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Declarations under Rule 4.17 :

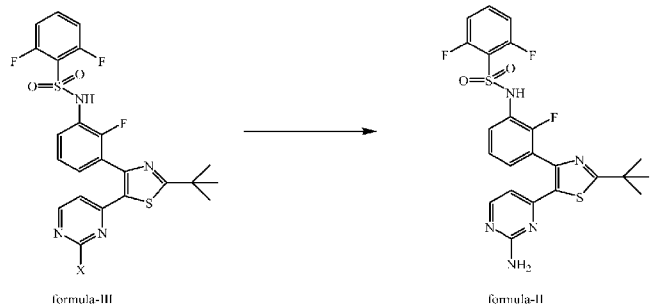
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.1 7(H))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.1 7(in))*

Published:

— *with international search report (Art. 21(3))*

(54) **Title:** PROCESSES FOR THE PREPARATION OF DABRAFENIB



formula-III formula-II

(57) **Abstract:** **A** process for the preparation of dabrafenib and pharmaceutically acceptable salts thereof comprising the step of reacting formula-Ill (wherein "X" is a leaving group) with formamide in the presence of a base to get formula- 11

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PROCESSES FOR THE PREPARATION OF DABRAFENIB

CROSS-REFERENCE TO RELATED APPLICATIONS

This application, in its entirety, claims the benefit of earlier Indian provisional patent application No. 5115/CHE/2014 filed on October 13, 2014.

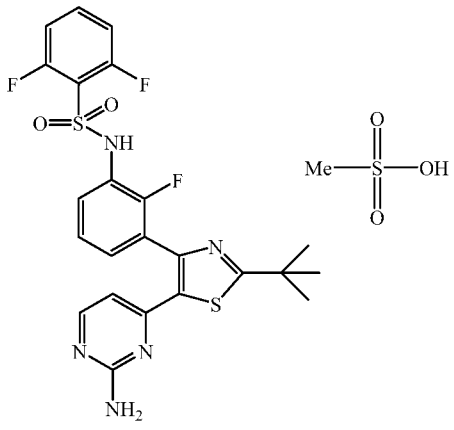
BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to the field of pharmaceutical sciences and more specifically a process for the preparation of dabrafenib or its pharmaceutically acceptable salts.

BACKGROUND OF THE INVENTION

Dabrafenib is chemically known as N-{3-[5-(2-amino-4-pyrimidinyl)-2-(l,l-dimethylethyl)-l,3-thiazol-4-yl]2fluorophenyl}2,6-difluorobenzenesulfonamide. The methane sulfonate salt of dabrafenib, chemically known as N-{3-[5-(2-amino-4-pyrimidinyl)-2-(l,l-dimethylethyl)-l,3-thiazol-4-yl]2-fluorophenyl}2,6-difluorobenzenesulfonamide, methane sulfonate salt, is structurally represented below as Formula-I.



Formula-1

Dabrafenib mesylate is marketed under the trade name TAFINLAR® by Novartis Pharmaceuticals Corporation. TAFINLAR® is indicated for the treatment of BRAF V600E mutation-positive unresectable or metastatic melanoma.

Dabrafenib and a process for the preparation thereof are disclosed in U.S. Patent No. 7,994,185, which is hereby incorporated by reference.

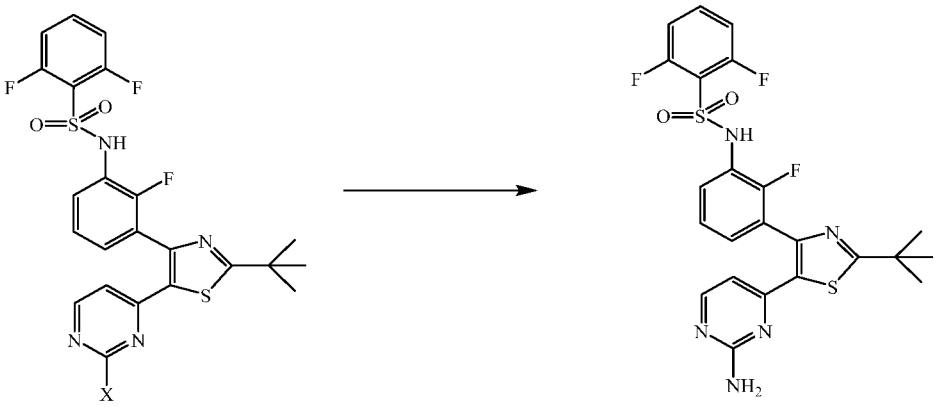
The present invention provides a novel process for the preparation of dabrafenib or pharmaceutically acceptable salts thereof.

