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Processes For The Preparation of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-[(2,4,6-trifluorophenyl)methyl]-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5] pyrazino[2,1-b][1,3]oxazepine-10-carboxamide And Pharmaceutically Acceptable Salts Thereof

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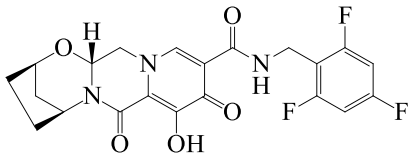
Processes for the preparation of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-[(2,4,6-trifluorophenyl)methyl]-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5] pyrazino[2,1-b][1,3]oxazepine-10-carboxamide and pharmaceutically acceptable salts thereof

Field of the Invention:

The present invention provides various processes for the preparation of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-[(2,4,6-trifluorophenyl)methyl]-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide represented by the following structural formula-1 and pharmaceutically acceptable salts thereof.



Formula-1

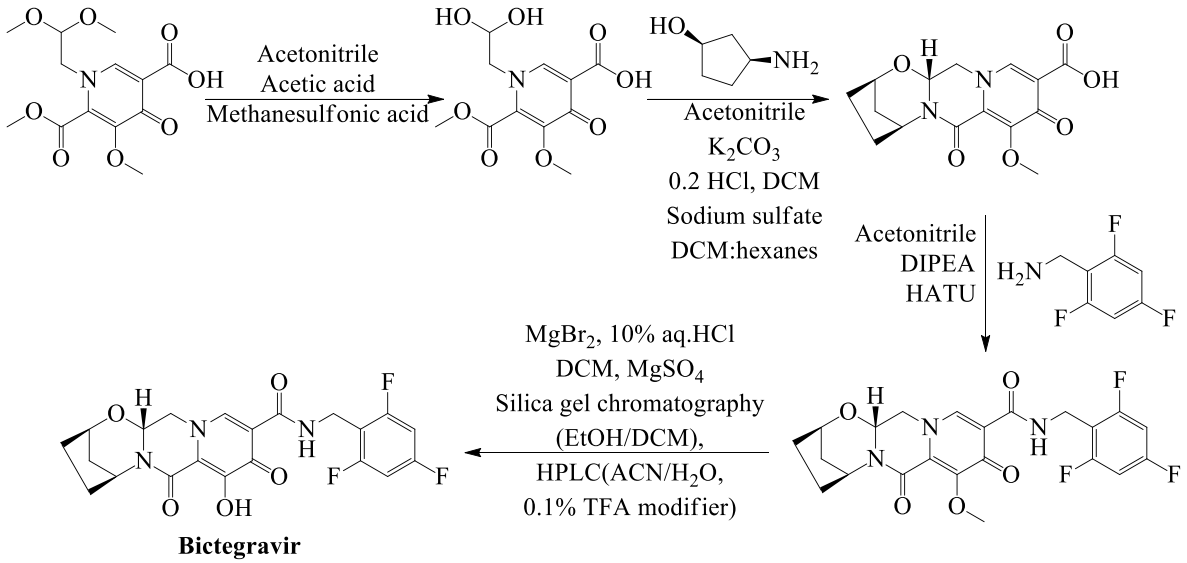
Background of the Invention:

Sodium (2R,5S,13aR)-7,9-dioxo-10-[(2,4,6-trifluorobenzyl)carbamoyl]-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate is commonly known as Bictegravir sodium.

Bictegravir sodium was designed and developed by Gilead Sciences Inc., which was approved by USFDA on February 07, 2018 in combination with Emtricitabine and Tenofovir alafenamide fumarate and it belongs to the class of polycyclic carbamoylpyridone compounds. It is marketed under the brand name BIKTARVY®, and is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults.

US9216996B2 and US9708342B2 describes (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-[(2,4,6-trifluorophenyl)methyl]-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5] pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (Bictegravir), its salts and processes for preparation thereof.

The process for the preparation of Bictegravir described in US9216996 B2 is schematically shown below;



Bictegravir

WO2015195656 A2 and WO2018229798 A1 describe various processes for the preparation of Bictegravir and its intermediate compounds.

Still, there is a need in the art for the development of improved and efficient process for the preparation of Bictegravir and its pharmaceutically acceptable salts, which is suitable for the commercial scale manufacturing in high yield and high purity.

Brief description of the invention:

The first aspect of the present invention is to provide a process for the preparation of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-[(2,4,6-trifluorophenyl)methyl]-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide compound of formula-1 and its pharmaceutically acceptable salts.

The second aspect of the present invention provides another process for the preparation of compound of formula-1 and its pharmaceutically acceptable salts.

The third aspect of the present invention provides alternate process for the preparation of compound of formula-1 and its pharmaceutically acceptable salts.

Brief description of the drawings:

Figure-1: PXRD pattern of compound of formula-6a obtained according to example-9

Figure-2: PXRD pattern of compound of formula-8a obtained according to example-10

Figure-3: PXRD pattern of compound of formula-1b obtained according to example-11

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

The "suitable base" used in the present invention can be selected from but not limited 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, cesium hydroxide and the like; "alkali metal hydrides" such as sodium hydride, potassium hydride, lithium hydride and the like; "alkali metal amides" such as sodium amide, potassium amide, lithium amide and the like; ammonia; "organic bases" like "alkali metal alkoxides" such as sodium methoxide, sodium

ethoxide, potassium methoxide, potassium ethoxide, lithium methoxide, lithium ethoxide, sodium tert.butoxide, potassium tert.butoxide, lithium tert.butoxide and the like; alkali metal and alkali earth metal salts of acetic acid such as sodium acetate, potassium acetate, magnesium acetate, calcium acetate and the like; dimethylamine, diethylamine, diisopropyl mine, diisopropylethylamine (DIPEA), diisobutylamine, trimethylamine, triethylamine, triisopropylamine, tributylamine, tert.butyl amine, pyridine, piperidine, 4-dimethylamino pyridine (DMAP), quinoline, imidazole, N-methylimidazole, l,8-diazabicyclo[5.4.0]undec-7-ene (DBU), l,5-diazabicyclo[4.3.0]non-5-ene (DBN), dimethylaniline, N-methylmorpholine (NMM), l,4-diazabicyclo[2.2.2]octane (DABCO), 2,6-lutidine and the like; "organolithium bases" such as methyl lithium, n-butyl lithium, lithium diisopropylamide (LDA) and the like; "organosilicon bases" such as lithium hexamethyldisilazide (LiHMDS), sodium hexamethyldisilazide (NaHMDS), potassium hexamethyldisilazide (KHMDS) and the like or mixtures thereof.

The "suitable acid" used in the present invention can be selected from but not limited to "inorganic acids" such as hydrofluoric acid, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, boric acid, perchloric acid, carbonic acid; and "organic acids" such as formic acid, acetic acid, trifluoroacetic acid, propionic acid, butyric acid, valeric acid, capric acid, oxalic acid, malonic acid, maleic acid, fumaric acid, lactic acid, succinic acid, citric acid, uric acid, tartaric acid, benzoic acid, 4-hydroxybenzoic acid, salicylic acid, oleic acid, octanoic acid, stearic acid, mandelic acid, adepic acid, pivalic acid, camphorsulfonic acid, substituted/unsubstituted alkyl/aryl sulfonic acids such as methanesulfonic acid, ethanesulfonic acid, propanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid and the like.

