FORM-2

THE PATENT ACT 1970

(39 of 1970)

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The Patents Rules, 2003

COMPLETE SPECIFICATION

(See section 10 and rule 13)

1. TITLE OF THE INVENTION

A process for the preparation of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide or its salts

2. APPLICANT (S)

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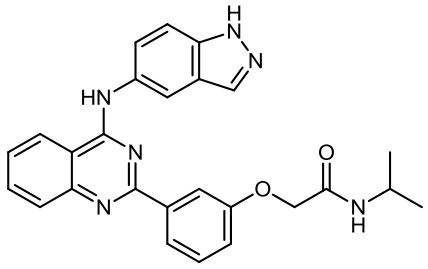
3. PREAMBLE TO THE DESCRIPTION

COMPLETE

The following specification particularly describes the invention and the manner in which itis to be performed.

Field of the invention:

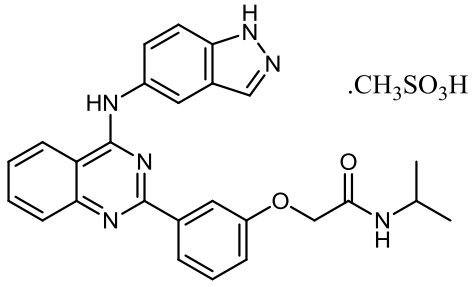
The present application relates to a process for the preparation of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide represented by the following structural formula-1, which is referred to as Belumosudil. The present invention also provides a process for the preparation salts of Belumosudil. The present invention also relates a process for the preparation Belumosudil intermediates.



Formula-1.

Background of the invention:

2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide methanesulfonate (1:1) of formula-1a is commonly known as Belumosudil mesylate. It is a kinase inhibitor indicated for the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy. The brand name is Rezurock®.



Formula-1a

US. Patent number 8357693 describe certain methods for making Belumosudil or its salts and intermediates. The said patent also discloses column chromatographic purification for the purification of the intermediates and Belumosudil, which are tedious and lengthy process.

Advantages of the present invention:

- Avoids the column purifications
- Simple and cost effective process
- Cheaper raw materials

Brief summary of the invention:

The present invention is to provide the process for the preparation of Belumosudil or its and its intermediate compounds.

The first embodiment of the present invention is to provide the process for the preparation of N-isopropyl-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)phenoxy) acetamide formula 4.

The second embodiment of the present invention is to provide a process for the preparation of compound of formula-7.

The third embodiment of the present invention is to provide a process for the preparation of 2-(3-hydroxyphenyl)quinazolin-4(3H)-one formula-11.

The fourth embodiment of the present invention is to provide a process for the preparation of tert-butyl 5-amino-1H-indazole-1-carboxylate formula 6a.

The fifth embodiment of the present invention is to provide a process for the preparation of Belumosudil or its salts.

Detailed description of the Invention:

The “suitable solvent” used in the present invention can be selected from but not limited to “hydrocarbon solvents” such as n-pentane, n-hexane, n-heptane, cyclohexane, petroleum ether, benzene, toluene, xylene and mixtures thereof; “ether

solvents" such as dimethyl ether, diethyl ether, diisopropyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxane and mixtures thereof; "ester solvents" such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, tert-butyl acetate and mixtures thereof; "polar aprotic solvents" such as dimethylacetamide, dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone (NMP) and mixtures thereof; "chloro solvents" such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and mixtures thereof; "ketone solvents" such as acetone, methyl ethyl ketone, methyl isobutyl ketone and mixtures thereof; "nitrile solvents" such as acetonitrile, propionitrile, isobutyronitrile and mixtures thereof; "alcohol solvents" such as methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, 2-butanol, tert-butanol, ethane-1,2-diol, propane-1,2-diol and mixtures thereof; "polar solvents" such as water; formic acid, acetic acid and the like or mixture of any of the afore mentioned solvents.

The term "base" used in the present invention refers to inorganic bases selected from "alkali metal carbonates" such as sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate and the like; "alkali metal bicarbonates" such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, cesium bicarbonate and the like; "alkali metal hydroxides" such as sodium hydroxide, potassium hydroxide, lithium hydroxide and the like; "alkyl metals" such as n-butyl lithium and like; "metal hydrides" such as lithium hydride, sodium hydride, potassium hydride and the like; "alkali metal phosphates" such as disodium hydrogen phosphate, dipotassium hydrogen phosphate; ammonia such as aqueous ammonia, ammonia gas, methanolic ammonia and like and "organic bases" selected from but not limited to methyl amine, ethyl amine, diisopropyl amine, diisopropylethyl amine (DIPEA), diisobutylamine, triethylamine, tert.butyl amine, pyridine, N-methyl piperazine, 4-dimethylaminopyridine (DMAP), N-methyl morpholine (NMM), N-methyl pyridine (NMP), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0] non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane

(DABCO), imidazole; “alkalimetal alkoxides” such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, sodium tert.butoxide, potassium tert.butoxide and the like; “alkali metal amides” such as sodium amide, potassium amide, lithium amide, lithiumdiisopropyl amide (LDA), sodium bis(trimethylsilyl)amide (NaHMDS), potassiumbis(trimethylsilyl)amide, lithium bis(trimethysilyl)amide (LiHMDS) and the like; or mixtures thereof.

