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Process for the preparation of Risdiplam and its intermediates

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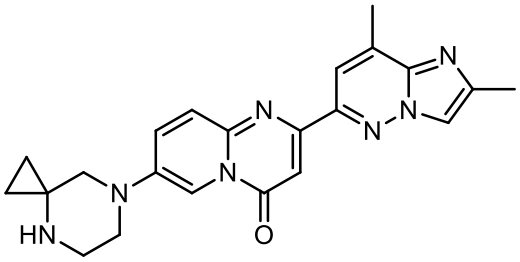
Process for the preparation of Risdiplam and its intermediates

Field of the invention:

The present application relates to a process for the preparation of 7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido-4H-[1,2-a]pyrimidin-4-one of formula-1 and its intermediate compounds.



Formula-1.

Background of the invention:

7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido-4H-[1,2-a]pyrimidin-4-one of formula-1 is commonly known as Risdiplam. Risdiplam is approved by USA Food and drug administration and by European Medicines Agency under the brand name of Evrysdi and it is a survival of motor neuron 2 (SMN2) splicing modifier indicated for the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older.

Risdiplam and its process for the preparation described in the patent document WO2015173181A1. The process described for the preparation of Risdiplam intermediate in this patent proceeds through reaction temperatures above 100°C to 250°C, also requires the multiple chromatography purifications and use of chromatography methods for isolation of Risdiplam intermediates are considered to be tedious and expensive when carried on large scale preparations.

PCT (Patent cooperation treaty) publication number WO2019057740A1 describes the process for the preparation of Risdiplam.

There is always a need for simple, cost-effective, commercially scalable, feasible and environment friendly process for the preparation of Risdiplam of Formula-1 and its intermediates which results in yield improvement.

Advantages of the present invention:

- Present invention avoids multiple column chromatography purifications.
- Present invention avoids high temperature reactions.
- Present invention uses the easily available raw materials.

Brief summary of the invention:

The first embodiment of the present invention is to provide the process for the preparation of Risdiplam of formula 1 and its intermediate compounds.

The second embodiment of the present invention is to provide the process for the preparation novel process of Risdiplam.

The third embodiment of the present invention provides a process for the preparation of compound of formula 4.

Detailed description of the Invention:

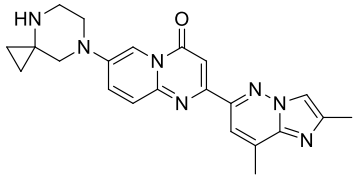
The "suitable solvent" used in the present invention can be selected from but not limited to "hydrocarbon solvents" such as n-pentane, n-hexane, n-heptane, cyclohexane, petroleum ether, benzene, toluene, xylene and mixtures thereof; "ether solvents" such as dimethyl ether, diethyl ether, diisopropyl 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 “acyl” denotes in the present invention refers to alkyl or aryl group linked to carbonyl group. An example of acyl group includes formyl, acetyl, propionyl, acrylyl, benzoyl, and the like.

The term “halogen” denotes in the present inventions refers to fluorine, chloride, bromine and iodine.

The term “boronic ester” denotes in the present invention refers to trimethylene glycol ester and pinacol ester.

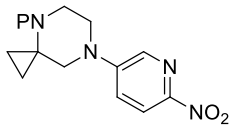
The first embodiment of the present invention provides a process for the preparation of Risdiplam of formula 1,



Formula 1

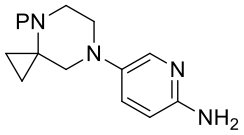
comprising one or more of the following steps:

a) reducing the compound of formula-4



Formula 4

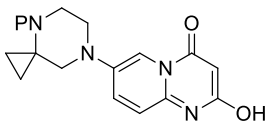
in presence of a reducing agent in a solvent to provide compound of formula-5,



Formula 5

wherein P is -C_1-C_6 acyl, -benzoyl, -trityl, -Si(C_1-C_6 alkyl)$_3$, mesyl, tosyl, benzenesulfonyl, triflate;

