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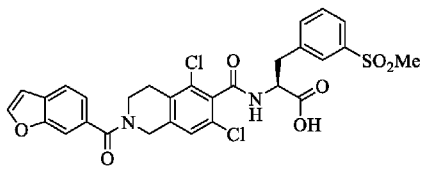
(54) **Title:** PROCESSES FOR THE PREPARATION OF (S)-2-(2-(BENZOFURAN-6-CARBONYL)-5,7-DICHLORO-l,2,3,4-TETRAHYDROISOQUINOLINE-6-CARBOXAMIDO)-3-(3-(METHYLSULFONYL)PHENYL) PROPANOIC ACID AND POLYMORPHS THEREOF



Formula- 1

(57) **Abstract:** The present invention relates to various processes for the preparation of (S)-2-(2- (benzofuran-6-carbonyl)-5 ,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3- (methylsulfonyl)phenyl)propanoic acid represented by the following structural formula- 1. The said processes for the preparation of compound of formula- 1 proceed through various novel intermediate compounds. The present invention also relates to novel crystalline polymorphs of compound of formula-1 and processes for preparation thereof.

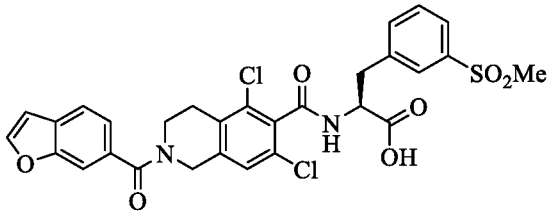
Processes for the preparation of (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl) propanoic acid and polymorphs thereof

Related Applications:

This application claims the benefit of priority of our Indian patent applications 201741030292 filed on Aug 28, 2017, 201741041739 filed on Nov 22, 2017, 201841004875 filed on Feb 08, 2018 and 201841019947 filed on May 28, 2018 which are incorporated herein as reference.

Field of the Invention:

The present invention provides processes for the preparation of (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methyl sulfonyl)phenyl)propanoic acid represented by the following structural formula-1 and polymorphs thereof.



Formula-1

Background of the Invention:

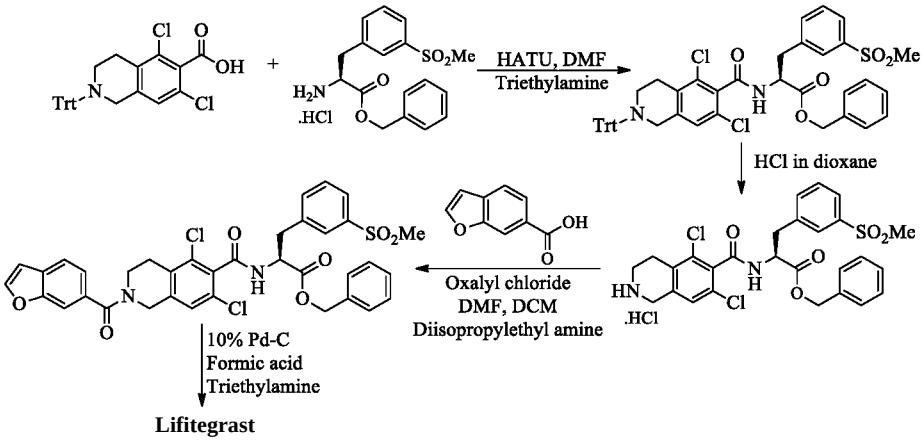
(S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid, commonly known as Lifitegrast was initially designed and developed by SARcode Bioscience which was acquired by Shire in 2013. Lifitegrast was approved by USFDA on July 11, 2016 and is marketed under the brand name XIIDRA™. Xiidra (Lifitegrast ophthalmic solution) 5% is a lymphocyte function-associated antigen-1 (LFA-1) antagonist indicated for the treatment of the signs and symptoms of dry eye disease (DED).

US7314938B2 and US8084047B2 describes (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl) propanoic acid and its analogous compounds.

US7314938B2 and US8084047B2 didn't disclose any specific method for the synthesis of Lifitegrast.

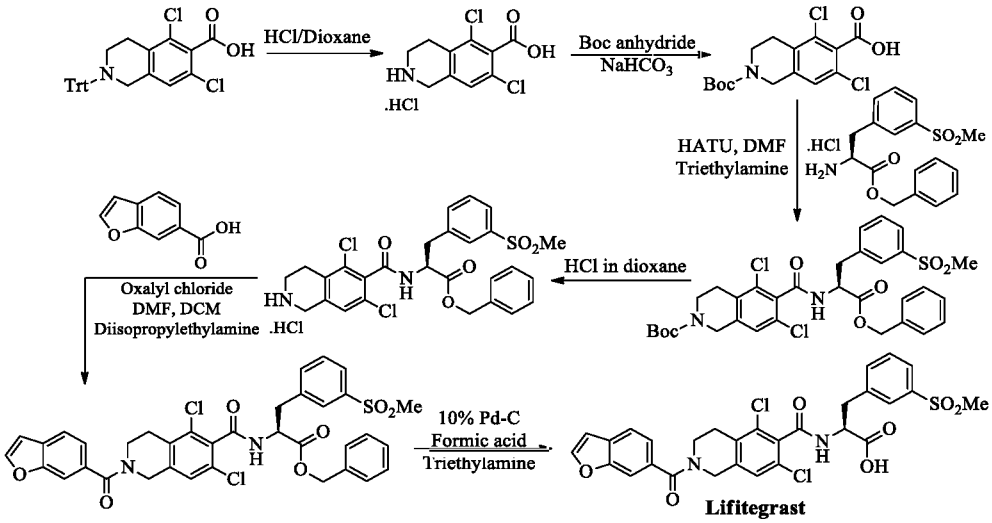
US8080562B2 (herein after referred as US'562 patent) discloses a process for the synthesis of Lifitegrast and its various intermediate compounds in scheme-3 & scheme-5 which is shown below.

Scheme-A;



Alternative process for the preparation of Lifitegrast has been described in scheme-6 of the above US'562 patent which is schematically shown below.

Scheme-B:



The above described prior-art processes has many disadvantages. They involve more number of steps viz., protection of amine as well as carboxylic acid functional groups at various stages of the synthetic processes and deprotection of the same in the subsequent steps to produce the final compound. As these processes involve more number of synthetic steps, the overall reaction time cycle is high and there is more scope for the formation of lot of unwanted by-products. The formation of unwanted by-products greatly decreases the quality of the product. Hence, additional purification(s) may be required to remove the unwanted compounds from the product which in turn decreases the yield of the product.

It is well known to the person skilled in the art that increasing the number of synthetic steps decreases the overall productivity and increases the cost of the production of the target compound.

In view of all these disadvantages, the above described processes are not suitable to adopt on commercial scale.

Hence, there is a significant need in the art to develop a process for the preparation of Lifitegrast which involves lesser number of synthetic steps and produces the product with high yield and better quality.

The present inventors after numerous trails and earnest efforts developed a process for the preparation of Lifitegrast which involves less number of steps, low reaction time cycle, simple operations and easy to carry out chemical conversions.

The process described in the present invention is simple, safe, economic and suitable for the production of Lifitegrast and its intermediates on commercial scale.

US8367701B2 describes five crystalline polymorphic forms of Lifitegrast namely form-A, form-B, form-C, form-D, form-E and amorphous form.

WO2014018748 describes crystalline form-II of Lifitegrast and process for its preparation.

IPCOM000250248D describes a crystalline polymorph of Lifitegrast and process for its preparation.

IPCOM000250498D discloses three crystalline forms of Lifitegrast namely form-i, form-ii, form-iii and processes for their preparation.

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 crystalline forms that a formulation scientist has available for designing a pharmaceutical dosage form with desired characteristics.

After numerous trials and earnest efforts, the present inventors surprisingly found novel crystalline polymorphs of Lifitegrast having advantageous properties which are useful and well suitable for the preparation of various pharmaceutical compositions.

Brief description of the invention:

The first aspect of the present invention is to provide a process for the preparation of (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid compound of formula-1.

The second aspect of the present invention is to provide an improved process for the preparation of compound of formula-1.

The third aspect of the present invention is to provide a novel crystalline polymorph of compound of formula-1, herein after designated as form-M.

The fourth aspect of the present invention is to provide a novel crystalline polymorph of compound of formula-1, herein after designated as form-S.

The fifth aspect of the present invention is to provide a novel crystalline polymorph of compound of formula-1, herein after designated as crystalline form-N.

The sixth aspect of the present invention is to provide a novel crystalline polymorph of compound of formula-1, herein after designated as crystalline form-L.

The seventh aspect of the present invention is to provide a process for the preparation of compound of formula-1.

The eighth aspect of the present invention is to provide a novel process for the preparation of compound of formula-1.

The ninth aspect of the present invention is to provide alternate process for the preparation of compound of formula-1.

The tenth aspect of the present invention is to provide a novel process for the preparation of compound of formula-1.

The eleventh aspect of the present invention is to provide another novel process for the preparation of compound of formula-1.

The twelfth aspect of the present invention is to provide another process for the preparation of compound of formula-1.

The thirteenth aspect of the present invention is to provide a novel process for the preparation of compound of formula-1.

Brief Description of the Drawings:

Figure-1: Illustrates powder X-Ray diffraction (PXRD) pattern of compound of formula-5

Figure-2: Illustrates the PXRD pattern of crystalline form-M of compound of formula-1

Figure-3: Illustrates the PXRD pattern of crystalline form-S of compound of formula-1

Figure-4: Illustrates the PXRD pattern of crystalline form-N of compound of formula-1 obtained according to example-5

Figure-5: Illustrates the PXRD pattern of crystalline polymorph of compound of formula-1 obtained according to example-6

Figure-6: Illustrates the PXRD pattern of compound of formula-1 obtained according to example-13

Figure-7: Illustrates the PXRD pattern of crystalline form-L of compound of formula-1

Figure-8: Illustrates the PXRD pattern of compound of formula-1 obtained after drying the crystalline form-L at 100°C for 10 hr

Figure-9: Illustrates the PXRD pattern of compound of formula-3a

Figure-10: Illustrates the PXRD pattern of compound of formula-5a

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 hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid; and "organic acids" such as formic acid, acetic acid, propionic acid, butyric acid, valeric acid, capric acid, oxalic acid, malonic acid, maleic acid, fumaric acid, succinic acid, citric acid, tartaric acid, benzoic acid, salicylic 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), 0-(benzotriazol-l-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), N-hydroxysuccinamide (HOSu), N-hydroxysulfosuccinimide (Sulfo-NHS) and the like.

In the present invention, the suitable "amine protecting group" or "N-protecting group" 'PG' can be selected from but not limited to alkoxycarbonyl such methoxycarbonyl (Moc), ethoxycarbonyl, tert-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz), p-methoxybenzyl carbonyl (Moz or MeOZ), 9-fluorenylmethyloxy carbonyl (Fmoc), acetyl (Ac), benzoyl (Bz), benzyl (Bn), carbamate group, p-methoxyphenyl (PMP), p-methoxybenzyl (PMB), 3,4-dimethoxybenzyl (DMPM), tosyl (Ts), tnfluoroacetyl (TFA), trichloroethoxycarbonyl (Troc), pivaloyl (Piv), triphenylmethyl (trityl or Trt) and the like.

The suitable amine protecting agent can be selected such that it is capable of protecting the nitrogen atom with any of the above mentioned amine protecting groups.

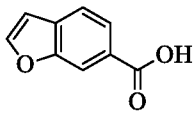
Suitable amine protecting agent can be selected from but not limited to di-tert.butyl dicarbonate (DIBOC), benzyl chloroformate, fluorenylmethyloxy carbonyl chloride (Fmoc chloride), acetyl chloride, acetic anhydride, benzoyl halides, benzyl halides, alkyl haloformates such as methyl chloroformate, ethyl chloroformate, isopropyl chloroformate and the like, tosyl halides, tosyl anhydrides, alkyl trifluoroacetates such as methyl trifluoroacetate, ethyl trifluoroacetate, isopropyl trifluoroacetate, vinyl trifluoroacetate, trifluoroacetic acid, tnfluoroacetyl chloride, trichloroethoxycarbonyl chloride, pivaloyl chloride, triphenylmethyl chloride (trityl chloride) and the like.

The "suitable deprotecting agent" can be selected based on the protecting group employed. The "suitable deprotecting agent" can be selected from but not limited to acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, aq.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; 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(Ci-C_6)alkylsilanes, tri(Ci-C_6) alkylsilyl halides and the like.

In the present invention, 'X' represents halogen such as F, CI, Br & I.

The first aspect of the present invention provides a process for the preparation of (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid compound of formula-1, comprising;

a) reacting benzofuran-6-carboxylic acid compound of formula-2



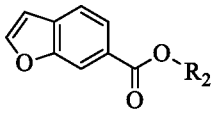
Formula-2

with compound of general formula

R_2-OH

wherein, 'R_2' represents substituted or unsubstituted aryl and the substituents wherever used can be independently selected from halogens such as F, CI, Br & I, $N0_2$ and the substitution can be takes place at single or multiple positions on aryl group;

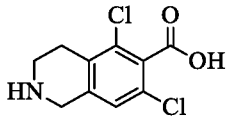
in a suitable solvent optionally in presence of a suitable coupling agent and/or a suitable base to provide compound of general formula-3,



Formula-3

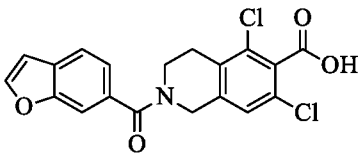
wherein, 'R_2' is same as defined above;

b) reacting compound of general formula-3 with 5,7-dichloro-l,2,3,4-tetrahydro isoquinoline-6-carboxylic acid compound of formula-4 or its salt



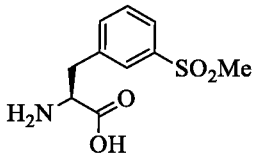
Formula-4

in a suitable solvent optionally in presence of a suitable base to provide 2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxylic acid compound of formula-5,



Formula-5

c) reacting compound of formula-5 with (S)-2-amino-3-(3-(methylsulfonyl)phenyl) propanoic acid compound of formula-6 or its salt



Formula-6

in a suitable solvent optionally in presence of a suitable coupling agent and/or a suitable base to provide compound of formula- 1.

Wherein, in step-a) & step-c) the suitable coupling agent is selected from the coupling agents as described above;

In step-a), step-b) & step-c) the suitable base is selected from organic bases, inorganic bases, organolithium bases, organosilicon bases or mixtures thereof;

In step-a) to step-c) the suitable solvent wherever necessary is selected from hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents or mixtures thereof.

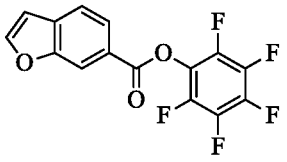
In the above described process, the compound of formula-3 can be optionally isolated from the reaction mixture as a solid and purified from a suitable solvent or mixture of solvents as defined above to provide pure compound of formula-3.

In one embodiment of the present invention, the activated compounds which are formed by reacting compound of formula-2 or compound of formula-5 with suitable coupling agent optionally in presence of a suitable base in a suitable solvent can optionally be isolated from the reaction mixture in solid form and can be further purified from a suitable solvent or mixture of solvents. Then the said activated compounds can be further reacted with compound of formula R_2-OH (in case of compound of formula-2) or compound of formula-6 or its salt (in case of compound of formula-5) in a suitable solvent optionally in presence of a suitable base to provide compound of formula-3 or compound of formula- 1 respectively.

In another embodiment of the present invention, the said activated compounds are not isolated from the reaction mixture and are reacted in-situ with the subsequent compounds to provide the corresponding products.

A preferred embodiment of the present invention provides a process for the preparation of compound of formula-1, comprising;

a) reacting compound of formula-2 with pentafluorophenol in a suitable solvent optionally in presence of a suitable coupling agent and/or a suitable base to provide perfluorophenyl benzofuran-6-carboxylate compound of formula-3a,

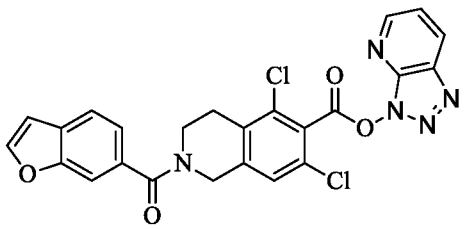


Formula-3a

b) optionally isolating compound of formula-3a as a solid,

c) reacting compound of formula-3a with compound of formula-4 or its salt in a suitable solvent optionally in presence of a suitable base to provide compound of formula-5,

d) reacting compound of formula-5 with l-[bis(dimethylamino)methylene]-lH-l,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluoro phosphate in a suitable solvent optionally in presence of a suitable base to provide 3H-[l,2,3]triazolo[4,5-b]pyridin-3-yl 2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxylate compound of formula-5a,



Formula-5a

e) optionally isolating compound of formula-5a as a solid,

f) reacting compound of formula-5a with compound of formula-6 or its salt in a suitable solvent optionally in presence of a suitable base to provide compound of formula-1.

Wherein, in step-a) the suitable coupling agent, suitable base and the suitable solvent are same as defined in step-a) of the first aspect of the present invention;

In step-c), step-d) & step-f) the suitable base and the suitable solvent are same as defined in step-b) of the first aspect of the present invention.

A more preferred embodiment of the present invention provides a process for the preparation of compound of formula-1, comprising;

a) reacting compound of formula-2 with pentafluorophenol in presence of oxalyl chloride and N,N-diisopropylethylamine in tetrahydrofuran and catalytic amount of dimethylformamide to provide compound of formula-3a,
b) isolating compound of formula-3a as a solid,
c) reacting compound of formula-3a with 5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid hydrochloride compound of formula-4a in presence of N,N-diisopropylethylamine in acetonitrile to provide compound of formula-5,
d) reacting compound of formula-5 with HATU in presence of triethylamine in acetonitrile to provide compound of formula-5a,
e) isolating compound of formula-5a as a solid,
f) reacting compound of formula-5a with (S)-2-amino-3-(3-(methylsulfonyl)phenyl) propanoic acid hydrochloride compound of formula-6a in presence of triethylamine in dimethylsulfoxide to provide compound of formula-1.

