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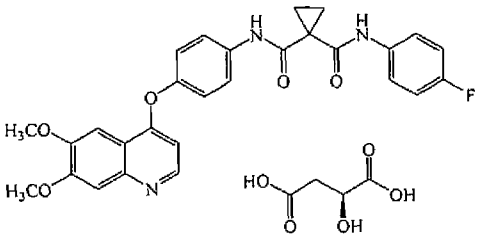
(54) Title: PROCESS FOR THE PREPARATION OF N-(4-(6,7-DIMETHOXYQUINOLIN-4-YLOXY) PHENYL)-N'-(4-FLUOROPHENYL)CYCLOPROPANE-1, 1-DICARBOXAMIDE, (2S)-HYDROXYBUTANEDIOATE AND ITS POLYMORPHS THEREOF

(57) Abstract: The present invention also relates to process for the preparation of N-(4-(6,7-dimethoxy quinolin-4-yloxy)phenyl)-N' -(4-fluorophenyl)cyclopropane-1, 1-dicarboxamide (S)-malate compound of formula-1a and its polymorphs thereof, represented by the following structural.



Formula-1

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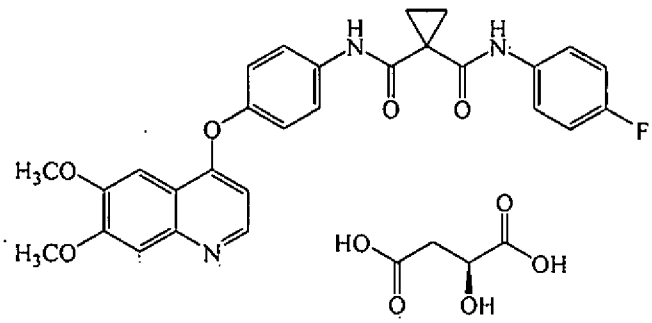
Process for the preparation of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluoro phenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate and its polymorphs thereof

Related Applications:

This application claims the benefit of priority of our Indian patent application numbers 201641041767 filed on 7th December 2016 and 201741020998 filed on 15th June 2017 which are incorporated herein by reference.

Field of the Invention:

The present invention relates to novel crystalline forms of N-(4-(6,7-dimethoxy quinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.



Formula-1a

The present invention also relates to novel crystalline forms of N-(4-(6,7-dimethoxy quinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b.

Background of the Invention:

Cabozantinib (S)-malate is a kinase inhibitor indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer and advanced renal cell carcinoma in people who have received prior anti-angiogenic therapy.

Cabozantinib has been approved by the US FDA as COMETRIQ for the treatment of patients with progressive, metastatic medullary thyroid cancer.

COMETRIQ has also been approved by the European Commission for the Treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma.

Cabozantinib chemically known as N-{4-[(6,7-dimethoxyquinolin-4-yloxy]phenyl}-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide.

International (PCT) publication No. WO 2005030140 A1 first disclosed Cabozantinib and process for its preparation.

International (PCT) publication No. WO 2010083414 A1 discloses amorphous forms of Cabozantinib L- and D-malate as well as the N-1 and N-2 polymorphs of crystalline Cabozantinib L- and D-malate and process for its preparation.

International (PCT) publication No. WO 2016150966 A1 discloses crystalline Cabozantinib hydrochloride as well as crystalline Cabozantinib phosphate and process for its preparation.

CN104961680 A discloses crystal A and crystal B of hydrochloride salt of Cabozantinib and process for its preparation.

CN104961681 A discloses various acid addition salts of Cabozantinib and process for its preparation.

Brief description of the Invention:

The first aspect of the present invention is to provide novel crystalline form of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, herein after designated as form-M and process for its preparation.

The second aspect of the present invention is to provide an improved process for the preparation of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide (S)-malate compound of formula-1a.

The third aspect of the present invention is to provide novel crystalline form of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, herein after designated as form-S and process for its preparation.

The fourth aspect of the present invention is to provide novel crystalline form of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, herein after designated as form-N and process for its preparation.

The fifth aspect of the present invention is to provide novel crystalline form of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, herein after designated as form-R and process for its preparation.

The sixth aspect of the present invention is to provide novel crystalline form of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, herein after designated as form-M and process for its preparation.

The seventh aspect of the present invention is to provide novel crystalline form of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, herein after designated as form-S and process for its preparation.

The eighth aspect of the present invention is to provide a process for the preparation of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

Brief description of the Drawings:

Figure 1: Illustrates the PXRD pattern of crystalline form-M of N-(4-(6,7-dimethoxy quinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b.

Figure 2: Illustrates the PXRD pattern of crystalline form-S of N-(4-(6,7-dimethoxy quinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b.

Figure 3: Illustrates the PXRD pattern of crystalline form-N of N-(4-(6,7-dimethoxy quinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b.

Figure 4: Illustrates the PXRD pattern of crystalline form-R of N-(4-(6,7-dimethoxy quinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b.

Figure 5: Illustrates the PXRD pattern of crystalline form-M of N-(4-(6,7-dimethoxy quinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

Figure 6: Illustrates the PXRD pattern of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

Detailed description of the Invention:

As used herein the term "suitable solvent" used in the present invention refers to "hydrocarbon solvents" such as n-hexane, n-heptane, cyclohexane, pet ether, toluene, pentane, cycloheptane, methylcyclohexane, m-, o-, or p-xylene, and the like; "ether solvents" such as dimethoxy methane, tetrahydrofuran, 1,3-dioxane, 1,4-dioxane, furan, diethyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethylene glycol diethyl ether, triethylene glycol dimethyl ether, anisole, t-butyl methyl ether, 1,2-dimethoxy ethane and the like; "ester solvents" such as methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate and the like; "polar-aprotic solvents such as dimethylacetamide (DMA), dimethylformamide (DMF), dimethyl sulfoxide (DMSO), 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 isobutylketone and the like; "nitrile solvents" such as acetonitrile, propionitrile, isobutyronitrile and the like; "alcoholic solvents" such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, ethylene glycol, propylene glycol, 2-methoxyethanol, l, 2-ethoxyethanol, diethylene glycol, 1, 2, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monoethyl ether, cyclohexanol, anisole, benzyl alcohol, phenol, or glycerol and the like; "polar solvents" such as water or mixtures thereof.

The term "suitable base" used herein the present invention until unless specified is selected from inorganic bases like "alkali metal hydroxides" such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; "alkali metal carbonates" such as sodium carbonate, potassium carbonate, lithium carbonate and the like; "alkali metal bicarbonates" such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate and the

like; "alkali metal hydrides" such as potassium hydride, lithium hydride and the like; ammonia; and organic bases such "alkali metal alkoxides" such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium methoxide, potassium ethoxide, potassium tert-butoxide and the like; triethyl amine, methyl amine, ethyl amine, 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo(4.3.0)non-5-ene (DBN), lithium dioisopropyl amide (LDA), n-butyl lithium, tribenzylamine, isopropyl amine, diisopropyl amine, diiso propylethylamine, N-methylmorpholine, N-ethylmorpholine, piperidine, dimethylamino pyridine, morpholine, pyridine, 2,6-lutidine, 2,4,6-collidine, imidazole, 1-methyl imidazole, 1,2,4-triazole, 1,4-diazabicyclo[2.2.2]octane (DABCO) or mixtures thereof.

The "hydrochloric acid source" used herein the present invention is selected from hydrochloric acid gas, aqueous hydrochloric acid, ethanolic-HCl, methanolic-HCl, ethyl acetate-hydrochloric acid, isopropanol-hydrochloric acid, diisopropyl ether-hydrochloric acid, diethylether- hydrochloric acid, and trimethylchlorosilane.

The first aspect of the present invention provides a crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, characterized by its powder x-ray diffraction pattern having peaks at 6.4, 7.8, 8.6, 9.5, 10.4, 10.8, 12.0, 12.7, 13.4, 14.7, 16.0, 17.2, 17.5, 18.6, 20.2, 20.8, 21.5, 22.1, 22.7, 23.2, 24.1, 26.5, 26.8 and 27.2 ± 0.2 degrees two theta as depicted in figure-1.

Further, In an embodiment of the present invention also provides a process for the preparation of crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, comprising of:

a) Adding a suitable solvent to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt of compound of formula-1b,
b) stirring the reaction mixture for 3 hours at 25-30°C,

c) filtering the reaction mixture and drying to get crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b.

Wherein, in step-a) the suitable solvent is selected from chloro solvents, alcohol solvents, ester solvents, nitrile solvents, polar aprotic solvents, hydrocarbon solvents, ether solvents, ketone solvents, polar solvents such as water or mixtures.

The preferred embodiment of the present invention provides a process for the preparation of crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, comprising of:

a) Adding isopropanol to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt of compound of formula-1b,
b) stirring the reaction mixture for 3 hours at 25-30°C,
c) filtering the reaction mixture and drying to get crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b.

The second aspect of the present invention provides an improved process for the preparation of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of the following steps:

a) Reacting 1-((4-fluorophenyl)carbamoyl)cyclopropane carboxylic acid compound of formula-2 with chlorinating agent in a suitable solvent to provide 1-(4-fluorophenyl carbamoyl)cyclopropanecarbonylchloride compound of formula-3,
b) reacting the compound of formula-3 in-situ with 4-(6,7-dimethoxyquinolin-4-yloxy) aniline compound of formula-4 in the presence of a suitable base in a suitable solvent to provide N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide compound of formula-1,

c) treating the compound of formula-1 in-situ with a suitable hydrochloric acid source in a suitable solvent to provide N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b,

d) purifying the compound of formula-1b using a suitable solvent,

e) treating the compound of formula-1b with a suitable base in a suitable solvent to provide N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide compound of formula-1 which on in-situ treating with (L)-malic acid in a suitable solvent to provide N-(4-(6,7-dimethoxyquinolin-4-yloxy) phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

Wherein, in step-a) the suitable chlorinating agent is selected from pivaloyl chloride, thionyl chloride, sulfuryl chloride, phosphorus oxychloride, oxalyl chloride, phosphorus trichloride, phosphorus pentachloride; in step-b) & step-e) the suitable base is selected from inorganic or organic base; in step-c) the suitable hydrochloric acid source is selected from hydrochloric acid gas, aqueous hydrochloric acid, ethyl acetate-hydrochloric acid, ethanolic-HCl, methanolic-HCl, isopropanol-hydrochloric acid, diisopropyl ether-hydrochloric acid, diethylether-hydrochloric acid, and trimethylchlorosilane;
in step-a) to step-e) the suitable solvent is selected from chloro solvents, alcohol solvents, ester solvents, nitrile solvents, polar aprotic solvents, hydrocarbon solvents, ether solvents, ketone solvents, polar solvents such as water or mixtures.

The preferred embodiment of the present invention provides an improved process for the preparation of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of the following steps:

a) Reacting 1-((4-fluorophenyl)carbamoyl)cyclopropane carboxylic acid compound of formula-2 with thionyl chloride in tetrahydrofuran to provide 1-(4-fluorophenyl carbamoyl)cyclopropanecarbonylchloride compound of formula-3,

b) reacting the compound of formula-3 in-situ with 4-(6,7-dimethoxyquinolin-4-yloxy) aniline compound of formula-4 in the presence of potassium carbonate in a mixture of water and tetrahydrofuran to provide N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide compound of formula-1,

c) treating the compound of formula-1 in-situ with aqueous hydrochloric acid to provide N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b,

d) purifying the compound of formula-1b using isopropanol and then followed by using dimethyl sulfoxide and ethyl acetate,

