Title: IMIDAZOLE DERIVATIVES AND COMPOSITIONS FOR TREATING MELANOMA

Abstract: The present invention relates to novel imidazole derivatives or pharmaceutically acceptable salts thereof, preparation methods thereof and pharmaceutical compositions for prevention and treatment of melanoma containing the same as active ingredients. The novel imidazole derivatives or pharmaceutically acceptable salts thereof according to the present invention have excellent inhibitory effects on various protein kinases, which cause melanoma, such as B- Raf, C-Raf, Aurora-A, BTK, Flt3, Ret, KDR/VEGFR2, P38a/MAPK14, RAF1, FMS, and the like, so they can be used for the prevention and treatment of melanoma.
Description

Title of Invention: IMIDAZOLE DERIVATIVES AND COMPOSITIONS FOR TREATING MELANOMA

Technical Field

[1] The present invention relates to novel imidazole derivatives or pharmaceutically acceptable salts thereof, preparation methods thereof and pharmaceutical compositions for prevention and treatment of melanoma containing the same as active ingredients.

[2] Background Art

[3] Melanoma is a kind of skin cancers which occurs due to an abnormal growth of melanocyte in a basal skin. It is known that the melanoma more frequently occurs in white people, but less in colored people. In particular, people who work outdoors are more subject to melanoma. Why the melanoma occurs is not known, but it is known that the melanoma generally occurs when melanocyte or nevus, which is skin cells, becomes malignant and also family genetic factor is one of main reasons for melanoma. The malignant melanoma does not have any subjective symptoms such as itches or pains and is indicated with black spots or cuts, which leads to a difficult self-diagnosis.

[4] The initial stage melanoma can be surgically treated, but when it starts transferring to other organs, it shows a strong resistance to all existing anti-cancer agent. The so-far developed treatment for medicine is a symptom relaxation agent, not a treatment agent, which leads to a variety of side effects. The research and development of therapeutics for melanoma continues, and the research on the molecular target is being most widely performed.

[5] The V600E, which is one of the point mutations of B-RAF, is an important molecular target found in more than 60% of melanoma, which was proved through in vitro or in vivo (LiangS. et al., Cancer Res. 67(12), 5814-5820 (2007)). In addition, when inhibiting mutant B-RAF by using siRNA in melanoma cell of a human being, both MEK and ERK are inhibited, so the growth of tumor cells stops for thereby accelerating the death of cells (Sharma, et al., Cancer Res. 65:2412-2412 (2005); and Wellbrock et al., Cancer Res. 64: 2338-2342 (2004)), and in a short-hairpin RNA xenograft model experiment, which has a target on B-RAF mutants, it is known that the inhibition of B-RAF can induce an inhibitory effect on tumor and can be reversely adjusted (Hoeftlich et al., Cancer Res. 66: 999-1006 (2006)). Therefore, the B-RAF cellular signal transduction system is deeply involved in the growth of tumor, in particular in the growth of melanoma, as a result of which it can confirm that B-RAF
can be an important target of anti-melanoma treatment.

In recent years, a lot of melanoma patients who do not have B-RAF V600E mutants have been founded (>33%), which means that it is necessary to develop a treatment agent in other directions as compared to the development of V600E B-RAF inhibitor.

As a new target of melanoma, it is most likely suspected that the C-RAF, which is very close to B-RAF, is involved in abnormal proliferation in melanoma. The C-RAF is connected with plasma membrane and involved in activating a MAPK signal transduction system like B-RAF (Kyriakis JM et al. (1992) Nature 358: 417-421), but C-RAF controls lower proteins such as MST-2 and ASK-1 irrespective of MAPK signal transduction system as compared to B-RAF (Chen J et al., (2001), Proc Natl Acad Sci USA 98: 7783-7788). In addition, it is known that C-RAF affects mitochondria for thereby controlling the inhibition of apoptosis, which is obtained with the help of phosphorylation of BAD through a direct coupling with Bcl-2 (von Gise A et al., (2001), Mol Cell Biol 21: 2324-2336). C-RAF seems to be clearly related with the mutants of NRAS (Dumaz N et al., (2006), Cancer Res 66:9483-9491). A recent study, which shows that B-RAF can directly phosphorylate C-RAF (Dhomen N, Marais R. (2007), Curr Opin Genet Dev 17:31-39), emphasizes the value of C-RAF as a target protein for melanoma therapeutics.

In the course of developing a new melanoma therapeutics which has less side effects, the inventors have found novel imidazole derivatives as a small molecular compound having less side effects, which derivatives have excellent anti-growth effects on melanoma tumor cells and have excellent inhibitory effects on a variety of protein kinase such as B-RAF, C-RAF, Aurora-A, BTK, Flt3, Ret, KDR/VEGFR2, P38a/MAPK14, RAF1, FMS, and the like which lead to the prevention and treatment agent of melanoma.

Disclosure of Invention

Technical Problem

It is an object of the present invention to provide novel imidazole derivatives or pharmaceutically acceptable salts thereof.

It is another object of the present invention to provide methods for preparing the novel imidazole derivatives or pharmaceutically acceptable salts thereof.

It is a further object of the present invention to provide pharmaceutical compositions for prevention and treatment of melanoma containing the novel imidazole derivatives or pharmaceutically acceptable salts thereof as active ingredients.

Solution to Problem
To achieve the above objects, herein is provided a novel imidazole derivatives or pharmaceutically acceptable salts thereof, preparation methods thereof and pharma-ceutical compositions for prevention and treatment of melanoma containing the novel imidazole derivatives or pharmaceutically acceptable salts thereof as active in-gredients.

**Advantageous Effects of Invention**

Since the novel imidazole derivatives or pharmaceutically acceptable salts thereof according to the present invention have excellent inhibitory effects on a variety of protein kinase, which cause melanoma, such as B-RAF, C-RAF, Aurora-A, BTK, Flt3, Ret, KDR/VEGFR2, P38a/MAPK14, RAF1, FMS, and the like.

**Best Mode for Carrying out the Invention**

The present invention will be described in details.

The present invention provides an imidazole derivatives represented by the following Chemical Formula 1 or pharmaceutically acceptable salts thereof.

[Chemical Formula 1]

\[
\begin{align*}
\text{R}^1 & \text{N} & \text{X} & \text{N} \\
& & & \text{R}^2
\end{align*}
\]

wherein,

- \( \text{X} \) is carbon or nitrogen,
- \( \text{R}^1 \) is hydrogen; a straight or branched \( \text{C}_{1} \sim \text{C}_{6} \) alkyl; a \( \text{C}_{2} \sim \text{C}_{8} \) alkenyl; a \( \text{C}_{2} \sim \text{C}_{8} \) alkynyl; a \( \text{C}_{1} \sim \text{C}_{6} \) alkoxy; a \( \text{C}_{5} \sim \text{C}_{12} \) aryl \( \text{C}_{1} \sim \text{C}_{6} \) alkyl which is unsubstituted or substituted with at least one substituent selected from among a straight or branched \( \text{C}_{1} \sim \text{C}_{6} \) alkyl, a \( \text{C}_{2} \sim \text{C}_{8} \) alkenyl, a \( \text{C}_{2} \sim \text{C}_{8} \) alkynyl, a \( \text{C}_{1} \sim \text{C}_{6} \) alkoxy, halogen or \( \text{OH} \); a \( \text{C}_{5} \sim \text{C}_{12} \) heteroaryl \( \text{C}_{1} \sim \text{C}_{6} \) alkyl which is unsubstituted or substituted with at least one substituent selected from among a straight or branched \( \text{C}_{1} \sim \text{C}_{6} \) alkyl, a \( \text{C}_{2} \sim \text{C}_{8} \) alkenyl, a \( \text{C}_{2} \sim \text{C}_{8} \) alkynyl, a \( \text{C}_{1} \sim \text{C}_{6} \) alkoxy, halogen or \( \text{OH} \); a \( \text{C}_{5} \sim \text{C}_{12} \) cycloalkyl which is unsubstituted or substituted with at least one substituent selected from among a straight or branched \( \text{C}_{1} \sim \text{C}_{6} \) alkyl, a \( \text{C}_{2} \sim \text{C}_{8} \) alkenyl, a \( \text{C}_{2} \sim \text{C}_{8} \) alkynyl, a \( \text{C}_{1} \sim \text{C}_{6} \) alkoxy, halogen or \( \text{OH} \); or a \( \text{C}_{5} \sim \text{C}_{12} \) hetero-cycloalkyl which is unsubstituted or substituted with at least one substituent selected from among a straight or branched \( \text{C}_{1} \sim \text{C}_{6} \) alkyl, a \( \text{C}_{2} \sim \text{C}_{8} \) alkenyl, a \( \text{C}_{2} \sim \text{C}_{8} \) alkynyl, a \( \text{C}_{1} \sim \text{C}_{6} \) alkoxy, halogen or \( \text{OH} \).
[24] \( R^2 \) is

\[
\begin{align*}
\text{or }
\end{align*}
\]

, wherein \( L \) is \(-\text{NH}-; -\text{NRC(O)}--; -\text{NRC(0)NR}--; -\text{NRC(S)NR}--; -\text{NRC(0)S}--; -\text{C(0)NR}--; -\text{C(0)NRC(0)R}; \) or \(-\text{NRS(O)2R}--; \) and \( R \) is hydrogen, a straight or branched \( \text{C}_1-\text{C}_4 \) alkyl.

[25] \( R^3 \) is hydrogen; a \( \text{C}_5-\text{C}_2 \) aryl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched \( \text{C}_1-\text{C}_6 \) alkyl, a \( \text{C}_1-\text{C}_6 \) alkoxy, trifluoromethyl and morpholino; a \( \text{C}_5-\text{C}_2 \) heteroaryl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched \( \text{C}_1-\text{C}_6 \) alkyl, a \( \text{C}_1-\text{C}_6 \) alkoxy, trifluoromethyl and morpholino; a \( \text{C}_5-\text{C}_2 \) aryl \( \text{C}_1-\text{C}_6 \) alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched \( \text{C}_1-\text{C}_6 \) alkyl, a \( \text{C}_1-\text{C}_6 \) alkoxy, trifluoromethyl and morpholino; a \( \text{C}_5-\text{C}_2 \) heteroaryl \( \text{C}_1-\text{C}_6 \) alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched \( \text{C}_1-\text{C}_6 \) alkyl, a \( \text{C}_1-\text{C}_6 \) alkoxy, trifluoromethyl and morpholino; a \( \text{C}_5-\text{C}_2 \) cycloalkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched \( \text{C}_1-\text{C}_6 \) alkyl, a \( \text{C}_1-\text{C}_6 \) alkoxy, trifluoromethyl and morpholino; or a \( \text{C}_5-\text{C}_2 \) heterocycloalkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched \( \text{C}_1-\text{C}_6 \) alkyl, a \( \text{C}_1-\text{C}_6 \) alkoxy, trifluoromethyl and morpholino.