SUMMARY OF THE INVENTION

One aspect of the present invention provides a process for the preparation of dabrafenib or pharmaceutically acceptable salts thereof.

One embodiment of the present invention provides a process for the preparation of dabrafenib or pharmaceutically acceptable salts thereof, which include the following steps:

a) reacting formula-Ill with formamide in the presence of a base to get formula-II, where X is a leaving group defined further below; and



formula-TTT formula-TT

b) optionally converting dabrafenib into a pharmaceutically acceptable salt thereof.

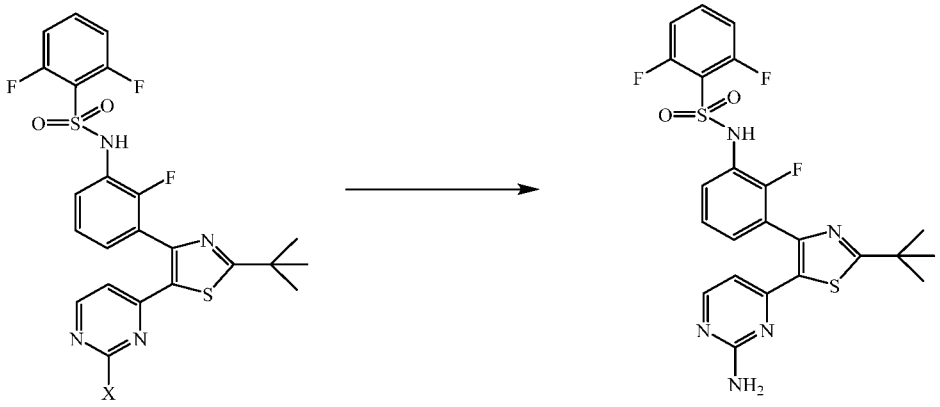
DETAILED DESCRIPTION OF THE INVENTION

It is to be understood that the description of the present invention has been simplified to illustrate elements that are relevant for a clear understanding of the invention, while eliminating, for purposes of clarity, other elements that may be well known.

The present invention provides a novel process for the preparation of dabrafenib and pharmaceutically acceptable salts thereof.

One embodiment of the present invention provides a process for the preparation of dabrafenib which may be carried out by the following steps:

a) reacting formula-Ill with formamide in the presence of a base to get formula-II.



formula-Ill formula-II

Within the context of the present invention, the "X" substituent in formula-Ill is a leaving group. As used herein, a "leaving group" refers to a functional group which may be, for example, halo (for example, chloro, fluoro, bromo, or iodo), methanesulfonyloxy, p-toluenesulfonyloxy, trifluoromethanesulfonyloxy, nonafluorobutanesulfonyloxy, (4-bromo-benzene)sulfonyloxy, (4-nitro-benzene)sulfonyloxy, (2-nitro-benzene)-sulfonyloxy, (4-isopropyl-benzene)sulfonyloxy, (2,4,6-tri-isopropyl-benzene)-sulfonyloxy, (2,4,6-trimethyl-benzene)sulfonyloxy, (4-tertbutyl-benzene)sulfonyloxy, benzenesulfonyloxy, (4-methoxy-benzene)sulfonyloxy, and alkoxy. The term alkoxy, as used herein, refers to straight chain or branched chain alkyl groups. Examples of suitable alkoxy groups include methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy, 1, 1-dimethyl ethoxy, and 1-methylpropoxy. Within the context of the present invention, an alkoxy leaving group may be unsubstituted or substituted by one or more halogens. In some

embodiments of the present invention the use of a methoxy, an ethoxy, a trifluoromethoxy, or a chloro leaving group was found to be particularly useful.

