



(51) International Patent Classification:

A61K 31/519 (2006.01) C07D 487/04 (2006.01)
C07D 401/04 (2006.01) C07D 211/56 (2006.01)

(21) International Application Number:

PCT/IN2016/000106

(22) International Filing Date:

22 April 2016 (22.04.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

2055/CHE/2015 22 April 2015 (22.04.2015) IN

(71) Applicants: **MSN LABORATORIES PRIVATE LIMITED** [IN/IN]; SY. No. 317 & 323, Rudraram (Vil), Patancheru (Mdl), Medak (Dist), Hyderabad, Telangana (IN). **MADHUSUDHAN, Gutta** [IN/IN]; SY. No. 317 & 323, Rudraram (Vil), Patancheru (Mdl), Medak (Dist), Hyderabad, Telangana (IN). **SEETHA RAMA SARMA, Peri** [IN/IN]; SY. No. 317 & 323, Rudraram (Vil), Patancheru (Mdl), Medak (Dist), Hyderabad, Telangana (IN).

(72) Inventors; and

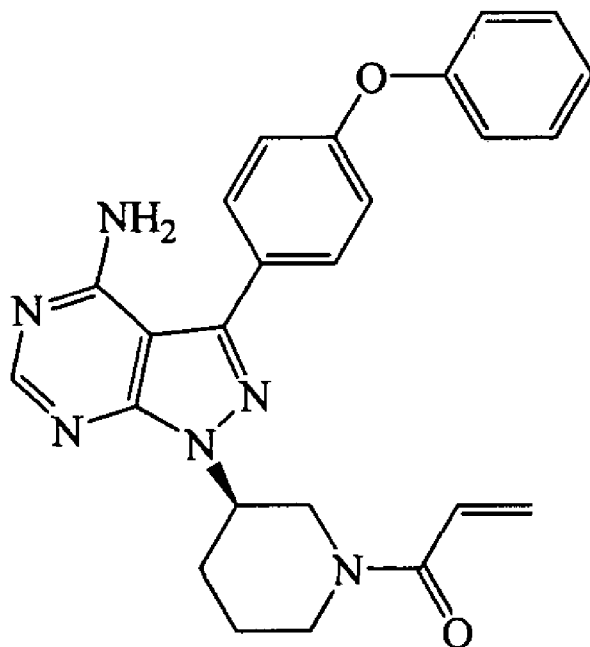
(71) Applicants : **THIRUMALAI RAJAN, Srinivasan** [IN/IN]; SY. No. 317 & 323, Rudraram (Vil), Patancheru (Mdl), Medak (Dist), Hyderabad, Telangana (IN). **ESWARAIAH, Sajja** [IN/IN]; SY. No. 317 & 323, Rudraram (Vil), Patancheru (Mdl), Medak (Dist), Hyderabad, Telangana (IN).

(74) Agent: **THIRUMALAI, RAJAN, Srinivasan**; SY. No. 317 & 323, Rudraram (Vil), Patancheru (Mdl), Medak (Dist), Hyderabad, Telangana (IN).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

[Continued on next page]

(54) Title: PROCESS FOR THE PREPARATION OF 1-[(3R)-3-[4-AMINO-3-(4-PHENOXYPHENYL)-1H-PYRAZOLO[3,4-D]PYRIMIDIN-1-YL]-1-PIPERIDINYL]-2-PROPEN-1-ONE AND ITS POLYMORPHS THEREOF



Formula-1

(57) Abstract: The present invention relates to an improved process for the preparation of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula- 1 and its polymorphs thereof, which is represented by the following structural formula:



(84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

Process for the preparation of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one and its polymorphs thereof

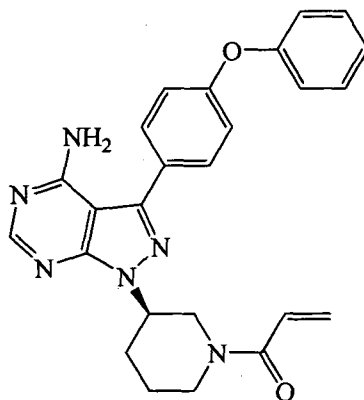
5 Related Applications:

This application claims the benefit of priority of our Indian patent application number 2055/CHE/2015 filed on 22nd Apr. 2015 which is incorporated herein by reference.

Field of the invention:

10

The present invention relates to an improved process for the preparation of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, which is represented by the following structural formula:



15

Formula-1

Further, the present invention also provides an improved process for the preparation of amorphous, crystalline Form-C and crystalline Form-A of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1.

20

Background of the invention:

1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one is commonly known as Ibrutinib. Ibrutinib is marketed

under the brand name Imbruvica by Pharmacyclics Inc. It is approved in United States as Ibrutinib on 12th Feb 2014. Ibrutinib is indicated for the treatment of patients with Mantle cell lymphoma (MCL) who have received at least one prior therapy, Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

5 US pat. No. 7,514,444 first discloses 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one, its pharmaceutically acceptable salts and process for the preparation thereof. Further the obtained compound of formula-1 was purified by flash chromatography provides amorphous compound, which is a laborious and time consuming process.

10 US2013338172 describes the process for the preparation of crystalline forms-A, B, C & D of the compound of formula-1.

Hence, there is a need in the art to develop an improved, economical viable and efficient, simple process for the preparation of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1 with
15 high yield and purity.

The present invention relates to an improved, economical viable and efficient, simple process for the preparation of amorphous form of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1 with high yield and purity. The present invention also provides a process for the preparation
20 of amorphous, crystalline form-C & crystalline form-A of the compound of formula-1 with high yield and purity.

Brief description of the invention:

The first aspect of the present invention is to provide a process for the preparation of
25 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1.

The second aspect of the present invention is to provide a process for the preparation of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13.

30 The third aspect of the present invention is to provide a crystalline form of (S)-tert-

butyl-3-(tosyloxy)piperidine-1-carboxylate compound of formula-11a, hereinafter designated as crystalline form-M and its process for the preparation.

The fourth aspect of the present invention is to provide a crystalline form of (S)-tert-butyl-3-((methylsulfonyl)oxy)piperidine-1-carboxylate compound of formula-11b, herein
5 after designated as crystalline form-S and its process for the preparation.

The fifth aspect of the present invention is to provide a crystalline form of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13, herein after designated as crystalline form-N and its process for the preparation.

10 The sixth aspect of the present invention is to provide an alternate process for the preparation of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1.

The seventh aspect of the present invention is to provide another alternative process for the preparation of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]
15 pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1.

The eighth aspect of the present invention is to provide a process for the preparation of amorphous form of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1.

The ninth aspect of the present invention is to provide an improved process for the
20 preparation of 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine compound of formula-9.

The tenth aspect of the present invention is to provide an improved process for the preparation of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1.

25 The eleventh aspect of the present invention is to provide a process for the preparation of amorphous 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1.

The twelfth aspect of the present invention is to provide a process for the preparation of crystalline form-C of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]
30 pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1.

The thirteenth aspect of the present invention is to provide a process for the preparation of crystalline form-A of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1.

5 Brief description of Drawings:

Figure-1: Illustrates the PXRD pattern of crystalline form-M of (S)-tert-butyl-3-(tosyloxy)piperidine-1-carboxylate compound of formula-11a.

Figure-2: Illustrates the PXRD pattern of crystalline form-S of (S)-tert-butyl-3-((methylsulfonyl)oxy)piperidine-1-carboxylate compound of formula-11b.

10 **Figure-3:** Illustrates the PXRD pattern of crystalline form-N of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13.

Figure-4: Illustrates the PXRD pattern of amorphous form of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one

15 compound of formula-1.

Detailed description of the invention:

The term "suitable solvent" used in the present invention refers to "hydrocarbon solvents" such as n-hexane, n-heptane, cyclohexane, pet.ether, benzene, toluene, pentane, 20 cycloheptane, methylcyclohexane, ethylbenzene, m-, o-, or p-xylene, octane, indane, nonane, or naphthalene and the like; "ether solvents" such as dimethoxymethane, 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 25 solvents" such as methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, n-butyl acetate, isobutylacetate and the like; "polar-aprotic solvents such as dimethylacetamide, dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone 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; 30 "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, 2-methoxyethanol, 1-ethoxyethanol, 2-ethoxyethanol, diethylene glycol, 1-pentanol, 2-pentanol, 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monoethyl ether, cyclohexanol, benzyl alcohol, phenol, or glycerol and the like; "polar solvents" such as water or mixtures thereof.

The term "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, cesium carbonate and the like; "alkali metal bicarbonates" such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, cesium bicarbonate and the like; "alkali metal hydrides" such as sodium hydride, potassium hydride, lithium hydride and the like; "alkali metal alkoxides" such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium methoxide, potassium ethoxide, potassium tert-butoxide and the like; ammonia; and organic bases such as 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 diisopropylamide (LDA), n-butyl lithium, tribenzylamine, isopropyl amine, diisopropylamine, diisopropylethylamine, N-methylmorpholine, N-ethylmorpholine, piperidine, dimethylaminopyridine, morpholine, pyridine, 2,6-lutidine, 2,4,6-collidine, imidazole, 1-methylimidazole, 1,2,4-triazole, 1,4-diazabicyclo[2.2.2]octane (DABCO) or mixtures thereof.

The term "acid" used in the present invention refers to inorganic acid selected from hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, sulfamic acid and the like; organic acid such as formic acid, acetic acid, trifluoro acetic acid, methane sulfonic acid, ethane sulfonic acid, benzene sulfonic acid, trifluoromethane sulfonic acid, p-toluene sulfonic acid, tartaric acid, mandelic acid, malic acid, maleic acid, succinic acid, malonic acid, oxalic acid, dibenzoyl tararic acid, lactic acid, cinnamic acid and the like.