An embodiment of the present invention provides a process for the preparation of compound of formula-1, comprising reacting compound of formula-5 with compound of formula-6 or its salt in a suitable solvent optionally in presence of a suitable coupling agent and/or a suitable base to provide compound of formula-1.

Wherein, the suitable coupling agent, suitable base and the suitable solvent are same as defined in step-a) of the first aspect of the present invention.

In one embodiment of the present invention, the activated compound which is formed by reacting compound of formula-5 with suitable coupling agent optionally in presence of a suitable base in a suitable solvent can optionally be isolated from the reaction mixture in

solid form and can be further purified from a suitable solvent or mixture of solvents. Then the activated compound can be further reacted with compound of formula-6 or its salt in a suitable solvent optionally in presence of a suitable base to provide compound of formula-1.

In another embodiment of the present invention, the said activated compound is not isolated from the reaction mixture and is reacted in-situ with compound of formula-6 or its salt to provide compound of formula-1.

A preferred embodiment of the present invention provides a process for the preparation of compound of formula-1, comprising;

a) reacting compound of formula-5 with HATU in a suitable solvent optionally in presence of a suitable base to provide compound of formula-5a,
b) optionally isolating compound of formula-5a as a solid,
c) reacting compound of formula-5a with compound of formula-6 or its salt in a suitable solvent optionally in presence of a suitable base to provide compound of formula-1.

Wherein, in step-a) & step-c) the suitable base and the suitable solvent are same as defined in step-a) of the first aspect of the present invention.

A more preferred embodiment of the present invention provides a process for the preparation of compound of formula-1, comprising;

a) reacting compound of formula-5 with HATU in presence of triethylamine in acetonitrile to provide compound of formula-5a,
b) isolating compound of formula-5a as a solid,
c) reacting compound of formula-5a with compound of formula-6a in presence of triethylamine in dimethylsulfoxide to provide compound of formula-1.

The other embodiment of the present invention provides a process for the preparation of compound of formula-5, comprising reacting compound of formula-2 with compound of formula-4 or its salt in a suitable solvent optionally in presence of a suitable coupling agent and/or a suitable base to provide compound of formula-5.

Wherein the suitable coupling agent, the suitable base and the suitable solvent are same as defined in step-a) of the first aspect of the present invention.

In this case also, the activated compound which is formed by reacting compound of formula-2 with a suitable coupling agent in a suitable solvent optionally in presence of a suitable base can be optionally isolated from the reaction mixture and can be further purified from a suitable solvent or mixture of solvents. Then the activated compound can be reacted with compound of formula-4 or its salt in a suitable solvent optionally in presence of a suitable base to provide compound of formula-5.

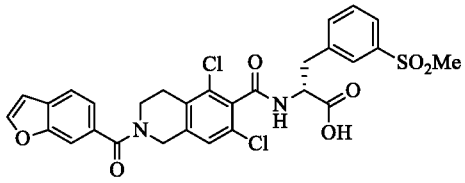
The compound of formula-1 obtained by various processes of the present invention can be purified from a suitable solvent or mixture of solvents to provide pure compound of formula-1.

Wherein, the suitable solvent is selected from hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents or mixtures thereof.

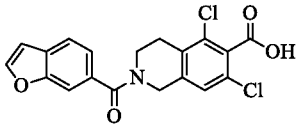
In one aspect of the present invention, the suitable solvent is selected from ketone solvents.

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-1 by the process of the present invention.



R-isomer impurity



Benzofuran isoquinoline acid impurity

The process for the preparation of compound of formula-1 developed by the present inventors produces highly pure compound of formula-1 with excellent 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- 1 produced by various processes of the present invention is having purity of greater than 99%, preferably greater than 99.5%, more preferably greater than 99.7% by HPLC.

The compound of formula-3a and compound of formula-5a which are formed in the processes of the present invention are novel compounds.

An embodiment of the present invention provides the use of said novel compounds as intermediates for the preparation of compound of formula- 1.

An embodiment of the present invention provides compound of formula-3a as a solid.

The other embodiment of the present invention provides a crystalline polymorph of compound of formula-3a. The said crystalline polymorph is characterized by its PXRD pattern having peaks at 8.9, 9.9, 12.4, 13.8, 14.2, 19.4, 19.9, 20.8, 21.7, 22.5, 24.6, 25.2, 27.9 and 30.4 ± 0.2° of 2Θ. The said crystalline polymorph is further characterized by its PXRD pattern as illustrated in figure-9.

An embodiment of the present invention provides compound of formula-5a as a solid.

The other embodiment of the present invention provides a crystalline polymorph of compound of formula-5a, characterized by its PXRD pattern having peaks at 8.2, 13.1, 13.4, 14.1, 15.1, 16.2, 17.0, 17.6, 18.4, 19.5, 20.2, 21.4, 21.9, 22.1, 23.0, 23.3, 24.2, 24.8, 25.7, 26.5, 27.2, 28.1, 28.7, 29.8 and 30.5 ± 0.2° of 2Θ. The said crystalline polymorph is further characterized by its PXRD pattern as illustrated in figure- 10.

An embodiment of the present invention provides a process for the purification of compound of formula-5, comprising;

a) treating compound of formula-5 with a suitable base in a suitable solvent,
b) treating reaction mixture with a suitable acid in a suitable solvent,
c) filtering the solid and drying to provide pure compound of formula-5.

Wherein, in step-a) the suitable base is selected from inorganic bases, organic bases or mixtures thereof; preferably inorganic bases.

In step-b) the suitable acid is selected from "inorganic acids" such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid; and "organic acids" such as formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, trifluoroacetic acid, trifluoromethanesulfonic acid, oxalic acid, malonic acid, maleic acid, fumaric acid, malic acid, succinic acid, citric acid, aspartic acid, tartaric acid, mandelic acid, benzoic acid, salicylic 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 or mixtures thereof.

In step-a) and step-b) the suitable solvent is independently selected from hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents or mixtures thereof.

A preferred embodiment of the present invention provides a process for the purification of compound of formula-5, comprising;

a) treating compound of formula-5 with aqueous potassium carbonate in a mixture of ethyl acetate and water,
b) separating the organic and aqueous layers,
c) treating aqueous layer with aqueous hydrochloric acid,
d) filtering the solid and drying to provide pure compound of formula-5.

The second aspect of the present invention provides an improved process for the preparation of compound of formula-1, comprising;

a) reacting compound of formula-2 with compound of formula-4 or its salt in a suitable solvent optionally in presence of a suitable base and/or a suitable coupling agent to provide compound of formula-5,
b) optionally purifying compound of formula-5 from a suitable solvent,
c) reacting compound of formula-5 with compound of formula-6 or its salt in a suitable solvent optionally in presence of a suitable base and/or a suitable coupling agent to provide compound of formula-1.

Wherein, in step-a) & step-c) the suitable base is selected from but not limited to organic bases, inorganic bases, organolithium bases, organosilicon bases or mixtures thereof;

The suitable coupling agent can be selected from coupling agents described above;

From step-a) to step-c) the suitable solvent wherever necessary is selected from but not limited to hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents, formic acid, acetic acid or mixtures thereof.

In an embodiment of the present invention, the term "salt" in relation to compound of formula-4 and compound of formula-6 represents acid-addition salts of said compounds formed with suitable acids.

In the present invention, the "suitable acid" refers to "inorganic acids" such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid; and "organic acids" such as formic acid, acetic acid, propionic acid, butyric acid, valeric acid, capric acid, oxalic acid, malonic acid, maleic acid, fumaric acid, succinic acid, citric acid, tartaric acid, benzoic acid, salicylic 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.

In one embodiment of the present invention, the activated esters which are formed by reacting compound of formula-2 or compound of formula-5 with suitable coupling agents optionally in presence of a suitable base in a suitable solvent can optionally be isolated from the reaction mixture in solid form and can be further purified from a suitable solvent or mixture of solvents. Then the said activated ester can be further reacted with compound of formula-4 or its salt (in case of compound of formula-2) or with compound of formula-6 or its salt (in case of compound of formula-5) in a suitable solvent optionally in presence of a suitable base to provide compound of formula-5 and compound of formula-1 respectively.

In another embodiment of the present invention, the said activated esters are not isolated from the reaction mixture and are reacted in-situ with the subsequent compounds to provide the corresponding products.

A preferred embodiment of the present invention provides a process for the preparation of compound of formula-1, comprising;

a) reacting compound of formula-2 with HATU in presence of triethylamine in dimethylformamide followed by reacting obtained activated compound with compound of formula-4a in presence of triethylamine in dichloromethane to provide compound of formula-5,
b) reacting compound of formula-5 with DCC/HOBt in presence of triethylamine in dichloromethane followed by reacting obtained activated compound with compound of formula-6a in presence of diisopropylethyl amine in dichloromethane to provide compound of formula-1.

Another preferred embodiment of the present invention provides a process for the preparation of compound of formula-1, comprising;

a) reacting compound of formula-2 with DCC/HOBt in dichloromethane followed by reacting obtained activated compound with compound of formula-4a in presence of triethylamine in dichloromethane to provide compound of formula-5,
b) reacting compound of formula-5 with DCC/HOBt in presence of triethylamine in dichloromethane followed by reacting obtained activated compound with compound of formula-6a in presence of diisopropylethyl amine in dichloromethane to provide compound of formula-1.

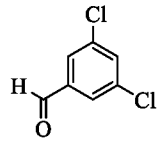
The compound of formula-2, compound of formula-4 or its salt and compound of formula-6 or its salt utilized in various processes of the present invention can be synthesized by any of the processes known in the art or they can be procured from any commercial sources available.

In one embodiment, the compound of formula-2 can be prepared according to any of the processes described in US8378105B2.

In the other embodiment, the compound of formula-4 or its salts and compound of formula-6 or its salts can be prepared by the processes as described below.

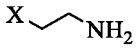
An embodiment of the present invention provides a process for the preparation of compound of formula-4 or its salts, comprising;

a) reacting 3,5-dichlorobenzaldehyde compound of formula-7



Formula-7

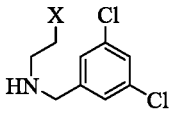
with 2-haloethanamine compound of general formula-8 or its acid-addition salt



Formula-8

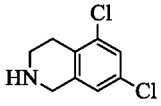
wherein, 'X' represents halogen;

in presence of a suitable reducing agent in a suitable solvent to provide 2-halo-N-(3,5-dichlorobenzyl)ethanamine compound of general formula-9,



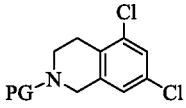
Formula-9

b) treating compound of general formula-9 with a suitable Lewis acid optionally in presence of a suitable solvent to provide 5,7-dichloro-l,2,3,4-tetrahydroisoquinoline compound of formula-10,



Formula-10

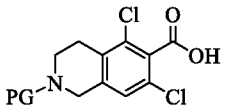
c) treating compound of formula-10 with a suitable amine protecting agent optionally in presence of a suitable solvent to provide compound of general formula-11,



Formula-11

wherein, **'PG'** represents amine protecting group;

d) converting compound of general formula-11 to compound of general formula-12 under suitable conditions,



Formula- 12

e) treating compound of general formula- 12 with a suitable deprotecting agent optionally in presence of a suitable solvent to provide compound of formula-4 or its salt,

f) isolating/purifying compound of formula-4 or its salt from a suitable solvent or mixture of solvents.

Wherein, in step-a) the suitable reducing agent is selected from but not limited to sodium triacetoxy borohydride (NaBH(OAc)3), sodium cyanoborohydride ($NaCNBH_3$), sodium bis(2-methoxyethoxy)aluminumhydride (Red-Al or Vitride), diisobutylaluminium hydride (DIBAL), lithium aluminium hydride ($LiAlH_4$), sodium borohydride ($NaBH_4$), catalytic hydrogenation in presence of Pd, Pt, Rh, Raney Ni, $Pt0_2$ and the like;

In step-b) the suitable Lewis acid is selected from but not limited to $A1C1_3$, $FeCl_3$, $T1CI_4$, BF_3, $BC1_3$, BBr_3, $ZnCl_2$, $SnCl_4$ and the like;

In step-c) the suitable amine protecting agent is selected based on the amine protecting group employed and it can be selected from the amine protecting agents described above. For instance, when the amine protecting group 'PG' represents Boc, then step-c) can be carried out by treating compound of formula- 10 with di-tert.butyl dicarbonate (DIBOC) optionally in presence of a suitable base selected from but not limited to organic bases, inorganic bases, organosilicon bases or their mixtures optionally in presence of a suitable solvent to provide compound of general formula- 11.

In step-d) the said conversion can be carried out by carboxylation of compound of general formula- 11 with carbon dioxide ($C0_2$) to provide compound of general formula- 12. This step can be performed in presence of organolithium compounds such as n-BuLi, lithium diisopropylamide (LDA) optionally in presence of tetramethyl ethylenediamine (TMEDA), alkyl/aryl magnesium halides (Grignard reagents), organoboron compounds, organozinc compounds, Lewis acids such as $A1X_3$ (X= halogen) optionally in presence of (a) metals such as Al, Zn or (b) silyl halides having the general formula $(Ci\text{-}C_6$ straight/branched chain alkyl$)_m$(aryl$)_{3-m}$SiX, wherein 'm' is an integer selected from 0,1,2,3 and 'X' represents halogen; and when 'm' is 2 or 3, the alkyl groups can be same or different.

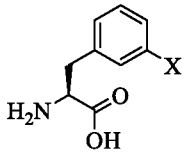
In one embodiment, the said carboxylation reaction can be carried out according to any of the processes described in *ChemSusChem, 2017, 10, 3317-3332* or the procedures cited therein preferably under anhydrous conditions.

In step-e) the suitable deprotecting agent is selected based on the protecting group employed and it can be selected from the deprotecting agents as described above. For instance, when the amine protecting group 'PG' represents Boc, then the deprotection step can be performed by treating compound of general formula-12 with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, aq.phosphoric acid, trifluoroacetic acid, methanesulfonic acid, p-toluenesulfonic acid and the like or with acetyl chloride in combination with alcohols;

In step-a) to step-f) the suitable solvent wherever necessary is selected from but not limited to hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents, formic acid, acetic acid or mixtures thereof.

The other embodiment of the present invention provides a process for the preparation of compound of formula-6 or its salt, comprising;

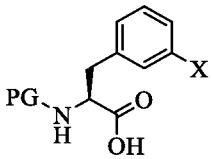
a) reacting compound of general formula-13



Formula-13

wherein, 'X' represents halogen;

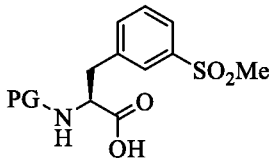
with a suitable amine protecting agent optionally in presence of a suitable solvent to provide compound of general formula-14,



Formula-14

wherein, 'PG' represents amine protecting group;

b) reacting compound of general formula-14 with $NaSO_2Me$ in a suitable solvent to provide compound of general formula-15,



Formula-15

c) treating compound of general formula-15 with a suitable deprotecting agent optionally in presence of a suitable solvent to provide compound of formula-6 or its salt,

d) isolating/purifying compound of formula-6 or its salt from a suitable solvent or mixture of solvents.

Wherein, in step-a) the suitable amine protecting agent is selected from the amine protecting agents as defined above. For instance, when the amine protecting group 'PG' represents Boc, then step-a) can be carried out by treating compound of formula-13 with di-tert.butyl dicarbonate (DIBOC) optionally in presence of a suitable base selected from but not limited to organic bases, inorganic bases, organosilicon bases or their mixtures optionally in presence of a suitable solvent to provide compound of general formula-14.

Step-b) can be carried out in presence of copper or palladium reagents selected from CuCl, CuBr, Cul, $Cu(OAc)_2$, Cu_20, $Cu(OTf)_2$, $Cu(OTf)_2PhH$, $Pd(OAc)_2$, $Pd_2(DBA)_3$ optionally in presence of a suitable base selected from but not limited to inorganic bases, organic bases, organolithium bases, organosilicon bases; This step is carried out optionally in presence of N,N'-dimethylethylamine, N,N-dimethylglycine, N,N'-dimethylamine, 1,10-phenanthroline, L-proline, L-hydroxyproline, neocuproine, 2-(hydroxymethyl)-2-methylpropane-l,3-diol, trans-1,2-diaminocyclohexane (DACH), 1,2-dimethylethylene diamine (DMEDA), D-glucosamine, xantophos and the like and optionally involves the usage of phase transfer catalyst such as tetra($Ci-C_6$)alkyl ammonium halides;

In step-c) the suitable deprotecting agent is selected based on the protecting group employed and the deprotecting agent can be selected from the deprotecting agents as described above. For instance, when the amine protecting group 'PG' represents Boc, then the deprotection step can be performed by treating compound of general formula-15 with

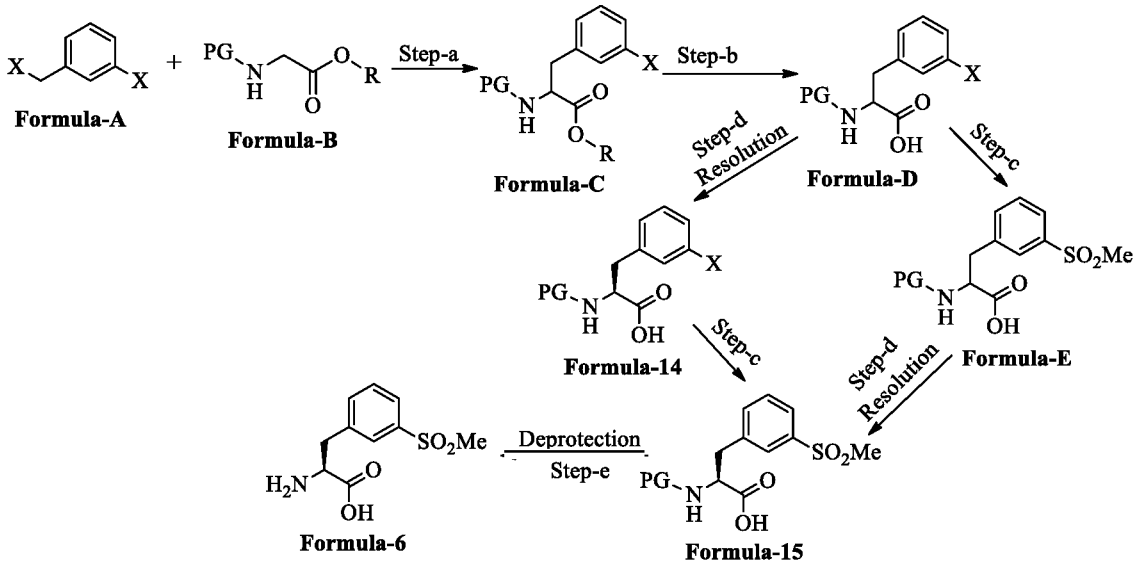
acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, aq.phosphoric acid, trifluoroacetic acid, methanesulfonic acid, p-toluenesulfonic acid and the like or with acetyl chloride in combination with alcohols.

