



- (51) **International Patent Classification:** Not classified
- (74) **Agent:** DARAE IP FIRM; (KIPS, Yeoksam-dong), 10th Floor, 131, Teheran-ro, Gangnam-gu, Seoul 135-080 (KR).
- (21) **International Application Number:** PCT/KR2012/003905
- (81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (22) **International Filing Date:** 17 May 2012 (17.05.2012)
- (84) **Designated States** (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:** 10-2011-0047490 19 May 2011 (19.05.2011) KR
- (71) **Applicant** (for all designated States except US): **HANMI FINE CHEMICAL CO., LTD.** [KR/KR]; (Jeongwang-dong), 59, Kyoungje-ro, Siheung-si, Gyeonggi-do 429-848 (KR).
- (72) **Inventors; and**
- (75) **Inventors/Applicants** (for US only): **JO, Nam-hyun** [KR/KR]; 402-2205, Poonglim 4 Cha Apt., Wolgotdong, Siheung-si, Gyeonggi-do 429-928 (KR). **LEE, Young Ju** [KR/KR]; 102-604, Donga Hangaram Apt., Pungnap 1-dong, Songpa-gu, Seoul 138-780 (KR). **CHU, Junho** [KR/KR]; 102-603, Boseong Apt., Jeongwang 4-dong, Siheung-si, Gyeonggi-do 429-768 (KR). **JEONG, Jiweon** [KR/KR]; 202-1103, Gwiin Hyundai Hometown, Pyeongchon-dong, Dongan-gu, Anyang-si, Gyeonggi-do 431-070 (KR).
- Published:**
— without international search report and to be republished upon receipt of that report (Rule 48.2(g))



(54) **Title:** MANUFACTURING METHOD OF AZILSARTAN

(57) **Abstract:** Disclosed is a method of manufacturing azilsartan, which treats a compound containing an amino-alcohol derivative with N,N'-carbonyldiimidazole, an inorganic base and a solvent to proceed both of cyclization and hydrolysis in a single reactor, 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.

Description

Title of Invention: MANUFACTURING METHOD OF AZILSARTAN

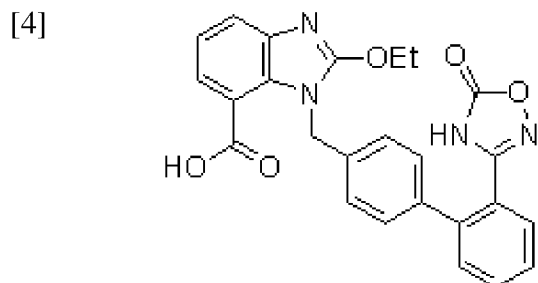
Technical Field

- [1] The present invention relates to a method of manufacturing azilsartan 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]

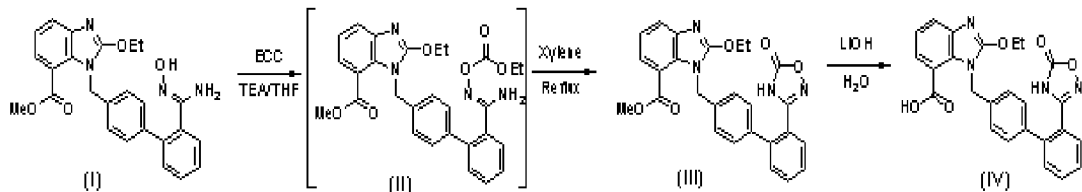


- [5] Angiotensin II causes vasoconstriction, promotes secretion of aldosterone leading to sodium and water content retention, which in turn causes an increase in body fluid, thus raising blood pressure. Vasoconstriction described above is fatal to patients suffering from hypertension.
- [6] Azilsartan 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]

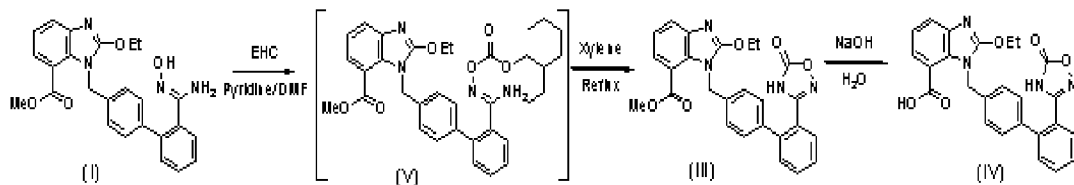
[10]



[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]

[13]



[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 generally involves a low yield of 23%, hence causing a decrease in yield of azilsartan.

