

New preparation method of Compound and New Crystalline Form

Technical Field

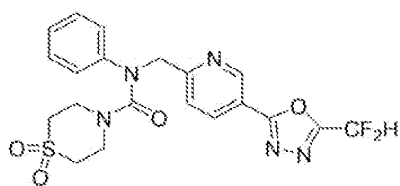
The present disclosure relates to a novel method for preparing N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, a novel method for preparing intermediates used in synthesis of the compound, and a novel crystalline form of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide.

Background

N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1 is a material having an effect of preventing or treating histone deacetylase 6 activity-related diseases.

A method for preparing a compound represented by Chemical Formula 1 below is disclosed in Korean Registered Patent No. 10-1799010.

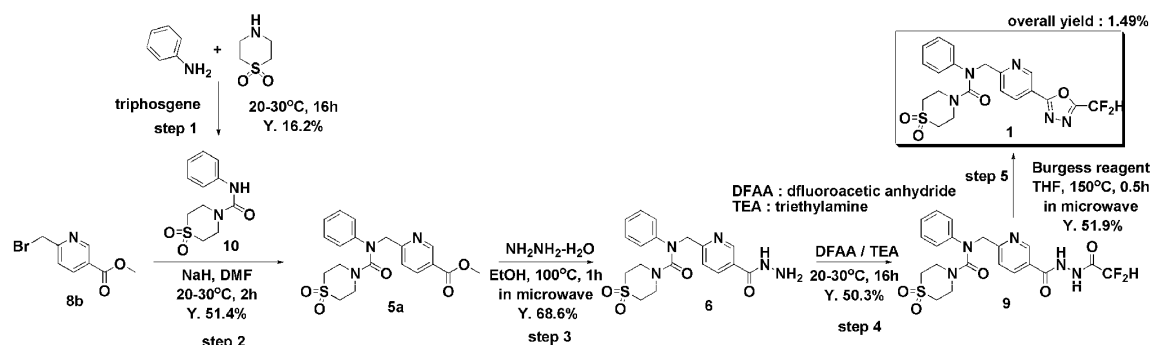
[Chemical Formula 1]



In the conventional preparation method which is disclosed in the above patent, as shown in the following [Reaction Formula 1], a compound of Chemical Formula 10 obtained by reacting aniline with a thiomorpholine derivative in the presence of triphosgene is subjected into N-alkylation reaction with a compound of Chemical Formula 8b to prepare a compound of Chemical Formula 5a. A compound of Chemical Formula 6 obtained by reacting the synthesized compound of Chemical Formula 5a with a

hydrazine hydrate is reacted with a difluoroacetic anhydride to prepare a compound of Chemical Formula 9, and a compound represented by Chemical Formula 1 is prepared by using 1-methoxy-N-triethylammoniosulfonyl-methaneimide (Burgess reagent).

[Reaction Formula 1]



However, the synthesis method through the path of the reaction formula 1 has a number of problems during the preparation process.

The triphosgene used when preparing the compound of Chemical Formula 10 has very high reactivity, and thus has low stability, is easily decomposed when coming into contact with moisture, and releases toxic gas, which is vulnerable to work safety, thus causing a big problem in mass production. In addition, a long reaction time of 16 hours and a low reaction yield of 20% or less are problematic for preparation efficiency and commercial potential. Furthermore, the base used when preparing the compound of Chemical Formula 5a from the compound of Chemical Formula 10 is sodium hydride, which is an inflammable material, and the reaction yield is also low. Moreover, according to the conventional method, when preparing the compound represented by Chemical Formula 6 and the compound represented by Chemical Formula 1, there is a problem in that the reaction is performed under a high temperature condition of 100°C or more using microwaves, and a reagent which is not generally used well and expensive, such as a Burgess reagent, should be used. Besides, column chromatography needs to be used for purification at all stages of reaction, and thus industrial mass production is

impossible.

In other words, according to the conventional method, the preparation of the compound of Chemical Formula 1, which is a target material, has a total yield of only about 1.5% through a total of five steps, and equipment and reagents used in the reaction are expensive and has a long reaction time, and the use of inflammable materials or reagents having low safety is required, and thus industrial mass production is almost impossible with very low economic efficiency.

In the above patent, the compound represented by Chemical Formula 1 is only prepared in an oil state. However, a compound in an oil state is not suitable for development as a medicament, and has a disadvantage in that it is difficult to remove the residual solvent and that the compound is not easy to industrially handle.

Therefore, there is a need for developing a compound in a solid form, which is pharmaceutically useful, easy to handle during preparation, and capable of stable production, and a preparation method thereof.

Prior Art Reference

Patent Document

(Patent Document 0001) Korean Registered Patent No. KR 1799010 B1

(Patent Document 0002) International Patent Publication WO 2015/082616 A1

(Patent Document 0003) International Patent Publication WO 2021/246781 A1

(Patent Document 0004) International Patent Publication WO 2000/060044 A1

(Patent Document 0005) International Patent Publication WO 2001/055115 A1

(Patent Document 0006) International Patent Publication WO 2019/182938 A1

(Patent Document 0007) International Patent Publication WO 2002/000626 A1

(Patent Document 0008) Chinese Patent Publication CN 103265479 A

Description of the Invention**Technical Problem**

To solve the problems of the existing preparation method, the present disclosure may provide a novel method for preparing N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholin-4-carboxamide 1,1-dioxide, which is a compound represented by Chemical Formula 1, or a pharmaceutically acceptable salt thereof in an economical, efficient, and safe mass-production manner.

In addition, the present disclosure may provide a novel method for preparing a compound represented by Chemical Formula 8a, a compound represented by Chemical Formula 3, a compound represented by Chemical Formula 5, and a compound represented by Chemical Formula 6, which are main intermediates used in the novel method for preparing the compound of Chemical Formula 1 or a pharmaceutically acceptable salt thereof.

The novel preparation method of the present disclosure may relatively simplify a preparation process by reducing synthesis steps in comparison with an existing known preparation method, and may provide the compound represented by Chemical Formula 1 with high yield and purity due to the efficiency of a post-treatment procedure and a purification method.

Furthermore, reagents and reaction equipment used in the reaction are also easily available, safe reagents and equipment are used, and the reaction conditions are relatively mild. In addition, a process such as column chromatography, etc., is not required and a process procedure is efficient, thereby enabling a large-scale production, a safe production process, and an economical production due to remarkably reduced costs.

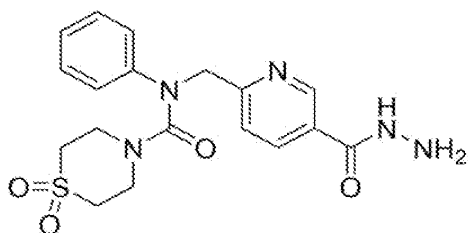
The present disclosure provides a novel crystalline form of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide and a preparation method thereof.

Technical Solution

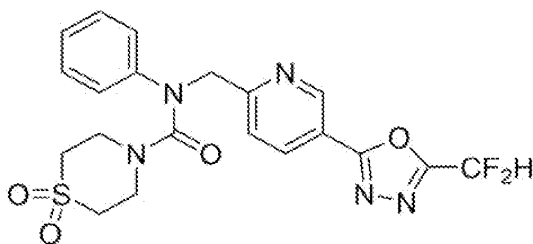
The present disclosure provides a novel method for preparing a compound represented by Chemical Formula 1 and intermediates used for preparing the compound represented by Chemical Formula 1, which are a compound represented by Chemical Formula 8a, a compound represented by Chemical Formula 3, a compound represented by Chemical Formula 5, and a compound represented by Chemical Formula 6.

The present disclosure provides a method for preparing a compound represented by Chemical Formula 1 below, the method including in-situ preparation of a compound represented by Chemical Formula 1 below from a compound represented by Chemical Formula 6 below:

[Chemical Formula 6]



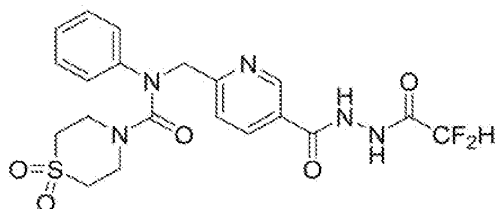
[Chemical Formula 1]



In the related art, a compound represented by Chemical Formula 9 below is prepared through an N-acylation reaction from the compound represented by Chemical Formula 6, which is then separated and purified to obtain a compound represented by Chemical Formula 9. After that, the compound represented by Chemical Formula 1 is prepared from the compound represented by Chemical Formula 9

below through a cyclization reaction using expensive 1-methoxy-N-triethylammoniosulfonyl-methanimidate (Burgess reagent):

[Chemical Formula 9]



However, the present disclosure does not use the expensive 1-methoxy-N-triethylammoniosulfonyl-methanimidate (Burgess reagent) and does not discretely separate and purify the compound represented by Chemical Formula 9 from the compound represented by Chemical Formula 6 unlike the above related art to prepare the compound represented by Chemical Formula 1 by continuously performing two reactions (N-acylation reaction/cyclization reaction) through in-situ synthesis.

In addition, the present disclosure may prepare the compound represented by Chemical Formula 1 using only a general reaction device employed for preparing the compound without a special reaction device such as a microwave.

Further, the present disclosure may obtain the compound represented by Chemical Formula 1 without a separation and purification process such as column chromatography, and thus may enable the mass production of the compound represented by Chemical Formula 1 on an industrial scale and may be economical due to a high production yield. Furthermore, the compound represented by Chemical Formula 1 may be obtained with high purity without using column chromatography.

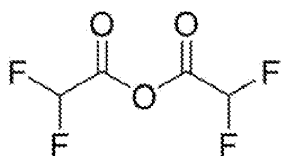
In other words, the present disclosure may mass-produce the compound represented by Chemical Formula 1 at a high yield without a complicated process, and at the same time, may obtain the compound represented by Chemical Formula 1 with a high purity.

In an exemplary embodiment of the present invention, the step of in-situ preparing the compound represented by Chemical Formula 1 from the compound represented by Chemical Formula 6 may be performed in the presence of a base. When the preparation is performed under the base, the reaction yield and purity may be excellent. For example, the base may be triethylamine, N,N-diisopropylethylamine (DIPEA), pyridine, imidazole, or a mixture thereof.

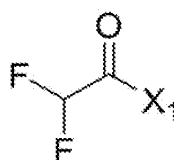
In an exemplary embodiment of the present invention, the base may be imidazole. When the base is imidazole, not only reaction yield may be improved but also reaction selectivity may be excellent to minimize the occurrence of by-products, thus requiring no complicated purification process.

In an exemplary embodiment of the present invention, the compound represented by Chemical Formula 1 may be prepared by using at least one of a compound represented by [Chemical Formula A] below and a compound represented by [Chemical Formula B] below, and the compound represented by Chemical Formula 6 as a reaction material.

[Chemical Formula A]



[Chemical Formula B]



In above Chemical Formula B, X₁ may be F, Cl, Br or I.

In an exemplary embodiment of the present invention, the compound represented by Chemical Formula 6 may directly react with the compound represented by Chemical Formula A or B to prepare the compound represented by Chemical Formula 1. In this case, both the N-acylation reaction and the intramolecular cyclization reaction may be performed in an in-situ manner to prepare the compound represented by Chemical Formula 1 from the compound represented by Chemical Formula 6 without a

different separation and purification process for the compound represented by Chemical Formula 9 unlike the related art, thereby remarkably simplifying the reaction process.

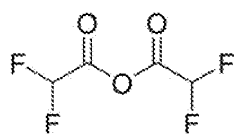
In an exemplary embodiment of the present invention, the method for preparing the compound represented by Chemical Formula 1 from the compound represented by Chemical Formula 6 may be performed in the presence of a base. In this case, the occurrence of by-products may be remarkably reduced, and the yield may also be remarkably improved, which may be advantageous for mass production.

In an exemplary embodiment of the present invention, the method for preparing the compound represented by Chemical Formula 1 from the compound represented by Chemical Formula 6 in the presence of a base may include:

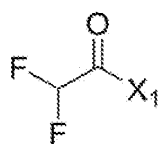
a) preparing a reaction part 1 including a compound represented by Chemical Formula A or B below and a base; and

b) mixing the reaction part 1 with a reaction part 2 including the compound represented by Chemical Formula 6 to prepare the compound represented by Chemical Formula 1:

[Chemical Formula A]



[Chemical Formula B]



In above Chemical Formula B, X₁ may be F, Cl, Br or I.

In an exemplary embodiment of the present invention, in the preparation method, a reaction between the compound represented by Chemical Formula 6 and the compound represented by Chemical Formula A, such as difluoroacetic anhydride, or the compound represented by Chemical Formula B (particularly, the compound represented by Chemical Formula A) may be performed in the presence of

a base. When the reaction is performed under the base, the reaction yield and purity may be excellent. For example, the base may be triethylamine, N,N-diisopropylethylamine (DIPEA), pyridine, imidazole, or a mixture thereof.

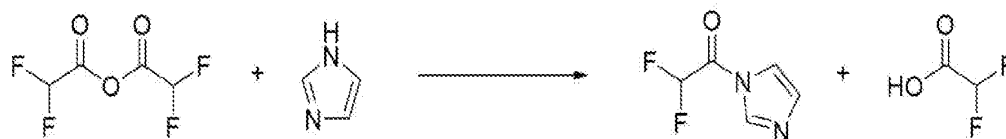
In an exemplary embodiment of the present invention, the base may be imidazole, particularly, when the compound represented by the Chemical Formula 6 is reacted with the compound represented by Chemical Formula A, such as difluoroacetic anhydride, the base may be imidazole. When the base is imidazole, not only reaction yield may be further improved but also reaction selectivity may be excellent to minimize occurrence of by-products, and thus a complicated purification process may not be required.

In an exemplary embodiment of the present invention, the amount of the compound represented by Chemical Formula A or Chemical Formula B, particularly difluoroacetic anhydride and the base, which are used, may be 2.0 to 4.0 equivalents, particularly 2.5 to 3.5 equivalents, per 1 equivalent of the compound represented by Chemical Formula 6.

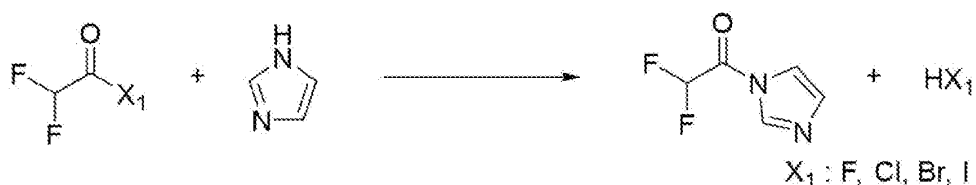
In an exemplary embodiment of the present invention, a reaction molar ratio of the compound represented by Chemical Formula A or B, particularly difluoroacetic anhydride and the base may be 2:1 to 1:2, particularly 1.2:1 to 1:1.2, and more particularly 1:1.

In an exemplary embodiment of the present invention, in Step a), the compound represented by Chemical Formula A or B, particularly difluoroacetic anhydride, may react with imidazole to produce a carboimidazole derivative (the compound represented by Chemical Formula C).

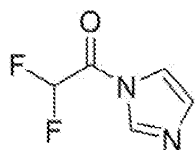
[Reaction formula A]



[Reaction formula B]



[Reaction formula C]



Even when the compound represented by Chemical Formula A or B used in the method for preparing the compound represented by Chemical Formula 1, particularly difluoroacetic anhydride directly reacts with the compound represented by Chemical Formula 6 as a reaction material without first reacting with a base, an in-situ reaction may be performed at a high yield. In this case, however, the reaction may rapidly proceed to produce not only the compound represented by Chemical Formula 1 but also three or more by-products, and out of which by-products with the difluoromethyl group ($-\text{CF}_2$) removed from the compound represented by Chemical Formula 1 may be hardly removed by a general purification method used in mass production such as recrystallization, which may be somewhat disadvantageous for mass production.

When the compound represented by Chemical Formula A or Chemical Formula B, particularly, difluoroacetic anhydride reacts with a base, for example, imidazole, a carboimidazole derivative such as the compound represented by Chemical Formula C may react with the compound represented by Chemical Formula 6. In this case, the occurrence of by-products may be remarkably inhibited and the compound represented by Chemical Formula 1 may be produced in-situ from the compound represented by Chemical Formula 6, which may be more advantageous for mass production.

According to an example of the present invention, in the step of preparing reaction part 1 of

above Step a), the mixture containing the solvent and the base, for example, imidazole may be mixed with the compound represented by Chemical Formula A or B, particularly, difluoroacetic anhydride, in which a temperature may be maintained at 30°C or less, particularly 0°C to 30°C, more particularly 10 to 25°C, and even more particularly 10 to 20°C.

According to an exemplary embodiment of the present invention, Step a) may include:

preparing a mixture including imidazole and a solvent;

cooling the mixture to 0 to 10°C; and

adding the compound represented by Chemical Formula A or Chemical Formula B, particularly difluoroacetic anhydride, to the cooled mixture.

In an exemplary embodiment of the present invention, there may be further included a step of stirring after completely adding the compound represented by Chemical Formula A or Chemical Formula B, in which the step of stirring may be more advantageous for the production of a carboimidazole derivative such as the compound represented by Chemical Formula C, and the stirring may be performed at room temperature for one hour or more.

In an exemplary embodiment of the present invention, in the mixture including imidazole and solvent, the solvent used may be dichloromethane, N,N-dimethylacetamide, N,N-dimethylformamide, tetrahydrofuran, dimethylsulfoxide, acetonitrile, toluene, xylene, or a mixture thereof. Preferably, the solvent used may be dichloromethane, acetonitrile, N,N-dimethylacetamide, toluene, tetrahydrofuran, or a mixture thereof, and particularly dichloromethane.

In an exemplary embodiment of the present invention, in Step b), the compound represented by Chemical Formula 1 may be prepared through an N-acylation reaction of a carboimidazole derivative, which is the intermediate prepared in Step a), with the compound represented by Chemical Formula 6, and a subsequent intramolecular cyclization reaction. In other words, both the N-acylation reaction and

the intramolecular cyclization reaction in Step b) may be performed in-situ to prepare the compound represented by Chemical Formula 1 from the compound represented by Chemical Formula 6 without a different separation and purification process for the compound represented by Chemical Formula 9 unlike the related art, thereby remarkably simplifying the reaction process, remarkably reducing the occurrence of by-products, and remarkably enhancing the yield, which may be advantageous for mass production.

In an exemplary embodiment of the present invention, Step b) may include:

preparing a reaction part 2 including the compound represented by Chemical Formula 6 and a solvent; and

reacting the reaction part 2 and the reaction part 1.

In an exemplary embodiment of the present invention, the step of reacting the reaction part 2 and the reaction part 1 may be performed by adding the reaction part 1 to the reaction part 2, or may be performed by adding the reaction part 2 to the reaction part 1, and particularly may be performed by adding the reaction part 1 to the reaction part 2.

According to exemplary embodiments of the present invention, in Step b), a reaction part 1 including a base (e.g., imidazole) and a carboimidazole derivative such as a compound represented by Chemical Formula A or Chemical Formula B, particularly, a compound represented by Chemical Formula C generated by a reaction with difluoroacetic anhydride, may be added to a reaction part 2 including the solvent and the compound represented by Chemical Formula 6.

In exemplary embodiments of the present invention, a temperature may be maintained at 5°C or less, particularly at -15 to 5°C, and more particularly at -10 to 5°C during the step of adding the reaction part 1 to the reaction part 2.

In exemplary embodiments of the present invention, after adding the reaction part 1 to the reaction part 2, the mixture including the reaction part 1 and the reaction part 2 may be heated to 20°C or higher, particularly 20 to 45°C, and more particularly 30 to 40°C.

In exemplary embodiments of the present invention, the solvent used in the reaction part 2 may be dichloromethane, N,N-dimethylacetamide, N,N-dimethylformamide, tetrahydrofuran, dimethylsulfoxide, acetonitrile, toluene, xylene, or a mixture thereof. Preferably, the solvent used may be dichloromethane, acetonitrile, N,N-dimethylacetamide, toluene, tetrahydrofuran, or a mixture thereof, and particularly dichloromethane.

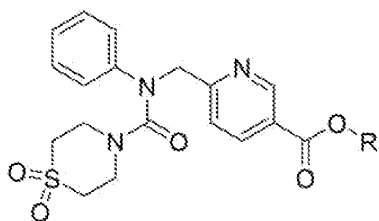
In exemplary embodiments of the present invention, the solvent included in a reaction part 1 and the solvent included in a reaction part 2 may be the same or different, particularly the same, and more particularly dichloromethane.

The present invention provides a method for preparing a compound represented by Chemical Formula 6 below.

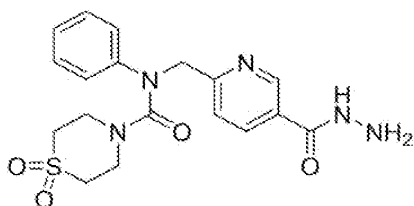
In the present disclosure, the method for preparing the compound represented by the Chemical Formula 6 may include:

preparing a compound represented by Chemical Formula 6 below from hydrazine (N₂H₄) or a hydrate thereof and a compound represented by Chemical Formula 5 below in the presence of a solvent including a C1 to C6 linear or branched alcohol or including a mixture of a C1 to C6 linear or branched alcohol and water.

[Chemical Formula 5]



[Chemical Formula 6]



In above Chemical Formula 5, R may be C1-C6 linear or branched alkyl or benzyl, particularly methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl or benzyl, more particularly methyl, ethyl, isopropyl, and even more particularly methyl.

In exemplary embodiments of the present invention, the reaction may proceed at a high yield under mild conditions without the use of microwaves.

In exemplary embodiments of the present invention, the preparation method may be a step of obtaining a compound of Chemical Formula 6, which is a hydrazide derivative, through a hydrazidation reaction of the compound represented by Chemical Formula 5 and hydrazine or a hydrate thereof.

In exemplary embodiments of the present invention, when the solvent is a C1 to C6 linear or branched alcohol, the C1 to C6 linear or branched alcohol may be methanol, isopropyl alcohol, butanol, or a mixture thereof, and particularly methanol. In a small production of about 100 g or less, alcohol (e.g., methanol) may be used alone as the solvent.

In exemplary embodiments of the present invention, the solvent may be a C1 to C6 linear or branched alcohol and water (e.g., distilled water), in which the C1 to C6 linear or branched alcohol may be a mixture of water and at least one selected from methanol, ethanol, isopropyl alcohol, and butanol, and particularly the solvent may be a mixture of methanol and water.

In exemplary embodiments of the present invention, the use of mixture including alcohol and water as the solvent may increase the stability of hydrazine or a hydrate thereof and simultaneously increase the reactivity. When only alcohol is used as a single solvent in a production process requiring a scale of Kg unit or more, a phenomenon may occur in which the compound represented by Chemical

Formula 6 is precipitated during the reaction, and subsequently the compound represented by Chemical Formula 5, which is a starting material, may be also precipitated, such that the reaction may not be completed. Particularly, the compound represented by Chemical Formula 6 is well dissolved in distilled water in a production process required by a scale of Kg unit or more. Thus, when the distilled water is mixed in the solvent, precipitation of the compound represented by Chemical Formula 6 may not occur during the reaction and the reaction may continue to proceed, such that the reaction may be completed.

In exemplary embodiments of the present invention, when the solvent is a mixture of alcohol and water (e.g., distilled water), a volume ratio of alcohol:water (e.g., distilled water) may be about 10:1 to about 1:1, and particularly about 2:1.

In exemplary embodiments of the present invention, the amount of hydrazine or a hydrate thereof used may be 3 to 10 equivalents, particularly 5 to 7 equivalents, per 1 equivalent of the compound represented by Chemical Formula 5.

In exemplary embodiments of the present invention, the reaction of the compound represented by Chemical Formula 5 with hydrazine or a hydrate thereof may be performed at 75°C or less, particularly at 40 to 70°C, and more particularly at 58 to 68°C.

In exemplary embodiments of the present invention, there may be further included a step of purifying the compound represented by Chemical Formula 6 generated by the reaction of the compound represented by Chemical Formula 5 with hydrazine or a hydrate thereof.

In exemplary embodiments of the present invention, in the step of purifying, a C1 to C6 linear or branched alcohol may be added as a solvent, particularly methanol, ethanol, isopropyl alcohol, butanol or a mixture thereof may be added as a solvent, and more particularly ethanol may be added as a solvent.

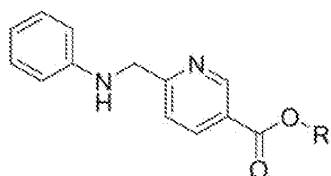
In exemplary embodiments of the present invention, the solvent used in the reaction of the compound represented by Chemical Formula 5 with hydrazine or a hydrate thereof may include a mixture of methanol and water (e.g., distilled water), and ethanol may be added as a solvent in the step of

purifying the compound represented by Chemical Formula 6.

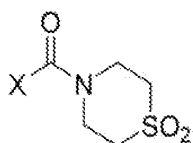
The present disclosure provides a method for preparing a compound represented by Chemical Formula 5 below.

In the present disclosure, the method for preparing the compound represented by Chemical Formula 5 may include a step of reacting the compound represented by Chemical Formula 3 with the compound represented by Chemical Formula 4 in the presence of a base to prepare the compound represented by Chemical Formula 5:

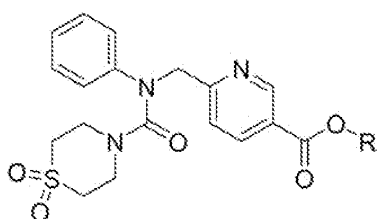
[Chemical Formula 3]



[Chemical Formula 4]



[Chemical Formula 5]



In above Chemical Formulas 3 and 5, R is C1-C6 linear or branched alkyl or benzyl. In above Chemical Formula 4, X may be F, Cl, Br or I. Particularly, in above Chemical Formulas 3 and 5, R may be methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, or benzyl. In above Chemical Formula 4, X may be Cl, Br or I. More particularly, in Chemical Formulas 3 and 5, R may be methyl or benzyl. In

above Chemical Formula 4, X may be Cl, and even more particularly R may be methyl and X may be Cl.

In exemplary embodiments of the present invention, the reaction of the compound represented by Chemical Formula 3 with the compound represented by Chemical Formula 4 may be performed in the presence of a base, and the base used may be triethylamine, N,N-diisopropylethylamine, imidazole, pyridine, sodium hydrogen carbonate, sodium carbonate, potassium hydrogen carbonate, potassium carbonate, or a mixture thereof, particularly triethylamine, N,N-diisopropylethylamine, imidazole, sodium hydrogen carbonate, or a mixture thereof, and more particularly N,N-diisopropylethylamine.

In exemplary embodiments of the present invention, the base may be used in an amount of 1.0 to 3.0 equivalents, and particularly in an amount of 1.3 to 2.0 equivalents, per 1 equivalent of the compound represented by Chemical Formula 3.

In exemplary embodiments of the present invention, the compound represented by Chemical Formula 4 may be used in an amount of 1.0 to 3.0 equivalents, and particularly in an amount of 1.1 to 1.5 equivalents, per 1 equivalent of the compound represented by Chemical Formula 3.

In exemplary embodiments of the present invention, in the reaction of the compound represented by Chemical Formula 3 with the compound represented by Chemical Formula 4, the solvent used may be N,N-dimethylacetamide, N,N-dimethylformamide, tetrahydrofuran, dimethylsulfoxide, toluene, benzene, xylene or a mixture thereof, particularly N,N-dimethylacetamide, tetrahydrofuran, toluene or a mixture thereof, and more particularly toluene.

In exemplary embodiments of the present invention, a reaction temperature of the compound represented by above Chemical Formula 3 and the compound represented by above Chemical Formula 4 may be performed at 60 to 110°C, particularly 75 to 100°C, and more particularly 75 to 90°C.

In exemplary embodiments of the present invention, after the reaction of the compound represented by Chemical Formula 3 and the compound represented by Chemical Formula 4, a purification process may be performed to obtain the compound represented by Chemical Formula 5 having a high

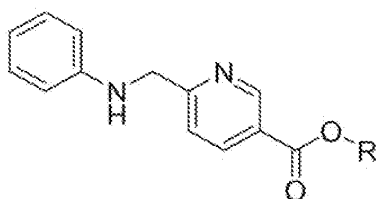
purity of 99% or more.

In exemplary embodiments of the present invention, the solvent used in the purification process may be methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl tertiary butyl ether (MTBE), diisopropyl ether, heptane, hexane, or a mixture thereof, and the compound represented by Chemical Formula 5 may be purified through slurring or recrystallization in the solvent. Particularly, the solvent used in the purification process may be methanol, ethanol, isopropyl alcohol, methyl tertiary butyl ether (MTBE), diisopropyl ether, or a mixture thereof, and more particularly at least one selected from the group consisting of methanol and methyl tertiary butyl ether (MTBE). For example, both methanol and methyl tertiary butyl ether (MTBE) may be used.

In examples of the present invention, the purification process for the compound represented by Chemical Formula 5 may be performed at 30 to 70°C, and particularly at 30 to 65°C.

The present disclosure may provide a method for preparing the compound represented by Chemical Formula 3:

[Chemical Formula 3]

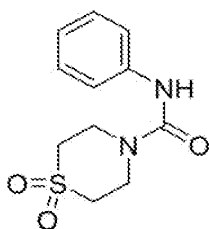


In above Chemical Formula 3, R may be C1-C6 linear or branched alkyl or benzyl, particularly methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl or benzyl, more particularly methyl, ethyl, isopropyl, and even more particularly methyl.

In the related art, the compound represented by Chemical Formula 6 may be prepared from a compound represented by Chemical Formula 10 below, which is obtained by reacting aniline with a

thiomorpholine derivative in the presence of triphosgene, through a substitution reaction and a hydrazidation reaction, but there are problems such as the use of triphosgene, which is vulnerable for stability, and sodium hydride, which is an inflammable material, long reaction time, low preparation yield, low preparation efficiency, low economic efficiency, as well as the use of microwaves in the hydrazidation reaction, which may be unsuitable for mass production.

[Chemical Formula 10]



In the preparation method according to the present invention, the compound represented by Chemical Formula 3, which may be easily obtained at high yield and with high purity, may be used as an intermediate.

In the preparation method according to the present invention, the compound represented by Chemical Formula 3 may use reaction reagents and preparation equipment which are generally easy to obtain and have stability and safety confirmed, may prepare a target compound with high purity on the basis of a short reaction time and a high preparation yield, may enable commercial mass-production due to an efficient process procedure, and may achieve safety and economic cost reduction.

In exemplary embodiments of the present invention, the preparation of the compound represented by Chemical Formula 3 may be performed by the following two methods.

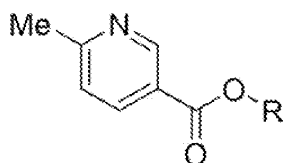
In the present disclosure, a preparation method 1 of a compound represented by Chemical Formula 3 below may include:

- a) preparing a compound represented by Chemical Formula 8 below from a compound

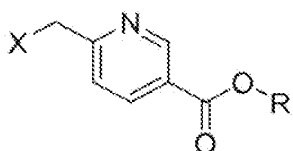
represented by Chemical Formula 7 below by using a halogenating reagent; and

b) preparing the compound represented by Chemical Formula 3 by reacting the compound represented by Chemical Formula 8 below with aniline in the presence of a base:

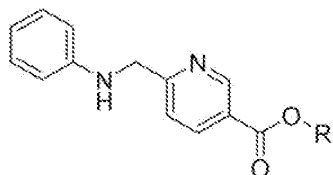
[Chemical Formula 7]



[Chemical Formula 8]



[Chemical Formula 3]



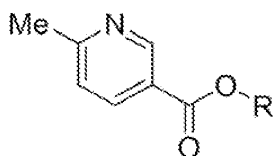
In above Chemical Formulas 3, 7 and 8, R may be C1-C6 linear or branched alkyl or benzyl. In Chemical Formula 8, X may be F, Cl, Br or I. Particularly, in above Chemical Formulas 3, 7 and 8, R may be methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, or benzyl. In above Chemical Formula 8, X may be Cl, Br or I. More particularly, in above Chemical Formulas 3, 7 and 8, R may be methyl or benzyl. In above Chemical Formula 8, X may be Cl, and even more particularly, R may be methyl and X may be Cl.

In exemplary embodiments of the present invention, the preparation method 1 of the compound represented by Chemical Formula 3 is performed in two steps, but when preparing the compound

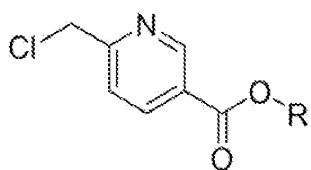
represented by Chemical Formula 3, the method may use the compound represented by Chemical Formula 7, which is a low-priced starting material. In the process of preparing the compound represented by Chemical Formula 8, a different purification and separation process may not be required, and dangerous reagents may not be used, which may be advantageous for mass production with an excellent production yield and safety. In other words, in a concentrate state with the solvent concentrated after preparing the compound represented by Chemical Formula 8, the compound represented by Chemical Formula 8 may be used as a reactant for preparing the compound represented by Chemical Formula 3 in the concentrate state per se without separating the compound into a solid state.

The present disclosure provides a method for preparing a compound represented by Chemical Formula 8a below from a compound represented by Chemical Formula 7 below by using a trichloroisocyanuric acid (TCCA) reagent alone:

[Chemical Formula 7]



[Chemical Formula 8a]



In above Chemical Formulas 7 and 8a, R may be C1-C6 linear alkyl or benzyl. Particularly, in above Chemical Formulas 7 and 8a, R may be methyl, ethyl, n-propyl, n-butyl, n-pentyl, or benzyl, more particularly in Chemical Formulas 7 and 8a, R may be methyl or benzyl, and even more particularly R may be methyl.

In exemplary embodiments of the present invention, in the method for preparing the compound

represented by above Chemical Formula 3, the halogenating reagent of Step a) may be iodine, copper iodide, bromine, N-bromosuccinimide (NBS), N-chlorosuccinimide (NCS), trichloroisocyanuric acid (TCCA) or a mixture thereof, particularly N-bromosuccinimide (NBS), trichloroisocyanuric acid (TCCA) or a mixture thereof, and more particularly trichloroisocyanuric acid (TCCA).

In exemplary embodiments of the present invention, in the method for preparing the compound represented by Chemical Formula 3, above X may be Cl in Step a). In this case, the halogenating reagent may be trichloroisocyanuric acid (TCCA). In the present invention, a halogenation reaction (particularly, a chlorination reaction) may be performed by using trichloroisocyanuric acid (TCCA) in one step, thereby increasing reaction efficiency and simplifying the reaction process, which may be advantageous for mass production.

In exemplary embodiments of the present invention, the halogenating reagent used in the method for preparing the compound represented by Chemical Formula 8a from the compound represented by Chemical Formula 7 may be trichloroisocyanuric acid (TCCA) alone.

In exemplary embodiments of the present invention, in Step a) in the method for preparing the compound represented by Chemical Formula 3, and in the method for preparing a compound represented by Chemical Formula 8a from the compound represented by Chemical Formula 7, a step of preparing a compound represented by Chemical Formula 8, particularly Chemical Formula 8a from the compound represented by Chemical Formula 7 using a halogenating reagent may be performed without using a benzamide catalyst.

In the related art, a step of treating the compound represented by Chemical Formula 7 with a halogenating reagent to obtain a benzyl halide derivative may be synthesized by the known methods (WO 2021/246781, WO 2000/060044, WO 2001/055115, WO 2019/182938, WO 2002/000626), but has disadvantages of long reaction time and low yield. Particularly, methods for chlorinating the compound represented by Chemical Formula 7 have a disadvantage in that chlorination is enabled through two steps

via an oxidation step and a chlorination step. However, the present disclosure has solved such problem by using trichloroisocyanuric acid (TCCA) for a successful chlorination within a short reaction time through only one step, and may prepare the compound represented by Chemical Formula 8, particularly Chemical Formula 8a from the compound represented by Chemical Formula 7 with high efficiency and simple processes.

In addition, among the methods known in the art, there is also a method (CN 103265479) using trichloroisocyanuric acid (TCCA), but a substituent introduced in pyridine is limited to a material of a tertiary butyl ester group, and a benzamide catalyst needs to be used. If a pyridine derivative with the tert-butyl ester group introduced thereinto is used as an intermediate by applying a conventionally known method, a hydrazidation reaction of the compound to be prepared later with hydride or a hydrate thereof may not proceed.

The present disclosure may provide an efficient chlorination reaction using trichloroisocyanuric acid (TCCA) alone without using a benzamide catalyst in the compound represented by Chemical Formula 8, when X is Cl, in which a starting material is a material, in which a substituent capable of facilitating even a hydrazidation reaction is introduced into a pyridine derivative, such as a methyl ester group, unlike the conventional method.

In exemplary embodiments of the present invention, the solvent used in Step a) of the method for preparing the compound represented by Chemical Formula 3 and in the method for preparing the compound represented by Chemical Formula 8 from the compound represented by Chemical Formula 7 by using a halogenating reagent may be tetrahydrofuran, ethyl acetate, acetic acid, toluene, xylene, benzene, dichloromethane, dichloroethane, chloroform, diisopropyl ether, methyl tertiary butyl ether, or a mixture thereof.

In exemplary embodiments of the present invention, when the halogenating reagent is N-bromosuccinimide (NBS), acetic acid may be used as a solvent, and when the halogenating reagent is

trichloroisocyanuric acid (TCCA), dichloromethane may be used as a solvent.

In exemplary embodiments of the present invention, when a halogenating reagent is N-bromosuccinimide (NBS) in Step a) of the method for preparing the compound represented by Chemical Formula 3 and in the method for preparing the compound represented by Chemical Formula 8 from the compound represented by Chemical Formula 7 by using the halogenating reagent, the halogenating reagent may be used in an amount of 2.0 to 4.0 equivalents, particularly 3.0 to 3.5 equivalents, per 1 equivalent of the compound represented by Chemical Formula 7 as a starting material.

In exemplary embodiments of the present invention, when a halogenating reagent is trichloroisocyanuric acid (TCCA) in Step a) of the method for preparing the compound represented by Chemical Formula 3 and in the method for preparing the compound represented by Chemical Formula 8a from the compound represented by Chemical Formula 7 by using the halogenating reagent, the halogenating reagent may be used in an amount of 1.0 to 2.0 equivalents, particularly 1.1 to 1.5 equivalents, per 1 equivalent of the compound represented by Chemical Formula 7, which is a starting material.

In exemplary embodiments of the present invention, when a halogenating reagent is N-bromosuccinimide (NBS) in Step a) of the method for preparing the compound represented by Chemical Formula 3, a reaction temperature may be performed at 50 to 80°C, and particularly at 55 to 65°C.

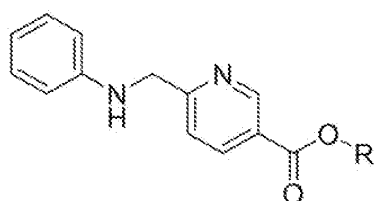
In exemplary embodiments of the present invention, when a halogenating reagent is trichloroisocyanuric acid (TCCA) in Step a) of the method for preparing the compound represented by Chemical Formula 3 and in the method for preparing the compound represented by Chemical Formula 8a from the compound represented by Chemical Formula 7 by using the halogenating reagent, a reaction temperature may be performed at 10 to 30°C, and particularly at 15 to 20°C.

In exemplary embodiments of the present invention, the compound represented by Chemical Formula 8 may be subjected into N-alkylation reaction with aniline in the presence of a base to obtain

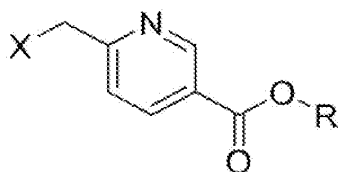
the compound represented by Chemical Formula 3.