From step-a) to step-d) the suitable solvent wherever necessary is selected from but not limited to hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents, formic acid, acetic acid or mixtures thereof.

The compound of formula-7 and compound of general formula-13 utilized in the above processes can be prepared by any of the processes known in the art or they can be procured from any commercial sources available.

Another embodiment of the present invention provides a process for the preparation of compound of formula-6 or its salts. The said process is schematically provided below.

Scheme:



Wherein, 'X' represents halogen such as F, CI, Br & I; 'PG' represents 'N-protecting group" or "amine protecting group", '**R**' represents Ci-C_6 straight/branched chain alkyl group.

Wherein in the above process, in step-a) the suitable base is selected from organic bases, inorganic bases, organolithium bases, organosilicon bases or their mixture;

In step-b) the hydrolysis can be carried out in presence of a suitable inorganic acid or a suitable inorganic base;

Step-c) can be carried out by reacting compound of general formula-D or compound of general formula- 14 with $NaSO_2Me$ in analogous manner to the procedure described above *(see.,* conversion of formula- 14 to formula- 15 above);

In step-d) the resolution process can be carried out by reacting compound of general formulae-D or E with chiral bases selected from but not limited to (R)-(+)-a-methylbenzylamine, (S)-(-)-a-methylbenzylamine, (R)-(+)-a-ethylbenzylamine, (S)-(-)-a-ethylbenzylamine, (R)-(+)-l-(2-naphthyl)ethylamine, (S)-(-)-l-(2-naphthyl)ethylamine, (R)-(-)- 1-amino-2-propanol, (S)-(+)- 1-amino-2-propanol, (R)-(+)- 1-(4-bromophenyl)ethylamine, (S)-(-)-l-(4-bromophenyl)ethylamine, (R)-4-chloro-a-methylbenzylamine, (S)-4-chloro-a-methylbenzylamine, (R)-(+)-N,a-dimethylbenzylamine, (S)-(-)-N,a-dimethylbenzylamine and the like;

Step-e) can be carried out by treating compound of general formula- 15 with a suitable deprotecting agent described above under suitable conditions. For example, when 'PG' represents Boc, then the deprotecting agent can be selected from acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, aq.phosphoric acid, trifluoroacetic acid, methanesulfonic acid, p-toluenesulfonic acid and the like, acetyl chloride in combination with alcohols.

Step-a) to step-e) can be carried out optionally in presence of suitable solvent 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 or mixtures thereof.

The third aspect of the present invention provides a novel crystalline polymorph of compound of formula- 1, herein after designated as form-M.

The said novel crystalline form-M of compound of formula- 1 is characterized by its PXRD pattern having peaks at 5.3, 9.8, 10.6, 14.5, 17.4, 17.8, 19.6, 20.9, 22.1, 24.3, 25.2, 26.3, 29.0, 30.0, 34.3 and 36.1 ± 0.2° of 2Θ.

The novel crystalline form-M is further characterized by its PXRD pattern having peaks at 6.3, 11.7, 12.1, 17.0, 17.5, 18.4, 20.4, 21.8, 22.9, 24.6, 25.8, 27.8, 29.7, 31.6, 38.4, 39.5 and 42.5 ± 0.2° of20.

In another embodiment, the novel crystalline polymorph is further characterized by its PXRD pattern having peaks at 5.3, 9.8, 10.6, 12.1, 14.5, 17.4, 19.6, 20.4, 21.8, 22.1, 22.9, 25.2, 26.3, 30.0 and 36.1 ± 0.2° of 2Θ.

In another embodiment of the present invention, the novel crystalline form-M of compound of formula-1 is characterized by its PXRD pattern as illustrated in figure-2.

An embodiment of the present invention provides a process for the preparation of crystalline form-M of compound of formula-1, comprising;

a) adding a suitable solvent to compound of formula-1,
b) optionally heating the reaction mixture to a suitable temperature,
c) stirring the reaction mixture,
d) optionally cooling the reaction mixture to a suitable temperature,
e) filtering the solid and drying to provide crystalline form-M of compound of formula-1.

Wherein, in step-a) the suitable solvent is selected from ester solvents, hydrocarbon solvents, chloro solvents, ether solvents, nitrile solvents or mixtures thereof;

In step-b) the suitable temperature ranges from 30°C to reflux temperature of the solvent used; and

In step-d) suitable temperature ranges from 0-30°C.

In an embodiment of the present invention, a small amount of crystalline form-M can optionally be added as seed material to the reaction mixture at any stage of step-a) to step-c) of the above described process.

A preferred embodiment of the present invention provides a process for the preparation of crystalline form-M of compound of formula-1, comprising;

a) adding isopropyl acetate to compound of formula-1 at 25-30°C,
b) heating the reaction mixture to 35-40°C,
c) stirring the reaction mixture,
d) filtering the solid and drying to provide crystalline form-M of compound of formula-1.

Another preferred embodiment of the present invention provides a process for the preparation of crystalline form-M of compound of formula-1, comprising;

a) adding isopropyl acetate to compound of formula-1 at 25-30°C,
b) adding a small amount of crystalline form-M of compound of formula-1 as seed crystal to the reaction mixture,
c) heating the reaction mixture to 35-40°C and stirring,
d) filtering the solid and drying to provide crystalline form-M of compound of formula-1.

The fourth aspect of the present invention provides a novel crystalline polymorph of compound of formula-1, herein after designated as form-S.

The crystalline form-S of compound of formula-1 of the present invention is characterized by its PXRD pattern having peaks at 10.5, 14.1, 14.7, 15.2, 15.9, 17.2, 19.6, 21.8, 24.1, 24.4, 25.3, 26.0, 27.0 and 28.7 ± 0.2° of 2Θ.

The novel crystalline form-S of compound of formula-1 is further characterized by its PXRD pattern having peaks at 10.5, 14.1, 14.7, 15.0, 15.2, 15.4, 15.9, 17.2, 19.6, 20.7, 21.8, 24.1, 24.4, 25.1, 25.3, 26.0, 27.0 and 28.7 ± 0.2° of 2Θ.

In another embodiment of the preset invention, the novel crystalline form-S of compound of formula-1 is characterized by its PXRD pattern as illustrated in figure-3.

An embodiment of the present invention provides a process for the preparation of crystalline form-S of compound of formula-1, comprising;

a) adding a suitable solvent to compound of formula-1,
b) optionally heating the reaction mixture to a suitable temperature,
c) adding a suitable second solvent to the reaction mixture,
d) optionally cooling the reaction mixture to a suitable temperature,
e) filtering the solid and drying to provide crystalline form-S of compound of formula-1.

Wherein, in step-a) the suitable solvent is selected from alcohol solvents, ester solvents, chloro solvents, nitrile solvents, ketone solvents, polar solvents or mixtures thereof;

In step-b) the suitable temperature ranges from 30°C to reflux temperature of the solvent used;

In step-c) the suitable second solvent is selected from hydrocarbon solvents, ester solvents, polar-aprotic solvents, ether solvents or mixtures thereof;

In step-d) the suitable temperature ranges from 0-30°C.

A preferred embodiment of the present invention provides a process for the preparation of crystalline form-S of compound of formula-1, comprising;

a) adding ethanol and dichloromethane to compound of formula-1 at 25-30°C,
b) heating the reaction mixture to 40-45 °C,
c) adding a mixture of cyclohexane and n-heptane to the reaction mixture,
d) cooling the reaction mixture to 0-5 °C,
e) filtering the solid and drying to provide crystalline form-S of compound of formula-1.

The fifth aspect of the present invention provides a novel crystalline polymorph of compound of formula-1, herein after designated as crystalline form-N. The said novel crystalline form-N is characterized by its PXRD pattern as illustrated in figure-4.

An embodiment of the present invention provides a process for the preparation of crystalline form-N of compound of formula-1, comprising;

a) adding compound of formula-1 to methanol or to a mixture of methanol and water,
b) stirring the reaction mixture,
c) optionally cooling the reaction mixture,
d) filtering the solid and drying to provide crystalline form-N of compound of formula-1.

Wherein, in one embodiment step-a) can be carried out at a suitable temperature ranges from 35°C to 70°C;

In step-b) stirring of the reaction mixture can be done for 15 min to 10 hr;

In step-c) the reaction mixture can be optionally cooled to a suitable temperature ranges from -50°C to 30°C.

In one embodiment of the present invention, a suitable solvent selected from ketone solvents, nitrile solvents, alcohol solvents such as ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, 2-butanol, tert-butanol and the like or mixtures thereof can be used instead of water in step-a) of the above described process.

A preferred embodiment of the present invention provides a process for the preparation of crystalline form-N of compound of formula-1, comprising;

a) adding compound of formula-1 to a pre-heated mixture of methanol and water at 60-65°C,
b) stirring the reaction mixture,
c) cooling the reaction mixture to 25-30°C,
d) filtering the solid and drying to provide crystalline form-N of compound of formula-1.

The sixth aspect of the present invention provides a novel crystalline polymorph of compound of formula-1, herein after designated as crystalline form-L. The said crystalline form-L is characterized by its PXRD pattern as illustrated in figure-7.

An embodiment of the present invention provides a process for the preparation of crystalline form-L of compound of formula-1, comprising;

a) adding n-propanol to compound of formula-1,
b) heating the reaction mixture to a suitable temperature,
c) adding water to the reaction mixture,
d) cooling the reaction mixture to a suitable temperature,
e) filtering the solid and drying to provide crystalline form-L of compound of formula-1.

Wherein, step-a) is carried out at 25-30°C;
In step-b) the suitable temperature ranges from 35°C to 100°C;
In step-d) the suitable temperature ranges from -30°C to 30°C.

A preferred embodiment of the present invention provides a process for the preparation of crystalline form-L of compound of formula-1, comprising;

a) adding n-propanol to compound of formula-1 at 25-30°C,
b) heating the reaction mixture to 60-65°C,
c) adding water to the reaction mixture,
d) cooling the reaction mixture to 25-30°C,
e) filtering the solid and drying to provide crystalline form-L of compound of formula-1.

The crystalline polymorphs of compound of formula-1 of the present invention are prepared by the processes as illustrated in the present invention and they are useful for the preparation of various pharmaceutical compositions.

An embodiment of the present invention provides the use of crystalline polymorphs of compound of formula-1 of the present invention for the preparation of pharmaceutical formulations.

The other embodiment of the present invention provides pharmaceutical composition comprising crystalline polymorphs of compound of formula-1 of the present invention and at least one pharmaceutically acceptable excipient.

Another embodiment of the present invention provides a method of treating or preventing a condition or disease comprising administering to the patient a therapeutically effective amount of any of the crystalline polymorphs of compound of formula-1 of the present invention.

The compound of formula-1 which is used as input in the above processes for the preparation of various crystalline polymorphs of compound of formula-1 of the present invention can be prepared by any of the processes known in the art.

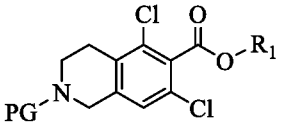
The novel crystalline polymorphs of compound of formula-1 of the present invention can be utilized as input for the preparation of any of the known polymorphic forms of compound of formula-1 and they can also be used as input for the preparation of other novel crystalline polymorphs of compound of formula-1.

The novel crystalline polymorphs of compound of formula-1 of the present invention are useful and well suitable for the preparation of various pharmaceutical compositions formulated in a manner suitable for the route of administration to be used where at least a portion of compound of formula-1 is present in the composition in particular polymorphic form mentioned. Such pharmaceutical compositions may comprise compound of formula-1 present in the composition in a range of between 0.005% and 100% (wt/wt), with the balance of the pharmaceutical composition comprising additional substances such as excipients, diluents, lubricants, binders, wetting agents, disintegrating agents, glidants, sweetening

agents, flavoring agents, emulsifying agents, solubilizing agents, pH buffering agents, perfuming agents, surface stabilizing agents, suspending agents and other conventional pharmaceutically inactive agents.

The seventh aspect of the present invention provides a process for the preparation of compound of formula-1, comprising;

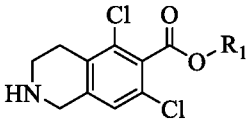
a) treating protected compound of general formula-16



Formula-16

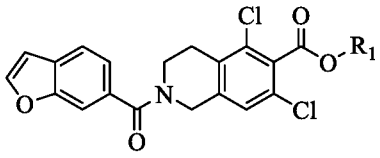
wherein, 'PG' represents amine protecting group or N-protecting group; 'Ri' represents Ci-C_6 straight chain or branched chain alkyl group;

with a suitable deprotecting agent optionally in a suitable solvent to provide compound of general formula-17 or its salt,



Formula-17

b) coupling of compound of general formula-17 or its salt with compound of formula-2 in presence of a suitable base in a suitable solvent optionally in presence of a suitable coupling agent to provide compound of general formula-18,



Formula-18

c) hydrolyzing compound of general formula-18 in presence of a suitable acid or a suitable base optionally in a suitable solvent to provide compound of formula-5,

d) coupling of compound of formula-5 with compound of formula-6 or its salt in presence of a suitable base in a suitable solvent optionally in presence of a suitable coupling agent to provide compound of formula-1.

Wherein, in step-a) the suitable deprotecting agent is selected based on the type of the protecting group employed. In one embodiment, it can be selected from the deprotecting agents as described above.

In step-b) & step-d) the suitable base is selected from organic bases, inorganic bases, organolithium bases, organosilicon bases or their mixtures; and the suitable coupling agent is same as defined above in step-a) of the first aspect of the present invention.

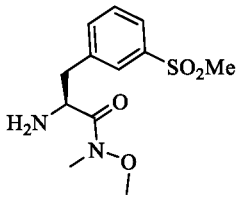
In step-c) the suitable acid is selected from inorganic acids and the suitable base can be selected from inorganic bases.

In step-a) to step-d) the suitable solvent wherever necessary is selected from but not limited to hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents, formic acid, acetic acid or mixtures thereof.

The compound of general formula-16, compound of formula-2 and compound of formula-6 or its salt which are used in the above process can be obtained from any commercial sources or they can be synthesized by any of the processes known in the art.

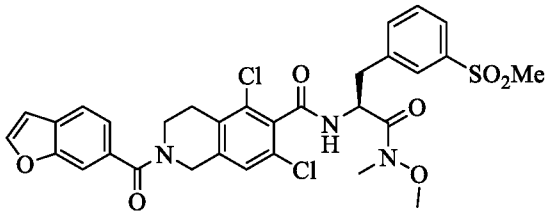
The eighth aspect of the present invention provides a novel process for the preparation of compound of formula-1, comprising;

a) reacting compound of formula-5 with (S)-2-amino-N-methoxy-N-methyl-3-(3-(methyl sulfonyl)phenyl)propanamide compound of formula-20 or its salt



Formula-20

in presence of a suitable base in a suitable solvent optionally in presence of a suitable coupling agent to provide (S)-2-(benzofuran-6-carbonyl)-5,7-dichloro-N-(l-(methoxy (methyl)amino)-3-(3-(methylsulfonyl)phenyl)- 1-oxopropan-2-yl)- 1,2,3,4-tetrahydro isoquinoline-6-carboxamide compound of formula-21,



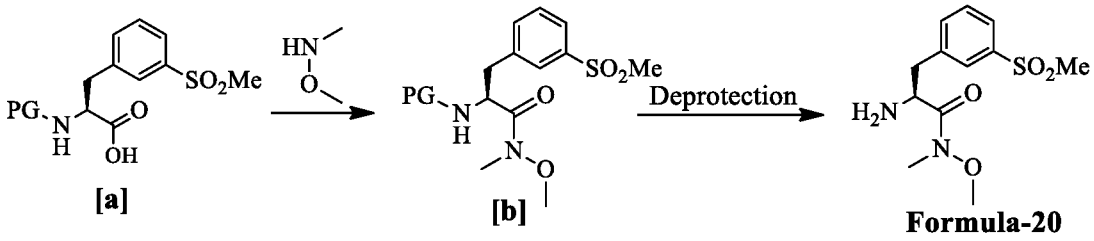
Formula-21

b) hydrolyzing compound of formula-21 in presence of a suitable acid or a suitable base optionally in a suitable solvent to provide compound of formula- 1.

