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

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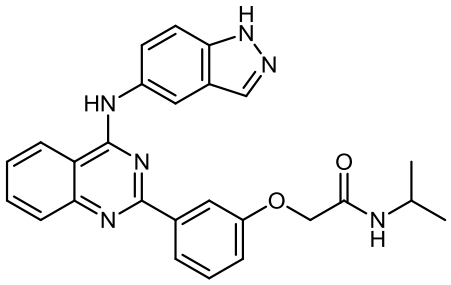
A process for the preparation of 2-{3-[4-(1H-indazol-5-ylamino)-2-quinazolinyl] phenoxy}-N-(propan-2-yl) acetamide and its salts

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 and its intermediate preparation thereof.

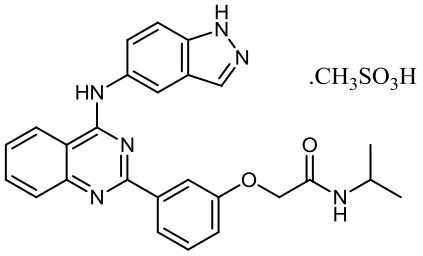


Formula-1.

The present application also relates to novel crystalline forms of Belumosudil, its mesylate and its intermediate and preparation thereof.

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 with the brand name of Rezurock®.



Formula-1a .

US. Patent number 8357693 describes certain methods for making Belumosudil or its salts and intermediates. The said patent discloses deprotection of tert-butyl 5-((2-(3-(2-(isopropylamino)-2-oxoethoxy)phenyl)quinazolin-4- yl)amino)-1H-indazole-1-carboxylate using trifluoro acetic acid.

IPCOM000270633D describes the deprotection of tert-butyl 5-((2-(3-(2-(isopropylamino)-2-oxoethoxy)phenyl)quinazolin-4- yl)amino)-1H-indazole-1-carboxylate using methanesulfonic acid in methanol to provide Belumosudil mesylate with HPLC purity of > 95%.

PCT Publication No. WO2022020850A1 describes various crystalline and amorphous forms of Belumosudil and its salts.

There is a still develop further solid state forms or polymorphs of Belumosudil mesylate to meet the pharmaceuticals requirements.

Since the development of new polymorphic forms of an active pharmaceutical ingredient provides new opportunity to improve the performance characteristics of pharmaceutical finished product, the development of new polymorphic forms is always encouraged.

Furthermore, solid state study of an active pharmaceutical ingredient aims to widen the variety of polymorphs that a formulation scientist has available for designing a pharmaceutical dosage form with desired characteristics.

The present inventors after significant efforts have surprisingly found crystalline form of Belumosudil mesylate which are useful for the preparation of various pharmaceutical compositions.

Brief Description of the Drawings:

Figure-1: Illustrates the PXRD pattern compound of formula-2 obtained in example-1.

Figure-2: Illustrates the PXRD pattern compound of formula-2 obtained in example-2.

Figure-3: Illustrates the PXRD pattern crystalline form-S of Belumosudil Mesylate of formula-1a.

Figure-4: Illustrates the PXRD pattern crystalline form-S of Belumosudil of formula-1.

Figure-5: Illustrates the PXRD pattern crystalline form of Belumosudil mesylate obtained according to example-12.

Figure-6: Illustrates the PXRD pattern amorphous form of Belumosudil mesylate obtained according to example-13.

Brief summary of the invention:

The first embodiment of the present invention provides Belumosudil of formula-1 or it's pharmaceutically acceptable salts.

The second embodiment of the present invention provides a process for the preparation of Belumosudil of formula-1 or it's pharmaceutically acceptable salts.

Third embodiment of the present invention provides a process for the purification of tert-butyl 5-((2-(3-(2-(isopropylamino)-2-oxoethoxy) phenyl) quinazolin-4- yl)amino)-1H-indazole-1-carboxylate of formula-2 .

Fourth embodiment of the present invention provides a novel crystalline form of Belumosudil mesylate of formula-1a, herein after designated as crystalline form-S and its process for the preparation.

Fifth embodiment of the present invention provides a novel crystalline form of Belumosudil of formula-1, herein after designated as crystalline form-S.