The present disclosure may provide a method for preparing a compound represented by Chemical Formula 3 below by reacting a compound represented by Chemical Formula 8 below with aniline in the presence of a base:

[Chemical Formula 3]



[Chemical Formula 8]



In above Chemical Formulas 3 and 8, R may be C1-C6 linear or branched alkyl or benzyl. In Chemical Formula 8, X may be F, Cl, Br or I. Particularly, in above Chemical Formulas 3 and 8, R may be methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, or benzyl. In above Chemical Formula 8, X may be Cl, Br or I. More particularly, in Chemical Formulas 3 and 8, R may be methyl or benzyl. In above Chemical Formula 8, X may be Cl, and even more particularly R may be methyl and X may be Cl.

In the related art (WO 2015/082616), N-alkylation is performed using aniline substituted with a protecting group, and then a deprotection reaction is performed to obtain a hydrochloride of a compound represented by Chemical Formula 3, but in the preparation method of the present disclosure, a reaction may be directly performed without a protection/deprotection reaction, thereby shortening a process step.

In exemplary embodiments of the present invention, when X is Cl in the compound represented

by Chemical Formula 8, in order to increase a reaction rate, a halogen exchange reagent, etc., such as potassium bromide, potassium iodide, tetrabutylammonium bromide (TBAB) or a mixture thereof may be used, and particularly potassium iodide may be used, in which the halogen exchange reagent may be used in an amount of 0.1 to 1.0 equivalents, and particularly 0.3 to 0.5 equivalents per 1 equivalent of the compound represented by Chemical Formula 8.

In exemplary embodiments of the present invention, the solvent used in the step of reacting the compound represented by Chemical Formula 8 with aniline may be N,N-dimethylacetamide, N,N-dimethylformamide, tetrahydrofuran, dimethyl sulfoxide, acetonitrile or a mixture thereof. Specifically, N,N-dimethylacetamide, N,N-dimethylformamide, or a mixture thereof may be used, and more specifically N,N-dimethylacetamide may be used.

In exemplary embodiments of the present invention, the base used in the step of reacting the compound represented by Chemical Formula 8 with aniline may be sodium hydrogen carbonate, sodium carbonate, potassium hydrogen carbonate, potassium carbonate, triethylamine, diisopropylethylamine, or a mixture thereof, and particularly sodium hydrogen carbonate or sodium carbonate.

In exemplary embodiments of the present invention, in the step of reacting the compound represented by Chemical Formula 8 with aniline, the base may be used in an amount of 1.0 to 3.0 equivalents, particularly 1.5 to 2.0 equivalents per 1 equivalent of the compound represented by Chemical Formula 8.

In exemplary embodiments of the present invention, the aniline may be used in an amount of 1.0 to 3.0 equivalents, and particularly in an amount of 2.0 to 2.5 equivalents per 1 equivalent of the compound represented by Chemical Formula 8.

In exemplary embodiments of the present invention, the preparation method 1 may further include a purification process for the compound represented by Chemical Formula 3. Through the

purification process, the compound represented by Chemical Formula 3 may be obtained with a purity of 95% or more.

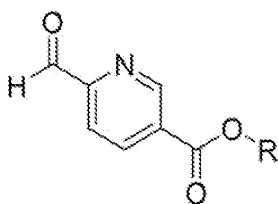
In exemplary embodiments of the present invention, in the purification process, the compound represented by Chemical Formula 3 may be purified through slurring or recrystallization using methanol, ethanol, isopropyl alcohol, butanol, water (e.g., distilled water), or a mixture thereof as a solvent. Particularly, the solvent used in the purification process may be a mixture of one alcohol selected from methanol, ethanol, and isopropyl alcohol with water (e.g., distilled water), and more particularly a mixture of methanol and distilled water.

In exemplary embodiments of the present invention, the purification process for the compound represented by Chemical Formula 3 may be performed at 40 to 60°C, and particularly at 45 to 55°C.

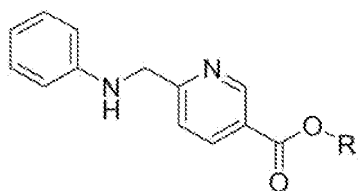
In the present disclosure, a preparation method 2 of the compound represented by above Chemical Formula 3 may include:

preparing a compound represented by Chemical Formula 3 below from a compound represented by Chemical Formula 2 below in the presence of aniline and a reducing agent:

[Chemical Formula 2]



[Chemical Formula 3]



In above Chemical Formula 2 or 3, R may be C1-C6 linear or branched alkyl or benzyl, particularly methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl or benzyl, more particularly methyl, ethyl, isopropyl, and even more particularly methyl.

In exemplary embodiments of the present invention, the preparation method 2 may perform a reductive amination reaction between a compound represented by Chemical Formula 2 and aniline to prepare a compound represented by Chemical Formula 3.

In exemplary embodiments of the present invention, the aniline may be used in an amount of 0.95 to 1.3 equivalents, and particularly in an amount of 0.95 to 1.05 equivalents per 1 equivalent of the compound represented by Chemical Formula 2.

In exemplary embodiments of the present invention, the reducing agent may include sodium borohydride (NaBH_4), sodium cyanoborohydride (NaBH_3CN), sodium triacetoxyborohydride ($\text{NaBH}(\text{OAc})_3$), or a mixture thereof, and particularly sodium triacetoxyborohydride ($\text{NaBH}(\text{OAc})_3$).

In exemplary embodiments of the present invention, the reducing agent may be used in an amount of 1.0 to 2.0 equivalents, and particularly in an amount of 1.3 to 1.7 equivalents per 1 equivalent of the compound represented by Chemical Formula 2.

In exemplary embodiments of the present invention, the reaction for preparing the compound represented by Chemical Formula 3 through the reaction of the compound represented by Chemical Formula 2 with aniline may be performed at a temperature of 10 to 30°C, and particularly at a temperature of 15 to 25°C.

In exemplary embodiments of the present invention, a step of preparing a compound represented

by Chemical Formula 3 below from the compound represented by Chemical Formula 2 may include:

preparing a mixture including the compound of Chemical Formula 2 and aniline; and
reacting the mixture with the reducing agent.

In exemplary embodiments of the present invention, a step of preparing a compound represented by Chemical Formula 3 below from the compound represented by Chemical Formula 2 may include:

preparing a reaction part 1 including the compound represented by Chemical Formula 2, aniline and the solvent; and
reacting the reaction part 1 and a reaction part 2 including the reducing agent and the solvent.

In exemplary embodiments of the present invention, the step of reacting the reaction part 2 and the reaction part 1 may be a step of adding the reaction part 1 to the reaction part 2.

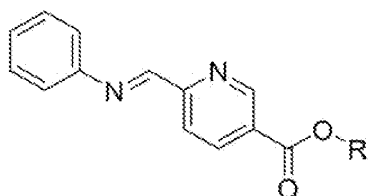
In exemplary embodiments of the present invention, the solvents used in the reaction part 1 and the reaction part 2 may be the same or different, and the solvent used may be tetrahydrofuran, methanol, ethanol, isopropyl alcohol, acetonitrile, dichloromethane, toluene, or a mixture thereof, particularly dichloromethane, and particularly the solvents used in the reaction part 1 and the reaction part 2 may be all dichloromethane.

In exemplary embodiments of the present invention, the compound represented by Chemical Formula 2 may produce an imine intermediate through a reaction with aniline, and after the imine intermediate is produced, a reaction part 1 including the imine intermediate may be added to a reaction part 2 including a reducing agent to perform a reaction.

In exemplary embodiments of the present invention, the preparation of the reaction part 1 may be performed by reacting the compound represented by Chemical Formula 2 with aniline to synthesize an imine intermediate. In this case, the imine intermediate may be synthesized by stirring a mixture of the compound represented by Chemical Formula 2 and a reaction part 1 including aniline, and the stirring may be performed for one to two hours.

In exemplary embodiments of the present invention, the imine intermediate may be a compound represented by Chemical Formula 11 below.

[Chemical Formula 11]



In above Chemical Formula 11, R may be C1-C6 linear or branched alkyl or benzyl, particularly methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl or benzyl, more particularly methyl, ethyl, isopropyl, and even more particularly methyl.

In exemplary embodiments of the present invention, in the step of adding the reaction part 1 to the reaction part 2, the reaction part 1 may be added to the reaction part 2 cooled down to 5°C or less, particularly 0°C to 5°C while maintaining a temperature of 10°C or less, particularly 0°C to 10°C.

In exemplary embodiments of the present invention, after the addition is completed, a temperature of a mixing part including the reaction part 1 and the reaction part 2 may be increased to 15 to 30°C, and particularly to 15 to 25°C.

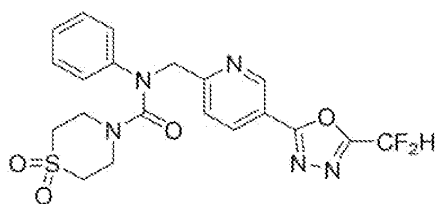
In exemplary embodiments of the present invention, a step of preparing the compound represented by Chemical Formula 3 from the compound represented by Chemical Formula 2 may be performed in the presence of an acid. Particularly, in order to accelerate a reaction rate of production of the imine intermediate, the reaction part 1 may further include an acid additive such as acetic acid. Activation may be sufficiently performed without including an additive in the reaction part 1, but when the acid additive is further included, a reaction in which the compound represented by Chemical Formula 2 is reduced per se may be reduced, and thus the purity of the compound represented by Chemical Formula 3 may be relatively improved.

The present disclosure provides a preparation method 1 for preparing a compound represented by Chemical Formula 1 below.

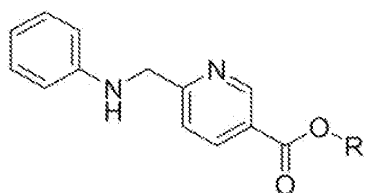
In the present disclosure, a preparation method 1 of the compound represented by Chemical Formula 1 may include:

- 1) preparing a compound represented by Chemical Formula 8 below from a compound represented by Chemical Formula 7 below by using a halogenating reagent;
- 2) preparing a compound represented by Chemical Formula 3 by reacting the compound represented by Chemical Formula 8 with aniline in the presence of a base;
- 3) obtaining a compound represented by Chemical Formula 5 below by reacting the compound represented by Chemical Formula 3 with a compound represented by Chemical Formula 4 below in the presence of a base;
- 4) obtaining a compound represented by Chemical Formula 6 below by reacting hydrazine or a hydrate thereof with the compound represented by Chemical Formula 5; and
- 5) in-situ preparing the compound represented by Chemical Formula 1 from the compound represented by Chemical Formula 6:

[Chemical Formula 1]

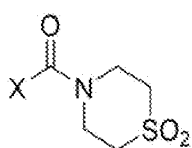


[Chemical Formula 3]



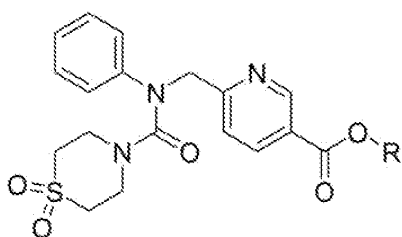
(in above Chemical Formula 3, R may be C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



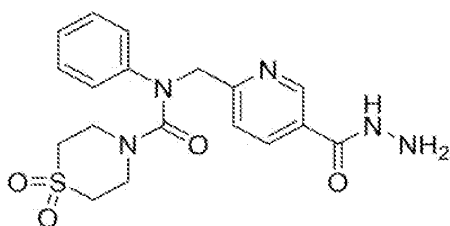
(in above Chemical Formula 4, X may be F, Cl, Br or I)

[Chemical Formula 5]

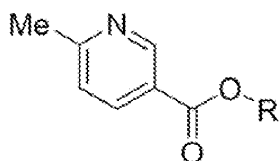


(in above Chemical Formula 5, R may be C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 6]

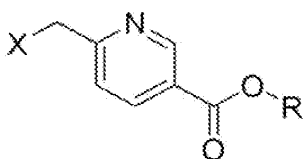


[Chemical Formula 7]



(in above Chemical Formula 7, R may be C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 8]



(in above Chemical Formula 8, R may be C1-C6 linear or branched alkyl or benzyl, and X may be F, Cl, Br or I).

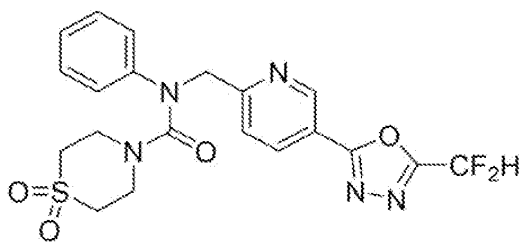
In an exemplary embodiment of the present invention, all of the above-described contents in the method for preparing the compound represented by Chemical Formula 8a, the method for preparing the compound represented by Chemical Formula 3, the method for preparing the compound represented by Chemical Formula 5, the method for preparing the compound represented by Chemical Formula 6, and the method for preparing the compound represented by Chemical Formula 1 may be applied to the above Step 1), Step 2), Step 3), Step 4), and Step 5) of the preparation method 1 for preparing the compound of Chemical Formula 1, which uses the compound represented by Chemical Formula 7 as a starting material and uses the compound represented by Chemical Formula 8, the compound represented by Chemical Formula 3, the compound represented by Chemical Formula 4, the compound represented by Chemical Formula 5, and the compound represented by Chemical Formula 6, unless they are contradictory to each other. For example, reaction conditions, effects and the like such as a solvent, a reducing agent, a halogenating reagent, a base, a temperature, a content, etc., may be all applied to the preparation method 1 for preparing the compound of Chemical Formula 1.

The present disclosure provides a preparation method 2 for preparing a compound represented by Chemical Formula 1 below.

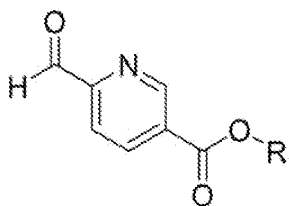
In the present disclosure, a preparation method 2 for preparing the compound represented by Chemical Formula 1 below may include:

- 1) preparing a compound represented by Chemical Formula 3 below from a compound represented by Chemical Formula 2 below in the presence of aniline and a reducing agent;
- 2) obtaining a compound represented by Chemical Formula 5 below by reacting the compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 below in the presence of a base;
- 3) obtaining a compound represented by Chemical Formula 6 below by reacting hydrazine or a hydrate thereof with the compound represented by Chemical Formula 5 below; and
- 4) in-situ preparing the compound represented by Chemical Formula 1 below from the compound represented by Chemical Formula 6 below:

[Chemical Formula 1]

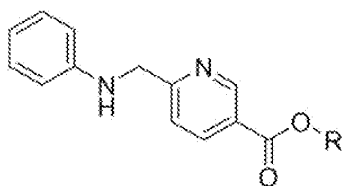


[Chemical Formula 2]



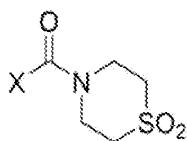
(in above Chemical Formula 2, R may be C1-C6 alkyl or benzyl)

[Chemical Formula 3]



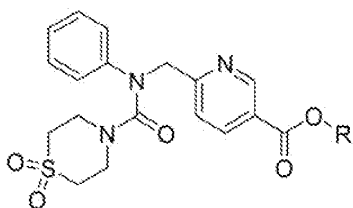
(in above Chemical Formula 3, R may be C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



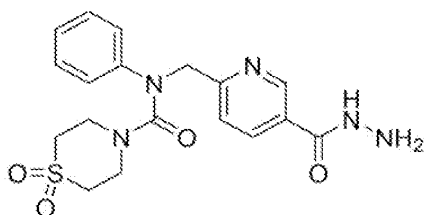
(in which, in above Chemical Formula 4, X may be F, Cl, Br or I)

[Chemical Formula 5]



(in above Chemical Formula 5, R may be C1-C6 linear or branched alkyl or benzyl)

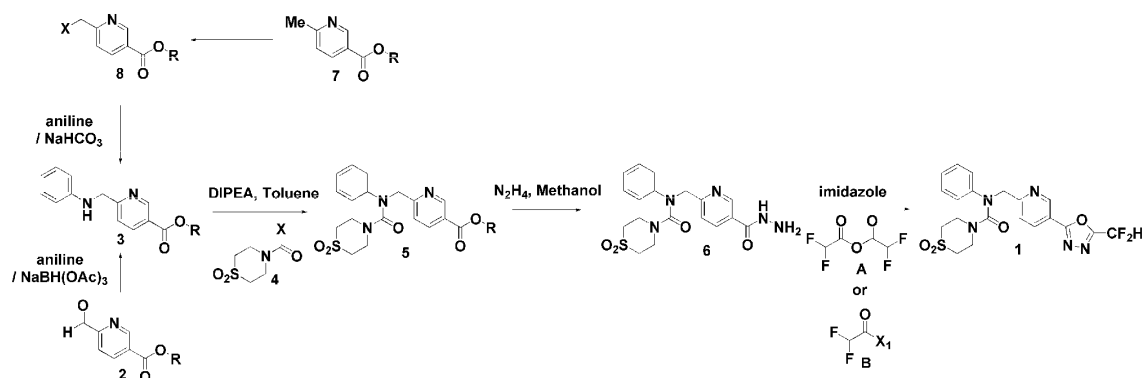
[Chemical Formula 6]



In an exemplary embodiment of the present invention, all of the above-described contents in method 2 for preparing a compound represented by Chemical Formula 3, the method for preparing a compound represented by Chemical Formula 5, the method for preparing a compound represented by Chemical Formula 6, and the method for preparing the compound represented by Chemical Formula 1 may be applied to above Step 1), Step 2), Step 3), and Step 4) of the preparation method 2 for preparing the compound of Chemical Formula 1 which uses the compound represented by Chemical Formula 2 as a starting material and uses the compound represented by Chemical Formula 3, the compound represented by Chemical Formula 4, the compound represented by Chemical Formula 5, and the compound represented by Chemical Formula 6, unless they are contradictory to each other. For example, reaction conditions, effects and the like such as a solvent, a reducing agent, a halogenating reagent, a base, a temperature, a content, etc., may be all applied to the preparation method 2 for preparing the compound of above Chemical Formula 1.

If represented by a reaction formula, preparation methods 1 and 2 for preparing the compound of Chemical Formula 1 according to the present disclosure are the same as represented by [Reaction Formula 2] shown in FIG. 1.

[Reaction Formula 2]



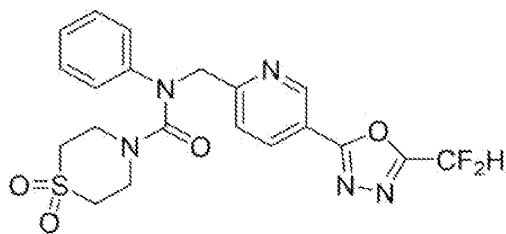
In above reaction formula 2, R may be C1 to C6 linear or branched alkyl or benzyl, above X may be F, Cl, Br or I, and above X1 may be F, Cl, Br or I.

The present disclosure provides a preparation method 3 for preparing a compound represented by Chemical Formula 1 below.

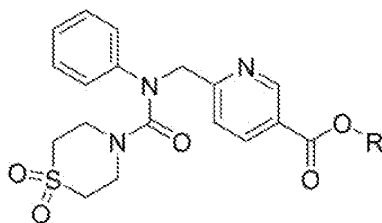
In the present disclosure, preparation method 3 for preparing the compound represented by Chemical Formula 1 below may include:

- 1) obtaining a compound represented by Chemical Formula 6 below by reacting hydrazine or a hydrate thereof with a compound represented by Chemical Formula 5 below; and
- 2) in-situ preparing the compound represented by Chemical Formula 1 below from the compound represented by Chemical Formula 6 below:

[Chemical Formula 1]

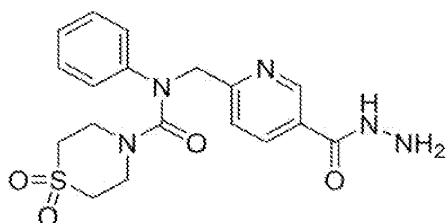


[Chemical Formula 5]



(in above Chemical Formula 5, R may be C1-C6 linear or branched alkyl or benzyl)

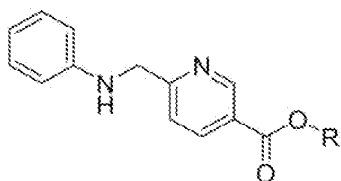
[Chemical Formula 6]



In exemplary embodiments of the present invention, in the preparation method 3 for preparing the compound represented by Chemical Formula 1, the method for preparing the compound represented by Chemical Formula 5 may include:

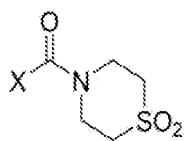
reacting a compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 below in the presence of a base to prepare the compound represented by Chemical Formula 5:

[Chemical Formula 3]



(in above Chemical Formula 3, R may be C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



(in which, in above Chemical Formula 4, X may be F, Cl, Br or I)

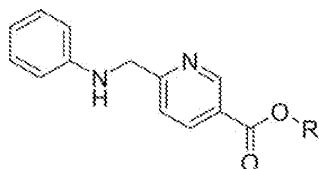
In exemplary embodiments of the present invention, in the preparation method 3 for preparing the compound represented by Chemical Formula 1,

the method for preparing the compound represented by Chemical Formula 5 may include:

preparing a compound represented by Chemical Formula 3 by reacting a compound represented by Chemical Formula 8 below with aniline in the presence of a base; and

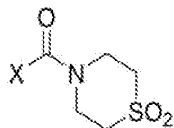
reacting a compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 below in the presence of a base to prepare a compound represented by Chemical Formula 5:

[Chemical Formula 3]



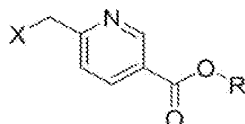
(in above Chemical Formula 3, R may be C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



(in above Chemical Formula 4, X may be F, Cl, Br or I)

[Chemical Formula 8]



(in above Chemical Formula 8, R may be C1-C6 linear or branched alkyl or benzyl, and X may be F, Cl, Br or I)

In exemplary embodiments of the present invention, in the preparation method 3 for preparing the compound represented by Chemical Formula 1,

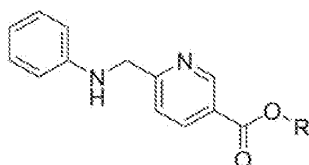
the method for preparing the compound represented by Chemical Formula 5 may include:

preparing a compound represented by Chemical Formula 8 below from a compound represented by Chemical Formula 7 below by using a halogenating reagent;

preparing a compound represented by Chemical Formula 3 by reacting the compound represented by Chemical Formula 8 below with aniline below in the presence of a base; and

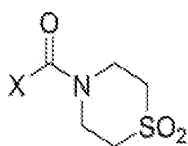
reacting a compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 below in the presence of a base to prepare the compound represented by Chemical Formula 5:

[Chemical Formula 3]



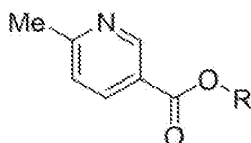
(in which, in above Chemical Formula 3, R may be C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



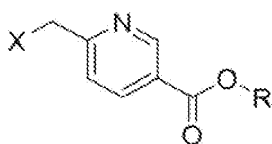
(in which, in above Chemical Formula 4, X may be F, Cl, Br or I)

[Chemical Formula 7]



(in which, in above Chemical Formula 7, R may be C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 8]



(in which, in above Chemical Formula 8, R may be C1-C6 linear or branched alkyl or benzyl, and X may be F, Cl, Br or I)

In exemplary embodiments of the present invention, in the preparation method 3 for preparing the compound represented by above Chemical Formula 1,

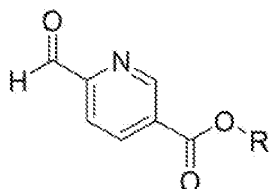
the method for preparing the compound represented by Chemical Formula 5 may include:

preparing a compound represented by Chemical Formula 3 below from a compound represented by Chemical Formula 2 below in the presence of aniline and a reducing agent; and

reacting a compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 below in the presence of a base to prepare the compound represented by

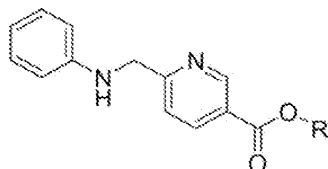
Chemical Formula 5 below:

[Chemical Formula 2]



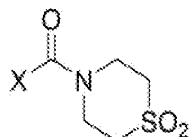
(in above Chemical Formula 2, R may be C1-C6 alkyl or benzyl)

[Chemical Formula 3]



(in above Chemical Formula 3, R may be C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



(in above Chemical Formula 4, X may be F, Cl, Br or I)

In an exemplary embodiment of the present invention, all of the above-described contents in the method for preparing a compound represented by Chemical Formula 8a, method 1 for preparing the compound represented by Chemical Formula 3, method 2 for preparing the compound represented by Chemical Formula 3, the method for preparing the compound represented by Chemical Formula 5, the method for preparing the compound represented by Chemical Formula 6, and the method for preparing

the compound represented by Chemical Formula 1 may be applied to the preparation method 3 for preparing the compound of Chemical Formula 1, unless they are contradictory to each other. For example, reaction conditions, effects and the like such as a solvent, a reducing agent, a halogenating reagent, a base, a temperature, a content, etc., may be all applied to the preparation method 3 for preparing the compound of above Chemical Formula 1.

The present disclosure provides a preparation method 1 for preparing a compound represented by Chemical Formula 5 below.

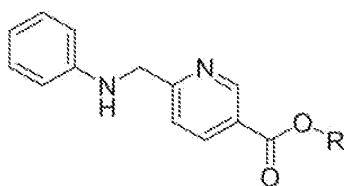
In the present disclosure, the preparation method 1 for preparing the compound represented by Chemical Formula 5 may include:

1) preparing a compound represented by Chemical Formula 8 below from a compound represented by Chemical Formula 7 below by using a halogenating reagent;

2) preparing a compound represented by Chemical Formula 3 by reacting the compound represented by Chemical Formula 8 below with aniline in the presence of a base; and

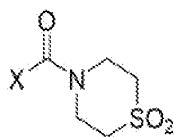
3) reacting a compound represented by Chemical Formula 3 below with a compound represented by formula 4 below in the presence of a base to obtain a compound represented by Chemical Formula 5 below:

[Chemical Formula 3]



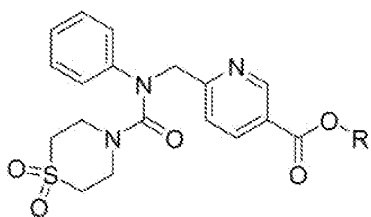
(in above Chemical Formula 3, R may be C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



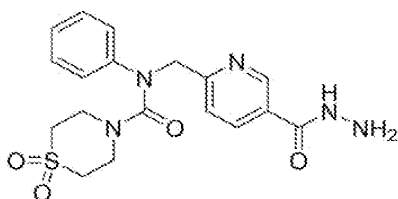
(in above Chemical Formula 4, X may be F, Cl, Br or I)

[Chemical Formula 5]

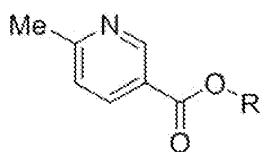


(in above Chemical Formula 5, R may be C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 6]

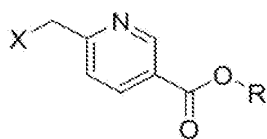


[Chemical Formula 7]



(in above Chemical Formula 7, R may be C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 8]



(in above Chemical Formula 8, R may be C1-C6 linear or branched alkyl or benzyl, and X may be F, Cl, Br or I)

In an exemplary embodiment of the present invention, all of the above-described contents in method 1 for preparing the compound represented by Chemical Formula 3 and the method for preparing the compound represented by Chemical Formula 5 using the compound represented by Chemical Formula 3 as a starting material may be applied to all of above Step 1), Step 2) and Step 3) in the preparation method 1 for preparing a compound of Chemical Formula 5 which uses the compound represented by Chemical Formula 7 as a starting material and uses the compound represented by Chemical Formula 8, the compound represented by Chemical Formula 3, and the compound represented by Chemical Formula 4, , unless they are contradictory to each other. For example, reaction conditions, effects and the like such as a solvent, a reducing agent, a halogenating reagent, a base, a temperature, a content, etc., may be all applied to the preparation method 1 for preparing the compound of above Chemical Formula 5.

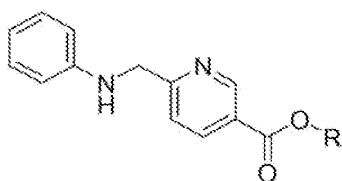
The present disclosure provides a preparation method 2 for preparing a compound represented by Chemical Formula 5 below.

In the present disclosure, the preparation method 2 for preparing the compound represented by Chemical Formula 5 below may include:

- 1) preparing a compound represented by Chemical Formula 3 by reacting a compound represented by Chemical Formula 8 below with aniline in the presence of a base; and
- 2) reacting a compound represented by Chemical Formula 3 below with a compound represented

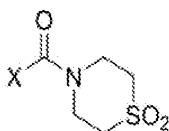
by Chemical Formula 4 below in the presence of a base to obtain a compound represented by Chemical Formula 5 below:

[Chemical Formula 3]



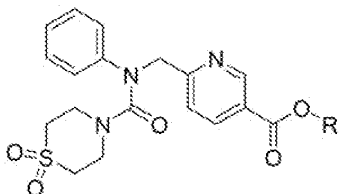
(in above Chemical Formula 3, R may be C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



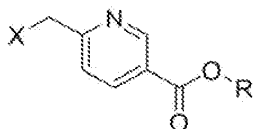
(in above Chemical Formula 4, X may be F, Cl, Br or I)

[Chemical Formula 5]



(in above Chemical Formula 5, R may be C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 8]



(in above Chemical Formula 8, R may be C1-C6 linear or branched alkyl or benzyl, and X may

be F, Cl, Br or I)

In an exemplary embodiment of the present invention, all of the above-described contents in method 1 for preparing the compound represented by Chemical Formula 3 and the method for preparing the compound represented by Chemical Formula 5 by using the compound represented by Chemical Formula 3 as a starting material may be applied to above Step 1) and Step 2) in the preparation method 2 for preparing the compound of Chemical Formula 5 which uses the compound represented by Chemical Formula 8 as a starting material and uses the compound represented by Chemical Formula 3 and the compound represented by Chemical Formula 4, unless they are contradictory to each other. For example, reaction conditions, effects and the like such as a solvent, a reducing agent, a halogenating reagent, a base, a temperature, a content, etc., may be all applied to the preparation method 2 for preparing the compound of above Chemical Formula 5.

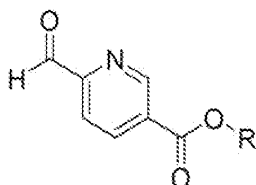
The present disclosure provides a preparation method 3 for preparing a compound represented by Chemical Formula 5 below.

In the present disclosure, the preparation method 3 for preparing the compound represented by Chemical Formula 5 below may include:

1) preparing a compound represented by Chemical Formula 3 below from a compound represented by Chemical Formula 2 below in the presence of aniline and a reducing agent; and

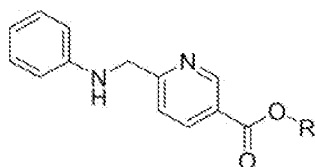
2) reacting a compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 below in the presence of a base to obtain a compound represented by Chemical Formula 5 below:

[Chemical Formula 2]



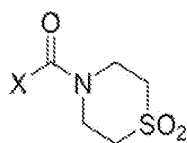
(in above Chemical Formula 2, R may be C1-C6 alkyl or benzyl)

[Chemical Formula 3]



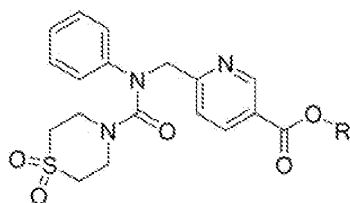
(in above Chemical Formula 3, R may be C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



(in above Chemical Formula 4, X may be F, Cl, Br or I)

[Chemical Formula 5]



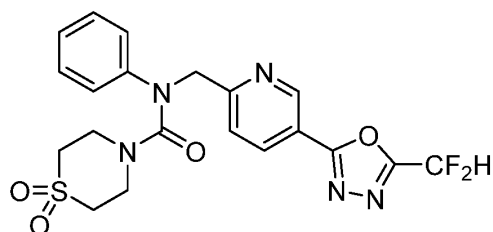
(in above Chemical Formula 5, R may be C1-C6 linear or branched alkyl or benzyl)

In an exemplary embodiment of the present invention, all of the above-described contents in method 2 for preparing the compound represented by Chemical Formula 3, the method for preparing the

compound represented by Chemical Formula 5, the method for preparing the compound represented by Chemical Formula 6, and the method for preparing the compound represented by above Chemical Formula 1 may be applied to above Step 1) and Step 2) in the preparation method 3 for preparing the compound of Chemical Formula 5 which uses the compound represented by Chemical Formula 2 as a starting material and uses the compound represented by Chemical Formula 3 and a compound represented by Chemical Formula 4, unless they are contradictory to each other. For example, reaction conditions, effects and the like such as a solvent, a reducing agent, a halogenating reagent, a base, a temperature, a content, etc., may be all applied to the preparation method 3 for preparing the compound of above Chemical Formula 5.

The present disclosure provides a novel crystalline form of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1:

[Chemical Formula 1]



Particularly, the present disclosure provides novel Crystalline Form I, Crystalline Form II and Crystalline Form III of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide.

In Korean Patent No. 10-1799010, which discloses the compound of Chemical Formula 1, the compound of Chemical Formula 1 is only obtained in an oil state, the compound represented by Chemical Formula 1 in the oil state may be prepared in a solid form having a foam-type shape through additional

drying, but it is also not in a crystalline form.

The oil state or the solid having a foam-type shape is not suitable for development as a medicament, and has a disadvantage in that it is difficult to remove the residual solvent and it is not easy to industrially handle.

However, Crystalline Form I, Crystalline form II and Crystalline Form III of the compound represented by Chemical Formula 1 have excellent properties associated with solid forms such as handling and stability, and have suitable solubility in formulation. Particularly, Crystalline Form I, Crystalline Form II and Crystalline Form III of the compound represented by Chemical Formula 1 have excellent long-term and accelerated stability, thermodynamic stability, photostability and crystal stability, low hygroscopicity, and favorable properties for the removal of the residual solvent, and thus has excellent safety and suitable solubility in formulation.

Further, since Crystalline Form I, Crystalline Form II and Crystalline Form III of the compound represented by Chemical Formula 1 according to the present disclosure have excellent storage stability, mechanical stability and fluidity, have uniform particles, and are easily processed into pharmaceuticals and the crystalline forms can be maintained unchanged even after storage and formulation of API(Active Pharmaceutical Ingredient), the medicament can secure a long shelf life and exhibit sufficient solubility for commercial production, and thus can be easily formulated as a medicament and prepared with commercial reproducibility.

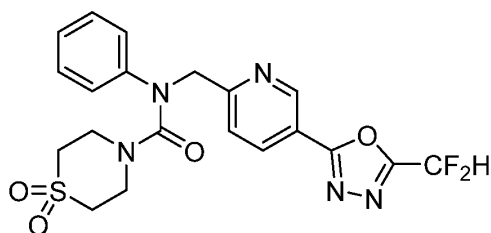
In addition, changes in pharmacological properties, safety and pharmacokinetics properties occur, and thus may cause unexpected reactions when a plurality of crystalline forms or mixtures of crystalline and amorphous forms are produced since low crystalline stability can easily lead to changes in crystalline form, but Crystalline Form I, Crystalline Form II and Crystalline Form III of the compound represented by Chemical Formula 1 have excellent stability, and thus can maintain a pure single crystal form for a long period of time.

Therefore, since Crystalline Form I, Crystalline Form II, and Crystalline Form III of the compound represented by Chemical Formula 1 can maintain a constant content due to excellent thermodynamic stability and crystal stability and low hygroscopicity, the crystalline forms have a long storage and distribution period, has suitable solubility in formulation, and can enable the production of medicaments without deviations in efficacy and safety.

Crystalline Form I of compound represented by Chemical Formula 1 (Form I)

The present disclosure provides Crystalline Form I of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1.

[Chemical Formula 1]



According to the examples of the present invention, the X-ray powder diffraction pattern of Crystalline Form I of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is the compound represented by Chemical Formula 1, may include diffraction peaks at three or more (for example, three, four, five, six, or seven) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 7.85° , 14.54° , 17.14° , 18.09° , 19.62° , 21.41° and 23.58° ($2\theta \pm 0.2^\circ$).

It is to be understood that any 2θ diffraction angle specified herein means the specified value $\pm 0.2^\circ$. For example, when a described example or a claim specifies a 2θ of 7.85° , this is to be

understood to mean $7.85^{\circ} \pm 0.2^{\circ}$, that is, a 2θ diffraction angle of from 7.65° to 8.05° .

For example, in the X-ray powder diffraction pattern, the diffraction angle(2θ) of 7.85° may be substantially the same as $7.85^{\circ} \pm 0.2^{\circ}$, the diffraction angle(2θ) of 14.54° may be substantially the same as $14.54^{\circ} \pm 0.2^{\circ}$, the diffraction angle(2θ) of 17.14° may be substantially the same as $17.14^{\circ} \pm 0.2^{\circ}$, the diffraction angle(2θ) of 18.09° may be substantially the same as $18.09^{\circ} \pm 0.2^{\circ}$, the diffraction angle(2θ) of 19.62° may be substantially the same as $19.62^{\circ} \pm 0.2^{\circ}$, the diffraction angle(2θ) of 21.41° may be substantially the same as $21.41^{\circ} \pm 0.2^{\circ}$ and the diffraction angle(2θ) of 23.58° may be substantially the same as $23.58^{\circ} \pm 0.2^{\circ}$.

For example, the X-ray powder diffraction pattern of Crystalline Form I of the compound represented by Chemical Formula 1 which includes diffraction peaks at three or more (for example, three, four, five, six or seven) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^{\circ}$) of 7.85° , 14.54° , 17.14° , 18.09° , 19.62° , 21.41° and 23.58° ($2\theta \pm 0.2^{\circ}$) may be substantially the same as the the X-ray powder diffraction pattern of Crystalline Form I represented by Chemical Formula 1 below:

the X-ray powder diffraction pattern which includes diffraction peaks at three or more (for example, three, four, five, six or seven) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^{\circ}$) of 7.90° , 14.59° , 17.20° , 18.15° , 19.68° , 21.49° and 23.65° ;

the X-ray powder diffraction pattern which includes diffraction peaks at three or more (for example, three, four, five, six or seven) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^{\circ}$) of 7.86° , 14.54° , 17.12° , 18.09° , 19.61° , 21.42° and 23.59° ; or

the X-ray powder diffraction pattern which includes diffraction peaks at three or more (for example, three, four, five, six or seven) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^{\circ}$) of 7.83° , 14.52° , 17.11° , 18.08° , 19.59° , 21.41° and 23.56° .

In an exemplary embodiment of the present invention, the X-ray powder diffraction pattern of Crystalline Form I of the compound represented by Chemical Formula 1 may include diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 7.85° , 14.54° , 17.14° , 18.09° , 19.62° , 21.41° and 23.58° .

It is to be understood that any 2θ diffraction angle specified herein means the specified value $\pm 0.2^\circ$.

For example, the X-ray powder diffraction pattern of Crystalline Form I represented by Chemical Formula 1 which includes diffraction peaks at diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 7.85° , 14.54° , 17.14° , 18.09° , 19.62° , 21.41° and 23.58° ($2\theta \pm 0.2^\circ$) may be substantially the same as the the X-ray powder diffraction pattern of Crystalline Form I represented by Chemical Formula 1 below:

the X-ray powder diffraction pattern which includes diffraction peaks at diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 7.90° , 14.59° , 17.20° , 18.15° , 19.68° , 21.49° and 23.65° ;

the X-ray powder diffraction pattern which includes diffraction peaks at diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 7.86° , 14.54° , 17.12° , 18.09° , 19.61° , 21.42° and 23.59° ; or

the X-ray powder diffraction pattern which includes diffraction peaks at diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 7.83° , 14.52° , 17.11° , 18.08° , 19.59° , 21.41° and 23.56° .