The "suitable oxidizing agent" used herein the present invention is selected from peroxides such as oxygen, oxygen/Pt, ozone, hydrogen peroxide, hydrogen peroxide/HCl in presence of hydroxyl amine hydrochloride, peroxydisulfuric acid, peroxymono sulfuric acid; nascent oxygen, chlorite, chlorate, perchlorates of alkali and alkaline earth metals such as

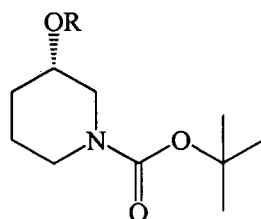
sodium chlorite, sodium chlorate, sodium hypochlorite, calcium chlorite, sodium chlorite/H₂O₂, calcium hypochlorite and the like; oxalyl chloride in combination with dimethyl sulfoxide, trichloroisocyanuric acid in combination with TEMPO, nitric acid, silver nitrate, potassium nitrate, silver oxide, copper (II) oxide, sodium perborate, hypochlorous acid, tollen's reagent (silver nitrate/ammonia), lithium bromide/ triethylamine, Br₂/sodium acetate/ acetic acid; hexavalent chromium compounds such as chromic and dichromic acids and chromium trioxide, chromium trioxide/H₂SO₄ pyridinium chlorochromate (PCC), chromyl chlorite, chromate/dichromate compounds such as potassium dichromate, sodium dichromate, sodium dichromate optionally in presence of sulfuric acid; permanganate compounds such as potassium permanganate and the like; manganate compounds such as potassium manganate and the like; peracids such as perbenzoic acid, Peroxy acetic acid, m-chloroperbenzoic acid, trifluoro peracetic acid and the like; chromium complexes such as (1,10-phenonthrolin)H₂CrOCl₅ (1,10-phenonthrolin) CrOCl₃, (α, α'-bipyridyl) H₂CrOCl₅, (α, α'-bipyridyl) CrOCl₃ and other well-known oxidizing agents that will convert aldehydes into carboxylic acids.

The term "suitable methylating agent" is selected from methyl halides such as methyl chloride, methyl bromide, methyl iodide optionally in presence of silver oxide; dimethylsulfate, trimethylsilyldiazomethane, dimethylsulfoxide, methyl trifluoromethane sulfonate, methyl p-toluene sulphonate, Trimethyloxonium tetrafluoroborate, trimethyl phosphate, dimethylcarbonate optionally in presence of a base such as DBU (or) DABCO and/or dimethylaminopyridine and formaldehyde/formic acid and all other known methylating agents which are suitable for the conversion of alcohols into its methyl ether compound.

The term "Boc-protecting agent" refers to a protecting agent which is useful to protecting the tert-butoxycarbonyl group (BOC group). The suitable Boc-protecting agent is selected from dry HCl, methanolic-HCl, ethylacetate in hydrochloric acid, isopropyl alcohol in hydrochloric acid, hydrochloric acid in ether and the like.

The first aspect of the present invention provides a process for the preparation of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidiny]-2-propen-1-one compound of formula-1, comprising of:

- a) Reacting 4-fluorobenzaldehyde compound of formula-2 with phenol compound of formula-3 in presence of a base in a suitable solvent to provide 4-phenoxybenzaldehyde compound of formula-4,
- b) oxidizing compound of formula-4 with a suitable oxidizing agent optionally in presence of an acid in a suitable solvent to provide 4-phenoxybenzoic acid compound of formula-5,
- c) converting the compound of formula-5 into its derivative such as acid chloride or acid anhydride or ester by using a suitable agent in presence or absence of a solvent,
- d) reacting the compound obtained in step-(c) with malononitrile in presence of a base in a suitable solvent provides 2-(hydroxy(4-phenoxyphenyl)methylene) malononitrile compound of formula-6,
- e) methylating compound of formula-6 with a suitable methylating agent optionally in presence of a base in a suitable solvent provides 2-(methoxy(4-phenoxyphenyl)methylene)malononitrile compound of formula-7,
- f) reacting compound of formula-7 with hydrazine hydrate in a suitable solvent provides 3-amino-5-(4-phenoxyphenyl)-1H-pyrazole-4-carbonitrile compound of formula-8,
- g) reacting compound of formula-8 with formamide in a suitable solvent provides 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine compound of formula-9,
- h) reacting the compound of formula-9 with compound of general formula-11



Formula-11

wherein, 'R' represents methanesulfonyl group or p-toluene sulfonyl group,

in presence of a base in a suitable solvent to provide (R)-tert-butyl 3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate compound of formula-12,

5 i) treating the compound of formula-12 with a suitable Boc-deprotecting agent in a suitable solvent provides (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo [3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13,

j) treating the compound of formula-13 with a base in a suitable solvent, followed by treating the obtained compound with acryloyl chloride in presence of a base in a suitable solvent provides 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1.

10 wherein,

in step-a) the suitable base is inorganic base or organic base,

in step-b) the suitable acid is selected from inorganic acid,

in step-c) the conversion of compound of formula-5 into its derivative such as acid chloride

15 or acid anhydride or ester by treating it with a suitable agent selected from thionyl chloride, phosphorous trichloride, phosphorous penta chloride, oxalyl chloride, pivaloyl chloride, alkyl or aryl chloroformates such as methyl chloroformate, ethyl chloroformate, isobutyl chloroformate, isopropenyl chloroformate, phenyl chloroformate, benzyl chloroformate, p-nitrophenyl chloroformate and the like, 20 alcohols such as methanol, ethanol, propanol, isopropanol, butanol, isobutanol, pentanol, n-hexanol and the like,

in step-d) the base is organic base,

in step-e) & step-h) the base is inorganic base,

in step-j) the base is inorganic base or organic base,

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

The compound of general formula-11 (wherein, 'R' represents methane sulfonyl group or p-toluene sulfonyl group) used herein the present invention can be prepared from (S)-tert-butyl-3-hydroxypiperidine-1-carboxylate by treating it with methane sulfonyl chloride or p-

toluene sulfonyl chloride in presence of a base such as inorganic base or organic base in a suitable solvent.

In the above aspect, the compound of formula-9 can be treated with (S)-tert-butyl 3-chloropiperidine-1-carboxylate in presence of a suitable base in a suitable solvent provides compound of formula-12. (S)-tert-butyl 3-chloropiperidine-1-carboxylate can be prepared from its corresponding hydroxy compound by using a suitable chlorinating agent such as sulfuryl chloride, chlorine, thionyl chloride, phosphoryl chloride, N-chloro succinamide and all other well-known reagents for chlorination.

A preferred embodiment of the present invention provides a process for the preparation of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, comprising of :

- a) Reating 4-fluorobenzaldehyde compound of formula-2 with phenol compound of formula-3 in presence of potassium carbonate in dimethylformamide provides 4-phenoxybenzaldehyde compound of formula-4,
- b) oxidizing compound of formula-4 with sodium chlorite in presence of sulphamic acid in water to provide 4-phenoxybenzoic acid compound of formula-5,
- c) converting the compound of formula-5 into its acid anhydride derivative by treating it with pivaloyl chloride,
- d) reacting the compound obtained in step-(c) with malononitrile in presence of diisopropylethylamine and dimethylaminopyridine in tetrahydrofuran provides 2-(hydroxy(4-phenoxyphenyl)methylene) malononitrile compound of formula-6,
- e) methylating compound of formula-6 with dimethyl sulfate in presence of potassium carbonate in 1,4-dioxane provides 2-(methoxy(4-phenoxyphenyl)methylene) malononitrile compound of formula-7,
- f) reacting compound of formula-7 with hydrazine hydrate in methanol provides 3-amino-5-(4-phenoxyphenyl)-1H-pyrazole-4-carbonitrile compound of formula-8,
- g) reacting compound of formula-8 with formamide in methanol provides 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine compound of formula-9,

h) reacting the compound of formula-9 with compound of general formula-11 in presence of cesium carbonate in N-methylpyrrolidine to provide (R)-tert-butyl 3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate compound of formula-12,

5 i) treating the compound of formula-12 with ethylacetate-HCl in isopropyl alcohol provides (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13,

j) treating the compound of formula-13 with sodium carbonate in dichloromethane, followed by treating the obtained compound with acryloyl chloride in presence of triethylamine in dichloromethane provides 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1.

Alternatively, the compound of formula-13 obtained in step-(i) is basified with a suitable base to provide (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. The obtained compound is further treated with a suitable chiral acid in presence or absence of a solvent to provide its corresponding acid addition salt, which is again treated with a base and the obtained compound utilized for synthesis of Ibrutinib compound of formula-1. The conversion compound of formula-13 into its chiral acid addition salt will enhance the chiral purity of the compound of formula-14 as well as final compound of formula-1.

The suitable chiral acid is selected from tartaric acid, mandelic acid, acetyl mandelic acid, D-glutamic acid, di-p-toluoyl tartaric acid, dibenzoyl tartaric acid, di-p-anisoyl tartaric acid, camphor sulfonic acid, lactic acid, malic acid, L-glutamic acid, menthyloxy acetic acid, menthyl chloroformate, methyl mandelate, gluconic acid, lysine etc. The chiral acid used in the present invention is selected from either its D-isomer or L-isomer.

The second aspect of the present invention provides a process for the preparation of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13, comprising of treating the (R)-tert-butyl 3-(4-

amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate compound of formula-12 with a suitable Boc-deprotecting agent such as dry HCl, ethyl acetate-HCl, isopropyl alcohol-HCl, methanolic-HCl, ether-HCl in a suitable solvent selected from hydrocarbon solvents, ether solvents, ester solvents, chloro solvents, alcoholic solvents, polar aprotic solvents, ketone solvents, nitrile solvents, polar solvents or mixtures thereof, preferably alcoholic solvents provides compound of formula-13.

US7514444B2 reported the deprotection of compound of formula-12 by using dioxane-HCl, which is toxic hence, the usage of dioxane and aqueous hydrochloric acid solvent for deprotection is not suitable for commercial scale up. The problem is solved by the present invention by utilizing the ethylacetate-HCl or methanolic HCl for deprotection.

The third aspect of the present invention provides a crystalline form of (S)-tert-butyl-3-(tosyloxy)piperidine-1-carboxylate compound of formula-11a, hereinafter designated as crystalline form-M. The crystalline form-M is characterized by:

- a) its powder X-ray diffraction pattern having peaks at 11.0, 18.8, 19.3, 20.3, 20.9 and 21.3 ± 0.2 degrees of two-theta,
- b) further characterized by its powder X-ray diffraction pattern having peaks at 7.9, 8.4, 13.7, 14.9 and 16.7 ± 0.2 degrees of two-theta; and
- c) its powder X-ray diffraction pattern as shown in figure-1.

