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(54) **Title**: NOVEL PROCESSES FOR THE PREPARATION OF VEMURAFENIB

(57) **Abstract**: The present invention provides novel intermediates of vemurafenib or a pharmaceutically acceptable salt thereof and processes for its preparation. The present invention also provides novel processes for preparation of vemurafenib or a pharmaceutically acceptable salt thereof using the novel intermediates.

"NOVEL PROCESSES FOR THE PREPARATION OF VEMURAFENIB"

PRIORITY

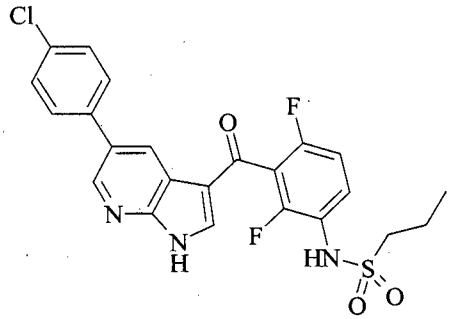
This application claims the benefit under Indian Provisional Application No. 5395/CHE/2013 filed on 22 November 2013 entitled "A novel process for preparing Vemurafenib" and 3113/CHE/2014 filed on 26 June 2014 entitled "A novel process for preparation of Vemurafenib", the content of which are incorporated by reference herein.

FIELD OF THE INVENTION

The present invention generally relates to novel processes for the preparation of Vemurafenib or a pharmaceutically acceptable salt thereof using novel intermediates.

BACKGROUND OF THE INVENTION

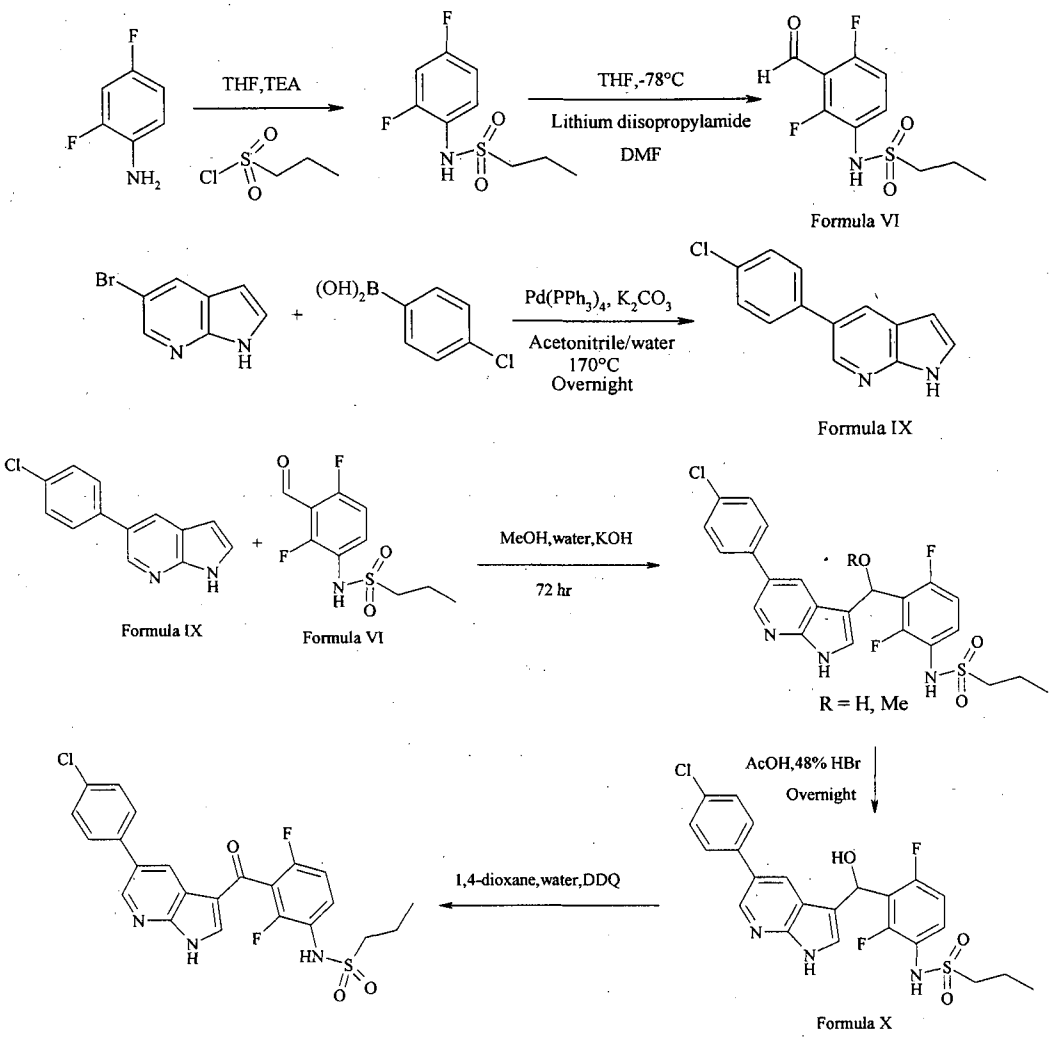
Vemurafenib, also known as propane-1-sulfonic acid {3-[-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4difluoro-phenyl}-amide, is represented by the following structure of Formula I:



Formula I

Vemurafenib is marketed by Hoffmann La Roche under the trade name ZELBORAF® is a kinase inhibitor and indicated for the treatment of patients with unresectable or metastatic melanoma with $BRAF^{V600E}$ mutation as detected by an FDA-approved test.

U.S. Patent No. 7,504,509 ("the '509 patent"), 7,863,288 ("the '288 patent") and 8,143,271 ("the '271 patent") discloses a variety of pyrrolo-pyridine and their derivatives such as vemurafenib. Particularly the '288 patent discloses a process for preparation of vemurafenib by condensation of 5-(4-chloro-phenyl)-azaindole and (2,4-difluoro-3-formyl-phenyl)-amide in presence of potassium hydroxide and methanol. The process disclosed in the '288 patent is schematically represented as follows:



The synthesis of Vemurafenib as discussed in the '288 patent have certain drawbacks as it involves:

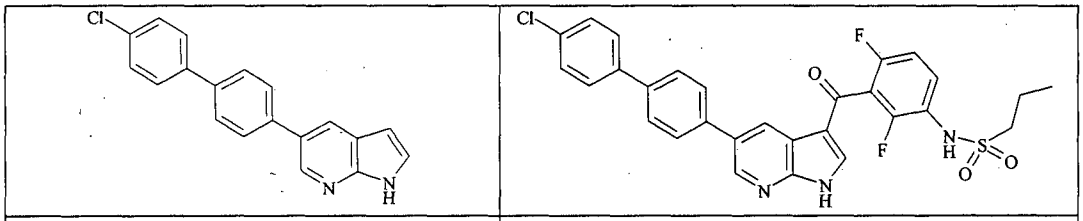
a) formylation of difluoro sulfonamide intermediate in presence of a pyrophoric reagent like Lithium diisopropylamine at a very lower temperature of -78°C;

b) the process involves methoxy intermediate, which is formed due to use of methanol as solvent in the reaction of 5-(4-chlorophenyl)-7-azaindole of Formula IX and formyl intermediate of Formula VI, which is then deprotection and finally converted to Vemurafenib; the additional steps like formation of methoxy compound followed by deprotection reaction are time consuming and makes the process more costly; and

c) Further formation and deprotection of methoxy compound involves prolonged period of reaction maintenance of about 72 hrs for methoxy compound preparation and about 12 hours for deprotection reaction, which process leads, to an increase in the manufacturing cycle time and decrease in the product yield and quality.

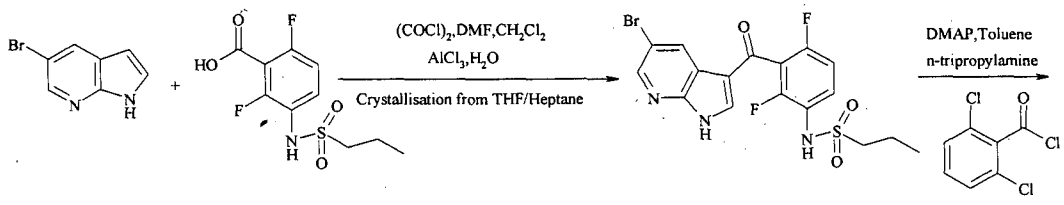
Further the process disclosed in the '288 patent involves preparation of 5-(4-chlorophenyl)-azaindole of Formula IX by Suzuki coupling of 5-bromo- azaindole and

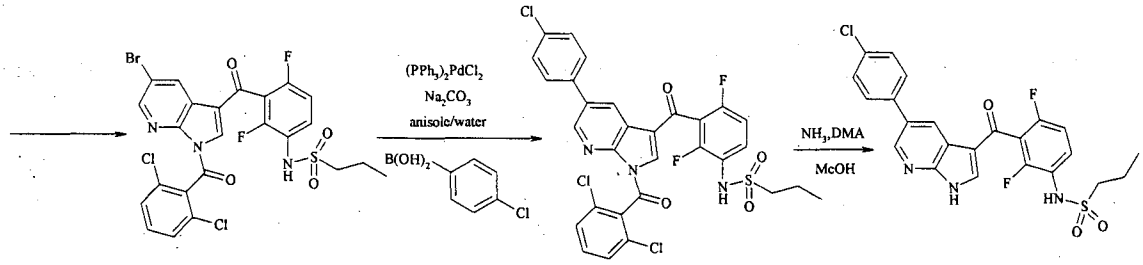
p-chlorophenyl boronic acid in presence of acetonitrile and water at a higher temperature of 170°C for a prolonged period of reaction time and followed by silica-gel column purification by eluting with ethyl acetate/hexane. The disadvantage associated with the '288 patent disclosed process involves formation of substantial amounts of biphenyl impurity of Formula A, which is formed due to use of acetonitrile as solvent for coupling of 5-bromo- azaindole and p-chlorophenyl boronic acid. Use of acetonitrile as solvent in this step requires higher temperature and extended time to complete reaction leads to formation of substantial amounts of biphenyl impurity of Formula A. The biphenyl impurity of Formula A, which is further proceeded to form compound of Formula B as impurity in the final vemurafenib, which is very difficult to remove from the final product and extensive multiple purification procedures are required to remove the same from the final API. Also the '288 patent disclosed process involves tedious chromatographic purifications makes the process not viable for large scale manufacturing.



Formula A | Formula B

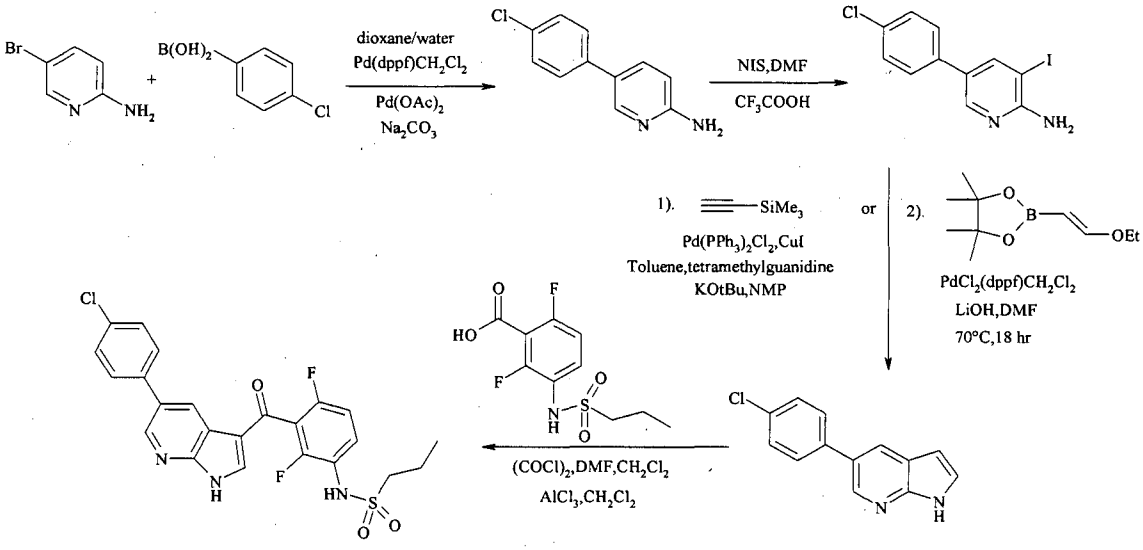
U.S. Patent No. 8,329,724 ("the '724 patent") discloses a process for the preparation of vemurafenib by acylation of 5-bromo-7-azaindole with 2,6-difluoro-3-[(propylsulfonyl)amino]benzoyl chloride in presence of aluminium trichloride, in a solvent like methylene chloride, the obtained azaindole intermediate amine was protected with 2,6-dichloro benzoyl chloride. The obtained protected compound was subjected to Suzuki-coupling in presence of 4-chlorophenyl boronic acid to obtain amine protected vemurafenib, finally deprotecting the obtained compound in presence of ammonia to obtain vemurafenib. The process disclosed in the '724 patent is schematically represented as follows:



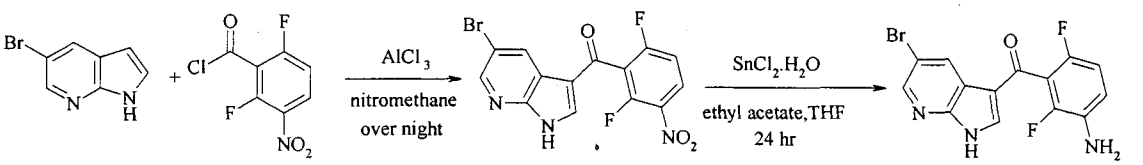


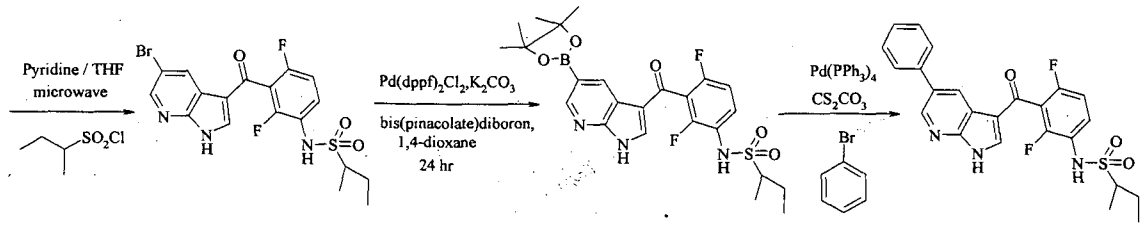
The process disclosed in the '724 patent has certain disadvantages, which includes additional process steps like protection and deprotection of azaindole with dichloro benzoyl chloride, which in turn result to an increase in the manufacturing time cycle and cost.

U.S. Patent No. 8,779,150 ("the '150 patent") discloses a process for the preparation of vemurafenib by involving azaindole cyclisation. The process disclosed in the '150 application is schematically represented as follows:



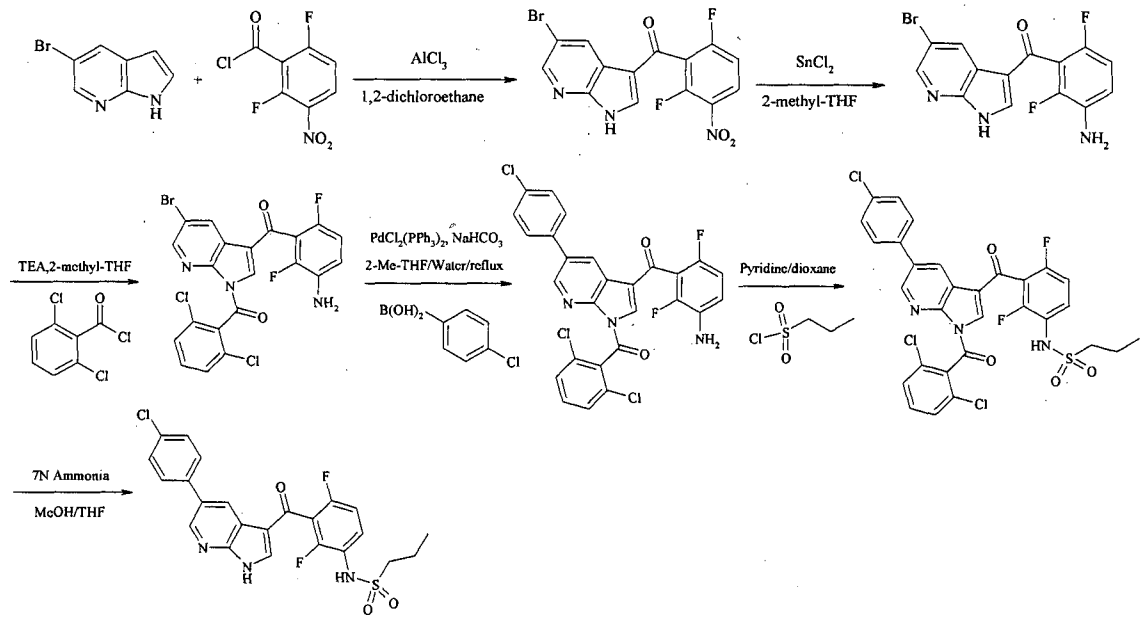
Patent Publication No. WO2012/109075 ("the 075 publication") discloses a process for preparation of vemurafenib analogous. The process disclosed in the '075 publication is schematically represented as follows:





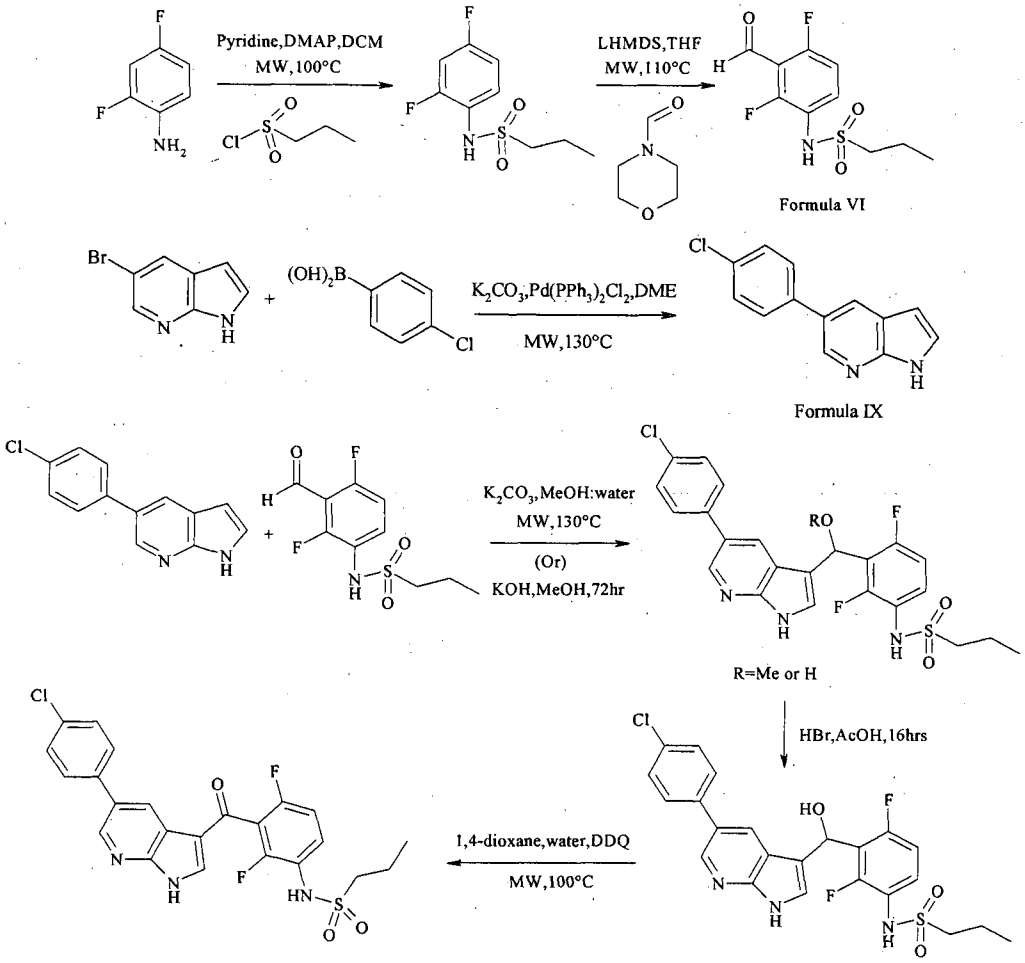
The WO '075 publication process has some disadvantages like use of cumbersome microwave irradiation reactions, which are difficult at large scale preparation.

