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(54) Title: PROCESS FOR THE PREPARATION OF N-PHENYL-2-PYRIMIDINE-AMINE DERIVATIVES

(57) Abstract: Disclosed is a novel method of preparing an N-phenyl-2-pyrimidine-amine derivative. As compared to a conventional method, the disclosed preparation method is efficient in that the method requires low production cost due to production process reduction, a simplified purification method, and high yield/purity by a selective reaction, and also is environmentally friendly and consistent.



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## Description

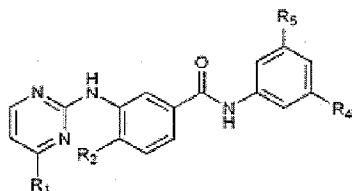
### PROCESS FOR THE PREPARATION OF N-PHENYL-2-PYRIMIDINE-AMINE DERIVATIVES

#### Technical Field

[1] The present invention relates to a novel method of preparing an N-phenyl-2-pyrimidine-amine derivative represented by Formula 1:

[2] [Formula 1]

[3]



[4] in which,  $R_1$  represents thiazole, imidazole, or pyrazine, each of which is substituted or unsubstituted (herein, a substituent group is an amino group or lower alkyl),  $R_2$  represents hydrogen, halogen, lower alkyl, or lower alkoxy,  $R_4$  represents lower alkyl or lower alkyl substituted with 1 to 3 halogen atoms, and  $R_5$  represents: a C5 to C10 aliphatic group; a saturated or unsaturated monocyclic radical or a bi or tri-cyclic radical fused with any benzene ring, each of which contains 1 to 3 heteroatoms selected from the group including nitrogen, oxygen, and sulfur, and contains 5 to 7 ring members; or piperazinyl or homopiperazinyl, each of which is substituted with lower alkyl.

[5]

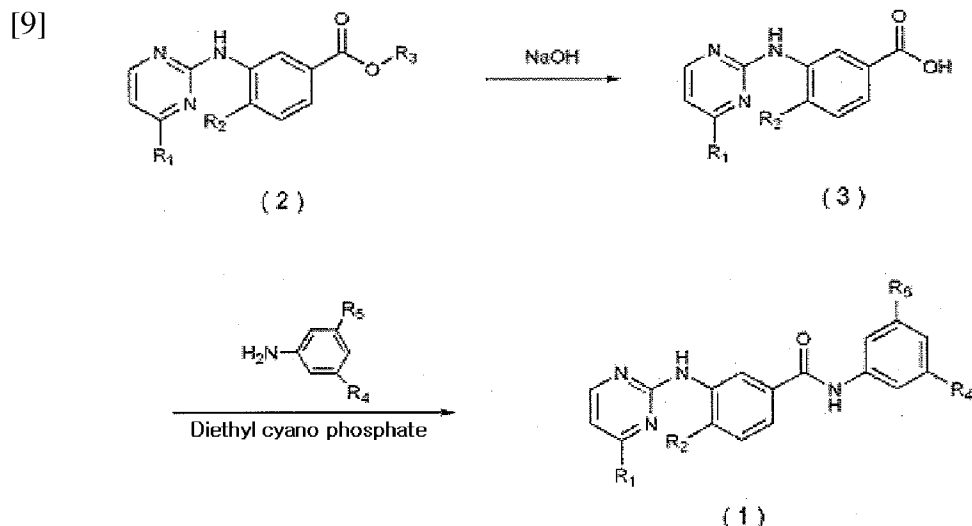
#### Background Art

[6] The compound represented by Formula 1 was disclosed in Korea Patent Registration No. 10-0674813. A preferred compound according to Formula 1 includes 4-methyl-N-[3-(4-methylimidazole-1-yl)-5-trifluoromethyl-phenyl]-3-(4-pyrazine-2-yl-pyrimidine-2-yl amino)benzamide. It has been known that the compound represented by Formula 1 can inhibit at least one kind of tyrosine kinase, for example, c-Abl, Bcr-Abl, and receptor tyrosine kinases (PDGF-R, Flt3, VEGF-R, EGF-R and c-Kit). Accordingly, the compound represented by Formula 1 may be used for treatment of various kinds of cancers in a warm blooded animal, such as lung cancer, stomach cancer, colon cancer, pancreatic cancer, liver cancer, prostate cancer, breast cancer, chronic or acute leukemia, hematological malignancy, brain tumor, bladder cancer, rectal cancer, uterine cervical cancer, lymphoma, etc.