As used herein the term “acid” in the present invention refers to inorganic acid and organic acid; inorganic acid is selected from such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, sulfuric acid; organic acids such as acetic acid, maleic acid, malic acid, oxalic acid, succinic acid, fumaric acid, trifluoroacetic acid, methane sulfonic acid, p-toluene sulfonic acid; chiral acids such as S-(+) mandelic acid, R-(-) mandelic acid, L-(+)tartaric acid, D-(-)tartaric acid, L-malic acid, D-malic acid, D-maleic acid, (-)-naproxen, (+)-naproxen, (1R)-(-)-camphor sulfonic acid, (IS)-(+)-camphor sulfonic acid (1R)-(+)-bromocamphor-10-sulfonic acid, (1S)-(-)-bromocamphor-10-sulfonic acid, (-)-Dibenzoyl-L-tartaric acid, (-)-Dibenzoyl-L-tartaricacid monohydrate, (+) -Dibenzoyl-D-tartaric acid, (+)-Dibenzoyl-D-tartaric acid monohydrate, (+)-dipara-tolyl-D-tataric acid, (-)-diparatolyl-L-tataricacid, L(-)-pyroglutamic acid, L(+)-pyroglutamic acid, (-)-lactic acid.

The first embodiment of the present invention provides a process for the preparation of N-isopropyl-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)phenoxy) acetamide formula 4 comprising reacting 2-aminobenzamide of formula-2 with 2-(3-formylphenoxy)-N-isopropylacetamide of formula-3 in the presence of cyclizing agent in a solvent.

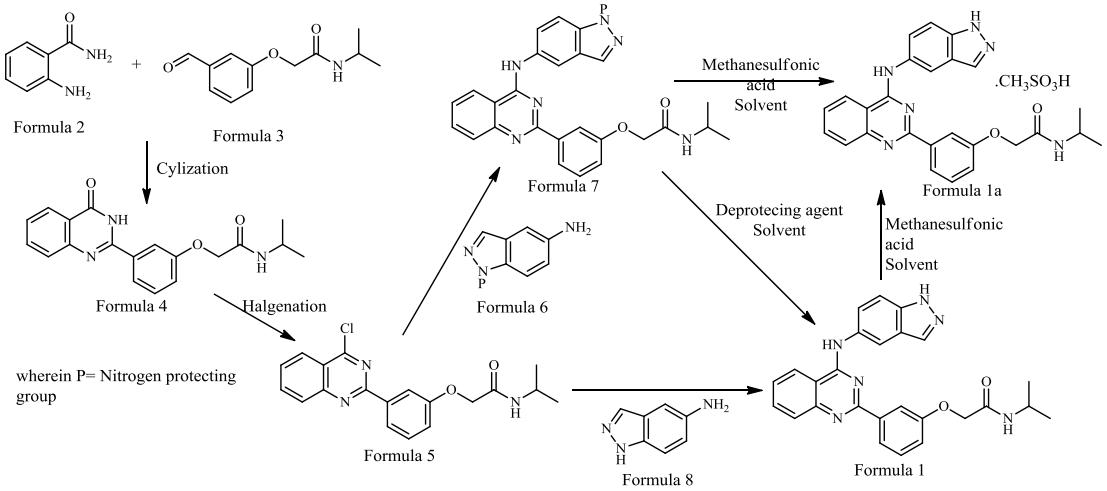
The first aspect of the first embodiment, wherein cyclizing agent selected from copper(II) chloride dihydrate, copper (II) bromide, Iodine, iodine/potassium iodide, sodium bisulfate; solvent is selected from alcohol solvents, chloro solvents, ester solvents, ketone solvents, ether solvents, hydrocarbon solvents, nitrile solvents,

polar aprotic solvents, and polar solvents such as water; nitrogen protecting group is selected from pivaloyl, pyrrolidinylmethyl, t-butoxycarbonyl, benzyl, silyl (such as TES), acetyl, benzyloxycarbonyl (Cbz) and trimethylsilyethoxymethyl (SEM).

In the second aspect of the first embodiment, the process can be carried out at a temperature ranging from at least 20°C to the reflux temperature of the solvent used.

In the third aspect of the first embodiment, the conversion of compound of formula-4 to compound of formula 1 or its salts can be carried out by the process described in CN106916145B or by the process described in the present invention.

A process according to the first embodiment of the present invention is depicted in Scheme 1 as follows:



Scheme-1

The second embodiment of present invention provides a process for the preparation of compound of formula 7 comprising reacting compound of formula 15 with 2-iodo-N-isopropylacetamide of formula 16a in the presence of a base in a solvent.

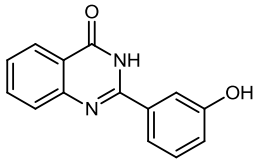
Base is selected from inorganic bases selected from “alkali metal carbonates” such as sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate