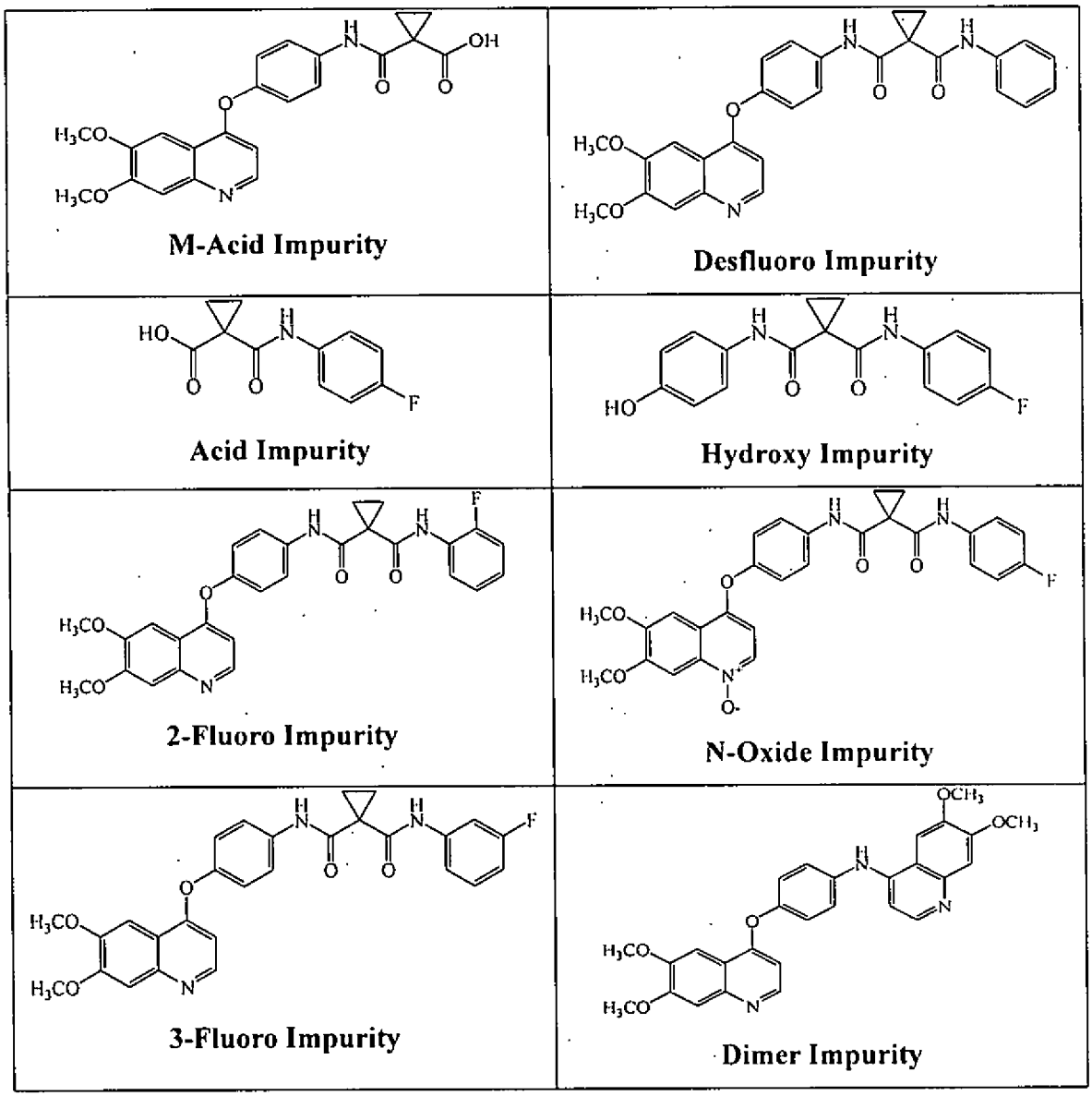
e) treating the compound of formula-1b with aqueous sodium carbonate solution to provide N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide compound of formula-1 which on in-situ treating with (L)-malic acid in a mixture of tetrahydrofuran, water and methyl isobutyl ketone to provide N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide (S)-malate compound of formula-1a.

US7579473 B2 involves purification of crude Cabozantinib by preparative column chromatography which is expensive, tedious, time consuming and inevitably decrease yield of the product. Hence this process is not suitable for commercial scale. Therefore, there is an unmet need to develop a purification process which can be performed at industrial scale.

The present invention have overcame the problems associated with the prior art, by simply converting the crude Cabozantinib into its acid addition salt and then treating the acid addition salt of Cabozantinib with a suitable base to provide Cabozantinib free base compound of formula-1 with enhanced purity.

N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a obtained according to the present invention is having 1-((4-((6,7-dimethoxyquinolin-4-yloxy)phenyl)carbamoyl)cyclopropane carboxylic acid {*M-Acid Impurity*}; 1-((4-fluorophenyl)carbamoyl)cyclopropane carboxylic acid {*Acid Impurity*}; N-(4-fluorophenyl)-N-(4-hydroxyphenyl)cyclopropane-1,1-di

carboxamide {*Hydroxy Impurity*}; N-(4-((6,7-dimethoxyquinolin-4-yloxy)phenyl)-N-phenyl cyclopropane-1,1-dicarboxamide {*Desfluoro Impurity*}; N-(4-((6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N-(2-fluorophenyl)cyclopropane-1,1-dicarboxamide {*2-Fluoro Impurity*}; 4-(4-(1-((4-fluorophenyl)carbamoyl)cyclopropanecarboxamido)phenoxy)-6,7-dimethoxyquinoline 1-oxide {*N-Oxide Impurity*}; N-(4-((6,7-dimethoxyquinolin-4-yloxy)phenyl)-N-(3-fluoro phenyl)cyclopropane-1,1-dicarboxamide {*3-Fluoro Impurity*}; and N-(4-((6,7-dimethoxy quinolin-4-yloxy)phenyl)-6,7-dimethoxyquinolin-4-amine {*Dimer Impurity*} less than 0.05% as measured by HPLC.



N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a obtained according to the present invention is having particle size distribution $D_{90} < 100$ µm.

The third aspect of the present invention provides a crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloric acid salt compound of formula-1b, characterized by its powder x-ray diffraction pattern having peaks at 5.1, 6.5, 7.9, 8.6, 9.7, 10.5, 12.8, 13.4, 15.2, 16.1, 17.2, 17.9, 18.5, 19.1, 19.4, 20.4, 20.9, 22.0, 23.0, 23.7, 24.8, 26.8, 28.4, 29.1, 29.8 and 40.6 ± 0.2 degrees two theta as depicted in figure-2.

In another embodiment of the present invention provides a process for the preparation of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, comprising of the following steps:

a) Adding a suitable solvent to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride compound of formula-1b,
b) stirring the reaction mixture,
c) filtering the reaction mixture,
d) adding a suitable solvent to the filtrate obtained in step-c),
e) stirring the reaction mixture,
f) filtering the precipitated solid and drying to get the crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b.

Wherein, in step-a) and step-d) the suitable solvent is selected from chloro solvents, alcohol solvents, ester solvents, nitrile solvents, polar aprotic solvents, hydrocarbon solvents, ether solvents, ketone solvents, polar solvents such as water or mixtures.

The preferred embodiment of the present invention provides a process for the preparation of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-

fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, comprising of the following steps:

a) Adding dimethyl sulfoxide to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride compound of formula-1b,
b) stirring the reaction mixture,
c) filtering the reaction mixture,
d) adding ethyl acetate to the filtrate obtained in step-c),
e) stirring the reaction mixture,
f) filtering the precipitated solid and drying to get the crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b.

The fourth aspect of the present invention provides a crystalline form-N of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloric acid salt compound of formula-1b, characterized by its powder x-ray diffraction pattern having peaks at 4.0, 5.1, 6.3, 7.5, 8.0, 8.6, 9.4, 10.5, 11.2, 11.8, 12.6, 13.3, 13.5, 15.0, 15.3, 16.0, 16.3, 17.5, 17.9, 18.9, 19.9, 20.5, 21.2, 22.3, 22.7, 23.2, 23.8, 25.8, 26.4 and 27.4 ± 0.2 degrees two theta as depicted in figure-3.

In another embodiment of the present invention provides a process for the preparation of crystalline form-N of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, comprising of:

a) Adding a suitable solvent to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt of compound of formula-1b,
b) stirring the reaction mixture for 5 hours,
c) filtering the reaction mixture and drying to get crystalline form-N of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b.

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

The preferred embodiment of the present invention provides a process for the preparation of crystalline form-N of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, comprising of:

a) Adding isopropanol to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluoro phenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt of compound of formula-1b,
b) stirring the reaction mixture 5 hours,
c) filtering the reaction mixture and drying to get crystalline form-N of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b.

The fourth aspect of the present invention provides a crystalline form-R of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, characterized by its powder x-ray diffraction pattern having peaks at 8.5, 9.3, 10.5, 11.6, 11.8, 12.1, 12.5, 12.9, 13.2, 13.7, 14.5, 15.5, 16.1, 16.8, 17.2, 17.6, 17.8, 19.3, 19.7, 20.0, 20.4, 21.3, 21.8, 22.2, 22.7, 23.2, 23.7, 24.0, 25.2, 25.7, 25.9, 27.0, 27.4, 27.6, 28.5, 30.0, 30.6, 31.9 and 32.3 ±0.2 degrees two theta as depicted in figure-4.

In another embodiment of the present invention provides a process for the preparation of crystalline form-R of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, comprising of the following steps:

a) Adding a suitable solvent to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide compound of formula-1,
b) adding suitable hydrochloric acid salt to the reaction mixture,

c) stirring the reaction mixture,
d) filtering the reaction mixture,
e) adding a suitable solvent to the compound obtained in step-d),
f) stirring the reaction mixture,
g) filtering the reaction mixture and drying to get the crystalline form-R of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b.

Wherein, in step-a) and step-e) the suitable solvent is selected from chloro solvents, alcohol solvents, ester solvents, nitrile solvents, polar aprotic solvents, hydrocarbon solvents, ether solvents, ketone solvents, polar solvents such as water or mixtures thereof;
in step-b) the suitable hydrochloric acid source is same as defined in step-(c) of the second aspect of the present invention.

The preferred embodiment of the present invention provides a process for the preparation of crystalline form-R of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, comprising of the following steps:

a) Adding a mixture of tetrahydrofuran and ethyl acetate to N-(4-(6,7-dimethoxy quinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide compound of formula-1,
b) adding aqueous hydrochloric acid salt to the reaction mixture,
c) stirring the reaction mixture,
d) filtering the reaction mixture,
e) adding isopropanol to the compound obtained in step-d),
f) stirring the reaction mixture,
g) filtering the reaction mixture and drying to get the crystalline form-R of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b.

The crude compound of formula-1 was treated with a suitable acid selected from

inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or phosphoric acid; and organic acids such as oxalic acid, maleic acid, malonic acid, tartaric acid, fumaric acid, citric acid, malic acid, succinic acid, mandelic acid, lactic acid, acetic acid, propionic acid, 2-chloromandelate, p-toluene sulfonic acid, ethane-1,2-disulfonic acid, camphor sulfonic acid, ethane sulfonic acid, methane sulfonic acid, naphthalene-2-sulfonic acid, benzene sulfonic acid, adipic acid, glutaric acid, glutamic acid, palmitic acid or aspartic acid to provide its corresponding acid addition salt of compound of formula-1 and further neutralizing the acid addition salt of compound of formula-1 with a suitable base selected from a group consisting of alkali metal carbonates like sodium carbonate, lithium carbonate, potassium carbonate; or an alkali metal hydroxide like sodium hydroxide, potassium hydroxide, lithium hydroxide; or alkali metal bicarbonates like sodium bicarbonate, potassium bicarbonate; or an organic base like triethylamine, tributylamine, diisopropylethlyamine to provide pure compound of formula-1.

The sixth aspect of the present invention provides novel crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, characterized by its powder x-ray diffraction pattern having peaks at 7.0, 7.4, 7.8, 9.4, 11.0, 11.4, 11.9, 12.6, 13.6, 14.0, 15.4, 15.6, 16.1, 17.2, 18.4, 19.2, 19.9, 21.1, 21.8, 22.1, 22.4, 23.1, 24.0, 24.2, 25.8, 26.2, 27.1, 27.6, 28.9, 29.3, 29.9, 30.1, 31.6, 32.5, 33.8, 35.3, 36.8, 37.6 and 39.9 ±0.2 degrees two theta as depicted in figure-5.

In another embodiment of the present invention provides a process for the preparation of crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of the following steps:

a) Adding a suitable solvent to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide compound of formula-1,
b) heating the reaction mixture to a suitable temperature,
c) adding (L)-malic acid to the reaction mixture,
d) stirring the reaction mixture,

e) cooling the reaction mixture to a suitable temperature and stirring the reaction mixture,
f) filtering the precipitated solid and drying to get the crystalline form-M of N-{4-[(6,7-dimethoxyquinolin-4-yloxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

Wherein, in step-a) the suitable solvent is selected from chloro solvents, alcohol solvents, ester solvents, nitrile solvents, polar aprotic solvents, hydrocarbon solvents, ether solvents, ketone solvents, polar solvents such as water or mixtures thereof;
in step-b) the suitable temperature is ranging from 30°C to reflux temperature of the solvent used in the reaction;
in step-e) the suitable temperature is ranging from -50°C to 0°C.

