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An improved process for the preparation of (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-4 [4,3-h][2,5,11]Benzoxadiazacyclo tetradecine-3-carbonitrile and its intermediates thereof

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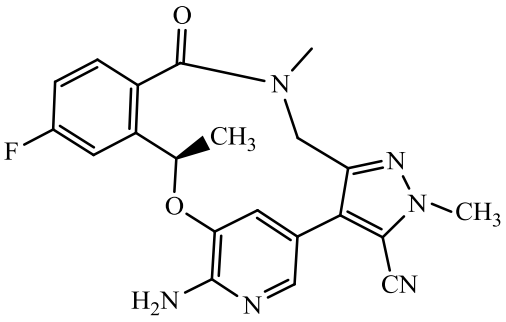
An improved process for the preparation of (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-4,8-methenopyrazolo [4,3-h][2,5,11]Benzoxadiazacyclo tetradecine-3-carbonitrile and its intermediates thereof

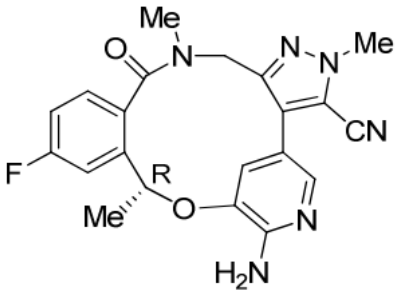
Field of the invention:

The present invention relates to an improved process for the preparation of (10*R*)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-4,8-methenopyrazolo [4,3-*h*][2,5,11] benzoxadiazacyclotetradecine-3-carbonitrile represented by following structural formula-1



Formula-1

[OR]

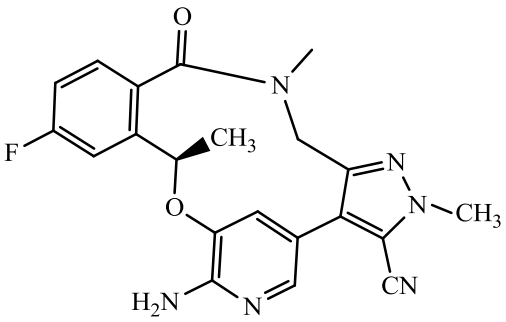


Formula-1.

The present invention also relates to an improved process for the preparation of intermediate compounds of formula-5 and formula-6.

Background of the invention:

(10*R*)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-4,8-methenopyrazolo[4,3-*h*][2,5,11] benzoxadiazacyclotetradecine-3-carbonitrile is commonly known as Lorlatinib, which was approved in US & Europe under the brand names of Lorbrena and Lorviqua respectively for the treatment of anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer.



Formula-1

US 8680111 B2 patent discloses the process for the preparation of Lorlatinib.

US 9637500 B2 patent describes hydrated crystalline forms and acetic acid solvate form 3 of Lorlatinib and their process for the preparation.

Journal of Medicinal Chemistry, 2014, 57 (11), 4720-4744 discloses the process for the preparation of Lorlatinib.

European Journal of Medicinal Chemistry, 2017, 134, 348-356 discloses the process for the preparation of Lorlatinib.

Organic Process Research & Development, 2018, 22(9), 1289-1293 discloses the process for the preparation of Lorlatinib.

All prior art processes for the preparation of compound of formula-6 involves the usage of carbon monoxide in presence of palladium complex as catalyst.

Carbon monoxide is a health hazard and environmental pollutant. Carbon monoxide exposure leads several health problems. Hence the usage of Carbon monoxide in large scale production is not suggestible.

Palladium complex as catalyst is costly and toxic reagent. Removing of palladium from the reaction mixture is very difficult and it requires consumption of excess of solvents which increases the production cost and also generates lot of spent and unwanted wastes which are difficult to dispose and leads to pollution of the environment.

Thus, there remains a need to develop an improved process for the preparation Lorlatinib, which is simple, economic, eco-friendly and industrially viable process with high yield and purity.

After numerous trials and earnest efforts, the present inventors developed an

improved industrially viable economic process for the preparation of Lorlatinib by overcoming the above said drawbacks.