Further, the present invention provides a process for the preparation of crystalline form-M of (S)-tert-butyl-3-(tosyloxy)piperidine-1-carboxylate compound of formula-11a, comprising of;

- a) Adding a suitable solvent to (S)-tert-butyl-3-(tosyloxy)piperidine-1-carboxylate compound of formula-11a at a suitable temperature,
- b) stirring the reaction mixture,
- c) cooling the reaction mixture to a suitable temperature,
- d) stirring the reaction mixture,
- e) filtering the solid, washing with suitable solvent and then drying to get crystalline form-M of compound of formula-11a.

Wherein,

in step-a) & e) the suitable solvent is selected from hydrocarbon solvents, ether solvents, ester solvents, chloro solvents, alcoholic solvents, polar aprotic solvents, ketone solvents, nitrile solvents, polar solvents or mixtures thereof, preferably the suitable solvent is selected from hydrocarbon solvents;

- 5 in step-a) the suitable temperature is ranging from 25-30°C;
in step-c) the suitable temperature is below 15°C.

The fourth aspect of the present invention provides a crystalline form of (S)-tert-butyl-3-((methylsulfonyl)oxy)piperidine-1-carboxylate compound of formula-11b,
10 hereinafter designated as crystalline form-S. The crystalline form-S is characterized by:

- a) its powder X-ray diffraction pattern having peaks at 8.2, 13.6, 18.7 and 20.0 $\pm$ 0.2 degrees of two-theta,
b) further characterized by its powder X-ray diffraction pattern having peaks at 9.3, 11.5, 14.4, 15.3, 15.6, 16.8, 21.0, 22.2, 22.6, 23.3 and 24.9 $\pm$ 0.2 degrees of two-theta; and
15 c) its powder X-ray diffraction pattern as shown in figure-2.

Further, the present invention provides a process for the preparation of crystalline form-S of (S)-tert-butyl-3-((methylsulfonyl)oxy)piperidine-1-carboxylate compound of formula-11b, comprising of;

- 20 a) Adding a suitable solvent to (S)-tert-butyl-3-((methylsulfonyl)oxy)piperidine-1-carboxylate compound of formula-11b at a suitable temperature,
b) stirring the reaction mixture,
c) cooling the reaction mixture to a suitable temperature,
d) stirring the reaction mixture,
25 e) filtering the solid, washing with suitable solvent and then drying to get crystalline form-S of compound of formula-11b.

Wherein,

in step-a) & e) the suitable solvent is selected from hydrocarbon solvents, ether solvents, ester solvents, chloro solvents, alcoholic solvents, polar aprotic solvents, ketone

solvents, nitrile solvents, polar solvents or mixtures thereof, preferably the suitable solvent is selected from hydrocarbon solvents;

in step-a) the suitable temperature is ranging from 25-30°C;

in step-c) the suitable temperature is below 15°C.

5

The fifth aspect of the present invention provides crystalline form of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13, herein designated as crystalline form-N. The crystalline form-N is characterized by:

- 10 a) its powder X-ray diffraction pattern having peaks at 3.7, 7.4, 9.0, 14.2 and 22.3 ± 0.2 degrees of two-theta ,
b) its powder X-ray diffraction pattern as shown in figure-3.

15 Further, the present invention provides a process for the preparation of crystalline form-N of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13, comprising of:

- a) Dissolving the (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13 in a suitable solvent or in a mixture of solvents by heating to a suitable temperature,
20 b) cooling the reaction mixture to a suitable temperature,
c) stirring the reaction mixture,
d) filtering the solid, washing with suitable solvent and then drying to provide crystalline form-N of compound of formula-13.

Wherein,

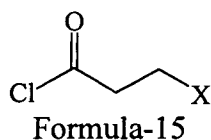
- 25 in step-a) and d) the suitable solvent is selected from hydrocarbon solvents, ether solvents, ester solvents, chloro solvents, alcoholic solvents, polar aprotic solvents, ketone solvents, nitrile solvents, polar solvents or mixtures thereof, preferably the suitable solvent is selected from alcohol solvents and polar solvent or mixtures thereof;
in step-a) the suitable temperature is 40°C to reflux temperature of a solvent ,
30 in step-b) the suitable temperature is below 10°C.

A preferred embodiment of the present invention provides a process for the preparation of crystalline form-N of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13, comprising of:

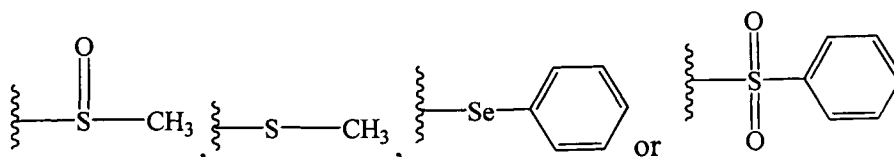
- a) Dissolving the (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13 in aqueous isopropyl alcohol by heating to 75-80°C,
- b) cooling the reaction mixture to 0-5°C,
- c) stirring the reaction mixture,
- d) filtering the solid, washing with isopropyl alcohol and then drying to get crystalline form-N of compound of formula-13.

The sixth aspect of the present invention provides alternative process for the preparation of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, comprising of:

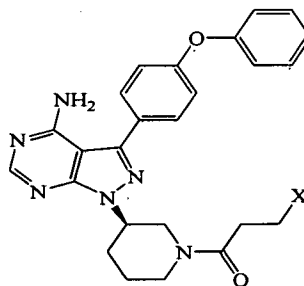
- a) Treating the (R)-tert-butyl 3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate compound of formula-12 with a suitable boc-deprotecting agent in a suitable solvent provides (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13,
- b) treating the compound of formula-13 with a base in a suitable solvent, followed by treating the obtained compound with compound of general formula-15



wherein, 'X' represents halogen such as chlorine, bromine, iodine; dimethylamine, or a group selected from



in presence of a base in a suitable solvent to provide compound of general formula-16,



Formula-16

wherein, 'X' is same as defined above,

- c) treating the compound of general formula-16 with a suitable reagent optionally in
 5 presence of a base in a suitable solvent to provide compound of formula-1,
 d) optionally purifying the obtained compound with a suitable solvent or mixtures thereof
 provides the pure compound of formula-1.

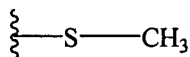
Wherein,

in step-b) the suitable base is inorganic base or organic base,

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

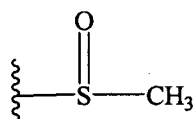
in step-c)

- 15 (i) when 'X' represents halogen then the suitable reagent for carrying out the step-(c) is
 selected from inorganic bases such as alkali metal hydroxide and alkoxides, for
 example sodium hydroxide, potassium hydroxide, sodium methoxide, sodium
 ethoxide, sodium tert-butoxide, potassium methoxide, potassium ethoxide, potassium
 tert-butoxide; and organic bases such as triethylamine, DBU or mixtures thereof
 optionally in presence of hydroquinone;
 20 (ii) when 'X' represents dimethylamine then the suitable reagent for carrying out the step-
 (c) is selected from triethylamine or 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT)
 in presence of triethylamine;
 (iii) when 'X' represents



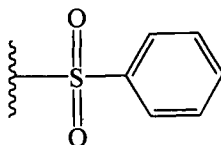
then the suitable reagent for carrying out the step-(c) is selected from alkali metal alkoxide such as potassium methoxide, potassium ethoxide, potassium tert-butoxide, sodium methoxide, sodium ethoxide, sodium tert-butoxide and the like; alkali metal bicarbonate such as sodium bicarbonate, potassium bicarbonate optionally in presence of methyl trifluoromethane sulfonate; and also the above reaction was carried out by utilizing oxidizing agents such as sodium periodate or hydrogen peroxide or meta-chloro perbenzoic acid and followed by heating the obtained compound to higher temperatures.

(iv) when 'X' represents



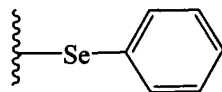
then the suitable reagent for carrying out the step-(c) is selected from alkali metal alkoxides such as potassium methoxide, potassium ethoxide, potassium tert-butoxide, sodium methoxide, sodium ethoxide, sodium tert-butoxide and the like; alkali metals hydroxides such as sodium hydroxide, potassium hydroxide; or pyrolysis (i.e., by heating the compound to higher temperature) optionally in presence of alkali metal carbonate such as calcium carbonate.

(v) when 'X' represents



then the suitable reagent for carrying out the step-(c) is selected from inorganic bases such as alkali metal hydroxides such as sodium hydroxide, potassium hydroxide and the like; alkali metal alkoxide such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium methoxide, potassium ethoxide, potassium tert-butoxide and the like; organic bases such as triethylamine, DBU and/or mixtures thereof; quaternary ammonium salts such as tetrabutyl ammonium bromide, tetrabutyl ammonium fluoride and the like.

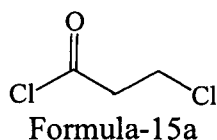
(vi) when 'X' represents



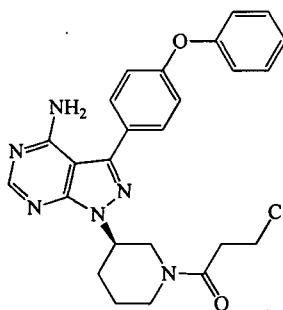
then the step-(c) was carried out by oxidizing the compound with hydrogen peroxide followed by treating the obtained compound with a base such as sodium thiosulfate.

5 The preferred embodiment of the present invention provides an alternative process for the preparation of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, comprising of:

- 10 a) Treating the (R)-tert-butyl 3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate compound of formula-12 with ethylacetate-HCl in isopropyl alcohol provides (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13,
- b) reacting the compound of formula-13 with sodium carbonate in dichloromethane, followed by treating the obtained compound with compound of formula-15a



in presence of triethylamine in dichloromethane provides compound of formula-16a,

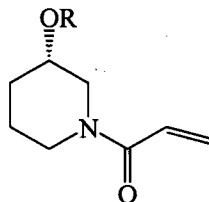


Formula-16a

- 20 c) treating the compound of formula-16a with triethylamine in presence of 1,8-Diazabicyclo [5.4.0]undec-7-ene and hydroquinone in acetonitrile provides compound of formula-1,
- d) purifying the obtained compound of formula-1 with a mixture of dichloromethane and methanol provides pure compound of formula-1.

The seventh aspect of the present invention provides another alternative process for the preparation of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, comprising of reacting the 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine compound of formula-9 with

5 compound of general formula-10



Formula-10

wherein, 'R' represents 'H' or methane sulfonyl group or p-toluene sulfonyl group, in presence of a base in a suitable solvent to provide compound of formula-1.

