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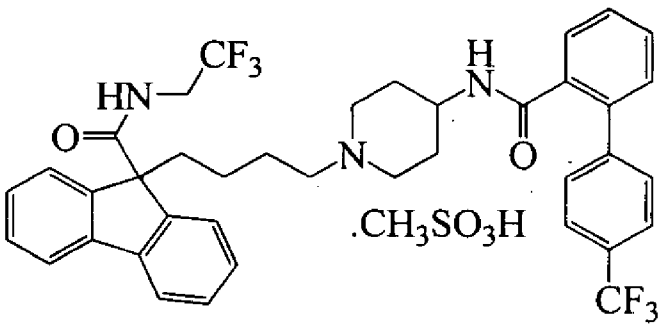
— *of inventorship (Rule 4.17(iv))*

[Continued on next page]

(54) **Title**: CRYSTALLINE POLYMORPH OF N-(2,2,2-TRIFLUOROETHYL-9-[4-[R4-R[[[I4'- (TRIFLUOROMETHYL) [1,1 ' -BIPHENYL] -2-YL] CARBONYL] AMINO] -1 -PIPERIDINYL] BUTYL] -9H- FLUORENE-9-CARBOXAMIDE METHANESULFONATE AND PROCESS FOR PREPARATION THEREOF



Formula-1a

(57) **Abstract**: The present invention relates to,, crystalline polymorph of N-(2,2.2-trifluoroethyl)-9- [4- [4- [[[4,-(trifluoromethyl) [1,1 '-biphenyl] -2-yl] carbonyl] amino] - 1 -piperidinyl] butyl] -9H- fluorene-9-carboxamide methanesulfonate salt represented by the following structural formula- la and process for preparation thereof.

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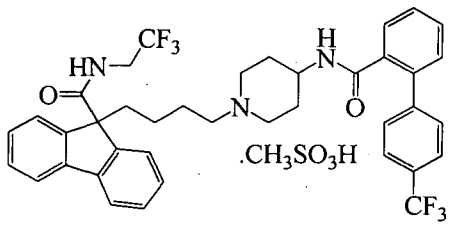
Crystalline polymorph of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate and process for preparation thereof

Related Application:

This application claims the benefit of priority of our Indian patent application IN6561/CHE/2015 filed on Dec 08, 2015 which is incorporated herein as reference.

Field of the Invention:

The present invention provides crystalline polymorph of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate salt represented by the following structural formula-1a and process for preparation thereof.



Formula-1a

The present invention also provides process for the preparation of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate compound of formula-1a.

Background of the Invention:

N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl] amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide (commonly known as Lomitapide; marketed as Juxtapid in the US and as Lojuxta in the EU) is a drug for the treatment of familial hypercholesterolemia, developed by Aegerion Pharmaceuticals. The US Food and Drug Administration (FDA) approved Lomitapide as its mesylate salt as an orphan drug to reduce LDL cholesterol, total cholesterol, apolipoprotein B and non-high-density lipoprotein (non-HDL) cholesterol in patients with homozygous familial hypercholesterolemia (HoFH).

Lomitapide, its pharmaceutically acceptable salts and process for their preparation is first reported in US5712279A.

US5712279A didn't provide any specific method for the preparation of mesylate salt of Lomitapide.

WO2015121877A2 has described and characterized the amorphous form of Lomitapide mesylate and process for its preparation.

Still, there is a significant need in the art to develop crystalline polymorph of Lomitapide mesylate which is advantageous over the prior known amorphous form to meet the pharmaceutical requirements.

In the process of research for the advantageous polymorph for Lomitapide mesylate, the present inventors have surprisingly found novel crystalline polymorph of Lomitapide mesylate which is well suitable for the preparation of various pharmaceutical compositions.

Brief description of the invention:

The first aspect of the present invention is to provide novel crystalline polymorph of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate, herein after designated as crystalline form-M.

The second aspect of the present invention is to a provide process for the preparation of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate compound of formula-1a.

The third aspect of the present invention is to provide process for the preparation of crystalline form-M of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate compound of formula-1a.

The fourth aspect of the present invention is to provide a process for the preparation of compound of general formula-3.

The fifth aspect of the present invention is to provide a process for the preparation of tert-butyl 1-(4-(9-(2,2,2-trifluoroethylcarbamoyl)-9H-fluoren-9-yl)butyl)piperidin-4-ylcarbamate compound of formula-6.

The sixth aspect of the present invention is to provide process for the preparation of 9-(4-(4-aminopiperidin-1-yl)butyl)-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide compound of formula-7 or its salt.

The seventh aspect of the present invention is to provide process for the preparation of crystalline N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl] carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide compound of formula-1.

The eighth aspect of the present invention is to provide a process for the preparation of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl] carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate compound of formula-1a.

Brief Description of the Drawings:

Figure-1: Illustrates the PXRD pattern of crystalline form-M of compound of formula-1a obtained according to example-6

Figure-2: Illustrates the PXRD pattern of crystalline form-M of compound of formula-1a obtained according to example-7

Figure-3: Illustrates the PXRD pattern of crystalline form-M of compound of formula-1a obtained according to example-8

Figure-4: Illustrates the PXRD pattern of compound of formula-1

Figure-5: Illustrates the PXRD pattern of 9-(4-bromobutyl)-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide (Formula-4a)

Figure-6: Illustrates the PXRD pattern of tert-butyl 1-(4-(9-(2,2,2-trifluoroethylcarbamoyl)-9H-fluoren-9-yl)butyl)piperidin-4-ylcarbamate (Formula-6)

Figure-7: Illustrates the PXRD pattern of 9-(4-(4-aminopiperidin-1-yl)butyl)-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide dihydrochloride (Formula-7a).

Figure-8: Illustrates the PXRD pattern of crystalline form-M of compound of formula-1a obtained according to example-16

Figure-9: Illustrates the DSC thermogram of crystalline form-M of compound of formula-1a obtained according to example-16.

Figure-10: Illustrates the PXRD pattern of tert-butyl 1-(4-(9-(2,2,2-trifluoroethylcarbamoyl)-9H-fluoren-9-yl)butyl)piperidin-4-ylcarbamate compound of formula-6 obtained according to example-13.

Detailed description of the Invention:

The term "suitable solvent" used in the present invention refers to "hydrocarbon solvents" such as n-pentane, n-hexane, n-heptane, cyclohexane, methyl cyclohexane, pet 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, t-butanol, ethane-1,2-diol, propane-1,2-diol, cyclohexanol and the like; "polar solvents" such as water; formic acid, acetic acid or mixture of any of the aforementioned solvents.

The term "suitable base" used in the present invention refers to "inorganic bases" selected from "alkali metal carbonates" such as sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate and the like; "alkali metal bicarbonates" such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, cesium bicarbonate and the like; "alkali metal hydroxides" such as sodium hydroxide, potassium hydroxide, lithium hydroxide and the like; "alkali metal alkoxides" such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, sodium tert.butoxide, potassium tert.butoxide, lithium tert.butoxide 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; alkali metal and alkali earth metal salts of acetic acid such as sodium acetate, potassium acetate, magnesium acetate, calcium acetate and the like; ammonia; "organic bases" like dimethylamine, diethylamine, diisopropyl mine, diisopropylethylamine, diisobutylamine, triethylamine, triisopropyl amine, tributylamine, tert.butyl amine, pyridine, 4-dimethylaminopyridine, imidazole, N-methylimidazole, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), N-methyl morpholine, 1,4-diazabicyclo[2.2.2]octane (DABCO), 2,6-lutidine and the like; "organolithium bases" such as methyl lithium, n-butyl lithium, lithium diisopropylamide and the like; "organosilicon bases" such as lithium hexamethyldisilazide, sodium hexamethyldisilazide, potassium hexamethyldisilazide and the like or their mixtures.

The term "suitable acid" used in the present invention refers to hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, formic acid, acetic acid, trifluoroacetic acid, alkyl/aryl sulfonic acids such as methane sulfonic acid, ethane sulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, malic acid, maleic acid, fumaric acid, tartaric acid, mandelic acid, acetyl mandelic acid, oxalic acid, citric acid, succinic acid and the like.

The first aspect of the present invention provides novel crystalline polymorph of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate compound of formula-1a, herein after designated as crystalline form-M. The crystalline form-M of compound of formula-1a of the present invention is characterized by its PXRD pattern having characteristic peaks at 4.7, 9.5, 10.1, 10.8, 12.1, 13.4, 14.3, 15.9, 17.9, 18.9, 21.7, 22.5, 23.5, 24.6, 36.2 ± 0.2° of 2-theta values. The crystalline form-M of compound of formula-1a of the present invention is further characterized by its PXRD patterns as illustrated in any of the figures-1, 2, 3 and 8.

The crystalline form-M of compound of formula-1a of the present invention is useful 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-1a is present in the composition in particular polymorphic form mentioned. Such pharmaceutical

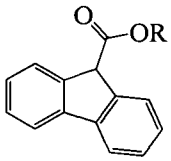
compositions may comprise compound of formula-1a present in the composition in a range of between 0.005% and 100% (wt/wt), with the balance of the pharmaceutical composition comprising additional substances such as excipients, diluents, lubricants, binders, wetting agents, disintegrating agents, glidants, sweetening agents, flavoring agents, emulsifying agents, solubilizing agents, pH buffering agents, perfuming agents, surface stabilizing agents, suspending agents and other conventional pharmaceutically inactive agents.

An embodiment of the present invention provides pharmaceutical composition comprising crystalline polymorph form-M of compound of formula-1a and at least one pharmaceutically acceptable excipient.

The crystalline polymorph form-M of compound of formula-1a of the present invention is stable and well suitable for the preparation of various pharmaceutical compositions.

The second aspect of the present invention provides a process for the preparation of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate compound of formula-1a, comprising of;

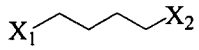
a) alkylation of compound of general formula-2



Formula-2

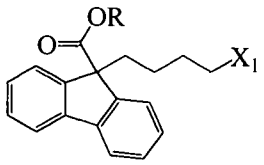
wherein, 'R' represents H, alkyl, aryl group;

with 1,4-disubstitued butane represented by the following formula



wherein, 'X_1', 'X_2' are independently selected form leaving groups such as halogens, alkyl/aryl sulfonyloxy groups which may be optionally substituted;

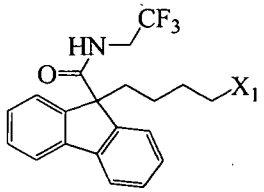
in presence of a suitable base in a suitable solvent to provide compound of general formula-3,



Formula-3

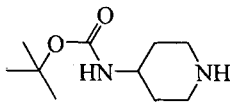
wherein, 'X_1' is same as defined above;

b) reacting the compound of general formula-3 with 2,2,2-trifluoroethylamine or its salt in presence of a suitable coupling agent and/or a suitable base in a suitable solvent to provide compound of general formula-4,



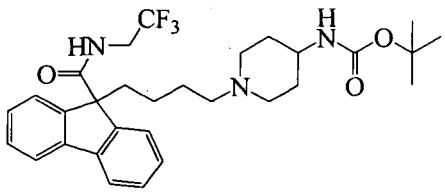
Formula-4

c) reacting the compound of general formula-4 by reacting it with tert-butyl piperidin-4-ylcarbamate compound of formula-5



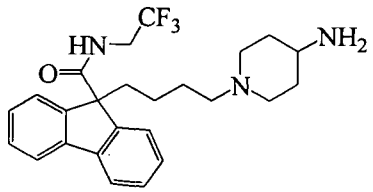
Formula-5

in presence of a suitable base in a suitable solvent optionally in presence of a suitable catalyst to provide tert-butyl 1-(4-(9-(2,2,2-trifluoroethylcarbamoyl)-9H-fluoren-9-yl)butyl)piperidin-4-ylcarbamate compound of formula-6,



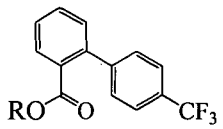
Formula-6

d) deprotection of compound of formula-6 by treating it with a suitable deprotecting agent in a suitable solvent to provide 9-(4-(4-aminopiperidin-1-yl)butyl)-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide compound of formula-7 or its salt,



Formula-7

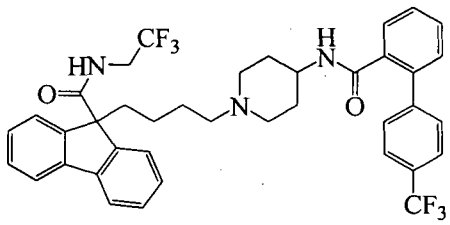
e) reacting the compound of formula-7 or its salt with compound of general formula-8



Formula-8

wherein, 'R' is as defined above;

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



Formula-1

f) treating the compound of formula-1 with methanesulfonic acid in a suitable solvent to provide its methanesulfonate salt compound of formula-1a,

g) purifying the compound of formula-1a from a suitable solvent to provide pure compound of formula-1a.

