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# Process for the preparation of (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline -6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid and polymorphs thereof

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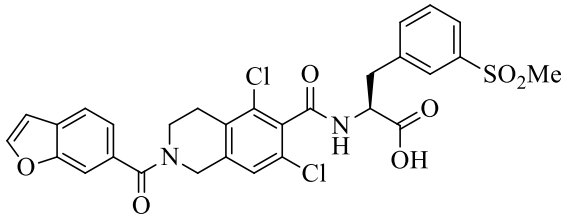
# Process for the preparation of (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid and polymorphs thereof

## Field of the Invention:

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




Formula-1

## Background of the Invention:

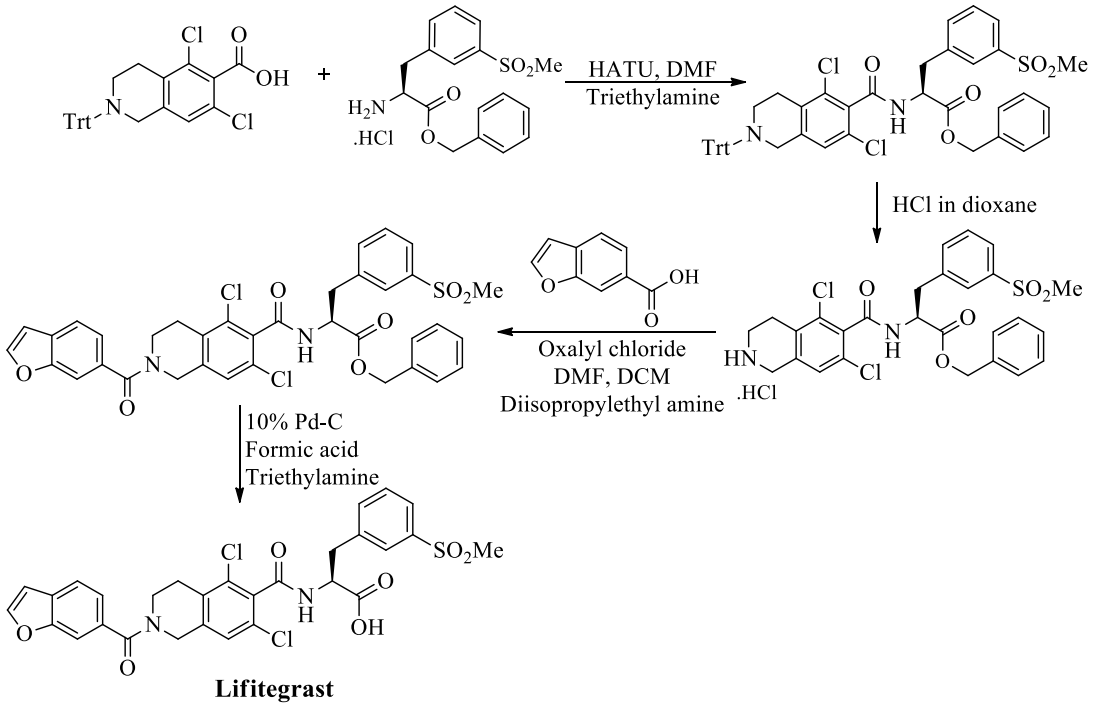
(S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxami-do)-3-(3-(methylsulfonyl)phenyl)propanoic acid, commonly known as Lifitegrast was initially designed and developed by SARcode Bioscience which was acquired by Shire in 2013. Lifitegrast was approved by USFDA on July 11, 2016 and is marketed under the brand name XIIDRA$^{TM}$. 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 US8084047 B2 describes (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl) propanoic acid and its analogous compounds.

US7314938B2 and US8084047 B2 didn’t disclose any specific method for the synthesis of Lifitegrast.

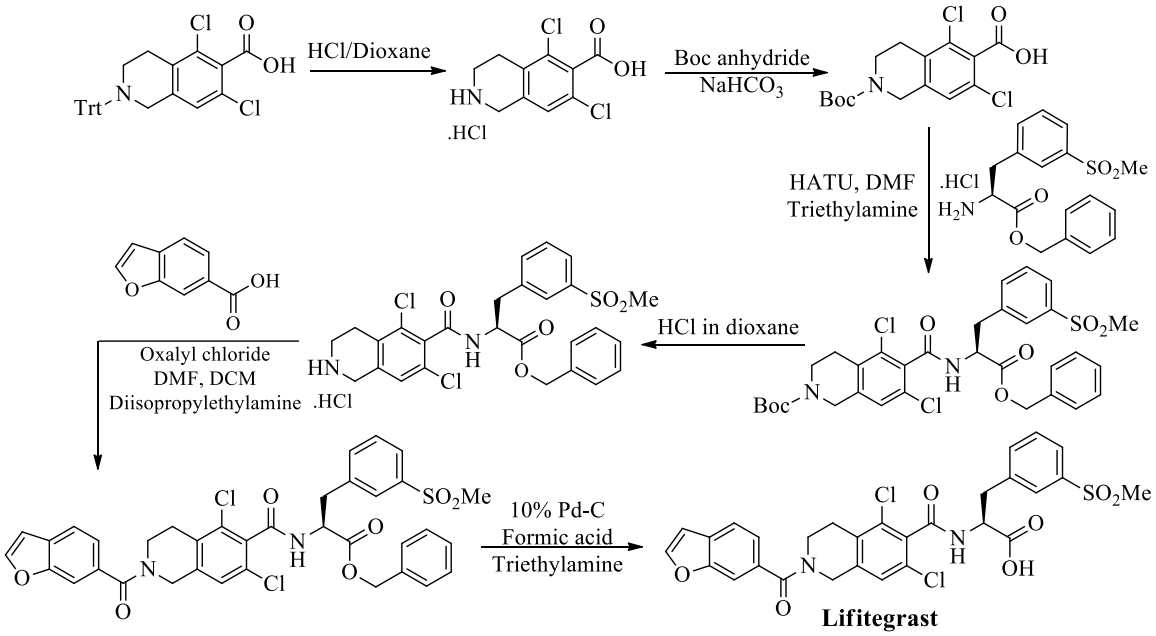
US8080562B2 (herein after referred as US’562 patent) discloses a process for the synthesis of Lifitegrast and its various intermediate compounds in scheme-3 & scheme-5 which is shown below.