[7] According to a conventional method, the compound represented by Formula 1 is synthesized through hydrolysis of ethyl ester into carboxylic acid and then a reaction with aniline, and herein, diethyl cyano phosphonate is used as a coupling agent (see

Reaction Scheme 1).

[8] [Reaction Scheme 1]



[10] The above method requires a process of hydrolyzing ethyl ester (2) into carboxylic acid (3). In order to obtain the compound represented by Formula 3 as shown in Reaction Scheme 1, a preparation process and a purifying process require a long time. Also, in the condensation reaction, there have been problems such as high production cost due to a low yield (30 to 40%) of the compound represented by Formula 1. Especially, it is very difficult to treat carboxylic acid (3) after purification and reaction, due to its very low solubility in general organic solvent. Also, diethyl cyano phosphonate used for the condensation reaction is an expensive reagent, and an environmentally harmful and very toxic material, which has LD50 values of 25mg/Kg and 4mg/Kg in mice and rabbits (that is, rodents), respectively. Therefore, there is a requirement for an alternative method of conveniently, consistently, efficiently and rapidly preparing a high-purity compound (represented by Formula 1) with low production cost in high yield, which is not harmful for humans and the environment.

[11]

## Disclosure of Invention

### Technical Problem

[12] Accordingly, the present invention provides an alternative method of efficiently preparing a compound (represented by Formula 1) with high purity in consistent high yield.

[13] Also, the present invention provides a method of preparing the compound represented by Formula 1, which can reduce production cost by using inexpensive reagents.

[14] Furthermore, the present invention provides a method of preparing the compound

represented by Formula 1, which is harmless to humans and the environment by using safety reagents.

[15] The present invention has been made to solve the above-mentioned problems occurring in the conventional synthesis method as shown in Reaction Scheme 1, thereby increasing the total yield by 70 to 90%.

[16]

### Technical Solution

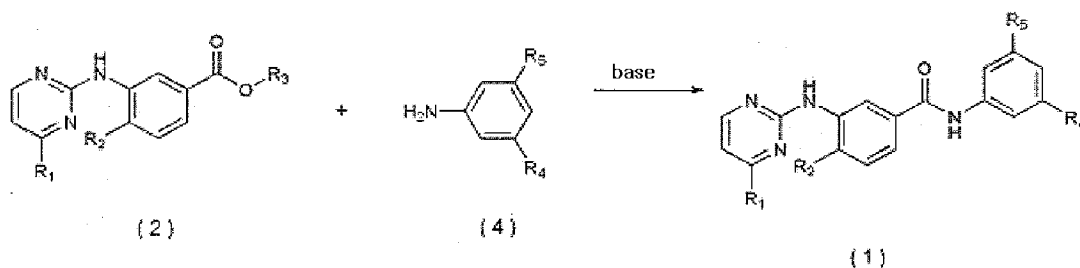
[17] Hereinafter, an exemplary embodiment of the present invention will be described.

[18] The present invention provides a novel method including a reaction for preparing the compound represented by Formula 1, that is, an N-phenyl-2-pyrimidine-amine derivative, through direct condensation of the compound represented by Formula 2 and the compound represented by Formula 4, as starting materials, and a strong base, as a catalyst, as shown in Reaction Scheme 2.

[19]

[20] [Reaction Scheme 2]

[21]



[22]

[23] In the above Reaction Scheme,

[24]  $R_1$  represents thiazole, imidazole, or pyrazine, each of which is substituted or unsubstituted (herein, a substituent group is an amino group or lower alkyl),

[25]  $R_2$  represents hydrogen, halogen, lower alkyl, or lower alkoxy,

[26]  $R_3$  represents lower alkyl, phenyl, phenyl-lower alkyl or substituted phenyl,

[27]  $R_4$  represents lower alkyl or lower alkyl substituted with 1 to 3 halogen atoms,

[28]  $R_5$  represents: a C5 to C10 aliphatic group; a saturated or unsaturated monocyclic radical or a bi or tri-cyclic radical fused with any benzene ring, each of which contains 1 to 3 heteroatoms selected from the group including nitrogen, oxygen, and sulfur, and contains 5 to 7 ring members; or piperazinyl or homopiperazinyl, each of which is substituted with lower alkyl.