In one more embodiment of the present invention, compound of Formula-Ill is prepared by following prior art procedures for example as disclosed in prior arts US. Patent No. 8,415,345 and Drugs of the Future Volume 37 year 2012, page 469-474, which is hereby incorporated by references.

According to the present invention, formula-Ill may then be reacted with formamide in the presence of a base to get formula-II. Examples of suitable bases include alkaline metal hydroxides, alkaline metal bicarbonates, alkaline metal carbonates, and alkaline alkoxides. Examples of suitable alkaline metal hydroxides include sodium hydroxide and potassium hydroxide. Suitable alkaline metal bicarbonates includes, as examples, sodium bicarbonate and potassium bicarbonate. Suitable alkaline metal carbonates include, as examples, sodium carbonate, potassium carbonate, and cesium carbonate. Examples of suitable alkaline alkoxides include sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium propoxide, and potassium tert-butoxide.

Within the context of the present invention, the reacting of formula-Ill with formamide to get formula-II may be carried out in presence of a solvent. The solvent may be, for example, acetone, acetonitrile dimetylacetamide, dimethylformamide, N-methylpyrrolidone, or dimethylsulfoxide.

Within the context of the present invention, this step may be carried out at temperatures of about 70 °C to about 130 °C, which may be at about 70 °C, 75 °C, 80 °C, 85 °C, 90 °C, 95 °C, 100 °C, 105 °C, 110 °C, 115 °C, 120 °C, 125 °C, or 130 °C or between any of the aforementioned temperatures.

Within the context of the present invention, dabrafenib of formula-II may be optionally converted into a pharmaceutically acceptable salt of dabrafenib.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are

commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al, describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977), which is hereby incorporated by reference. Within the context of the present invention, pharmaceutically acceptable salts of dabrafenib may be prepared in situ during isolation and purification of the compounds disclosed herein. Alternatively, pharmaceutically acceptable salts of dabrafenib may be prepared separately by reacting a free basic functional group of dabrafenib with a suitable reagent. For example, a free basic functional group of dabrafenib (e.g., the primary amine group) can be reacted with a suitable acid to form a pharmaceutically acceptable acid addition salt of dabrafenib. Examples of pharmaceutically acceptable acid addition salts of dabrafenib include, as examples, salts formed with inorganic acids or organic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid. Examples of suitable organic acids include acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid.

Within the context of the present invention, formation of a pharmaceutically acceptable salt of dabrafenib may also be carried out using other methods, for example, ion exchange. Examples of other pharmaceutically acceptable salts of dabrafenib include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, (R,S)-malate, (S)-malate, maleate, malonate, mesylate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3- phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, and valerate salts. In certain embodiments, the mesylate salt was found to be a particularly useful salt of dabrafenib.

Within the context of the present invention, dabrafenib may be converted to its salts according to prior art processes, such as those disclosed in U.S. Patent No. 7,994,185.

Dabrafenib or salts thereof may optionally be isolated purified by methods well known in the art, for example, by filtering the product mixture, by performing solvent extractions, by chromatography, or by any combination thereof.

With all of the reactions disclosed above, one of skill in the art will recognize that the reaction conditions (e.g., reaction time or temperature) may be adjusted to achieve appropriate yield without undertaking undue experimentation and without departing from the scope of the present disclosure.

The dabrafenib disclosed herein may be incorporated into oral dosage forms, for example, a capsule for oral administration. One of skill in in the art will recognize a wide variety of excipients that may be include in such a capsule formulation, including, for example, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, povidone, and colloidal silicon dioxide. Coatings of formulations in capsule form may contain ferric oxide red, ferric oxide yellow, lecithin, hypromellose, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. Within the context of the present invention, dosage forms may have about 50 and 75 milligrams of dabrafenib.

The dabrafinib and pharmaceutically acceptable salts as prepared by the methods disclosed herein may be useful in the treatment of BRAF V600E mutation-positive unresectable or metastatic melanoma. Dabrafinib or pharmaceutically acceptable salts thereof may be used singly or in combination with other drugs (or pharmaceutically acceptable salts thereof), such as trematinib.