**Scheme-A:**

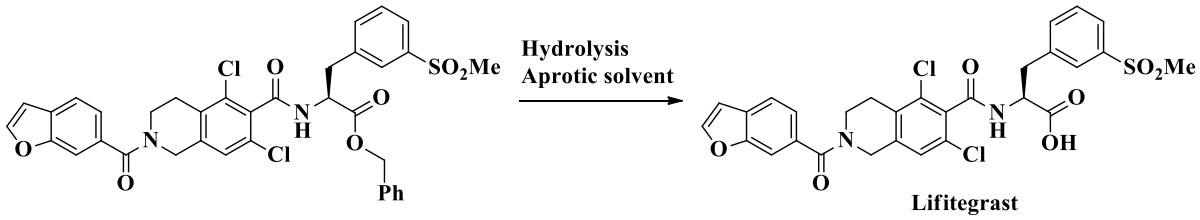



Alternative process for the preparation of Lifitegrast has been described in scheme-6 of the above US'562 patent which is schematically shown below.

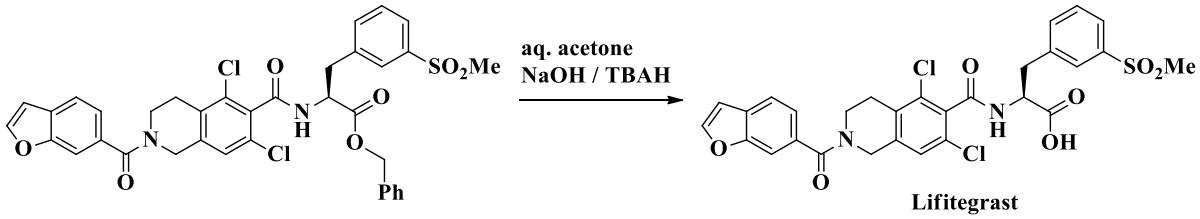
**Scheme-B:**



US8378105B2 (herein after referred as US'105 patent) discloses a process for the synthesis of Lifitegrast, which is shown below.




US9085553B2 (herein after referred as US'553 patent) discloses a process for the synthesis of Lifitegrast, which is shown below.




The prior art processes herein described above have some drawbacks such as more number of process steps, formation of unwanted by products which decreases the quality of the product. Hence, additional purifications may be required to remove the unwanted compounds from the product which leads to decrease in the yield of the product. Hence, there is a need for the development of improved and efficient process for the preparation of Lifitegrast.

**Advantages of the present invention:**

- The process described in the present invention controlled the formation of critical dimer impurities.
- The process described in the present invention controlled the racemization of Lifitegrast.
- The process described in the present invention is simple, safe, economic and suitable for the production of Lifitegrast and its intermediates on commercial scale.
- The process described in the present invention provides Lifitegrast with high yield and high purity.

**Brief description of the invention:**

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

The second aspect of the present invention is to provide a process for the preparation of compound of general formula-6.

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

**Brief Description of the Drawings:**

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

**Figure-2:** Illustrates the PXRD pattern of compound of formula-1 obtained according to example-8

**Detailed description of the Invention:**

The "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 “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, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), dimethylaniline, N-methylmorpholine (NMM), 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 (LDA) and the like; “organosilicon bases” such as lithium hexamethyldisilazide (LiHMDS), sodium hexamethyldisilazide (NaHMDS), potassium hexamethyldisilazide (KHMDS) and the like or mixtures thereof.

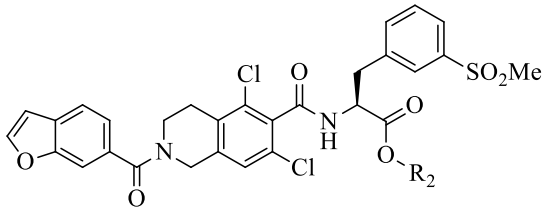
The “coupling agent” used in the present invention can be selected from but not limited to N,N'-dicyclohexylcarbodiimide (DCC), N,N’-diisopropyl carbodiimide (DIC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl), N,N’-carbonyl diimidazole (CDI), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b] pyridinium 3-oxid hexafluorophosphate (HATU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), 1H-benzotriazolium 1-[bis(dimethylamino)methylene]-5chloro-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-1-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), 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.

The "acid" used in the present invention can be selected from but not limited to "inorganic acids" such as hydrofluoric acid, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, boric acid, perchloric acid, carbonic acid and hypochlorous 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, lactic acid, succinic acid, citric acid, tartaric acid, benzoic acid, salicylic acid, oleic acid, stearic acid and the like; 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 term “straight chain or branched chain $C_1$-$C_6$ alkyl group” as used herein refers to an aliphatic hydrocarbon group which may be straight or branched having C1-C6 carbon atoms in the chain. The alkyl groups include but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl.