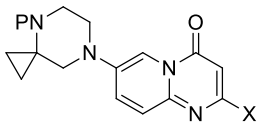
b) reacting the compound of formula-5 with C_{1-6} branched or straight chain alkyl esters of malonic acid or bis(2,4,6-trichlorophenyl) malonate in presence of a solvent to provide compound of formula-6,



Formula 6 ,

wherein P is -C_1-C_6 acyl, -benzoyl, -trityl, -Si(C_1-C_6 alkyl)$_3$, mesyl, tosyl, benzenesulfonyl, triflate;

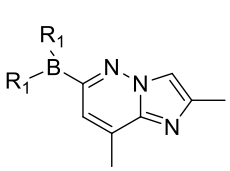
c) converting compound of formula-6 to the compound of formula-7,



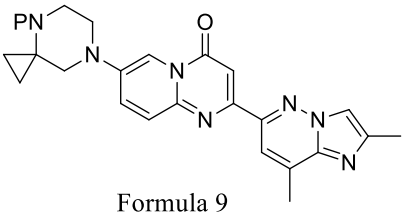
Formula 7 ,

wherein P is -C_1-C_6 acyl, -benzoyl, -trityl, -Si(C_1-C_6 alkyl)$_3$, mesyl, tosyl, benzenesulfonyl, triflate; wherein X is halogen, O-triflate, O-tosyl, O-benzenesulfonyl, O-mesyl or like;

d) reacting the compound of formula-7 with compound of formula-8 in the presence of palladium catalyst and a base in a solvent to provide compound of formula-9,



Formula 8 ,



Formula 9 ,

wherein P is -C_1-C_6 acyl, -benzoyl, -trityl, -Si(C_1-C_6 alkyl)$_3$, mesyl, tosyl, benzenesulfonyl, triflate; R_1 is OH, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkoxyl, or together they form a C_{2-3} alkylenedioxy group optionally substituted by C_{1-6} alkyl, or a benzyldioxy group optionally substituted by C_{1-6} alkyl;

e) deprotecting the compound of formula-9 with suitable deprotecting agent to provide the Risdiplam or its salts of formula-1.

Reducing agent in step-a) is selected from catalytic hydrogenation (using hydrogen gas) and a catalyst such as Pt, Pt/C, PtO 2 , Pd, Pd/C, Rh, Ru, Ni or Raney

Ni; Zn, Sn or Fe and an acid; AlH_3-$AlCl_3$; hydrazine and a catalyst; $[Fe_3(CO)_{12}]$-methanol; hot liquid paraffin; formic acid or ammonium formate and a catalyst such as Pd/C; $LiAlH_4$; and sulfides such as NaHS, $(NH_4)_2S$ or polysulfides.

Converting the compound of formula-6 to formula-7 in step c) by reacting the compound of formula-6 with a suitable reagents such as methanesulfonyl chloride, tosyl chloride, benzenesulfonyl chloride, phosphorous pentachloride, phosphorous oxychloride, thionyl chloride, oxalyl chloride, sodium iodide, cupper iodide, hydrobromic acid, HI and like and optionally in presence of organic or inorganic base.

Palladium catalyst in step-d) is selected from the group comprises $Pd(PPh_3)_4$, $PdCl_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$, $Pd(PPh_3)_2Cl_2$, $PdCl_2$(dppf), PdCl2(dppf).CH_2Cl_2, $PdCl_2$(dppp), Cyclo pentadienyl allyl palladium, allylpalladium(II) chloride dimer $(Pd(allyl)Cl)_2$, (2-Butenyl) chloropalladium dimer, (2-Methylallyl) palladium(II) chloride dimer, palladium(1-phenylallyl)chloride dimer, di-μ-chlorobis[2-(amino-N)[1,1'-bi phenyl] -2-yl-C] dipalladium (II), di-μ-chlorobis[2-(dimethylamino) methyl]phenyl-C,N]di palladium(II), dichloro[9,9-dimethyl-4,5-bis (diphenylphosphino)xanthene] palladium ($Pd(XantPhos)Cl_2$).