10

Wherein, the base is selected from inorganic base or organic base; and the suitable solvent is selected from hydrocarbon solvents, ether solvents, ester solvents, chloro solvents, alcoholic solvents, polar aprotic solvents, ketone solvents, nitrile solvents, polar solvents or mixtures thereof.

15

Alternatively, in the above aspect the compound of formula-9 can be treated with (S)-1-(3-chloropiperidin-1-yl)prop-2-en-1-one in presence of a suitable base in a suitable solvent provides compound of formula-1. The (S)-1-(3-chloropiperidin-1-yl)prop-2-en-1-one can be prepared from its corresponding hydroxy compound by chlorinating the compound with

20 sulfuryl chloride, chlorine, thionyl chloride, phosphoryl chloride, N-chlorosuccinamide and all other well-known reagents for chlorination.

The eighth aspect of the present invention provides a process for the preparation of amorphous form of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, which is characterized by its

25 powder X-ray diffraction pattern as depicted in figure-4. The process comprises the following steps of:

- a) Adding a solution of 10% methanol in dichloromethane to 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1 at a suitable temperature ranges from 15-40°C, preferably 25-30°C,
- 5 b) stirring the reaction mixture,
- c) distilling off the solvent from the reaction mixture and then drying to get amorphous form of compound of formula-1.

The amorphous form of compound of formula-1 of the present invention can be prepared by techniques that are known in the art such as distillation, recrystallization, isolation, solvent- anti solvent technique, lyophilization etc by utilizing a suitable solvent selected from hydrocarbon solvents, ether solvents, ester solvents, chloro solvents, alcoholic solvents, polar aprotic solvents, ketone solvents, nitrile solvents, polar solvents or mixtures thereof.

15 The ninth aspect of the present invention provides a process for the preparation of 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine compound of formula-9, comprising of:

- a) Reacting 4-fluorobenzaldehyde compound of formula-2 with phenol compound of formula-3 in presence of a base in a suitable solvent to provide 4-phenoxybenzaldehyde compound of formula-4,
- 20 b) oxidizing compound of formula-4 in-situ with a suitable oxidizing agent in a suitable solvent to provide 4-phenoxybenzoic acid compound of formula-5,
- c) converting the compound of formula-5 into its acid chloride by using a suitable chlorinating agent in presence or absence of a solvent,
- 25 d) reacting the compound obtained in step-(c) with malononitrile in presence of a base in a suitable solvent provides 2-(hydroxy(4-phenoxyphenyl)methylene) malononitrile compound of formula-6,
- e) methylating the compound of formula-6 in-situ with a suitable methylating agent optionally in presence of a base in a suitable solvent provides 2-(methoxy(4-
- 30

phenoxyphenyl) methylene)malononitrile compound of formula-7,

f) reacting the compound of formula-7 with hydrazine hydrate in a suitable solvent provides 3-amino-5-(4-phenoxyphenyl)-1H-pyrazole-4-carbonitrile compound of formula-8,

5 g) reacting the compound of formula-8 with formamide in presence of a suitable catalyst at a suitable temperature in a suitable solvent provides 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine compound of formula-9,

h) optionally, purifying the compound obtained in step-g) in a suitable solvent provides pure compound of formula-9.

10 wherein,

in step-a) the suitable base is inorganic base or organic base,

in step-d) the base is organic base,

in step-e) the base is inorganic base,

in step-a) to step-h) the suitable solvent is selected from hydrocarbon solvents, ether

15 solvents, ester solvents, chloro solvents, alcoholic solvents, polar aprotic solvents, ketone solvents, nitrile solvents, polar solvents or mixtures thereof,

A preferred embodiment of the present invention provides a process for the preparation of 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine compound of
20 formula-9, comprising of :

a) Reacting 4-fluorobenzaldehyde compound of formula-2 with phenol compound of formula-3 in presence of potassium carbonate in dimethylformamide provides 4-phenoxybenzaldehyde compound of formula-4,

25 b) oxidizing compound of formula-4 in-situ with potassium permanganate in water to provide 4-phenoxybenzoic acid compound of formula-5,

c) converting the compound of formula-5 into its acid chloride derivative by treating it with thionyl chloride,

30 d) reacting the compound obtained in step-(c) with malononitrile in presence of diisopropylethylamine in toluene provides 2-(hydroxy(4-phenoxyphenyl)methylene) malononitrile compound of formula-6,

- e) methylating compound of formula-6 in-situ with dimethyl sulfate in presence of sodium bicarbonate in acetone provides 2-(methoxy(4-phenoxyphenyl)methylene) malononitrile compound of formula-7,
- f) reacting compound of formula-7 with hydrazine hydrate in methanol provides 3-amino-5-(4-phenoxyphenyl)-1H-pyrazole-4-carbonitrile compound of formula-8,
- g) reacting compound of formula-8 with formamide in presence of zinc chloride in O-xylene at a temperature ranging from 110°C to 120°C provides 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine compound of formula-9,
- h) purifying the compound obtained in step-g) in water provides pure compound of formula-9.

The tenth aspect of the present invention provides an improved process for the preparation of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, comprising of:

- a) Reacting 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine compound of formula-9 with (S)-tert-butyl 3-hydroxypiperidine-1-carboxylate compound of formula-17 in presence of diisopropylazodicarboxylate and triphenylphosphine in tetrahydrofuran provides (R)-tert-butyl 3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate compound of formula-12,
- b) treating the compound of formula-12 in-situ with a suitable hydrochloric acid source in a suitable solvent provides (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13,
- c) optionally purifying the obtained compound from a suitable solvent or mixture thereof,
- d) reacting the compound of formula-13 with acryloyl chloride in presence of a suitable base in a suitable solvent provides compound of formula-1.

Wherein, the suitable hydrochloric acid source used in step-b) is selected from HCl gas, aqueous HCl, dry HCl, ethylacetate-HCl, IPA-HCl, ethanol-HCl, methanol-HCl; the suitable base used in step-c) is organic base; the suitable solvent used in step-b), c) & d) are same as defined in the first aspect of the present invention.

A preferred embodiment of the present invention provides an improved process for the preparation of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, comprising of:

- 5 a) Reating 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine compound of formula-9 with (S)-tert-butyl 3-hydroxypiperidine-1-carboxylate compound of formula-17 in presence of diisopropylazodicarboxylate and triphenylphosphine in tetrahydrofuran provides (R)-tert-butyl 3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate compound of formula-12,
- 10 b) treating the compound of formula-12 in-situ with methanolic HCl in ethylacetate provides (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13,
- c) purifying the obtained compound from aqueous isopropanol provides pure compound of formula-13,
- 15 d) reacting the compound of formula-13 with acryloyl chloride in presence of diisopropylethylamine in a mixture of dichloromethane and methanol provides compound of formula-1.

The eleventh aspect of the present invention provides an improved process for the preparation of amorphous 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, comprising of:

- 20 a) Dissolving 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1 in a suitable first solvent,
- b) adding the solution obtained in step-a) to a suitable second solvent,
- c) filtering the obtained solid,
- 25 d) optionally, slurring the solid obtained in step-c) in a suitable third solvent provides amorphous form of the compound of formula-1.

wherein,

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

30 the suitable second solvent used in step-b) is selected from polar solvents, hydrocarbon

solvents or mixtures thereof.

the suitable third solvent used in step-c) is selected from polar solvents.

A preferred embodiment of the present invention provides an improved process for the preparation of amorphous 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, comprising of:

- a) Dissolving crystalline Form-C of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1 in dimethylformamide,
- b) adding the solution obtained in step-a) to water,
- c) filtering the obtained solid,
- d) slurring the solid obtained in step-c) in water provides amorphous form of the compound of formula-1.

The twelfth aspect of the present invention provides an improved process for the preparation of crystalline form-C of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, comprising of:

- a) Reacting the (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13 with acryloyl chloride in presence of a suitable base in a suitable solvent provides 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1,
- b) purifying the compound of formula-1 obtained in step-a) in a suitable solvent provides pure crystalline form-C of the compound of formula-1.

Wherein, the suitable base used in step-a) is organic base; the suitable solvent used in step-a) & b) are same as defined in the first aspect of the present invention;

A preferred embodiment of the present invention provides an improved process for the preparation of crystalline form-C of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, comprising of :

- a) Reacting the (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13 with acryloyl chloride in presence of diisopropyl ethylamine in dichloromethane provides 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1,
- b) dissolving the compound of formula-1 obtained in step-a) in a mixture of methanol and dichloromethane,
- c) treating the reaction mixture with carbon,
- d) cooling the reaction mixture,
- e) filtering the solid obtained in step-d) to get pure crystalline form-C of the compound of formula-1.

The thirteenth aspect of the present invention provides a process for the preparation of crystalline form-A of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo [3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, comprising of:

- a) Reacting the (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13 with acryloyl chloride in presence of a base in a suitable solvent provides 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1,
- b) purifying the compound of formula-1 obtained in step-a) in a suitable solvent provides pure crystalline form-A of the compound of formula-1.

Wherein, the suitable base used in step-a) is organic base; the suitable solvent used in step-a) & b) are same as defined in the first aspect of the present invention;

A preferred embodiment of the present invention provides an improved process for the preparation of crystalline form-A of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, comprising of :

- a) Reacting the (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13 with acryloyl chloride in presence of diisopropyl ethylamine in dichloromethane provides 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1,
- b) dissolving the compound of formula-1 obtained in step-a) in a mixture of methanol and dichloromethane,
- c) treating the reaction mixture with carbon,
- d) cooling the reaction mixture,
- e) filtering the obtained solid,
- f) slurrying the solid in a mixture of isopropanol and water,
- g) filtering the obtained solid and drying to get pure crystalline form-C of the compound of formula-1.

A preferred embodiment of the present invention provides an improved process for the preparation of crystalline form-A of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, comprising of :

- a) Reacting the (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13 with acryloyl chloride in presence of diisopropyl ethylamine in dichloromethane provides 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1,
- b) dissolving the compound of formula-1 obtained in step-a) in the mixture of ethanol and dichloromethane,
- c) treating the reaction mixture with carbon,
- d) cooling the reaction mixture,
- e) filtering the solid obtained in step-d) to get pure crystalline form-A of the compound of formula-1.