[29] According to the preparation method in the present invention, the direct condensation of aniline (4) and ester (2) may generate the compound represented by Formula 1 through catalysis by a strong base such as potassium tert-butoxide. Also, other base materials, such as metal hydride, metal halide, bulky alkyl lithium, metal alkoxide,

metal bis(trimethylsilyl)amide or lithium dialkylamide, or a mixture thereof, may be used. The metal may be lithium, sodium, magnesium or potassium.

[30] Although there is no particular limitation in an organic solvent that may be used in the preparation method of the present invention, at least one organic solvent selected from the group including tetrahydrofuran, dimethylformamide, dimethylsulfoxide, toluene, N,N-dimethylacetamide, xylene, benzene and N-methylpyrrolidinone may be used.

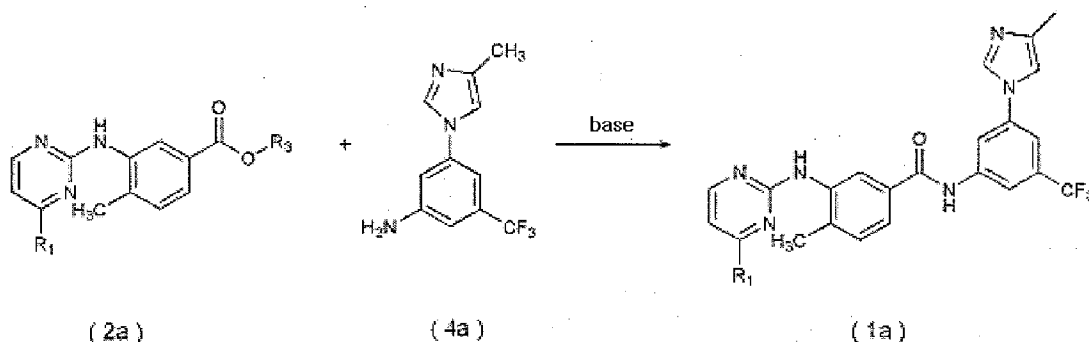
[31] In a preparation method according to a preferred embodiment of the present invention, the compound represented by Formula 1 may be prepared by the steps of: dissolving 1.0 equivalent of compound represented by Formula 4 in at least one organic solvent selected from the group including tetrahydrofuran, dimethylformamide, dimethylsulfoxide, toluene, N,N-dimethylacetamide, xylene, benzene and N-methylpyrrolidinone, at -50 to 50°C, preferably at -20 to 30°C, in the presence of 3.0 to 5.0 equivalents of base, preferably of 3.5 to 4.5 equivalents, dropwise adding the compound and stirring the mixture; and dissolving 1.0 to 1.2 equivalents of compound represented by Formula 2, preferably of 1.1 equivalents of the compound, in the selected organic solvent, dropwise adding the compound and stirring the mixture.

[32] According to the preferred embodiment of the present invention, the above described method includes the following reaction.

[33]

[34] [Reaction Scheme 3]

[35]



[36]

[37] In the above Reaction Scheme,

[38] R<sub>1</sub> represents thiazole, imidazole, or pyrazine, each of which is substituted or unsubstituted (herein, a substituent group is an amino group or lower alkyl), and

[39] R<sub>3</sub> represents lower alkyl, phenyl, phenyl-lower alkyl or substituted phenyl.

[40] The compound represented by Formula 4a may be prepared by using the method disclosed in Korea Patent Registration No. 10-0674813. The present invention is intended to include the disclosed method.

[41] As shown in Reaction Scheme 3 according to the embodiment of the present

invention, an N-phenyl-2-pyrimidine-amine derivative represented by Formula 1a may be prepared by a one-step condensation reaction through catalysis of a strong base with starting materials, that is, aniline (4a) and ester (2a).

[42] As compared to a conventional method, the preparation method according to the present invention is efficient in that the method requires low production cost due to production process reduction, a simplified purification method, and high yield/purity by a selective reaction.