Wherein, in step-a) the suitable coupling agent, suitable base and the suitable solvent are same as defined in step-a) of the first aspect of the present invention;

In step-b) the suitable acid, suitable base and the suitable solvent are same as defined in step-c) of the seventh aspect of the present invention.

The compound of formula-20 or its salt used in the above process can be prepared by the process as shown in the following synthetic scheme;



Wherein, 'PG' represents amine protecting group or N-protecting group.

Compound of formula-[b] is prepared by reacting compound of formula-[a] with N,O-dimethyl hydroxylamine or its salt in presence of a suitable base in a suitable solvent optionally in presence of a suitable coupling agent. Wherein, the suitable coupling agent, suitable base and the suitable solvent are same as defined in step-a) of the first aspect of the present invention.

Compound of formula-20 or its salt is prepared by deprotection of compound of formula-[b] with a suitable deprotecting agent as described in the present invention optionally in presence of a suitable solvent.

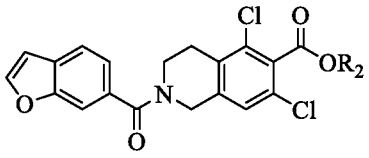
The ninth aspect of the present invention provides alternate process for the preparation of compound of formula-1, comprising;

a) reacting compound of formula-5 with compound of general formula

R_2-OH

wherein, 'R_2' represents substituted or unsubstituted aryl and the substituents are independently selected from halogens such as F, CI, Br, I, $N0_2$,

in presence of a suitable base in a suitable solvent optionally in presence of a suitable coupling agent to provide compound of general formula-19,



Formula-19

wherein, 'R_2' is same as defined above,

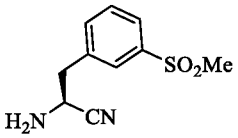
b) optionally isolating compound of general formula-19 from the reaction mixture,

c) reacting compound of general formula-19 with compound of formula-6 or its salt in a suitable solvent optionally in presence of a base to provide compound of formula-1.

Wherein, in step-a) & step-c) the suitable coupling agent, the suitable base and the suitable solvent are same as defined in step-a) of the first aspect of the present invention.

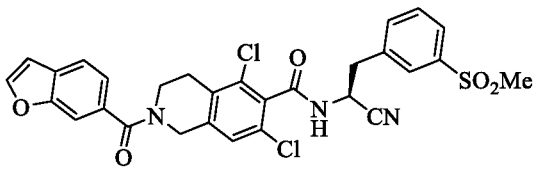
The tenth aspect of the present invention provides a novel process for the preparation of compound of formula-1, comprising;

a) reacting compound of formula-5 with (S)-2-amino-3-(3-(methylsulfonyl)phenyl) propane nitrile compound of formula-22 or its salt



Formula-22

in presence of a suitable base in a suitable solvent optionally in presence of a suitable coupling agent to provide (S)-2-(benzofuran-6-carbonyl)-5,7-dichloro-N-(l-cyano-2-(3-(methylsulfonyl)phenyl)ethyl)- 1,2,3,4-tetrahydroisoquinoline-6-carboxamide compound of formula-23,



Formula-23

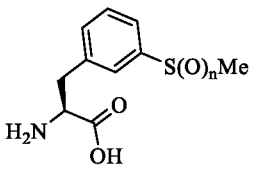
b) hydrolyzing compound of formula-23 in presence of a suitable acid or a suitable base optionally in presence of a suitable solvent to provide compound of formula- 1.

Wherein, in step-a) the suitable coupling agent, the suitable base and the suitable solvent are same as defined in step-a) of the first aspect of the present invention;

In step-b) the suitable acid, the suitable base and the suitable solvent are same as defined in step-c) of the seventh aspect of the present invention.

The eleventh aspect of the present invention provides another novel process for the preparation of compound of formula- 1, comprising;

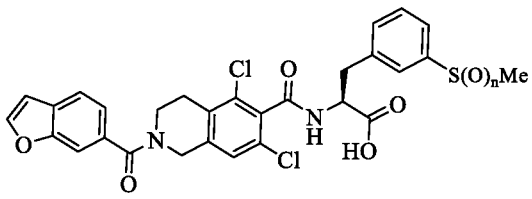
a) reacting compound of formula-5 or compound of general formula- 19 with compound of general formula-27 or its salt



Formula-27

wherein, 'n' is 0 or 1;

in presence of a suitable base in a suitable solvent optionally in presence of a suitable coupling agent to provide compound of general formula-28,



Formula-28

b) oxidizing compound of general formula-28 with a suitable oxidizing agent in a suitable solvent to provide compound of formula- 1.

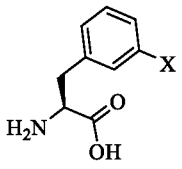
Wherein, in step-a) the suitable coupling agent, the suitable base and the suitable solvent are same as defined in step-a) of the first aspect of the present invention;

In step-b) the suitable oxidizing agent is selected from but not limited to oxone (potassium peroxymonosulfate), hydrogen peroxide (H_20_2), urea-hydrogen peroxide adduct, tert-butyl hydroperoxide (t-BuOOH or TBHP), cumene hydroperoxide (CHP), peracetic acid, trifluoroperacetic acid (TFPAA), dimethyldioxirane (DMDO), o-Iodoxybenzoic acid, m-chloroperbenzoic acid (MCPBA), molecular oxygen, (diacetoxyiodo)benzene, ammonium cerium(IV) nitrate, $Mη0_2$, $KMn0_4$, $Ru0_4$, periodic acid (H_5IO_6), sodium periodate, sodium perborate, HNO_3, sodium hypochlorite (NaOCl), calcium hypochlorite ($Ca(OCl)_2$) and the like or their mixtures; and the suitable solvent is same as defined in step-a) of the first aspect of the present invention.

The said oxidation step is carried out optionally in presence of a titanium, vanadium or a molybdenum catalyst selected from but not limited to titanium isopropoxide, vanadium pentoxide, vanadyl acetylacetonate [$VO(acac)_2$], molybdenum acetylacetonate and the like.

The twelfth aspect of the present invention provides another process for the preparation of compound of formula-1, comprising;

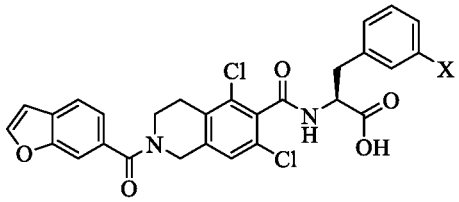
a) reacting compound of formula-5 or compound of general formula-19 with compound of general formula-13 or its salt



Formula-13

wherein, 'X' represents halogen such as F, CI, Br and I;

in presence of a suitable base in a suitable solvent optionally in presence of a suitable coupling agent to provide compound of general formula-26,



Formula-26

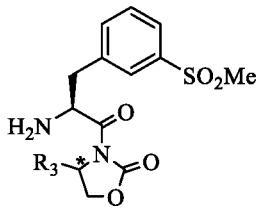
b) reacting compound of general formula-26 with $NaSO_2Me$ in a suitable solvent to provide compound of formula-1.

Wherein, in step-a) the suitable coupling agent, suitable base and the suitable solvent are same as defined in step-a) of the first aspect of the present invention;

In step-b) the suitable solvent is same as defined in step-a) of the first aspect of the present invention. This step is carried out in presence of copper or palladium reagents such as CuCl, CuBr, CuI, $Cu(OAc)_2$, Cu_2O, $Cu(OTf)_2$, $Cu(OTf)_2PhH$, $Pd(OAc)_2$, $Pd_2(DBA)_3$ optionally in presence of a suitable base selected from but not limited to inorganic bases, organic bases, organolithium bases, organosilicon bases; This step is carried out optionally in presence of N,N'-dimethylethylamine, N,N-dimethylglycine, N,N'-dimethylamine, 1,10-phenanthroline, L-proline, L-hydroxyproline, neocuproine, 2-(hydroxymethyl)-2-methylpropane-l,3-diol, trans-1,2-diaminocyclohexane (DACH), 1,2-dimethylethylene diamine (DMEDA), D-glucosamine, xantophos and the like and optionally involves the usage of phase transfer catalyst such as tetra(C_1-C_6)alkyl ammonium halides.

The thirteenth aspect of the present invention provides a novel process for the preparation of compound of formula-1, comprising;

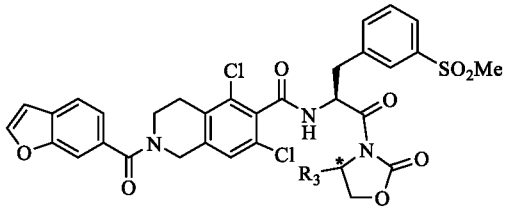
a) reacting compound of formula-5 with compound of general formula-24 or its salt



Formula-24

wherein, 'R_3' can be selected from phenyl(Ph), benzyl (Bn) & '*'represents chiral center and the configuration at said chiral center can be (R) or (S);

in presence of a suitable base in a suitable solvent optionally in presence of a suitable coupling agent to provide compound of general formula-25,



Formula-25

b) converting compound of general formula-25 to compound of formula- 1.

Wherein, in step-a) the suitable coupling agent, the suitable base and the suitable solvent are same as defined in step-a) of the first aspect of the present invention;

In step-b) the conversion of compound of general formula-25 to compound of formula- 1 can be done by acid or base hydrolysis optionally in presence of a suitable solvent. The acid can be selected from inorganic acids, the base can be selected from inorganic bases and the suitable solvent is same as defined in step-a) of the first aspect of the present invention. This step can be carried out optionally in presence of hydrogen peroxide or lithium peroxide (LiOOH).

HPLC Method of Analysis;

The compound of formula- 1 produced by the process of the present invention was analyzed by HPLC under the following conditions;

Apparatus: A liquid chromatograph equipped with variable wavelength UV detector; Column: Zodiac C18 250 X 4.6 mm, 3 μπι (or) equivalent; Wavelength: 215 nm; Column temperature: 40°C; Auto sampler temperature: 5°C; Injection volume: 5 μL; Diluent: Mobile phase-A: Mobile phase-B (80:20 v/v); Elution: Gradient; Sample concentration: 0.5 mg/mL; Buffer preparation: Accurately transfer 1000 mL of milli-Q-water into a suitable clean and dry beaker. Transfer accurately 1.32 gm of diammonium hydrogen ortho phosphate in 1000 mL of milli-Q-water. Adjust its pH to 7.2 with dilute ortho phosphoric acid solution (transfer 1 mL of ortho phosphoric acid solution (85%) in 10 mL of water). Filter this solution through 0.45 μπι durapore PVDF filter paper; Mobile phase-A: Accurately transfer 900 ml of Buffer and 100 ml of acetonitrile into a 1000 mL mobile phase bottle, mix well and sonicate to degas it; Mobile phase-B: Accurately transfer 600 mL of acetonitrile and 400 mL of buffer into a 1000 mL mobile phase bottle, mix well and sonicate to degas it.

The chiral purity of compound of formula-1 produced by the process of the present invention was analyzed by HPLC under the following conditions;
Apparatus: A liquid chromatograph equipped with variable wavelength UV detector; Column: CHIRALPAK IA-3 250 X 4.6 mm, 3 μπι (or) equivalent; Wavelength: 254 nm; Column temperature: 40°C; Injection volume: 15 μL; Diluent: 0.05% triethylamine in ethanol; Elution: Isocratic; Mobile phase composition: n-Heptane:Isopropyl alcohol:Dichloromethane:TFA (70:20:10:0.2 v/v/v/v).

PXRD Method of Analysis:

The PXRD analysis of compounds of the present invention was carried out using BRUKER/D8 ADVANCE X-Ray diffractometer using CuKa radiation of wavelength 1.5406A^0 and at a continuous scan speed of 0.03°/min.

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

An embodiment of the present invention provides compound of formula-1 with particle size distribution of D90 less than 50 μπι, preferably less than 20 μπι.

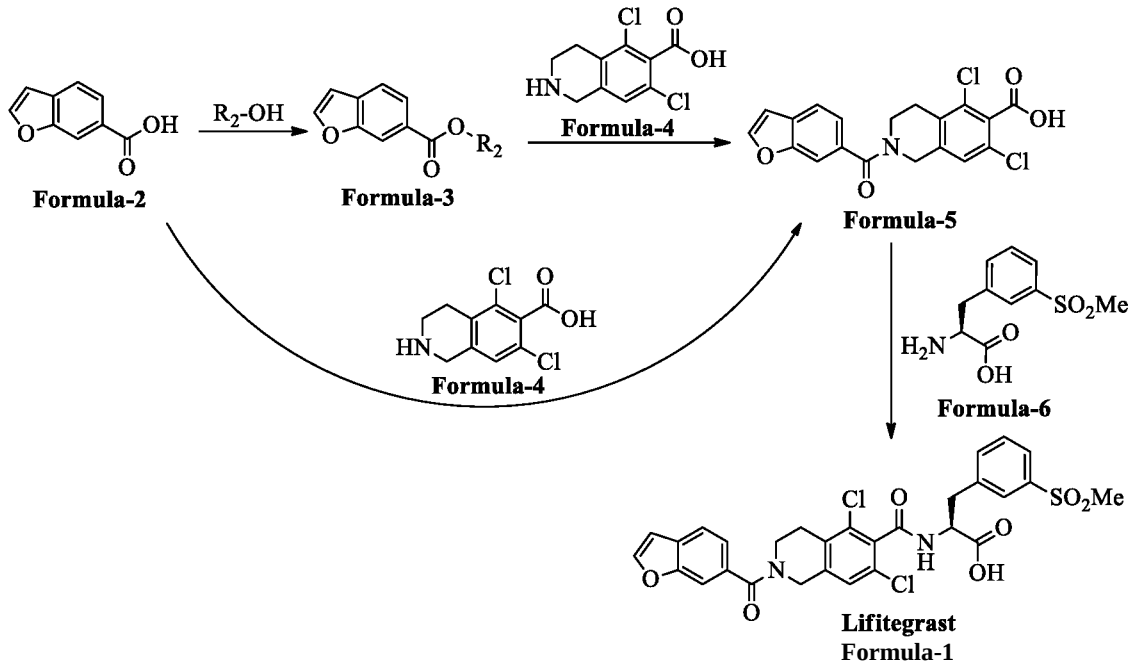
Particle size distribution (PSD) method of analysis:

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

The compound of formula-1 produced by the processes 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 or micronization may be performed before drying or after drying of the product.

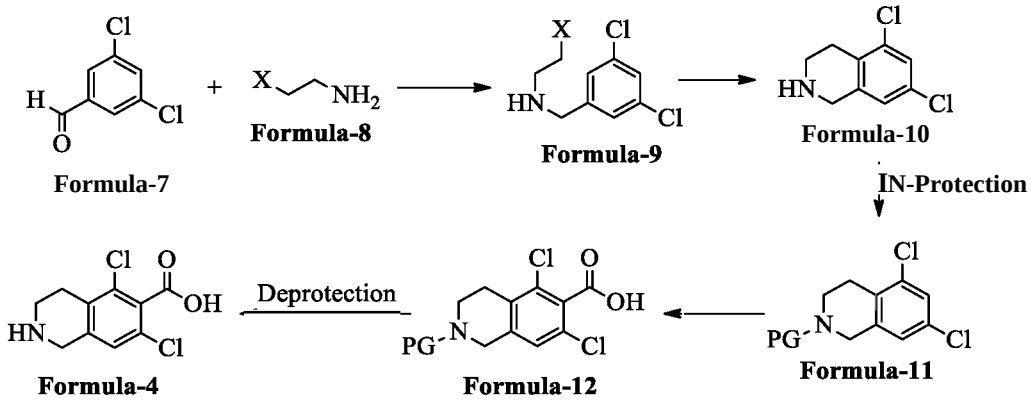
The present invention is schematically represented as follows;

Scheme-I:



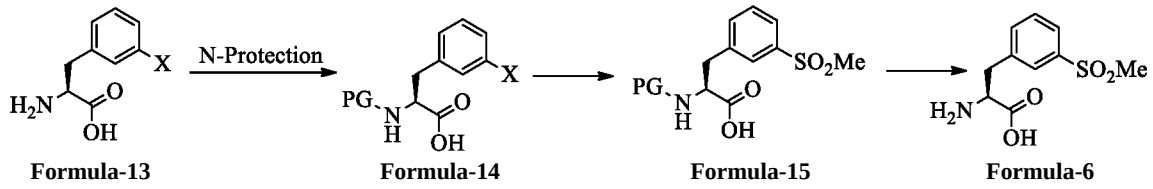
Wherein, 'R_2' represents substituted or unsubstituted aryl and the substituents wherever used can be independently selected from halogens such as F, Cl, Br & I, $N0_2$ and the substitution can be takes place at single or multiple positions on aryl group.

Scheme-II:



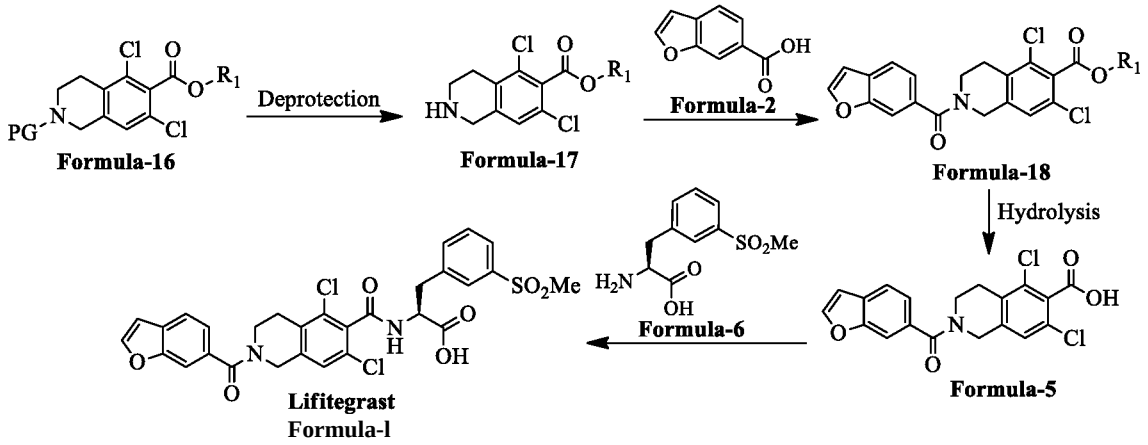
Wherein, 'X' represents halogen such as F, Cl, Br & I; and 'PG' represents 'N-protectin^; group" or "amine protecting group".

