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(54) Title: PROCESS FOR THE PREPARATION OF PYRAZOLE SUBSTITUTED AMINOHETEROARYL COMPOUNDS

(57) Abstract: The present invention relates to an improved process for the preparation of pyrazole substituted aminoheteroaryl compounds. More particularly, the present invention provides highly pure 3-[(1R)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-5-(1-piperidin-4-ylpyrazol-4- yl)pyridin-2-amine, its intermediates and preparation thereof. The process of the present invention is simple, convenient, does not use expensive chemicals and avoids use of tedious purification techniques. Invention also provides process intermediates, useful not only in the synthesis, but also useful for providing desired compound with high purity.

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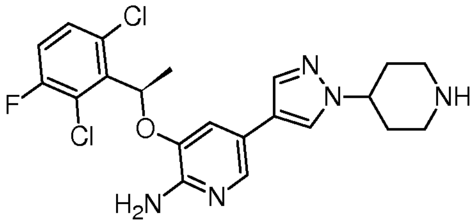
PROCESS FOR THE PREPARATION OF PYRAZOLE SUBSTITUTED AMINOHETEROARYL COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to an improved process for the Preparation of pyrazole substituted aminoheteroaryl compounds, more particularly 3-[(1R)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-5-(1-piperidin-4-ylpyrazol-4-yl)pyridin-2-amine and its intermediates which is simple, convenient, economical and industrially viable.

BACKGROUND OF THE INVENTION

The compound (R)-3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-pyridin-2-ylamine, also known as Crizotinib, is represented by the Formula (I):

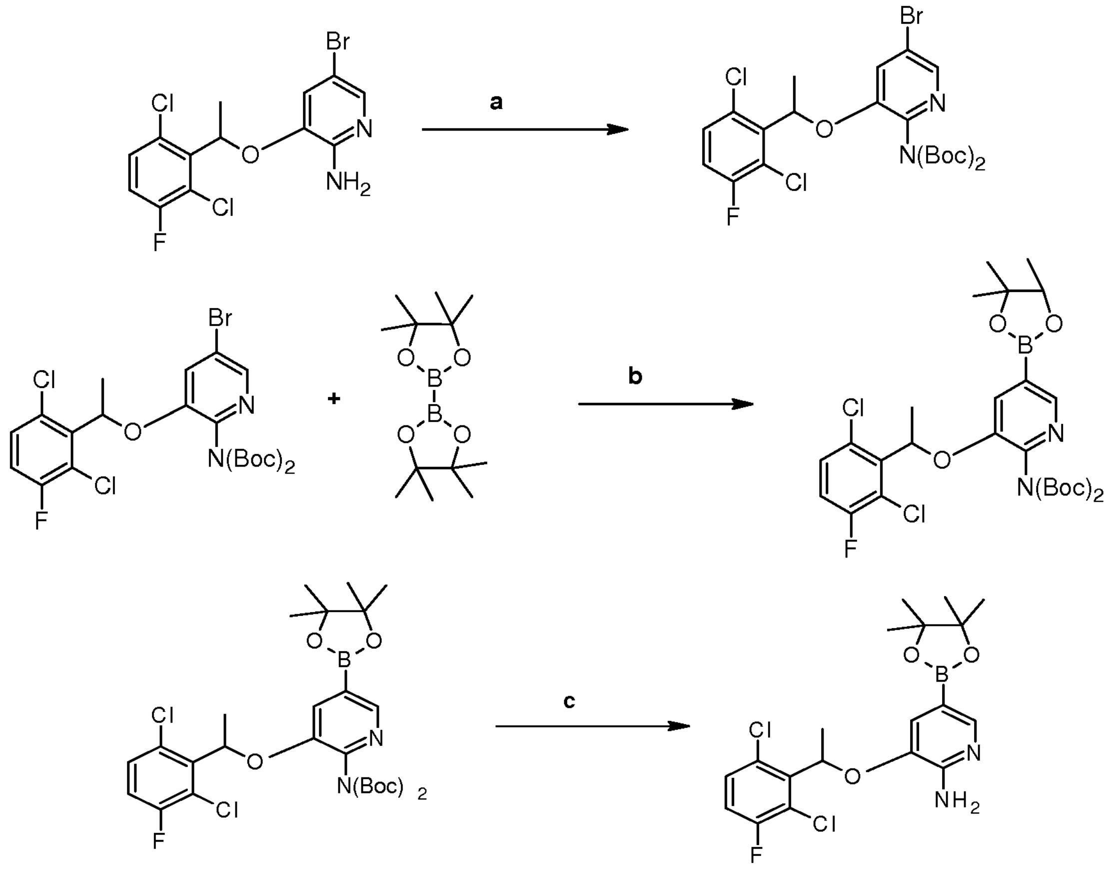


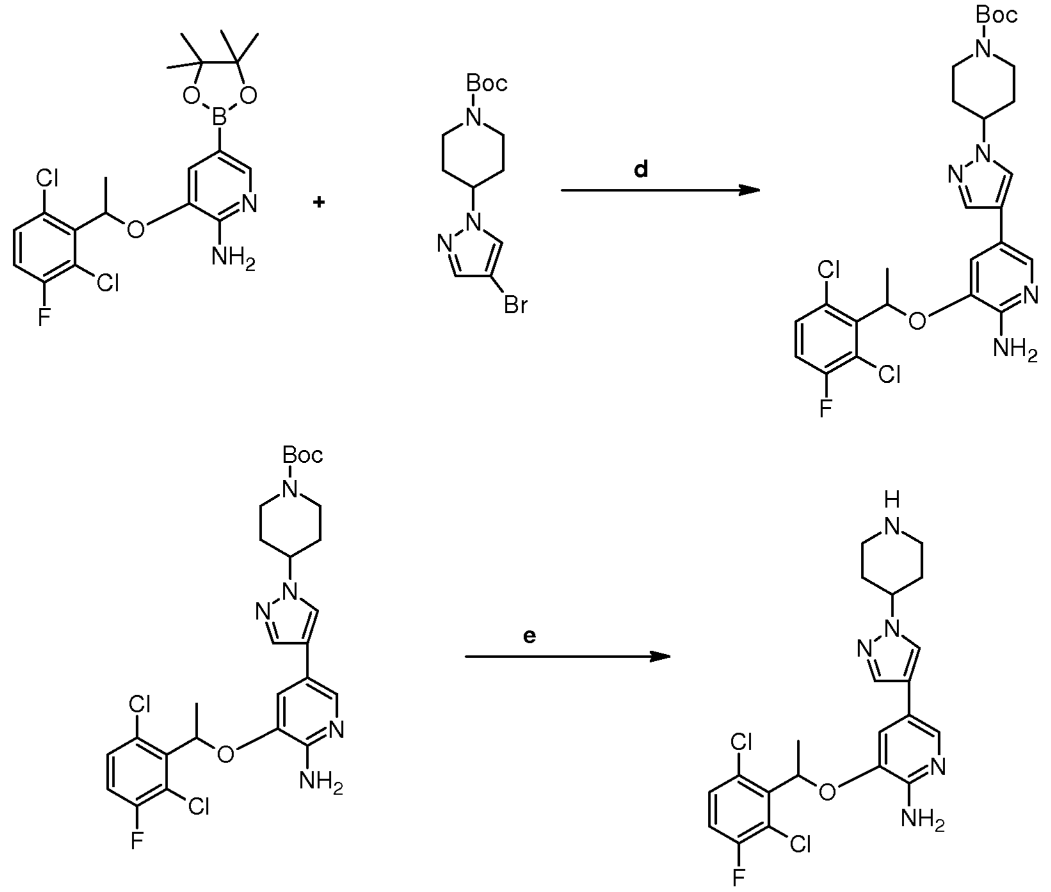
Formula (I)