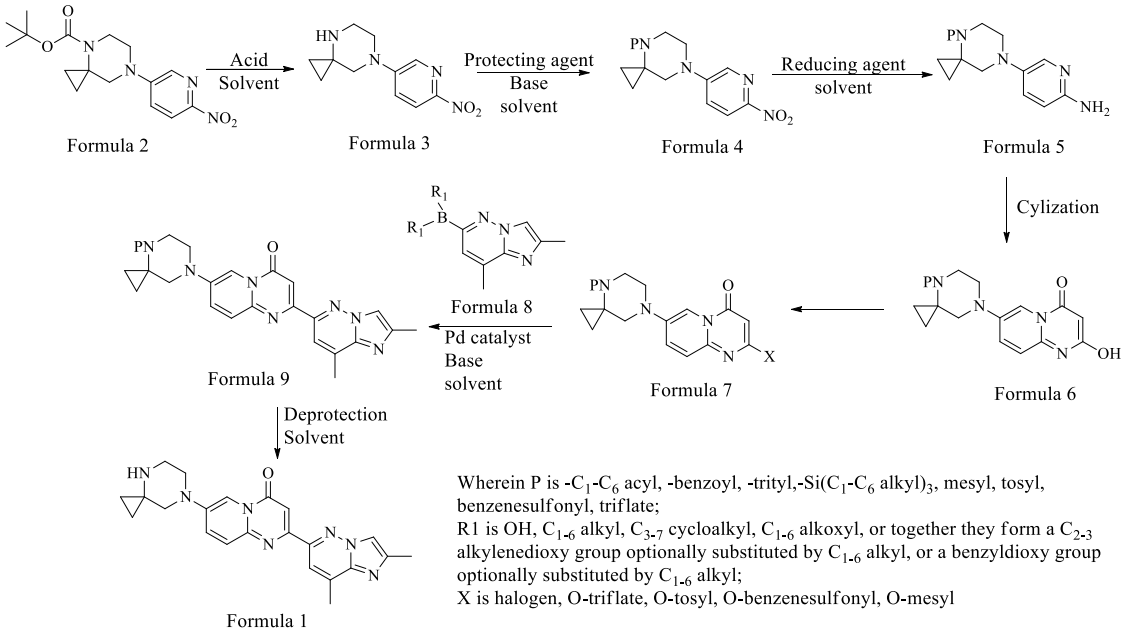
Base in step-d) and step-e) is selected from inorganic bases selected from "alkali metal carbonates" such as sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate and the like; "alkali metal bicarbonates" such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, cesium 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.

Deprotecting agent in step-e) is selected from the base or acid; wherein "base" as defined above; 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-tartaricacid, (-)-Dibenzoyl-L-tartaricacid monohydrate, (+) -Dibenzoyl-D-tartaric acid, (+)-Dibenzoyl-D-tartaric acid monohydrate, (+)-dipara-tolyl-D-tataric acid, (-)-diparatolyl-L-tataricacid, L(-)-pyroglutamic acid

Solvent in steps a) to e) is selected from alcohol solvents, chloro solvents, ether solvents, ester solvents, polar aprotic solvents, hydrocarbon solvents, ketone solvents, and polar solvents such as water or mixtures thereof.

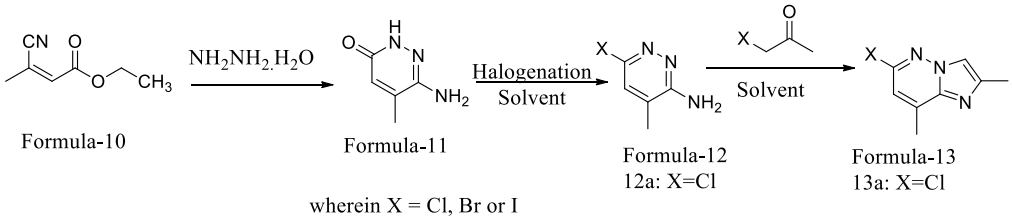
The first embodiment of the present invention is described in the following scheme:



Scheme-I

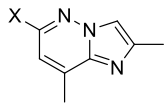
Compound of formula-2 of present application is prepared by the process described in PCT (Patent cooperation treaty) publication number WO2016058501 or by any other process.