In an exemplary embodiment of the present invention, the X-ray powder diffraction pattern of Crystalline Form I of the compound represented by Chemical Formula 1 may further include diffraction peaks at one or more (for example, one, two, three, four, five, six or seven) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 15.64° , 17.55° , 20.78° , 21.04° , 23.27° ,

24.24°, and 30.38° in addition to three or more (for example, three, four, five, six or seven) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 7.85°, 14.54°, 17.14°, 18.09°, 19.62°, 21.41° and 23.58°.

It is to be understood that any 2θ diffraction angle specified herein means the specified value $\pm 0.2^\circ$.

For example, the X-ray powder diffraction pattern of Crystalline Form I of the compound represented by Chemical Formula 1 which further includes diffraction peaks at one or more (for example, one, two, three, four, five, six or seven) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 15.64°, 17.55°, 20.78°, 21.04°, 23.27°, 24.24° and 30.38° in addition to three or more (for example, three, four, five, six or seven) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 7.85°, 14.54°, 17.14°, 18.09°, 19.62°, 21.41° and 23.58°, may be substantially the same as the the X-ray powder diffraction pattern of Crystalline Form I represented by Chemical Formula 1 below:

the X-ray powder diffraction pattern which includes diffraction peaks at one or more (for example, one, two, three, four, five, six or seven) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 15.70°, 17.61°, 20.84°, 21.10°, 23.34°, 24.30° and 30.44° in addition to three or more (for example, three, four, five, six or seven) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 7.90°, 14.59°, 17.20°, 18.15°, 19.68°, 21.49° and 23.65°;

the X-ray powder diffraction pattern which includes diffraction peaks at one or more (for example, one, two, three, four, five, six or seven) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 15.66°, 17.55°, 20.77°, 21.04°, 23.27°, 24.23° and 30.38° in addition to three or (for example, three, four, five, six or seven) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 7.86°, 14.54°, 17.12°, 18.09°, 19.61°, 21.42° and 23.59°; or

the X-ray powder diffraction pattern which includes diffraction peaks at one or more (for

example, one, two, three, four, five, six or seven) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 15.64° , 17.54° , 20.77° , 21.04° , 23.26° , 24.23° and 30.37° in addition to three or more (for example, three, four, five, six or seven) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 7.83° , 14.52° , 17.11° , 18.08° , 19.59° , 21.41° and 23.56° .

In an exemplary embodiment of the present invention, the X-ray powder diffraction pattern of Crystalline Form I of the compound represented by Chemical Formula 1 may further include diffraction peaks at one or more (for example, one, two, three, four, five, six or seven, etc.) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 9.40° , 11.62° , 11.77° , 13.49° , 14.92° , 15.64° , 17.55° , 18.82° , 20.78° , 21.04° , 22.69° , 23.27° , 24.24° , 26.35° , 27.58° , 28.91° , 30.38° , 33.57° and 36.74° in addition to three or more (for example, three, four, five, six or seven) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 7.85° , 14.54° , 17.14° , 18.09° , 19.62° , 21.41° and 23.58° .

It is to be understood that any 2θ diffraction angle specified herein means the specified value $\pm 0.2^\circ$.

For example, the X-ray powder diffraction pattern of Crystalline Form I of the compound represented by Chemical Formula 1 which further includes diffraction peaks at one or more (for example, one, two, three, four, five, six or seven, etc.) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 9.40° , 11.62° , 11.77° , 13.49° , 14.92° , 15.64° , 17.55° , 18.82° , 20.78° , 21.04° , 22.69° , 23.27° , 24.24° , 26.35° , 27.58° , 28.91° , 30.38° , 33.57° and 36.74° in addition to three or more (for example, three, four, five, six or seven) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 7.85° , 14.54° , 17.14° , 18.09° , 19.62° , 21.41° and 23.58° may be substantially the same as the the X-ray powder diffraction pattern of Crystalline Form I represented by Chemical Formula 1 below:

the X-ray powder diffraction pattern of Crystalline Form I of the compound represented by Chemical Formula 1 which further includes diffraction peaks at one or more (for example, one, two,

three, four, five, six or seven, etc.) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 9.45° , 11.65° , 11.86° , 13.55° , 14.98° , 15.70° , 17.61° , 18.88° , 20.84° , 21.10° , 22.74° , 23.34° , 24.30° , 26.41° , 27.65° , 28.96° , 30.44° , 33.65° and 36.81° in addition to three or more (for example, three, four, five, six or seven) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 7.90° , 14.59° , 17.20° , 18.15° , 19.68° , 21.49° and 23.65° ;

the X-ray powder diffraction pattern of Crystalline Form I of the compound represented by Chemical Formula 1 which further includes diffraction peaks at one or more (for example, one, two, three, four, five, six or seven, etc.) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 9.39° , 11.62° , 11.80° , 13.48° , 14.91° , 15.66° , 17.55° , 18.82° , 20.77° , 21.04° , 22.68° , 23.27° , 24.23° , 26.37° , 27.59° , 28.92° , 30.38° , 33.57° and 36.74° in addition to three or more (for example, three, four, five, six or seven) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 7.86° , 14.54° , 17.12° , 18.09° , 19.61° , 21.42° and 23.59° ; or

the X-ray powder diffraction pattern of Crystalline Form I of the compound represented by Chemical Formula 1 which further includes diffraction peaks at one or more (for example, one, two, three, four, five, six or seven, etc.) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 9.40° , 11.60° , 11.78° , 13.49° , 14.92° , 15.64° , 17.54° , 18.82° , 20.77° , 21.04° , 22.68° , 23.26° , 24.23° , 26.36° , 27.55° , 28.89° , 30.37° , 33.57° and 36.71° in addition to three or more (for example, three, four, five, six or seven) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 7.83° , 14.52° , 17.11° , 18.08° , 19.59° , 21.41° and 23.56° .

In an exemplary embodiment of the present invention, Crystalline Form I of the compound represented by Chemical Formula 1 may have substantially the same peak positions in the X-ray powder diffraction pattern as the peak positions in the X-ray powder diffraction pattern shown in FIGs. 2, 4, 6 or 14. In an exemplary embodiment of the present invention, Crystalline Form I of the compound

represented by Chemical Formula 1 may have X-ray powder diffraction pattern peak positions, which appear at substantially the same positions as the diffraction angles ($2\theta \pm 0.2^\circ$) shown in Tables 1, 2, 3 or 6.

In an exemplary embodiment of the present invention, Crystalline Form I of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is the compound represented by Chemical Formula 1 may have an endothermic peak at $132^\circ\text{C} (\pm 0.5^\circ\text{C})$ to $143^\circ\text{C} (\pm 0.5^\circ\text{C})$ during differential scanning calorimetry (DSC) analysis when the heating rate is $10^\circ\text{C}/\text{min}$.

In an exemplary embodiment of the present invention, Crystalline Form I of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is the compound represented by Chemical Formula 1 may have an endothermic peak at $134^\circ\text{C} (\pm 0.5^\circ\text{C})$ to $143^\circ\text{C} (\pm 0.5^\circ\text{C})$ during differential scanning calorimetry (DSC) analysis when the heating rate is $10^\circ\text{C}/\text{min}$.

In an exemplary embodiment of the present invention, Crystalline Form I of the compound represented by Chemical Formula 1 may have an endothermic peak at $138^\circ\text{C} (\pm 3^\circ\text{C})$ during differential scanning calorimetry (DSC) analysis when the heating rate is $10^\circ\text{C}/\text{min}$.

In an exemplary embodiment of the present invention, Crystalline Form I of the compound represented by Chemical Formula 1 may have an endothermic onset temperature of $134.1^\circ\text{C} (\pm 0.5^\circ\text{C})$ and an endothermic peak at a temperature of $138.0^\circ\text{C} (\pm 0.5^\circ\text{C})$; an endothermic onset temperature of $134.7^\circ\text{C} (\pm 0.5^\circ\text{C})$ and an endothermic peak at a temperature of $139.2^\circ\text{C} (\pm 0.5^\circ\text{C})$; or an endothermic onset temperature of $134.64^\circ\text{C} (\pm 0.5^\circ\text{C})$ and an endothermic peak at a temperature of $138.27^\circ\text{C} (\pm 0.5^\circ\text{C})$ during differential scanning calorimetry (DSC) analysis when the heating rate is $10^\circ\text{C}/\text{min}$.

More particularly, Crystalline Form I of the compound represented by Chemical Formula 1 may have substantially the same differential scanning calorimetry (DSC) endothermic peaks as the

endothermic peaks shown in FIGs. 3, 5 or 15.

Crystalline Form I of the compound represented by Chemical Formula 1 according to the present invention is suitable for development as a medicament, has improved preparation efficiency, is suitable for mass production and easy to handle industrially, and has excellent characteristics related to pharmaceuticals in a solid form, such as handleability and stability. Particularly, Crystalline Form I of the compound represented by Chemical Formula 1 has excellent long-term and accelerated stability, thermodynamic stability, photostability and crystal stability, low hygroscopicity, and favorable properties for the removal of the residual solvent, and thus has excellent safety and suitable solubility in formulation.

Further, since Crystalline Form I of the compound represented by Chemical Formula 1 according to the present invention has excellent storage stability, mechanical stability and fluidity, has uniform particles, and is easily processed into pharmaceuticals and the crystalline form can be maintained unchanged even after long-term storage of API and even with changes in the surrounding environment such as temperature and humidity, the medicament can secure a long shelf life and exhibit sufficient solubility for commercial production, and thus can be easily formulated as a medicament and prepared with commercial reproducibility.

In addition, since a crystalline form having weak crystalline stability can easily undergo changes in crystalline form, a plurality of crystalline forms or mixtures of crystalline and amorphous forms are produced, so that changes in pharmacological properties, safety and pharmacokinetics properties occur, which may cause unexpected reactions, but Crystalline Form I of the compound represented by Chemical Formula 1 has excellent stability, and thus can maintain a pure single crystal form for a long period of time.

In particular, since Crystalline Form I of the compound represented by Chemical Formula 1 has excellent stability, it is possible to maintain an anhydride state in which moisture is hardly absorbed even in a humid environment, and a single crystalline form maintains its Crystalline Form I without being

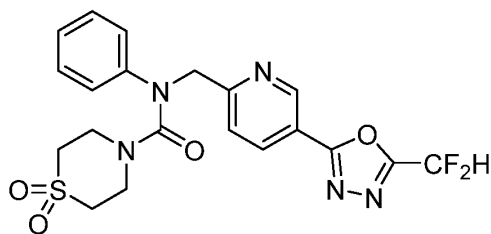
changed to another crystalline form or amorphous form for a long period of time even in a heating environment of 40°C or higher, so that during the preparation process or storage process, a demanding environment is not required, and the crystalline form may be stably maintained.

Therefore, since Crystalline Form I of the compound represented by Chemical Formula 1 can maintain a constant content due to excellent thermodynamic stability and crystal stability and low hygroscopicity, the crystalline form has a long storage and distribution period, has suitable solubility in formulation, and can enable the production of medicaments without deviations in efficacy and safety.

Crystalline Form II of compound represented by Chemical Formula 1 (Form II)

The present disclosure provides Crystalline Form II of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1.

[Chemical Formula 1]



According to the examples of the present disclosure, the X-ray powder diffraction pattern of Crystalline Form II of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is the compound represented by Chemical Formula 1, may include diffraction peaks at three or more (for example, three, four, five, six, or seven) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 7.83° , 12.22° , 19.02° , 19.67° , 21.40° , 22.35° and 26.44° .

It is to be understood that any 2θ diffraction angle specified herein means the specified

value $\pm 0.2^\circ$. For example, when a described example or a claim specifies a 2θ of 7.83° , this is to be understood to mean $7.83^\circ \pm 0.2^\circ$, that is, a 2θ diffraction angle of from 7.63° to 8.03° .

For example, in the X-ray powder diffraction pattern, the diffraction angle(2θ) of 7.83° may be substantially the same as $7.83^\circ \pm 0.2^\circ$, the diffraction angle(2θ) of 12.22° may be substantially the same as $12.22^\circ \pm 0.2^\circ$, the diffraction angle(2θ) of 19.02° may be substantially the same as $19.02^\circ \pm 0.2^\circ$, the diffraction angle(2θ) of 19.67° may be substantially the same as $19.67^\circ \pm 0.2^\circ$, the diffraction angle(2θ) of 21.40° may be substantially the same as $21.40^\circ \pm 0.2^\circ$, the diffraction angle(2θ) of 22.35° may be substantially the same as $22.35^\circ \pm 0.2^\circ$ and the diffraction angle(2θ) of 26.44° may be substantially the same as $26.44^\circ \pm 0.2^\circ$.

For example, the X-ray powder diffraction pattern of Crystalline Form II of the compound represented by Chemical Formula 1 which includes diffraction peaks at three or more (for example, three, four, five, six or seven) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 7.83° , 12.22° , 19.02° , 19.67° , 21.40° , 22.35° and 26.44° ($2\theta \pm 0.2^\circ$) may be substantially the same as the X-ray powder diffraction pattern of Crystalline Form II represented by Chemical Formula 1 below:

the X-ray powder diffraction pattern which includes diffraction peaks at three or more (for example, three, four, five, six or seven) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 7.83° , 12.22° , 19.02° , 19.67° , 21.39° , 22.35° and 26.42° .

In an exemplary embodiment of the present invention, the X-ray powder diffraction pattern of Crystalline Form II of the compound represented by Chemical Formula 1 may include diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 7.83° , 12.22° , 19.02° , 19.67° , 21.40° , 22.35° and 26.44° .

It is to be understood that any 2θ diffraction angle specified herein means the specified value $\pm 0.2^\circ$.

For example, the X-ray powder diffraction pattern of Crystalline Form II of the compound

represented by Chemical Formula 1 which includes diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 7.83° , 12.22° , 19.02° , 19.67° , 21.40° , 22.35° and 26.44° may be substantially the same as the the X-ray powder diffraction pattern of Crystalline Form II represented by Chemical Formula 1 below:

the X-ray powder diffraction pattern which includes diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 7.83° , 12.22° , 19.02° , 19.67° , 21.39° , 22.35° and 26.42° .

In an exemplary embodiment of the present invention, the X-ray powder diffraction pattern of Crystalline Form II of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by Chemical Formula 1 may further include diffraction peaks at one or more (for example, one, two, three, four, five, six or seven, etc.) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 11.41° , 11.78° , 13.28° , 15.70° , 16.64° , 17.48° , 18.28° , 19.37° , 20.71° , 24.58° , 27.35° and 33.73° in addition to three or more (for example, three, four, five, six or seven) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 7.83° , 12.22° , 19.02° , 19.67° , 21.40° , 22.35° and 26.44° .

It is to be understood that any 2θ diffraction angle specified herein means the specified value $\pm 0.2^\circ$.

For example, the X-ray powder diffraction pattern of Crystalline Form II of the compound represented by Chemical Formula 1 which further includes diffraction peaks at one or more (for example, one, two, three, four, five, six or seven, etc.) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 11.41° , 11.78° , 13.28° , 15.70° , 16.64° , 17.48° , 18.28° , 19.37° , 20.71° , 24.58° , 27.35° and 33.73° in addition to three or more (for example, three, four, five, six or seven) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 7.83° , 12.22° , 19.02° , 19.67° , 21.40° , 22.35° and 26.44° may be substantially the same as the the X-ray powder diffraction pattern of Crystalline Form II represented by Chemical Formula 1 below:

the X-ray powder diffraction pattern of Crystalline Form II of the compound represented by Chemical Formula 1 which includes diffraction peaks at one or more (for example, one, two, three, four, five, six or seven, etc.) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 11.39° , 11.77° , 13.26° , 15.72° , 16.60° , 17.48° , 18.27° , 19.35° , 20.67° , 24.56° , 27.34° and 33.72° in addition to three or more (for example, three, four, five, six or seven) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 7.83° , 12.22° , 19.02° , 19.67° , 21.39° , 22.35° and 26.42° .

In an exemplary embodiment of the present invention, the X-ray powder diffraction pattern of Crystalline Form II of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by Chemical Formula 1 may further include diffraction peaks at one or more (for example, one, two, three, four, five, six or seven, etc.) diffraction angles selected from the group consisting of 10.72° , 10.92° , 11.41° , 11.78° , 13.28° , 15.70° , 16.64° , 16.97° , 17.48° , 18.28° , 19.37° , 20.71° , 24.58° , 27.35° , 30.49° , 32.19° , 33.73° , 35.44° and 35.91° in addition to three or more (for example, three, four, five, six or seven.) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 7.83° , 12.22° , 19.02° , 19.67° , 21.40° , 22.35° and 26.44° .

It is to be understood that any 2θ diffraction angle specified herein means the specified value $\pm 0.2^\circ$.

For example, the X-ray powder diffraction pattern of Crystalline Form II of the compound represented by Chemical Formula 1 which further includes diffraction peaks at one or more more (for example, one, two, three, four, five, six or seven, etc.) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 10.72° , 10.92° , 11.41° , 11.78° , 13.28° , 15.70° , 16.64° , 16.97° , 17.48° , 18.28° , 19.37° , 20.71° , 24.58° , 27.35° , 30.49° , 32.19° , 33.73° , 35.44° and 35.91° in addition to three or more (for example, three, four, five, six or seven, etc.) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 7.83° , 12.22° , 19.02° , 19.67° , 21.40° , 22.35° and 26.44° may be substantially the same as the the X-ray powder diffraction pattern of Crystalline Form II represented by

Chemical Formula 1 below:

the X-ray powder diffraction pattern of Crystalline Form II of the compound represented by Chemical Formula 1 which includes diffraction peaks at one or more more (for example, one, two, three, four, five, six or seven, etc.) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 10.68° , 10.88° , 11.39° , 11.77° , 13.26° , 15.72° , 16.60° , 16.95° , 17.48° , 18.27° , 19.35° , 20.67° , 24.56° , 27.34° , 30.49° , 32.17° , 33.72° , 35.45° and 35.94° in addition to three or more (for example, three, four, five, six or seven, etc.) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 7.83° , 12.22° , 19.02° , 19.67° , 21.39° , 22.35° and 26.42° .

In an exemplary embodiment of the present invention, Crystalline Form II of the compound represented by Chemical Formula 1 may have substantially the same peak positions in the X-ray powder diffraction pattern as the peak positions in the diffraction pattern shown in FIGs. 7 or 16.

In an exemplary embodiment of the present invention, Crystalline Form II of the compound represented by Chemical Formula 1 may have X-ray powder diffraction pattern peak positions, which appear at substantially the same positions as the diffraction angles ($2\theta \pm 0.2^\circ$) shown in Tables 4 or 7.

In an exemplary embodiment of the present invention, Crystalline Form II of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is the compound represented by Chemical Formula 1 may have an endothermic peak at 124°C ($\pm 0.5^\circ\text{C}$) to 138°C ($\pm 0.5^\circ\text{C}$) during differential scanning calorimetry (DSC) analysis when the heating rate is $10^\circ\text{C}/\text{min}$.

In an exemplary embodiment of the present invention, Crystalline Form II of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is the compound represented by Chemical Formula 1 may have an endothermic peak at 125°C ($\pm 0.5^\circ\text{C}$) to 138°C ($\pm 0.5^\circ\text{C}$) during differential scanning calorimetry (DSC) analysis when the heating rate is $10^\circ\text{C}/\text{min}$.

In an exemplary embodiment of the present invention, Crystalline Form II of the compound represented by Chemical Formula 1 may have an endothermic peak at 130 °C ($\pm 5^{\circ}\text{C}$) during differential scanning calorimetry (DSC) analysis when the heating rate is 10°C/min.

In an exemplary embodiment of the present invention, Crystalline Form II of the compound represented by Chemical Formula 1 may have an endothermic onset temperature of 125.7°C ($\pm 0.5^{\circ}\text{C}$) and an endothermic peaks at a temperature of 132.2°C ($\pm 0.5^{\circ}\text{C}$); or an endothermic onset temperature of 125.61°C ($\pm 0.5^{\circ}\text{C}$) and an endothermic peaks at a temperature of 130.43°C during differential scanning calorimetry (DSC) analysis when the heating rate is 10°C/min.

More particularly, Crystalline Form II of the compound represented by Chemical Formula 1 may have substantially the same differential scanning calorimetry (DSC) endothermic peaks as the endothermic peaks shown in FIGs. 8 or 17.

Crystalline Form II of the compound represented by Chemical Formula 1 according to the present disclosure is suitable for development as a medicament, has improved preparation efficiency, is suitable for mass production and easy to handle industrially, and has excellent characteristics related to a solid form, such as handleability and stability. Particularly, Crystalline Form II of the compound represented by Chemical Formula 1 has excellent long-term and accelerated stability, thermodynamic stability, photostability and crystal stability, low hygroscopicity, and is favorable for the removal of the residual solvent, and thus has excellent safety and suitable solubility in formulation.

Further, since Crystalline Form II of the compound represented by Chemical Formula 1 according to the present disclosure has excellent storage stability, mechanical stability and fluidity, has uniform particles, and is easily processed into pharmaceuticals and the crystalline form can be maintained unchanged even after long-term storage of API and even with changes in the surrounding environment such as temperature and humidity, the medicament can secure a long shelf life and exhibit sufficient solubility for commercial production, and thus can be easily formulated as a medicament and prepared

with commercial reproducibility.

Changes in crystalline form, a plurality of crystalline forms or mixtures of crystalline and amorphous forms are produced, so that changes in pharmacological properties, safety and pharmacokinetics properties occur, which may cause unexpected reactions, but Crystalline Form II of the compound represented by Chemical Formula 1 has excellent stability, and thus can maintain a pure single crystal form for a long period of time even with changes in the surrounding environment such as accelerated stability condition.

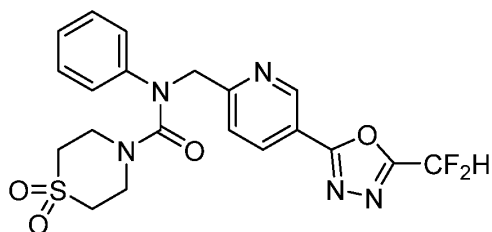
In particular, since Crystalline Form II of the compound represented by Chemical Formula 1 has excellent stability, it is possible to maintain an anhydride state in which moisture is hardly absorbed even in a humid environment, and a single crystalline form maintains its Crystalline Form II without being changed to another crystalline form or amorphous form for a long period of time, so that during the preparation process or storage process, a demanding environment is not required, and the crystalline form may be stably maintained.

Therefore, since Crystalline Form II of the compound represented by Chemical Formula 1 can maintain a constant content due to excellent thermodynamic stability and crystal stability and low hygroscopicity, the crystalline form has a long storage and distribution period, has suitable solubility in formulation, and can enable the production of medicaments without deviations in efficacy and safety.

Crystalline Form III of compound represented by Chemical Formula 1 (Form III)

The present disclosure provides Crystalline Form III of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1.

[Chemical Formula 1]



According to the examples of the present invention, the X-ray powder diffraction pattern of Crystalline Form III of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is the compound represented by Chemical Formula 1, may include diffraction peaks at three or more (for example, three, four, five or six) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 8.75° , 10.98° , 12.44° , 16.86° , 22.92° and 28.49° .

It is to be understood that any 2θ diffraction angle specified herein means the specified value $\pm 0.2^\circ$. For example, when a described example or a claim specifies a 2θ of 8.75° , this is to be understood to mean $8.75^\circ \pm 0.2^\circ$, that is, a 2θ diffraction angle of from 8.55° to 8.95° .

For example, in the X-ray powder diffraction pattern, the diffraction angle(2θ) of 8.75° may be substantially the same as $8.75^\circ \pm 0.2^\circ$, the diffraction angle(2θ) of 10.98° may be substantially the same as $10.98^\circ \pm 0.2^\circ$, the diffraction angle(2θ) of 12.44° may be substantially the same as $12.44^\circ \pm 0.2^\circ$, the diffraction angle(2θ) of 16.86° may be substantially the same as $16.86^\circ \pm 0.2^\circ$, the diffraction angle(2θ) of 22.92° may be substantially the same as $22.92^\circ \pm 0.2^\circ$, the diffraction angle(2θ) of 28.49° may be substantially the same as $28.49^\circ \pm 0.2^\circ$.

For example, the X-ray powder diffraction pattern of Crystalline Form III of the compound represented by Chemical Formula 1 which includes diffraction peaks at three or more (for example, three, four, five or six) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 8.75° , 10.98° , 12.44° , 16.86° , 22.92° and 28.49° may be substantially the same as the X-ray powder diffraction pattern of Crystalline Form I represented by Chemical Formula 1 below:

the X-ray powder diffraction pattern of Crystalline Form III of the compound represented by Chemical Formula 1 which includes diffraction peaks at three or more (for example, three, four, five or six) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 8.73° , 10.95° , 12.40° , 16.84° , 22.90° and 28.47° .

In an exemplary embodiment of the present invention, the X-ray powder diffraction pattern of Crystalline Form III of the compound represented by Chemical Formula 1 may include diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 8.75° , 10.98° , 12.44° , 16.86° , 22.92° and 28.49° .

It is to be understood that any 2θ diffraction angle specified herein means the specified value $\pm 0.2^\circ$.

For example, the X-ray powder diffraction pattern of Crystalline Form III of the compound represented by Chemical Formula 1 which includes diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 8.75° , 10.98° , 12.44° , 16.86° , 22.92° and 28.49° may be substantially the same as the X-ray powder diffraction pattern of Crystalline Form III represented by Chemical Formula 1 below:

the X-ray powder diffraction pattern of Crystalline Form III of the compound represented by Chemical Formula 1 which includes diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 8.73° , 10.95° , 12.40° , 16.84° , 22.90° and 28.47° .

In an exemplary embodiment of the present invention, the X-ray powder diffraction pattern of Crystalline Form III of the compound represented by Chemical Formula 1 may further include diffraction peaks at one or more (for example, one, two, three, four, five, six, or seven, etc.) diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 17.48° , 19.95° , 20.49° , 20.79° , 21.55° , 21.87° , 22.07° , 24.04° , 24.72° , 24.99° and 26.30° in addition to three or more (for example, three, four, five or six) diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 8.75° , 10.98° , 12.44° ,

16.86°, 22.92° and 28.49°.

It is to be understood that any 2θ diffraction angle specified herein means the specified value $\pm$ 0.2°.

For example, the X-ray powder diffraction pattern of Crystalline Form III of the compound represented by Chemical Formula 1 which further includes diffraction peaks at one or more (for example, one, two, three, four, five, six, or seven, etc.) diffraction angles selected from the group consisting of diffraction angles (2θ $\pm$ 0.2°) of 17.48°, 19.95°, 20.49°, 20.79°, 21.55°, 21.87°, 22.07°, 24.04°, 24.72°, 24.99° and 26.30° in addition to three or more (for example, three, four, five or six) diffraction angles (2θ $\pm$ 0.2°) selected from the group consisting of 8.75°, 10.98°, 12.44°, 16.86°, 22.92° and 28.49° may be substantially the same as the X-ray powder diffraction pattern of Crystalline Form III represented by Chemical Formula 1 below:

the X-ray powder diffraction pattern of Crystalline Form III of the compound represented by Chemical Formula 1 which further includes diffraction peaks at one or more (for example, one, two, three, four, five, six, or seven, etc.) diffraction angles selected from the group consisting of diffraction angles (2θ $\pm$ 0.2°) of 17.47°, 19.93°, 20.45°, 20.77°, 21.53°, 21.84°, 22.05°, 24.02°, 24.70°, 24.96° and 26.27° in addition to three or more (for example, three, four, five or six) diffraction angles (2θ $\pm$ 0.2°) selected from the group consisting of 8.73°, 10.95°, 12.40°, 16.84°, 22.90° and 28.47°.

In an exemplary embodiment of the present invention, the X-ray powder diffraction pattern of Crystalline Form III of the compound represented by Chemical Formula 1 may further include diffraction peaks at one or more (for example, one, two, three, four, five, six, or seven, etc.) diffraction angles selected from the group consisting of 14.28°, 15.45°, 17.48°, 18.49°, 18.77°, 19.95°, 20.49°, 20.79°, 21.55°, 21.87°, 22.07°, 24.04°, 24.72°, 24.99°, 26.30°, 29.22°, 30.20°, 31.40°, 34.10°, 37.13° and 38.86° in addition to three or more (for example, three, four, five or six) diffraction angles (2θ $\pm$ 0.2°) selected

from the group consisting of 8.75°, 10.98°, 12.44°, 16.86°, 22.92° and 28.49°.

It is to be understood that any 2θ diffraction angle specified herein means the specified value $\pm$ 0.2°.

For example, the X-ray powder diffraction pattern of Crystalline Form III of the compound represented by Chemical Formula 1 which further includes diffraction peaks at one or more (for example, one, two, three, four, five, six, or seven, etc.) diffraction angles selected from the group consisting of 14.28°, 15.45°, 17.48°, 18.49°, 18.77°, 19.95°, 20.49°, 20.79°, 21.55°, 21.87°, 22.07°, 24.04°, 24.72°, 24.99°, 26.30°, 29.22°, 30.20°, 31.40°, 34.10°, 37.13° and 38.86° in addition to three or more (for example, three, four, five or six) diffraction angles (2θ $\pm$ 0.2°) selected from the group consisting of 8.75°, 10.98°, 12.44°, 16.86°, 22.92° and 28.49° may be substantially the same as the X-ray powder diffraction pattern of Crystalline Form I represented by Chemical Formula 1 below:

the X-ray powder diffraction pattern of Crystalline Form III of the compound represented by Chemical Formula 1 which further includes diffraction peaks at one or more (for example, one, two, three, four, five, six, or seven, etc.) diffraction angles selected from the group consisting of 14.20°, 15.45°, 17.47°, 18.44°, 18.75°, 19.93°, 20.45°, 20.77°, 21.53°, 21.84°, 22.05°, 24.02°, 24.70°, 24.96°, 26.27°, 29.20°, 30.18°, 31.39°, 34.09°, 37.09° and 38.82° in addition to three or more (for example, three, four, five or six) diffraction angles (2θ $\pm$ 0.2°) selected from the group consisting of 8.73°, 10.95°, 12.40°, 16.84°, 22.90° and 28.47°.

In an exemplary embodiment of the present invention, Crystalline Form III of the compound represented by Chemical Formula 1 may have substantially the same peak positions in the X-ray powder diffraction pattern as the peak positions in the diffraction pattern shown in FIGs. 9 or 18.

In an exemplary embodiment of the present invention, Crystalline Form III of the compound represented by Chemical Formula 1 may have X-ray powder diffraction pattern peak positions, which appear at substantially the same positions as the diffraction angles (2θ $\pm$ 0.2°) shown in Tables 5 or 8.

In an exemplary embodiment of the present invention, Crystalline Form III of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is the compound represented by Chemical Formula 1 may have an endothermic peak at 120°C ($\pm 0.5^\circ\text{C}$) to 130°C ($\pm 0.5^\circ\text{C}$) during differential scanning calorimetry (DSC) analysis when the heating rate is 10°C/min.

In an exemplary embodiment of the present invention, Crystalline Form III of the compound represented by Chemical Formula 1 may have an endothermic peak at 125°C ($\pm 5^\circ\text{C}$) during differential scanning calorimetry (DSC) analysis when the heating rate is 10°C/min.

In an exemplary embodiment of the present invention, Crystalline Form III of the compound represented by Chemical Formula 1 may have an endothermic onset temperature of 120.5°C ($\pm 0.5^\circ\text{C}$) and endothermic peaks at a temperature of 124.7 °C ($\pm 0.5^\circ\text{C}$); or an endothermic onset temperature of 120.4°C ($\pm 0.5^\circ\text{C}$) and endothermic peaks at a temperature of 124.8°C ($\pm 0.5^\circ\text{C}$) during differential scanning calorimetry (DSC) analysis when the heating rate is 10°C/min.

Crystalline Form III of the compound represented by Chemical Formula 1 according to the present disclosure is suitable for development as a medicament, has improved preparation efficiency, is suitable for mass production and easy to handle industrially, and has excellent characteristics related to a solid form, such as handleability and stability. Particularly, Crystalline Form III of the compound represented by Chemical Formula 1 has excellent long-term and accelerated stability, thermodynamic stability, photostability and crystal stability, low hygroscopicity, and favorable properties for the removal of the residual solvent, and thus has excellent safety and suitable solubility in formulation.

Further, since Crystalline Form III of the compound represented by Chemical Formula 1 according to the present disclosure has excellent storage stability, mechanical stability and fluidity, has uniform particles, and is easily processed into pharmaceuticals and the crystalline form can be maintained unchanged even after long-term storage of API and even with changes in the surrounding environment

such as temperature and humidity, the medicament can secure a long shelf life and exhibit sufficient solubility for commercial production, and thus can be easily formulated as a medicament and prepared with commercial reproducibility.

In addition, since a crystalline form having weak crystalline stability can easily undergo changes in crystalline form, a plurality of crystalline forms or mixtures of crystalline and amorphous forms are produced, so that changes in pharmacological properties, safety and pharmacokinetics properties occur, which may cause unexpected reactions, and Crystalline Form III of the compound represented by Chemical Formula 1 has excellent stability, and thus can maintain a pure single crystal form for a long period of time.

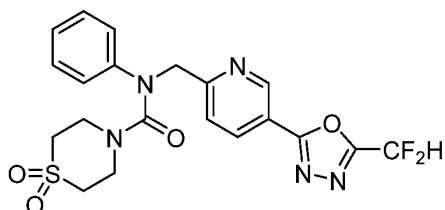
In particular, since Crystalline Form III of the compound represented by Chemical Formula 1 has excellent stability, it is possible to maintain an anhydride state in which moisture is hardly absorbed even in a humid environment, and a single crystalline form maintains its Crystalline Form III without being changed to another crystalline form or amorphous form for a long period of time, so that during the preparation process or storage process, a demanding environment is not required, and the crystalline form may be stably maintained.

Therefore, since Crystalline Form III of the compound represented by Chemical Formula 1 can maintain a constant content due to excellent thermodynamic stability and crystal stability and low hygroscopicity, the crystalline form has a long storage and distribution period, has suitable solubility in formulation, and can enable the production of medicaments without deviations in efficacy and safety.

Pharmaceutical composition including Crystalline Form I, II or III

The present disclosure provides a pharmaceutical composition including a novel crystalline form of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1:

[Chemical Formula 1]



In an exemplary embodiment of the present invention, the pharmaceutical composition may prevent or treat a disease associated with histone deacetylase 6 activity.

In an exemplary embodiment of the present invention, the disease associated with histone deacetylase 6 activity includes an infectious disease such as a prion disease; a neoplasm such as benign tumors (for example, myelodysplastic syndrome) or malignant tumors (for example, multiple myeloma, lymphoma, leukemia, lung cancer, colorectal cancer, colon cancer, prostate cancer, urothelial carcinoma, breast cancer, melanoma, skin cancer, liver cancer, brain cancer, stomach cancer, ovarian cancer, pancreatic cancer, head and neck cancer, oral cancer or glioma); endocrine, nutritional and metabolic diseases such as Wilson's disease, amyloidosis or diabetes; mental and behavioral disorders such as depression or Rett's syndrome; a neurological disease such as central nervous system atrophy (for example, Huntington's disease, spinal muscular atrophy (SMA), spinocerebellar ataxia (SCA)), a neurodegenerative disease (for example, Alzheimer's disease), a motor disorder (for example, Parkinson's disease), a neuropathy (for example, a hereditary neuropathy (Charcot-Marie-Tooth disease), a sporadic neuropathy, an inflammatory neuropathy, and a drug-induced neuropathy), a motor neuron disease (for example, amyotrophic lateral sclerosis (ALS)) or a central nervous system demyelinating disease (for example, multiple sclerosis (MS)); an eye and adnexal disease such as uveitis; a circulatory disease such as stroke; a respiratory disease such as asthma; a digestive disease such as alcoholic liver disease, inflammatory bowel disease, Crohn's disease or ulcerative bowel disease; a skin and subcutaneous tissue disease such as psoriasis; a musculoskeletal system and connective tissue disease, such as rheumatoid

arthritis, osteoarthritis or systemic lupus erythematosus (SLE); and congenital malformations, deformations and chromosomal abnormalities, such as autosomal dominant polycystic kidney disease, and may also include other symptoms or diseases associated with the abnormal function of histone deacetylase 6.

In an exemplary embodiment of the present invention, the X-ray powder diffraction patterns and the endothermic peaks of differential scanning calorimetry (DSC) analysis of Crystalline Form I, Crystalline Form II or Crystalline Form III of the compound represented by Chemical Formula 1 included in the pharmaceutical composition are as described above.

In an exemplary embodiment of the present invention, Crystalline Form I, Crystalline Form II and Crystalline Form III of the compound represented by Chemical Formula 1 included in the pharmaceutical composition may exhibit excellent physicochemical properties, and as a result, the pharmaceutical composition including Crystalline Form I, Crystalline Form II or Crystalline Form III of the compound represented by Chemical Formula 1 exhibits excellent crystalline stability, facilitates commercial mass production, can be reproducibly prepared, and the physicochemical properties can be maintained for a long period of time as at the time of initial preparation, a long distribution period may be secured, and separate demanding storage conditions may not be required.

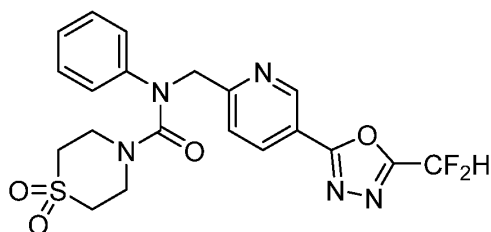
The pharmaceutical composition of the present invention may further include one or more pharmaceutically acceptable additives, and the additives may be those typically used in the art.

The pharmaceutical composition of the present invention may be formulated in an appropriate form, if necessary, and may be, for example, a patch, a liquid, a pill, capsules, granules, a tablet, a suppository, and the like. These preparations may be formulated by typical methods used for formulation in the art or by the methods disclosed in Remington's Pharmaceutical Sciences (latest edition), Mack Publishing Company, Easton PA, and may be formulated into various preparations according to each disease or according to each component.

Preparation method of Crystalline Form I, Crystalline Form II and Crystalline Form III of compound represented by Chemical Formula 1

The present disclosure provides a method for preparing novel Crystalline Form I, Crystalline Form II and Crystalline Form III of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is a compound represented by the following Chemical Formula 1.

[Chemical Formula 1]



by Chemical Formula 1 may include the following steps:

(a) obtaining a solution by dissolving N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide in a solvent selected from the group consisting of ethyl acetate, ethanol, methanol, isopropyl alcohol, butyl alcohol, methyl tertiary butyl ether (MTBE), diisopropyl ether, acetone, methylisobutylketone (MIBK), methyl ethyl ketone, dichloromethane, dimethylformamide, N-methyl-2-pyrrolidone, toluene, tetrahydrofuran, heptane, hexane, acetonitrile and a mixture thereof; and

(b) producing a solid from the solution.

In an exemplary embodiment of the present invention, in the preparation of Crystalline Form I of the compound represented by Chemical Formula 1, the solvent of Step (a) may be one or more alcohols selected from the group consisting of ethanol, methanol, isopropyl alcohol and butyl alcohol, ethyl acetate, or a mixture of the alcohol and ethyl acetate.

In an exemplary embodiment of the present invention, in the preparation of Crystalline Form I of the compound represented by Chemical Formula 1, the solvent of Step (a) may be a mixture of one or more alcohols selected from the group consisting of ethanol, methanol, isopropyl alcohol and butyl alcohol, and ethyl acetate.

In an exemplary embodiment of the present invention, in the preparation of Crystalline Form I of the compound represented by Chemical Formula 1, the obtaining of the solution (a) may include:

(a1) obtaining a mixture by adding a compound represented by Chemical Formula 1 to a solvent; and

(a2) warming the mixture to a temperature exceeding 40°C.

In an exemplary embodiment of the present invention, the warming in (a2) may be performed at a temperature more than 40°C, 45°C or more, particularly in a range of 45°C to 70°C, more particularly

in a range of 45°C to 65°C, and even more particularly, 50°C to 65°C.

In an exemplary embodiment of the present invention, in the method for preparing Crystalline Form I of the compound represented by Chemical Formula 1, the producing of the solid of Step (b) may include:

(b1) preparing a mixture by additionally adding one or more alcohols selected from the group consisting of ethanol, methanol, isopropyl alcohol and butyl alcohol to the solution obtained in Step (a); and

(b2) stirring the mixture after adding the alcohol of Step (b1).