An embodiment of the present invention provides a process for the preparation of (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid of formula-1, comprising hydrolysis of compound of general formula-7 in presence of formic acid optionally in presence of a solvent.



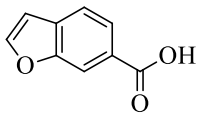
Formula-7

wherein, '$R_2$' is a straight chain or branched chain $C_1$-$C_6$ alkyl group.

Wherein, the 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.

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

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



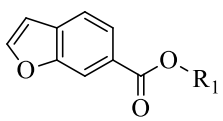
Formula-2

with compound of general formula

$R_1$-OH

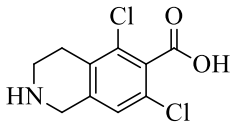
wherein, '$R_1$' represents substituted or unsubstituted aryl and the substituents wherever used can be independently selected from halogens such as F, Cl, Br & I, $NO_2$ and the substitution can be at one or more positions on aryl group;

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



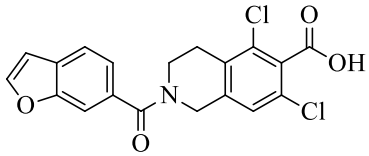
Formula-3

b) reacting compound of general formula-3 with 5,7-dichloro-1,2,3,4-tetrahydro isoquinoline-6-carboxylic acid compound of formula-4 or its hydrochloride salt,



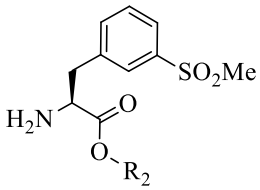
Formula-4

optionally in presence of a base and/or a solvent to provide 2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid compound of formula-5,



Formula-5

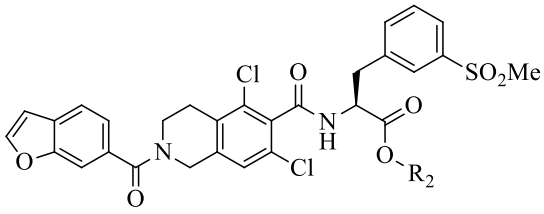
c) reacting compound of formula-5 with compound of general formula-6



Formula-6

wherein, '$R_2$' is a straight chain or branched chain $C_1$-$C_6$ alkyl group;

optionally in presence of a suitable coupling agent and/or a base in a solvent to provide compound of general formula-7,



Formula-7

d) hydrolysis of compound of general formula-7 in presence of an acid or a base optionally in presence of a solvent to provide compound of formula-1.

The coupling agent in step-a) & step-c) can be selected from the coupling agents as described above;

The base in step-a) to step-c) can be selected from organic bases, inorganic bases, organolithium bases, organosilicon bases or mixtures thereof;

The acid in step-d) can be selected form organic acids, inorganic acids or mixtures thereof.

In one embodiment, the organic acids and inorganic acids can be selected from those described above.

In another embodiment, the organic acid is selected from formic acid, acetic acid, trifluoroacetic acid and the like; and the inorganic acid is selected from hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, boric acid, perchloric acid, carbonic acid and the like.

The base in step-d) can be selected from inorganic bases or mixtures thereof. In one embodiment, the inorganic base is selected from but not limited to alkali metal carbonates, alkali metal bicarbonates, alkali metal hydroxides and the like or mixtures thereof.

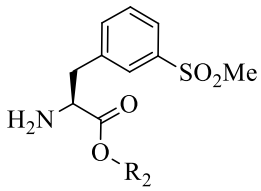
In another embodiment, the base can be selected from organic bases such as alkali metal alkoxides.

The solvent in step-a) to step-d) wherever necessary can be 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 mixtures thereof.

In one embodiment, the solvent in step-d) can be selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, formic acid, acetic acid, water and the like or mixtures thereof.

In one embodiment of the present invention, the above sequential process for the preparation of compound of formula-1 can be carried out as a single-pot process. i.e., the above process can be carried out in a sequential manner without isolating any of the process intermediate from the reaction mixture.

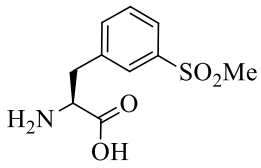
The second aspect of the present invention provides a process for the preparation of compound of general formula-6,



Formula-6

wherein, '$R_2$' is same as defined above;

comprising, reacting (S)-2-amino-3-(3-(methylsulfonyl)phenyl)propanoic acid compound of formula-8 or its hydrochloride salt,



Formula-8

with $R_2$-OH or $R_2$-OAc in presence of an acid or an acid source optionally in presence of a solvent to provide compound of general formula-6.

The solvent in the process of second aspect can be selected from but not limited to hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, polar solvents or mixtures thereof as described above.

The acid in the process of second aspect can be selected from organic acids, inorganic acids or mixtures thereof as described above.

In one embodiment, acid is selected from perchloric acid, sulfuric acid and the like.

In one embodiment, the acid source can be selected from phosphoryl chloride, sulfuryl chloride, thionyl chloride, oxalyl chloride and the like.

The third aspect of the present invention provides a process for the purification of compound of formula-1, comprising:

a) dissolving compound of formula-1 in a solvent at a suitable temperature,
b) optionally filtering the reaction mixture,
c) combining the solution with an anti-solvent at a suitable temperature.

