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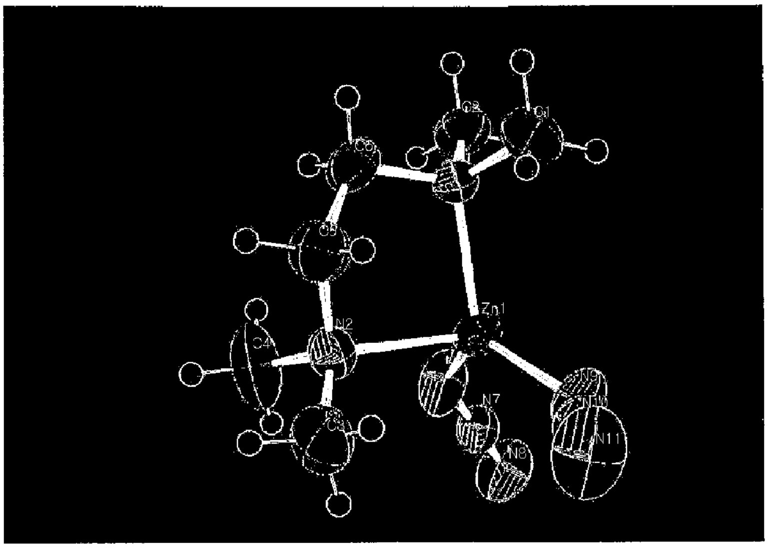
(54) **Title**: NOVEL ZINC AZIDE COMPLEX AND A PROCESS FOR PREPARING TETRAZOLE DERIVATIVES USING THE SAME

[Fig. 1]



(57) **Abstract**: The present invention relates to a novel zinc azide complex. The present invention also relates to a process for preparing 5-substituted-1H-tetrazole derivatives from nitrile derivatives by using the zinc azide complex. According to the present invention, in particular, pharmaceutically active compounds for treating hypertension or intermediates useful for preparation thereof can be prepared effectively.

WO 2012/148148 A2

Description

Title of Invention: NOVEL ZINC AZIDE COMPLEX AND A PROCESS FOR PREPARING TETRAZOLE DERIVATIVES USING THE SAME

Technical Field

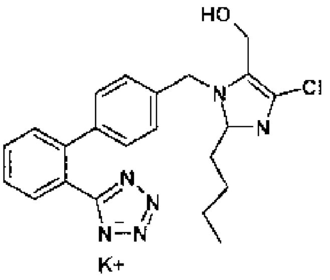
[1] The present invention relates to a novel zinc azide complex. The present invention also relates to a process for preparing 5-substituted-1H-tetrazole derivatives from nitrile derivatives by using the zinc azide complex. According to the present invention, in particular, pharmaceutically active compounds for treating hypertension or intermediates useful for preparation thereof can be prepared effectively.

[2]

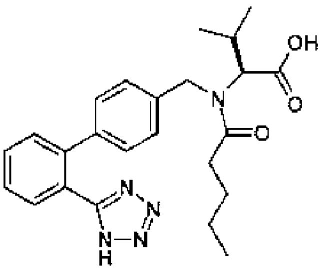
Background Art

[3] In general, tetrazole groups are often used as metabolism-resistant isosteric replacement for carboxylic acids in a living body. Thus, they act as an essential component in agents for treating various important diseases. In particular, the compounds such as Losartan-potassium, Valsartan, Candesartan cilexetil, Irbesartan, Olmesartan medoxomil and Fimasartan of the following chemical formulas, which are widely known as angiotensin II receptor blockers (ARBs) and so used for treating hypertension and congestive heart failure, have in common a tetrazole group.

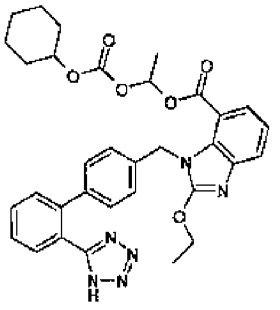
[4]



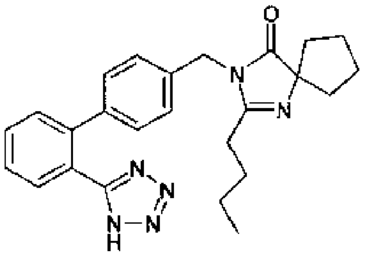
Losartan-potassium



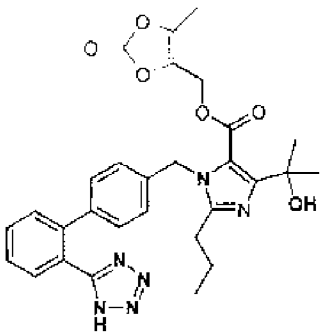
Valsartan



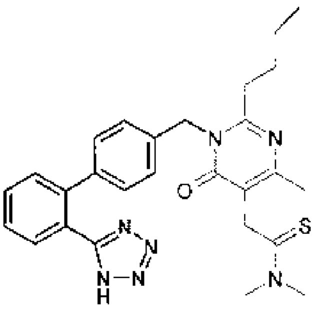
Candesartan cilexetil



Irbesartan



Olmesartan medoxomil



Fimasartan

[5] For the above ARB series compounds, many known patents and articles have already reported their preparation processes using various synthesis routes. Among them, processes for preparing tetrazole compounds from nitrile compounds are disclosed in the following:

[6] As for Losartan-potassium, US Patent No. 5,138,069 and International Publication Nos. WO 2007/020654 and WO 2007/026375. As for Valsartan, US Patent Nos. 5,965,592 and 5,399,579, and International Publication No. WO 2007/014412. As for Candesartan cilexetil, US Patent No. 5,705,517, European Patent No. 459,136, and International Publication Nos. WO 2006/015134, WO 2007/094015 and WO 2007/054965. As for Irbesartan, US Patent Nos. 5,270,317, 5,629,331 and 7,211,676, US Patent Publication No. 20090286990 and International Publication No. WO 2007/013101. As for Olmesartan medoxomil, European Patent No. 503,785.