Crizotinib is a potent small-molecule inhibitor of c-Met/HGFR (hepatocyte growth factor receptor) kinase and ALK (anaplastic lymphoma kinase) activity. Enantiomerically pure compound of formula I was first disclosed in US Patent No. 7,858,643. Additionally, the racemate of compound of formula I was disclosed in U.S. patent application 2006/0128724, both of these references discloses similar methods for the synthesis of Compound of Formula I.

Conventionally, the compounds of formula I are prepared by reacting Bis(pinacolato)diboron with protected 5-bromo-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine in the presence of Pd catalyst. The obtained product after deprotection is reacted with N-protected 4-(4-bromo-pyrazol-1-yl)-piperidine in the presence of Pd Catalyst. The obtained product is filtered through celite pad and purified by Column Chromatography. The final product of formula I was obtained by deprotection of the purified compound by using HCl/dioxane.

US Patent No. 7,858,643 provides enantiomerically pure aminoheteroaryl compounds, particularly aminopyridines and aminopyrazines, having protein tyrosine kinase activity. More particularly, US 7,858,643 describes process for the preparation of 3-[(1R)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-5-(1-piperidin-4-ylpyrazol-4-yl)pyridin-2-amine. The Scheme is summarized below in Scheme-1:





Scheme-1

wherein, "Boc" means tert-butoxycarbonyl; and **a**) $(Boc)_2$, DMF, Dimethylaminopyridine **b**) Pd(dppf)Cl_2, KOAc, Dichloromethane; c) HCl, Dioxane, Dichloromethane; d) $Pd(PPh_3)_2Cl_2$, Na_2CO_3, DME/H_2O; **e**) 4M HCl/Dioxane, Dichloromethane

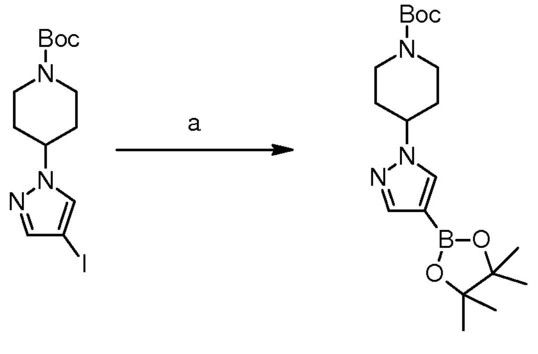
A similar process has been disclosed in the U.S. patent application 2006/0128724 for the preparation of Crizotinib. *J. Jean Cui et. al.* in J. Med. Chem. 2011, 54, 6342-6363, also provides a similar process for the preparation of Crizotinib and its derivatives.

However, above mentioned synthetic process requires stringent operational conditions such as filtration at several steps through celite pad. Also column chromatography is required at various steps which is not only tedious but also results in significant yield loss.

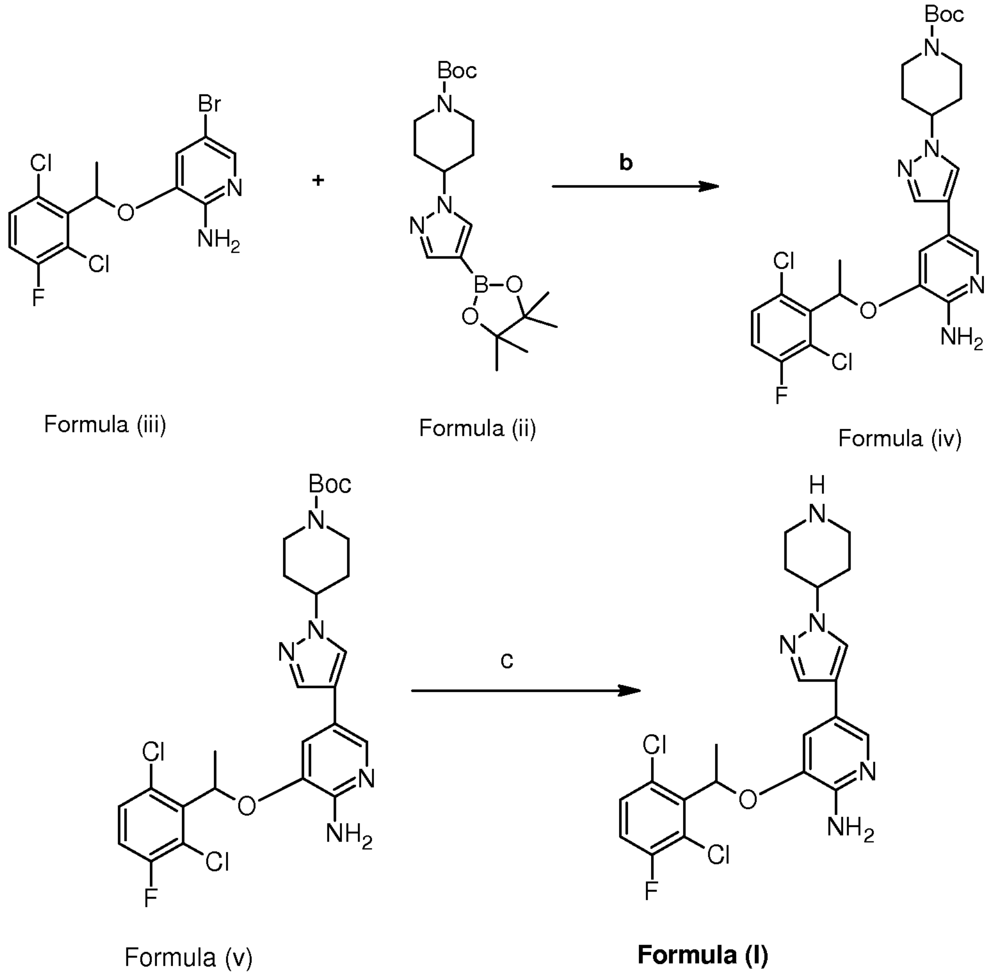
Another disadvantage of above process involves extensive use of palladium catalysts, hence metal scavengers are required to remove palladium content from the desired product at various steps which makes this process inefficient for commercial scale.