Patent Publication No. WO 2013/181415 ("the '415 publication") discloses a process for preparation of vemurafenib. The process disclosed in the '415 publication is schematically represented as follows:



The process disclosed in the '415 publication also involves additional process steps like protection and deprotection of azaindole with dichloro benzoyl chloride, which makes the process lengthy, thereby increase in the manufacturing time cycle.

Jason R Buck et al discloses a process for preparation of vemurafenib in *Tetrahedron Letters 53 (2012) 4161–4165 & Tetrahedron Letters 55 (2014) 169–173* by rapid microwave-assisted organic synthesis. The process disclosed by Jason R Buck et al is schematically represented as follows:



The process disclosed by Jason R Buck et al includes all reaction steps are carried out by microwave-assisted organic synthesis, which is not suitable for large scale production.

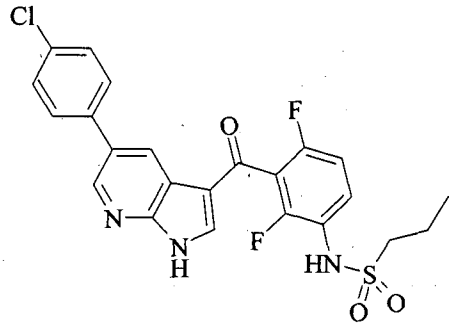
Based on the drawbacks mentioned in all the literatures above, there is a vital need to develop a process for the preparation of vemurafenib, which is readily amenable to large scale production.

Hence, present inventors focused research to simplify the process for the preparation of vemurafenib with fewer steps, greater yield, and higher purity by using novel intermediates to obviate the problems associated with the reported processes.

The present invention provides novel processes for the preparation of vemurafenib using novel intermediates.

SUMMARY OF THE INVENTION

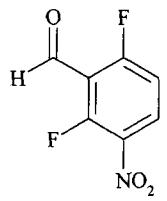
In accordance with a first embodiment, the present invention provides a novel process for the preparation of vemurafenib of Formula I or a pharmaceutically acceptable salt thereof:



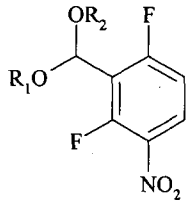
Formula I

comprising:

a) reacting 2,6-difluoro-3-nitro benzaldehyde with a suitable protecting group to obtain a compound of Formula II; wherein R_1 and R_2 independently represents an alkyl, or R_1 and R_2 taken together form an optionally substituted alkylene ring;

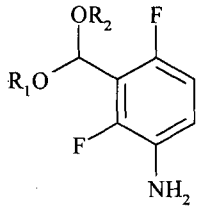


2,6-difluoro-3-nitro benzaldehyde



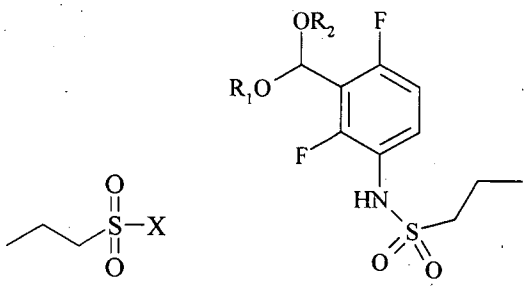
Formula II

b) nitro reduction of compound of Formula II with a suitable reducing agent to obtain a compound of Formula III; wherein R_1 and R_2 are defined as above:



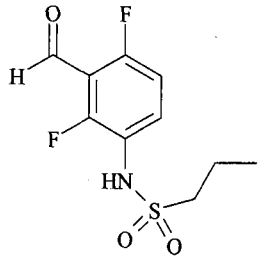
Formula III

c) reacting the compound of Formula III with a compound of Formula IV, wherein 'X' represents suitable leaving group; in presence of a suitable base to obtain a compound of Formula V, wherein R_1 and R_2 are defined as above:



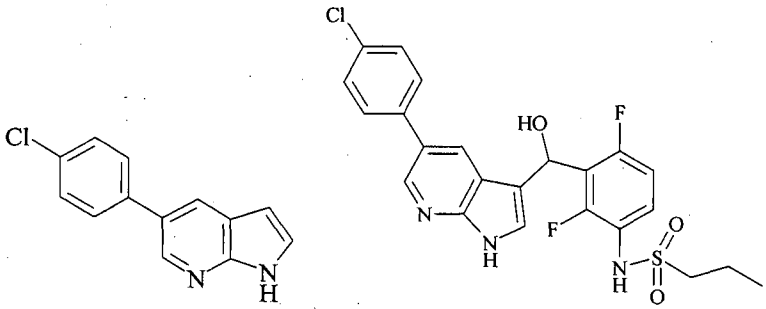
Formula IV Formula V

d) deprotecting the compound of Formula V in presence of a suitable deprotecting agent to obtain a compound of Formula VI:



Formula VI

e) reacting the compound of Formula VI with a compound of Formula IX in presence of a suitable base to obtain a compound of Formula X; and



Formula IX Formula X

f) converting the obtained compound of Formula X in to vemurafenib or a pharmaceutically acceptable salt thereof.

In accordance with a second embodiment, the present invention provides a novel process for the preparation of vemurafenib or a pharmaceutically acceptable salt thereof, comprising:

a) reacting 2,6-difluoro-3-nitro benzaldehyde with a suitable protecting group to obtain a compound of Formula II; wherein R_1 and R_2 independently represents an alkyl, or R_1 and R_2 taken together form an optionally substituted alkylene ring;

b) nitro reduction of compound of Formula II with a suitable reducing agent to obtain a compound of Formula III; wherein R_1 and R_2 are defined as above;

c) reacting the compound of Formula III with a compound of Formula IV, wherein 'X' represents suitable leaving group; in presence of a suitable base to obtain a compound of Formula V, wherein R_1 and R_2 are defined as above;

d) deprotecting the compound of Formula V in presence of a suitable deprotecting agent to obtain a compound of Formula VI; and
e) converting the compound of Formula VI in to vemurafenib or a pharmaceutically acceptable salt thereof.

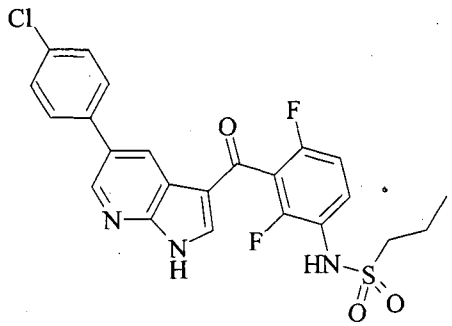
In accordance with a third embodiment, the present invention provides a novel process for the preparation of vemurafenib or a pharmaceutically acceptable salt thereof, comprising:

a) reacting 2,6-difluoro-3-nitro benzaldehyde with a suitable protecting group to obtain a compound of Formula II; wherein R_1 and R_2 independently represents an alkyl, or R_1 and R_2 taken together form an optionally substituted alkylene ring;
b) nitro reduction of compound of Formula II with a suitable reducing agent to obtain a compound of Formula III; wherein R_1 and R_2 are defined as above;
c) reacting the compound of Formula III with a compound of Formula IV, wherein 'X' represents suitable leaving group; in presence of a suitable base to obtain a compound of Formula V, wherein R_1 and R_2 are defined as above; and
d) converting the compound of Formula V in to vemurafenib or a pharmaceutically acceptable salt thereof.

In accordance with a fourth embodiment, the present invention provides a novel process for the preparation of vemurafenib or a pharmaceutically acceptable salt thereof, comprising:

a) reacting 2,6-difluoro-3-nitro benzaldehyde with a suitable protecting group to obtain a compound of Formula II; wherein R_1 and R_2 independently represents an alkyl, or R_1 and R_2 taken together form an optionally substituted alkylene ring;
b) nitro reduction of compound of Formula II with a suitable reducing agent to obtain a compound of Formula III; wherein R_1 and R_2 are defined as above; and
c) converting the compound of Formula III in to vemurafenib or a pharmaceutically acceptable salt thereof.

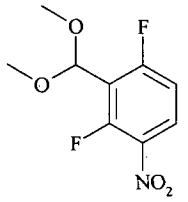
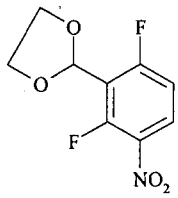
In accordance with a fifth embodiment, the present invention provides a novel process for the preparation of vemurafenib or a pharmaceutically acceptable salt thereof of Formula I:



Formula I

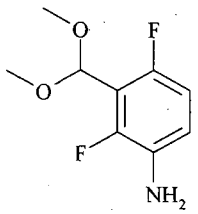
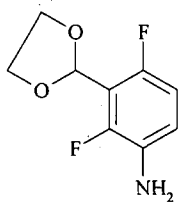
comprising:

a) reacting 2,6-difluoro-3-nitro benzaldehyde with trimethyl orthoformate or ethylene glycol to obtain a compound of Formula IIa or Formula IIb;

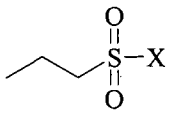
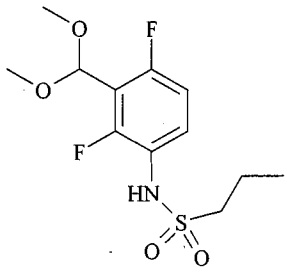
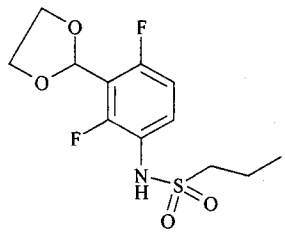
Formula IIa or Formula IIb

b) nitro reduction of compound of Formula IIa or Formula IIb with a suitable reducing agent to obtain a compound of Formula IIIa or Formula IIIb:

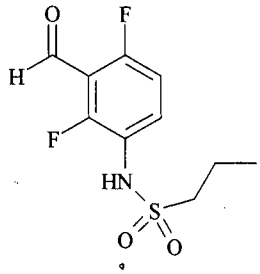
Formula IIIa or Formula IIIb

c) reacting the compound of Formula IIIa or Formula IIIb with a compound of Formula IV, wherein 'X' represents suitable leaving group; in presence of a suitable base to obtain a compound of Formula Va or Formula Vb:

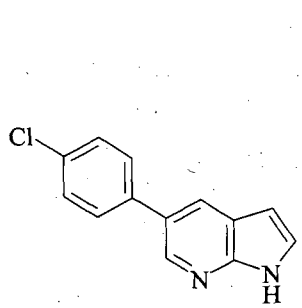
Formula IV Formula Va or Formula Vb

d) deprotecting the compound of Formula Va or Formula Vb in presence of a suitable deprotecting agent to obtain a compound of Formula VI:

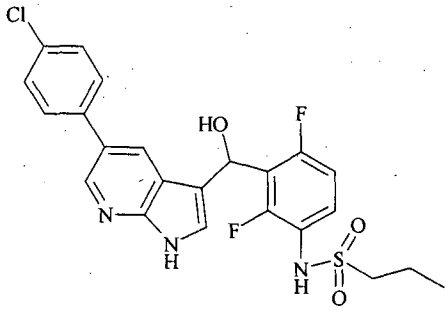


Formula VI

e) reacting the compound of Formula VI with a compound of Formula IX in presence of a suitable base to obtain a compound of Formula X; and



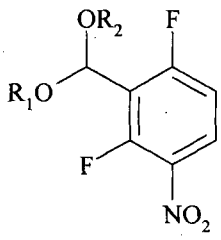
Formula IX



Formula X

f) converting the obtained compound of Formula X in to vemurafenib or a pharmaceutically acceptable salt thereof.

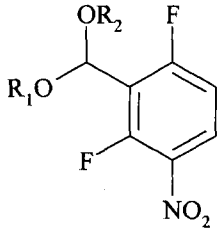
In accordance with a sixth embodiment, the present invention provides a compound of Formula II or a pharmaceutically acceptable salt thereof.



Formula II

wherein R_1 and R_2 independently represents an alkyl, or R_1 and R_2 taken together form an optionally substituted alkylene ring.

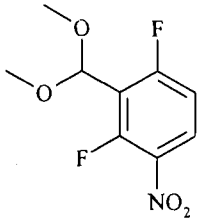
In accordance with a seventh embodiment, the present invention provides a compound of Formula II or a pharmaceutically acceptable salt thereof.



Formula II

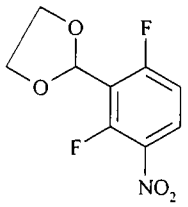
wherein R_1 and R_2 independently represents an alkyl; or R_1 and R_2 taken together form an optionally substituted alkylene ring; wherein the alkyl is selected from the group consisting of methyl, ethyl, propyl, butyl and the like; alkylene is selected from the group consisting of methylene, ethylene, propylene, butylene, pentylene and the like.

In accordance with an eighth embodiment, the present invention provides a compound of Formula IIa or a pharmaceutically acceptable salt thereof.



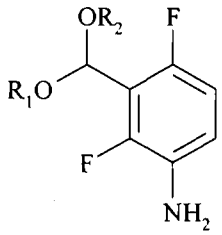
Formula IIa

In accordance with a ninth embodiment, the present invention provides a compound of Formula IIb or a pharmaceutically acceptable salt thereof.



Formula IIb

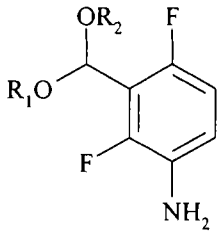
In accordance with a tenth embodiment, the present invention provides a compound of Formula III or a pharmaceutically acceptable salt thereof.



Formula III

wherein R_1 and R_2 independently represents an alkyl, or R_1 and R_2 taken together form an optionally substituted alkylene ring.

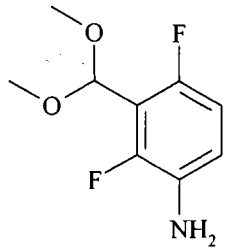
In accordance with an eleventh embodiment, the present invention provides a compound of Formula III or a pharmaceutically acceptable salt thereof.



Formula III

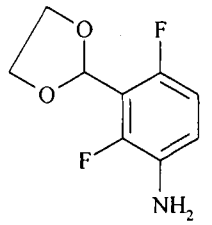
wherein R_1 and R_2 independently represents an alkyl; or R_1 and R_2 taken together form an optionally substituted alkylene ring; wherein the alkyl is selected from the group consisting of methyl, ethyl, propyl, butyl and the like; alkylene is selected from the group consisting of methylene, ethylene, propylene, butylene, pentylene and the like.

In accordance with a twelfth embodiment, the present invention provides a compound of Formula IIIa or a pharmaceutically acceptable salt thereof.



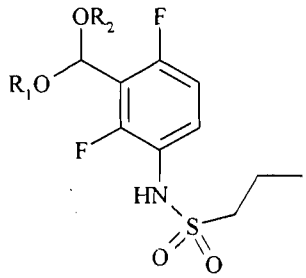
Formula IIIa

In accordance with a thirteenth embodiment, the present invention provides a compound of Formula IIIb or a pharmaceutically acceptable salt thereof.



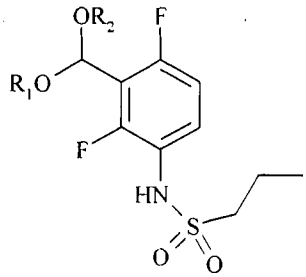
Formula IIIb

In accordance with a fourteenth embodiment, the present invention provides a compound of Formula V; wherein R_1 and R_2 independently represents an alkyl, or R_1 and R_2 taken together form an optionally substituted alkylene ring.



Formula V

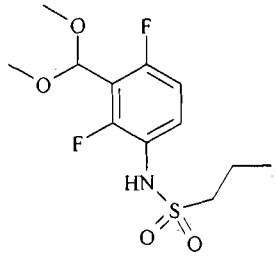
In accordance with a fifteenth embodiment, the present invention provides a compound of Formula V or a pharmaceutically acceptable salt thereof;



Formula V

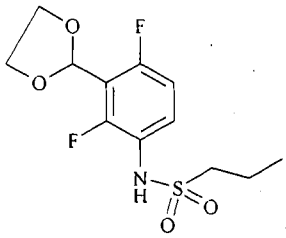
wherein R_1 and R_2 independently represents an alkyl; or R_1 and R_2 taken together form an optionally substituted alkylene ring; wherein the alkyl is selected from the group consisting of methyl, ethyl, propyl, butyl and the like; alkylene is selected from the group consisting of methylene, ethylene, propylene, butylene, pentylene and the like.

In accordance with a sixteenth embodiment, the present invention provides a compound of Formula Va or a pharmaceutically acceptable salt thereof;



Formula Va

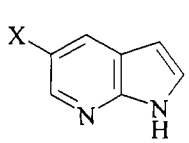
In accordance with a seventeenth embodiment, the present invention provides a compound of Formula Vb or a pharmaceutically acceptable salt thereof;



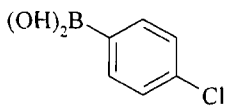
Formula Vb

In accordance with an eighteenth embodiment, the present invention provides a process for preparation of vemurafenib of Formula I or a pharmaceutically acceptable salt thereof, comprising:

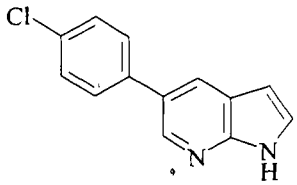
a) reacting a compound of Formula VII; wherein 'X' represents halo with 4-chlorophenyl boronic acid of Formula VIII in presence of a suitable palladium catalyst and a base in a suitable solvent selected from the group consisting of ketones, ethers, amides, aromatic hydrocarbons, water or mixture thereof, to obtain a compound of Formula IX; and



Formula VII



Formula VIII

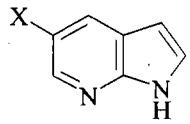


Formula IX

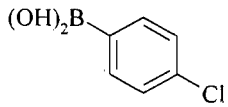
b) converting the compound of Formula IX in to vemurafenib or a pharmaceutically acceptable salt thereof.

In accordance with a nineteenth embodiment, the present invention provides a process for preparation of vemurafenib of Formula I or a pharmaceutically acceptable salt thereof, comprising:

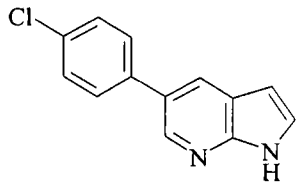
a) reacting a compound of Formula VII; wherein 'X' represents halo with 4-chlorophenyl boronic acid of Formula VIII in presence of a suitable palladium catalyst and a base in a suitable solvent selected from the group consisting of ketones, ethers, amides, aromatic hydrocarbons, water or mixture thereof, to obtain a compound of Formula IX;



Formula VII



Formula VIII



Formula IX

b) purifying the compound of Formula IX with a suitable solvent to obtain pure compound of Formula IX; and

c) converting the compound of Formula IX in to vemurafenib or a pharmaceutically acceptable salt thereof.