[7] As a classical process for synthesizing a tetrazole compound from a nitrile compound, there is a known method in which the nitrile compound is reacted with sodium azide in the presence of ammonium chloride in N,N-dimethylformamide solvent at a reaction temperature of 120°C (W.G. Finnegan et al., *J. Am. Chem. Soc.*, 1958, 80, 3908). However, when the nitrile compound is sterically hindered, this method has problems of very low yield and purity, and risk of explosion due to the

sublimating ammonium azide generated during the reaction, and thus is difficult to employ in large-scale production facilities.

[8] It has been also known that a method of using trimethyltin azide or tributyltin azide can prepare tetrazole compounds with a relatively good yield (J.V. Duncia et al., *J. Org. Chem.*, 1991, 56, 2395). However, in the case of using trialkyltin azide compounds, because of their toxicity special care is required during the production process, environmental problems may be caused, and the production cost increases due to the requirement of further steps for recovering the tin compound from the waste.

[9] Recently, International Publication No. WO 2005/014602 and Korean Laid-open Patent Publication No. 2006/0038994 reported that as an alternative of the aforesaid trialkyltin azide compounds, organic boron azide or organic aluminum azide can be used for preparing tetrazole compounds with high yield and low production cost, providing the advantage of an environment-friendly process with no toxicity. However, the handling of organic boron azide and organic aluminum azide requires special care such as perfectly anhydrous condition, and inert atmosphere like nitrogen or argon environment. Furthermore, Example 12 of Korean Laid-open Patent Publication No. 2006/0038994 shows that the preparation of Valsartan using diisobutyl-Al-azide resulted in a low conversion rate of about 77% and the remaining about 23% of the starting material, although the Al-azide was added two times (1.4 equivalents for the first and 0.8 equivalent for the second) and the reaction was conducted at high temperature (110~130°C).

[10] In addition, a method of using a zinc salt (Zn salt) (for example, zinc chloride ($ZnCl_2$) or zinc bromide ($ZnBr_2$)) and sodium azide is known as a safe and effective method for preparing tetrazole derivatives (B.M. Sharpless et al., *J. Org. Chem.*, 2001, 66, 7945), and such methods are disclosed in International Publication No. WO 1996/037481, US Patent No. 5,502,191, etc. However, sterically hindered nitriles such as biphenyl nitriles like Valsartan require a long reaction time at high temperature and excessive zinc salt and sodium azide in order to complete the reaction. Accordingly, the method of using zinc salt and sodium azide is insufficient to resolve the aforesaid problems.

[11]

Disclosure of Invention

Technical Problem

[12] The present inventors have conducted intensive research to develop a process which can remarkably improve the aforesaid problems that conventional processes have in preparing ARB series compounds. The aforesaid problems are long reaction time, use of highly toxic tin metal, use of excessive azide salt, low reaction conversion rate and

yield, risk of explosion due to sublimating byproduct, etc. This invention has come from our efforts to develop a process that is economical, environment-friendly and suitable for large-scale commercial production by overcoming the aforesaid problems.

[13]

Solution to Problem

[14] The present invention relates to a novel zinc azide complex of the following formula 3:

[15] [Formula 3]

[16] $L_aZn(N_3)_bX_c$

[17] wherein

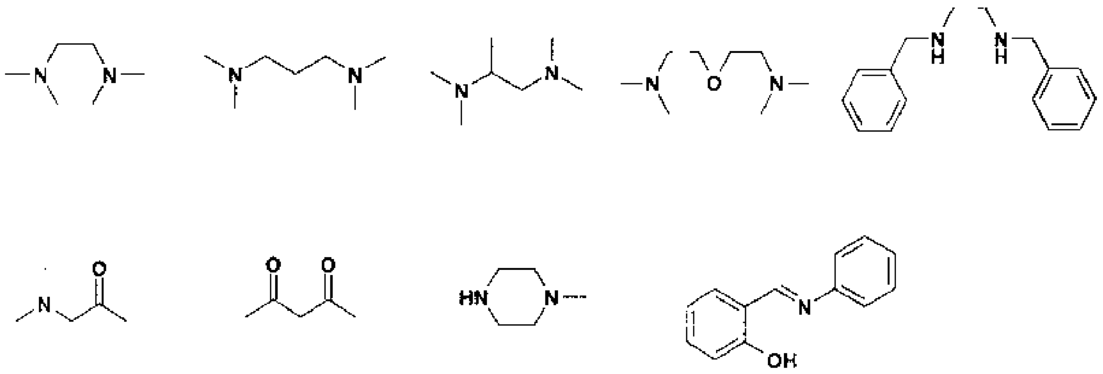
[18] X represents NO_3, OH, Cl, Br, I or a combination thereof,

[19] L represents an amine ligand that can coordinate with Zn, and

[20] a, b and c satisfy $0<a<2$, $0<b<4$ and $0\leq c<2$, respectively.

[21] Preferably, L represents a bidentate ligand selected from the following group:

[22]



[23] Among the above, N,N,N',N'-tetramethylethylenediamine (TMEDA) is most preferred.

[24] For preparing the novel zinc azide complex of formula 3, a zinc compound (for example, zinc nitrate hexahydrate, zinc chloride, zinc bromide or zinc iodide) is dissolved in water and added into a reactor together with an alkali metal azide (for example, lithium azide, sodium azide or potassium azide), and the reaction mixture is heated to 45~60℃ with stirring. An amine ligand (for example, N,N,N',N'-tetramethylethylenediamine (TMEDA)) is slowly added thereto dropwise. The generated solid is filtered, washed with water and dried under nitrogen or vacuum to obtain the desired zinc azide complex.

