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(54) Title: MANUFACTURING METHOD OF HETEROCYCLIC COMPOUND

(57) Abstract: Disclosed is a method of manufacturing a heterocyclic compound, which treats a compound containing an acyl derivative with water and an active material to concurrently proceed cyclization and hydrolysis, so that one-pot reaction may be performed to hence achieve advantages such as a simple and convenient working process, reduction in processing time, and production of a compound with high purity of more than 98% and high yield, compared to typical stepwise processes known in related art.



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Description

Title of Invention: MANUFACTURING METHOD OF HETEROCYCLIC COMPOUND

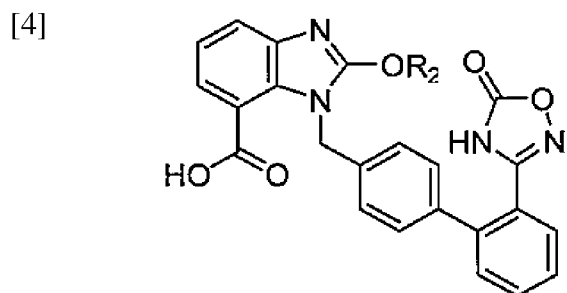
Technical Field

- [1] The present invention relates to a method of manufacturing a heterocyclic compound by continuously proceeding a reaction (one-pot reaction) in a single reactor, compared to typical processes known in prior art which are generally carried out in steps.

Background Art

- [2] A heterocyclic compound represented by Formula 1 below, in particular, azilsartan having R₂ denoted as an ethyl group, *i.e.*, 2-ethoxy-1-[[2'-(2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid is an angiotensin II receptor blocker (ARB).

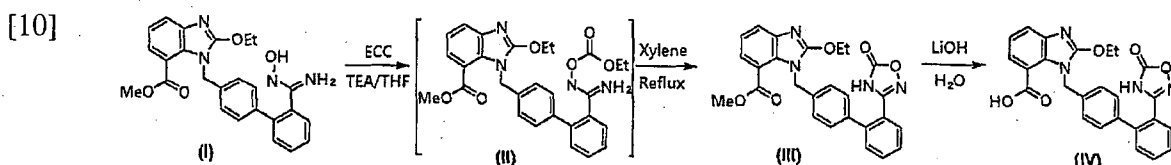
- [3] [Formula 1]



- [5] Angiotensin II causes vasoconstriction, promotes secretion of aldosterone leading to sodium and water content retention, which in turn causes an increase in body fluid, thus raising blood pressure. Vasoconstriction described above is fatal to patients suffering from hypertension.
- [6] Azilsartan is a blocker of angiotensin II receptors and hence inhibits combination of angiotensin II with AT₁ receptor, to control vasoconstriction and aldosterone secretion and thereby lower blood pressure. Also, azilsartan exhibits excellent anti-hypertensive effects, compared to Diovan (name of component: valsartan) or Olmetec (name of component; Olmesartan) which are commercially available in the market.
- [7] The Food and Drug Administration (FDA) in the United States has approved azilsartan medoxomil as a hypertension drug, which is a prodrug of azilsartan.
- [8] Conventionally, Korean Patent Registration No. 233,689 (registered on September 14, 1999) disclosed production of azilsartan according to a process illustrated in Reaction Scheme 1 below. As shown in Reaction Scheme 1, the foregoing technique has produced a compound III by reacting a compound I with ethyl chloroformate (ECC) to form a compound II and refluxing the same in the presence of a xylene

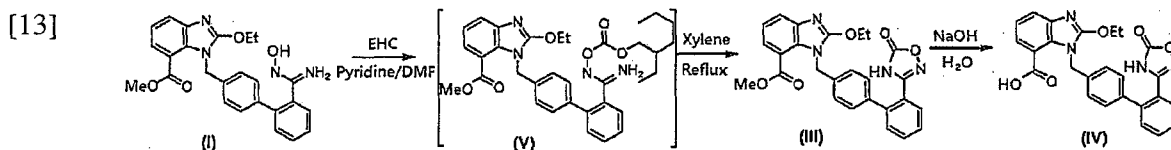
solvent to execute a cyclization reaction. In addition, the compound IV (azilsartan) was prepared by adding lithium hydroxide (LiOH) to the compound III to progress hydrolysis. However, since the above known technique includes purification using column chromatography, it cannot be used in mass-production and may entail difficulties in commercial application.