Sixth embodiment of the present invention provides a process for the preparation of crystalline form of Belumosudil mesylate.

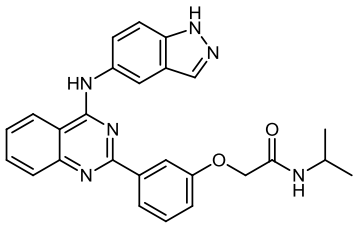
Detailed description of the Invention:

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 pharmaceutically acceptable salts of present invention include the conventional nontoxic salts or quaternary ammonium salts of the compounds, e.g., from non-toxic organic or inorganic acids. For example, Such conventional nontoxic salts include those derived from inorganic acids such as hydrochloride, hydrobromic, Sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicyclic, sulfanilic, 2-acetoxybenzoic, fumaric, toluene-sulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic and the like.

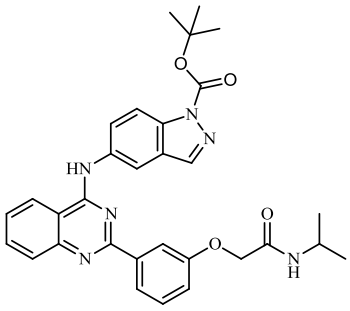
First embodiment, the present invention provides Belumosudil of formula-1 or

it’s pharmaceutically acceptable salts.



Formula-1.

Second embodiment, the present invention provides a process for the preparation of Belumosudil or it’s pharmaceutically acceptable salts of formula-1 comprising de-protecting the tert-butyl 5-((2-(3-(2-(isopropylamino)-2-oxoethoxy) phenyl)quinazolin-4- yl)amino)-1H-indazole-1-carboxylate of formula-2



Formula-2

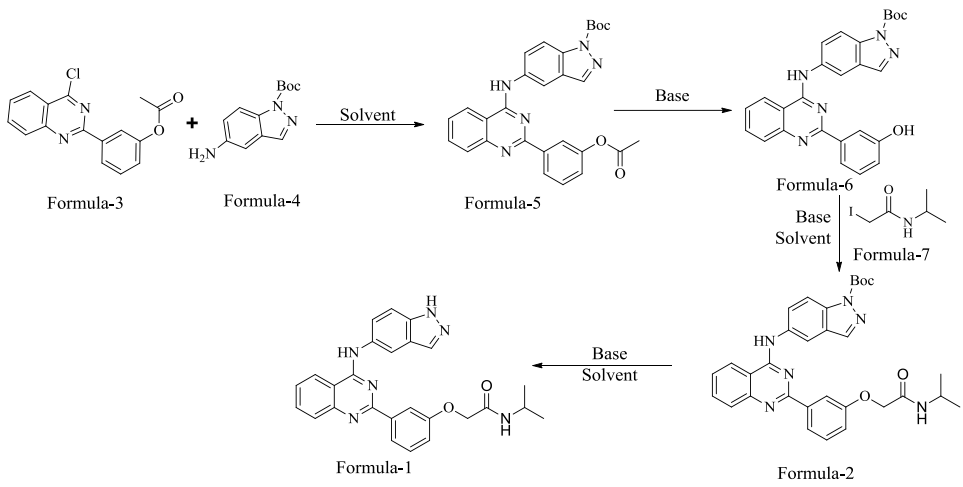
in the absence of an acid to provide Belumosudil of fromula-1 or it’s pharmaceutically acceptable salts.

The first aspect of the second embodiment, wherein deprotection carried out by using organic base or inorganic base optionally in presence of a solvent.

The second aspect of the second embodiment, wherein “organic base” used in the present invention selected from but not limited to methyl amine, ethyl amine, diisopropyl amine, diisopropylethyl amine (DIPEA), diisobutylamine, triethylamine, tert.butyl amine, pentylamine, dibutylamine, pyridine, cyclohexylamine, cyclopentylamine, 4-dimethylaminopyridine (DMAP), N-methyl morpholine (NMM), N-methyl pyridine (NMP), piperazine, N-methyl piperazine, 1,8-

diazabicyclo[5.4.0]undec-7-ene (DBU), morpholine, 1,5-diazabicyclo[4.3.0] non-5-ene (DBN), 1,4-diazabicyclo [2.2.2]octane (DABCO), imidazole, 2-methoxy propyl amine; inorganic base is 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 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.