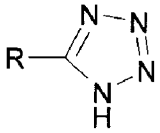
[25] The zinc azide complex obtained as such is in a mixture form and is represented by formula 3. It can also be used after purification. However, there is no significant difference in the results from a use of mixture form complex and that of purified form. The structure of the zinc azide complex obtained after purification is represented in Figure 1.

[26] For detail reaction conditions, an article (J. Rollin et al. *Synthesis*, 1990, 130-132) may be referred to, and molar ratio of the zinc compound, sodium azide and amine ligand depends on the target complex structure.

[27] $Zn(TMEDA)(N_3)_2$, which is a zinc azide complex of formula 3 wherein a is 1, b is 2, c is 0, and L is N,N,N',N'-tetramethylethylenediamine (TMEDA), may be referred to as the representative zinc azide complex according to the present invention. In addition, [$Zn(NO_3)_2 \cdot 6H_2O$, NaN_3 and TMEDA] mixture or [$ZnCl_2$, NaN_3 and TMEDA] mixture may be referred to as the corresponding mixture.

[28] The present invention also relates to a process for preparing a substituted tetrazole derivative of formula 1. This process comprises reacting the zinc azide complex of formula 3, which is prepared by the complex formation reaction, with a nitrile compound of formula 2 after isolation or *in situ*.

[29] [Formula 1]

[30] 

[31] [Formula 2]

[32] R—CN

[33] [Formula 3]

[34] $L_aZn(N_3)_bX_c$

[35] wherein

[36] R represents an organic residual group, and

[37] X, L, a, b and c are the same as defined above.

[38] Preferably,

[39] 1) R represents linear or branched C_1-C_6-alkyl or C_3-C_6-cycloalkyl, each of which is optionally substituted with one or more (preferably, 1 to 4) substituents selected from:

[40] halogen;

[41] hydroxy;

[42] C_1-C_6-alkyl;

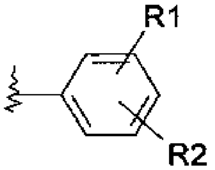
[43] C_1-C_6-alkoxy; and

[44] phenyl, pyridine, pyrimidine, imidazole, thiophene and furan, each of which is optionally substituted with one or more (preferably, 1 to 4) substituents selected from the group consisting of C_1-C_6-alkyl, halogen, hydroxy, nitro and C_1-C_6-alkoxy,

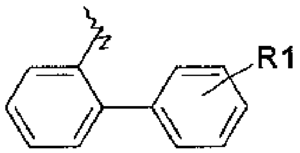
[45] or

[46] 2) R represents phenyl or biphenyl of the following formula:

[47]



or



[48] wherein

[49] each of R1 and R2 is independently selected from the group consisting of

[50] hydrogen;

[51] halogen;

[52] hydroxy;

[53] nitro;

[54] C_1-C_6-alkyl (for example, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, hexyl);

[55] C_3-C_6-cycloalkyl (for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl);

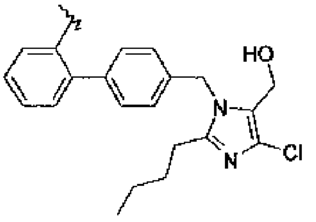
[56] C_1-C_6-alkoxy;

[57] phenylmethyl, pyridylmethyl, pyrimidylmethyl, imidazolylmethyl, benzimidazolylmethyl, thiophenylmethyl and furanylmethyl, each of which is optionally substituted with one to four substituents selected from the group consisting of halogen, carboxy, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxy-C_1-C_6-alkyl, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkoxycarbonyl-C_1-C_6-alkyl, C_3-C_6-alkanediyl, di(C_1-C_6 -alkyl)aminothiocarbonyl-C_1-C_6-alkyl, cilexetiloxycarbonyl and medoxomiloxycarbonyl; and

[58] amino or amino-C_1-C_6-alkyl, each of which is optionally substituted with one or two substituents selected from the group consisting of C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_1-C_6 -alkylcarbonyl, carboxy-C_1-C_6-alkyl and C_1-C_6-alkoxycarbonyl-C_1-C_6-alkyl (for example, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, diisopropylamino, cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino).

[59] In the compounds of formula 1 prepared according to the present invention, some concrete structures of the substituent R are as follows:

[60]



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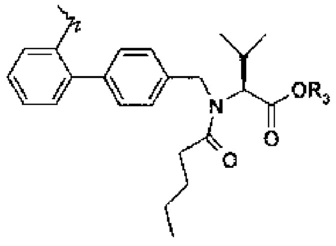
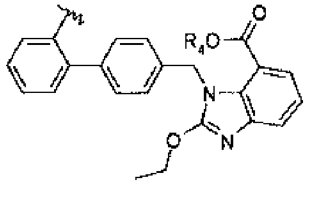
a

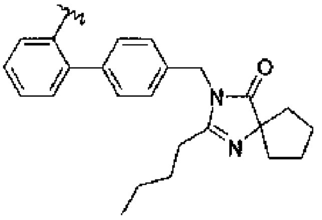


,

b



c



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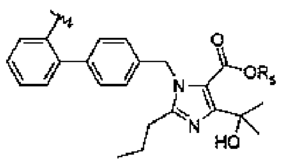
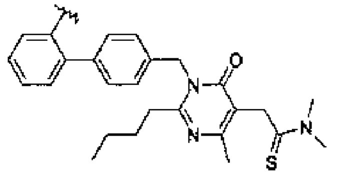
d



,

e



f

[61] In structure b, R_3 represents hydrogen or methyl.