The "suitable coupling agent" used in the present invention can be selected from but not limited to N,N'-dicyclohexylcarbodiimide (DCC), N,N'-diisopropyl carbodiimide (DIC), l-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HC1), N,N'-carbonyl diimidazole (CDI), l-[bis(dimethylamino)methylene]-lH-l,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU), 2-(lH-benzotriazol-l-yl)-l,l,3,3-tetramethyluronium

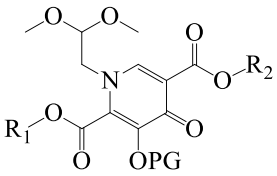
hexafluorophosphate (HBTU), lH-benzotriazolium l-[bis(dimethylamino)methylene]-5-chloro-hexafluorophosphate (1-) 3 -oxide (HCTU), alkyl/aryl/aralkyl chloroformates such as methyl chloroformate, ethyl chloroformate, isopropyl chloroformate, phenyl chloroformate, benzyl chloroformate and the like; diphenylphosphoroazidate (DPPA), thionyl chloride, oxalyl chloride, phosphorous oxychloride, phosphorous pentachloride, 4-methyl-2-oxopentanoyl chloride (i-BuCOCOCl), (benzotriazol-l-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate (BOP), benzotriazol-l-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), alkyl/aryl sulfonyl chlorides such as methanesulfonyl chloride, ethanesulfonyl chloride, benzenesulfonyl chloride, p-toluenesulfonyl chloride and the like optionally in combination with 1-hydroxy-7-azatriazole (HOAt), 1-hydroxy benzotriazole (HOBt), l-hydroxy-lH-l,2,3-triazole-4-carboxylate (HOCt), O-(benzotriazol-l-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), N-hydroxysuccinamide (HOSu), N-hydroxysulfosuccinimide (Sulfo-NHS) and the like.

The "suitable deprotecting agent" can be selected from but not limited to acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, trifluoroacetic acid, methanesulfonic acid, p-toluenesulfonic acid; acetyl chloride in combination with alcohols; bases such as alkali metal hydroxides, alkali metal carbonates, cesium carbonate/imidazole, alkali metal bicarbonates, ammonia, aqueous ammonia, ammonium cerium(IV) nitrate (CAN); and organic bases such as methylamine, ethylamine, diethylamine, triethylamine, piperidine, alkali metal alkoxides; hydrogenating agents such as Pd/C, $Pd(OH)_2/C$ (Pearlman's catalyst), palladium acetate, platinum oxide, platinum black, sodium borohydride, Na-liquid ammonia, Raney-Ni, Zn-acetic acid, tri(C_1-C_6)alkylsilanes, tri(C_1-C_6)alkylsilyl halides; Lewis acids such as but not limited to aluminium chloride, aluminium bromide, aluminium triiodide, boron trifluoride, boron trichloride, boron tribromide, iron bromide, iron chloride, lithium chloride, lithium bromide, lithium iodide, trimethylsilyl iodide, magnesium chloride, magnesium bromide, tin chloride and the like; fluoride ion sources such as NaF, tetra n-butyl ammonium fluoride (TBAF), HF-Pyridine, HF-triethylamine) and the like.

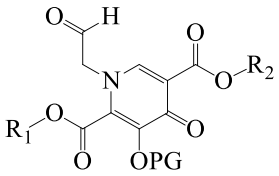
In the present invention the protecting group 'PG' can be selected from but not limited to methyl, ethyl, tert-butyl, acetyl, pivaloyl, benzyl, benzoyl, silyl protecting groups such as trimethylsilyl, triethylsilyl, triisopropylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl and the like; tetrahydropyranyl, tetrahydrofuranyl, triphenyl methyl (trityl), methoxymethyl acetal (MOM), methoxypropyl acetal (MOP), ethoxyethyl acetal, benzyloxymethyl acetal (BOM), methoxymethyl, benzyloxymethyl, tert-butoxymethyl, methoxyphenyl, methoxytrityl (MMT), dimethoxytrityl (DMT) and the like.

The first aspect of the present invention provides a process for the preparation of compound of formula-1 and its pharmaceutically acceptable salts, comprising;

a) treating the compound of general formula-2 with an acid optionally in presence of a solvent to provide compound of general formula-3,



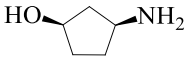
Formula-2



Formula-3

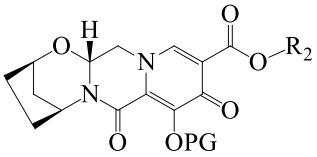
wherein, 'R_1' & 'R_2' are same or different and can be independently selected from C_1-C_6 straight chain/branched chain alkyl groups; and 'PG' represents protecting group;

b) reacting compound of general formula-3 with (1R,3S)-3-aminocyclopentanol compound of formula-4 or its salt



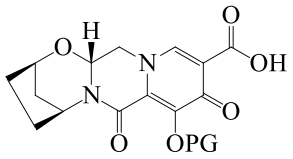
Formula-4

optionally in presence of an acid or a base in a solvent to provide compound of general formula-5



Formula-5

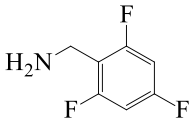
c) hydrolyzing the compound of general formula-5 in presence of an acid or a base optionally in presence of a solvent to provide compound of general formula-6,



Formula-6

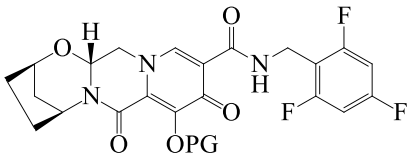
d) optionally purifying the compound of general formul-6,

e) reacting compound of general formula-6 with 2,4,6-trifluorobenzylamine compound of formula-7



Formula-7

in a solvent optionally in presence of a coupling agent and/or a base to provide compound of genera formula-8,



Formula-8

f) deprotecting the compound of general formula-8 with a deprotecting agent optionally in presence of a solvent to provide compound of formula-1,

g) converting compound of formula-1 to its pharmaceutically acceptable salts.

Wherein, the acid in step-a) is selected from inorganic acids and organic acids;

The acid in step-b) is selected from inorganic acids and organic acids; and the base is selected from inorganic bases and organic bases;

The acid in step-c) is selected from inorganic acids and the base is selected from inorganic bases;

The coupling agent in step-e) can be selected from the coupling agents described above and the base can be selected from inorganic bases, organic bases or mixtures thereof;

The deprotecting agent in step-f) can be selected from the deprotecting agents as described above;

In step-g) the compound of formula-1 can be further converted to its pharmaceutically acceptable salts.

In one embodiment, the compound of formula-1 produced by various processes of the present invention can be converted to its sodium salt by treating it with a sodium source optionally in presence of a solvent.

Wherein, the sodium source can be selected from sodium hydroxide, sodium alkoxides such as sodium methoxide, sodium ethoxide, sodium tert.butoxide and the like.