The second embodiment of the present invention is described in the below scheme:



Scheme-II

The second embodiment of the present invention provides a process for the preparation of compound of formula-13,



Formula-13,

which comprises:

a) reacting the ethyl 3-cyanobut-2-enoate of formula-10 with hydrazine hydrate in a solvent to provide 6-amino-5-methylpyridazin-3(2H)-one of formula-11,

b) halogenating the 6-amino-5-methylpyridazin-3(2H)-one of formula-11 with a halogenating agent in a solvent to provide compound of formula-12,

c) reacting the compound of formula-12 with 1-bromo acetone or 1-chloro acetone or 1-iodo acetone optionally in presence of a base in a solvent to provide the compound of formula-13.

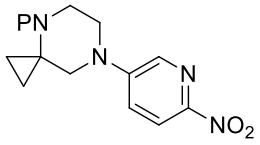
Halogenation in step-b) comprises chlorination, bromination, fluorination, or iodination. Bromination using a brominating agent selected from bromine, HBr-Acetic acid, 1,4-dibromo-dimethylhydantoin, N-bromosuccinimide; chlorination using chlorinating reagent is selected from phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride, thionyl chloride, NCS (N-chlorosuccinimide). Base in step-c) is selected from organic or inorganic base.

Solvent in steps a) to c) selected from alcohol solvents, chloro solvents, ether solvents, ester solvents, polar aprotic solvents, hydrocarbon solvents, ketone solvents, and polar solvents such as water or mixtures thereof.

Compound of formula-13 of present application can be converted to the compound of formula-8 by the known process such as the process described in US Patent number US9969754B2 or by any other process.

Compound of formula-10 is prepared by the process described journal article Journal of Organic Chemistry, 2013, 78(4), 1525-1533 or by any other literature.

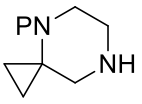
The third embodiment of the present invention provides a process for the preparation of compound of formula 4,



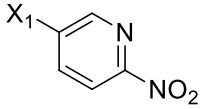
Formula 4

wherein P is selected from -C_1-C_6 acyl, -benzoyl, -trityl, -Si(C_1-C_6 alkyl)$_3$, mesyl, tosyl, benzenesulfonyl, triflate and X_1 is chloro, bromo and iodo;

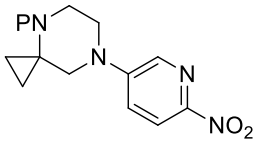
comprising reacting the compound of formula-14 with compound of formula-15 in presence of base in a solvent to provide the compound of formula-4,



Formula-14,



Formula-15,

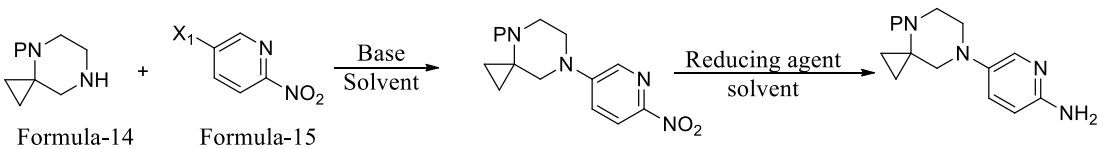


Formula 4

wherein P is -C_1-C_6 acyl, -benzoyl, -trityl, -Si(C_1-C_6 alkyl)$_3$, mesyl, tosyl, benzenesulfonyl, triflate and X_1 is chloro, bromo and iodo.

In an aspect, the base is selected organic and inorganic bases as defined above; Reducing agent is selected from catalytic hydrogenation (using hydrogen gas) and a catalyst such as Pt, Pt/C, PtO 2 , Pd, Pd/C, Rh, Ru, Ni or Raney Ni; Zn, Sn or Fe and an acid; AlH_3-$AlCl_3$; hydrazine and a catalyst; [$Fe_3(CO)_{12}$]-methanol; hot liquid paraffin; formic acid or ammonium formate and a catalyst such as Pd/C; $LiAlH_4$; and sulfides such as NaHS, $(NH_4)_2S$ or polysulfides.

