formula (XII) into contact with 3-chloro-2-methylaniline.

[0074] The solvent in bringing the compound represented by the above formula (VIII) into contact with CDI may be a solvent that is not reactive with the compound represented by the above formula (VIII) and CDI, and, for example, N,N-dimethylformamide, N,N-dimethylacetamide, etc., are suitable for use as the solvent. In addition, the temperature and the time for bringing the compound represented by the above formula (VIII) into contact with CDI are not particularly limited as long as the compound represented by the above formula (XII) can be obtained, and the reaction may be carried out at a temperature condition of 5 to 50°C, 10 to 40°C or 20 to 30°C for 10 minutes to 24 hours, 20 minutes to 6 hours, or 30 minutes to 2 hours, for example. The equivalent relationship in bringing the compound represented by the above formula (VIII) into contact with CDI is not particularly limited as long as the compound represented by the above formula (XII) can be obtained at a high yield (e.g., a yield of 90% or

more) from the compound represented by the above formula (VIII), and the equivalent of CDI may be, for example, 1.00 to 2.00, 1.05 to 1.40, or 1.10 to 1.20 equivalents per equivalent of the compound represented by the above formula (VIII).

[0075] The solvent in bringing the compound represented by the above formula (XII) into contact with 3-chloro-2-methylaniline may be a solvent that is not reactive with the compound represented by the above formula (XII) and 3-chloro-2-methylaniline, and, for example, N,N-dimethylformamide, N,N-dimethylacetamide, etc., are suitable for use as the solvent. In addition, the temperature and the time for bringing the compound represented by the above formula (XII) into contact with 3-chloro-2-methylaniline are not particularly limited as long as the compound represented by the above formula (I) can be obtained, and reaction may be carried out at a temperature of 40 to 70°C or 50 to 60°C for 10 minutes to 168 hours, 1 to 72 hours, or 6 to 30 hours, for example. The equivalent relationship in bringing the compound represented by the above formula (XII) into contact with 3-chloro-2-methylaniline is not particularly limited as long as the compound represented by the above formula (I) can be obtained at a high yield (e.g., a yield of 90% or more) relative to the compound represented by the above formula (XII), and the equivalent of 3-chloro-2-methylaniline may be, for example, 1.1 to 10, 1.5 to 5.0, or 2.0 to 3.0 per equivalent of the compound represented by the above formula (XII). In addition, bringing the compound represented by the above formula (XII) into contact with 3-chloro-2-methylaniline may be carried out in the presence of a compound having a carboxyl group such as benzoic acid.

[0076] Bringing the compound represented by the above formula (VIII) into contact with CDI and bringing the compound represented by the above formula (XII) into contact with 3-chloro-2-methylaniline may be performed in one reaction vessel (one pot). In this case, for example, this may be performed by bringing the compound represented by the above formula (VIII) into contact with CDI in N,N-dimethylformamide, and then adding 3-chloro-2-methylaniline and benzoic acid into the reaction solution.

[0077] Bringing the compound represented by the above formula (I) into contact with N,N-dimethylacetamide to obtain the N,N-dimethylacetamide solvate of the compound represented by the above formula (I) can be performed by a method commonly used by those skilled in the art, and can be performed, for example, by adding DMA or a mixed solution containing DMA (e.g., a mixed solution of DMA and water) to a solvent in which the compound represented by the above formula (I) in any form (e.g., the free form of the compound represented by the above formula (I)) is dissolved, and performing incubation. In one embodiment, this may be performed by adding a mixed solution of DMA and water to the solution after bringing the compound represented by the above formula (XII) into contact with 3-

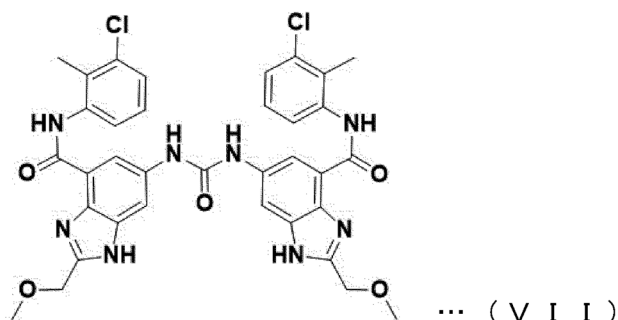
chloro-2-methylaniline. In this case, the temperature condition may be, for example, 40 to 70°C or 50 to 60°C, and the incubation time may be, for example, 10 minutes to 24 hours.

[0078] By the fourth step and the fifth step described above, the N,N-dimethylacetamide solvate of the compound represented by the above formula (I) is obtained with the compound represented by the above formula (II), as a starting material. That is, in one embodiment, it can be said that a step of converting the compound represented by the above formula (II) into the N,N-dimethylacetamide solvate of the compound represented by the above formula (I), is performed by a combination of the fourth step and the fifth step.

[0079] <Sixth step>

A sixth step is a step of purifying a crude product of the N,N-dimethylacetamide solvate of the compound (compound A) represented by the above formula (I), by recrystallization. In one embodiment, the sixth step is a step of purifying the N,N-dimethylacetamide solvate of the compound represented by the above formula (I) and obtained in the fifth step, by recrystallization. Recrystallization of the crude product of the N,N-dimethylacetamide solvate of the compound represented by the above formula (I) may be performed in N,N-dimethylacetamide or a mixed solvent containing N,N-dimethylacetamide, and may be performed in a mixed solvent of N,N-dimethylacetamide and water in one embodiment. Also, in one preferred embodiment, recrystallization of the crude product of the N,N-dimethylacetamide solvate of the compound represented by the above formula (I) may be performed in a mixed solvent of N,N-dimethylacetamide and water in which the content of N,N-dimethylacetamide is 50 vol% or more, 60 vol% or more, 70 vol% or more, 75 vol% or more, or 78 vol% or more and is 99 vol% or less, 95 vol% or less, 90 vol% or less, or 80 vol% or less, and may be performed, for example, in a mixed solvent of N,N-dimethylacetamide and water in which the content of N,N-dimethylacetamide is 75 vol% or more, or is 75 vol% or more and 99 vol% or less. If recrystallization is performed in such a solvent, the N,N-dimethylacetamide solvate of the compound represented by the above formula (I) can be obtained at a high yield and a high purity. Also, if recrystallization is performed in such a solvent, a refined product, of the N,N-dimethylacetamide solvate of the compound represented by the above formula (I), in which the content of a compound (hereinafter also referred to as “compound B”) which is formed in the process of production, which may be involved in mutagenicity, and which is represented by the following formula (VII):

[Chem. 68]



is reduced. In particular, if a mixed solvent of N,N-dimethylacetamide and water in which the content of N,N-dimethylacetamide is 70 vol% or more, 75 vol% or more, or 78 vol% or more is used, a refined product, of the N,N-dimethylacetamide solvate of the compound represented by the above formula (I), in which the content of the compound B is further reduced, can be obtained. In these cases, the content of the compound B being reduced may be that the content of the compound B in the refined product (crystal) obtained by recrystallization is, for example, 1800×10^{-4} mass% or less, 1000×10^{-4} mass% or less, 500×10^{-4} mass% or less, 400×10^{-4} mass% or less, 300×10^{-4} mass% or less, 200×10^{-4} mass% or less, or 170×10^{-4} mass% or less, and, in particular, if a mixed solvent of N,N-dimethylacetamide and water in which the content of N,N-dimethylacetamide is 70 vol% or more, 75 vol% or more, or 78 vol% or more is used, a refined product (crystal) in which the content of the compound B is, for example, 1000×10^{-4} mass% or less, 500×10^{-4} mass% or less, 400×10^{-4} mass% or less, 300×10^{-4} mass% or less, 200×10^{-4} mass% or less, or 170×10^{-4} mass% or less, can be obtained.

[0080] <Seventh step>

A seventh step is a step of converting the N,N-dimethylacetamide solvate of the compound (compound A) represented by the above formula (I) into a p-toluenesulfonate of the compound (compound A) represented by the above formula (I). In one embodiment, the seventh step is a step of converting the refined product (crystal) of the N,N-dimethylacetamide solvate of the compound represented by the above formula (I) obtained in the sixth step into the p-toluenesulfonate of the compound represented by the above formula (I). The seventh step is normally performed by bringing the N,N-dimethylacetamide solvate of the compound represented by the above formula (I) into contact with p-toluenesulfonic acid (tosic acid, 4-methylbenzenesulfonate). The conditions for bringing the N,N-dimethylacetamide solvate of the compound represented by the above formula (I) into contact with p-toluenesulfonic acid are not particularly limited as long as the N,N-dimethylacetamide solvate of the compound represented by the above formula (I) is converted into the p-toluenesulfonate of the compound represented by the above formula (I), and the solvent may be, for example, N,N-

dimethylformamide, acetonitrile, or a mixed solvent thereof, and may be a mixed solvent of N,N-dimethylformamide and acetonitrile (e.g., a mixed solvent with a mass ratio of about 1:6) as a specific example. The temperature for this contact may be, for example, 30 to 70°C or 45 to 60°C. The time for this contact may be, for example, 10 minutes to 24 hours, or 1 hour to 12 hours. In addition, the form of p-toluenesulfonic acid to be added is not particularly limited, and p-toluenesulfonic acid may be added to the solvent as a hydrate, for example. As for the equivalent relationship in the reaction system, the equivalent of p-toluenesulfonic acid or its hydrate may be, for example, 1.01 to 2.00, 1.03 to 1.50, or 1.05 to 1.20 equivalents per equivalent of the N,N-dimethylacetamide solvate of the compound represented by the above formula (I).

[0081] <Eighth step>

An eighth step is a step of obtaining a Form-I crystal of the p-TsOH salt of the compound A from a crude product of the p-toluenesulfonate (p-TsOH salt) of the compound (compound A) represented by the above formula (I). In one embodiment, the eighth step is a step of obtaining a Form-I crystal of the p-TsOH salt of the compound A from a crude product of the p-toluenesulfonate of the compound represented by the above formula (I) obtained in the seventh step. In one embodiment, the eighth step includes purifying the p-toluenesulfonate of the compound represented by the above formula (I) by bringing the p-toluenesulfonate into contact with activated carbon, and recrystallizing the p-toluenesulfonate of the compound represented by the above formula (I) after being brought into contact with the activated carbon, to obtain a Form-I crystal of the p-TsOH salt of the compound A, in this order.

[0082] Purifying the p-toluenesulfonate of the compound represented by the above formula (I) by bringing the p-toluenesulfonate into contact with activated carbon is performed by adding activated carbon to a solution of the p-toluenesulfonate of the compound represented by the above formula (I), incubating the solution, and then removing the activated carbon by filtration or the like. The solvent is not particularly limited as long as the p-toluenesulfonate of the compound represented by the above formula (I) is dissolved in the solvent and the form of the salt is maintained, and, for example, N,N-dimethylformamide is suitable for use as the solvent. The contact may be performed, for example, at a temperature condition of about 30 to 60°C or 40 to 50°C for about 5 minutes to 24 hours or 10 minutes to 6 hours, and a specific example is 1 hour. The amount of the activated carbon to be brought into contact with the p-toluenesulfonate of the compound represented by the above formula (I) may be, for example, 0.04 times or more, 0.05 times or more, 0.08 times or more, 0.09 times or more, 0.10 times or more, 0.14 times or more, or 0.15 times or more the mass of the p-toluenesulfonate of the compound, may be 1.00 times or less, 0.50 times or less, or 0.20 times or less the mass of the p-

toluenesulfonate of the compound, and may be 0.08 times or more the mass of the p-toluenesulfonate of the compound in one preferred embodiment. If the amount of the activated carbon to be brought into contact with the p-toluenesulfonate of the compound represented by the above formula (I) is the above lower limit or more, the compound B, which is an impurity that may be involved in mutagenicity, can be efficiently removed.