[43] Unless otherwise noted, specific terms of the present invention have meanings as described below.

[44] Lower alkyl includes 1 to 6 carbon atoms, and is linear or branched, and a preferable lower alkyl residue includes butyl (for example, n-butyl, sec-butyl, isobutyl, tert-butyl), propyl (for example, n-propyl or isopropyl), ethyl or methyl. Especially, a preferable lower alkyl residue includes methyl, ethyl, n-propyl or tert-butyl. Also, aliphatic indicates alkenyl, alkynyl, or alkyl. Also, lower alkoxy indicates a group containing a linear or branched, saturated aliphatic hydrocarbon residue having preferably 1 to 6 carbon atoms, and specifically includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentoxy, isopentoxy, hexoxy, etc.

[45] Halogen indicates fluorine, chlorine, bromine, or iodine, and especially, fluorine, chlorine, or bromine.

### **Advantageous Effects**

[46] As compared to a conventional method, the disclosed preparation method is efficient in that the method requires low production cost due to production process reduction, a simplified purification method, and high yield/purity by a selective reaction, and also is environmentally friendly and consistent.

[47]

### **Best Mode for Carrying out the Invention**

[48] Hereinafter, the present invention will be described in detail with reference to following Examples. However, the following examples are illustrative only, and the scope of the present invention is not limited thereto.

[49]

#### **Example 1**

[51] Synthesis of 4-methyl-N-[3-(4-methylimidazole-1-yl)-5-trifluoromethyl-phenyl] - 3-(4-thiazole-2-yl-pyrimidine-2-yl amino)benzamide

[52]

#### **Method A**

[54] In a reactor, potassium tert-butoxide (20.9g, 186.56mmol) was dissolved in tetrahydrofuran (167ml), and then was cooled to  $-20\pm 5^{\circ}\text{C}$ . To the resultant product,

3-(4-methyl-imidazole-1-yl)-5-trifluoromethyl-phenylamine (10g, 41.46mmol) dissolved in tetrahydrofuran (80ml) was added and stirred for 30 minutes. When the stirring was completed, 4-methyl-3-(4-thiazole-2-yl-pyrimidine-2-yl amino)benzoic acid ethyl ester (15.5g, 45.60mmol) dissolved in tetrahydrofuran (90ml) was slowly added to the resultant product. After the addition, the temperature of the mixture was slowly elevated to room temperature, and stirring was carried out until the reaction was completed. When the reaction was completed, the reaction mixture was cooled to 5-10°C, and then 15% sodium chloride aqueous solution (337ml) was slowly added to the reaction mixture. After the addition, the temperature of the reaction mixture was slowly elevated to room temperature again, and then water (170ml) was added thereto and an organic layer was extracted and separated.

[55] To the organic layer, ethyl acetate (400ml) was added. Then, the layer was washed with water (200ml), separated and was subjected to vacuum concentration. When the concentration was completed, methanol (220ml) was added thereto. Then, the resultant layer was subjected to reflux-stirring for 1 hour, cooled to room temperature, and then stirred for 2 hours.

[56] The obtained solid was filtered, sufficiently washed with methanol (100ml), and then dried to provide a pale yellow solid final compound (17.51g, yield 81%).

[57] <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>, δ= 2.19(s,3H), 2.36(s,3H), 7.24(s,1H), 7.35(m,2H), 7.47(s,1H), 7.64(d,1H), 7.71(d,1H), 7.92(d,1H), 8.01(s,1H), 8.11(s,1H), 8.30(s,2H), 8.47(d,1H), 9.00(s, 1H), 10.49(s,1H)

[58]

[59] Method B

[60] A pale yellow solid final compound (17.8g, yield 80%) was obtained by reacting 3-(4-methyl-imidazole-1-yl)-5-trifluoromethyl-phenylamine (10g, 41.46mmol) with 4-methyl-3-(4-thiazole-2-yl-pyrimidine-2-yl amino)-benzoic acid methyl ester in a similar manner as described in Method A of Example 1, except that 4-methyl-3-(4-thiazole-2-yl-pyrimidine-2-yl amino)-benzoic acid methyl ester (14.9g, 45.60mmol) was used, instead of 4-methyl-3-(4-thiazole-2-yl-pyrimidine-2-yl amino)benzoic acid ethyl ester.