In an exemplary embodiment of the present invention, Step (b1) and (b2) may be performed at a temperature more than 40°C, particularly, at a temperature more than 40°C and 60°C or less.

In an exemplary embodiment of the present invention, a solid may be produced during the stirring process of Step (b2).

In an exemplary embodiment of the present invention, a cooling process may be further performed, and the cooling may be performed at a temperature of 10°C or less, particularly 0°C to 10°C, and more particularly 0°C to 7°C.

In an exemplary embodiment of the present invention, the compound represented by Chemical Formula 1, which is the starting material of Step (a) of the method for preparing Crystalline Form I is not limited in its physical state and can be any physical state as long as it is a compound represented by Chemical Formula 1, and particularly, the compound can be in a liquid or solid state such as a solution or a suspension, and the solid state can also be in a foam form, an amorphous form, or the like, and more particularly, the compound may be in the form of an oil or foam, or an amorphous solid, and more particularly an amorphous form with an oil or foam type shape, but is not limited thereto.

In an exemplary embodiment of the present invention, the compound represented by Chemical Formula 1 may be prepared by the preparation method known in the art, and for example, the compound

represented by Chemical Formula 1 may be prepared by the preparation method disclosed in Korean Registered Patent No. 10-1799010.

In an exemplary embodiment of the present invention, the method for preparing Crystalline Form I of the compound represented by Chemical Formula 1 may further include, before performing Step (a), producing a concentrated residue by dissolving the compound represented by Chemical Formula 1 in dichloromethane, and then performing primary concentration; and adding ethyl acetate to the concentrated residue and performing secondary concentration.

In the present disclosure, a method for preparing Crystalline Form II of the compound represented by Chemical Formula 1 may include the following steps:

- (a) preparing a mixture by adding N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is the compound represented by Chemical Formula 1 to a solvent selected from the group consisting of methanol, ethanol, isopropyl alcohol, butyl alcohol, diisopropyl ether, tetrahydrofuran, heptane, hexane and a mixture thereof;
- (b) obtaining a solution by warming the mixture to a temperature of 30°C to 40°C; and
- (c) producing a solid from the solution at a temperature of 40°C or less.

In an exemplary embodiment of the present invention, in the preparation of Crystalline Form II of the compound represented by Chemical Formula 1, the solvent of Step (a) may be ethanol, isopropyl alcohol or a mixture thereof.

In an exemplary embodiment of the present invention, in the preparation of Crystalline Form II of the compound represented by Chemical Formula 1, the solvent of Step (a) may be ethanol.

In an exemplary embodiment of the present invention, in the preparation of Crystalline Form II of the compound represented by Chemical Formula 1, the warming of Step (b) may be performed at 40°C or less, particularly, in a temperature range of 30°C to 40°C.

In an exemplary embodiment of the present invention, in the preparation of Crystalline Form II

of the compound represented by Chemical Formula 1, the production of the solid from the solution at a temperature of 40°C or less in Step (c) may include stirring the solution at a temperature of 40°C or less.

In an exemplary embodiment of the present invention, in the preparation of Crystalline Form II of the compound represented by Chemical Formula 1, Step (c) may be performed at 40°C or less, more particularly 20°C to 40°C, and more particularly in a temperature range of 30°C to 40°C.

In an exemplary embodiment of the present invention, the compound represented by Chemical Formula 1, which is the starting material of Step (a) of the method for preparing Crystalline Form II is not limited in its physical state and can be any physical state as long as it is the compound represented by Chemical Formula 1, and particularly, the compound can be in a liquid or solid state such as a solution or a suspension, and the solid state can also be in a foam form, an amorphous form, or the like, and more particularly, the compound may be in the form of an oil or foam, or an amorphous solid, and more particularly an amorphous form with an oil or foam type shape, but is not limited thereto.

In an exemplary embodiment of the present invention, the compound represented by Chemical Formula 1 may be prepared by the preparation method known in the art, and for example, the compound represented by Chemical Formula 1 may be prepared by the preparation method disclosed in Korean Registered Patent No. 10-1799010.

In an exemplary embodiment of the present invention, forming the solid in Step (c) may include stirring the solution.

In an exemplary embodiment of the present invention, a solid may be produced during the stirring process.

In an exemplary embodiment of the present invention, the method for preparing Crystalline Form II of the compound represented by Chemical Formula 1 may further include, before performing Step (a), producing a concentrated residue by dissolving the compound represented by Chemical Formula 1 in dichloromethane, and then performing primary concentration; and

adding ethanol to the concentrated residue and performing secondary concentration.

In the present disclosure, a method for preparing Crystalline Form III of the compound represented by Chemical Formula 1 may include the following steps:

(a) producing a slurry by adding amorphous N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by Chemical Formula 1 to a solvent selected from the group consisting of methyl tertiary butyl ether (MTBE), heptane, octane, hexane, pentane and a mixture thereof; and

(b) obtaining a solid from the slurry.

In an exemplary embodiment of the present invention, in the preparation of Crystalline Form III of the compound represented by Chemical Formula 1, the solvent of Step (a) may be methyl tertiary butyl ether (MTBE), heptane or a mixture thereof.

In an exemplary embodiment of the present invention, in the preparation of Crystalline Form III of the compound represented by Chemical Formula 1, the producing of the slurry of (a) may be performed for 12 hours to 20 days, particularly 12 hours to 7 days, and more particularly, 12 hours to 3 days. For example, the producing of the slurry of (a) may be performed for 12 hours to 36 hours, particularly 15 hours to 30 hours and more particularly 20 hours to 27 hours.

In an exemplary embodiment of the present invention, in the method for preparing Crystalline Form III of the compound represented by Chemical Formula 1, the obtaining of the solid of (b) may include:

filtering the slurry obtained in Step (a).

In an exemplary embodiment of the present invention, the producing of the slurry of (a) and the obtaining of the solid of (b) may be performed at 30°C or less, particularly 20°C to 30°C, and more particularly 20°C to 25°C.

In an exemplary embodiment of the present invention, crystalline forms I to III of the compound represented by Chemical Formula 1 may be prepared using the compound represented by Chemical Formula 1 prepared according to the method of the present disclosure as a starting material.

In an exemplary embodiment of the the present invention, when the starting material is the compound represented by the Chemical Formula 1 which is prepared by the method according the present disclosure, a method for preparing Crystalline Form I of the compound represented by Chemical Formula 1 may include the following steps:

(a) obtaining a solution by dissolving N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl) methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide in a solvent selected from the group consisting of ethyl acetate, ethanol, methanol, isopropyl alcohol, butyl alcohol, methyl tertiary butyl ether (MTBE), diisopropyl ether, acetone, methylisobutylketone (MIBK), methyl ethyl ketone, dichloromethane, dimethylformamide, N-methyl-2-pyrrolidone, toluene, tetrahydrofuran, heptane, hexane, acetonitrile and a mixture thereof; and

(b) producing a solid from the solution.

In an exemplary embodiment of the present invention, in the preparation of Crystalline Form I of the compound represented by Chemical Formula 1, the solvent of Step (a) may be one or more alcohols selected from the group consisting of ethanol, methanol, isopropyl alcohol and butyl alcohol, ethyl acetate, or a mixture of the alcohol and ethyl acetate.

In an exemplary embodiment of the present invention, in the preparation of Crystalline Form I of the compound represented by Chemical Formula 1, the solvent of Step (a) may be a mixture of one or more alcohols selected from the group consisting of ethanol, methanol, isopropyl alcohol and butyl alcohol, and ethyl acetate.

In an exemplary embodiment of the present invention, in the preparation of Crystalline Form I of the compound represented by Chemical Formula 1, the obtaining of the solution (a) may include:

- (a1) obtaining a mixture by adding a compound represented by Chemical Formula 1 to a solvent;
- and
- (a2) warming the mixture to a temperature exceeding 40°C .

In an exemplary embodiment of the present invention, the warming in (a2) may be performed at a temperature more than 40°C, 45°C or more, particularly in a range of 45°C to 70°C, more particularly in a range of 45°C to 65°C, and even more particularly, 50°C to 65°C.

In exemplary embodiments of the present invention, in the method for preparing Crystalline Form I of the compound represented by Chemical Formula 1, the producing of the solid of Step (b) may include:

- (b1) preparing a mixture by additionally adding one or more alcohols selected from the group consisting of ethanol, methanol, isopropyl alcohol and butyl alcohol to the solution obtained in Step (a);
- and
- (b2) stirring the mixture after adding the alcohol of Step (b1).

In exemplary embodiments of the present invention, Steps (b1) and (b2) may be performed at a temperature more than 40°C, particularly, at a temperature more than 40°C and 60°C or less.

In exemplary embodiments of the present invention, a solid may be produced during the stirring process of Step (b2).

In exemplary embodiments of the present invention, a cooling process may be further performed, and the cooling may be performed at a temperature of 10°C or less, particularly 0°C to 10°C, and more particularly 0°C to 7°C.

In exemplary embodiments of the present invention, the compound represented by Chemical Formula 1, which is the starting material of Step (a) of the method for preparing Crystalline Form I is

not limited in its physical state and can be any physical state as long as it is a compound represented by Chemical Formula 1, and particularly, the compound can be in a liquid or solid state such as a solution or a suspension, and the solid state can also be in a foam form, an amorphous form, or the like, and more particularly, the compound may be in the form of an oil or foam, or an amorphous solid, and more particularly an amorphous form with an oil or foam type shape, but is not limited thereto.

In exemplary embodiments of the present invention, in the method for preparing Crystalline Form I of the compound represented by Chemical Formula 1, the compound represented by above Chemical Formula 1 as the starting material may be prepared according to the method for preparing the compound represented by Chemical Formula 1 described in detail above, but is not limited thereto. For example, in the method for preparing Crystalline Form I, the starting material may be the compound represented by Chemical Formula 1 prepared by the novel method described herein, or may be prepared according to a conventionally known method.

In exemplary embodiments of the present invention, the method for preparing Crystalline Form I of the compound represented by Chemical Formula 1 may further include a step of adding ethyl acetate to the compound represented by Chemical Formula 1 and concentrating the resulting mixture before performing Step (a). In this case, the compound represented by Chemical Formula 1 may be the compound represented by Chemical Formula 1 obtained by the novel preparation method described herein, in which the compound represented by Chemical Formula 1 may be in an oil state, but is not limited thereto.

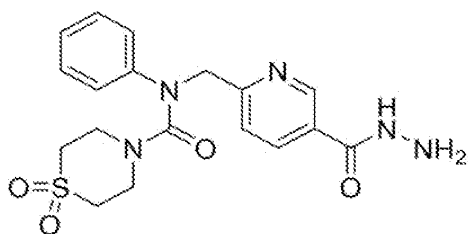
In exemplary embodiments of the present invention, in the method for preparing the Crystalline Form I of the compound represented by Chemical Formula 1, the compound represented by the Chemical Formula 1 as the starting material may be prepared by the methods described herein. Particularly, the compound represented by Chemical Formula 1 may be prepared in-situ from the compound represented by Chemical Formula 6. In this case, the reactants and the reaction conditions may be the same as

previously described herein.

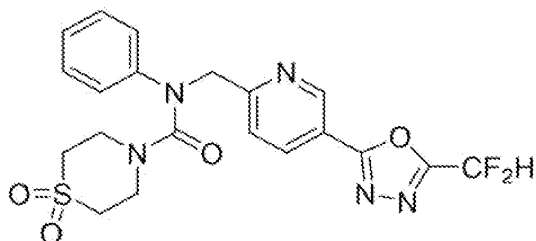
More particularly, the Crystalline Form I of the compound represented by Chemical Formula 1 may be prepared by the method including (1) to (3) below:

(1) in-situ preparing a compound represented by Chemical Formula 1 below from a compound represented by Chemical Formula 6 below:

[Chemical Formula 6]



[Chemical Formula 1]



(2) obtaining a solution by dissolving the compound represented by Chemical Formula 1 obtained in Step (1) in a solvent selected from the group consisting of ethyl acetate, ethanol, methanol, isopropyl alcohol, butyl alcohol, methyl tertiary butyl ether (MTBE), diisopropyl ether, acetone, methylisobutylketone (MIBK), methyl ethyl ketone, dichloromethane, dimethylformamide, N-methyl-2-pyrrolidone, toluene, tetrahydrofuran, heptane, hexane, acetonitrile and a mixture thereof; and

(3) producing a solid from the solution.

In the method for preparing the Crystalline Form I of the compound represented by Chemical Formula 1, the Step (1) may be substantially the same as the method for preparing the compound represented by Chemical Formula 1 from the compound represented by Chemical Formula 6 previously described herein. For example, the reactants, the reaction conditions and the particular reaction detail substantially the same as previously described herein. In the method for preparing the Crystalline Form I of the compound represented by Chemical Formula 1, the Step (2) and Step (3) may be substantially the same as Step (a) and Step (b) of the method for preparing Crystalline Form I of the compound represented by Chemical Formula 1 using the compound represented by Chemical Formula 1 as a starting material which may be prepared according to the present disclosure previously described. For example, the reactants, the reaction conditions and the particular reaction detail substantially the same as previously described herein.

In exemplary embodiments of the present invention, the method for preparing Crystalline Form I of the compound represented by Chemical Formula 1 may further include, before performing Step (2), adding ethyl acetate into the compound represented by Chemical Formula 1 and performing concentration. In this case, the compound represented by Chemical Formula 1 may be prepared by the novel method described herein, wherein the compound represented by Chemical Formula 1 may be oil state, but is not limited thereto.

In exemplary embodiments of the present invention, the X-ray powder diffraction pattern and differential scanning calorimetry (DSC) analysis when the heating rate is 10°C/min may be the same as those previously described herein with regard to Crystalline Form I of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is the compound represented by Chemical Formula 1.

In exemplary embodiments of the present invention, when the starting material is the compound

represented by Chemical Formula I prepared by the method according to the present disclosure, a method for preparing Crystalline Form II of the compound represented by Chemical Formula 1 may include the following steps:

(a) preparing a mixture by adding N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl) pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is the compound represented by Chemical Formula 1 to a solvent selected from the group consisting of methanol, ethanol, isopropyl alcohol, butyl alcohol, diisopropyl ether, tetrahydrofuran, heptane, hexane and a mixture thereof;

(b) obtaining a solution by warming the mixture to a temperature of 30°C to 40°C; and

(c) producing a solid from the solution at a temperature of 40°C or less.

In an exemplary embodiment of the present invention, in the preparation of Crystalline Form II of the compound represented by Chemical Formula 1, the solvent of Step (a) may be ethanol, isopropyl alcohol or a mixture thereof.

In an exemplary embodiment of the present invention, in the preparation of Crystalline Form II of the compound represented by Chemical Formula 1, the solvent of Step (a) may be ethanol.

In an exemplary embodiment of the present invention, in the preparation of Crystalline Form II of the compound represented by Chemical Formula 1, the warming of Step (b) may be performed at 40°C or less, particularly, in a temperature range of 30°C to 40°C.

In an exemplary embodiment of the present invention, in the preparation of Crystalline Form II of the compound represented by Chemical Formula 1, the producing of the solid from the solution at a temperature of 40°C or less in Step (c) may include stirring the solution at a temperature of 40°C or less.

In an example of the present invention, in the preparation of Crystalline Form II of the compound represented by above Chemical Formula 1, Step (c) may be performed at 40°C or less, more particularly 20°C to 40°C, and more particularly in a temperature range of 30°C to 40°C.

In an exemplary embodiment of the present invention, the compound represented by Chemical Formula 1, which is the starting material of Step (a) of the method for preparing Crystalline Form II is not limited in its physical state and can be any physical state as long as it is the compound represented by Chemical Formula 1, and particularly, the compound can be in a liquid or solid state such as a solution or a suspension, and the solid state can also be in a foam form, an amorphous form, or the like, and more particularly, the compound may be in the form of an oil or foam, or an amorphous solid, and more particularly an amorphous form with an oil or foam type shape, but is not limited thereto.

In exemplary embodiments of the present invention, in the method for preparing Crystalline Form II of the compound represented by Chemical Formula 1, the compound represented by Chemical Formula 1 as the starting material may be prepared according to the novel method for preparing the compound represented by Chemical Formula 1 described in detail above in the present specification, but is not limited thereto. For example, in the method for preparing Crystalline Form II, the starting material may be the compound represented by Chemical Formula 1 prepared by the novel method described herein.

In an exemplary embodiment of the present invention, forming the solid in step (c) may include stirring the solution.

In an exemplary embodiment of the present invention, a solid may be produced during the stirring process.

In an exemplary embodiment of the present invention, the method for preparing Crystalline Form II of the compound represented by Chemical Formula 1 may further include a step of:

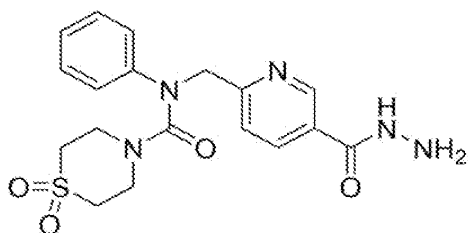
adding ethanol to the compound represented by Chemical Formula 1 and concentrating the resulting mixture before performing Step (a). In this case, the compound represented by Chemical Formula 1 may be the compound represented by Chemical Formula 1 obtained by the novel preparation method described in the present specification, in which the compound represented by Chemical Formula 1 may be in an oil state, but is not limited thereto.

In exemplary embodiments of the present invention, the compound represented by the Chemical Formula 1 may be prepared by the methods previously described herein. Particularly, the compound represented by Chemical Formula 1 may be prepared in-situ from the compound represented by Chemical Formula 6. In this case, the reactants and the reaction conditions may be the same as previously described herein.

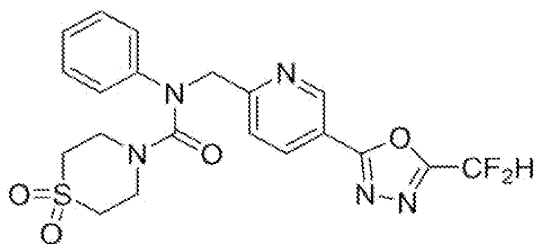
More particularly, the Crystalline Form II of the compound represented by Chemical Formula 1 may be prepared by the method including (1) to (4) below:

(1) in-situ preparing a compound represented by Chemical Formula 1 below from a compound represented by Chemical Formula 6 below:

[Chemical Formula 6]



[Chemical Formula 1]



(2) preparing a mixture by adding N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is the compound represented by Chemical Formula 1 to a solvent selected from the group consisting of methanol, ethanol, isopropyl alcohol, butyl alcohol, diisopropyl ether, tetrahydrofuran, heptane, hexane and a mixture thereof;

- (3) obtaining a solution by warming the mixture to a temperature of 30°C to 40°C; and
- (4) producing a solid from the solution at a temperature of 40°C or less.

In the method for preparing the Crystalline Form II of the compound represented by Chemical Formula 1, the Step (1) may be substantially the same as the method for preparing the compound represented by Chemical Formula 1 from the compound represented by Chemical Formula 6 previously described herein. For example, the reactants, the reaction conditions and the particular reaction detail substantially the same as previously described herein.

In the method for preparing the Crystalline Form II of the compound represented by Chemical Formula 1, the Step (2), Step (3) and Step (4) may be substantially the same as Step (a), Step (b) and Step (C) of the method for preparing Crystalline Form II of the compound represented by Chemical Formula 1 using the compound represented by Chemical Formula 1 as a starting material which may be prepared according to the present disclosure previously described. For example, the reactants, the reaction conditions and the particular reaction detail substantially the same as previously described herein.

In exemplary embodiments of the present invention, the method for preparing Crystalline Form II of the compound represented by Chemical Formula 1 may further include, before performing Step (2), adding ethanol into the compound represented by Chemical Formula 1 and performing concentration. In this case, the compound represented by Chemical Formula 1 may be prepared by the novel method described herein, wherein the compound represented by Chemical Formula 1 may be oil state, but is not limited thereto.

In exemplary embodiments of the present invention, the X-ray powder diffraction pattern and differential scanning calorimetry (DSC) analysis when the heating rate is 10°C/min may be the same as those previously described herein with regard to Crystalline Form II of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is the compound represented by Chemical Formula 1.

In the present disclosure, a method for preparing Crystalline Form III of the compound represented by Chemical Formula 1 may include the following steps:

(a) producing a slurry by adding amorphous N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by Chemical Formula 1 to a solvent selected from the group consisting of methyl tertiary butyl ether (MTBE), heptane, octane, hexane, pentane and a mixture thereof; and

(b) obtaining a solid from the slurry.

In an exemplary embodiment of the present invention, in the preparation of Crystalline Form III of the compound represented by Chemical Formula 1, the solvent of Step (a) may be methyl tertiary butyl ether (MTBE), heptane or a mixture thereof.

In an exemplary embodiment of the present invention, in the preparation of Crystalline Form III of the compound represented by Chemical Formula 1, the producing of the slurry of (a) may be performed for 12 hours to 20 days, particularly 12 hours to 7 days, and more particularly, 12 hours to 3 days. For example, the producing of the slurry of (a) may be performed for 12 hours to 36 hours, particularly, 15 hours to 30 hours, and even more particularly 20 hours to 27 hours.

In an exemplary embodiment of the present invention, in the method for preparing Crystalline Form III of the compound represented by Chemical Formula 1, the obtaining of the solid of (b) may include:

filtering the slurry obtained in Step (a).

In an exemplary embodiment of the present invention, the producing of the slurry of (a) and the obtaining of the solid of (b) may be performed at 30°C or less, particularly 20°C to 30°C, and more particularly 20°C to 25°C.

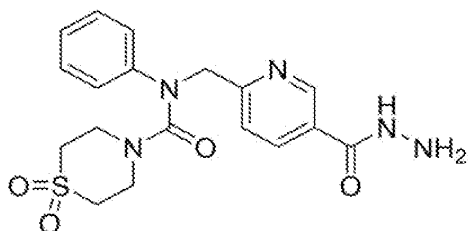
In exemplary embodiments of the present invention, in the method for preparing Crystalline

Form III of the compound represented by Chemical Formula 1, the compound represented by above Chemical Formula 1 as the starting material may be prepared according to the novel method for preparing the compound represented by Chemical Formula 1 described in detail above herein, but is not limited thereto. For example, in the method for preparing Crystalline Form III, the amorphous form of the compound represented by Chemical Formula 1 as the starting material may be prepared from the compound represented by Chemical Formula 1 prepared by the novel method described herein, or may be prepared according to a conventionally known method.

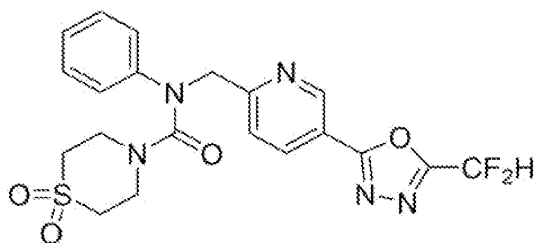
More particularly, the Crystalline Form III of the compound represented by Chemical Formula 1 may be prepared by the method including (1) to (4) below:

(1) in-situ preparing a compound represented by Chemical Formula 1 below from a compound represented by Chemical Formula 6 below:

[Chemical Formula 6]



[Chemical Formula 1]



(2) vacuum-drying the compound represented by Chemical Formula 1 obtained in (1) to prepare

an amorphous form of the compound represented by Chemical Formula 1;

(3) producing a slurry by adding amorphous form of the compound represented by Chemical Formula 1 to a solvent selected from the group consisting of methyl tertiary butyl ether (MTBE), heptane, octane, hexane, pentane and a mixture thereof; and

(4) obtaining a solid from the slurry.

In the method for preparing the Crystalline Form III of the compound represented by Chemical Formula 1, the Step (1) may be substantially the same as the method for preparing the compound represented by Chemical Formula 1 from the compound represented by Chemical Formula 6 previously described herein. For example, the reactants, the reaction conditions and the particular reaction detail substantially the same as previously described herein.

In the method for preparing the Crystalline Form III of the compound represented by Chemical Formula 1, Step (3) and Step (4) may be substantially the same as Step (a) and Step (b) of the method for preparing Crystalline Form III of the compound represented by Chemical Formula 1. For example, the reactants, the reaction conditions and the particular reaction detail substantially the same as previously described herein.

In exemplary embodiments of the present invention, the X-ray powder diffraction pattern and differential scanning calorimetry (DSC) analysis when the heating rate is 10°C/min may be the same as those previously described herein with regard to Crystalline Form II of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is the compound represented by Chemical Formula 1.

Advantageous Effects

The novel preparation method of the present invention can simplify synthesis steps as compared

with conventional preparation methods, use easily available reagents and reaction equipment in reactions, mild reaction conditions, efficient process procedures, and not require the use of column chromatography, enable mass production, and have remarkably excellent stability and economic efficiency essential for mass production.

Accordingly, the novel preparation method can be a very efficient method since an overall yield is about 60%, which is increased about 40 times compared to 1.5% of the conventional preparation method, when obtaining the compound represented by Chemical Formula 1. In addition, due to a simple post-treatment procedure and an effective purification method, the compound of Chemical Formula 1 having a HPLC purity of 99% or more can be obtained without column chromatography.

The N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide crystalline forms of the present disclosure have excellent long-term and accelerated stability, thermodynamic stability, photostability and crystalline stability, and have solubility suitable for formulation. Further, the crystalline forms maintain a constant content without being denatured by the surrounding environment even during long-term storage due to low hygroscopicity, and have advantageous characteristics for removing the residual solvent.

In addition, the crystalline forms of the present invention have excellent storage stability, mechanical stability and fluidity, and do not require a complicated process for formulation due to uniform particles, and the crystalline forms can be easily obtained with high purity and high yield by a simple method.

Furthermore, the method for preparing a crystalline form according to the present disclosure can be easily applied to production (scale-up) and can stably prepare crystals, and is suitable for industrial production because an economical preparation process can be established due to an inexpensive solvent used for production (scale-up).

Brief description of the drawings

FIG. 1 is a view showing reaction formula 2 for preparing a compound of Chemical Formula 1 according to an example of the present invention.

FIGS. 2, 4 and 6 show results of X-ray powder diffraction (XRPD) analysis on Crystalline Form I of the compound represented by Chemical Formula 1 according to one example of the present invention.

FIGS. 3 and 5 show results of differential scanning calorimetry (DSC) thermogram on Crystalline Form I of the compound represented by Chemical Formula 1 according to one example of the present invention.

FIG. 7 shows results of X-ray powder diffraction (XRPD) analysis on Crystalline Form II of the compound represented by Chemical Formula 1 according to one example of the present invention.

FIG. 8 shows results of differential scanning calorimetry (DSC) thermogram on Crystalline Form II of the compound represented by Chemical Formula 1 according to one example of the present invention.

FIG. 9 shows results of X-ray powder diffraction (XRPD) analysis on Crystalline Form III of the compound represented by Chemical Formula 1 according to one example of the present invention.

FIG. 10 shows results of differential scanning calorimetry (DSC) thermogram on Crystalline Form III of the compound represented by Chemical Formula 1 according to one example of the present invention.

FIGS. 11 and 12 show results of X-ray powder diffraction (XRPD) analysis on an amorphous form of the compound represented by Chemical Formula 1.

FIG. 13 shows the differential scanning calorimetry (DSC) thermal analysis (thermogram) results of amorphous form of the compound represented by Chemical Formula 1 according to one preparation example of the present invention.

FIG. 14 shows the X-ray powder diffraction (XRPD) analysis results of Crystalline Form I of

the compound represented by Chemical Formula 1 according to one example of the present invention (Start: 3.0°-End: 39.999°/Step: 0.020°-step time: 46.5 s /Operation: Strip kAlpha2 0.5000/Background 1.000, 1.000).

FIG. 15 shows the differential scanning calorimetry (DSC) thermal analysis (thermogram) results of Crystalline Form I of the compound represented by Chemical Formula 1 according to one example of the present invention;

FIG. 16 shows the X-ray powder diffraction (XRPD) analysis results of Crystalline Form II of the compound represented by Chemical Formula 1 according to one example of the present invention (Start: 3.0°- End: 39.999°/Step: 0.020°- step time: 46.5 s /Operation: Strip kAlpha2 0.5000/Background 1.000, 1.000).

FIG. 17 shows the differential scanning calorimetry (DSC) thermal analysis (thermogram) results of Crystalline Form II of the compound represented by Chemical Formula 1 according to one example of the present invention.

FIG. 18 shows the X-ray powder diffraction (XRPD) analysis results of Crystalline Form III of the compound represented by Chemical Formula 1 according to one example of the present invention (Start: 3.0°- End: 39.999°/Step: 0.020°- step time: 46.5 s /Operation: Strip kAlpha2 0.5000/Background 1.000, 1.000).

FIG. 19 shows the differential scanning calorimetry (DSC) thermal analysis (thermogram) results of Crystalline Form III of the compound represented by Chemical Formula 1 according to one example of the present invention.

FIG. 20 shows the dynamic vapor sorption (DVS) results of Crystalline Form I of the compound represented Chemical by Formula 1 according to one example of the present invention.

FIG. 21 shows the dynamic vapor sorption (DVS) results of Crystalline Form II of the compound represented by Chemical Formula 1 according to one example of the present invention.

FIG. 22 shows the dynamic vapor sorption (DVS) results of Crystalline Form III of the compound represented by Chemical Formula 1 according to one example of the present invention.

FIG. 23 shows the dynamic vapor sorption (DVS) results of an amorphous form of the compound represented Chemical by Formula 1 according to one preparation example of the present invention.

FIG. 24 shows the ^1H NMR results of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is a compound represented by Chemical Formula 1.

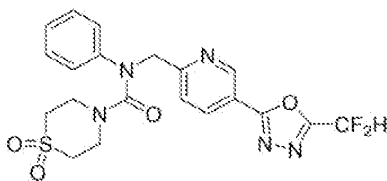
FIG. 25 shows the ^{13}C NMR results of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is a compound represented by Chemical Formula 1.

Embodiments

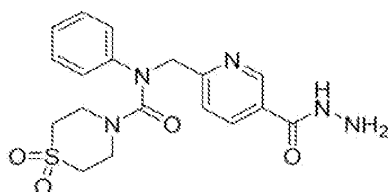
Embodiment 1. A method for preparing a compound represented by Chemical Formula 1 below, the method comprising:

in-situ preparing a compound represented by Chemical Formula 1 below from a compound represented by Chemical Formula 6 below:

[Chemical Formula 1]



[Chemical Formula 6]



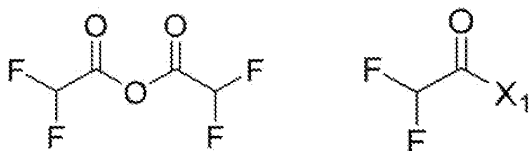
Embodiment 2. The method according to Embodiment 1, wherein the preparing of the compound represented by Chemical Formula 1 from the compound represented by Chemical Formula 6 is performed in the presence of a base.

Embodiment 3. The method according to Embodiment 1 or 2, wherein the base comprises imidazole.

Embodiment 4. The method according to any one of Embodiments 1 to 3, wherein the compound represented by Chemical Formula 1 is prepared by using at least one selected from a compound represented by [Chemical Formula A] below and a compound represented by [Chemical Formula B], and the compound represented by Chemical Formula 6 as a reaction material:

[Chemical Formula A]

[Chemical Formula B]



in above Chemical formula B, X₁ is F, Cl, Br or I.

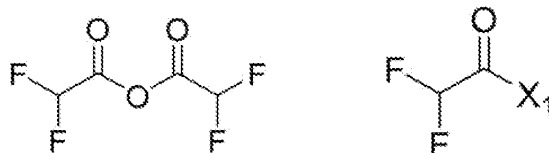
Embodiment 5. The method according to any one of Embodiments 1 to 4 wherein the preparing of the compound represented by Chemical Formula 1 from the compound represented by Chemical Formula 6 comprises:

- a) preparing a reaction part 1 including a compound represented by Chemical Formula A or B below and a base; and
- b) mixing the reaction part 1 with a reaction part 2 including the compound represented by

Chemical Formula 6 to prepare the compound represented by Chemical Formula 1:

[Chemical Formula A]

[Chemical Formula B]



in above Chemical Formula B, X₁ is F, Cl, Br or I.

Embodiment 6. The method according to any one of Embodiments 1 to 5, wherein Step a) is performed by mixing a mixture comprising a base and a solvent with the compound represented by Chemical Formula A or B.

Embodiment 7. The method according to any one of Embodiments 1 to 6, wherein Step a) comprises:

preparing the mixture including the base and the solvent; and

adding the compound represented by Chemical Formula A or Chemical Formula B to the mixture.

Embodiment 8. The method according to any one of Embodiments 1 to 7, the method further comprises:

cooling the mixture into 0-10°C after preparing the mixture including the base and the solvent.

Embodiment 9. The method according to any one of Embodiments 1 to 8, further comprising:

stirring after adding the compound represented by Chemical Formula A or Chemical Formula B to the mixture.

Embodiment 10. The method according to any one of Embodiments 1 to 9, wherein the reaction part 2 in Step b) comprises the compound represented by Chemical Formula 6 and the solvent.

Embodiment 11. The method according to any one of Embodiments 1 to 10, wherein mixing the reaction part 2 and the reaction part 1 in the Step b) is performed by adding the reaction part 1 to the

reaction part 2.

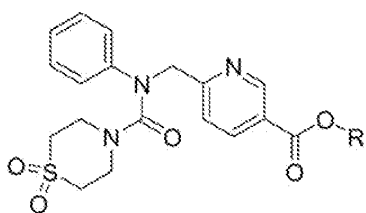
Embodiment 12. The method according to any one of Embodiments 1 to 11, wherein adding the reaction part 1 to the reaction part 2 is performed at -15°C to 5°C.

Embodiment 13. The method according to any one of Embodiments 1 to 12, further comprising: heating to a temperature of 20 to 45°C after completely mixing in Step b).

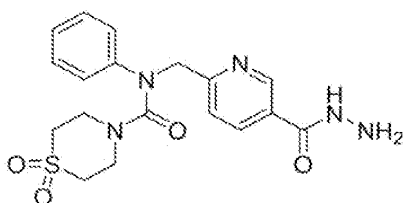
Embodiment 14. A method for preparing a compound represented by Chemical Formula 6 below, the method comprising:

preparing a compound represented by Chemical Formula 6 below from hydrazine(N₂H₄) or a hydrate thereof and a compound represented by Chemical Formula 5 below in the presence of a solvent including a C1 to C6 linear or branched alcohol or a mixture of a C1 to C6 linear or branched alcohol and water:

[Chemical Formula 5]



[Chemical Formula 6]



in above Chemical Formula 5, R is C1-C6 linear or branched alkyl or benzyl.

Embodiment 15. The method according to Embodiment 14, wherein the solvent is methanol or a mixture of methanol and water.

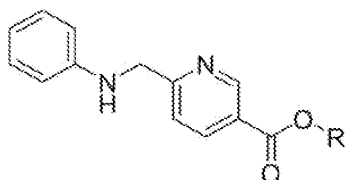
Embodiment 16. The method according to Embodiment 14 or 15, wherein a volume ratio of the alcohol and the water is 10:1 to 1:1.

Embodiment 17. The method according to any one of Embodiment 14 to 16, wherein R is methyl.

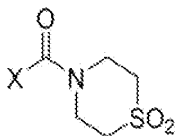
Embodiment 18. A method for preparing a compound represented by Chemical Formula 5, the method comprising:

reacting a compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 in the presence of a base to prepare a compound represented by Chemical Formula 5:

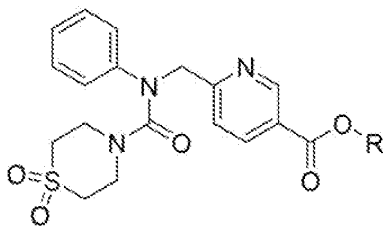
[Chemical Formula 3]



[Chemical Formula 4]



[Chemical Formula 5]



in above Chemical Formulas 3 and 5, R is C1-C6 linear or branched alkyl or benzyl, and in above Chemical Formula 4, X is F, Cl, Br or I.

Embodiment 19. The method according to Embodiment 18, wherein R is methyl and X is Cl.

Embodiment 20. The method according to Embodiment 18 or 19, wherein the base is triethylamine, N,N-diisopropylethylamine, imidazole, pyridine, sodium hydrogen carbonate, sodium carbonate, potassium hydrogen carbonate, potassium carbonate, or a mixture thereof.

Embodiment 21. The method according to any one of Embodiments 18 to 20, the method further comprising:

purifying the compound represented by Chemical Formula 5.

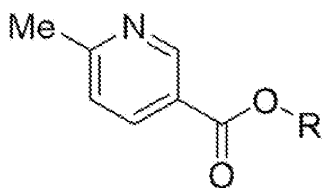
Embodiment 22. The method according to any one of Embodiments 18 to 21, wherein the purifying is performed in a solvent selected from the group consisting of methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl tertiary butyl ether (MTBE), diisopropyl ether, heptane, hexane, and a mixture thereof.

Embodiment 23. A method for preparing a compound represented by Chemical Formula 3 below, the method comprising:

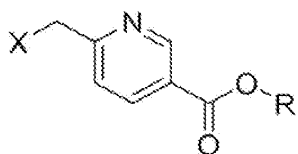
preparing a compound represented by Chemical Formula 8 below from a compound represented by Chemical Formula 7 below by using a halogenating reagent; and

preparing a compound represented by Chemical Formula 3 below by reacting a compound represented by Chemical Formula 8 below with aniline in the presence of a base:

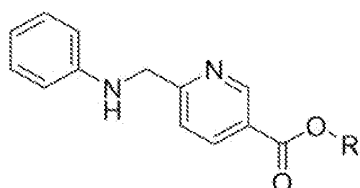
[Chemical Formula 7]



[Chemical Formula 8]



[Chemical Formula 3]



wherein, in above Chemical Formulas 3, 7 and 8, R is C1-C6 linear or branched alkyl or benzyl, and in Chemical Formula 8, X is F, Cl, Br or I.

Embodiment 24. The method according to Embodiment 23, wherein R is methyl and X is Cl.

Embodiment 25. The method according to Embodiment 23 or 24, wherein the halogenating reagent is iodine, copper iodide, bromine, N-bromosuccinimide (NBS), N-chlorosuccinimide (NCS), trichloroisocyanuric acid (TCCA), or a mixture thereof.

Embodiment 26. The method according to Embodiment 24, wherein X of the compound represented by above Chemical Formula 8 is Cl, and the halogenating reagent is N-chlorosuccinimide (NCS), trichloroisocyanuric acid (TCCA), or a mixture thereof.

Embodiment 27. The method according to any one of Embodiments 24 to 26, wherein the base is selected from the group consisting of sodium hydrogen carbonate, sodium carbonate, potassium hydrogen carbonate, potassium carbonate, triethylamine, diisopropylethylamine, and a mixture thereof.

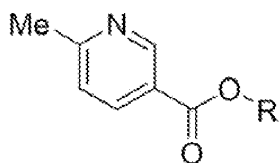
Embodiment 28. The method according to any one of Embodiments 24 to 27, wherein the reacting of the compound represented by Chemical Formula 8 with aniline is performed in the presence of potassium bromide, potassium iodide, tetrabutylammonium bromide (TBAB), or a mixture thereof.

Embodiment 29. A method for preparing a compound represented by Chemical Formula 8a below,

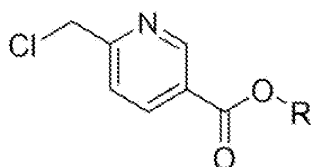
the method comprising:

preparing a compound represented by Chemical Formula 8a below by using only a trichloroisocyanuric acid (TCCA) reagent alone in a compound represented by Chemical Formula 7 below:

[Chemical Formula 7]



[Chemical Formula 8a]

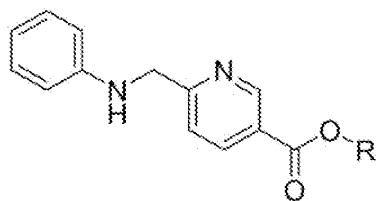


in above Chemical Formulas 7 and 8a, R is C1-C6 linear alkyl or benzyl.