The solvent in step-a) is selected from acetic acid, formic acid, polar-aprotic solvents, ketone solvents, ether solvents, ester solvents or mixtures thereof; and the suitable temperature ranges from 25°C to 100°C;

In one embodiment the solvent is selected from acetic acid, formic acid, dimethylsulfoxide, dimethylformamide, methyl ethyl ketone, tetrahydrofuran or mixtures thereof.

The anti-solvent in step-c) can be selected from hydrocarbon solvents, ether solvents, ester solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents such as water or mixtures thereof; and the suitable temperature ranges from 25°C to 100°C.

An embodiment of the present invention provides a process for the purification of compound of formula-1, comprising:

a) dissolving compound of formula-1 in acetic acid,
b) combining the solution with water to provide pure compound of formula-1.

The compound of formula-1 obtained by the above purification process is crystalline in nature and is characterized by its PXRD pattern as illustrated in figure-1. The said crystalline form is herein designated as crystalline form-L.

In one embodiment of the present invention, a small amount of crystalline form-L can be added as seeding material to facilitate the crystallization process and provide the compound of formula-1 as a free flow solid.

Another embodiment of the present invention provides a process for the purification of compound of formula-1, comprising recrystallizing it from a solvent selected from hydrocarbon solvents, ether solvents, ester solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents, polar solvents such as water, polar-aprotic solvents or mixtures thereof.

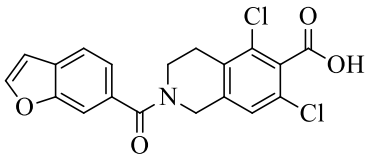
In one embodiment of the present invention, the solvent is selected from aqueous solutions of esters, ketones, nitriles and acids.

In an embodiment, the solvent is selected from aqueous mixture of esters such as ethyl acetate and water, tert-butyl acetate and water, isopropyl acetate and water; aqueous mixture of ketones such as acetone and water, methyl ethyl ketone and water; aqueous mixture of nitriles such as acetonitrile and water and aqueous mixture of acids such as formic acid and water, acetic acid and water and the like.

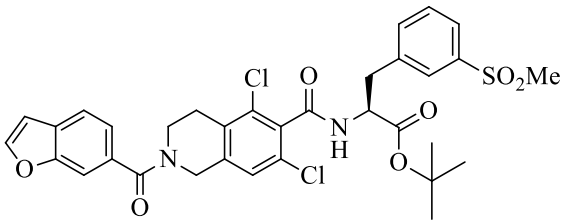
The benzofuran-6-carboxylic acid compound of formula-2, 5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid compound of formula-4 or its HCl salt and (S)-2-amino-3-(3-(methylsulfonyl)phenyl)propanoic acid compound of formula-8 or its HCl salt utilized in above processes can be synthesized by any of the processes known in the art.

Compound of formula-1 produced by the process of the present invention is substantially pure. The term “substantially pure” in relation to compound of formula-1 refers to the compound having purity of greater than about 99%, or about 99.5%, or about 99.6%, or about 99.7%, or about 99.8%, or about 99.9% by HPLC.

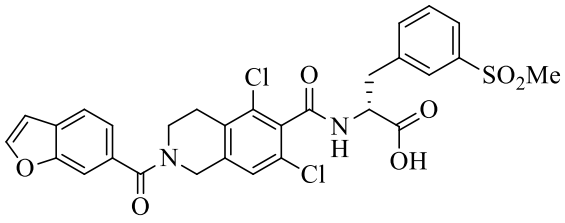
The formation of following compounds as impurities has been observed during the synthesis of compound of formula-1 by the process of the present invention.




**Benzofuran isoquinoline acid impurity**




**Tertiary butyl ester impurity**




**(R)-Isomer 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.

**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: Primesil C18, 3 µm, 4.6 X 250 mm or equivalent; Wavelength: 215 nm; Column temperature: 25°C; Injection volume: 5 µL; Diluent: Acetonitrile:Methanol (1:1 v/v); Elution: Gradient; Buffer: Accurately transfer 1000 mL of milli-Q-water into a suitable clean and dry beaker. Transfer 2.0 mL of perchloric acid (70%) into 1000 mL of milli-Q-water and mix well. Filter this solution through 0.22 µm Durapore PVDF filter paper and sonicate to degas it; Mobile phase-A: Buffer (100%); Mobile phase-B: Accurately transfer 700 mL of acetonitrile and 300 mL of buffer into a 1000 mL mobile phase bottle, mix well and sonicate to degas it.

Enantiomeric purity of compound of formula-1 of the present invention was analyzed by HPLC under the following conditions;

Apparatus: A liquid chromatograph equipped with variable wavelength UV-detector; Column: CHIRALPAK IE-3, 3 µm, 4.6 X 250 mm or equivalent; Wavelength: 260 nm; Column temperature: 25°C; Injection volume: 15 µL; Diluent: Acetonitrile:Methanol (1:1 v/v); Elution: Isocratic; Buffer: Accurately transfer 950 mL of methanol, 50 mL of water and 1.0 mL of trifluoroacetic acid into a mobile phase bottle and mix well. Filter this solution through 0.22 µm Durapore PVDF filter paper; Mobile phase: Buffer (100%).

**PXRD Method of Analysis:**

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

An embodiment of the present invention provides a pharmaceutical composition comprising substantially pure compound of formula-1 obtained by the process of the present invention and at least one pharmaceutically acceptable excipient.