[26] Preferably,

[27] \( X \) is carbon or nitrogen,

[28] \( R^1 \) is hydrogen, methyl, ethyl, propyl, 3-hydroxypropyl,

[29] \( R^2 \) is

\[
\begin{align*}
\text{or }
\end{align*}
\]
, wherein L is -NH-; -NRC(O)-; -NRC(0)NR-; -NRC(0)S- or -NRC(S)NR-, and R is hydrogen, methyl or ethyl,

31. R³ is hydrogen; (3,4-di-methoxyphenyl)methyl; 2,4-dimethylphenyl; 2,3-dichlorophenyl; 3,4-dichlorophenyl; 2,4,5-trichlorophenyl; 3-(trifluoromethyl)phenyl; 4-chloro-3-(trifluoromethyl)phenyl; 3-(4-hydroxypiperidin-1-yl)-5-(trifluoromethyl)phenyl; 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl; 3-morpholino-5-(trifluoromethyl)phenyl; 3-(4-methylpiperazin-1-yl)-5-trifluoromethyl)phenyl; 4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl; 3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl; 4-((1-methylpiperidin-4-yloxy)-3-(trifluoromethyl)phenyl; 5-bromothiophene; naphthyl; benzo[b]thiophenyl; furanyl; isoxazolyl; pyrazolyl; pyridazinyl; thiazolyl; pyrazinyl; thienyl; pyrimidinyl; imidazolyl; pyrrolyl; dihydropyrrolyl; oxazolyl; triazolyl; thiadiazolyl; benimidazolyl; quinoline; tetrahydroquinolinyl; benzothiazolyl; methylbenzothiazolyl; benzothiazolephenyl; benzodioxolyl; imidazolyl; indolyl; indoly; dihydroindolyl or dihydrobenzofuran.

32. More preferably,

33. X is nitrogen,

34. R¹ is 3-hydroxypropyl,

35. R² is

36. L is -NH-; -NHC(O)-; -NHC(0)NH-; -NRC(0)S- or -NHC(S)NH-, and R³ is hydrogen; 4-chloro-3-(trifluoromethyl)phenyl; 3-morpholino-5-(trifluoromethyl)phenyl; 6-methylbenzothiazol-2-yl; 3,4-dichlorophenyl; 2,4,5-trichlorophenyl; 4-chloro-3-(trifluoromethyl)phenyl;
3-(4-methylpiperazin-1-yl)-5-trifluoromethyl)phenyl; 3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl; 5-methylisoxazolyl; 4-chlorophenyl-isoxazolyl; 4-methoxyphenylfuranyl; 3-chloro-5-(trifluoromethyl)phenylfuranyl; 4-methoxyphenyl-5-trifluoromethyl-pyrazolyl; pyridin-4-yl-thiazolyl.

[37] The detailed compound of the imidazole derivatives represented by the Chemical Formula 1 according to the present invention is as follows.

[38] (1) (S)-1-(4-(2-(3-aminophenyl)-1H-imidazol-2-ylamino)propan-2-ol; (2) (S)-1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)imidazol-2-yl)phenyl)urea; (3) (S)-1-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(3-morpholino-5-(trifluoromethyl)phenyl)urea; (4) (S)-1-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(6-methylbenzo[d]thiazol-2-yl)urea; (5) (S)-1-(3,4-dichlorophenyl)-3-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)urea; (6) (S)-1-(4-(2-(3,4-dichlorophenyl)ureido)phenyl)-1H-imidazol-1-yl)pyrimidin-2-ylamino)propan-2-yl acetate; (7) (S)-1-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(2,4,5-trichlorophenyl)urea; (8) (S)-1-(3-chlorophenyl)-3-(3-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)urea; (9) (S)-1-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(4-morpholinophenyl)urea; (10) (S)-1-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(3-(trifluoromethyl)phenyl)urea; (11) (S)-1-(3,4-dichlorophenyl)-3-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)urea; (12) (S)-1-(3,4-dichlorophenyl)-3-(4-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)urea; (13) (S)-1-(4-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(2,4,5-trichlorophenyl)urea; (14) (S)-1-(4-chlorophenyl)-3-(4-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)thiourea;
(S)-1-(4-chlorophenyl)-3-(4-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)furan-2-carboxamide;

(S)-1-(4-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(4-morpholinophenyl)urea;

(S)-1-(4-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(3-(trifluoromethyl)phenyl)urea;

(S)-5-(3-chloro-5-(trifluoromethyl)phenyl)-N-(4-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)furan-2-carboxamide;

(S)-5-(2-chloro-5-(trifluoromethyl)phenyl)-N-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)isoxazole-3-carboxamide;

(S)-5-(4-chlorophenyl)-N-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-5-methylisoxazole-3-carboxamide;

(S)-5-(4-chlorophenyl)-N-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)isoxazole-3-carboxamide;

(S)-5-(4-chlorophenyl)-NK4-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)isoxazole-3-carboxamide;

(S)-5-(3-chloro-5-(trifluoromethyl)phenyl)-N-(4-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)furan-2-carboxamide;
(33) (S)-N-(4-((2-hydroxypropylamino)-pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-l-(4-methoxyphenyl)-5-(trifluoromethyl)-IH-pyrazole-4-carboxamide;

(34) (S)-N-(4-((2-hydroxypropylamino)-pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-2-(pyridin-4-yl)thiazole-4-carboxamide;

(35) (S)-1-((4-chlorophenyl)-3-(trifluoromethyl)phenyl)-3-((2-(2-hydroxypropylamino)-pyrimidin-4-yl)-1H-imidazol-2-carbonyl)phenyl)urea; and

(36) (S)-4-chloro-N-(1-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-1H-imidazole-2-carbonyl)phenyl)-3-(trifluoromethyl)benzamide.

The imidazole derivatives represented by the Chemical Formula 1 according to the present invention may be used in a form of pharmaceutically acceptable salt in which salt is preferably acid addition salt formed by means of pharmaceutically acceptable free acid. The expression of pharmaceutically acceptable salt represents a certain organic or inorganic addition salt of the Chemical Formula 1 which is not toxic to patients with a concentration having a non-harmful effective operation and has a side effect which does not worsen a beneficial effect of the compound of the Chemical Formula 1. In the above salt, free acid consists of inorganic acid and organic acid, and the inorganic acid can be hydrochloric acid, bromic acid, nitric acid, sulfuric acid, perchloric acid, phosphoric acid, and the like, and the organic acid can be citric acid, acetic acid, lactic acid, maleic acid, fumaric acid, gluconic acid, glycolic acid, succinic acid, tartaric acid, galacturonic acid, embonic acid, glutamic acid, aspartic acid, oxalic acid, D- or L-malic acid, methanesulfonic acid, ethanesulfonic acid, 4-toluene sulfonic acid, salicylic acid, benzoic acid or malonic acid. The salts may consist of alkaline metallic salt (sodium salt, potassium salt, and the like.) and alkaline earth metallic salt (calcium salt, magnesium salt, and the like.) For example, the acid addition salt may be acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camcilate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iode, isethionate, lactate, maleate, maleate, malonate, mesylate, methylsulfate, naphthylate, 2-naphsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/di-hydrogen phosphate, saccharate, stearate, succinate, tartarate, tosylate, trifluoroacetate, aluminum, arginine, benzathine, calcium, choline, diethyamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine, and the like, among which hydrochloride and trifluoroacetate are preferred.

Also, the imidazole derivatives represented by the Chemical Formula 1 according to
The present invention includes pharmaceutically acceptable salts as well as all salts and hydrates and solvates thereof which can be prepared using a conventional method.

The addition salts according to the present invention may be prepared using conventional methods. For example, they may be prepared by dissolving the compound of Chemical Formula 1 in a water-miscible organic solvent, such as acetone, methanol, ethanol or acetonitrile and adding an excess of organic acids or an excess of aqueous inorganic acid solutions so as to precipitate or crystallize. These addition salts may be obtained by distilling the solvent or excess of acids from the solution or by suctioning and filtering the precipitates.

Also, the present invention provides methods for preparing the novel imidazole derivatives represented by the Chemical Formula 1 or pharmaceutically acceptable salts thereof.

The compound of the Chemical Formula 1 according to the present invention may be prepared by the methods of the following Reaction Schemes 1-5.

The preparation methods will be described with reference to the Reaction Scheme.

Preparation method 1

The method for preparing the imidazole derivatives of the Chemical Formula 1 or pharmaceutically acceptable salts thereof of the present invention may be comprised, as represented by the Reaction Scheme 1:

(1) reacting a compound of Chemical Formula 2 as a starting material with a compound of Chemical Formula 3 to obtain a compound of Chemical Formula 4;

(2) conducting Buchwald amination reaction with the compound of Chemical Formula 4 of step 1 and a compound of Chemical formula 5 to obtain a compound of Chemical Formula 6;

(3) oxidating the compound of Chemical Formula 6 of step 2 to obtain a compound of Chemical Formula 7;

(4) reacting the compound of Chemical Formula 7 of step 3 with R’NH₂ to obtain a compound of Chemical Formula 8; and

(5) reducting the compound of Chemical Formula 8 of step 4 to obtain a compound of Chemical Formula 1a;

[Reaction Scheme 1]
[91] (wherein, \( R \) is as defined in Chemical Formula 1, and the compound of the Chemical Formula 1a belongs to the compound of the Chemical Formula 1).

[92] In more details, the step 1 consists of a step for mixing the compound of the Chemical Formula 2 with methanol and 25% of sodium methoxide methanol solution and agitating the mixture, a step for adding acetic acid, amino acetaldehyde dimethylacetal (Chemical Formula 3) and agitating the mixture, and a step for lowering the temperature to a room temperature, adding methanol and 6N HCl aqueous solution and agitating and circulating the mixture for 3 hours at 70 °C, from which the compound of the Chemical Formula 4 can be prepared.

[93] The step 2 can be performed by using the conventional Buchwald amination reaction. For example, the compound of the Chemical Formula 4, the compound of the Chemical Formula 5, Pd(OAC)\(_2\), BINAP and K\(_3\)PO\(_4\) are all dissolved in toluene, and are agitated and circulated for 3 hours at 130 °C for thereby preparing the compound of the Chemical Formula 6.

[94] In the step 3, the compound of the Chemical Formula 7 may be prepared by using the conventional oxidation method.

[95] In the step 4, the compound of the Chemical Formula 8 may be prepared by reacting the compound of the Chemical Formula 7 with \( R' \)NH\(_2\) and the conventional substitution reaction.
In the step 5, the compound of the Chemical Formula 1a in which -NO substitute is reduced with -NH₂ by using the conventional reduction reaction.

Preparation method 2

In accordance with another aspect thereof, the method for preparing the derivatives of the Chemical Formula 1 or pharmaceutically acceptable salts thereof of the present invention may be further comprises, as represented by the Reaction Scheme 2:

(6) reacting the compound of the Chemical Formula 1a with the isocyanate compound through the coupling reaction to obtain a compound of Chemical Formula 1b;

[Reaction Scheme 2]

<table>
<thead>
<tr>
<th>(Reaction Scheme 2)</th>
</tr>
</thead>
</table>

In more details, in the step 6, the compound of the Chemical Formula 1b is prepared by mixing Tetrahydrofuran (THF) with the compound of the Chemical Formula 1a and the R³-NCO compound as a reaction solvent and by performing the coupling reaction at a room temperature.

Preparation method 3
In accordance with a further another aspect thereof, the method for preparing the derivatives of the Chemical Formula 1 or pharmaceutically acceptable salts thereof of the present invention may be further comprises, as represented by the Reaction Scheme 3:

(6') reacting the compound of the Chemical Formula 1a with carboxyl acid compound through a coupling reaction to obtain a compound of Chemical Formula 1c;

[Reaction Scheme 3]

![Chemical Reaction Scheme 3]

(1') reacting a compound of Chemical Formula 9 as a starting material with a...
compound of Chemical Formula 10 to obtain a compound of Chemical Formula 11;

(2) conducting Buchwald amination reaction with the compound of Chemical Formula 11 of step 1' and a compound of Chemical formula 5 to obtain a compound of Chemical Formula 12;

(3) oxidating the compound of Chemical Formula 12 of step 2 to obtain a compound of Chemical Formula 13;

(4) reacting the compound of Chemical Formula 13 of step 3 with R'NH₂ to obtain a compound of Chemical Formula 14;

(5) reducting the compound of Chemical Formula 14 of step 4 to obtain a compound of Chemical Formula 15; and

(6) reacting the compound of Chemical Formula 15 with the isocyanate through the coupling reaction to obtain a compound of Chemical Formula 1d;

[Reaction Scheme 4]

(wherein, R¹ and R³ are as defined in Chemical Formula 1, and the compounds of the Chemical Formula 1d belongs to the compound of Chemical Formula 1).