Wherever necessary, the solvent in step-a) to step-g) of the above process can be selected from hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents, formic acid, acetic acid and/or mixtures thereof.

In one embodiment of the present invention, the compound of general formula-6 obtained in step-c) of the above process can be purified from a suitable solvent or mixture of solvents as described above.

In another embodiment, compound of general formula-6 can be purified by a process which comprising treating the compound of general formula-6 with a base optionally in presence of a solvent to provide corresponding salt of compound of general formula-6 and treating the obtained salt with an acid optionally in presence of a solvent to provide pure compound of general formula-6.

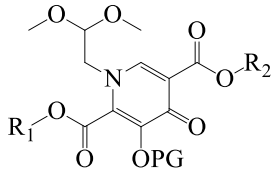
Wherein, the base is selected from inorganic bases such as alkali metal hydroxides, alkali metal alkoxides and the like; organic amines selected from monoalkyl amines such as methyl amine, ethyl amine, n-propyl amine, isopropyl amine, n-butyl amine, iso-butyl amine, tert.butyl amine and the like; dialkyl amines such as dimethylamine, diethyl amine, dipropyl amine, dibutyl amine and the like; dicyclohexylamine, benzyl amine, N,N’-dibenzylethylene diamine, phenylethyl amine, ethanolamine, diethanolamine, tromethamine and the like.

The acid can be selected from inorganic acids and organic acids as described above.

The solvent can be selected from hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents, formic acid, acetic acid and/or mixtures thereof.

The second aspect of the present invention provides another process for the preparation of compound of formula-1 and its pharmaceutically acceptable salts, comprising;

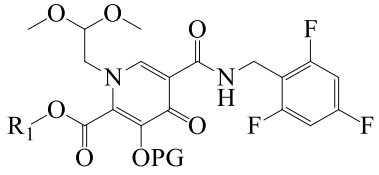
a) reacting compound of general formula-2



Formula-2

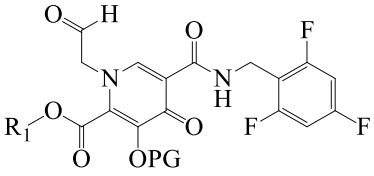
wherein, 'R_1' & 'R_2' are same or different and can be independently selected from C_1-C_6 straight chain/branched chain alkyl groups; and 'PG' represents protecting group;

with compound of formula-7 in presence of an acid at a suitable temperature optionally in presence of a solvent to provide compound of general formula-9,



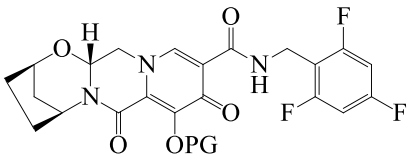
Formula-9

b) treating the compound of general formula-9 with an acid optionally in presence of a solvent to provide compound of general formula-10,



Formula-10

c) reacting compound of general formula-10 with compound of formula-4 or its salt optionally in presence of an acid or a base in a solvent to provide compound of general formula-8,



Formula-8

d) deprotecting compound of general formula-8 with a deprotecting agent optionally in presence of a solvent to provide compound of formula-1,

e) converting compound of formula-1 to its pharmaceutically acceptable salt.

Wherein, the acid in step-a) is selected from organic acids, inorganic acids; and the suitable temperature ranges from 20°C-150°C;

The acid in step-b) is selected from inorganic acids and organic acids;

The acid in step-c) is selected from inorganic acids and organic acids; and the base is selected from inorganic bases and organic bases;

The deprotecting agent in step-d) can be selected from the deprotecting agents as described above;

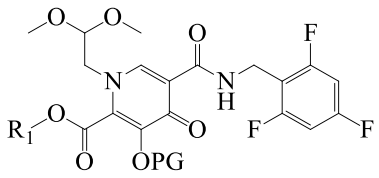
In step-e) the compound of formula-1 can be further converted to its pharmaceutically acceptable salts.

In one embodiment, compound of formula-1 can be converted to its sodium salt by the process as described above.

Wherever necessary, the solvent in step-a) to step-e) of the above process can be selected from hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents, formic acid, acetic acid and/or mixtures thereof.

The third aspect of the present invention provides alternate process for the preparation of compound of formula-1 and its pharmaceutically acceptable salts, comprising;

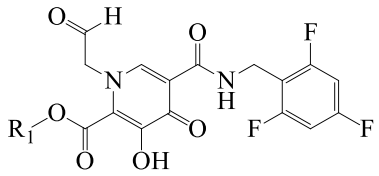
a) converting compound of general formula-9



Formula-9

wherein, 'R_1' represents C_1-C_6 straight chain/branched chain alkyl group; and 'PG' represents protecting group;

to compound of general formula-11



Formula-11

b) reacting compound of general formula-11 with compound of formula-4 or its salt optionally in presence of an acid or base in a solvent to provide compound of formula-1,

c) optionally converting the compound of formula-1 to its pharmaceutically acceptable salt.

Wherein, the acid in step-b) is selected from inorganic acids, organic acids; and the base is selected from inorganic bases and organic bases.

In the above process, compound of general formula-9 can be treated with an acid selected from inorganic acids and organic acids optionally in presence of a solvent to provide aldehyde compound of formula-10 which upon treatment with a deprotecting agent selected from those described above optionally in presence of a solvent to provide compound of general formula-11.

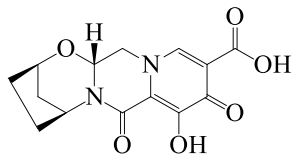
Wherever necessary, the solvent(s) in step-a) to step-c) of the above process can be selected from hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents, formic acid, acetic acid and/or mixtures thereof.

The compound of formula-1 produced by various processes of the present invention can be further converted to its pharmaceutically acceptable salts selected from sodium, potassium, calcium, magnesium salt and the like.

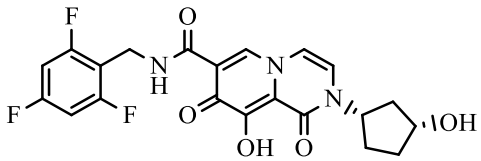
The compound of formula-2, compound of formula-4 and compound of formula-7 which are utilized in the present invention can be synthesized by any of the processes known in the art or they can be procured from any commercial sources available.

The process developed by the present inventors is simple, safe, eco-friendly and commercially viable and involves the usage of simple and commercially available raw materials, reagents and solvents.

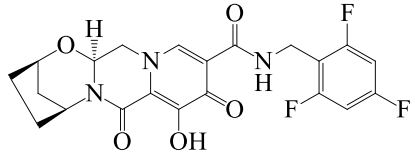
The formation of following compounds as impurities has been observed during the synthesis of compound of formula-1a by the process of the present invention.



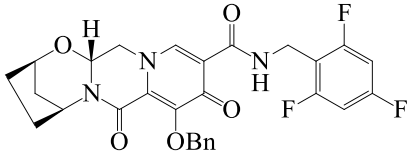
Debenzylated acid impurity



Hydroxy impurity



(2R,5S,13aS)-Diasteriomer impurity



Benzyloxy impurity (Formula-8a)

Wherein, 'Bn' represents benzyl protecting group.