The crystalline form-C of compound of formula-1 obtained according to the present invention is useful for the preparation of amorphous form of the compound of formula-1.

The compound of formula-1 obtained by the present invention can be further micronized or milled 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.

P-XRD Method of Analysis:

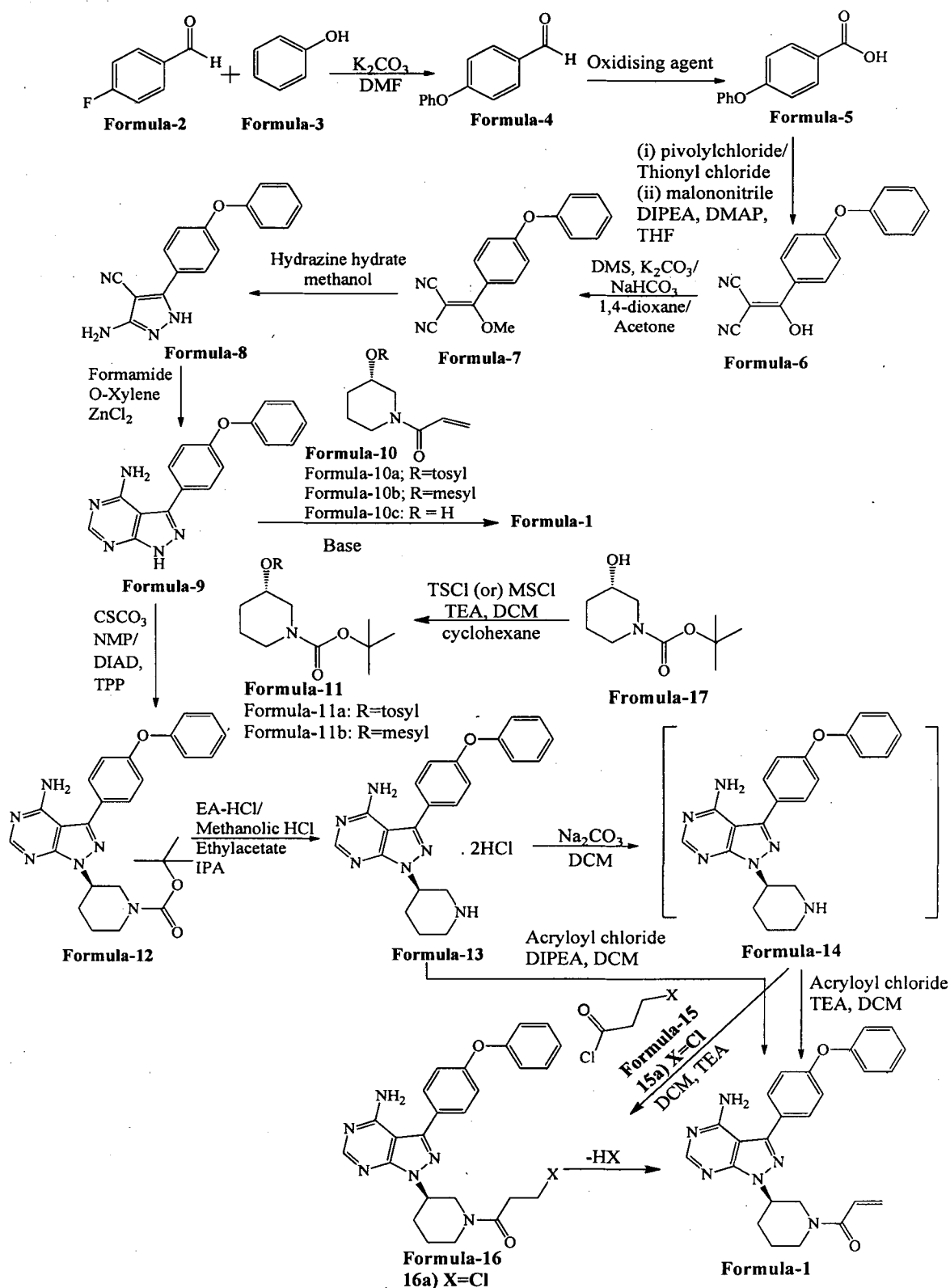
PXRD analysis of compound of formula-1 was carried out by using BRUKER/D8 ADVANCE diffractometer using Cu K α radiation of wavelength 1.5406 Å and continuous scan speed of 0.03°/min.

HPLC Method of Analysis:

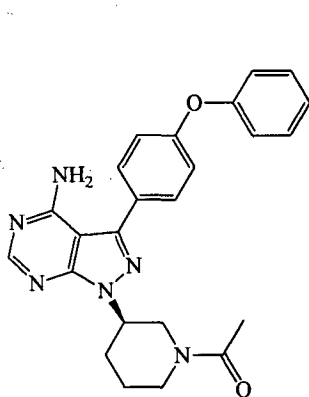
1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1

Apparatus: A liquid chromatographic system is to be equipped with variable wavelength UV-detector; Column: Xselect HSS T3 150*4.6mm, 3.5 µm or Equivalent; Flow Rate: 1.0 mL/min; Wavelength : 210 nm; Column temperature: 30°C; Injection volume: 5 µL; Run time: 48 minutes; Auto sampler temperature: 5°C; Buffer: Dissolve 1.36 gm of potassium dihydrogen phosphate in 1000mL of Milli-Q- Water and mix well. Adjust its pH to 5.5 with diluted potassium hydroxide and filtered through 0.22 µm nylon membrane and degas it. Mobile phase-A: Buffer: Acetonitrile (95: 05) v/v; Mobile phase-B: Acetonitrile: Water (90:10) v/v; Diluent: Acetonitrile: water (70:30) v/v; Needle wash: Diluent; Elution: Gradient.

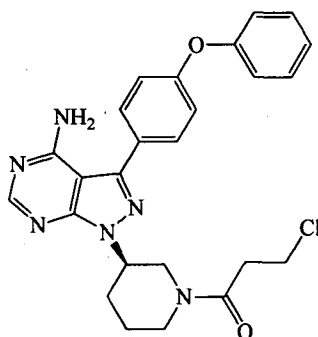
The process of the present invention is represented schematically as follows:



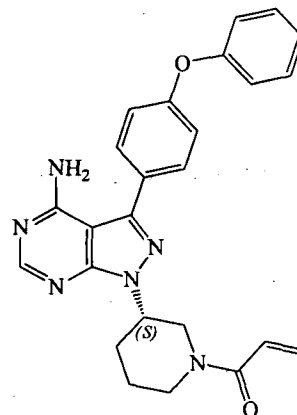
The possible impurities that are formed during the process for the preparation of compound of formula-1, which are well controlled in the present invention as per the ICH guidelines. The said impurities are represented by the following structural formulae:



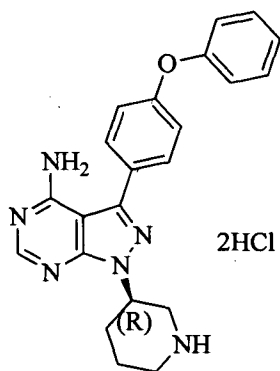
Acetyl impurity



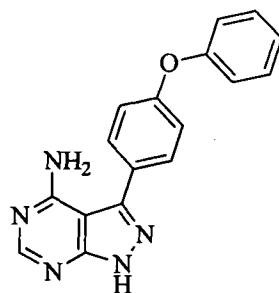
Chloro impurity



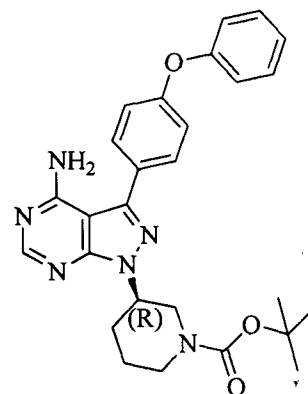
S-Isomer impurity



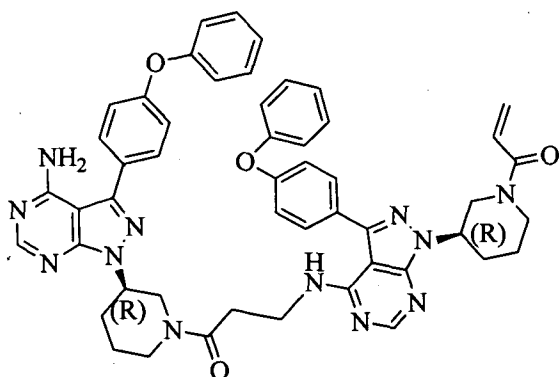
Amino piperidine impurity



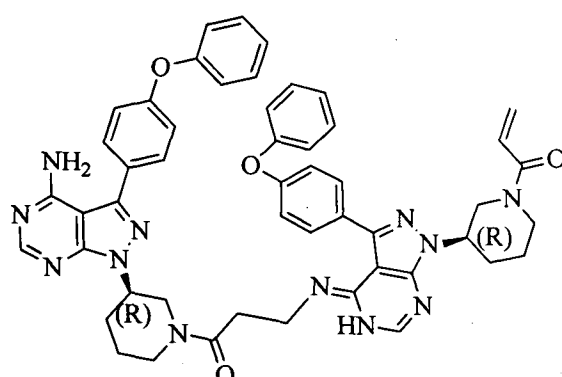
Amine impurity



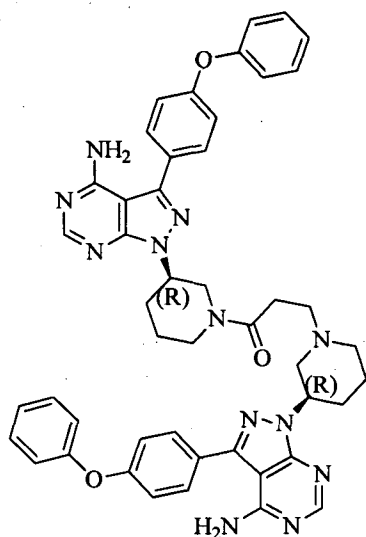
BoC amine impurity



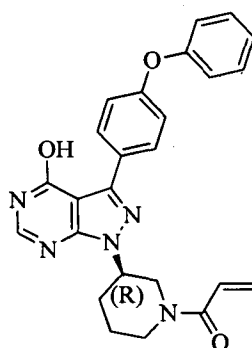
Dimer impurity



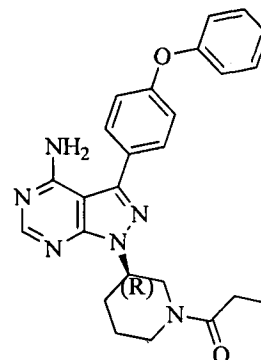
Di-piepridine impurity



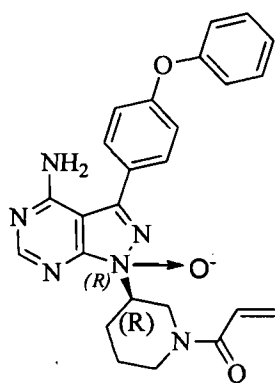
Diamine impurity



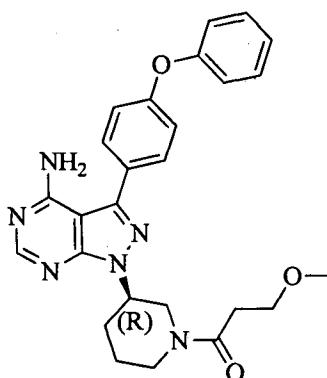
Hydroxy impurity



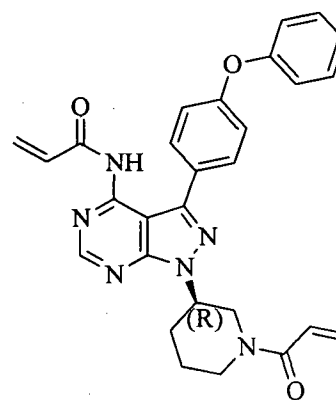
Propionamide impurity



N-Oxide impurity



Methoxy impurity



Diamide impurity

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

Examples:

Example-1: Preparation of 2-(hydroxy(4-phenoxyphenyl)methylene)malononitrile (Formula-6)

Pivoyl chloride (135 gms) was added to a mixture of 4-phenoxybenzoic acid compound of formula-5 (200 gms), tetrahydrofuran (100 ml), malononitrile (74 gms),

dimethylaminopyridine (11.5 gms) and diisopropylethylamine (277.5 gms) at 0-5°C under nitrogen atmosphere. Heated the reaction mixture to 65-70°C and stirred for 8 hrs at the same temperature. Cooled the reaction mixture to 25-30°C. Ethyl acetate and water were added to the reaction mixture. Both the organic and aqueous layers were separated and the aqueous layer was extracted with ethyl acetate. Combined the organic layers and then cooled to 10-15°C. The organic layer was washed with aqueous potassium carbonate solution and followed by dilute hydrochloric acid solution. Further, the organic layer was washed with aqueous sodium chloride solution. Distilled off the solvent from the organic layer completely under reduced pressure to get the title compound. Yield: 242 gms.

Example-2: Preparation of 2-(hydroxy(4-phenoxyphenyl)methylene)malononitrile (Formula-6)

Thionyl chloride (33.2 ml) was added to a mixture of 4-phenoxybenzoic acid compound of formula-5 (50 gms), tetrahydrofuran (50 ml) and dimethylformamide (2 ml) at 0-5°C under nitrogen atmosphere. Heated the reaction mixture to 65-70°C and stirred for 6 hrs at the same temperature. Distilled off the solvent from the reaction mixture completely under reduced pressure. Cooled the obtained compound to 25-30°C. Tetrahydrofuran (200 ml) followed by malononitrile (18.5 gms) and diisopropylethylamine (94 ml) were added to the reaction mixture at 25-30°C. Heated the reaction mixture to 65-70°C and stirred for 30 hrs. Cooled the reaction mixture to 25-30°C. Water followed by ethyl acetate was added to the reaction mixture. Both the organic and aqueous layers were separated. The aqueous layer was extracted with ethyl acetate. Combined the organic layers and then cooled to 10-15°C. The organic layer was washed with aqueous potassium carbonate solution and followed by dilute hydrochloric acid solution. Further, the organic layer was washed with aqueous sodium chloride solution. Distilled off the solvent completely from the organic layer under reduced pressure to get the title compound. Yield: 61.21 gms.

Example-3: Preparation of 2-(methoxy(4-phenoxyphenyl)methylene)malononitrile (Formula-7)

Dimethyl sulfate (211.6 gms) and sodium carbonate (141 gms) were added to a mixture of 2-(hydroxy(4-phenoxyphenyl)methylene)malononitrile (220 gm) and 1,4-dioxane (1100 ml) at 0-5°C. Heated the reaction mixture to 70-75°C and stirred for 5 hrs. Cooled the

reaction mixture to 25-30°C. Water followed by ethyl acetate were added to the reaction mixture. Both the organic and aqueous layers were separated. Aqueous layer was extracted with ethyl acetate. Organic layers were combined and washed with water. Distilled off the solvent from the organic layer completely under reduced pressure and co-distilled with isopropyl alcohol. Isopropyl alcohol (220 ml) was added to the obtained compound at 25-30°C. The reaction mixture was cooled to 0-5°C and stirred for 2 hrs at the same temperature. Filtered the precipitated solid, washed with isopropyl alcohol and dried to get the title compound. Yield: 86 gms; Melting range: 70-75°C.

Example-4: Preparation of 3-amino-5-(4-phenoxyphenyl)-1H-pyrazole-4-carbonitrile (Formula-8)

80% Hydrazine hydrate (32.5 ml) was added to a mixture of 2-(methoxy(4-phenoxyphenyl)methylene)malononitrile (48 gms) and methanol (192 ml) at 25-30°C and stirred for 2 hrs at the same temperature. Water was added to the reaction mixture at 25-30°C. Cooled the reaction mixture to 0-5°C and stirred for 60 mins at the same temperature. Filtered the precipitated solid, washed with water and dried to get the title compound. Yield: 46 gms; Melting range: 172-176°C; purity: 96.89%

Example-5: Preparation of 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (Formula-9)

A mixture of 3-amino-5-(4-phenoxyphenyl)-1H-pyrazolo-4-carbonitrile compound of formula-8 (46 gms) and formamide (230 ml) was heated to 165-170°C and stirred for 12 hrs. Cooled the reaction mixture to 25-30°C. Water was added to the reaction mixture at 25-30°C and stirred for 60 mins at the same temperature. Filtered the precipitated solid, washed with a mixture of water and methanol. Dimethyl formamide (380 ml) was added to the obtained compound. Heated the reaction mixture to 70-75°C and stirred for 30 mins. Carbon was added to the reaction mixture at 70-75°C and stirred for 30 mins. Filtered the reaction mixture through hyflow bed and washed with dimethylformamide. The filtrate was cooled to 25-30°C. Water was added to the reaction mixture at 25-30°C and stirred for 60 mins. Filtered the precipitated solid, washed with water and dried to get the title compound.

Yield: 40.3 gms; Purity: 95.35%; Melting range: 248-253°C.

Example-6: Preparation of (S)-tert-butyl-3-(tosyloxy)piperidine-1-carboxylate (Formula-11a)

4-dimethylaminopyridine (6.7 gms) and p-toluene sulfonylchloride (67 gms) were added to a mixture of (S)-tert-butyl-3-hydroxypiperidine-1-carboxylate compound of formula-10 (50 gms) and dichloromethane (250 ml) at 0-5°C. Triethyl amine (75.2 gms) was added to the reaction mixture at 0-5°C and stirred the reaction mixture for 60 mins at the same temperature. Raised the temperature of the reaction mixture to 25-30°C and stirred for 10 hrs. Water was added to the reaction mixture. Both the organic and aqueous layers were separated. The aqueous layer was extracted with dichloromethane. Organic layers were combined and cooled to 0-5°C and acidify the reaction mixture with 10% HCl solution. Both the organic and aqueous layers were separated. The organic layer was washed with 10% aqueous sodium bicarbonate solution followed by 5% aqueous sodium chloride solution. Distilled off the solvent from the organic layer completely under reduced pressure and co-distilled with cyclohexane under reduced pressure. Cyclohexane (150 ml) was added to the obtained compound at 25-30°C and stirred for 30 mins. Cooled the reaction mixture to 10-15°C and stirred for 60 mins. Filtered the reaction mixture, washed with cyclohexane and dried to get the title compound. Yield: 72 gms; Melting range: 80-85°C.

Powder X-ray diffraction pattern of the obtained compound is shown in figure-1.

Example-7: Preparation of (S)-tert-butyl-3-((methylsulfonyl)oxy)piperidine-1-carboxylate (formula-11b)

Methanesulfonyl chloride (3.7 gms) and 4-dimethylaminopyridine (0.66 gms) were added to a mixture of (S)-tert-butyl-3-hydroxypiperidine-1-carboxylate compound of formula-10 (5 gms) and dichloromethane (25 ml) at 0-5°C. Triethyl amine (7.5 gms) was slowly added to the reaction mixture at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 2 hrs. Water was added to the reaction mixture. Both the organic and aqueous layers were separated. The aqueous layer was extracted with dichloromethane. Organic layers were combined and cooled to 0-5°C and acidify the reaction mixture with 10% HCl solution. Both the organic and aqueous layers were separated. The organic layer was washed with aqueous sodium bicarbonate solution followed by aqueous sodium chloride solution. Distilled off the solvent from the organic layer completely under reduced pressure

and co-distilled with cyclohexane. Cyclohexane (150 ml) was added to the obtained compound at 25-30°C and stirred for 30 mins at the same temperature. Cooled the reaction mixture to 10-15°C and stirred for 60 mins at the same temperature. Filtered the precipitated solid, washed with cyclohexane and dried to get the title compound.

5 Yield: 5.4 gms; Melting range: 85-90°C.

Powder X-ray diffraction pattern of the obtained compound is shown in figure-2.

Example-8: Preparation of (R)-tert-butyl-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate (Formula-12)

10 A mixture of 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine compound of formula-9 (60 gms), NMP (480 ml), (S)-tert-butyl-3-(tosyloxy)piperidine-1-carboxylate compound of formula-11a (86 gms) and cesium carbonate (161 gms) was heated to 70-75°C under nitrogen atmosphere and stirred for 12 hrs. Cooled the reaction mixture to 25-30°C. Ethyl acetate was added to the reaction mixture at 25-30°C. Filtered the reaction mixture and washed with ethyl acetate. Water was added to the filtrate at 25-30°C and stirred for 15 mins.
15 Both the organic and aqueous layers were separated. The organic layer was washed with water. Distilled off the solvent from the organic layer completely under reduced pressure to get the title compound. Yield: 77 gms.