[0083] Recrystallizing the p-toluenesulfonate of the compound represented by the above formula (I) after being brought into contact with the activated carbon, to obtain a Form-I crystal of the p-TsOH salt of the compound A, can be performed by a method commonly used by those skilled in the art. In one embodiment, this may be performed by adding, if necessary, a seed crystal of the p-toluenesulfonate of the compound represented by the above formula (I) to a filtrate obtained by removing the activated carbon by filtration after purifying the p-toluenesulfonate of the compound represented by the above formula (I) by bringing the p-toluenesulfonate into contact with activated carbon, and then heating and cooling the filtrate.

[0084] If the eighth step includes purifying the p-toluenesulfonate of the compound represented by the above formula (I) by bringing the p-toluenesulfonate into contact with activated carbon, and recrystallizing the p-toluenesulfonate of the compound represented by the above formula (I) after being brought into contact with the activated carbon, to obtain the Form-I crystal of the p-TsOH salt of the compound A in this order, the content of the compound B, which is an impurity that may be involved in mutagenicity, in the refined product (Form-I crystal of the p-TsOH salt of the compound A) obtained by recrystallization can be significantly reduced compared to the case where only recrystallization is performed. More specifically, the content of the compound B in the refined product (Form-I crystal of the p-TsOH salt of the compound A) obtained by recrystallization can be reduced to 100×10^{-4} mass% or less, 70×10^{-4} mass% or less, 50×10^{-4} mass% or less, 40×10^{-4} mass% or less, 30×10^{-4} mass% or less, 20×10^{-4} mass% or less, 15×10^{-4} mass% or less, 12×10^{-4} mass% or less, or 10×10^{-4} mass% or less.

[0085] <Embodiments of production method according to fifth aspect>

One embodiment of the fifth aspect of the present disclosure can be a production method for a Form-I crystal of the p-TsOH salt of the compound A or a composition containing the same, including at least one of the steps described above. One specific embodiment of the fifth aspect of the present disclosure can be a production method for a Form-I crystal of the p-TsOH salt of the compound A or a composition containing the same, including the seventh step. One embodiment of the fifth aspect of the present disclosure can be a production method for a Form-I crystal of the p-TsOH salt of the compound A or a composition containing the same, including the fourth step and the seventh step in this order. One embodiment of the fifth aspect of the present disclosure can be a production method for a Form-I crystal of the p-TsOH salt of

the compound A or a composition containing the same, including the second/third step, the fourth step, and the seventh step in this order. One embodiment of the fifth aspect of the present disclosure can be a production method for a Form-I crystal of the p-TsOH salt of the compound A or a composition containing the same, including the fourth step, the fifth step, and the seventh step in this order. One embodiment of the fifth aspect of the present disclosure can be a production method for a Form-I crystal of the p-TsOH salt of the compound A or a composition containing the same, including the second/third step, the fourth step, the fifth step, and the seventh step in this order. One embodiment of the fifth aspect of the present disclosure can be a production method for a Form-I crystal of the p-TsOH salt of the compound A or a composition containing the same, including the first step, the second/third step, the fourth step, the fifth step, and the seventh step in this order. One embodiment of the fifth aspect of the present disclosure can be a production method for a Form-I crystal of the p-TsOH salt of the compound A or a composition containing the same, further including the sixth step immediately before the seventh step in these embodiments. One embodiment of the fifth aspect of the present disclosure can be a production method for a Form-I crystal of the p-TsOH salt of the compound A or a composition containing the same, further including the eighth step immediately after the seventh step in these embodiments.

[0086] <Production method for Form-III crystal of p-TsOH salt of compound A>

The sixth aspect of the present disclosure is a production method for a Form-III crystal of the p-TsOH salt of the compound A. In one embodiment, the sixth aspect of the present disclosure may be a production method for the Form-III crystal of the p-TsOH salt of the compound A according to one embodiment of the second aspect of the present disclosure. In one embodiment, the sixth aspect of the present disclosure may be a production method for a Form-III crystal of the p-TsOH salt of the compound A, including a step of producing a Form-I crystal of the p-TsOH salt of the compound A by the production method according to one embodiment of the fifth aspect of the present disclosure.

[0087] The sixth aspect of the present disclosure may include a step of exposing the p-TsOH salt of the compound A to a temperature condition equal to or higher than a predetermined lower limit in one embodiment, may include a step of exposing a Form-I crystal of the p-TsOH salt of the compound A to a temperature condition equal to or higher than a predetermined lower limit in one preferred embodiment, and may include a step of exposing a Form-I crystal of the p-TsOH salt of the compound A in a solid state to a temperature condition equal to or higher than a predetermined lower limit in a more preferred embodiment. The predetermined lower limit in these cases may be, for example, 130°C, 140°C, 150°C, or 160°C. In one preferred embodiment, the Form-I crystal of the p-TsOH salt of the compound A to be exposed to a

temperature condition equal to or higher than a predetermined lower limit may be a crystal produced by the production method according to one embodiment of the fifth aspect of the present disclosure. That is, a production method according to one preferred embodiment of the sixth aspect of the present disclosure may be a production method for a Form-III crystal of the p-TsOH salt of the compound A, including a step of producing a Form-I crystal of the p-TsOH salt of the compound A by the production method according to one embodiment of the fifth aspect of the present disclosure, and a step of exposing the obtained Form-I crystal of the p-TsOH salt of the compound A to a temperature condition equal to or higher than a predetermined lower limit. In another embodiment, the p-TsOH salt of the compound A to be exposed to a temperature condition equal to or higher than a predetermined lower limit may be an amorphous substance obtained from the p-TsOH salt of the compound A produced by a production method including at least the seventh step out of the steps of the production method according to one embodiment of the fifth aspect of the present disclosure. That is, a production method according to one embodiment of the seventh aspect of the present disclosure may be a production method for a Form-III crystal of the p-TsOH salt of the compound A, including a step of producing an amorphous substance obtained from the p-TsOH salt of the compound A produced by a production method including at least the seventh step out of the steps of the production method according to one embodiment of the fifth aspect of the present disclosure, and a step of exposing the obtained amorphous substance of the p-TsOH salt of the compound A to a temperature condition equal to or higher than a predetermined lower limit.

[0088] <Production method for Form-IV crystal of p-TsOH salt of compound A>

The seventh aspect of the present disclosure is a production method for a Form-IV crystal of the p-TsOH salt of the compound A. In one embodiment, the seventh aspect of the present disclosure may be a production method for the Form-IV crystal of the p-TsOH salt of the compound A according to one embodiment of the third aspect of the present disclosure. In one embodiment, the seventh aspect of the present disclosure may be a production method for a Form-IV crystal of the p-TsOH salt of the compound A, including a step of producing a Form-I crystal of the p-TsOH salt of the compound A by the production method according to one embodiment of the fifth aspect of the present disclosure. In one embodiment, the seventh aspect of the present disclosure may be a production method for a Form-IV crystal of the p-TsOH salt of the compound A, including a step of producing an amorphous substance of the p-TsOH salt of the compound A by a production method including at least the seventh step out of the steps of the production method according to one embodiment of the fifth aspect of the present disclosure.

[0089] In one embodiment, the seventh aspect of the present disclosure may include a

step of exposing the p-TsOH salt of the compound A to a temperature condition equal to or higher than a predetermined lower limit after bringing the p-TsOH salt of the compound A into contact with acetonitrile, and may include a step of exposing a Form-I crystal of the p-TsOH salt of the compound A to a temperature condition equal to or higher than a predetermined lower limit after bringing the Form-I crystal of the p-TsOH salt of the compound A into contact with acetonitrile. The predetermined lower limit in these cases may be, for example, 90°C, 100°C, 110°C, 120°C, 130°C, 140°C, 150°C, or 160°C. In one embodiment, the Form-I crystal of the p-TsOH salt of the compound A to be exposed to a temperature condition equal to or higher than a predetermined lower limit may be a crystal produced by the production method according to one embodiment of the fifth aspect of the present disclosure. That is, a production method according to one embodiment of the seventh aspect of the present disclosure may be a production method for a Form-IV crystal of the p-TsOH salt of the compound A, including a step of producing a Form-I crystal of the p-TsOH salt of the compound A by the production method according to one embodiment of the fifth aspect of the present disclosure, and a step of exposing the obtained Form-I crystal of the p-TsOH salt of the compound A to a temperature condition equal to or higher than a predetermined lower limit after bringing the obtained Form-I crystal of the p-TsOH salt of the compound A into contact with acetonitrile. In another embodiment, the p-TsOH salt of the compound A to be exposed to a temperature condition equal to or higher than a predetermined lower limit may be an amorphous substance obtained from the p-TsOH salt of the compound A produced by a production method including at least the seventh step out of the steps of the production method according to one embodiment of the fifth aspect of the present disclosure. That is, a production method according to one embodiment of the seventh aspect of the present disclosure may be a production method for a Form-IV crystal of the p-TsOH salt of the compound A, including a step of producing an amorphous substance obtained from the p-TsOH salt of the compound A produced by a production method including at least the seventh step out of the steps of the production method according to one embodiment of the fifth aspect of the present disclosure, and a step of exposing the obtained amorphous substance of the p-TsOH salt of the compound A to a temperature condition equal to or higher than a predetermined lower limit after bringing the obtained amorphous substance of the p-TsOH salt of the compound A into contact with acetonitrile.

[0090] <Pharmaceutical composition and inhibitor>

An eighth aspect of the present disclosure is a pharmaceutical composition containing, as an active ingredient, the crystal according to one embodiment of the first aspect of the present disclosure, the crystal according to one embodiment of the second aspect of the present disclosure, the crystal according to one embodiment of the third aspect of the present

disclosure, or the composition according to one embodiment of the fourth aspect of the present disclosure. In the present disclosure, the pharmaceutical composition means a composition administered for the purpose of treatment and/or prevention in a subject to whom the composition is administered. A ninth aspect of the present disclosure is a membrane-bound prostaglandin E synthase-1 inhibitor (mPGES-1 inhibitor) containing, as an active ingredient, the crystal according to one embodiment of the first aspect of the present disclosure, the crystal according to one embodiment of the second aspect of the present disclosure, the crystal according to one embodiment of the third aspect of the present disclosure, or the composition according to one embodiment of the fourth aspect of the present disclosure.