When administered to human and non-human patients, formulations of dabrafenib may be adjusted to compensate for the age, weight, and physical condition of the patient. Dabarfenib may be administered over a wide dosage range from about 50 to 150 milligrams twice per day.

All patents and patent applications cited herein by reference in incorporated by reference in their entirety. In view of the above description and the examples below, one of ordinary skill in the art will be able to practice the invention as claimed without undue experimentation. The foregoing will be better understood with reference to the following examples that detail certain procedures for the preparation of molecules, compositions and Formulations according to the

present invention. All references made to these examples are for the purposes of illustration. The following examples should not be considered exhaustive, but merely illustrative of only a few of the many aspects and embodiments contemplated by the present disclosure.

EXAMPLES

Example 1: Process for the preparation of dabrafenib

In a flask, N-{3-[5-(2-chloro-4-pyrimidinyl)-2-(l, l-dimethylethyl)-l, 3-thiazol-4-yl]-2-fluorophenyl}-2, 6-difluorobenzenesulfonamide (100 g) and dimethylsulfoxide (600 ml) were combined. To this, formamide (125.3 g) and potassium carbonate (76.7 g) were added. The reaction mass temperature was raised to 70-130 °C and stirred at this temperature for 2-5 hours. The reaction mass was cooled to 20-30 °C and to this, dichloromethane (2000 ml) and water (500 ml) were added. The pH of the reaction mass was adjusted to 5.0-7.0 using aqueous hydrochloric acid and the aqueous and organic layers were separated. Dichloromethane was added to the aqueous layer and the layers were again separated. The combined dichloromethane layers were washed with water and concentrated under vacuum at 30-50 °C. To this ethyl acetate (300 ml) was added and the reaction mass was heated to 50-60 °C. To this, heptane (900 ml) was added slowly at 50-60 °C. The reaction mass was heated to reflux, then cooled to 0-10 °C and maintained for 2-4 hours at same temperature. The obtained solid was filtered and washed with heptanes (200 ml) and dried under vacuum at 30-60 °C to yield crude dabrafenib (N-{3-[5-(2-amino-4-pyrimidinyl)-2-(l,l-dimethylethyl)-l,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide) (70 g). The (crude) product was further purified by using silica gel column chromatography (eluent: dichloromethane: methanol 95: 05 & 90:10). The product eluent was then concentrated to get dabrafenib (N-{3-[5-(2-amino-4-pyrimidinyl)-2-(l, 1-dimethylethyl)-l, 3-thiazol-4-yl]-2-fluorophenyl}-2, 6-difluorobenzenesulfonamide) (60 g).

Example 2: Process for preparation of dabrafenib

In a flask, N-{3-[5-(2-chloro-4-pyrimidinyl)-2-(l, l-dimethylethyl)-l, 3-thiazol-4-yl]-2-fluorophenyl}-2, 6-difluorobenzenesulfonamide (100 g) and dimethylsulfoxide (600 ml) were

combined. To this, formamide (125.3 g) and potassium tert-butoxide (104.1 g) were added. The reaction mass temperature was raised to 70-130 °C and stirred at this temperature for 2-5 hours. The reaction mass was cooled to 20-30 °C and to this dichloromethane (2000 ml) and water (500 ml) were added. The pH of the reaction mass was adjusted to 5.0-7.0 using aqueous hydrochloric acid and the aqueous and organic layers were separated. Dichloromethane was added to the aqueous layer and the layers were separated. The combined dichloromethane layers were washed with water and concentrated under vacuum at 30-50 °C. To this ethyl acetate (300 ml) was added and heated the reaction mass to 50-60 °C. To this, heptanes (900 ml) was added slowly at 50-60 °C. After addition of heptanes, the reaction mass was heated to reflux then cooled to 0 - 10 °C and maintained for 2-4 hours at same temperature. The obtained solid was filtered and washed with heptanes (200 ml) and dried under vacuum at 30-60 °C to yield crude dabrafenib (N-{3-[5-(2-amino-4-pyrimidinyl)-2-(l,l-dimethylethyl)-l,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide) (70 g). The crude product was further purified by using silica gel column chromatography (Eluent: dichloromethane: methanol 95: 05 & 90:10). The product eluents to were concentrated to get dabrafenib (N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1, l-dimethylethyl)-l, 3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide) (60 g).