Wherein, in step-a) to step-g) wherever necessary the suitable solvent 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 or their mixtures;

In step-a), step-b), step-c) & step-e) the suitable base is selected from but not limited to organic bases, inorganic bases, organolithium bases, organosilicon bases or their mixtures;

In step-b) and step-e) the suitable coupling agent is selected from but not limited to 1,1'-carbonyldiimidazole (CDI), N,N'-dicyclohexylcarbodiimide (DCC), N,N'-diisopropyl

carbodiimide (DIC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluoro phosphate (HATU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluoro phosphate (HBTU), 1H-benzotriazolium 1-[bis(dimethylamino)methylene]-5chloro-hexafluorophosphate (1-) 3-oxide (HCTU), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyl uronium tetrafluoroborate (TBTU), alkyl/aryl haloformates selected from but not limited to ethyl chloroformate, benzylchloroformate; diphenylphosphoroazidate (DPPA), thionyl chloride, oxalyl chloride, phosphorous oxychloride, phosphorous pentachloride, 4-methyl-2-oxopentanoyl chloride (i-BuCOCOCl), (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate (BOP), benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), methane sulfonyl chloride, p-toluenesulfonyl chloride and the like optionally in combination with 1-hydroxy-7-azatriazole (HOAt), 1-hydroxybenzotriazole (HOBt), 1-hydroxy-1H-1,2,3-triazole-4-carboxylate (HOCt), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), N-hydroxysuccinamide (HOSu), N-hydroxysulfosuccinimide (Sulfo-NHS) and the like;

In step-c) the suitable catalyst is selected from but not limited to alkali metal halides such as lithium bromide, lithium iodide, sodium bromide, sodium, iodide, potassium bromide, potassium iodide and the like;

In step-d) the suitable deprotecting agent is selected from but not limited to acids such as hydrochloric acid, hydrobromic acid, formic acid, acetic acid, trifluoroacetic acid, alkyl/aryl sulfonic acids such as methane sulfonic acid, p-toluenesulfonic acid and the like; the suitable acid source such as acetyl chloride in presence of alcohol solvent, trialkylsilyl halide; tetrabutylammonium fluoride, ceric ammonium nitrate and the like.

In the above deprotection step, deprotection of compound of formula-6 can also be done by treating it with a suitable hydrochloric acid source such as conc. HCl, aq.HCl, HCl gas, ethyl acetate-HCl, isopropyl acetate-HCl, methanol-HCl, ethanol-HCl, isopropanol-HCl, HCl in dioxane and the like.

Instead of tert.butoxycarbonyl (Boc) protecting group in compound of formula-5, other amine protecting groups known in the art can also be employed. The said amine protecting group can be deprotected by treating with a suitable deprotecting agent based on

the type of the protecting group employed. The said amine protecting groups include but not limited to benzyloxycarbonyl (Cbz), trityl, acetyl, benzyl, benzoyl, alkyl/aryl sulfonyl, Fmoc, -COOR (R can be alkyl or aryl) and the like.

The third aspect of the present invention provides a process for the preparation of crystalline form-M of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate compound of formula-1a, comprising of;

a) Adding cyclohexane to compound of formula-1a,
b) heating the reaction mixture,
c) slowly adding water to the reaction mixture,
d) cooling the reaction mixture,
e) filtering the solid and drying the material to provide crystalline form-M of compound of formula-1a.

Wherein, in step-a) the compound of formula-1a which is used as input can be prepared by reacting compound of formula-1 with methanesulfonic acid in presence of a suitable solvent or mixture of solvents followed by removal of the solvent from the reaction mixture to provide compound of formula-1a; In this process the suitable solvent can be selected from the solvents as defined in second aspect of the present invention;

In step-b) the reaction mixture is heated to a suitable temperature ranges from 35°C to reflux temperature of the solvent used;

In step-d) the reaction mixture is cooled to a suitable temperature ranges from 30°C to -70°C; after cooling the reaction mixture, stirring is stopped and holding the reaction mixture for sufficient time ranges from 0.5-72 hrs to facilitate the completion of crystal formation followed by further stirring the reaction mixture and filtering the solid to provide form-M.

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

a) Adding cyclohexane to compound of formula-1a,
b) heating the reaction mixture to 75-80°C,

c) slowly 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-M of compound of formula-1a.

An embodiment of the present invention provides a process for the preparation of crystalline form-M of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate compound of formula-1a, comprising of;

a) Combining the compound of formula-1a with water,
b) stirring the reaction mixture,
c) filtering the solid and drying the material to provide crystalline form-M of compound of formula-1a.

Wherein, the reaction mixture is stirred for 0.5-10 hrs at 25-30°C.

Another embodiment of the present invention provides an alternate process for the preparation of crystalline form-M of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate compound of formula-1a, comprising of;

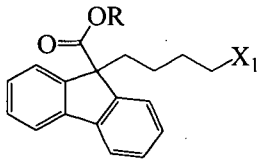
a) Combining the compound of formula-1a with a suitable hydrocarbon solvent,
b) heating the reaction mixture,
c) filtering the solid and drying the material to provide crystalline form-M of compound of formula-1a.

Wherein the suitable hydrocarbon solvent is selected from n-pentane, n-hexane, n-heptane, cyclohexane, methyl cyclohexane, pet ether, benzene, toluene, xylene or mixtures thereof; and the reaction mixture is heated to a suitable temperature ranging from 30-70°C.

A preferred embodiment of the present invention provides a process for the preparation of crystalline form-M of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate compound of formula-1a, comprising of;

a) Combining the compound of formula-1a with cyclohexane,
b) heating the reaction mixture to 55-60°C,
c) filtering the solid and drying the material to provide crystalline form-M of compound of formula-1a.

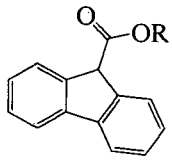
The fourth aspect of the present invention provides a process for the preparation of compound of general formula-3,



Formula-3

wherein, 'R' represents H, alkyl, aryl group and 'X_1', 'X_2' are independently selected form leaving groups such as halogens, alkyl/aryl sulfonyloxy groups which may be optionally substituted;

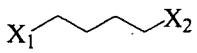
comprising of, alkylation of compound of general formula-2



Formula-2

wherein, 'R' is as defined above;

with 1,4-disubstitued butane represented by the following formula



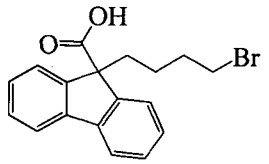
wherein, 'X_1', 'X_2' are as defined above;

in presence of a suitable base in a suitable solvent to provide compound of general formula-3.

Wherein, in the above process the suitable solvent 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 or their mixtures; preferably hydrocarbon solvents.

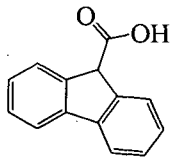
The suitable base is selected from but not limited to organic bases, inorganic bases, organolithium bases, organosilicon bases or their mixtures. The suitable base is preferably selected from inorganic bases, more preferably selected from alkali metal alkoxides.

A preferred embodiment of the present invention provides a process for the preparation of 9-(4-bromobutyl)-9H-fluorene-9-carboxylic acid compound of formula-3a,



Formula-3a

comprising of, reacting the 9H-fluorene-9-carboxylic acid compound of formula-2a



Formula-2a

with 1,4-dibromobutane in presence of sodium tert.butoxide in toluene to provide compound of formula-3a.

The fifth aspect of the present invention provides a process for the preparation of tert-butyl 1-(4-(9-(2,2,2-trifluoroethylcarbamoyl)-9H-fluoren-9-yl)butyl)piperidin-4-yl carbamate compound of formula-6, comprising of reacting the compound of general formula-4 with tert-butyl piperidin-4-ylcarbamate compound of formula-5 in presence of a suitable base in a suitable solvent optionally in presence of suitable catalyst to provide compound of formula-6.

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

In the above step, the suitable base is preferably selected from inorganic bases and the suitable solvent is preferably selected from ketone solvents.

A preferred embodiment of the present invention provides a process for the preparation of tert-butyl 1-(4-(9-(2,2,2-trifluoroethylcarbamoyl)-9H-fluoren-9-yl)butyl)piperidin-4-ylcarbamate compound of formula-6, comprising of reacting the 9-(4-bromobutyl)-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide compound of formula-4a with tert-butyl piperidin-4-ylcarbamate compound of formula-5 in presence of potassium carbonate and sodium iodide in acetone in to provide compound of formula-6.

The sixth aspect of the present invention provides a process for the preparation of 9-(4-(4-aminopiperidin-1-yl)butyl)-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide compound of formula-7 or its salt, comprising of deprotecting the tert-butyl 1-(4-(9-(2,2,2-trifluoroethylcarbamoyl)-9H-fluoren-9-yl)butyl)piperidin-4-ylcarbamate compound of formula-6 with a suitable deprotecting agent in a suitable solvent to provide compound of formula-7 or its salt.

Wherein the suitable deprotecting agent and the suitable solvent are same as defined in step-d) of the second aspect of the present invention.

In the above process, the suitable deprotecting agent is preferably selected from suitable hydrochloric acid source such as conc.HCl, aq.HCl, HCl gas, ethyl acetate-HCl, isopropyl acetate-HCl, methanol-HCl, ethanol-HCl, isopropanol-HCl, HCl in dioxane and the like.

A preferred embodiment of the present invention provides a process for the preparation of 9-(4-(4-aminopiperidin-1-yl)butyl)-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide dihydrochloride compound of formula-7a, comprising of deprotecting the tert-butyl 1-(4-(9-(2,2,2-trifluoroethylcarbamoyl)-9H-fluoren-9-yl)butyl)piperidin-4-ylcarbamate compound of formula-6 with ethyl acetate-HCl in presence of ethyl acetate as solvent to provide compound of formula-7a.