In more details, the step 1' consists of a step for mixing the compound of the Chemical Formula 9 with triethylamine and pyridine and agitating at below 0°C, and a step for adding the compound of the Chemical Formula 10 and increasing the tem-
temperature to a room temperature and agitating the mixture, from which the compound of the Chemical Formula 1 may be prepared.

[131] The steps 2-6 are performed in the same method as the method of the Reaction Scheme 2.

[132] Preparation method 5

[133] In accordance with a further another aspect thereof, the method for preparing the derivatives of the Chemical Formula 1 or pharmaceutically acceptable salts thereof of the present invention may be further comprises, as represented by the Reaction Scheme 5:

[135] (6') reacting the compound of the Chemical Formula 15 with carboxyl acid compound through a coupling reaction to obtain a compound of Chemical Formula 1e;

[136] [Reaction Scheme 5]

(9) reacting the compound of the Chemical Formula 9 with carboxyl acid compound through a coupling reaction to obtain a compound of Chemical Formula 10;

[137] [Reaction Scheme 5]

(10) reacting the compound of the Chemical Formula 10 with carboxyl acid compound through a coupling reaction to obtain a compound of Chemical Formula 11;

[138] (wherein, R¹ and R³ are as defined in Chemical Formula 1, and the compounds of the Chemical Formula 1e belongs to the compound of the Chemical Formula 1).

[139] In more details, the steps 1'-5 are performed in the same method as the method of the Reaction Scheme 4, and the step 6' is performed in the same method as the method of the Reaction Scheme 4 from which the compound according to the present invention may be prepared.
The present invention provides pharmaceutical compositions for prevention and treatment of melanoma containing the imidazole derivatives represented by the Chemical Formula 1 or pharmaceutically acceptable salt thereof as active ingredients.

The present invention provides a melanoma treatment method which includes a step for administrating the imidazole derivatives represented by the Chemical Formula 1 or pharmaceutically acceptable salts thereof to patients who need the same by the therapy-effective amount.

The present invention provides a usage of the imidazole derivatives or pharmaceutically acceptable salts thereof in the preparation of a melanoma treatment agent.

The V600E, which is one of the point mutations of B-RAF, is an important molecular target found in more than 60% of melanoma, which was proved through an experiment tube (in vitro) or animal experiment (in vivo) (Liang S. et al. Cancer Res 2007 67(12), 5814-5820). In addition, when inhibiting mutant B-RAF by using siRNA in melanoma cell of a human being, both MEK and ERK are inhibited, so the growth of tumor cells stops for thereby accelerating the death of cells (Sharma, et al. Cancer Res. 65:2412-2412 (2005); and Wellbrock et al., Cancer Res. 64:2338-2342 (2004)), and in a short-hairpin RNA xenograft model experiment, which has a target on B-RAF mutants, it is known that the inhibition of B-RAF can induce an inhibitory effect on tumor and can be reversely adjusted (Hoeflich et al., Cancer Res. 66:999-1006 (2006). Summarizing the above descriptions, the B-RAF in vivo signal transduction system is deeply involved in the growth of tumor, in particular in the growth of melanoma, as a result of which it can confirm that B-RAF can be an important target of anti-melanoma treatment.

The imidazole derivatives represented by the Chemical Formula 1 or pharmaceutically acceptable salts thereof showed an excellent inhibitory effect as a result of the growth inhibitory activity experiment of A375P and WM3629 human melanoma cell lines, which showed that GI₅₀ values were 10 or below 10 μM (refer to Tables 1 and 2).

Also, the imidazole derivatives represented by the Chemical Formula 1 or pharmaceutically acceptable salts thereof showed an excellent inhibitory effect on a variety of protein kinases, for example, B-RAF, C-RAF, Aurora-A, BTK, Flt3, Ret, KDR/VEGFR2, MAPK14, RAF1, FMS, and the like, which cause melanoma (refer to Tables 3 and 4).

Therefore, pharmaceutical compositions containing the imidazole derivatives or pharmaceutically acceptable salts thereof as active ingredients can be used for
prevention and treatment of melanoma.

[151] The compounds according to the present invention may be clinically administrated in oral or non-oral forms. It is usually formulated using diluent or additive, such as a filler, a diluent, a binder, a wetting agent, a disintegrant, a surfactant, and the like.

[152] The solid agents intended for oral administration may be tablets, pills, powers, granules, capsules, trochess, and the like. The solid agents are prepared by adding to the compound of the present invention at least one of additives such as starch, calcium carbonate, sucrose or lactose, or gelatin. In addition, a lubricant such as magnesium, stearate, talc, and the like, can be used in addition to common additives. The liquid agents for oral administration may be suspensions, solutions, emulsions, syrups, and the like. In addition to a simple diluent such as water or liquid paraffin, various excipients, such as wetting agents, sweetening agents, aromatics, preservatives, and the like may be contained in the liquid agents for the oral administration of the compound of the present invention.

[153] The compound of the present invention may be administered via a non-oral route. For this, sterile aqueous solutions, non-aqueous solvents, suspensions, emulsions, lyophilics, suppositories, and the like may be used. Injectable propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and esters such as ethyl oleate may be suitable for non-aqueous solvents and suspensions. The basic materials of suppositories include witepsol, macrogol, tween 61, cacao butter, laurin butter, glycerol, gelatin, and the like.

[154] Depending on the conditions of patients, including age, body weight, sex, administration route, health state, and disease severity, the effective administration dosage of the compound of the present invention to humans may vary. Typically, the compound of the present invention is administrated at a dosage from 0.001 to 100 mg/kg/day, and preferably at a dosage from 0.01 to 35 mg/kg/day. When the weight of a patient is 70 kg, the effective dosage is from 0.07 to 7000 mg/day, preferably from 0.7 to 2500 mg/day. The administration can be done once per day or a couple times per day at regular intervals depending on the decision of a doctor or a pharmacist.

[155] Mode for the Invention

[159] The Examples of the present invention will be described as follows. The following Examples are proposed only for the illustrative purposes, the contents of which are not limited by the following disclosed descriptions.
Step 1: Preparation of 2-(3-nitrophenyl)-1H-imidazole

3-nitrobenzonitrile (1.0 g, 6.75 mmol), methanol (3.38 ml) and 25% sodium methoxide methanol solution (0.145 ml) were mixed and stirred for 5 hours. Upon the completion of the reaction, acetic acid (78 mmol), aminoacetaldehyde dimethylacetal (735.5 mmol) were slowly added and stirred for 1 hour at 70 °C. Upon the completion of the reaction, the reaction mixture was cooled to room temperature, and methanol (4.5 ml) and 6N HCl aqueous solution (3.38 ml) were added and stirred under reflux for 3 hours at 70 °C. Upon the completion of the reaction, the solvent was removed under reduced pressure, and saturated potassium carbonate aqueous solution was slowly added, and the pH value was adjusted to 8-10. The mixture was extracted three times with ethyl acetate, dried over magnesium sulfate and filtered. The filtrate was distilled under reduced pressure, and the concentrated residue was purified and separated by column chromatography (silica gel, methylene chloride/methanol=9/1) for thereby preparing a target compound (890 mg, 70%).

Η NMR (400 MHz, DMSO-d$_6$) δ 12.91 (1H, s), 8.78 (1H, s), 8.34 (1H, d, J = 9.82 Hz), 8.17 (1H, dd, J = 1.49 Hz, J = 1.53 Hz), 7.74 (1H, t, J = 16.0 Hz), 7.24 (2H, br).

Step 2: Preparation of 2-(methylthio)-4-(2-3-nitrophenyl)-1H-imidazol-1-ylpyrimidine

2-(3-nitrophenyl)-1H-imidazole (200 mg, 1.057 mmol) prepared in the step 1, 4-chloro-2-(methylthio)pyrimidine (169.81 mg, 1.057 mmol), Pd(OAC)$_2$ (23.8 mg, 0.106 mmol), BINAP (66.0 1 mg, 0.106 mmol) and K$_3$PO$_4$ (448.8 mg, 2.11 mmol) were dissolved in toluene (5.23 ml) and stirred under reflux for 3 hours at 130 °C. Upon the completion of the reaction, the reaction mixture was cooled to room temperature and filtered with celite, and the filtrate was distilled and concentrated under reduced pressure. The residue was purified with column chromatography (silica gel, hexane/ethyl acetate=1/1) for thereby preparing a target compound (207 mg, 61.4%).

Η NMR (400 MHz, DMSO-d$_6$) δ 8.74 (1H, d, J = 5.41Hz), 8.37 (1H, s), 8.28 (1H, d,
\[ J = 5.8 \text{ Hz}, \ 7.99 \ (1\ H, \ d, \ J = 1.46 \text{ Hz}), \ 7.83 \ (1\ H, \ d, \ J = 1.06 \text{ Hz}), \ 7.69 \ (1\ H, \ t, \ J = 8.2 \text{ Hz}), \ 7.34 \ (1\ H, \ s), \ 7.33 \ (1\ H, \ d, \ J = 0.96 \text{ Hz}), \ 2.07 \ (3\ H, \ s) \]

[171]

Step 3: Preparation of 2-(methylsulfonyl)-4-(2-3-nitrophenyl)-lH-imidazol-1-vDpyrimidine

\[
\begin{align*}
\text{MeO}_2S &- \underline{\text{N}} & & N \\
& & & & \underline{\text{N}} & & & & \underline{\text{N}} \\
& & & & & & & & \text{NO}_2
\end{align*}
\]

[174] 2\'(methylthio)-4-(2-3-nitrophenyl)-lH-imidazol-1-yl)pyrimidine (207 mg, 0.661 mmol) prepared in the step 2 and 70\% m-CPBA (488.5 mg, 1.982 mmol) were dissolved in methylene chloride (6.6 ml) and stirred for 8 hours at a room temperature. Upon the completion of the reaction, the reaction mixture was extracted with ethyl acetate, and washed with sodium hydrogen carbonate saturated aqueous solution. The extracted organic layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was distilled under reduced pressure. The residue was purified with column chromatography (silica gel, methylene chloride/methanol=10/1) for thereby preparing a target compound of 2-(methylsulfonyl)-4-(2-3-nitrophenyl)-lH-imidazol-1-yl)pyrimidine (220 mg, 96\%).

[175] \[ \text{NMR} \ (400 \text{ MHz, CDCl}_3) \delta 8.86 \ (1\ H, \ d, \ J = 7.32 \text{ Hz}), \ 8.38 \ (1\ H, \ s), \ 8.32 \ (1\ H, \ d, \ J = 10.9 \text{ Hz}), \ 7.82 \ (1\ H, \ d, \ J = 10.3 \text{ Hz}), \ 7.78 \ (1\ H, \ s), \ 7.65 \ (1\ H, \ t, \ J = 10.6 \text{ Hz}), \ 7.37 \ (1\ H, \ s), \ 7.21 \ (1\ H, \ d, \ J = 7.33 \text{ Hz}), \ 3.22 \ (3\ H, \ s) \]

Step 4: Preparation of (SVl-(4-(2-3-nitrophenylV1 H -imidazol-1-yl)pyrimidin2-ylamino)propan-2-ol

\[
\begin{align*}
\text{HO} &- \underline{\text{N}} & & N \\
& & & & \underline{\text{N}} & & & & \underline{\text{N}} \\
& & & & & & & & \text{NO}_2
\end{align*}
\]

[179] 2-(methyl sulfonyl)-4-(2-3-nitrophenyl)-lH-imidazol-1-yl)pyrimidine (150 mg, 0.434 mmol) prepared in the step 3 and (S)-l-aminopropan-2-ol (48.94 mg, 0.652 mmol) were dissolved in THF (4.3 ml) and stirred for 8 hours at 60 °C. Upon the completion of the reaction, the reaction mixture was cooled at room temperature and distilled under reduced pressure, and the residue was purified with column chromatography (silica gel, ethyl acetate) for thereby preparing a target compound (110 mg, 75\%).