Yet another disadvantage of above process is the cost of Bis(pinacolato)diboron. This reagent is used in excess in the reaction mixture resulting in considerable cost, especially during large-scale syntheses.

US Patent No. 7,825,137 also discloses a process for the preparation of Crizotinib where Boc protected 4-(4-iodo-pyrazol-1-yl)-piperidine is first reacted with Bis(pinacolato)diboron in the presence of Pd catalyst. The reaction mixture is filtered through a bed of celite and the obtained filtrate is concentrated and purified by silica gel chromatography to give to form tert-butyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]piperidine-1-carboxylate. To this compound, 5-bromo-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine is added in the presence of a Pd catalyst. The reaction mixture is stirred for 16h at 87°C. The reaction mixture is filtered through celite pad and the concentrated filtrate is purified on silica gel column to obtain (4-{6-amino-5-[(R)-1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyri- din-3-yl}-pyrazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester of 95% purity. To the solution of resulting compound in dichloromethane 4N HCl/Dioxane is added and thereby getting the reaction suspension is filtered in Buchner funnel lined with filter paper. The obtained solid is dissolved in HPLC water and pH is adjusted to 10 with the addition of Na_2CO_3. Compound is extracted using dichloroform and is purified on a silica gel column by eluting with CH_2Cl_2/MeOH/NEt_3 system to obtain Crizotinib. The scheme is summarized below in scheme 2:



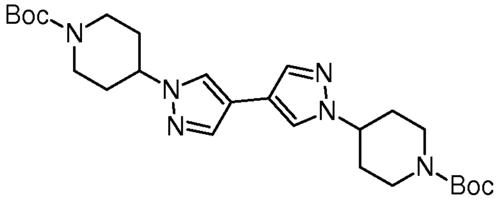
Formula (i) Formula (ii)



Scheme-2

wherein, "Boc" means tert-butoxycarbonyl; and **a**) Bis(pinacolato)diboron, Potassium Acetate, DMSO, dichlorobis(triphenylphosphino)palladium (II), 80^0 C **b**) $Pd(PPh_3)_2Cl_2$, DME/H_2O, Na_2CO_3; **c**) 4M HCl/Dioxane, CH_2Cl_2, Na_2CO_3

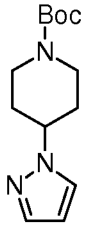
The inventors of present invention have found that, compound of Formula (ii) obtained by following the process of Scheme-2 contain (pyrazol-1-yl)-piperidine dimer as an impurity as represented by Formula (A), hence reduces the yield of the desired compound.



Wherein, "Boc" means tert-butoxycarbonyl

Formula (A)

Additionally the compound of Formula (ii) thus prepared also contain other impurities such as unreacted starting material i.e. compound of Formula (i), other by-products such as compound of Formula (B), as represented hereinbelow:



Formula (B)

HPLC assay of the crude reaction mixture for the preparation of compound of Formula (ii) by following the process of Scheme-2 is provided hereinbelow in **Table-1**:

Compound	**% in the Reaction Mixture**
Compound of Formula (i)	26.61%
Compound of Formula (ii)	8.87%
Compound of Formula (A)	7.75%
Compound of Formula (B)	13.09%

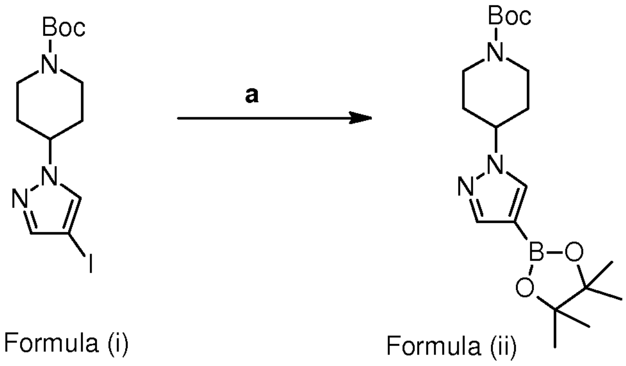
From Table-1, it is evident that compound of Formula (ii) prepared by following the process of Scheme-2 is only 8.87% that means reaction does not proceed to completion and contain starting material in significant amount with other major byproduct or impurities.

Accordingly, to remove such byproducts or impurities these processes involve stringent operational conditions such as filtration at several steps through celite pad or Buchner funnel. Also column chromatography is required at various steps which needless to mention, are not only tedious but also results in significant yield loss.

Another disadvantage of hereinabove mentioned prior art processes i.e. Scheme-1 and as well in Scheme-2 is the use of highly expensive Bis(pinacolato)diboron. This reagent is used in excess in the reaction mixture resulting in considerable cost, especially during large-scale synthesis, which renders such methods as particularly not having any significant economic, industrial or commercial viability, application or advantage.

The prior art, as known to the inventor additionally includes the process disclosed *in Org. Process Res. Dev. 2011, 15, 1018-1026.* This describes a process that obviates the use of bis(pinacolato)diboron for the preparation of compound of Formula (ii) as used in conventional methods.

This process involves the reaction of Boc-protected 4-(4-iodo-pyrazol-1-yl)-piperidine with i-PrMgCl in THF at 20°C, which was quenched with 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane yielding tert-butyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]piperidine-1-carboxylate in a modest 70-80% yield after workup, precipitation from ethanol and water and subsequent recrystallization. The reaction scheme is summarized as below in scheme 3:



Scheme 3

a) (i) i-PrMgCl in THF, 0^0C, then warm to 20^0C; (ii) 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, THF, 20^0-30^0C, then EtOAc; (iii) EtOH/water cryt, 70-80%.

However, in this process particular care was required to ensure that sufficient water was added during the crystallization process to maximize recovery of the compound. Also, inventors of the present invention found that, by following the same procedure and conditions as mentioned in *Org. Process Res. Dev. 2011, 15, 1018-1026,* solid compound of Formula (ii) was not obtained.

Inventors further revealed that, reaction does not proceed to completion and starting material i.e. compound of Formula (i) was detected in HPLC assay even after 9h of reaction time period. The HPLC assay of the crude is provided hereinbelow in **Table-2:**

Compound	% in the Reaction Mixture
Compound of Formula (ii)	67.95%
Compound of Formula (i)	15.61%

In addition to above, major content of about 13.17% of an unknown impurity was found in the HPLC assay of the reaction mixture.

Additionally, it was observed by the inventors that, inadequate purification of compound of Formula (ii) at this stage lead to unacceptable impurities in the forthcoming reaction steps, which involves the reaction with highly expensive compound of Formula (iii).

It was found that, if purity of compound of Formula (ii) is less than 90%, the reaction does not proceed to completion for the preparation of compound of Formula (iv) and difficulties were encountered in the isolation of compound of Formula (iv).