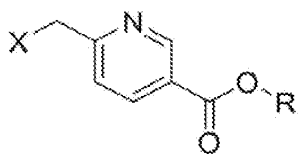
Embodiment 30. A method for preparing a compound represented by Chemical Formula 3, the method comprising:

preparing a compound represented by Chemical Formula 3 below by reacting a compound represented by Chemical Formula 8 below with aniline in the presence of a base:

[Chemical Formula 3]



[Chemical Formula 8]



in above Chemical Formulas 3 and 8, R is C1-C6 linear or branched alkyl or benzyl and in above Chemical Formula 8, X is F, Cl, Br, or I.

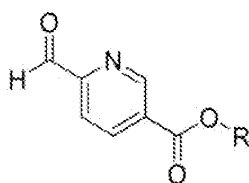
Embodiment 31. The method according to Embodiment 30, wherein the base is selected from the group consisting of sodium hydrogen carbonate, sodium carbonate, potassium hydrogen carbonate, potassium carbonate, triethylamine, diisopropylethylamine, and a mixture thereof.

Embodiment 32. The method according to Embodiment 30 or 31, wherein the reacting of the compound represented by Chemical Formula 8 with aniline is performed in the presence of potassium bromide, potassium iodide, tetrabutylammonium bromide (TBAB), or a mixture thereof.

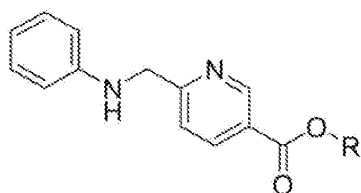
Embodiment 33. A method for preparing a compound represented by Chemical Formula 3, the method comprising:

preparing a compound represented by Chemical Formula 3 below from a compound represented by Chemical Formula 2 below in the presence of aniline and a reducing agent:

[Chemical Formula 2]



[Chemical Formula 3]



in above Chemical Formula 2 or 3, R is C1-C6 linear or branched alkyl or benzyl.

Embodiment 34. The method according to Embodiment 33, wherein the preparing of the compound represented by Chemical Formula 3 from the compound represented by Chemical Formula 2 comprises:

preparing a mixture including the compound represented by Chemical Formula 2 and aniline;
and
reacting the mixture with the reducing agent.

Embodiment 35. The method according to Embodiment 33 or 34, wherein the preparing of the compound represented by Chemical Formula 3 from the compound represented by Chemical Formula 2 comprises:

preparing reaction part 1 including the compound represented by Chemical Formula 2, aniline and a solvent; and
mixing the reaction part 1 and reaction part 2 including the reducing agent and the solvent.

Embodiment 36. The method according to any one of Embodiments 33 to 35, wherein the reducing agent comprises one or more selected from the group consisting of sodium borohydride (NaBH_4), sodium cyanoborohydride (NaBH_3CN), and sodium triacetoxyborohydride ($\text{NaBH}(\text{OAc})_3$).

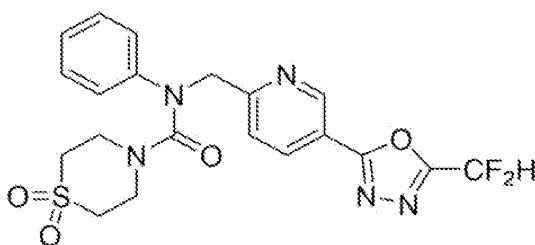
Embodiment 37. The method according to any one of Embodiments 33 to 36, wherein the preparing of the compound represented by Chemical Formula 3 from the compound represented by Chemical Formula 2 is performed in the presence of an acid.

Embodiment 38. A method for preparing a compound represented by Chemical Formula 1 below,

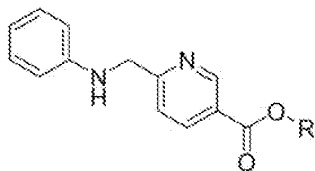
the method comprising:

- 1) preparing a compound represented by Chemical Formula 8 below from a compound represented by Chemical Formula 7 below by using a halogenating reagent;
- 2) preparing a compound represented by Chemical Formula 3 by reacting the compound represented by Chemical Formula 8 below with aniline in the presence of a base;
- 3) obtaining a compound represented by Chemical Formula 5 below by reacting the compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 below in the presence of a base;
- 4) obtaining a compound represented by Chemical Formula 6 below by reacting hydrazine or a hydrate thereof with the compound represented by Chemical Formula 5 below; and
- 5) in-situ preparing the compound represented by Chemical Formula 1 below from the compound represented by Chemical Formula 6 below:

[Chemical Formula 1]

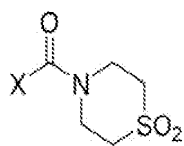


[Chemical Formula 3]



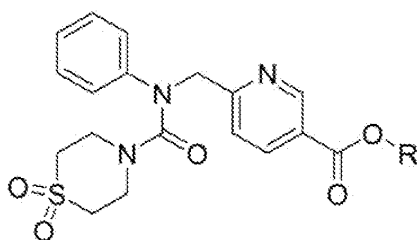
(in above Chemical Formula 3, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



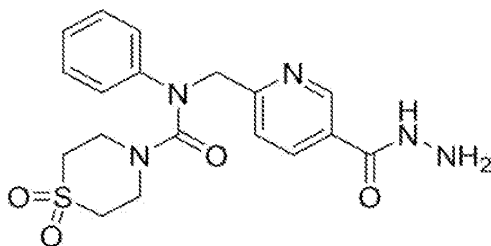
(in above Chemical Formula 4, X is F, Cl, Br or I)

[Chemical Formula 5]

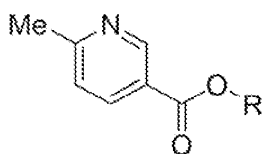


(in above Chemical Formula 5, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 6]

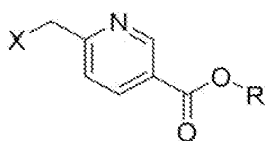


[Chemical Formula 7]



(in above Chemical Formula 7, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 8]

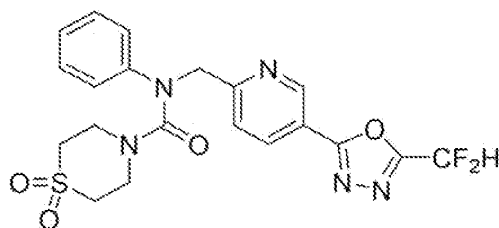


(in above Chemical Formula 8, R is C1-C6 linear or branched alkyl or benzyl, and X is F, Cl, Br or I).

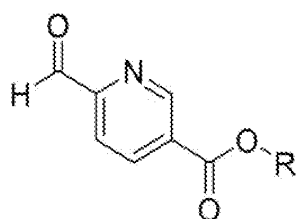
Embodiment 39. A method for preparing a compound represented by Chemical Formula 1 below, the method comprising:

- 1) preparing a compound represented by Chemical Formula 3 below from a compound represented by Chemical Formula 2 below in the presence of aniline and a reducing agent;
- 2) obtaining a compound represented by Chemical Formula 5 below by reacting the compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 below in the presence of a base;
- 3) obtaining a compound represented by Chemical Formula 6 below by reacting hydrazine or a hydrate thereof with the compound represented by Chemical Formula 5 below; and
- 4) in-situ preparing the compound represented by Chemical Formula 1 below from the compound represented by Chemical Formula 6 below:

[Chemical Formula 1]

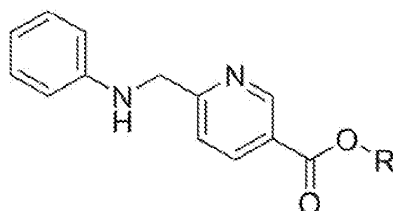


[Chemical Formula 2]



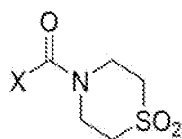
(in above Chemical Formula 2, R is C1-C6 alkyl or benzyl)

[Chemical Formula 3]



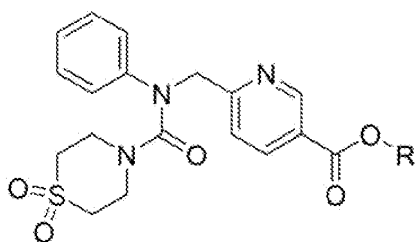
(wherein, in above Chemical Formula 3, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



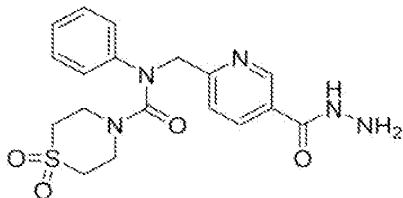
(wherein, in above Chemical Formula 4, X may be F, Cl, Br or I)

[Chemical Formula 5]



(wherein, in above Chemical Formula 5, R is C1-C6 linear or branched alkyl or benzyl)

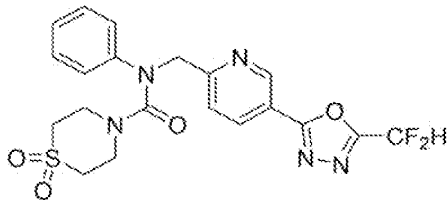
[Chemical Formula 6]



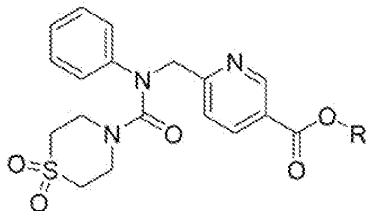
Embodiment 40. A method for preparing a compound represented by Chemical Formula 1 below, the method comprising:

- 1) obtaining a compound represented by Chemical Formula 6 below by reacting hydrazine or a hydrate thereof with a compound represented by Chemical Formula 5 below; and
- 2) in-situ preparing the compound represented by Chemical Formula 1 below from a compound represented by Chemical Formula 6 below:

[Chemical Formula 1]

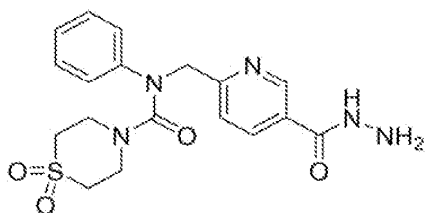


[Chemical Formula 5]



(in above Chemical Formula 5, R is C1-C6 linear or branched alkyl or benzyl)

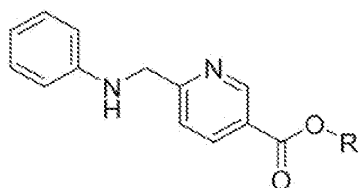
[Chemical Formula 6]



Embodiment 41. The method according to Embodiment 40, wherein the method for preparing the compound represented by above Chemical Formula 5 comprises:

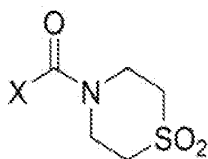
reacting a compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 below in the presence of a base to prepare the compound represented by Chemical Formula 5:

[Chemical Formula 3]



(in above Chemical Formula 3, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



(in above Chemical Formula 4, X is F, Cl, Br or I).

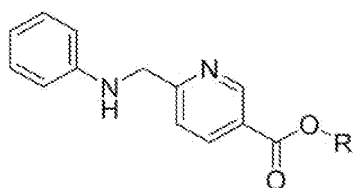
Embodiment 42. The method according to Embodiment 40 or 41, wherein the method for preparing the compound represented by Chemical Formula 5 comprises:

preparing a compound represented by Chemical Formula 3 by reacting a compound represented

by Chemical Formula 8 below with aniline in the presence of a base; and

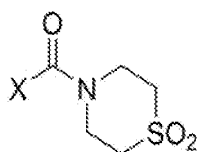
reacting a compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 below in the presence of a base to prepare the compound represented by Chemical Formula 5:

[Chemical Formula 3]



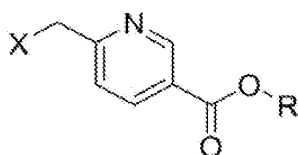
(in above Chemical Formula 3, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



(in above Chemical Formula 4, X is F, Cl, Br or I)

[Chemical Formula 8]



(in above Chemical Formula 8, R is C1-C6 linear or branched alkyl or benzyl, and X is F, Cl, Br or I).

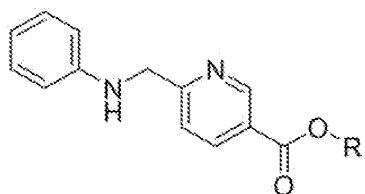
Embodiment 43. The method according to any one of Embodiments 40 to 42, wherein the method for preparing the compound represented by Chemical Formula 5 comprises:

Preparing a compound represented by Chemical Formula 8 below from a compound represented by Chemical Formula 7 below by using a halogenating reagent;

preparing a compound represented by Chemical Formula 3 below by reacting the compound represented by Chemical Formula 8 with aniline in the presence of a base;

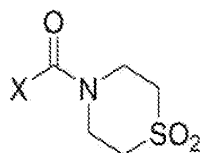
reacting the compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 below in the presence of a base to prepare the compound represented by Chemical Formula 5:

[Chemical Formula 3]



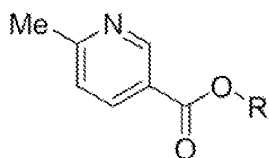
(in above Chemical Formula 3, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



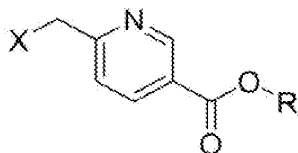
(in above Chemical Formula 4, X is F, Cl, Br or I)

[Chemical Formula 7]



(in above Chemical Formula 7, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 8]



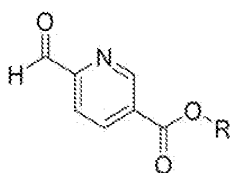
(in above Chemical Formula 8, R is C1-C6 linear or branched alkyl or benzyl, and X is F, Cl, Br or I)

Embodiment 44. The method according to any one of Embodiments 40 to 43, wherein the method for preparing the compound represented by Chemical Formula 5 comprises:

preparing a compound represented by Chemical Formula 3 below from a compound represented by Chemical Formula 2 below in the presence of aniline and a reducing agent; and

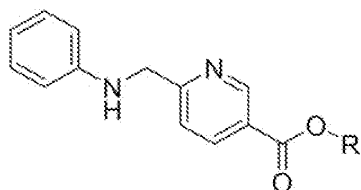
reacting the compound represented by Chemical Formula 3 with a compound represented by Chemical Formula 4 below in the presence of a base to prepare a compound represented by Chemical Formula 5 below:

[Chemical Formula 2]



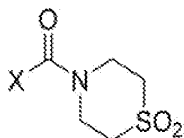
(in above Chemical Formula 2, R is C1-C6 alkyl or benzyl)

[Chemical Formula 3]



(in above Chemical Formula 3, R is C1-C6 linear or branched alkyl or benzyl)

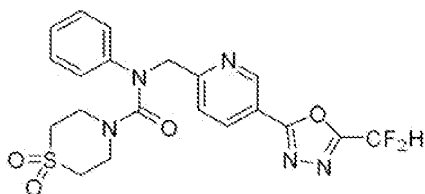
[Chemical Formula 4]



(in above Chemical Formula 4, X is F, Cl, Br, or I).

Embodiment 45. Crystalline Form I of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1, wherein an X-ray powder diffraction pattern comprises diffraction peaks at three or more diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 7.85° , 14.54° , 17.14° , 18.09° , 19.62° , 21.41° and 23.58° :

[Chemical Formula 1]



Embodiment 46. The Crystalline Form I according to Embodiment 45, wherein the X-ray powder diffraction pattern further comprises diffraction peaks at one or more diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 15.64° , 17.55° , 20.78° , 21.04° , 23.27° , 24.24° and 30.38° .

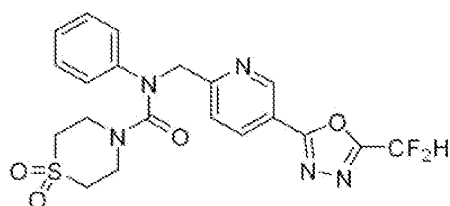
Embodiment 47. The Crystalline Form I according to Embodiment 45 or 46, wherein the X-ray powder diffraction pattern further comprises one or more diffraction peaks selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 9.40° , 11.62° , 11.77° , 13.49° , 14.92° , 15.64° , 17.55° , 18.82° , 20.78° , 21.04° , 22.69° , 23.27° , 24.24° , 26.35° , 27.58° , 28.91° , 30.38° , 33.57° and 36.74° .

Embodiment 48. The Crystalline Form I according to any one of Embodiments 45 to 47, wherein Crystalline Form I has an endothermic peak at 132 °C($\pm 0.5^{\circ}\text{C}$) to 143°C($\pm 0.5^{\circ}\text{C}$) during differential scanning calorimetry (DSC) analysis when the heating rate is 10°C/min.

Embodiment 49. The Crystalline Form I according to any one of Embodiments 45 to 48, wherein Crystalline Form I has an endothermic peak at 138°C ($\pm 3^{\circ}\text{C}$) during differential scanning calorimetry (DSC) analysis when the heating rate is 10°C/min.

Embodiment 50. Crystalline Form II of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1, wherein an X-ray powder diffraction pattern comprises three or more diffraction peaks selected from the group consisting of diffraction angles ($2\theta \pm 0.2^{\circ}$) of 7.83°, 12.22°, 19.02°, 19.67°, 21.40°, 22.35° and 26.44°:

[Chemical Formula 1]



Embodiment 51. The Crystalline Form II according to Embodiment 50, wherein the X-ray powder diffraction pattern further comprises diffraction peaks at one or more diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^{\circ}$) of 11.41°, 11.78°, 13.28°, 15.70°, 16.64°, 17.48° 18.28°, 19.37°, 20.71°, 24.58°, 27.35° and 33.73°.

Embodiment 52. The Crystalline Form II according to Embodiment 50 or 51, wherein the X-ray powder diffraction pattern further comprises diffraction peaks at one or more diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^{\circ}$) of 10.72°, 10.92°, 11.41°, 11.78°, 13.28°, 15.70°, 16.64°, 16.97°, 17.48°, 18.28°, 19.37° 20.71°, 24.58°, 27.35°, 30.49°, 32.19°, 33.73°, 35.44° and

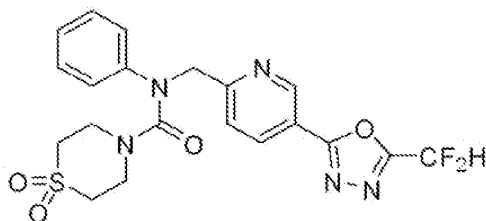
35.91°

Embodiment 53. The Crystalline Form II according to any one of Embodiments 50 to 52, wherein Crystalline Form II has an endothermic peak at 124 °C ($\pm 0.5^{\circ}\text{C}$) to 138°C ($\pm 0.5^{\circ}\text{C}$) during differential scanning calorimetry (DSC) analysis when the heating rate is 10°C/min.

Embodiment 54. The Crystalline Form II according to any one of Embodiments 50 to 53, wherein Crystalline Form II has an endothermic peak at 130°C ($\pm 5^{\circ}\text{C}$) during differential scanning calorimetry (DSC) analysis when the heating rate is 10°C/min.

Embodiment 55. Crystalline Form III of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1, wherein an X-ray powder diffraction pattern comprises diffraction peaks at three or more diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^{\circ}$) of 8.75°, 10.98°, 12.44°, 16.86°, 22.92° and 28.49°:

[Chemical Formula 1]



Embodiment 56. The Crystalline Form III according to Embodiment 55, wherein the X-ray powder diffraction pattern further comprises diffraction peaks at one or more diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^{\circ}$) of 17.48°, 19.95°, 20.49°, 20.79°, 21.55°, 21.87°, 22.07°, 24.04°, 24.72°, 24.99° and 26.30°.

Embodiment 57. The Crystalline Form III according to Embodiment 55 or 56, wherein the X-ray powder diffraction pattern further comprises diffraction peaks at one or more diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^{\circ}$) of 14.28°, 15.45°, 17.48°, 18.49°,

18.77°, 19.95°, 20.49°, 20.79°, 21.55°, 21.87°, 22.07°, 24.04°, 24.72°, 24.99°, 26.30°, 29.22°, 30.20°, 31.40°, 34.10°, 37.13° and 38.86°.

Embodiment 58. The Crystalline Form III according to any one of Embodiments 55 to 57, wherein Crystalline Form III has an endothermic peak at 120°C (±0.5°C) to 130°C (±0.5°C) during differential scanning calorimetry (DSC) analysis when the heating rate is 10°C/min.

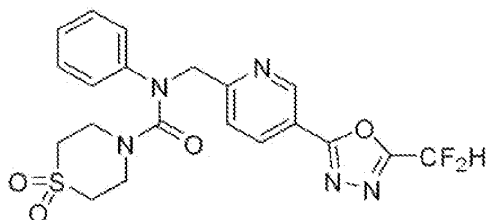
Embodiment 59. The Crystalline Form III according to any one of Embodiments 55 to 57, wherein Crystalline Form III has an endothermic peak at 125°C (±5°C) during differential scanning calorimetry (DSC) analysis when the heating rate is 10°C/min.

Embodiment 60. A method for preparing Crystalline Form I of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is a compound represented by the following Chemical Formula 1, the method comprising:

(a) obtaining a solution by dissolving N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1 in a solvent selected from the group consisting of ethyl acetate, ethanol, methanol, isopropyl alcohol, butyl alcohol, methyl tertiary butyl ether (MTBE), diisopropyl ether, acetone, methylisobutylketone (MIBK), methyl ethyl ketone, dichloromethane, dimethylformamide, N-methyl-2-pyrrolidone, toluene, tetrahydrofuran, heptane, hexane, acetonitrile and a mixture thereof; and

(b) producing a solid from the solution:

[Chemical Formula 1]



Embodiment 61. The method according to Embodiment 60, wherein in Step (a), the solvent is

one or more alcohols selected from the group consisting of ethanol, methanol, isopropyl alcohol and butyl alcohol, ethyl acetate, or a mixture of the alcohol and ethyl acetate.

Embodiment 62. The method according to Embodiment 60 or 61, wherein the obtaining of the solution (a) comprises:

(a1) obtaining a mixture by adding the compound represented by Chemical Formula 1 to the solvent; and

(a2) warming the mixture to a temperature exceeding 40°C.

Embodiment 63. The method according to any one of Embodiments 60 to 62, wherein the producing of the solid of Step (b) further comprises:

(b1) additionally adding one or more alcohols selected from the group consisting of ethanol, methanol, isopropyl alcohol and butyl alcohol to the solution of Step (a); and

(b2) stirring the mixture after adding the alcohol of Step (b1).

Embodiment 64. The method according to any one of Embodiments 60 to 63, wherein Steps (b1) and (b2) are performed at a temperature exceeding 40°C.

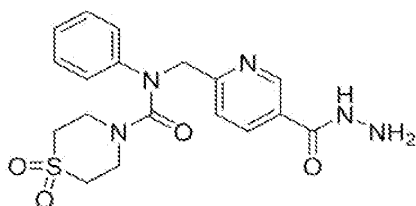
Embodiment 65. The method according to any one of Embodiments 60 to 64, further comprising, before performing Step (a),

producing a concentrated residue by dissolving the compound represented by Chemical Formula 1 in dichloromethane, and then performing primary concentration; and

adding ethyl acetate to the concentrated residue and performing secondary concentration.

Embodiment 66. The method according to Embodiment 60, the compound represented by Chemical Formula 1 is in-situ prepared from a compound represented by Chemical Formula 6:

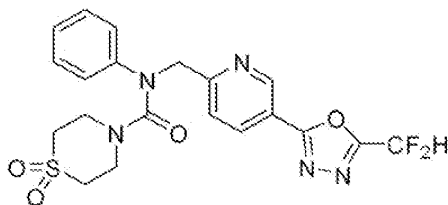
[Chemical Formula 6]



Embodiment 67. A method for preparing Crystalline Form II of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is a compound represented by the following Chemical Formula 1, the method comprising:

- (a) preparing a mixture by adding N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1 to a solvent selected from the group consisting of methanol, ethanol, isopropyl alcohol, butyl alcohol, diisopropyl ether, tetrahydrofuran, heptane, hexane and a mixture thereof;
- (b) obtaining a solution by warming the mixture to a temperature of 40°C or less; and
- (c) producing a solid from the solution at a temperature of 40°C or less;

[Chemical Formula 1]



Embodiment 68. The method according to Embodiment 67, wherein in Step (a), the solvent is ethanol, isopropanol or a mixture thereof.

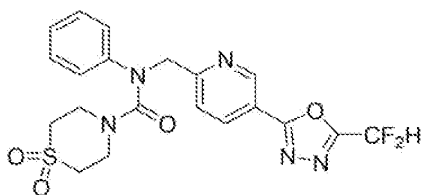
Embodiment 69. The method according to Embodiment 67 or 68, further comprising, before performing Step (a),

producing a concentrated residue by dissolving the compound represented by Chemical Formula 1 in dichloromethane, and then performing primary concentration;

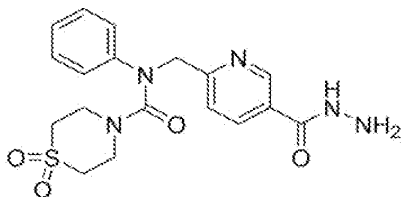
adding ethanol to the concentrated residue and performing secondary concentration.

Embodiment 70. The method according to any one of Embodiments 67 to 69, the compound represented by Chemical Formula 1 is in-situ prepared from a compound represented by Chemical Formula 6:

[Chemical Formula 1]



[Chemical Formula 6]

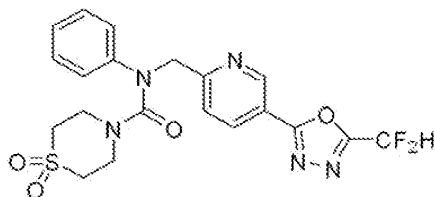


Embodiment 71. A method for preparing Crystalline Form III of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is a compound represented by the following Chemical Formula 1, the method comprising:

(a) producing a slurry by adding amorphous N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1 to a solvent selected from the group consisting of methyl tertiary butyl ether (MTBE), heptane, octane, hexane, pentane and a mixture thereof; and

(b) obtaining a solid from the slurry:

[Chemical Formula 1]



Embodiment 72. The method according to Embodiment 71, wherein the solvent of Step (a) is methyl tertiary butyl ether (MTBE), heptane or a mixture thereof.

Embodiment 73. The method according to Embodiment 71 or 72, wherein (a) the producing of the slurry is performed for 12 hours to 20 days.

Embodiment 74. The method according to any one of Embodiments 71 to 73, wherein (b) the obtaining of the solid further comprises filtering the slurry.

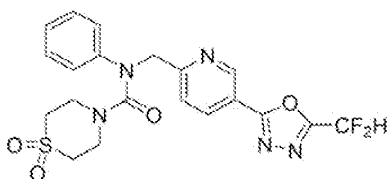
Embodiment 75. The method according to Embodiments 71 to 74, wherein (a) the producing of the slurry and (b) the obtaining of the solid are performed at a temperature of 30°C or less.

Embodiment 76. The method according to Embodiments 71 to 75, wherein preparing the amorphous form of the compound represented by Chemical Formula 1 comprising:

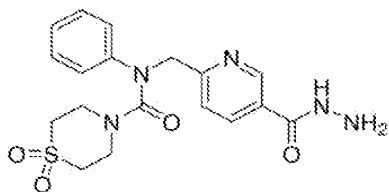
in-situ preparing the compound represented by Chemical Formula 1 from a compound represented by Chemical Formula 6; and

vacuum-drying the compound represented by Chemical Formula 1.

[Chemical Formula 1]



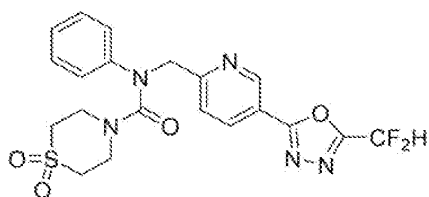
[Chemical Formula 6]



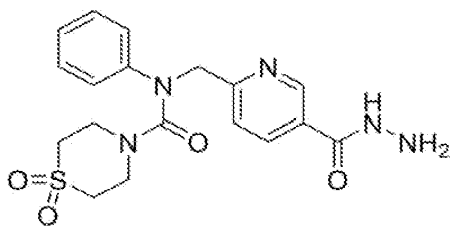
Embodiment A1. A method for preparing a compound represented by Chemical Formula 1 below, the method comprising:

in-situ preparing a compound represented by Chemical Formula 1 below from a compound represented by Chemical Formula 6 below:

[Chemical Formula 1]



[Chemical Formula 6]



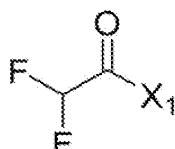
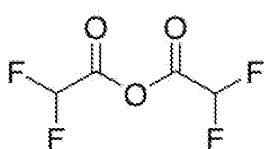
Embodiment A 2. The method according to Embodiment A1, wherein the preparing of the compound represented by Chemical Formula 1 from the compound represented by Chemical Formula 6 is performed in the presence of a base.

Embodiment A3. The method according to Embodiment A2, wherein the base comprises imidazole.

Embodiment A4. The method according to any one of Embodiments A1 to A3, wherein the compound represented by Chemical Formula 1 is prepared by using at least one selected from a compound represented by [Chemical Formula A] below and a compound represented by [Chemical Formula B], and the compound represented by Chemical Formula 6 as a reaction material:

[Chemical Formula A]

[Chemical Formula B]



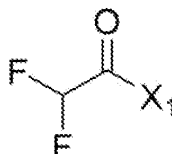
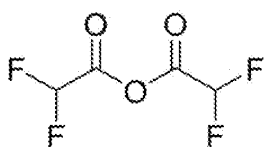
wherein, in above Chemical formula B, X₁ is F, Cl, Br or I.

Embodiment A 5. The method according to any one of Embodiments A1 to A3, wherein the preparing of the compound represented by Chemical Formula 1 from the compound represented by Chemical Formula 6 comprises:

- a) preparing a reaction part 1 including a compound represented by Chemical Formula A or B below and a base; and
- b) mixing the reaction part 1 with a reaction part 2 including the compound represented by Chemical Formula 6 to prepare the compound represented by Chemical Formula 1:

[Chemical Formula A]

[Chemical Formula B]



wherein, in above Chemical Formula B, X₁ is F, Cl, Br or I.

Embodiment A6. The method according to Embodiments A5, wherein Step a) is performed by mixing a mixture comprising a base and a solvent with the compound represented by Chemical Formula A or B.

Embodiment A7. The method according to Embodiment A5 or A6, wherein Step a) comprises:
preparing the mixture including the base and the solvent;
cooling the mixture to 0 to 10 °C; and
adding the compound represented by Chemical Formula A or Chemical Formula B to the cooled mixture.

Embodiment A8. The method according to any one of Embodiments A5 to A7, further comprising:
stirring after adding the compound represented by Chemical Formula A or Chemical Formula B to the mixture.

Embodiment A9. The method according to any one of Embodiments A5 to A8, wherein Step b) comprises:
preparing a reaction part 2 including the compound represented by Chemical Formula 6 and the solvent; and
reacting the reaction part 2 and the reaction part 1.

Embodiment A10. The method according to any one of Embodiments A5 to A9, wherein the reacting of the reaction part 2 and the reaction part 1 in the Step b) is performed by adding the reaction part 1 to the reaction part 2.

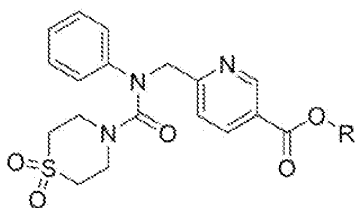
Embodiment A11. The method according to Embodiment A10, wherein the adding of the reaction part 1 to the reaction part 2 is performed at -15 °C to 5 °C.

Embodiment A12. The method according to Embodiment A10 or A11, further comprising:
heating to a temperature of 20 to 45 °C after completely adding in Step b).

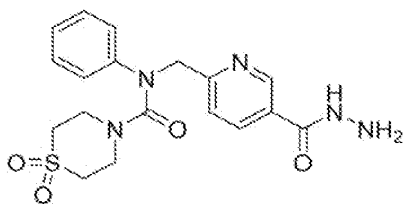
Embodiment A13. A method for preparing a compound represented by Chemical Formula 6 below, the method comprising:

preparing a compound represented by Chemical Formula 6 below from hydrazine or a hydrate thereof and a compound represented by Chemical Formula 5 below in the presence of a solvent including a C1 to C6 linear or branched alcohol or a mixture of a C1 to C6 linear or branched alcohol and water:

[Chemical Formula 5]



[Chemical Formula 6]



wherein, in above Chemical Formula 5, R is C1-C6 linear or branched alkyl or benzyl.

Embodiment A14. The method according to Embodiment A13, wherein the solvent is methanol or a mixture of methanol and water.

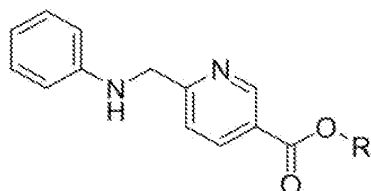
Embodiment A15. The method according to Embodiment A13 or 14, wherein a volume ratio of the alcohol and the water is 10:1 to 1:1.

Embodiment A16. A method for preparing a compound represented by Chemical Formula 5, the method comprising:

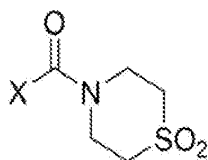
reacting a compound represented by Chemical Formula 3 below with a compound represented by

Chemical Formula 4 in the presence of a base to prepare a compound represented by Chemical Formula 5:

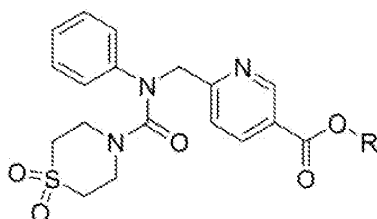
[Chemical Formula 3]



[Chemical Formula 4]



[Chemical Formula 5]



wherein, in above Chemical Formulas 3 and 5, R is C1-C6 linear or branched alkyl or benzyl, and in above Chemical Formula 4, X is F, Cl, Br or I.

Embodiment A17. The method according to Embodiment A16, wherein R is methyl and X is Cl.

Embodiment A18. The method according to Embodiment A16 or A17, wherein the base is triethylamine, N,N-diisopropylethylamine, imidazole, pyridine, sodium hydrogen carbonate, sodium carbonate, potassium hydrogen carbonate, potassium carbonate, or a mixture thereof.

Embodiment A19. The method according to any one according to Embodiments A16 to A18, the

method further comprising: purifying the compound represented by Chemical Formula 5.

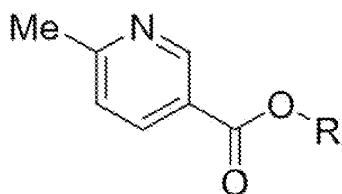
Embodiment A20. The method according to Embodiment A19, wherein the purifying is performed in a solvent selected from the group consisting of methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl tertiary butyl ether (MTBE), diisopropyl ether, heptane, hexane, and a mixture thereof.

Embodiment A21. A method for preparing a compound represented by Chemical Formula 3 below, the method comprising:

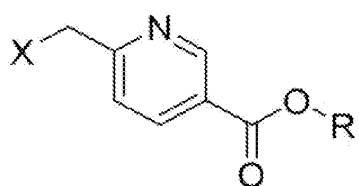
preparing a compound represented by Chemical Formula 8 below from a compound represented by Chemical Formula 7 below by using a halogenating reagent; and

preparing a compound represented by Chemical Formula 3 below by reacting a compound represented by Chemical Formula 8 below with aniline in the presence of a base:

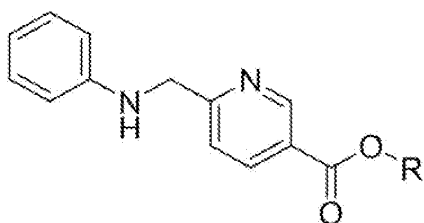
[Chemical Formula 7]



[Chemical Formula 8]



[Chemical Formula 3]



wherein, in above Chemical Formulas 3, 7 and 8, R is C1-C6 linear or branched alkyl or benzyl, and in Chemical Formula 8, X is F, Cl, Br or I.

Embodiment A22. The method according to Embodiment A21, wherein the halogenating reagent is iodine, copper iodide, bromine, N-bromosuccinimide (NBS), N-chlorosuccinimide (NCS), trichloroisocyanuric acid (TCCA), or a mixture thereof.

Embodiment A23. The method according to Embodiment A21 or A22, wherein X of the compound represented by above Chemical Formula 8 is Cl, and the halogenating reagent is N-chlorosuccinimide (NCS), trichloroisocyanuric acid (TCCA), or a mixture thereof.

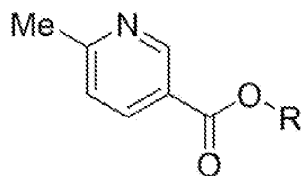
Embodiment A24. The method according to any one of Embodiments A21 to A23, wherein the base is selected from the group consisting of sodium hydrogen carbonate, sodium carbonate, potassium hydrogen carbonate, potassium carbonate, triethylamine, diisopropylethylamine, and a mixture thereof.

Embodiment A25. The method according to any one of Embodiments A21 to A24, wherein the reacting of the compound represented by Chemical Formula 8 with aniline is performed in the presence of potassium bromide, potassium iodide, tetrabutylammonium bromide (TBAB), or a mixture thereof.

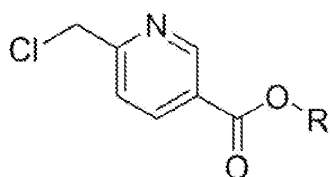
26. A method for preparing a compound represented by Chemical Formula 8a below, the method comprising:

preparing a compound represented by Chemical Formula 8a below by using only a trichloroisocyanuric acid (TCCA) reagent alone in a compound represented by Chemical Formula 7 below:

[Chemical Formula 7]



[Chemical Formula 8A]

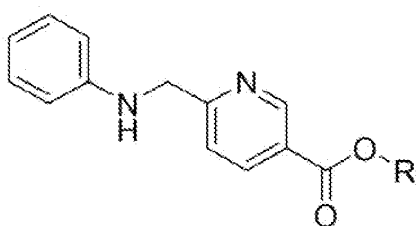


wherein, in above Chemical Formulas 7 and 8a, R is C1-C6 linear alkyl or benzyl.

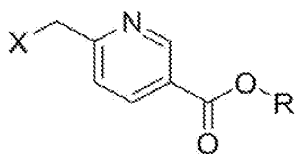
Embodiment A27. A method for preparing a compound represented by Chemical Formula 3, the method comprising:

preparing a compound represented by Chemical Formula 3 below by reacting a compound represented by Chemical Formula 8 below with aniline in the presence of a base:

[Chemical Formula 3]



[Chemical Formula 8]



wherein, in above Chemical Formulas 3 and 8, R is C1-C6 linear or branched alkyl or benzyl.

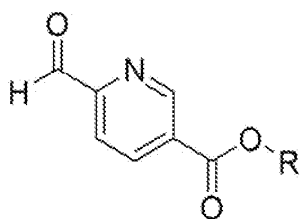
Embodiment A28. The method according to Embodiment A27, wherein the base is selected from the group consisting of sodium hydrogen carbonate, sodium carbonate, potassium hydrogen carbonate, potassium carbonate, triethylamine, diisopropylethylamine, and a mixture thereof.

Embodiment A29. The method according to Embodiment A27 or A28, wherein the reacting of the compound represented by Chemical Formula 8 with aniline is performed in the presence of potassium bromide, potassium iodide, tetrabutylammonium bromide (TBAB), or a mixture thereof.

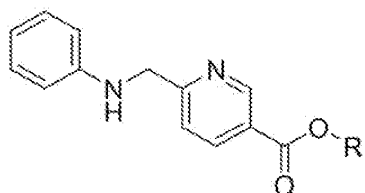
Embodiment A30. A method for preparing a compound represented by Chemical Formula 3, the method comprising:

preparing a compound represented by Chemical Formula 3 below from a compound represented by Chemical Formula 2 below in the presence of aniline and a reducing agent:

[Chemical Formula 2]



[Chemical Formula 3]



wherein, in above Chemical Formula 2 or 3, R is C1-C6 linear or branched alkyl or benzyl.