Example 3: Process for preparation of methyl-3-amino-2-fluorobenzoate

Methyl-2-fluoro-3-nitrobenzoate (100 g) was added to a mixture of tetrahydrofuran (1000 ml) and methanol (300 ml). The reaction mixture was stirred and palladium on charcoal (10 g) was added. The reaction mass temperature was raised to 50-60 °C and stirred under 3.0-10 kg hydrogen pressure for 3-24 hours. The reaction mass was filtered and washed with tetrahydrofuran. The obtained filtrate was concentrated under vacuum to give methyl-3-amino-2-fluorobenzoate (70 g).

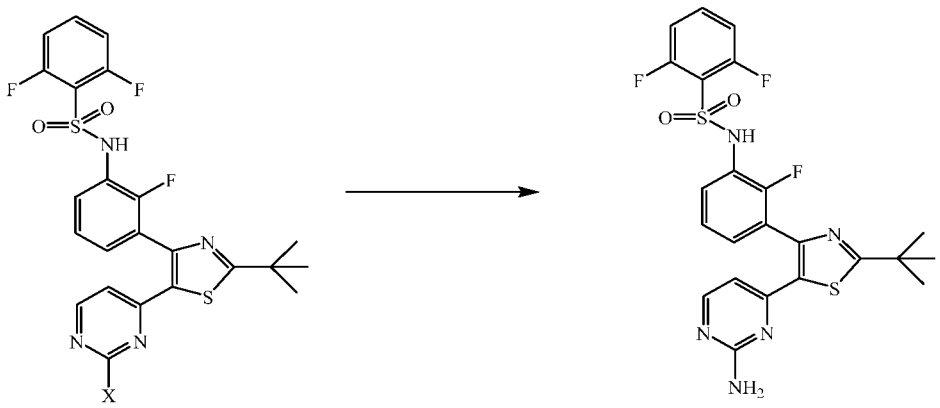
Example 4: Process for preparation of (N-{3-[5-(2-chloro-4-pyrimidinyl)-2-(l, 1-dimethylethyl)-l, 3-thiazol-4-yl]-2-fluorophenyl}-2, 6-difluorobenzenesulfonamide.

N-{3-[(2-chloro-4-pyrimidinyl) acetyl]-2-fluorophenyl}-2, 6-difluorobenzenesulfonamide (100 g) was added to dichloromethane (1000 ml) and the reaction mixture was cooled to 0-10 °C. To this, N-bromosuccinimide (40.3 g) was added in 3 equal portions. After the addition of N-bromosuccinimide, the reaction mixture was heated to 20 °C and stirred for 1-3 hours. Water

was added to the reaction mixture and the organic and aqueous layers were separated. Dichloromethane was added to the aqueous and the layers were again separated. The combined organic layer was concentrated to a volume of 400 ml. To this, ethyl acetate (700 ml) was added and the reaction mixture was concentrated to a volume of 400 ml. Dimethylacetamide (900 ml) and β-cyclodextrin (100 g) were added to the reaction mixture and cooled to 0-10 °C. To this, 2, 2-dimethylpropanethioamide (26.6 g) was added in 3 equal portions. The reaction mixture was warmed to 20-30 °C and stirred. The reaction was further heated to 70-80 °C and stirred for 1-3 hours. The reaction mixture was cooled to 0-10 °C and water (900 ml) was slowly added at 0-10 °C. To this, ethyl acetate (400 ml) was added and the pH of reaction mass was adjusted to 6.0-8.0 with aqueous ammonia solution. The reaction mixture was stirred and the layers were separated. Ethyl acetate was added to the aqueous layer and the layers were again separated. The combined organic layers were washed with twice with water. The organic layer was treated with activated charcoal (10 g), filtered, and washed with ethyl acetate (100 ml). The filtrate was then concentrated under vacuum at 30-50 °C. To this, ethyl acetate (400 ml) was added and the reaction mass was heated to 50-60 °C. Heptanes (400 ml) were slowly added to the reaction mixture at 50-60 °C. After addition of heptanes, the reaction mass was heated to reflux then cooled to 0-10 °C and maintained for 2-4 hours at same temperature. The solid was filtered and washed with heptanes (200 ml) and dried under vacuum at 30-60 °C to get formula-Ill (N-{3-[5-(2-chloro-4-pyrimidinyl)-2-(l,l-dimethylethyl)-l,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide) (70 g).