and the like; “alkali metal bicarbonates” such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, cesium bicarbonate and the like; “alkali metal hydroxides” such as sodium hydroxide, potassium hydroxide, lithium hydroxide and the like; “alkyl metals” such as n-butyl lithium and like; “metal hydrides” such as lithium hydride, sodium hydride, potassium hydride and the like; “alkali metal phosphates” such as disodium hydrogen phosphate, dipotassium hydrogen phosphate; ammonia such as aqueous ammonia, ammonia gas, methanolic ammonia and like and “organic bases” selected from but not limited to methyl amine, ethyl amine, diisopropyl amine, diisopropylethyl amine (DIPEA), diisobutylamine, triethylamine, tert.butyl amine, pyridine, 4-dimethylaminopyridine (DMAP), N-methyl morpholine (NMM), nmethyl pyridine (NMP), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0] non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO), imidazole; “alkalimetal alkoxides” such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, sodium tert.butoxide, potassium tert.butoxide and the like; “alkali metal amides” such as sodium amide, potassium amide, lithium amide, lithiumdiisopropyl amide (LDA), sodium bis(trimethylsilyl) amide (NaHMDS), potassiumbis(trimethylsilyl)amide, lithium bis(trimethysilyl) amide (LiHMDS) and the like; or mixtures thereof; solvent is selected from alcohol solvents, chloro solvents, ester solvents, ketone solvents, ether solvents, hydrocarbon solvents, nitrile solvents, polar aprotic solvents, and polar solvents such as water; nitrogen protecting group is selected from pivaloyl, pyrrolidinylmethyl, t-butoxycarbonyl, benzyl, silyl (such as TES), acetyl, benzyloxycarbonyl (Cbz) and trimethylsilyethoxymethyl (SEM).

In an aspect of the second embodiment of the present invention, further, the compound of formula-7 is converted to Belumosudil formula-1 or its salts by using suitable deprotecting agents like acid or base.

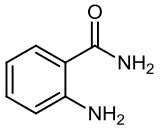
The compound of formula-15 and compound of formula-16 are used in the preparation of Belumosudil or its salts prepared by the by process described in WO2006105081A2 or according to the present invention.

Third embodiment of the present invention provides a process for the preparation of 2-(3-hydroxyphenyl)quinazolin-4(3H)-one formula-11

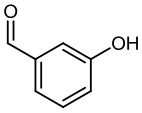


Formula-11

comprising reacting 2-aminobenzamide formula-9 with 3-hydroxybenzaldehyde formula-10,



Formula-9

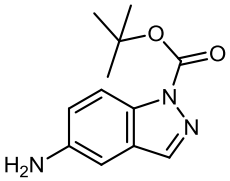


Formula-10

in the presence iron chloride, optionally in presence of a solvent.

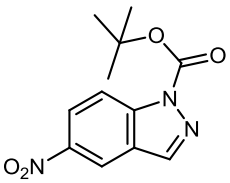
In an aspect of the third embodiment of the present invention wherein solvent is selected from alcohol solvents, polar aprotic solvents, water or mixture thereof.

Fourth embodiment of the present invention provides a process for the preparation of tert-butyl 5-amino-1H-indazole-1-carboxylate formula 6a



Formula-6a

comprising reducing the tert-butyl 5-nitro-1H-indazole-1-carboxylate formula-17a,



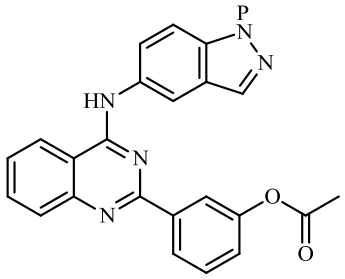
Formula-17a

in presence of Raney Nickel and hydrogen gas in a solvent to provide tert-butyl 5-amino-1H-indazole-1-carboxylate formula 6a.

In an aspect of the fourth embodiment wherein solvent is selected from alcohol solvents, chloro solvents, ester solvents, ketone solvents, ether solvents, hydrocarbon solvents, nitrile solvents, polar aprotic solvents, and polar solvents such as water.

Fifth embodiment of the present invention provides a process for the preparation of Belumosudil or its salts comprises:

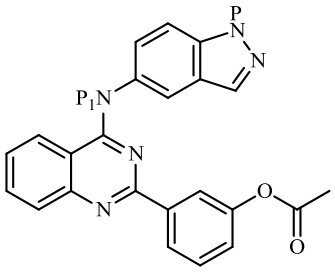
a) protecting the compound of formula-14



Formula 14

Formula-14a: P= Boc

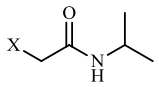
suitable nitrogen protecting agent in presence of base a solvent to provide compound of formula-18,



Formula 18

Formula-18a: P= Boc & P1= Boc

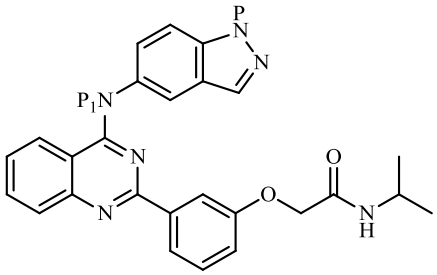
b) coupling of compound of formula-18 with compound of formula-16