[0091] A pharmaceutical composition according to one embodiment of the eighth aspect of the present disclosure and an inhibitor according to one embodiment of the ninth aspect of the present disclosure may each be formulated as a formulation for treatment and/or prevention, and the form of the formulation is not particularly limited, and may be, for example, a tablet, capsule, powder, granule, or fine granule formulation. The pharmaceutical composition according to one embodiment of the eighth aspect of the present disclosure, the inhibitor according to one embodiment of the ninth aspect, and formulations each containing the pharmaceutical composition or the inhibitor may be administered orally or parenterally. The doses of the pharmaceutical composition according to one embodiment of the eighth aspect of the present disclosure, the inhibitor according to one embodiment of the ninth aspect, and the formulations each containing the pharmaceutical composition or the inhibitor are preferably adjusted taking into consideration the conditions of a patient such as age, weight, and type and severity of disease, an administration route, etc. Normally, the effective amount of the p-TsOH salt of the compound A for adult, in the case of oral administration, is suitably within a range of 0.01 mg to 5 g/day, and preferably 1 mg to 500 mg/day. In some cases, a smaller amount may be sufficient or a larger amount may be required. Usually, the dosage can be administered once a day or can be divided and administered several times a day, or in the case of intravenous administration, the dosage can be administered rapidly or sustainably within 24 hours.

[0092] The pharmaceutical composition according to one embodiment of the eighth aspect of the present disclosure and the inhibitor according to one embodiment of the ninth aspect of the present disclosure may each contain a pharmaceutically acceptable additive in addition to the crystal according to one embodiment of the first aspect of the present disclosure, the crystal according to one embodiment of the second aspect of the present disclosure, the crystal according to one embodiment of the third aspect of the present disclosure, or the composition according to one embodiment of the fourth aspect of the present disclosure, which are active ingredients, and may each contain, for example, an excipient, a buffer, a stabilizer, an

antioxidant, a binder, a disintegrant, a filler, an emulsifier, or a flow control additive, or at least one additive selected from the group consisting of these additives.

[0093] The pharmaceutical composition according to one embodiment of the eighth aspect of the present disclosure, the inhibitor according to one embodiment of the ninth aspect of the present disclosure, and the formulations each containing the pharmaceutical composition or the inhibitor can be used, by virtue of the mPGES-1 inhibitory activity of the p-TsOH salt of the compound A, for example, as a preventive agent or a therapeutic agent for inflammatory colitis, irritable bowel syndrome, migraine headache, headache, lumbago, lumbar spinal canal stenosis, herniated disc, temporomandibular joint disorder, cervicobrachial syndrome, cervical spondylosis, endometriosis, adenomyosis, preterm labor, threatened preterm labor, dysmenorrhea, overactive bladder, nocturia, interstitial cystitis, neurodegenerative diseases (e.g., Alzheimer's disease, multiple sclerosis), psoriasis, rheumatoid arthritis, rheumatic fever, fibromyalgia, neuralgia, complex regional pain syndrome, myofascial disorders, viral infections (e.g., influenza, cold, herpes zoster, AIDS), bacterial infections, fungal infections, inflammation and pain after burns, surgery, injury, and tooth extraction, malignancies (e.g., leukemia, malignant lymphomas, multiple myeloma, myelodysplastic syndrome, head and neck cancer, esophageal cancer, esophageal adenocarcinoma, gastric cancer, duodenal cancer, colon cancer, colonic cancer, rectal cancer, liver cancer, gallbladder/bile duct cancer, biliary tract cancer, pancreatic cancer, thyroid cancer, breast cancer, lung cancer, ovarian cancer, cervical cancer, uterine body cancer, endometrial cancer, vaginal cancer, vulvar cancer, kidney cancer, renal pelvis and ureter cancers, urothelial cancer, penile cancer, prostate cancer, testicular tumor, bone and soft tissue sarcoma, malignant bone tumor, skin cancer, thymoma, mesothelioma, and cancer of unknown primary), atherosclerosis, apoplexy, gout, arthritis, osteoarthritis, juvenile arthritis, ankylosing spondylitis, tenosynovitis, ligament ossification, systemic lupus erythematosus, vasculitis, pancreatitis, nephritis, chronic prostatitis, chronic pelvic pain syndrome, conjunctivitis, iritis, scleritis, uveitis, wound healing, dermatitis, eczema, osteoporosis, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, allergic diseases, familial adenomatous polyposis, scleroderma, bursitis, uterine fibroids, and pain from cancer.

EXAMPLES

[0094] Hereinafter, the present disclosure will be described more specifically by means of examples, but the present disclosure is not limited to the examples below.

[0095] In the examples below, the following abbreviations are used.

IPC = In-Process Control test

dba = Dibenzylideneacetone

XPhos = 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

IPA = 2-Propanol

CDI = 1,1'-Carbonyldiimidazole

DMF = N,N-Dimethylformamide

DMAc, DMA = N,N-Dimethylacetamide

pTsOH-H₂O = p-Toluenesulfonic acid monohydrate

MeCN = Acetonitrile

HPLC = High performance liquid chromatography

[0096] ¹H-NMR spectra in the examples were measured by a JNM-ECS400 type nuclear magnetic resonance apparatus (manufactured by JEOL RESONANCE Inc.). The observed peaks are expressed as chemical shift values δ (ppm) (s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, m = multiplet, dd = double doublet, dt = double triplet).

[0097] X-ray powder diffraction spectra in Examples 1 to 11 were measured by MiniFlex 600 (manufactured by Rigaku Corporation) (voltage: 40 kv, current: 15 mA, wavelength: CuK α , solar slit: 5.0 degrees, scanning range: 4 to 40 degrees, scanning speed/counting time: 20.0) unless otherwise specified.

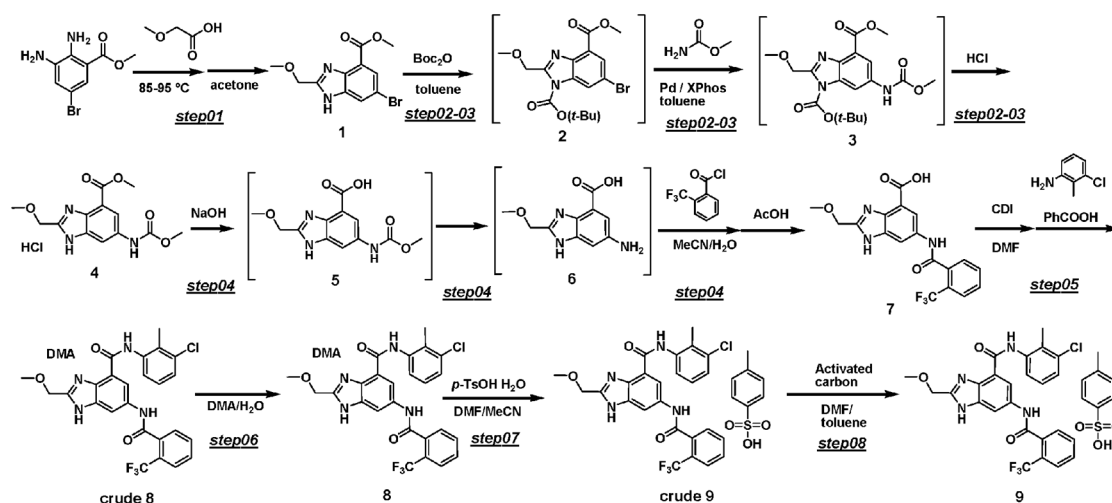
[0098] DSC in Examples 1 to 11 was measured by DSC-60A (manufactured by SHIMADZU CORPORATION) (cell: alumina (open), gas: nitrogen (20.0 mL/min), heating rate: 10.0°C/min, hold temperature: 300°C, hold time: 0 min) unless otherwise specified.

[0099] TG/DTA in Examples 1 to 11 was measured by TG-8120 (manufactured by Rigaku Corporation) (cell: alumina (open), gas: nitrogen, heating rate: 10.0°C/min, hold temperature: 300°C, hold time: 0 min) unless otherwise specified.

[0100] [Example 1: Production of Form-I crystal of p-TsOH salt of compound A]

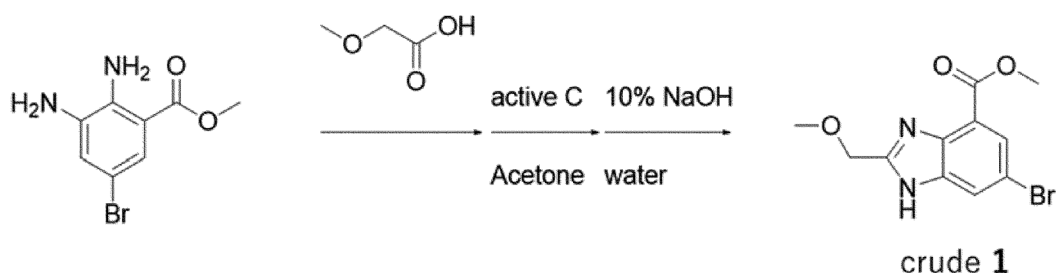
A Form-I crystal of the p-TsOH salt of the compound A was produced by a production method outlined below.

[Chem. 69]



[0101] [Step 1: Synthesis of methyl 6-bromo-2-(methoxymethyl)-1H-benzimidazole-4-carboxylate (compound 1)]

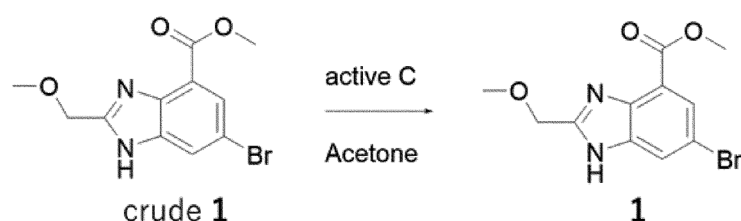
[Chem. 70]



80.0 kg of methyl 2,3-diamino-5-bromobenzoate and methoxyacetic acid (294 kg) were added to a stirring tank purged with nitrogen. The temperature in the stirring tank was heated to 85°C or higher, and a reaction was carried out for 10 hours while maintaining the internal temperature at 80°C to 95°C. After confirming the completion of the reaction by HPLC based on the fact that the peak area of methyl 2,3-diamino-5-bromobenzoate, which was a raw material, reached 1% or less of the sum of the areas of all detected peaks, the reaction solution was cooled to 20 to 30°C. Then, acetone (506 kg) was added to the reaction solution, the reaction solution was stirred, then diatomaceous earth (8.0 kg), activated carbon (16.0 kg), and acetone (129 kg) were added to the reaction solution, and the reaction solution was further stirred for 1 hour or longer while maintaining the temperature of the reaction solution at 20 to 30°C. The insoluble material was filtered off, and the trapped insoluble material was washed with acetone (378 kg). Then, the collected filtrate was concentrated to 390 L by removing the solvent under reduced pressure while maintaining the temperature outside the vessel at 50°C or lower. Then, water (800 L) was added thereto while maintaining the temperature of the reaction solution at 20 to 50°C. Then, the reaction solution was cooled to 15°C or lower, and

then about 1100 kg of a 10% sodium hydroxide solution was added such that the pH of the solution was 5.5 to 7.5, while maintaining the temperature of the reaction solution at 20°C or lower. The reaction solution was stirred for 30 minutes or longer while maintaining the temperature of the reaction solution at 20 to 30°C, then the slurry was filtered to collect the insoluble material, and the collected insoluble material was washed with water (602 kg), and then dried under reduced pressure while maintaining the temperature outside the vessel at 60°C or lower to obtain a crude product (crude) of methyl 6-bromo-2-(methoxymethyl)-1H-benzimidazole-4-carboxylate (compound 1), which was a target product, as 91.6 kg of a powder (yield: 94%).