Wherein, the excipient can be selected from diluents, disintegrants, glidants, surfactants, binders and lubricants which are generally used by the person of ordinary skilled in the art in the field of pharmaceutical formulations.

The other embodiment of the present invention provides a method of treating a patient comprising administering to the patient a therapeutically effective amount of compound of formula-1 obtained by the process of the present invention.

The compound of formula-1 produced by the process of the present invention is having particle size distribution of $D_{90}$ less than about 400 µm, preferably less than about 300 µm, more preferably less than about 200 µm.

In one embodiment of the present invention, the compound of formula-1 is having particle size distribution of $D_{90}$ less than about 100 µm, preferably less than about 50 µm.

In another embodiment of the present invention, the compound of formula-1 is having particle size distribution of $D_{90}$ less than about 20 µm, preferably less than about 10 µm.

The other embodiment of the present invention provides compound of formula-1 having particle size distribution of $D_{90}$ less than about 5 µm, preferably less than about 3 µm.

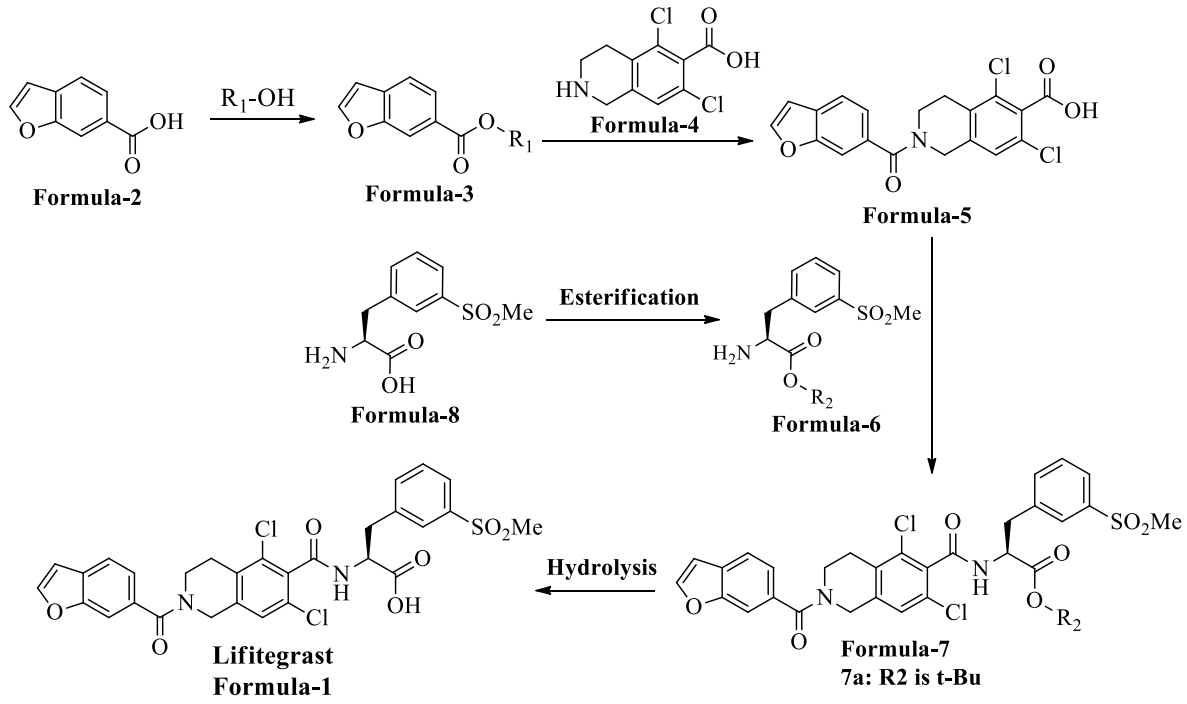
**Particle size distribution (PSD) method of analysis:**

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

The compound of formula-1 obtained 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/micronization may be performed before drying or after drying of the product.

The present invention is schematically represented as follows.

**Synthetic scheme:**




'$R_1$' represents substituted or unsubstituted aryl and the substituents wherever used can be independently selected from halogens such as F, Cl, Br & I, $NO_2$ and the substitution can be at one or more positions on aryl group; and

'$R_2$' is straight/branched chain $C_1$-$C_6$ alkyl group.

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

**Examples:**

**Example-1: Preparation of 2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (Formula-5)**

A mixture of benzofuran-6-carboxylic acid compound of formula-2 (25 gm), toluene (200 ml) and dimethylformamide (5 ml) was stirred for 15 min at 25-30°C. Cooled the reaction mixture to 15-20°C and oxalyl chloride (25.44 gm) was slowly added to it at the same temperature under nitrogen atmosphere. Raised the temperature of the reaction mixture to 25-30°C and stirred for 6 hr at the same temperature. A solution of pentafluorophenol (28.37 gm) in toluene (25 ml) was added to the reaction mixture at 25-30°C. Cooled the reaction mixture to 0-5°C and diisopropylethylamine (79.71 gm) was slowly added to it. Raised the temperature of the reaction mixture to 25-30°C and stirred for 90 min at the same temperature. Water was added to the reaction mixture at 25-30°C and stirred the reaction mixture for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with aqueous sodium bicarbonate solution followed by with water. Distilled off the solvent from the organic layer under reduced pressure and co-distilled with acetonitrile.