The preferred embodiment of the present invention provides a process for the preparation of crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of the following steps:

a) Adding xylene to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide compound of formula-1,
b) heating the reaction mixture to 70-75°C,
c) adding (L)-malic acid to the reaction mixture,
d) stirring the reaction mixture,
e) cooling the reaction mixture to -50°C and stirring the reaction mixture,
f) filtering the precipitated solid and drying to get the crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

The another preferred embodiment of the present invention provides a process for the preparation of crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of the following steps:

a) Adding n-heptane to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluoro phenyl)cyclopropane-1,1-dicarboxamide compound of formula-1,
b) heating the reaction mixture to 65-70°C,
c) adding (L)-malic acid to the reaction mixture,
d) stirring the reaction mixture,
e) cooling the reaction mixture to -50°C and stirring the reaction mixture,
f) filtering the precipitated solid and drying to get the crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

The another preferred embodiment of the present invention provides a process for the preparation of crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of the following steps:

a) Adding methyl tert-butyl ether to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide compound of formula-1,
b) heating the reaction mixture to 50-55°C,
c) adding (L)-malic acid to the reaction mixture,
d) stirring the reaction mixture,
e) cooling the reaction mixture to -50°C and stirring the reaction mixture,
f) filtering the precipitated solid and drying to get the crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

The preferred embodiment of the present invention provides a process for the preparation of crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of the following steps:

a) Adding toluene to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide compound of formula-1,
b) heating the reaction mixture to 70-75°C,

c) adding (L)-malic acid to the reaction mixture,

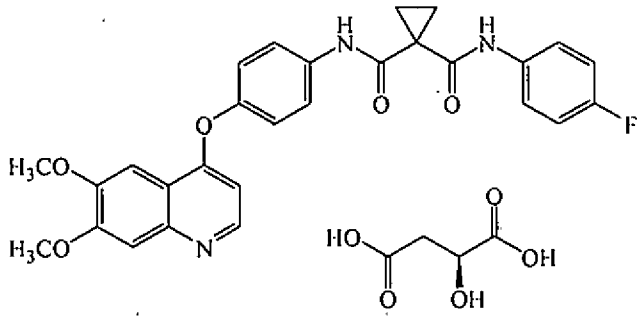
d) stirring the reaction mixture,

e) cooling the reaction mixture to -50°C and stirring the reaction mixture,

f) filtering the precipitated solid and drying to get the crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a and hydrochloride salt compound of formula-1b respectively produced according to the present invention are useful in the preparation of pharmaceutical formulation.

The seventh aspect of the present invention provides novel crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a,



Formula-1a

characterized by its powder x-ray diffraction pattern having peaks at 6.6, 7.6, 8.2, 10.0, 10.5, 12.5, 13.3, 15.1, 16.4, 18.2, 19.0, 20.2, 20.6, 21.6, 22.6, 25.1, 26.1, 27.0, 28.1, 29.8 and 32.8 ± 0.2 degrees two theta as depicted in figure-1.

In an embodiment of the present invention provides a process for the preparation of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide (S)-malate compound of formula-1, comprising of;

a) Adding a suitable solvent to crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a,
b) heating the reaction mixture to a suitable temperature and stirring the reaction mixture,
c) optionally, filtering the reaction mixture,
d) adding the obtained filtrate in step-c) to a pre-cooled suitable anti-solvent at suitable temperature,
e) stirring the reaction mixture,
f) filtering the precipitated solid and drying to get crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-di carboxamide (S)-malate compound of formula-1a.

Wherein, in step-b) the suitable temperature is ranging from ambient temperature to the reflux temperature of the solvent used in the reaction;
in step-d) the suitable anti-solvent is selected from chloro solvents and hydrocarbon solvents; the suitable temperature is ranging from -10°C to 20°C;
in step-a) and d) the suitable solvent is selected from chloro solvents, alcohol solvents, ester solvents, nitrile solvents, polar aprotic solvents, hydrocarbon solvents, ether solvents, ketone solvents, polar solvents such as water or mixture thereof.

The preferred embodiment of the present invention provides a process for the preparation of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of;

a) Adding a mixture of tetrahydrofuran and water to crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a,
b) heating the reaction mixture to 60-65°C and stirring the reaction mixture,
c) filtering the reaction mixture through hyflow bed,
d) adding the obtained filtrate in step-c) to a pre-cooled dichloromethane at 0-5°C,
e) stirring the reaction mixture,

f) filtering the precipitated solid and drying to get crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-di carboxamide (S)-malate compound of formula-1a.

The crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluoro phenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a obtained according to the present invention can be prepared by using crystalline form-M of compound of formula-1a disclosed in the present invention or any of the free base compound of frormula-1 or compound of formula-1a known in the prior art.

Thermal stability at 60°C:

Samples of crystalline form-S of Cabozantinib (S)-malate (3.0 gms) is subjected to heating in a vacuum dryer at 60°C for 24 hours. The P-XRD pattern was results to show that crystalline form-S of Cabozantinib (S)-malate is stable.

Hygroscopic stability for 24 hours:

Samples of crystalline form-S of Cabozantinib (S)-malate (3.0 gms) is kept in the desiccator for 24 hours. The P-XRD pattern was results to show that crystalline form-S of Cabozantinib (S)-malate is stable.

The eighth aspect of the present invention provides a process for the preparation of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of:

a) Treating N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide hydrochloride salt with a suitable base in a suitable solvent,
b) adding a suitable solvent to the reaction mixture and stirring the reaction mixture,
c) separating both the organic and aqueous layers,
d) optionally treating the organic layer with carbon,
e) optionally filtering the organic layer through hyflow bed,
f) optionally heating the obtained filtrate to a suitable temperature,
g) adding malic acid to the filtrate,

h) adding a suitable anti-solvent to the reaction mixture and stirring the reaction mixture,
i) cooling the reaction mixture to a suitable temperature,
j) filtering the precipitated solid and dried to provide crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

Wherein, in step-a) the suitable base is selected from organic or inorganic bases; in step-b) the suitable solvent is selected from alcohol solvents, ester solvents, ketone solvents, ether solvents, hydrocarbon solvents, polar aprotic solvents, nitrile solvents, polar solvents like water or mixture thereof; in step-f) the suitable temperature is ranging from 30°C to reflux temperature of the solvent used; in step-h) the suitable anti-solvent is selected from chloro solvents; in step-i) the suitable temperature is ranging from 20°C to -20°C.

The preferred embodiment of the present invention provides a process for the preparation of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of:

a) Treating N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide hydrochloride salt with aqueous sodium carbonate and water,
b) adding a mixture of ethyl acetate and tetrahydrofuran to the reaction mixture and stirring the reaction mixture,
c) separating both the organic and aqueous layers,
d) treating the organic layer with carbon,
e) filtering the organic layer through hyflow bed,
f) heating the obtained filtrate to 40-45°C,
g) adding malic acid to the filtrate at 40-45°C,
h) adding dichloromethane to the reaction mixture and stirring the reaction mixture at 40-45°C,
i) cooling the reaction mixture to 0-5°C,

j) filtering the precipitated solid and dried to provide crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

The preferred embodiment of the present invention provides a process for the preparation of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of:

a) Treating N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide hydrochloride salt with aqueous sodium carbonate and water,
b) adding a mixture of ethyl acetate and tetrahydrofuran to the reaction mixture and stirring the reaction mixture,
c) separating both the organic and aqueous layers,
d) treating the organic layer with carbon,
e) filtering the organic layer through hyflow bed,
f) heating the obtained filtrate to 40-45°C,
g) adding dichloromethane to the reaction mixture and stirring the reaction mixture at 40-45°C,
h) adding malic acid to the filtrate at 40-45°C,
i) cooling the reaction mixture to 0-5°C,
j) filtering the precipitated solid and dried to provide crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

The preferred embodiment of the present invention provides a process for the preparation of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of:

a) Treating N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide hydrochloride salt with aqueous sodium carbonate and water,
b) adding a mixture of ethyl acetate and tetrahydrofuran to the reaction mixture and stirring the reaction mixture,
c) separating both the organic and aqueous layers,
d) treating the organic layer with carbon,
e) filtering the organic layer through hyflow bed,
f) adding a mixture of ethyl acetate, tetrahydrofuran and malic acid to the filtrate,
g) adding dichloromethane to the reaction mixture and stirring the reaction mixture,
h) cooling the reaction mixture to 0-5°C,
i) filtering the precipitated solid and dried to provide crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

In another embodiment of the present invention provides a process for the preparation of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of:

a) Treating N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide hydrochloride salt with a suitable base in a suitable solvent,
b) adding a suitable solvent to the reaction mixture and stirring the reaction mixture,
c) separating both the organic and aqueous layers,
d) optionally treating the organic layer with carbon,
e) optionally filtering the organic layer through hyflow bed,
f) optionally heating the obtained filtrate to a suitable temperature,
g) adding malic acid to the filtrate,
h) adding the reaction mixture obtained in step-g) to a pre-cooled solvent and stirring the reaction mixture,

i) filtering the precipitated solid and dried to provide crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

Wherein, in step-a) the suitable base is selected from organic or inorganic bases; in step-b) the suitable solvent is selected from alcohol solvents, ester solvents, ketone solvents, ether solvents, hydrocarbon solvents, polar aprotic solvents, nitrile solvents, polar solvents like water or mixture thereof; in step-h) the suitable solvent is selected from chloro solvents.

The preferred embodiment of the present invention provides a process for the preparation of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a. comprising of:

a) Treating N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt with aqueous sodium carbonate in water,
b) adding a mixture of ethyl acetate and tetrahydrofuran to the reaction mixture and stirring the reaction mixture,
c) separating both the organic and aqueous layers,
d) treating the organic layer with carbon,
e) filtering the organic layer through hyflow bed,
f) adding malic acid to the filtrate,
g) adding the reaction mixture obtained in step-f) to a pre-cooled dichloromethane and stirring the reaction mixture at 0-5°C,
h) filtering the precipitated solid and dried to provide crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

The crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluoro phenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a according to the present invention is having purity greater than 99.95% by HPLC.

The starting materials compound of formula-2 and compound of formula-4 used in the present invention can be prepared by any of the prior known process.

Crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluoro phenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a obtained according to the present invention is having particle size distribution $D_{90} < 100$ µm.

N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide compound of formula-1a and formula-1b produced by the present invention can be further micronized or milled in a conventional techniques to get the 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 include, but not limited to ball, roller and hammer mills, and jet mills. Milling or micronization may be performed before drying, or after the completion of drying of the product.

The invention also encompasses pharmaceutical compositions comprising compound of formula-1 or salts thereof of the present invention. As used herein, the term "pharmaceutical compositions" or "pharmaceutical formulations" include tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

The N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a obtained according to the present invention is having purity greater than 99.9 % by HPLC.

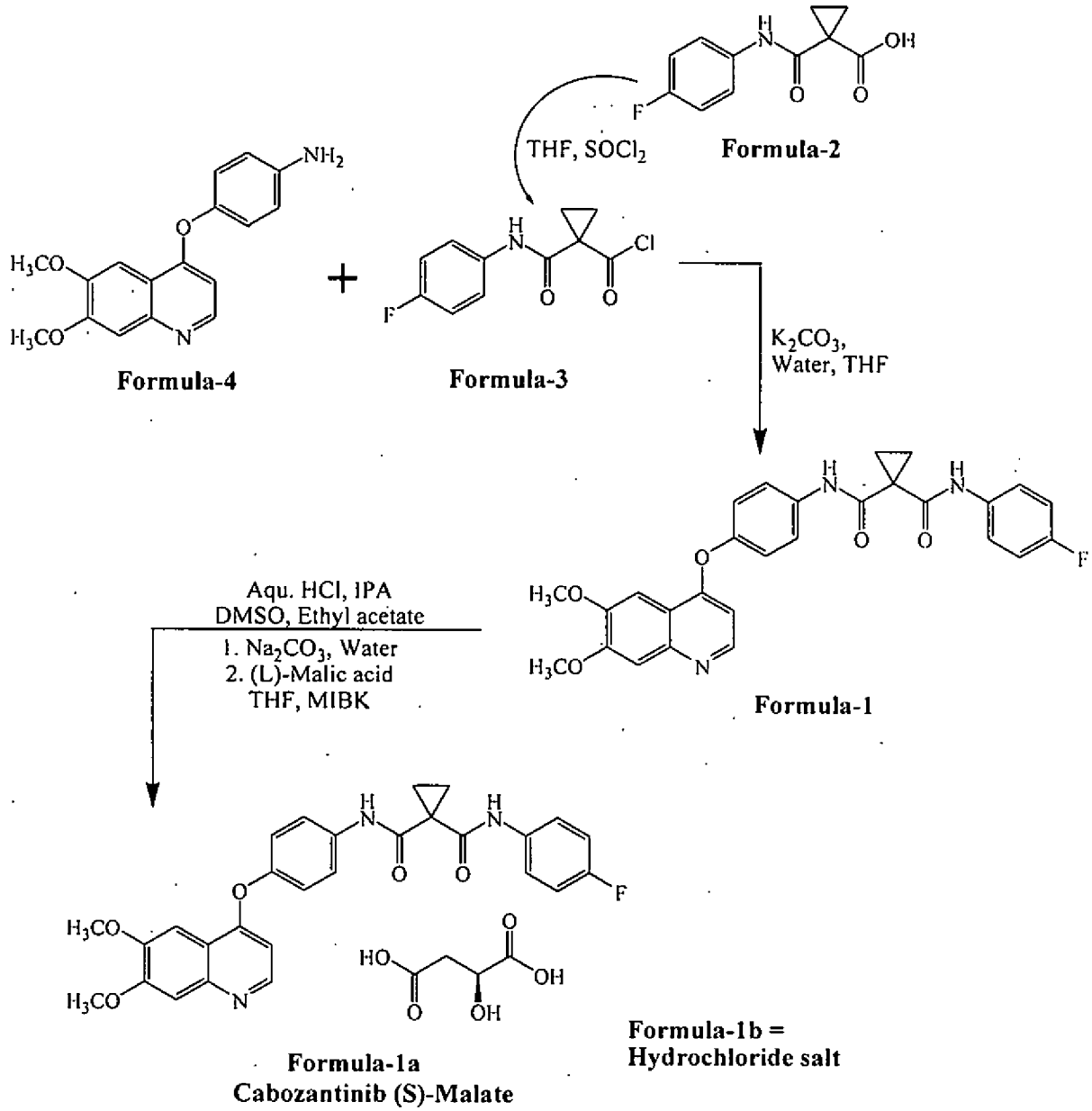
P-XRD Method of Analysis:

PXRD analysis of compounds produced by the present invention were carried out using BRUKER D8 ADVANCE/AXS X-Ray diffractometer using Cu Kα radiation of wavelength 1.5406 A° and continuous scan speed of 0.03°/min.