[0102] [Chem. 71]



The obtained crude product of the compound 1 (91.5 kg) and acetone (1011 kg) were added to a stirring tank purged with nitrogen. The temperature in the stirring tank was raised to 35 to 45°C, and the compound 1 was dissolved in acetone. Activated carbon (9.2 kg) and acetone (73.2 kg) were added to the solution, and the reaction solution was then stirred for 1 hour or longer while maintaining the temperature of the reaction solution at 35 to 45°C. The insoluble material including the activated carbon was removed by filtration, and the trapped insoluble material was washed with acetone (434 kg). Then, the filtrate was concentrated to 640 L by removing the solvent while raising the temperature. The obtained solution was cooled to 20 to 30°C, and was stirred for 12 hours or longer while maintained at 20 to 30°C. Then, the solution was cooled to 10°C or lower over 1 hour or longer, and was stirred for 1 hour or longer while maintained at 0 to 10°C. The slurry was filtered to collect the insoluble material, and the collected insoluble material (cake) was washed with cooled acetone (73.1 kg). Then, the collected insoluble material was dried under reduced pressure while maintaining the temperature outside the vessel at 60°C or lower, to obtain methyl 6-bromo-2-(methoxymethyl)-1H-benzimidazole-4-carboxylate (compound 1) as 79.3 kg of a powder (yield: 87%).

[0103] The spectrum data of the obtained compound 1 was as follows.

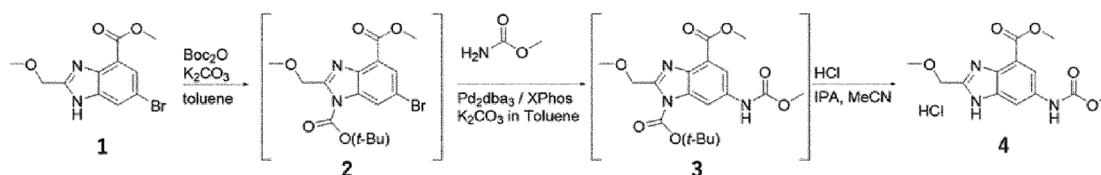
ESI-MS (-): calculated value 297.0, measured value 297.0 (M-H)

¹H NMR (Chloroform-d, δ in ppm) 10.47 (br, 1H), 8.04 (d, J = 1.3 Hz, 1H), 8.00 (d, J = 1.9 Hz, 1H), 4.76 (s, 2H), 4.00 (s, 3H), 3.51 (s, 3H)

[0104] [Step 2/3: Synthesis of methyl 6-[(methoxycarbonyl)amino]-2-(methoxymethyl)-

1H-benzimidazole-4-carboxylate hydrochloride (compound 4)]

[Chem. 72]



The compound 1 (79.2 kg) obtained in step 1, potassium carbonate (54.9 kg), and toluene (688 kg) were added to a stirring tank purged with nitrogen gas. Di-*t*-butyl dicarbonate (86.8 kg) was added to the mixture at a temperature of 15 to 30 °C, then the temperature of the reaction solution was raised to 40 to 50°C, and a reaction was carried out for 20 hours or longer. After confirming the completion of the reaction by HPLC based on the fact that the peak area of the compound 1, which was a raw material, reached 0.6% or less of the sum of the areas of all detected peaks, the reaction solution was cooled to 30°C to obtain a solution containing a compound 2 (compound 2 solution).

Methyl carbamate (39.8 kg), potassium carbonate (73.3 kg), and toluene (138 kg) were added to another stirring tank purged with nitrogen gas, and vacuum degassing was performed. The compound 2 solution and toluene (550 kg) were added to the mixture, and vacuum degassing was performed. 64.7%-Pd₂(dba)₃ (1.88 kg) and XPhos (2.54 kg) were added to the mixture, and vacuum degassing was performed. The reaction solution was heated to 88 to 97°C, and a reaction was carried out at 88 to 97°C for 4 hours. After confirming the completion of the reaction by HPLC based on the fact that the peak area of the compound 2, which was a raw material, reached 1.0% or less of the sum of the areas of all detected peaks, the reaction solution was cooled to 20 to 30°C. The insoluble material was removed by filtration, and the trapped insoluble material was washed with acetonitrile (437 kg). Then, 2-propanol (310 kg) was added to the collected filtrate containing a compound 3, and concentrated hydrochloric acid (81.6 kg) was further added thereto while maintaining the temperature of the solution at 30°C or lower. The temperature of the reaction solution was raised to 50 to 60°C, and a reaction was carried out for 1 hour or longer while maintaining the temperature at 50 to 60°C. After confirming the completion of the reaction by HPLC based on the fact that the peak area of the compound 3, which was a raw material, reached 0.1% or less of the sum of the areas of all detected peaks, the reaction solution was cooled to 25°C or lower and incubated at 15 to 25°C for 1 hour. The slurry was filtered to collect the insoluble material, and the collected insoluble material (cake) was washed with acetonitrile (683 kg). Then, the collected insoluble material was dried under reduced pressure while maintaining the temperature outside the vessel at 60°C or lower, to obtain methyl 6-[(methoxycarbonyl)amino]-2-(methoxymethyl)-1H-

benzimidazole-4-carboxylate hydrochloride (compound 4) as 76.0 kg of a powder (yield: 87%).

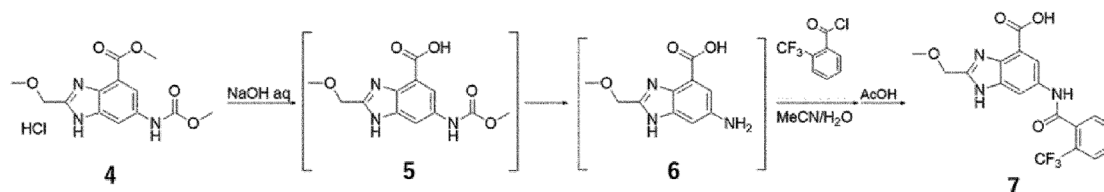
[0105] The spectrum data of the obtained compound 4 was as follows.

ESI-MS(+): calculated value 294.1, measured value 294.0 (M+H)

¹H NMR (DMSO-d₆, δ in ppm) 10.19 (s, 1H), 8.24 (d, J = 1.9 Hz, 1H), 8.13 (d, J = 1.9 Hz, 1H), 4.94 (s, 2H), 3.96 (s, 3H), 3.68 (s, 3H), 3.44 (s, 3H)

[0106] [Step 4: Synthesis of 2-(methoxymethyl)-6-(2-(trifluoromethyl)benzamido)-1H-benzimidazole-4-carboxylic acid (compound 7)]

[Chem. 73]



Water (76.2 kg) and a 30% sodium hydroxide solution (153 kg) were added to a stirring tank purged with nitrogen gas and were mixed. The compound 4 (75.6 kg) obtained in step 2/3 was added to the mixture, and degassing was performed with nitrogen gas. The reaction solution was heated to raise the temperature thereof to 50 to 60°C, and a reaction was carried out for 6 hours or longer while maintaining the temperature at 50 to 60°C. After confirming the completion of the reaction by HPLC based on the fact that the peak area of a compound 5, which was a reaction intermediate, reached 1.0% or less of the sum of the areas of all detected peaks, the reaction solution was cooled to 30°C, and water (756 L) and acetic acid (13.7 kg) were added to the reaction solution. Acetonitrile (356 kg) was added to the reaction solution, and the solution was cooled to 0°C or lower. 47.9 kg of 2-(trifluoromethyl)benzoyl chloride was added dropwise to the solution at -5 to 5°C, and a reaction was carried out for 15 minutes or longer while maintaining the temperature at -5 to 5°C. After confirming the completion of the reaction by HPLC based on the fact that the peak area of a compound 6, which was a reaction intermediate, reached 1.0% or less of the sum of the areas of all detected peaks, the reaction solution was heated to raise the temperature thereof to 60°C or higher, and a reaction was carried out for 2 hours or longer while maintaining the temperature at 60 to 70°C. After confirming the completion of the reaction by HPLC based on the fact that the sum of the peak areas of compounds obtained by reaction of two or three molecules of 2-(trifluoromethyl)benzoyl chloride, which was a byproduct of the previous reaction, with the compound 6 reached 0.1% or less of the sum of the areas of all detected peaks, acetonitrile (238 kg) was added at a temperature of 70°C or lower, and acetic acid (55.0 kg) was added over 30 minutes or longer while maintaining the temperature at 60 to 70°C. The reaction solution was stirred for 1 hour or longer while maintained at 60 to 70°C, then cooled to 30°C or lower, and

further stirred for 1 hour or longer while maintained at 20 to 30°C. The slurry was filtered to collect the insoluble material, and the collected insoluble material (cake) was washed with a mixed solution of MeCN (142 kg) and water (182 kg), water (183 kg), and 2-propanol (144 kg) in this order. Then, the collected insoluble material was dried under reduced pressure while maintaining the temperature outside the vessel at 60°C or lower, to obtain 2-(methoxymethyl)-6-(2-(trifluoromethyl)benzamido)-1H-benzimidazole-4-carboxylic acid (compound 7) as 85.1 kg of a powder (yield: 94%).

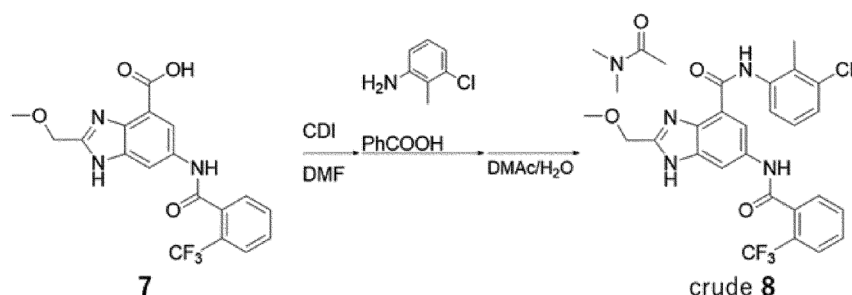
[0107] The spectrum data of the obtained compound 7 was as follows.