Scheme-Ill:



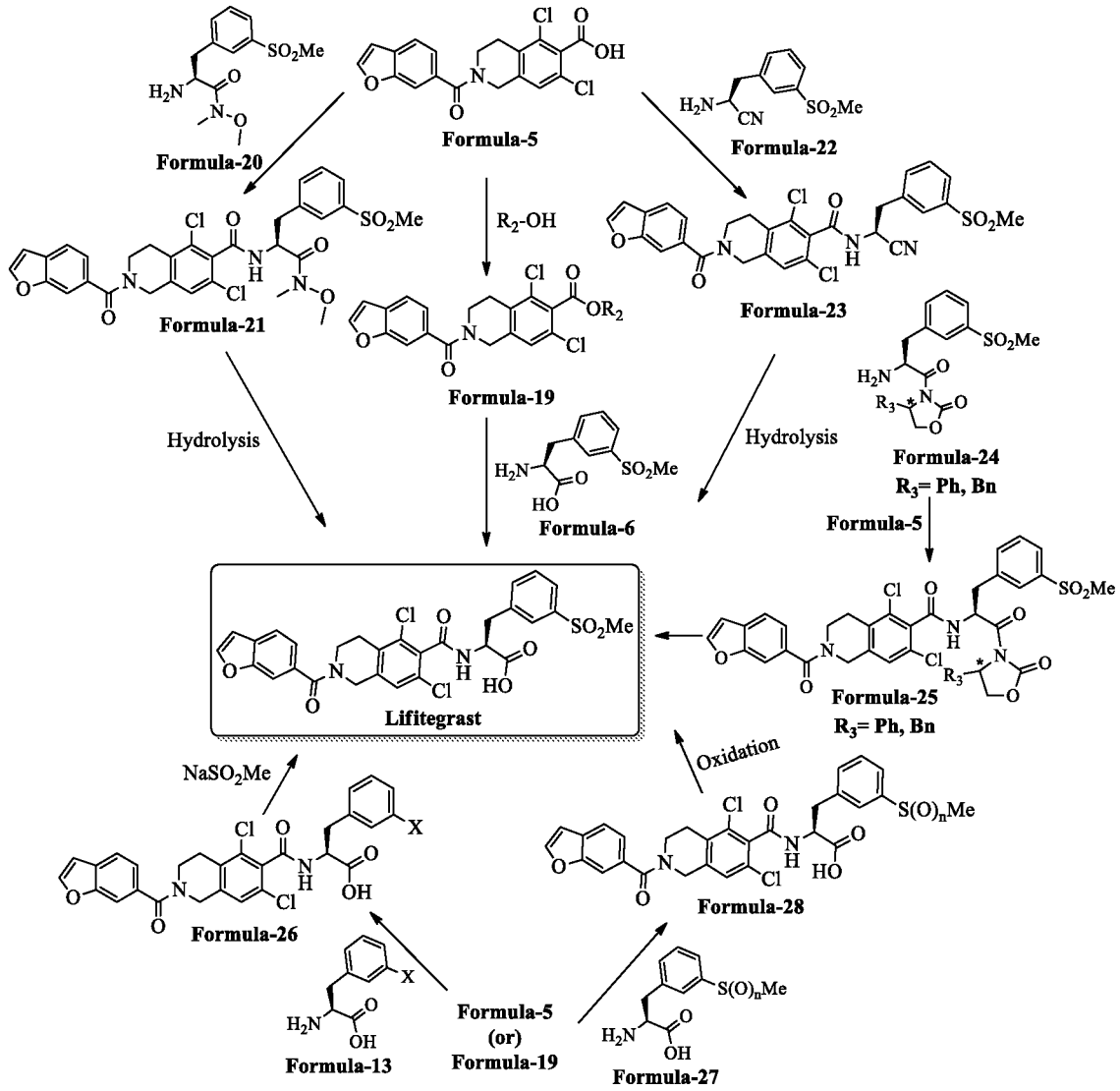
Wherein, 'X' represents halogen such as F, CI, Br & I; and 'PG' represents 'N-protecting group" or "amine protecting group".

Scheme-IV:



Wherein, 'PG' represents amine protecting group or N-protecting group; and 'R_1' represents Ci-C_6 straight chain or branched chain alkyl group.

Scheme-V:



Wherein, 'R_2' represents substituted or unsubstituted aryl and the substituents wherever used can be independently selected from halogens such as F, CI, Br & I, $N0_2$; 'n' is 0 or 1; 'X' represents halogen.

In the compounds of formulae-24&25 of the present invention, '*' mark on carbon atom represents chiral center and the configuration at the said carbon atom can be (R) or (S).

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: Preparation of compound of formula-5

Oxalyl chloride (29.35 gm) was slowly added to a pre-cooled mixture of compound of formula-2 (25 gm), dimethylformamide (5 ml) and tetrahydrofuran (325 ml) at 0-5°C under nitrogen atmosphere. Raised the temperature of the reaction mixture to 25-30°C and stirred for 6 hr at the same temperature. Slowly added the reaction mixture to a pre-cooled mixture of tetrahydrofuran (175 ml), N,N-diisopropylethyl amine (99.64 gm) and pentafluorophenol (31.21 gm) at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 2 hr at the same temperature. Water and methyl tert.butyl ether were added to the reaction mixture at 25-30°C and stirred for 10 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with 10% aqueous sodium bicarbonate solution followed by with water. Distilled off the solvent completely from the organic layer. The obtained compound was slowly added to a mixture of acetonitrile (250 ml), N,N-diisopropylethylamine (79.71 gm) and compound of formula-4a (56.63 gm) at 25-30°C. Heated the reaction mixture to 60-65°C and stirred for 3 hr at the same temperature. Cooled the reaction mixture to 0-5°C, 50% aq.HCl solution was slowly added to it and stirred the reaction mixture for 1 hr at the same temperature. Filtered the solid and washed with water. Methanol (200 ml) was added to the obtained compound at 25-30°C and stirred the reaction mixture for 1 hr at the same temperature. Filtered the solid, washed with methanol and dried to get the title compound. Yield: 47.0 gm.

Example-2: Alternate process for the preparation of compound of formula-5

Oxalyl chloride (29.35 gm) was slowly added to a pre-cooled mixture of compound of formula-2 (25 gm), dimethylformamide (5 ml) and tetrahydrofuran (325 ml) at 0-5°C under nitrogen atmosphere. Raised the temperature of the reaction mixture to 25-30°C and stirred for 5 hr at the same temperature. A solution of pentafluorophenol (31.21 gm) in tetrahydrofuran (25 ml) was added to the reaction mixture at 25-30°C. Cooled the reaction mixture to 0-5°C and N,N-diisopropylethyl amine (99.64 gm) was slowly added to it at the same temperature. Raised the temperature of the reaction mixture to 25-30°C and stirred for 90 min at the same temperature. Methyl tert.butyl ether and water were added to the reaction mixture at 25-30°C and stirred the reaction mixture for 10 min at the same temperature. Both

the organic and aqueous layers were separated and washed the organic layer with 10% aqueous sodium bicarbonate solution followed by with water. Distilled off the solvent completely from the organic layer and co-distilled with acetonitrile. Compound of formula-4a (47.92 gm), acetonitrile (250 ml) and N,N-diisopropylethylamine (59.78 gm) were added to the obtained compound at 25-30°C and stirred the reaction mixture for 40 min at the same temperature. Heated the reaction mixture to 60-65 °C and stirred for 3 hr at the same temperature. Cooled the reaction mixture to 5-10°C, 50% aq.HCl solution was slowly added to it and stirred the reaction mixture for 2 hr at the same temperature. Filtered the solid and washed with water. Ethyl acetate (175 ml) and water (250 ml) were added to the obtained compound at 25-30°C. Slowly basified the reaction mixture by using 10% aqueous potassium carbonate solution (25 gm of potassium carbonate in 250 ml of water) at 25-30°C and stirred the reaction mixture for 10 min at the same temperature. Both the organic and aqueous layers were separated and washed the aqueous layer with ethyl acetate. Slowly acidified the aqueous layer by using 50% aqueous hydrochloric acid solution (25 ml of hydrochloric acid in 25 ml of water) at 25-30°C and stirred the reaction mixture for 3 hr at the same temperature. Filtered the solid, washed with acetone and dried the material to get the title compound. The PXRD pattern of the obtained compound is illustrated in figure- 1.
Yield: 49.0 gm.

Example-3: Preparation of compound of formula-1

Triethylamine (31.06 gm) was added to a mixture of dimethylformamide (300 ml), l-[bis(dimethylamino)methylene]-lH-l,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluoro phosphate (43.84 gm) and compound of formula-5 (30 gm) at 25-30°C under nitrogen atmosphere and stirred the reaction mixture for 3 hr at the same temperature. Filtered the solid and washed with dichloromethane. The obtained compound was dissolved in dichloromethane (900 ml) and the resulting solution was slowly added to a mixture of compound of formula-6a (27.95 gm), dichloromethane (300 ml) and triethylamine (11.64 gm) at 25-30°C. Triethylamine (19.41 gm) was added to the reaction mixture at 25-30°C and stirred for 16 hr at the same temperature. Filtered the reaction mixture and washed with dichloromethane. Water was added to the filtrate at 25-30°C and stirred for 10 min at the same temperature. Both the organic and aqueous layers were separated and washed the

organic layer with 10% aqueous sodium bicarbonate solution followed by with 5% aqueous hydrochloric acid solution. Distilled off the solvent completely from the organic layer and co-distilled with methyl ethyl ketone. Methyl ethyl ketone (210 ml) was added to the obtained compound at 25-30°C and stirred the reaction mixture for 11 hr at the same temperature. Filtered the solid, washed with methyl ethyl ketone and dried to get the title compound. The PXRD pattern of the obtained compound is similar to the PXRD pattern of crystalline form-A illustrated in figure-6 of US8367701B2. Yield: 28.2 gm.

Example-4: Purification of compound of formula-1

Methyl ethyl ketone (25 ml) was added to compound of formula-1 (5 gm) at 25-30°C and stirred the reaction mixture for 30 min at the same temperature. Filtered the solid and washed with methyl ethyl ketone. A mixture of dichloromethane (30 ml) and methanol (30 ml) was added to the obtained solid at 25-30°C and stirred the reaction mixture for 30 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. Methyl ethyl ketone (30 ml) was added to the obtained compound at 25-30°C. Cooled the reaction mixture to 0-5°C and stirred for 13 hr at the same temperature. Filtered the solid, washed with methyl ethyl ketone and dried the material to get the title compound. The PXRD pattern of the obtained compound is similar to the PXRD pattern of crystalline form-A illustrated in figure-6 of US8367701B2. Yield: 4.0 gm.

Example-5: Preparation of crystalline form-N of compound of formula-1

Compound of formula-1 (50 gm) was added to a pre-heated mixture of methanol (675 ml) and water (75 ml) at 60-65°C and stirred the reaction mixture for 2 hr at the same temperature. Cooled the reaction mixture to 25-30°C. Filtered the solid, washed with methanol and dried the material to get the title compound. The PXRD pattern of the obtained compound is illustrated in figure-4. Yield: 42.0 gm.

Example-6: Preparation of crystalline polymorph of compound of formula-1

A mixture of compound of formula-1 (72 gm), ethanol (972 ml) and water (108 ml) was heated to 60-65°C. Cooled the reaction mixture to 25-30°C. Filtered the solid, washed

with ethanol and dried the material to get the title compound. The PXRD pattern of the obtained compound is illustrated in figure-5. Yield: 70.0 gm.

Example-7: Preparation of crystalline form-A of compound of formula-1

A mixture of compound of formula-1 (56 gm) and acetone (560 ml) was heated to 50-55°C. Cooled the reaction mixture to 25-30°C. Filtered the solid, washed with acetone and dried the material to get the title compound. The PXRD pattern of the obtained compound is similar to the PXRD pattern of crystalline form-A illustrated in figure-6 of US8367701B2. Yield: 48.0 gm.

Example-8: Preparation of compound of formula-5

Process-1: A mixture of compound of formula-2 (10 gm), HATU (35.17 gm), triethylamine (12.45 gm) and dimethylformamide (100 ml) was stirred for 5 hr at 25-30°C under N_2 atmosphere. Cooled the reaction mixture to 5-10°C, water was added to it and stirred for 30 min at same temperature. Filtered the solid, washed with water. The obtained compound was added to a mixture of dichloromethane (100 ml), Compound of formula-4a (17.42 gm) and triethylamine (15.58 gm) at 25-30°C under N_2 atmosphere and stirred the reaction mixture for 4 hr at same temperature. Filtered the reaction mixture and washed with dichloromethane. 50% Aqueous HC1 solution was added to the filtrate at 25-30°C and stirred the reaction mixture for 15 min at the same temperature. Filtered the precipitated solid, washed with water and dried the material to get the title compound. Yield: 16.0 gm.

Process-2: DCC (19.13 gm) and HOBt (2.5 gm) were added to a mixture of compound of formula-2 (10 gm) and dichloromethane (100 ml) at 25-30°C under N_2 atmosphere and stirred the reaction mixture for 5 hr at the same temperature. Filtered the reaction mixture and washed with dichloromethane. Distilled off the solvent completely from the filtrate and co-distilled with cyclohexane. Cyclohexane (50 ml) was added to the obtained compound at 25-30°C and stirred the reaction mixture for 1 hr at the same temperature. Filtered the solid, washed with cyclohexane and dried the material. The obtained compound was added to a mixture of compound of formula-4a (17.4 gm), triethylamine (15.58 gm) and dichloromethane (150 ml) at 25-30°C under N_2 atmosphere and stirred the reaction mixture for 4 hr at the same temperature. Filtered the reaction mixture and washed with

dichloromethane. 50% Aq.HCl solution was added to the filtrate at 25-30°C and stirred the reaction mixture for 15 min at the same temperature. Filtered the precipitated solid, washed with water and dried the material to get the title compound. Yield: 18.0 gm.

Example-9: Preparation of compound of formula-1

A mixture of compound of formula-5 (7.5 gm), DCC (5.96 gm), HOBt (0.77 gm), triethylamine (1.94 gm) and dichloromethane (75 ml) was stirred for 3 hr at 25-30°C under N_2 atmosphere. Filtered the reaction mixture, washed with dichloromethane. Distilled off the solvent completely from the filtrate. Ethyl acetate (37.5 ml) was added to the obtained compound at 25-30°C and stirred the reaction mixture for 1 hr at the same temperature. Filtered the solid and washed with ethyl acetate. Dichloromethane (150 ml) was added to the obtained compound at 25-30°C under N_2 atmosphere and stirred the reaction mixture for 15 min at same temperature. Compound of formula-6a (6.4 gm) and diisopropylethyl amine (10.04 ml) were added to the reaction mixture at 25-30°C and stirred for 16 hr at the same temperature. 10% Aq.HCl solution was added to the reaction mixture at 25-30°C and stirred for 10 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Distilled off the solvent completely from the organic layer. Ethyl acetate was added to the obtained compound at 25-30°C and stirred the reaction mixture for 15 min at the same temperature. 10% Aq.$NaHC0_3$ solution was added to the reaction mixture at 25-30°C and stirred for 10 min at the same temperature. Both the organic and aqueous layers were separated and ethyl acetate was added to the aqueous layer. Acidified the reaction mixture by using acetic acid. Both the organic and aqueous layers were separated and distilled off the solvent completely from the organic layer. Ethyl acetate (7.5 ml) and methyl tert.butyl ether (7.5 ml) were added to the obtained compound at 25-30°C and stirred the reaction mixture for 1 hr at the same temperature. Filtered the solid, washed with methyl tert.butyl ether and dried the material to get the title compound. Yield: 8.0 gm.

Example-10: Preparation of crystalline form-M of compound of formula-1

Process-1: Isopropyl acetate (60 ml) was added to compound of formula-1 (2 gm) at 25-30°C. Heated the reaction mixture to 35-40°C and stirred for 5 days at the same temperature. Filtered the solid and dried to get the title compound. Yield: 1.6 gm.

Process-2: Isopropyl acetate (90 ml) was added to compound of formula-1 (3 gm) at 25-30°C. Form-M seed crystal (0.3 gm) was added to the reaction mixture at 25-30°C. Heated the reaction mixture to 35-40°C and stirred for 24 hr at the same temperature. Filtered the solid and dried to get the title compound. The PXRD pattern of the obtained compound is illustrated in figure-2. Yield: 2.7 gm.

Process-3: Isopropyl acetate (60 ml) was added to compound of formula-1 (2 gm) and stirred the reaction mixture for 5 days at 25-30°C. Filtered the solid and dried to get the title compound. Yield: 1.6 gm.