From the foregoing, it would be thus apparent that the reported methods for the preparation of Crizotinib suffer from one or more of the following disadvantages or limitations *viz.*

a) Scavenger support for the removal of metal values especially palladium makes reported processes cost extensive;

b) Formation of significant amounts of undesired compounds e.g. compounds of Formula (A) and Formula (B);

c) Utilization of tedious chromatographic, extraction, and/or multiple crystallization techniques for separation and removal of said undesired compounds;

d) Use of expensive reactants like bis(pinacolato)diboron makes the reported processes cost extensive;

e) Palladium Catalyzed boronation involves high level of dimerization impurities, resulting in wastage of expensive materials and reducing yield of the reaction;

f) Strict adherence to critical reaction conditions and parameters e.g. inadequate purification after the coupling reaction leading to the formation unacceptable impurities in the forthcoming reaction steps.

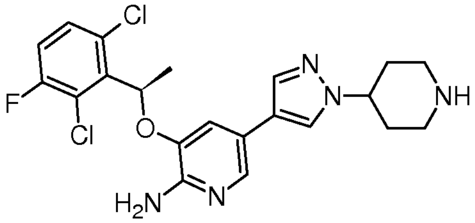
Considering the therapeutic and commercial importance of Crizotinib, a need, therefore, exists for a method for synthesis of Crizotinib, which is simple, convenient, economical, industrially viable.

OBJECT OF THE INVENTION

It is an object of the invention to overcome the drawbacks of the prior art. It is another object of the invention to provide a method for synthesis of Crizotinib and its intermediates which is simple, convenient, economical and industrially viable.

SUMMARY OF INVENTION

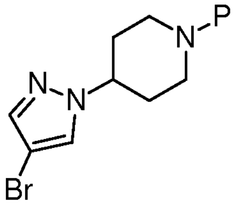
In first embodiment, the present invention provides an improved process for the preparation of a compound of Formula (I) or its pharmaceutically acceptable salt,



Formula (I)

comprising the steps of:

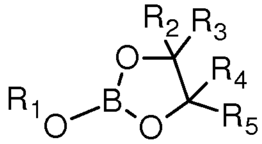
a) reaction of a compound of Formula (II),



Formula (II)

wherein, P represents a protecting group

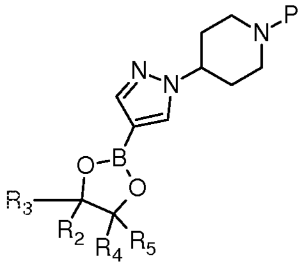
with the compound of Formula (III),



Formula (III)

wherein, R_1, R_2, R_3, R_4 or R_5 may be independently selected from the group comprising of hydrogen or straight or branched chain alkyl, alkylene, alkene or alkoxy group

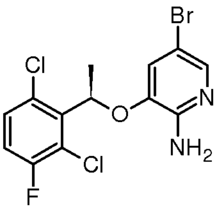
in the presence of a base to obtain a compound of Formula (IV),



Formula (IV)

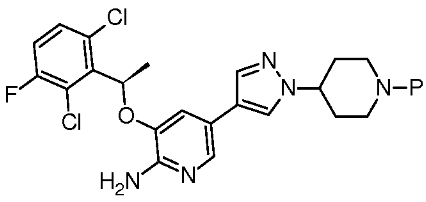
wherein R_1, R_2, R_3, R_4 or R_5 have the meanings given under Formula (III) and P represents a protecting group;

b) coupling the compound of Formula (IV) with compound of Formula (iii),



Formula (iii)

to obtain a compound of Formula (V),

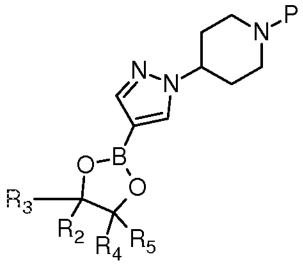


Formula (V)

wherein, P represents a protecting group; and

c) deprotecting the compound of Formula (V) with an Acid to obtain the compound of Formula (I) of high purity.

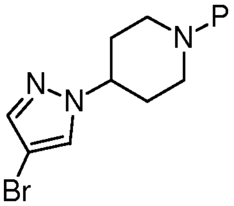
In second embodiment, the present invention provides a process for the preparation of a compound of Formula (IV),



Formula (IV)

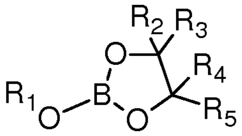
wherein, R_1, R_2, R_3, R_4 or R_5 may be independently selected from the group comprising of hydrogen or straight or branched chain alkyl, alkylene, alkene or alkoxy group and P represents a protecting group

by reacting a compound of Formula (II),



Formula (II)

wherein, P represents a protecting group in the presence of a base with a compound of Formula (III),

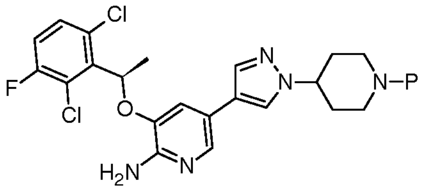


Formula (III)

wherein, R_1, R_2, R_3, R_4 or R_5 have the meanings given under Formula (IV).

In another embodiment, the compound of Formula (IV) may be converted to compound of Formula (I).

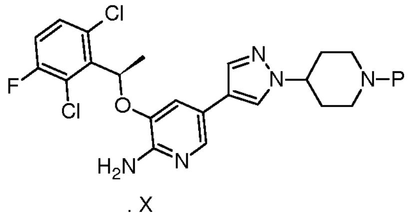
In third embodiment the present invention provides a process for the purification of the compound of Formula (V).



Formula (V)

wherein, P represents a protecting group comprising the steps of:

a) preparing an acid addition salt of the compound of Formula (V) to obtain a compound of Formula (VI);



Formula (VI)

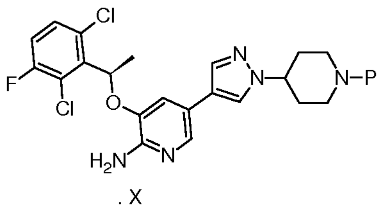
wherein, X includes organic or inorganic acids and P represents a protecting group;

and

b) isolating the purified compound of Formula (V) by adjusting the pH in the range of 6-9.

Yet, in another embodiment, the purified compound of Formula (V) may be converted to compound of Formula (I).

In fourth embodiment the present invention provides an intermediate of Formula (VI),



Formula (VI)

wherein, X represents organic or inorganic acids and P represents a protecting group.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is detailed as hereinunder.

The compound of Formula (II) as used herein may be obtained by treating 4-bromopyrazole with N-protected methanesulfonyloxy-piperidine in the conventional manner known in the art or by methods as described in US 7,858,643; which is incorporated herein for reference purpose only.