ESI-MS(+): calculated value 394.1, measured value 394.0 (M+H)

¹H NMR (Methanol-d₄, δ in ppm) 8.28 (d, J = 2.6 Hz, 1H), 8.12 (d, J = 1.9 Hz, 1H), 7.64-7.81 (m, 4H), 4.72 (s, 2H), 3.46 (s, 3H)

[0108] [Step 5: Synthesis of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-({[2-(trifluoromethyl)phenyl]carbonyl}amino)-1H-benzimidazole-4-carboxamide DMA solvate (compound 8)]

[Chem. 74]

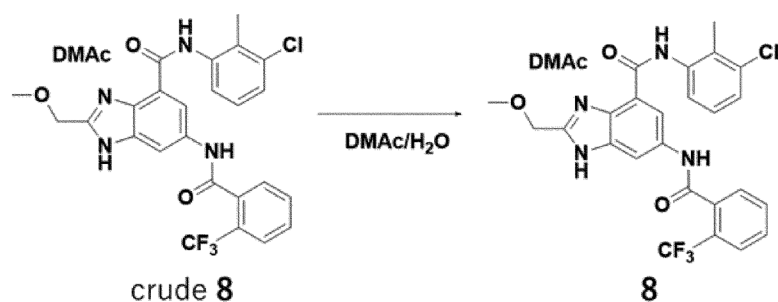


The compound 7 (82.8 kg) obtained in step 4 and DMF (235 kg) were added to a stirring tank purged with nitrogen gas. 1,1'-carbonyldiimidazole (38.8 kg) was added to the solution while stirring the solution at 30°C or lower, and a reaction was carried out for 1 hour or longer while maintaining the temperature of the reaction solution at 20 to 30°C. After confirming the completion of the reaction by HPLC based on the fact that the peak area of the compound 7, which was a starting material, reached 1.0% or less of the sum of the areas of all detected peaks, the reaction solution was cooled to 20 to 30°C, and 74.3 kg of 3-chloro-2-methylaniline and benzoic acid (1.28 kg) were added to the reaction solution. The reaction solution was heated to raise the temperature thereof, and a reaction was carried out at 50 to 60°C for 20 hours or longer. After confirming the completion of the reaction by HPLC based on the fact that the peak area of a reaction intermediate having a carbonyl imidazole structure reached 2.0% or less of the sum of the areas of all detected peaks, DMAc (465 kg) was added to the reaction solution at 50 to 60°C. Water (331 kg) was added dropwise to the reaction solution while maintaining the temperature of the reaction solution at 50 to 60°C, and then the reaction

solution was stirred at 50 to 60°C for 1 hour or longer. The reaction solution was cooled to 25°C or lower, and was stirred for 2 hours or longer while maintaining the temperature of the reaction solution at 20 to 25°C. The slurry was filtered to collect the insoluble material, and the collected insoluble material (cake) was washed with a mixed solution of DMAc (183 kg) and water (195 kg), and water (293 kg) in this order. Then, the collected insoluble material was dried under reduced pressure while maintaining the temperature outside the vessel at 60°C or lower, to obtain a crude product of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide DMA solvate (compound 8) as 115 kg of a powder (yield: 91%).

[0109] [Step 6: Purification of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide DMA solvate (compound 8)]

[Chem. 75]



The crude product of the compound 8 (105 kg) obtained in step 5 and DMAc (322 kg) were added to a stirring tank. The mixed solution was heated to raise the temperature thereof to 70 to 80°C, and water (90.3 kg) was added to the solution at 70 to 80°C. The mixed solution was cooled to 25°C or lower over 90 minutes or longer, and was stirred at 20 to 30°C for 30 minutes or longer. The slurry was filtered to collect the insoluble material, and the collected insoluble material (cake) was washed with a mixed solution of DMAc (98.4 kg) and water (105 kg), and then water (211 kg). Then, the collected insoluble material was dried under reduced pressure while maintaining the temperature outside the vessel at 60°C or lower, to obtain N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide DMA solvate (compound 8) as 98.7 kg of a powder (yield: 94%).

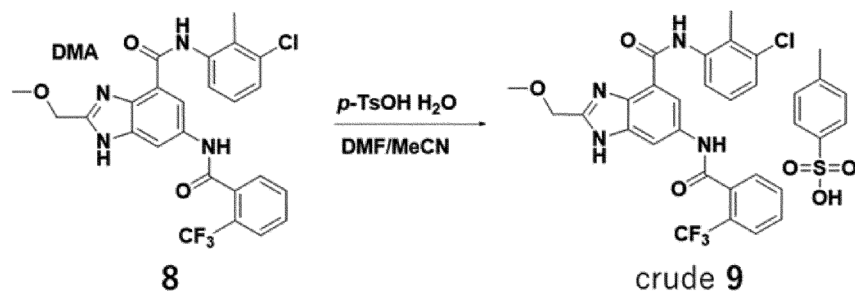
[0110] The spectrum data of the obtained compound 8 was as follows.

ESI-MS(+): calculated value for the desolvated free form 517.1, measured value 517.0 (M+H)

¹HNMR (DMSO-d₆, δ in ppm) 11.88 (s, 1H), 10.80 (s, 1H), 8.35 (d, J = 2.3 Hz, 1H), 8.24 (dd, J = 6.9 and 2.3 Hz, 1H), 8.13 (d, J = 1.8 Hz, 1H), 7.67-7.84 (m, 4H), 7.21-7.27 (m, 2H), 4.75 (s,

2H), 3.40 (s, 3H), 2.90 (s, 3H), 2.74 (s, 3H), 2.53 (s, 3H), 1.92 (s, 3H)

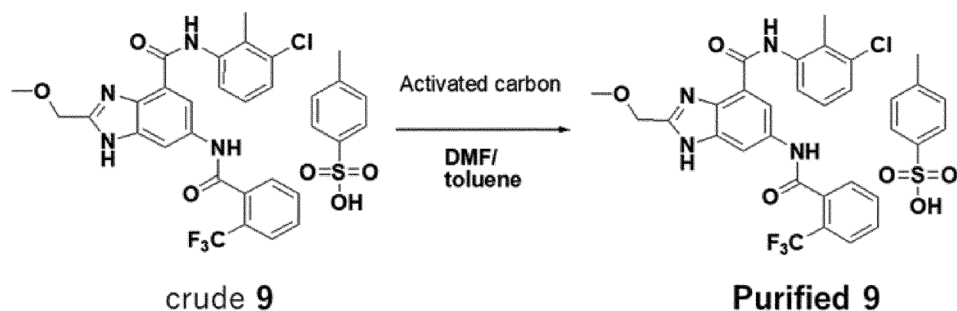
[0111] [Step 7: Synthesis of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-({[2-(trifluoromethyl)phenyl]carbonyl}amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate (compound 9 (synonymous with “p-TsOH salt of compound A”))] [Chem. 76]



The compound 8 (98.0 kg) obtained in step 6 and DMF (231 kg) were added to a stirring tank. The solution was heated to raise the temperature thereof to 50 to 60°C, and the compound 8 was dissolved in DMF. Then, MeCN (576 kg) was added to the solution at 45 to 60°C. In a state of being maintained at 45 to 60°C, a solution of pTsOH-H₂O (33.9 kg) dissolved in MeCN (307 kg) was added dropwise to this solution, and MeCN (461 kg) was further added to the solution while maintaining the temperature at 45 to 60°C. Then, the reaction solution was stirred for 5 hours or longer while maintained at 50 to 60°C. The slurry was filtered to collect the insoluble material, and the collected insoluble material (cake) was washed with a mixed solution of DMF (23.1 kg) and MeCN (134 kg) and then MeCN (230 kg). Then, the collected insoluble material was dried under reduced pressure while maintaining the temperature outside the vessel at 60°C or lower, to obtain a crude product of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-({[2-(trifluoromethyl)phenyl]carbonyl}amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate (compound 9) as 96.5 kg of a powder (yield: 86%).

[0112] [Step 8: Preparation of Form-I crystal of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-({[2-(trifluoromethyl)phenyl]carbonyl}amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate (p-TsOH salt of compound A)]

[Chem. 77]



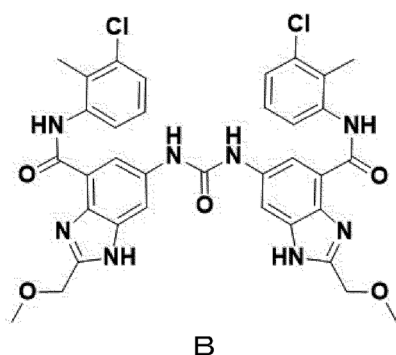
The crude product of the compound 9 (48.0 kg) obtained in step 7 and DMF (113 kg) were added to a stirring tank, and the temperature inside the stirring tank was raised to 35 to 40°C to dissolve the crude product. Activated carbon (4.8 kg) was added to the solution, and then the reaction solution was heated to raise the temperature thereof to 40 to 50°C, and was stirred for 1 hour while maintained at 40 to 50°C. The slurry was filtered to remove the insoluble material, and the trapped insoluble material was washed with a mixed solution of DMF (22.6 kg) and toluene (41.5 kg). Toluene (208 kg) was added to the obtained filtrate at a temperature of 20 to 30°C. A Form-I crystal of the compound 9 (48.0 g) was added to the filtrate, toluene (872 kg) was then added dropwise thereto at a temperature of 20 to 30°C, and the solution was stirred for 5 hours or longer while maintained at 20 to 30°C. A seed crystal of the compound 9 (240 g) was added to the solution, and the solution was then heated to raise the temperature thereof to 50 to 60°C, and was stirred at 50 to 60°C for 5 hours or longer. The solution was cooled to 20 to 30°C, and was then further stirred at 20 to 30°C for 12 hours or longer. The slurry was filtered to collect the insoluble material, and the collected insoluble material (cake) was washed with toluene (125 kg) and then MeCN (75.2 kg). Then, the collected insoluble material was dried under reduced pressure while maintaining the temperature outside the vessel at 60°C or lower, to obtain a Form-I crystal of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate (compound 9), that is, a Form-I crystal of the p-TsOH salt of the compound A, as 44.9 kg of a powder (yield: 94%). The results of X-ray powder diffraction of the obtained Form-I crystal of the p-TsOH salt of the compound A are shown in FIG. 1. According to FIG. 1, peaks were observed at $2\theta = 7.1^\circ$, 14.3° , 15.8° , and 18.3° . Furthermore, the obtained powder was analyzed by HPLC, and as a result, the purity of the compound 9 based on the peak area at 230 nm was 99.95%. Moreover, the amounts of toluene and N,N-dimethylformamide as solvents remaining in the obtained Form-I crystal of the p-TsOH salt of the compound A were 460 ppm and 514 ppm, respectively, and no acetonitrile was detected.

[0113] The results of differential scanning calorimetry (DSC) of the Form-I crystal of the p-TsOH salt of the compound A are shown in FIG. 2. The results of thermophysical property measurement by differential thermal analysis (DTA) and thermogravimetric analysis (TGA) of the Form-I crystal of the p-TsOH salt of the compound A are shown in FIG. 3. According to FIG. 2, the Form-I crystal of the p-TsOH salt of the compound A had an endothermic peak at 265.76°C in DSC. In addition, according to FIG. 3, the Form-I crystal of the p-TsOH salt of the compound A had an endothermic peak at 263.0°C in DTA, and was stable without any weight change or endothermic or exothermic heat until decomposition at 200°C or higher.

[0114] <Test Example 1: Purification efficiency and impurity removal efficiency in step 6>

For the powder of the compound 8 or its crude product, the content of the compound B represented by the following formula, which is an impurity whose content is required to be controlled in the order of ppm, was measured before purification in step 6 was performed, after purification in step 6 was performed using a solvent in which the volume ratio of DMA to H₂O was 79:21, and after purification in step 6 was performed using a solvent in which the volume ratio of DMA to H₂O was 69:31.