Example-11: Preparation of crystalline form-S of compound of formula-1

A mixture of compound of formula-1 (1 gm), ethanol (5 ml) and dichloromethane (5 ml) was slowly heated to 40-45°C and stirred the reaction mixture for 30 min at the same temperature. A mixture of cyclohexane (30 ml) and n-heptane (15 ml) was added to the reaction mixture at 40-45°C and stirred for 60 min at the same temperature. Slowly cooled the reaction mixture to 0-5°C and stirred for 2 hr at same temperature. Filtered the solid and dried to get the title compound. The PXRD pattern of the obtained compound is illustrated in figure-3. Yield: 0.6 gm.

Example-12: Preparation of compound of formula-5

A mixture of compound of formula-2 (25 gm), tetrahydrofuran (325 ml) and dimethylformamide (5 ml) was stirred for 15 min at 25-30°C under nitrogen atmosphere. Oxalyl chloride (25.44 gm) was slowly added to the reaction mixture at 25-30°C and stirred for 6 hr at the same temperature. A solution of pentafluorophenol (31.21 gm) in tetrahydrofuran (25 ml) was added to the reaction mixture at 25-30°C. Cooled the reaction mixture to 0-5°C and N,N-diisopropylethylamine (79.71 gm) was slowly added to it at the same temperature. Raised the temperature of the reaction mixture to 25-30°C and stirred for 90 min at the same temperature. Methyl tert-butyl ether and water were added to the reaction mixture at 25-30°C and stirred for 10 min at the same temperature. Both the organic and aqueous layers were separated, washed the organic layer with 10% aqueous sodium bicarbonate solution followed by with water. Distilled off the solvent from the organic layer and co-distilled with acetonitrile. The PXRD pattern of the obtained compound is illustrated in figure-9. Yield: 48.0 gm.

Acetonitrile (250 ml), compound of formula-4a (39.2 gm) and N,N-diisopropylethylamine (79.71 gm) were added to the obtained compound at 25-30°C and stirred the reaction mixture for 30 min at the same temperature. Heated the reaction mixture to 60-65°C and stirred for 4 hr at the same temperature. Cooled the reaction mixture to 5-10°C, 50% aqueous HCl solution (125 ml of conc.HCl in 125 ml of water) was slowly added to it and stirred the reaction mixture for 3 hr at the same temperature. Filtered the solid and washed with water. Water and ethyl acetate were added to the obtained solid at 25-30°C. Slowly basified the reaction mixture by using 10% aqueous potassium carbonate solution at 25-30°C and stirred for 10 min at the same temperature. Both the organic and aqueous layers were separated and washed the aqueous layer with ethyl acetate. Slowly acidified the aqueous layer using 50% aqueous HCl solution at 25-30°C and stirred the reaction mixture for 3 hr at the same temperature. Filtered the solid, washed with acetone and dried the material to get the title compound. The PXRD pattern of the obtained compound is similar to figure-1.

Yield: 46.0 gm; M.P.: 185-191°C.

Purity by HPLC: 99.64%; Highest individual unspecified impurity: 0.05%.

Example-13: Preparation of compound of formula-1

HATU (31.66 gm) and triethylamine (25.88 gm) were added to a mixture of compound of formula-5 (25 gm) and acetonitrile (250 ml) at 25-30°C under nitrogen atmosphere and stirred the reaction mixture for 5 hr at the same temperature. Water (100 ml) was added to the reaction mixture at 25-30°C and stirred for 1 hr at the same temperature. Filtered the solid and washed with water. The PXRD pattern of the obtained compound is illustrated in figure-10. Yield: 50.0 gm.

Compound of formula-6a (19.7 gm), dimethylsulfoxide (250 ml) and triethylamine (12.9 gm) were added to the obtained compound at 25-30°C under nitrogen atmosphere and stirred the reaction mixture for 3 hr at the same temperature. Cooled the reaction mixture to 5-10°C, ethyl acetate and aqueous potassium carbonate solution were added to it and stirred for 10 min at the same temperature. Both the organic and aqueous layers were separated. Ethyl acetate was added to the aqueous layer. Slowly acidified the reaction mixture by using 50% aqueous hydrochloric acid solution at 25-30°C and stirred the reaction mixture for 10 min at

the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. Distilled off the solvent from the organic layer and co-distilled with methanol. Methanol (200 ml) was added to the obtained compound at 25-30°C and stirred the reaction mixture for 3 hr at the same temperature. Filtered the solid, washed with methanol and dried to get the title compound. The PXRD pattern of the obtained compound is illustrated in figure-6. Yield: 26.0 gm; M.P.: 154-156°C.

Example-14: Purification of compound of formula-1

A mixture of compound of formula-1 (30 gm), dichloromethane (120 ml) and methanol (120 ml) was stirred for 40 min at 25-30°C. Filtered the reaction mixture through hyflow bed and washed with dichloromethane. Distilled off the solvent from the organic layer and co-distilled with methanol. 30% Aqueous acetone (180 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 5-10°C and stirred for 2 hr at the same temperature. Filtered the solid, washed with 30% aqueous acetone and dried the material to get the title compound. PXRD pattern of obtained compound is similar to PXRD pattern of crystalline form-A illustrated in figure-6 of US8367701B2. Yield: 25.0 gm;

Water content by KFR: 2.4% w/w; Purity by HPLC: 99.7%; Benzofuran isoquinoline acid impurity: 0.05%; Highest individual unspecified impurity: 0.04%; R-isomer: Not detected.

Particle size distribution:

Before micronization: D(0.1) is 2.80 μιη; D(0.5) is 7.02 μιη; D(0.9) is 20.76 μιη.

After micronization: D(0.1) is 1.46 μιη; D(0.5) is 3.41 μιη; D(0.9) is 11.50 μιη.

Example-15: Preparation of crystalline form-L of compound of formula-1

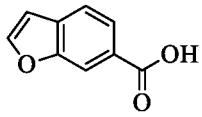
n-Propanol (65 ml) was added to compound of formula-1 (5 gm) at 25-30°C. Heated the reaction mixture to 60-65°C and stirred for 10 min at the same temperature. Water (10 ml) was added to the reaction mixture at 60-65°C and stirred for 15 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 45 min at the same temperature. Filtered the solid and dried at 25-30°C for 2 hr to get the title compound. The PXRD pattern of the obtained compound is illustrated in figure-7. Yield: 4.8 gm.

The obtained compound is dried at 100°C for 10 hr. The PXRD pattern of the obtained compound is illustrated in figure-8. Yield: 4.4 gm.

We Claim:

1. A process for the preparation of (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-l, 2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid compound of formula- 1, comprising;

a) reacting benzofuran-6-carboxylic acid compound of formula-2



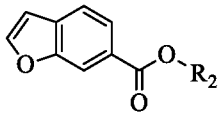
Formula-2

with compound of general formula

R_2-OH

wherein, 'R_2' represents substituted or unsubstituted aryl and the substituents wherever used can be independently selected from halogens such as F, CI, Br & I, $N0_2$ and the substitution can be takes place at single or multiple positions on aryl group;

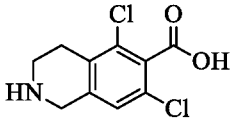
in a suitable solvent optionally in presence of a suitable coupling agent and/or a suitable base to provide compound of general formula-3,



Formula-3

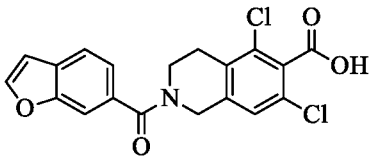
wherein, 'R_2' is same as defined above;

b) reacting compound of general formula-3 with 5,7-dichloro-l,2,3,4-tetrahydro isoquinoline-6-carboxylic acid compound of formula-4 or its salt



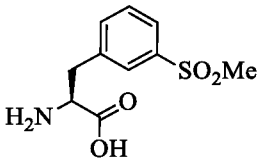
Formula-4

in a suitable solvent optionally in presence of a suitable base to provide 2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxylic acid compound of formula-5,



Formula-5

c) reacting compound of formula-5 with (S)-2-amino-3-(3-(methylsulfonyl)phenyl) propanoic acid compound of formula-6 or its salt



Formula-6

in a suitable solvent optionally in presence of a suitable coupling agent and/or a suitable base to provide compound of formula-1.

2. The process according to claim 1, wherein,

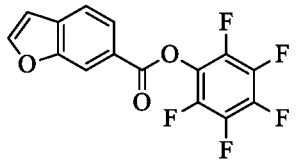
in step-a) & step-c) the suitable coupling agent is selected from N,N'-dicyclohexyl carbodiimide (DCC), N,N'-diisopropyl carbodiimide (DIC), l-ethyl-3-(3-dimethylamino propyl)carbodiimide hydrochloride (EDC.HC1), N,N'-carbonyl diimidazole (CDI), 1-[bis(dimethylamino)methylene]-lH-l,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluoro phosphate (HATU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-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-1-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-1,2,3-triazole-4-carboxylate (HOCt), 0-(benzotriazol- l-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), N-hydroxysuccinamide (HOSu), N-hydroxysulfosuccinimide (Sulfo-NHS) and the like;

in step-a), step-b) & step-c) the suitable base is selected from organic bases, inorganic bases, organolithium bases, organosilicon bases or mixtures thereof;

in step-a) to step-c) the suitable solvent is selected from hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents or mixtures thereof.

3. A process for the preparation of (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-l, 2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid compound of formula-1, comprising;

a) reacting benzofuran-6-carboxylic acid compound of formula-2 with pentafluorophenol in a suitable solvent optionally in presence of a suitable coupling agent and/or a suitable base to provide perfluorophenyl benzofuran-6-carboxylate compound of formula-3a,

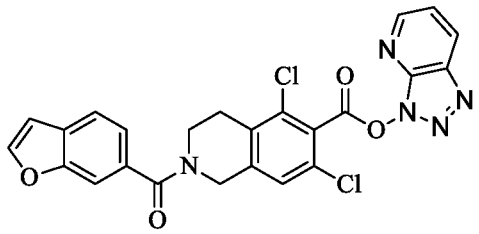


Formula-3a

b) optionally isolating compound of formula-3a as a solid,

c) reacting compound of formula-3a with 5,7-dichloro-l,2,3,4-tetrahydro isoquinoline-6-carboxylic acid compound of formula-4 or its hydrochloride salt in a suitable solvent optionally in presence of a suitable base to provide 2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxylic acid compound of formula-5,

d) reacting compound of formula-5 with HATU in a suitable solvent optionally in presence of a suitable base to provide 3H-[l,2,3]triazolo[4,5-b]pyridin-3-yl 2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxylate compound of formula-5a,



Formula-5a

e) optionally isolating compound of formula-5a as a solid,

f) reacting compound of formula-5a with (S)-2-amino-3-(3-(methylsulfonyl)phenyl) propanoic acid compound of formula-6 or its salt in a suitable solvent optionally in presence of a suitable base to provide compound of formula-1.

4. The process according to claim 3, wherein,

in step-a) the suitable coupling agent is selected from the coupling agents defined in step-a) of claim 1;

in step-a), step-c), step-d) & step-f) the suitable base is selected from organic bases, inorganic bases, organolithium bases, organosilicon bases or mixtures thereof;

in step-a) to step-f) the suitable solvent is selected from hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents or mixtures thereof.

5. A process for the preparation of (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-l, 2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid compound of formula-1, comprising;
   a) reacting benzofuran-6-carboxylic acid compound of formula-2 with pentafluorophenol in presence of oxalyl chloride and N,N-diisopropylethylamine in tetrahydrofuran and catalytic amount of dimethylformamide to provide perfluorophenyl benzofuran-6-carboxylate compound of formula-3a,
   b) isolating compound of formula-3a as a solid,
   c) reacting compound of formula-3a with 5,7-dichloro-l,2,3,4-tetrahydro isoquinoline-6-carboxylic acid hydrochloride compound of formula-4a in presence of N,N-diisopropylethylamine in acetonitrile to provide 2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxylic acid compound of formula-5,
   d) reacting compound of formula-5 with HATU in presence of triethylamine in acetonitrile to provide 3H-[l,2,3]triazolo[4,5-b]pyridin-3-yl 2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxylate compound of formula-5a,
   e) isolating compound of formula-5a as a solid,
   f) reacting compound of formula-5a with (S)-2-amino-3-(3-(methylsulfonyl)phenyl) propanoic acid hydrochloride compound of formula-6a in presence of triethylamine in dimethylsulfoxide to provide compound of formula-1.

6. A process for the preparation of (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-l, 2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid compound of formula-1, comprising reacting 2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxylic acid compound of formula-5 with (S)-2-amino-3-(3-(methylsulfonyl)phenyl)propanoic acid compound of formula-6 or its salt in a suitable solvent optionally in presence of a suitable coupling agent and/or a suitable base to provide compound of formula-1.

7. The process according to claim 6, wherein the suitable coupling agent, suitable base and the suitable solvent are selected from those defined in step-a) of claim 1.

8. The process according to claim 6, wherein the activated compound which is formed by reacting compound of formula-5 with a suitable coupling agent optionally in presence of a suitable base in a suitable solvent can optionally be isolated from the reaction mixture in solid form before reacting it with compound of formula-6 or its salt.

9. A process for the preparation of (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-l, 2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid compound of formula-1, comprising;

a) reacting 2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxylic acid compound of formula-5 with HATU in a suitable solvent optionally in presence of a suitable base to provide 3H-[l,2,3]triazolo[4,5-b]pyridin-3-yl 2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxylate compound of formula-5a,

b) optionally isolating compound of formula-5a as a solid,

c) reacting compound of formula-5a with (S)-2-amino-3-(3-(methylsulfonyl)phenyl) propanoic acid compound of formula-6 or its salt in a suitable solvent optionally in presence of a suitable base to provide compound of formula-1.

10. The process according to claim 9, wherein,

in step-a) & step-c) the suitable base is selected from organic bases, inorganic bases, organolithium bases, organosilicon bases or mixtures thereof; and

the suitable solvent is selected from hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents or mixtures thereof.

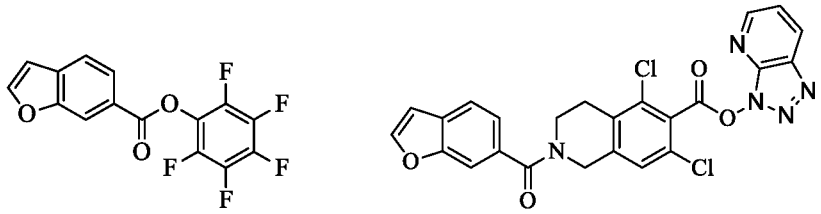
11. The process for the preparation of compound of formula-1 according to claim 9, comprising;

a) reacting compound of formula-5 with HATU in presence of triethylamine in acetonitrile to provide compound of formula-5a,

b) isolating compound of formula-5a as a solid,

c) reacting compound of formula-5a with (S)-2-amino-3-(3-(methylsulfonyl)phenyl) propanoic acid hydrochloride compound of formula-6a in presence of triethylamine in dimethylsulfoxide to provide compound of formula- 1.

12. Compounds having following structural formulae;



13. Use of compounds according to claim 12, for the preparation of (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methyl sulfonyl)phenyl)propanoic acid compound of formula- 1.

14. Perfluorophenyl benzofuran-6-carboxylate compound of formula-3a as a solid.

15. Crystalline polymorph of perfluorophenyl benzofuran-6-carboxylate compound of formula-3a, characterized by its PXRD pattern having peaks at 8.9, 9.9, 12.4, 13.8, 14.2, 19.4, 19.9, 20.8, 21.7, 22.5, 24.6, 25.2, 27.9 and 30.4 ± 0.2° of 2Θ

16. The crystalline polymorph of compound of formula-3a according to claim 15, which is further characterized by its PXRD pattern as illustrated in figure-9.

17. A process for the preparation of perfluorophenyl benzofuran-6-carboxylate compound of formula-3a, comprising reacting benzofuran-6-carboxylic acid compound of formula-2 with pentafluorophenol in a suitable solvent optionally in presence of a suitable coupling agent and/or a suitable base to provide compound of formula-3a.

18. The process according to claim 17, wherein the suitable coupling agent, the suitable base and the suitable solvent are selected from those defined in step-a) of claim 1.

19. The process for the preparation of compound of formula-3a according to claim 17, comprising reacting benzofuran-6-carboxylic acid compound of formula-2 with pentafluorophenol in presence of oxalyl chloride and N,N-diisopropylethylamine in tetrahydrofuran and catalytic amount of dimethylformamide to provide compound of formula-3a.

20. 3H-[l,2,3]triazolo[4,5-b]pyridin-3-yl 2-(benzofuran-6-carbonyl)-5,7-dichloro- 1,2,3,4-tetrahydroisoquinoline-6-carboxylate compound of formula-5a as a solid.

21. Crystalline polymorph of 3H-[l,2,3]triazolo[4,5-b]pyridin-3-yl 2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxylate compound of formula-5a, characterized by its PXRD pattern having peaks at 8.2, 13.1, 13.4, 14.1, 15.1, 16.2, 17.0, 17.6, 18.4, 19.5, 20.2, 21.4, 21.9, 22.1, 23.0, 23.3, 24.2, 24.8, 25.7, 26.5, 27.2, 28.1, 28.7, 29.8 and 30.5 ± 0.2° of 2Θ.

22. The crystalline polymorph of compound of formula-5a according to claim 21, which is further characterized by its PXRD pattern as illustrated in figure- 10.

23. A process for the preparation of 3H-[l,2,3]triazolo[4,5-b]pyridin-3-yl 2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxylate compound of formula-5a, comprising reacting 2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetra hydroisoquinoline-6-carboxylic acid compound of formula-5 with HATU in a suitable solvent optionally in presence of a suitable base to provide compound of formula-5a.

24. The process according to claim 23, wherein the suitable base is selected from organic bases, inorganic bases, organolithium bases, organosilicon bases or mixtures thereof; and the suitable solvent is selected from hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents or mixtures thereof.