The third embodiment of the present invention is described in the following scheme:



Formula-14
14a: P is acetyl

Formula-15

Formula 4
4a: P= acetyl

Formula 5
5a: P= acetyl

Wherein P is -C_1-C_6 acyl, -benzoyl, -trityl,-Si(C_1-C_6 alkyl)$_3$, mesyl, tosyl, benzenesulfonyl, triflate;
X_1- is Cl, Br or I

Scheme-III

The compound of formula-1 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.

Fourth embodiment of present invention, the novel intermediates obtained as per the present invention are useful in the preparation of Risdiplam of formula-1.

Fifth embodiment of present invention provides one or more novel intermediates of Risdiplam selected from compound of formula-4, compound of formula-5, compound of formula-6, compound of formula-7, compound of formula-9 and compound of formula-11.

Sixth embodiment of the present invention provides the use of Risdiplam of formula-1 of the present invention for the preparation of various pharmaceutical formulations.

Seventh embodiment of the present invention provides pharmaceutical composition comprising Risdiplam of formula-1 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.

Risdiplam of formula-1 produced by the present invention are useful survival of motor neuron 2 (SMN2) splicing modifier indicated for the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older.

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

Examples:

Example-1: Preparation of 1-((tert-butoxycarbonyl)amino)-cyclopropane carboxylic acid

Aqueous sodium bicarbonate solution (sodium bicarbonate 415.4 g in 750 ml of water) was added to the mixture of 1-aminocyclopropane carboxylic acid (200 g), 1,4-dioxane (1500 ml), water (750 ml) at 5-10°C. Di-tert-butyl dicarbonate (518. 1 g) was slowly added to the above reaction mixture at the same temperature, raised the temperature of the reaction mixture to 25-30°C and stirred at the same temperature. Filtered reaction mixture and washed with water. Ethyl acetate was added to the filtrate, separated the both organic and aqueous layers and aqueous layer was cooled to 0-5°C. Acidified the aqueous layer using aqueous citric acid solution and stirred at the same temperature. Filtered the solid and washed with water. Slurried the obtained compound in n-Heptane. Filtered the solid, washed with n-heptane and dried to get the title compound. Yield: 240 g

Example-2: Preparation of ethyl 2-(N-benzyl-1-((tertbutoxycarbonyl)amino) cyclopropanecarboxamido)acetate

Ethyl 2-bromoacetate (300 g) was slowly added to the mixture of benzylamine (423.46 g) and dichloromethane (2400 ml) at 5-10°C, raised the temperature to 25-30°C and stirred at the same temperature. Filtered the reaction mixture, washed with dichloromethane and water was added to the obtained filtrate. Separated the both organic and aqueous layers and organic layer was distilled to get the ethyl 2-(benzylamino)acetate. Dichloromethane (1840 ml) was added to the obtained compound at 25-30°C and cooled to 0-5°C. Diisopropylamine (443.17 g), 1-Ethyl-3-

(3-dimethylaminopropyl)carbodiimide hydrochloride (327 g), 1-((tert-butoxycarbonyl)amino)-cyclopropanecarboxylic acid (300 g), hydroxybenzotriazole (154.76 g) were added to the reaction mixture at 0-5°C, raised the temperature of the reaction mixture to 25-30°C and stirred at the same temperature. Water added to the reaction mixture at 25-30°C, separated the both organic and aqueous layers and aqueous layer was extracted with dichloromethane. Combined the organic layers and washed with aqueous citric acid solution, aqueous sodium bicarbonate solution and followed by with water. Distilled off solvent completely from the organic layer. Slurried the obtained compound in n-heptane. Filtered the solid, washed with n-heptane and dried to get the title compound. Yield: 345 g

Example-3: Preparation of 7-benzyl-4,7-diazaspiro[2.5]octane-5,8-dione

Mixture of ethylene glycol (1720 ml) and ethyl 2-(N-benzyl-1-((tertbutoxycarbonyl) amino)cyclopropanecarboxamido)acetate (344 g) was heated to 150-155°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C, added the reaction mixture into pre-cooled water solution at 5-10°C and stirred at the same temperature. Filtered the solid and washed with water. Slurried the obtained compound in n-heptane. Filter the solid, washed with n-heptane and dried to get the title compound. Yield: 176 g.