Acetonitrile (250 ml), 5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid hydrochloride compound of formula-4a (39.2 gm) and 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, quenched with 50% aqueous HCl solution and stirred for 3 hr at the same temperature. Filtered the solid and washed with water. Water (125 ml) and ethyl acetate (100 ml) were added to the obtained compound at 25-30°C. Aqueous sodium carbonate solution (12.5 gm of sodium carbonate in 125 ml of water) was slowly added to the reaction mixture at 25-30°C and stirred the reaction mixture for 15 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

aqueous HCl solution at 25-30°C and stirred the reaction mixture for 3 hr at the same temperature. Filtered the solid and washed with water. Acetone (75 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 acetone and dried to get the title compound.

Yield: 45.6 gm; M.R.: 258-260°C.

**Example-2: Preparation of 3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylate**

Triethylamine (71.89 ml) was slowly added to a solution of 2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid compound of formula-5 (50 gm) in dimethylformamide (100 ml) at 25-30° C under nitrogen atmosphere. Heated the reaction mixture to 45-50°C, HATU solution (58.46 gm of HATU in 100 ml of DMF) was slowly added to it and stirred for 2 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 and washed with dichloromethane to get the title compound.

Yield: 55.0 gm.

**Example-3: Preparation of (S)-tert-butyl 2-amino-3-(3-(methylsulfonyl)phenyl) propanoate (Formula-6a)**

Perchloric acid (16 ml) was slowly added to a pre-cooled mixture of (S)-2-amino-3-(3-(methylsulfonyl)phenyl)propanoic acid hydrochloride compound of formula-8a (35 gm) and tert-butyl acetate (525 ml) at 0-5°C under nitrogen atmosphere. Raised the temperature of the reaction mixture to 25-30°C and stirred for 14 hr at the same temperature. Water 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 extracted the organic layer with water. Combined both the aqueous layers and dichloromethane was added to it. Cooled the reaction mixture to 5-10°C, slowly basified it by using aqueous ammonia solution and stirred for 10 min at 25-30°C. Both the organic and aqueous layers were separated and distilled off the solvent completely from the organic layer to get the title compound.

Yield: 35.0 gm.

**Example-4: Preparation of ((S)-tert-butyl 2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoate (Formula-7a)**

3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylate (55 gm) was added to a mixture of (S)-tert-butyl 2-amino-3-(3-(methylsulfonyl)phenyl)propanoate compound of formula-6a (35 gm), dichloromethane (550 ml) and triethylamine (60.7 ml) at 25-30°C and stirred the reaction mixture for 9 hr at the same temperature. Water and dichloromethane were added to the reaction mixture and stirred for 10 min. Both the organic and aqueous layers were separated and washed the organic layer with 5% aqueous sodium carbonate solution followed by with 0.5N HCl solution and finally with water. Distilled off the solvent from organic layer to get title compound. Yield: 58.0 gm.

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

A mixture of ((S)-tert-butyl 2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoate compound of formula-7a (58 gm) and formic acid (290 ml) was heated to 40-45°C and stirred the reaction mixture for 4 hr at the same temperature. Water and ethyl acetate 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 extracted the aqueous layer with ethyl acetate. Combined the organic layers, methanol (696 ml) was added to it at 25-30°C and stirred the reaction mixture for 3 hr at the same temperature. Filtered the solid, washed with methanol and dried the material to get the title compound.

Yield: 50.0 gm.

**Example-6: Preparation of compound of formula-1**

Perchloric acid (70 ml) was slowly added to a pre-cooled mixture of (S)-2-amino-3-(3-(methylsulfonyl)phenyl)propanoic acid hydrochloride compound of formula-8a (150.5 gm) and tert-butyl acetate (1950 ml) at 0-5°C. Raised the temperature of the reaction mixture to 20-25°C and stirred for 7 hr at the same temperature. Water was added to the reaction mixture and stirred for 5 min. Both the organic and aqueous layers were separated and

dichloromethane was added to the aqueous layer. Cooled the reaction mixture to 0-5°C and slowly basified the reaction mixture by using aqueous ammonia solution. Raised the temperature of the reaction mixture to 25-30°C and stirred for 40 min at the same temperature. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Combined the organic layers and kept aside.

Triethylamine (213 ml) was slowly added to a mixture of 2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid compound of formula-5 (150 gm) and dimethylformamide (600 ml) at 25-30°C under nitrogen atmosphere. Heated the reaction mixture to 45-50°C, a solution of HATU (175 gm) in dimethylformamide (600 ml) was slowly added to it and stirred for 2 hr at the same temperature. Reduced the temperature of the reaction mixture to 25-30°C and the organic layer obtained above was added to it and stirred the reaction mixture for 6 hr at the same temperature. Water 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 extracted the aqueous layer with dichloromethane. Combined the organic layers and washed with aqueous sodium carbonate solution followed by with 0.5N HCl solution and then finally with aqueous sodium chloride solution. Distilled off the solvent from the organic layer and formic acid (750 ml) was added to the obtained compound at 25-30°C. Heated the reaction mixture to 60-65°C and stirred for 5 hr at the same temperature. The obtained reaction mixture was slowly added to chilled water (3000 ml) at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 30 min at the same temperature. Filtered the solid and washed with water. The obtained compound was added to water (1500 ml) at 25-30°C and stirred the reaction mixture for 60 min at the same temperature. Filtered the compound and washed with water.