Disclosure of Invention

Technical Problem

[15] Therefore, compared to typically stepwise processes known in the related art, an object of the present invention is to provide a method of manufacturing azilsartan capable of continuously proceeding cyclization and hydrolysis (one-pot reaction) in a

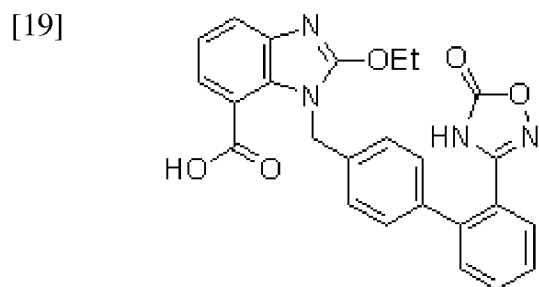
single reactor by treating a compound containing an amino-alcohol derivative with N,N'-carbonyldiimidazole, an inorganic base and a solvent.

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

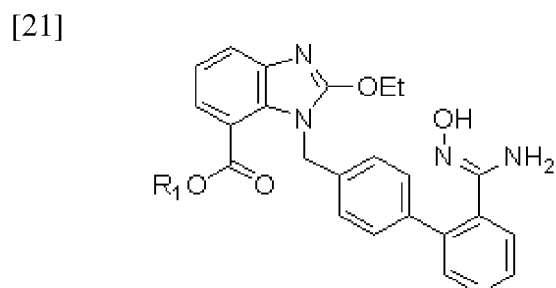
Solution to Problem

[17] In order to achieve the above purposes, there is provided a method of manufacturing azilsartan represented by the following Formula 1, which includes reacting a compound represented by the following Formula 2 with N,N'-carbonyldiimidazole, an inorganic base and a solvent.

[18] [Formula 1]



[20] [Formula 2]



[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).

[23] In particular, N,N'-carbonyldiimidazole and the inorganic base are sequentially added to the compound represented by Formula 2 or, otherwise, both N,N'-carbonyldiimidazole and the inorganic base are simultaneously added thereto, thus conducting a reaction.

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

[25] The solvent may be at least one selected from a group consisting of tetrahydrofuran, 1,4-dioxane and water.

[26] N,N'-carbonyldiimidazole described above is used in an amount of 1 to 5 equivalents to 1 equivalent of the compound represented by Formula 2, while the inorganic base is used in an amount of 1 to 10 equivalents to 1 equivalent of the compound represented

by Formula 2.

[27] Also, N,N'-carbonyldiimidazole is used in an amount of 0.1 to 5 equivalents to 1 equivalent of the inorganic base.

[28] In this regards, a reaction temperature may be more than 0 to 110°C.

Advantageous Effects of Invention

[29] The present invention adopts a one-pot reaction starting from a compound containing an amino-alcohol derivative wherein cyclization and hydrolysis are continuously carried out, 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.

[30] 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.

[31] 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

[32] The present invention describes a method of manufacturing azilsartan represented by Formula 1, which includes conducting cyclization and hydrolysis in a single vessel treating a compound containing an amino-alcohol derivative with N,N'-carbonyldiimidazole, an inorganic base and a solvent, 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, reduction in processing time, and production of a final compound with high yield (60 to 80%) and high purity (not less than 98%) without additional purification.

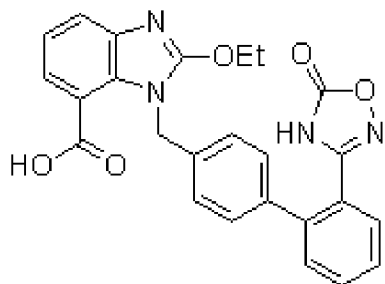
[33] Hereinafter, the present invention will be described in detail.

[34] According to the present invention, azilsartan 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 amino-alcohol derivative represented by Formula 2 with N,N'-carbonyldiimidazole, an inorganic base and a solvent.