[9] [Reaction Scheme 1]



[11] Further, *The Journal of Medicinal Chemistry* 1996, 39, 5228~5235, disclosed a method for production of azilsartan based on Reaction Scheme 2 below. This includes reacting a compound I with 2-ethylhexyl chloroformate (EHC) to prepare a compound V and refluxing the prepared compound in the presence of a xylene solvent to proceed cyclization reaction, thus forming a compound III, as shown in Reaction Scheme 2. In addition, by adding sodium hydroxide (NaOH) to the compound III, hydrolysis occurs to form a compound IV (azilsartan).

[12] [Reaction Scheme 2]



[14] Conventional technologies used for preparation of azilsartan, as described above, generally use xylene, which is a carcinogenic material harmful to a human body, by heating and refluxing the same at a high temperature and hence may cause a worker to be exposed to xylene gas. Further, when xylene is removed through vacuum distillation after completing a cyclization reaction, difficulties may be encountered in relation to generation of xylene waste which is hard to treat and/or dispose of. Furthermore, since the reaction is conducted at a high temperature, impurities may occur to deteriorate purity and yield. The cyclization reaction (hereinafter referred to as 'cyclization') using xylene involves a low yield of 23%, hence causing a decrease in yield of azilsartan.

Disclosure of Invention

Technical Problem

[15] Therefore, compared to typical stepwise processes known in the related art, an object of the present invention is to provide a method of manufacturing a heterocyclic

compound capable of continuously proceeding cyclization and hydrolysis (one-pot reaction) by treating a compound containing an acyl derivative with an active material as well as water.

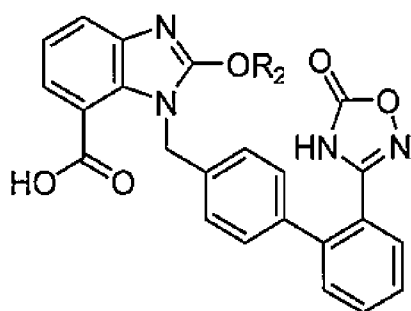
- [16] Also, another object of the present invention is to provide a method of manufacturing a heterocyclic compound with high purity and yield.

Solution to Problem

- [17] In order to achieve the above objects, there is provided a method of manufacturing a heterocyclic compound represented by the following Formula 1, which includes reacting a compound represented by the following Formula 2 with water and an active material.

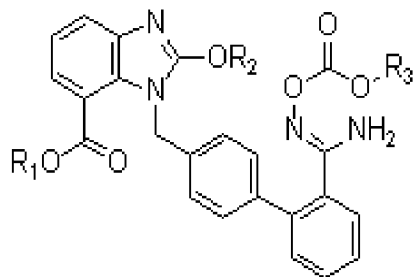
[18] [Formula 1]

[19]



[20] [Formula 2]

[21]



- [22] (wherein R₁ is selected from a group consisting of alkyl groups having 1 to 6 carbon atoms and cycloalkyl groups having 3 to 6 carbon atoms, and R₂ and R₃ are each selected from a group consisting of alkyl groups having 1 to 8 carbon atoms).

- [23] The above active material may be at least one selected from a group consisting of inorganic bases and pyridine.

- [24] The inorganic base may be a hydroxyl salt of an alkali metal wherein the hydroxyl salt of the alkali metal may be at least one selected from sodium hydroxide, lithium hydroxide and potassium hydroxide.