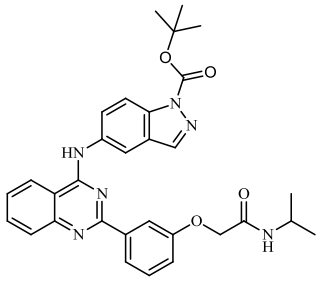
The present invention is depicted in the following scheme-1:



Scheme-1

Tert-butyl 5-((2-(3-hydroxyphenyl)quinazolin-4-yl)amino)-1H-indazole-1-carboxylate, 3-(4-chloroquinazolin-2-yl) phenyl acetate, tert-butyl 5-amino-1H-indazole-1-carboxylate and 2-iodo-N-isopropylacetamide used as an input in the present application obtained according to the process described in our co-pending application IN202241047970 or by the process described in the literature or within the common general knowledge of person skilled in art.

Third embodiment of the present invention a process for the purification of tert-butyl 5-((2-(3-(2-(isopropylamino)-2-oxoethoxy)phenyl)quinazolin-4- yl)amino)-1H-indazole-1-carboxylate of formula-2



Formula-2

comprising the following steps:

a) dissolving or suspending the compound of formula-2 in solvent or mixture of solvents,

b) isolating the pure compound of formula-2.

Solvent in step-a) and step-b) 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; isolating the compound of formula-2 in step-b) refers to the compound obtained can be isolated by one or more of filtration, filtration under vacuum, evaporation or distillation, decantation, or by adding a suitable anti-solvent or also can be isolated upon cooling.

An aspect of the third embodiment, wherein the tert-butyl 5-((2-(3-(2-(isopropylamino)-2-oxoethoxy) phenyl)quinazolin-4- yl)amino)-1H-indazole-1-carboxylate of formula-2 having purity of greater than about 99% by HPLC.

Fourth embodiment of the present invention provides a novel crystalline form of Belumosudil mesylate of formula-1a, herein after the said crystalline form is designated as crystalline form-S.

The first aspect of fourth embodiment provides the crystalline form-S of Belumosudil mesylate characterized by its powder X-Ray diffractogram illustrated in

figure-3.

The second aspect of the fourth embodiment, the present invention provides process for the preparation of crystalline form-S of Belumosudil mesylate, comprising:

a) dissolving or suspending Belumosudil mesylate of formula-1a in solvent or mixture of solvents,

b) isolating crystalline form-S of Belumosudil mesylate.

wherein the solvent in step-a) is selected from water, chloro solvents, alcohol solvents, ether solvent, ketone solvents, ester solvents and/or mixtures thereof; isolating crystalline form-S of Belumosudil mesylate in step-b) is by solvent removal by known techniques which are selected from distillation, decanting, filtration, cooling the mixture to lower temperatures to precipitate the solid followed by filtration of the mixture, crystallization or by combining with an anti-solvent.

Fifth embodiment of the present invention provides a novel crystalline form of Belumosudil of formula-1, herein after designated as crystalline form-S and its process for the preparation.

The first aspect of fifth embodiment provides the crystalline form-S of Belumosudil of formula-1 characterized by its powder X-Ray diffractogram illustrated in figure-4.

Sixth embodiment of the present invention provides a process for the preparation of crystalline form of Belumosudil mesylate comprises:

a) suspending Belumosudil mesylate in paraffin oil,

b) isolating crystalline form of Belumosudil mesylate,

wherein suspending Belumosudl mesylate in paraffin oil at a temperature about 170°C to 220°C; isolating crystalline form of Belumosudil mesylate in step-b) is by solvent removal by known techniques which are selected from, concentrating, filtration, cooling the mixture to lower temperatures followed by filtration of the

mixture, or by combining with a second solvent which is selected from “hydrocarbon solvent” is selected from n-pentane, n-hexane, n-heptane, cyclohexane, petroleum ether, benzene, toluene, xylene and mixtures thereof;

First aspect of the sixth embodiment, wherein the crystalline form of Belumosudil mesylate PXRD pattern is depicted in figure-5.