Example-9: Preparation of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride (Formula-13)

20 Ethyl acetate-HCl (291 ml) was added to a mixture of (R)-tert-butyl-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate compound of formula-12 (110 gms) and isopropyl alcohol (220 ml) at 25-30°C and stirred for 16 hrs. Filtered the reaction mixture, washed with ethyl acetate and dried to get the title compound. The obtained compound was dissolved in a mixture of isopropyl alcohol (360 ml) and water
25 (52 ml) at 75-80°C. Cooled the reaction mixture to 0-5°C and stirred for 60 mins at the same temperature. Filtered the precipitated solid, washed with isopropyl alcohol and dried to get the title compound. Yield: 36 gms; MR: 260-265°C; Chiral purity by HPLC: 99.52%, other isomer: 0.48%; chloride content: 15.52%

Powder X-ray diffraction pattern of the obtained compound is shown in figure-3.

Example-10: Preparation of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (Formula-1)

A mixture of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13 (12 gms), dichloromethane (450 ml) and water (30 ml) was cooled to 10-15°C and basify the reaction mixture with 10% aqueous sodium carbonate solution. Both the organic and aqueous layers were separated. The aqueous layer was extracted with dichloromethane. Combined the organic layers and washed with water. Distilled off the solvent from the organic layer completely under reduced pressure. Dichloromethane (350 ml) was added to the obtained compound at 25-30°C. Cooled the reaction mixture to -45 to -40°C. Triethyl amine (3.65 ml) was added to the reaction mixture at -45 to -40°C. A mixture of acryloyl chloride (2.1 gms) and dichloromethane (50 ml) was added to the reaction mixture at -45 to -40°C and stirred the reaction mixture for 20 mins. Ethanol was added to the reaction mixture followed by the addition of 1% aqueous sodium hydroxide solution and water at -45 to -40°C. Raised the temperature of the reaction mixture to 0-5°C. Both the organic and aqueous layers were separated. The organic layer was washed with 10% aqueous citric acid solution, followed by 10% aqueous sodium bicarbonate solution and 5% aqueous sodium chloride solution. Distilled off the solvent from the organic layer completely under reduced pressure and co-distilled with toluene. Toluene was added to the above obtained compound at 25-30°C and stirred for 60 mins. Filtered the solid, washed with toluene and dried to get the title compound.

Yield: 6.5 gms; MR: 145-150°C; Purity by HPLC: 96.11%; Chiral purity by HPLC: 99.10%, other isomer: 0.90%.

Example-11: Preparation of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-3-chloropropane-1-one (Formula-16a)

A mixture of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13 (5 gms), dichloromethane (185 ml) and water (10 ml) was cooled to 10-15°C and basify the reaction mixture with 10% sodium carbonate solution. Both the organic and aqueous layers were separated. The aqueous layer was extracted with dichloromethane. Combined the organic layers and washed with

water. Distilled off the solvent from the organic layer completely under reduced pressure. Dichloromethane was added to the obtained compound at 25-30°C. Cooled the reaction mixture to -45 to -40°C. Triethyl amine (1.3 gms) was added to the reaction mixture at -45 to -40°C. A mixture of 3-chloropropionyl chloride compound of formula-15a (1.1 gms) and dichloromethane (25 ml) was added to the reaction mixture at -45 to -40°C and stirred for 20 mins. Ethanol and water were added to the reaction mixture followed by the addition of 1% aqueous sodium hydroxide solution at -45 to -40°C. Raised the temperature of the reaction mixture to 0-5°C. Both the organic and aqueous layers were separated. The organic layer was washed with 1N HCl solution, followed by 10% aqueous sodium carbonate solution and 5% aqueous sodium chloride solution. Distilled off the solvent from the organic layer completely under reduced pressure and co-distilled with acetonitrile. Pet ether (20 ml) was added to the above obtained compound at 25-30°C and stirred for 60 mins. Filtered the precipitated solid, washed with pet ether and dried to get the title compound. Yield: 2.5 gms.

Example-12: Preparation of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (Formula-1)

Hydroquinone (0.2 gms), triethylamine (0.52 gms) and 1,8-Diazabicyclo [5.4.0]undec-7-ene (0.015 gms) were added to a mixture of (R)-1-(3-(4-amino-3-(4-phenoxy phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-3-chloropropane-1-one compound of formula-16a (0.5 gms) and acetonitrile (2 ml) at 25-30°C and stirred for 16 hrs. Distilled off the solvent completely from the reaction mixture under reduced pressure. Dichloromethane and water were added to the obtained compound at 25-30°C. Both the organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane. The organic layer was washed with water, followed by aqueous citric acid solution, aqueous sodium carbonate solution and aqueous sodium chloride solution. Distilled off the solvent from the organic layer completely under reduced pressure and co-distilled with methyl tert-butyl ether. Methyl tert-butyl ether (10 ml) was added to the obtained compound at 25-30°C and stirred for 60 mins. Filtered the precipitated solid, washed with methyl tert-butyl ether and dried to get the title compound.

Yield: 0.25 gms; Purity by HPLC: 96.88%; Melting range: 140-145°C. Chloro impurity: 0.11% by HPLC.

Example-13: Preparation of amorphous form of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (Formula-1)

A solution of 10% Methanol in dichloromethane (2.5 ml) was added to 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1 (0.5 gms) at 25-30°C and stirred for 10 mins. Dry distilling the solvent completely from the reaction mixture under reduced pressure to get amorphous form of compound of formula-1. Yield: 0.3 gms; Melting range: 91-92°C.

Powder X-ray diffraction pattern of the obtained compound is shown in figure-4.

Example-14: Preparation of (S)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one

A mixture of (S)-(3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride (1 gm) and dichloromethane (30 ml) was cooled to -30 to -35°C. Triethylamine (0.7 gms) followed by a solution of acryloyl chloride (0.23 gms) in dichloromethane (5 ml) was added to the reaction mixture at -30 to -35°C and stirred for 20 mins. Water was added to the reaction mixture at -30 to -35°C. Raised the temperature of the reaction mixture to 25-30°C. Both the organic and aqueous layers were separated. The organic layer was washed with 5% aqueous citric acid solution followed by 10% aqueous sodium carbonate solution and 5% aqueous sodium chloride solution. Distilled off the solvent from the organic layer completely under reduced pressure to get the title compound.

Yield: 0.8 gms.

Example-15: Preparation of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)ethanone

A mixture of (R)-(3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (1 gm) and dichloromethane (30 ml) was cooled to -40 to -45°C. Diisopropylethylamine (0.66 gms) followed by a solution of acetyl chloride (0.2 gms) in dichloromethane (15 ml) was added to the reaction mixture at -40 to -45°C and stirred for 20 mins. Ethanol and water were added to the reaction mixture at -40 to -45°C. 1% aqueous sodium hydroxide solution was added to the reaction mixture at -40 to -45°C and raised the temperature of the reaction mixture to 0-5°C. Both the organic and aqueous layers were separated. The organic layer was washed with 1N hydrochloric acid solution followed by 5%

aqueous sodium carbonate solution and 5% aqueous sodium chloride solution. Distilled off the solvent completely from the organic layer under reduced pressure to get the title compound. Yield: 1 gm.

Example-16: Preparation of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-3-chloropropane-1-one (Formula-16a)

Diisopropylethylamine (16.8 gms) was added to a mixture of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13 (20 gms) and dichloromethane (600 ml) at -45 to -40°C. 3-chloropropionyl chloride compound of formula-15a (5.25 gms) in dichloromethane (40 ml) solution was slowly added to the reaction mixture at -45 to -40°C within 90 minutes and stirred for 30 minutes at the same temperature. Water (100 ml) was added to the reaction mixture at -45 to -40°C and raised the temperature to 0-5°C. Both the organic and aqueous layers were separated at 0-5°C and extracted the aqueous layer with dichloromethane. Combined the organic layers and washed with aqueous sulfuric acid followed by aqueous sodium bicarbonate solution and aqueous sodium chloride solution at 0-5°C. Distilled off the solvent completely from the organic layer under reduced pressure. Petroleum ether (40 ml) was added to the obtained crude compound at 25-30°C and stirred for 60 minutes at the same temperature. Filtered the precipitated solid, washed with petroleum ether and dried to get the title compound.

Yield: 17.8 gms; Purity by HPLC: 91.34%.

Example-17: Purification of (R)-1-(3-(4-Amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one compound of formula-1:

A mixture of (R)-1-(3-(4-Amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (50 gms), dichloromethane (250 ml), triethylamine (57.32 gms) and 1,8-Diaza bicycloundec-7-ene (3.45 ml) was stirred for 10 hours at 25-30°C. Water (150 ml) was added to the reaction mixture 25-30°C. Both the organic and aqueous layers were separated at 0-5°C and the organic layer was washed with aqueous sulfuric acid, then aqueous sodium bicarbonate followed by sodium chloride solution at 0-5°C. Distilled off the solvent completely from the organic layer under reduced pressure.

Dichloromethane (27.25 ml) and methanol (522.5 ml) were added to the obtained crude compound at 25-30°C and stirred for 30 minutes at the same temperature. Neutral carbon (0.5 gms) was added to the reaction mixture at 25-30°C and stirred for 30 minutes at the same temperature. Filtered the reaction mixture through highflow bed and washed with mixture of
5 dichloromethane and methanol. Cooled the obtained filtrate to 0-3°C and stirred for 3 hours at the same temperature. Filtered the precipitated solid, washed with methanol and dried to get the title compound.

Yield: 15 gms; Purity by HPLC: 99.54%. Chloro impurity: Not detected;

**Example-18: Preparation of (S)-1-(3-hydroxypiperidin-1-yl)prop-2-en-1-one compound
10 of formula-10c:**

N,N-dicyclohexylcarbodiimide (8.98 gms) was slowly added to a mixture of acrylic acid (2.61 gms) and dichloromethane (25 ml) at 0-5°C. Dimethylaminopyridine (0.21 gms) was added to the reaction mixture at 0-5°C and stirred for 60 minutes at the same temperature. A mixture of 3-hydroxy piperidine hydrochloride (5 gms) and dichloromethane
15 (15 ml) was added to the reaction mixture at 0-5°C. Diisopropylethylamine (14.1 gms) was slowly added to the reaction mixture at 0-5°C. Raised the reaction mixture temperature to 25-30°C and stirred for 90 minutes at the same temperature. Filtered the reaction mixture and washed with dichloromethane. The obtained filtrate was washed with 2% hydrochloride solution. Both the organic and aqueous layers were separated and organic layer was washed
20 with 2% sodium bicarbonate solution and followed by water. Distilled off the solvent completely from the organic layer to get the title compound.