The process for the preparation of compound of formula-1a developed by the present inventors produces highly pure compound of formula-1a with good yield. All the related substances and residual solvents are controlled well within the limits as suggested by ICH guidelines and most of the related substances are controlled in non-detectable levels.

The compound of formula-1a produced by the process of the present invention is having purity of greater than 99.5%, preferably greater than 99.7%, more preferably greater than 99.9% by HPLC.

Compound of formula-2a was analyzed by HPLC under the following conditions; Apparatus: A liquid chromatograph equipped with variable wavelength UV detector; Column: Kromasil C18, 250 × 4.6 mm, 5 µm or equivalent; Column temperature: 25°C; Wavelength: 254 nm; Auto sampler temperature: 25°C; Injection volume: 5 µL; Elution: Gradient; Diluent: Methanol:Acetonitrile (70:30 v/v); Buffer: 0.2% orthophosphoric acid; Mobile phase-A: 0.2% orthophosphoric acid: Acetonitrile (90:10 v/v); Mobile phase-B: Acetonitrile: Methanol: Water: (80:10:10 v/v/v).

Compound of formula-1a was analyzed by HPLC under the following conditions; Apparatus: A liquid chromatograph equipped with variable wavelength UV detector; Column: X-Bridge C18, 3.5 µm, 4.6 X 150 mm; Column temperature: 20°C; Wavelength: 220 nm; Auto sampler temperature: 10°C; Injection volume: 5 µL; Elution: Gradient; Diluent: 2% Formic acid in Acetonitrile; Buffer: Transfer 1000 mL of milli-Q-water into a suitable cleaned and dry beaker. Transfer 1.36 g of Potassium dihydrogen phosphate and 1.74 g of Dipotassium hydrogen phosphate into the above 1000 mL of milli-Q-water and mix well. Adjust the pH to 6.5 ± 0.05 with diluted ortho phosphoric acid. Filter the solution through 0.22µm Durapore PVDF filter paper and sonicate to degas it; Mobile phase-A: Transfer 950 mL of Buffer and 50 mL of Acetonitrile into a 1000 mL Mobile phase bottle, mix well and sonicate to degas it; Mobile phase-B: Transfer 900 mL of acetonitrile and 100 mL of water into a Mobile phase bottle, mix well and sonicate to degas it.

The PXRD analysis of compounds of the present invention was carried out using BRUKER/D8 ADVANCE X-Ray diffractometer using CuKα radiation of wavelength 1.5406A° and at a continuous scan speed of 0.03°/min.

The compound of formula-1a produced by the process of the present invention is having particle size distribution of D_{90} less than 300 µm, preferably less than 200 µm, more preferably less than 100 µm.

An embodiment of the present invention provides compound of formula-1a with particle size distribution of D_{90} less than 50 µm, preferably less than 20 µm.

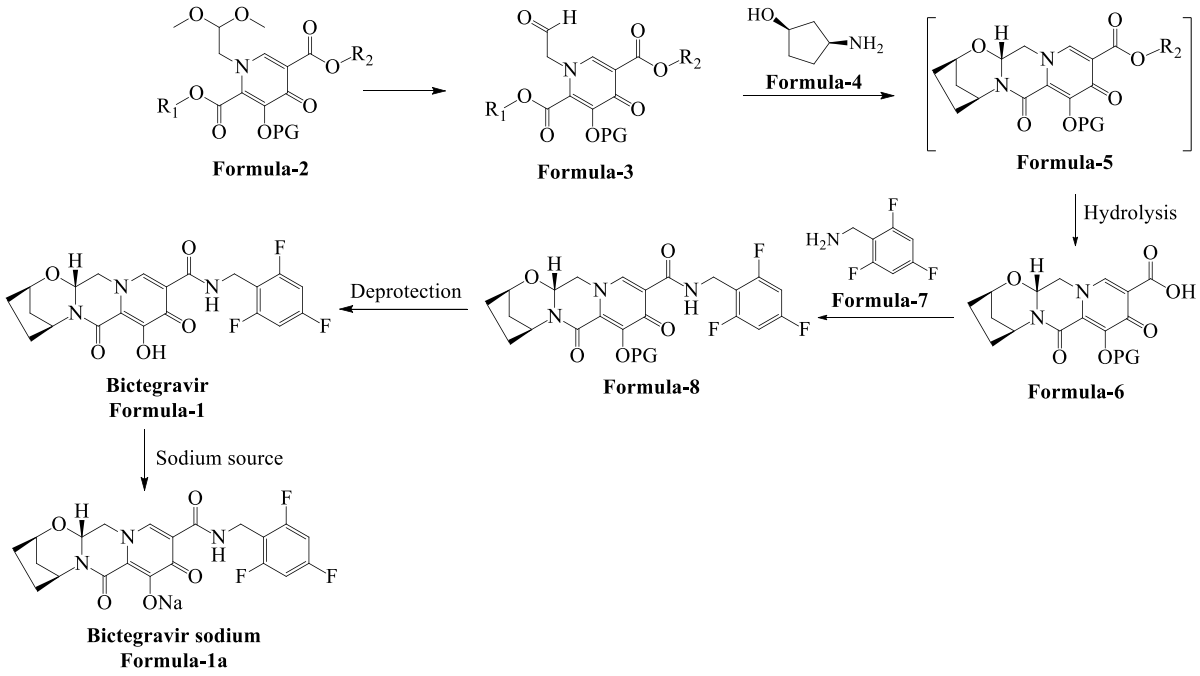
Particle size distribution (PSD) method of analysis:

The particle size distribution analysis was carried out by using Malvern Mastersizer 3000 instrument.

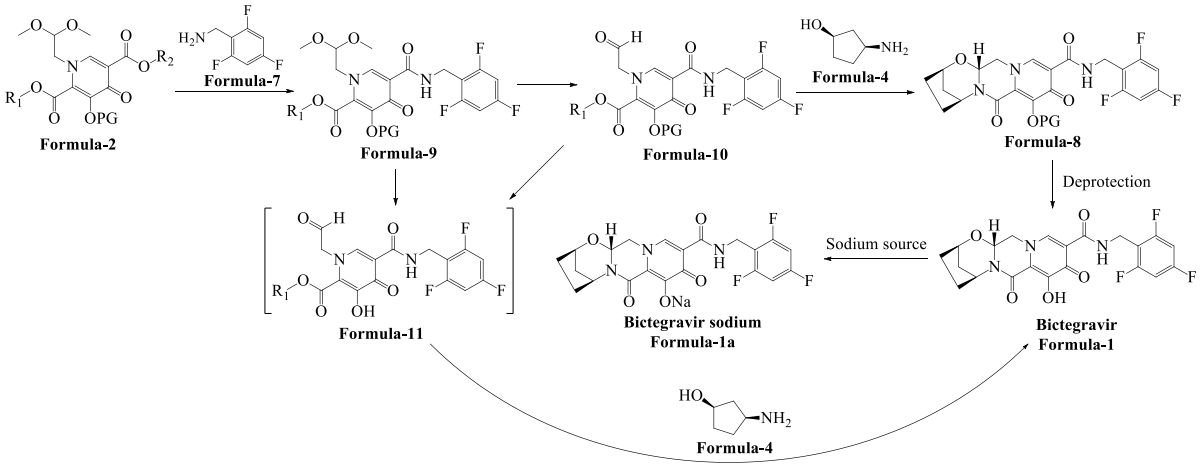
The compound of formula-1a obtained by the process of the present invention can be further micronized or milled to get desired particle size to achieve desired solubility profile based on different forms of pharmaceutical composition requirements. Techniques that may be used for particle size reduction includes but not limited to 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/micronization may be performed before drying or after drying of the product.