[180] \[ \text{NMR} \ (300 \text{ MHz, CDCl}_3) \delta 8.42 \ (1\ H, \ s), \ 8.26 \ (1\ H, \ s), \ 8.24 \ (1\ H, \ s), \ 7.85 \ (1\ H, \ d, \ J = 7.67 \text{ Hz}), \ 7.58 \ (2\ H, \ m), \ 7.30 \ (1\ H, \ s), \ 6.29 \ (1\ H, \ s), \ 3.84 \ (2\ H, \ m), \ 3.30 \ (1\ H, \ m), \ 1.16 \]
Step 5: Preparation of (S)-l-(4-(2-(3-aminophenyl)-lH-imidazol-1-yl)pyrimidin-2-ylamino)propan-2-ol

(S)-l-(4-(2-(3-nitrophenyl)-lH-imidazol-1-yl)pyrimidin-2-ylamino)propan-2-ol (110 mg, 0.323 mmol) prepared in the step 4 was dissolved in methanol (3.23 mL), and 10% Pd/C (11 mg) was added, and the mixture was stirred for 6 hours at room temperature in hydrogen gas environment. Upon the completion of the reaction, the reaction mixture was filtered with celite, and the filtrate was distilled under reduced pressure. The residue was purified with column chromatography (slica gel, methylene chloride/methanol=10/1) for thereby preparing (S)-l-(4-(2-(3-aminophenyl)-lH-imidazol-1-yl)pyrimidin-2-ylamino)propan-2-ol (50 mg, 50%).

^H NMR (400 MHz, CDC13) δ 8.13 (1H, d, J = 5.34 Hz), 7.56 (1H, s), 7.18 (1H, d, J = 1.30 Hz), 7.10 (1H, t, J = 8.10 Hz), 6.86 (1H, s), 6.73 (2H, m), 6.15 (1H, br), 5.68 (1H, br), 3.97 (1H, br), 3.48 (1H, m), 3.25 (2H, m), 1.21 (3H, d, J = 6.05 Hz)

Example 2: Preparation of
(S)-1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-lH-imidazol-2-yl)phenyl)urea

(S)-l-(4-(2-(3-aminophenyl)-lH-imidazol-1-yl)pyrimidin-2-ylamino)propan-2-ol (6 mg, 0.019 mmol) prepared in the Example 1 and 1-chloro-4-isocyanato-2-(trifluoromethyl)benzene (6.425 mg, 0.029 mmol) were added to THF (0.2 mL) and stirred for 12 hours at room temperature. Upon the completion of the reaction, the reaction mixture was extracted with ethyl acetate and washed with sodium hydrogen carbonate saturated aqueous solution. The washed organic layer was dried over anhydrous sulfuric acid magnesium and was filtered, and the filtrate was distilled under reduced pressure. The residue was purified with column chromatography (slica gel, methylene chloride/methanol=10/1) for thereby preparing a target compound (6 mg, 59.4%).
The following compounds were prepared in the same method as the Example 2.

<Example 3> Preparation of (S)-1-(3-(1-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(3-morpholino-5-(trifluoromethyl)phenyl)urea

<Example 4> Preparation of (S)-1-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(6-methylbenzo[d]thiazol-2-yl)urea

<Example 5> Preparation of (S)-1-(3,4-dichlorophenyl)-3-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)urea
[204] ¹H NMR (400 MHz, CDCl₃) δ 8.20 (IH, s), 8.16 (IH, s), 7.55-7.51 (2 H, m), 7.27 (IH, s), 7.23-7.18 (3 H, m), 7.13-7.07 (3 H, m), 6.91 (IH, J = 7.13 Hz), 6.22 (IH, s), 5.61-5.60 (IH, br), 4.98-4.96 (IH, br), 3.48-3.47 (IH, m), 3.18-3.00 (2 H, m), 1.27 (3 H, t, J = 9.24 Hz)

[205]  

[206] <Example 6> Preparation of (S)-l-(4-(2-(3-(3,4-dichlorophenyl)ureido)phenyl)-lH-imidazol-1-yl)pyrimidin-2-ylamino)propan-2-yl acetate

[207]  

[208] ¹H NMR (400 MHz, CDCl₃) δ 8.17 (IH, s), 8.09 (IH, s), 7.69-7.63 (2 H, m), 7.52-7.45 (3 H, m), 7.32-7.29 (2 H, m), 7.21-7.18 (3 H, m), 6.28 (IH, s), 5.91-5.90 (IH, br), 3.74-3.73 (IH, m), 3.49-3.46 (2 H, m), 2.12 (3 H, s), 1.25 (3 H, t, J = 2.88 Hz)

[209]  

[210] <Example 7> Preparation of (S)-l-(3-(l-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-lH-imidazol-2-yl)phenyl)-3-(2,4,5-trichlorophenyl)urea

[211]  

[212] ¹H NMR (400 MHz, CDCl₃) δ 9.45 (IH, s), 8.44 (IH, s), 8.28 (IH, s), 8.19 (IH, d, J = 5.13 Hz), 7.40-7.22 (3 H, m), 7.18 (IH, s), 7.09 (IH, s), 6.90 (IH, d, J = 3.68 Hz), 6.22 (IH, s), 5.81-5.80 (IH, br), 5.59 (IH, d, J = 4.04 Hz), 5.04-5.02 (IH, br), 3.92-3.90 (IH, m), 3.50-3.48 (2 H, m), 1.23 (3 H, t, J = 10.7 Hz)

[213]  

[214] <Example 8> Preparation of (S)-l-(3-chlorophenyl)-3-(3-(l-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-lH-imidazol-2-yl)phenyl)urea

[215]
[216] ¹H NMR (400 MHz, DMSO-d₆) δ 9.19 (1 H, s), 9.02 (1 H, s), 8.26 (1 H, d, J = 5.21 Hz), 7.78 (1 H, s), 7.66 (1 H, s), 7.58 (1 H, m), 7.50 (1 H, d), 7.36 (1 H, d, J = 18.96 Hz), 7.34-7.30 (3 H, d, J = 9.19 Hz), 7.23 (1 H, d, J = 14.5 Hz), 7.18 (1 H, s), 7.14 (1 H, d, J = 1.24 Hz), 6.35-6.16 (1 H, s), 4.69-4.54 (1 H, s), 3.77-3.58 (1 H, broad-d), 2.93 (2 H, s), 1.0 (3 H, br)

[217]  <Example 9> Preparation of (S)-1-(3-(l-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-lH-imidazol-2-yl)phenyl)-3-(4-morpholinophenyl)urea

[219]  <Example 9> Preparation of (S)-1-(3-(l-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-lH-imidazol-2-yl)phenyl)-3-(4-morpholinophenyl)urea

[220] ¹H NMR (400 MHz, DMSO-d₆) δ 9.19 (1 H, s), 9.02 (1 H, s), 8.26 (1 H, d, J = 5.21 Hz), 7.78 (1 H, s), 7.66 (1 H, s), 7.58 (1 H, m), 7.50 (1 H, d), 7.36 (1 H, d, J = 18.96 Hz), 7.34-7.30 (3 H, d, J = 9.19 Hz), 7.23 (1 H, d, J = 14.5 Hz), 7.18 (1 H, s), 7.14 (1 H, d, J = 1.24 Hz), 6.35-6.16 (1 H, s), 4.69-4.54 (1 H, s), 3.77-3.58 (1 H, broad-d), 2.93 (2 H, s), 1.0 (3 H, br)

[221]  <Example 10> Preparation of (S)-1-(3-(l-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-lH-imidazol-2-yl)phenyl)-3-(3-(trifluoromethyl)phenyl)urea

[223]  <Example 10> Preparation of (S)-1-(3-(l-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-lH-imidazol-2-yl)phenyl)-3-(3-(trifluoromethyl)phenyl)urea

[224] ¹H NMR (400 MHz, DMSO-d₆) δ 9.19 (1 H, s), 9.02 (1 H, s), 8.26 (1 H, d, J = 5.21 Hz), 8.01 (1 H, s), 7.66 (1 H, s), 7.58 (1 H, m), 7.50 (1 H, d), 7.47 (2 H, d, J = 18.96 Hz), 7.34-7.30 (3 H, d, J = 9.19 Hz), 7.18 (1 H, s), 7.14 (1 H, d, J = 1.24 Hz), 6.35-6.16 (1 H, s), 4.69-4.54 (1 H, s), 3.77-3.58 (1 H, broad-d), 2.93 (2 H, s), 1.0 (3 H, br)

[225]  <Example 11> Preparation of (S)-1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-l(2-(2-hydroxypropylamino)-pyrimi
din-4-yl)-1H-imidazol-2-yl)phenyl)urea

[228] H NMR (400 MHz, CDCl$_3$) $\delta$ 8.49 (IH, s), 8.23 (IH, d, J = 5.18 Hz), 8.01 (IH, d, J = 8.26 Hz), 7.87-7.74 (2H, m), 7.55-7.49 (2H, m), 7.42 (IH, s), 7.35 (IH, d, J = 8.68 Hz), 6.66 (2H, d, J = 8.62 Hz), 6.55 (IH, d, J = 4.99 Hz), 5.43-5.33 (IH, br), 4.83-4.80 (IH, br), 3.49-3.43 (IH, m), 3.02-2.95 (2H, m), 1.28 (3H, t, J = 9.7 Hz)

[229] <Example 12> Preparation of (S)-l-(3,4-dichlorophenyl)-3-(4-(l-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)urea

[231] H NMR (400 MHz, DMSO-d$_6$) $\delta$ 9.07 (IH, s), 9.00 (IH, s), 8.28 (IH, d, J = 5.24 Hz), 7.88 (IH, d, J = 2.49 Hz), 7.68-7.62 (IH, m), 7.53-41 (3H, m), 7.34-7.31 (4H, m), 7.14 (IH, d, J = 1.4 Hz), 6.35-6.16 (IH, br), 4.69-4.54 (IH, br), 3.58-3.32 (IH, m), 3.17-2.93 (2H, m), 1.05 (3H, t, J = 9.3 Hz)

[233] <Example 13> Preparation of (S)-l-(4-((l-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(2,4,5-trichlorophenyl)urea

[235] H NMR (400 MHz, CDCl$_3$) $\delta$ 9.44 (IH, s), 8.53 (IH, s), 8.28 (IH, s), 8.21 (IH, d, J = 4.15 Hz), 7.44-7.25 (3H, m), 7.20 (IH, s), 7.08 (IH, s), 6.86 (IH, d, J = 2.98 Hz), 6.24 (IH, s), 5.80-5.78 (IH, br), 5.60 (IH, d, J = 4.12 Hz), 5.04-5.02 (IH, br), 3.90-3.84 (IH, m), 3.53-3.44 (2H, m), 1.25 (3H, t, J = 6.34 Hz)

[237] <Example 14> Preparation of (S)-l-(4-chlorophenyl)-3-(4-(l-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)thiourea
[239] \[
\text{H NMR } (400 \text{ MHz, } \text{CDCl}_3) \delta 8.59 (1\text{H}, s), 8.47 (1\text{H}, s), 8.21 (1\text{H}, d, J = 5.13 \text{ Hz}), 7.44-7.29 (10 \text{H}, m), 7.20 (1\text{H}, d, J = 1.08 \text{ Hz}), 6.22-6.14 (1\text{H}, br), 5.51 (1\text{H}, d, J = 3.52 \text{ Hz}), 3.82-3.21 (3 \text{H}, m), 1.25 (3 \text{H}, t, J = 7.16 \text{ Hz})
\]