The examples of suitable protecting agents for the protection of methanesulfonyloxy-piperidine include, but are not limited to, those that lead to the formation of carbamates or amides or cyclic imide derivatives or N-Alkyl or N-Aryl amines or imine derivatives or enamine derivatives. In certain exemplary embodiments, the protecting agent may be selected from the group comprising of acetic anhydride, di-tert-butyl dicarbonate (i.e., Boc anhydride) or 9-fluorenylmethoxy carbonyl reagent (i.e., Fmoc reagent).

R_1, R_2, R_3, R_4 or R_5 in the compound of Formula III, may be independently selected from the group comprising of hydrogen or straight or branched chain alkyl, alkylene, alkene or alkoxy group. Preferably, R_1, R_2, R_3, R_4 or R_5 may be independently selected from the group comprising of methyl, ethyl or propyl etc.

In first embodiment of the present invention, Step a) provides a process for the reaction (generally referred herein as boronation) of compound of Formula (II) with compound of Formula (III) to obtain a compound of Formula (IV). The reaction may be performed in the presence of a suitable base. Suitable base may be selected from the group comprising of metal hydrides such as sodium hydride or the like or metal hydroxides such as sodium hydroxide, potassium hydroxide, lithium hydroxide, barium hydroxide or the like or metal carbonates such as sodium carbonate, calcium carbonate, cesium carbonate or the like or metal alkoxides such as sodium methoxide, sodium ethoxide, potassium t-butoxide or the like or sodium hydrogen carbonate such as sodium hydrogen carbonate or the like or organic amines such as triethylamine, diisopropylethylamine, 1,8-Diazabicyclo[5.4.0]undec-7-ene, 2,6-lutidine or the like or pyridine or alkyl lithiums such as n-butyllithium, sec- butyllithium, tert- butyllithium or the like. Preferably, the reaction may be performed in the presence of n-butyllithium.

The reaction may be carried out in the presence of a suitable solvent. Suitable solvent may be selected from the group comprising of alcohols, halogenated hydrocarbons, non-polar solvents, polar aprotic solvents, polar protic solvents, water, ketones, esters, ethers or mixtures thereof. Suitable solvent may be selected from the group comprising of alcohols such as methanol, ethanol, t-butanol, n-butanol, isopropanol or the like mixtures thereof or halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane or the like or mixture thereof or non-polar solvents such as benzene, toluene, dioxane, ethers, halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane or the like or mixtures thereof or polar aprotic solvents such as tetrahydrofuran, ethyl acetate, acetone, dimethylformamide, acetonitrile, dimethyl sulfoxide or the like or mixtures thereof or polar protic solvents such as methanol, ethanol, t-butanol, n-butanol, isopropanol, formic acid, acetic acid, nitromethane or the like or mixture thereof or water or ketones such as acetone, diisobutyl ketone, cyclohexanone, methylcyclohexanone, methyl ethyl ketone, methyl isobutyl ketone, acetylacetone or the like or mixture thereof or esters such as methyl acetate, ethyl acetate or the like or mixture thereof or ethers such as Dimethyl ether, Diethyl ether, Tetrahydrofuran, Dioxane or the like or mixture thereof. Preferably, the reaction may be carried out in tetrahydrofuran.

The reaction may be performed at a temperature range of about -100 to 50°C. Preferably, the reaction may be carried out at a temperature range of -70°C to about -80°C.

It was found that in the reaction of compound of Formula (II) with compound of Formula (III) for the preparation of compound of Formula (IV), a very significant reduction of undesired impurities could be achieved by carrying the reaction in the presence of a suitable base. It was observed that selection of base in this reaction is very critical. It was found that by the selection of an appropriate base the compound of Formula (IV) can be obtained with high purity and free of undesired impurities. Typically, it was found that, compound of Formula (IV) obtained by following the process of present invention has a purity ≥ 98% and was essentially free of starting material or reagents or any corresponding dimer of (pyrazol-1-yl)-piperidine, such as represented by Formula (**A**) hereinbefore.

In first embodiment of the present invention, Step b) provides a process for the coupling of compound of Formula (IV) with compound of Formula (iii) to obtain a compound of Formula (V). The reaction may be carried out in the presence of a suitable catalyst. Suitable catalyst may be selected from the group comprising of 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane, Palladium-tetrakis(triphenylphosphine), Palladium(II) chloride, Tris(dibenzylideneacetone)dipalladium(0), Palladium(0) bis(dibenzylideneacetone) or the like.

The reaction may be performed in the presence of a suitable base. Suitable base may be selected from the group comprising of metal hydrides such as sodium hydride or the like or metal hydroxides such as sodium hydroxide, potassium hydroxide, lithium hydroxide, barium hydroxide or the like or metal carbonates such as sodium carbonate, calcium carbonate, cesium carbonate or the like or metal alkoxides such as sodium methoxide, sodium ethoxide, potassium t-butoxide or the like or sodium hydrogen carbonate such as sodium hydrogen carbonate or the like or organic amines such as triethylamine, diisopropylethylamine, 1,8-Diazabicyclo[5.4.0]undec-7-ene, 2,6-lutidine or the like or pyridine or alkyl lithiums such as n-butyllithium, sec- butyllithium, tert- butyllithium or the like. Preferably, the reaction may be performed in sodium carbonate, calcium carbonate, cesium carbonate or the like.

The reaction may be carried out in the presence of a suitable phase transfer catalyst. Suitable phase transfer catalyst may be selected from the group comprising of tetramethylammonium chloride, tetramethylammonium bromide, benzyltriethylammonium chloride, methyltrioctylammonium chloride, tetrabutylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium hydrogen sulfate, tetrabutylphosphonium chloride, tetraphenyl phosphonium bromide, tetraphenylphosphonium chloride, triphenylmethyl phosphonium bromide, triphenylmethylphosphonium chloride or 4-dialkylaminopyridinium salts such as tetraphenylarsonium chloride, bis[tris(dimethylamino)phosphine]iminium chloride and tetratris[tris(dimethylamino)phosphinimino]phosphonium chloride. Preferably, reaction may be performed in the presence of tetrabutylammonium bromide.

The reaction may be carried out in the presence of a suitable solvent. Suitable solvent may be selected from the group comprising of alcohols, halogenated hydrocarbons, non-polar solvents, polar aprotic solvents, polar protic solvents, water, ketones, esters, ethers or mixtures thereof. Suitable solvent may be selected from the group comprising of alcohols such as methanol, ethanol, t-butanol, n-butanol, isopropanol or the like mixtures thereof or halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane or the like or mixture thereof or non-polar solvents such as benzene, toluene, dioxane, ethers, halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane or the like or mixtures thereof or polar aprotic solvents such as tetrahydrofuran, ethyl acetate, acetone, dimethylformamide, acetonitrile, dimethyl sulfoxide or the like or mixtures thereof or polar protic solvents such as methanol, ethanol, t-butanol, n-butanol, isopropanol, formic acid, acetic acid, nitromethane or the like or mixtures thereof or water or ketones such as acetone, diisobutyl ketone, cyclohexanone, methylcyclohexanone, methyl ethyl ketone, methyl isobutyl ketone, acetylacetone or the like or mixture thereof or esters such as methyl acetate, ethyl acetate or the like or mixture thereof or ethers such as Dimethyl ether, Diethyl ether, Tetrahydrofuran, Dioxane or the like or mixture thereof. Preferably, the reaction may be performed in water or toluene or the like or in the mixture thereof.