[61]

[62] Method C

[63] A pale yellow solid final compound (17.3g, yield 78%) was obtained by reacting 3-(4-methyl-imidazole-1-yl)-5-trifluoromethyl-phenylamine (10g, 41.46mmol) with 4-methyl-3-(4-thiazole-2-yl-pyrimidine-2-yl amino)benzoic acid methyl ester (14.9g, 45.60mmol) in a similar manner as described in Method A of Example 1, except that sodium tert-butoxide was used, instead of potassium tert-butoxide.

[64]

[65]     Method D

[66]     A pale yellow solid final compound (15.53g, yield 70%) was obtained by reacting 3-(4-methyl-imidazole-1-yl)-5-trifluoromethyl-phenylamine (10g, 41.46mmol) with 4-methyl-3-(4-thiazole-2-yl-pyrimidine-2-yl amino)benzoic acid phenyl ester in a similar manner as described in Method A of Example 1, except that 4-methyl-3-(4-thiazole-2-yl-pyrimidine-2-yl amino)benzoic acid phenyl ester (17.7g, 45.60mmol) was used, instead of 4-methyl-3-(4-thiazole-2-yl-pyrimidine-2-yl amino)benzoic acid ethyl ester.

[67]

[68]     **Example 2**

[69]     Synthesis of 4-methyl-N-[3-(4-methylimidazole-1-yl)-5-trifluoromethyl-phenyl] - 3-(4-pyrazine-2-yl-pyrimidine-2-yl amino)benzamide

[70]

[71]     Method A

[72]     A pale yellow solid final compound (18.7g, yield 85%) was obtained by reacting 3-(4-methyl-imidazole-1-yl)-5-trifluoromethyl-phenylamine (10g, 41.46mmol) with 4-methyl -3-(4-pyrazine-2-yl-pyrimidine-2-yl amino)-benzoic acid ethyl ester in a similar manner as described in Method A of Example 1, except that 4-methyl-3-(4-pyrazine-2-yl-pyrimidine-2-yl amino)-benzoic acid ethyl ester (15.3g, 45.60mmol) was used, instead of 4-methyl-3-(4-thiazole-2-yl-pyrimidine-2-yl amino)benzoic acid ethyl ester.

[73]     <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>, δ= 2.21(s,3H), 2.38(s,3H), 7.35(s,1H), 7.39(s,1H), 7.54(s,1H), 7.63(d,1H), 7.75(d,1H), 8.14(d,2H), 8.38(d,2H), 8.54(d,2H), 8.68(s,1H), 9.06(s,1H), 9.45(s, 1H), 10.56(s,1H)

[74]

[75]     Method B

[76]     A pale yellow solid final compound (18.3g, yield 83%) was obtained by reacting 3-(4-methyl-imidazole-1-yl)-5-trifluoromethyl-phenylamine (10g, 41.46mmol) with 4-methyl -3-(4-pyrazine-2-yl-pyrimidine-2-yl amino)-benzoic acid methyl ester in a similar manner as described in Method A of Example 1, except that 4-methyl-3-(4-pyrazine-2-yl-pyrimidine-2-yl amino)-benzoic acid methyl ester (14.7g, 45.60mmol) was used, instead of 4-methyl-3-(4-thiazole-2-yl-pyrimidine-2-yl amino)benzoic acid ethyl ester.

[77]

[78]     Method C

[79]     A pale yellow solid final compound (17.2g, yield 78%) was obtained by reacting 3-(4-methyl-imidazole-1-yl)-5-trifluoromethyl-phenylamine (10g, 41.46mmol) with 4-methyl-3-(4-pyrazine-2-yl-pyrimidine-2-yl amino)benzoic acid methyl ester (14.7g,



45.60mmol) in a similar manner as described in Method A of Example 1, except that sodium tert-butoxide was used, instead of potassium tert-butoxide.