PSD method of Analysis:

Particle size distribution (PSD) analysis was performed using Malvern Mastersizer 2000 instrument.

The process of the present invention can be represented schematically as follows:



The process described in the present invention was demonstrated in examples illustrated below. These examples are provided as illustration only and therefore should not be construed as limitation of the scope of the invention.

Examples:

Example-1:

Preparation of crystalline form-M of Cabozantinib hydrochloride salt (Formula-1b):

Thionyl chloride (180.4 gms) was slowly added to the mixture of 1-((4-fluorophenyl) carbamoyl)cyclopropane carboxylic acid (112.9 gms) and tetrahydrofuran (600 ml) at 25-30°C and stirred for 5 hours at the same temperature. The reaction mixture was slowly added to a pre-cooled mixture of 4-((6,7-dimethoxyquinolin-4-yloxy)aniline (100 gms), aqueous potassium carbonate solution (418.5 gms of potassium carbonate in 600 ml of water) and tetrahydrofuran (600 ml) at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 2 hours at the same temperature. Both the organic and aqueous layers were separated. Extracted the aqueous layer with ethyl acetate. Combined the organic layers. Aqueous hydrochloric acid solution (75 ml of HCl in 725 ml of water) was added to the organic layer at 25-30°C and stirred the reaction mixture for 3 hours at the same temperature. Filtered the precipitated solid, washed with tetrahydrofuran and ethyl acetate, To the obtained compound, isopropanol (22.0 lts) was added at 25-30°C and stirred for 3 hours at the same temperature. Filtered the solid, washed with isopropanol and dried to get the title compound.

Yield: 152 gms; Chloride content: 7.0%.

The P-XRD pattern of the obtained compound was depicted in figure-1.

Example-2: Preparation of crystalline form-S of Cabozantinib hydrochloride salt (Formula-1b):

Dimethyl sulfoxide (700 ml) was added to the obtained compound in example-1 at 25-30°C and stirred for 45 minutes at the same temperature. Filtered the reaction mixture. Ethyl acetate (2.1 lts) was added to the obtained filtrate at 25-30°C and stirred for 3 hours at the same temperature. Filtered the precipitated solid, washed with ethyl acetate and dried to get the title compound.

Yield: 169.3 gms; M.R: 185-190°C; Chloride content: 7.3%; Purity by HPLC: 99.83%.

The P-XRD pattern of the obtained compound was depicted in figure-2.

Example-3: Preparation of Cabozantinib (S)-malate (Formula-1a):

A mixture of water (840 ml) and N-(4-((6,7-dimethoxyquinolin-4-yloxy)phenyl)-N-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide hydrochloride (120 gms) was stirred for 10 minutes at 25-30°C. Aqueous sodium carbonate solution was added to the reaction mixture at 25-30°C and stirred for 10 minutes at the same temperature. Tetrahydrofuran (900 ml) and ethyl acetate (900 ml) were added to the reaction mixture at 25-30°C and stirred for 10

minutes at the same temperature. Both the organic and aqueous layers were separated and aqueous layer was extracted twice with tetrahydrofuran and ethyl acetate mixture. Combined the organic layers and washed with aqueous sodium chloride solution. Carbon powder was added to the organic layer at 25-30°C and stirred for 15 minutes at the same temperature. Filtered the reaction mixture through hyflow bed and washed with tetrahydrofuran. Distilled off the solvent completely from the obtained filtrate under reduced pressure and co-distilled with tetrahydrofuran. To the obtained compound, tetrahydrofuran (1300 ml) and water (14 ml) were added at 25-30°C. Heated the reaction mixture to 60-65°C and stirred for 15 minutes at the same temperature. The reaction mixture was slowly added to a solution of L-malic acid (34.5 gms) and methyl isobutyl ketone (3.0 lts) and seeding crystals of compound of formula-1a at 25-30°C and stirred the reaction mixture for 3 hours at the same temperature. Filtered the reaction mixture and washed with methyl isobutyl ketone. To the obtained compound, methyl isobutylketone was added at 25-30°C and stirred for 3 hours at the same temperature. Filtered the reaction mixture, washed with methyl isobutylketone and dried to get the title compound.

Yield: 113.2 gms; M.R: 182-187°C; Purity by HPLC: 99.98%; M-Acid impurity: Not detected; Acid impurity: Not detected; Hydroxy impurity: Not detected; Desfluoro impurity: 0.04%; 2-fluoro impurity: Not detected; 3-fluoro impurity: Not detected; N-oxide impurity: Not detected and HIUI: 0.05%.

Before micronization: Particle size distribution: D_{90}: 47.97 µm; D_{50}: 8.82 µm; D_{10}: 3.26 µm.

After micronization: Particle size distribution: D_{90}: 15.5 µm; D_{50}: 7.4 µm; D_{10}: 2.8 µm.

Example-4: Preparation of crystalline form-N of Cabozantinib hydrochloride salt (Formula-1b):

Aqueous hydrochloric acid solution was added to N-{4-[(6,7-dimethoxyquinolin-4-yl oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide compound of formula-1 (163 gm) at 25-30°C and stirred for 3 hours at the same temperature. Filtered the precipitated solid, washed with tetrahydrofuran and ethyl acetate, To the obtained compound, isopropanol (2.2 lts) was added at 25-30°C and stirred for 5 hours at the same temperature. Filtered the solid, washed with isopropanol and dried to get the title compound.

Yield: 152 gms; Chloride content: 6.4%.

The P-XRD pattern of the obtained compound was depicted in figure-3.

Example-5: Preparation of crystalline form-R of Cabozantinib hydrochloride salt (Formula-1b):

Tetrahydrofuran (1080 ml) and ethyl acetate (720 ml) were added to N-{4-[(6,7-dimethoxyquinolin-4-yloxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (150 gms) at 25-30°C. Aqueous hydrochloric acid (67.5 ml of hydrochloric acid in 900 ml of water) was added to the reaction mixture at 25-30°C and stirred for 3 hours at the same temperature. Filtered the reaction mixture and washed with a mixture of ethyl acetate and tetrahydrofuran. Washed the obtained compound with water and isopropanol. To the obtained compound, isopropanol (2.0 lts) was added at 25-30°C and stirred for 3 hours at the same temperature. Filtered the solid, washed with isopropanol and dried to get the title compound. Yield: 149.02 gms; M.R: 240-245°C; Chloride content: 6.3%; Purity by HPLC: 99.80%.

The P-XRD pattern of the obtained compound was depicted in figure-4.

Example-6: Preparation of crystalline form-M of Cabozantinib (S)-malate:

A mixture of toluene (50 ml) and N-{4-[(6,7-dimethoxyquinolin-4-yloxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (5 gms) was stirred for 10 minutes at 25-30°C. Heated the reaction mixture to 70-75°C. L-malic acid (1.6 gms) was added to the reaction mixture at 70-75°C and stirred for 60 minutes at the same temperature. Cooled the reaction mixture to -50°C and stirred for 60 minutes at the same temperature. Filtered the precipitated solid and dried to get the title compound. Yield: 4.0 gms; Malate content: 23.6%.

The P-XRD pattern of the obtained compound was depicted in figure-5.

Example-7: Preparation of crystalline form-M of Cabozantinib (S)-malate:

A mixture of xylene (50 ml) and N-{4-[(6,7-dimethoxyquinolin-4-yloxy]phenyl}-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide (5 gms) was stirred for 10 minutes at 25-30°C. Heated the reaction mixture to 70-75°C. L-malic acid (1.6 gms) was added to the reaction mixture at 70-75°C and stirred for 60 minutes at the same temperature. Cooled the reaction mixture to -50°C and stirred for 60 minutes at the same temperature. Filtered the precipitated solid and dried to get the title compound. Yield: 4.5 gms; Malate content: 22.8%.

The P-XRD pattern of the obtained compound was depicted in figure-5.

Example-8: Preparation of crystalline form-M of Cabozantinib (S)-malate:

A mixture of n-heptane (20 ml) and N-{4-[(6,7-dimethoxyquinolin-4-yloxy]phenyl}-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide (2 gms) was stirred for 10 minutes at 25-30°C. Heated the reaction mixture to 70-75°C. L-malic acid (0.64 gms) was added to the reaction mixture at 70-75°C and stirred for 60 minutes at the same temperature. Cooled the reaction mixture to -50°C and stirred for 60 minutes at the same temperature. Filtered the precipitated solid and dried to get the title compound. Yield: 1.2 gms; Malate content: 22.8%. The P-XRD pattern of the obtained compound was depicted in figure-5.

Example-9: Preparation of crystalline form-M of Cabozantinib (S)-malate:

A mixture of methyl tert-butyl ether (20 ml) and N-{4-[(6,7-dimethoxyquinolin-4-yloxy]phenyl}-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide (2 gms) was stirred for 10 minutes at 25-30°C. Heated the reaction mixture to 50-55°C. L-malic acid (0.64 gms) was added to the reaction mixture at 50-55°C and stirred for 60 minutes at the same temperature. Cooled the reaction mixture to -50°C and stirred for 60 minutes at the same temperature. Filtered the precipitated solid and dried to get the title compound.

Yield: 1.2 gms; Malate content: 23.1%.

The P-XRD pattern of the obtained compound was depicted in figure-5.

Example-10: Preparation of crystalline form-M of Cabozantinib (S)-malate:

A mixture of xylene (250 ml) and N-{4-[(6,7-dimethoxyquinolin-4-yloxy]phenyl}-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide (25 gms) was stirred for 10 minutes at 25-30°C. Heated the reaction mixture to 70-75°C. L-malic acid (8.5 gms) was added to the reaction mixture at 70-75°C and stirred for 60 minutes at the same temperature. Cooled the reaction mixture to -50°C and stirred for 60 minutes at the same temperature. Filtered the precipitated solid and dried to get the title compound.

Yield: 24.0 gms.

The P-XRD pattern of the obtained compound was depicted in figure-5.

Example-11: Preparation of crystalline form-S of Cabozantinib (S)-malate:

Tetrahydrofuran (500 ml) and water (50 ml) were added to N-(4-(6,7-dimethoxy quinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate (50 gms) at 25-30°C and stirred for 10 minutes at the same temperature. Heated the reaction mixture to 60°C and stirred for 15 minutes at the same temperature. The obtained clear

solution was slowly added to pre-cooled dichloromethane (1000 ml) at 0-5°C and stirred for 60 minutes at the same temperature. Filtered the precipitated solid and dried to get the title compound. Yield: 43.0 gms.

Water content: 2.4%; L-malic acid content: 20.6%; Purity by HPLC: 99.97%;

The P-XRD pattern of the obtained compound is depicted in figure-6.

Particle size distribution: D_{90}: 29.02 µm; D_{50}: 9.99 µm.

Example-12: Preparation of crystalline form-S of Cabozantinib (S)-malate:

Tetrahydrofuran (500 ml) and water (50 ml) were added to crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate (50 gms) at 25-30°C and stirred for 10 minutes at the same temperature. Heated the reaction mixture to 60°C and stirred for 15 minutes at the same temperature. Filtered the reaction mixture to through hyflow bed. The obtained particle free clear solution was slowly added to pre-cooled dichloromethane (1000 ml) at 0-5°C and stirred for 60 minutes at the same temperature. Filtered the precipitated solid and dried to get the title compound. Yield: 39.9 gms.