[Chem. 78]



[0115] The results are shown in Table 1 below. According to Table 1, even when recrystallization was performed under any of the solvent conditions, the refined product of the compound 8 was obtained at a high yield, and the content of the compound B, which is an impurity, decreased. Furthermore, when the solvent conditions were compared, the content of the compound B was significantly decreased under the condition that the volume ratio of DMA to H₂O was 79:21. That is, the removal efficiency of the compound B was higher under the condition that the volume ratio of DMA to H₂O was 79:21. This indicates that, if N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide, which is a synthetic intermediate of the compound 9, is obtained as a DMA solvate (compound 8), the impurity that is required to be controlled in the order of ppm can be removed with high efficiency by the recrystallization method.

[0116] [Table 1]

Purification in step 6	DMA/H ₂ O ratio (v/v)	Compound B (ppm)	Yield (%)
Before	-	1855	-
After	3.27/0.86 (79:21)	158	96.7
After	3.27/1.47 (69:31)	1675	99.1

[0117] <Test Example 2: Purification efficiency and impurity removal efficiency in step 8>

For the compound 9 obtained before purification in step 8, after purification was performed in step 8 only by recrystallization without contact with activated carbon, and after purification was performed by recrystallization after contact with activated carbon whose mass was 0.05 times, 0.10 times, or 0.15 times the mass of the crude product of the compound 9 as in step 8, the content of the compound B, which is an impurity, was measured.

[0118] The results are shown in Table 2 below. Unexpectedly, the compound B could not be effectively removed by recrystallization of the compound 9 alone. On the other hand, when contact with activated carbon was included before recrystallization, the compound B could be effectively removed, and, especially when the mass of activated carbon contacted was 0.10 times and 0.15 times the mass of the crude product of the compound 9, the compound B could be more efficiently removed.

[0119] [Table 2]

Activated carbon treatment	Recrystallization	Compound B (ppm)
No	No	112
No	Yes	108
Yes, 5 wt%	Yes	31.0
Yes, 10 wt%	Yes	13.8
Yes, 15 wt%	Yes	9.73

[0120] [Preparation Example 1: Preparation of amorphous substance of p-TsOH salt of compound A]

The Form-I crystal of the p-TsOH salt of the compound A (10 g) obtained in Example 1 was suspended in methanol (1 L) and the suspension was concentrated to dryness under reduced pressure at an external temperature of 55°C to obtain an amorphous substance of the p-TsOH salt of the compound A. The results of X-ray powder diffraction of the obtained

amorphous substance are shown in FIG. 4, and are shown in FIG. 5 in an enlarged manner in the vertical axis direction. No peaks were observed in the analysis results, and it was confirmed that the obtained product was an amorphous substance of the p-TsOH salt of the compound A.

[0121] [Example 2: Production 1 of Form-III crystal of p-TsOH salt of compound A]

The amorphous substance of the p-TsOH salt of the compound A (14 g) obtained in Preparation Example 1 was placed in an electric furnace and heated at 210°C for 1 hour, and as a result, a Form-III crystal of the p-TsOH salt of the compound A (13.5 g) was obtained at a yield of 96%. The results of X-ray powder diffraction of the obtained Form-III crystal of the p-TsOH salt of the compound A are shown in FIG. 6. The results of thermophysical property measurement by differential thermal analysis (DTA) and thermogravimetric analysis (TGA) of the obtained Form-III crystal of the p-TsOH salt of the compound A are shown in FIG. 7. According to FIG. 6, peaks were observed at $2\theta = 6.3^\circ$, 15.0° , 16.4° , 17.9° , and 22.7° . In addition, according to FIG. 7, the Form-III crystal of the p-TsOH salt of the compound A had an endothermic peak at 247.4°C in DTA.

[0122] [Example 3: Production 1 of Form-IV crystal of p-TsOH salt of compound A]

The amorphous substance of the p-TsOH salt of the compound A (14 g) obtained in Preparation Example 1 was added to acetonitrile (1 L), the mixture was stirred, and as a result, a crystal was precipitated. The mixed solution was stirred overnight, then the crystal was filtered off, and the obtained crystal was dried at room temperature under normal pressure overnight to obtain, as an intermediate product, a crystal for which the results of X-ray powder diffraction are as shown in FIG. 8 and the results of thermophysical property measurement by differential thermal analysis (DTA) and thermogravimetric analysis (TGA) are as shown in FIG. 9. From the results of $^1\text{H-NMR}$, it was found that this crystal was an acetonitrile solvate in which one molecule of the compound A was solvated with 1/2 molecule of acetonitrile (hereinafter, the crystal obtained here is also referred to as “1/2 acetonitrile solvate crystal of the p-TsOH salt of the compound A obtained in Example 3”). The obtained crystal was placed in an electric furnace and heated at 160°C for 1.5 hours, and as a result, a Form-IV crystal of the p-TsOH salt of the compound A (12.7 g) was obtained at a yield of 91%. The results of X-ray powder diffraction of the obtained Form-IV crystal of the p-TsOH salt of the compound A are shown in FIG. 10. The results of thermophysical property measurement by differential thermal analysis (DTA) and thermogravimetric analysis (TGA) of the obtained Form-IV crystal of the p-TsOH salt of the compound A are shown in FIG. 11. According to FIG. 10, peaks were observed at $2\theta = 7.4^\circ$, 8.0° , 14.5° , 16.1° , and 20.6° . In addition, according to FIG. 11, the Form-IV crystal of the p-TsOH salt of the compound A had an endothermic peak at 212.5°C in DTA.

[0123] [Comparative Example 1: Production of Form-V crystal of p-TsOH salt of compound A]

The amorphous substance of the p-TsOH salt of the compound A (14 g) obtained in Preparation Example 1 was added to chloroform (0.8 L), the mixture was stirred, and as a result, a crystal was precipitated. The mixed solution was stirred overnight, and then the crystal was filtered off to obtain, as an intermediate product, a crystal for which the results of X-ray powder diffraction are as shown in FIG. 12 and the results of thermophysical property measurement by differential thermal analysis (DTA) and thermogravimetric analysis (TGA) are as shown in FIG. 13. From the results of ^1H -NMR, it was found that this crystal was a chloroform solvate. The obtained crystal was placed in an electric furnace and heated at 170°C for 1.5 hours, and as a result, a Form-V crystal of the p-TsOH salt of the compound A (12.9 g) was obtained at a yield of 92%. The results of X-ray powder diffraction of the obtained Form-V crystal of the p-TsOH salt of the compound A are shown in FIG. 14. The results of thermophysical property measurement by differential thermal analysis (DTA) and thermogravimetric analysis (TGA) of the obtained Form-V crystal of the p-TsOH salt of the compound A are shown in FIG. 15.

[0124] [Comparative Example 2: Production of Form-VI crystal of p-TsOH salt of compound A]

The amorphous substance of the p-TsOH salt of the compound A (15 g) obtained in Preparation Example 1 was added to 2,2,2-trifluoroethanol (TFE, 60 mL) cooled to 5°C, the mixture was stirred, and as a result, a crystal was precipitated. The mixed solution was stirred for 5 days, and then the crystal was filtered off to obtain, as an intermediate product, a crystal for which the results of X-ray powder diffraction are as shown in FIG. 16. From the results of ^1H -NMR, it was found that this crystal was a trifluoroethanol solvate. The obtained crystal was placed in an electric furnace and heated at 150°C for 30 minutes, and as a result, a Form-VI crystal of the p-TsOH salt of the compound A (12.5 g) was obtained at a yield of 83%. The results of X-ray powder diffraction of the obtained Form-VI crystal of the p-TsOH salt of the compound A are shown in FIG. 17. The results of thermophysical property measurement by differential thermal analysis (DTA) and thermogravimetric analysis (TGA) of the obtained Form-VI crystal of the p-TsOH salt of the compound A are shown in FIG. 18.

[0125] [Comparative Example 3: Production of Form-VII crystal of p-TsOH salt of compound A]

The amorphous substance of the p-TsOH salt of the compound A (15 g) obtained in Preparation Example 1 was added to 2,2,2-trifluoroethanol (TFE, 60 mL) cooled to 5°C, the mixture was stirred, and as a result, a crystal was precipitated. The mixed solution was stirred

for 6 days, and then the crystal was filtered off to obtain, as an intermediate product, a crystal for which the results of X-ray powder diffraction are as shown in FIG. 16. The filtered crystal was left on a funnel overnight, and as a result, a crystal for which the results of X-ray powder diffraction are as shown in FIG. 19 was obtained. From the results of $^1\text{H-NMR}$, it was found that this crystal was a trifluoroethanol solvate. The obtained crystal was placed in an electric furnace and heated at 150°C for 1 hour, and as a result, a Form-VII crystal of the p-TsOH salt of the compound A (12.7 g) was obtained at a yield of 85%. The results of X-ray powder diffraction of the obtained Form-VII crystal of the p-TsOH salt of the compound A are shown in FIG. 20. The results of thermophysical property measurement by differential thermal analysis (DTA) and thermogravimetric analysis (TGA) of the obtained Form-VII crystal of the p-TsOH salt of the compound A are shown in FIG. 21.

[0126] [Example 4: Production 2 of Form-III crystal of p-TsOH salt of compound A]

The Form-IV crystal of the p-TsOH salt of the compound A obtained in Example 3 was heated at 205°C , and as a result, a Form-III crystal of the p-TsOH salt of the compound A was obtained.

[0127] [Example 5: Production 3 of Form-III crystal of p-TsOH salt of compound A]

The Form-V crystal of the p-TsOH salt of the compound A obtained in Comparative Example 1 was heated at 205°C for 10 minutes, and as a result, a Form-III crystal of the p-TsOH salt of the compound A was obtained. In addition, from this result, it was found that the Form-III crystal of the p-TsOH salt of the compound A had higher stability than the Form-V crystal.

[0128] [Example 6: Production 4 of Form-III crystal of p-TsOH salt of compound A]

The Form-VI crystal of the p-TsOH salt of the compound A obtained in Comparative Example 2 was heated at 190°C for 10 minutes, and as a result, a Form-III crystal of the p-TsOH salt of the compound A was obtained. In addition, from this result, it was found that the Form-III crystal of the p-TsOH salt of the compound A had higher stability than the Form-VI crystal.

[0129] [Example 7: Production 5 of Form-III crystal of p-TsOH salt of compound A]

About 10 mg of the 1/2 acetonitrile solvate crystal of the p-TsOH salt of the compound A obtained in Example 3 was placed in an open pan having a capacity of 100 μL , was heated to just above the desolvation temperature using a TG/DTA apparatus, and was held and desolvated at this temperature until the weight loss became stabilized (10 min). Then, the sample was cooled to the ambient temperature, and analysis thereof by XRPD was performed and showed that a Form-III crystal of the p-TsOH salt of the compound A was obtained.