Brief description of the invention:

The first embodiment of the present invention provides an improved process for the preparation of Lorlatinib.

The second embodiment of the present invention provides an improved process for the preparation of Lorlatinib.

The third embodiment of the present invention provides an improved process for the preparation of Lorlatinib.

The fourth embodiment of the present invention provides an improved process for the preparation of compound of formula-5.

The fifth embodiment of the present invention provides an improved process for the preparation of compound of formula-6.

The sixth embodiment of the present invention provides an improved process for the preparation of compound of formula-6.

Detailed description of the invention:

As used herein the term “suitable solvent” or solvent used in the present invention refers to “hydrocarbon solvents” such as n-hexane, n-heptane, cyclohexane, pet ether, benzene, toluene, pentane, cycloheptane, methyl cyclohexane, ethylbenzene, m-, o-, or p-xylene, or naphthalene and the like; “ether solvents” such as dimethoxymethane, tetrahydrofuran, 1,3-dioxane, 1,4-dioxane, furan, diethyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethylene glycol diethyl ether, triethylene glycol dimethyl ether, anisole, t-butyl methyl ether, 1,2-dimethoxy ethane and the like; “ester solvents” such as methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate and the like; “polar-aprotic solvents such as dimethylacetamide (DMA), dimethylformamide (DMF), dimethylsulfoxide (DMSO), N-methylpyrrolidone (NMP) and the like; “chloro solvents” such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and the like; “ketone solvents” such as acetone, methyl ethyl ketone, methyl

isobutylketone and the like; “nitrile solvents” such as acetonitrile, propionitrile, isobutyronitrile and the like; “alcohol solvents” such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, ethylene glycol, 1,2-propanediol (propylene glycol), 2-methoxyethanol, l, 2-ethoxyethanol, diethylene glycol, 1, 2, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monoethyl ether, cyclohexanol, benzyl alcohol, phenol, or glycerol and the like; “polar solvents” such as water or mixtures thereof.

As used herein the term “acid" used in the present invention refers to hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, formic acid, acetic acid, trifluoroacetic acid, alkyl/aryl sulfonic acids such as methane sulfonic acid, ethane sulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like.

As used herein the term “Grignard reagent” or RMgX refers to an organo magnesium halide. Wherein R is selected from substituted or unsubstituted alkyl group or aryl group.

The first embodiment of the present invention provides an improved process for the preparation of Lorlatinib, which comprises:

a) converting compound of formula-4 to compound of formula-5,
b) converting compound of formula-5 to Lorlatinib.

Converting compound of formula-4 to compound of formula-5 in step-a) of the first embodiment can be done by reacting compound of formula-4 with Grignard reagent in a solvent followed by reacting with carbon dioxide to provide compound of formula-5; wherein the solvent can be selected from chloro solvents, ether solvents, hydrocarbon solvents, polar aprotic solvents and mixtures thereof.

Compound of formula-4 used in step-a) of the first embodiment can be prepared by any of the processes disclosed in literature such as US 8680111 B2 or other references.

The second embodiment of the present invention provides an improved process for the preparation of Lorlatinib, which comprises:

a) converting compound of formula-5 to compound of formula-6,
b) converting compound of formula-6 to Lorlatinib.

Converting compound of formula-5 to compound of formula-6 in step-a) of the second embodiment can be done by treating compound of formula-5 with an acid in an alcohol solvent to provide compound of formula-6; wherein alcohol solvent is selected from methanol, ethanol, propanol, isopropanol and the like; acid is selected from hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, formic acid, acetic acid, trifluoroacetic acid, alkyl/aryl sulfonic acids such as methane sulfonic acid, ethane sulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like.

Compound of formula-5 used in step-a) of the second embodiment can be prepared by the process described in the first embodiment.

Converting compound of formula-6 to Lorlatinib in step-b) of the second embodiment can be done by any of the processes disclosed in literature such as US 8680111 B2 or other references.

The third embodiment of the present invention provides an improved process for the preparation of Lorlatinib, which comprises:

a) converting compound of formula-4 to compound of formula-5,
b) converting compound of formula-5 to compound of formula-6,
c) converting compound of formula-6 to Lorlatinib.