The present invention is schematically represented as follows:

Scheme-I:



Scheme-II:



wherein in the above schemes, 'R_1' & 'R_2' are same or different and can be independently selected from C_1-C_6 straight chain/branched chain alkyl groups; and 'PG' represents protecting group.

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

Examples:

Example-1: Purification of 5-ethyl 2-methyl 3-(benzyloxy)-1-(2,2-dimethoxyethyl)-4-oxo-1,4-dihydropyridine-2,5-dicarboxylate (Formula-2a)

A mixture of compound of formula-2a (50 gm) and cyclohexane (200 ml) was stirred for 15 min at 25-30°C. Heated the reaction mixture to 65-70°C and stirred for 90 min at the same temperature. Cooled the reaction mixture to 10-15°C, ethyl acetate (50 ml) was added to it and stirred for 3 hr at the same temperature. Filtered the solid, washed with cyclohexane and dried it. Ethyl acetate (50 ml) was added to the obtained solid at 25-30°C and stirred the reaction mixture for 15 min at the same temperature. Heated the reaction mixture to 65-70°C and stirred for 90 min at the same temperature. Filtered the reaction mixture through hyflow bed and washed the hyflow bed with ethyl acetate. Cooled the reaction mixture to 0-5°C and stirred for 3 hr at the same temperature. Filtered the solid, washed with methyl tert-butyl ether and dried the material to get the pure title compound.

Yield: 30.0 gm; M.R.: 57-61°C; Purity by HPLC: 97.1%.

Example-2: Preparation of (2R,5S,13aR)-ethyl 8-(benzyloxy)-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxylate (Formula-5a)

A pre-cooled aqueous sulfuric acid solution (3.8 ml of sulfuric acid in 2.2 ml of water at 0-5°C) was slowly added to a mixture of compound of formula-2a (20 gm) and formic acid (60 ml) at 25-30°C and stirred the reaction mixture for 6 hr at the same temperature. Cooled the reaction mixture to 0-5°C and aqueous sodium chloride solution was slowly added drop wise to it. Raised the temperature of the reaction mixture to 25-30°C and stirred for 15 min at the same temperature. Dichloromethane was added to the reaction mixture and stirred for 15 min. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Combined the organic layers and washed with aqueous sodium

chloride solution. Distilled off the solvent from the organic layer under reduced pressure. Acetonitrile (45 ml), (1R,3S)-3-aminocyclopentanol hydrochloride compound of formula-4a (5.5 gm) followed by potassium acetate (8.83 gm) were added to the obtained compound at 25-30°C under nitrogen atmosphere and stirred the reaction mixture for 15 hr at the same temperature. Dichloromethane and water were added to the reaction mixture at 25-30°C and stirred for 20 min at the same temperature. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Combined the organic layers and distilled off the solvent under reduced pressure. Methanol (45 ml) was added to the obtained compound at 25-30°C. Cooled the reaction mixture to -10 to -5°C and stirred for 1 hr at the same temperature. Filtered the reaction mixture and washed with methyl tert-butyl ether. Distilled off the solvent completely from the filtrate under reduced pressure. Methyl tert-butyl ether (10 ml) was added to the obtained compound at 25-30°C and stirred the reaction mixture for 2 hr at the same temperature. Filtered the solid, washed with methyl tert-butyl ether and dried the solid to get the title compound. Yield: 9.0 gm.

Example-3: Preparation of (2R,5S,13aR)-8-(benzyloxy)-7,9-dioxo-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxylic acid (Formula-6a)

Aqueous sodium hydroxide solution (1.6 gm of sodium hydroxide in 46 ml of water) was added to a pre-cooled mixture of compound of formula-5a (17 gm) and methanol (46 ml) at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 3 hr at the same temperature. Dichloromethane and water were added to the reaction mixture at 25-30°C. Cooled the reaction mixture to 0-5°C and quenched with 20% acetic acid solution. Raised the temperature of the reaction mixture to 25-30°C and stirred for 20 min at the same temperature. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Combined the organic layers, distilled off the solvent completely under reduced pressure and co-distilled with methyl tert-butyl ether. Methyl tert-butyl ether (51 ml) was added to the obtained compound at 25-30°C and stirred the reaction mixture for 90 min at the same temperature. Filtered the solid, washed with methyl tert-butyl ether and dried the material to get the title compound. Yield: 11.0 gm.

Example-4: Alternate process for the preparation of compound of formula-6a

Aqueous sodium hydroxide solution (1.6 gm of sodium hydroxide in 46 ml of water) was added to a pre-cooled mixture of compound of formula-5a (17 gm) and methanol (46 ml) at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 3 hr at the same temperature. Dichloromethane and water were added to the reaction mixture at 25-30°C. Cooled the reaction mixture to 0-5°C and quenched with 20% acetic acid solution. Raised the temperature of the reaction mixture to 25-30°C and stirred for 20 min at the same temperature. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Combined the organic layers, distilled off the solvent completely under reduced pressure and co-distilled with methyl tert-butyl ether. Methyl tert-butyl ether (51 ml) was added to the obtained compound at 25-30°C and stirred the reaction mixture for 90 min at the same temperature. Filtered the solid and washed with methyl tert-butyl ether. Water (102 ml) was added to the obtained compound at 25-30°C and slowly basified the reaction mixture by using 10% aqueous sodium hydroxide solution. Ethyl acetate was added to the reaction mixture and stirred for 20 min. Both the organic and aqueous layers were separated and dichloromethane was added to the aqueous layer. Slowly acidified the reaction mixture by using 20% acetic acid solution (75 ml) at 25-30°C and stirred for 20 min at the same temperature. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Combined the organic layers and distilled off the solvent completely under reduced pressure. Methyl tert-butyl ether (51 ml) was added to the obtained compound at 25-30°C and stirred the reaction mixture for 90 min at the same temperature. Filtered the solid and washed with methyl tert-butyl ether. Dimethyl sulfoxide (34 ml) was added to the obtained compound at 25-30°C and heated the reaction mixture to 60-65°C. A solution of tertiary butyl amine (1.9 gm) in dimethyl sulfoxide (22 ml) was slowly added to the reaction mixture at 60-65°C and stirred for 3 hr at the same temperature. Cooled the reaction mixture to 20-25°C and stirred for 3 hr at the same temperature. Filtered the solid and washed with methyl tert-butyl ether. Dichloromethane (68 ml) and water (68 ml) were added to the obtained compound. 20% Acetic acid solution (70 ml) was slowly added to the reaction mixture at 25-30°C and stirred for 20 min at the same temperature. Both the organic and aqueous layers were separated and extracted the aqueous layer with

dichloromethane. Combined the organic layers and distilled off the solvent under reduced pressure. Methyl tert-butyl ether (26 ml) was added to the obtained compound at 25-30°C and stirred the reaction mixture for 90 min at the same temperature. Filtered the solid, washed with methyl tert-butyl ether and dried to get the title compound. Yield: 5.0 gm.