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

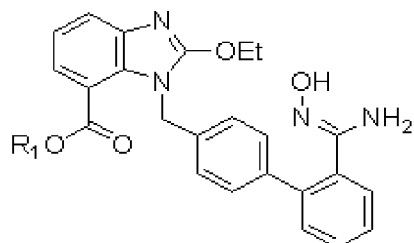
[36] [Formula 1]

[37]



[38] [Formula 2]

[39]



[40] (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).

[41] N,N' -carbonyldiimidazole is used to conduct cyclization may be used in an amount of 1 to 5 equivalents, and preferably, 1.1 to 1.2 equivalents to 1 equivalent of the compound represented by Formula 2. If the amount of N,N' -carbonyldiimidazole 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 5 equivalents, impurities tend to increase with time.

[42] The inorganic base is used to conduct hydrolysis, and in particular, may include hydroxyl salts of alkali metals, for example, at least one or two or more selected from a group consisting of sodium hydroxide, lithium hydroxide and potassium hydroxide. More preferably, sodium hydroxide is used.

[43] 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.

[44] Alternatively, N,N' -carbonyldiimidazole may be used in an amount of 0.1 to 5 equivalents, and preferably, 0.2 to 1 equivalent to 1 equivalent of the inorganic base. If the amount of N,N' -carbonyldiimidazole is less than 0.1 equivalent to 1 equivalent of the inorganic base, yield may be decreased. On the other hand, when the amount is more than 5 equivalents, impurities tend to increase with time.

[45] The solvent may be at least one or two or more selected from a group consisting of tetrahydrofuran, 1,4-dioxane and water. Particularly, N,N' -carbonyldiimidazole may be

used together with tetrahydrofuran or 1,4-dioxane as the solvent, while the inorganic base may be used with water as the solvent. However, the use of inorganic base is not particularly limited to the foregoing, instead, the inorganic solvent may also be used alone without using any solvent.

- [46] The compound represented by Formula 1 may be prepared by adding N,N'-carbonyldiimidazole, an inorganic base and a solvent to the compound represented by Formula 2 then agitating the mixture at a temperature of more than 0 to 110°C, and preferably, 20 to 100°C, for 2 to 5 hours. If a reaction temperature is less than 0°C, cyclization and hydrolysis may not occur. On the other hand, when the reaction temperature exceeds 110°C, impurities may be increased.
- [47] For instance, a method of manufacturing the compound represented by Formula 1 may include adding N,N'-carbonyldiimidazole and 1,4-dioxane (or tetrahydrofuran) to the compound represented by Formula 2 and agitating the mixture at 20 to 110°C for 1 to 3 hours to perform cyclization, and then, adding an aqueous solution of the inorganic base thereto and agitating the mixture at a temperature of more than 0 to 100°C for 2 to 3 hours to perform hydrolysis.
- [48] For instance, another method of manufacturing the compound represented by Formula 1 may include adding N,N'-carbonyldiimidazole, 1,4-dioxane (or tetrahydrofuran) and an aqueous solution of the inorganic base to the compound represented by Formula 2 and agitating the mixture at a temperature of more than 0 to 110°C for 1 to 3 hours to perform continuous cyclization and hydrolysis.
- [49] After completing cyclization and hydrolysis starting from the compound represented by Formula 2 to the compound represented by Formula 1, the reaction mixture may be controlled by using acid to reach a pH value of 2 to 3, and then, be subjected to separation of the compound represented by Formula 1. If necessary, such separation may be conducted using a water-immiscible solvent, in particular, ethyl acetate.
- [50] 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 represented by Formula 1 may be produced with high yield (60 to 80%) and high purity (not less than 98%).
- [51] Hereinafter, preferred embodiments of the present invention will be described in detail to more concretely understand the present invention with reference to examples and comparative 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.
- [52]
- [53] **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-car**

boxylic acid

[54] After introducing 5.0g of methyl 2-ethoxy-1-[[2'-hydroxycarbonylmimidoyl]biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate into a vessel, 100 ml of 1,4-dioxane was added and dissolved therein and 2.2g of N,N'-carbonyldiimidazole was also added thereto. Then, the mixture was refluxed at 80°C for 2 hours and the reaction mixture was cooled to 50°C and 50 ml of a 1M sodium hydroxide solution was added and stirred at 50°C for 3 hours. The reaction mixture including the 1M sodium hydroxide solution was further cooled to 25°C and provided with 100 ml of water as well as 200 ml of ethyl acetate. Thereafter, the reaction mixture was cooled again to 5°C and controlled to reach pH of 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 3.76g of a purposed compound (yield: 75.0%).