In accordance with a twentieth embodiment, the present invention provides a process for purification of compound of Formula IX, comprising:

i) dissolving compound of Formula IX in one or more suitable solvents at a temperature of about 30°C to about reflux temperature,

ii) cooling the obtained solution to less than 20°C, and

iii) filtering the compound of Formula IX.

In accordance with a twenty first embodiment, the present invention provides a process for the preparation of vemurafenib of Formula I or a pharmaceutically acceptable salt thereof, comprising:

a) reacting a compound of Formula VI with a compound of Formula IX in presence of a suitable base in a non-alcoholic solvent to obtain a compound of Formula X; and

b) converting the obtained compound of Formula X in to vemurafenib or a pharmaceutically acceptable salt thereof.

In accordance with a twenty second embodiment, the present invention provides a process for the preparation of vemurafenib of Formula I or a pharmaceutically acceptable salt thereof; comprising:

a) reacting 2,6-difluoro-3-nitro benzaldehyde with trimethyl orthoformate or ethylene glycol to obtain a compound of Formula IIa or Formula IIb;

b) nitro reduction of compound of Formula IIa or Formula IIb with a suitable reducing agent to obtain a compound of Formula IIIa or Formula IIIb:

c) reacting the compound of Formula IIIa or Formula IIIb with a compound of Formula IV, wherein 'X' represents suitable leaving group; in presence of a suitable base to obtain a compound of Formula Va or Formula Vb:

d) deprotecting the compound of Formula Va or Formula Vb in presence of a suitable deprotecting agent to obtain a compound of Formula VI:

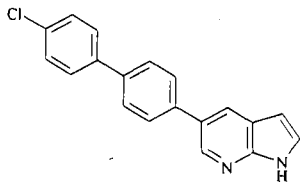
e) reacting a compound of Formula VII; wherein 'X' represents halo with 4-chlorophenyl boronic acid of Formula VIII in presence of a suitable palladium catalyst and a base in a suitable solvent selected from the group consisting of ketones, ethers, amides, aromatic hydrocarbons, water or mixture thereof, to obtain a compound of Formula IX;

f) optionally purifying the compound of Formula IX with a suitable solvent to obtain a pure compound of Formula IX,

g) reacting the compound of Formula VI with a compound of Formula IX in presence of a suitable base in a non-alcoholic solvent to obtain a compound of Formula X; and

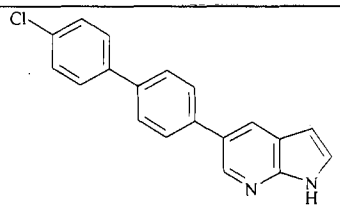
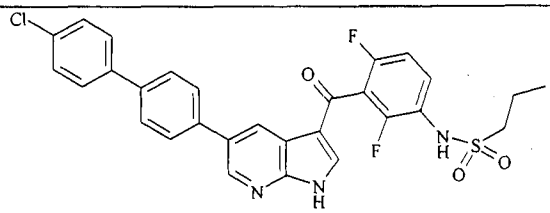
h) converting the compound of Formula X in to vemurafenib or a pharmaceutically acceptable salt thereof.

In accordance with a twenty third embodiment, the present invention provides a compound of Formula IX having less than 0.02% as measured by HPLC of Formula A:



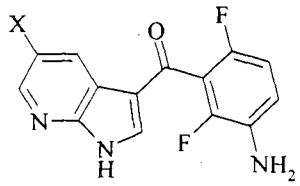
Formula A

In accordance with a twenty fourth embodiment, the present invention provides vemurafenib having less than 0.02% as measured by HPLC each of compound of Formula A or Formula B:

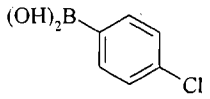
	
Formula A	Formula B

In accordance with a twenty fifth embodiment, the present invention provides a novel process for the preparation of vemurafenib or a pharmaceutically acceptable salt thereof of Formula I: comprising:

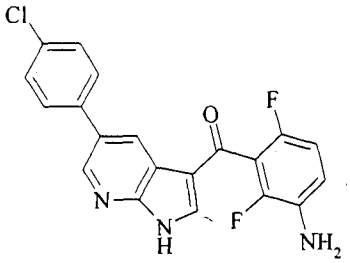
a) reacting a compound of Formula XI, wherein 'X' represents halo; with 4-chlorophenyl boronic acid of Formula VIII in presence of a suitable palladium catalyst and a base to obtain a compound of Formula XII;



Formula XI

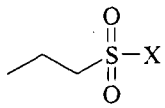


Formula VIII



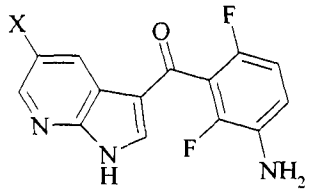
Formula XII; and

b) condensing the obtained compound of Formula XII with a compound of Formula IV, wherein 'X' represents suitable leaving group; in presence of a base to obtain vemurafenib.



Formula IV

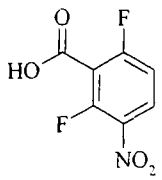
In accordance with a twenty sixth embodiment, the present invention provides a process for the preparation of a compound of Formula XI, wherein 'X' represents halo;



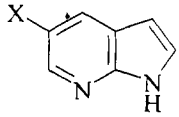
Formula XI

comprising:

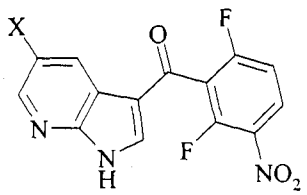
a) reacting 2,6-difluoro-3-nitrobenzoic acid or a reactive derivative of Formula XIII with 5-halo-7-azaindole of Formula VII; wherein 'X' represents halo; in presence of a Lewis acid in a suitable solvent to obtain a compound of Formula XIV:



Formula XIII



Formula VII

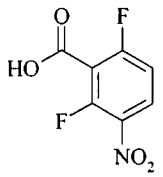


Formula XIV; and

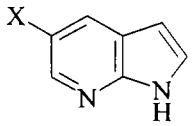
b) nitro reduction of the compound of Formula XIV with a suitable reducing agent to obtain a compound of Formula XI, wherein 'X' represents halo.

In accordance with a twenty seventh embodiment, the present invention provides a novel process for the preparation of vemurafenib or a pharmaceutically acceptable salt thereof of Formula I: comprising:

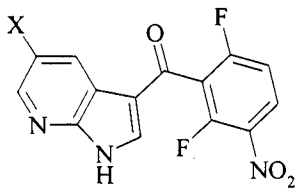
a) reacting 2,6-difluoro-3-nitrobenzoic acid or a reactive derivative of Formula XIII with 5-halo-7-azaindole of Formula VII; wherein 'X' represents halo; in presence of a Lewis acid in a suitable solvent to obtain a compound of Formula XIV:



Formula XIII

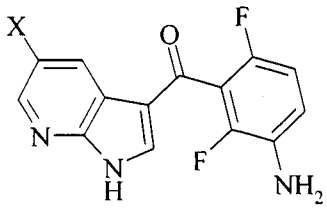


Formula VII



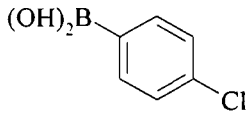
Formula XIV

b) nitro reduction of the compound of Formula XIV with a suitable reducing agent to obtain a compound of Formula XI, wherein 'X' represents halo;

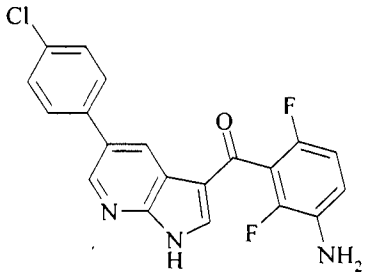


Formula XI

c) coupling the compound of Formula XI with 4-chlorophenyl boronic acid of Formula VIII in presence of a suitable palladium catalyst and a base to obtain a compound of Formula XII; and

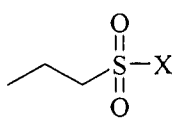


Formula VIII



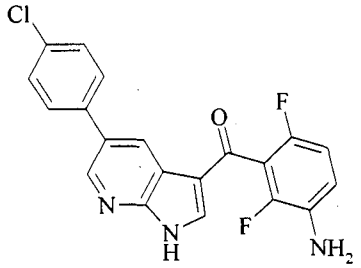
Formula XII

d) condensing the obtained compound of Formula XII with a compound of Formula IV, wherein 'X' represents suitable leaving group; in presence of a base to obtain vemurafenib.

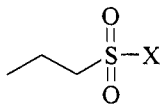


Formula IV

In accordance with a twenty eighth embodiment, the present invention provides a novel process for the preparation of vemurafenib or a pharmaceutically acceptable salt thereof of Formula I: comprising: reacting a compound of Formula XII with a compound of Formula IV, wherein 'X' represents suitable leaving group; in presence of a base to obtain vemurafenib.

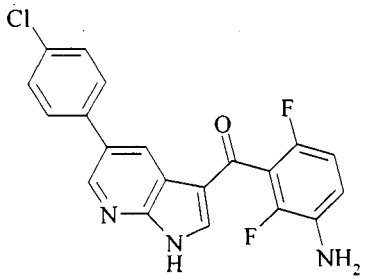


Formula XII



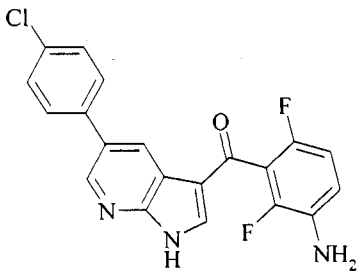
Formula IV

In accordance with a twenty ninth embodiment, the present invention provides a compound of Formula XII or a pharmaceutically acceptable salt thereof.



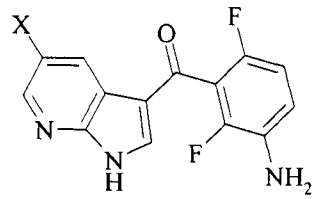
Formula XII

In accordance with a thirtieth embodiment, the present invention provides a process for the preparation of compound of Formula XII or a pharmaceutically acceptable salt thereof:

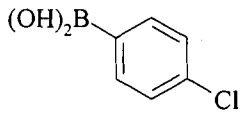


Formula XII

comprising: reacting a compound of Formula XI, wherein 'X' represents halo; with 4-chlorophenyl boronic acid of Formula VIII in presence of a suitable palladium catalyst and a base to obtain a compound of Formula XII.



Formula XI



Formula VIII

In accordance with a thirty first embodiment, the present invention provides a process for purification of vemurafenib or a pharmaceutically acceptable salt thereof, comprising:

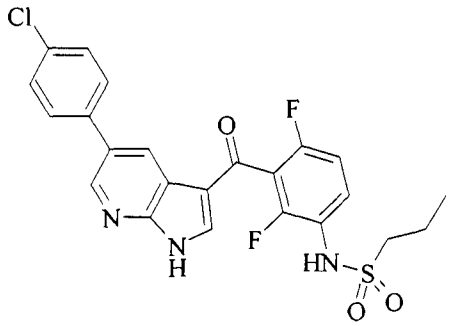
a) dissolving or suspending vemurafenib in a mixture of suitable water immiscible solvent and water,
b) adding a suitable base to the step a),
c) separating the organic layer and aqueous layer,
d) optionally treating the aqueous layer with a suitable water immiscible solvent,
e) adding an acid to the aqueous solution, and
f) isolating the vemurafenib.

In accordance with a thirty second embodiment, the present invention provides a pharmaceutical composition, comprising vemurafenib or a pharmaceutically acceptable salt thereof prepared by the processes of the present invention and at least one pharmaceutically acceptable excipient.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel processes for the preparation of vemurafenib using novel intermediates.

In one embodiment, the present invention provides a novel process for the preparation of vemurafenib of Formula I or a pharmaceutically acceptable salt thereof:

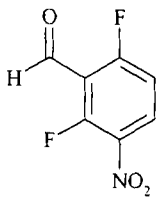


Formula I

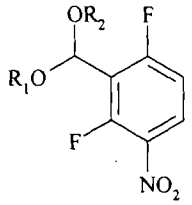
comprising:

a) reacting 2,6-difluoro-3-nitro benzaldehyde with a suitable protecting group to obtain a compound of Formula II; wherein R_1 and R_2 independently represents an

alkyl, or R_1 and R_2 taken together form an optionally substituted alkylene ring; and

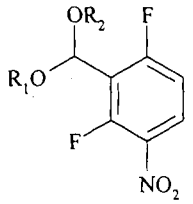


2,6-difluoro-3-nitro benzaldehyde

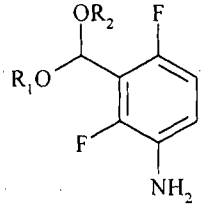


Formula II

b) nitro reduction of compound of Formula II with a suitable reducing agent to obtain a compound of Formula III; wherein R_1 and R_2 are defined as above:

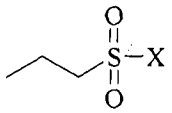


Formula II

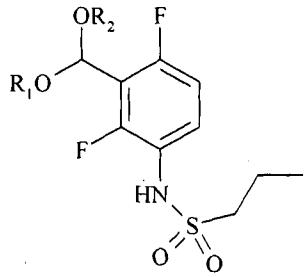


Formula III

c) reacting the compound of Formula III with a compound of Formula IV, wherein 'X' represents suitable leaving group; in presence of a suitable base to obtain a compound of Formula V, wherein R_1 and R_2 are defined as above:

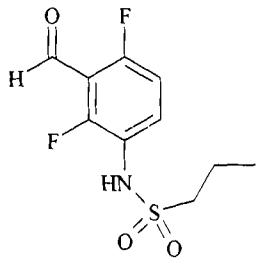


Formula IV



Formula V

d) deprotecting the compound of Formula V in presence of a suitable deprotecting agent to obtain a compound of Formula VI:



Formula VI

e) converting the obtained compound of Formula VI in to vemurafenib or a pharmaceutically acceptable salt thereof.

Unless otherwise specified the term "alkyl" used herein the specification represents C_1 to C_5 alkyl and is selected from but not limited to methyl, ethyl, propyl, isopropyl, butyl and the like.

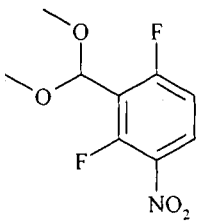
Unless otherwise specified the term "alkylene ring" used herein the specification represents methylene, ethylene, propylene, butylene, pentylene and the like, optionally substituted with C_1 to C_5 alkyl.

Unless otherwise specified the term "suitable leaving group" used herein the specification represents a halo group such as Cl, Br, I; OTf (triflate); OTs (tosylate) and the like.

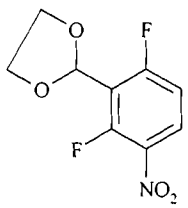
The starting material of 2,6-difluoro-3-nitro benzaldehyde, 5-halo7-azaindole of Formula VII are known in the art and can be prepared by any known method, for example 2,6-difluoro-3-nitro benzaldehyde may be synthesized as disclosed in PCT Publication No. 2010/003025, compound of Formula VII may be synthesized as disclosed in *Heterocycles vol. 50, nb. 2, (1999), page 1065 – 1080.*

In an embodiment of the present invention, the step a) of reacting 2,6-difluoro-3-nitro benzaldehyde with a suitable protecting group is carried out in presence of suitable dehydrating agent to obtain a compound of Formula II; wherein R_1 and R_2 independently represents an alkyl as defined as above; preferably methyl, or R_1 and R_2 taken together form an optionally substituted alkylene ring as defined as above, preferably ethylene ring.

In another embodiment, the compound of Formula II specifically represented as following Formula IIa or Formula IIb:



Formula IIa



Formula IIb

The suitable protecting group includes but is not limited to trimethyl orthoformate, triethyl orthoformate, tripropyl orthoformate, tributyl orthoformate, tripentyl orthoformate, methylene glycol, ethylene glycol, propylene glycol, butylene glycol, pentylene glycol and the like; preferably trimethyl orthoformate or ethylene glycol.

The suitable dehydrating agent includes but is not limited to p-toluenesulfonic acid (PTSA), camphorsulfonic acid (CSA), pyridinium p-toluenesulfonate (PPTS), sulfonic

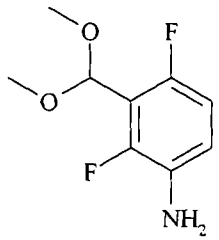
acid exchange resins (Amberlyst, Dowex), sulfuric acid, nitric acid and the like and mixtures thereof; preferably p-toluenesulfonic acid or sulfuric acid.

The reaction of 2,6-difluoro-3-nitro benzaldehyde with a suitable protecting group and a dehydrating agent may be carried out in a suitable solvent. The suitable solvent includes but is not limited to alcohols, ethers, esters, halogenated solvents, aromatic hydrocarbons, cyclic hydrocarbons, amides, nitriles, water and mixtures thereof. Preferably alcohols include, but are not limited to methanol, ethanol, propanol, isopropanol and the like; Ethers include, but are not limited to tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and the like; esters include, but are not limited to methyl acetate, ethyl acetate, isopropyl acetate and the like; halogenated solvents include, but are not limited to methylene chloride, ethylene chloride, chloroform and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like; cyclic hydrocarbons include, but are not limited to hexane, cyclohexane, heptane and the like; amides include, but are not limited to dimethyl formamide, dimethylsulfoxide, dimethyl acetamide, N-methyl pyrrolidinone and the like; nitriles include, but are not limited to acetonitrile, propionitrile and like and mixtures thereof; preferably methanol, ethanol, toluene, xylene or mixtures thereof.

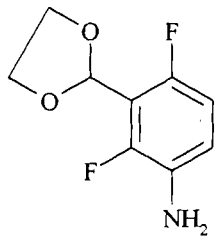
The reaction of 2,6-difluoro-3-nitro benzaldehyde with a suitable protecting group and a dehydrating agent is carried out at a temperature of about 25°C to reflux temperature; preferably at about 60°C to about 110°C.

The step b) of nitro reduction process of the aforementioned process involves reduction of the nitro group in the compound of Formula II; wherein R_1 and R_2 are defined as above; in presence of a suitable reducing agent in an organic solvent to obtain a compound of Formula III, wherein R_1 and R_2 are defined as above.

In another embodiment, the compound of Formula III specifically represented as following Formula IIIa or Formula IIIb:



Formula IIIa



Formula IIIb

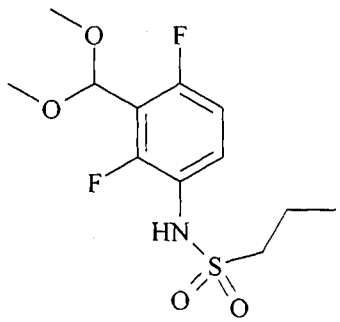
The suitable reducing agent used herein is selected from the group consisting of Palladium on carbon, Raney nickel, Platinum oxide, Sodium hydrosulfite, Zinc and the like; preferably Palladium on carbon.

The organic solvent for nitro reduction is used herein is selected from the group consisting of alcohols, ethers, aromatic hydrocarbons and mixtures thereof. The alcohols include, but are not limited to methanol, ethanol, propanol, isopropanol and the like; ethers include, but are not limited to tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like and mixtures thereof; preferably methanol, ethanol, tetrahydrofuran and mixtures thereof.

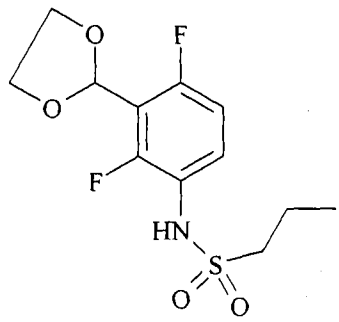
The nitro reduction is carried out at a temperature of about 25°C to about reflux. After completion of the reaction, the reaction mass is subjected to filtration and the resultant reaction mass may be concentrated under vacuum to obtain a compound of Formula III as residue; wherein R_1 and R_2 are defined as above.