25. The process for the preparation of compound of formula-5a according to claim 23, comprising reacting compound of formula-5 with HATU in presence of triethylamine in acetonitrile to provide compound of formula-5a.

26. A process for the purification of 2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxylic acid compound of formula-5, comprising;
    a) treating compound of formula-5 with a suitable base in a suitable solvent,
    b) treating reaction mixture with a suitable acid in a suitable solvent,
    c) filtering the solid and drying to provide pure compound of formula-5.

27. The process according to claim 26, wherein,

    in step-a) the suitable base is selected from inorganic bases, organic bases or mixtures thereof;

in step-b) the suitable acid is selected from "inorganic acids" such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid; and "organic acids" such as formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, trifluoroacetic acid, trifluoromethanesulfonic acid, oxalic acid, malonic acid, maleic acid, fumaric acid, malic acid, succinic acid, citric acid, aspartic acid, tartaric acid, mandelic acid, benzoic acid, salicylic 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 or mixtures thereof;

in step-a) and step-b) the suitable solvent is independently selected from hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents or mixtures thereof.

28. The process for the purification of compound of formula-5 according to claim 26, comprising;
    a) treating compound of formula-5 with aqueous potassium carbonate in a mixture of ethyl acetate and water,
    b) separating the organic and aqueous layers,
    c) treating aqueous layer with aqueous hydrochloric acid,
    d) filtering the solid and drying to provide pure compound of formula-5.

29. Crystalline form-M of (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydro isoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid compound of formula- 1, characterized by;
    a) its PXRD pattern having peaks at 5.3, 9.8, 10.6, 14.5, 17.4, 17.8, 19.6, 20.9, 22.1, 24.3, 25.2, 26.3, 29.0, 30.0, 34.3 and 36.1 ± 0.2° of 2Θ; and
    b) its PXRD pattern as illustrated in figure-2.

30. A process for the preparation of crystalline form-M of compound of formula- 1 according to claim 29, comprising;
    a) adding a suitable solvent to compound of formula- 1,
    b) optionally heating the reaction mixture to a suitable temperature,
    c) stirring the reaction mixture,
    d) optionally cooling the reaction mixture to a suitable temperature,

e) filtering the solid and drying to provide form-M of compound of formula-1 .

31. The process according to claim 30, wherein,

in step-a) the suitable solvent is selected from ester solvents, hydrocarbon solvents, chloro solvents, ether solvents, nitrile solvents or mixtures thereof;

in step-b) the suitable temperature ranges from 30°C to reflux temperature of the solvent used; and

in step-d) suitable temperature ranges from 0-30°C.

32. A process for the preparation of crystalline form-M of compound of formula-1 according to claim 29, comprising;

a) adding isopropyl acetate to compound of formula-1 at 25-30°C,
b) optionally adding a small amount of crystalline form-M of compound of formula-1 as seed crystal to the reaction mixture,
c) heating the reaction mixture to 35-40°C,
d) filtering the solid and drying to provide form-M of compound of formula-1 .

33. Crystalline form-S of (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydro isoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid compound of formula-1, characterized by;

a) its PXRD pattern having peaks at 10.5, 14.1, 14.7, 15.2, 15.9, 17.2, 19.6, 21.8, 24.1, 24.4, 25.3, 26.0, 27.0 and 28.7 ± 0.2° of 2Θ; and
b) its PXRD pattern as illustrated in figure-3.

34. A process for the preparation of crystalline form-S of compound of formula-1 according to claim 33, comprising;

a) adding a suitable solvent to compound of formula-1,
b) optionally heating the reaction mixture to a suitable temperature,
c) adding a suitable second solvent to the reaction mixture,
d) optionally cooling the reaction mixture to a suitable temperature,
e) filtering the solid and drying the material to provide crystalline form-S of compound of formula-1.

35. The process according to claim 34, wherein,

in step-a) the suitable solvent is selected from alcohol solvents, ester solvents, chloro solvents, nitrile solvents, ketone solvents, polar solvents or mixtures thereof;

in step-b) the suitable temperature ranges from 30°C to reflux temperature of the solvent used;

in step-c) the suitable second solvent is selected from hydrocarbon solvents, ester solvents, polar-aprotic solvents, ether solvents or mixtures thereof;

in step-d) the suitable temperature ranges from 0-30°C.

36. A process for the preparation of crystalline form-S of compound of formula-1 according to claim 34, comprising;

a) adding ethanol and dichloromethane to compound of formula-1 at 25-30°C,
b) heating the reaction mixture to 40-45°C,
c) adding a mixture of cyclohexane and n-heptane to the reaction mixture,
d) cooling the reaction mixture to 0-5°C,
e) filtering the solid and drying to provide crystalline form-S of compound of formula-1.

37. Crystalline form-N of (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydro isoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid compound of formula-1, characterized by its PXRD pattern as illustrated in figure-4.

38. A process for the preparation of crystalline form-N of compound of formula-1 according to claim 37, comprising;

a) adding compound of formula-1 to methanol or to a mixture of methanol and water,
b) stirring the reaction mixture,
c) optionally cooling the reaction mixture,
d) filtering the solid and drying to provide form-N of compound of formula-1.

39. The process according to claim 38, wherein,

step-a) can be carried out at a suitable temperature ranges from 35°C to 70°C;

in step-b) stirring of the reaction mixture can be done for 15 min to 10 hr;

in step-c) the reaction mixture can be optionally cooled to a suitable temperature ranges from -50°C to 30°C;

a suitable solvent selected from ketone solvents, nitrile solvents, alcohol solvents such as ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, 2-butanol, tert-butanol and the like or mixtures thereof can be used instead of water in step-a).

40. A process for the preparation of crystalline form-N of compound of formula-1 according to claim 38, comprising;
    a) adding compound of formula-1 to a pre-heated mixture of methanol and water at 60-65°C,
    b) stirring the reaction mixture,
    c) cooling the reaction mixture to 25-30°C,
    d) filtering the solid and drying to provide form-N of compound of formula-1.

41. Crystalline form-L of (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydro isoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid compound of formula-1, characterized by its PXRD pattern as illustrated in figure-7.

42. A process for the preparation of crystalline form-L of compound of formula-1 according to claim 41, comprising;
    a) adding n-propanol to compound of formula-1,
    b) heating the reaction mixture to a suitable temperature,
    c) adding water to the reaction mixture,
    d) cooling the reaction mixture to a suitable temperature,
    e) filtering the solid and drying to provide crystalline form-L of compound of formula-1.

43. The process according to claim 42, wherein,
    step-a) is carried out at 25-30°C;
    in step-b) the suitable temperature ranges from 35°C to 100°C; and
    in step-d) the suitable temperature ranges from -30°C to 30°C.

44. A process for the preparation of crystalline form-L of compound of formula-1 according to claim 42, comprising;
    a) adding n-propanol to compound of formula-1 at 25-30°C,
    b) heating the reaction mixture to 60-65°C,
    c) adding water to the reaction mixture,
    d) cooling the reaction mixture to 25-30°C,
    e) filtering the solid and drying to provide crystalline form-L of compound of formula-1.

45. Use of any of the crystalline polymorphs of compound of formula-1 according to claims 29, 33, 37, 41 for the preparation of pharmaceutical formulations.

46. Pharmaceutical composition comprising any of the crystalline polymorphs of compound of formula-1 according to claims 29, 33, 37, 41 and at least one pharmaceutically acceptable excipient.

47. A method of treating or preventing a condition or disease comprising administering to the patient a therapeutically effective amount of any of the crystalline polymorphs of compound of formula-1 according to claims 29, 33, 37, 41.

48. (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-l,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid compound of formula-1 having particle size distribution of D90 less than 100 μιη.

49. The compound of formula-1 according to claim 48, having particle size distribution of D90 less than 50 μιη.

50. The compound of formula-1 according to claim 49, having particle size distribution of D90 less than 20 μιη.

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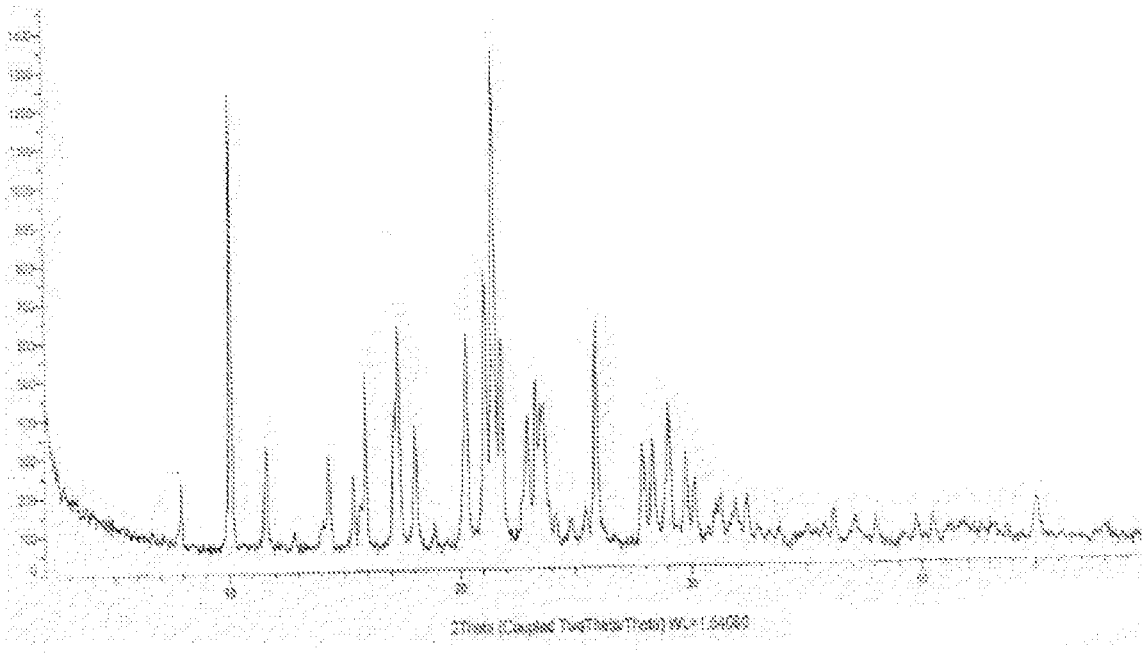