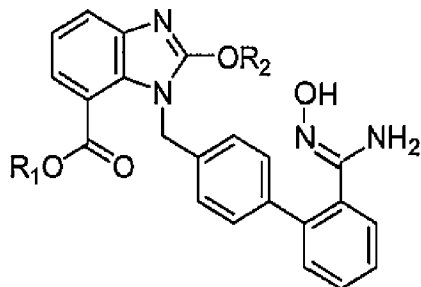
- [25] The inorganic base may be used in an amount of 1 to 10 equivalents to 1 equivalent of the compound represented by Formula 2, while pyridine may be used in amount of 1 to 30 ml to 1g of the compound represented by Formula 2. If the inorganic base and pyridine are used together, pyridine may be used in an amount of 0.5 to 200

equivalents to 1 equivalent of the inorganic base.

[26] Meanwhile, a compound represented by the following Formula 3 may react with alkyl chloroformate to prepare the compound represented by Formula 2.

[27] [Formula 3]

[28]



[29] (wherein R₁ is selected from a group consisting of alkyl groups having 1 to 6 carbon atoms and cycloalkyl groups having 3 to 6 carbon atoms, and R₂ is selected from a group consisting of alkyl groups having 1 to 8 carbon atoms).

[30] The alkyl chloroformate may be ethyl chloroformate or 2-ethylhexyl chloroformate.

Advantageous Effects of Invention

[31] The present invention adopts a one-pot reaction starting from a compound containing an acyl derivative wherein cyclization and hydrolysis are continuously carried out, and therefore, may have advantages such as a simple working process, mass-production and short processing time by as much as half that of typical processes.

[32] In addition, 2-ethoxy-1-[[2'-(2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid produced according to the present invention may have purity of not less than 98% and does not need further purification. Moreover, if necessary, it may have higher purity of 99.5% or more through purification.

[33] The present invention may perform a one-pot reaction under mild conditions, compared to typical processes using xylene through refluxing at a high temperature, thereby accomplishing higher yield.

Mode for the Invention

[34] The present invention describes a method of manufacturing a heterocyclic compound represented by Formula 1, which includes conducting cyclization and hydrolysis in a single reactor treating a compound containing an acyl derivative with water and an active material, to proceed a 'one-pot' reaction, compared to typical processes proceeding in steps, thereby attaining various advantages such as a simple and convenient working process, decrease in processing time, and production of a final compound with high purity (not less than 98%) and high yield (70 to 85%) without additional purification.

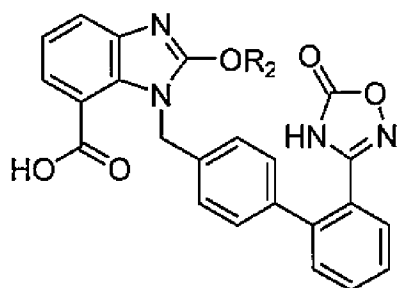
[35] Hereinafter, the present invention will be described in detail.

[36] According to the present invention, the heterocyclic compound represented by Formula 1 may be prepared by a one-pot reaction wherein cyclization and hydrolysis are continuously proceeded by reacting the compound containing an acyl derivative represented by Formula 2 with water and an active material.

[37] Herein, 'one-pot' reaction denotes continuous progress of a reaction(s) in a single reactor.

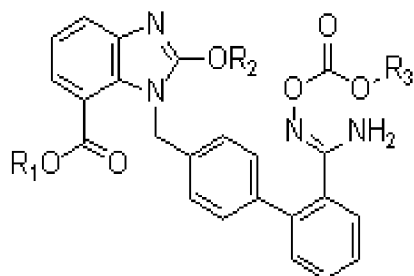
[38] [Formula 1]

[39]



[40] [Formula 2]

[41]



[42] (wherein R_1 is selected from a group consisting of alkyl groups having 1 to 6 carbon atoms and cycloalkyl groups having 3 to 6 carbon atoms, and R_2 and R_3 are each selected from a group consisting of alkyl groups having 1 to 8 carbon atoms).