Formula 16

X= Cl, Br, I

in presence of base in solvent to provide compound of formula-19,



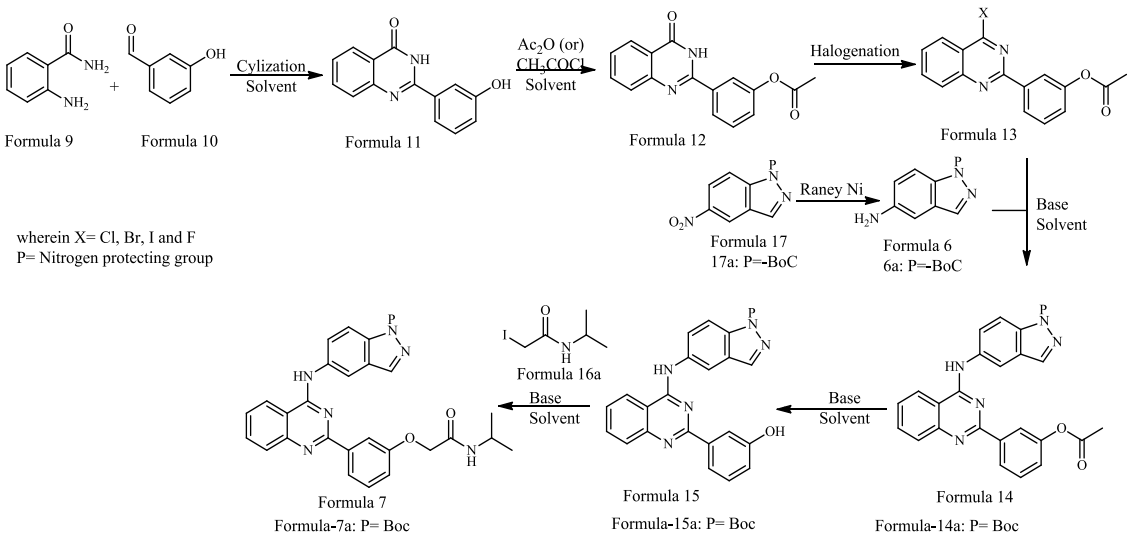
Formula-19

Formula-19a; P and P1 = Boc

c) deprotecting the compound of formula-19 to provide Belumosudil or its salts using suitable deprotecting agents.

Wherein suitable nitrogen protecting agent is selecting from pivaloyl chloride, benzyloxycarbonyl chloride, trimethylsilyethoxymethyl chloride, acetyl chloride, trimethyl silyl chloride, trimethylsilyethoxymethyl chloride, di-tert-butyl dicarbonate, t-butoxycarbonyl chloride; base in step-a) and b) is defined above; deprotecting agent is selected from acid or base as defined above.

The process according to the above embodiments of the present invention is depicted in scheme-2 as follows:



Scheme-2.

The compound of formula-1 or its pharmaceutically acceptable salts produced by the processes of the present invention can be further micronized or milled to get desired particle sizes to achieve desired solubility profile based on different forms of pharmaceutical composition requirements. Techniques that may be used for particle size reduction include but not limited to a single or multi-stage micronization using cutting mills, pin/cage mills, hammer mills, jet mills, fluidized bed jet mills, ball mills and roller mills. Milling or micronization may be performed before drying or after drying of the product.

An embodiment of the present invention provides the use of Belumosudil or its salts of the present invention for the preparation of various pharmaceutical formulations.

Another embodiment of the present invention provides pharmaceutical composition comprising Belumosudil or its salts and their polymorphs or mixture thereof obtained according to the present invention and at least one pharmaceutically acceptable excipient.

As used herein, the term "pharmaceutical compositions" or "pharmaceutical formulations" include tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

The term “pharmaceutically acceptable excipients” selected from but not limited to binders, diluents, disintegrants, surfactants and lubricants. Suitable binders that can be include polyvinylpyrolidone, copovidone, starches such as pregelatinized starch, cellulose derivatives such as hydroxypropylmethyl cellulose, ethylcellulose, hydroxypropylcellulose and carboxymethylcellulose, gelatine, acacia, agar, alginic acid, carbomer, chitosan, dextrates, cyclodextrin, dextrin, glycerol dibehenate, guargum, hypromellose, maltodextrin, poloxamer, polycarbophil, polydextrose, polyethylene oxide, polymethacrylates, sodium alginate, sucrose, mixtures thereof; suitable diluents that can be include anhydrous lactose, lactose monohydrate, modified lactose, dibasic calcium phosphate, tribasic calcium phosphate, microcrystalline cellulose, silicified microcrystalline cellulose, powdered cellulose, maize starch, pregelatinized starch, calcium carbonate, sucrose, glucose, dextrates, dextrins, dextrose, fructose, lactitol, mannitol, sorbitol starch, calcium lactate or mixtures thereof; suitable disintegrants that can be include magnesium aluminometa silicate (or magnesium aluminum silicate), starch, pregelatinized starch, sodium starch glycolate, crospovidone, croscarmellose sodium, low-substituted hydroxypropyl cellulose, alginic acid, carboxy methyl cellulose sodium, sodium alginate, calcium alginate and chitosan; suitable lubricants that can be include (but are not limited to) magnesium stearate, stearic acid, palmitic acid, talc, and aerosil. Suitable surfactants that can be include (but are not limited to) polysorbate 80, polyoxyethylene sorbitan, polyoxyethylene-polyoxy-propylene copolymer and sodium lauryl sulphate; beta-cyclodextrin include (but are not limited to) sulfobutylalkyl ether-beta-cyclodextrin, betadex-sulfobutylether sodium, or hydroxypropyl-beta-cyclodextrin.

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

Examples:

Example-1: Preparation of 2-(3-formylphenoxy)-N-isopropylacetamide of formula-3

Potassium carbonate (45.26 g) added to the mixture of 3-hydroxybenzaldehyde (20 g) and acetonitrile (200 ml) at 25-30°C and stirred at the same temperature. 2-chloro-N-isopropylacetamide (26.6 g) and potassium iodide (5.43 g) were added to the mixture at 25-30°C, heated to 80-85°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C and water added. Separated the both organic and aqueous layers and aqueous layer is extracted with ethyl acetate. Combined the organic layers, washed with aqueous sodium chloride solution. Distilled off the solvent completely from organic layer to get the title compound.