Example-5: Preparation of (2R,5S,13aR)-8-(benzyloxy)-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (Formula-8a)

A mixture of compound of formula-6a (7 gm), carbonyldiimidazole (7.11 gm) and dichloromethane (42 ml) was stirred for 4 hr at 25-30°C under nitrogen atmosphere. Cooled the reaction mixture to 5-10°C and a solution of 2,4,6-trifluorobenzylamine compound of formula-7 (5.66 gm) in dichloromethane (14 ml) was slowly added to it at the same temperature. Raised the temperature of the reaction mixture to 25-30°C and stirred for 3 hr at the same temperature. Cooled the reaction mixture to 5-10°C and acidified it by adding aqueous HCl solution. Raised the temperature of the reaction mixture to 25-30°C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Combined the organic layers and washed with aqueous sodium bicarbonate solution. Distilled off the solvent from the organic layer under reduced pressure. Methyl tert-butyl ether (21 ml) was added to the obtained compound at 25-30°C and stirred the mixture for 3 hr at the same temperature. Filtered the solid, washed with methyl tert.butyl ether and dried to get title compound. Yield: 7.0 gm; M.R: 178-185°C.

Example-6: Preparation of compound of formula-1

5% Pd/C (1.26 gm) was added to a mixture of compound of formula-8a (6 gm), tetrahydrofuran (54 ml) and methanol (6 ml) at 25-30°C under nitrogen atmosphere in an autoclave vessel. 3-4 Kg/Cm^2 hydrogen gas pressure was applied to the reaction mixture at 25-30°C. Heated the reaction mixture to 40-45°C and stirred for 36 hr at the same temperature. Cooled the reaction mixture to 25-30°C and released the hydrogen gas from the autoclave vessel. Dichloromethane and methanol were added to the reaction mixture at 25-30°C and stirred for 20 min at the same temperature. Filtered the reaction mixture through hyflow bed and washed the hyflow bed with a mixture of dichloromethane and methanol.

Distilled off the solvent completely from the filtrate under reduced pressure. Methanol (18 ml) was added to the obtained compound at 25-30°C and stirred the reaction mixture for 15 min at the same temperature. Methyl tert-butyl ether (180 ml) was added to reaction mixture at 25-30°C and stirred for 90 min at the same temperature. Filtered the solid, washed with methyl tert-butyl ether and dried to get the title compound. Yield: 4.0 gm.

Example-7: Preparation of compound of formula-1a

A pre-heated (60-65°C) solution of compound of formula-1 (0.5 gm) in methanol (4 ml) was slowly added drop wise to aqueous sodium hydroxide solution (0.04 gm of sodium hydroxide in 4 ml of water) at 25-30°C and stirred the reaction mixture for 90 min at the same temperature. Filtered the precipitated solid, washed with water and dried to get the title compound. Yield: 0.4 gm.

Example-8: Alternate process for the preparation of compound of formula-6a

Step-1: A pre-cooled aqueous sulfuric acid solution (3.8 ml of sulfuric acid in 2.2 ml of water at 0-5°C) was added to a mixture of compound of formula-2a (20 gm) and formic acid (60 ml) at 25-30°C and stirred the reaction mixture for 6 hr at the same temperature. Cooled the reaction mixture to 0-5°C and aqueous sodium chloride solution was slowly added to it. Raised the temperature of the reaction mixture to 25-30°C and stirred for 15 min at the same temperature. Dichloromethane was added to the reaction mixture and stirred for 15 min. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Combined the organic layers and washed with aqueous sodium chloride solution. Distilled off the solvent from the organic layer under reduced pressure.

Step-2: A mixture of compound of formula-4a (4.5 gm), acetonitrile (45 ml) and potassium carbonate (8.28 gm) was heated to 85-90°C under nitrogen atmosphere and stirred for 3 hr at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 3 hr at same temperature. Filtered the reaction mixture and distilled off the solvent from the filtrate.

Step-3: Acetonitrile (100 ml) was added to the compound obtained in step-1 at 25-30°C under nitrogen atmosphere. The compound obtained in step-2 was added to the reaction mixture at 25-30°C. Heated the reaction mixture to 85-90°C and stirred for 5 hr at the same temperature. Cooled the reaction mixture to 25-30°C, dichloromethane and water were added

to it and stirred the reaction mixture for 20 min at the same temperature. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Combined the organic layers and distilled off the solvent under reduced pressure. Methanol (16.74 ml) was added to the obtained compound at 25-30°C. Cooled the reaction mixture to 0-5°C and aqueous sodium hydroxide solution (1.13 gm of sodium hydroxide in 16.74 ml of water) was added to it. Raised the temperature of the reaction mixture to 25-30°C and stirred for 3 hr at the same temperature. Dichloromethane was added to the reaction mixture at 25-30°C and cooled to 0-5°C. Quenched the reaction mixture with aq.HCl solution at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 20 min at the same temperature. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Combined the organic layers and distilled off the solvent under reduced pressure. Methyl tert-butyl ether (10 ml) was added to the obtained compound at 25-30°C and stirred the mixture for 90 min at the same temperature. Filtered the solid, washed with methyl tert-butyl ether and dried to get the title compound. Yield: 10.0 gm.

Example 9: Preparation of compound of formula-6a

Aqueous solution of sulfuric acid (diluted 13.3 ml of sulfuric acid with 7.7 ml of water at 0-5°C) was added to a mixture of compound of formula-2a (70 gm) and formic acid (210 ml) at 25-30°C and stirred the reaction mixture for 7 hr at the same temperature. Cooled the reaction mixture to 0-5°C and aqueous sodium chloride solution was slowly added drop-wise to it at the same temperature. Raised the temperature of the reaction mixture to 25-30°C and stirred for 15 min at the same temperature. Dichloromethane was added to the reaction mixture and stirred for 15 min. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Combined the organic layers and washed with water. Compound of formula-4a (24.8 gm) and potassium acetate (29.48 gm) were added to the organic layer at 25-30°C and stirred the reaction mixture for 24 hr at 30-35°C. Water was added to the reaction mixture at 25-30°C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Combined the organic layers and washed with water. Distilled off the solvent from the organic layer and co-distilled with methanol. Methanol (168 ml) was