The step c) of the aforementioned process involves reaction of compound of Formula III; wherein R_1 and R_2 are defined as above; with a compound of Formula IV; wherein 'X' represents halo; in presence of a base to obtain a compound of Formula V; wherein R_1 and R_2 are defined as above.

In another embodiment, the compound of Formula V specifically represented as following Formula Va or Formula Vb:



Formula Va



Formula Vb

The base used herein for the reaction of compound of Formula III and compound of Formula IV; wherein R_1 and R_2 are defined as above; include but is not limited to inorganic bases selected from alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate and the like; and organic bases selected from the group consisting of triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine, pyridine and the like and mixtures thereof; preferably pyridine, triethylamine, potassium carbonate and mixtures thereof.

The reaction of compound of Formula III and Formula IV; wherein R_1 and R_2 are defined as above; may be carried out in a suitable solvent. The suitable solvent include but is not limited to esters, ketones, amides, nitriles, ethers, halogenated hydrocarbons, aromatic hydrocarbons and mixtures thereof. The esters include, but are not limited to methyl acetate, ethyl acetate, isopropyl acetate and the like; ketones include, but are not limited to acetone, methyl isobutyl ketone, methyl ethyl ketone and the like; amides include, but are not limited to dimethyl formamide, dimethyl acetamide, N-methyl pyrrolidinone and the like; nitriles include, but are not limited to acetonitrile, propionitrile and the like; ethers include, but are not limited to tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and the like; halogenated hydrocarbons include, but are not limited to methylene chloride, ethylene chloride, chloroform, carbon tetrachloride and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like and mixture thereof; preferably tetrahydrofuran, dimethyl formamide, methylene chloride or mixture thereof.

The reaction of compound of Formula III and Formula IV; wherein R_1 and R_2 are defined as above; is carried out at a temperature of about 0°C to reflux temperature; preferably at about 25°C to about 35°C.

The step d) of deprotecting the compound of Formula V; wherein R_1 and R_2 are defined as above; is carried out in presence of a suitable deprotecting agent to obtain a compound of Formula VI.

The suitable deprotecting agent used herein is selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, trifluoro acetic acid, trichloro acetic acid, methane sulfonic acid and the like and mixture thereof; preferably hydrochloric acid.

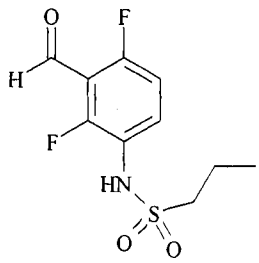
The source of acid may be in the form of an aqueous, anhydrous or gas form, for example aqueous hydrochloric acid or solvent containing hydrochloric acid or hydrochloric acid gas.

The deprotection of compound of Formula V; wherein R_1 and R_2 are defined as above; may be carried out in a suitable organic solvent. The suitable organic solvent includes but is not limited to esters, ketones, nitriles, ethers, halogenated hydrocarbons and mixtures thereof. The esters include, but are not limited to methyl acetate, ethyl acetate, isopropyl acetate and the like; ketones include, but are not limited to acetone, methyl isobutyl ketone, methyl ethyl ketone and the like; nitriles include, but are not limited to acetonitrile, propionitrile and the like; ethers include, but are not limited to tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and the like; halogenated hydrocarbons include, but are not limited to methylene

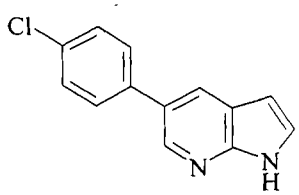
chloride, ethylene chloride, chloroform, carbon tetrachloride and the like; preferably tetrahydrofuran, acetonitrile, methylene chloride or mixture thereof.

The deprotection of Formula V is carried out at a temperature of about 25°C to reflux temperature; preferably at about 60°C to about 70°C.

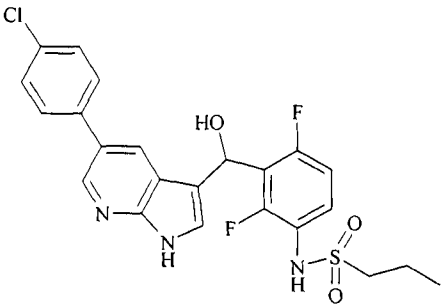
In another embodiment, the compound of Formula VI thus obtained may be converted in to vemurafenib of Formula I by reacting the compound of Formula VI with a compound of Formula IX in presence of a suitable base to obtain a compound of Formula X; and converting the compound of Formula X into vemurafenib or a pharmaceutically acceptable salt thereof.



Formula VI



Formula IX



Formula X

The step of reacting the compound of Formula VI with a compound of Formula IX can be carried out according to processes known in the art, for example the reaction is carried out in presence of a suitable base in a suitable solvent at a temperature of about 25°C to reflux temperature to obtain a compound of Formula X, which is then converted into vemurafenib as procedure known in the art.

In another embodiment, the present invention provides a process for the preparation of vemurafenib of Formula I or a pharmaceutically acceptable salt thereof, comprising:

a) reacting a compound of Formula VI with a compound of Formula IX in presence of a suitable base in a non-alcoholic solvent to obtain a compound of Formula X; and
b) converting the obtained compound of Formula X in to vemurafenib or a pharmaceutically acceptable salt thereof.

The '288 patent discloses a process for preparation of vemurafenib, which involves formation of methoxy intermediate, which is formed due to the presence of alcoholic solvent such as methanol in the reaction of compound of Formula VI and Formula IX. The methoxy compound is converted in to vemurafenib through deprotection of methyl moiety. The additional process steps such as formation of methoxy compound and then deprotection to remove methyl moiety, which process involves prolonged period of reaction time of about 72 hours for formation of methoxy compound and about 12 hours

for deprotection reaction; which process leads to an increase in the manufacturing cycle time and decrease in the product yield and quality.

The present inventors have found that use of non alcoholic solvent in the reaction of compound of Formula VI with a compound of Formula IX avoids the formation of such alkyl derivatives, which eliminates the additional process steps to remove alkyl moiety, thereby the process substantially decreases the reaction time cycle and improves the product yield.

The non-alcoholic solvent used herein in the reaction of compound of Formula VI and compound of Formula IX includes but is not limited to ethers, amides, nitriles, water and mixtures thereof. Ethers include, but are not limited to tetrahydrofuran, 1,4-dioxane and the like; amides such as dimethyl formamide, dimethylsulfoxide, dimethyl acetamide, N-methyl pyrrolidinone and the like; nitriles such as acetonitrile, propionitrile and the like and mixtures thereof; preferably tetrahydrofuran, dimethyl formamide, acetonitrile, water or mixture thereof.

The suitable base used herein for the reaction of compound of Formula VI and compound of Formula IX include but is not limited to inorganic bases selected from alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate and the like; and organic bases selected from the group consisting of triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine, pyridine and the like; guanidine bases such as 1,1,3,3-Tetramethylguanidine (TMG) and the like and mixtures thereof; preferably 1,1,3,3-Tetramethylguanidine (TMG), potassium hydroxide, sodium carbonate or cesium carbonate.

The reaction of compound of Formula VI and compound of Formula IX is carried out at a temperature of about 25°C to reflux temperature; preferably at about 25°C to about 35°C.

In another embodiment, the compound of Formula X thus obtained by the processes described as above may be optionally purified and converting it into vemurafenib by the processes known in the art.

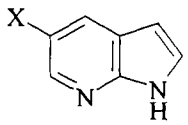
The purification step of compound of Formula X may be carried out by dissolving it in a suitable solvent. The suitable solvent may be selected from the group comprising halogenated hydrocarbons include, but are not limited to methylene chloride, ethylene chloride, chloroform, carbon tetrachloride and the like; ethers such as methyl tertiary

butyl ether, diethyl ether, diisopropyl ether and the like and mixtures thereof; preferably methylene chloride. Further step of heating to obtain a solution at a temperature of from about ambient temperature to about reflux temperature; then, the reaction solution may be cooled at a temperature from about 20°C or less such that the compound of Formula X can be isolated by conventional techniques.

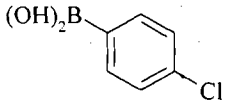
The conversion of the compound of Formula X in to vemurafenib is carried out by the process known in the art for e.g., as process described in the '288 patent or in presence of suitable oxidising agent such as 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), potassium dichromate, pyridinium chloro chromate, hydrogen peroxide and in a suitable solvent to obtain vemurafenib.

In another embodiment, the present invention provides a process for the preparation of vemurafenib of Formula I or a pharmaceutically acceptable salt thereof, comprising:

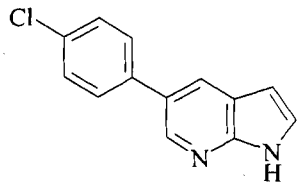
a) reacting a compound of Formula VII; wherein 'X' represents halo with 4-chlorophenyl boronic acid of Formula VIII in presence of a suitable palladium catalyst and a base in a suitable solvent selected from the group consisting of ketones, ethers, amides, aromatic hydrocarbons, water or mixture thereof, to obtain a compound of Formula IX; and



Formula VII



Formula VIII



Formula IX

b) converting the compound of Formula IX in to vemurafenib or a pharmaceutically acceptable salt thereof.

The reported literatures for example, the '288 patent discloses preparation of compound of Formula IX by coupling of 5-bromo-azaindole of Formula VII and p-chlorophenyl boronic acid in presence of acetonitrile and water at a temperature of about 170°C for extended periods and silica-gel column purification with ethyl acetate/hexane. This process has certain drawbacks as it involves formation of substantial amounts of biphenyl impurity of Formula A, which is formed due to the presence of acetonitrile as solvent. If the compound of Formula IX contains the biphenyl impurity of Formula A as an impurity, which readily produces Formula B as an impurity during the formation of final vemurafenib API. The said impurity of Formula B is very difficult to remove from the vemurafenib product; it requires multiple purification procedures to remove such impurity, which process is not viable for large scale manufacturing. Thus control of Formula A during the reaction between Formula VII and Formula VIII itself is advantageous.

The present inventors have found that use of other than acetonitrile as reaction solvent during the reaction of Formula VII and Formula VIII substantially reduces the formation of Formula A as an impurity; which eliminates the additional purification steps, thereby the process substantially decreases the reaction time cycle and improves the product yield.

In a preferred embodiment, the compound of Formula VII; wherein 'X' represents halo such as bromo, chloro, or iodo; preferably bromo is reacted with 4-chlorophenyl boronic acid of Formula VIII in presence of a suitable palladium catalyst and a base in a suitable solvent as stated above.

The suitable palladium catalyst used herein is selected from the group consisting of tetrakis (triphenylphosphine) palladium(0), tetrakis(tri(otolyl) phosphine) palladium(0), $Pd_2(dba)_3$, [1,1'Bis(diphenylphosphino)ferrocene]dichloropalladium(II) ($Pd(dppf)_2Cl_2$), Palladium(II)acetate and the like and mixtures thereof; preferably tetrakis (triphenylphosphine) palladium.

The base used herein for the reaction of a compound of Formula VII and a compound of Formula VIII include but is not limited to alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate and the like; and organic bases such as triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine, pyridine and the like and their mixtures thereof; preferably sodium methoxide, potassium carbonate, potassium tert-butoxide or sodium tert-butoxide; more preferably potassium carbonate.

The suitable solvent for reaction of a compound of Formula VII and a compound of Formula VIII include but is not limit to ketones, ethers, amides, aromatic hydrocarbons, water and mixtures thereof. The ketones include, but are not limited to acetone, methyl isobutyl ketone, methyl ethyl ketone and the like; ethers include, but are not limited to tetrahydrofuran, dimethyl ether, diethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane, 1,2-domethoxy ethane, and the like; amides include, but are not limited to dimethyl formamide, dimethyl acetamide, dimethyl sulfoxide, N-methyl pyrrolidinone and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like; water and mixture thereof; preferably 1,4-dioxane, tetrahydrofuran, water and mixture thereof; more preferably 1,4-dioxane, water and mixtures thereof.

The reaction of a compound of Formula VII and a compound of Formula VIII is advantageously carried out at a temperature of about 25°C to reflux temperature;

preferably at about 65°C to 95°C, more preferably at about 80°C to 90°C. After completion of the reaction, the obtained reaction mass may be separated off and the obtained product containing organic layer may be cooled to about 0°C to 5°C to precipitate out the compound IX.

The present invention provides a compound of Formula IX prepared by the process described as above having a purity of at least about 97%, as measured by HPLC, preferably at least about 98% as measured by HPLC, and more preferably at least about 99.5%, as measured by HPLC; and content of Formula A is less than about 0.1%, as measured by HPLC, more preferably less than about 0.05% as measured by HPLC.

In another embodiment, compound of Formula IX thus obtained may be purified by treating the compound of Formula IX in a suitable solvent.

In another embodiment, the present invention provides a process for purification of compound of Formula IX, comprising:

i) dissolving compound of Formula IX in one or more suitable solvent at a temperature of about 30°C to about reflux temperature,
ii) cooling the obtained solution to less than 20°C, and
iii) filtering the compound of Formula IX.

The suitable solvent used herein for purification of compound of Formula IX include but is not limited to alcohols, ethers, esters, amides, nitriles, ketones, halogenated hydrocarbons, aromatic hydrocarbons, water and mixtures thereof. The alcohols include, but are not limited to methanol, ethanol, isopropanol, n-propanol, t-butanol and the like; ethers include, but are not limited to tetrahydrofuran, methyl tertiary butyl ether, diethyl ether and the like; esters include, but are not limited to methyl acetate, ethyl acetate, isopropyl acetate and the like; amides include, but are not limited to dimethyl formamide, dimethyl sulfoxide, dimethyl acetamide and the like; nitriles include, but are not limited to acetonitrile, propionitrile and the like; ketones include, but are not limited to acetone, methyl isobutyl ketone, methyl ethyl ketone and the like; halogenated hydrocarbons include, but are not limited to methylene chloride, chloroform and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like; water and mixtures thereof; preferably tetrahydrofuran, acetonitrile, ethyl acetate or mixtures thereof; more preferably tetrahydrofuran.

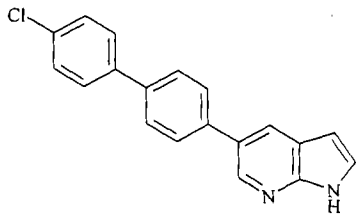
The solution may be heated to dissolve the compound of Formula IX. The temperature suitable for dissolving compound of Formula IX depends on the solvent used and the amount of compound of Formula IX in the solution. Typically, the solution is heated at a temperature of at least about 30°C to about reflux; preferably at about 60°C to about 65°C. The resultant reaction solution may be cooled at a temperature from about 20°C or less such that the compound of Formula IX can be isolated by conventional techniques,

for example filtration. In the event that stirring is involved, the temperature during stirring can range from about – 10°C to about +20°C, preferably at about -10 to about + 10°C, more preferably at temperature between 0°C to 5°C.

The present invention provides a compound of Formula IX prepared by the purification as described above having a purity of at least about 97%, as measured by HPLC, preferably at least about 98% as measured by HPLC, and more preferably at least about 99.8%, as measured by HPLC; and content of Formula A is less than about 0.05%, as measured by HPLC, more preferably less than about 0.02% as measured by HPLC.

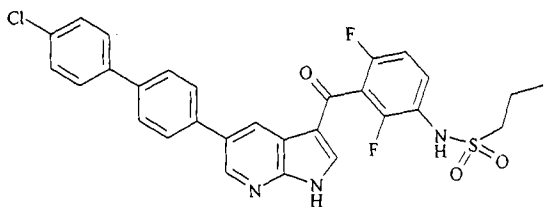
In another embodiment, the present invention provides a process for the preparation of vemurafenib or a pharmaceutically acceptable salt thereof, comprising providing a compound of Formula IX as obtained by the process described above, as a starting material or as an intermediate by the process known in the art, for example as per the '288 patent, where the purity of the vemurafenib having at least about 98% as measured by HPLC, preferably at least about 99.8% as measured by HPLC and substantially free of impurity of Formula A or Formula B; wherein the word "substantially free" refers to vemurafenib having less than about 0.15% of Formula A or Formula B as measured by HPLC, preferably less than about 0.1% of Formula A or Formula B as measured by HPLC; more preferably less than about 0.05% of Formula A or Formula B as measured by HPLC; still more preferably less than about 0.02% of Formula A or Formula B as measured by HPLC.

In another embodiment, the present invention provides a compound of Formula IX having less than 0.02% of Formula A:



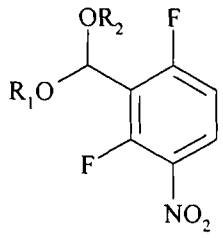
Formula A

In another embodiment, the present invention provides vemurafenib having less than 0.02% each of compound of Formula A or Formula B:



Formula B

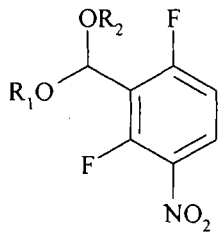
In another embodiment, the present invention provides a compound of Formula II or a pharmaceutically acceptable salt thereof;



Formula II

wherein R_1 and R_2 independently represents an alkyl, or R_1 and R_2 taken together form an optionally substituted alkylene ring.

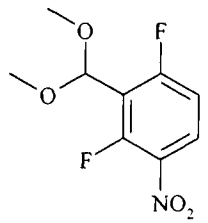
In another embodiment, the present invention provides a compound of Formula II or a pharmaceutically acceptable salt thereof;



Formula II

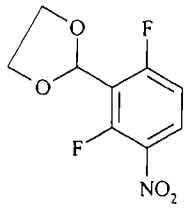
wherein R_1 and R_2 independently represents an alkyl; or R_1 and R_2 taken together form an optionally substituted alkylene ring; wherein the alkyl is selected from the group consisting of methyl, ethyl, propyl, butyl and the like; alkylene is selected from the group consisting of methylene, ethylene, propylene, butylene, pentylene and the like.

In another embodiment, the present invention provides a compound of Formula IIa or a pharmaceutically acceptable salt thereof.



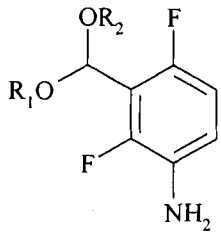
Formula IIa

In another embodiment, the present invention provides a compound of Formula IIb or a pharmaceutically acceptable salt thereof.



Formula IIb

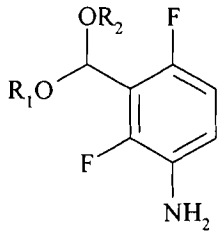
In another embodiment, the present invention provides a compound of Formula III or a pharmaceutically acceptable salt thereof;



Formula III

wherein R_1 and R_2 independently represents an alkyl, or R_1 and R_2 taken together form an optionally substituted alkylene ring.

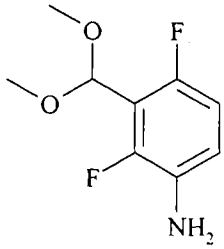
In another embodiment, the present invention provides a compound of Formula III or a pharmaceutically acceptable salt thereof;



Formula III

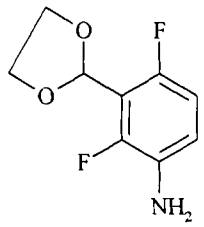
wherein R_1 and R_2 independently represents an alkyl; or R_1 and R_2 taken together form an optionally substituted alkylene ring; wherein the alkyl is selected from the group consisting of methyl, ethyl, propyl, butyl and the like; alkylene is selected from the group consisting of methylene, ethylene, propylene, butylene, pentylene and the like.

In another embodiment, the present invention provides a compound of Formula IIIa or a pharmaceutically acceptable salt thereof.