Yield: 35 g.

Example-2: Preparation of N-isopropyl-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl) phenoxy)acetamide formula-4

2-(3-formylphenoxy)-N-isopropylacetamide (17.07 g) and copper (II) chloride dihydrate (25.06 g) were added to the solution of 2-aminobenzamide (10 g) in ethanol (50 ml) at 25-30°C. Heated the reaction mixture to 80-85°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C and quenched into water. Filtered the precipitated solid and washed with water. Slurried the obtained compound in water. Filtered the solid, washed with water and dried to get the title compound.

Yield: 21 g.

Example-3: Preparation of 2-(3-(4-chloroquinazolin-2-yl)phenoxy)-N-isopropylacetamide formula-5

Thionyl chloride (15 ml) was slowly added to the pre-cooled mixture of N-isopropyl-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)phenoxy)acetamide (10 g) and

dimethylformamide (160 ml) at 0-5°C, raised the temperature to 25-30°C and stirred at the same temperature. Reaction mixture was poured into water at 25-30°C and stirred at the same temperature. Methyl tertiary butyl ether was added to the mixture and separated the both organic and aqueous layers. Filtered the solid, washed with methyl tertiary butyl ether and dried to get the title compound.

Yield: 4.6 g

Example-4: Preparation of 2-(3-hydroxyphenyl) quinazolin-4(3H)-one formula-11

2-aminobenzamide (150 g) followed by Cupper chloride dihydrate (383 g) was added to the solution of 3-hydroxybenzaldehyde (137.2 g) in ethanol (3000 ml) at 25-30°C and stirred. Heated the reaction mixture to 75-80°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C and poured the reaction mixture into chilled water at 0-5°C and stirred at the same temperature. Filtered the solid and washed with water. Obtained compound was slurried in water, filtered and washed with methyl tertiary butyl ether. Dried the obtained compound to get the title compound.

Yield: 369 g.

Example-5: Preparation of 3-(4-oxo-3,4-dihydroquinazolin-2-yl)phenyl acetate formula 12

Acetic anhydride (1950 ml) added to the pre-cooled mixture of 2-(3-hydroxyphenyl) quinazolin-4(3H)-one (150 g) and pyridine (210 ml) at 0-5°C and stirred. Heated the reaction mixture to 105-110°C and stirred at the same temperature. Cooled the reaction mixture. Poured the reaction mixture into pre-cooled water at 0-5°C, raised the temperature to 25-30°C and stirred at the same temperature. Filtered the solid and washed with of water. The obtained compound slurried in the mixture of n-heptane and methyl tertiary butyl ether at 25-30°C. Filtered the solid, washed with mixture of n-heptane and methyl tertiary butyl ether and dried to get the title compound.

Yield: 164 g.

Example-6: Preparation of 3-(4-chloroquinazolin-2-yl)phenyl acetate formula 13

Dimethyl formamide (6.25 ml) added to the mixture of 3-(4-oxo-3,4-dihydroquinazolin-2-yl)phenyl acetate (25 g) and thionyl chloride (75 ml) at 25-30°C and stirred. Heated the reaction mixture to 65-70°C and stirred at the same temperature. Distilled off the reaction mixture and co-distilled with toluene. Dichloromethane added to obtained compound at 25-30°C and cooled to 0-5°C. Obtained solution washed with aqueous sodium bicarbonate solution and followed by with aqueous sodium chloride solution. Distilled off the solvent completely from the organic layer. The obtained compound slurried in methyl tertiary butyl ether to get the title compound.

Yield: 12.5 g.

Example-7: Preparation of tert-butyl 5-((2-(3-acetoxyphenyl)quinazolin-4-yl)amino)-1*H*-indazole-1-carboxylate formula 14a

Tert-butyl 5-amino-*1H*-indazole-1-carboxylate (7.8 g) was added to the mixture of 3-(4-chloroquinazolin-2-yl)phenyl acetate (10 g) and isopropanol (300 ml) at 25-30°C. Heated the reaction mixture to 85-90°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C and stirred at the same temperature. Filtered the solid, washed with isopropanol and dried to get the title compound.

Yield: 14.7 g.

Example-8: Preparation of tert-butyl 5-((2-(3-hydroxyphenyl)quinazolin-4-yl)amino)-1H-indazole-1- carboxylate formula 15a

Aqueous ammonia (30 ml) added to the solution of tert-butyl 5-((2-(3-acetoxyphenyl)quinazolin-4-yl)amino)-1H-indazole-1-carboxylate (10 g) in methanol (700 ml) at 25-30°C and stirred at the same temperature. Filtered the solid, washed with water and dried to get the title compound.

Yield: 3.7 g.

Example-9: Preparation of 2-chloro-N-isopropylacetamide

Potassium carbonate (105.2 g) added to the mixture of propane-2-amine (25.0 g) and dichloromethane (50.0 ml) at 25-30°C and cooled to 0-10°C. 2-chloroacetyl chloride

(50.4 ml) in dichloromethane (50.0 ml) was slowly added to the above mixture at 0-10°C, raised the temperature to 25-30°C and stirred at the same temperature. Water and ethyl acetate were added to it, separated both the organic and aqueous layers. The aqueous layer was extracted with ethyl acetate. Combined the organic layers, washed with aqueous sodium bicarbonate solution and followed by with aqueous sodium chloride solution. Distilled off the solvent from the organic layer to get the title compound.