The P-XRD pattern of the obtained compound is depicted in figure-6.

Example-13: Preparation of crystalline form-S of Cabozantinib (S)-malate:

Aqueous sodium carbonate solution was added to a mixture of N-(4-(6,7-dimethoxy quinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride (10 gms) and water (70 ml) at 25-30°C and stirred for 10 minutes at the same temperature. Ethyl acetate (75 ml) and tetrahydrofuran (75 ml) were added to the reaction mixture at 25-30°C and stirred for 10 minutes at the same temperature. Both the organic and aqueous layers were separated and aqueous layer was extracted with a mixture of tetrahydrofuran and ethyl acetate. Combined the organic layers and washed with aqueous sodium chloride solution. Carbon powder (1 gm) was added to organic layer at 25-30°C and stirred for 10 minutes at the same temperature. Filtered the reaction mixture through hyflow bed and washed with tetrahydrofuran. Heated the obtained filtrate to 40-45°C. Malic acid (2.8 gms) was slowly added to the obtained filtrate at 40-45°C. Dichloromethane was slowly added to the reaction mixture at 40-45°C and stirred for 10 minutes at the same temperature. Cooled the reaction mixture to 0-5°C and stirred for 3 hours at the same temperature. Filtered the precipitated

solid and dried to get the title compound.

Yield: 8.0 gms.

The P-XRD pattern of the obtained compound is depicted in figure-6.

Example-14: Preparation of crystalline form-S of Cabozantinib (S)-malate:

Aqueous sodium carbonate solution was added to a mixture of N-(4-(6,7-dimethoxy quinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride (10 gms) and water (70 ml) at 25-30°C and stirred for 10 minutes at the same temperature. Ethyl acetate (75 ml) and tetrahydrofuran (75 ml) were added to the reaction mixture at 25-30°C and stirred for 10 minutes at the same temperature. Both the organic and aqueous layers were separated and aqueous layer was extracted with a mixture of tetrahydrofuran and ethyl acetate. Combined the organic layers and washed with aqueous sodium chloride solution. Carbon powder (1 gm) was added to organic layer at 25-30°C and stirred for 10 minutes at the same temperature. Filtered the reaction mixture through hyflow bed and washed with tetrahydrofuran. Heated the obtained filtrate to 40-45°C. Dichloromethane (100 ml) was added to the obtained filtrate at 40-45°C. Malic acid (2.8 gms) was added to the reaction mixture at 50-55°C and stirred for 10 minutes at the same temperature. Cooled the reaction mixture to 0-5°C and stirred for 3 hours at the same temperature. Filtered the precipitated solid and dried to get the title compound.

Yield: 7.8 gms.

The P-XRD pattern of the obtained compound is depicted in figure-6.

Example-15: Preparation of crystalline form-S of Cabozantinib (S)-malate:

Aqueous sodium carbonate solution was added to a mixture of N-(4-(6,7-dimethoxy quinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride (50 gms) and water (350 ml) at 25-30°C and stirred for 10 minutes at the same temperature. Ethyl acetate (375 ml) and tetrahydrofuran (375 ml) were added to the reaction mixture at 25-30°C and stirred for 10 minutes at the same temperature. Both the organic and aqueous layers were separated and aqueous layer was extracted with a mixture of tetrahydrofuran and ethyl acetate. Combined the organic layers and washed with aqueous sodium chloride solution. Carbon powder (4.0 gms) was added to organic layer at 25-30°C and stirred for 10 minutes at the same temperature. Filtered the reaction mixture through hyflow bed and washed with

tetrahydrofuran. Malic acid (14.4 gms) was added to the obtained filtrate at 25-30°C. The reaction mixture was slowly added to a pre-cooled dichloromethane at 0-5°C and stirred for 1 ½ hour at the same temperature. Filtered the precipitated solid, washed with dichloromethane and dried to get the title compound.

Yield: 41.0 gms.

The P-XRD pattern of the obtained compound is depicted in figure-6.

Example-16: Preparation of crystalline form-S of Cabozantinib (S)-malate:

Aqueous sodium carbonate solution was added to a mixture of N-(4-(6,7-dimethoxy quinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride (50 gms) and water (350 ml) at 25-30°C and stirred for 10 minutes at the same temperature. Ethyl acetate (375 ml) and tetrahydrofuran (375 ml) were added to the reaction mixture at 25-30°C and stirred for 10 minutes at the same temperature. Both the organic and aqueous layers were separated and aqueous layer was extracted with a mixture of tetrahydrofuran and ethyl acetate. Combined the organic layers and washed with aqueous sodium chloride solution. Carbon powder (4.0 gms) was added to organic layer at 25-30°C and stirred for 10 minutes at the same temperature. Filtered the reaction mixture through hyflow bed and washed with tetrahydrofuran. Malic acid was dissolved in a mixture of ethyl acetate and tetrahydrofuran and this solution was added to the obtained filtrate at 25-30°C. Dichloromethane was added to the reaction mixture at 25-30°C. Cooled the reaction mixture to 0-5°C and stirred for 60 minutes at the same temperature. Filtered the precipitated solid, washed with dichloromethane and dried to get the title compound.

Yield: 43.0 gms.

The P-XRD pattern of the obtained compound is depicted in figure-6.

Example-17: Preparation of Cabozantinib hydrochloride salt (Formula-1b):

Thionyl chloride (36.10 kgs) was slowly added to the mixture of 1-((4-fluorophenyl) carbamoyl)cyclopropane carboxylic acid (22.60 kgs) and tetrahydrofuran (120 lts) at 25-30°C and stirred for 9 hours at the same temperature. The reaction mixture was slowly added to a pre-cooled mixture of 4-((6,7-dimethoxyquinolin-4-yloxy)aniline (20.0 kgs), aqueous potassium carbonate solution (83.70 kgs of potassium carbonate in 120 lts of water) and tetrahydrofuran (120 lts) at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C

and stirred for 2 hours at the same temperature. Both the organic and aqueous layers were separated and water was added to the aqueous layer at 25-30°C. Extracted the aqueous layer with ethyl acetate. Combine the organic layers. Aqueous hydrochloric acid solution (15 lts of HCl in 145 lts of water) was added to the organic layer at 25-30°C and stirred the reaction mixture for 3 hours at the same temperature. Filtered the precipitated solid, washed with tetrahydrofuran and ethyl acetate. To the obtained compound, water (lot-4) was added at 25-30°C and stirred for 2 hours at the same temperature. Filtered the reaction mixture and washed with water. To the obtained compound, water (595 lts) and hydrochloric acid (1.0 lts) were added at 25-30°C and stirred for 2 hours at the same temperature. Filtered the reaction mixture and washed with water. To the obtained compound, isopropanol (435 lts) was added at 25-30°C and stirred for 3 hours at the same temperature. Filtered the solid, washed with isopropanol and dried to get the title compound. Dimethyl sulfoxide (235 lts) was added to the obtained compound at 25-30°C and stirred for 45 minutes at the same temperature. Filtered the reaction mixture. Ethyl acetate (720 lts) was added to the obtained filtrate at 25-30°C and stirred for 3 hours at the same temperature. Filtered the precipitated solid, washed with ethyl acetate and dried to get the title compound.

Yield: 32.99 kgs; Purity by HPLC: 99.85%.

Example-18: Preparation of Cabozantinib (S)-malate (Formula-1a):

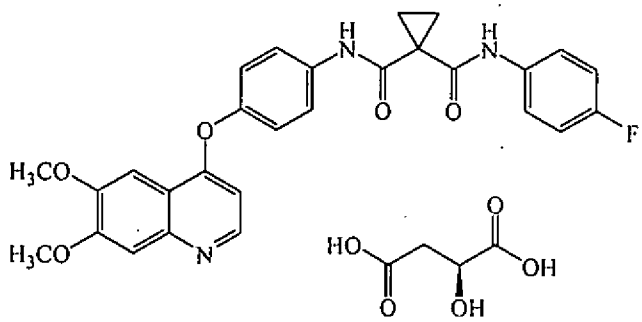
A mixture of water (135 lts) and N-(4-((6,7-dimethoxyquinolin-4-yloxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride (20.0 kgs) was stirred for 10 minutes at 25-30°C. Aqueous sodium carbonate solution was added to the reaction mixture at 25-30°C and stirred for 10 minutes at the same temperature. Tetrahydrofuran (150 lts) and ethyl acetate (15 lts) were added to the reaction mixture at 25-30°C and stirred for 10 minutes at the same temperature. Both the organic and aqueous layers were separated and aqueous layer was extracted twice with tetrahydrofuran and ethyl acetate mixture. Combined the organic layers and washed with aqueous sodium chloride solution. Carbon powder was added to the organic layer at 25-30°C and stirred for 15 minutes at the same temperature. Filtered the reaction mixture through hyflow bed and washed with tetrahydrofuran. Distilled off the solvent completely from the obtained filtrate under reduced pressure and co-distilled with tetrahydrofuran. To the obtained compound, tetrahydrofuran (216 lts) and water (2.2 lts) were

added at 25-30°C. Heated the reaction mixture to 60-65°C and stirred for 20 minutes at the same temperature. The reaction mixture was slowly added to a solution of L-malic acid (5.70 kgs) and methyl isobutyl ketone (500 lts) and seeding crystals of compound of formuls-1a at 25-30°C and stirred the reaction mixture for 3 hours at the same temperature. Filtered the reaction mixture and washed with methyl isobutyl ketone. To the obtained compound, methyl isobutylketone (40 lts) was added at 25-30°C and stirred for 3 hours at the same temperature. Filtered the reaction mixture, washed with methyl isobutylketone and dried to get the title compound. The obtained compound was micronized using conventional techniques to get the desired particle size. Methyl isobutyl ketone (200 lts) was added to the micronized compound at 25-30°C and stirred form 3 hours at the same temperature. Filtered the compound and washed with methyl isobutyl ketone and dried to get title compound.

Yield: 21.34 kgs; Purity by HPLC: 99.96%.

We Claim:

1. Crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-*N'*-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a,



Formula-1a

characterized by its powder x-ray diffraction pattern having peaks at 6.6, 7.6, 8.2, 10.0, 10.5, 12.5, 13.3, 15.1, 16.4, 18.2, 19.0, 20.2, 20.6, 21.6, 22.6, 25.1, 26.1, 27.0, 28.1, 29.8 and 32.8 ± 0.2 degrees two theta.

2. Crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluoro phenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a obtained according to claim 1 is further characterized by P-XRD pattern as depicted in figure-1.

3. A process for the preparation of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1, comprising of;
   a) Adding a suitable solvent to crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a,
   b) heating the reaction mixture to a suitable temperature and stirring the reaction mixture,
   c) optionally, filtering the reaction mixture,
   d) adding the obtained filtrate in step-c) to a pre-cooled suitable anti-solvent at suitable temperature,
   e) stirring the reaction mixture,
   f) filtering the precipitated solid and drying to get crystalline form-S of N-(4-(6,7-

dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-di carboxamide (S)-malate compound of formula-1a.

4. The process according to claim 3, wherein, in step-b) the suitable temperature is ranging from ambient temperature to the reflux temperature of the solvent used in the reaction;
in step-d) the suitable anti-solvent is selected from chloro solvents and hydrocarbon solvents; the suitable temperature is ranging from -10°C to 20°C;
in step-a) and d) the suitable solvent is selected from chloro solvents, alcohol solvents, ester solvents, nitrile solvents, polar aprotic solvents, hydrocarbon solvents, ether solvents, ketone solvents, polar solvents such as water or mixture thereof.

5. A process for the preparation of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of;
   a) Adding a mixture of tetrahydrofuran and water to crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a,
   b) heating the reaction mixture to 60-65°C and stirring the reaction mixture,
   c) filtering the reaction mixture through hyflow bed,
   d) adding the obtained filtrate in step-c) to a pre-cooled dichloromethane at 0-5°C,
   e) stirring the reaction mixture,
   f) filtering the precipitated solid and drying to get crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-di carboxamide (S)-malate compound of formula-1a.

6. A process for the preparation of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of:
   a) Treating N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide hydrochloride salt with a suitable base in a suitable solvent,

b) adding a suitable solvent to the reaction mixture and stirring the reaction mixture,
c) separating both the organic and aqueous layers,
d) optionally treating the organic layer with carbon,
e) optionally filtering the organic layer through hyflow bed,
f) optionally heating the obtained filtrate to a suitable temperature,
g) adding malic acid to the filtrate,
h) adding a suitable anti-solvent to the reaction mixture and stirring the reaction mixture,
i) cooling the reaction mixture to a suitable temperature,
j) filtering the precipitated solid and dried to provide crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

7. The process according to claim 6, wherein, in step-a) the suitable base is selected from organic or inorganic bases; in step-b) the suitable solvent is selected from alcohol solvents, ester solvents, ketone solvents, ether solvents, hydrocarbon solvents, polar aprotic solvents, nitrile solvents, polar solvents like water or mixture thereof;
in step-f) the suitable temperature is ranging from 30°C to reflux temperature of the solvent used; in step-h) the suitable anti-solvent is selected from chloro solvents;
in step-i) the suitable temperature is ranging from 20°C to -20°C.