As mentioned hereinabove, compound of Formula (V) can be converted to compound of Formula (I) by any of the known literature methods, specifically by the process of step c) of the first embodiment of the present invention.

In first embodiment of the present invention, Step c) provides a process for the deprotection of compound of Formula (V) to obtain a compound of Formula (I). The reaction may be carried out in the presence of a suitable acid. Suitable acid may be selected from the group comprising of inorganic acids such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid and the like; or organic acids such as formic acid, acetic acid, citric acid, trifluoroacetic acid, p-toluenesulfonic acid and the like. Preferably, the reaction may be performed in organic acids such as hydrochloric acid.

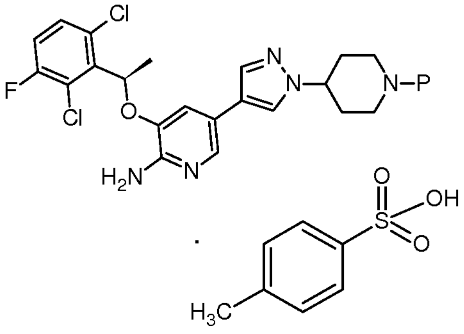
The reaction may be carried out in the presence of a suitable solvent. Suitable solvent may be selected from the group comprising of alcohols, halogenated hydrocarbons, non-polar solvents, polar aprotic solvents, polar protic solvents, water, ketones, esters, ethers or mixtures thereof. Suitable solvent may be selected from the group comprising of alcohols such as methanol, ethanol, t-butanol, n-butanol, isopropanol or the like mixtures thereof or halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane or the like or mixture thereof or non-polar solvents such as benzene, toluene, dioxane, ethers, halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane or the like or mixtures thereof or polar aprotic solvents such as tetrahydrofuran, ethyl acetate, acetone, dimethylformamide, acetonitrile, dimethyl sulfoxide or the like or mixtures thereof or polar protic solvents such as methanol, ethanol, t-butanol, n-butanol, isopropanol, formic acid, acetic acid, nitromethane or the like or mixtures thereof or water or ketones such as acetone, diisobutyl ketone, cyclohexanone, methylcyclohexanone, methyl ethyl ketone, methyl isobutyl ketone, acetylacetone or the like or mixture thereof or esters such as methyl acetate, ethyl acetate or the like or mixture thereof or ethers such as Dimethyl ether, Diethyl ether, Tetrahydrofuran, Dioxane or the like or mixture thereof. Preferably, the reaction may be performed in tetrahydrofuran or dioxane.

The reaction may be carried out at a temperature range from -20°C to room temperature. Preferably, reaction may be carried at 0°C.

In second embodiment of the present invention, the reaction may be carried out under same parameters as defined hereinabove for Step a) of the first embodiment.

In third embodiment of the present invention provides a process for the purification of compound of Formula (V).

In third embodiment of the present invention, step a) provides a process for the preparation of compound of Formula (VI) from the compound of Formula (V). The compound of Formula (VI) may be prepared by treating compound of Formula (V) with an organic or inorganic acid. An organic or inorganic acid may be selected from the group comprising of halogen acids such as hydrochloric acid, sulfuric acid, phosphoric acid, boric acid, carboxylic acids, sulfonic acids, fumaric acid methansulfonic acid, toluenesulphonic acid etc. Preferably, the reaction may be performed in an organic acid such as toluenesulphonic acid. A preferred compound of Formula (VI) is a compound of Formula (VII),



Formula (VII)

wherein, P represents a protecting group.

The reaction may be carried out in the presence of a suitable solvent. Suitable solvent may be selected from the group comprising of alcohols, halogenated hydrocarbons, non-polar solvents, polar aprotic solvents, polar protic solvents, water, ketones, esters, ethers or mixtures thereof. Suitable solvent may be selected from the group comprising of alcohols such as methanol, ethanol, t-butanol, n-butanol, isopropanol or the like mixtures thereof or halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane or the like or mixture thereof or non-polar solvents such as benzene, toluene, dioxane, ethers, halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane or the like or mixtures thereof or polar aprotic solvents such as tetrahydrofuran, ethyl acetate, acetone, dimethylformamide, acetonitrile, dimethyl sulfoxide or the like or mixtures thereof or polar protic solvents such as methanol, ethanol, t-butanol, n-butanol, isopropanol, formic acid, acetic acid, nitromethane or the like or mixtures thereof or water or ketones such as acetone, diisobutyl ketone, cyclohexanone, methylcyclohexanone, methyl ethyl ketone, methyl isobutyl ketone, acetylacetone or the like or mixture thereof or esters such as methyl acetate, ethyl acetate or the like or mixture thereof or water or ethers such as Dimethyl ether, Diethyl ether, Tetrahydrofuran, Dioxane or the like or mixture thereof. Preferably, the reaction may be performed in acetone or the like.

In third embodiment of the present invention, Step b) provides a process for the isolation of purified compound of Formula (V). The purified compound of Formula (V) may be obtained from compound of Formula (VI) by adjusting the pH in the range of 6.0-9.0. The pH of the solution may be adjusted by using a suitable base. Suitable base may be selected from the group comprising of metal hydrides such as sodium hydride or the like or metal hydroxides such as sodium hydroxide, potassium hydroxide, lithium hydroxide, barium hydroxide or the like or metal carbonates such as sodium carbonate, calcium carbonate, cesium carbonate or the like or metal alkoxides such as sodium methoxide, sodium ethoxide, potassium t-butoxide or the like or sodium hydrogen carbonate such as sodium hydrogencarbonate or the like or organic amines such as triethylamine, diisopropylethylamine, 1,8-Diazabicyclo[5.4.0]undec-7-ene, 2,6-lutidine or the like or pyridine or alkyl lithiums such as n-butyllithium, sec-butyllithium, tert- butyllithium or the like. Preferably, the pH of the solution may be adjusted by using alkali metal hydrogencarbonate such as sodium hydrogen carbonate.

It was found that purification of compound of Formula (V) achieves a significant reduction of palladium content in the isolated compound without using any tedious purification techniques or by using highly expensive metal scavenger as used in the reported methods.

It was found that palladium contents were reduced from ~1500 ppm to ~105 ppm by using the process of present invention and compound of Formula (V) was obtained with purity ≥99%.

The purified compound of Formula (V) can be optionally converted to compound of Formula (I) by any of the known literature methods. It was found that palladium content in the compound of Formula (I) obtained by the process of the present invention was well within the prescribed regulatory guidance. More specifically, palladium content in the compound of Formula (I) was in the range of ~ 0.3 ppm to ~ 0.4 ppm with purity ≥99% in a reproducible yield.