[43] The active material is used for cyclization and hydrolysis, and more particularly, may be at least one or two or more selected from a group consisting of inorganic bases and pyridine.

[44] Specific examples of the inorganic base may include hydroxyl salts of alkali metals, and more particularly, at least one or two or more selected from a group consisting of sodium hydroxide, lithium hydroxide and potassium hydroxide. More preferably, sodium hydroxide may be used.

[45] The inorganic base may be used in an amount of 1 to 10 equivalents, and preferably, 4 to 5 equivalents to 1 equivalent of the compound represented by Formula 2. If the amount of the inorganic base is less than 1 equivalent to 1 equivalent of the compound represented by Formula 2, yield may be decreased. On the other hand, when the amount exceeds 10 equivalents, impurities may be increased.

[46] Also, pyridine may be used in an amount of 1 to 30 ml, and preferably, 10 to 20 ml to

1g of the compound represented by Formula 2. If an amount of the active material is less than 1 ml to 1g of the compound represented by Formula 2, agitation is not efficient while a yield may be decreased. On the other hand, when the amount is more than 30 ml, a reaction time may be prolonged or, after completing the reaction, a time for removing a solvent may be delayed to cause a decrease in yield.

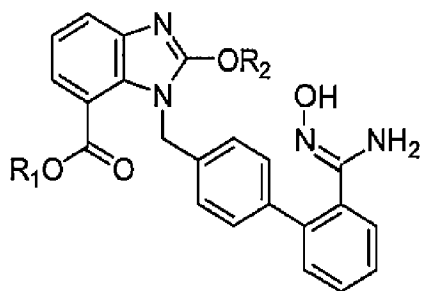
[47] Alternatively, in the case where an inorganic base and pyridine are used together as the active material, 0.5 to 200 equivalents, and preferably, 10 to 40 equivalents of pyridine to 1 equivalent of the inorganic base may be used. If an amount of pyridine is less than 0.5 equivalent to 1 equivalent of the inorganic base, agitation is not efficient while a yield may be decreased. On the other hand, when the amount exceeds 200 equivalents, a reaction time may be prolonged or a yield may be decreased.

[48] The compound represented by Formula 1 may be prepared by adding water and an active material to the compound represented by Formula 2 then agitating the mixture at a temperature of more than 0 to 100°C, and preferably, 40 to 80°C, for 1 to 10 hours. If the temperature is less than 0°C, a yield may be decreased. On the other hand, when the temperature is more than 100°C, impurities tend to increase with time.

[49] Meanwhile, the compound represented by Formula 2 may be prepared by reacting a compound represented by Formula 3 with alkyl chloroformate.

[50] [Formula 3]

[51]



[52] (wherein R₁ is selected from a group consisting of alkyl groups having 1 to 6 carbon atoms and cycloalkyl groups having 3 to 6 carbon atoms, and R₂ is selected from a group consisting of alkyl groups having 1 to 8 carbon atoms).

[53] Alkyl chloroformate described above is used for acylation of amine alcohol and may include, for example, ethyl chloroformate or 2-ethylhexyl chloroformate. More preferably, ethyl chloroformate is used.

[54] The compound represented by Formula 2 may be prepared by adding alkyl chloroformate to the compound represented by Formula 3 and agitating the mixture at -10 to 25°C, and preferably, more than 0 to 25°C for 1 to 3 hours.

[55] After completing cyclization and hydrolysis starting from the compound represented by Formula 2 into the compound represented by Formula 1, a pH value may be adjusted in the range of 2 to 3 using acid, so as to separate the compound represented

by Formula 1. In addition, a water-immiscible solvent, more particularly, ethyl acetate may be optionally used to separate the above compound.

[56] According to the manufacturing method of the present invention, 2-ethoxy-1-[[2'-(2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid may be produced with high yield (70 to 85%) and high purity (not less than 98%).