Embodiment A31. The method according to Embodiment A30, wherein the preparing of the compound represented by Chemical Formula 3 from the compound represented by Chemical Formula 2 comprises:

- preparing a mixture including the compound of Chemical Formula 2 and aniline; and
- reacting the mixture with the reducing agent.

Embodiment A32. The method according to Embodiment A30 or A31, wherein the preparing of the compound represented by Chemical Formula 3 from the compound represented by Chemical Formula 2 comprises:

- preparing reaction part 1 including the compound represented by Chemical Formula 2, aniline and a solvent; and
- reacting the reaction part 1 and reaction part 2 including the reducing agent and the solvent.

Embodiment A33. The method according to any one of Embodiments A30 to A32, wherein the reducing agent comprises one or more selected from the group consisting of sodium borohydride (NaBH_4), sodium cyanoborohydride (NaBH_3CN), and sodium triacetoxyborohydride ($\text{NaBH}(\text{OAc})_3$).

Embodiment A34. The method according to any one of Embodiments A30 to A33, wherein the preparing of the compound represented by Chemical Formula 3 from the compound represented by Chemical Formula 2 is performed in the presence of acid.

Embodiment A35. A method for preparing a compound represented by Chemical Formula 1 below, the method comprising:

1) preparing a compound represented by Chemical Formula 8 below from a compound represented by Chemical Formula 7 below by using a halogenating reagent;

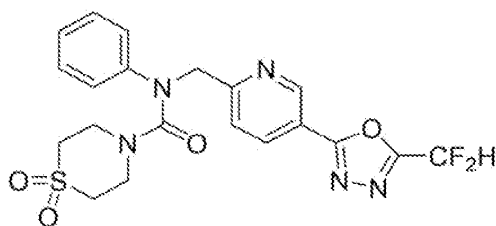
2) preparing a compound represented by Chemical Formula 3 by reacting the compound represented by Chemical Formula 8 below with aniline in the presence of a base;

3) obtaining a compound represented by Chemical Formula 5 below by reacting the compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 below in the presence of a base;

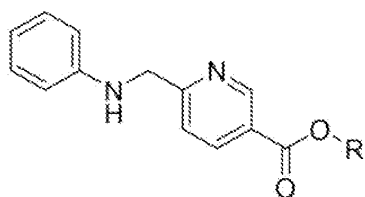
4) obtaining a compound represented by Chemical Formula 6 below by reacting hydrazine or a hydrate thereof with the compound represented by Chemical Formula 5 below; and

5) in-situ preparing the compound represented by Chemical Formula 1 below from the compound represented by Chemical Formula 6 below:

[Chemical Formula 1]

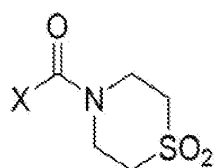


[Chemical Formula 3]



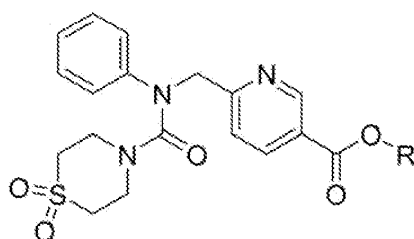
(wherein, in above Chemical Formula 3, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



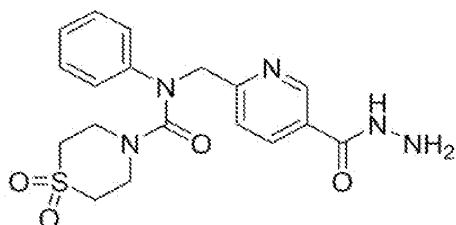
(wherein, in above Chemical Formula 4, X is F, Cl, Br or I)

[Chemical Formula 5]

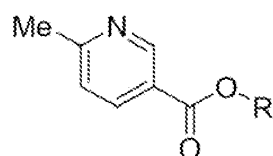


(wherein, in above Chemical Formula 5, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 6]

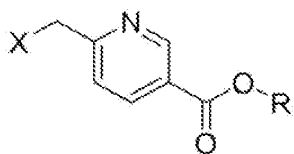


[Chemical Formula 7]



(wherein, in above Chemical Formula 7, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 8]



(wherein, in above Chemical Formula 8, R is C1-C6 linear or branched alkyl or benzyl, and X is F, Cl, Br or I)

Embodiment A36. A method for preparing a compound represented by Chemical Formula 1 below, the method comprising:

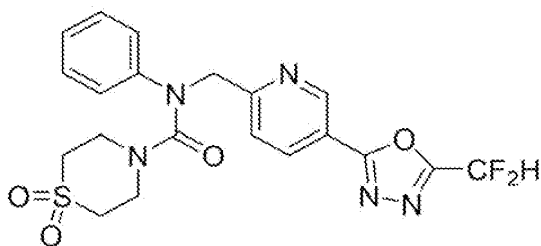
1) preparing a compound represented by Chemical Formula 3 below from a compound represented by Chemical Formula 2 below in the presence of aniline and a reducing agent;

2) obtaining a compound represented by Chemical Formula 5 below by reacting the compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 below in the presence of a base;

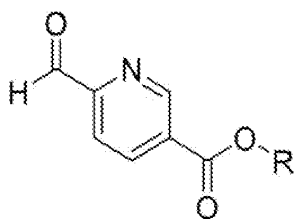
3) obtaining a compound represented by Chemical Formula 6 below by reacting hydrazine or a hydrate thereof with the compound represented by Chemical Formula 5 below; and

4) in-situ preparing the compound represented by Chemical Formula 1 below from the compound represented by Chemical Formula 6 below:

[Chemical Formula 1]

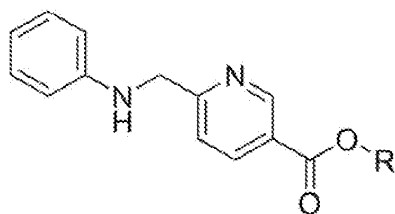


[Chemical Formula 2]



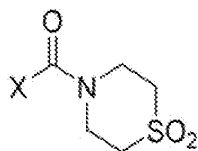
(wherein, in above Chemical Formula 2, R is C1-C6 alkyl or benzyl)

[Chemical Formula 3]



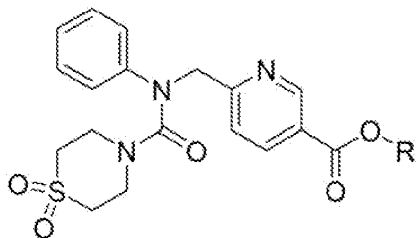
(wherein, in above Chemical Formula 3, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



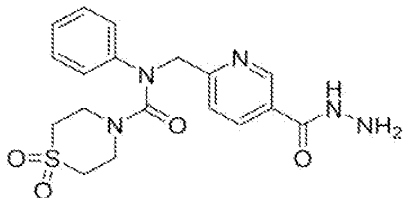
(wherein, in above Chemical Formula 4, X may be F, Cl, Br or I)

[Chemical Formula 5]



(wherein, in above Chemical Formula 5, R is C1-C6 linear or branched alkyl or benzyl)

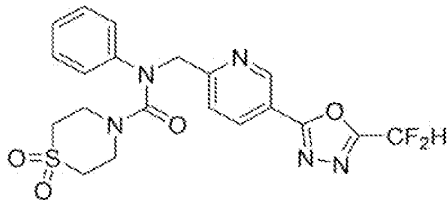
[Chemical Formula 6]



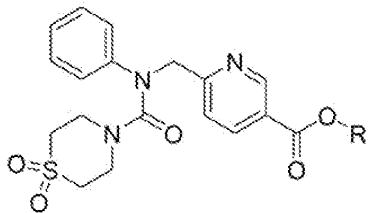
Embodiment A37. A method for preparing a compound represented by Chemical Formula 1 below, the method comprising:

- 1) obtaining a compound represented by Chemical Formula 6 below by reacting hydrazine or a hydrate thereof with a compound represented by Chemical Formula 5 below; and
- 2) in-situ preparing the compound represented by Chemical Formula 1 below from a compound represented by Chemical Formula 6 below:

[Chemical Formula 1]

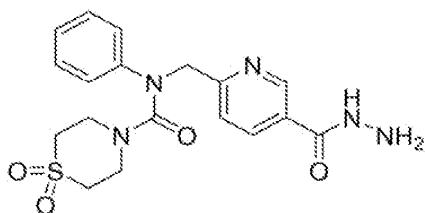


[Chemical Formula 5]



(wherein, in above Chemical Formula 5, R is C1-C6 linear or branched alkyl or benzyl)

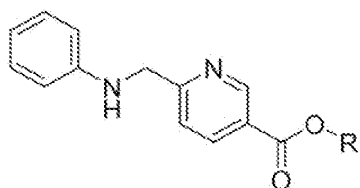
[Chemical Formula 6]



Embodiment A38. The method according to Embodiment 37, wherein the method for preparing the compound represented by above Chemical Formula 5 comprises:

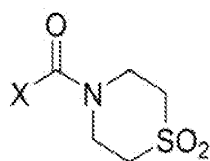
reacting a compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 below in the presence of a base to prepare the compound represented by Chemical Formula 5:

[Chemical Formula 3]



(wherein, in above Chemical Formula 3, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



(wherein, in above Chemical Formula 4, X is F, Cl, Br or I).

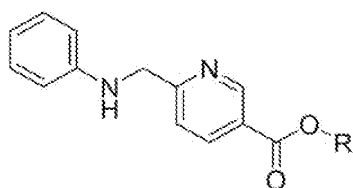
Embodiment A39. The method according to Embodiment A37, wherein the method for preparing the compound represented by Chemical Formula 5 comprises:

preparing a compound represented by Chemical Formula 3 by reacting a compound represented

by Chemical Formula 8 below with aniline in the presence of a base; and

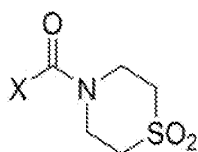
reacting a compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 below in the presence of a base to prepare the compound represented by Chemical Formula 5:

[Chemical Formula 3]



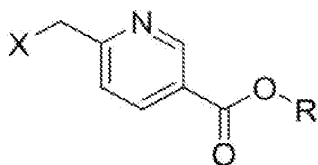
(wherein, in above Chemical Formula 3, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



(wherein, in above Chemical Formula 4, X is F, Cl, Br or I)

[Chemical Formula 8]



(wherein, in above Chemical Formula 8, R is C1-C6 linear or branched alkyl or benzyl, and X is F, Cl, Br or I).

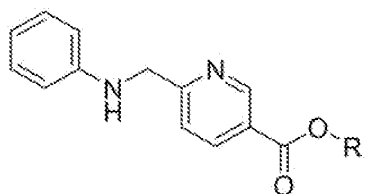
Embodiment A40. The method according to Embodiment A37, wherein the method for preparing the compound represented by Chemical Formula 5 comprises:

Preparing a compound represented by Chemical Formula 8 below from a compound represented by Chemical Formula 7 below by using a halogenating reagent;

preparing a compound represented by Chemical Formula 3 below by reacting the compound represented by Chemical Formula 8 with aniline in the presence of a base;

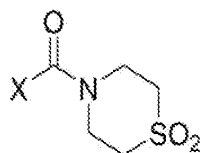
reacting the compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 below in the presence of a base to prepare the compound represented by Chemical Formula 5:

[Chemical Formula 3]



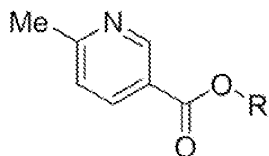
(wherein, in above Chemical Formula 3, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



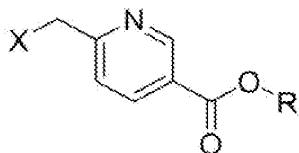
(wherein, in above Chemical Formula 4, X is F, Cl, Br or I)

[Chemical Formula 7]



(wherein, in above Chemical Formula 7, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 8]



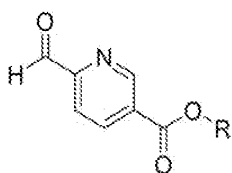
(wherein, in above Chemical Formula 8, R is C1-C6 linear or branched alkyl or benzyl, and X is F, Cl, Br or I)

Embodiment A41. The method according to Embodiment A37, wherein the method for preparing the compound represented by Chemical Formula 5 comprises:

preparing a compound represented by Chemical Formula 3 below from a compound represented by Chemical Formula 2 below in the presence of aniline and a reducing agent; and

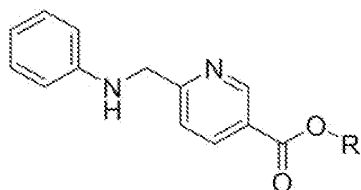
reacting the compound represented by Chemical Formula 3 with a compound represented by Chemical Formula 4 below in the presence of a base to prepare a compound represented by Chemical Formula 5 below:

[Chemical Formula 2]



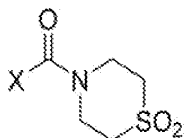
(wherein, in above Chemical Formula 2, R is C1-C6 alkyl or benzyl)

[Chemical Formula 3]



(wherein, in above Chemical Formula 3, R is C1-C6 linear or branched alkyl or benzyl)

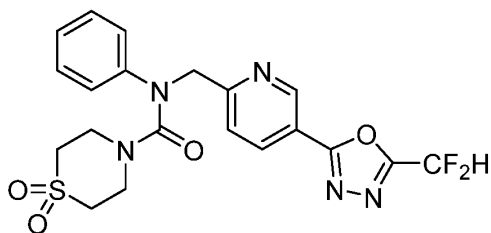
[Chemical Formula 4]



(Wherein, in above Chemical Formula 4, X is F, Cl, Br, or I).

Embodiment B1. Crystalline Form I of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1, wherein an X-ray powder diffraction pattern comprises diffraction peaks at three or more diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 7.83° , 14.52° , 17.11° , 18.08° , 19.59° , 21.41° and 23.56° :

[Chemical Formula 1]



Embodiment B2. The Crystalline Form I according to Embodiment B1, wherein the X-ray powder diffraction pattern further comprises diffraction peaks at one or more diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 15.64° , 17.54° , 20.77° , 21.04° , 23.26° , 24.23° , and 30.37° .

Embodiment B3. The Crystalline Form I according to Embodiment B1, wherein the X-ray powder diffraction pattern further comprises one or more diffraction peaks selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 9.40° , 11.60° , 11.78° , 13.49° , 14.92° , 15.64° , 17.54° , 18.82° , 20.77° ,

21.04°, 22.68°, 23.26°, 24.23°, 26.36°, 27.55°, 28.89°, 30.37°, 33.57° and 36.71°.

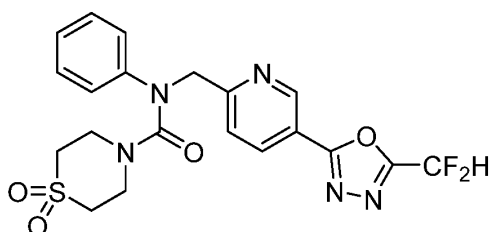
Embodiment B4. The Crystalline Form I according to any one of Embodiments B1 to B3, wherein Crystalline Form I has an endothermic peak at 134°C ($\pm 0.5^\circ\text{C}$) to 142°C ($\pm 0.5^\circ\text{C}$) during differential scanning calorimetry (DSC) analysis when the heating rate is 10°C/min.

Embodiment B5. The Crystalline Form I according to any one of Embodiments B1 to B4, wherein Crystalline Form I has an endothermic peak at 138°C ($\pm 3^\circ\text{C}$) during differential scanning calorimetry (DSC) analysis when the heating rate is 10°C/min.

Embodiment B6. The Crystalline Form I according to any one of Embodiments B1 to B5, wherein Crystalline Form I has endothermic peaks at an onset temperature of 134.64°C ($\pm 0.5^\circ\text{C}$) and a temperature of 138.27°C ($\pm 0.5^\circ\text{C}$) during differential scanning calorimetry (DSC) analysis when the heating rate is 10°C/min.

Embodiment B7. Crystalline Form II of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1, wherein an X-ray powder diffraction pattern comprises three or more diffraction peaks selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 7.83°, 12.22°, 19.02°, 19.67°, 21.39°, 22.35° and 26.42°:

[Chemical Formula 1]



Embodiment B8. The Crystalline Form II according to Embodiment B7, wherein the X-ray powder diffraction pattern further comprises diffraction peaks at one or more diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 11.39°, 11.77°, 13.26°, 15.72°, 16.60°, 18.27°, 19.35°,

20.67°, 24.56°, 27.34° and 33.72°.

Embodiment B9. The Crystalline Form II according to Embodiment B7, wherein the X-ray powder diffraction pattern further comprises diffraction peaks at one or more diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 10.68°, 10.88°, 11.39°, 11.77°, 13.26°, 15.72°, 16.60°, 16.95°, 17.48°, 18.27°, 19.35°, 20.67°, 21.59°, 24.56°, 27.34°, 30.49°, 32.17°, 33.72°, 35.45° and 35.94°.

Embodiment B10. The Crystalline Form II according to any one of Embodiments B7 to B9, wherein Crystalline Form II has an endothermic peak at 125°C ($\pm 0.5^\circ\text{C}$) to 135°C ($\pm 0.5^\circ\text{C}$) during differential scanning calorimetry (DSC) analysis when the heating rate is 10°C/min.

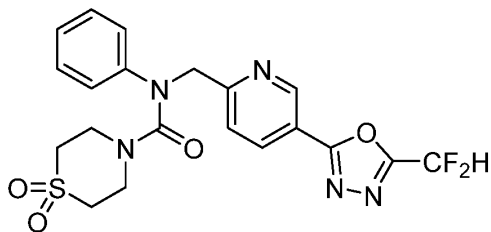
Embodiment B11. The Crystalline Form II according to any one of Embodiments B7 to B10, wherein Crystalline Form II has an endothermic peak at 130°C ($\pm 5^\circ\text{C}$) during differential scanning calorimetry (DSC) analysis when the heating rate is 10°C/min.

Embodiment B12. The Crystalline Form II according to any one of Embodiments B7 to B11, wherein Crystalline Form II has endothermic peaks at an onset temperature of 125.61°C ($\pm 0.5^\circ\text{C}$) and a temperature of 130.43°C ($\pm 0.5^\circ\text{C}$) during differential scanning calorimetry (DSC) analysis when the heating rate is 10°C/min.

Embodiment B13. A method for preparing Crystalline Form I of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is a compound represented by the following Chemical Formula 1, the method comprising: (a) obtaining a solution by dissolving N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1 in a solvent selected from the group consisting of ethyl acetate, ethanol, methanol, isopropyl alcohol, butyl alcohol, methyl tertiary butyl ether (MTBE), diisopropyl ether, acetone, methylisobutylketone (MIBK), methyl ethyl ketone, dichloromethane, dimethylformamide, N-methyl-2-pyrrolidone, toluene, tetrahydrofuran, heptane, hexane, acetonitrile and a mixture thereof; and

(b) producing a solid from the solution:

[Chemical Formula 1]



Embodiment B14. The method according to Embodiment B13, wherein in Step (a), the solvent is one or more alcohols selected from the group consisting of ethanol, methanol, isopropyl alcohol and butyl alcohol, ethyl acetate, or a mixture of the alcohol and ethyl acetate.

Embodiment B15. The method according to Embodiment B14 or 15, wherein the obtaining of the solution (a) comprises:

(a1) obtaining a mixture by adding the compound represented by Chemical Formula 1 to the solvent; and

(a2) warming the mixture to a temperature exceeding 40°C.

Embodiment B16. The method according to any one of Embodiments B13 to 15, wherein the producing of the solid of Step (b) further comprises:

(b1) additionally adding one or more alcohols selected from the group consisting of ethanol, methanol, isopropyl alcohol and butyl alcohol to the solution of Step (a); and

(b2) stirring the mixture after adding the alcohol of Step (b1).

Embodiment B17. The method according to Embodiment B16, wherein Steps (b1) and (b2) are performed at a temperature exceeding 40°C.

Embodiment B18. The method according to Embodiments B13 to B17, further comprising, before performing Step (a),

producing a concentrated residue by dissolving the compound represented by Chemical Formula

1 in dichloromethane, and then performing primary concentration; and

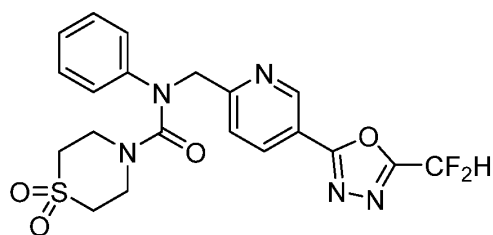
adding ethyl acetate to the concentrated residue and performing secondary concentration.

Embodiment B19. A method for preparing Crystalline Form II of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is a compound represented by the following Chemical Formula 1, the method comprising: (a) preparing a mixture by adding N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1 to a solvent selected from the group consisting of methanol, ethanol, isopropyl alcohol, butyl alcohol, diisopropyl ether, tetrahydrofuran, heptane, hexane and a mixture thereof;

(b) obtaining a solution by warming the mixture to a temperature of 40°C or less; and

(c) producing a solid from the solution at a temperature of 40°C or less:

[Chemical Formula 1]



Embodiment B20. The method according to Embodiment B19, wherein in Step (a), the solvent is ethanol, isopropanol or a mixture thereof.

Embodiment B21. The method according to Embodiment B19 or B20, further comprising, before performing Step (a),

producing a concentrated residue by dissolving the compound represented by Chemical Formula 1 in dichloromethane, and then performing primary concentration;

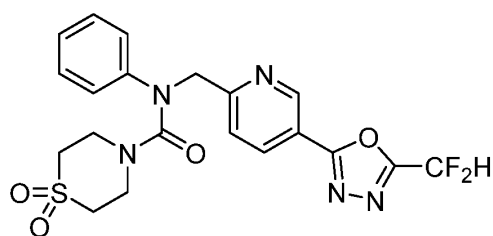
adding ethanol to the concentrated residue and performing secondary concentration.

Embodiment B22. A method for preparing Crystalline Form III of N-((5-(5-(difluoromethyl)-1,3,4-

oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is a compound represented by the following Chemical Formula 1, the method comprising: (a) producing a slurry by adding amorphous N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1 to a solvent selected from the group consisting of methyl tertiary butyl ether (MTBE), heptane, octane, hexane, pentane and a mixture thereof; and

(b) obtaining a solid from the slurry:

[Chemical Formula 1]



Embodiment B23. The method according to Embodiment B22, wherein the solvent of Step (a) is methyl tertiary butyl ether (MTBE), heptane or a mixture thereof.

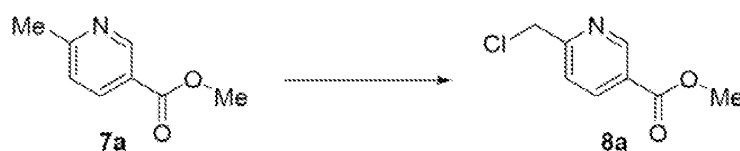
Embodiment B24. The method according to Embodiment B22 or B23, wherein (a) the producing of the slurry is performed for 3 days to 20 days.

Embodiment B25. The method according to any one of Embodiments B22 to B24, wherein (b) the obtaining of the solid further comprises filtering the slurry.

Embodiment B26. The method according to any one of Embodiments B28 to B31, wherein (a) the producing of the slurry and (b) the obtaining of the solid are performed at a temperature of 30°C or less.

Detailed description of exemplary embodiments

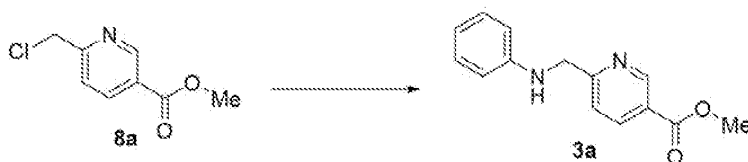
Hereinafter, the present invention will be described in detail with reference to Examples to help understand the present invention. However, the following Examples are only for exemplifying the present invention, and the scope of the present invention is not limited to the following Examples. The Examples of the present invention are provided for more completely describing the present invention to a person with ordinary skill in the art.

<Example 1> Preparation of methyl 6-(chloromethyl)nicotinate (8a)

Methyl 6-methylnicotinate (380 g, 7a) and dichloromethane (5.7 L) were added to a reaction part, and trichloroisocyanuric acid (701 g) was added in portions thereto at 15-22°C for one hour. The added mixture was stirred at 17-22°C for 2-4 hours, cooled down to 5°C or less, and filtered. The solid obtained by filtration was washed with dichloromethane (760 mL) and an insoluble solid was removed. A 20% sodium sulfite aqueous solution (1.9L) was slowly added dropwise to the filtrate obtained through the filtration at 25°C or less and stirred at 20-25°C for one hour. The stirred mixture was filtered through celite and washed with dichloromethane (760 mL), and an organic layer was separated. The separated organic layer was washed sequentially with distilled water (1.9 L) and a 10% sodium chloride aqueous solution (1.9 L), and moisture was removed using sodium sulfate (380 g). A reaction product was concentrated to remove the solvent to obtain the title compound (466.6 g, yield 100%) with a HPLC purity of 93.08%.

TLC (EA/Hx = 1/4) : R_f 0.3

¹H NMR (400 MHz, CDCl₃) δ 9.15 (d, J=2.0Hz, 1H), 8.32 (dd, J=8.1, 2.1Hz, 1H), 7.58(d, J=8.1Hz, 1H), 4.71 (s, 2H), 3.95 (s, 3H)

<Example 2> Preparation of methyl 6-((phenylamino)methyl)nicotinate (3a)

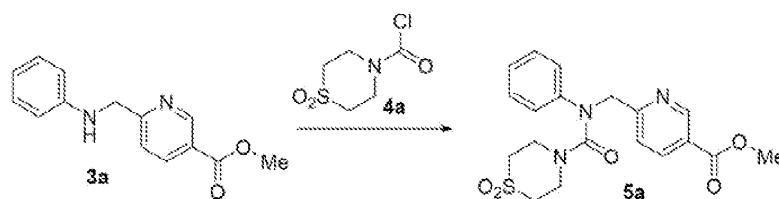
Methyl 6-(chloromethyl)nicotinate (466.6 g, 8a) prepared in Example 1, sodium hydrogen carbonate (422.3 g), potassium iodide (125.19 g), dimethylacetamide (1.4 L), and aniline (468.21 g) were added to a reaction part and stirred at 25-30 °C for three hours to react. After the reaction, a temperature was cooled down to room temperature, and ethyl acetate (3.7 L) and a 10% ammonium chloride aqueous solution (2.3 L) were added thereto, and stirred for 0.5 hours. An organic layer was separated, washed sequentially with 15% aqueous ammonium chloride solution (2.3 L) and 9% sodium hydrogen carbonate aqueous solution (2.3 L), and the solvent was concentrated to remove therefrom.

Methanol (2.3 L) was added to the concentrated residue, which was then dissolved at 45-50 °C, cooled down to room temperature and stirred for two hours. Distilled water (2.3 L) was slowly added dropwise to the reactant at room temperature and stirred for two hours. After stirring, a temperature was cooled down to 0-5 °C, stirred for 1-2 hours, and filtered. The solid obtained by filtration was washed with distilled water (930 mL) and vacuum-dried for 12 hours to obtain the title compound (501.2 g, yield: 82.4%) having a HPLC purity of 95.54%.

TLC (EA/Hx = 1/2) : R_f 0.3

¹H NMR (400 MHz, CDCl₃) δ 9.18 (dd, J=2.2, 0.8Hz, 1H), 8.23 (dd, J=8.1, 2.1Hz, 1H), 7.42 (dd, J=8.2, 0.7Hz, 1H), 7.19-7.15 (m, 2H), 6.75-6.71 (m, 1H), 6.65-6.62 (m, 2H), 4.52 (s, 2H), 3.94 (s, 3H)

<Example 3> Preparation of methyl 6-((1,1-dioxido-N-phenylthiomorpholin-4-carboxamido)methyl)nicotinate (5a)



Methyl 6-((phenylamino)methyl)nicotinate (500 g, 3a) prepared in Example 2, thiomorpholin-4-carbonyl chloride 1,1-dioxide (469 g, 4a), N,N-diisopropylethylamine (DIPEA, 346.8 g), and toluene (1.5 L) were added into a reaction part, heated to 75-85 °C, and then stirred for 2-3 hours.

After cooling down a temperature to 20-30 °C, dichloromethane (3.5 L) was added dropwise thereto and stirred at room temperature for 0.5-1 hour. An organic layer was separated, and a 10% ammonium chloride aqueous solution (2.5 L) was added thereto, and stirred at 20-30 °C for 0.5 hours. After stirring, the organic layer was separated therefrom, and washed by sequentially using 10% ammonium chloride aqueous solution (2.5 L) and distilled water (2.5 L).

The reactant was concentrated to remove the solvent, and then methanol (2.5 L) was added thereto, and stirred at 55-65 °C for 2-3 hours. After cooling down a temperature to 45-55 °C, methyl tertiary butyl ether (4 L) was slowly added thereto and stirred at 35-45 °C for 1-2 hours. A temperature was cooled down to 0-5 °C, stirred for 1-2 hours, and then filtered. The solid obtained by filtration was washed with methyl tertiary butyl ether (1 L) and vacuum-dried for six hours to obtain the title compound (731.7 g, yield: 87.9%) having a HPLC purity of 99.65%.

TLC (EA/Hx = 1/2) : R_f 0.1

¹H NMR (400 MHz, CDCl₃) δ 9.12 (dd, J=2.1, 0.8Hz, 1H), 8.26 (dd, J=8.1, 2.2Hz, 1H), 7.39 (dd, J=8.1, 0.7Hz, 1H), 7.33-7.31 (m, 2H), 7.16-7.13 (m, 3H), 5.06 (s, 2H), 3.94 (s, 3H), 3.72-3.69 (m, 4H), 2.96-2.94 (m, 4H)

<Example 4> Preparation of N-((5-(hydrazinecarbonyl)pyridin-2-yl)methyl)-N-phenylthiomorpholin-4-carboxamide 1,1-dioxide (6)



Methyl 6-((1,1-dioxido-N-phenylthiomorpholin-4-carboxamido)methyl)nicotinate (700 g, 5a) prepared in Example 3, hydrazine monohydrate (434.3 g), methanol (2.8 L), and distilled water (1.4 L) were added to a reaction part, heated to 58-68 °C, and then stirred for 3-5 hours.

A temperature was cooled down to 20-30 °C and then stirred for one hour, after which anhydrous ethanol (2.8 L) was slowly added dropwise to the reactant. A temperature was cooled down to 0-5 °C, stirred for one hour, and then filtered. The solid obtained by filtration was washed with a mixture of anhydrous ethanol:distilled water (5:1 (v:v), 1.4 L) and vacuum-dried at 50-55 °C for 12 hours to obtain a primarily purified title compound.

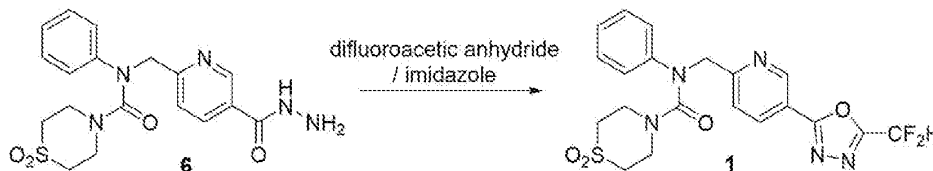
The title compound, which was primarily purified, and dichloromethane (4.9 L) were added to a reaction part, stirred at 25-35 °C for two hours, and then cooled down to 0-5 °C. The cooled mixture was stirred for one hour and then filtered. The solid obtained by filtration was washed with dichloromethane (1.4 L) and vacuum-dried at 50-55 °C for 12 hours to obtain the title compound (631.5 g, yield: 90.2%) having a HPLC purity of 99.63%.

TLC (MC/MeOH = 10/1) : R_f 0.2

¹H NMR (400 MHz, DMSO) δ 9.90 (s, 1H), 8.85 (dd, J=2.2, 0.7Hz, 1H), 8.11 (dd, J=8.2, 2.2Hz, 1H), 7.49-7.48 (m, 1H), 7.36-7.32 (m, 2H), 7.26-7.24 (m, 2H), 7.12 (t, J=7.3Hz, 1H), 4.98 (s, 2H), 4.38 (s, 2H), 3.56 (s, 4H), 3.00-2.98 (m, 4H)

<Example 5> Preparation of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-

yl)methyl)-N-phenylthiomorpholin-4-carboxamide 1,1-dioxide (1) and Crystalline Form I thereof



Imidazole (303.73 g) and dichloromethane (0.9 L) were added to reaction part 1 and a temperature was cooled down to 0-10 °C. Difluoroacetic anhydride (776.5 g) was slowly added to the cooled mixture while maintaining a temperature at 25 °C or less, and then the mixture was stirred at room temperature for 1-2 hours.

N-((5-(hydrazinecarbonyl)pyridin-2-yl)methyl)-N-phenylthiomorpholin-4-carboxamide 1,1-dioxide (600 g, 6) prepared in Example 4 and dichloromethane (2.7 L) were added to another reaction part 2 and a temperature was cooled down to 0 °C or less.

The mixed solution of reaction part 1 was slowly added to the mixed solution of reaction part 2 cooled down to 0 °C or less while maintaining a temperature at -10-5 °C. After the addition was completed, a temperature was raised to 35-40 °C and then stirred for 3-4 hours. After the stirring, the reactant was cooled down to room temperature, and 10% ammonium chloride aqueous solution (3 L) was added thereto and stirred for 0.5 hours. An organic layer was separated, after which 9% sodium hydrogen carbonate aqueous solution (3 L) was added thereto and stirred for 0.5 hours, and then an organic layer was separated and washed with distilled water (3 L). Sodium sulfate (600 g) was added to the organic layer and moisture was removed therefrom while stirring for 0.5 hours, after which the reactant was filtered and the solvent was concentrated to obtain the title compound (689 g) represented by Chemical Formula 1 having a HPLC purity of 99.60%.

Ethyl acetate (600 mL) was injected into the compound represented by Chemical Formula 1 obtained as described above to perform additional concentration. Ethyl acetate (900 mL) and anhydrous

ethanol (1.2 L) were added to the concentrated residue, which was then dissolved by raising a temperature to 55-65 °C. Anhydrous ethanol (2.4 L) was added and stirred at 40-50 °C for three hours to precipitate a solid. Anhydrous ethanol (2.4 L) was further added thereto, stirred at 40-50 °C for 2-4 hours, cooled down to 5 °C or less, stirred for one hour, and then filtered. The solid obtained by filtration was washed with anhydrous ethanol (1.2 L) and vacuum-dried at 35-40 °C for six hours to obtain Crystalline Form I (632.3 g, yield: 91.7%) of the compound represented by Chemical Formula 1 having a HPLC purity of 99.84%.

NMR analysis results of the compound represented by Chemical Formula 1 obtained in Example 5 are as follows.

TLC (EA/Hx = 1/2) : Rf 0.6

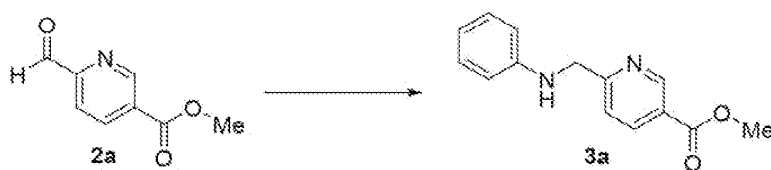
¹H NMR (400 MHz, CDCl₃) δ 9.22 (dd, J=2.2, 0.8Hz, 1H), 8.37 (dd, J=8.2, 2.2Hz, 1H), 7.53 (dd, J=8.2, 0.8Hz, 1H), 7.37-7.33 (m, 2H), 7.20-7.16 (m, 3H), 6.93 (t, J=51.6Hz, 1H), 5.09 (s, 2H), 3.72-3.70 (m, 4H), 2.94-2.91 (m, 4H)

In addition, the X-ray powder diffraction (XRPD) pattern of the Crystalline Form I obtained in above Example 5 was shown in FIG. 2 and Table 1, and the results of differential scanning calorimetry (DSC) analysis were shown in FIG. 3.

[Table 1]

Caption	Legend	Angle	d value	Intensity	Intensity %
		2-Theta °	Angstrom	Count	%
2T=7.85 °		7.85	11.25179	14903	55.3
2T=9.40 °		9.40	9.39786	502	1.9
2T=11.62 °		11.62	7.61179	1786	6.6
2T=11.77 °		11.77	7.51504	2074	7.7
2T=13.49 °		13.49	6.56003	2406	8.9
2T=14.54 °		14.54	6.0868	4674	17.3
2T=14.92 °		14.92	5.93288	1628	6
2T=15.64 °		15.64	5.66063	4492	16.7
2T=17.14 °		17.14	5.16815	6323	23.5
2T=17.55 °		17.55	5.04932	2284	8.5
2T=18.09 °		18.09	4.89943	7762	28.8
2T=18.82 °		18.82	4.71149	561	2.1
2T=19.62 °		19.62	4.52007	26950	100
2T=20.78 °		20.78	4.27198	3372	12.5
2T=21.04 °		21.04	4.21823	3908	14.5
2T=21.41 °		21.41	4.14638	16768	62.2
2T=22.69 °		22.69	3.91636	985	3.7
2T=23.27 °		23.27	3.82034	2304	8.5
2T=23.58 °		23.58	3.77029	3226	12
2T=24.24 °		24.24	3.66895	3798	14.1
2T=26.35 °		26.35	3.37974	2867	10.6
2T=27.07 °		27.07	3.29081	1067	4
2T=27.58 °		27.58	3.2318	1000	3.7
2T=28.91 °		28.91	3.08634	1671	6.2
2T=29.96 °		29.96	2.97996	1354	5
2T=30.38 °		30.38	2.94003	2302	8.5
2T=33.57 °		33.57	2.66716	1367	5.1
2T=36.74 °		36.74	2.44412	1423	5.3
2T=37.42 °		37.42	2.40135	508	1.9

<Example 6> Preparation of methyl 6-((phenylamino)methyl)nicotinate (3a)



Methyl 6-formylnicotinate (180 g, 2a) and dichloromethane (900 mL) were added to reaction part 1, after which aniline (101.5 g) was slowly added thereto while maintaining a temperature of 10-30 °C, and then stirred at a temperature of 20-30 °C for 1-2 hours.

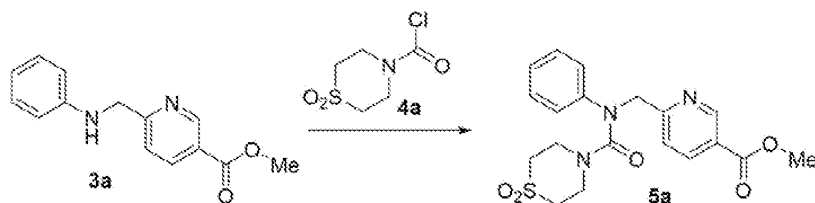
Sodium triacetoxyborohydride (346.5 g) and dichloromethane (1.62 L) were added to another reaction part 2 and cooled down to a temperature of 5 °C or less.

The mixed solution of reaction part 1 was slowly added to the mixed solution of reaction part 2 cooled down to 5 °C or less while maintaining a temperature of 10 °C or less, and after the addition, a small amount of the mixed solution remaining in reaction part 1 was washed with dichloromethane (180 mL) and added to reaction part 2. After the addition was completed, a temperature was raised to 15-25 °C and then stirred for 2-3 hours. After stirring, 1N hydrochloric acid aqueous solution (1.8 L) and 9% sodium hydrogen carbonate aqueous solution (360 mL) were slowly and sequentially added and stirred at 20-30 °C for 0.5 hours. An organic layer was separated, after which 9% sodium hydrogen carbonate aqueous solution (1.44 L) was added thereto and stirred for 0.5 hours, and then the organic layer was separated and washed with aqueous sodium chloride solution (1.8 L). Moisture was removed from the organic layer by using sodium sulfate (180 g), and the resulting product was filtered and the solvent was concentrated to obtain the title compound (264.07 g, yield 100%) having a HPLC purity of 99.01%.