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.

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

Eighth 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 tert-butyl 5-((2-(3-(2-(isopropylamino)-2-oxoethoxy) phenyl)quinazolin-4- yl)amino)-1H-indazole-1-carboxylate of formula-2

A solution of 2-iodo-N-isopropylacetamide (175.2 g) in acetonitrile (2000 ml) added to mixture of tert-butyl 5-((2-(3-hydroxyphenyl)quinazolin-4-yl)amino)-1H-indazole-1- carboxylate (250 g), acetonitrile (3000 ml) and potassium carbonate (304.7 g) at 25-30°C, heated to 85-90°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C and stirred at the same temperature. Water added to the reaction mixture at 25-30°C and stirred at the same temperature. Filtered the solid, washed with water and dried to get the title compound. Slurried the obtained compound in the mixture of methanol (62.5 ml) and dichloromethane (1187.5 ml). Filtered the solid, washed with mixture of methanol and dichloromethane. Acetonitrile (1250 ml) added to the above obtained compound at 25-30°C, stirred at the same temperature. Distilled off the organic solvent to get the title compound.

PXRD pattern of the obtained compound is depicted in the figure-1.

Example-2: Purification of tert-butyl 5-((2-(3-(2-(isopropylamino)-2-oxoethoxy) phenyl)quinazolin-4- yl)amino)-1H-indazole-1-carboxylate of formula-2

Slurried the compound obtained in example-1 in the mixture of methanol (62.5 ml) and dichloromethane (1187.5 ml) at 25-30°C and filtered the solid, washed with mixture of methanol and dichloromethane and dried to get the title compound.

Yield: 193. 0 g; PXRD pattern of the obtained compound is depicted in the figure-2.

Example-3: Preparation of Belumosudil

A mixture of tert-butyl 5-((2-(3-(2-(isopropylamino)-2-oxoethoxy)phenyl)quinazolin-4- yl)amino)-1H-indazole-1-carboxylate (275 g) and N-methyl piperazine (1375 ml) heated to 90-100°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C and stirred at the same temperature. Quenched the mixture into water at 25-30°C and stirred at the same temperature. Filtered the solid and washed with water. Slurried the obtained solid in the mixture of acetonitrile (2750 ml) and water (2750 ml) at 25-30°C, filtered the solid, washed with mixture of acetonitrile and water. Acetonitrile (1275 ml) added to the obtained solid and distilled off solvent completely. Slurried the obtained compound in the mixture of methanol (110 ml) and dichloromethane (2090 ml) at 25-30°C, filtered the solid, washed with mixture of

methanol and dichloromethane and dried to get the title compound.

Yield: 189 g.

Example-4: Preparation of Belumosudil

3-Methoxy propylamine (250 ml) slowly added to the mixture of tert-butyl 5-((2-(3-(2-(isopropylamino)-2-oxoethoxy)phenyl)quinazolin-4- yl)amino)-1H-indazole-1-carboxylate (25 g) and acetonitrile (250 ml) at 25-30°C, heated to 80-90°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C, water added and stirred at the same temperature. Filtered the solid and washed with mixture of acetonitrile and water. Acetonitrile (125 ml) added to the obtained solid and distilled off the solvent completely to get the title compound.

Yield: 17.5 g;

Example-5: Preparation of Belumosudil

Heated the mixture of 3-Methoxy propylamine (15 ml) and tert-butyl 5-((2-(3-(2-(isopropylamino)-2-oxoethoxy)phenyl)quinazolin-4- yl)amino)-1H-indazole-1-carboxylate (3 g)) to 90-100°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C. The water added to the above reaction mixture and stirred at the same temperature. Filtered the solid, washed with water and dried to get the title compound.

Yield: 2.5 g;

Example-6: Preparation of Crystalline form-S of Belumosudil Mesylate

Belumosudil mesylate (17 g) added to 255 ml of water at 25-30°C, heated to 95-100°C and stirred at the same temperature. Cooled the mixture to 45-55°C and stirred at the same temperature. Filtered the solid, washed with water and dried to get the title compound.