Converting compound of formula-4 to compound of formula-5 in step-a) of the third embodiment can be done by reacting compound of formula-4 with Grignard reagent in a solvent followed by reacting with carbon dioxide to provide compound of formula-5; wherein the solvent can be selected from chloro solvents, ether solvents, hydrocarbon solvents, polar aprotic solvents and mixtures thereof.

Compound of formula-4 used in step-a) of the third embodiment can be prepared by any of the processes disclosed in literature such as US 8680111 B2 or other references.

Converting compound of formula-5 to compound of formula-6 in step-b) of the third embodiment can be done by treating compound of formula-5 with an acid in an alcohol solvent to provide compound of formula-6; wherein alcohol solvent is selected from methanol, ethanol, propanol, isopropanol and the like; acid is selected from hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, formic acid, acetic acid,

trifluoroacetic acid, alkyl/aryl sulfonic acids such as methane sulfonic acid, ethane sulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like.

Converting compound of formula-6 to Lorlatinib in step-c) of the third embodiment can be done by any of the processes disclosed in literature such as US 8680111 B2 or other references.

The fourth embodiment of the present invention provides an improved process for the preparation of compound of formula-5, which comprises converting compound of formula-4 to compound of formula-5.

Converting compound of formula-4 to compound of formula-5 in the fourth embodiment can be done by reacting compound of formula-4 with Grignard reagent in a solvent followed by reacting with carbon dioxide to provide compound of formula-5; wherein solvent can be selected from chloro solvents, ether solvents, hydrocarbon solvents, polar aprotic solvents and mixtures thereof.

Compound of formula-4 used in the fourth embodiment can be prepared by any of the processes disclosed in literature such as US 8680111 B2 or other references.

The fifth embodiment of the present invention provides an improved process for the preparation of compound of formula-6, which comprises converting compound of formula-5 to compound of formula-6.

Converting compound of formula-5 to compound of formula-6 in the fifth embodiment can be done by treating compound of formula-5 with an acid in an alcohol solvent to provide compound of formula-6; wherein alcohol solvent is selected from methanol, ethanol, propanol, isopropanol and the like; acid is selected from hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, formic acid, acetic acid, trifluoroacetic acid, alkyl/aryl sulfonic acids such as methane sulfonic acid, ethane sulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like.

Compound of formula-5 used in the fifth embodiment can be prepared by the process described in the first embodiment.

The sixth embodiment of the present invention provides an improved process for the

preparation of compound of formula-6, which comprises:

a) converting compound of formula-4 to compound of formula-5,

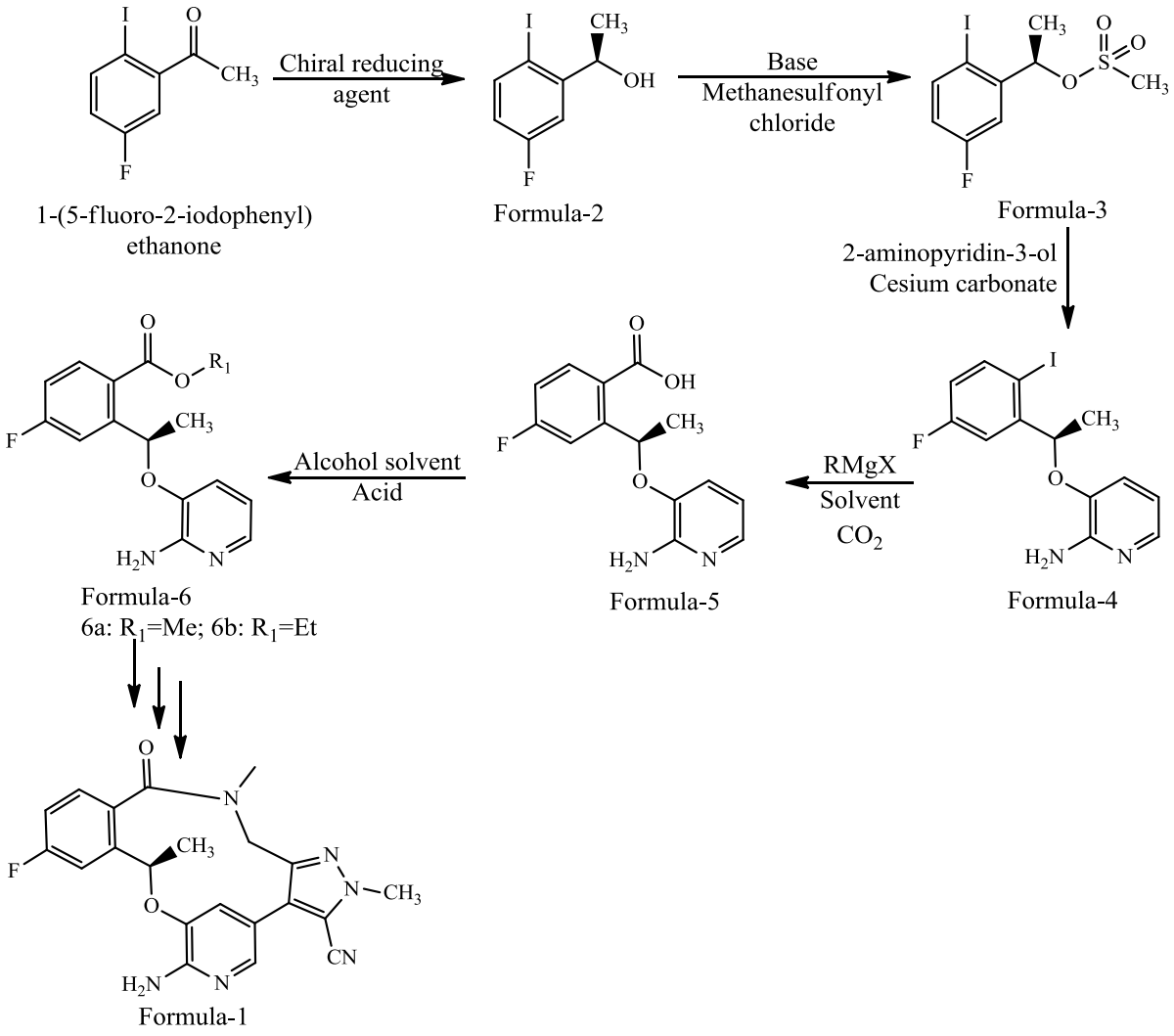
b) converting compound of formula-5 to compound of formula-6.

Converting compound of formula-4 to compound of formula-5 in step-a) of the sixth embodiment can be done by reacting compound of formula-4 with Grignard reagent in a solvent followed by reacting with carbon dioxide to provide compound of formula-5; wherein the solvent can be selected from chloro solvents, ether solvents, hydrocarbon solvents, polar aprotic solvents and mixtures thereof.

Compound of formula-4 in step-a) of the sixth embodiment can be prepared by any of the processes disclosed in literature such as US 8680111 B2 or other references.

Converting compound of formula-5 to compound of formula-6 in step-b) of the sixth embodiment can be done by treating compound of formula-5 with an acid in an alcohol solvent to provide compound of formula-6; wherein alcohol solvent is selected from methanol, ethanol, propanol, isopropanol and the like; acid is selected from hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, formic acid, acetic acid, trifluoroacetic acid, alkyl/aryl sulfonic acids such as methane sulfonic acid, ethane sulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like.

First to sixth embodiments of the present invention are schematically illustrated as follows:



Wherein R, R_1 are selected from substituted or unsubstituted alkyl group or aryl group

1-(5-fluoro-2-iodophenyl)ethanone which is used in the present invention is commercially available in the market (or) it can be prepared by any of the processes known in the prior art.

The best mode of carrying out the present invention is illustrated by the below mentioned examples. These examples are provided as illustration only and hence should not be considered as limitation of the scope of the invention.