[62] In structure c, R_4 represents hydrogen, methyl, ethyl or cilexetil.

[63] In structure e, R_5 represents hydrogen, methyl, ethyl or medoxomil.

[64] In preparing the tetrazole derivative of formula 1, it is possible to use a compound that is obtained through forming the zinc azide complex of formula 3 and then isolating it by filtering and drying. Alternatively, the starting material of formula 2 may be added to and react *in situ* with the zinc azide complex that is obtained by the zinc azide complex formation reaction without the filtering and drying steps. Preferably, the zinc azide complex is isolated and then used.

[65] The reaction for preparing the formula 1 compound according to the present invention uses a single or mixture solvent selected from the group consisting of toluene; xylene; ethylbenzene; halogenated aromatic solvents such as chlorobenzene, o-, m- or p-chlorotoluene, dichlorobenzene, trifluoromethylbenzene; aprotic polar solvents such as dimethylformamide, dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide; protic polar solvents such as ethanol, propanol, isopropanol, butanol, t-butanol, pentanol, cyclopropanol, cyclobutanol, cyclopentanol, cyclohexanol; and mixtures thereof.

[66] The reaction is preferably conducted at a temperature of 90~130°C since it is advantageous in achieving a higher conversion rate in a given time. The temperature of 100~120°C is more preferred. The reaction time is preferably 10~30 hours and more preferably 15~24 hours, and may vary according to the starting material.

[67] When the starting material comprises a reactive substituent or a substituent capable of reacting with azide, the process of the present invention may further comprise the

steps of: protecting the reactive substituent, forming a tetrazole ring, and then removing the corresponding protecting group, by using conventionally known methods for protecting and deprotecting a functional group.

[68]

Advantageous Effects of Invention

[69] According to the present invention, in particular, pharmaceutically active compounds for treating hypertension or intermediates useful for preparation thereof can be prepared effectively and economically in an environment-friendly manner.

[70]

Brief Description of Drawings

[71] Figure 1 represents the X-ray structure of pure $Zn(N_3)_2TMEDA$ which was obtained by purifying the zinc azide complex prepared according to Example 1.

[72]

Mode for the Invention

[73] The present invention is explained in more detail by the following Examples and Comparative Examples. However, these Examples seek to facilitate the understanding of the present invention only, and the scope of the present invention is not limited by the Examples in any manner.

[74]

[75] **Example 1-1: Preparation of zinc azide complex**

[76] 6.25kg of zinc nitrate hexahydrate and 4.0L of water were added into a reactor and stirred at room temperature for complete dissolution. A solution of 2.73kg of sodium azide completely dissolved in 7.5L of water was added into the reactor. After the reaction temperature was elevated to 45~50℃, 2.5kg of N,N,N’,N’-tetramethylethylenediamine was slowly added thereto dropwise over 1 hour, and the mixture was stirred for 3 hours at the same temperature. After the reaction mixture was cooled to room temperature, the generated solid was filtered, washed with water (11.0L) and dried under nitrogen to obtain the title compound.

[77] ^1H NMR (δ ppm, DMSO-d_6, 300MHz), 2.3 (s, 6H), 2.5 (s, 4H)

[78] ^{13}C NMR (δ ppm, DMSO-d_6, 75MHz), 47, 57

[79] Elemental Analysis: C 22.8%, H 5.3%, N 40.2%

[80] Zn^{2+}-EDTA titration: 31% wt/wt

[81] TMEDA ^1H-NMR titration: 33% (External standard material: sodium acetate)

[82] Water content: 5%

[83] Infrared spectrum: 2981, 2915, 2856, 2064(N3 stretching), 1464, 947 cm^{-1}

[84]

[85] **Example 1-2: Preparation of zinc azide complex**

[86] 2.86kg of zinc chloride and 4.0L of water were added into a reactor and stirred at room temperature for complete dissolution. A solution of 2.73kg of sodium azide completely dissolved in 7.5L of water was added into the reactor. After the reaction temperature was elevated to 45~50°C, 2.5kg of N,N,N',N'-tetramethylethylenediamine was slowly added thereto dropwise over 1 hour, and the mixture was stirred for 3 hours at the same temperature. After the reaction mixture was cooled to room temperature, the generated solid was filtered, washed with water (11.0L) and dried under nitrogen to obtain the title compound.

[87]

[88] Comparative Example 1: Preparation of 5-(4'-methyl[1,1'-biphenyl]-2-yl)-1H-tetrazole

[89] Comparative Example 1-1: Method using the isolated zinc azide complex of the present invention

[90] 2-(p-tolyl)benzonitrile (2.1g) and toluene (5.0ml) were added into a reaction vessel, and the solid compound (4.3g) obtained in Example 1-1 was added thereto while stirring the mixture. The reaction mixture was heated and refluxed, and after 24 hours the reaction conversion rate of 99.2% was confirmed with HPLC. The reaction mixture was cooled to room temperature and phase-separated by using 1N-HCl and ethyl acetate. The obtained organic layer was concentrated and made into slurry with n-hexane to obtain the pure, white crystalline title compound (purity: 98.6%, yield: 84%).

[91] HPLC: Agilent 1100 series, solvent: TFA 0.1%, acetonitrile(30→100)/water(70→0), flow rate:1.5ml/min., wavelength:225nm, column: CAPCELL PAK C_{18} (4.6mm I.D × 250 mm, 5 ㎛, TYPE AQ)

[92]

[93] Comparative Example 1-2: Method using $(CH_3)_3SnN_3$

[94] 2-(p-tolyl)benzonitrile (2.1g) and toluene (5.0ml) were added into a reaction vessel, and $(CH_3)_3SnN_3$ (3.3g) was added thereto while stirring the mixture. The reaction mixture was heated and refluxed, and after 24 hours the reaction conversion rate of 79.8% was confirmed with HPLC.