added to the obtained compound at 25-30°C and stirred the reaction mixture for 5 hr at the same temperature. Filtered the reaction mixture and washed with 50% aqueous methanol solution. Cooled the filtrate to 5-10°C, slowly added aqueous sodium hydroxide solution (8.01 gm of sodium hydroxide in 154 ml of water) to it at the same temperature and stirred the reaction mixture for 3 hr at the same temperature. Dichloromethane was added to the reaction mixture and slowly acidified the reaction mixture by using aqueous acetic acid solution at 5-10°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloroethane. Combined the organic layers and washed with water. Distilled off the solvent from the organic layer under reduced pressure. Methyl tert.butyl ether (175 ml) was added to the obtained compound at 25-30°C and stirred the reaction mixture for 90 min at the same temperature. Filtered the solid and washed with methyl tert.butyl ether. Dimethyl sulfoxide (98 ml) was added to the obtained compound at 25-30°C. Heated the reaction mixture to 60-65°C and stirred for 90 min at the same temperature. Filtered the reaction mixture and washed with dimethyl sulfoxide. Cooled the filtrate to 25-30°C, tert.butyl amine (12.81 gm) was slowly added to it and stirred the reaction mixture for 6 hr at the same temperature. Cooled the reaction mixture to 20-25°C and stirred for 2 hr at the same temperature. Filtered the solid and washed with methyl tert.butyl ether. Dichloromethane (350 ml) and water (210 ml) were added to the obtained compound at 25-30°C and stirred the reaction mixture for 10 min at the same temperature. Cooled the reaction mixture to 5-10°C ad slowly acidified it by using aqueous acetic acid solution. Raised the temperature of the reaction mixture to 25-30°C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Combined the organic layers and washed with water. Distilled off the solvent from the organic layer under reduced pressure. Methyl tert.butyl ether (210 ml) was added to the obtained compound at 25-30°C and stirred the reaction mixture for 90 min at the same temperature. Filtered the solid, washed with methyl tert.butyl ether and dried the material to get the title compound. The PXRD pattern of the obtained compound is shown in figure-1. Yield: 22.0 gm; M.P.: 230-235°C; Purity by HPLC: 98.43%.

Example-10: Preparation of compound of formula-8a

Carbonyldiimidazole (51.08 gm) was added to a mixture of compound of formula-6a (50 gm) and dichloromethane (500 ml) at 25-30°C under nitrogen atmosphere and stirred the reaction mixture for 4 hr at the same temperature. Cooled the reaction mixture to -40°C to -35°C, a solution of compound of formula-7 (35.56 gm) in dichloromethane (100 ml) was slowly added to it and stirred the reaction mixture for 45 min at the same temperature. Water was added to the reaction mixture at -40°C to -35°C. Raised the temperature of the reaction mixture to 25-30°C, water was added to it and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with aqueous ammonia solution. Both the aqueous layers were combined and extracted with dichloromethane. Combined the total organic layers and washed with water. Distilled off the solvent from the organic layer under reduced pressure and co-distilled with methanol. Methanol (350 ml) was added to the obtained compound at 25-30°C. Heated the reaction mixture to 60-65°C and stirred for 90 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 3 hr at the same temperature. Filtered the solid and washed with methanol. Dimethyl sulfoxide (225 ml) was added to the obtained solid at 25-30°C. Heated the reaction mixture to 90-95°C and stirred for 50 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 4 hr at the same temperature. Filtered the solid, washed with methanol and suck dried the material. Dimethyl sulfoxide (200 ml) was added to the obtained compound at 25-30°C. Heated the reaction mixture to 90-95°C and stirred for 50 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 4 hr at the same temperature. Filtered the solid, washed with methanol and suck dried the material. Dimethyl sulfoxide (175 ml) was added to the obtained solid at 25-30°C. Heated the reaction mixture to 90-95°C and stirred for 50 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 4 hr at the same temperature. Filtered the solid, washed with methanol and dried the material to get the title compound. The PXRD pattern of the obtained compound is shown in figure-2. Yield: 35.0 gm; M.P.: 217-220°C. Purity by HPLC: 99.85%.

Example-11: Preparation of lithium (2R,5S,13aR)-7,9-dioxo-10-[(2,4,6-trifluorobenzyl)carbamoyl]-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5] pyrazino[2,1-b][1,3]oxazepin-8-olate (Formula-1b)

Lithium chloride (39.28 gm) was added to a mixture of compound of formula-8a (100 gm), tetrahydrofuran (500 ml) and isopropyl alcohol (200 ml) at 25-30°C. Heated the reaction mixture to 60-65°C and stirred for 15 hr at the same temperature. Cooled the reaction mixture to 25-30°C, water was slowly added to it and stirred for 3 hr at the same temperature. Filtered the solid and washed with isopropyl alcohol. Dichloromethane (500 ml) and water (500 ml) were added to the obtained compound at 25-30°C and cooled the reaction mixture to 5-10°C. Acidified the reaction mixture by using aqueous acetic acid solution at 5-10°C and stirred for 30 min at the same temperature. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Combined the organic layers and washed with aqueous sodium bicarbonate solution followed by with water. Distilled off the solvent from the organic layer and methanol (500 ml) was added to the obtained compound at 25-30°C. Heated the reaction mixture to 60-65°C and stirred for 1 hr at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 2 hr at the same temperature. Filtered the compound and washed with methanol. Methanol (500 ml) was added to the obtained compound at 25-30°C. Aqueous lithium hydroxide solution (8.76 gm of lithium hydroxide hydrate in 500 ml of water) was slowly added to the reaction mixture at 25-30°C and stirred for 4 hr at the same temperature. Filtered the solid, washed with methanol and dried the material to get the title compound. The PXRD pattern of the obtained compound is shown in figure-3. Yield: 50.0 gm.

Water content by KFR: 1.80% w/w; Purity by HPLC: 99.93%.

Example-12: Preparation of compound of formula-1a

Aqueous acetic acid solution (19.8 ml of acetic acid in 46.2 ml of water) was slowly added to a pre-cooled mixture of compound of formula-1b (66 gm), dichloromethane (330 ml) and water (330 ml) at 5-10°C and stirred the reaction mixture for 20 min at the same temperature. Raised the temperature of the reaction mixture to 25-30°C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and

extracted the aqueous layer with dichloromethane. Combined the organic layers and washed with aqueous sodium bicarbonate solution followed by with water. Distilled off the solvent from the organic layer under reduced pressure and methanol (528 ml) was added to the obtained compound at 25-30°C. Aqueous sodium hydroxide solution (6.95 gm of sodium hydroxide in 528 ml of water) was slowly added to the reaction mixture at 25-30°C and stirred for 3 hr at the same temperature. Filtered the solid, washed with methanol and dried the material to get the title compound. Yield: 62.0 gm.

Water content by KFR: 0.32% w/w; Purity by HPLC: 99.93%; Debenzylated acid impurity: Not detected; Hydroxy impurity: Not detected; Diastereomer impurity: 0.01%; Benzyloxy impurity: 0.01%; Highest individual unspecified impurity: 0.02%.