[240] <Example 15> Preparation of
(S)-l-(4-(l-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-l H-imidazol-2-yl)phenyl)urea

[233]

[243] \[
\text{H NMR } (400 \text{ MHz, } \text{DMSO-d}_6) \delta 9.19 (1\text{H}, s), 9.02 (1\text{H}, s), 8.27 (1\text{H}, d, J = 5.21 \text{ Hz}), 8.01 (1\text{H}, s), 7.66 (1\text{H}, s), 7.58 (1\text{H}, m), 7.50 (1\text{H}, d), 7.36 (1\text{H}, d, J = 18.96 \text{ Hz}), 7.34-7.30 (3 \text{H}, d, J = 9.19 \text{ Hz}), 7.23 (1\text{H}, d, J = 14.5 \text{ Hz}), 7.18 (1\text{H}, s), 7.14 (1\text{H}, d, J = 1.24 \text{ Hz}), 6.35-6.16 (1\text{H}, s), 4.69-4.54 (1\text{H}, s), 3.77-3.58 (1\text{H}, broad-d), 2.93 (2 \text{H}, s), 1.0 (3 \text{H}, br)
\]

[244] <Example 16> Preparation of
(S)-l-(4-(l-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-l H-imidazol-2-yl)phenyl)-3-(4-morpholinophenyl)urea

[247] \[
\text{H NMR } (400 \text{ MHz, } \text{DMSO-d}_6) \delta 8.76 (1\text{H}, s), 8.48 (1\text{H}, s), 8.27 (1\text{H}, d, J = 5.24 \text{ Hz}), 7.72-7.54 (2 \text{H}, br), 7.47 (2\text{H}, d, J = 8.43 \text{ Hz}), 7.29 (3 \text{H}, d, J = 9.19 \text{ Hz}), 7.25 (1\text{H}, s), 7.17 (1\text{H}, s), 6.91 (1\text{H}, d, J = 8.09 \text{ Hz}), 6.87 (1\text{H}, d, J = 9.05 \text{ Hz}), 6.35-6.16 (1\text{H}, s), 4.69-4.54 (1\text{H}, s), 3.77-3.58 (1\text{H}, broad-d), 3.72 (4\text{H}, t, J = 4.15 \text{ Hz}), 3.01 (4\text{H}, t, J = 4.15 \text{ Hz}), 2.93 (2 \text{H}, s), 1.0 (3 \text{H}, br)
\]

[248] <Example 17> Preparation of
(S)-l-(4-(l-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-l H-imidazol-2-yl)phenyl)-3-(3-(trifluoromethyl)phenyl)urea

[250] \[
\text{H NMR } (400 \text{ MHz, } \text{DMSO-d}_6) \delta 8.76 (1\text{H}, s), 8.48 (1\text{H}, s), 8.27 (1\text{H}, d, J = 5.24 \text{ Hz}), 7.72-7.54 (2 \text{H}, br), 7.47 (2\text{H}, d, J = 8.43 \text{ Hz}), 7.29 (3 \text{H}, d, J = 9.19 \text{ Hz}), 7.25 (1\text{H}, s), 7.17 (1\text{H}, s), 6.91 (1\text{H}, d, J = 8.09 \text{ Hz}), 6.87 (1\text{H}, d, J = 9.05 \text{ Hz}), 6.35-6.16 (1\text{H}, s), 4.69-4.54 (1\text{H}, s), 3.77-3.58 (1\text{H}, broad-d), 3.72 (4\text{H}, t, J = 4.15 \text{ Hz}), 3.01 (4\text{H}, t, J = 4.15 \text{ Hz}), 2.93 (2 \text{H}, s), 1.0 (3 \text{H}, br)
\]
[251] 

[252] H NMR (400 MHz, DMSO-d$_6$) δ 9.19 (1 H, s), 9.02 (1 H, s), 8.26 (1 H, d, J = 5.21 Hz), 8.01 (1 H, s), 7.66 (1 H, s), 7.58 (1 H, m), 7.50 (1 H, d), 7.47 (2 H, d, J = 18.96 Hz), 7.34-7.30 (3 H, d, J = 9.19 Hz), 7.18 (1 H, s), 7.14 (1 H, d, J = 1.24 Hz), 6.35-6.16 (1 H, s), 4.69-4.54 (1 H, s), 3.77-3.58 (1 H, broad-d), 2.93 (2 H, s), 1.0 (3 H, br)

[253] <Example 18> Preparation of (S)-4-chloro-N-(3-(l-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-lH-imidazol-2-yl)phenyl)-3-(trifluoromethyl)benzamide

[254] The following compounds were prepared in the same method as Example 18.

[255] <Example 19> Preparation of (S)-N-(3-(l-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-lH-imidazol-2-yl)phenyl)-3-(trifluoromethyI)benzamide
[262] 4-methylpiperazin-1-yl)-5-(trifluoromethyl)benzamide

[263] ^1H NMR (400 MHz, DMSO-d$_6$) δ 10.42 (IH, s), 8.29 (IH, d, J = 5.28 Hz), 7.94 (1H, s), 7.84 (IH, d, J = 7.45 Hz), 7.74-7.68 (2 H, m), 7.59 (IH, s), 7.37-7.30 (3 H, m), 7.19 (IH, d, J = 1.15 Hz), 7.08-7.07 (IH, br), 4.60-4.59 (IH, br), 3.75-3.73 (IH, m), 3.64-3.47 (2 H, m), 2.50 (8 H, s), 2.24 (3 H, s), 1.03 (3 H, t, J = 8.42 Hz)

[264] <Example 20> Preparation of (S)-N-(3-(l-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-lH-imidazol-2-yl)phenyl)-3-(4-methyl-lH-imidazol-1-yl)-5-(trifluoromethyl)benzamide

[265] 4-methylpiperazin-1-yl)-5-(trifluoromethyl)benzamide

[266] <Example 21> Preparation of (S)-N-(3-(l-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-lH-imidazol-2-yl)phenyl)-4-morpholino-3-(trifluoromethyl)benzamide

[267] ^1H NMR (400 MHz, CDC1$_3$) δ 10.20 (IH, s), 8.23-8.05 (4 H, m), 7.83 (IH, s), 7.62-7.47 (3 H, m), 7.38 (IH, s), 7.00-6.92 (3 H, m), 6.16 (IH, s), 5.92-5.91 (IH, br), 3.89-3.88 (IH, m), 3.25-3.14 (2 H, m), 2.17 (3 H, s), 1.18 (3 H, t, J = 6.78 Hz)

[268] <Example 21> Preparation of (S)-N-(3-(l-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-lH-imidazol-2-yl)phenyl)-4-morpholino-3-(trifluoromethyl)benzamide

[269] ^1H NMR (400 MHz, CDC1$_3$) δ 9.21 (1 H, s), 8.18 (1 H, d, J = 1.73 Hz), 8.14 (1 H, d, J = 5.37 Hz), 8.06 (1 H, dd, J = 1.84 Hz, J = 1.88 Hz), 7.75-7.66 (3 H, m), 7.49 (1 H, d, J = 1.22 Hz), 7.34-7.28 (2 H, m), 7.14 (1 H, s), 7.09 (1 H, d, J = 7.60 Hz), 6.23-6.21 (1
H, br), 5.79-5.78 (1 H, br), 3.83-3.81 (4 H, m), 3.62-3.61 (1 H, m), 3.23-3.18 (2 H, m), 2.99-2.96 (4 H, m), 1.19 (3 H, d, J = 2.90 Hz)

[272]

<Example 22> Preparation of
(S)-N-(3-(1-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-1 H-imidazol-2-yl)phenyl)-3-(trifluoromethyl)benzamide

[274]

\[
\text{HO-} \begin{array}{c}
  \text{N} \\
  \text{N} \\
  \text{O} \\
\end{array} \begin{array}{c}
  \text{CF}_3 \\
  \text{OH} \\
  \text{OMe} \\
\end{array} 
\]

[275] Η NMR (400 MHz, CDCl₃) δ 9.17 (1 H, s), 8.21-8.15 (2 H, m), 8.10 (1 H, d, J = 7.91 Hz), 7.77-7.69 (4 H, m), 7.53-7.50 (2 H, m), 7.33 (1 H, t, J = 7.88 Hz), 7.16 (1 H, d, J = 1.38 Hz), 7.13 (1 H, d, J = 5.58 Hz), 6.26-6.24 (1 H, br), 5.85-5.84 (1 H, br), 3.48-3.46 (1 H, m), 3.20-3.13 (2 H, m), 1.24 (3 H, d, J = 3.22 Hz)

[276]

<Example 23> Preparation of
(S)-N-(3-(1-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-1 H-imidazol-2-yl)phenyl)-5-(4-methoxyphenyl)furan-2-carboxamide

[278]

\[
\text{HO-} \begin{array}{c}
  \text{N} \\
  \text{N} \\
  \text{O} \\
\end{array} \begin{array}{c}
  \text{OMe} \\
  \text{O} \\
  \text{Cl} \\
\end{array} 
\]

[279] Η NMR (400 MHz, CDCl₃) δ 8.68 (1 H, s), 8.26 (1 H, s), 8.20 (1 H, d, J = 5.32 Hz), 7.87-7.79 (2 H, m), 7.74 (1 H, s), 7.67 (1 H, s), 7.50 (1 H, d, J = 1.48 Hz), 7.39 (1 H, t, J = 6.19 Hz), 7.30 (1 H, d, J = 3.5 Hz), 7.21 (1 H, d, J = 1.48 Hz), 6.98 (1 H, s), 6.94 (1 H, s), 6.65 (1 H, d, J = 3.64 Hz), 6.27-6.26 (1 H, br), 5.52-5.47 (1 H, br), 3.83 (3 H, s), 3.62-3.42 (1 H, m), 3.18-3.11 (2 H, m), 1.32 (3 H, d, J = 3.53 Hz)

[280]

<Example 24> Preparation of
(S)-5-(2-chloro-5-(trifluoromethyl)phenyl)-N-(3-(1-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-1 H-imidazol-2-yl)phenyl)furan-2-carboxamide

[282]

\[
\text{HO-} \begin{array}{c}
  \text{N} \\
  \text{N} \\
  \text{O} \\
\end{array} \begin{array}{c}
  \text{Cl} \\
  \text{Cl} \\
  \text{Cl} \\
\end{array} 
\]

[283] Η NMR (400 MHz, CDCl₃) δ 8.46 (1 H, s), 8.20 (1 H, d, J = 5.34 Hz), 8.12 (1 H, d,
J = 1.59 Hz), 7.88-7.70 (2 H, m), 7.65 (1 H, s), 7.61 (1 H, s), 7.55 (1 H, d, J = 1.92 Hz), 7.49 (1 H, d, J = 3.62 Hz), 7.39-7.35 (2 H, m), 7.27 (1 H, s), 7.21 (1 H, d, J = 1.48 Hz), 6.15-6.11 (1 H, br), 5.49-5.47 (1 H, br), 3.53-3.47 (1 H, m), 3.20-3.14 (2 H, m), 1.22 (3 H, d, J = 4.98 Hz)

[284]
<Example 25> Preparation of (S)-5-(4-chlorophenyl)-N-(3-(1-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)isoxazole-3-carboxamide

[285]

[286]