Yield: 47 g

Example-10: Preparation of 2-iodo-N-isopropylacetamide formula 16a

Potassium iodide (110.2 g) added to the solution of 2-chloro-N-isopropylacetamide (90.0 g) in dimethylformamide (450.0 ml) at 25-30°C and stirred at the same temperature. Water added to the reaction mixture. Separated both the organic and aqueous layers. The aqueous layer was extracted with methyl tertiary butyl ether and combined the organic layers. Organic layer washed with aqueous sodium bisulfate solution and followed by with aqueous sodium chloride solution. Distilled off the solvent completely from the organic layer to get the title compound.

Yield: 66 g.

Example-11: Preparation of tert-butyl 5-((2-(3-(2-(isopropylamino)-2-oxoethoxy)phenyl)quinazolin-4- yl)amino)-1H-indazole-1-carboxylate formula 7a [P=Boc in Formula 7]

Potassium carbonate (24.37 g) added to the mixture of tert-butyl 5-((2-(3-hydroxyphenyl)quinazolin-4-yl)amino)-1H-indazole-1- carboxylate (20 g) in dimethylformamide (200 ml) at 25-30°C and stirred. 2-iodo-N-isopropylacetamide (13.01 g) in dimethylformamide (40 ml) was added to the above mixture at 25-30°C and stirred at the same temperature. Poured the reaction mixture into water at 25-30°C and stirred. Filtered the solid and washed with water. Methanol (40 ml) added to the obtained solid at 25-30°C and stirred at the same temperature. Filtered the solid, washed with methanol and dried to get the title compound.

Yield: 17 g

Example-12: Preparation of 2-(3-(4-((1H-indazol-5-yl)amino)quinazolin-2-yl)phenoxy)-N-isopropylacetamide formula 1

Hydrochloric acid (36.0 ml) added to the mixture of tert-butyl 5-((2-(3-(2-(isopropylamino)-2-oxoethoxy)phenyl)quinazolin-4-yl)amino)-1H -indazole-1-carboxylate (12.0 g) and acetonitrile (60.0 ml) at 25-30°C and stirred at the same temperature. Acetonitrile (36 ml) added to the above reaction mixture. Filtered the solid and washed with acetonitrile. Water added to the obtained compound at 25-30°C and basified using aqueous sodium hydroxide solution. Filtered the compound and washed with water. Obtained compound slurried in acetonitrile to get the title compound.

Yield: 8.2 g.

Example-13: Preparation of Belumosudil mesylate formula 1a

Methane sulfonic acid (0.31 ml) in ethanol (3.4 ml) added to the mixture of 2-(3-(4-((1H-indazol-5-yl)amino)quinazolin-2-yl)phenoxy)-N-isopropylacetamide (2.0 g) and ethanol (40.0 ml) at 25-30°C, heated to 45-55°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C and stirred. Filtered the solid and washed with ethanol. Obtained compound slurried in ethanol and dried to get the title compound.

Yield: 1.2 g

Example-14: Preparation of Belumosudil mesylate formula 1a

Methane sulfonic acid (0.31 ml) in isopropyl alcohol (3.1 ml) added to the mixture of 2-(3-(4-((1H-indazol-5-yl)amino)quinazolin-2-yl)phenoxy)-N-isopropylacetamide (2.0 g) and Isopropanol (40.0 ml) at 25-30°C, heated to 50-55°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C, filtered the solid and washed with isopropanol. Obtained compound slurried in isopropanol to get the title compound.

Yield: 1.32 g

Example-15: Preparation of 2-iodo-N-isopropylacetamide formula 16a

Potassium carbonate (350.70 g) added to the pre-cooled solution of propane-2-amine

(100 g) in toluene (300 ml) at 0-10°C. 2-Chloroacetyl chloride (175 ml) in toluene (400 ml) was slowly added to the above mixture at -5°Cto 5°C, raised the temperature to 25-30°C and stirred at the same temperature. Cooled the reaction mixture to 0-10°C and quenched it with pre-cooled water. Raised the reaction mixture temperature to 25-30°C, separated both the organic and aqueous layers. The aqueous layer extracted with toluene and combined the organic layers. Dimethylformamide (50 ml) and potassium iodide (337 g) added to the organic layer at 25-30°C. Heated the reaction mixture to 65-70°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C, water added to the reaction mixture. Basified the mixture with aqueous sodium carbonate solution. Separated both the organic and aqueous layers. Aqueous layer was extracted with ethyl acetate. Combined the organic layers, washed with aqueous sodium bisulfate solution and followed by with aqueous sodium chloride solution. Distilled off the solvent completely from the organic layer and co-distilled with methyl tertiary butyl ether. The obtained compound was recrystallized using methyl tertiary butyl ether and dried to get the title compound.

Yield: 225.02 g.

Example-16: Preparation of 2-(3-hydroxyphenyl) quinazolin-4(3H)-one formula 11

Ferric chloride (178.8 g) was slowly added into two equal lots to the mixture of 2-aminobenzamide (100 g), 3-hydroxybenzaldehyde (94.2 g) and water (1000 ml) at 25-30°C and stirred at the same temperature. Heated the reaction mixture to 95-105°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C. Added the mixture of water and isopropyl alcohol to the above reaction mixture at 25-30°C and stirred at the same temperature. Filtered the precipitated solid and washed with the mixture of water and isopropyl alcohol. Dried the obtained compound to get the title compound.