The seventh aspect of the present invention provides a process for the preparation of crystalline N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl] carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide compound of formula-1, comprising of;

a) Combining the compound of formula-1 with a suitable solvent selected from water or aqueous alcohol,
b) heating the reaction mixture,
c) cooling the reaction mixture,
d) filtering the solid and optionally drying the material to provide crystalline compound of formula-1.

Wherein, in step-a) the alcohol solvent is selected from C_1-C_6 straight chain or branched chain alcohol. The alcohol solvent is preferably selected from methanol, ethanol, n-propanol, isopropyl alcohol, n-butanol, iso-butanol, 2-butanol, tert.butanol, n-pentanol and the like or their mixtures;

In step-b) the reaction mixture is heated to a suitable temperature ranges from 30°C to reflux temperature of the solvent used;

In step-c) the reaction mixture is cooled to a suitable temperature ranges from 30°C to -70°C.

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

a) Combining the compound of formula-1 with water,
b) heating the reaction mixture,
c) cooling the reaction mixture,
d) filtering the solid and optionally drying the material to provide crystalline compound of formula-1.

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

a) Combining the compound of formula-1 with aqueous methanol or aqueous ethanol,

b) heating the reaction mixture,

c) cooling the reaction mixture,

d) filtering the solid and optionally drying the material to provide crystalline compound of formula-1.

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

a) Combining the compound of formula-1 with aqueous isopropyl alcohol,

b) heating the reaction mixture,

c) cooling the reaction mixture,

d) filtering the solid and optionally drying to provide crystalline compound of formula-1.

The eighth aspect of the present invention provides a process for the preparation of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate compound of formula-1a, comprising of;

a) Providing N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide compound of formula-1 and methane sulfonic acid in a suitable solvent,

b) optionally filtering the reaction mixture,

c) combining the obtained solution with a suitable second solvent,

d) removing the solvent from the reaction mixture to provide compound of formula-1a.

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

In step-c) the suitable second solvent is selected from hydrocarbon solvents or mixture of hydrocarbon solvents; and combining the solution of step-a) or step-b) with suitable second solvent can be carried out at a suitable temperature ranging from 25°C to reflux temperature of the second solvent used;

In step-d) removal of the solvent can be carried out by distillation optionally under reduced pressure, evaporation, evaporation by rotational distillation, spray drying, freeze drying, agitated thin film drying (ATFD), filtration, decantation, centrifugation; and the reaction mixture can be optionally cooled to lower temperature before the removal of solvent.

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

a) Providing compound of formula-1 and methane sulfonic acid in ethyl acetate,
b) optionally filtering the reaction mixture,
c) combining the obtained solution with cyclohexane,
d) removing the solvent from the reaction mixture to provide compound of formula-1a.

The compound of formula-1 and compound of formula-1a obtained by the processes of the present invention are having purity of greater than 99%, more preferably greater than 99.5%, most preferably greater than 99.8% by HPLC with all the impurities and residual solvents well within the limits as suggested by ICH.

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

Apparatus: A liquid chromatographic system equipped with variable wavelength UV detector; Column: Zorbax Bonus RP, 250 × 4.6 mm, 5 µm or equivalent; Column temperature: 25°C; Wave length: 210 nm; Injection volume: 5 µL; Elution: Gradient; Diluent: Acetonitrile:Water (50:50 v/v); Buffer: Transfer 2.0 mL of orthophosphoric acid (85%) and add 3.0 gm of 1-octane sulphonic acid sodium salt anhydrous into 1000 mL of milli-Q-water, mix well and filter this solution through 0.22 µm Nylon membrane filter paper; Mobile phase-A: Buffer (100%); Mobile phase-B: Acetonitrile: Water (90:10 v/v).

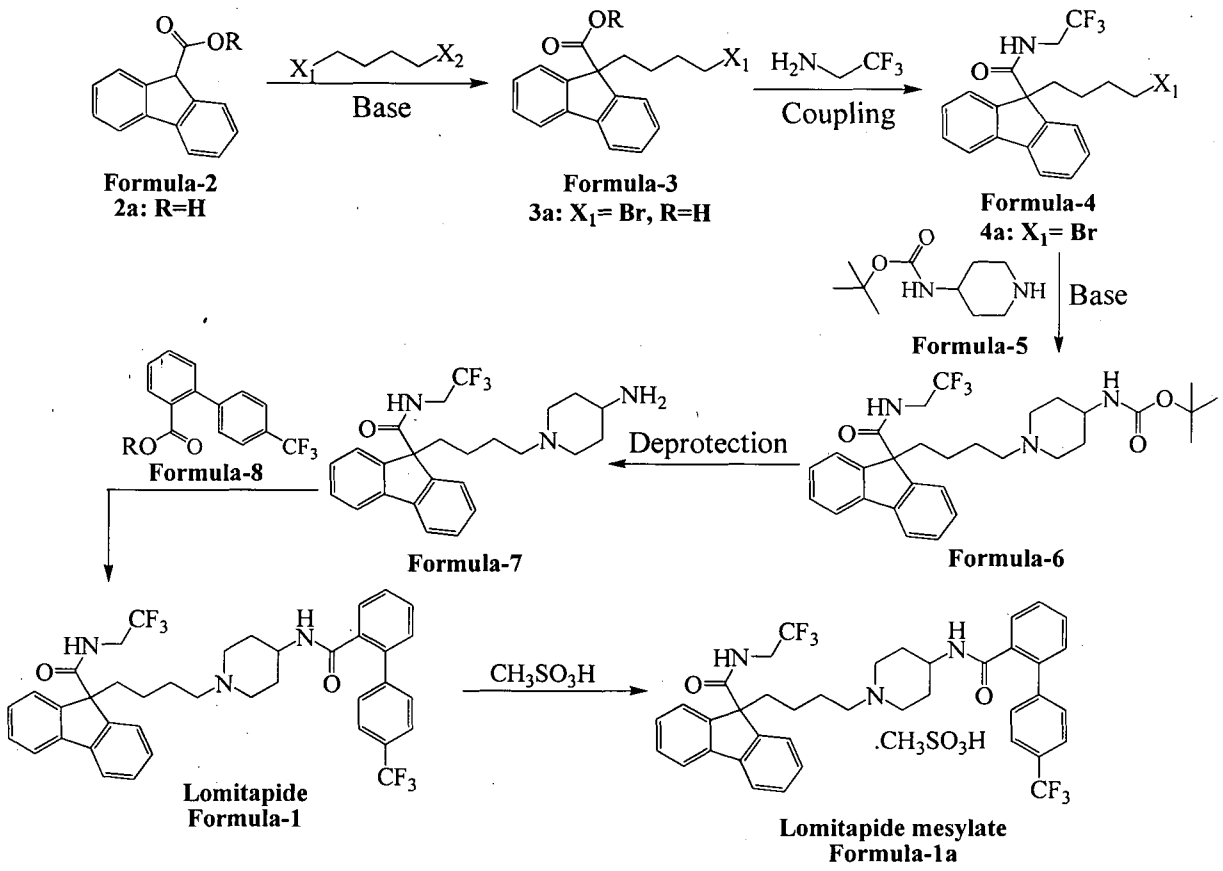
The PXRD analysis of compound of formula-1a of the present invention was carried out using BRUKER/AXS X-Ray diffractometer using CuKα radiation of wavelength 1.5406 A° and at a continuous scan speed of 0.03°/min.

Differential scanning calorimetric (DSC) analysis was performed on a Q2000 V24.11 Build 124 calorimeter with aluminium pans. Samples held in a closed pan were analyzed at a heating rate of 10°C/min.

The crystalline form-M of compound of formula-1a 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:



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 9-(4-bromobutyl)-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide (Formula-4a)

A mixture of 9H-fluorene-9-carboxylic acid compound of formula-2a (100 gm), 1,4-dibromobutane (308 gm) and toluene (1000 ml) was stirred for 15 min at 25-30°C under nitrogen atmosphere. Cooled the reaction mixture to 5-10°C, sodium tert.butoxide (100.5 gm) was slowly added to it and stirred the reaction mixture for 3 hrs at the same temperature. Water was added to the reaction mixture at 25-30°C and stirred for 15 min at the same temperature. Filtered the reaction mixture through hyflow bed and washed the hyflow bed with water. Both the organic and aqueous layers were separated and washed the aqueous layer with toluene. Acidified the aqueous layer using aqueous hydrochloric acid solution at 25-30°C and stirred the reaction mixture for 20 min at the same temperature. Dichloromethane was added to the reaction mixture at 25-30°C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with aqueous citric acid solution. Distilled off the solvent completely from the organic layer. Dichloromethane (500 ml) was added to the reaction mixture at 25-30°C and stirred for 15 min at the same temperature. N,N-dimethylformamide (6.9 gm) followed by oxalyl chloride (66.4 gm) were slowly added to the reaction mixture at 25-30°C and stirred for 2 hrs at the same temperature. Distilled off the solvent completely from the reaction mixture under nitrogen atmosphere and co-distilled with dichloromethane under reduced pressure. Dichloromethane (500 ml) was added to the obtained compound at 25-30°C and stirred for 15 min at the same temperature. The obtained compound was slowly added to a pre-cooled mixture of water (500 ml), 2,2,2-trifluoroethylamine hydrochloride (64.4 gm) and sodium carbonate (75.6 gm) at 5-10°C and stirred the reaction mixture for 45 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with aqueous hydrochloric acid solution followed by with aqueous sodium bicarbonate solution and then finally washed with water. Distilled off the solvent completely from the

organic layer and then co-distilled with n-heptane under reduced pressure. n-Heptane (100 ml) and isopropanol (5 ml) were added to the reaction mixture at 25-30°C. Heated the reaction mixture to 55-60°C and stirred for 1 hr at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 1 hr at the same temperature. Filtered the precipitated solid, washed with n-heptane and then dried the material to provide the title compound. The PXRD pattern of the obtained compound is shown in figure-5. Yield: 155.0 gm; M.R: 95-102°C.

Example-2: Preparation of tert-butyl 1-(4-(9-(2,2,2-trifluoroethylcarbamoyl)-9H-fluoren-9-yl)butyl)piperidin-4-ylcarbamate (Formula-6)

9-(4-bromobutyl)-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide compound of formula-4a (100 gm) and sodium iodide (3.5 gm) were added to a mixture of tert-butyl piperidin-4-ylcarbamate compound of formula-5 (47 gm), diisopropylethylamine (121 gm) and N,N-dimethylformamide (300 ml) at 25-30°C. Heated the reaction mixture to 70-75°C and stirred for 5 hrs at the same temperature. Cooled the reaction mixture to 25-30°C, water was added and stirred for 15 min at the same temperature. Ethyl acetate was added to the reaction mixture at 25-30°C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with aqueous sodium chloride solution. Distilled off the solvent completely from the organic layer and co-distilled with n-heptane under reduced pressure. Cooled the reaction mixture to 25-30°C, tetrahydrofuran (200 ml) was added and stirred for 15 min at the same temperature. n-Heptane (800 ml) was added to the reaction mixture at 25-30°C. Heated the reaction mixture to 75-80°C and stirred for 1 hr at the same temperature. Cooled the reaction mixture to 25-30°C. Filtered the reaction mixture through hyflow bed and washed with n-heptane. Distilled off the solvent completely from the filtrate and under reduced pressure. Tetrahydrofuran (50 ml) and n-heptane (400 ml) were added to the obtained compound at 25-30°C. Heated the reaction mixture to 95-100°C and stirred for 40 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 40 min at the same temperature. Filtered the precipitated solid and washed with a mixture of tetrahydrofuran and n-heptane and then dried the material to provide the title compound. PXRD pattern of obtained compound is shown in figure-6. Yield: 102.5 gm; M.R: 135-138°C.