The obtained compound was slowly added to pre-cooled aqueous sodium carbonate solution at 10-15°C. Ethyl acetate was added to the reaction mixture at 10-15°C and stirred for 10 min. Both the organic and aqueous layers were separated and washed the aqueous layer with ethyl acetate. Dichloromethane (1500 ml) was added to the aqueous layer at 25-30°C and slowly acidified the reaction mixture by using aqueous HCl solution at the same temperature. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Combined the organic layers and distilled off the solvent completely.

Acetic acid (900 ml) was added to the obtained compound at 25-30°C and stirred the reaction mixture for 10 min at the same temperature. Filtered the reaction mixture through hyflow bed and washed the hyflow bed with acetic acid. Water (1050 ml) was added to the filtrate. Heated the reaction mixture to 50-55°C and stirred for 50 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 4 hr at the same temperature. Filtered the solid, washed with water and dried the material to get the title compound.

Yield: 150 gm.

**Example-7: Purification of compound of formula-1**

A mixture of compound of formula-1 (10 gm) and acetic acid (100 ml) was heated to 50-55°C and stirred for 30 min at the same temperature. Cooled the reaction mixture to 25-30°C, filtered to make it particle free and washed with acetic acid. Water (100 ml) was slowly added to the filtrate at 25-30°C and stirred the reaction mixture for 6 hr at the same temperature. Filtered the solid, washed with water and dried to get the title compound.

The PXRD pattern of the obtained compound is similar to figure-1.

Yield: 7.0 gm.

**Example-8: Purification of compound of formula-1**

A mixture of compound of formula-1 (10 gm) and acetic acid (100 ml) was heated to 50-55°C and stirred for 30 min at the same temperature. Cooled the reaction mixture to 25-30°C, filtered to make it particle free and washed with acetic acid. Methanol (100 ml) was slowly added to the filtrate at 25-30°C and stirred the reaction mixture for 6 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 as illustrated in figure-2.

Yield: 7.0 gm.

**Example-9: Purification of compound of formula-1**

A mixture of compound of formula-1 (100 gm), ethyl acetate (800 ml) and water (400 ml) was heated to 50-55°C and stirred for 60 min at the same temperature. Filtered the reaction mixture through hyflow bed and washed with ethyl acetate. Both the organic and aqueous layers were separated and the aqueous layer was extracted with ethyl acetate.

Combined the organic layers, methanol (500 ml) was added to it at 25-30°C and stirred the reaction mixture for 3 hr at the same temperature. Filtered the solid, washed with methanol and dried the material to get the title compound.

The PXRD pattern of the obtained compound is similar to figure-2.

Yield: 75.0 gm.

**Example-10: Preparation of compound of formula-1**

Perchloric acid (79.75 ml) was slowly added to a pre-cooled mixture of (S)-2-amino-3-(3-(methylsulfonyl)phenyl)propanoic acid hydrochloride compound of formula-8a (172.05 gm) and tert-butyl acetate (2250 ml) at 0-5°C. Raised the temperature of the reaction mixture to 20-25°C and stirred for 7 hr at the same temperature. Water was added to the reaction mixture and stirred for 5 min. Both the organic and aqueous layers were separated and dichloromethane was added to the aqueous layer. Cooled the reaction mixture to 0-5°C and slowly basified the reaction mixture by using aqueous ammonia solution. Raised the temperature of the reaction mixture to 25-30°C and stirred for 40 min at the same temperature. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Combined the organic layers, washed with water and kept the organic layer aside.

Triethylamine (213 ml) was slowly added to a mixture of 2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid compound of formula-5 (150 gm) and dimethylformamide (600 ml) at 25-30°C under nitrogen atmosphere. Heated the reaction mixture to 45-50°C, a solution of HATU (175 gm) in dimethylformamide (600 ml) was slowly added to it and stirred for 2 hr at the same temperature. Reduced the temperature of the reaction mixture to 25-30°C and the organic layer obtained above was added to it and stirred the reaction mixture for 6 hr at the same temperature. Water 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 extracted the aqueous layer with dichloromethane. Combined the organic layers and washed with aqueous sodium carbonate solution followed by with aqueous HCl solution and then finally with aqueous sodium chloride solution. Distilled off the solvent from the organic layer and formic acid (825 ml) was added to the obtained compound at 25-30°C. Heated the reaction mixture to 60-65°C and stirred for 7 hr

at the same temperature. The obtained reaction mixture was slowly added to chilled water (5250 ml) at 0-5°C and stirred for 2 hr at the same temperature. Filtered the solid and washed with water. The obtained compound was added to water (1500 ml) at 25-30°C and stirred the mixture for 60 min at the same temperature. Filtered the compound and washed with water. The obtained compound was slowly added to pre-cooled aqueous sodium carbonate solution at 10-15°C. Ethyl acetate was added to the reaction mixture at 10-15°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. Dichloromethane (1500 ml) was added to the aqueous layer at 25-30°C and slowly acidified the reaction mixture by using aqueous HCl solution at the same temperature. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Combined the organic layers and distilled off the solvent completely. Acetic acid (975 ml) was added to the obtained compound at 25-30°C. Heated the reaction mixture to 50-55°C and stirred for 50 min at the same temperature. Filtered the reaction mixture and washed with acetic acid. Water (1050 ml) was added to the filtrate at 25-30°C and stirred the reaction mixture for 3 hr at the same temperature. Crystalline form-L of compound of formula-1 (0.15 gm) was added as a seeding material to the reaction mixture at 25-30°C and stirred the reaction mixture for 14 hr at the same temperature. Filtered the solid, washed with water and dried the material to get the title compound. Yield: 150.0 gm; Purity by HPLC: 93.3% by HPLC.