8. A process for the preparation of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of:
a) Treating N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide hydrochloride salt with aqueous sodium carbonate and water,
b) adding a mixture of ethyl acetate and tetrahydrofuran to the reaction mixture and stirring the reaction mixture,
c) separating both the organic and aqueous layers,
d) treating the organic layer with carbon,
e) filtering the organic layer through hyflow bed,

f) heating the obtained filtrate to 40-45°C,

g) adding malic acid to the filtrate at 40-45°C,

h) adding dichloromethane to the reaction mixture and stirring the reaction mixture at 40-45°C,

i) cooling the reaction mixture to 0-5°C,

j) filtering the precipitated solid and dried to provide crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

9. A process for the preparation of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of:

a) Treating N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide hydrochloride salt with aqueous sodium carbonate and water,

b) adding a mixture of ethyl acetate and tetrahydrofuran to the reaction mixture and stirring the reaction mixture,

c) separating both the organic and aqueous layers,

d) treating the organic layer with carbon,

e) filtering the organic layer through hyflow bed,

f) heating the obtained filtrate to 40-45°C,

g) adding dichloromethane to the reaction mixture and stirring the reaction mixture at 40-45°C,

h) adding malic acid to the filtrate at 40-45°C,

i) cooling the reaction mixture to 0-5°C,

j) filtering the precipitated solid and dried to provide crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

10. A process for the preparation of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of:
    a) Treating N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide hydrochloride salt with aqueous sodium carbonate and water,
    b) adding a mixture of ethyl acetate and tetrahydrofuran to the reaction mixture and stirring the reaction mixture,
    c) separating both the organic and aqueous layers,
    d) treating the organic layer with carbon,
    e) filtering the organic layer through hyflow bed,
    f) adding a mixture of ethyl acetate, tetrahydrofuran and malic acid to the filtrate,
    g) adding dichloromethane to the reaction mixture and stirring the reaction mixture,
    h) cooling the reaction mixture to 0-5°C,
    i) filtering the precipitated solid and dried to provide crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

11. A process for the preparation of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of:
    a) Treating N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide hydrochloride salt with a suitable base in a suitable solvent,
    b) adding a suitable solvent to the reaction mixture and stirring the reaction mixture,
    c) separating both the organic and aqueous layers,
    d) optionally treating the organic layer with carbon,
    e) optionally filtering the organic layer through hyflow bed,
    f) optionally heating the obtained filtrate to a suitable temperature,
    g) adding malic acid to the filtrate,

h) adding the reaction mixture obtained in step-g) to a pre-cooled solvent and stirring the reaction mixture,

i) filtering the precipitated solid and dried to provide crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

12. The process according to claim 11, wherein, in step-a) the suitable base is selected from organic or inorganic bases; in step-b) the suitable solvent is selected from alcohol solvents, ester solvents, ketone solvents, ether solvents, hydrocarbon solvents, polar aprotic solvents, nitrile solvents, polar solvents like water or mixture thereof; in step-h) the suitable solvent is selected from chloro solvents.

13. A process for the preparation of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of:

a) Treating N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide hydrochloride salt with aqueous sodium carbonate in water,

b) adding a mixture of ethyl acetate and tetrahydrofuran to the reaction mixture and stirring the reaction mixture,

c) separating both the organic and aqueous layers,

d) treating the organic layer with carbon,

e) filtering the organic layer through hyflow bed;

f) adding malic acid to the filtrate,

g) adding the reaction mixture obtained in step-f) to a pre-cooled dichloromethane and stirring the reaction mixture at 0-5°C,

h) filtering the precipitated solid and dried to provide crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

14. An improved process for the preparation of N-(4-(6,7-dimethoxyquinolin-4-yloxy) phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of the following steps:
    a) Reacting 1-((4-fluorophenyl)carbamoyl)cyclopropane carboxylic acid compound of formula-2 with chlorinating agent in a suitable solvent to provide 1-(4-fluorophenyl carbamoyl)cyclopropanecarbonylchloride compound of formula-3,
    b) reacting the compound of formula-3 in-situ with 4-(6,7-dimethoxyquinolin-4-yloxy) aniline compound of formula-4 in the presence of a suitable base in a suitable solvent to provide N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide compound of formula-1,
    c) treating the compound of formula-1 in-situ with a suitable hydrochloric acid source in a suitable solvent to provide N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b,
    d) purifying the compound of formula-1b using a suitable solvent,
    e) treating the compound of formula-1b with a suitable base in a suitable solvent to provide N-(4-[(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide compound of formula-1 which on in-situ treating with (L)-malic acid in a suitable solvent to provide N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

15. The process according to claim 14, wherein, in step-a) the suitable chlorinating agent is selected from pivaloyl chloride, thionyl chloride, sulfuryl chloride, phosphorusoxy chloride, oxalyl chloride, phosphorus trichloride, phosphorus pentachloride;
in step-b) & step-e) the suitable base is selected from inorganic or organic bases;
in step-c) the suitable hydrochloric acid source is selected from hydrochloric acid gas, aqueous hydrochloric acid, ethanolic-HCl, methanolic-HCl, ethyl acetate-hydrochloric acid, isopropanol-hydrochloric acid, diisopropyl ether-hydrochloric acid, diethylether-hydrochloric acid, and trimethyl chloro silane; in step-a) to step-e) the suitable solvent is selected from chloro solvents, alcohol solvents, ester solvents, nitrile solvents, polar

aprotic solvents, hydrocarbon solvents, ether solvents, ketone solvents, polar solvents such as water or mixtures thereof.

16. An improved process for the preparation of N-(4-(6,7-dimethoxyquinolin-4-yloxy) phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of the following steps:
    a) Reacting 1-((4-fluorophenyl)carbamoyl)cyclopropane carboxylic acid compound of formula-2 with thionyl chloride in tetrahydrofuran to provide 1-(4-fluorophenyl carbamoyl)cyclopropanecarbonylchloride compound of formula-3,
    b) reacting the compound of formula-3 in-situ with 4-(6,7-dimethoxyquinolin-4-yloxy) aniline compound of formula-4 in the presence of potassium carbonate in a mixture of water and tetrahydrofuran to provide N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide compound of formula-1,
    c) treating the compound of formula-1 in-situ with aqueous hydrochloric acid to provide N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b,
    d) purifying the compound of formula-1b using isopropanol and then followed by using dimethyl sulfoxide and ethyl acetate,
    e) treating the compound of formula-1b with aqueous sodium carbonate solution to provide N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide compound of formula-1 which on in-situ treating with (L)-malic acid in a mixture of tetrahydrofuran, water and methyl isobutyl ketone to provide N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide (S)-malate compound of formula-1a.

17. Crystalline forms of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide hydrochloride salt, which includes:
    a) Crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluoro phenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, characterized by its powder x-ray diffraction pattern having peaks at 6.4, 7.8, 8.6, 9.5,

10.4, 10.8, 12.0, 12.7, 13.4, 14.7, 16.0, 17.2, 17.5, 18.6, 20.2, 20.8, 21.5, 22.1, 22.7, 23.2, 24.1, 26.5, 26.8 and 27.2 ± 0.2 degrees two theta as depicted in figure-1.

b) Crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluoro phenyl)cyclopropane-1,1-dicarboxamide hydrochloric acid salt compound of formula-1b, characterized by its powder x-ray diffraction pattern having peaks at 5.1, 6.5, 7.9, 8.6, 9.7, 10.5, 12.8, 13.4, 15.2, 16.1, 17.2, 17.9, 18.5, 19.1, 19.4, 20.4, 20.9, 22.0, 23.0, 23.7, 24.8, 26.8, 28.4, 29.1, 29.8 and 40.6 ± 0.2 degrees two theta as depicted in figure-2.

c) Crystalline form-N of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluoro phenyl)cyclopropane-1,1-dicarboxamide hydrochloric acid salt compound of formula-1b, characterized by its powder x-ray diffraction pattern having peaks at 4.0, 5.1, 6.3, 7.5, 8.0, 8.6, 9.4, 10.5, 11.2, 11.8, 12.6, 13.3, 13.5, 15.0, 15.3, 16.0, 16.3, 17.5, 17.9, 18.9, 19.9, 20.5, 21.2, 22.3, 22.7, 23.2, 23.8, 25.8, 26.4 and 27.4 ± 0.2 degrees two theta as depicted in figure-3.

d) Crystalline form-R of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluoro phenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, characterized by its powder x-ray diffraction pattern having peaks at 8.5, 9.3, 10.5, 11.6, 11.8, 12.1, 12.5, 12.9, 13.2, 13.7, 14.5, 15.5, 16.1, 16.8, 17.2, 17.6, 17.8, 19.3, 19.7, 20.0, 20.4, 21.3, 21.8, 22.2, 22.7, 23.2, 23.7, 24.0, 25.2, 25.7, 25.9, 27.0, 27.4, 27.6, 28.5, 30.0, 30.6, 31.9 and 32.3 ±0.2 degrees two theta as depicted in figure-4.

18. Crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluoro phenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, characterized by its powder x-ray diffraction pattern having peaks at 7.0, 7.4, 7.8, 9.4, 11.0, 11.4, 11.9, 12.6, 13.6, 14.0, 15.4, 15.6, 16.1, 17.2, 18.4, 19.2, 19.9, 21.1, 21.8, 22.1, 22.4, 23.1, 24.0, 24.2, 25.8, 26.2, 27.1, 27.6, 28.9, 29.3, 29.9, 30.1, 31.6, 32.5, 33.8, 35.3, 36.8, 37.6 and 39.9 ±0.2 degrees two theta as depicted in figure-5.

19. A process for the preparation of crystalline form-M of N-(4-((6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, comprising of:

a) Adding a suitable solvent to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt of compound of formula-1b,
b) stirring the reaction mixture for 3 hours at 25-30°C,
c) filtering the reaction mixture and drying to get crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b.

20. The process according to claim 19, wherein, in step-a) the suitable solvent is selected from chloro solvents, alcohol solvents, ester solvents, nitrile solvents, polar aprotic solvents, hydrocarbon solvents, ether solvents, ketone solvents, polar solvents such as water or mixtures thereof.

21. A process for the preparation of crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, comprising of:
a) Adding isopropanol to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluoro phenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt of compound of formula-1b,
b) stirring the reaction mixture for 3 hours at 25-30°C,
c) filtering the reaction mixture and drying to get crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b.

22. A process for the preparation of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, comprising of the following steps:
a) Adding a suitable solvent to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride compound of formula-1b,
b) stirring the reaction mixture and filtering the reaction mixture,

c) adding a suitable solvent to the filtrate obtained in step-b),

d) stirring the reaction mixture and filtering the precipitated solid to get the crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide hydrochloride salt compound of formula-1b.

23. The process according to claim 22, wherein, in step-a) the suitable solvent is selected from chloro solvents, alcohol solvents, nitrile solvents, polar aprotic solvents, hydrocarbon solvents, ether solvents, ketone solvents, polar solvents such as water or mixtures; in step-c) the suitable solvent is selected from ester solvents.

24. A process for the preparation of crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, comprising of the following steps:

a) Adding dimethylsulfoxide to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride compound of formula-1b,

b) stirring the reaction mixture and filtering the reaction mixture,

c) adding ethyl acetate to the filtrate obtained in step-b),

d) stirring the reaction mixture and filtering the precipitated solid to get the crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide hydrochloride salt compound of formula-1b.

25. A process for the preparation of crystalline form-N of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, comprising of:

a) Adding a suitable solvent to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt of compound of formula-1b,

b) stirring the reaction mixture and filtering the reaction mixture to get crystalline form-N of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b.

26. The process according to claim 25, wherein, in step-a) the suitable solvent is selected from chloro solvents, alcohol solvents, ester solvents, nitrile solvents, polar aprotic solvents, hydrocarbon solvents, ether solvents, ketone solvents, polar solvents such as water or mixtures.

27. A process for the preparation of crystalline form-N of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, comprising of:
    a) Adding isopropanol to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluoro phenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt of compound of formula-1b,
    b) stirring the reaction mixture for 5 hours and filtering the reaction mixture to get crystalline form-N of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluoro phenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b.