[95]

[96] Comparative Example 1-3: Method using $(CH_3CH_2)_2AlN_3$

[97] Into a dried reaction vessel, toluene (5.0ml) and sodium azide (1.0g) were added, and the mixture was cooled to 0°C. Diethylaluminum chloride 1.0 M solution (14.8ml) was slowly added thereto dropwise. The reaction mixture was stirred at room temperature for 12 hours or more. Then, 2-(p-tolyl)benzonitrile (2.1g) and toluene (5.0ml) were added into the reaction vessel, the mixture was heated and refluxed, and after 24 hours the reaction conversion rate of 86.1% was confirmed with HPLC.

[98]

[99] **Example 2: Preparation of 2-butyl-4-chloro-5-hydroxymethyl-1-[(2'-(1H-tetrazol-5-yl)-biphenyl-4-yl)-methyl]-imidazole (Losartan) (Method 1)**

[100] 2-butyl-4-chloro-5-hydroxymethyl-1-[(2'-cyano-biphenyl-4-yl)-methyl]-imidazole (379.9g) and n-butanol (1.5L) were added into a reactor, and the solid compound (370.7g) obtained in Example 1-1 was added thereto while stirring the mixture. The reaction mixture was stirred for 24 hours while maintaining the internal temperature of the reaction mixture at 100~120℃. The temperature inside the reactor was cooled to room temperature, and 28% ammonia water (1.0L) and water (1.0L) were added thereto dropwise for phase separation. To the obtained organic layer, water (1.7L) and sodium hydroxide (240.0g) were added, and the mixture was stirred at room temperature for 2 hours, and then phase preparation was conducted again. To the obtained organic layer, water (1.5L), sodium hydroxide (64.0g) and sodium chloride (400g) were added, and phase preparation was conducted again. Finally, water (1.8L) was added to the organic layer, and with stirring the pH of the mixture was adjusted to 3~4 by using sulfuric acid, and then the mixture was stirred for 15~17 hours. The generated solid was filtered, washed with n-butanol (0.9L) and dried under nitrogen to obtain the title compound (361.2g, yield: 85.4%).

[101] ^{1}H NMR (δ ppm, DMSO-d_6), 0.79 (t, 3H), 1.22 (m, 2H), 1.44 (m, 2H), 2.49 (t, 2H), 4.32 (s, 2H), 5.23 (s, 2H), 7.03 (d, 2H), 7.08 (d, 2H), 7.52 (d, 1H), 7.57 (t, 1H), 7.66 (m, 2H)

[102]

[103] **Example 3: Preparation of 2-butyl-4-chloro-5-hydroxymethyl-1-[(2'-(1H-tetrazol-5-yl)-biphenyl-4-yl)-methyl]-imidazole (Losartan) (Method 2)**

[104] n-butanol (1.5L) was added into a reactor, and with stirring sodium azide (189.0g) and zinc chloride (200.1g) were added thereto. N,N,N',N'-tetramethylethylenediamine (168.5g) was slowly added thereto dropwise. The reaction mixture was stirred at 100~120℃ for 3 hours or more and cooled to room temperature. Then, 2-butyl-4-chloro-5-hydroxymethyl-1-[(2'-cyano-biphenyl-4-yl)-methyl]-imidazole (379.8g) was added thereto, and the mixture was heated again. The reaction was conducted for 24 hours while maintaining the internal temperature as 100~120℃. The internal temperature was cooled to room temperature, and 28% ammonia water (1.0L) and water (1.0L) were added thereto dropwise for phase separation. To the obtained organic layer, water (1.7L) and sodium hydroxide (240.0g) were added, and the mixture was stirred at room temperature for 2 hours, and then phase preparation was conducted again. To the obtained organic layer, water (1.5L), sodium hydroxide

(64.0g) and sodium chloride (400g) were added, and phase preparation was conducted again. Finally, water (1.8L) was added to the organic layer, and with stirring the pH of the mixture was adjusted to 3~4 by using sulfuric acid, and then the mixture was stirred for 15~17 hours. The generated solid was filtered, washed with n-butanol (0.9L) and dried under nitrogen to obtain the title compound (351.0g, yield: 83.0%).

[105]

[106] **Example 4: Preparation of 2-butyl-4-chloro-5-hydroxymethyl-1-[(2'-(1H-tetrazol-5-yl)-biphenyl-4-yl)-methyl]-imidazole (Losartan) (Method 3)**

[107] n-butanol (1.5L) was added into a reactor, and with stirring sodium azide (189.0g) and zinc nitrate hexahydrate (445.3g) were added thereto. N,N,N',N'-tetramethylethylenediamine (168.5g) was slowly added thereto dropwise. The reaction mixture was stirred at 100~120℃ for 3 hours or more and cooled to room temperature. Then, 2-butyl-4-chloro-5-hydroxymethyl-1-[(2'-cyano-biphenyl-4-yl)-methyl]-imidazole (379.8g) was added thereto, and the mixture was heated again. The reaction was conducted for 24 hours while maintaining the internal temperature at 100~120℃. The internal temperature was cooled to room temperature, and 28% ammonia water (1.0L) and water (1.0L) were added thereto dropwise for phase separation. To the obtained organic layer, water (1.7L) and sodium hydroxide (240.0g) were added, the mixture was stirred at room temperature for 2 hours, and then phase preparation was conducted again. To the obtained organic layer, water (1.5L), sodium hydroxide (64.0g) and sodium chloride (400g) were added, and phase preparation was conducted again. Finally, water (1.8L) was added to the organic layer, and with stirring the pH of the mixture was adjusted to 3~4 by using sulfuric acid, and then the mixture was stirred for 15~17 hours. The generated solid was filtered, washed with n-butanol (0.9L) and dried under nitrogen to obtain the title compound (355.2g, yield: 84.0%).