[80]

[81]     Method D

[82]     A pale yellow solid final compound (16.1g, yield 73%) was obtained by reacting 3-(4-methyl-imidazole-1-yl)-5-trifluoromethyl-phenylamine (10g, 41.46mmol) with 4-methyl-3-(4-pyrazine-2-yl-pyrimidine-2-yl amino)benzoic acid phenyl ester in a similar manner as described in Method A of Example 1, except that 4-methyl-3-(4-pyrazine-2-yl-pyrimidine-2-yl amino)-benzoic acid phenyl ester (17.5g, 45.60mmol) was used, instead of 4-methyl-3-(4-thiazole-2-yl-pyrimidine-2-yl amino)benzoic acid ethyl ester.

[83]

[84]     **Example 3**

[85]     Synthesis of 3-(4-imidazole-1-yl-pyrimidine-2-yl amino)-4-methyl-N-[3-(4-methyl-imidazole-1-yl)-5- trifluoromethyl-phenyl] benzamide

[86]

[87]     Method A

[88]     A pale yellow solid final compound (15.7g, yield 73%) was obtained by reacting 3-(4-methyl-imidazole-1-yl)-5-trifluoromethyl-phenylamine (10g, 41.46mmol) with 3-(4-imidazole-1-yl-pyrimidine-2-yl amino)-4-methyl-benzoic acid ethyl ester in a similar manner as described in Method A of Example 1, except that 3-(4-imidazole-1-yl-pyrimidine-2-yl amino)-4-methyl-benzoic acid ethyl ester (14.75g, 45.60mmol) was used, instead of 4-methyl-3-(4-thiazole-2-yl-pyrimidine-2-yl amino)benzoic acid ethyl ester.

[89]     <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>, δ= 2.27(s,3H), 2.30(s,3H), 6.84(d,1H), 7.24(s,1H), 7.39(s,1H), 7.56(d,2H), 7.89(m,3H), 7.92(d,2H), 8.07(s,1H), 8.35(s,1H), 8.42(d,1H), 9.40(s,1H), 9.89(s,1H)

[90]

[91]     Method B

[92]     A pale yellow solid final compound (16.1g, yield 75%) was obtained by reacting 3-(4-methyl-imidazole-1-yl)-5-trifluoromethyl-phenylamine (10g, 41.46mmol) with 3-(4-imidazole-1-yl-pyrimidine-2-yl amino)-4-methyl-benzoic acid methyl ester in a similar manner as described in Method A of Example 1, except that 3-(4-imidazole-1-yl-pyrimidine-2-yl amino)-4-methyl-benzoic acid methyl ester (14.1g, 45.60mmol) was used, instead of 4-methyl-3-(4-thiazole-2-yl-pyrimidine-2-yl amino)benzoic acid ethyl ester.

[93]

[94]      Method C

[95]      A pale yellow solid final compound (16.3g, yield 76%) was obtained by reacting 3-(4-methyl-imidazole-1-yl)-5-trifluoromethyl-phenylamine (10g, 41.46mmol) with 3-(4-imidazole-1-yl-pyrimidine-2-yl amino)-4-methyl-benzoic acid methyl ester (14.1g, 45.60mmol) in a similar manner as described in Method A of Example 1, except that sodium tert-butoxide was used, instead of potassium tert-butoxide.

[96]

[97]      Method D

[98]      A pale yellow solid final compound (15.3g, yield 71%) was obtained by reacting 3-(4-methyl-imidazole-1-yl)-5-trifluoromethyl-phenylamine (10g, 41.46mmol) with 3-(4-imidazole-1-yl-pyrimidine-2-yl amino)-4-methyl-benzoic acid phenyl ester in a similar manner as described in Method A of Example 1, except that 3-(4-imidazole-1-yl-pyrimidine-2-yl amino)-4-methyl-benzoic acid phenyl ester (16.9g, 45.60mmol) was used, instead of 4-methyl-3-(4-thiazole-2-yl-pyrimidine-2-yl amino)benzoic acid ethyl ester.

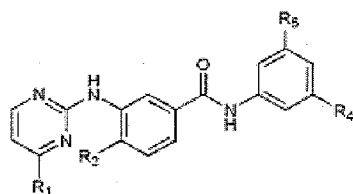
[99]

[100]      Although an exemplary embodiment of the present invention has been described for illustrative purposes, those skilled in the art will appreciate that various modifications, additions and substitutions are possible, without departing from the scope and spirit of the invention as disclosed in the accompanying claims.