28. A process for the preparation of crystalline form-R of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, comprising of the following steps:
    a) Adding a suitable solvent to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide compound of formula-1,
    b) adding suitable hydrochloric acid source to the reaction mixture,
    c) stirring the reaction mixture and filtering the reaction mixture,
    d) adding a suitable solvent to the compound obtained in step-c),
    e) stirring the reaction mixture and filtering the reaction mixture to get the crystalline form-R of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide hydrochloride salt compound of formula-1b.

29. The process according to claim 28, wherein, in step-a) the suitable solvent is selected from chloro solvents, ester solvents, nitrile solvents, polar aprotic solvents, hydrocarbon solvents, ether solvents, ketone solvents, polar solvents such as water or mixtures;

in step-b) the suitable hydrochloric acid source is selected from hydrochloric acid gas, aqueous hydrochloric acid, ethanolic-HCl, ethyl acetate-hydrochloric acid, methanolic-HCl, isopropanol-hydrochloric acid, diisopropyl ether-hydrochloric acid, diethylether-hydrochloric acid, and trimethylchlorosilane; in step-d) the suitable solvent is selected from alcohol solvents.

30. A process for the preparation of crystalline form-R of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b, comprising of the following steps:
    a) Adding a mixture of tetrahydrofuran and ethyl acetate to N-(4-(6,7-dimethoxy quinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide compound of formula-1,
    b) adding aqueous hydrochloric acid to the reaction mixture,
    c) stirring the reaction mixture and filtering the reaction mixture,
    d) adding isopropanol to the compound obtained in step-c),
    e) stirring the reaction mixture and filtering the reaction mixture to get the crystalline form-R of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclo propane-1,1-dicarboxamide hydrochloride salt compound of formula-1b.

31. A process for the purification of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide compound of formula-1, comprising of treating the compound of formula-1 with a suitable acid in a suitable solvent to provide its corresponding acid addition salt of compound of formula-1 and further neutralizing the acid addition salt of compound of formula-1 with a suitable base in a suitable solvent to provide pure compound of formula-1.

32. The process according to claim 31, wherein the suitable acid is selected from inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or phosphoric acid; and organic acids such as oxalic acid, maleic acid, malonic acid, tartaric acid, fumaric acid, citric acid, malic acid, succinic acid, mandelic acid, lactic acid, acetic acid, propionic acid, 2-chloromandelate, p-toluene sulfonic acid, ethane-1,2-disulfonic acid,

camphor sulfonic acid, ethane sulfonic acid, methane sulfonic acid, naphthalene-2-sulfonic acid, benzene sulfonic acid, adipic acid, glutaric acid, glutamic acid, palmitic acid or aspartic acid; the suitable solvent is selected from chloro solvents, ether solvents, alcohol solvents, ester solvents, nitrile solvents, polar aprotic solvents, hydrocarbon solvents, polar aprotic solvents, ketone solvents, polar solvents such as water or mixtures; the suitable base is selected from a group consisting of alkali metal carbonates like sodium carbonate, lithium carbonate, potassium carbonate; or an alkali metal hydroxide like sodium hydroxide, potassium hydroxide, lithium hydroxide; or alkali metal bicarbonates like sodium bicarbonate, potassium bicarbonate; or an organic base like triethylamine, tributylamine, diisopropylethylamine.

33. A process for the preparation of crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of the following steps:
    a) Adding a suitable solvent to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide compound of formula-1,
    b) heating the reaction mixture to a suitable temperature,
    c) adding (L)-malic acid to the reaction mixture,
    d) stirring the reaction mixture,
    e) cooling the reaction mixture to a suitable temperature and stirring the reaction mixture,
    f) filtering the precipitated solid to get the crystalline form-M of N-(4-(6,7-dimethoxy quinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

34. The process according to claim 33, wherein, in step-a) the suitable solvent is selected from chloro solvents, alcohol solvents, ester solvents, nitrile solvents, polar aprotic solvents, hydrocarbon solvents, ether solvents, ketone solvents, polar solvents such as water or mixtures; in step-b) the suitable temperature is ranging from 30°C to reflux temperature of the solvent used in the reaction; in step-e) the suitable temperature is ranging from -50°C to 0°C.

35. A process for the preparation of crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of the following steps:
    a) Adding xylene to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluoro phenyl)cyclopropane-1,1-dicarboxamide compound of formula-1,
    b) heating the reaction mixture to 70-75°C,
    c) adding (L)-malic acid to the reaction mixture,
    d) stirring the reaction mixture,
    e) cooling the reaction mixture to -50°C and stirring the reaction mixture,
    f) filtering the precipitated solid to get the crystalline form-M of N-(4-(6,7-dimethoxy quinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

36. A process for the preparation of crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of the following steps:
    a) Adding n-heptane to N-{4-[(6,7-dimethoxyquinolin-4-yloxy]phenyl}-N'-(4-fluoro phenyl)cyclopropane-1,1-dicarboxamide compound of formula-1,
    b) heating the reaction mixture to 65-70°C,
    c) adding (L)-malic acid to the reaction mixture,
    d) stirring the reaction mixture,
    e) cooling the reaction mixture to -50°C and stirring the reaction mixture,
    f) filtering the precipitated solid to get the crystalline form-M of N-(4-(6,7-dimethoxy quinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

37. A process for the preparation of crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of the following steps:
    a) Adding methyl tert-butyl ether to N-{4-[(6,7-dimethoxyquinolin-4-yloxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide compound of formula-1,

b) heating the reaction mixture to 50-55°C,

c) adding (L)-malic acid to the reaction mixture,

d) stirring the reaction mixture,

e) cooling the reaction mixture to -50°C and stirring the reaction mixture,

f) filtering the precipitated solid to get the crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

38. A process for the preparation of crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a, comprising of the following steps:

a) Adding toluene to N-(4-(6,7-dimethoxyquinolin-4-yl oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide compound of formula-1,

b) heating the reaction mixture to 70-75°C,

c) adding (L)-malic acid to the reaction mixture,

d) stirring the reaction mixture,

e) cooling the reaction mixture to -50°C and stirring the reaction mixture,

f) filtering the precipitated solid to get the crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a.

39. N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a having purity greater than 99.5%; preferably 99.75%; most preferably 99.9% by HPLC.

40. Crystalline form-S and form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a are useful in the preparation of pharmaceutical composition.

41. Crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a according to the preceding claims having purity greater than 99.5%; preferably 99.75% by HPLC.

42. Crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a obtained according to the preceding claims having particle size distribution of D_{90} < 150 µm, preferably < 100 µm; more preferably < 50 µm.

43. Use of crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluoro phenyl)cyclopropane-1,1-dicarboxamide (S)-malate in the preparation of crystalline form-S of compound of formula-1a.

44. N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a obtained according to the preceding claims having particle size distribution of D_{90} < 150 µm, preferably < 100 µm; more preferably < 50 µm.

45. N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (S)-malate compound of formula-1a obtained according to the preceding claims having M-acid impurity; acid impurity; hydroxy impurity; desfluoro impurity; 2-fluoro impurity; N-oxide impurity; 3-fluoro impurity; and dimer impurity less than 0.04% as measured by HPLC.

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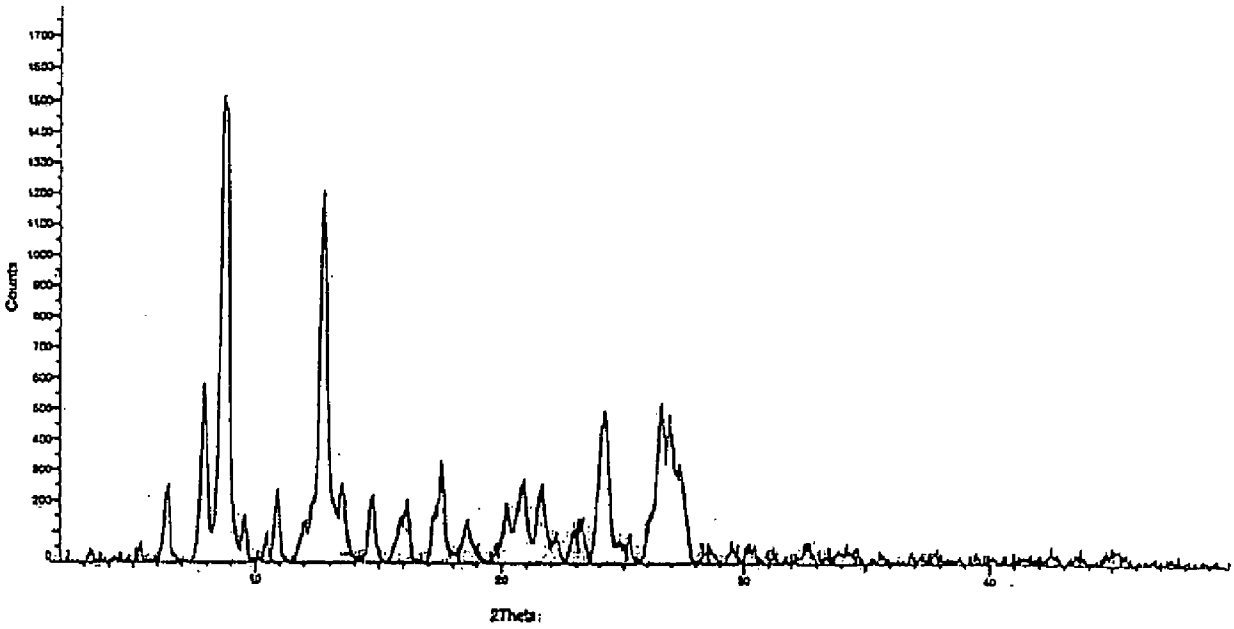