[108]

[109] **Example 5: Preparation of 2-butyl-4-chloro-5-hydroxymethyl-1-[(2'-(1H-tetrazol-5-yl)-biphenyl-4-yl)-methyl]-imidazole potassium salt (Losartan potassium)**

[110] 2-butyl-4-chloro-5-hydroxymethyl-1-[(2'-(1H-tetrazol-5-yl)-biphenyl-4-yl)-methyl]-imidazole (122.6g) prepared according to the method of Example 2 was suspended in isopropanol (580mL). A solution of potassium hydroxide (19.2g) dissolved in isopropanol (580mL) was slowly added thereto dropwise. After the mixture was dissolved completely, the temperature was elevated to simply distill 60~70% of the used isopropanol. After distillation was completed, the temperature was cooled to 40~50℃ and cyclohexane (580mL) was slowly added thereto dropwise over about 1 hour. After the

dropwise addition, the mixture was slowly cooled to room temperature and then stirred for 2 hours, and the generated solid was filtered and washed twice with a mixture liquid of isopropanol and cyclohexane, and dried under nitrogen to obtain the title compound (125.4g, yield: 93.7%).

[111] ^{1}H NMR (δ ppm, DMSO-d_6), 0.80 (t, 3H), 1.24 (m, 2H), 1.48 (m, 2H), 2.49 (t, 2H), 4.31 (d, 2H), 5.20 (s, 2H), 6.90 (d, 2H), 7.10 (d, 2H), 7.28 (d, 1H), 7.35 (m, 2H), 7.53 (d, 1H)

[112]

[113] **Example 6: Preparation of N-pentanoyl-N-[(2'-cyanobiphenyl-4-yl)methyl]-(L)-valine methyl ester**

[114] Potassium carbonate (37.5g) was added and completely dissolved in water (90mL), and then N-[(2'-cyanobiphenyl-4-yl)methyl]-(L)-valine methyl ester (35.9g) and toluene (900mL) were added thereto and stirred at room temperature for complete dissolution. After the reactants were dissolved, valeryl chloride (18.0g) was slowly added to the reactor. After the reaction was completed, water (900mL) was further added for phase separation. The obtained organic layer was washed with water (900mL) to obtain the title compound (purity: 98.0%). The organic layer was directly used in the next reaction without any separate purification procedure.

[115] ^{1}H NMR (400MHz, $CDCl_3$): δ 7.81-7.77 (1H, m), 7.70-7.64 (1H, m), 7.58-7.46 (4H, m), 7.35-7.30 (2H, m), 5.13 and 4.3 (2 d, J = 15.6, 1H), 5.02-5.00 (d, J = 10.4, 1H), 4.77-4.73 (1H, m), 3.49 (1H, s), 3.41 (1H, s), 2.69-2.65 and 2.41-2.31 (2H, m), 1.79-1.66 and 1.48-1.31 (6H, m), 1.04-0.97 (4H, m), 0.95-0.88 (5H, m)

[116]

[117] **Example 7: Preparation of N-pentanoyl-N-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-(L)-valine (Valsartan) (Method 1)**

[118] The solid compound (35.0g) obtained in Example 1-1 was added to the toluene solution of N-pentanoyl-N-[(2'-cyanobiphenyl-4-yl)methyl]-(L)-valine methyl ester obtained in Example 6, and the mixture was heated and refluxed for 24 hours or more. The reaction mixture was cooled to 45~55°C, and water (50mL) and 28% ammonia water (50mL) were added thereto for phase separation. The organic layer was washed with 5% brine solution (100mL), and water (50mL) and sulfuric acid (14.8g) were added thereto and stirred at room temperature for 2 hours or more. The mixture was phase-separated and washed with water (50mL), and then water (50mL) and sodium hydroxide (10.0g) were added thereto, and the mixture was stirred at room temperature for 12 hours or more. After the hydrolysis reaction was completed, stirring was stopped and phase separation was conducted, and then dichloromethane (100mL) was added to the aqueous layer obtained through phase separation. A solution of sulfuric

acid (24.5g) diluted in water (50mL) was added thereto at room temperature, and the mixture was stirred for 1 hour. An organic layer was obtained by phase separation and then washed twice with water (50mL). n-hexane (150mL) was slowly added thereto and the mixture was stirred at room temperature for 20 hours or more. The generated solid was filtered, washed with n-hexane (50mL) and dried to obtain the title compound (38.7g).

[119] ^{1}H NMR (DMSO-d_6), 0.62~0.95 (m, 9H), 1.05~1.65 (m, 4H), 1.95~2.3 (m, 2H), 2.35~2.55(m, 2H), 2.5(m, 1H), 4.37~4.68(m, 2H), 6.88~7.25 (m, 4H), 7.45~7.68 (m, 4H), 12.25~13.0(br, 1H)

[120]

[121] **Example 8: Preparation of N-pentanoyl-N-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-(L)-valine (Valsartan) (Method 2)**

[122] Sodium azide (20.2g) and zinc chloride (21.8g) were added to the toluene solution of N-pentanoyl-N-[(2'-cyanobiphenyl-4-yl)methyl]-(L)-valine methyl ester obtained in Example 6. The mixture was heated to 50~60°C and stirred for 1 hour, and then N,N,N',N'-tetramethylethylenediamine (18.6g) was slowly added thereto dropwise. The reactants were heated and refluxed for 24 hours or more, the internal temperature was then cooled to 45~55°C, and water (50mL) and 28% ammonia water (50mL) were added thereto for phase separation. The organic layer was washed with 5% brine solution (100mL), and water (100mL) and sulfuric acid (19.6g) were added thereto and stirred at room temperature for 2 hours or more. The mixture was phase-separated and washed with water (100mL), and then water (100mL) and sodium hydroxide (20.0g) were added thereto, and the mixture was stirred at room temperature for 12 hours or more for phase separation. After phase separation was conducted, dichloromethane (200mL) and a solution of sulfuric acid (29.4g) diluted in water (100mL) were added to the aqueous layer obtained through phase separation at room temperature, and the mixture was stirred for 1 hour. An organic layer was obtained by phase separation and then washed twice with water (100mL). n-hexane (300mL) was slowly added thereto at room temperature, and the mixture was stirred for 20 hours or more. The generated solid was filtered, washed with n-hexane (100mL) and dried to obtain the title compound (36.9g).