TLC (EA/Hx = 1/2) : R_f 0.3

¹H NMR (400 MHz, CDCl₃) δ 9.18 (dd, J=2.2, 0.8 Hz, 1H), 8.23 (dd, J=8.1, 2.1 Hz, 1H), 7.42 (dd, J=8.2, 0.7 Hz, 1H), 7.19-7.15 (m, 2H), 6.75-6.71 (m, 1H), 6.65-6.62 (m, 2H), 4.52 (s, 2H), 3.94 (s, 3H)

<Example 7> Preparation of methyl 6-((1,1-dioxido-N-phenylthiomorpholin-4-carboxamido)methyl)nicotinate (5a)



Methyl 6-((phenylamino)methyl)nicotinate (264.07 g, 3a) prepared in Example 6, thiomorpholin-4-carbonyl chloride (280 g, 4a), N,N-diisopropylethylamine (DIPEA, 281.7 g), and toluene (3.43 L) were added into a reaction part, heated to 90-100 °C, and then stirred for 2-3 hours.

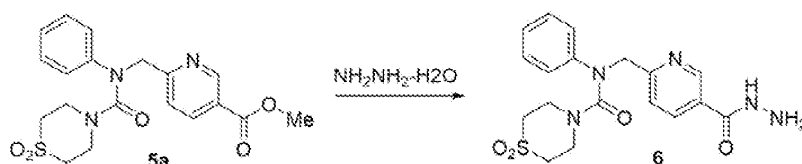
After cooling down a temperature to 65-70 °C, distilled water (792 mL) was added dropwise and stirred at 65-70 °C for one hour. 2-butanol (792 mL) was added to a reactant at 65-70 °C, and a temperature was cooled down to 35-40 °C, after which dichloromethane (528 mL) was added dropwise and stirred at 35-40 °C for 0.5 hours. An organic layer was separated, filtered through celite, and washed with 2-butanol (528 mL). Distilled water (1.85 L) was added and stirred at 25-30 °C for 0.5 hours, after which the organic layer was separated and washed sequentially using 10% ammonium chloride aqueous solution (2.6 L) and distilled water (1.3 L).

The reactant was concentrated to remove the solvent, and then methanol (1.3 L) was added thereto and stirred at 55-65 °C for two hours. After cooling down a temperature to 50-55 °C, methyl tertiary butyl ether (2.1 L) was slowly added thereto and stirred at 35-45 °C for one hour. A temperature was cooled down to 0-5 °C, stirred for 1-2 hours, and then filtered. The solid obtained by filtration was washed with methyl tertiary butyl ether (528 mL) and vacuum-dried for six hours to obtain the title compound (372 g, yield: 84.6%) having a HPLC purity of 99.72%.

TLC (EA/Hx = 1/2) : R_f 0.1

^1H NMR (400 MHz, CDCl_3) δ 9.12 (dd, $J=2.1, 0.8\text{Hz}$, 1H), 8.26 (dd, $J=8.1, 2.2\text{Hz}$, 1H), 7.39 (dd, $J=8.1, 0.7\text{Hz}$, 1H), 7.33-7.31 (m, 2H), 7.16-7.13 (m, 3H), 5.06 (s, 2H), 3.94 (s, 3H), 3.72-3.69 (m, 4H), 2.96-2.94 (m, 4H)

<Example 8> Preparation of N-((5-(hydrazinecarbonyl)pyridin-2-yl)methyl)-N-phenylthiomorpholin-4-carboxamide 1,1-dioxide (6)



Methyl 6-((1,1-dioxido-N-phenylthiomorpholin-4-carboxamido)methyl)nicotinate (370 g, 5a) prepared in Example 7, hydrazine monohydrate (229.5 g), methanol (1.48 L), and distilled water (740 mL) were added to a reaction part, heated to 58-68 °C, and then stirred for 3-5 hours.

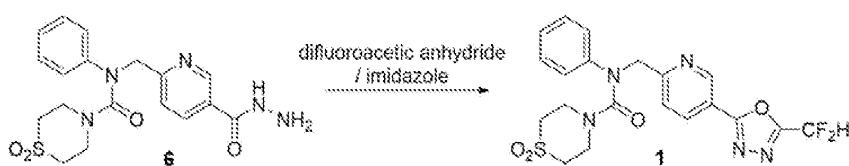
A temperature was cooled down to 20-30 °C and then stirred for one hour, and anhydrous ethanol (2.22 L) was slowly added dropwise to the reactant. A temperature was cooled down to 0-5 °C, stirred for one hour, and then filtered. The solid obtained by filtration was washed with a mixture of anhydrous ethanol:distilled water (5:1 (v:v), 740 mL) and vacuum-dried at 50-55 °C for 12 hours to obtain a primarily purified title compound.

The title compound, which was primarily purified, and dichloromethane (1.85 L) were added to the reaction part, stirred at 25-35 °C for two hours, and then cooled down to 0-5 °C. The cooled mixture was stirred for one hour and then filtered. The solid obtained by filtration was washed with dichloromethane (740 mL) and vacuum-dried at 50-55 °C for 12 hours to obtain the title compound (333 g, yield: 90%) having a HPLC purity of 99.56%.

TLC (MC/MeOH = 10/1) : R_f 0.2

^1H NMR (400 MHz, DMSO) δ 9.90 (s, 1H), 8.85 (dd, $J=2.2, 0.7\text{Hz}$, 1H), 8.11 (dd, $J=8.2, 2.2\text{Hz}$, 1H), 7.49-7.48 (m, 1H), 7.36-7.32 (m, 2H), 7.26-7.24 (m, 2H), 7.12 (t, $J=7.3\text{Hz}$, 1H), 4.98 (s, 2H), 4.38 (s, 2H), 3.56 (s, 4H), 3.00-2.98 (m, 4H)

<Example 9> Preparation of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholin-4-carboxamide 1,1-dioxide (1) and crystalline form I thereof



Imidazole (164.83 g) and dichloromethane (1.3 L) were added to reaction part 1 and a temperature was cooled down to 0-10°C. Difluoroacetic anhydride (421.4 g) was slowly added to the cooled mixture while maintaining a temperature at 20°C or less, and then the mixture was stirred at room temperature for 1-2 hours.

N-((5-(hydrazinecarbonyl)pyridin-2-yl)methyl)-N-phenylthiomorpholin-4-carboxamide 1,1-dioxide (325.6 g, 6) prepared in Example 8 and dichloromethane (1.63 L) were added to another reaction part 2 and a temperature was cooled down to 0°C or less.

The mixture of reaction part 1 was slowly added to the mixed solution of reaction part 2 cooled down to 0°C or less while maintaining a temperature at -10-0°C. After the addition was completed, a temperature was raised to 35-40°C and then stirred for 3-4 hours. After the stirring, the reactant was cooled down to room temperature, and 10% ammonium chloride aqueous solution (3.26 L) was added thereto and stirred for 0.5 hours. An organic layer was separated, after which 9% sodium hydrogen carbonate aqueous solution (3.26 L) was added thereto and stirred for 0.5 hours, and then the organic layer was separated and washed with distilled water (1.63 L). Sodium sulfate (326 g) was added to the

organic layer and moisture was removed therefrom while stirring for 0.5 hours, after which the reactant was filtered and the solvent was concentrated to obtain the title compound (374 g) represented by Chemical Formula 1 having a HPLC purity of 99.69%.

Ethyl acetate (326 mL) was injected into the compound represented by Chemical Formula 1 obtained as described above to perform additional concentration. Ethyl acetate (326 mL) and anhydrous ethanol (1.3 L) were added to the concentrated residue, which was then dissolved by raising a temperature to 50-60°C. Anhydrous ethanol (1.95 L) was further added thereto, stirred at 45-50°C for three hours, cooled down to 5°C or less, and then filtered. The solid obtained by filtration was washed with anhydrous ethanol (652 mL) and vacuum-dried at 35-40°C for six hours to obtain the title compound (343.2 g, yield 91.8%) having a HPLC purity of 99.83%.

NMR analysis results of the compound represented by Chemical Formula 1 obtained in Example 9 are as follows.

TLC (EA/Hx = 1/2) : R_f 0.6

¹H NMR (400 MHz, CDCl₃) δ 9.22 (dd, J=2.2, 0.8Hz, 1H), 8.37 (dd, J=8.2, 2.2Hz, 1H), 7.53 (dd, J=8.2, 0.8Hz, 1H), 7.37-7.33 (m, 2H), 7.20-7.16 (m, 3H), 6.93 (t, J=51.6Hz, 1H), 5.09 (s, 2H), 3.72-3.70 (m, 4H), 2.94-2.91 (m, 4H)

The X-ray powder diffraction (XRPD) pattern of the Crystalline Form I obtained in above Example 9 was shown in FIG. 4 and Table 2, and the results of differential scanning calorimetry (DSC) analysis were shown in FIG. 5.

[Table 2]

Caption	Legend	Angle	d value	Intensity	Intensity %
		2-Theta °	Angstrom	Count	%
2T=7.90 °		7.90	11.17711	13891	48.1
2T=9.45 °		9.45	9.34721	445	1.5
2T=11.65 °		11.65	7.59304	1793	6.2
2T=11.86 °		11.86	7.45895	2040	7.1
2T=13.55 °		13.55	6.52994	2250	7.8
2T=14.59 °		14.59	6.06712	4297	14.9
2T=14.98 °		14.98	5.90849	1494	5.2
2T=15.70 °		15.70	5.63935	4254	14.7
2T=17.20 °		17.20	5.1517	5803	20.1
2T=17.61 °		17.61	5.03338	2148	7.4
2T=18.15 °		18.15	4.88325	6814	23.6
2T=18.88 °		18.88	4.6957	514	1.8
2T=19.68 °		19.68	4.50839	28859	100
2T=20.84 °		20.84	4.25979	3095	10.7
2T=21.10 °		21.10	4.20802	3862	13.4
2T=21.49 °		21.49	4.13252	17179	59.5
2T=22.74 °		22.74	3.90728	1097	3.8
2T=23.34 °		23.34	3.80878	2117	7.3
2T=23.65 °		23.65	3.75917	3410	11.8
2T=24.30 °		24.30	3.65925	3931	13.6
2T=26.41 °		26.41	3.37262	2735	9.5
2T=27.13 °		27.13	3.28406	1020	3.5
2T=27.65 °		27.65	3.22402	1113	3.9
2T=28.96 °		28.96	3.08039	1916	6.6
2T=30.03 °		30.03	2.97332	1314	4.6
2T=30.44 °		30.44	2.93392	2214	7.7
2T=33.65 °		33.65	2.66149	1378	4.8
2T=36.81 °		36.81	2.43986	1500	5.2
2T=37.50 °		37.50	2.39637	608	2.1

<Example 10> Preparation of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholin-4-carboxamide 1,1-dioxide (compound represented by

Chemical Formula 1) and Crystalline Form I thereof

Imidazole (1.61 kg) and dichloromethane (15.9 L) were added to reaction part 1 and a temperature was cooled down to 5-10°C. Difluoroacetic anhydride (4.12 kg) was slowly added to the cooled mixture while maintaining a temperature at 30°C or less, and then the mixture was stirred at room temperature for one hour.

N-((5-(hydrazinecarbonyl)pyridin-2-yl)methyl)-N-phenylthiomorpholin-4-carboxamide 1,1-dioxide (3.18 kg) and dichloromethane (15.9 L) were added to another reaction part 2 and a temperature was cooled down to 0°C or less.

The mixture of reaction part 1 was slowly added to the mixed solution of reaction part 2 cooled down to 0°C or less while maintaining a temperature at 5°C or less. After the addition was completed, a temperature was raised to 35 to 40°C for one hour and then stirred for two hours. After the completion of the reaction was confirmed by HPLC, the reactant was cooled down to room temperature, and 10% ammonium chloride aqueous solution (31.8 L) was added thereto and stirred for 0.5 hours. An organic layer was separated, and 9% sodium hydrogen carbonate aqueous solution (31.8 L) was added thereto and stirred for 0.5 hours. After that, the organic layer was separated and washed with distilled water (15.9 L). Sodium sulfate (3.18 kg) was added to the organic layer and moisture was removed therefrom while stirring for 0.5 hours, after which the reactant was filtered and the solvent was concentrated to obtain the title compound (3.65 kg) represented by Chemical Formula 1 having a HPLC purity of 99.69%.

Ethyl acetate (3.18 L) was injected into 3.65 kg of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholin-4-carboxamide 1,1-dioxide, which is the compound represented by Chemical Formula 1 obtained as described above, and further concentrated. Ethyl acetate (3.18 L) and ethanol (12.72 L) were added to the concentrated residue, which was then dissolved by raising a temperature to 50-55°C. Ethanol (19.08 L) was further added thereto, stirred at 50 - 55°C for 1.5 hours, cooled down to 5°C or less, and then filtered. The solid obtained by filtration was washed with

ethanol (6.36 L) and vacuum-dried for 14 hours to obtain the title compound (Crystalline Form I of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholin-4-carboxamide 1,1-dioxide) (3.38 kg, yield 92.3%) with a HPLC purity of 99.90%.

The X-ray powder diffraction (XRPD) pattern of the Crystalline Form I obtained in Example 10 was shown in FIG. 6 and Table 3.

[Table 3]

Caption	Legend	Angle	d value	Intensity	Intensity %
		2-Theta °	Angstrom	Count	%
2T=7.86 °		7.86	11.24575	10437	38.5
2T=9.39 °		9.39	9.41598	395	1.5
2T=11.62 °		11.62	7.61004	879	3.2
2T=11.80 °		11.80	7.49658	1482	5.5
2T=13.48 °		13.48	6.56281	2175	8
2T=14.54 °		14.54	6.08936	3337	12.3
2T=14.91 °		14.91	5.93629	1258	4.6
2T=15.66 °		15.66	5.65563	3529	13
2T=17.12 °		17.12	5.17414	4995	18.4
2T=17.55 °		17.55	5.05042	1804	6.7
2T=18.09 °		18.09	4.89887	5808	21.4
2T=18.82 °		18.82	4.7103	459	1.7
2T=19.61 °		19.61	4.52274	27115	100
2T=20.77 °		20.77	4.2724	2683	9.9
2T=21.04 °		21.04	4.21921	3509	12.9
2T=21.42 °		21.42	4.14551	14735	54.3
2T=22.68 °		22.68	3.91795	955	3.5
2T=23.27 °		23.27	3.82006	1609	5.9
2T=23.59 °		23.59	3.76875	3302	12.2
2T=24.23 °		24.23	3.66964	3398	12.5
2T=26.37 °		26.37	3.37776	2556	9.4
2T=27.06 °		27.06	3.29246	945	3.5
2T=27.59 °		27.59	3.23075	1108	4.1
2T=28.92 °		28.92	3.08441	1164	4.3
2T=29.96 °		29.96	2.97979	1149	4.2
2T=30.38 °		30.38	2.94011	1975	7.3
2T=33.57 °		33.57	2.66719	1320	4.9
2T=36.74 °		36.74	2.4443	1392	5.1
2T=37.43 °		37.43	2.40086	510	1.9

<Example 11> Preparation of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-

yl)methyl)-N-phenylthiomorpholin-4-carboxamide 1,1-dioxide (compound represented by Chemical Formula 1) and Crystalline Form II thereof

Imidazole (405.4 g) and dichloromethane (4.45 L) were added to reaction part 1 and a temperature was cooled down to 0 to 5 °C. Difluoroacetic anhydride (1.04 kg) was slowly added to the cooled mixture while maintaining a temperature at 0-10 °C, and then the mixture was stirred at room temperature for one hour.

N-((5-(hydrazinecarbonyl)pyridin-2-yl)methyl)-N-phenylthiomorpholin-4-carboxamide 1,1-dioxide (890 g) and dichloromethane (8.9 L) were added to another reaction part 2 and a temperature was cooled down to 0-5 °C.

The mixture of reaction part 1 was slowly added to the cooled mixture of reaction part 2 while maintaining a temperature at 0-5 °C. After the addition was completed, a temperature was raised to 35 to 40 °C for one hour and then stirred for four hours. After the completion of the reaction was confirmed by HPLC, the reactant was cooled down to room temperature, and 10% ammonium chloride aqueous solution (8.9 L) was added thereto and stirred for 0.5 hours. An organic layer was separated, and 9% sodium hydrogen carbonate aqueous solution (8.9 L) was added thereto and stirred for 0.5 hours. After that, the organic layer was separated and washed with distilled water (4.45 L). Sodium sulfate (890 g) was added to the organic layer and moisture was removed therefrom while stirring for 0.5 hours, after which the reactant was filtered and the solvent was concentrated to obtain the title compound represented by Chemical Formula 1.

Ethanol (2 L) was injected into N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholin-4-carboxamide 1,1-dioxide (1022.4 g), which is the compound represented by Chemical Formula 1 obtained as described above, and concentrated. Ethanol (7.15 L) was added to the concentrated residue, a temperature was increased to 35 to 40 °C, and the mixture was stirred

for 13 hours. The precipitated mixture was filtered while stirring. The solid obtained by filtration was washed with ethanol (2 L) and dried for 14 hours to obtain the title compound (Crystalline Form II of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholin-4-carboxamide 1,1-dioxide) (985.8 g, yield 96.4%) with a HPLC purity of 99.6%.

The X-ray powder diffraction (XRPD) pattern of the Crystalline Form II obtained in Example 11 was shown in FIG. 7 and Table 4, and the results of differential scanning calorimetry (DSC) analysis were shown in FIG. 8.

[Table 4]

Caption	Legend	Angle	d value	Intensity	Intensity %
		2-Theta °	Angstrom	Count	%
2T=7.83 °		7.83	11.28765	1573	18.4
2T=10.72 °		10.72	8.24294	967	11.3
2T=10.92 °		10.92	8.09606	901	10.6
2T=11.41 °		11.41	7.74839	1723	20.2
2T=11.78 °		11.78	7.50745	1202	14.1
2T=12.22 °		12.22	7.23998	8082	94.8
2T=13.28 °		13.28	6.66402	2829	33.2
2T=15.70 °		15.70	5.63885	1186	13.9
2T=16.64 °		16.64	5.32306	3369	39.5
2T=16.97 °		16.97	5.22143	990	11.6
2T=17.48 °		17.48	5.06861	2339	27.4
2T=18.28 °		18.28	4.84969	3394	39.8
2T=19.02 °		19.02	4.6613	7463	87.5
2T=19.37 °		19.37	4.57809	3027	35.5
2T=19.67 °		19.67	4.50952	8529	100
2T=20.34 °		20.34	4.36311	2340	27.4
2T=20.71 °		20.71	4.28555	3983	46.7
2T=21.40 °		21.40	4.14935	4741	55.6
2T=21.58 °		21.58	4.11539	3413	40
2T=21.87 °		21.87	4.0607	1766	20.7
2T=22.35 °		22.35	3.97457	4855	56.9
2T=22.83 °		22.83	3.89151	1031	12.1
2T=24.58 °		24.58	3.61867	1484	17.4
2T=26.44 °		26.44	3.36782	2187	25.6
2T=27.35 °		27.35	3.2579	1962	23
2T=30.49 °		30.49	2.92998	917	10.8
2T=32.19 °		32.19	2.77871	769	9
2T=33.73 °		33.73	2.65504	1446	16.9
2T=35.44 °		35.44	2.53098	656	7.7
2T=35.91 °		35.91	2.49893	422	4.9

<Example 12> Preparation of amorphous N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-

yl)pyridin-2-yl)methyl)-N-phenylthiomorpholin-4-carboxamide 1,1-dioxide (compound represented by Chemical Formula 1) and Crystalline Form III thereof

Imidazole (15.2g) and dichloromethane (150mL) were added to reaction part 1 and a temperature was cooled down to 0 to 5°C. Difluoroacetic anhydride (38.8g) was slowly added to the cooled mixture while maintaining a temperature at 20°C or less, and then the mixture was stirred at room temperature for one hour.

N-((5-(hydrazinecarbonyl)pyridin-2-yl)methyl)-N-phenylthiomorpholin-4-carboxamide 1,1-dioxide (30 g) and dichloromethane (150mL) were added to another reaction part 2 and a temperature was cooled down to 0-5°C.

The mixture of reaction part 1 was slowly added to the cooled mixture of reaction part 2 while maintaining a temperature at 0-5°C. After the addition was completed, a temperature was raised to 35 to 40°C for one hour and then stirred for three hours. After the completion of the reaction was confirmed by HPLC, the reactant was cooled down to room temperature, and 10% ammonium chloride aqueous solution (300mL) was added thereto and stirred for 0.5 hours. An organic layer was separated, and 9% sodium hydrogen carbonate aqueous solution (300mL) was added thereto and stirred for 0.5 hours. After that, the organic layer was separated and washed with distilled water (150mL). Sodium sulfate (30g) was added to the organic layer and moisture was removed therefrom while stirring for 0.5 hours. Then, the compound represented by Chemical Formula 1 obtained by filtration and concentration of the solvent was dried under vacuum for 14 hours at room temperature to obtain the amorphous solid of the compound represented by Chemical Formula 1(34.46g).

Methyl tertiary butyl ether (MTBE, 400 mL) was added to 20 g of compound represented by Chemical Formula 1 as the amorphous solid and the reactant was slurried at 20°C to 25°C for 24 hours, and then filtered. The solid obtained by filtration was washed with methyl tertiary butyl ether (MTBE, 40 mL) and dried under vacuum for 14 hours to obtain the title compound (Crystalline Form III of N-

((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide)(18.6 g, yield 93%) with an HPLC purity of 99.86%.

The X-ray powder diffraction (XRPD) pattern of the Crystalline Form III obtained in Example 12 was shown in FIG. 9 and Table 5, and the results of differential scanning calorimetry (DSC) analysis were shown in FIG. 10.

[Table 5]

Caption	Legend	Angle	d value	Intensity	Intensity %
		2-Theta °	Angstrom	Count	%
	2T=8.75 °	8.75	10.09272	1992	23.6
	2T=10.98 °	10.98	8.05302	1997	23.7
	2T=12.44 °	12.44	7.11189	2838	33.6
	2T=14.28 °	14.28	6.19797	244	2.9
	2T=15.45 °	15.45	5.73053	207	2.5
	2T=16.86 °	16.86	5.25529	8437	100
	2T=17.48 °	17.48	5.06812	786	9.3
	2T=18.49 °	18.49	4.79564	422	5
	2T=18.77 °	18.77	4.72338	670	7.9
	2T=19.95 °	19.95	4.44756	1151	13.6
	2T=20.49 °	20.49	4.33042	1213	14.4
	2T=20.79 °	20.79	4.26833	693	8.2
	2T=21.55 °	21.55	4.12027	1825	21.6
	2T=21.87 °	21.87	4.0611	1312	15.5
	2T=22.07 °	22.07	4.02461	1558	18.5
	2T=22.92 °	22.92	3.87674	3364	39.9
	2T=24.04 °	24.04	3.69912	898	10.6
	2T=24.72 °	24.72	3.59881	734	8.7
	2T=24.99 °	24.99	3.56045	921	10.9
	2T=26.30 °	26.30	3.38569	687	8.1
	2T=28.49 °	28.49	3.13045	1040	12.3
	2T=29.22 °	29.22	3.05439	326	3.9
	2T=30.20 °	30.20	2.95739	283	3.4
	2T=31.40 °	31.40	2.8469	443	5.3
	2T=34.10 °	34.10	2.6272	380	4.5
	2T=37.13 °	37.13	2.41977	219	2.6
	2T=38.86 °	38.86	2.31571	258	3.1

Meanwhile, the X-ray powder diffraction (XRPD) pattern of the amorphous compound represented by Chemical Formula 1 used in the preparation process of Crystalline Form III was shown in FIG. 11.

<Preparation Example>**Preparation Example 1. Preparation of amorphous form of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide**

20 g of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide (a compound represented by Chemical Formula 1) was dissolved in 400 mL of dichloromethane, and then the resulting solution was concentrated. The concentrated solution was dried under vacuum at 20 to 30°C for 14 hours to obtain 20 g of an amorphous form (melting point: 129.5°C) of the title compound (N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide with an HPLC purity of 99.77%. The X-ray powder diffraction (XRPD) pattern thereof is shown in FIG. 12, and the differential scanning calorimetry (DSC) analysis results are shown in FIG. 13.

Example 13. Preparation of Crystalline Form I of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide

34.5 g of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide (a compound represented by Chemical Formula 1) was completely dissolved by injecting dichloromethane (600 mL), and then the resulting solution was concentrated. After ethyl acetate (30 mL) was injected into the concentrated residue and the resulting mixture was concentrated, ethyl acetate (30 mL) and ethanol (120 mL) were added thereto, and the resulting mixture was dissolved by heating to 50°C to 55°C. Ethanol (180 mL) was additionally added, and the mixture was stirred at 50 to 55°C for 3 hours to precipitate a solid, and then the precipitated solid was cooled to 5°C or less and filtered. The solid obtained by filtration was washed with ethanol (60 mL) and dried under vacuum for 14 hours to obtain the title compound (Crystalline Form I of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide

1,1-dioxide)(32.5 g, yield 94.3%, melting point: 138.3°C) with an HPLC purity of 99.91%. The X-ray powder diffraction (XRPD) pattern of Crystalline Form I is shown in FIG. 14 and Table 6, and the differential scanning calorimetry (DSC) analysis results are shown in FIG. 15.

[Table 6]

Caption	Legend	Angle	d value	Intensity	Intensity %
		2-Theta °	Angstrom	Count	%
	2T=7.83 °	7.83	11.28856	17432	44.9
	2T=9.40 °	9.40	9.40436	579	1.5
	2T=11.60 °	11.60	7.62081	1341	3.5
	2T=11.78 °	11.78	7.50713	1756	4.5
	2T=13.49 °	13.49	6.5567	1798	4.6
	2T=14.52 °	14.52	6.09616	5159	13.3
	2T=14.92 °	14.92	5.93134	997	2.6
	2T=15.64 °	15.64	5.66122	3444	8.9
	2T=17.11 °	17.11	5.17815	5187	13.4
	2T=17.54 °	17.54	5.05231	2982	7.7
	2T=18.08 °	18.08	4.90133	4894	12.6
	2T=18.82 °	18.82	4.71205	676	1.7
	2T=19.59 °	19.59	4.52794	38792	100
	2T=20.77 °	20.77	4.27374	3569	9.2
	2T=21.04 °	21.04	4.21878	3407	8.8
	2T=21.41 °	21.41	4.14661	21818	56.2
	2T=22.68 °	22.68	3.91749	802	2.1
	2T=23.26 °	23.26	3.82141	2426	6.3
	2T=23.56 °	23.56	3.77284	4346	11.2
	2T=24.23 °	24.23	3.67068	3388	8.7
	2T=26.36 °	26.36	3.37876	1754	4.5
	2T=27.06 °	27.06	3.2931	572	1.5
	2T=27.55 °	27.55	3.23475	1513	3.9
	2T=28.89 °	28.89	3.08773	1542	4
	2T=29.96 °	29.96	2.98053	861	2.2
	2T=30.37 °	30.37	2.94109	2107	5.4
	2T=33.57 °	33.57	2.66748	1367	3.5
	2T=36.71 °	36.71	2.4462	2095	5.4
	2T=37.41 °	37.41	2.40178	535	1.4

Example 14. Preparation of Crystalline Form II of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide

23 g of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-

phenylthiomorpholine-4-carboxamide 1,1-dioxide (a compound represented by Chemical Formula 1) was completely dissolved in dichloromethane (400 mL), and then the resulting solution was concentrated. After ethanol (40 mL) was injected into the concentrated residue and the resulting mixture was concentrated, ethanol (140 mL) was added thereto, the resulting mixture was dissolved by heating to 35°C to 40°C to prepare a solution, and then the solution was stirred for 1 to 2 hours. A solid precipitated during stirring was filtered. The solid obtained by filtration was dried for 14 hours to obtain the title compound (Crystalline Form II of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide)(20.9 g, yield 91%, melting point: 130.4°C) with an HPLC purity of 99.6%. The X-ray powder diffraction (XRPD) pattern of Crystalline Form II is shown in FIG. 16 and Table 7, and the differential scanning calorimetry (DSC) analysis results are shown in FIG. 17.

[Table 7]

Caption	Legend	Angle	d value	Intensity	Intensity %
		2-Theta °	Angstrom	Count	%
2T=7.83 °		7.83	11.28867	2130	18.3
2T=10.68 °		10.68	8.27461	843	7.2
2T=10.88 °		10.88	8.1258	587	5
2T=11.39 °		11.39	7.76509	1682	14.4
2T=11.77 °		11.77	7.5105	1731	14.8
2T=12.22 °		12.22	7.2397	7828	67.2
2T=13.26 °		13.26	6.67311	2704	23.2
2T=15.72 °		15.72	5.63283	1664	14.3
2T=16.60 °		16.60	5.3353	3270	28.1
2T=16.95 °		16.95	5.22708	1133	9.7
2T=17.48 °		17.48	5.06991	2479	21.3
2T=18.27 °		18.27	4.85108	4068	34.9
2T=19.02 °		19.02	4.66301	7613	65.3
2T=19.35 °		19.35	4.58254	3546	30.4
2T=19.67 °		19.67	4.51074	11656	100
2T=20.33 °		20.33	4.36463	2726	23.4
2T=20.67 °		20.67	4.29281	3228	27.7
2T=21.39 °		21.39	4.15091	4909	42.1
2T=21.59 °		21.59	4.11314	3109	26.7
2T=21.85 °		21.85	4.065	1695	14.5
2T=22.35 °		22.35	3.9744	4881	41.9
2T=22.82 °		22.82	3.89312	1020	8.8
2T=24.56 °		24.56	3.62191	1654	14.2
2T=26.42 °		26.42	3.37061	2432	20.9
2T=27.34 °		27.34	3.25896	2273	19.5
2T=30.49 °		30.49	2.92925	1041	8.9
2T=32.17 °		32.17	2.77995	761	6.5
2T=33.72 °		33.72	2.65603	1560	13.4
2T=35.45 °		35.45	2.53015	715	6.1
2T=35.94 °		35.94	2.497	251	2.2

Example 15. Preparation of Crystalline Form III of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide

Methyl tertiary butyl ether (MTBE, 400 mL) was added to 20 g of the amorphous solid N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide (a compound represented by Chemical Formula 1) obtained in Preparation Example 1, and the resulting mixture was slurried at 20°C to 25°C for 24 hours, and then filtered. The solid obtained by filtration was washed with methyl tertiary butyl ether (MTBE, 40 mL) and dried under vacuum for 14 hours to obtain the title compound (Crystalline Form III of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide) (18.5 g, yield 92.5%, melting point: 125.0°C) with an HPLC purity of 99.8%. The X-ray powder diffraction (XRPD) pattern of Crystalline Form III is shown in FIG. 18 and Table 8, and the differential scanning calorimetry (DSC) analysis results are shown in FIG. 19.

[Table 8]

Caption	Legend	Angle	d value	Intensity	Intensity %
		2-Theta °	Angstrom	Count	%
2T=8.73 °		8.73	10.12463	1921	23.9
2T=10.95 °		10.95	8.07318	1794	22.3
2T=12.40 °		12.40	7.13131	2642	32.9
2T=14.20 °		14.20	6.23375	127	1.6
2T=15.45 °		15.45	5.73263	223	2.8
2T=16.84 °		16.84	5.26091	8035	100
2T=17.47 °		17.47	5.0722	750	9.3
2T=18.44 °		18.44	4.80664	402	5
2T=18.75 °		18.75	4.72916	568	7.1
2T=19.93°		19.93	4.45195	1043	13
2T=20.45 °		20.45	4.33963	1209	15
2T=20.77 °		20.77	4.27334	662	8.2
2T=21.53 °		21.53	4.12446	1878	23.4
2T=21.84 °		21.84	4.06566	1181	14.7
2T=22.05 °		22.05	4.02856	1415	17.6
2T=22.90 °		22.90	3.88005	3415	42.5
2T=24.02 °		24.02	3.70158	832	10.4
2T=24.70 °		24.70	3.60209	685	8.5
2T=24.96 °		24.96	3.56528	745	9.3
2T=26.27 °		26.27	3.38961	675	8.4
2T=28.47 °		28.47	3.13233	1030	12.8
2T=29.20 °		29.20	3.05598	347	4.3
2T=30.18 °		30.18	2.95922	259	3.2
2T=31.39 °		31.39	2.84758	385	4.8
2T=34.09 °		34.09	2.62775	401	5
2T=37.09 °		37.09	2.42178	179	2.2
2T=38.82 °		38.82	2.31781	224	2.8

<Experimental Examples>

Experimental Example 1. Crystal stability and accelerated stability test of amorphous and

Crystalline Forms I, II and III

The crystalline form of a compound may be changed to another crystalline form according to the surrounding environment, and such a crystalline form that has weak crystal stability easily undergoes a crystalline form change, and thus may be present as a plurality of crystalline forms.

In this case, an unexpected pharmacokinetic reaction may be induced as the pharmacokinetic properties of a final drug are changed. Therefore, a crystal stability and accelerated stability test (accelerated condition: $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$, $75\% \text{ RH} \pm 5\%$) was performed on the amorphous N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, Crystalline Form I, Crystalline Form II and Crystalline Form III, and 6 months later, the purity and the X-ray powder diffraction (XPRD) pattern were checked again, and the analysis results thereof are shown in Table 9.

[Table 9]

	Purity (HPLC)/ crystalline form			
	Amorphous	Crystalline Form I	Crystalline Form II	Crystalline Form III
Initial	99.9 % / Amorphous	99.9 % / Crystalline Form I	99.6 % / Crystalline Form II	99.8 % / Crystalline Form III
40°C / 75% RH 1 month	99.9 % / Amorphous	99.9 % / Crystalline Form I	99.6 % / Crystalline Form II	99.8 % / Crystalline Form III
40°C / 75% RH 3 months	99.9 % / Crystalline Form I	99.9 % / Crystalline Form I	99.6 % / Crystalline Form II	99.8 % / Crystalline Form III
40°C / 75% RH 6 months	94.6 % / Crystalline Form I	99.9 % / Crystalline Form I	99.6 % / Crystalline Form II	99.8 % / Crystalline Form III

As shown in Table 9, since Crystalline Form I, Crystalline Form II, and Crystalline Form III have excellent crystal stability, the crystals are stably maintained for 6 months without any change in purity and crystalline form, confirming the ease of storage.

However, in the case of the amorphous form, although there was no change in purity under accelerated conditions, it was confirmed that the amorphous form was easily converted to Crystalline Form I in 3 months. In addition, it was observed the purity of the amorphous form was reduced into 94.6% in 6 months. . Based on the observations, it was confirmed that the amorphous form was relatively unstable.

Therefore, Crystalline Form I, Crystalline Form II and Crystalline Form III according to the present invention exhibit enough excellent stability to be used in pharmaceuticals, and can be stored for a long period of time without any change in pharmacological effects, safety and pharmacokinetic properties because the crystalline forms are stably maintained when manufactured as a pharmaceutical, so that it can be seen that the crystalline forms can maintain an excellent therapeutic effect for a long period of time and also have remarkably excellent economic feasibility.

Experimental Example 2. Hygroscopicity test

A hygroscopic compound is not useful for formulation because it easily absorbs moisture, is difficult to handle, and does not flow smoothly. In addition, since the compound has weak stability, there are limitations in long-term storage, and it is difficult to derive reproducible results because the content is not constant.

Accordingly, the hygroscopicity of the N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide crystalline forms was evaluated. The hygroscopicity of the crystalline form of the present application was confirmed through a water sorption analyzer (dynamic vapor sorption, DVS), and compared to the measurement results for the amorphous compound, which is shown in Table 10 and FIGS. 20 to 23.

<Water sorption analysis (dynamic vapor sorption, DVS)>

The mass changes in crystalline and amorphous forms were measured under the delta mass/delta

time (dm/dt) conditions by changing the relative humidity stepwise by 10% from the initial 0% to 95% at 25°C using a water sorption analyzer (dynamic vapor sorption, DVS) (DVS Intrinsic Model of Surface Measurement Systems). The change in mass according to the humidity change is illustrated in FIG. 20 (Crystalline Form I), FIG. 21 (Crystalline Form II), FIG. 22 (Crystalline Form III) and FIG. 23 (amorphous), and the confirmation of hygroscopicity by mass change at humidity 25°C/80% RH is shown in the following Table 10 below.

[Table 10]

Hygroscopicity test conditions	Crystalline Form I	Crystalline Form II	Crystalline Form III	Amorphous
DVS (25°C/80% RH)	Non-hygroscopic (0.02 %)	Non-hygroscopic (0.11 %)	Non-hygroscopic (0.05 %)	Slightly hygroscopic (1.73 %)

As confirmed in FIGS. 20 to 23, it can be seen that Crystalline Form I, Crystalline Form II, and Crystalline Form III according to the present invention stably maintained an anhydrous state without being affected by changes in the surrounding relative humidity. However, the amorphous form showed a tendency to absorb 1% to 2.5% water according to high relative humidity (70 to 90% RH) compared to the crystalline forms.

Furthermore, as can be seen in Table 10, it could be seen that the water weight% of Crystalline Form I, Crystalline Form II and Crystalline Form III according to the present invention was maintained substantially unchanged even at a relative humidity of 80%, whereas it was confirmed by an increased water weight% that the amorphous form absorbs water.

Therefore, Crystalline Form I, Crystalline Form II, and Crystalline Form III according to the present invention are stable crystal forms with low hygroscopicity, may be stably maintained for a long period of time without being affected by the surrounding humidity and thus do not require separate storage conditions during storage, and are advantageous for formulation because physicochemical

properties may be stably maintained without being affected by the surrounding moisture, a preparation with an excellent content uniformity may be obtained, and excellent therapeutic effects may be stably maintained for a long period of time, so that it can be seen that the crystalline forms have excellent reproducibility and economic feasibility.

Experimental Example 3. Residual solvent removal test of amorphous form, Crystalline Forms I, II and III

All residual solvents have no therapeutic benefit, and thus need to be removed to a level suitable for product specifications, good pharmaceutical manufacturing practices (GMP) or other quality standards and residual solvents above should not be contained beyond the level permitted by safety data in preparations. Further, residual levels need to be regulated according to ICH guidelines in order to protect patients from potential adverse reactions due to the toxicity of the residual solvent. Therefore, residual solvent management is as important as impurity management in the final API, and the efficiency of removing the residual solvent may vary greatly according to the type of crystalline form. Accordingly, the residual solvent removal degrees of the amorphous form and the crystalline forms of the present application were evaluated.

In the following Table 11, the residual solvent removal degrees of the amorphous form and Crystalline Forms I, II and III of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide by commonly used drying methods (vacuum drying and humidified drying) were tested, and the results are shown in the following Table 11.

In the residual solvent removal experiment, vacuum drying was performed at a temperature of 20°C to 30°C, humidified drying was performed at a temperature of 20°C to 30°C and a relative humidity of 80% to 90%, and the amorphous form was dried under vacuum, and then subjected to humidified drying, as described in Preparation Example 1.

[Table 11]

Solid form	Amount of residual solvent after vacuum drying for 14 hours	Amount of residual solvent after humidified drying for 6 days	Residual solvent concentration limit (ICH guideline criteria)
Amorphous	Dichloromethane 22,000 ppm	Dichloromethane 9561 ppm	Dichloromethane 600 ppm
Crystalline Form I	Ethyl acetate 246 ppm Ethanol 603 ppm	-	Ethyl acetate 5000 ppm Ethanol 5000 ppm
Crystalline Form II	Ethanol 291 ppm	-	Ethanol 5000 ppm
Crystalline Form III	Methyl tertiary butyl ether 3944 ppm	-	Methyl tertiary butyl ether 5000 ppm

As shown in Table 11, it was confirmed that Crystalline Form I, Crystalline Form II, and Crystalline Form III of the present invention are suitable as pharmaceutical substances because it can be seen that the residual solvent was removed below the ICH guideline criteria even by general vacuum drying alone, whereas it is difficult to remove the residual solvent of the amorphous form below the ICH specified value even though humidified drying is additionally performed after vacuum drying. That is, it was confirmed that the residual solvent can be effectively removed from Crystalline Form I, Crystalline Form II and Crystalline Form III of the present invention compared to the amorphous form.