[55] 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).

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

[57] **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**

[58] After introducing 1.0g of methyl 2-ethoxy-1-[[2'-hydroxycarbonylmimidoyl]biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate into a vessel, 20 ml of 1,4-dioxane was added and dissolved therein and 0.44g of N,N'-carbonyldiimidazole and 10 ml of a 1M sodium hydroxide solution were also added thereto, followed by refluxing the same at 80°C for 1 hour. The reaction mixture was cooled to 25°C and 10 ml of water as well as 40 ml of ethyl acetate were added thereto. Thereafter, the reaction mixture 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 10 ml of water, the organic layer was concentrated under reduced pressure at 40°C, followed by crystallization, thereby yielding 0.55g of a purposed compound (yield: 60.2%).

[59] 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).

[60] Measurement of purity (HPLC): 98.64%

[61]

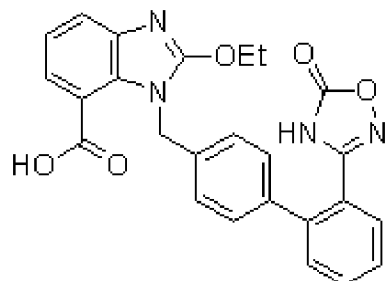
[62] **Comparative Example 1: Preparation of methyl 2-ethoxy-1-[[2'-(2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate**

- [63] To a suspension prepared by agitating 30 ml of tetrahydrofuran (THF), 0.2g of triethylamine 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 mixture and, after removing an insoluble material by filtration, the remaining filtrate was concentrated to dryness. 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 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%).
- [64] **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**
- [65] 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%).
- [66] Measurement of purity (HPLC): 91.0%.
- [67] 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.

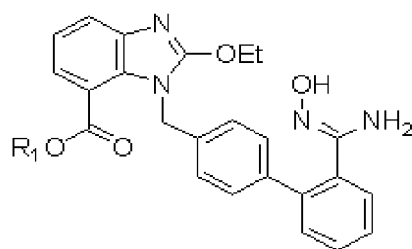
Claims

[Claim 1] A method of manufacturing azilsartan represented by the following Formula 1, comprising reacting a compound represented by the following Formula 2 with N,N'-carbonyldiimidazole, an inorganic base and a solvent:

[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).

[Claim 2] The method according to claim 1, wherein the reaction is executed by sequentially adding N,N'-carbonyldiimidazole and the inorganic base to the compound represented by Formula 2.

[Claim 3] The method according to claim 1, wherein the reaction is executed by simultaneously adding N,N'-carbonyldiimidazole and the inorganic base to the compound represented by Formula 2.

[Claim 4] The method according to any one of claims 1 to 3, wherein the inorganic base is a hydroxyl salt of an alkali metal.

[Claim 5] The method according to claim 4, wherein the hydroxyl salt of the alkali metal is at least one selected from a group consisting of sodium hydroxide, lithium hydroxide and potassium hydroxide.

[Claim 6] The method according to claim 1, wherein the solvent is at least one selected from a group consisting of tetrahydrofuran, 1,4-dioxane and water.

[Claim 7] The method according to any one of claims 1 to 3, wherein the

N,N'-carbonyldiimidazole is used in an amount of 1 to 5 equivalents to 1 equivalent of the compound represented by Formula 2.

[Claim 8] The method according to any one of claims 1 to 3, 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 9] The method according to any one of claims 1 to 3, wherein the N,N'-carbonyldiimidazole is used in an amount of 0.1 to 5 equivalents to 1 equivalent of the inorganic base.

[Claim 10] The method according to claim 1, wherein a reaction temperature is more than 0 to 110°C.