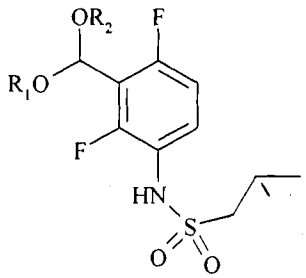
Formula IIIa

In another embodiment, the present invention provides a compound of Formula IIIb or a pharmaceutically acceptable salt thereof.



Formula IIIb

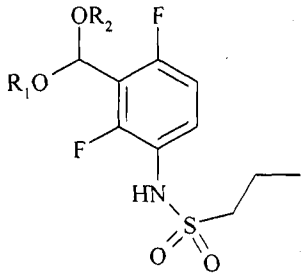
In another embodiment, the present invention provides a compound of Formula V or a pharmaceutically acceptable salt thereof;



Formula V

wherein R_1 and R_2 independently represents an alkyl, or R_1 and R_2 taken together form an optionally substituted alkylene ring.

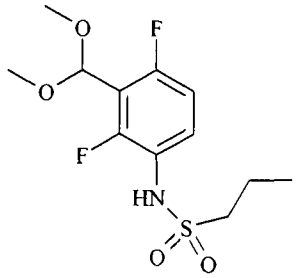
In another embodiment, the present invention provides a compound of Formula V or a pharmaceutically acceptable salt thereof;



Formula V

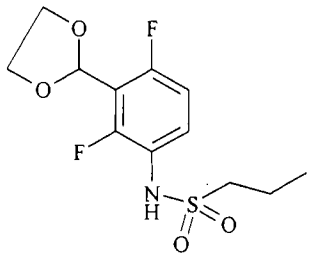
wherein R_1 and R_2 independently represents an alkyl; or R_1 and R_2 taken together form an optionally substituted alkylene ring; wherein the alkyl is selected from the group consisting of methyl, ethyl, propyl, butyl and the like; alkylene is selected from the group consisting of methylene, ethylene, propylene, butylene, pentylene and the like.

In another embodiment, the present invention provides a compound of Formula Va or a pharmaceutically acceptable salt thereof.



Formula Va

In another embodiment, the present invention provides a compound of Formula Vb or a pharmaceutically acceptable salt thereof.



Formula Vb

In a preferred embodiment, the present invention provides a process for the preparation of vemurafenib of Formula I or a pharmaceutically acceptable salt thereof; comprising:

a) reacting 2,6-difluoro-3-nitro benzaldehyde with trimethyl orthoformate or ethylene glycol in presence of a dehydrating agent such as PTSA or sulfuric acid to obtain a compound of Formula IIa or Formula IIb;

b) nitro reduction of compound of Formula IIa or Formula IIb with a suitable reducing agent such as palladium on carbon to obtain a compound of Formula IIIa or Formula IIIb:

c) reacting the compound of Formula IIIa or Formula IIIb with a compound of Formula IV, wherein 'X' represents a suitable leaving group such as chloro; in presence of a suitable base such as pyridine to obtain a compound of Formula Va or Formula Vb:

d) deprotecting the compound of Formula Va or Formula Vb in presence of a suitable deprotecting agent such as hydrochloric acid to obtain a compound of Formula VI:

e) reacting a compound of Formula VII; wherein 'X' represents halo specifically bromo with 4-chlorophenyl boronic acid of Formula VIII in presence of a suitable palladium catalyst and a base such as potassium carbonate in a suitable solvent selected from 1,4-dioxane, water or mixture thereof, to obtain a compound of Formula IX;

f) optionally purifying the compound of Formula IX with a suitable solvent such as tetrahydrofuran to obtain a pure compound of Formula IX,

g) reacting the compound of Formula VI with a compound of Formula IX in presence of 1,1,3,3-Tetramethylguanidine in a non-alcoholic solvent selected from tetrahydrofuran, water or mixtures thereof to obtain a compound of Formula X; and

h) optionally purifying the compound of Formula X with a suitable solvent such as methylene chloride to obtain a pure compound of Formula X, and

i) converting the compound of Formula X in to vemurafenib or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a process for purification of vemurafenib or a pharmaceutically acceptable salt thereof, comprising:

a) dissolving or suspending vemurafenib in a mixture of suitable water immiscible solvent and water,

b) adding a suitable base to the step a),

c) separating the organic layer and aqueous layer,

d) optionally treating the aqueous layer with a suitable water immiscible solvent,

e) adding an acid to the aqueous solution, and

f) isolating the vemurafenib.

The starting material of vemurafenib may be prepared by the processes of the present invention described above or by the process known in the art can be used for purification process.

The step a) process involves providing dissolving or suspending vemurafenib in a suitable water immiscible solvent and water at a temperature of about 25-35°C.

The suitable water immiscible solvent used herein for purification of vemurafenib include but is not limited to methyl tertiary butyl ether, diethyl ether, ethyl acetate, methylene chloride, chloroform toluene, xylene and the like and mixtures thereof; preferably methylene chloride, ethyl acetate or toluene.

The base used herein for step b) is selected from the group consisting of ammonia, sodium hydroxide, potassium hydroxide and the like; preferably sodium hydroxide.

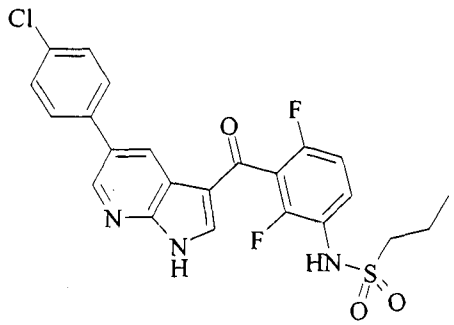
Then, separating the organic and aqueous layers and the aqueous layer may be optionally treated with the water immiscible solvent. The resultant aqueous layer containing product may be treating with an acid to precipitating out the product. The acid may be selected from the group comprising hydrochloric acid, sulfuric acid, acetic acid and the like; preferably hydrochloric acid. Advantageously the acid may be added at a temperature of less than about 20°C, preferably less than 10°C.

The precipitated vemurafenib can be recovered by any conventional techniques known in the art, for example filtration. Typically, if stirring is involved, the temperature during stirring can range from about 0°C to about 15°C, preferably at about 5°C to about 10°C.

In another embodiment, vemurafenib obtained by the processes described as above, having purity of at least about 98% as measured by HPLC, preferably at least about 99.8% as measured by HPLC and substantially free of impurity of Formula A or Formula B; wherein the word "substantially free" refers to vemurafenib having less than about 0.15% of Formula A or Formula B as measured by HPLC, preferably less than about 0.1% of Formula A or Formula B as measured by HPLC; more preferably less than about 0.05% of Formula A or Formula B as measured by HPLC; still more preferably less than about 0.02% of Formula A or Formula B as measured by HPLC.

As used herein, the pharmaceutical acceptable salts include acid addition salts formed with inorganic acids or with organic acids. The inorganic acids may be selected from hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, sulfamic acid, and the like; organic acids may be selected from acetic acid, oxalic acid, fumaric acid, citric acid, succinic acid, tartaric acid, salicylic acid, benzoic acid, glycolic acid, methane sulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, lactic acid, maleic acid, malonic acid, malic acid, isethionic acid, lactobionic acid, mandelic acid, p-coumaric acid, ferulic acid, sinapic acid, caffeic acid, chlorogenic acid, caftaric acid, coutaric acid, p-hydroxy benzoic acid, vanillic acid, syringic acid, 4-(4-phenoxybenzoyl) benzoic acid, gentisic acid, protocatechuic acid, gallic acid, lipoic acid, aspartic acid and the like.

In another embodiment, the present invention provides a novel process for the preparation of vemurafenib or a pharmaceutically acceptable salt thereof of Formula I:

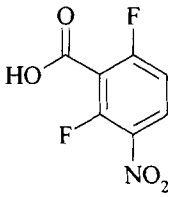


Formula I

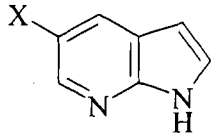
comprising:

a) reacting 2,6-difluoro-3-nitrobenzoic acid or a reactive derivative of Formula XIII with 5-halo-7-azaindole of Formula VII; wherein 'X' represents halo; in

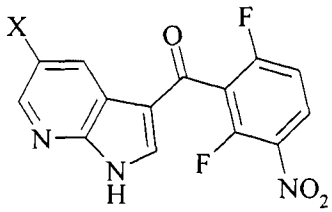
presence of a Lewis acid in a suitable solvent to obtain a compound of Formula XIV:



Formula XIII

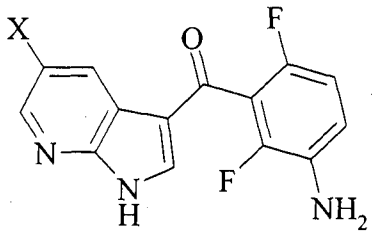


Formula VII



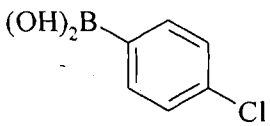
Formula XIV

b) nitro reduction of the compound of Formula XIV with a suitable reducing agent to obtain a compound of Formula XI, wherein 'X' represents halo;

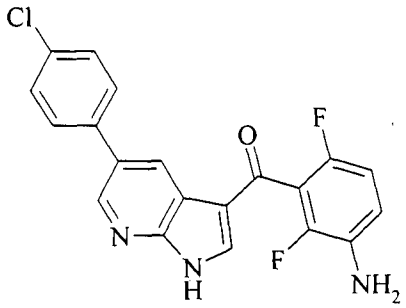


Formula XI

c) coupling the compound of Formula XI with 4-chlorophenyl boronic acid of Formula VIII in presence of a suitable palladium catalyst and a base to obtain a compound of Formula XII; and

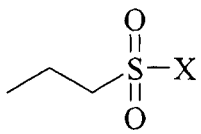


Formula VIII



Formula XII

d) condensing the obtained compound of Formula XII with a compound of Formula IV, wherein 'X' represents suitable leaving group; in presence of a base to obtain vemurafenib.

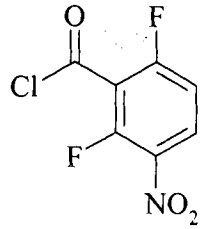


Formula IV

The starting material of compound of Formula XIII or a reactive derivative, preferably chloro derivative and Formula XIII are known in the art and can be prepared by any known method, for example starting compound of Formula XIII and Formula VII may be synthesized as disclosed in PCT Publication No. 2012/109075.

The reaction of 2,6-difluoro-3-nitrobenzoic acid or a reactive derivative of Formula XIII, preferably its chloro derivative with 5-halo-7-azaindole of Formula VII; wherein 'X' represents halo; preferably bromo is carried out in presence of a Lewis acid catalyst and in a suitable solvent to obtain a compound of Formula XIV, wherein 'X' is bromo.

The reactive derivative of 2,6-difluoro-3-nitrobenzoic acid of Formula XIII may be prepared by reacting compound of Formula XIII with source of chlorine like oxalyl chloride or thionyl chloride and in a chlorinated solvent like methylene chloride to obtain acid chloride of compound of Formula XIII a.



Formula XIII a

The suitable Lewis acid catalyst for the reaction of compound of Formula XIII and Formula VII is selected from the group consisting of aluminum chloride, aluminum bromide, ferric chloride, tin chloride, stannic chloride and the like; preferably aluminum chloride.

The compound of Formula XIII and Formula VII may be reacted in a suitable solvent. The suitable solvent includes but is not limited to ethers, halogenated hydrocarbons, aromatic hydrocarbons and mixtures thereof. ethers include, but are not limited to tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and the like; halogenated hydrocarbons include, but are not limited to methylene chloride, ethylene chloride, chloroform, carbon tetrachloride and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like; preferably methylene chloride.

The reaction of compound of Formula XIII and Formula VII is carried out at a temperature of about 0°C to about reflux temperature; preferably at about 5°C to about 40°C.

The nitro reduction process of the aforementioned process involves reduction of the nitro group in the compound of Formula XIV in presence of a suitable reducing agent and in an organic solvent to obtain a compound of Formula XI, wherein the 'X' is bromo.

The suitable reducing agent for nitro reduction is selected from the group consisting of Fe/HCl, Fe/NH_4Cl, $SnCl_2$ and the like; preferably the suitable reducing agent is Fe/HCl.

The organic solvent for nitro reduction of compound of Formula XIV includes but is not limited to alcohols, ethers, aromatic hydrocarbons and mixtures thereof. The alcohols include, but are not limited to methanol, ethanol, propanol, isopropanol and the like; ethers include, but are not limited to tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane and the like; aromatic hydrocarbons include, but are not limited to toluene, xylene and the like and mixtures thereof; preferably the solvent mixture for reduction is tetrahydrofuran, ethanol and mixtures thereof.

The nitro reduction is carried out at a temperature of about 30°C to about reflux; preferably at about 60°C to about 80°C.

After completion of the reaction, the reaction mass is subjected to filtration and the resultant reaction mass may be concentrated under vacuum to obtain residue. The compound of Formula XI, wherein 'X' is bromo is isolated from the residue so obtained by methods known in the art, for example solvent crystallization, solvent slurry and the like.

In another embodiment, the present invention provides a process for the preparation of vemerafenib of Formula I, comprising reacting a compound of Formula XI, wherein 'X' represents bromo; as obtained by the process described above or may be obtained by any known process, as a starting material or as an intermediate with 4-chlorophenyl boronic acid of Formula VIII in presence of a suitable palladium catalyst and a base to obtain a compound of Formula XII and converting the compound of Formula XII into vemurafenib or a pharmaceutically acceptable salts thereof according step c) and d) of the above.

The palladium catalyst for coupling of compound of Formula XI and Compound of Formula VIII include but are not limit to tetrakis (triphenylphosphine) palladium (0), tetrakis(tri(otolyl)phosphine)palladium(0),$Pd_2(dba)_3$,[1,1'Bis(diphenylphosphino)ferrocene]dichloropalladium(II) ($Pd(dppf)_2CH_2Cl_2$), Palladium(II)acetate and mixtures thereof; preferably mixture of $Pd(dppf)_2CH_2Cl_2$ and Palladium(II)acetate.

The base for coupling of compound of Formula XI and Compound of Formula VIII include inorganic bases selected from alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and the like; and alkali metal bicarbonates such as sodium bicarbonate and potassium bicarbonate and the like; and organic bases such as triethylamine, isopropyl

ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine, pyridine and the like and their mixtures thereof; preferable potassium carbonate.

The base can be added either as solution in water or it may be added as solid to the solution of reaction mixture.

The reaction of compound of Formula XI and Formula VIII is advantageously carried out in a suitable solvent. The suitable solvents include but are not limit to ketones, amides, nitriles, ethers, halogenated hydrocarbons, aromatic hydrocarbons, water and mixtures thereof. Preferably acetone, methyl isobutyl ketone, methyl ethyl ketone, dimethyl formamide, dimethyl acetamide, N-methyl pyrrolidinone , acetonitrile, propionitrile, tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane, methylene chloride, ethylene chloride, chloroform, toluene, xylene; water and mixture thereof; preferably acetone, 1,4-dioxane, tetrahydrofuran, dimethyl formamide and mixtures thereof; more preferably 1,4-dioxane.

The coupling reaction of compound of Formula XI and Formula VIII is advantageously carried out at a temperature of about 30°C to 120°C; preferably at about 40°C to about 90°C.

In another embodiment, the present invention provides a process for the preparation of vemerafenib of Formula I, comprising reacting a compound of Formula XII as obtained by the process described above, as a starting material or as an intermediate with a compound of Formula IV, wherein 'X' represents suitable leaving group; preferably chloro, according to step d) of the above.

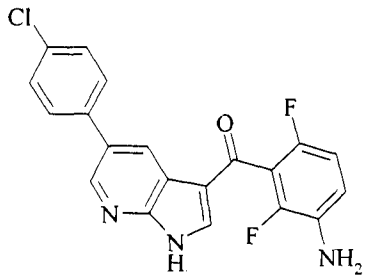
The suitable base used herein for the reaction of compound of Formula XII and compound of Formula IV include but is not limited to inorganic bases selected from alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and the like; and alkali metal bicarbonates such as sodium bicarbonate and potassium bicarbonate and the like; and organic bases selected from the group consisting of triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine, pyridine and the like and their mixtures thereof; preferably pyridine, triethylamine or potassium carbonate; more preferably pyridine.

The reaction of compound of Formula XII and Formula IV is advantageously carried out in a suitable solvent. The suitable solvent include but is not limited to esters, ketones, amides, nitriles, ethers, halogenated hydrocarbons, aromatic hydrocarbons and mixtures

thereof. Preferably ethyl acetate, isopropyl acetate acetone, methyl isobutyl ketone, methyl ethyl ketone dimethyl formamide, dimethyl acetamide, N-methyl pyrrolidinone acetonitrile, propionitrile, tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane, methylene chloride, ethylene chloride, chloroform, toluene, xylene and mixture thereof; preferably tetrahydrofuran, dimethyl formamide or methylene chloride.

The reaction of compound of Formula XII and Formula IV is carried out at a temperature of about 0°C to reflux temperature; preferably at about 25°C to about 65°C. After completion of the reaction, the resultant product may be isolated by known methods, for example one or more solvent extractions followed by solvent evaporation.

In another embodiment, the present invention provides a compound of Formula XII or a pharmaceutically acceptable salt thereof.



Formula XII

In another embodiment, the present invention provides vemurafenib or a pharmaceutically acceptable salt thereof and its intermediates, obtained by the above process, as analyzed using high performance liquid chromatography ("HPLC") with the conditions are tabulated below:

Column	X-Terra phenyl, (250 X 4.6)mm
Column temperature	30°C
Mobile phase	Mobile Phase-A: Buffer: Acetonitrile (90:10) v/v Mobile Phase-B: Buffer: Acetonitrile: Methanol (30:50:20)v/v
Buffer	Ammonium dihydrogen orthophosphate
Diluent	Acetonitrile: Methanol (80:20)v/v
Flow rate	0.7 mL/min
Wavelength	230 nm
Injection Volume	10 µL
Elution	Gradient (T%B): 0/25, 5/25, 10/50, 20/50, 30/85, 60/85,65/25 and 70/25

Column	X-Terra phenyl, (250 X 4.6)mm

Column temperature	40°C
Mobile phase	Mobile Phase-A: Buffer: Acetonitrile (80:20) v/v Mobile Phase-B: Buffer: Acetonitrile (30:70)v/v
Buffer	disodium hydrogen phosphate
Flow rate	0.8 mL/min
Diluent	Acetonitrile
Wavelength	230 nm
Injection Volume	10 µL
Elution	Gradient (T%/B): 0/15, 5/15, 10/30, 15/45, 25/80, 35/80,40/15 and 45/15

In another embodiment, the present invention provides a pharmaceutical composition, comprising vemurafenib or a pharmaceutically acceptable salt thereof prepared by the processes of the present invention and at least one pharmaceutically acceptable excipient. Such pharmaceutical composition may be administered to a mammalian patient in any dosage form, e.g., solid, liquid, powder, injectable solution, etc.

EXAMPLES

The following non limiting examples illustrate specific embodiments of the present invention. They are not intended to be limiting the scope of the present invention in any way.

EXAMPLE 1: Preparation of 5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine of Formula IX

A 250 ml round bottom flask fitted with a mechanical stirrer, reflux condenser, thermometer socket was charged 5-bromoazaindole (10gm) of Formula VII, 4-chlorophenyl boronic acid (7.1gm) of Formula VIII in 1,4-dioxane (100ml) at room temperature and stirred for 10min. To the reaction mass aqueous potassium carbonate (10.5gm dissolved in 40ml water), $Pd(PPh_3)_4$ was charged and heated to 85°C to 90°C for 3hr. After completion of the reaction cooled the temperature to 55°C to 60°C and separated organic and aqueous layers and followed by cooling the organic layer to 0°C to 5°C and stirred for 1hr to precipitate solid compound. The precipitated solid was isolated by filtration, washed with n-heptane (30ml) to get crude compound.