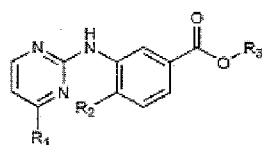
## Claims

- [1] A method of preparing a compound represented by Formula 1, the method comprising a reaction of a compound represented by Formula 2 with a compound represented by Formula 4 through catalysis by a strong base in an organic solvent:

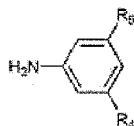
[Formula 1]



[Formula 2]



[Formula 4]



wherein  $R_1$  represents thiazole, imidazole, or pyrazine, each of which is substituted or unsubstituted (herein, a substituent group is an amino group or lower alkyl);

$R_2$  represents hydrogen, halogen, lower alkyl, or lower alkoxy;

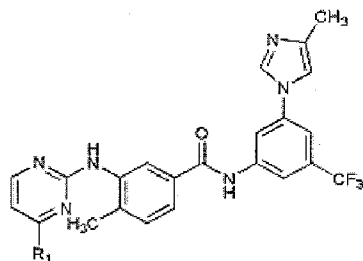
$R_3$  represents lower alkyl, phenyl, phenyl-lower alkyl or substituted phenyl;

$R_4$  represents lower alkyl or lower alkyl substituted with 1 to 3 halogen atoms; and

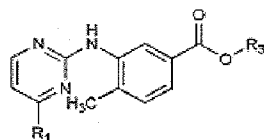
$R_5$  represents: a C5 to C10 aliphatic group; a saturated or unsaturated monocyclic radical or a bi or tri-cyclic radical fused with any benzene ring, each of which contains 1 to 3 heteroatoms selected from the group including nitrogen, oxygen, and sulfur, and contains 5 to 7 ring members; or piperazinyl or homopiperazinyl, each of which is substituted with lower alkyl.

- [2] A method of preparing a compound represented by Formula 1a, the method comprising a reaction of a compound represented by Formula 4a with a compound represented by Formula 2a through catalysis by a strong base in an organic solvent:

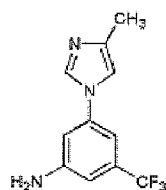
[Formula 1a]



[Formula 2a]



[Formula 4a]



wherein  $R_1$  represents thiazole, imidazole, or pyrazine, each of which is substituted or unsubstituted (herein, a substituent group is an amino group or lower alkyl), and

$R_3$  represents lower alkyl, phenyl, phenyl-lower alkyl or substituted phenyl.

- [3] The method as claimed in claim 1 or 2, wherein the base is at least one material selected from the group including metal hydride, metal halide, bulky alkyl lithium, metal alkoxide, metal bis(trimethylsilyl)amide and lithium dialkylamide.
- [4] The method as claimed in claim 3, wherein metal is selected from the group including lithium, sodium, magnesium and potassium.
- [5] The method as claimed in claim 3, wherein the base is potassium tert-butoxide.
- [6] The method as claimed in claim 1 or 2, wherein the organic solvent is at least one material selected from the group including tetrahydrofuran, dimethylformamide, dimethylsulfoxide, toluene, N,N-dimethylacetamide, xylene, benzene and N-methylpyrrolidinone.

**A. CLASSIFICATION OF SUBJECT MATTER***C07D 239/18(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)

IPC 8 as above

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)

eKIPASS(KIPO internal), PubMed, NCBI, Esp@snet, PAJ, USPTO, Google

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2003/066613 A1 (NOVARTIS PHARMA GMBH) 14 August 2003 See the abstract, page 4~12, claims 8~13	1-6
X	KR 10-0674813 B1 (IL-YANG PHARM. CO., LTD.) 19 January 2007 See the abstract, page 2~6, claims 1~4	1-6
A	WO 2004/005281 A1 (NOVARTIS PHARMA GMBH) 15 January 2004 See the whole documents.	1-6



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

"&amp;" document member of the same patent family

Date of the actual completion of the international search

08 JULY 2009 (08.07.2009)

Date of mailing of the international search report

**08 JULY 2009 (08.07.2009)**

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**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

**PCT/KR2008/006850**

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