Example-3: Preparation of 9-(4-(4-aminopiperidin-1-yl)butyl)-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide dihydrochloride (Formula-7a)

Ethyl acetate-HCl (200 ml) was slowly added to a pre-cooled mixture of tert-butyl 1-(4-(9-(2,2,2-trifluoroethylcarbamoyl)-9H-fluoren-9-yl)butyl)piperidin-4-ylcarbamate compound of formula-6 (50 gm) and ethyl acetate (100 ml) at 5-10°C. Heated the reaction mixture to 45-50°C and stirred for 1 hr at the same temperature. Distilled off the solvent completely from the reaction mixture under reduced pressure and co-distilled with dichloromethane. Dichloromethane (250 ml) was added to the obtained compound at 25-30°C. Heated the reaction mixture to 40-45°C and stirred for 30 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 1 hr at the same temperature. Filtered the solid, washed with dichloromethane and then dried the material to provide the title compound. The PXRD pattern of the obtained compound is shown in figure-7.

Yield: 42.0 gm; M.R: 185-195°C.

Example-4: Preparation of compound of formula-1

1-Hydroxybenzotriazole (3.4 gm) was added to a mixture of 4'-(trifluoromethyl)biphenyl-2-carboxylic acid compound of formula-8a (5.1 gm), toluene (15 ml) and ethyl acetate (15 ml) at 25-30°C and stirred the reaction mixture for 10 min at the same temperature. Cooled the reaction mixture to 0-5°C. A solution of dicyclohexylcarbodiimide (5.9 gm) in a mixture of toluene (10 ml) and ethyl acetate (10 ml) was slowly added to the reaction mixture at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 90 min at the same temperature. Cooled the reaction mixture to 0-5°C, stirred for 90 min at the same temperature and filtered the reaction mixture. The obtained filtrate was slowly added to a pre-cooled mixture of 9-(4-(4-aminopiperidin-1-yl)butyl)-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide dihydrochloride compound of formula-7a (10 gm), sodium carbonate (6.1 gm) and water (50 ml) at 5-10°C and stirred the reaction mixture for 1 hr at the same temperature. Raised the temperature of the reaction mixture to 25-30°C. Both the organic and aqueous layers were separated and washed the organic layer with aqueous HCl solution followed by with aqueous sodium carbonate solution and then finally with aqueous sodium chloride solution. Distilled off the solvent completely from the organic layer under reduced pressure and co-distilled with cyclohexane.

Cyclohexane (40 ml) and ethyl acetate (20 ml) were added to the obtained compound at 25-30°C. Heated the reaction mixture to 75-80°C and stirred for 30 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 90 min at the same temperature. Filtered the precipitated solid, washed with a mixture of cyclohexane and ethyl acetate. Ethanol (40 ml) and water (10 ml) were added to the obtained compound at 25-30°C. Heated the reaction mixture to 85-90°C and stirred for 40 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 2 hrs at the same temperature. Filtered the precipitated solid and washed with aqueous ethanol. To the obtained compound, ethanol (30 ml) and water (10 ml) were added at 25-30°C. Heated the reaction mixture to 85-90°C and stirred for 40 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 2 hrs at the same temperature. Filtered the precipitated solid, washed with aqueous ethanol and then dried the material to provide the title compound.

The PXRD pattern of the obtained compound is shown in figure-4.

Yield: 6.5 gm.

Example-5: Preparation of compound of formula-1a

A mixture of compound of formula-1 (30 gm) and dichloromethane (1050 ml) was stirred for 15 min at 25-30°C. Filtered the reaction mixture, methanesulfonic acid (4.15 gm) was added to the filtrate at 25-30°C and stirred for 15 min at the same temperature. Distilled off the solvent completely from the reaction mixture under reduced pressure to provide the title compound. Yield: 25.0 gm.

Example-6: Preparation of crystalline form-M of compound of formula-1a

A mixture of compound of formula-1a (500 mg) and water (10 ml) was stirred for 5 hrs at 25-30°C. Filtered the solid and suck dried the material to provide the title compound.

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

Yield: 400.0 mg.

Example-7: Preparation of crystalline form-M of compound of formula-1a

A mixture of compound of formula-1a obtained in the above example and cyclohexane (10 ml) was slowly heated to 55-60°C and stirred the reaction mixture for 6 hrs

at the same temperature. Filtered the solid and dried the material under reduced pressure to provide the title compound. PXRD pattern of the obtained compound is shown in figure-2.
Yield: 260.0 mg.

Example-8: Preparation of crystalline form-M of compound of formula-1a

A mixture of compound of formula-1a (500 mg) and cyclohexane (5 ml) was slowly heated to 55-60°C and stirred the reaction mixture for 25 hrs at the same temperature. Filtered the solid and then dried to provide the title compound.
The PXRD pattern of the obtained compound is shown in figure-3.
Yield: 395.0 mg.

Example-9: Preparation of amorphous form of compound of formula-1a

A mixture of compound of formula-1a (500 mg) and cyclohexane (10 ml) was slowly heated to 45-50°C. Water (10 ml) was added to the reaction mixture. Heated the reaction mixture to 55-60°C and stirred for 15 hrs at the same temperature. Filtered the solid and dried the material to provide the title compound.
Yield: 300.0 mg.

Example-10: Preparation of amorphous form of compound of formula-1a

A mixture of compound of formula-1a (500 mg) and n-heptane (5 ml) was slowly heated to 65-70°C and stirred the reaction mixture for 25 hrs at the same temperature. Filtered the solid and dried the material to provide the title compound.
Yield: 310.0 mg.

Example-11: Preparation of amorphous form of compound of formula-1a

A mixture of compound of formula-1a (500 mg) and methyl cyclohexane (7 ml) was slowly heated to 55-60°C and stirred the reaction mixture for 25 hrs at the same temperature. Filtered the solid and dried the material to provide the title compound.
Yield: 360.0 mg.

Example-12: Preparation of 9-(4-bromobutyl)-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide (Formula-4a)

A mixture of 9H-fluorene-9-carboxylic acid compound of formula-2a (5 Kg), 1,4-dibromobutane (15.4 Kg) and toluene (50 Lt) was stirred for 15 min at 25-30°C under nitrogen atmosphere. Cooled the reaction mixture to 5-10°C, sodium tert.butoxide (5 Kg) was slowly added to it and stirred the reaction mixture for 2 hrs at the same temperature. Water was slowly added to the reaction mixture. Raised the temperature of the reaction mixture to 25-30°C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the aqueous layer with toluene. Adjusted the pH of the aqueous layer using aqueous hydrochloric acid solution at 25-30°C and stirred the reaction mixture for 20 min at the same temperature. Dichloromethane was added to the reaction mixture at 25-30°C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with aqueous citric acid solution. Distilled off the solvent completely from the organic layer. Dichloromethane (25 Lt) was added to the obtained compound at 25-30°C and stirred for 15 min at the same temperature. N,N-dimethylformamide (0.33 Lt) was added to the reaction mixture. Oxalyl chloride (3.32 Kg) was slowly added to the reaction mixture at 25-30°C and stirred for 2 hrs at the same temperature. Distilled off the solvent completely from the reaction mixture under nitrogen atmosphere and co-distilled with dichloromethane under reduced pressure. Dichloromethane (10 Lt) was added to the obtained compound at 25-30°C and stirred for 15 min at the same temperature. The obtained reaction mixture was slowly added to a pre-cooled mixture of dichloromethane (25 Lt), 2,2,2-trifluoroethylamine hydrochloride (3.22 Kg) and triethylamine (4.8 Kg) at 5-10°C and stirred the reaction mixture for 1 hr at the same temperature. Water was slowly added to the reaction mixture at 5-10°C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with aqueous hydrochloric acid solution followed by with aqueous sodium bicarbonate solution and then finally washed with water. Distilled off the solvent completely from the organic layer. Water (25 Lt) was added to the obtained compound at 25-30°C and stirred for 1 hr at the same temperature. Filtered the solid, washed with water and then dried

the material to provide the title compound. PXRD pattern of obtained compound is similar to figure-5. Yield: 7.4 Kg; Purity by HPPLC: 91.9%.

Example-13: Preparation of tert-butyl 1-(4-(9-(2,2,2-trifluoroethylcarbamoyl)-9H-fluoren-9-yl)butyl)piperidin-4-ylcarbamate (Formula-6)

9-(4-bromobutyl)-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide compound of formula-4a (7 Kg) and sodium iodide (0.24 Kg) were added to a mixture of tert-butyl piperidin-4-ylcarbamate compound of formula-5 (3.29 Kg), acetone (21 Lt) and potassium carbonate (4.54 Kg) at 25-30°C and stirred the reaction mixture for 5-10 min at the same temperature. Heated the reaction mixture to 55-60°C and stirred for 6 hrs at the same temperature. Distilled off the solvent completely from the reaction mixture under reduced pressure. Water was added to the reaction mixture at 25-30°C and stirred for 15 min at the same temperature. Ethyl acetate was added to the reaction mixture at 25-30°C and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated and extracted the aqueous layer with ethyl acetate. Combined the organic layers and washed with water. Distilled off the solvent completely from the organic layer under reduced pressure and co-distilled with cyclohexane. Cooled the obtained compound to 25-30°C, cyclohexane (35 Lt) was added and stirred the reaction mixture for 15 min at the same temperature. Heated the reaction mixture to 50-55°C and stirred for 1 hr at the same temperature. Cooled the reaction mixture to 25-30°C. Filtered the solid, washed with cyclohexane and then dried the material to provide the title compound. PXRD pattern of obtained compound is shown in figure-10. Yield: 7.1 Kg; Purity by HPLC: 90.5%.

Example-14: Preparation of 9-(4-(4-aminopiperidin-1-yl)butyl)-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide dihydrochloride (Formula-7a)

A mixture of tert-butyl 1-(4-(9-(2,2,2-trifluoroethylcarbamoyl)-9H-fluoren-9-yl)butyl)piperidin-4-ylcarbamate compound of formula-6 (6 Kg) and ethyl acetate (18 Lt) was cooled to 5-10°C and ethyl acetate-HCl (24 Lt) was slowly added to it. Heated the reaction mixture to 45-50°C and stirred for 45 min at the same temperature. Distilled off the solvent completely from the reaction mixture under reduced pressure and co-distilled with dichloromethane. Dichloromethane (42 Lt) was added to the obtained compound at 25-30°C.

Heated the reaction mixture to 35-40°C and stirred for 45 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 1 hr at the same temperature. Filtered the solid, washed with dichloromethane and dried the material to provide the title compound. The PXRD pattern of the obtained compound is similar to figure-7. Yield: 4.2 Kg; Purity by HPLC: 99.3%.

Example-15: Preparation of compound of formula-1

Step-a) Oxalyl chloride (2.94 Kg) was slowly added to a mixture of 4'-(trifluoromethyl)biphenyl-2-carboxylic acid compound of formula-8a (2.05 Kg) and dichloromethane (12 Lt) at 25-30°C and stirred the reaction mixture for 4 hr at the same temperature. Distilled off the solvent completely from the reaction mixture and co-distilled with dichloromethane. Dichloromethane (8 Lt) was added to the obtained compound and the solution containing the acid chloride is kept aside.