Yield: 7.2 gm
Purity by HPLC: 94.8%
Formula A by HPLC: 0.1%

Purification of Formula IX:

A 250 ml round bottom flask fitted with a mechanical stirrer, reflux condenser, thermometer socket was charged above obtained crude product (7.2gm) and

tetrahydrofuran (110ml) at room temperature and heated to 65°C for 1 hr, then distilled the tetrahydrofuran till the reaction mass volume 35-40 ml in the flask. Then the reaction mass temperature was cooled to room temperature and followed by 0°C to 5°C and allowed to stir for 1 hr. The precipitated solid was isolated by filtration, washed with n-heptane (15ml) to get cream color solid. Same purification was repeated once again to obtaine pure compound of Formula IX.
Yield: 4.2 gm
Purity by HPLC: 99.9%
Formula A by HPLC: 0.02%

EXAMPLE 2: Preparation of 2,6-difluoro-3-nitrobenzaldehyde

A 250 ml round bottom flask fitted with a mechanical stirrer, thermometer socket was added sulfuric acid (50ml) to 2,6-difluorobenzaldehyde (10gm) over a period of 10-15min at 0°C to 5°C. To the reaction mass a mixture of nitric acid (6.4ml) and sulfuric acid (4.2ml) was added drop by drop at 0°C to 10°C over a period of 30-45min. Reaction mass temperature was raised to room temperature and stirred for 2hr. Afetr completion of the reaction, reaction mass was quenched in to ice and water (100gm) at 0°C to 5°C and stirred for 1hr at same temperature. The precipitated solid was isolated by filtration, washed with water (50ml) to get title compound as a cream color solid.
Yield: 9.5gm
Purity by HPLC: 99.6%

EXAMPLE 3: Preparation of 2-(dimethoxymethyl)-1,3-difluoro-4-nitrobenzene of Formula IIa

A 250 ml round bottom flask fitted with a mechanical stirrer, thermometer socket was charged 2,6-difluoro-3-nitrobenzaldehyde (10gm), *p*-toluene sulfonic acid monohydrate (0.3gm) or conc. H_2SO_4 (0.1 mL), trimethylorthoformate in methanol (100ml) at room temperature and heated to 65°C and stirred for 2hr. After completion of the reaction concentrated reaction mass completely under vacuum at 40°C and charged methylene chloride (50ml), washed the organic layer successively with 5% sodium bicarbonate (50ml), water (2×50ml) and brine (30ml) and finally dried the organic layer with anhydrous sodium sulphate. Distilled the organic layer under vacuum to obtain solid compound and charged n-heptane (20ml) to the solid, stirred for 1hr. The obtained solid was isolated by filtration and washed with n-heptane (10ml) to obtain title compound as a cream colored solid.
Yield: 9.5gm .
Purity by HPLC: 99.5%
^{1}HNMR (DMSO-d6): δ 3.42 (s, 6H), 5.56 (s, 1H), 6.93-6.7.03 (m, 1H), 7.97-8.09 (m, 1H)
MS (ESI)[M-H$^-$]$^-$: 202 (M^+-OMe+1)

EXAMPLE 4: Preparation of 3-(dimethoxymethyl)-2,4-difluoroaniline of Formula IIIa

A 250 ml of autoclave was charged 2-(dimethoxymethyl)-1,3-difluoro-4-nitrobenzene (10gm) of Formula II a, 10% Pd/C (2gm) in methanol (100ml) was hydrogenated at room temperature for 3hr. After completion of the reaction, reaction mass was filtered on celite bed and washed with methanol (30ml). The obtained filterate was concentrated under vacuum at 35°C to obtain title compound as a light brown color residue.
Yield: 8gm
Purity by HPLC: 92.5%
^{1}HNMR (DMSO-d6): δ 3.23 (s, 6H), 4.92 (bs, NH_2, D_2O exchangeable), 5.40 (s, 1H), 6.60-6.73 (m, 2H);
MS (ESI)$[M+H^+]^+$: 204

EXAMPLE 5: Preparation of 2-(2,6-difluoro-3-nitrophenyl)-1,3-dioxolane of Formula IIb

A 250 ml round bottom flask fitted with a mechanical stirrer, thermometer socket was charged 2,6-difluoro-3-nitrobenzaldehyde (10gm),p-toluene sulfonic acid monohydrate (0.3gm) or conc. H_2SO_4 (0.1 mL), ethylene glycol (9ml) in toluene at room temperature and heated to 110°C under dean-stork and stirred for 2hr. After completion of the reaction, temperature was cooled to room temperature and washed the reaction mass successively with 5% sodium bicarbonate solution (50ml), water (50ml), brine (50ml) and finally dried the organic layer with anhydrous sodium sulphate. Distilled the organic layer under vacuum to obtain solid and charged n-heptane (20ml) to the solid compound and stirred for 1hr. The obtained solid was isolated by filtration and washed with n-heptane (10ml) to obtain title compound as a cream colored solid.
Yield: 9.5gm
^{1}HNMR (DMSO-d6): δ 3.97-4.17 (m, 4H), 6.18 (s, 1H), 7.36-7.46 (m, 1H), 8.27-8.38 (m, 1H);
MS (ESI)$[M+H^+]^+$: 232

EXAMPLE 6: Preparation of 3-(1,3-dioxolan-2-yl)-2,4-difluoroaniline of Formula IIIb

A 250 ml of autoclave was charged 2-(2,6-difluoro-3-nitrophenyl)-1,3-dioxolane of Formula IIb, 10% Pd/C (2gm) in methanol (100ml) was hydrogenated at room temperature for 3hr. After completion of the reaction, reaction mass was filtered on celite bed and washed with methanol (30ml). The obtained filterate was concentrated under vacuum at 35°C to obtain title compound as a light brown color solid.
Yield: 8gm
Purity by HPLC: 98%
^{1}HNMR (DMSO-d6): δ 3.89-4.11 (m, 4H), 5.04 (bs, NH2, D2O exchangeable), 6.03 (s, 1H), 6.74-6.83 (m, 2H);

MS (ESI)$[M+H^+]^+$: 202

EXAMPLE 7: Preparation of N-[3-(dimethoxymethyl)-2,4-difluorophenyl]propane-1-sulfonamide of Formula Va

A 250 ml round bottom flask fitted with a mechanical stirrer, thermometer socket was charged 3-(dimethoxymethyl)-2,4-difluoroaniline of Formula IIIa (10gm) in tetrahydrofuran (100ml) at room temperature under nitrogen atmosphere. To the reaction mass pyridine (30ml) was charged at room temperature and stirred for 10min, followed by addition of 1-propanesulfonyl chloride (13.8ml) in tetrahydrofuran (14ml) over a period of 30-45min and stirred for 24hr at same temperature. After completion of the reaction, reaction mass was concentrated under vacuum at 40°C to 42°C and charged ethyl acetate (100ml), 1N HCl at room temperature. Organic layer and aqueous layers was separated, aqueous layer was back extracted with ethyl acetate (50ml). Combined organic layer was successively washed with water (100ml), brine (100ml), dryed over anhydrous sodium sulphate and concentrated under vacuum to obtain residue of compound of Formula Va.

Yield: 13gm

^{1}HNMR (DMSO-d6): δ 0.97 (t, 3H, J=7.3 Hz), 1.68-1.79 (m, 2H), 3.01-3.10 (m, 2H), 3.35 (s, 6H), 5.57 (s, 1H), 7.05-7.15 (m, 1H), 7.38-7.49 (m, 1H), 9.62 (s, NH, D_2O exchangeable).

EXAMPLE 8: Preparation of N-[3-(1,3-dioxolan-2-yl)-2,4-difluorophenyl]propane-1-sulfonamide of Formula Vb

A 250 ml round bottom flask fitted with a mechanical stirrer, thermometer socket was charged 3-(1,3-dioxolan-2-yl)-2,4-difluoroaniline of Formula IIIb (10gm) in tetrahydrofuran (100ml) at room temperature under nitrogen atmosphere. To the reaction mass pyridine (30ml) was charged at room temperature and stirred for 10min, followed by addition of 1-propanesulfonyl chloride (13.8ml) in tetrahydrofuran (14ml) over a period of 30-45min at same temperature and stirred for 24hr. After completion of the reaction, reaction mass was concentrated under vacuum at 40°C to 42°C and charged ethyl acetate (100ml), 1N HCl at room temperature. Organic layer and aqueous layers was separated, aqueous layer was back extracted with ethyl acetate (50ml), combined organic layer was successively washed with water (100ml), brine (100ml), dryed over anhydrous sodium sulphate and concentrated under vacuum to obtain residue of compound of Formula Vb.

Yield: 12gm

^{1}HNMR (DMSO-d6): δ 0.97 (t, 3H, J=7.5 Hz), 1.65-1.82 (m, 2H), 3.02-3.15 (m, 2H), 3.93-4.14 (m, 4H), 6.09 (s, 1H), 7.06-7.17 (m, 1H), 7.42-7.53 (m, 1H), 9.64 (s, NH, D_2O exchangeable).

EXAMPLE 9: Preparation of N-(2,4-difluoro-3-formylphenyl)propane-1-sulfonamide of Formula VI

A 250 ml round bottom flask fitted with a mechanical stirrer, thermometer socket was charged N-[3-(dimethoxymethyl)-2,4-difluorophenyl]propane-1-sulfonamide of Formula Va (13gm), tetrahydrofuran (100ml), 6N HCl (10ml) at room temperature and heated to 65°C to 70°C, stirred for 2hr at same temperature. After completion of the reaction cooled the reaction mass to room temperature and ethyl acetate (150ml), water (100ml) was charged and stirred for 15min. Organic layer and aqueous layers were separated, aqueous layer was back extracted with ethyl acetate (100ml). Combined organic layer was successively washed with water (100ml), brine (100ml), dried over anhydrous sodium sulphate and concentrated under vacuum and charged n-heptane (50ml), stirred for 1hr. The obtained solid was isolated by filtration and washed with n-heptane (10ml) to obtain title compound as a light brown colored solid.
Yield: 10gm
Purity by HPLC: 98.2%

EXAMPLE 10: Preparation of N-(2,4-difluoro-3-formylphenyl)propane-1-sulfonamide of Formula VI

A 250 ml round bottom flask fitted with a mechanical stirrer, thermometer socket was charged N-[3-(1,3-dioxolan-2-yl)-2,4-difluorophenyl]propane-1-sulfonamide of Formula Vb (12gm), tetrahydrofuran (100ml), 6N HCl (10ml) at room temperature and heated to 65°C, stirred for 2hr at same temperature. After completion of the reaction, ethyl acetate (150ml), water (100ml) was charged and stirred for 15min. Organic layer and aqueous layers were separated, aqueous layer was back extracted with ethyl acetate (100ml), combined organic layer was successively washed with water (100ml), brine (100ml), dried over anhydrous sodium sulphate and concentrated under vacuum and charged n-heptane (50ml), stirred for 1hr. The solid was isolated by filtration and washed with n-heptane (10ml) to obtain title compound as a light brown colored solid.
Yield: 10 gm
Purity by HPLC: 99%

EXAMPLE 11: Preparation of Propane-1-sulfonic acid (3-{[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-yl]-hydroxy-methyl}-2,4-difluoro-phenyl)-amide of Formula X

A 500 ml round bottom flask fitted with a mechanical stirrer, thermometer socket was charged 5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine of Formula IX (10gm), N-(2,4-difluoro-3-formylphenyl)propane-1-sulfonamide of Formula VI (15gm) in tetrahydrofuran (100ml) at room temperature and stirred for 10min. To the reaction mass 1,1,3,3-tetramethylguanidine (40.3gm), water (100ml) was charged at room temperature

and stirred for 24 hr at same temperature. After completion of the reaction, pH of the reaction mass was adjusted to 7.0 with 4N HCl and charged ethyl acetate (100ml).Organic layer was separated, aqueous layer was back extracted with ethyl acetate (100ml). Combined organic layer was successively washed with 5% sodium bisulfite (2×100ml), water (100ml), dried over anhydrous sodium sulphate and concentrated under vacuum to obtain residue. To the obtained residue methylene chloride (100ml) was charged at room temperature and stirred for 1 hr. The solid was isolated by filtration and washed with methylene chloride (20 ml) to obtain title compound as a cream colored solid.

Yield: 20gm

Purity by HPLC: 96%

EXAMPLE 12: Preparation of Vemurafenib

A 250 ml round bottom flask fitted with a mechanical stirrer, thermometer socket was charged Propane-1-sulfonic acid (3-{[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-yl]-hydroxy-methyl}-2,4-difluoro-phenyl)-amide of Formula X (10gm), 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (6gm) in 1,4-dioxane (80ml), water (3.5ml) at room temperature and stirred for 3hr. After completion of the reaction, added 5% aqueous saturated sodium bicarbonate solution over a period of 20-30 min and stirred for 10min. Reaction mass was concentrated under vacuum to remove 1,4-dioxane and charged water (100ml), ethyl acetate (150ml), tetrahydrofuran (50ml) and stirred for 15min. Organic layer and aqueous layers were separated and aqueous layer was extracted with ethyl acetate (2×100ml). Combined organic layer was successively washed with water (200ml), brine (200ml), dried over anhydrous sodium sulphate, concentrated under vacuum and charged methanol (50ml) at room temperature, stirred for 1 hr. The solid was isolated by filtration and washed with methanol (10ml) to obtain crude compound. The crude compound was further purified from tetrahydrofuran and n-heptane to obtain title compound as a cream color solid. The solid obtained was taken in 50 mL of water and adjusted to pH 13.0 with 1N NaOH and reaction mass washed with 50 mL of methylene chloride twice and aqueous layer pH was adjusted to 6.0 with 1N HCl to precipitate solids. Filtered the obtained solids and washed with water (2× 20 mL), dried under vacuum at 60-65 °C for 5 hr to obtain the title compound as an off-white color solid.

Yield: 4gm

Purity by HPLC: 99.8%

Formula B by HPLC: 0.02%

EXAMPLE 13:

Purification of vemurafenib

A 2000 ml round bottom flask fitted with a mechanical stirrer, thermometer socket was charged vemurafenib (23 gm), water (460 ml) and methylene chloride (460 ml) at 25°C to 30°C.Reaction mass was cooled to 8°C to 10°C and adjusted pH to 13.0 with 1N sodium hydroxide (206 ml) and stirred for 20 to 30 min at same temperature. Organic layer was separated and filtered through 0.45µ filter paper and adjusted pH to 5.9 with 1N hydrochloric acid (193 ml) at 8°C to 10°C and stirred for 1 hr at same temperature. The obtained solids were filtered and washed with water (460 ml) to yield pure vemurafenib.

Yield: 21.5 gm.

Purity by HPLC: 99.8%

EXAMPLE 14:

Preparation of (5-bromo-1H-pyrrolo [2,3-b]pyridin-3-yl)(2,6-difluoro-3-nitrophenyl) methanone of Formula XIV

A 250 ml round bottom flask fitted with a mechanical stirrer, thermometer socket was charged 2,6-difluoro-3-nitrobenzoic acid, methylene chloride (60 ml) at 30-35°C and stirred for 10 min. To the reaction mass dimethylformamide (2 ml) was charged, cooled to 10-15°C and stirred for 5min. To the reaction mass oxalyl chloride (18.7 ml) was added over a period of 30-40 min and stirred for 3 hr at 30-35°C. To a another 1 L round bottom flask aluminium trichloride (33.85 gm), methylene chloride (400 ml) was charged, temperature of the reaction mass was cooled to 5°C. To the reaction mass 5-bromo-7-azaindole (10 gm) was charged and stirred for 15 min. To the reaction mass, the above obtained acid chloride was added over period of 40-50 min at 5°C. After addition reaction mass heated to 40°C and stirred for 4 hr. After completion of the reaction, to the reaction mass ice cold water (500 ml) was added at 5°C and stirred for 15 min. The obtained solids were filtered and washed with water (200 ml), dryed at 40-45°C to obtain title compound.

Yield: 8.5 gm.

EXAMPLE 15:

Preparation of (3-amino-2,6-difluorophenyl)(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone of Formula XI

A 500 ml round bottom flask fitted with a mechanical stirrer, reflux condenser, thermometer socket was charged tetrahydrofuran (100 ml), ethanol (100 ml), (5-bromo-1H-pyrrolo [2,3-b]pyridin-3-yl)(2,6-difluoro-3-nitrophenyl)methanone (10 gm), concentrated hydrochloric acid (26 ml) at 30-35°C and stirred for 10 min. Charged Iron powder (14.6 gm), heated to 75°C-80°C and allowed to stirred for 2-3 hr. After completion of the reaction, reaction mass cooled to 30-35°C, filtered the reaction mass

and washed with tetrahydrofuran (30 ml). The obtained solvent was concentrated and charged water (300 ml) at 30-35°C and stirred for 1 hr. The obtained solids were filtered and washed with purified water (50 ml), dryed at 40-45°C to obtain title compound.
Yield: 7.0 gm.

EXAMPLE 16:

Preparation of (3-amino-2,6-difluorophenyl)[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone of Formula XII

A 500 ml round bottom flask fitted with a mechanical stirrer, reflux condenser, thermometer socket was charged (3-amino-2,6-difluorophenyl)(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)methanone (10 gm), 4-chlorophenyl boronic acid (5.32 gm) in 1,4-dioxane (200 ml) at room temperature. To the reaction mass was charged potassium carbonate (5.8 gm in purified water 40 ml), heated to 42°C and purged with nitrogen for 15 min. To the reaction mass $PdCl(dppf)CH_2Cl_2$ (1.14 gm), Palladium (II) acetate (0.31 gm) was charged and purged with nitrogen for 15 min, reaction mass heated to 90°C and stirred for 6 hr. After completion of the reaction cooled to 25°C to 30°C and separated organic, concentrated organic layer under vacuum to obtain residue. To the residue 1,4-dioxane (30 ml) was charged and stirred for 1 hr. The obtained solids were filtered and washed with 1,4-dioxane (10 ml) fallowed by methanol (10 ml) to obtain title compound as a brown colored solid.
Yield: 5.2 gm
^{1}HNMR (DMSO-d6): δ 5.2 (s, 2H), 6.9 (s, 2H), 7.3 (d, 4H), 8.2 (s, 1H), 8.6 (d, 2H), 13 (s, 1H)
MS (ESI)$[M+H^+]^+$: 384.

EXAMPLE 17:

Preparation of vemurafenib

A 200 ml round bottom flask fitted with a mechanical stirrer, thermometer socket was charged (3-amino-2,6-difluorophenyl)[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]methanone (10 gm), tetrahydrofuran (50 ml), pyridine (50 ml) at 25-35°C under nitrogen atmosphere. To the reaction mass added propane sulfonyl chloride (10 ml) over a period of time 10-15 min and stirred for 8 hr. After completion of the reaction distilled pyridine and tetrahydrofuran completely under vacuum to obtain residue. To the obtained residue was added ethyl acetate (70 ml) tetrahydrofuran (70 ml) at 25-35°C. Organic layer was washed with 1N hydrochloride (100 ml) fallowed by water, brine and finally dryed over anhydride sodium sulphate. Distilled the organic layer under vacuum and charged acetone (30 ml) and stirred for 30 min. The obtained solids were filtered and washed with acetone (10 ml) to obtain title compound as a cream colored solid.

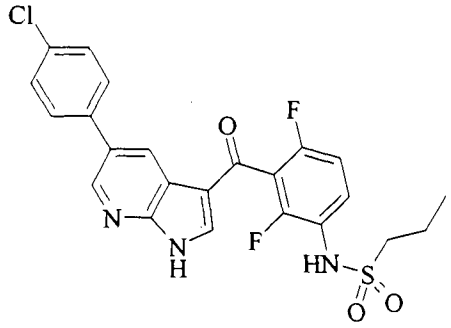
Yield: 8.5 gm.