Yield: 16 g; PXRD pattern of the obtained compound is depicted in the figure-3.

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

Tert-butyl 5-amino-*1H*-indazole-1-carboxylate (78 g) was added to the mixture of 3-(4-chloroquinazolin-2-yl)phenyl acetate (100 g) and isopropanol (1000 ml) at 25-

30°C. Heated the reaction mixture to 60-70°C and stirred at the same temperature. Methanol (500 ml) added to the reaction mixture at same temperature, heated to 70-80°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 mixture of methanol and isopropanol and dried to get tert-butyl 5-((2-(3-acetoxyphenyl)quinazolin-4-yl)amino)-1H-indazole-1-carboxylate.

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

Aqueous ammonia (1200 ml) added to the pre-cooled mixture of tert-butyl 5-((2-(3-acetoxyphenyl)quinazolin-4-yl)amino)-1H-indazole-1-carboxylate obtained in example-7 and water (500 ml) at 0-10°C and stirred at the same temperature. Isopropanol added to the reaction mixture at 0-10°C and stirred at the same temperature. Raised the reaction mixture temperature to 25-30°C and stirred at the same temperature. Isopropanol added to the reaction mixture at 25-30°C and stirred at the same temperature. Filtered the solid, washed with isopropanol and obtained compound is slurried in isopropanol to get the title compound.

Yield: 113.8 g; Purity by HPLC: 96.20%.

Example-9: Preparation of tert-butyl 5-((2-(3-(2-(isopropylamino)-2-oxoethoxy) phenyl)quinazolin-4- yl)amino)-1H-indazole-1-carboxylate of formula-2

Tert-butyl 5-((2-(3-hydroxyphenyl)quinazolin-4-yl)amino)-1H-indazole-1-carboxylate (100 g) is added to the mixture of 2-iodo-N-isopropylacetamide (70.09 g), acetonitrile (1500 ml) and cesium carbonate (93.40 g) at 25-30°C and stirred at the same temperature. Water added to the reaction mixture at 25-30°C, cooled to 5-15°C and stirred at the same temperature. Filtered the precipitated solid, washed with water and dried to get the title compound.

Yield: 110 g.

Example-10: Purification of tert-butyl 5-((2-(3-(2-(isopropylamino)-2-oxoethoxy) phenyl)quinazolin-4- yl)amino)-1H-indazole-1-carboxylate of formula-2

Recrystallized the obtained compound in example-9 from the mixture of methanol and dichloromethane to get the title compound.

Yield: 85 g.

Example-11: Preparation of Belumosudil

A mixture of tert-butyl 5-((2-(3-(2-(isopropylamino)-2-oxoethoxy)phenyl)quinazolin-4-yl)amino)-1H-indazole-1-carboxylate obtained in example-10, methanol (595 ml) and potassium carbonate (10.6 g) was heated to 45-55°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C, water added to it and stirred at the same temperature. Filtered the solid and washed with water. Slurried the obtained solid in water to get the title compound.

Yield: 63.5 g

Example-12: Preparation of crystalline form of Belumosudil Mesylate

A mixture of Belumosudil mesylate (10 g) and paraffin oil (100 ml), heated to 200-210°C and stirred at the same temperature. Cooled the mixture to 25-30°C, cyclohexane added and stirred at the same temperature. Filtered the solid, washed with cyclohexane and dried to get the title compound.

Yield: 8.5 g; PXRD pattern of the obtained compound is depicted in the figure-5.

Example-13: Preparation of amorphous Belumosudil mesylate

A mixture of Belumosudil (5 g) and paraffin oil (50 ml) heated to 70-75°C and stirred at the same temperature. Methane sulfonic acid (1.16 g) added to the reaction mixture at 70-75°C, heated to 180-185°C and stirred at the same temperature. Cooled the mixture to 25-30°C, cyclohexane added and stirred at the same temperature. Filtered the solid, washed with cyclohexane and dried to get the title compound.

Yield: 5 g; PXRD pattern of the obtained compound is depicted in the figure-6.