Example-4: Preparation of 7-benzyl-4,7-diazaspiro[2.5]octane

Sodium borohydride (144.4 g) was added in lot-wise to pre-cooled mixture of 7-benzyl-4,7-diazaspiro[2.5]octane-5,8-dione (175 g) and tetrahydrofuran (3500 ml) at -10° to -5°C and then boron trifluoride etherate (539.22 g) was added to it. Raised the reaction mixture temperature to 25-30°C, stirred, further heated the reaction mixture to 65-70°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C and quenched into the pre-cooled aqueous hydrochloric acid solution at 0-5°C. Heated the reaction mixture to 60-65°C and stirred at the same temperature. Distilled off the solvent completely from reaction mixture. The aqueous sodium hydroxide solution was added to the obtained distillate at 25-30°C and ethyl acetate was added to it. Separated the both organic and aqueous layers and aqueous layer was extracted

with ethyl acetate. Distilled off solvent completely from the organic layer to get the title compound.

Yield: 153 g

Example-5: Preparation of 1-(7-benzyl-4,7-diazaspiro[2.5]octan-4-yl)ethanone

Triethylamine (15 g) was added to the pre-cooled mixture of 7-benzyl-4,7-diazaspiro[2.5]octane (10 g) and dichloromethane (100 ml) at 0-5°C. Acetyl chloride (7.77 g) was slowly added to the reaction mixture at 0-5°C and stirred at the same temperature. Aqueous sodium bicarbonate solution was added to the reaction mixture and separated the both organic and aqueous layers. Aqueous layer was extracted with dichloromethane and distilled off solvent completely from the organic layer to get the title compound. Yield: 14 g

Example-6: Preparation of 1-(4,7-diazaspiro[2.5]octan-4-yl)ethanone of formula-14a

A mixture of 1-(7-benzyl-4,7-diazaspiro[2.5]octan-4-yl)ethanone (100 g), methanol (800 ml) and 10% Pd/C (25 g) in autoclave at 28-30°C and applied hydrogen pressure and stirred at the same temperature. Filter the reaction mixture, washed with methanol and distilled off solvent completely from the filtrate to get the title compound. Yield: 54 g.

Example-7: Preparation of 1-(7-(6-nitropyridin-3-yl)-4,7-diazaspiro[2.5]octan-4-yl)ethanone formula 4a

5-bromo-2-nitropyridine (50 g) to the solution of 1-(4,7-diazaspiro[2.5]octan-4-yl) ethanone (52.29 g) in dimethyl sulphoxide (250 ml) at 25-30°C. Lithium chloride (31.36 g) was slowly added to the above mixture. Tetramethylguanidine (85.10 g) was slowly added to the obtained mixture at 25-30°C and dimethylsuphoxide was added. Heated the reaction to 80-85°C and stirred at the same temperature. Cooled the reaction to 25-30°C and it was quenched with water. Filtered the solid and washed with water. Heptane (250 ml) was added to the obtained solid, heated to 50-55°C and stirred at the same temperature. Cooled the mixture to 25-30°C and stirred at the

same temperature. Filtered the solid, washed with heptane and dried to get the title compound. Yield: 42 g.

Example-8: Preparation of 1-(7-(6-aminopyridin-3-yl)-4,7-diazaspiro[2.5]octan-4-yl)ethanone formula 5a

1-(7-(6-nitropyridin-3-yl)-4,7-diazaspiro[2.5]octan-4-yl)ethanone (38 g) was dissolved in methanol (525 ml) and dichloromethane (525 ml), charcoal (3.8 g) was added to it at 25-30°C and stirred at the same temperature. Filtered the reaction mixture through the hyflow bed and obtained filtrate was taken into autoclave vessel. To this autoclave vessel 10% Pd/C (7 g) and applied hydrogen pressure was applied to it at 25-30°C and stirred the same temperature. Filtered the reaction mixture through hyflow bed, distilled off the solvent completely and co-distilled with n-heptane. n-Heptane (76 ml) was added to obtained residue at 25-30°C, stirred at the same temperature, dichloromethane **(**19 ml) was added and stirred at the same temperature. Filtered the solid, washed with n-heptane and dried to get the title compound.