[287] H NMR (400 MHz, CDC13) δ 8.74 (1 H, s), 8.18 (1 H, d, J = 5.33 Hz), 7.74 (1 H, s), 7.73 (1 H, s), 7.51 (1 H, d, J = 1.35 Hz), 7.47 (1 H, s), 7.44 (1 H, s), 7.40 (1 H, t, J = 7.86 Hz), 7.31 (1 H, d, J = 8.24 Hz), 7.22 (1 H, d, J = 1.26 Hz), 7.04 (1 H, s), 6.24-6.23 (1 H, br), 5.46-5.44 (1 H, br), 3.54-3.48 (1 H, m), 3.20-3.15 (2 H, m), 1.23 (3 H, d, J = 7.76 Hz)

[288]
<Example 26> Preparation of (S)-N-(3-(1-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-2-(pyridin-4-yl)thiazole-4-carboxamide

[289]

[290]

[291] H NMR (400 MHz, CDC13) δ 9.34 (1 H, s), 8.79 (1 H, d, J = 1.76 Hz), 8.76 (1 H, d, J = 2.88 Hz), 8.36 (1 H, s), 8.19 (1 H, d, J = 5.35 Hz), 7.94-7.80 (5 H, m), 7.51 (1 H, d, J = 4.75 Hz), 7.40 (1 H, t, J = 7.87 Hz), 7.30 (1 H, d, J = 6.88 Hz), 7.23 (1 H, d, J = 1.48 Hz), 6.27-6.26 (1 H, br), 5.52-5.47 (1 H, br), 3.52-3.49 (1 H, m), 3.19-3.16 (2 H, m), 1.21 (3 H, d, J = 5.91 Hz)

[292]
<Example 27> Preparation of (S)-N-(4-(1-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-morpholino-5-(trifluoromethyl)benzamide
[295] Ή NMR (400 MHz, CDCl$_3$) δ 9.28 (IH, s), 8.30 (IH, s), 8.18 (2 H, d, J = 4.58 Hz), 7.79-7.39 (7 H, m), 7.31-7.18 (3 H, m), 7.11 (IH, s), 6.23-6.20 (IH, br), 5.76-5.68 (IH, br), 3.88-3.81 (5 H, m), 3.28-3.20 (6 H, m), 1.25 (3 H, t, J = 7.16 Hz)

[296] <Example 28> Preparation of
(S)-N-(4-(1-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-4-morpholino-3-(trifluoromethyl)benz amide

[297] Ή NMR (400 MHz, CDCl$_3$) δ 8.63 (IH, s), 8.16 (IH, d, J = 5.22 Hz), 7.67 (2 H, d, J = 8.49 Hz), 7.54 (IH, s), 7.48 (2 H, d, J = 8.56 Hz), 7.22 (IH, d, J = 1.23 Hz), 6.53 (IH, s), 6.15 (IH, s), 5.35-6.26 (IH, br), 4.09-4.00 (IH, br), 3.67-3.55 (IH, m), 2.52 (3 H, s), 2.40-2.52 (2 H, m), 1.25 (3 H, t, J = 6.23 Hz)

[300] <Example 29> Preparation of
(S)-N-(4-(1-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-5-methylisoxazole-3-carboxamide

[304] <Example 30> Preparation of
(S)-5-(4-chlorophenyl)-N-(4-(1-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)isoazole-3-carboxamide

[306] ![Chemical structure](image)

[307] H NMR (400 MHz, DMSO-d$_6$) $\delta$ 10.94 (IH, s), 8.28 (IH, d, $J = 5.24$ Hz), 8.01 (2 H, d, $J = 8.56$ Hz), 7.85 (2 H, d, $J = 8.68$ Hz), 7.68 (2 H, d, $J = 9.24$ Hz), 7.58 (IH, s), 7.42 (2 H, d, $J = 7.84$ Hz), 7.17 (IH, d, $J = 1.44$ Hz), 6.28-6.16 (IH, br), 4.62-4.57 (IH, br), 3.68-3.61 (IH, m), 3.24-3.15 (2 H, m), 1.24 (3 H, t, $J = 6.65$ Hz)

[308] <Example 31> Preparation of

(S)-N-(4-(1-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-5-(4-methoxyphenyl)furan-2-carboxamide

[310] ![Chemical structure](image)

[311] H NMR (400 MHz, DMSO-d$_6$) $\delta$ 10.24 (IH, s), 8.28 (IH, d, $J = 5.52$ Hz), 7.91 (2 H, d, $J = 8.6$ Hz), 7.78 (2 H, d, $J = 10.8$ Hz), 7.67 (IH, br), 7.42-7.40 (IH, m), 7.17-7.13 (2 H, m), 7.07-7.03 (3 H, m), 6.32-6.22 (IH, br), 4.72-4.57 (IH, br), 3.65 (3 H, s), 3.64-3.63 (IH, m), 3.22-3.12 (2 H, m), 1.17 (3 H, t, $J = 7.23$ Hz)

[312] <Example 32> Preparation of

(S)-5-(3-chloro-5-(trifluoromethyl)phenyl)-N-(4-(1-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)furan-2-carboxamide

[314] ![Chemical structure](image)

[315] H NMR (400 MHz, CDC$_1$$_3$) $\delta$ 8.36 (IH, s), 8.17 (IH, s), 8.10 (IH, s), 7.68-7.62 (3 H, m), 7.55 (2 H, d, $J = 8.27$ Hz), 7.47 (2 H, d, $J = 8.28$ Hz), 7.38 (IH, d, $J = 3.66$ Hz), 7.27 (IH, d, $J = 3.74$ Hz), 7.23-7.21 (IH, br), 6.21-6.03 (IH, br), 5.39 (IH, s), 3.74-3.60 (IH, m), 2.57-2.29 (2 H, m), 1.23 (3 H, t, $J = 13.5$ Hz)

[316] <Example 33> Preparation of
(S)-N-(4-(l-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-lH-imidazol-2-yl)phenyl)-l-(4-methoxyphenyl)-5-(trifluoromethyl)-lH-pyrazole-4-carboxamide

\[ \text{H} \text{NMR (400 MHz, CDCl}_3 \} \delta 8.56 (1H, s), 8.17 (1H, d, J = 5.15 Hz), 8.00 (1H, s), 7.52-7.45 (3H, m), 7.45-7.35 (4H, m), 7.13 (1H, s), 7.00 (2H, d, J = 8.76 Hz), 6.22-6.15 (1H, br), 5.37 (1H, d, J = 5.6 Hz), 3.87 (3H, s), 3.80-3.41 (2H, m), 1.9-1.7 (2H, m), 1.26 (3H, t, J = 3.23 Hz) \]

<Example 34> Preparation of (S)-N-(4-(l-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-lH-imidazol-2-yl)phenyl)-2-(pyridin-4-yl)thiazole-4-carboxamide

\[ \text{H} \text{NMR (400 MHz, CDCl}_3 \} \delta 9.33 (1H, s), 8.79-8.78 (2H, m), 8.35 (1H, s), 8.17 (1H, d, J = 5.21 Hz), 7.87-7.85 (2H, m), 7.77 (2H, d, J = 8.05 Hz), 7.54-7.51 (3H, m), 7.23 (1H, d, J = 1.46 Hz), 6.15-6.12 (1H, br), 5.38 (1H, d, J = 5.96 Hz), 4.00-3.93 (1H, m), 3.66-3.45 (2H, m), 1.27 (3H, t, J = 2.56 Hz) \]

<Example 35> Preparation of (S)-1-(4-chlorophenyl)-3-(trifluoromethyl)phenyl)-3-(4-(l-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-lH-imidazole-2-carbonyl)phenyl)urea

Step 1: Preparation of 1H-imidazol-2-yl 4-nitrophenyLmethanon

Imidazole (300 mg, 4.407 mmol) and triethylamine (1.23 ml) were added to pyridine (2.2 ml) at 0 °C and stirred. 4-nitrobenzoylchloride (1.63 g, 8.813 mmol) was slowly added, and the temperature was increased to room temperature slowly. The reaction mixture was stirred for 3 hours. Upon the completion of the reaction, 6N NaOH aqueous solution (3 ml) was added and the reaction mixture was stirred for 1 hour at 100 °C. Upon the completion of the reaction, the temperature was lowered to room
temperature. The pH value was adjusted to 6-7 with 1N HCl, and the reaction mixture was extracted three times with ethyl acetate and washed with water and dried over magnesium sulfate. The filtrate was distilled under reduced pressure, and the concentrated residue was purified and separated by column chromatography (silica gel, ethyl acetate/hexane=1/1) for thereby preparing a target compound (150 mg).

\[329\] \( \text{H}^1 \text{NMR (400 MHz, DMSO-d}_6 \) \( \delta \) 13.69 (1H, s), 8.63 (2H, d, J=8.84 Hz), 8.36 (2H, d, J=8.84 Hz), 7.61 (1H, s), 7.36 (1H, s)

\[330\] Step 2-6: Preparation of
(S)-1-(4-chlorophenyl)-3-(trifluoromethyl)phenyl)-3-(4-(l-(2-hydroxypropylamino)-pyrimidin-4-yl)-1H-imidazole-2-carbonyl)phenyl)urea

\[332\] ![](image)

The steps 2-6 were performed in the same method as Example 2 for thereby preparing a target compound.

\[334\] \( \text{H}^1 \text{NMR (400 MHz, CDC1}_3 \) \( \delta \) 8.49 (1H, s), 8.23 (1H, d, J = 5.18 Hz), 8.01 (1H, d, J = 8.26 Hz), 7.87-7.74 (2H, m), 7.55-7.49 (2H, m), 7.42 (1H, s), 7.35 (1H, d, J = 8.68 Hz), 6.66 (2H, d, J = 8.62 Hz), 6.55 (1H, d, J = 4.99 Hz), 5.43-5.33 (1H, br), 4.83-4.80 (1H, br), 3.49-3.43 (1H, m), 3.02-2.95 (2H, m), 1.28 (3H, d, J = 9.7 Hz)

\[335\] <Example 36> Preparation of
(S)-4-chloro-N-(l-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-lH-imidazole-2-carbonyl)phenyl)-3-(trifluoromethyl)benzamide

\[337\] ![](image)

The step 1 was performed in the same method as Example 35, and the steps 2-6 were performed in the same method as Example 18 for thereby preparing a target compound.

\[339\] \( \text{H}^1 \text{NMR (400 MHz, CDC1}_3 \) \( \delta \) 8.51 (1H, s), 8.32 (1H, d, J = 5.26 Hz), 8.23 (1H, d, J
EXPERIMENTAL  EXAMPLE 1> The measurement of the growth inhibitory activity against A375P cell line (melanoma)

The A375P cells purchased from ATCC were cultured in DMEM medium (supplemented with 10% FBS, 1% penicillin/streptomycin) in a humidified atmosphere with 5% CO\(_2\) at 37 °C. The grown A375P cells were taken culture substrate with 0.05% trypsin-0.02% EDTA and plated at a density of 5x10^3 cells/well in a 96-well plates. MTT[3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] activation search method(CellTiter 96 Assay, Promega) was used in order to measure A357 cell viability. 15 \(\mu\)l of dye was added in each well, and the cells were incubated for 2 hours, and 100 \(\mu\)l of stop solution was added each well, and the absorbance was measured after 24 hours. The compounds were treated one day after plating. 10 mM of stock solution was prepared in the course of compound treatment. The representative compounds of examples were prepared by three fold serial dilution of 10 mM stock solution in DMSO, 12 point, and 0.5 \(\mu\)l of the representative compounds of examples were added (final concentration DMSO 0.5%). The absorbance at 590 nm was measured using EnVision 2103, and GI\(_{50}\) values were calculated using GraphPad Prism 4.0 software.

The results are shown in Table 1, below.