Purity by HPLC: 99.7%

It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be constructed as limiting, but merely as exemplifications of preferred embodiments. For example, the functions described above and implemented as the best mode for operating the present invention are for illustration purposes only. Other arrangements and methods may be implemented by those skilled in the art without departing from the scope and spirit of this invention. Moreover, those skilled in the art will envision other modifications within the scope and spirit of the specification appended hereto.

CLAIMS

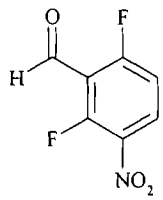
Claim 1: A novel process for the preparation of vemurafenib of Formula I or a pharmaceutically acceptable salt thereof:



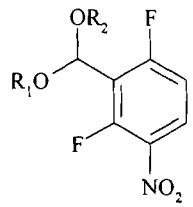
Formula I

comprising:

a) reacting 2,6-difluoro-3-nitro benzaldehyde with a suitable protecting group to obtain a compound of Formula II; wherein R_1 and R_2 independently represents an alkyl, or R_1 and R_2 taken together form an optionally substituted alkylene ring;

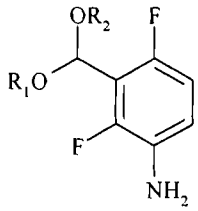


2,6-difluoro-3-nitro benzaldehyde



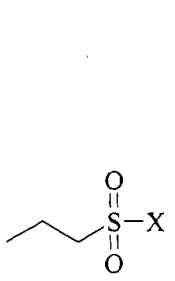
Formula II

b) nitro reduction of compound of Formula II with a suitable reducing agent to obtain a compound of Formula III; wherein R_1 and R_2 are defined as above:

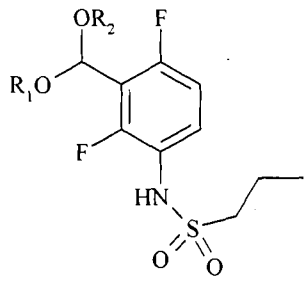


Formula III

c) reacting the compound of Formula III with a compound of Formula IV, wherein 'X' represents suitable leaving group; in presence of a suitable base to obtain a compound of Formula V, wherein R_1 and R_2 are defined as above:

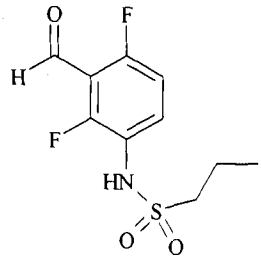


Formula IV



Formula V

d) deprotecting the compound of Formula V in presence of a suitable deprotecting agent to obtain a compound of Formula VI; and



Formula VI

e) converting the obtained compound of Formula VI in to vemurafenib or a pharmaceutically acceptable salt thereof.

Claim 2: The process of claim 1, wherein the alkyl represents C_1 to C_5 alkyl selected from the group consisting of methyl, ethyl, propyl, isopropyl and butyl.

Claim 3: The process of claim 1, wherein the alkylene ring is selected from the group consisting of methylene, ethylene, propylene, butylene and pentylene group.

Claim 4: The process of claim 1, wherein the alkyl is methyl.

Claim 5: The process of claim 1, wherein the alkylene ring is ethylene group.

Claim 6: The process of claim 1, wherein the suitable protecting group is selected from the group comprising trimethyl orthoformate, triethyl orthoformate, tripropyl orthoformate, tributyl orthoformate, tripentyl orthoformate, methylene glycol, ethylene glycol, propylene glycol, butylene glycol and pentylene glycol.

Claim 7: The process of claim 6, wherein the suitable protecting group is trimethyl orthoformate or ethylene glycol.

Claim 8: The process of claim 1, wherein the step a) is carried out in presence of a suitable dehydrating agent and a suitable solvent.

Claim 9: The process of claim 8, wherein the suitable dehydrating agent is selected from the group comprising p-toluenesulfonic acid (PTSA), camphorsulfonic acid (CSA), pyridinium p-toluenesulfonate (PPTS), sulfonic acid exchange resins (Amberlyst, Dowex), sulfuric acid and nitric acid.

Claim 10: The process of claim 9, wherein the suitable dehydrating agent is p-toluenesulfonic acid or sulfuric acid.

Claim 11: The process of claim 8, wherein the suitable solvent is selected from the group comprising alcohols, ethers, esters, halogenated solvents, aromatic hydrocarbons, cyclic hydrocarbons, amides, nitriles, water and mixtures thereof.

Claim 12: The process of claim 11, wherein the suitable solvent is methanol, ethanol, toluene, xylene or mixtures thereof.

Claim 13: The process of claim 1, wherein the nitro reduction is carried out with a suitable reducing agent in an organic solvent.

Claim 14: The process of claim 13, wherein the suitable reducing agent is selected from the group comprising Palladium on carbon, Raney nickel, Platinum oxide, Sodium hydrosulfite, Zinc and mixtures thereof.

Claim 15: The process of claim 14, wherein the suitable reducing agent is Palladium on carbon.

Claim 16: The process of claim 13, wherein the organic solvent is selected from the group consisting of alcohols, ethers, aromatic hydrocarbons and mixtures thereof.

Claim 17: The process of claim 16, wherein the organic solvent is methanol, ethanol, tetrahydrofuran and mixtures thereof.

Claim 18: The process of claim 1, wherein the suitable leaving group is chloro.

Claim 19: The process of claim 1, wherein the step c) is carried out in presence of a suitable base and a suitable solvent.

Claim 20: The process of claim 19, wherein the suitable base is selected form the group comprising alkali metal hydroxides, alkali metal alkoxides, alkali metal carbonates, alkali metal bicarbonates; organic bases selected from the group comprising triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine, pyridine and mixtures thereof.

Claim 21: The process of claim 20, wherein the suitable base is selected from the group consisting of pyridine, triethylamine and potassium carbonate.

Claim 22: The process of claim 19, wherein the suitable solvent is selected from the group comprising esters, ketones, amides, nitriles, ethers, halogenated hydrocarbons, aromatic hydrocarbons and mixtures thereof.

Claim 23: The process of claim 19, wherein the suitable base is pyridine and suitable solvent is tetrahydrofuran.

Claim 24: The process of claim 1, wherein the step d) is carried out with a suitable deprotecting agent and a suitable organic solvent.

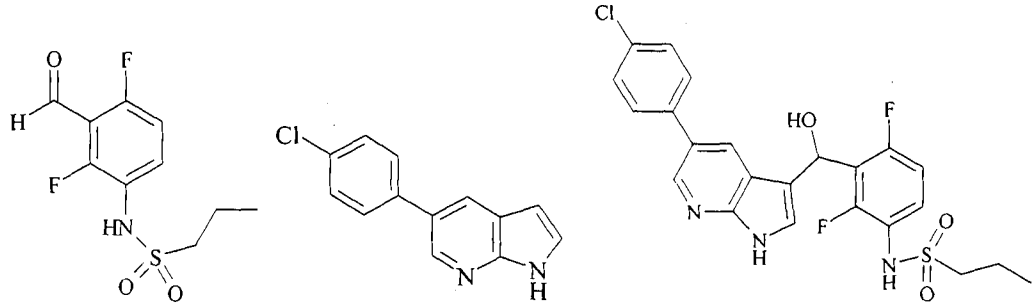
Claim 25: The process of claim 24, wherein the suitable deprotecting agent is selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, trifluoro acetic acid, trichloro acetic acid, methane sulfonic acid and mixture thereof.

Claim 26: The process of claim 25, wherein the suitable deprotecting agent is hydrochloric acid.

Claim 27: The process of claim 24, wherein the suitable organic solvent is selected from the group comprising esters, ketones, nitriles, ethers, halogenated hydrocarbons and mixtures thereof.

Claim 28: The process of claim 27, wherein the suitable organic solvent is selected from the group consisting of tetrahydrofuran, acetonitrile, methylene chloride or mixture thereof.

Claim 29: The process of claim 1, further comprising: reacting the compound of Formula VI with a compound of Formula IX in presence of a suitable base and a suitable solvent to obtain a compound of Formula X; and converting the compound of Formula X into vemurafenib or a pharmaceutically acceptable salt thereof.

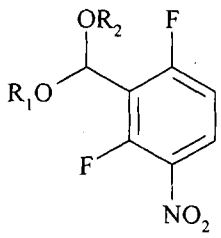


Formula VI Formula IX Formula X

Claim 30: The process of claim 29, wherein the suitable base is 1,1,3,3-Tetramethylguanidine.

Claim 31: The process of claim 29, wherein the suitable solvent is a non alcoholic solvent.

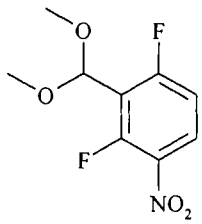
Claim 32: A compound of Formula II or a pharmaceutically acceptable salt thereof;



Formula II

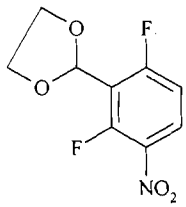
wherein R_1 and R_2 independently represents an alkyl selected from the group consisting of methyl, ethyl, propyl and butyl, or R_1 and R_2 taken together form an optionally substituted alkylene ring selected from the group consisting of methylene, ethylene, propylene, butylene and pentylene.

Claim 33: The compound of claim 32, wherein the compound is a compound of Formula IIa:



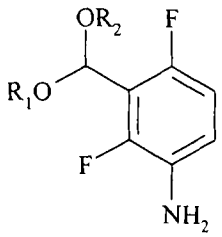
Formula IIa

Claim 34: The compound of claim 32, wherein the compound is a compound of Formula IIb:



Formula IIb

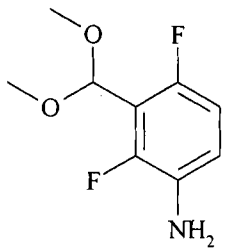
Claim 35: A compound of Formula III or a pharmaceutically acceptable salt thereof;



Formula III

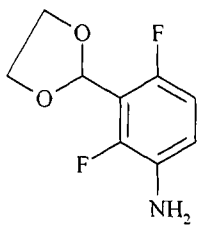
wherein R_1 and R_2 independently represents an alkyl selected from the group consisting of methyl, ethyl, propyl and butyl, or R_1 and R_2 taken together form an optionally substituted alkylene ring selected from the group consisting of methylene, ethylene, propylene, butylene and pentylene.

Claim 36: The compound of claim 35, wherein the compound is a compound of Formula IIIa:



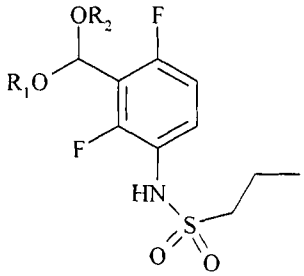
Formula IIIa

Claim 37: The compound of claim 35, wherein the compound is a compound of Formula IIIb:



Formula IIIb

Claim 38: A compound of Formula V or a pharmaceutically acceptable salt thereof;

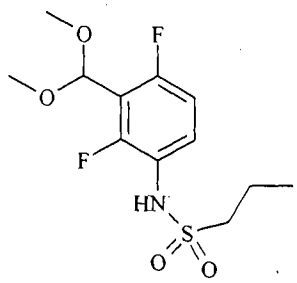


Formula V

wherein R_1 and R_2 independently represents an alkyl selected from the group consisting of methyl, ethyl, propyl and butyl, or R_1 and R_2 taken together form an optionally

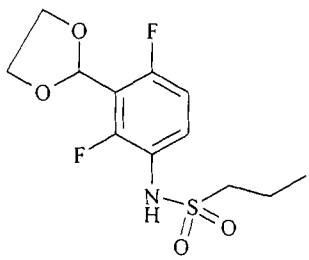
substituted alkylene ring selected from the group consisting of methylene, ethylene, propylene, butylene and pentylene.

Claim 39: The compound of claim 38, wherein the compound is a compound of Formula Va:



Formula Va

Claim 40: The compound of claim 38, wherein the compound is a compound of Formula Vb:

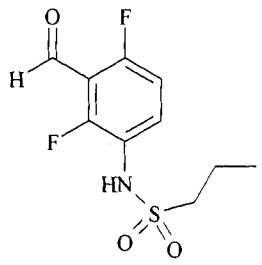


Formula Vb

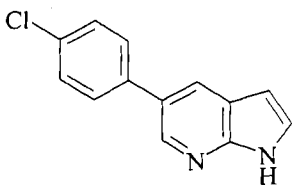
Claim 41: A process for the preparation of vemurafenib or a pharmaceutically acceptable salt thereof, comprising:

a) reacting a compound of Formula VI with a compound of Formula IX in presence of a suitable base in a non-alcoholic solvent to obtain a compound of Formula X; and

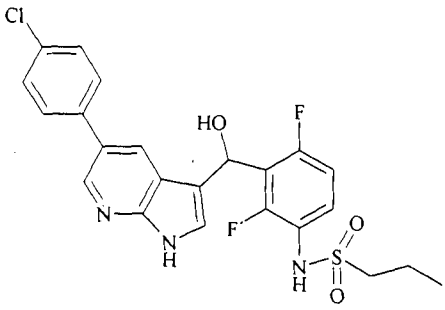
b) converting the obtained compound of Formula X in to vemurafenib or a pharmaceutically acceptable salt thereof.



Formula VI



Formula IX



Formula X

Claim 42: The process of claim 41, wherein the suitable base is selected from the group comprising inorganic bases selected from the group comprising lithium

hydroxide, sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate, potassium bicarbonate; and organic bases selected from the group consisting of triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine, pyridine; guanidine bases such as 1,1,3,3-Tetramethylguanidine (TMG) and mixtures thereof.

Claim 43: The process of claim 42, wherein the suitable base is 1,1,3,3-Tetramethylguanidine.

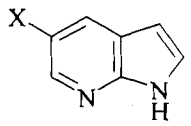
Claim 44: The process of claim 41, wherein the non-alcoholic solvent is selected from the group comprising ethers, amides, nitriles, water and mixtures thereof.

Claim 45: The process of claim 44, wherein the non-alcoholic solvent is selected from the group consisting of tetrahydrofuran, 1,4-dioxane, dimethyl formamide, dimethylsulfoxide, dimethyl acetamide, N-methyl pyrrolidinone, acetonitrile, propionitrile and mixtures thereof.

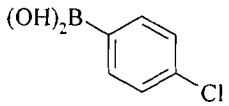
Claim 46: The process of claim 45, wherein the non-alcoholic solvent is a mixture of tetrahydrofuran and water.

Claim 47: A process for the preparation of vemurafenib of Formula I or a pharmaceutically acceptable salt thereof, comprising:

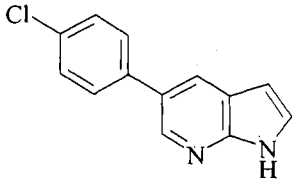
a) reacting a compound of Formula VII; wherein 'X' represents halo with 4-chlorophenyl boronic acid of Formula VIII in presence of a suitable palladium catalyst and a base in a suitable solvent selected from the group consisting of ketones, ethers, amides, aromatic hydrocarbons, water or mixture thereof, to obtain a compound of Formula IX; and



Formula VII



Formula VIII



Formula IX

b) converting the compound of Formula IX in to vemurafenib or a pharmaceutically acceptable salt thereof.

Claim 48: The process of claim 47, wherein the halo represents bromo.

Claim 49: The process of claim 47, wherein the suitable palladium catalyst is selected from the group consisting of tetrakis (triphenylphosphine) palladium(0), tetrakis(tri(otolyl) phosphine) palladium(0), [1,1'Bis(diphenylphosphino)ferrocene] dichloropalladium(II), Palladium(II)acetate and mixtures thereof.

Claim 50: The process of claim 49, wherein the suitable palladium catalyst is tetrakis (triphenylphosphine) palladium(0).

Claim 51: The process of claim 47, wherein the suitable solvent is selected from the group consisting of acetone, methyl isobutyl ketone, methyl ethyl ketone, tetrahydrofuran, dimethyl ether, diethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane, 1,2-domethoxy ethane, dimethyl formamide, dimethyl acetamide, dimethyl sulfoxide, N-methyl pyrrolidinone, toluene, xylene; water and mixture thereof.

Claim 52: The process of claim 51, wherein the suitable base is selected from the group comprising sodium methoxide, potassium carbonate, potassium tert-butoxide or sodium tert-butoxide.

Claim 53: The process of claim 51, wherein the suitable solvent is a mixture of 1,4-dioxane and water; and the base is potassium carbonate.

Claim 54: The process of claim 47, wherein the reaction is carried out at a temperature of about 65°C to about 95°C.

Claim 55: The process of claim 47, further comprising the steps of:

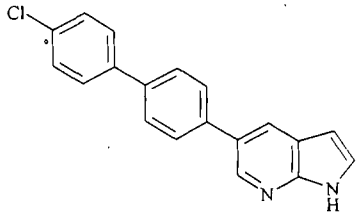
i) dissolving compound of Formula IX in one or more suitable solvent at a temperature of about 30°C to about reflux temperature,
ii) cooling the obtained solution to less than 20°C, and
iii) filtering the compound of Formula IX.

Claim 56: The process of claim 55, wherein the one or more suitable solvents are selected from the group comprising alcohols, ethers, esters, amides, nitriles, ketones, halogenated hydrocarbons, aromatic hydrocarbons, water and mixtures thereof.

Claim 57: The process of claim 56, wherein the solvent is tetrahydrofuran.

Claim 58: The process of claim 55, wherein the temperature at about 60°C to about 65°C.

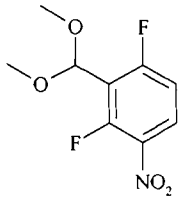
Claim 59: The process of claim 55, the compound of Formula IX is having less than 0.02% by HPLC of Formula A.



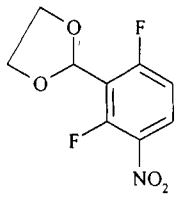
Formula A

Claim 60: A process for the preparation of vemurafenib of Formula I or a pharmaceutically acceptable salt thereof; comprising:

a) reacting 2,6-difluoro-3-nitro benzaldehyde with trimethyl orthoformate or ethylene glycol to obtain a compound of Formula IIa or Formula IIb;

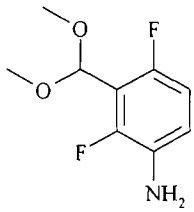


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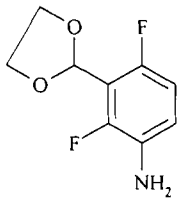


Formula IIa Formula IIb

b) nitro reduction of compound of Formula IIa or Formula IIb with a suitable reducing agent to obtain a compound of Formula IIIa or Formula IIIb:

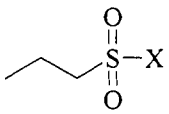


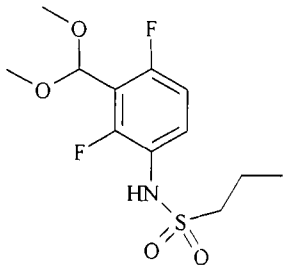
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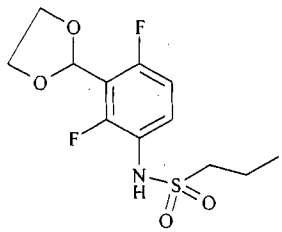
Formula IIIa Formula IIIb

c) reacting the compound of Formula IIIa or Formula IIIb with a compound of Formula IV, wherein 'X' represents suitable leaving group; in presence of a suitable base to obtain a compound of Formula Va or Formula Vb:



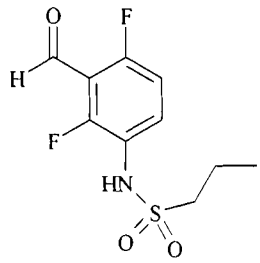


or



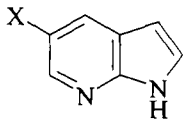
Formula IV Formula Va Formula Vb

d) deprotecting the compound of Formula Va or Formula Vb in presence of a suitable deprotecting agent to obtain a compound of Formula VI:

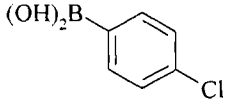


Formula VI

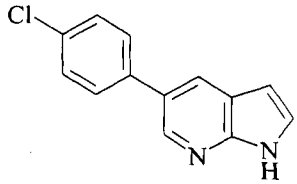
e) reacting a compound of Formula VII; wherein 'X' represents halo with 4-chlorophenyl boronic acid of Formula VIII in presence of a suitable palladium catalyst and a base in a suitable solvent selected from the group consisting of ketones, ethers, amides, aromatic hydrocarbons, water or mixture thereof, to obtain a compound of Formula IX;



Formula VII



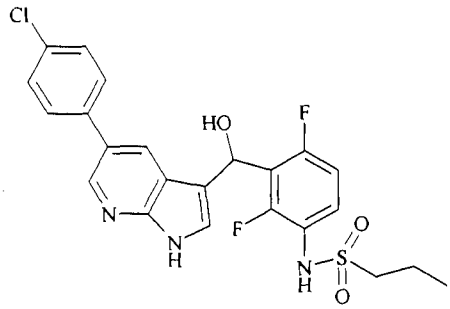
Formula VIII



Formula IX

f) optionally purifying the compound of Formula IX with a suitable solvent to obtain a pure compound of Formula IX,

g) reacting the compound of Formula VI with a compound of Formula IX in presence of a suitable base in a non-alcoholic solvent to obtain a compound of Formula X; and



Formula X

h) converting the compound of Formula X in to vemurafenib or a pharmaceutically acceptable salt thereof.