[57] Hereinafter, preferred embodiments of the present invention will be described in detail to more concretely understand the present invention with reference to examples, comparative examples, practical examples and experimental examples. However, it will be apparent to those skilled in the art that such embodiments are provided for illustrative purposes and do not limit subject matters to be protected as defined by the appended claims.

[58]

[59] **Preparative Example 1**

[60] 10.0g of methyl 2-ethoxy-1-[[2'-hydroxycarbamimidoyl]biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate was introduced into a vessel and then 200 ml of pyridine was added thereto and dissolved therein. Thereafter, 2.4 ml of ethyl chloroformate was slowly added thereto at 5°C, followed by agitating the same at 25°C for 1 hour, to thereby prepare methyl 2-ethoxy-1-[[2'-ethoxy carbonyloxycarbamimidoyl]biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate having an acyl derivative.

[61] **Preparative Example 2**

[62] 10.0g of methyl 2-ethoxy-1-[[2'-hydroxycarbamimidoyl]biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate was introduced into a vessel and then 3.5 ml of triethylamine was added thereto and dissolved therein. Thereafter, 2.36 ml of ethyl chloroformate was slowly added thereto at 5°C, followed by agitating the same at 25°C for 1 hour. Following this, solids were removed from the agitated reaction mixture by filtration and the remaining solution was concentrated under reduced pressure at 40°C, followed by crystallization using ethyl acetate and hexane, thereby yielding 10.8g (yield: 93.0%) of a compound having an acyl derivative.

[63] **Preparative Example 3**

[64] 10.0g of ethyl 2-ethoxy-1-[[2'-hydroxycarbamimidoyl]biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate was introduced into a vessel and then 200 ml of pyridine was added thereto and dissolved therein. Thereafter, 2.3 ml of ethyl chloroformate was slowly added thereto at 5°C, followed by agitating the same at 25°C for 1.5 hours, to thereby prepare

ethyl 2-ethoxy-1-[[2'-etoxy carbonyloxycarbamimidoyl]biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate having an acyl derivative.

[65] **Preparative Example 4**

[66] 10.0g of ethyl

2-ethoxy-1-[[2'-hydroxycarbamimidoyl]biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate was introduced into a vessel and then 150 ml of tetrahydrofuran was added thereto and dissolved therein. Thereafter, 2.3 ml of ethyl chloroformate was slowly added thereto at 5°C, followed by agitating the same at 25°C for 1 hour. Following this, solids were removed from the agitated reaction mixture by filtration and the remaining solution was concentrated under reduced pressure at 40°C, followed by crystallization using ethyl acetate and hexane, thereby yielding 10.6g (yield: 92.0%) of a compound having an acyl derivative.

[67]

[68] **Example 1: Preparation of 2-ethoxy-1-[[2'-(2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid**

[69] To the vessel including the compound having an acyl derivative prepared in Preparative Example 1 as well as pyridine, 100 ml of a 1M sodium hydroxide solution was added and agitated at 50°C for 4 hours. Then, the reaction mixture containing the 1M sodium hydroxide solution was cooled to 25°C and provided with 100 ml of water and 400 ml of ethyl acetate. The reaction mixture containing water and ethyl acetate was further cooled to 5°C and controlled to reach pH 3 using a 6M hydrochloric acid solution. After washing an isolated organic layer with 100 ml of a 1M hydrochloric acid solution and 100 ml of water, the organic layer was concentrated under reduced pressure at 40°C, followed by crystallization, thereby yielding 7.59g of a purposed compound (yield: 75.5%).

[70] ¹H NMR (400 MHz, DMSO) δ: 1.38(3H, t, J = 7.2), 4.59(2H, q, J = 7.2), 5.68(2H, s), 7.03-7.56(11H, m).