Table 1
As seen in Table 1, GI\textsubscript{50} values of the compound according to the present invention were 10 or below 10 µM, in more detail, GI\textsubscript{50} values were in the range of 0.001-10 µM. Therefore, the imidazole derivatives or pharmaceutically acceptable salts thereof according to the present invention can be used for prevention and treatment of melanoma by inhibiting the growth of the A375P human melanoma cell line in which B-raf-V600E mutants species are over-expressed.

EXPERIMENTAL  EXAMPLE 2> The measurement of the growth inhibitory activity against WM3629 cell line (melanoma)

WM3629 cell lines (KSM Smalley et al, CRAF inhibition induces apoptosis in
as melanoma cells with non-V600E BRAF mutations, 2009, Oncogene) provided from the US Wistar Institute were cultured Tu2 melanoma medium [mixture of 80% MCDB15, 20% L15 with 2 mmol/L Ca²⁺, heat-inactivated fetal bovine serum (2%), insulin (5 mg/mL)] in a humidified atmosphere with 5% CO₂ at 37 °C, and the growth inhibitory activity of the compound according to the present invention against WM3629 cell line was measured by MTT assay in the same manner as the experiment 1. The results of the are shown in Table 2, below.

<table>
<thead>
<tr>
<th>Example</th>
<th>Inhibitory activity against WM3629 cell line (GI₅₀, µM)</th>
<th>Example</th>
<th>Inhibitory activity against WM3629 cell line (GI₅₀, µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 3</td>
<td>&lt;10</td>
<td>Example 19</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Example 4</td>
<td>&lt;10</td>
<td>Example 20</td>
<td>&lt;10</td>
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<td>Example 5</td>
<td>&lt;10</td>
<td>Example 21</td>
<td>&lt;10</td>
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<tr>
<td>Example 6</td>
<td>&lt;10</td>
<td>Example 25</td>
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<td>Example 10</td>
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<td>Example 26</td>
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<td>Example 12</td>
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<td>&lt;10</td>
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<td>&lt;10</td>
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<tr>
<td>Example 17</td>
<td>&lt;10</td>
<td>Example 36</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Example 18</td>
<td>&lt;10</td>
<td>---------</td>
<td>----------------------------------------------------------</td>
</tr>
</tbody>
</table>

As seen in Table 2, GI₅₀ values of the compound according to the present invention were 10 or below 10 µM, in more detail, GI₅₀ values were in the range of 0.001-10 µM.

Therefore, the imidazole derivatives or pharmaceutically acceptable salts thereof
according to the present invention can be used for prevention and treatment of melanoma by inhibiting the growth of the WM3629 human melanoma cell line in which B-raf-D594G and C-RAP mutants species are over-expressed.

EXAMPLE 3> The measurement of the inhibitory activity against various kinases

The following experiments were performed in order to find the inhibitory activity against various kinases of the imidazole derivates or pharmaceutically acceptable salt s thereof according to the present invention.

The inhibitory activity against various kinases at the concentration of 10 µM of the compound prepared in the Example 2 using kinase profiling service (IC_{50} profiler express) of Millipore(Upstate). The results are shown in Table 3, below.

Also, the inhibitory activity against various kinases at the concentration of 1 µM of the compound prepared in the Example 3 by using kinase profiling service (IC_{50} profiler express) of Millipore(Upstate). The results are shown in Table 4, below.

Table 3
<table>
<thead>
<tr>
<th>kinase</th>
<th>Inhibitory activity of 10 μM of the compound of Example 2 (% compared with control)</th>
<th>Enzyme activity IC&lt;sub&gt;50&lt;/sub&gt; (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABL1</td>
<td>43.7</td>
<td></td>
</tr>
<tr>
<td>BRaf (V600E)</td>
<td>95.7</td>
<td>17.37</td>
</tr>
<tr>
<td>AKT1 (dPH, S473D)</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>ALK</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Aurora A</td>
<td>72.2</td>
<td></td>
</tr>
<tr>
<td>c-Kit</td>
<td>61.7</td>
<td></td>
</tr>
<tr>
<td>c-MET</td>
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<td></td>
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<tr>
<td>c-Src</td>
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<td></td>
</tr>
<tr>
<td>CDK1/cyclinB</td>
<td>21.4</td>
<td></td>
</tr>
<tr>
<td>CDK2/cyclinE</td>
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<td></td>
</tr>
<tr>
<td>CDK5/p25</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>CHK1</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>DMPK</td>
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<td></td>
</tr>
<tr>
<td>DNA-PK</td>
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<td></td>
</tr>
<tr>
<td>EGFR/ERBB1</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>ERK2/MAPK1 / P42MAPK</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td>FAK/PTK2</td>
<td>-0.3</td>
<td></td>
</tr>
<tr>
<td>FGFR1</td>
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<td></td>
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<tr>
<td>FLT3</td>
<td>81.6</td>
<td>3490</td>
</tr>
<tr>
<td>FMS</td>
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<td></td>
</tr>
<tr>
<td>GSK3b</td>
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<td></td>
</tr>
<tr>
<td>IGF-1R</td>
<td>3.5</td>
<td></td>
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<td>JAK3</td>
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<td></td>
</tr>
<tr>
<td>JNK1/MAPK8</td>
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<td></td>
</tr>
<tr>
<td>KDR/VEGFR2</td>
<td>91.3</td>
<td>11250</td>
</tr>
<tr>
<td>Protein</td>
<td>Value</td>
<td>Value</td>
</tr>
<tr>
<td>---------------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>LCK</td>
<td>57.6</td>
<td></td>
</tr>
<tr>
<td>LYN/LYN A</td>
<td>20.8</td>
<td></td>
</tr>
<tr>
<td>MEK1</td>
<td>-1.19</td>
<td></td>
</tr>
<tr>
<td>mTOR/FRAP1</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>P38α/MAPK14</td>
<td>88.8</td>
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[359] Table 4
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As seen in Table 3 and Table 4, it is known that a novel imidazole derivatives or pharmaceutically acceptable salts thereof according to the present invention have an excellent inhibitory effect on B-RAF, C-RAF, Aurora-A, BTK, Fli3, Ret, KDR/VEGFR2, P38a/MAPK14, RAF1, FMS and serve as selective inhibitors with a relatively lower activity against a lot of kinases.

The examples of the agents for composition according to the present invention are as follows.

<FORMULATION EXAMPLE 1> Preparation of pharmaceutical agents
Preparation of powder agent

Imidazole derivative of Chemical Formula 1 2 g
Lactose 1 g

The above components were mixed and filled in a seal pocket for thereby preparing powder agent.

Preparation of tablet agents

Imidazole derivative of Chemical Formula 1 100 mg
Corn starch 100 mg
Lactose 100 mg
Stearic acid magnesium 2 mg

The above components were mixed and tablet-processed by a conventional tablet preparation method for thereby preparing tablet agents.

Preparation of capsules

Imidazole derivative of Chemical Formula 1 100 mg
Corn starch 100 mg
Lactose 100 mg
Stearic acid magnesium 2 mg

The above components were mixed and filled in a gelatin capsule by a conventional capsule agent preparation method for thereby preparing capsule agents.

Preparation of liquid injection

Imidazole derivative of Chemical Formula 1 10 jg/ml
Diluting with hydrochloric acid until pH 3.5
Sodium chloride BP for injection 1 ml in max

The imidazole derivative according to the present invention was dissolved in sodium chloride BP for injection by a certain volume, and the pH value of the produced solution was adjusted to 3.5 with diluted hydrochloric acid BP, and the volume was adjusted with sodium chloride BP for injection, and the mixture was substantially mixed. The solution was filled in 5 ml type I ample made of visible glass, and the glass was dissolved for thereby sealing under the upper lattice of the air, and the solution was sterilized by autoclaving for more than 15 minutes at 120 °C for thereby preparing liquid injection.

As the present invention may be embodied in several forms without departing from the spirit or essential characteristics thereof, it should also be understood that the above-described examples are not limited by any of the details of the foregoing de-
scription, unless otherwise specified, but rather should be construed broadly within its spirit and scope as defined in the appended claims, and Therefore all changes and modifications that fall within the meets and bounds of the claims, or equivalences of such meets and bounds are Therefore intended to be embraced by the appended claims.
Claims

[Claim 1] An imidazole derivative represented by the following Chemical Formula 1 or pharmaceutically acceptable salt thereof;

[Chemical Formula 1]

\[
\begin{align*}
R^1 &\text{ is hydrogen; a straight or branched } C_1-C_6 \text{ alkyl; a } C_2-C_8 \text{ alkenyl; a } C_2-C_8 \text{ alkynyl; a } C_1-C_6 \text{ alkoxy; a } C_5-C_3 \text{ aryl } C_1-C_6 \text{ alkyl which is unsubstituted or substituted with at least one substituent selected from among a straight or branched } C_1-C_6 \text{ alkyl, a } C_2-C_8 \text{ alkenyl, a } C_2-C_8 \text{ alkynyl, a } C_1-C_6 \text{ alkoxy, halogen or OH; a } C_5-C_3 \text{ heteroaryl } C_1-C_6 \text{ alkyl which is unsubstituted or substituted with at least one substituent selected from among a straight or branched } C_1-C_6 \text{ alkyl, a } C_2-C_8 \text{ alkenyl, a } C_2-C_8 \text{ alkynyl, a } C_1-C_6 \text{ alkoxy, halogen or OH; a } C_5-C_3 \text{ cycloalkyl which is unsubstituted or substituted with at least one substituent selected from among a straight or branched } C_1-C_6 \text{ alkyl, a } C_2-C_8 \text{ alkenyl, a } C_2-C_8 \text{ alkynyl, a } C_1-C_6 \text{ alkoxy, halogen or OH; or a } C_5-C_3 \text{ heterocycloalkyl which is unsubstituted or substituted with at least one substituent selected from among a straight or branched } C_1-C_6 \text{ alkyl, a } C_2-C_8 \text{ alkenyl, a } C_2-C_8 \text{ alkynyl, a } C_1-C_6 \text{ alkoxy, halogen or OH,}
\end{align*}
\]

R^2 is

\[
\begin{align*}
\text{or }
\end{align*}
\]

, wherein L is -NH--; -NRC(O)--; -NRC(0)NR--; -NRC(S)NR--; -
NRC(0)S--; -C(0)NR--; -C(0)NRC(0)R; or -NRS(0)R--; and R is hydrogen, a straight or branched C_{1-4} alkyl, R^3 is hydrogen; a C_{5-12} aryl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; a C_{5-12} heteroaryl C_{1-6} alkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; or a C_{5-12} heterocycloalkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino; or a C_{5-12} heterocycloalkyl which is unsubstituted or substituted with at least one substituent selected from among halogen, a straight or branched C_{1-6} alkyl, a C_{1-6} alkoxy, trifluoromethyl and morpholino.

[Claim 2]
The imidazole derivative or pharmaceutically acceptable salt according to claim 1, wherein
X is carbon or nitrogen,
R^1 is hydrogen, methyl, ethyl, propyl, 3-hydroxypropyl,
R^2 is

\[ \begin{align*}
\text{L} & \quad \text{R}^3 \\
& \quad \end{align*} \]

or

\[ \begin{align*}
\text{O} & \quad \text{L} \quad \text{R}^3 \\
& \quad \end{align*} \]

, wherein L is -NH--; -NRC(O)-; -NRC(0)NR--; -NRC(0)S- or -NRC(S)NR-, and R is hydrogen, methyl or ethyl,
R^3 is hydrogen; (3,4-di-methoxyphenyl)methyl; 2,4-dimethylphenyl; 2,3-dichlorophenyl; 3,4-dichlorophenyl; 2,4,5-trichlorophenyl; 3-(trifluoromethyl)phenyl; 4-chloro-3-(trifluoromethyl)phenyl;
3-(4-hydroxypiperidin-1-yl)-5-(trifluoromethyl)phenyl;
4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl;
3-morpholin-5-(trifluoromethyl)phenyl;
3-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)phenyl;
4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl;
3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl;
4-(1-methylpiperidin-4-yloxy)-3-(trifluoromethyl)phenyl;
5-bromothiophene; naphthyl; benzothiophenyl; furanyl; isoxazolyl; pyrazolyl; pyridazinyl; thiazolyl; pyrazinyl; thienyl; pyrimidinyl; imidazolyl; pyrrolyl; dihydropyrrolyl; oxazolyl; triazolyl; thiadiazolyl; benzimidazolyl; quinoline; tetrahydroquinolinyl; benzothiazolyl; methylbenzothioazoyl; benzothiazolephenyl; benzodioxolyl; imidazolyl; indolyl; indolylyl; dihydroindolyl or dihydrobenzofuran.