Examples:

Example-1: Preparation of *(R)*-1-(5-fluoro-2-iodophenyl)ethanol compound of formula-2

(R)-Methyl oxazaborolidine (15.74 g) was added to the mixture of 1-(5-fluoro-2-iodophenyl)ethanone (25 g) and tetrahydrofuran (250 ml) at 25-30°C. Cooled the reaction mixture to -20°C to -25°C, Borane dimethyl sulfide (5.75 g) was slowly added to the reaction mixture and stirred for 1 hour at same temperature. Methanol was added to reaction mixture and raised the temperature of the reaction mixture to 15-20°C. Aqueous ammonium chloride solution was added to the above reaction mixture and stirred for 10 minutes. The reaction mixture extracted with ethyl acetate. Ethyl acetate layer was washed with water and dried with sodium sulfate. Distilled of the solvent completely from the organic layer to get the title compound.

Yield: 21 g.

Example-2: Preparation of compound of formula-3

Triethylamine (76.06 g) was slowly added to the mixture of *(R)*-1-(5-fluoro-2-iodophenyl)ethanol compound of formula-2 (100 g) and methyl tertiary butyl ether (1500 ml) at 0-5°C and stirred for 10 minutes at same temperature. Methanesulfonyl chloride (64.58 g) was slowly added to the reaction mixture at 0-5°C and stirred for 45 minutes. Raised the temperature of the reaction mixture to 25-30°C and stirred for 1 hour at same temperature. Filtered the reaction mixture. The obtained filtrate was washed with water and distilled of the solvent. Methyl tertiary butyl ether (100 ml) and n-heptane (500 ml) were added to the above obtained compound at 25-30°C. Cooled the mixture to 0-5°C and stirred for 1 hour at same temperature. Filtered the precipitated solid, washed with n-heptane and dried to get the title compound.

Yield:110 g.

Example-3: Preparation of compound of formula-4

The compound of formula-3 obtained in the example-2 was added to the mixture of 2-aminopyridin-3-ol (49.66 g), acetonitrile and cesium carbonate (244.9 g) at 25-30°C and stirred for 10 minutes at same temperature. Heated the reaction mixture to 70-75°C and

stirred for 1 hour at same temperature. Cooled the reaction mixture to 25-30°C. Ethyl acetate was added to the reaction mixture at 25-30°C and stirred for 10 minutes at same temperature. Filtered mixture though hyflow bed and washed with ethyl acetate. Charcoal treatment was given to the filtrate. Distilled of the solvent completely from the filtrate. Acetone was added to the above obtained residue at 25-30°C and stirred at same temperature. Filtered the solid, washed with acetone and dried to get the title compound.
Yield: 90 g.

Example-4: Preparation of compound of formula-5

Isopropyl magnesium chloride was slowly added to the solution of compound of formula-4 (50 g) in tetrahydrofuran (500 ml) at 5-10°C and stirred for 10 minutes at same temperature. Cooled the reaction mixture to -10 to -20°C and carbon dioxide gas passed into reaction mixture. Raised the temperature of reaction mixture to 25-30°C and stirred for 1 hour at same temperature. The reaction mixture was cooled to 5-10°C, 2M aqueous hydrochloric acid solution was added to the reaction mixture and stirred for 10 minutes at same temperature. Water and ethyl acetate were added to the mixture and stirred for 15 minutes. Both the organic and aqueous layers were separated. Aqueous layer was extracted with ethyl acetate. Distilled of the solvent completely from the organic layer. Ethyl acetate and cyclohexane were added to the above obtained compound at 25-30°C and stirred for 1 hour at same temperature. Filtered the solid and dried to get the title compound.

Example-5: Preparation of compound of formula-6a

Methanolic hydrochloride (100 ml) was added to compound of formula-5 obtained in example-4 at 25-30°C. Heated the reaction mixture to 60-65°C and stirred for 3 hours at same temperature. Distilled off the solvent from the reaction mixture. Cooled the obtained compound to 10-15°C and ethyl acetate was added to it. Neutralized mixture with aqueous sodium bicarbonate solution. The organic and aqueous layers were separated. Organic layer was washed with aqueous sodium chloride solution. Distilled of the solvent completely from the organic layer. Cyclohexane (30 ml) was added to the above obtained compound at 25-

30°C and stirred for 3 hours at same temperature. Filtered the solid, washed with cyclohexane and dried to get title compound.

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