In fourth embodiment of the present invention, an intermediate of Formula (VI) is provided.

Detailed experimental parameters suitable for the preparation of Crizotinib according to present invention are provided by the following examples, which are intended to be illustrative and not limiting of all possible embodiments of the invention.

Example-1

Preparation of Tert-butyl 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]piperidine-1-carboxylate

To a stirred solution of *tert*-butyl 4-(4-bromo-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (25.0g, 0.076 mole) in THF (500 ml) at – 70°C was added BuLi 1.6 M in Hexane solution (56.75 ml, 0.091 mole) dropwise followed by addition of 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (18.52 ml , 0.091 mole) at same temperature. Reaction mixture was stirred at -70°C for 1h then warmed to room temperature and continued stirring for 2h at room temperature. Reaction mixture was quenched with ammonium chloride solution (25 ml) water (500 ml), and ethyl acetate (750 ml) was added to reaction mixture, followed by extraction with ethylacetate (100 ml x 2). The combined organic layer was washed with brine, concentrated under vacuum to get crude product which was crystallized from n-Heptane to give pure title compound.

Yield: 51 % (14.7g)

HPLC Purity: 96.7 %

MS (m/z): 378 (M + 1)

^{1}HNMR (400 MHz, $CDCl_3$) δ: 7.81 (s, 1H), 7.75 (s, 1H), 4.27 (m, 3H), 2.9 (m, 2H), 2.14 (m, 2H), 1.91 (m, 2H), 1.49 (s, 9H), 1.33 (s, 12 H).

Example-2

Preparation of Tert-butyl 4-(4-{6-amino-5-[(1R)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]pyridin-3-yl}-1H-pyrazol-1-yl)piperidine-1-carboxylate

5-bromo-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine (17.0g, 0.044 moles), tert-butyl 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]piperidine-1-carboxylate (20.25g, 0.054 moles) and tetrabutylammonium bromide (0.0741g, 0.00223 moles) were dissolved in toluene (136 ml), and the resulting solution was added to a solution of cesium carbonate (46.6g, 0.143 moles) in water (102 ml) at room temperature. The resulting mixture was degassed with nitrogen. $PdCl_2$ $(dppf)_2$. CH_2Cl_2 (0.456 g, 0.00558 moles) was added to the mixture and reaction mixture was degassed again by purging nitrogen. The reaction mixture was heated to 90°C for 3h. After the completion of reaction solution was cooled to room temperature, filtered through celite bed and water (~170 ml) was added to filtrate. Organic layer was separated and aqueous layer was extracted with ethyl acetate (~85ml x 3). Combined organic layers were washed with water (170 ml), concentrated under vacuum to give gummy mass. Crude product was dissolved in toluene (~85 ml) at 50-60°C. Heptane (~170 ml) was added dropwise to this mixture at 50-60°C. Mixture was stirred at room temperature for 12h. The obtained solid was filtered and washed with heptane, dried under vacuum to give title compound.

Yield: 20 g (81 %)

HPLC Purity: 97 %

Example-3

Purification of Tert-butyl 4-(4-{6-amino-5-[(1R)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]pyridin-3-yl}-1H-pyrazol-1-yl)piperidine-1-carboxylate

To a stirred solution of material obtained in Example -2 (17.0 g, 0.0308 moles) in acetone (140 ml) was added p-toluenesulphonic acid (5.8g, 0.0308 moles) at room temperature. Reaction mixture was stirred at room temperature for 12h. Precipitated salt was filtered and washed with acetone (~20 ml x 2). Obtained product was taken in water (170 ml), pH was adjusted to 7.0-8.0, and the product was extracted with ethyl acetate (100 ml x 2). Combined organic layers were washed with water and concentrated under vacuum to get title compound.

Yield: 14.6g

HPLC purity: 99.15 %

^{1}HNMR (400 MHz, $CDCl_3$) δ: 7.75 (d, J = 1.6 Hz, 1H), 7.56 (s, 1H), 7.48 (s, 1H), 7.30 (dd, J = 9.2 Hz), 7.0 (m, 1H), 6.86 (d, J = 1.6 Hz, 1H), 6.07 (q, J= 6.8 Hz, 1H), 4.79 (brs, 1H), 4.25 (m, 3H), 2.89 (m, 2H), 2.14 (m, 2H), 1.92 (m, 2H), 1.88 (d, J= 6.8 Hz, 3H), 1.47 (s, 15H).

Example-4

Preparation of Crizotinib:

To a stirred solution of Tert-butyl 4-(4-{6-amino-5-[(1*R*)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]pyridin-3-yl}-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (material obtained in Example 3) (1.0g, 0.00181 moles) in dichloromethane (~13 ml) at 0°C was added 4.0 M dioxane HCl (6.7 ml, 0.0272 moles). Reaction mixture was stirred at room temperature for 4h. After the completion of reaction monitored by TLC, solid was filtered and washed with dichloromethane (10 ml). The obtained solid was dissolved in water (20 ml); aqueous layer was extracted with dichloromethane (10x2). The pH of aqueous layer was adjusted to 9-10 with Na_2CO_3 and compound was extracted with dichloromethane (10 x 3), combined organic layers were washed with water (20 ml), evaporated under vacuum to get solid product. The solid was stirred with ether (10 ml), filtered off, washed well with ether, dried under vacuum to get Crizotinib.

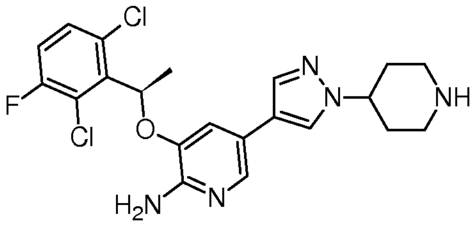
Yield: 0.45g (55 %)

HPLC Purity: 99.35 %

^{1}HNMR (400 MHz, $CDCl_3$) δ: 7.76 (d, J = 1.6 Hz, 1H), 7.56 (s, 1H), 7.49 (s, 1H), 7.30 (dd, J = 9.2 Hz), 7.0 (m, 1H), 6.86 (d, J = 1.6 Hz, 1H), 6.09 (q, J= 6.8 Hz, 1H), 4.75 (brs, 1H), 4.19 (m, 1H), 3.25 (m, 2H), 2.76 (m, 2H), 2.16 (m, 2H), 1.92 (m, 2H), 1.85 (d, J= 6.8 Hz, 3H), 1.67 (brs, 1H)

CLAIMS

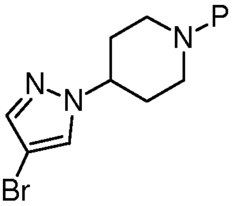
1. A process for the preparation of a compound of Formula (I),



Formula (I)

Comprising the steps of:

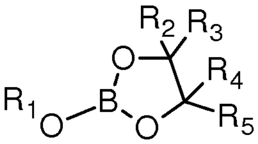
a) reacting a compound of Formula (II),



Formula (II)

wherein, P represents a protecting group

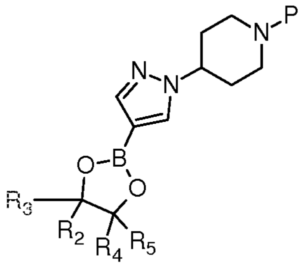
with a compound of Formula (III),



Formula (III)

wherein, R_1, R_2, R_3, R_4 or R_5 may be independently selected from the group comprising of hydrogen or straight or branched chain alkyl, alkylene, alkene or alkoxy group

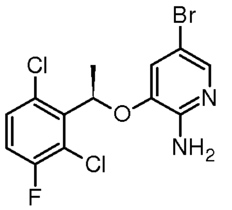
in the presence of a base to obtain a compound of Formula (IV),



Formula (IV)

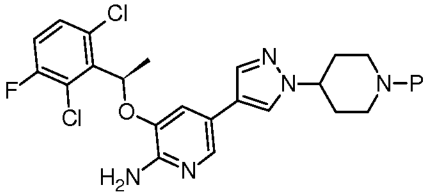
wherein R_1, R_2, R_3, R_4 or R_5 have the meanings given under Formula (III) and P represents a protecting group;

b) coupling of the compound of Formula (IV) with a compound of Formula (iii),



Formula (iii)

to obtain a compound of Formula (V),

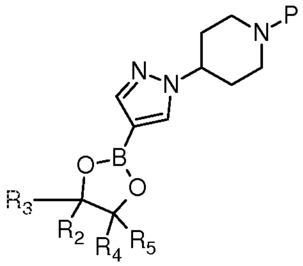


Formula (V)

wherein, P represents a protecting group; and

c) deprotecting the compound of Formula (V) to obtain the compound of Formula (I).

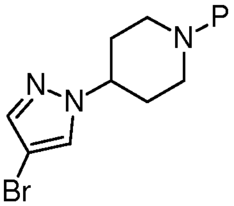
2. A process for the preparation of a compound of Formula (IV),



Formula (IV)

wherein, R_1, R_2, R_3 or R_4 may be independently selected from the group comprising of hydrogen or straight or branched chain alkyl, alkylene, alkene or alkoxy group and P represents a protecting group

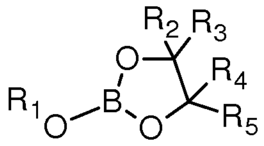
by reacting a compound of Formula (II),



Formula (II)

wherein, P represents a protecting group

in the presence of a base with a compound of Formula (III),



Formula (III)

wherein R_1, R_2, R_3, R_4 or R_5 have the meanings given under Formula (IV).

3. The process according to claim 1 or claim 2, wherein base is selected from the group comprising of metal hydrides, metal carbonates, metal hydroxides, metal alkoxides, alkyl lithiums or organic amines.

4. The process of claim 3, wherein base is n-butyllithium.

5. The process according to claim 1, wherein step a) is carried out in the presence of a solvent selected from the group comprising of alcohols, halogenated hydrocarbons, non-polar solvents, polar aprotic solvents, polar protic solvents, ketones, esters, ethers, water or mixtures thereof.

6. The solvent according to claim 5, wherein solvent is tetrahydrofuran.

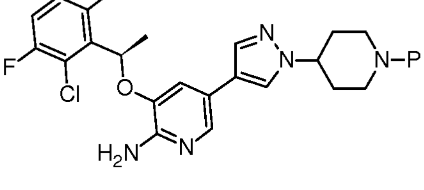
7. The process according to claim 1, wherein reaction is carried out at a temperature range of -100°C to 50°C.

8. The process according to claim 2, wherein reaction is carried out in the presence of a solvent selected from the group comprising of alcohols, halogenated hydrocarbons, non-polar solvents, polar aprotic solvents, polar protic solvents, ketones, esters, ethers, water or mixtures thereof.

9. The solvent according to claim 8, wherein solvent is tetrahydrofuran.

10. The process according to claim 2, wherein reaction is carried out at a temperature range of -100°C to 50°C.

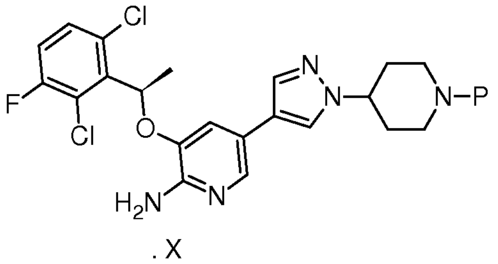
11. A process of purification of the compound of Formula (V),



Formula (V)

wherein, P represents a protecting group comprising the step of:

a) preparing an acid addition salt of a crude compound of Formula (V), to obtain a compound of Formula (VI),



Formula (VI)

wherein, X represents organic or inorganic acids and P represents a protecting group;

and

b) isolating the purified compound of Formula (V) by adjusting the pH in the range of 6.0-9.0.

12. The process according to claim 11, wherein acid addition salt is prepared in the presence of an organic or an inorganic acid.

13. The process of claim 12, wherein the acid is p-toluenesulphonic acid.

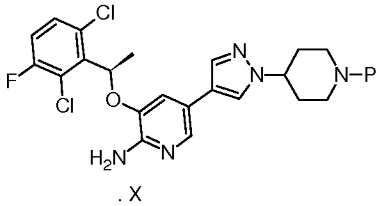
14. The process according to claim 11, wherein acid addition salt is prepared in the presence of a solvent selected from the group comprising of alcohols, halogenated hydrocarbons, non-polar solvents, polar aprotic solvents, polar protic solvents, ketones, esters, ethers, water or mixtures thereof.

15. The process according to claim 14, wherein solvent is acetone.

16. The process according to claim 11, wherein pH is adjusted in the presence of a base selected from the group comprising of metal hydrides, metal carbonates, metal alkoxides, metal hydrogen carbonates, organic amines or mixture thereof.

17. The process according to claim 16, wherein base is sodium hydrogen carbonate.

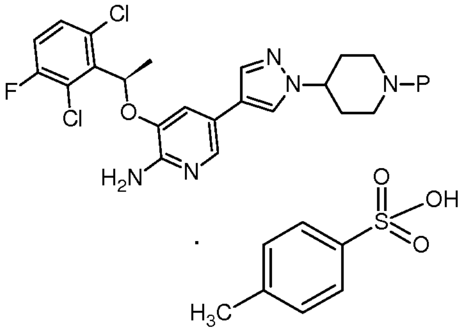
18. A compound of Formula (VI),



Formula (VI)

wherein, X represents organic or inorganic acids and P represents a protecting group.

19. The compound according to claim 18, wherein compound is of Formula (VII),



Formula (VII)

wherein, P represents a protecting group.