Step-b) Triethylamine (3.12 Kg) was slowly added to a mixture of 9-(4-(4-aminopiperidin-1-yl)butyl)-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide dihydrochloride compound of formula-7a (4 Kg) and dichloromethane (20 Lt) at 25-30°C and stirred the reaction mixture for 45 min at the same temperature. Filtered the reaction mixture and cooled the filtrate to 0-5°C. Acid chloride solution prepared in above step-a) was slowly added to the reaction mixture at 0-5°C and stirred for 90 min at the same temperature. Water was added to the reaction mixture at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Distilled of the solvent completely from the organic layer under reduced pressure. Water (20 Lt) was added to the obtained compound at 25-30°C. Heated the reaction mixture to 55-60°C and stirred for 30 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 2 hrs at the same temperature. Filtered the solid and washed with water. Methanol (28 Lt) and water (12 Lt) were added to the obtained compound at 25-30°C. Heated the reaction mixture to 65-70°C and stirred for 30 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 1 hr at the same temperature. Filtered the solid and washed with aqueous methanol. Isopropyl alcohol (20 Lt) and water (8 Lt) were added to the obtained compound at 25-30°C. Heated the reaction mixture to 80-85°C and stirred for 40 min at the same temperature. Cooled the reaction

mixture to 25-30°C and stirred for 3 hr at the same temperature. Filtered the solid, washed with aqueous isopropyl alcohol and dried the material to provide the title compound.
The PXRD pattern of the obtained compound is similar to figure-4.
Yield: 3.15 Kg; Purity by HPLC: 99.81%.

Example-16: Preparation of compound of formula-1a

A mixture of compound of formula-1 (3 Kg), methanesulfonic acid (0.42 Kg) and ethyl acetate (10.5 Lt) was stirred for 15 min at 25-30°C. Filtered the reaction mixture to make it particle free. The obtained filtrate was added to pre-heated cyclohexane (45 Lt) at 45-50°C and stirred for 45 min at the same temperature. Cooled the reaction mixture to 25-30°C and decanted the solvent completely. Cyclohexane (45 Lt) was added to the reaction mixture at 25-30°C. Heated the reaction mixture to 75-80°C. Slowly added purified water (1.5 Lt) to the reaction mixture at 75-80°C and stirred for 3 hrs at the same temperature. Cooled the reaction mixture to 25-30°C. Stopped the reaction mixture stirring and hold it for 42 hrs at 25-30°C. Again stirred the reaction mixture for 2 hrs at 25-30°C. Filtered the solid, washed with cyclohexane and then dried the material to provide the title compound.
The PXRD pattern of the obtained compound is shown in figure-8 and the DSC thermogram is shown in figure-9. Yield: 2.9 Kg; Purity by HPLC: 99.83%.

Example-17: Preparation of compound of formula-1

1-Hydroxybenzotriazole (14.32 gm) was added to a mixture of 4'-(trifluoromethyl)biphenyl-2-carboxylic acid compound of formula-8a (25.67 gm) and ethyl acetate (150 ml) at 25-30°C and stirred the reaction mixture for 10 min at the same temperature. Cooled the reaction mixture to 0-5°C. A solution of dicyclohexylcarbodiimide (21.88 gm) in ethyl acetate (150 ml) was added to the reaction mixture at 0-5°C and stirred for 90 min at the same temperature. Filtered the byproduct and washed with chilled ethyl acetate. The obtained filtrate was slowly added to a pre-cooled mixture of 9-(4-(4-aminopiperidin-1-yl)butyl)-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide dihydrochloride compound of formula-7a (50 gm), triethylamine (58.55 gm) and water (350 ml) at 5-10°C and stirred the reaction mixture for 90 min at the same temperature. Raised the temperature of the reaction mixture to 25-30°C and ethyl acetate was added. Both the organic

and aqueous layers were separated. Aqueous HCl solution was added to the organic layer at 25-30°C, cooled the reaction mixture to 5-10°C and stirred for 40 min at the same temperature. Filtered the reaction mixture through hyflow bed and washed the filtrate with aqueous potassium carbonate solution. n-Heptane (100 ml) was added to the reaction mixture at 25-30°C and distilled off the solvent completely under reduced pressure. Aqueous acetic acid solution was added to the reaction mixture at 25-30°C and stirred for 1 hr at the same temperature. Hyflow was added to the reaction mixture and stirred for 15 min. Filtered the reaction mixture and washed with aqueous acetic acid solution. Cooled the filtrate to 5-10°C, basified the reaction mixture using aqueous sodium hydroxide solution. Ethyl acetate was added to the reaction mixture, further basified with aqueous sodium hydroxide solution and stirred for 1 hr at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with water. n-Heptane was added to the organic layer, distilled off the solvent completely under reduced pressure and co-distilled with cyclohexane. Ethyl acetate (100 ml) and cyclohexane (25 ml) were added to the obtained compound at 25-30°C. Heated the reaction mixture to 75-80°C and stirred for 30 min at the same temperature. Cooled the reaction mixture to 35-40°C and cyclohexane (175 ml) was added. Heated the reaction mixture to 75-80°C and stirred for 40 min at the same temperature. Slowly cooled the reaction mixture to 25-30°C and stirred for 3 hrs at the same temperature. Filtered the solid and washed with a mixture of cyclohexane and ethyl acetate. Ethyl acetate (100 ml) and cyclohexane (25 ml) were added to the obtained compound at 25-30°C. Heated the reaction mixture to 75-80°C and stirred for 30 min at the same temperature. Cooled the reaction mixture to 40-45°C and cyclohexane (175 ml) was added. Heated the reaction mixture to 75-80°C and stirred for 40 min at the same temperature. Slowly cooled the reaction mixture to 25-30°C and stirred for 3 hrs at the same temperature. Filtered the solid and washed with a mixture of ethyl acetate and cyclohexane. Ethanol (200 ml) and water (100 ml) were added to the obtained compound at 25-30°C. Heated the reaction mixture to 60-65°C and stirred for 40 min at the same temperature. Slowly cooled the reaction mixture to 25-30°C and stirred for 3 hrs at the same temperature. Filtered the solid and washed with a mixture of ethanol and water. Ethanol (200 ml) and water (100 ml) were added to the obtained compound at 25-30°C. Heated the reaction mixture to 60-65°C and stirred for 40 min at the same temperature.

Slowly cooled the reaction mixture to 25-30°C and stirred for 3 hrs at the same temperature. Filtered the solid and washed with a mixture of ethanol and water. Ethyl acetate (750 ml) and water (125 ml) were added to the obtained compound at 25-30°C and stirred for 10 min at the same temperature. Both the organic and aqueous layers were separated, n-heptane was added to the organic layer and distilled off the solvent completely under reduced pressure. Water (250 ml) was added to the obtained compound at 25-30°C. Heated the reaction mixture to 65-70°C and stirred for 40 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 40 min at the same temperature. Filtered the solid, washed with water and dried the material to get the title compound. Yield: 40.5 gm.

Example-18: Preparation of compound of formula-1a

A mixture of compound of formula-1 (100 gm), methanesulfonic acid (4.15 gm) and ethyl acetate (350 ml) was stirred for 15 min at 25-30°C. Filtered the reaction mixture to make it particle free. The obtained filtrate was slowly added to pre-cooled cyclohexane (1500 ml) at 5-10°C and stirred for 2 hrs at the same temperature. Filtered the solid and washed with cyclohexane. Cyclohexane (2000 ml) was added to the obtained compound at 25-30°C and heated the reaction mixture to 75-80°C. Water (50 ml) was slowly added to the reaction mixture at 75-80°C and stirred for 3 hrs at the same temperature. Cooled the reaction mixture to 25-30°C and hold it for 40 hrs at the same temperature. Further stirred the reaction mixture for 2 hrs at 25-30°C. Filtered the solid, washed with cyclohexane and dried the material to get the title compound. Yield: 107.0 gm.

We Claim:

1. Crystalline polymorph of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate compound of formula-1a, characterized by its PXRD pattern having peaks at 4.7, 9.5, 10.1, 10.8, 12.1, 13.4, 14.3, 15.9, 17.9, 18.9, 21.7, 22.5, 23.5, 24.6, 36.2 ± 0.2° of 2-theta.

2. The crystalline polymorph according to claim 1, which is further characterized by its PXRD pattern as illustrated in any of the figures-1, 2, 3 and 8.

3. A process for the preparation of crystalline form-M of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate compound of formula-1a, comprising of;
   a) Adding cyclohexane to compound of formula-1a,
   b) heating the reaction mixture,
   c) slowly adding water to the reaction mixture,
   d) cooling the reaction mixture,
   e) filtering the solid and drying the material to provide crystalline form-M of compound of formula-1a.

4. The process according to claim 3, wherein

   in step-b) the reaction mixture is heated to a suitable temperature ranges from 30°C to reflux temperature of the solvent used;

   in step-d) the reaction mixture is cooled to a suitable temperature ranges from 30°C to -70°C.

5. A process for the preparation of crystalline form-M of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate compound of formula-1a, comprising of;
   a) Adding cyclohexane to compound of formula-1a,
   b) heating the reaction mixture to 75-80°C,
   c) slowly adding water to the reaction mixture,

d) cooling the reaction mixture to 25-30°C,

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

6. A process for the preparation of crystalline form-M of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate compound of formula-1a, comprising of;

a) Combining the compound of formula-1a with water,

b) stirring the reaction mixture,

c) filtering the solid and drying the material to provide crystalline form-M of compound of formula-1a.

7. The process according to claim 6, wherein the reaction mixture is stirred for 0.5-10 hrs at 25-30°C.

8. A process for the preparation of crystalline form-M of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate compound of formula-1a, comprising of;

a) Combining the compound of formula-1a with a suitable hydrocarbon solvent,

b) heating the reaction mixture,

c) filtering the solid and drying the material to provide crystalline form-M of compound of formula-1a.

9. The process according to claim 8, wherein the suitable hydrocarbon solvent is selected from n-pentane, n-hexane, n-heptane, cyclohexane, methyl cyclohexane, pet ether, benzene, toluene, xylene or mixtures thereof; and the reaction mixture is heated to a suitable temperature ranging from 35°C to 70°C.

10. A process for the preparation of crystalline form-M of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate compound of formula-1a, comprising of;

a) Combining the compound of formula-1a with cyclohexane,

b) heating the reaction mixture to 55-60°C,

c) filtering the solid and drying the material to provide crystalline form-M of compound of formula-1a.

11. A process for the preparation of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate compound of formula-1a, comprising of;

a) Providing N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide compound of formula-1 and methane sulfonic acid in a suitable solvent,

b) optionally filtering the reaction mixture,

c) combining the obtained solution with a suitable second solvent,

d) removing the solvent from the reaction mixture to provide compound of formula-1a.

12. The process according to claim 11, wherein,

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

in step-c) the suitable second solvent is selected from hydrocarbon solvents or mixture of hydrocarbon solvents; and combining the solution of step-a) or step-b) with suitable second solvent can be carried out at a suitable temperature ranging from 25°C to reflux temperature of the second solvent used;

in step-d) removal of the solvent can be carried out by distillation optionally under reduced pressure, evaporation, evaporation by rotational distillation, spray drying, freeze drying, agitated thin film drying (ATFD), filtration, decantation, centrifugation; and the reaction mixture can be optionally cooled to lower temperature before the removal of solvent.