Figure-1

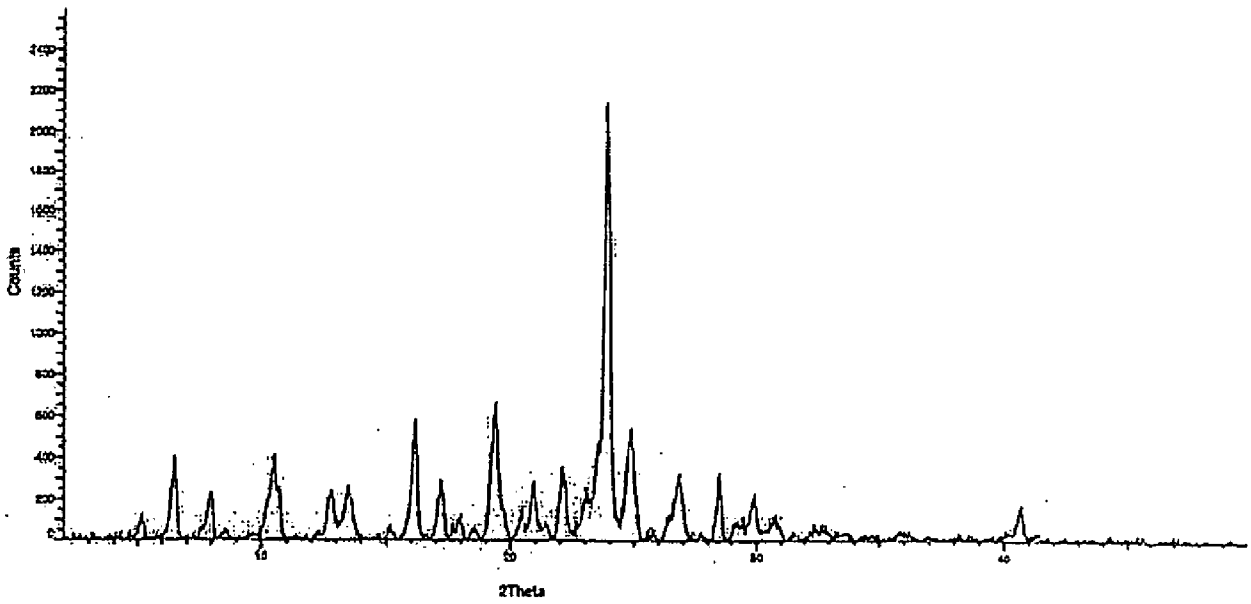

Figure-2

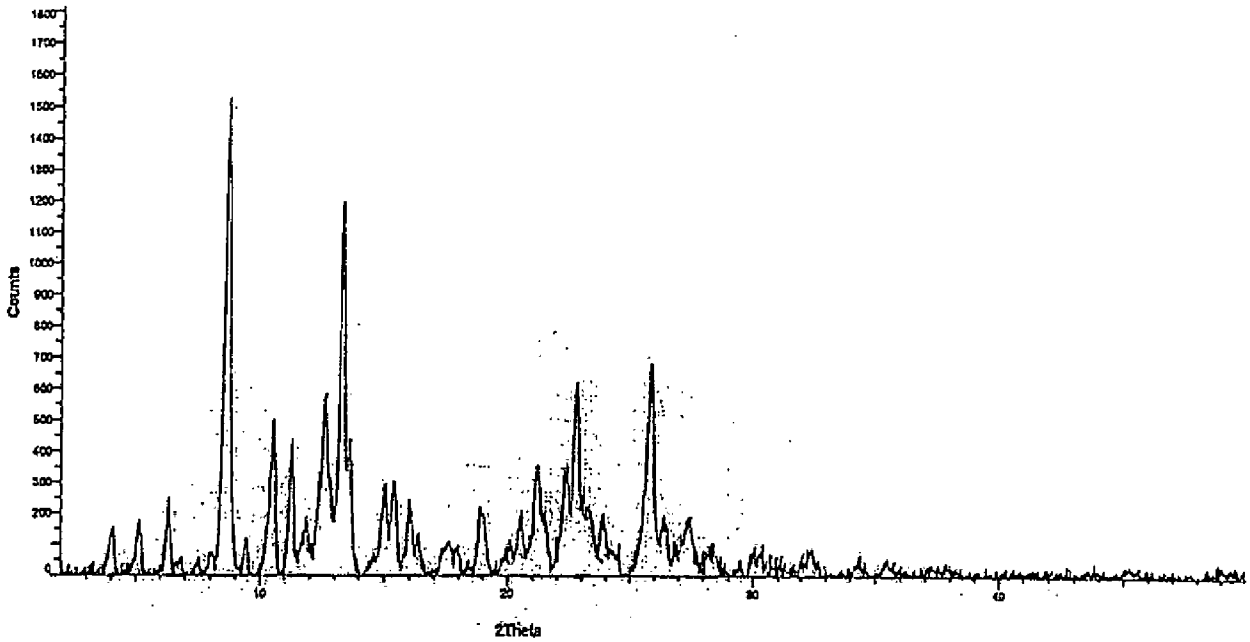

Figure-3

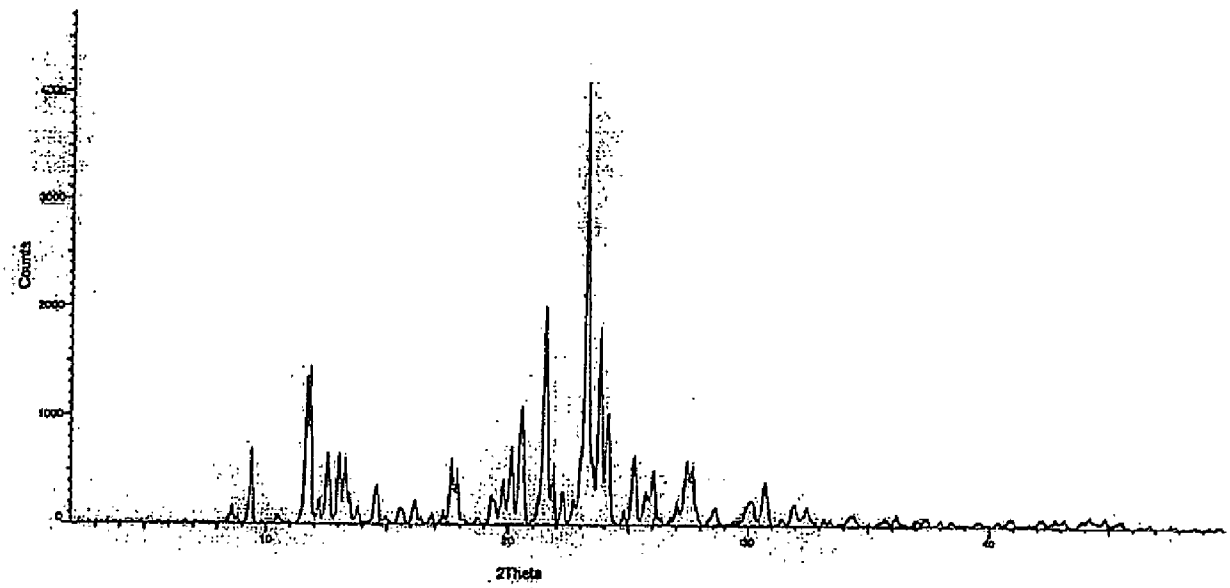

Figure-4

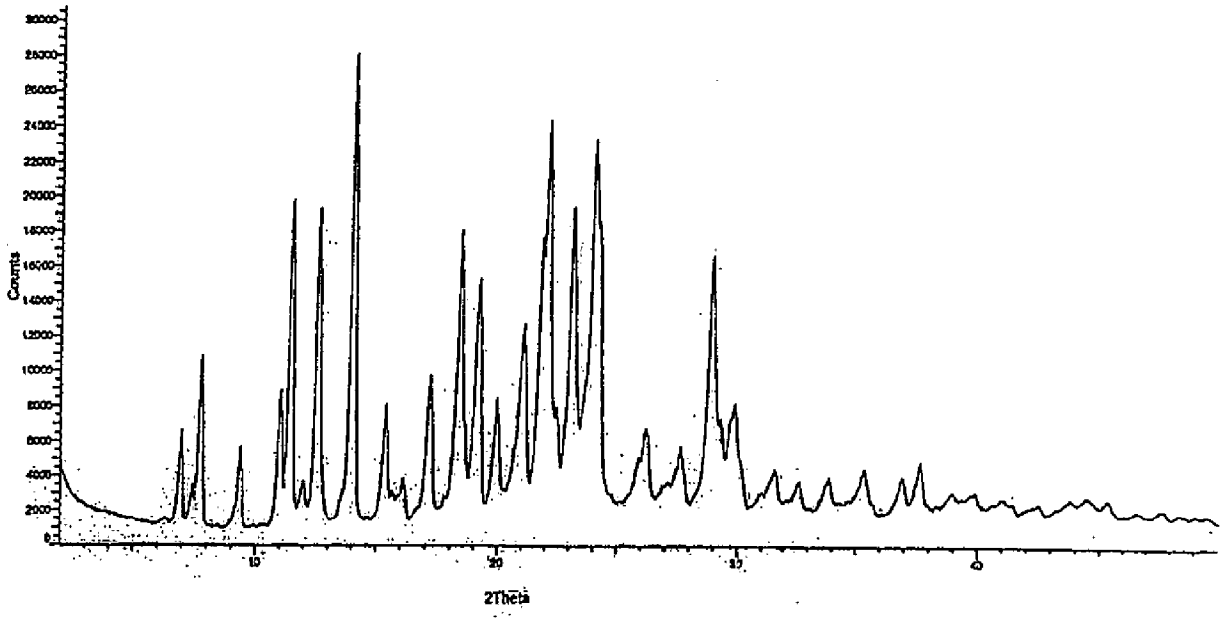

Figure-5

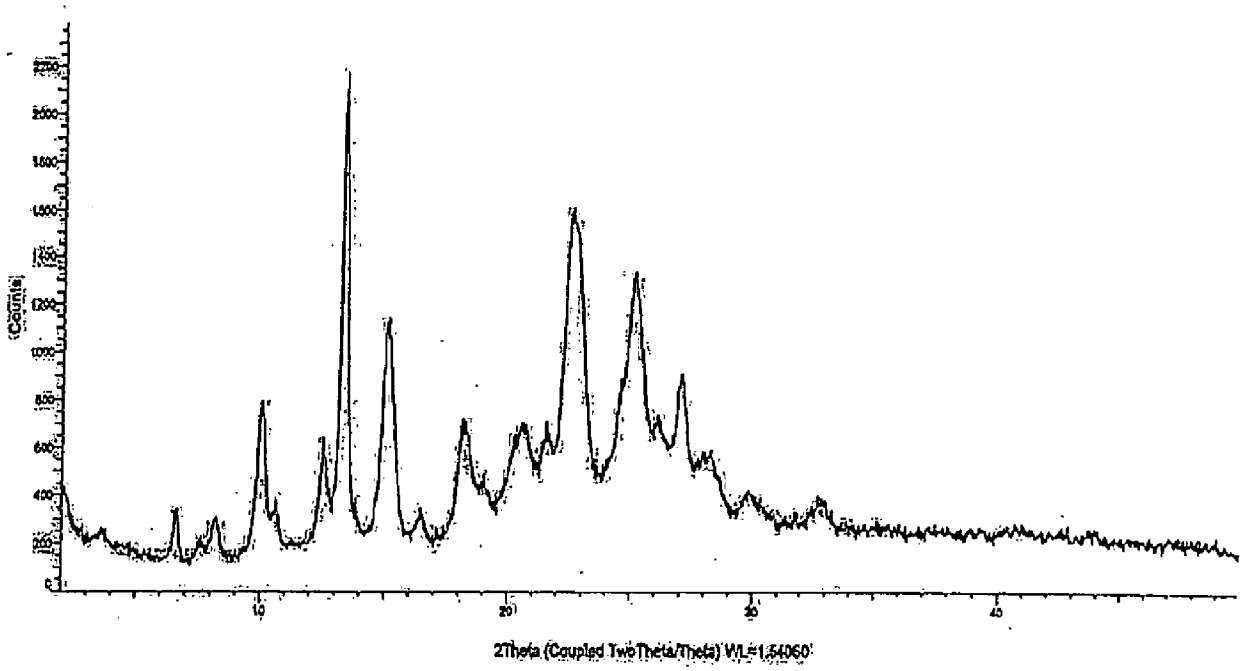

Figure-6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2017/000139

A. CLASSIFICATION OF SUBJECT MATTER
C07D215/233,A61K31/47 Version=2018.01

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D, A61K

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO2015/177758 A1 (MYLAN LABORATORIES LTD.[IN])26 November 2015 (26-11-2015) page 7, line 18-19; page 18, line 17-21	1-2 (part), 40(part)
X	WO2015/177758 A1 (MYLAN LABORATORIES LTD.[IN])26 November 2015 (26-11-2015) page-19, example 2, 3	3-5, 41-42

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12-03-2018	12-03-2018

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2017/000139

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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

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

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

This International Searching Authority found multiple inventions in this international application, as follows:
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Group I: Claims 1-2(part), 3-5, 40 (part), 41-42

The subject matter of these claims relates to Crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1- dicarboxamide (S)-malate compound of Formula-Ia and process [via the steps (a)- (f)] for preparing, purity, particle

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

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

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

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-2(part), 3-5, 40 (part), 41-42

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

Continuation of Observations where unity of invention is lacking(Box III)

size of the same.

Group II: Claims 1-2(part), 6-9

The subject matter of these claims relate to Crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1- dicarboxamide(S)-malate compound of Formula-1a, and process [via the steps (a)- (j)] for preparing the same.

Group III: Claims 1-2(part), 10-13

The subject matter of these claims relates to Crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1- dicarboxamide(S)-malate compound of Formula-1a, and another process [via the steps (a)- (i)] for preparing the same.

Group IV: Claims 14-16, 39, 44, 45

The subject matter of these claims relates to improved process for the preparation of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1- dicarboxamide(S)-malate compound of Formula-1a [via the steps (a)- (e)].

Group V: Claims 17 (part), 19-21

The subject matter of these claims relates to crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1- dicarboxamide hydrochloride salt compound of formula-1b and process for preparing the same.

Group VI: Claims 18, 33-38, 40(part), 43

The subject matter of these claims relates to crystalline form-M of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1- dicarboxamide (S)-malate compound of formula-1a, preparation of the same and use of the same compound.

Group VII: Claims 17 (part), 22-24

The subject matter of these claims relates to crystalline form-S of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1- dicarboxamide hydrochloride salt compound of formula-1b and process for preparing the same.

Group VIII: Claims 17 (part), 25-27

The subject matter of these claims relates to process for the preparation of crystalline form-N of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1- dicarboxamide hydrochloride salt compound of formula-1b and process for preparing the same.

Group IX: Claims 17 (part), 28-30

The subject matter of these claims relates to Crystalline form-R of N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluoro phenyl)cyclopropane-1,1-dicarboxamide hydrochloride salt compound of formula-1b and process for preparing the same.
Group X: Claims 31-32

The subject matter of these claims relates to processing for purification of
N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide compound
of formula-1.

These ten different inventions are related to N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1- dicarboxamide (Cabozantinib) and their different crystalline forms, salts and their preparations thereof. The common technical feature the compound Cabozantinib is already known from the Document WO2015/177758 A1 and the various crystalline forms of the compound of Cabozantinib salts and their preparation are also well known from the cited Document. Hence, this common technical feature could not be served as a special technical feature among these ten groups. Further, there is no other special technical feature which co-relates these ten groups of inventions. Hence, the international application does not comply with the requirement of unity of invention (Rules 13.1, 13.2 and 13.3).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2017/000139

Citation	Pub.Date	Family	Pub.Date
WO 2015/177758 A1	26-11-2015	IN 2561/CHE/2014 A	15-01-2016
		EP 3145913 A1	29-03-2017
		US 2017096395 A1	06-04-2017