Figure-1

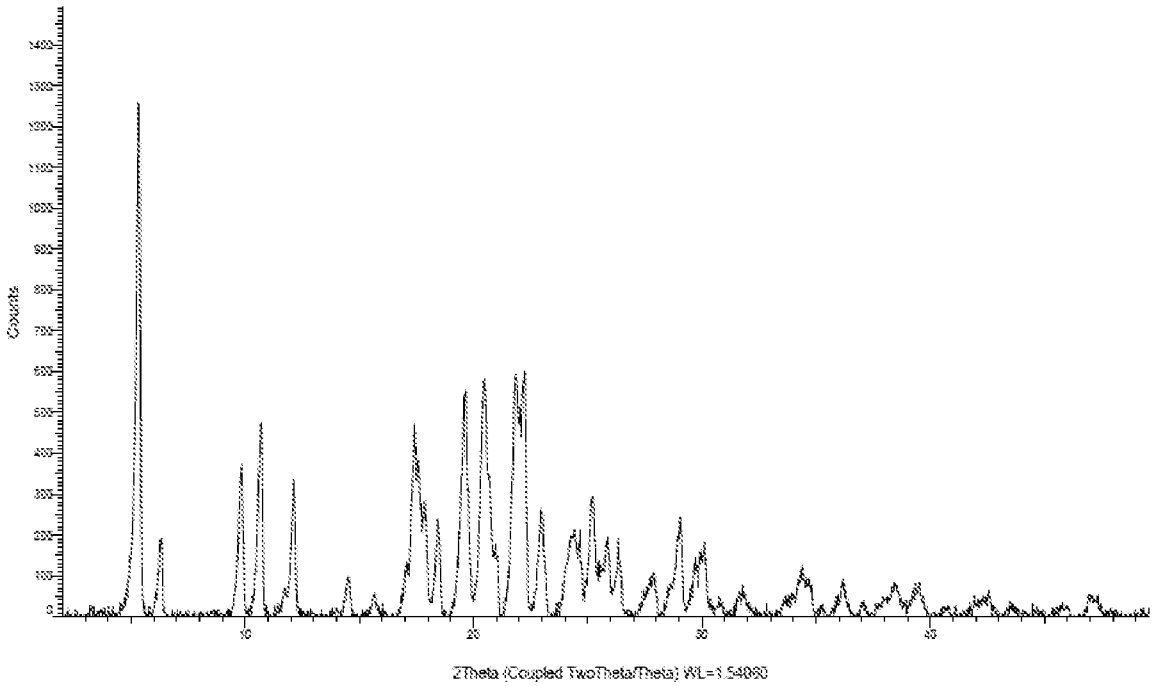

Figure-2

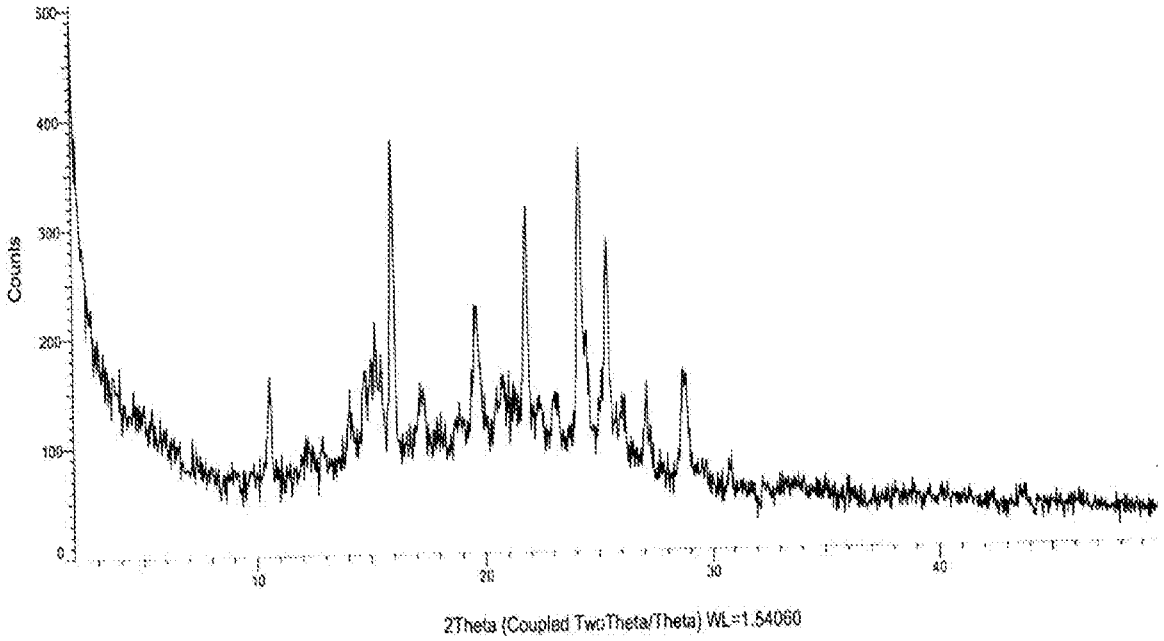

Figure-3

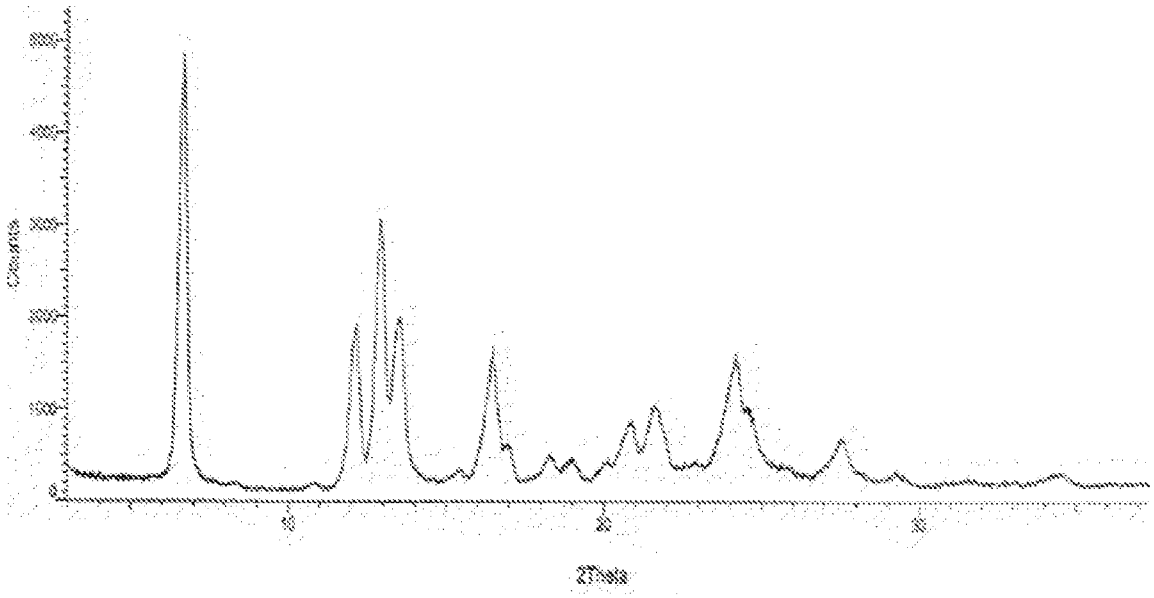

Figure-4

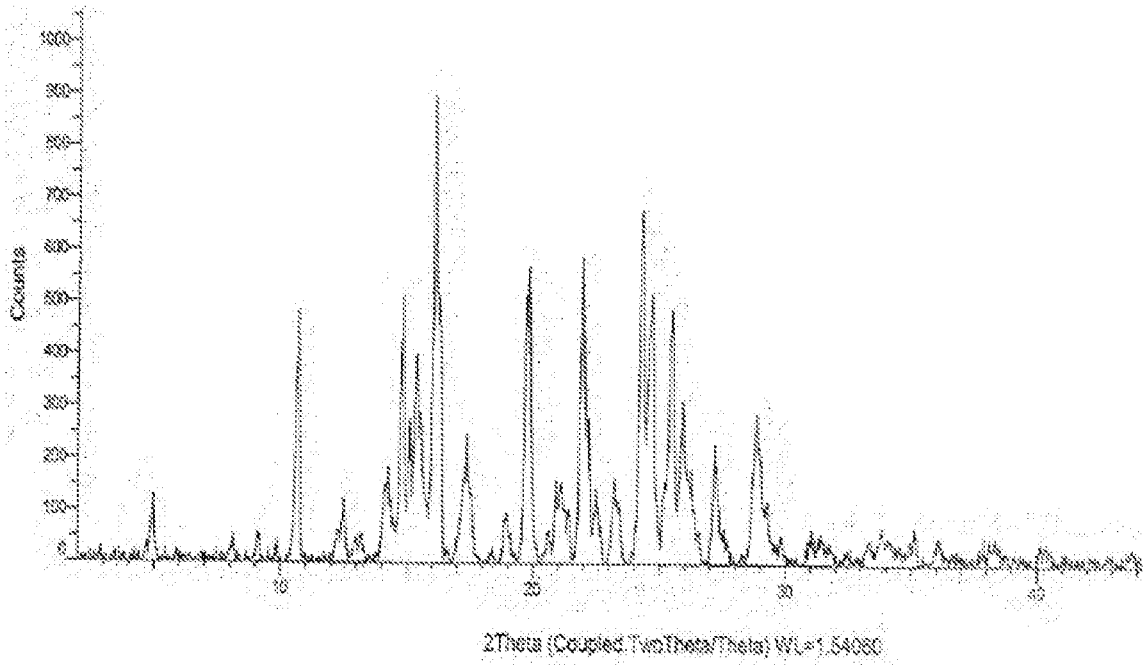

Figure-5

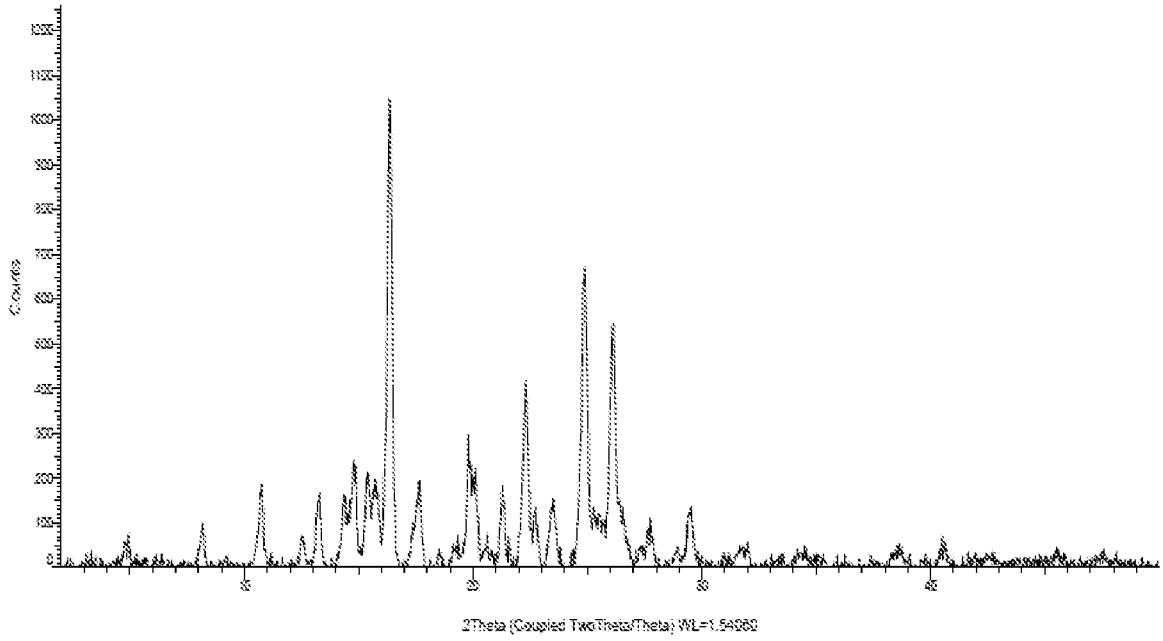

Figure-6

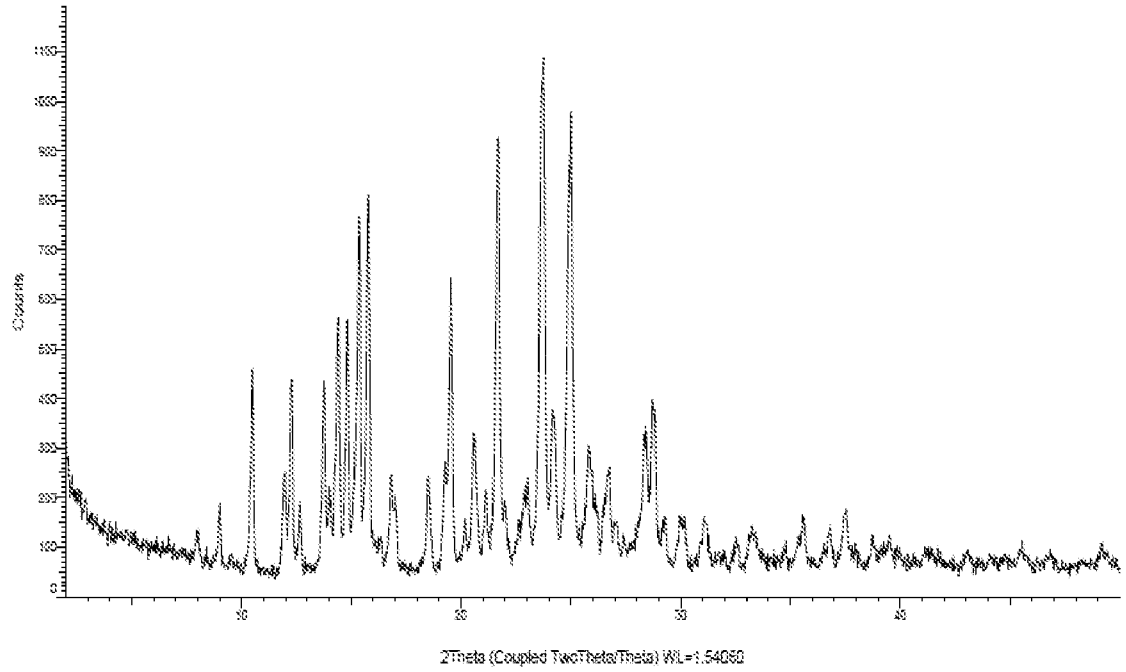

Figure-7

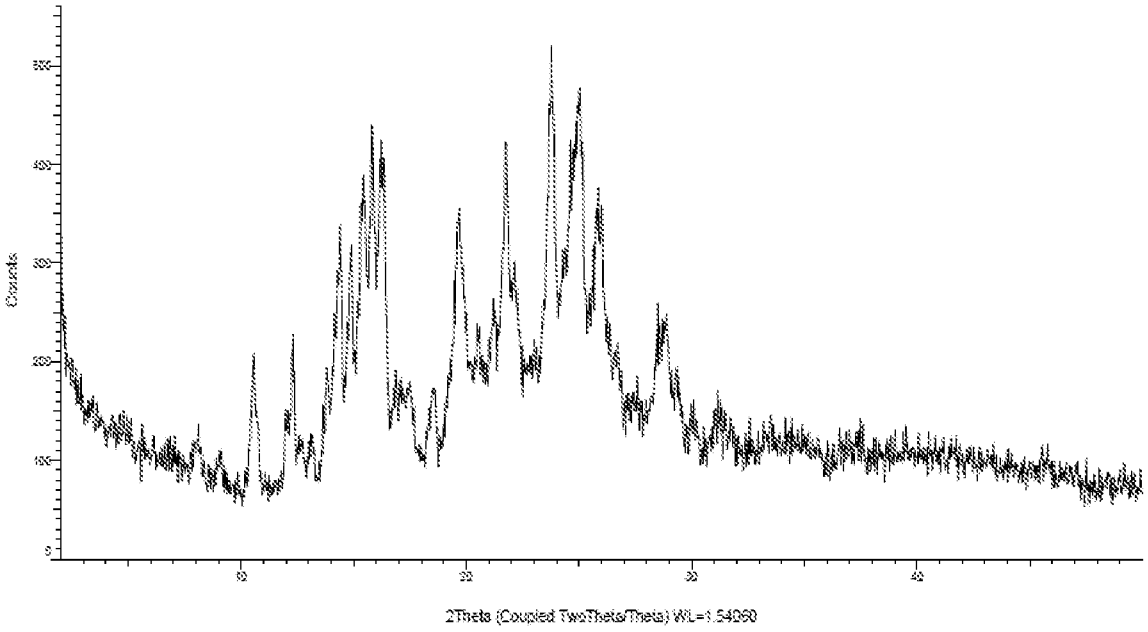

Figure-8

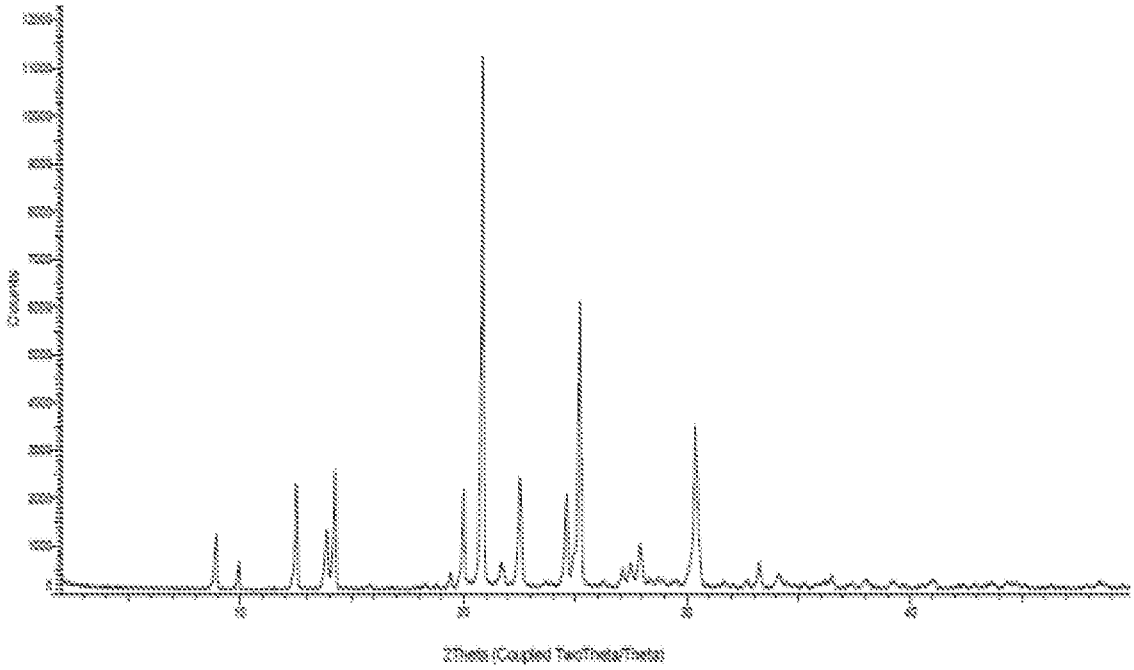

Figure-9

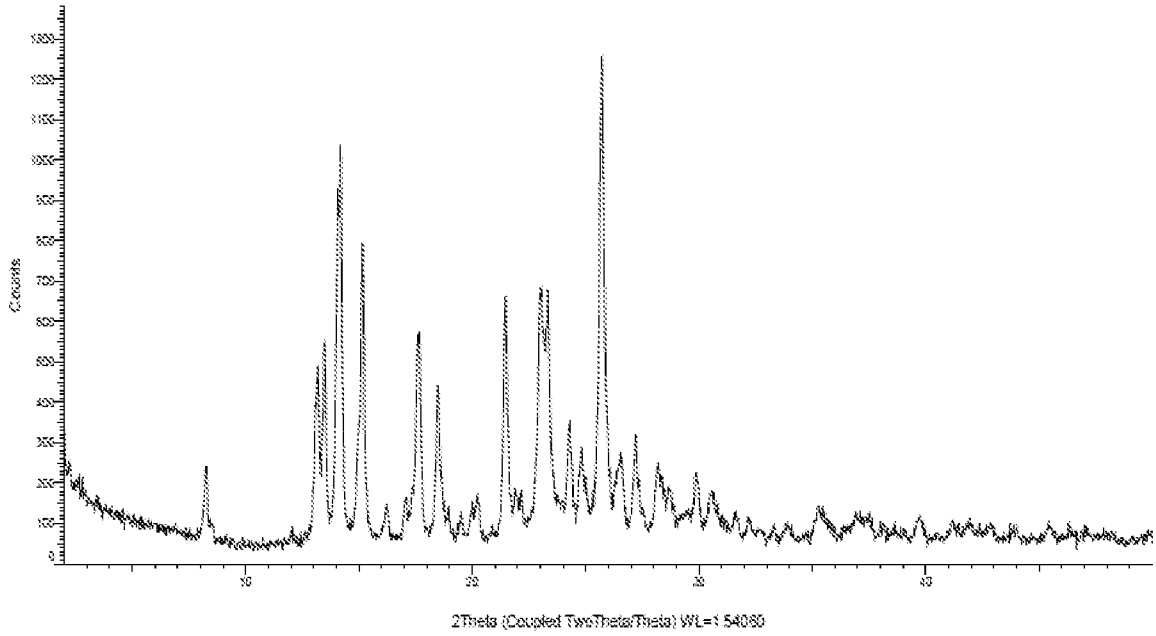

Figure-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2018/050552

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/00 Version=2018 .01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K31/444 Version=2018 .01

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

TotalPatent One, IPO Internal Database

C. DOCUMENTS **CONSIDERED** TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2011050175 (Al) SARCODE BIOSCIENCE INC [US] 28-04-2011 (28 APRIL 2011) Abstract, paragraphs [0002-0007, 0083, 0101, 0104-0108, 0160, 0167], scheme 5, tables, figures 2, 6, 13, 19, 22, and 25; claims	1-46, 48-50
Y	WO 2009139817 (A3) SARCODE CORPORATION [US] 07-01-2010 (07 JANUARY 2010) Abstract, paragraphs [0003-0011, 0018, 0031, 0114, 0121, and 0135-0137]; tables; figures 2, 6, 13, 19, 22 and 25; claims	1-46, 48-50
Y	WO 2005044817 (Al) SUNESIS PHARMACEUTICALS INC ET AL [US] 19-05-2005 (19 MAY 2005) Abstract, paragraphs [0006-0023, 0048], examples, schemes, claims	1-46, 48-50

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12-12-2018	12-12-2018

Name and mailing address of the ISA/	Authorized officer
Indian Patent Office Plot No. 32, Sector 14,Dwarka, New Delhi-110075 Facsimile No.	Dasari Ayodhya Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT

International application No.
PCT / IN2 018/ 050552

Box No. II Observations wbere certain claims were foand unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 47
because they relate to subject matter not reauired to be searched by this Authority, namely:
The subject matter of claim 47 appears to be related to a method for treatment of the human or animal body, which does not require an international search by this authority in accordance with PCT Article 17(2)(a)(i) and Rule 39.1(iv).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with ihe second and third sentences of Rule 6.4(a).

Box **No. Ill** Observations where **unity of invention** is lacking **(Continuation** of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
The present application is found to contravene the requirements of unity of invention according to Art. 3(4)(iii) PCT, Art. 34(3)(a) PCT and Rule 13 PCT for the following reasons: The following features have been identified which possibly lead to the following invention s / groups of inventions :
Invention 1: Claims 1-11, 13, and 48-50 relate to the various processes of the compound formula (1), its use and particle size distribution.
Invention 2: Claims 12 (partially) and 14-19, relates to the compound of formula (3a), its process and polymorphs thereof.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

.3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in ihe claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in ihe invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT / IN2 018/ 050552

Citation	Pub. Date	Family	Pub. Date
Wo 2011050175 Al	28-04-2011	US 8378105 B2	19-02-2013
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Continuation of Observations where unity of invention is lacking (Box III)

Invention 3: Claims 12 (partially) and 20-25, relates to the compound of formula (5a), its process and polymorphs thereof.
Invention 4: Claims 26-28, relates to the process and its purification of the compound of formula (5), its process and polymorphs thereof.
Invention 5: Claims 29-32 and 45-47 (partially), relates to a process for the preparation of crystalline form-M of compound formula-1 and characterized by powder-XRD .
Invention 6: Claims 33-36 and 45-47 (partially), relates to a process for the preparation of crystalline form-S of compound formula-1 and characterized by powder-XRD.
Invention 7: Claims 37-40 and 45-47 (partially), relates to a process for the preparation of crystalline form-N of compound formula-1 and characterized by powder-XRD.
Invention 8: Claims 41-44 and 45-47 (partially), relates to a process for the preparation of crystalline form-L of compound formula-1 and characterized by powder-XRD.
Though the amorphous and crystalline forms of compound formula-1 are common in all of above inventions, but in view of prior art, however, these elements do not provide a general inventive concept that links the claims. Each of the technical features corresponding to inventions 1-8 above is different and since they do not lead to the same product or process, the special technical features are not corresponding either. Hence, no same or corresponding special technical features can be identified amongst the different inventions 1-8 that can link them. Thus the present application lacks unity of invention.