13. A process for the preparation of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate compound of formula-1a, comprising of;

a) Providing N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide compound of formula-1 and methane sulfonic acid in ethyl acetate,

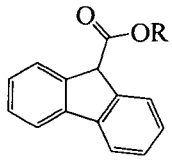
b) optionally filtering the reaction mixture,

c) combining the obtained solution with cyclohexane,

d) removing the solvent from the reaction mixture to provide compound of formula-1a.

14. A process for the preparation of N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide methanesulfonate compound of formula-1a, comprising of;

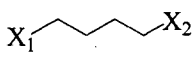
a) alkylation of compound of general formula-2



Formula-2

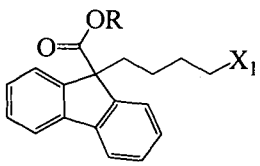
wherein, 'R' represents H, alkyl, aryl group;

with 1,4-disubstitued butane represented by the following formula



wherein, 'X_1', 'X_2' are independently selected form leaving groups such as halogens, alkyl/arylsulfonyloxy groups which may be optionally substituted;

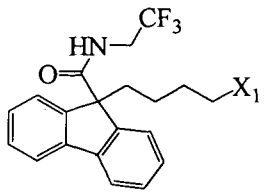
in presence of a suitable base in a suitable solvent to provide compound of general formula-3,



Formula-3

wherein, 'X_1' is same as defined above;

b) reacting the compound of general formula-3 with 2,2,2-trifluoroethylamine or its salt in presence of a suitable coupling agent and/or a suitable base in a suitable solvent to provide compound of general formula-4,

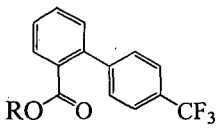


Formula-4

c) reacting the compound of general formula-4 by reacting it with tert-butyl piperidin-4-ylcarbamate compound of formula-5 in presence of a suitable base and a suitable catalyst in a suitable solvent to provide tert-butyl 1-(4-(9-(2,2,2-trifluoroethylcarbamoyl)-9H-fluoren-9-yl)butyl)piperidin-4-ylcarbamate compound of formula-6,

d) deprotection of compound of formula-6 by treating it with a suitable deprotecting agent in a suitable solvent to provide 9-(4-(4-aminopiperidin-1-yl)butyl)-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide compound of formula-7 or its salt,

e) reacting the compound of formula-7 or its salt with compound of general formula-8



Formula-8

wherein, 'R' is as defined above;

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

f) treating the compound of formula-1 with methanesulfonic acid in a suitable solvent to provide its methanesulfonate salt compound of formula-1a,

g) purifying the compound of formula-1a from a suitable solvent to provide pure compound of formula-1a.

15. The process according to claim 14, wherein

in step-a) to step-g) 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 their mixtures;

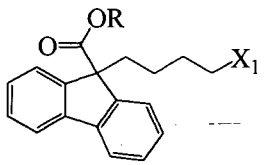
in step-a), step-b), step-c) & step-e) the suitable base is selected from organic bases, inorganic bases, organolithium bases, organosilicon bases or their mixtures;

in step-b) and step-e) the suitable coupling agent is selected from 1,1'-carbonyldiimidazole (CDI), N,N'-dicyclohexylcarbodiimide (DCC), N,N'-diisopropyl carbodiimide (DIC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluoro phosphate (HATU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluoro phosphate (HBTU), 1H-benzotriazolium 1-[bis(dimethylamino)methylene]-5chloro-hexafluorophosphate (1-) 3-oxide (HCTU), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyl uronium tetrafluoroborate (TBTU), alkyl/aryl haloformates selected from ethyl chloroformate, benzylchloroformate; diphenylphosphoroazidate (DPPA), thionyl chloride, oxalyl chloride, phosphorous oxychloride, phosphorous pentachloride, 4-methyl-2-oxopentanoyl chloride (i-BuCOCOCl), (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate (BOP), benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), methane sulfonyl chloride, p-toluenesulfonyl chloride optionally in combination with 1-hydroxy-7-azatriazole (HOAt), 1-hydroxybenzotriazole (HOBt), 1-hydroxy-1H-1,2,3-triazole-4-carboxylate (HOCt), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), N-hydroxysuccinamide (HOSu), N-hydroxysulfosuccinimide (Sulfo-NHS);

in step-c) the suitable catalyst is selected from alkali metal halides such as lithium bromide, lithium iodide, sodium bromide, sodium, iodide, potassium bromide, potassium iodide and the like;

in step-d) the suitable deprotecting agent is selected from acids such as hydrochloric acid, hydrobromic acid, formic acid, acetic acid, trifluoroacetic acid, alkyl/aryl sulfonic acids such as methane sulfonic acid, p-toluenesulfonic acid; the suitable acid source such as acetyl chloride in presence of alcohol solvent, trialkylsilyl halide, tetrabutylammonium fluoride, ceric ammonium nitrate; suitable HCl source such as conc.HCl, aq.HCl, HCl gas, ethyl acetate-HCl, isopropyl acetate-HCl, methanol-HCl, ethanol-HCl, isopropanol-HCl, HCl in dioxane.

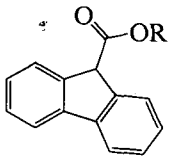
16. A process for the preparation of compound of general formula-3,



Formula-3

wherein, 'R' represents H, alkyl, aryl group and 'X_1', 'X_2' are independently selected form leaving groups such as halogens, alkyl/aryl sulfonyloxy groups which may be optionally substituted;

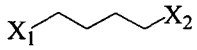
comprising of, alkylation of compound of general formula-2



Formula-2

wherein, 'R' is as defined above;

with 1,4-disubstitued butane represented by the following formula



wherein, 'X1', 'X2' are as defined above;

in presence of a suitable alkali metal alkoxide in a suitable solvent to provide compound of general formula-3.

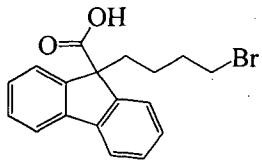
17. The process according to claim 16, wherein

the suitable alkali metal alkoxides is selected from sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, sodium tert.butoxide, potassium tert.butoxide, lithium tert.butoxide and the like;

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 their mixtures.

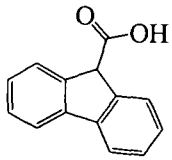
18. The process according to claim 17, wherein the suitable alkali metal alkoxide is preferably selected from sodium tert.butoxide, potassium tert.butoxide, lithium tert.butoxide and the suitable solvent is preferably selected from hydrocarbon solvents.

19. A process for the preparation of 9-(4-bromobutyl)-9H-fluorene-9-carboxylic acid compound of formula-3a,



Formula-3a

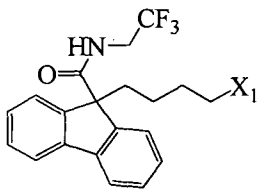
comprising of, reacting the 9H-fluorene-9-carboxylic acid compound of formula-2a



Formula-2a

with 1,4-dibromobutane in presence of sodium tert.butoxide in toluene to provide compound of formula-3a.

20. A process for the preparation of tert-butyl 1-(4-(9-(2,2,2-trifluoroethylcarbamoyl)-9H-fluoren-9-yl)butyl)piperidin-4-ylcarbamate compound of formula-6, comprising of reacting the compound of general formula-4



Formula-4

with tert-butyl piperidin-4-ylcarbamate compound of formula-5 in presence of a suitable base and a suitable catalyst in a suitable solvent to provide compound of formula-6.

21. The process according to claim 20, 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 their mixtures;

the suitable base is selected from organic bases, inorganic bases, organolithium bases, organosilicon bases or their mixtures;

the suitable catalyst is selected from alkali metal halides such as lithium bromide, lithium iodide, sodium bromide, sodium, iodide, potassium bromide, potassium iodide and the like.

22. The process according to claim 21, wherein the suitable base is preferably selected from inorganic bases and the suitable solvent is preferably selected from ketone solvents.

23. A process for the preparation of 9-(4-(4-aminopiperidin-1-yl)butyl)-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide compound of formula-7 or its salt, comprising of deprotecting the tert-butyl 1-(4-(9-(2,2,2-trifluoroethylcarbamoyl)-9H-fluoren-9-yl)butyl)piperidin-4-ylcarbamate compound of formula-6 with a suitable deprotecting agent selected from ethyl acetate-HCl, isopropyl acetate-HCl, methanol-HCl, ethanol-HCl, isopropanol-HCl, hydrobromic acid, formic acid, acetic acid, trifluoroacetic acid, alkyl/aryl sulfonic acids such as methane sulfonic acid, p-toluenesulfonic acid; the suitable acid source such as acetyl chloride in presence of alcohol solvent, trialkylsilyl halide; tetrabutylammonium fluoride, ceric ammonium nitrate.

24. A process according to claim 23, wherein the suitable deprotecting agent is preferably selected from ethyl acetate-HCl, isopropyl acetate-HCl, methanol-HCl, ethanol-HCl, isopropanol-HCl.

25. A process for the preparation of 9-(4-(4-aminopiperidin-1-yl)butyl)-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide dihydrochloride compound of formula-7a, comprising of deprotecting the tert-butyl 1-(4-(9-(2,2,2-trifluoroethylcarbamoyl)-9H-fluoren-9-yl)butyl)piperidin-4-ylcarbamate compound of formula-6 with ethyl acetate-HCl in presence of ethyl acetate as solvent to provide compound of formula-7a.

26. A process for the preparation of crystalline N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide compound of formula-1, comprising of;
    a) Combining the compound of formula-1 with a suitable solvent selected from water or aqueous alcohol,
    b) heating the reaction mixture,
    c) cooling the reaction mixture,
    d) filtering the solid and optionally drying the material to provide crystalline compound of formula-1.

27. The process according to claim 26, wherein

in step-a) the alcohol solvent is selected from C_1-C_6 straight chain or branched chain alcohol such as methanol, ethanol, n-propanol, isopropyl alcohol, n-butanol, iso-butanol, 2-butanol, tert.butanol, n-pentanol or their mixtures;

in step-b) the reaction mixture is heated to a suitable temperature ranges from 35°C to reflux temperature of the solvent used;

in step-c) the reaction mixture is cooled to a suitable temperature ranges from 30°C to -70°C.

28. A process for the preparation of crystalline N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide compound of formula-1, comprising of;
    a) Combining the compound of formula-1 with water,
    b) heating the reaction mixture,
    c) cooling the reaction mixture,
    d) filtering the solid and optionally drying the material to provide crystalline compound of formula-1.

29. A process for the preparation of crystalline N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide compound of formula-1, comprising of;

a) Combining the compound of formula-1 with aqueous methanol or aqueous ethanol,
b) heating the reaction mixture,
c) cooling the reaction mixture,
d) filtering the solid and optionally drying the material to provide crystalline compound of formula-1.

30. A process for the preparation of crystalline N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide compound of formula-1, comprising of;
a) Combining the compound of formula-1 with aqueous isopropyl alcohol,
b) heating the reaction mixture,
c) cooling the reaction mixture,
d) filtering the solid and optionally drying the material to provide crystalline compound of formula-1.

31. Use of crystalline polymorph according to claim 1 or 2 for the preparation of pharmaceutical composition.

32. Pharmaceutical composition comprising crystalline polymorph according to claim 1 or 2 and at least one pharmaceutically acceptable excipient.