Drawings

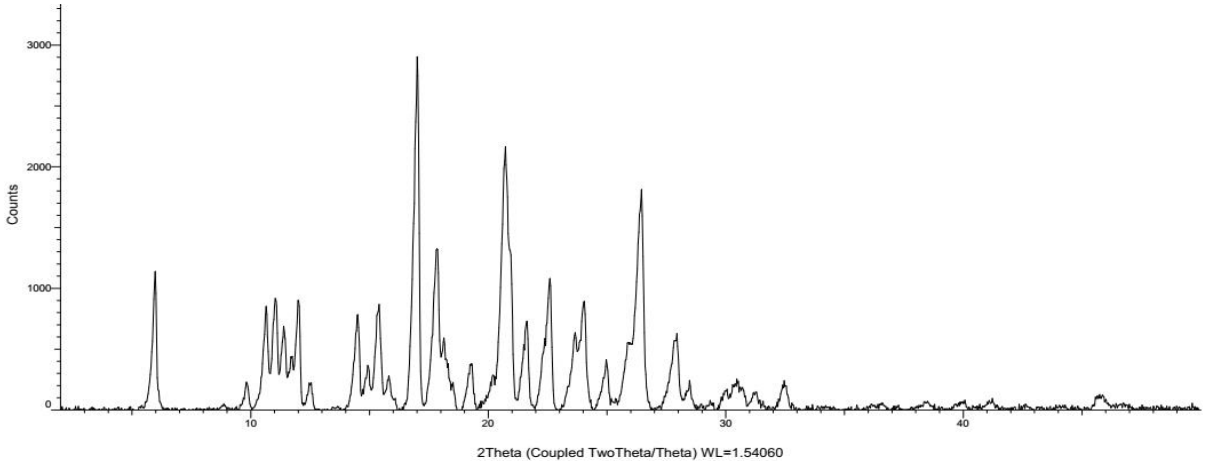


Figure-1

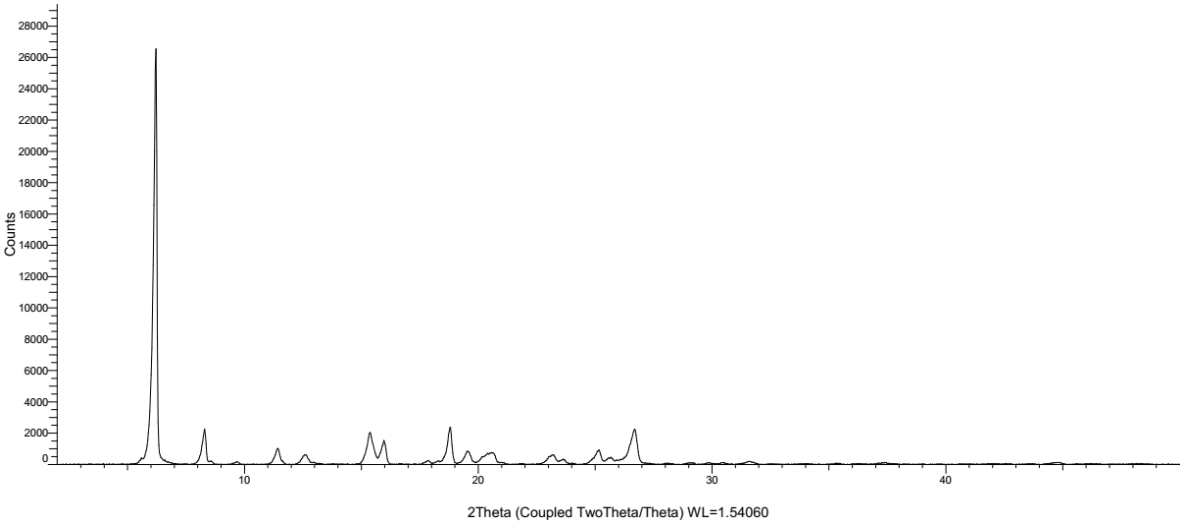


Figure-2