CLAIMS:

1. A process for the preparation of dabrafenib comprising the step of reacting formula-Ill with formamide in the presence of a base to get formula-II, wherein "X" is a leaving group.



formula-III formula-II

2. The process according to claim 1, wherein the leaving group is selected from the group consisting of chloro, fluoro, bromo, iodo, methanesulfonyloxy, p-toluenesulfonyloxy, trifluoromethanesulfonyloxy, nonafluorobutanesulfonyloxy, (4-bromo-benzene)sulfonyloxy, (4-nitro-benzene)sulfonyloxy, (2-nitro-benzene)-sulfonyloxy, (4-isopropyl-benzene)sulfonyloxy, (2,4,6-tri-isopropyl-benzene)-sulfonyloxy, (2,4,6-trimethyl-benzene)sulfonyloxy, (4-tertbutyl-benzene)sulfonyloxy, benzenesulfonyloxy, (4-methoxy-benzene)sulfonyloxy, and alkoxy.
3. The process according to claim 2, wherein the alkoxy leaving group is selected from the group consisting of substituted or unsubstituted methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy, 1, 1-dimethyl ethoxy, and 1-methylpropoxy.
4. The process according to claim 1, further comprising the step of converting dabrafenib into a pharmaceutically acceptable salt, after said reacting step.

5. The process according to claim 1, wherein the base is selected from the group consisting of alkaline metal hydroxides, alkaline metal bicarbonates, alkaline metal carbonates, and alkaline alkoxides.

6. The process according to claim 5, wherein the alkaline metal hydroxide is selected from the group consisting of sodium hydroxide and potassium hydroxide.

7. The process according to claim 5, wherein the alkaline metal bicarbonate is selected from the group consisting of sodium bicarbonate and potassium bicarbonate.

8. The process according to claim 5, wherein the alkaline metal carbonate is selected from the group consisting of sodium carbonate, potassium carbonate, and cesium carbonate.

9. The process according to claim 5, wherein the alkaline alkoxide is selected from the group consisting of sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium propoxide, and potassium tert-butoxide.

10. The process of claim 1, wherein the reaction is carried out in presence of solvent.

11. The process according to claim 10, wherein solvent is selected from the group consisting of acetone, acetonitrile dimetylacetamide, dimethylformamide, N-methylpyrrolidone, and dimethylsulfoxide, and mixtures thereof.

12. The process according to claim 4, wherein the pharmaceutically acceptable salt is a mesylate salt.

13. A process for preparing a pharmaceutical composition of dabrafenib, comprising the steps of:

a. obtaining a dabrafenib according to the process of any one of claims 1-12; and

b. combining the dabrafenib with a pharmaceutically acceptable excipient to obtain the pharmaceutical composition.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/057822

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D417/04
ADD.

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

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)
EPO-Internal , WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/137391 A2 (SMITHKLINE BEECHAM CORP [US]; ADAMS JERRY LEROY [US]; DICKERSON SCOTT) 12 November 2009 (2009-11-12) cited in the application the whole document; in particular, page 93, line 22 - page 94 line 19, pages 201, example 58a, and page 205, step D of example 58c --- -/--	1-13

[X] Further documents are listed in the continuation of Box C.

[X] 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" documentwhich may throw doubts on priority claim(s) orwhich is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 November 2015	15/12/2015

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/057822

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ARUMUGAM KODIMUTHALI ET AL: "A simple synthesis of aminopyridines: use of amides as amine source" , JOURNAL OF THE BRAZILIAN CHEMICAL SOCIETY, vol. 21, no. 8, 1 January 2010 (2010-01-01) , pages 1439-1445 , XP055232361 , BR ISSN: 0103-5053 , D0I : 10. 1590/S0103-50532010000800005 the whole document ----	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2015/057822

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009137391 A2	12-11-2009	AR 071617 Al	30-06-2010
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