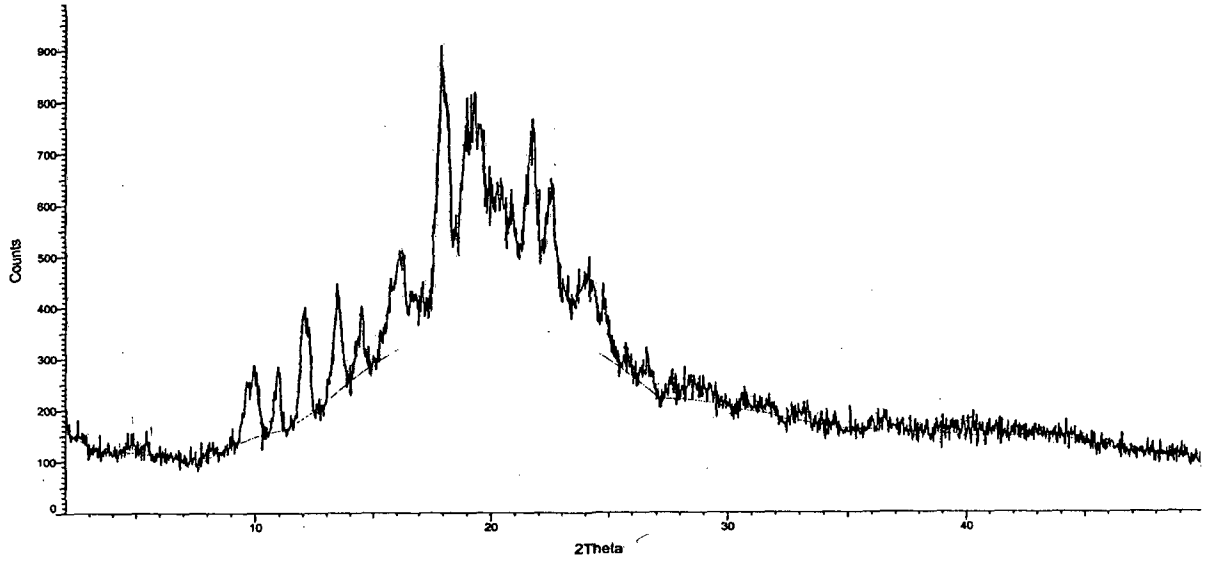


Figure-1

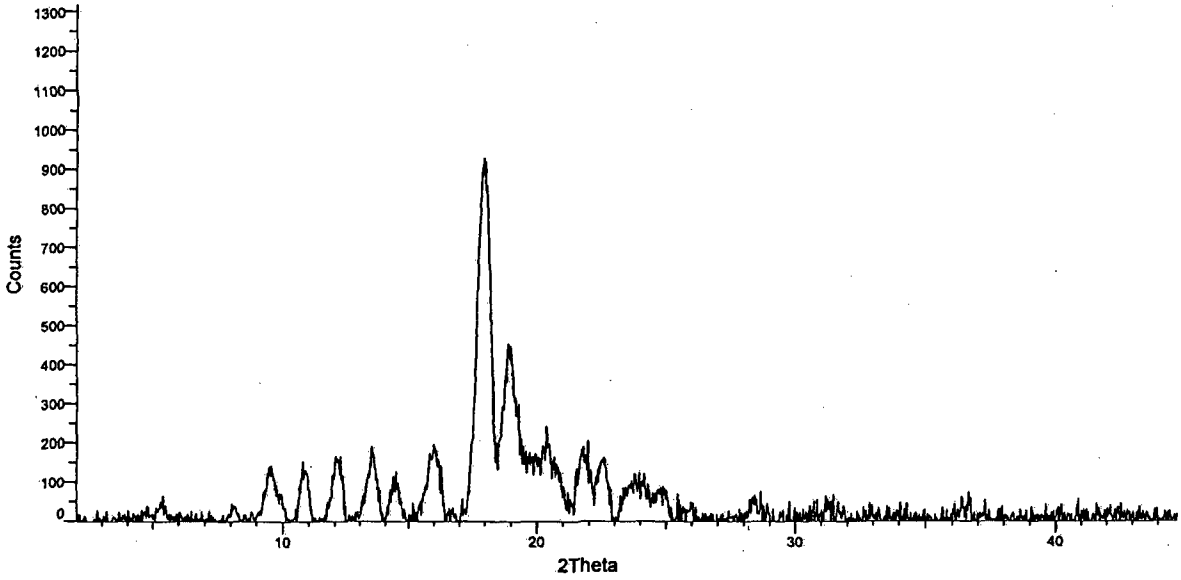


Figure-2

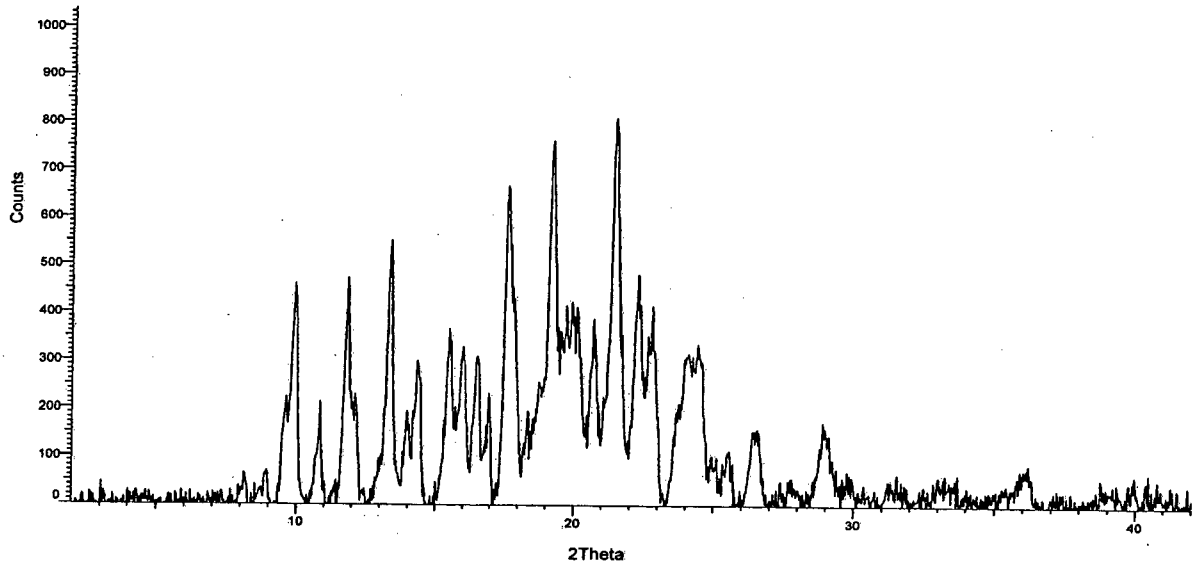


Figure-3

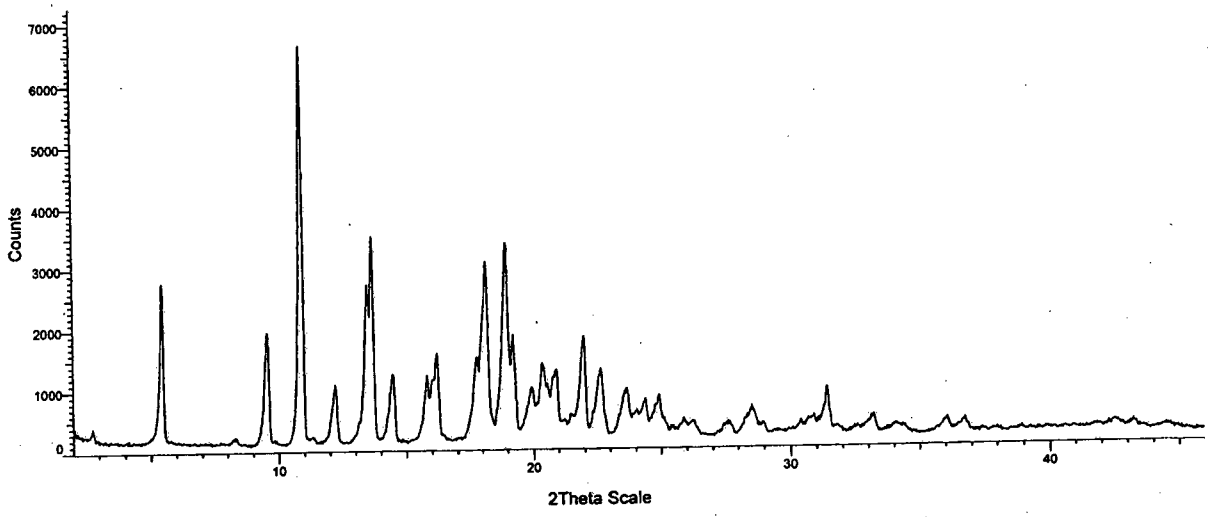


Figure-4

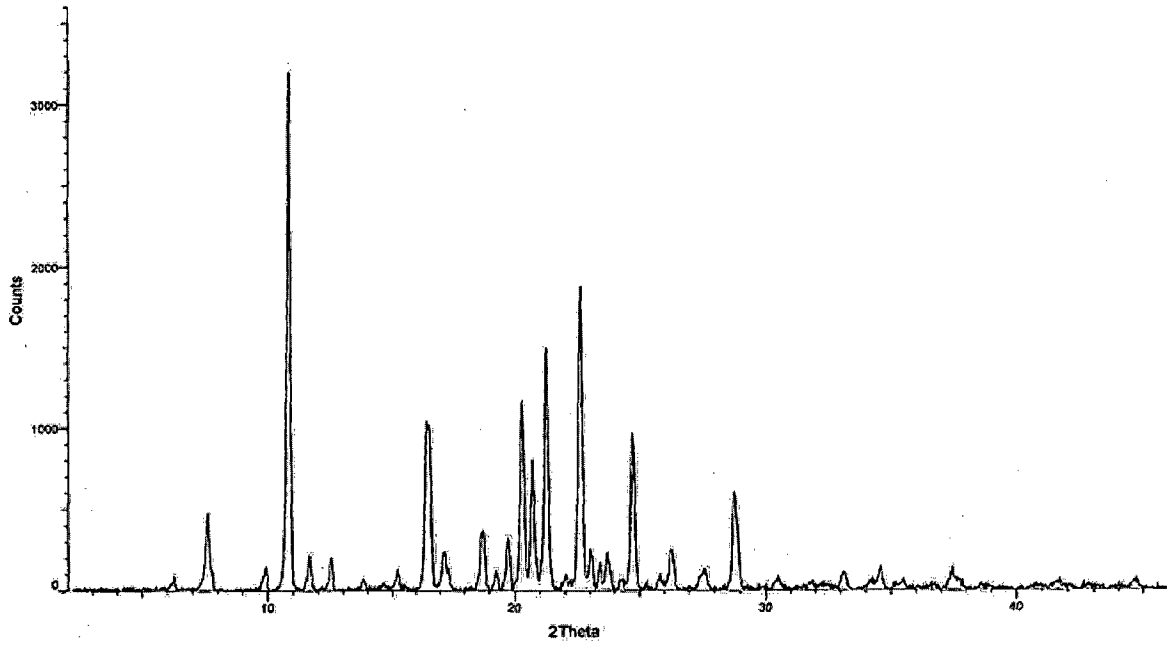


Figure-5

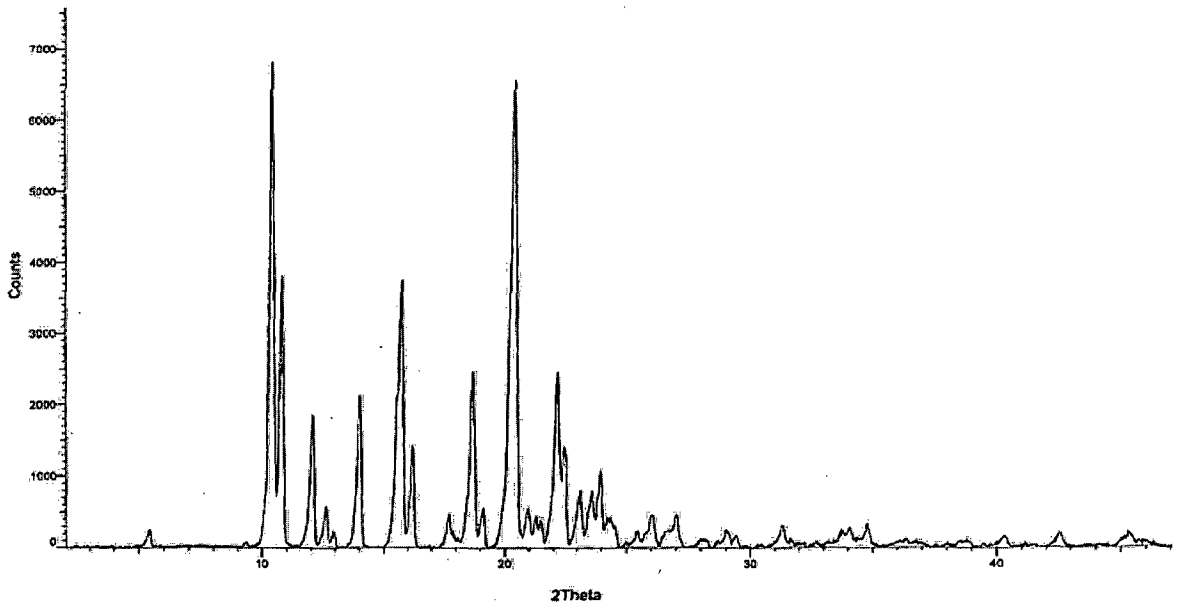


Figure-6

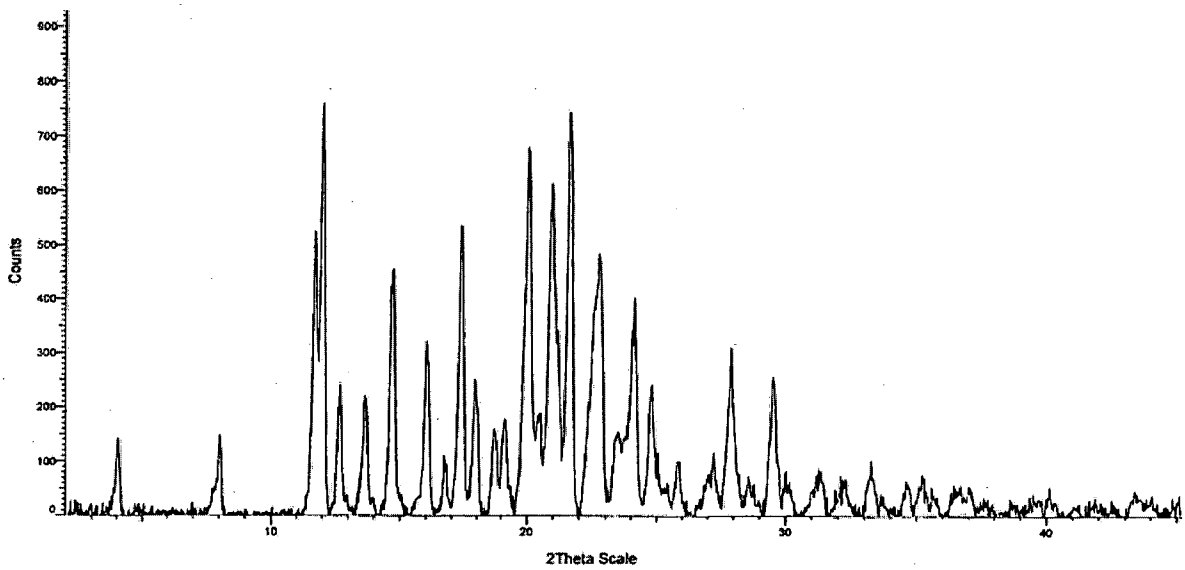


Figure-7

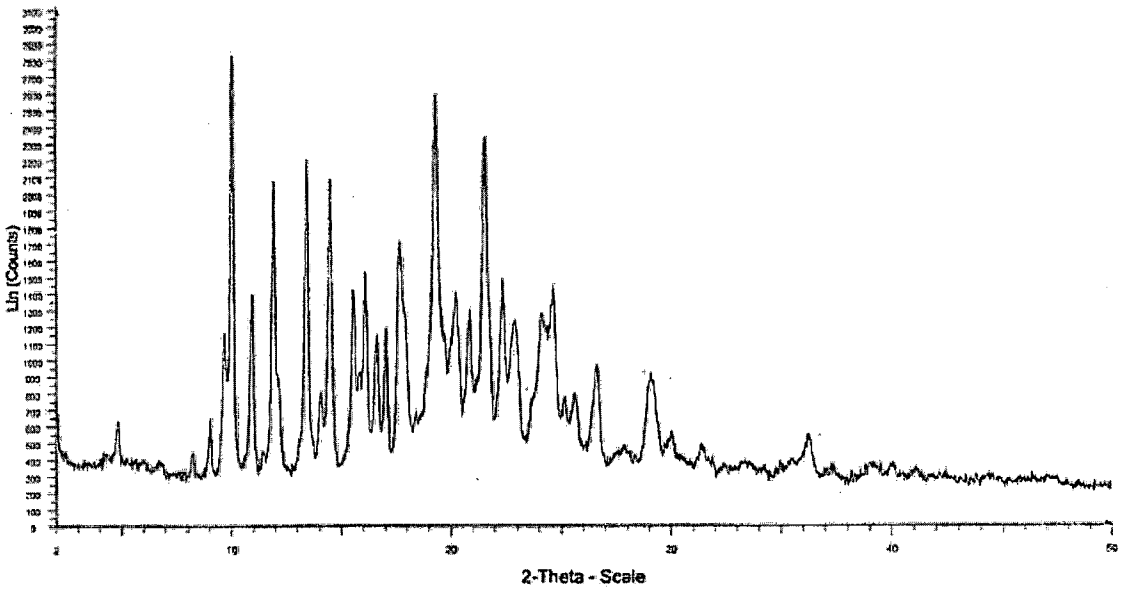


Figure-8

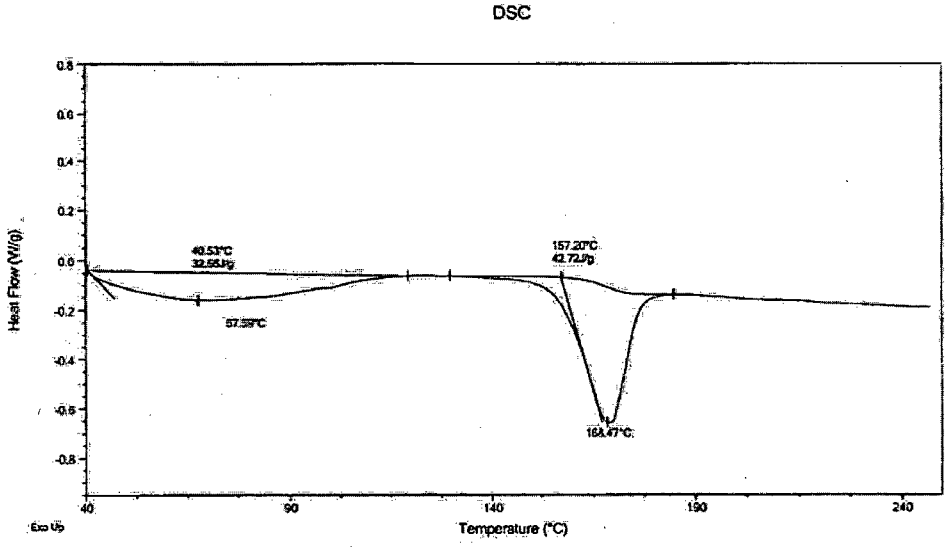


Figure-9

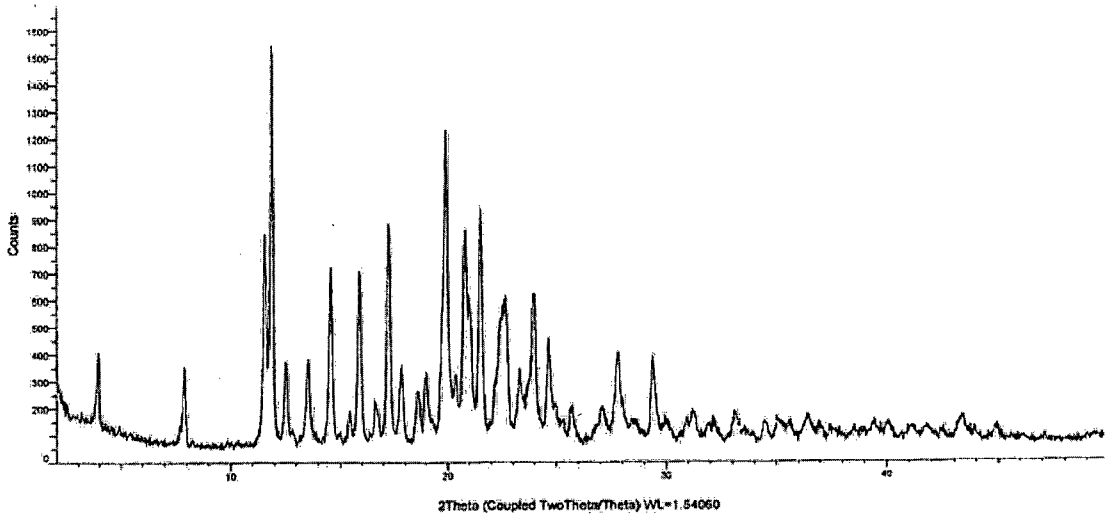


Figure-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2016/000283

A. CLASSIFICATION OF SUBJECT MATTER
C07C237/00 Version=2017.01

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)

C07C

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)

Patseer, IPO Internal Database,STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO2015121877 A2 HETERO RESEARCH FOUNDATION[IN] 20 AUGUST 2015 (20-08-2015) CLAIMS: 9,14-17 ; EXAMPLE 2	11-13, 16-19, 26-27, 29-32
Y	WO2015121877 A2 HETERO RESEARCH FOUNDATION[IN] 20 AUGUST 2015 (20-08-2015) CLAIMS: 1-17 ; EXAMPLES: 1-8	1-10, 14-15, 20-25, 28
Y	US5712279 A BRISTOL-MYERS SQUIBB COMPANY [US] 27 JANUARY 1998 (27-01-1998) SCHEME I-VI; EXAMPLES: 1-11	1-32

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

* Special categories of cited documents:
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"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
24-04-2017	24-04-2017

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

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2016/000283

Citation	Pub.Date	Family	Pub.Date
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