Yield: 30 g.

Example-9: Preparation of 7-(4-acetyl-4,7-diazaspiro[2.5]octan-7-yl)-2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one formula 6a

Bis(2,4,6-trichlorophenyl) malonate (89.11 g) was added in lot wise to mixture of 1-(7-(6-aminopyridin-3-yl)-4,7-diazaspiro[2.5]octan-4-yl)ethanone (30 g) and tetrahydrofuran (600 ml) at 65-70°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C and stirred at the same temperature. Filtered the solid and washed with ethyl acetate. Slurried the obtained compound in ethyl acetate. Filtered the solid, washed with ethyl acetate and dried to get the title compound.

Yield: 28 g.

Example-10: Preparation of 7-(4-acetyl-4,7-diazaspiro[2.5]octan-7-yl)-4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl 4-methylbenzenesulfonate formula-7a {P=acetyl; X=O-tosyl}

p-Toluene sulphonylchloride (16.67 g) was slowly added to mixture of 7-(4-acetyl-4,7-diazaspiro[2.5]octan-7-yl)-2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one (25 g), dichloromethane (250 ml) and triethylamine (19.71 g) at 5-10°C, raised the temperature to 25-30°C and stirred at the same temperature. p-Toluene sulfonyl chloride (4 g) was added to the reaction mixture at 25-30°C and stirred at the same temperature. Acidified the reaction mixture using hydrochloric acid and stirred at the same temperature. Separated the both organic and aqueous layers and organic layer was washed with water. Basified the organic layer using aqueous sodium hydroxide solution. Separated the both organic and aqueous layer and carbon treatment was given to organic layer. Distilled off solvent from organic layer and co-distilled with n-heptane. n-Heptane was added to obtained compound 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: 21.5 g.

Example-11: Preparation of 7-(4-acetyl-4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-4H-pyrido[1,2-a]pyrimidin-4-one formula-9a {P=acetyl }

Aqueous potassium carbonate solution (potassium carbonate 11.78 g in 32 ml of water) was added to the mixture of 7-(4-acetyl-4,7-diazaspiro[2.5]octan-7-yl)-4-oxo-4H-pyrido[1,2-a] pyrimidin-2-yl 4-methylbenzenesulfonate (20 g), 2,8-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-b]pyridazine (13.99 g) in acetonitrile (200 ml) and stirred under nitrogen atmosphere. $PdCl_2$(dppf). dichloromethane (1.74 g) was added to the above mixture under nitrogen atmosphere. Heated the reaction mixture to 90-95°C and stirred at the same temperature. Cooled the reaction mixture to 5-10°C, water was added and stirred at the same temperature. Filtered the solid and washed with ethyl acetate. Toluene (200 ml) was added to obtained solid at 25-30°C and heated to 90-95°C. 1-Propanol (10 ml) was added to the mixture at 90-95°C and stirred at the same temperature. Cooled to 25-30°C and

stirred at the same temperature. Filtered the solid, washed with toluene and dried to get the title compound.

Yield: 18.4 g.

Example-12: Preparation of Risdiplam formula 1

Ethyl acetate hydrochloric acid (5 ml) was added to the mixture of 7-(4-acetyl-4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (15 g) and toluene (150 ml) at 25-30°C, heated to 95-100°C. 1-Propanol (5 ml) was added to the above reaction mixture and stirred at the same temperature. Cooled the reaction mixture to 25-30°C, ethyl acetate and water added and separated both organic and aqueous layers. Basified with aqueous sodium hydroxide solution at 25-30°C and stirred at the same temperature. Filtered the solid, washed with water and dried to get the crude title compound.

Toluene (100 ml) was added to crude compound at 25-30°C, heated to 85-90°C and 1-propanol (10 ml) was added to it and stirred at the same temperature. Cooled the reaction mass to 25-30°C and stirred at the same temperature. Filtered the solid, washed with toluene and dried to get the title compound.