[0130] [Example 8: Production 2 of Form-IV crystal of p-TsOH salt of compound A]

About 10 mg of the 1/2 acetonitrile solvate crystal of the p-TsOH salt of the compound A obtained in Example 3 was allowed to stand at 40°C and a relative humidity of 75% for 7 days, and as a result, a Form-IV crystal of the p-TsOH salt of the compound A was obtained. In addition, from this result, it was found that the Form-IV crystal of the p-TsOH salt of the compound A had higher stability than the 1/2 acetonitrile solvate crystal of the p-TsOH salt of the compound A obtained in Example 3.

[0131] [Example 9: Relative stability between crystals of p-TsOH salt of compound A]

The crystals of the p-TsOH salt of the compound A prepared in Examples 1 to 3 and Comparative Examples 1 to 3 were each weighed in 100 mg, a total of 600 mg was added to 30 mL of a mixed solvent of DMF and toluene having a volume ratio of 1:9, and the mixture was stirred at 20°C or 55°C. After 3, 4, 7, and 8 days from the start of stirring at 20°C, and after 3 and 4 days from the start of stirring at 55°C, the crystal form of the p-TsOH salt of the compound A in the mixed solution was measured by X-ray powder diffraction. The results at 20°C are shown in FIG. 22. The results at 55°C are shown in FIG. 23. According to FIGS. 22 and 23, each of all crystals in the mixed solution became a Form-I crystal of the p-TsOH salt of the compound A after 8 days at 20°C and after 3 days at 55°C, so that it was found that the Form-I crystal was the most stable form of the p-TsOH salt of the compound A.

[0132] [Example 10: Stability test of Form-I crystal of p-TsOH salt of compound A when mixed with excipient]

The Form-I crystal of the p-TsOH salt of the compound A was mixed with each of various excipients at a mass ratio of 1:1 using a mortar, was allowed to stand in a thermo-hygrostat at a temperature of 40°C and a relative humidity of 75% in an open system for 2 weeks or 1 month, and then evaluated for the presence/absence of decomposition using HPLC and checked for color change by visual inspection. The stability of only the Form-I crystal of the p-TsOH salt of the compound A was also evaluated as a reference. The conditions for HPLC are as follows.

Instrument: SHIMADZU LC-2010 CHT

Column: COSMOSIL 3C18-MSII 4.6×100 mm

Column temperature: 40°C

Mobile phase: Liquid A; MeCN/H₂O/MsOH = 600/400/1

Liquid B: MeCN/H₂O/MsOH = 900/100/1

Gradient: 0-8 min; A = 100%

8-10 min; A to B

10-20 min; B = 100%

20-21 min; B to A

Flow rate: 0.5 mL/min

Wavelength: 230 nm

[0133] The results of the percentage (%) of the area of the peak of the Form-I crystal of the p-TsOH salt of the compound A in the observed peaks in HPLC and observation of the color of the crystal are shown in Table 3. According to Table 3, no decomposition of the Form-I crystal of the p-TsOH salt of the compound A was observed under the conditions of mixing with any of the excipients, and no color change occurred. From this, it was found that the Form-I crystal of the p-TsOH salt of the compound A was a crystal of the p-TsOH salt of the compound A having high stability.

[0134] [Table 3]

	Immediately after mixing	2 weeks	1 month
Crystal only	99.71	99.70	99.68
D-Mannitol	99.63	99.70	99.71
Crystalline cellulose	99.73	99.65	99.69
Lactose	99.64	99.74	99.58
Corn starch	99.71	99.66	99.66
		No color change under any conditions	No color change under any conditions

[0135] [Example 11: Stability evaluation of Form-I crystal of p-TsOH salt of compound A when exposed to various stimuli]

The Form-I crystal of the p-TsOH salt of the compound A and the free form crystal of the compound A prepared according to the method described in PATENT DOCUMENT 1 were exposed to heating stimulus (allowed to stand at 60°C for 24 hours), light stimulus (light source: D65 lamp, total intensity: 1.2 million lx·hr), or humidifying stimulus (allowed to stand at 30°C and a relative humidity of 90% for 24 hours), and the stability thereof was evaluated based on the percentage (%) of the area of the peak of the free form of the compound A or the Form-I crystal of the p-TsOH salt of the compound A in the observed peaks in HPLC with and without exposure to the stimuli. The results are shown in Table 4. According to Table 4, no decrease in purity was observed in the Form-I crystal of the p-TsOH salt of the compound A even after exposure to any of the stimuli, and no change in the color of the crystal was observed. From this, it was found that the Form-I crystal of the p-TsOH salt of the compound A was a stable crystal of the p-TsOH salt of the compound A.

[0136] [Table 4]

	Free form of compound A	Form-I crystal p-TsOH salt of compound A
No stimulus	99.78%	99.70%
Heating stimulus	99.76%	99.69%
Light stimulus	99.74%	99.72%
Humidifying stimulus	99.76%	99.68%

[0137] [Example 12: Stability of Form-I crystal of p-TsOH salt of compound A in exposure to mechanical stimulus and water]

X-ray powder diffraction measurement was performed for a crystal (pulverized) obtained by pulverizing the Form-I crystal of the p-TsOH salt of the compound A in a mortar, a crystal (water-treated) obtained by kneading the Form-I crystal of the p-TsOH salt of the compound A after adding water, a sample of the Form-I crystal of the p-TsOH salt of the compound A stored under a humidifying stimulus condition (30°C, relative humidity of 90%), and a sample obtained by tableting the Form-I crystal of the p-TsOH salt of the compound A (2,000 kgf × 30 min). The results are shown in FIG. 24 together with the results of the Form-I crystal of the p-TsOH salt of the compound A not undergoing any treatment (untreated). According to FIG. 24, no change in crystal form was observed under any of the conditions. From this, it was found that the Form-I crystal of the p-TsOH salt of the compound A was a stable crystal of the p-TsOH salt of the compound A. Powder X-ray diffraction spectra in this example were measured by RINT-Ultima III (manufactured by Rigaku Corporation) (target: Cu, voltage: 40 kv, current: 40 mA, scanning speed: 4 degrees/min).

[0138] [Example 13: Stability test of Form-III crystal of p-TsOH salt of compound A]

About 10 mg of the Form-III crystal of the p-TsOH salt of the compound A obtained in Example 2 was allowed to stand at 40°C and a relative humidity of 75% for 7 days or longer, and as a result, the Form-III crystal of the p-TsOH salt of the compound A was able to exist stably for 7 days or longer. From this, it was found that the Form-III crystal of the p-TsOH salt of the compound A was a crystal that can exist stably.

[0139] [Comparative Example 4: Production of Form-II crystal of p-TsOH salt of compound A]

The free form of the compound A (50 mg) obtained according to the method described in PATENT DOCUMENT 1 was added to ethyl acetate (1.0 mL). One equivalent of pTsOH-H₂O to the compound A was added to the mixture, the mixture was stirred at 50°C, and as a result, a crystal was precipitated such that gum was precipitated on a bottom wall and then became cloudy as a whole. The crystal was collected to obtain a Form-II crystal of the p-TsOH

salt of the compound A for which the results of X-ray powder diffraction are as shown in FIG. 25 and the results of thermophysical property measurement by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) are as shown in FIG. 26.

[0140] [Example 14: Examination of thermal stability of Form-II crystal of p-TsOH salt of compound A]

According to the results in FIG. 26, for the Form-II crystal of the p-TsOH salt of the compound A, an endothermic peak was observed at 177°C in DSC, but no mass change was observed in TGA, so that it was considered that crystal form transition occurred around 177°C. Therefore, for the Form-II crystal of the p-TsOH salt of the compound A, the crystal form was examined by X-ray powder diffraction while increasing the temperature to 30°C, 150°C, and 200°C, and then the crystal form was further examined by X-ray powder diffraction while cooling to 150°C and 30°C. The results are shown in FIG. 27. According to FIG. 27, the Form-II crystal of the p-TsOH salt of the compound A was unstable against heat. Furthermore, the Form-II crystal of the p-TsOH salt of the compound A transitioned to a Form-III crystal of the p-TsOH salt of the compound A under a condition of 200°C, so that it was found that the Form-III crystal of the p-TsOH salt of the compound A was rather stable against heat.

[0141] [Example 15: Examination of relative stability of Form-I crystal to Form-III crystal of p-TsOH salt of compound A]

As in Example 4, the Form-I crystal and the Form-II crystal of the p-TsOH salt of the compound A, the Form-I crystal and the Form-III crystal of the p-TsOH salt of the compound A, or the Form-II crystal and the Form-III crystal of the p-TsOH salt of the compound A were stirred in one solution, and the most stable form among these crystals was examined from the crystal form of the p-TsOH salt of the compound A in the solution. The Form-I crystal and the Form-II crystal of the p-TsOH salt of the compound A, the Form-I crystal and the Form-III crystal of the p-TsOH salt of the compound A, or the Form-II crystal and the Form-III crystal of the p-TsOH salt of the compound A were added to acetone at a mass ratio of 1:1, and the mixture was stirred at 30°C for 42 hours. Then, the crystal form of the p-TsOH salt of the compound A in the solution was examined by X-ray powder diffraction, and as a result, under all the three conditions, each of the crystals of the p-TsOH salt of the compound A in the solution transitioned to a Form-I crystal. Thus, it was shown that, among these three crystal forms, the Form-I crystal was the most stable form.

[0142] [Example 16: Confirmation of stability of Form-I crystal of p-TsOH salt of compound A in various solvents]

In order to facilitate the transition of the crystal form by a solvent, the Form-I crystal of the p-TsOH salt of the compound A was pulverized in a mortar. The obtained

pulverized material was added to methanol, ethyl acetate, or methyl ethyl ketone, and the mixture was stirred at 40°C for 115 hours. After stirring, the crystal form of the p-TsOH salt of the compound A in the solution was examined by X-ray powder diffraction, and the results are shown in FIG. 28. According to FIG. 28, no change in crystal form was observed under any of the conditions, so that it was found that the Form-I crystal of the p-TsOH salt of the compound A was a very stable crystal form.

[0143] [Example 17: Preparation 1 of crystal of p-TsOH salt of compound A under various conditions]

The amorphous substance of the p-TsOH salt of the compound A obtained in Preparation Example 1 was added to 1.4 mL of a solvent at a dose of 22 mg at room temperature. Then, while stirring at 600 rpm using a stirrer, two cycles of heating to a lower temperature out of $\pm 3^{\circ}\text{C}$ of the boiling point of the solvent and 100°C and cooling to 20°C at a rate of 0.2°C per minute were repeated, and then the crystal form was evaluated. As a result, a Form-I crystal of the p-TsOH salt of the compound A was obtained under a condition that acetone, acetonitrile, anisole, chloroform, cyclohexane, dichloromethane, 1,4-dioxane, ethanol, n-heptane, isopropyl acetate, methyl ethyl ketone, methyl tertiary-butyl ether (MTBE), 2-propanol, tetrahydrofuran, 2-methyltetrahydrofuran, or toluene was used as the solvent.

[0144] [Example 18: Preparation 2 of crystal of p-TsOH salt of compound A under various conditions]

The amorphous substance of the p-TsOH salt of the compound A obtained in Preparation Example 1 was added to acetic acid in a vial, and the vial was allowed to stand in a draft chamber with the vial lid open at room temperature to evaporate the acetic acid. As a result, a Form-I crystal of the p-TsOH salt of the compound A was obtained.