[71] Measurement of purity (HPLC): 98.7%

[72] **Example 2: Preparation of 2-ethoxy-1-[[2'-(2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid**

[73] To the vessel including 10.8g of the compound having an acyl derivative prepared in Preparative Example 2, 200 ml of pyridine and 100 ml of a 1M sodium hydroxide solution were added and agitated at 50°C for 4 hours. Then, the agitated reaction mixture was cooled to 25°C and provided with 100 ml of water and 400 ml of ethyl acetate. The reaction mixture containing water and ethyl acetate was further cooled to

5°C and controlled to reach pH 3 using a 6M hydrochloric acid solution. After washing a separated organic layer with 100 ml of a 1M hydrochloric acid solution and 100 ml of water, the organic layer was concentrated under reduced pressure at 40°C, followed by crystallization, thereby yielding 7.7g of a purposed compound (yield: 84.4%).

[74] ¹H NMR (400 MHz, DMSO) δ: 1.38(3H, t, *J* = 7.2), 4.59(2H, q, *J* = 7.2), 5.68(2H, s), 7.03-7.56(11H, m).

[75] Measurement of purity (HPLC): 99.04%

[76] **Example 3: Preparation of 2-ethoxy-1-[[2'-(2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid**

[77] To the vessel including the compound having an acyl derivative prepared in Preparative Example 3 as well as pyridine, 100 ml of a 1M sodium hydroxide solution was added and agitated at 50°C for 7 hours. Then, the reaction mixture containing the 1M sodium hydroxide solution was cooled to 25°C and provided with 100 ml of water and 400 ml of ethyl acetate. The reaction mixture containing water and ethyl acetate was further cooled to 5°C and controlled to reach pH 3 using a 6M hydrochloric acid solution. After washing a separated organic layer with 100 ml of a 1M hydrochloric acid solution and 100 ml of water, the organic layer was concentrated under reduced pressure at 40°C, followed by crystallization, thereby yielding 7.4g of a purposed compound (yield: 77.2%).

[78] ¹H NMR (400 MHz, DMSO) δ: 1.38(3H, t, *J* = 7.2), 4.59(2H, q, *J* = 7.2), 5.67(2H, s), 7.03-7.68(11H, m).

[79] Measurement of purity (HPLC): 98.7%

[80] **Example 4: Preparation of 2-ethoxy-1-[[2'-(2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid**

[81] To the vessel including 10.6g of the compound having an acyl derivative prepared in Preparative Example 4, 200 ml of pyridine and 100 ml of a 1M sodium hydroxide solution were added and agitated at 50°C for 7 hours. Then, the agitated reaction mixture was cooled to 25°C and provided with 100 ml of water and 400 ml of ethyl acetate. The reaction product containing water and ethyl acetate was further cooled to 5°C and controlled to reach pH 3 using a 6M hydrochloric acid solution. After washing a separated organic layer with 100 ml of a 1M hydrochloric acid solution and 100 ml of water, the organic layer was concentrated under reduced pressure at 40°C, followed by crystallization, thereby yielding 6.8g of a purposed compound (yield: 78.0%).

[82] ¹H NMR (400 MHz, DMSO) δ: 1.38(3H, t, *J* = 7.2), 4.59(2H, q, *J* = 7.2), 5.67(2H, s), 7.03-7.68(11H, m).

[83] Measurement of purity (HPLC): 99.5%

[84] **Example 5: Preparation of 2-ethoxy-1-[[2'-(2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid**

[85] To the vessel including 10.0g of the compound having an acyl derivative prepared in Preparative Example 2, 100 ml of a 1M sodium hydroxide solution was added and agitated at 80°C for 2 hours. Then, the agitated reaction mixture was cooled to 25°C and provided with 100 ml of water and 400 ml of ethyl acetate. The reaction mixture containing water and ethyl acetate was further cooled to 5°C and controlled to reach pH 3 using a 6M hydrochloric acid solution. After washing a separated organic layer with 100 ml of a 1M hydrochloric acid solution and 100 ml of water, the organic layer was concentrated under reduced pressure at 40°C, followed by crystallization, thereby yielding 6.2g of a purposed compound (yield: 71.0%).