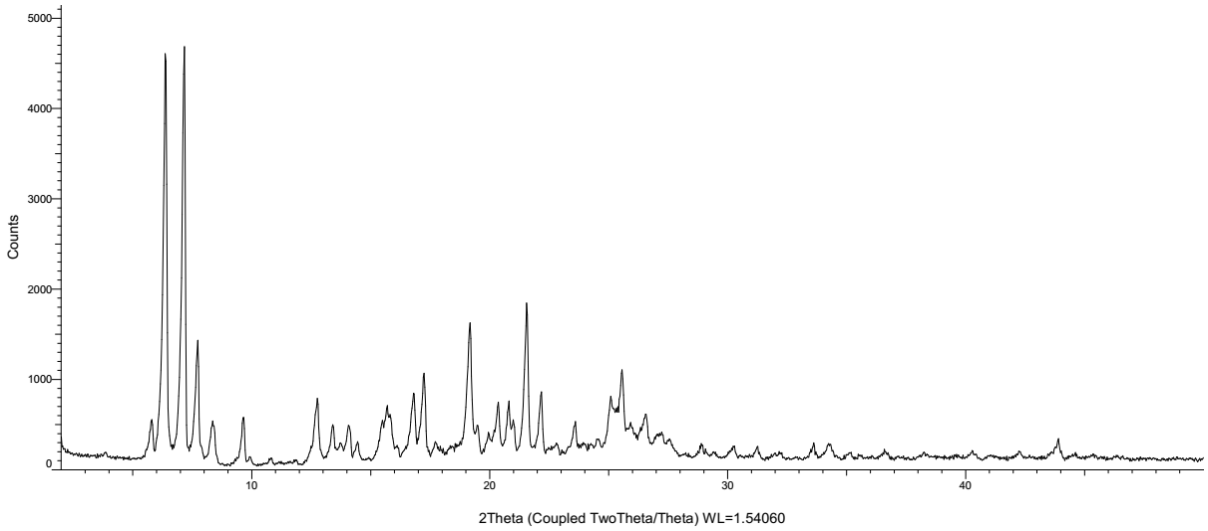


Figure-3

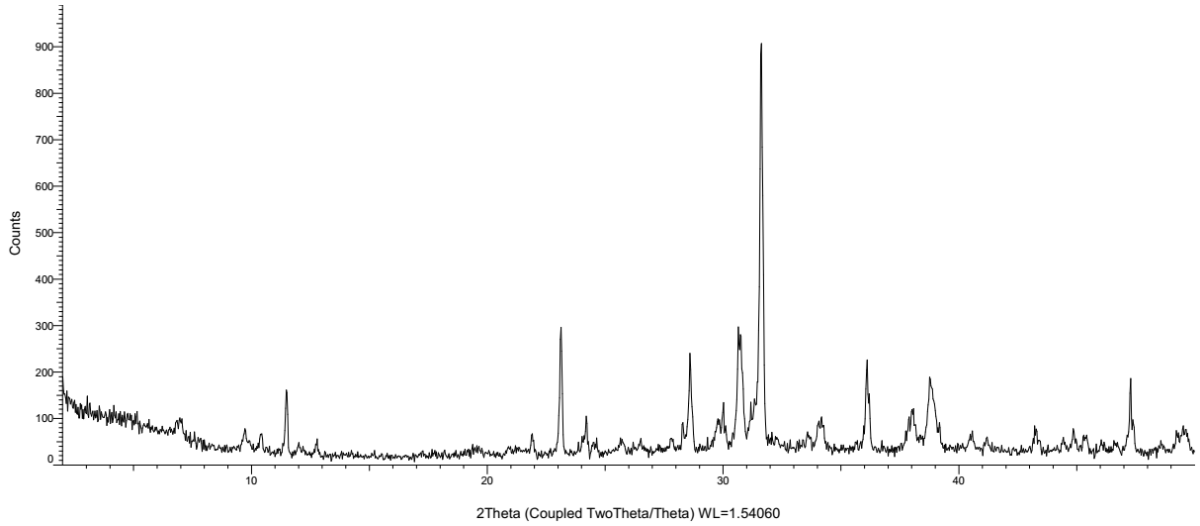


Figure-4

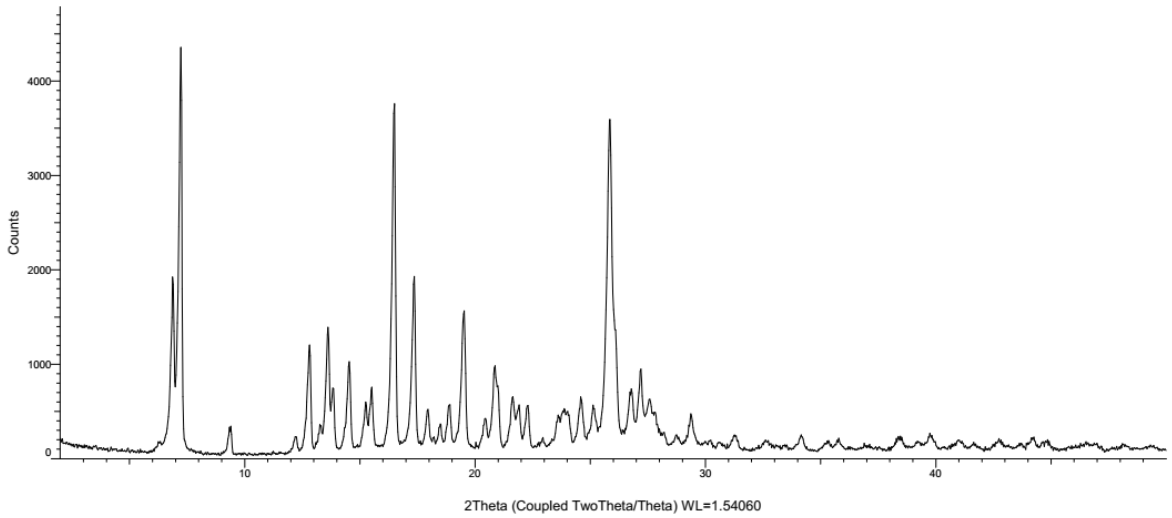