[123]

[124] **Example 9: Preparation of 2-butyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]spiro[2-imidazolin-4,1'-cyclopentan]-5-one (Irbesartan) (Method 1)**

[125] 2-butyl-3-[2'-{cyanobiphenyl-4-yl}methyl]-1,3-diazaspiro[4,4]non-1-en-4-one (5.0g) and toluene (15mL) were added into a reactor, and with stirring the solid compound

(5.1g) obtained in Example 1-1 was added thereto. The temperature inside the reactor was maintained at 100~120℃ and the reaction was conducted for 20 hours or more. After the reaction was completed, the internal temperature was cooled to 50~60℃, and 28% ammonia water (15mL) and water (15mL) were added thereto dropwise for phase separation. The obtained organic layer was washed with water (25mL), and stirred with maintaining pH 2~3 by using water (25mL) and 35% hydrochloric acid. The generated solid was filtered, washed with water (25mL) and dried under nitrogen to obtain the title compound (4.8g).

[126] ^{1}H NMR (DMSO-d_6), 0.78 (t, 3H), 1.17-1.30 (m, 2H), 1.40~1.50(m, 2H), 1.80~1.82 (m, 6H), 1.55 (m, 2H), 2.22~2.29 (t. 3H), 4.67 (s, 2H), 7.07 (s, 4H), 7.50~7.68 (m, 4H)

[127]

[128] **Example 10: Preparation of 2-butyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]spiro[2-imidazolin-4,1'-cyclopentan]-5-one (Irbesartan) (Method 2)**

[129] 2-butyl-3-[2'-{cyanobiphenyl-4-yl}methyl]-1,3-diazaspiro[4,4]non-1-en-4-one (5.0g) and toluene (15mL) were added into a reactor, and with stirring sodium azide (2.7g), zinc chloride (2.75g) and N,N,N',N'-tetramethylethylenediamine (2.3g) were added thereto. The temperature inside the reactor was maintained at 100~120℃, and the reaction was conducted for 24 hours or more. After the reaction was completed, the temperature inside the reactor was cooled to 50~60℃, and 28% ammonia water (15mL) and water (15mL) were added thereto dropwise for phase separation. The obtained organic layer was washed with water (25mL), and stirred with maintaining pH 2~3 by using water (25mL) and 35% hydrochloric acid. The generated solid was filtered, washed with water (25mL) and dried under nitrogen to obtain the title compound (4.6g).

[130]

[131] **Example 11: Preparation of 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]imidazol-5-carboxylic acid (Olmesartan)**

[132] 1-[{2'-cyanobiphenyl-4-yl}methyl]-4-(1-hydroxy-1-methylethyl)-2-propylimidazol-5-carboxylic acid ethyl ester (4.3g), ethanol (20mL) and n-butanol (20mL) were added into a reactor, and with stirring the solid compound (5.1g) obtained in Example 1-1 was added thereto. The reaction mixture was heated and refluxed, and reacted for 24 hours or more. After the completion of the reaction was confirmed by HPLC, the temperature inside the reactor was cooled to room temperature, and 28% ammonia water (20mL) and water (20mL) were added thereto dropwise for phase separation. The obtained organic layer was washed with water (20mL), and stirred for 1 hour or more with maintaining pH 2~3 by using water (20mL) and sulfuric acid. Phase separation

was conducted, the obtained organic layer was concentrated and dissolved by adding thereto THF (20mL) and water (10mL), and then LiOH (0.85g) was added thereto and the reaction was conducted at 25℃. After the completion of the reaction was confirmed by HPLC, the reaction mixture was neutralized with 1N-HCl and the generated solid was filtered to obtain the title compound (3.6g).

[133] ^{1}H NMR (DMSO-d_6), 0.82 (t, 3H), 1.49-1.51 (m, 8H), 2.54(t, 2H), 5.61 (s, 2H), 6.89~6.91 (m, 2H), 7.01~7.03 (m, 2H), 7.47~7.53 (m, 2H), 7.59~7.61 (m, 2H)

Claims

[Claim 1] A zinc azide complex of formula 3:

[Formula 3]

$L_aZn(N_3)_bX_c$

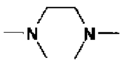
wherein

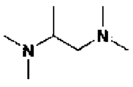
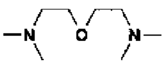
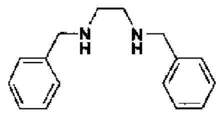
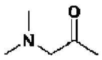
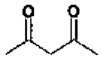
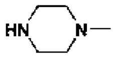
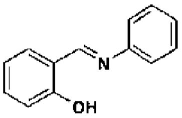
X represents NO_3, OH, Cl, Br, I or a combination thereof,

L represents an amine ligand that can coordinate with Zn, and

a, b and c satisfy $0<a<2$, $0<b<4$ and $0\leq c<2$, respectively.

[Claim 2] The zinc azide complex according to claim 1, wherein L represents a bidentate ligand selected from the following group:



[Claim 3] The zinc azide complex according to claim 2, wherein L is N,N,N',N'-tetramethylethylenediamine (TMEDA).