Example-17: Preparation of 3-(4-oxo-3,4-dihydroquinazolin-2-yl)phenyl acetate formula 12

Diisopropylethyl amine (338.0 ml) was added to the mixture of compound obtained in example-16 and toluene (500 ml) at 25-30°C. The mixture of acetic anhydride (104.1 ml) and toluene (200 ml) was added to the above reaction mixture at 25-30°C and stirred at the same temperature. Heated the reaction mixture to 40-50°C and stirred at the same temperature. Isopropyl alcohol (300 ml) was added to it at 40-50°C and stirred at the same temperature. Filtered the solid, washed with isopropyl alcohol and dried to get the title compound.

Yield: 155 g.

Example-18: Preparation of 3-(4-chloroquinazolin-2-yl)phenyl acetate formula 13

Dimethyl formamide (33 ml), oxalyl chloride (100.97 ml) in dichloromethane (220 ml) were slowly added to the pre cooled mixture of 3-(4-oxo-3,4-dihydroquinazolin-2-yl)phenyl acetate (110 g) and dichloromethane (550 ml) at 5-10°C. Raised the reaction mixture temperature to 25-30°C and stirred at the same temperature. Poured the reaction mixture into chilled water at 0-5°C and stirred at the same temperature. Raised the temperature to 25-30°C and stirred at the same temperature. Separated both the organic and aqueous layers. The aqueous layer was extracted with dichloromethane. Combined the organic layers, washed with aqueous sodium chloride solution, followed by with aqueous sodium bicarbonate solution and followed by with water. Distilled off the solvent from the organic layer and co-distilled with isopropyl alcohol. Obtained compound slurried in isopropyl alcohol, filtered and dried to get the title compound.

Yield: 100.5 g.

Example-19: Preparation of tert-butyl 5-amino-1H-indazole-1-carboxylate

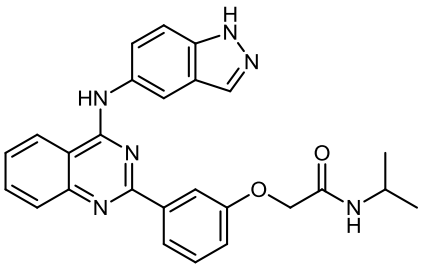
Di-tert-butyl dicarbonate (169 ml) in toluene (100 ml) added to the mixture of 5-nitro-1H-indazole(100 g), dimethylamino pyridine(11.23 g) and toluene(600 ml) at 25-30°C and stirred at the same temperature. Water added into the reaction mixture separated both the organic and aqueous layers. The aqueous layer was extracted with toluene. Combined the organic layers, washed with aqueous acetic acid solution and

followed by with aqueous sodium chloride solution. Distilled off the solvent from the organic layer and co distilled with isopropyl alcohol. The obtained compound dissolved in isopropyl alcohol (2560 ml) at 25-30°C in autoclave. Raney nickel (64.0 g) added to the reaction mixture and followed by applied hydrogen gas pressure at 25-30°C. Heated the reaction mixture to 50-55°C and stirred at the same temperature. Filtered the reaction mixture through hyflow bed and washed with isopropyl alcohol. Distilled off the solvent completely under vacuum. To the obtained residue, isopropyl alcohol (160 ml) added at 25-30°C and stirred at the same temperature. n-Heptane (640 ml) added to the mixture at 25-30°C and stirred at the same temperature. Filtered the solid, washed with n-heptane and dried to get the title compound.

Yield: 92.2 g.

We claim:

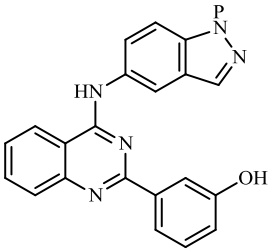
1. A process for the preparation of Belumosudil formula-1 or its salts



Formula-1.

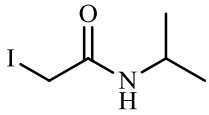
comprising:

a) reacting compound of formula 15



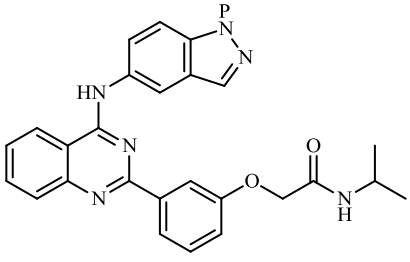
Formula-15

with 2-iodo-N-isopropylacetamide of formula 16a



Formula-16a

in the presence of a base in a solvent to provide compound of formula-7,



Formula-7

wherein P is nitrogen protecting group

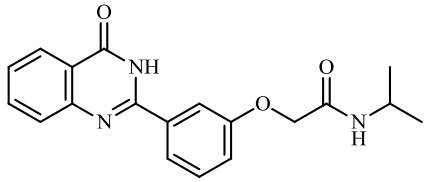
b) deprotecting the nitrogen protecting group of compound of formula-7 with acid or base in a solvent to provide compound of formula-1 or its salts.