[Claim 3]
The imidazole derivative or pharmaceutically acceptable salt according to claim 1, wherein
X is nitrogen,
R₁ is 3-hydroxypropyl,
R² is

\[
\begin{align*}
\text{or}
\end{align*}
\]

, wherein L is -NH--; -NHC(O)--; -NHC(0)NH--; -NRC(0)S-- or -NHC(S)NH--, and R³ is hydrogen; 4-chloro-3-(trifluoromethyl)phenyl;
3-morpholin-5-(trifluoromethyl)phenyl; 6-methylbenzothioazol-2-yl;
3,4-dichlorophenyl; 2,4,5-trichlorophenyl;
4-chloro-3-(trifluoromethyl)phenyl;
3-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)phenyl;
3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl;
5-methylisoxazolyl; 4-chlorophenyl-isoxazolyl;
4-methoxyphenyffuranyl; 3-chloro-5-(trifluoromethyl)phenylfuranyl;
4-methoxyphenyl-5-trifluoromethyl-pyrazolyl; pyridin-4-yl-thiazolyl.

[Claim 4]
The imidazole derivative or pharmaceutically acceptable salt according to claim 1, being selected from the group consisting of:
(1) (S)-1-(4-(2-(3-aminophenyl)-1H-imidazol-2-ylamino)pyrimidin-2-ylamino)propan-2-ol;

(2) (S)-1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)urea;

(3) (S)-1-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(3-morpholino-5-(trifluoromethyl)phenyl)urea;

(4) (S)-1-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(6-methylbenzo[d]thiazol-2-yl)urea;

(5) 1-(3,4-dichlorophenyl)-3-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)urea;

(6) (S)-1-(4-(2-(3-(3,4-dichlorophenyl)ureido)phenyl)-1H-imidazol-2-yl)pyrimidin-2-ylamino)propan-2-yl acetate;

(7) (S)-1-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(2,4,5-trichlorophenyl)urea;

(8) (S)-1-(3-chlorophenyl)-3-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)urea;

(9) (S)-1-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(4-morpholinophenyl)urea;

(10) (S)-1-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(3-(trifluoromethyl)phenyl)urea;

(11) (S)-1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)urea;

(12) (S)-1-(3,4-dichlorophenyl)-3-(4-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)urea;

(13) (S)-1-(4-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(2,4,5-trichlorophenyl)urea;

(14) (S)-1-(4-chlorophenyl)-3-(4-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)thiourea;

(15) (S)-1-(4-chlorophenyl)-3-(4-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)urea;
(16) (S)-1-(4-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(4-morpholinophenyl)urea;
(17) (S)-1-(4-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(3-(trifluoromethyl)phenyl)urea;
(18) (S)-4-chloro-N-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(trifluoromethyl)benzamide;
(19) (S)-N-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)benzamide;
(20) (S)-N-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)benzamide;
(21) (S)-N-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-4-morpholino-3-(trifluoromethyl)benzamide;
(22) (S)-N-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(trifluoromethyl)benzamide;
(23) (S)-N-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-5-(4-methoxyphenyl)furan-2-carboxamide;
(24) (S)-5-(2-chloro-5-(trifluoromethyl)phenyl)-N-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)furan-2-carboxamide;
(25) (S)-5-(4-chlorophenyl)-N-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)isoazole-3-carboxamide;
(26) (S)-N-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-2-(pyridin-4-yl)thiazole-4-carboxamide;
(27) (S)-N-(4-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-morpholine-5-(trifluoromethyl)benzamide;
(28) (S)-N-(4-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-4-morpholino-3-(trifluoromethyl)benzamide;
(29) (S)-N-(4-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-5-methylisoazole-3-carboxamide;
(30) (S)-5-(4-chlorophenyl)-N-(4-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)isoazole-3-carboxamide;
(31) (S)-N-(4-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-3-(trifluoromethyl)benzamide;
(32) (S)-N-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-4-morpholino-3-(trifluoromethyl)benzamide;
(33) (S)-N-(3-(1-(2-(2-hydroxypropylamino)pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-5-methylisoazole-3-carboxamide;
imidazol-2-yl)phenyl)-5-(4-methoxyphenyl)furan-2-carboxamide;
(32)
(S)-5-(3-chloro-5-(trifluoromethyl)phenyl)-N-(4-(1-(2-(2-hydroxypropylarnino)-pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)furan-2-carboxamide;
(33) (S)-N-(4-(1-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-1-(4-methoxyphenyl)-5-(trifluoromethyl)-IH-pyrazole-4-carboxamide;
(34) (S)-N-(4-(1-(2-(2-hydroxypropylamino)-pyrimidin-4-yl)-1H-imidazol-2-yl)phenyl)-2-(pyridin-4-yl)thiazole-4-carboxamide;
(35)
(S)-1-(4-chlorophenyl-3-(trifluoromethyl)phenyl)-3-(4-(1-(2-(2-hydroxypropylarnino)-pyrimidin-4-yl)-1H-imidazole-2-carbonyl)phenyl)urea; and
(36) (S)-4-chloro-N-4-(1-(2-(2-hydroxypropylarnino)-pyrimidin-4-yl)-1H-imidazole-2-carbonyl)phenyl)-3-(trifluoromethyl)benzamide.

[Claim 5]
A method for preparing the imidazole derivative according to claim 1, as represented by the following Reaction Scheme 1 comprising:
(1) reacting a compound of Chemical Formula 2 as a starting material with a compound of Chemical Formula 3 to obtain a compound of Chemical Formula 4
(2) conducting Buchwald amination reaction with the compound of Chemical Formula 4 of step 1 and a compound of Chemical formula 5 to obtain a compound of Chemical Formula 6
(3) oxidating the compound of Chemical Formula 6 of step 2 to obtain a compound of Chemical Formula 7
(4) reacting the compound of Chemical Formula 7 of step 3 with R'NH₂ to obtain a compound of Chemical Formula 8 and
(5) reducting the compound of Chemical Formula 8 of step 4 to obtain a compound of Chemical Formula 1a;

[Reaction Scheme 1]
A method for preparing the imidazole derivative according to claim 1, as represented by the following Reaction Scheme 2 comprising:

1. Reacting a compound of Chemical Formula 2 as a starting material with a compound of Chemical Formula 3 to obtain a compound of Chemical Formula 4;
2. Conducting Buchwald amination reaction with the compound of Chemical Formula 4 of step 1 and a compound of Chemical formula 5 to obtain a compound of Chemical Formula 6;
3. Oxidating the compound of Chemical Formula 6 of step 2 to obtain a compound of Chemical Formula 7;
4. Reacting the compound of Chemical Formula 7 of step 3 with R'NH₂ to obtain a compound of Chemical Formula 8;
5. Reducting the compound of Chemical Formula 8 of step 4 to obtain a compound of Chemical Formula 1a; and
6. Reacting the compound of the Chemical Formula 1a with the isocyanate compound through the coupling reaction to obtain a compound of Chemical Formula 1b;
A method for preparing the imidazole derivative according to claim 1, as represented by the following Reaction Scheme 3 comprising:

1. reacting a compound of Chemical Formula 2 as a starting material with a compound of Chemical Formula 3 to obtain a compound of Chemical Formula 4;
2. conducting Buchwald amination reaction with the compound of Chemical Formula 4 of step 1 and a compound of Chemical Formula 5 to obtain a compound of Chemical Formula 6;
3. oxidating the compound of Chemical Formula 6 of step 2 to obtain a compound of Chemical Formula 7;
4. reacting the compound of Chemical Formula 7 of step 3 with $R'NH_2$ to obtain a compound of Chemical Formula 8;
5. reducting the compound of Chemical Formula 8 of step 4 to obtain a compound of Chemical Formula 1a; and
6. reacting the compound of the formula 1a with carboxyl acid compound through a coupling reaction to obtain a compound of Chemical Formula 1c;
[Claim 8] A method for preparing the imidazole derivative according to claim 1, as represented by the following Reaction Scheme 4 comprising:

1. reacting a compound of Chemical Formula 9 as a starting material with a compound of Chemical Formula 10 to obtain a compound of Chemical Formula 11;
2. conducting Buchwald amination reaction with the compound of Chemical Formula 11 of step 1 and a compound of Chemical formula 5 to obtain a compound of Chemical Formula 12;
3. oxidating the compound of Chemical Formula 12 of step 2 to obtain a compound of Chemical Formula 13;
4. reacting the compound of Chemical Formula 13 of step 3 with R1 NH2 to obtain a compound of Chemical Formula 14;
5. reducting the compound of Chemical Formula 14 of step 4 to obtain a compound of Chemical Formula 15; and
6. reacting the compound of the Chemical Formula 15 with the isocyanate compound through the coupling reaction to obtain a compound of Chemical Formula 1d;

[Reaction Scheme 4]
A method for preparing the imidazole derivative according to claim 1, as represented by the following Reaction Scheme 5 comprising:

1. reacting a compound of Chemical Formula 9 as a starting material with a compound of Chemical Formula 10 to obtain a compound of Chemical Formula 11; 
2. conducting Buchwald amination reaction with the compound of Chemical Formula 11 of step 1' and a compound of Chemical formula 5 to obtain a compound of Chemical Formula 12;
3. oxidating the compound of Chemical Formula 12 of step 2 to obtain a compound of Chemical Formula 13;
4. reacting the compound of Chemical Formula 13 of step 3 with $\text{R}^1\text{NH}_2$ to obtain a compound of Chemical Formula 14;
5. reducting the compound of Chemical Formula 14 of step 4 to obtain a compound of Chemical Formula 15; and
6. reacting the compound of the Chemical Formula 15 with carboxyl acid compound through a coupling reaction to obtain a compound of Chemical Formula 1e;
[Claim 10] A pharmaceutical composition for the prevention and treatment of a melanoma comprising a imidazole derivative represented by Chemical Formula 1 of claim or pharmaceutically acceptable salt thereof as an active ingredient.

[Claim 11] The pharmaceutical composition according to claim 10, wherein the imidazole derivative or pharmaceutically acceptable salt thereof inhibit a growth of abnormal cells by inhibiting protein kinase.

[Claim 12] The pharmaceutical composition according to claim 11, wherein the protein kinase is selected from a group consisting of B-RAF, C-RAF, Aurora-A, BTK, Flt3, Ret, KDR/VEGFR2, P38a/MAPK14, RAF1 and FMS.

[Claim 13] The pharmaceutical composition according to claim 10, wherein the imidazole derivative or pharmaceutically acceptable salt thereof has growth inhibitory activity against A375P or WM3629 which are human melanoma cell lines.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

C07D 401/04(2006.01)i, C07D 401/02(2006.01)i, A61K 31/415(2006.01)i, A61P 35/00(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D 401/04; C07D 401/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: STN, imidazole, melanoma

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Relevant to claim No.</th>
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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search
25 JANUARY 2011 (25.01.2011)

Date of mailing of the international search report
25 JANUARY 2011 (25.01.2011)

Name and mailing address of the ISA/KR

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