[Claim 4] The zinc azide complex according to claim 1, wherein a is 1, b is 2, c is 0, and L is N,N,N',N'-tetramethylethylenediamine (TMEDA).

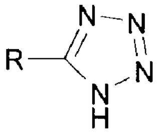
[Claim 5] A process for preparing the zinc azide complex of formula 3 according to claim 1, the process comprising: adding an amine ligand to a mixture of a zinc compound and an alkali metal azide, and conducting a reaction thereof.

[Claim 6] The process according to claim 5, wherein the zinc compound is selected from zinc nitrate hexahydrate, zinc chloride, zinc bromide and zinc iodide.

[Claim 7] The process according to claim 5, wherein the alkali metal azide is selected from lithium azide, sodium azide and potassium azide.

[Claim 8] A process for preparing a substituted tetrazole derivative of formula 1, the process comprising: reacting the zinc azide complex of formula 3, which is prepared by the complex formation reaction of claim 5, with a nitrile compound of formula 2 after isolation or *in situ*:

[Formula 1]



[Formula 2]

R—CN

wherein

R represents an organic residual group.

[Claim 9] The process according to claim 8, wherein

1) R represents linear or branched C_1-C_6-alkyl or C_3-C_6-cycloalkyl, each of which is optionally substituted with one or more substituents selected from:

halogen;

hydroxy;

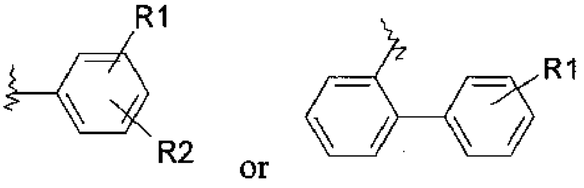
C_1-C_6-alkyl;

C_1-C_6-alkoxy; and

phenyl, pyridine, pyrimidine, imidazole, thiophene and furan, each of which is optionally substituted with one or more substituents selected from the group consisting of C_1-C_6-alkyl, halogen, hydroxy, nitro and C_1-C_6-alkoxy,

or

2) R represents phenyl or biphenyl of the following formula:



wherein

each of R1 and R2 is independently selected from the group consisting of

hydrogen;

halogen;

hydroxy;

nitro;

C_1-C_6-alkyl;

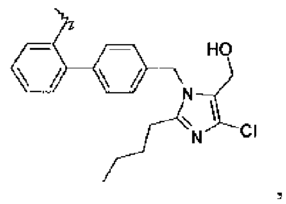
C_3-C_6-cycloalkyl;

C_1-C_6-alkoxy;

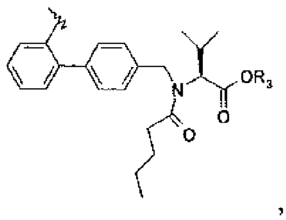
phenylmethyl, pyridylmethyl, pyrimidylmethyl, imidazolylmethyl, benzimidazolylmethyl, thiophenylmethyl and furanylmethyl, each of which is optionally substituted with one to four substituents selected from the group consisting of halogen, carboxy, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxy-C_1-C_6-alkyl, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkoxycarbonyl-C_1-C_6-alkyl, C_3-C_6-alkanediyl, di(C_1-C_6-alkyl)aminothiocarbonyl-C_1-C_6-alkyl, cilexetiloxycarbonyl and medoxomiloxycarbonyl; and

amino or amino-C_1-C_6-alkyl, each of which is optionally substituted with one or two substituents selected from the group consisting of C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_1-C_6-alkylcarbonyl, carboxy-C_1-C_6-alkyl and C_1-C_6-alkoxycarbonyl-C_1-C_6-alkyl.

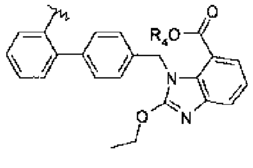
[Claim 10] The process according to claim 8, wherein R is selected from the following structures a to f:



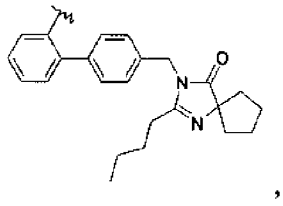
a



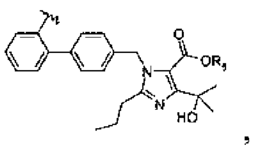
b



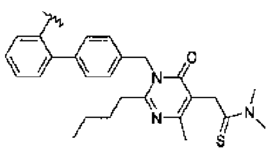
c



d



e



f

wherein

in structure b, R_3 represents hydrogen or methyl,

in structure c, R_4 represents hydrogen, methyl, ethyl or cilexetil, and

in structure e, R_5 represents hydrogen, methyl, ethyl or medoxomil.

[Claim 11] The process according to claim 8, which uses a single or mixture solvent selected from the group consisting of toluene, xylene, ethylbenzene, chlorobenzene, o-, m- or p-chlorotoluene, dichlorobenzene, trifluoromethylbenzene, dimethylformamide, dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, ethanol, propanol, isopropanol, butanol, t-butanol, pentanol, cyclopropanol, cyclobutanol, cyclopentanol, cyclohexanol and mixtures thereof.

[Claim 12] The process according to claim 8, wherein the reaction is conducted at a temperature of 90 to 130°C.

[Claim 13]	The process according to claim 12, wherein the reaction is conducted at a temperature of 100 to 120℃.
[Claim 14]	The process according to claim 8, when the compound of formula 2 comprises a reactive substituent or a substituent capable of reacting with azide, the process further comprising the steps of: protecting the reactive substituent, forming a tetrazole ring, and then removing the corresponding protecting group.

[Fig. 1]