2. The process as claimed in claim 1, wherein Base is selected from inorganic bases selected from “alkali metal carbonates” such as sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate and the like; “alkali metal bicarbonates” such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, cesium bicarbonate and the like; “alkali metal hydroxides” such as sodium hydroxide, potassium hydroxide, lithium hydroxide and the like; “alkyl metals” such as n-butyl lithium and like; “metal hydrides” such as lithium hydride, sodium hydride, potassium hydride and the like; “alkali metal phosphates” such as disodium hydrogen phosphate, dipotassium hydrogen phosphate; ammonia such as aqueous ammonia, ammonia gas, methanolic ammonia and like and “organic bases” selected from but not limited to methyl amine, ethyl amine, diisopropyl amine, diisopropylethyl amine (DIPEA), diisobutylamine, triethylamine, tert.butyl amine, pyridine, 4-dimethylaminopyridine (DMAP), N-methyl morpholine (NMM), N-methyl pyridine (NMP), N-methyl piperazine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0] non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO), imidazole; “alkalimetal alkoxides” such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, sodium tert.butoxide, potassium tert.butoxide and the like; “alkali metal amides” such as sodium amide, potassium amide, lithium amide, lithiumdiisopropyl amide (LDA), sodium bis(trimethylsilyl) amide (NaHMDS), potassiumbis(trimethylsilyl)amide, lithium bis(trimethysilyl) amide (LiHMDS) and the like; or mixtures thereof; solvent is selected from alcohol solvents, chloro solvents, ester solvents, ketone solvents, ether solvents, hydrocarbon solvents, nitrile solvents, polar aprotic solvents, and polar solvents such as water.

3. The process as claimed in claim 1, wherein nitrogen protecting group is selected from pivaloyl, pyrrolidinylmethyl, t-butoxycarbonyl, benzyl, silyl (such as TES),

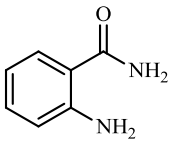
acetyl, benzyloxycarbonyl (Cbz) and trimethylsilyethoxymethyl (SEM).

4. A process for the preparation of N-isopropyl-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)phenoxy) acetamide formula 4



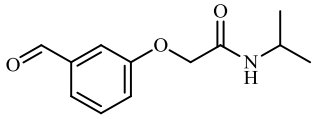
Formula-4

comprising reacting 2-aminobenzamide of formula-2



Formula-2

with 2-(3-formylphenoxy)-N-isopropylacetamide of formula-3

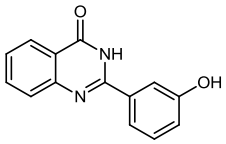


Formula-3

in the presence of cyclizing agent in a solvent.

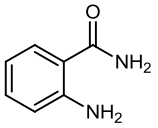
5. The process as claimed in claim 4, wherein cyclizing agent selected from copper(II) chloride dihydrate, copper (II) bromide, Iodine, iodine/potassium iodide, sodium bisulfate; solvent is selected from alcohol solvents, chloro solvents, ester solvents, ketone solvents, ether solvents, hydrocarbon solvents, nitrile solvents, polar aprotic solvents, and polar solvents such as water; nitrogen protecting group is selected from pivaloyl, pyrrolidinylmethyl, t-butoxycarbonyl, benzyl, silyl (such as TES), acetyl, benzyloxycarbonyl (Cbz) and trimethylsilyethoxymethyl (SEM).

6. A process for the preparation of 2-(3-hydroxyphenyl)quinazolin-4(3H)-one formula-11

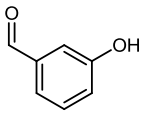


Formula-11

comprising reacting 2-aminobenzamide formula 9 with 3-hydroxybenzaldehyde formula 10



Formula-9

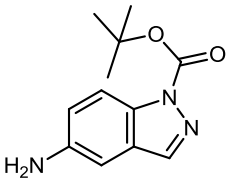


Formula-10

in the presence of iron chloride, optionally in presence of a solvent.

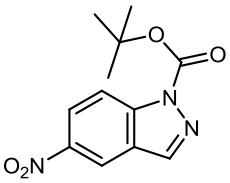
7. The process as claimed in claim 6, wherein solvent is selected from solvent is selected from alcohol solvents, polar aprotic solvents, water or mixture thereof.

8. A process for the preparation of tert-butyl 5-amino-1H-indazole-1-carboxylate formula 6a



Formula-6a

comprising reducing tert-butyl 5-nitro-1H-indazole-1-carboxylate formula-17a



Formula-17a

in presence of Raney Nickel and hydrogen in a solvent to provide tert-butyl 5-amino-1H-indazole-1-carboxylate formula 6a.

9. The process as claimed in claim 8, wherein selected is from alcohol solvents, chloro solvents, ester solvents, ketone solvents, ether solvents, hydrocarbon solvents, nitrile solvents, polar aprotic solvents, and polar solvents such as water.

Dated this day 23rd day of August 2023.

Authorized Signatory

(Srinivasan Thirumalai Rajan)

Head-IPM and Technical

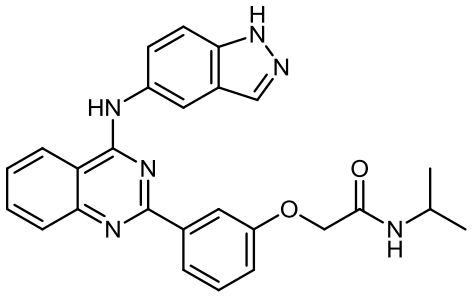
MSN Laboratories Private Limited, R&D Center.

****

Abstract

Title: A process for the preparation of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide or its salts

The present application relates to a process for the preparation of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-N-(propan-2-yl) acetamide represented by the following structural formula-1, which is referred to as Belumosudil. The present invention also provides a process for the preparation of salts of Belumosudil.



Formula-1.