Therefore, Crystalline Form I, Crystalline Form II and Crystalline Form III of the present invention are safe from toxicity due to the residual solvent, may satisfy excellent standards as pharmaceutical substances, and do not require complicated processes to remove the residual solvent, so that the crystalline forms can be easily used as pharmaceuticals, and thus are suitable for mass production, and can achieve excellent therapeutic effect and safety.

Experimental Example 4. NMR analysis test

An NMR analysis was performed on the N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-

yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide prepared by Preparation Example 1. An NMR spectrum was analyzed using a 700 MHz nuclear magnetic resonance spectrometer manufactured by Bruker, and the results are shown in FIG. 24 (^1H NMR) and FIG. 25 (^{13}C NMR).

The conditions for performing X-ray powder diffraction analysis, thermal analysis, and high performance liquid chromatography (HPLC) in the present invention are as follows.

1. X-ray powder diffraction analysis

An X-ray powder diffraction pattern was measured using an X-ray diffractometer (manufacturer: Bruker (Germany), model name: D8 ADVANCE) as a detector, and was measured at various angles (2θ) after a test sample was applied to a XPRD sample holder. Supply source $\text{CuK}\alpha$, $\lambda = 1.5406 \text{ \AA}$; Generator: 40 kV - 40 mA; Detector: PSD, Lynx Eye; DongShinFinetek DS-20.

Unless otherwise stated herein, X-ray powder diffraction analysis is measured using $\text{CuK}\alpha$ radiation as described above. For example, the X-ray powder diffraction (XRPD) patterns in Tables 1 to 8 was measured to use $\text{CuK}\alpha$ radiation.

2. Thermal analysis

Examples 1 to 12

A differential scanning calorimetry (DSC) analysis was performed using a thermal analysis device (manufacturer: Netzsch, model name: DSC204 F1 Phoenix)

About 1 to 10 mg of sample was weighed and placed in an aluminum pan with a lid. The sample was evaluated using a linear heating lamp at $10^\circ\text{C}/\text{min}$ in a range of 25°C to 400°C .

Examples 13 to 15

A differential scanning calorimetry (DSC) analysis was performed using a thermal analysis device (manufacturer: METTLER TOLEDO, model name: DSC823e (Crystalline Form I, Crystalline

Form II) / manufacturer: Netzsch, model name: DSC204 F1 Phoenix (amorphous, Crystalline Form III)).

About 1 to 10 mg of sample was weighed and placed in an aluminum pan with a lid. The sample was evaluated using a linear heating lamp at 10°C/min in a range of 25°C to 400°C.

3. High performance liquid chromatography (HPLC)

- Detector: UV absorbance photometer (detection wavelength 245 nm)
- Column: Waters Cortecs C18+ (3.0 x 100 mm, 2.7 µm)
- Column temperature: 35°C
- Flow rate: 0.7 mL/min
- Injection volume: 2.0 µl
- Mobile phase A: 0.1% Acetic acid in Water
- Mobile phase B: 0.1% Acetic acid in Acetonitrile
- Diluent: Mobile phase A: Mobile phase B = 50: 50 (v/v)
- Sample concentration: 0.5 mg/mL
- Mobile phase gradient conditions:

Time (min)	Mobile phase A (%)	Mobile phase B (%)
0	80	20
10	60	40
15	10	90
18	10	90
18.1	80	20
21	80	20

4. Hygroscopicity analysis

Water sorption analysis (dynamic vapor sorption, DVS)

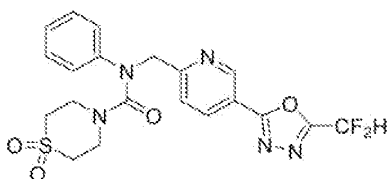
Water sorption was analyzed from 0% RH to 95% RH at 25°C using a water sorption analyzer (dynamic vapor sorption, DVS, DVS Intrinsic Model of Surface Measurement Systems). A change in mass of a crystalline form or amorphous form was measured under the condition of delta mass/delta time (dm/dt) by changing the relative humidity stepwise by 10% from the initial 0% to 95%.

Claims

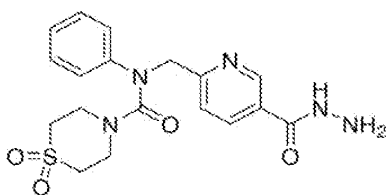
1. A method for preparing a compound represented by Chemical Formula 1 below, the method comprising:

in-situ preparing a compound represented by Chemical Formula 1 below from a compound represented by Chemical Formula 6 below:

[Chemical Formula 1]



[Chemical Formula 6]



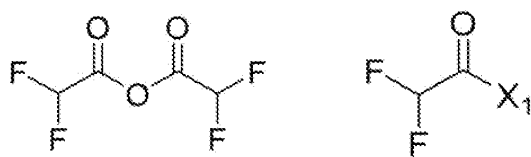
2. The method according to claim 1, wherein the preparing of the compound represented by Chemical Formula 1 from the compound represented by Chemical Formula 6 is performed in the presence of a base.

3. The method according to claim 2, wherein the base comprises imidazole.

4. The method according to claim 1, wherein the compound represented by Chemical Formula 1 is prepared by using at least one selected from a compound represented by [Chemical Formula A] below and a compound represented by [Chemical Formula B], and the compound represented by Chemical Formula 6 as a reaction material:

[Chemical Formula A]

[Chemical Formula B]



wherein, in above Chemical formula B, X_1 is F, Cl, Br or I.

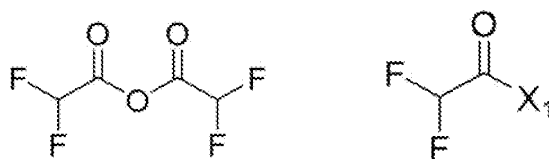
5. The method according to claim 1, wherein the preparing of the compound represented by Chemical Formula 1 from the compound represented by Chemical Formula 6 comprises:

a) preparing a reaction part 1 including a compound represented by Chemical Formula A or B below and a base; and

b) mixing the reaction part 1 with a reaction part 2 including the compound represented by Chemical Formula 6 to prepare the compound represented by Chemical Formula 1:

[Chemical Formula A]

[Chemical Formula B]



in above Chemical Formula B, X_1 is F, Cl, Br or I.

6. The method according to claim 5, wherein Step a) is performed by mixing a mixture comprising a base and a solvent with the compound represented by Chemical Formula A or B.

7. The method according to claim 5, wherein Step a) comprises:

preparing the mixture including the base and the solvent; and

adding the compound represented by Chemical Formula A or Chemical Formula B to the mixture.

8. The method according to claim 7, the method further comprises:

cooling the mixture into 0-10°C after preparing the mixture including the base and the solvent.

9. The method according to claim 5, further comprising:

stirring after adding the compound represented by Chemical Formula A or Chemical Formula B to the mixture.

10. The method according to claim 5, wherein the reaction part 2 in Step b) comprises the compound represented by Chemical Formula 6 and the solvent.

11. The method according to claim 5, wherein mixing the reaction part 2 and the reaction part 1 in the Step b) is performed by adding the reaction part 1 to the reaction part 2.

12. The method according to claim 11, wherein adding the reaction part 1 to the reaction part 2 is performed at -15°C to 5°C.

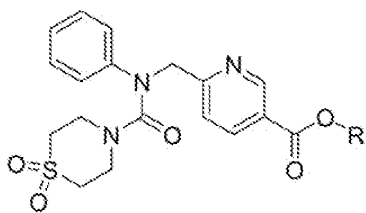
13. The method according to claim 12, further comprising:

heating to a temperature of 20 to 45°C after completely mixing in Step b).

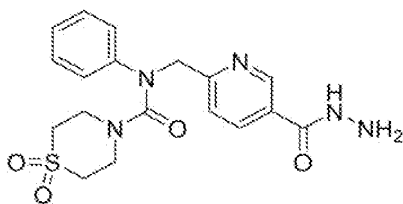
14. A method for preparing a compound represented by Chemical Formula 6 below, the method comprising:

preparing a compound represented by Chemical Formula 6 below from hydrazine(N₂H₄) or a hydrate thereof and a compound represented by Chemical Formula 5 below in the presence of a solvent including a C1 to C6 linear or branched alcohol or a mixture of a C1 to C6 linear or branched alcohol and water:

[Chemical Formula 5]



[Chemical Formula 6]



in above Chemical Formula 5, R is C1-C6 linear or branched alkyl or benzyl.

15. The method according to claim 14, wherein the solvent is methanol or a mixture of methanol and water.

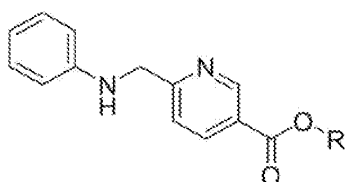
16. The method according to claim 14, wherein a volume ratio of the alcohol and the water is 10:1 to 1:1.

17. The method according to claim 14, wherein R is methyl.

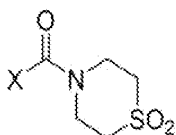
18. A method for preparing a compound represented by Chemical Formula 5, the method comprising:

reacting a compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 in the presence of a base to prepare a compound represented by Chemical Formula 5:

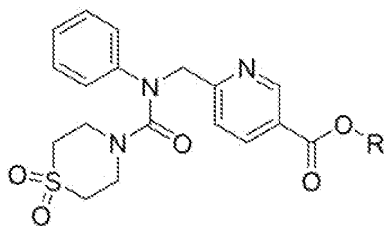
[Chemical Formula 3]



[Chemical Formula 4]

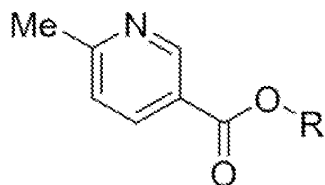


[Chemical Formula 5]

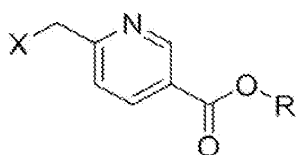


in above Chemical Formulas 3 and 5, R is C1-C6 linear or branched alkyl or benzyl, and in above Chemical Formula 4, X is F, Cl, Br or I.

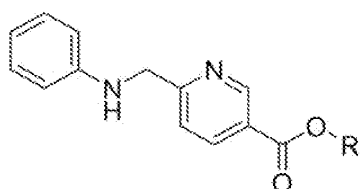
19. The method according to claim 18, wherein R is methyl and X is Cl.
20. The method according to claim 18, wherein the base is triethylamine, N,N-diisopropylethylamine, imidazole, pyridine, sodium hydrogen carbonate, sodium carbonate, potassium hydrogen carbonate, potassium carbonate, or a mixture thereof.
21. The method according to claim 18, the method further comprising:
purifying the compound represented by Chemical Formula 5.
22. The method according to claim 21, wherein the purifying is performed in a solvent selected from the group consisting of methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl tertiary butyl ether (MTBE), diisopropyl ether, heptane, hexane, and a mixture thereof.
23. A method for preparing a compound represented by Chemical Formula 3 below, the method comprising:
preparing a compound represented by Chemical Formula 8 below from a compound represented by Chemical Formula 7 below by using a halogenating reagent; and
preparing a compound represented by Chemical Formula 3 below by reacting a compound represented by Chemical Formula 8 below with aniline in the presence of a base:
[Chemical Formula 7]



[Chemical Formula 8]



[Chemical Formula 3]



wherein, in above Chemical Formulas 3, 7 and 8, R is C1-C6 linear or branched alkyl or benzyl, and in Chemical Formula 8, X is F, Cl, Br or I.

24. The method according to claim 23, wherein R is methyl and X is Cl.

25. The method according to claim 24, wherein the halogenating reagent is iodine, copper iodide, bromine, N-bromosuccinimide (NBS), N-chlorosuccinimide (NCS), trichloroisocyanuric acid (TCCA), or a mixture thereof.

26. The method according to claim 24, wherein X of the compound represented by above Chemical Formula 8 is Cl, and the halogenating reagent is N-chlorosuccinimide (NCS), trichloroisocyanuric acid (TCCA), or a mixture thereof.

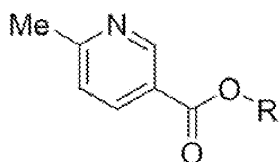
27. The method according to claim 24, wherein the base is selected from the group consisting of sodium hydrogen carbonate, sodium carbonate, potassium hydrogen carbonate, potassium carbonate, triethylamine, diisopropylethylamine, and a mixture thereof.

28. The method according to claim 24, wherein the reacting of the compound represented by Chemical Formula 8 with aniline is performed in the presence of potassium bromide, potassium iodide, tetrabutylammonium bromide (TBAB), or a mixture thereof.

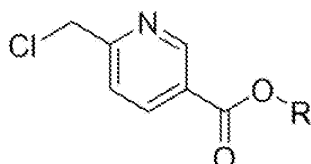
29. A method for preparing a compound represented by Chemical Formula 8a below, the method comprising:

preparing a compound represented by Chemical Formula 8a below by using only a trichloroisocyanuric acid (TCCA) reagent alone in a compound represented by Chemical Formula 7 below:

[Chemical Formula 7]



[Chemical Formula 8a]

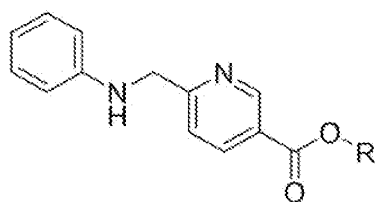


in above Chemical Formulas 7 and 8a, R is C1-C6 linear alkyl or benzyl.

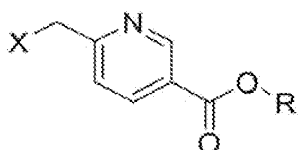
30. A method for preparing a compound represented by Chemical Formula 3, the method comprising:

preparing a compound represented by Chemical Formula 3 below by reacting a compound represented by Chemical Formula 8 below with aniline in the presence of a base:

[Chemical Formula 3]



[Chemical Formula 8]



in above Chemical Formulas 3 and 8, R is C1-C6 linear or branched alkyl or benzyl and in above Chemical Formula 8, X is F, Cl, Br, or I.

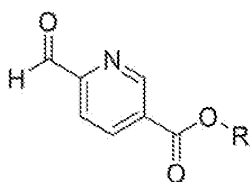
31. The method according to claim 30, wherein the base is selected from the group consisting of sodium hydrogen carbonate, sodium carbonate, potassium hydrogen carbonate, potassium carbonate, triethylamine, diisopropylethylamine, and a mixture thereof.

32. The method according claim 30, wherein the reacting of the compound represented by Chemical Formula 8 with aniline is performed in the presence of potassium bromide, potassium iodide, tetrabutylammonium bromide (TBAB), or a mixture thereof.

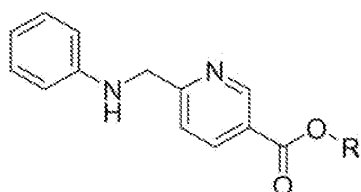
33. A method for preparing a compound represented by Chemical Formula 3, the method comprising:

preparing a compound represented by Chemical Formula 3 below from a compound represented by Chemical Formula 2 below in the presence of aniline and a reducing agent:

[Chemical Formula 2]



[Chemical Formula 3]



wherein, in above Chemical Formula 2 or 3, R is C1-C6 linear or branched alkyl or benzyl.

34. The method according to claim 33, wherein the preparing of the compound represented by Chemical Formula 3 from the compound represented by Chemical Formula 2 comprises:

preparing a mixture including the compound represented by Chemical Formula 2 and aniline;
and

reacting the mixture with the reducing agent.

35. The method according to claim 33, wherein the preparing of the compound represented by Chemical Formula 3 from the compound represented by Chemical Formula 2 comprises:

preparing reaction part 1 including the compound represented by Chemical Formula 2, aniline and a solvent; and

mixing the reaction part 1 and reaction part 2 including the reducing agent and the solvent.

36. The method according to claim 33, wherein the reducing agent comprises one or more selected from the group consisting of sodium borohydride (NaBH_4), sodium cyanoborohydride (NaBH_3CN), and sodium triacetoxyborohydride ($\text{NaBH}(\text{OAc})_3$).

37. The method according to claim 33, wherein the preparing of the compound represented by Chemical Formula 3 from the compound represented by Chemical Formula 2 is performed in the

presence of an acid.

38. A method for preparing a compound represented by Chemical Formula 1 below, the method comprising:

1) preparing a compound represented by Chemical Formula 8 below from a compound represented by Chemical Formula 7 below by using a halogenating reagent;

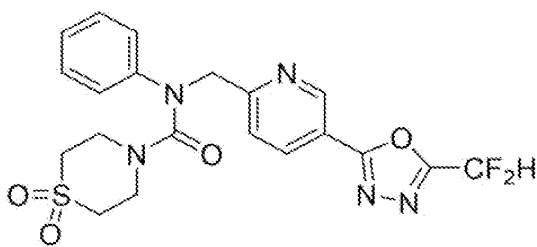
2) preparing a compound represented by Chemical Formula 3 by reacting the compound represented by Chemical Formula 8 below with aniline in the presence of a base;

3) obtaining a compound represented by Chemical Formula 5 below by reacting the compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 below in the presence of a base;

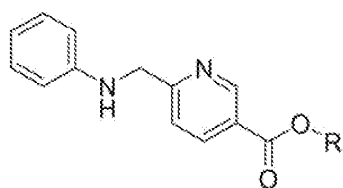
4) obtaining a compound represented by Chemical Formula 6 below by reacting hydrazine or a hydrate thereof with the compound represented by Chemical Formula 5 below; and

5) in-situ preparing the compound represented by Chemical Formula 1 below from the compound represented by Chemical Formula 6 below:

[Chemical Formula 1]

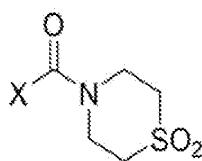


[Chemical Formula 3]



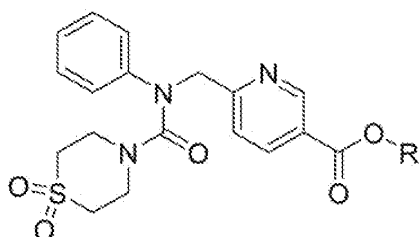
(in above Chemical Formula 3, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



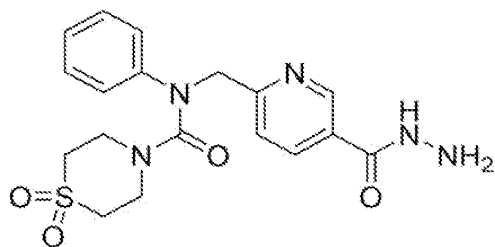
(in above Chemical Formula 4, X is F, Cl, Br or I)

[Chemical Formula 5]

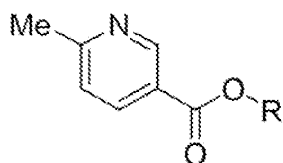


(in above Chemical Formula 5, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 6]

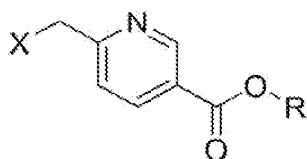


[Chemical Formula 7]



(in above Chemical Formula 7, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 8]



(in above Chemical Formula 8, R is C1-C6 linear or branched alkyl or benzyl, and X is F, Cl, Br or I).

39. A method for preparing a compound represented by Chemical Formula 1 below, the method comprising:

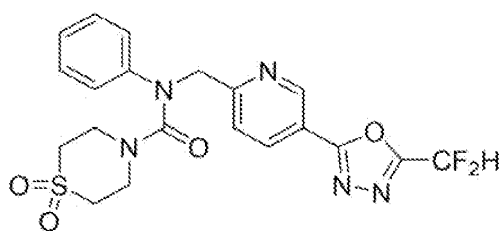
1) preparing a compound represented by Chemical Formula 3 below from a compound represented by Chemical Formula 2 below in the presence of aniline and a reducing agent;

2) obtaining a compound represented by Chemical Formula 5 below by reacting the compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 below in the presence of a base;

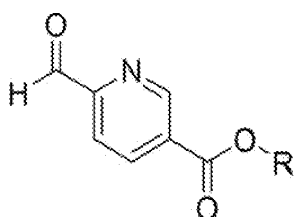
3) obtaining a compound represented by Chemical Formula 6 below by reacting hydrazine or a hydrate thereof with the compound represented by Chemical Formula 5 below; and

4) in-situ preparing the compound represented by Chemical Formula 1 below from the compound represented by Chemical Formula 6 below:

[Chemical Formula 1]

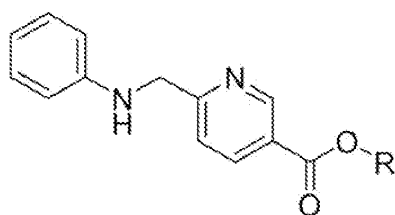


[Chemical Formula 2]



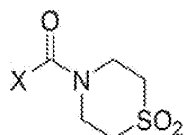
(wherein, in above Chemical Formula 2, R is C1-C6 alkyl or benzyl)

[Chemical Formula 3]



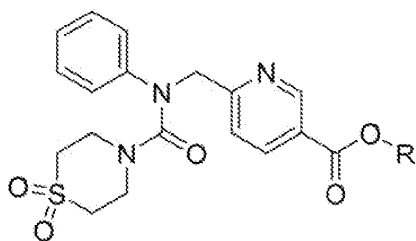
(in above Chemical Formula 3, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



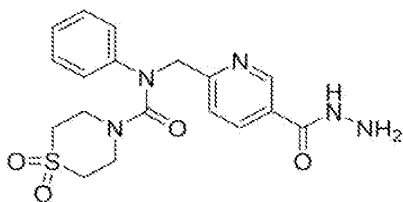
(in above Chemical Formula 4, X may be F, Cl, Br or I)

[Chemical Formula 5]



(in above Chemical Formula 5, R is C1-C6 linear or branched alkyl or benzyl)

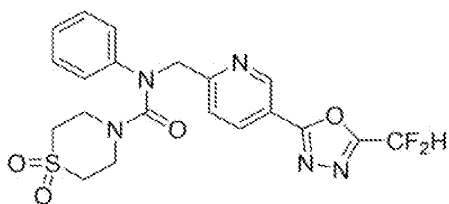
[Chemical Formula 6]



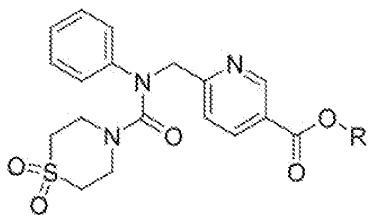
40. A method for preparing a compound represented by Chemical Formula 1 below, the method comprising:

- 1) obtaining a compound represented by Chemical Formula 6 below by reacting hydrazine or a hydrate thereof with a compound represented by Chemical Formula 5 below; and
- 2) in-situ preparing the compound represented by Chemical Formula 1 below from a compound represented by Chemical Formula 6 below:

[Chemical Formula 1]

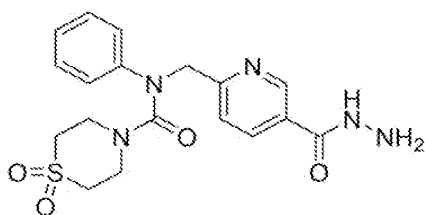


[Chemical Formula 5]



(wherein, in above Chemical Formula 5, R is C1-C6 linear or branched alkyl or benzyl)

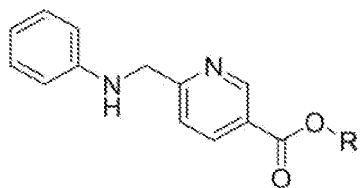
[Chemical Formula 6]



41. The method according to claim 40, wherein the method for preparing the compound represented by above Chemical Formula 5 comprises:

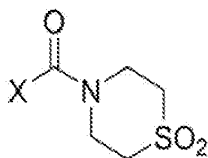
reacting a compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 below in the presence of a base to prepare the compound represented by Chemical Formula 5:

[Chemical Formula 3]



(in above Chemical Formula 3, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



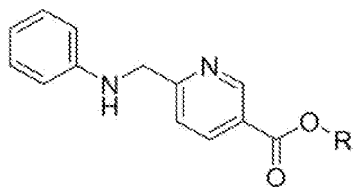
(in above Chemical Formula 4, X is F, Cl, Br or I).

42. The method according to claim 40, wherein the method for preparing the compound represented by Chemical Formula 5 comprises:

preparing a compound represented by Chemical Formula 3 by reacting a compound represented by Chemical Formula 8 below with aniline in the presence of a base; and

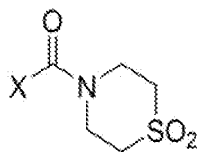
reacting a compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 below in the presence of a base to prepare the compound represented by Chemical Formula 5:

[Chemical Formula 3]



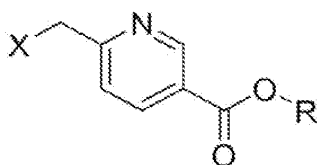
(in above Chemical Formula 3, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



(in above Chemical Formula 4, X is F, Cl, Br or I)

[Chemical Formula 8]



(in above Chemical Formula 8, R is C1-C6 linear or branched alkyl or benzyl, and X is F, Cl, Br or I).

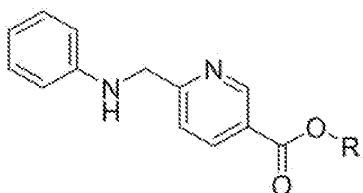
43. The method according to claim 40, wherein the method for preparing the compound represented by Chemical Formula 5 comprises:

Preparing a compound represented by Chemical Formula 8 below from a compound represented by Chemical Formula 7 below by using a halogenating reagent;

preparing a compound represented by Chemical Formula 3 below by reacting the compound represented by Chemical Formula 8 with aniline in the presence of a base;

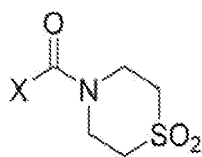
reacting the compound represented by Chemical Formula 3 below with a compound represented by Chemical Formula 4 below in the presence of a base to prepare the compound represented by Chemical Formula 5:

[Chemical Formula 3]



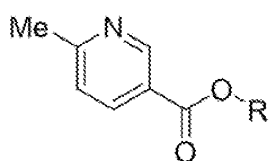
(in above Chemical Formula 3, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 4]



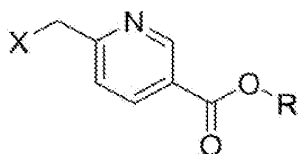
(in above Chemical Formula 4, X is F, Cl, Br or I)

[Chemical Formula 7]



(in above Chemical Formula 7, R is C1-C6 linear or branched alkyl or benzyl)

[Chemical Formula 8]



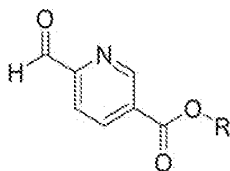
(wherein, in above Chemical Formula 8, R is C1-C6 linear or branched alkyl or benzyl, and X is F, Cl, Br or I).

44. The method according to claim 40, wherein the method for preparing the compound represented by Chemical Formula 5 comprises:

preparing a compound represented by Chemical Formula 3 below from a compound represented by Chemical Formula 2 below in the presence of aniline and a reducing agent; and

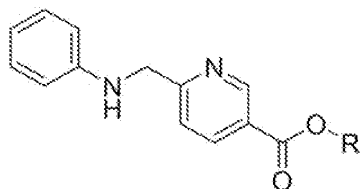
reacting the compound represented by Chemical Formula 3 with a compound represented by Chemical Formula 4 below in the presence of a base to prepare a compound represented by Chemical Formula 5 below:

[Chemical Formula 2]



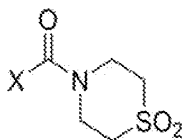
(in above Chemical Formula 2, R is C1-C6 alkyl or benzyl)

[Chemical Formula 3]



(in above Chemical Formula 3, R is C1-C6 linear or branched alkyl or benzyl)

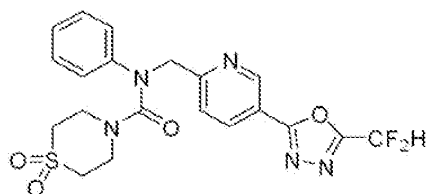
[Chemical Formula 4]



(in above Chemical Formula 4, X is F, Cl, Br, or I).

45. Crystalline Form I of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1, wherein an X-ray powder diffraction pattern comprises diffraction peaks at three or more diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 7.85° , 14.54° , 17.14° , 18.09° , 19.62° , 21.41° and 23.58° :

[Chemical Formula 1]



46. The Crystalline Form I according to claim 45, wherein the X-ray powder diffraction pattern further comprises diffraction peaks at one or more diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 15.64° , 17.55° , 20.78° , 21.04° , 23.27° , 24.24° and 30.38° .

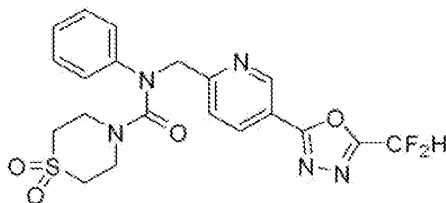
47. The Crystalline Form I according to claim 45, wherein the X-ray powder diffraction pattern further comprises one or more diffraction peaks selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 9.40° , 11.62° , 11.77° , 13.49° , 14.92° , 15.64° , 17.55° , 18.82° , 20.78° , 21.04° , 22.69° , 23.27° , 24.24° , 26.35° , 27.58° , 28.91° , 30.38° , 33.57° and 36.74° .

48. The Crystalline Form I according to claim 45, wherein Crystalline Form I has an endothermic peak at $132^\circ\text{C} (\pm 0.5^\circ\text{C})$ to $143^\circ\text{C} (\pm 0.5^\circ\text{C})$ during differential scanning calorimetry (DSC) analysis when the heating rate is $10^\circ\text{C}/\text{min}$.

49. The Crystalline Form I according to claim 45, wherein Crystalline Form I has an endothermic peak at $138^\circ\text{C} (\pm 3^\circ\text{C})$ during differential scanning calorimetry (DSC) analysis when the heating rate is $10^\circ\text{C}/\text{min}$.

50. Crystalline Form II of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1, wherein an X-ray powder diffraction pattern comprises three or more diffraction peaks selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 7.83° , 12.22° , 19.02° , 19.67° , 21.40° , 22.35° and 26.44° :

[Chemical Formula 1]



51. The Crystalline Form II according to claim 50, wherein the X-ray powder diffraction pattern further comprises diffraction peaks at one or more diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 11.41° , 11.78° , 13.28° , 15.70° , 16.64° , 17.48° , 18.28° , 19.37° , 20.71° , 24.58° , 27.35° and 33.73° .

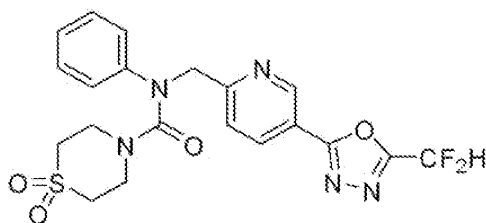
52. The Crystalline Form II according to claim 50, wherein the X-ray powder diffraction pattern further comprises diffraction peaks at one or more diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 10.72° , 10.92° , 11.41° , 11.78° , 13.28° , 15.70° , 16.64° , 16.97° , 17.48° , 18.28° , 19.37° , 20.71° , 24.58° , 27.35° , 30.49° , 32.19° , 33.73° , 35.44° and 35.91° .

53. The Crystalline Form II according to claim 50, wherein Crystalline Form II has an endothermic peak at 124°C ($\pm 0.5^\circ\text{C}$) to 138°C ($\pm 0.5^\circ\text{C}$) during differential scanning calorimetry (DSC) analysis when the heating rate is $10^\circ\text{C}/\text{min}$.

54. The Crystalline Form II according to claim 50, wherein Crystalline Form II has an endothermic peak at 130°C ($\pm 5^\circ\text{C}$) during differential scanning calorimetry (DSC) analysis when the heating rate is $10^\circ\text{C}/\text{min}$.

55. Crystalline Form III of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1, wherein an X-ray powder diffraction pattern comprises diffraction peaks at three or more diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 8.75° , 10.98° , 12.44° , 16.86° , 22.92° and 28.49° :

[Chemical Formula 1]



56. The Crystalline Form III according to claim 55, wherein the X-ray powder diffraction pattern further comprises diffraction peaks at one or more diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 17.48° , 19.95° , 20.49° , 20.79° , 21.55° , 21.87° , 22.07° , 24.04° , 24.72° , 24.99° and 26.30° .

57. The Crystalline Form III according to claim 55, wherein the X-ray powder diffraction pattern further comprises diffraction peaks at one or more diffraction angles selected from the group consisting of diffraction angles ($2\theta \pm 0.2^\circ$) of 14.28° , 15.45° , 17.48° , 18.49° , 18.77° , 19.95° , 20.49° , 20.79° , 21.55° , 21.87° , 22.07° , 24.04° , 24.72° , 24.99° , 26.30° , 29.22° , 30.20° , 31.40° , 34.10° , 37.13° and 38.86° .

58. The Crystalline Form III according to claim 55, wherein Crystalline Form III has an endothermic peak at 120°C ($\pm 0.5^\circ\text{C}$) to 130°C ($\pm 0.5^\circ\text{C}$) during differential scanning calorimetry (DSC) analysis when the heating rate is $10^\circ\text{C}/\text{min}$.

59. The Crystalline Form III according to claim 55, wherein Crystalline Form III has an endothermic peak at 125°C ($\pm 5^\circ\text{C}$) during differential scanning calorimetry (DSC) analysis when the heating rate is $10^\circ\text{C}/\text{min}$.

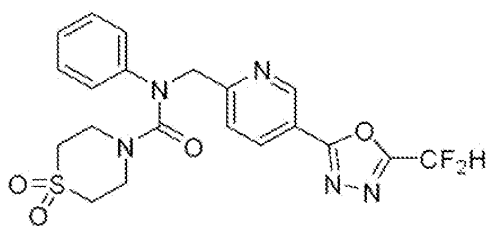
60. A method for preparing Crystalline Form I of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is a compound represented by the following Chemical Formula 1, the method comprising:

(a) obtaining a solution by dissolving N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1 in a solvent selected from the group consisting of ethyl acetate, ethanol, methanol, isopropyl

alcohol, butyl alcohol, methyl tertiary butyl ether (MTBE), diisopropyl ether, acetone, methylisobutylketone (MIBK), methyl ethyl ketone, dichloromethane, dimethylformamide, N-methyl-2-pyrrolidone, toluene, tetrahydrofuran, heptane, hexane, acetonitrile and a mixture thereof; and

(b) producing a solid from the solution:

[Chemical Formula 1]



61. The method according to claim 60 wherein in Step (a), the solvent is one or more alcohols selected from the group consisting of ethanol, methanol, isopropyl alcohol and butyl alcohol, ethyl acetate, or a mixture of the alcohol and ethyl acetate.

62. The method according to claim 60, wherein the obtaining of the solution (a) comprises:

(a1) obtaining a mixture by adding the compound represented by Chemical Formula 1 to the solvent; and

(a2) warming the mixture to a temperature exceeding 40°C.

63. The method according to claim 60, wherein the producing of the solid of Step (b) further comprises:

(b1) additionally adding one or more alcohols selected from the group consisting of ethanol, methanol, isopropyl alcohol and butyl alcohol to the solution of Step (a); and

(b2) stirring the mixture after adding the alcohol of Step (b1).

64. The method according to claim 63, wherein Steps (b1) and (b2) are performed at a temperature exceeding 40°C.

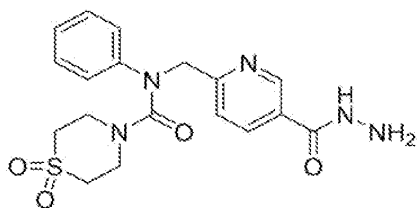
65. The method according to claim 60, further comprising, before performing Step (a),

producing a concentrated residue by dissolving the compound represented by Chemical Formula 1 in dichloromethane, and then performing primary concentration; and

adding ethyl acetate to the concentrated residue and performing secondary concentration.

66. The method according to claim 60, the compound represented by Chemical Formula 1 is in-situ prepared from a compound represented by Chemical Formula 6:

[Chemical Formula 6]



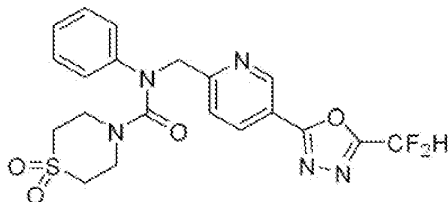
67. A method for preparing Crystalline Form II of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is a compound represented by the following Chemical Formula 1, the method comprising:

(a) preparing a mixture by adding N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1 to a solvent selected from the group consisting of methanol, ethanol, isopropyl alcohol, butyl alcohol, diisopropyl ether, tetrahydrofuran, heptane, hexane and a mixture thereof;

(b) obtaining a solution by warming the mixture to a temperature of 40°C or less; and

(c) producing a solid from the solution at a temperature of 40°C or less:

[Chemical Formula 1]

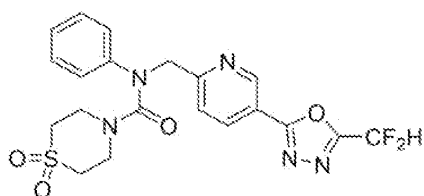


68. The method according to claim 67, wherein in Step (a), the solvent is ethanol, isopropanol or a mixture thereof.

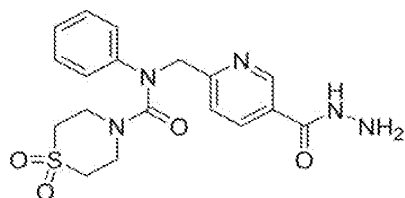
69. The method according to claim 67, further comprising, before performing Step (a), producing a concentrated residue by dissolving the compound represented by Chemical Formula 1 in dichloromethane, and then performing primary concentration; adding ethanol to the concentrated residue and performing secondary concentration.

70. The method according to claim 67, the compound represented by Chemical Formula 1 is in-situ prepared from a compound represented by Chemical Formula 6:

[Chemical Formula 1]



[Chemical Formula 6]



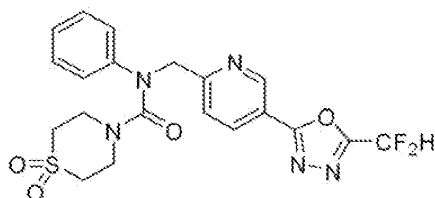
71. A method for preparing Crystalline Form III of N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide, which is a compound represented by the following Chemical Formula 1, the method comprising:

(a) producing a slurry by adding amorphous N-((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)methyl)-N-phenylthiomorpholine-4-carboxamide 1,1-dioxide represented by the following Chemical Formula 1 to a solvent selected from the group consisting of methyl tertiary butyl

ether (MTBE), heptane, octane, hexane, pentane and a mixture thereof; and

(b) obtaining a solid from the slurry:

[Chemical Formula 1]



72. The method according to claim 71, wherein the solvent of Step (a) is methyl tertiary butyl ether (MTBE), heptane or a mixture thereof.

73. The method according to claim 71, wherein (a) the producing of the slurry is performed for 12 hours to 20 days.

74. The method according to claim 71, wherein (b) the obtaining of the solid further comprises filtering the slurry.

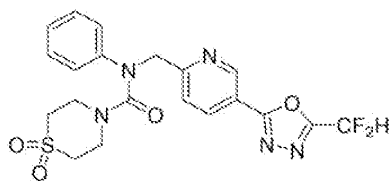
75. The method according to claim 71, wherein (a) the producing of the slurry and (b) the obtaining of the solid are performed at a temperature of 30°C or less.

76. The method according to claim 71, wherein preparing the amorphous form of the compound represented by Chemical Formula 1 comprising:

in-situ preparing the compound represented by Chemical Formula 1 from a compound represented by Chemical Formula 6; and

vacuum-drying the compound represented by Chemical Formula 1.

[Chemical Formula 1]



[Chemical Formula 6]