Yield: 6.2 g

Example-13: Preparation of 6-chloro-4-methylpyridazin-3-amine

A mixture of 3,6-dichloro-4-methyl-pyridazine (400 g) and ammonia (4000 ml) heated to 120 -125°C and stirred at the same temperature under pressure. Cooled the reaction mixture to 25-30°C, water added to it and stirred at the same temperature. Filtered the solid, washed with water and dried. Ethyl acetate (3200 ml) added to the obtained compound, heated to 75-80°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 ethyl acetate, distilled off the solvent completely and further slurried the obtained compound in n-heptane to get a mixture of 6-chloro-4-methylpyridazin-3-amine and 6-chloro-5-methylpyridazin-3-amine.

Yield: 200 g.

Example-14: Preparation of 6-chloro-2,7-dimethylimidazo[1,2-b]pyridazine

Chloroacetone (152.99 g) added to the mixture of 6-chloro-4-methylpyridazin-3-amine and 6-chloro-5-methylpyridazin-3-amine (200.0 g) and n-butanol (1800 ml) at 25-30°C, heated to 120-125°C and stirred at the same temperature. Cooled the reaction mixture to 50-55°C and distilled off the solvent. Water and dichloromethane were added to the obtained compound at 25-30°C and basified using aqueous ammonia. Separated both organic and aqueous layers and aqueous layer is extracted with dichloromethane. Organic layer washed with water and charcoal treatment was given. Distilled off the solvent from the organic layer and obtained compound is purified by using silica gel column chromatography, eluting with the mixture of cyclohexane and ethyl acetate. Concentrate the pure fractions and the obtained compound was slurried in n-heptane to get the title compound.

Yield: 100.0 g

Example-15: Preparation of 2,7-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-b]pyridazine formula 8a

A mixture of 6-chloro-2,7-dimethylimidazo[1,2-b]pyridazine (100.0 g) and Bis(pinacolato)diboron (209.77 g), tetrabutyl ammonium bromide (17.7 g), potassium acetate (134.89 g) and 1,1'-bis(diphenylphosphino)ferrocene (3.05 g) 1,4 dioxane (2000 ml) stirred at 25-30°C under Argon atmosphere. Palladium dichloride (1,1'-bis(diphenylphosphino) ferrocene). dichloromethane (8.99 g) was added to the reaction mixture , heated to 95-100°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C, water and methyl tertiary butyl ether added to it. Separated both organic and aqueous layers and aqueous layer was extracted with dichloromethane, combined the organic layers and distilled off the solvent completely and obtained compound slurried in n-heptane to get the title compound.

Yield: 110.0 gr

Example-16: Purification of 6-chloro-4-methylpyridazin-3-amine

6-chloro-4-methylpyridazin-3-amine (285.0 g) was recrystallized from ethanol (885 ml). Yield: 205.2 gr.

Example-17: Preparation of 7-(6-nitropyridin-3-yl)-4,7-diazaspiro[2.5]octane formula 3

Mixture of ethyl acetate hydrochloric acid (100 ml) and tert-butyl 7-(6-nitropyridin-3-yl)-4,7-diazaspiro[2.5]octane-4-carboxylate (10 g) heated to 60-65°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C and water added to it. Separated the organic and aqueous layers, aqueous layer is extracted with ethyl acetate and combined the organic layers. Aqueous layer is basified using aqueous sodium hydroxide solution at 0-5°C and stirred at the same temperature. Filtered the solid, washed with water and dried to get the title compound.

Yield: 6.8 g.

Example-18: Preparation of 1-(7-(6-nitropyridin-3-yl)-4,7-diazaspiro[2.5]octan-4-yl)ethanone formula 4a

Triethylamine (7.77 g) and acetyl chloride (4.02 g) were slowly added to the solution of 7-(6-nitropyridin-3-yl)-4,7-diazaspiro[2.5]octane (6 g) in dichloromethane (60 ml) at 0-5°C and stirred at the same temperature. Raised the reaction mixture temperature to 25-30°C and water added to it. Separated the both organic and aqueous layers and organic layer was washed with water. Distilled off the solvent completely from organic layer and obtained compound is slurried in n-heptane to get the title compound.

Yield: 7.6 g

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