[86] ¹H NMR (400 MHz, DMSO) δ: 1.38(3H, t, *J* = 7.2), 4.59(2H, q, *J* = 7.2), 5.68(2H, s), 7.03-7.56(11H, m).

[87] Measurement of purity (HPLC): 94.4%

[88] **Example 6: Preparation of 2-ethoxy-1-[[2'-(2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid**

[89] To the vessel including 10.0g of the compound having an acyl derivative prepared in Preparative Example 2, 100 ml of a 1M sodium hydroxide solution was added and agitated at 80°C for 4 hours. Then, the agitated reaction mixture was cooled to 25°C and provided with 100 ml of water and 400 ml of ethyl acetate. The reaction mixture containing water and ethyl acetate was further cooled to 5°C and controlled to reach pH 3 using a 6M hydrochloric acid solution. After washing a separated organic layer with 100 ml of a 1M hydrochloric acid solution and 100 ml of water, the organic layer was concentrated under reduced pressure at 40°C, followed by crystallization, thereby yielding 6.0g of a purposed compound (yield: 74.0%).

[90] ¹H NMR (400 MHz, DMSO) δ: 1.38(3H, t, *J* = 7.2), 4.59(2H, q, *J* = 7.2), 5.68(2H, s), 7.03-7.56(11H, m).

[91] Measurement of purity (HPLC): 88.0%

[92]

[93] **Comparative Example 1: Preparation of methyl 2-ethoxy-1-[[2'-(2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate**

[94] To a suspension prepared by blending and agitating 30 ml of tetrahydrofuran (THF), 0.2g of trimethylamine and 0.90g of methyl 2-ethoxy-1-[[2-(hydroxycarbamimidoyl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate, 0.22g of ethyl chlorocarbonate and 2 ml of methylene chloride were

added under ice cooling. The mixture was agitated at room temperature for 2 hours and, after removing an insoluble material by filtration, the remaining filtrate was concentrated and dried. 5 ml of ethyl acetate was added to the concentrated reaction mixture and, after removing an insoluble material by filtration, the remaining filtrate was concentrated and dried again. A mixture of residue in 10 ml of xylene was heated for 1.5 hours under refluxing. Ethyl acetate was added to the reaction mixture, and the mixture was washed with water, dried and concentrated, and then dried again. The residue was purified through a silica gel column-chromatography to obtain crystals. The crystals were subjected to recrystallization using ethyl acetate-isopropylether, thus yielding 0.22g of a colorless prism type product (yield: 23%).

[95] **Comparative Example 2: Preparation of 2-ethoxy-1-[[2'-(2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid**

[96] 0.166g of the compound prepared in Comparative Example 1 was dissolved in 12 ml of methanol and 1 ml of a 2N LiOH solution was added thereto, followed by heating the same for 3 hours under refluxing. Using 2N HCl, the heated mixture was controlled to reach pH 3. Then, the solvent was evaporated to dryness. After separating the remaining residue using 20 ml of water and 50 ml of chloroform, an organic layer was washed with water then dried. After distilling and drying the solvent, the remaining crystalline product was subjected to recrystallization using ethyl acetate, thus yielding in 0.135g of a colorless prism type product (yield: 84%).

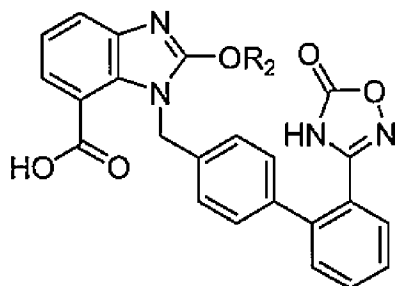
[97] Measurement of purity (HPLC): 91.0%.