[0145] [Example 19: Preparation 3 of crystal of p-TsOH salt of compound A under various conditions]

The amorphous substance of the p-TsOH salt of the compound A obtained in Preparation Example 1 was added to a solvent, and the slurry was stirred at 5°C . As a result, a Form-I crystal of the p-TsOH salt of the compound A was obtained under a condition that a mixed solution of DMF and toluene having a volume ratio of 1:9, acetone, ethanol, or tetrahydrofuran was used as the solvent.

[0146] [Example 20: Preparation 4 of crystal of p-TsOH salt of compound A under various conditions]

The amorphous substance of the p-TsOH salt of the compound A obtained in Preparation Example 1 was added to a solvent, and the slurry was stirred at 20°C . As a result, a Form-I crystal of the p-TsOH salt of the compound A was obtained under a condition that

acetone, ethanol, methyl tertiary-butyl ether (MTBE), or tetrahydrofuran was used as the solvent.

[0147] [Example 21: Preparation 5 of crystal of p-TsOH salt of compound A under various conditions]

The amorphous substance of the p-TsOH salt of the compound A obtained in Preparation Example 1 was added to a solvent, and the slurry was stirred at 50°C. As a result, a Form-I crystal of the p-TsOH salt of the compound A was obtained under a condition that a mixed solution of DMF and toluene having a volume ratio of 1:1, 1:2, 1:3, 1:4, or 1:9, a mixed solution of DMF and acetonitrile having a volume ratio of 1:1, 1:2, 1:3, or 1:4, a mixed solution of acetonitrile and toluene having a volume ratio of 1:1, acetone, chloroform, ethanol, methyl tertiary-butyl ether (MTBE), tetrahydrofuran, or toluene was used as the solvent.

[0148] [Example 22: Preparation 6 of crystal of p-TsOH salt of compound A under various conditions]

The amorphous substance of the p-TsOH salt of the compound A obtained in Preparation Example 1 was dissolved in DMF at a concentration of 350 mg/mL (for room temperature) or 500 mg/mL (for 50°C), and the solution was filtered through a 0.2 µm polytetrafluoroethylene filter. A poor solvent was added to 275 µL (for room temperature) or 250 µL (for 50°C) of the filtrate while stirring at 300 rpm, and the mixture was stirred for 2 hours. Then, when toluene was used as the poor solvent, the mixture was further stirred for 70 hours. When a solvent other than toluene was used as the poor solvent, a seed crystal of the p-TsOH salt of the compound A was added, and the mixture was further stirred for 70 hours. As a result, a Form-I crystal of the p-TsOH salt of the compound A was obtained when acetonitrile was used as the poor solvent and the mixture was stirred at 50°C, when 2-propanol was used as the poor solvent and the mixture was stirred at 50°C, when methyl ethyl ketone was used as the poor solvent and the mixture was stirred at room temperature or 50°C, or when toluene was used as the poor solvent and the mixture was stirred at room temperature or 50°C. The amount of the poor solvent added was 1.93 ml (room temperature) or 1.75 ml (50°C) for acetonitrile, 2.20 ml (room temperature) or 2.00 ml (50°C) for 2-propanol, 2.20 ml (room temperature) or 2.00 ml (50°C) for methyl ethyl ketone, and 2.48 ml (room temperature) or 2.25 ml (50°C) for toluene.

[0149] [Reference Example 1: Obtaining of Form-I crystal of compound 9 without using seed crystal]

N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide can be obtained by the method described in Example 11 of PATENT DOCUMENT 1. 480 ml of THF was added to 80 g of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide, and the mixture

was heated at 50°C for dissolution. 32.4 g of p-toluenesulfonic acid monohydrate was added thereto, the mixture was stirred at the same temperature for 1 hour or longer, and 960 ml of acetone was added thereto at 55°C while heating. The mixture was further stirred at 50°C for 2 hours or longer while heating, then cooled to room temperature, and stirred at the same temperature for 30 minutes. The slurry was filtered, and washing was performed with 50 ml of cold acetone. Drying was performed under reduced pressure while heating at an external temperature of 50°C or lower, to obtain 98.1 g of a white crystal at a yield of 92%.

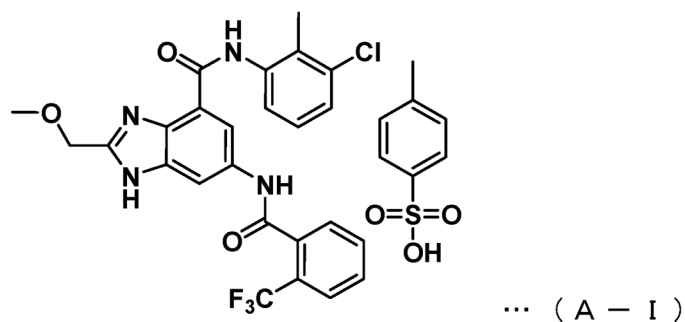
A portion of a white crystal obtained in the same manner as the obtaining method described above can be used as a seed crystal of the compound 9.

The results of X-ray powder diffraction of the obtained Form-I crystal of the compound 9 are shown in FIG. 29. The results of thermophysical property measurement by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) of the obtained Form-I crystal of the compound 9 are shown in FIG. 30. An X-ray powder diffraction spectrum in Reference Example 1 was measured by RINT-Ultima III (manufactured by Rigaku Corporation) (target: Cu, voltage: 40 kv, current: 40 mA, scanning speed: 4 degrees/min). DSC in Reference Example 1 was measured by DSC-50 (manufactured by SHIMADZU CORPORATION) (cell: alumina (open), gas: nitrogen (20.0 mL/min), heating rate: 10.0°C/min, hold temperature: 400°C, hold time: 0 min).

CLAIMS

1. A Form-I crystal of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate represented by the following formula (A-I):

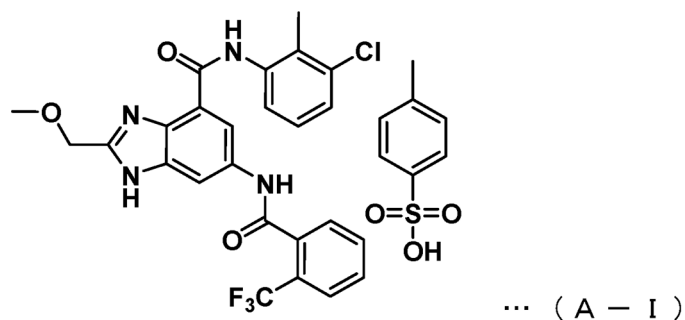
[Chem. 1]



the Form-I crystal having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 7.1° , 14.3° , 15.8° , and 18.3° in X-ray powder diffraction.

2. A Form-I crystal of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate represented by the following formula (A-I):

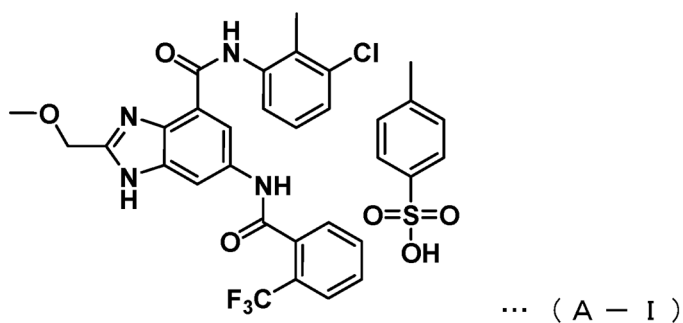
[Chem. 2]



the Form-I crystal having an endothermic peak at $265.8 \pm 3.0^\circ\text{C}$ in differential scanning calorimetry.

3. A Form-III crystal of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate represented by the following formula (A-I):

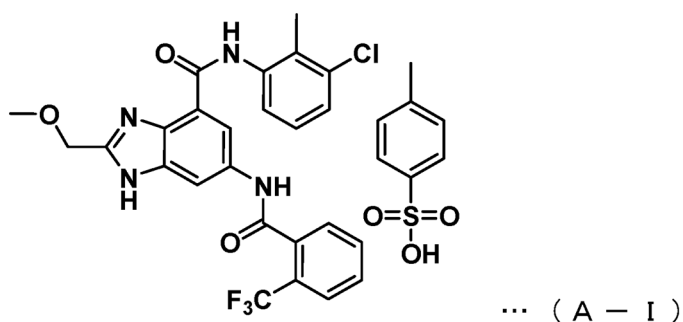
[Chem. 3]



the Form-III crystal having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 6.3° , 15.0° , 16.4° , 17.9° , and 22.7° in X-ray powder diffraction.

4. A Form-III crystal of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate represented by the following formula (A-I):

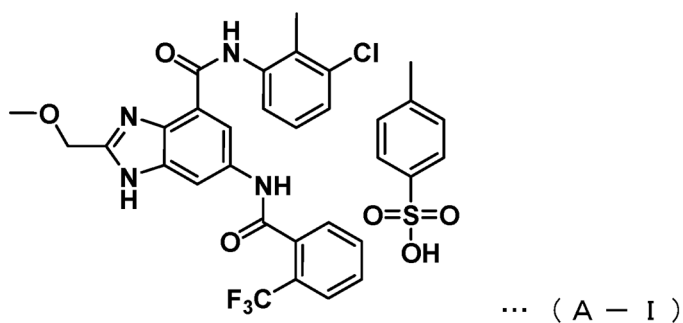
[Chem. 4]



the Form-III crystal having an endothermic peak at $247.4 \pm 3.0^\circ\text{C}$ in differential thermal analysis.

5. A Form-IV crystal of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate represented by the following formula (A-I):

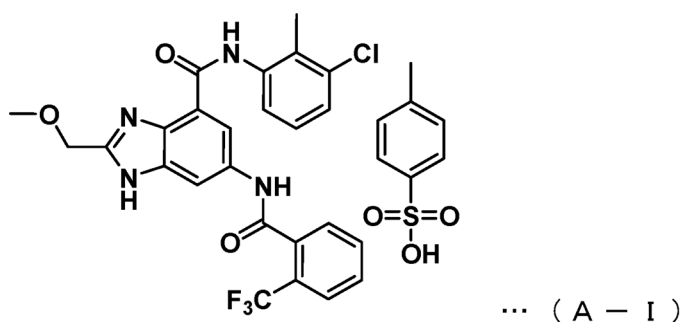
[Chem. 5]



the Form-IV crystal having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 7.4° , 8.0° , 14.5° , 16.1° , and 20.6° in X-ray powder diffraction.

6. A Form-IV crystal of N-(3-chloro-2-methylphenyl)-2-(methoxymethyl)-6-([2-(trifluoromethyl)phenyl]carbonyl)amino)-1H-benzimidazole-4-carboxamide 4-methylbenzenesulfonate represented by the following formula (A-I):

[Chem. 6]



the Form-IV crystal having an endothermic peak at $212.5 \pm 3.0^\circ\text{C}$ in differential thermal analysis.

7. A pharmaceutical composition containing the crystal according to any one of claims 1 to 6 as an active ingredient.
8. A membrane-bound prostaglandin E synthase-1 inhibitor containing the crystal according to any one of claims 1 to 6 as an active ingredient.