Drawings

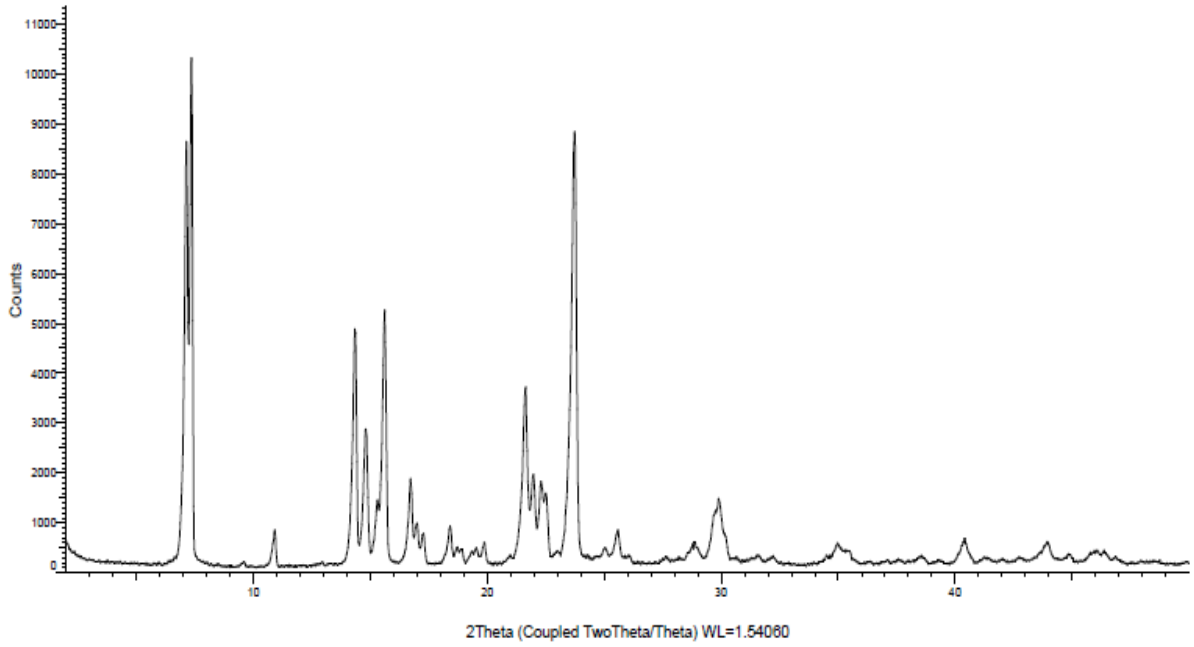


Figure-1

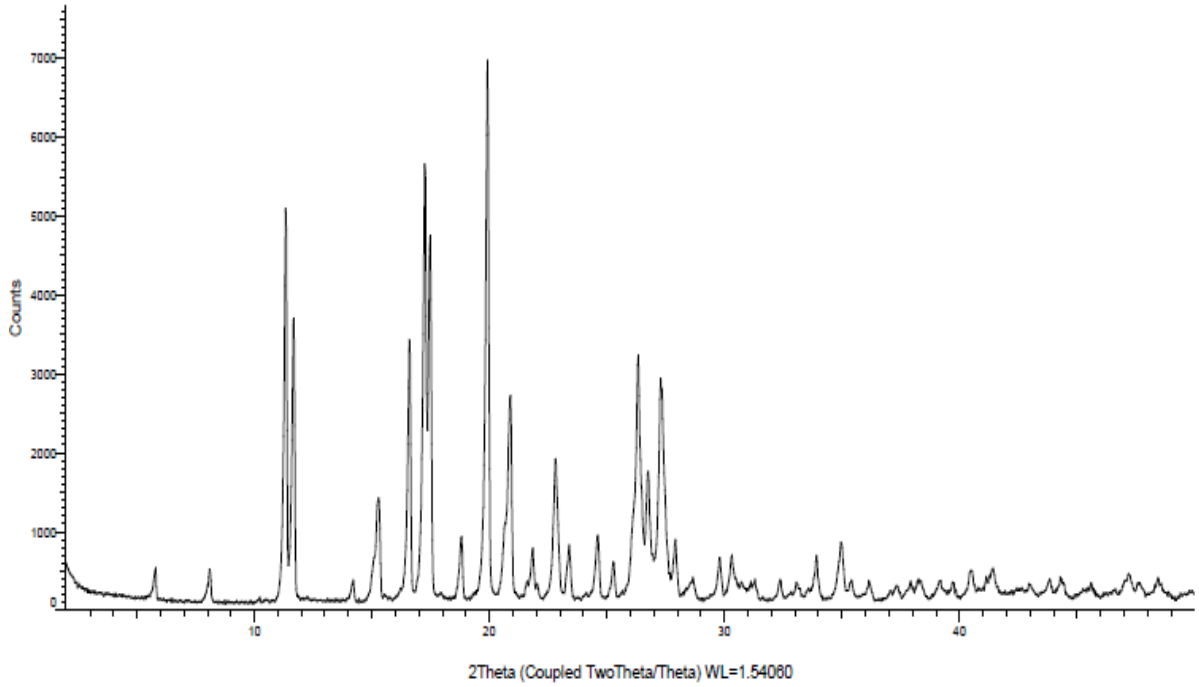


Figure-2

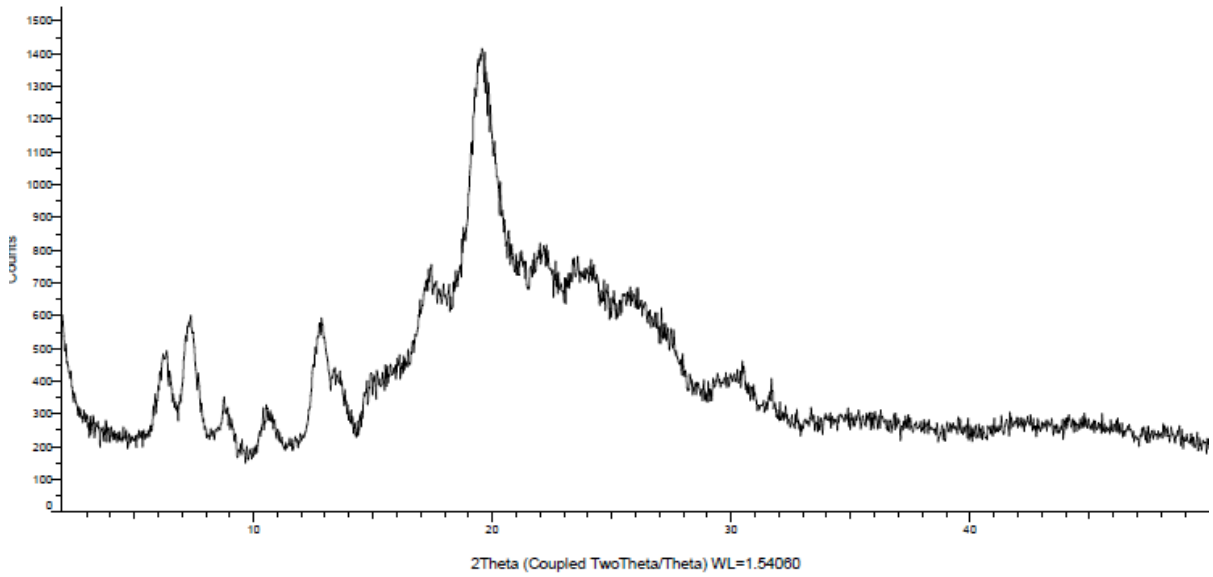


Figure-3

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