Claim 61: The process of claim 60, wherein the suitable reducing agent is selected from the group comprising Palladium on carbon, Raney nickel, Platinum oxide, Sodium hydrosulfite, Zinc and mixtures thereof.

Claim 62: The process of claim 60, wherein the suitable base is selected form the group comprising alkali metal hydroxides, alkali metal alkoxides, alkali metal carbonates, alkali metal bicarbonates; organic bases selected from the group comprising triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine, pyridine and mixtures thereof.

Claim 63: The process of claim 60, wherein the suitable deprotecting agent is selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, trifluoro acetic acid, trichloro acetic acid, methane sulfonic acid and mixture thereof.

Claim 64: The process of claim 60, wherein the suitable palladium catalyst is tetrakis (triphenylphosphine) palladium(0).

Claim 65: The process of claim 60, wherein the suitable solvent of step e) is a mixture of 1,4-dioxane and water; and the base is potassium carbonate.

Claim 66: The process of claim 60, wherein the suitable solvent of step f) is tetrahydrofuran.

Claim 67: The process of claim 60, wherein the suitable base of step g) is 1,1,3,3-Tetramethylguanidine.

Claim 68: The process of claim 60, wherein the non-alcoholic solvent is selected from the group consisting of tetrahydrofuran, 1,4-dioxane, dimethyl formamide, dimethylsulfoxide, dimethyl acetamide, N-methyl pyrrolidinone, acetonitrile, propionitrile and mixtures thereof.

Claim 69: The process of claim 68, wherein the non-alcoholic solvent is a mixture of tetrahydrofuran and water.

Claim 70: A process for purification of vemurafenib or a pharmaceutically acceptable salt thereof, comprising:

a) dissolving or suspending vemurafenib in a mixture of suitable water immiscible solvent and water,
b) adding a suitable base to the step a),
c) separating the organic layer and aqueous layer,
d) optionally treating the aqueous layer with a suitable water immiscible solvent,
e) adding an acid to the aqueous solution, and
f) isolating the vemurafenib.

Claim 71: The process of claim 70, wherein the suitable water immiscible solvent is selected from the group consisting of methyl tertiary butyl ether, diethyl ether, ethyl acetate, methylene chloride, chloroform, toluene, xylene and mixtures thereof.

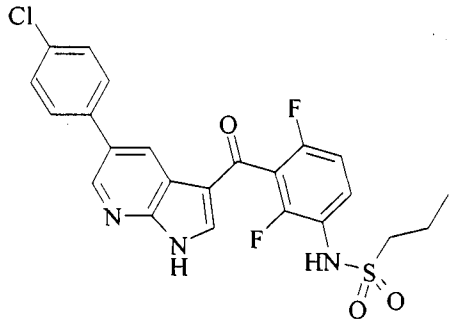
Claim 72: The process of claim 71, wherein the water immiscible solvent is methylene chloride.

Claim 73: The process of claim 70, where in suitable base is selected from ammonia, sodium hydroxide or potassium hydroxide.

Claim 74: The process of claim 70, where in the acid is selected from the group consisting of hydrochloric acid, sulfuric acid and acetic acid.

Claim 75: The process of claim 70, wherein the base is sodium hydroxide and acid is hydrochloric acid.

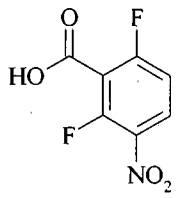
Claim 76: A novel process for the preparation of vemurafenib or a pharmaceutically acceptable salt thereof of Formula I:



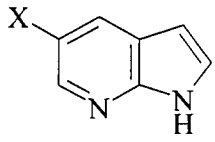
Formula I

comprising:

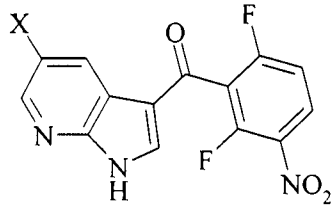
a) reacting 2,6-difluoro-3-nitrobenzoic acid or a reactive derivative of Formula XIII with 5-halo-7-azaindole of Formula VII; wherein 'X' represents halo; in presence of a Lewis acid in a suitable solvent to obtain a compound of Formula XIV:



Formula XIII

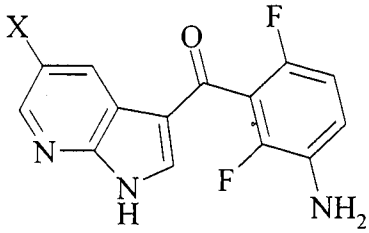


Formula VII



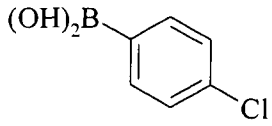
Formula XIV

b) nitro reduction of the compound of Formula XIV with a suitable reducing agent to obtain a compound of Formula XI, wherein 'X' represents halo;

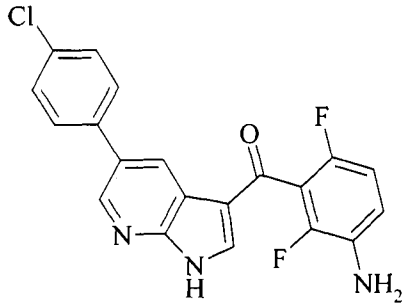


Formula XI

c) coupling the compound of Formula XI with 4-chlorophenyl boronic acid of Formula VIII in presence of a suitable palladium catalyst and a base to obtain a compound of Formula XII; and

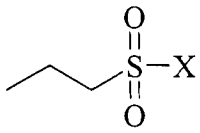


Formula VIII



Formula XII

d) condensing the obtained compound of Formula XII with a compound of Formula IV, wherein 'X' represents suitable leaving group; in presence of a base to obtain vemurafenib.



Formula IV

Claim 77: The process of claim 76, wherein the Lewis acid is selected from the group consisting of aluminum chloride, aluminum bromide, ferric chloride, tin chloride, stannic chloride and mixtures thereof.

Claim 78: The process of claim 76, wherein the suitable solvent is selected from the group comprising tetrahydrofuran, dimethyl ether, diisopropyl ether, methyl tertiary butyl ether, 1,4-dioxane, methylene chloride, ethylene chloride, chloroform, carbon tetrachloride, toluene, xylene and mixtures thereof.

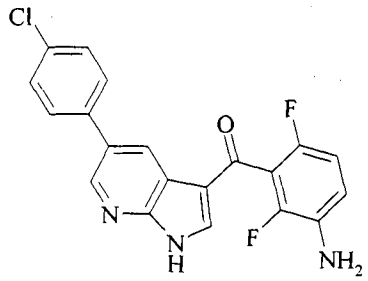
Claim 79: The process of claim 78, wherein the suitable solvent is methylene chloride.

Claim 80: The process of claim 76, wherein the suitable reducing agent is selected from Fe/HCl, Fe/NH_4Cl or $SnCl_2$.

Claim 81: The process of claim 76, wherein the palladium catalyst is selected from tetrakis (triphenylphosphine) palladium (0), tetrakis(tri(otolyl)phosphine)palladium(0), ,[1,1'Bis(diphenylphosphino)ferrocene]dichloropalladium(II), Palladium(II)acetate and mixtures thereof.

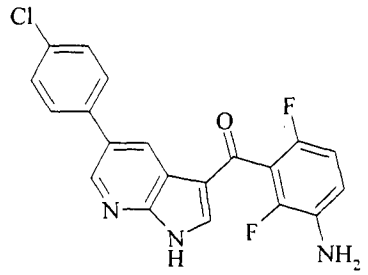
Claim 82: The process of claim 76, wherein the base of step d) is selected from pyridine, triethylamine or potassium carbonate.

Claim 83: A compound of Formula XII or a pharmaceutically acceptable salt thereof.



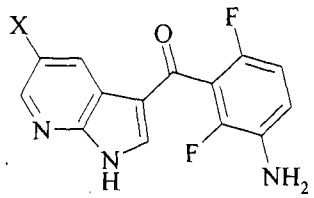
Formula XII

Claim 84: A process for the preparation of compound of Formula XII or a pharmaceutically acceptable salt thereof:

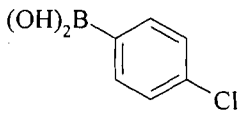


Formula XII

comprising: reacting a compound of Formula XI, wherein 'X' represents halo; with 4-chlorophenyl boronic acid of Formula VIII in presence of a suitable palladium catalyst and a base to obtain a compound of Formula XII.



Formula XI



Formula VIII

Claim 85: The process of claim 84, wherein the halo represents bromo.

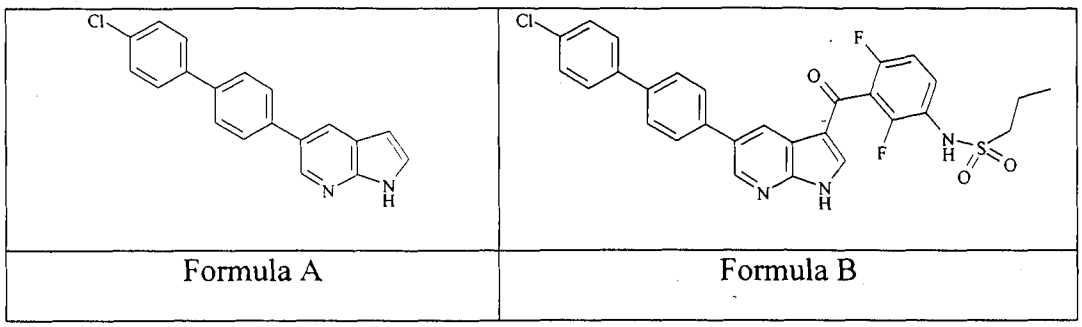
Claim 86: The process of claim 84, wherein the palladium catalyst is selected from tetrakis (triphenylphosphine) palladium (0), tetrakis(tri(otolyl)phosphine)palladium(0), [1,1'Bis(diphenylphosphino)ferrocene]dichloropalladium(II), Palladium(II)acetate and mixtures thereof.

Claim 87: The process of claim 84, wherein the base is selected from the group comprising sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate, potassium bicarbonate; and organic

bases such as triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine, pyridine; and their mixtures thereof.

Claim 88: The process of claim 87, wherein the base is potassium carbonate.

Claim 89: Vemurafenib substantially free of Formula A or Formula B as measured by HPLC.



Formula A | Formula B

Claim 90: A pharmaceutical composition, comprising vemurafenib or a pharmaceutically acceptable salt thereof prepared by the processes of claim 1-89 and at least one pharmaceutically acceptable excipient.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2014/000733

A. CLASSIFICATION OF SUBJECT MATTER
C07D471/04,A61K31/437,A61K31/517 Version=2014.01

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)

C07D471/04,A61K31/437,A61K31/517

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)

PATSEER, IPO Internal, STN (structure)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 7863288 B2, PLEXXIKON, INC., 04 January, 2011(04-01-2011), cited in the application, example 7, Scheme 19	1-32,35,38,90
Y	WO 2008/079909 A1, PLEXXIKON, INC., 03 July, 2008(03-07-2008), Examples 13, 18, Paras 0156-0157, 0188-0190, Scheme II	1-32,35,38,90
Y	WO 2008/079906 A1, PLEXXIKON, INC, 03 July, 2008(03-07-2008), Example 6, scheme 13, paras 0096-00105	1-32,35,38,90
Y	WO 2010/129570 A1, PLEXXIKON, INC, 11 November, 2010 (11-11-2010) , Example 23, schemes 25-26, paras 0305-0318 Example 23, schemes 25-26, paras 0305-0318	1-32,35,38,90

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30-03-2015	30-03-2015

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

International application No.
PCT/IN2014/000733

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
The authority has found the following separate groups of inventions in this international application

1. Group-I: Claims 1-31, 32, 35, 38, 90(partially)

Claims 1-28 define a novel process for the preparation of vemurafenib of Formula I or a pharmaceutically acceptable salt thereof comprising:
a) reacting 2,6-difluoro-3-nitro benzaldehyde with a suitable

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Claims 1-32, 35, 38, 90

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Continuation of Observations where unity of invention is lacking(Box III)

protecting group to obtain a compound of Formula II
b) nitro reduction of compound of Formula II with a suitable reducing agent to obtain a compound of Formula III
c) reacting the compound of Formula III with a compound of Formula IV in presence of a suitable base to obtain a compound of Formula V
d) deprotecting the compound of Formula V in presence of a suitable deprotecting agent to obtain a compound of Formula VI
e) converting the obtained compound of Formula VI into vemurafenib or a pharmaceutically acceptable salt thereof
Claims 29-31 defines a further process comprising: reacting the compound of Formula VI with a compound of Formula IX in presence of a suitable base and a suitable solvent to obtain a compound of Formula X; and converting the compound of Formula X into vemurafenib or a pharmaceutically acceptable salt thereof.
Claims 32, 35 and 38 define respectively intermediates II, III and V.

Claim 90 define a pharmaceutical composition, comprising vemurafenib or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient.
2. Group-II: Claims 41-46 and 90(partially)

Claims 41-46 define a process for the preparation of vemurafenib or a pharmaceutically acceptable salt thereof, comprising:
a) reacting a compound of Formula VI with a compound of Formula IX in presence of a suitable base in a non-alcoholic solvent to obtain a compound of Formula X; and
b) converting the obtained compound of Formula X in to vemurafenib or a pharmaceutically acceptable salt thereof.
3. Group-III: Claims 47-59 and 90(partially)

Claims 47-54 define a process for the preparation of vemurafenib of Formula I or a pharmaceutically acceptable salt thereof, comprising:
a) reacting a compound of Formula VII; wherein 'X' represents halo with 4- chlorophenyl boronic acid of Formula VIII in presence of a suitable palladium catalyst and a base in a suitable solvent selected from the group consisting of ketones, ethers, amides, aromatic hydrocarbons, water or mixture thereof, to obtain a compound of Formula IX; and
b) converting the compound of Formula IX in to vemurafenib or a pharmaceutically acceptable salt thereof.
Claims 55-59 define further process comprising the steps of:

i)dissolving compound of Formula IX in one or more suitable solvent at a temperature of about 30°C to about reflux temperature,
ii)cooling the obtained solution to less than 20°C, and

iii)filtering the compound of Formula IX.

4. Group-IV: Claims 60-69, 33-34, 36-37, 39-40 and 90(partially)

Claims 60-69 define a process for the preparation of vemurafenib of Formula I or a pharmaceutically acceptable salt thereof; comprising:
a) reacting 2,6-difluoro-3-nitro benzaldehyde with trimethyl

orthoformate or ethylene glycol to obtain a compound of Formula IIa or Formula IIb;
b) nitro reduction of compound of Formula IIa or Formula IIb with a suitable reducing agent to obtain a compound of Formula IIIa or Formula IIIb:
c) reacting the compound of Formula IIIa or Formula IIIb with a compound of Formula IV, wherein 'X' represents suitable leaving group; in presence of a suitable base to obtain a compound of Formula
Va or Formula Vb:
d) deprotecting the compound of Formula Va or Formula Vb in presence of a suitable deprotecting agent to obtain a compound of Formula VI:
61 Formula VI
e) reacting a compound of Formula VII; wherein 'X' represents halo with 4- chlorophenyl boronic acid of Formula VIII in presence of a suitable palladium catalyst and a base in a suitable solvent selected
from the group consisting of ketones, ethers, amides, aromatic hydrocarbons, water, or mixture thereof, to obtain a compound of Formula IX;
f) optionally purifying the compound of Formula IX with a suitable solvent to obtain a pure compound of Formula IX,
g) reacting the compound of Formula VI with a compound of Formula IX in presence of a suitable base in a non-alcoholic solvent to obtain a
compound of Formula X; and
h) converting the compound of Formula X in to vemurafenib or a pharmaceutically acceptable salt thereof.
Claims 33-34, 36-37 and 39-40 define respectively intermediates IIa-IIb, IIIa-IIIb and Va-Vb.
5. Group-V: Claims 70-75, 89 and 90(partially)

Claims 70-75 define a process for purification of vemurafenib or a pharmaceutically acceptable salt thereof, comprising:
a) dissolving or suspending vemurafenib in a mixture of suitable water immiscible solvent and water, b) adding a suitable base to the step a), c) separating the organic layer and aqueous layer, d) optionally treating the aqueous layer with a suitable water immiscible solvent, e) adding an acid to the aqueous solution, and f)
isolating the vemurafenib.
Claim 89 defines Vemurafenib substantially free of Formula A or Formula B as measured by HPLC.
6. Group-VI: Claims 76-83 and 90(partially)

Claims 76-82 define a novel process for the preparation of vemurafenib or a pharmaceutically acceptable salt thereof of Formula I: comprising:
a) reacting 2,6-difluoro-3-nitrobenzoic acid or a reactive derivative
of Formula XIII with 5-halo-7-azaindole of Formula VII;
wherein 'X' represents halo; in presence of a Lewis acid in a suitable solvent to obtain a compound of Formula XIV:
b) nitro reduction of the compound of Formula XIV with a suitable reducing agent to obtain a compound of Formula XI, wherein 'X'

represents halo; 64
c) coupling the compound of Formula XI with 4-chlorophenyl boronic acid of Formula VIII in presence of a suitable palladium catalyst and
a base to obtain a compound of Formula XII; and
d) condensing the obtained compound of Formula XII with a compound of
Formula IV,; in presence of a base to obtain vemurafenib.
Claim 83 define a compound of Formula XII or a pharmaceutically acceptable salt thereof.
7. Group-VII: Claims 84-88 and 90(partially)

Claims 84-88 define a process for the preparation of compound of Formula XII or a pharmaceutically acceptable salt thereof:
comprising: reacting a compound of Formula XI, wherein 'X' represents
halo; with 4-chlorophenyl boronic acid of Formula VIII in presence of a suitable palladium catalyst and a base to obtain a compound of Formula XII.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2014/000733

Citation	Pub.Date	Family	Pub.Date
US 7863288 B2	04-01-2011	AU 2006261993 A1	04-01-2007
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		EP 1893612 A1	05-03-2008
		IN KOLNP-2007-04938 A1	02-01-2009
		US 2010256365 A1	07-10-2010
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