**Example-11: Purification of compound of formula-1**

A mixture of compound of formula-1 (80 gm) and acetic acid (520 ml) was heated to 50-55°C and stirred for 50 min at the same temperature. Cooled the reaction mixture to 25-30°C, filtered to make it particle free and washed with acetic acid. Water (560 ml) was added to the filtrate at 25-30°C and stirred the reaction mixture for 3 hr at the same temperature. Crystalline form-L of compound of formula-1 (0.4 gm) was added to the reaction mixture at 25-30°C and stirred the reaction mixture for 14 hr at the same temperature. Filtered the solid, washed with water and dried the material to get the title compound.

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

Yield: 70.0 gm; Purity by HPLC: 99.7%.

# Drawings

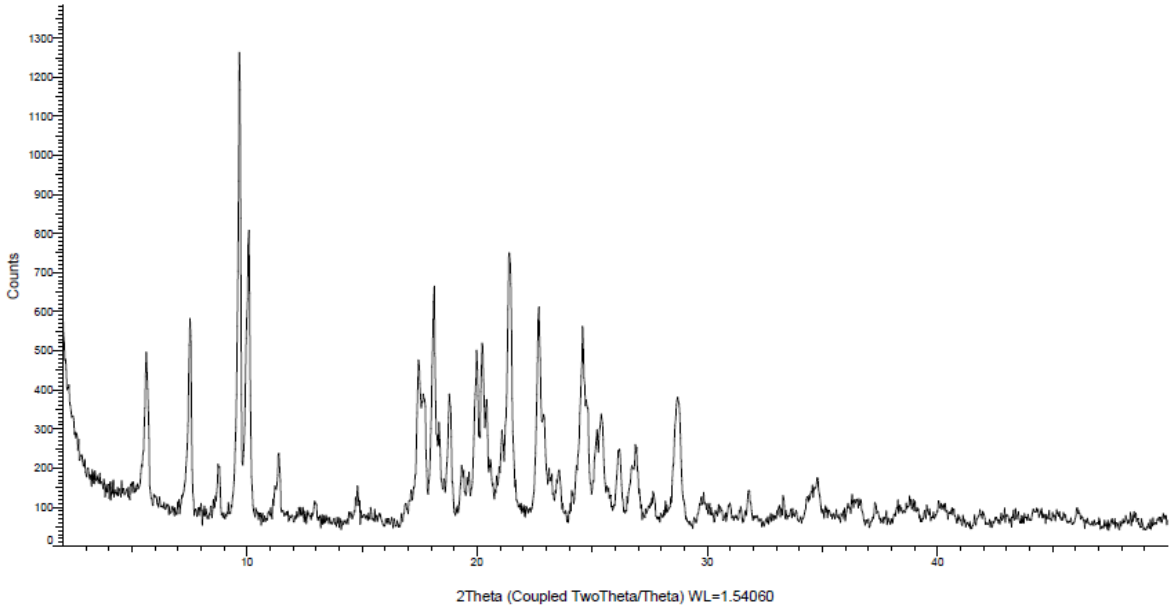



**Figure-1**

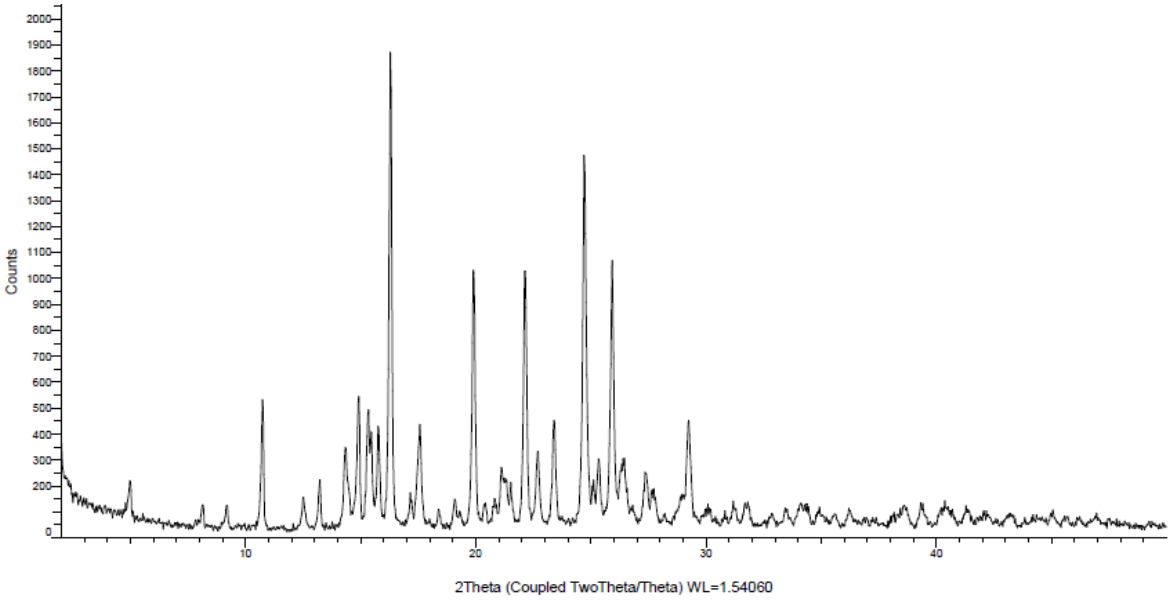



**Figure-2**