[98] Although preferred embodiments of the present invention have been described above in conjunction with the accompanying examples and experimental examples, those skilled in the art will appreciate that various modifications and alterations are possible without departing from the scope and spirit of the invention, based on the foregoing description and the appended claims.

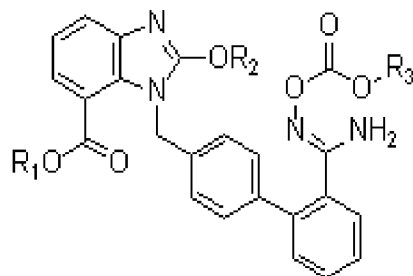
Claims

[Claim 1] A method of manufacturing a heterocyclic compound represented by the following Formula 1, comprising reacting a compound represented by the following Formula 2 with water and an active material:

[Formula 1]



[Formula 2]



(wherein R₁ is selected from a group consisting of alkyl groups having 1 to 6 carbon atoms and cycloalkyl groups having 3 to 6 carbon atoms, and R₂ and R₃ are each selected from a group consisting of alkyl groups having 1 to 8 carbon atoms).

[Claim 2] The method according to claim 1, wherein the active material is at least one selected from a group consisting of inorganic bases and pyridine.

[Claim 3] The method according to claim 2, wherein the inorganic base is a hydroxyl salt of alkali metal.

[Claim 4] The method according to claim 3, wherein the hydroxyl salt of alkali metal is at least one selected from a group consisting of sodium hydroxide, lithium hydroxide and potassium hydroxide.

[Claim 5] The method according to any one of claims 2 to 4, wherein the inorganic base is used in an amount of 1 to 10 equivalents to 1 equivalent of the compound represented by Formula 2.

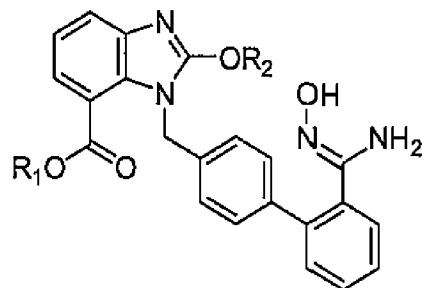
[Claim 6] The method according to claim 2, wherein the pyridine is used in an amount of 1 to 30 ml to 1g of the compound represented by Formula 2.

[Claim 7] The method according to claim 2, wherein the pyridine is used in an amount of 0.5 to 200 equivalents to 1 equivalent of the inorganic base.

[Claim 8] The method according to any one of claims 1 to 4, wherein a reaction temperature is more than 0 to 100°C.

[Claim 9] The method according to claim 1, wherein the compound represented by Formula 2 is prepared by reacting a compound represented by the following Formula 3 with alkyl chloroformate:

[Formula 3]



(wherein R₁ is selected from a group consisting of alkyl groups having 1 to 6 carbon atoms and cycloalkyl groups having 3 to 6 carbon atoms, and R₂ is selected from a group consisting of alkyl groups having 1 to 8 carbon atoms).

[Claim 10] The method according to claim 9, wherein the alkyl chloroformate is ethyl chloroformate or 2-ethylhexyl chloroformate.

A. CLASSIFICATION OF SUBJECT MATTER*C07D 413/10(2006.01)i, A61K 31/4184(2006.01)i, A61P 9/00(2006.01)i*

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D 413/10; A61K 31/4245; A61K 31/42; A61K 31/435; A61P 9/12

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

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

eKOMPASS(KIPO internal), CAplus

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5583141 A (NAKA, TAKEHIKO et al.) 10 December 1996 See the entire document.	1-10
A	US 2010-0016382 A1 (NOMURA, YUKIHIRO et al.) 21 January 2010 See the entire document.	1-10

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

26 OCTOBER 2012 (26.10.2012)

Date of mailing of the international search report

30 OCTOBER 2012 (30.10.2012)

Name and mailing address of the ISA/KR

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Telephone No. 82-42-481-8163



INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

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