Figure-5

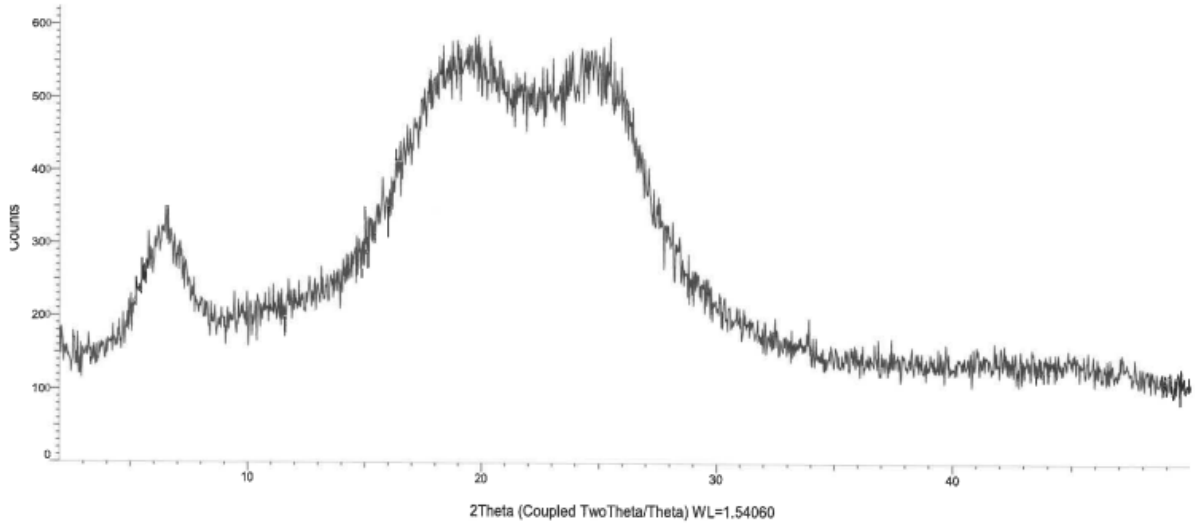


Figure-6

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