Yield: 2.0 gms.

Example-19: Preparation of 4-phenoxy benzoic acid (Formula-5)

Potassium carbonate (445 gms) and phenol (167 gms) were added to a mixture of
25 dimethyl formamide (600 ml) and 4-fluorobenzaldehyde (200 gms) at 25-30°C and stirred for 10 minutes at the same temperature. Heated the reaction mixture to 115-120°C and stirred for 4 hours at the same temperature. Cooled the reaction mixture to 25-30°C. Water and toluene were added to the reaction mixture at 25-30°C and stirred for 15 minutes at the same temperature. Both the organic and aqueous layers were separated and the aqueous layer was
30 extracted with toluene. Combined the organic layers and washed with aqueous sodium

hydroxide solution. Further, organic layer was washed with aqueous ammonium chloride solution. Distilled off the solvent from the organic layer under reduced pressure. Cooled the obtained residue to 25-30°C.

The obtained residue and acetone (100 ml) were added to the pre-cooled aqueous potassium permanganate solution at 0-5°C and stirred for 10 minutes at the same temperature. Slowly raised the temperature of reaction mixture to 25-30°C and stirred for 8 hours at the same temperature. Aqueous sodium sulfite solution was slowly added to the reaction mixture at 25-30°C and stirred for 2 hours at the same temperature. The reaction mixture was basified using aqueous sodium hydroxide solution. Heated the reaction mixture to 45-50°C and stirred for 30 minutes at the same temperature. Filtered the solid at 45-50°C. To the obtained wet compound, water was added at 25-30°C and stirred for 10 minutes at the same temperature. Heated the reaction mixture to 45-50°C and stirred for 30 minutes at the same temperature. Filtered the solid at 45-50°C. Combined the both filtrates and acidified using hydrochloric acid at 25-30°C and stirred for 2 hours at the same temperature. Filtered the precipitated solid, washed with water and dried to get the title compound.

Yield: 254 gms; M.R: 147-151°C.

Example-20: Preparation of 2-methoxy(4-phenoxyphenyl)methylene)malononitrile (Formula-7)

Toluene (600 ml) was added to a mixture of N,N-Dimethyl formamide (2 ml) and 4-phenoxy benzoic acid (200 gms) at 25-30°C and stirred for 10 minutes at the same temperature. Thionyl chloride (132 gms) was slowly added to the reaction mixture at 25-30°C. Heated the reaction mixture to 55-60°C and stirred for 3 hours at the same temperature. The reaction mixture was slowly added to a pre-cooled mixture of malononitrile (94 gms), N,N-diisopropylethylamine (362 gms) and toluene (200 ml) at 0-5°C. Raised the temperature of reaction mixture to 25-30°C and stirred for 2 hours at the same temperature. Toluene layer was separated from the reaction mixture. Toluene (400 ml) was added to the reaction mixture at 25-30°C and stirred for 10 minutes at the same temperature. Toluene layer was separated from the reaction mixture. Water (600 ml) and ethyl acetate (600 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

ethyl acetate. Aqueous layer was separated and extracted with ethyl acetate. Combined the organic layers and washed with aqueous hydrochloric acid solution. Further, organic layer was washed with 10% aqueous sodium bicarbonate solution and followed by aqueous sodium chloride solution. Distilled off the solvent completely from the organic layer under reduced pressure.

Acetone (1000 ml) was added to the obtained compound at 25-30°C and stirred for 10 minutes at the same temperature. Dimethylsulfate (153.1 gms) and sodium bicarbonate (118 gms) was added to the reaction mixture at 25-30°C. Heated the reaction mixture to 55-60°C and stirred for 10 hours at the same temperature. Cooled the reaction mixture to 25-30°C. Quenched the reaction mixture with water at 25-30°C and stirred for 10 minutes at the same temperature. Filtered the solid and washed with water. Toluene (600 ml) was added to the obtained filtrate 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 toluene. Combined the organic layers and washed with sodium chloride solution. Activated carbon (20 gms) 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 toluene. Distilled off the solvent completely from the obtained filtrate under reduced pressure and co-distilled with isopropyl alcohol and cyclohexane mixture at 55-60°C. Cooled the obtained compound to 25-30°C. Isopropyl alcohol and cyclohexane mixture was added to the compound at 25-30°C and stirred for 3 hours at the same temperature. Filtered the precipitated solid, washed with mixture of isopropyl alcohol and cyclohexane, dried to get the title compound. Yield: 165 gms; M.R: 70-75°C.

Example-21: Preparation of 3-amino-5-(4-phenoxyphenyl)-1H-pyrazole-4-carbonitrile (Formula-8):

Methanol (200 ml) was added to a mixture of water (400 ml) and hydrazine hydrate (30 ml) at 25-30°C and stirred for 10 minutes at the same temperature. 2-Methoxy (4-phenoxy phenyl) methylene)malononitrile (100 gms) was slowly added portion wise to the reaction mixture at 10-15°C. Slowly raised the temperature of the reaction mixture to 25-30°C and stirred for 3 hours at the same temperature. Filtered the precipitated solid and washed with water. To the obtained wet compound, methanol (150 ml) was added at 25-

30°C. Heated the reaction mixture to 45-50°C and stirred for 40 minutes at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 2 hours at the same temperature. Filtered the precipitated solid, washed with methanol and dried to get the title compound. Yield: 86 gms; M.R: 197-203°C.

5 **Example-22: Preparation of 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (Formula-9):**

Zinc chloride (44.4 gms) and formamide (540 ml) were added to a mixture of O-xylene (450 ml) and 3-amino-5-(4-phenoxyphenyl)-1H-pyrazole-4-carbonitrile (90 gms) at 25-30°C and stirred for 10 minutes at the same temperature. Heated the reaction mixture to 10 115-120°C and stirred for 20 hours at the same temperature. Cooled the reaction mixture to 25-30°C. Tetrahydrofuran (90 ml) was added to the reaction mixture at 25-30°C and stirred for 2 hours at the same temperature. Filtered the precipitated solid and washed with O-xylene. To the obtained wet compound, water (360 ml) was added at 25-30°C. Heated the reaction mixture to 50-55°C and stirred for 1 hour at the same temperature. Cooled the 15 reaction mixture to 25-30°C and stirred for 1 hour at the same temperature. Filtered the precipitated solid, washed with water and dried to get the title compound.

Yield: 75 gms; M.R: 250-255°C.

Example-23: Preparation of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo [3,4-d] pyrimidin-4-amine dihydrochloride (Formula-13):

20 A mixture of 3-(4-phenoxy phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine (100 gms), (S)-tert-butyl-2-(3-hydroxypiperidine-1-yl)acetate (116.1 gms), triphenylphosphine (303.3 gms) and tetrahydrofuran (1 lt) was stirred for 10 minutes at 25-30°C. Heated the reaction mixture to 45-50°C. Diisopropylazodicarboxylate (233.4 gms) in THF (100 ml) solution was slowly added to the reaction mixture at 55-60°C and stirred the reaction mixture 25 for 3 hours at the same temperature. Methanolic hydrochloric acid solution (700 ml) was added to the reaction mixture at 60-65°C and stirred for 6 hours at the same temperature. Ethylacetate (2500 ml) was added to the reaction mixture at 60-65°C. Cooled the reaction mixture to 40-45°C and stirred for 3 hours at the same temperature. Filtered the precipitated solid and washed with ethylacetate.

30 Isopropanol (700 ml) and water (66.6 ml) were added to the obtained wet compound

at 25-30°C. Heated the reaction mixture to 65-70°C and stirred for 1 hour at the same temperature. Cooled the reaction mixture to 10-15°C. Isopropanol (300 ml) was added to the reaction mixture at 10-15°C and stirred for 3 hours at the same temperature. Filtered the solid, washed with isopropanol and dried to get the title compound. Yield: 92 gms.

5 Example-24: Preparation of crystalline form-C of 1-[(3R)-3-[4-amino-3-(4-phenoxy phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (Formula-1)

(R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13 (100 gm) was added to a mixture of dichloromethane (3000 ml) and N,N-diisopropylethylamine (84.5 gm) at 25-30°C under nitrogen atmosphere. Cooled the reaction mixture to -45 to -40°C. A mixture of acryloyl chloride (19 gm) and dichloromethane (200 ml) was added to the reaction mixture at -45 to -40°C and stirred the reaction mixture for 60 minutes at the same temperature. Quenched the reaction mixture with water at below -15°C and stirred the reaction mixture for 20 minutes at the same temperature. Raised the temperature of the reaction mixture to 0-5°C. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Combined the organic layers and washed with dilute sulfuric acid solution, followed by aqueous sodium bicarbonate solution. The organic layer was washed with water followed by aqueous sodium chloride solution. Distilled off the solvent from the organic layer completely under reduced pressure. Methanol (720 ml) and dichloromethane (80 ml) was added to the above obtained compound and stirred the reaction mixture for 30 minutes at 25-30°C. Carbon (10 gm) was added to the reaction mixture at 25-30°C and stirred it for 30 minutes at the same temperature. Filtered the reaction mixture through hyflow bed and washed with the mixture of methanol and dichloromethane. Cooled the filtrate to 0-5°C and stirred it for 3 hours at the same temperature. Filtered the precipitated solid, washed with methanol and dried to get the title compound.

Yield: 59.5 gm; MR: 130-135°C;

Acetyl impurity: 0.11%; Chloro impurity: Not detected; Amino piperidine impurity: 0.01; BoC amine impurity: 0.02; Dimer impurity: 0.02%; Di-piperidine impurity: 0.10%; Diamine impurity: 0.02%; Hydroxy impurity: 0.03%; Propionamide impurity: 0.01%; N-Oxide impurity: Not detected and Diamide impurity: Not detected.

Particle size distribution before micronisation: D_{10} : 3.134 μm ; D_{50} : 20.606 μm ; D_{90} : 177.57 μm .

The Powder X-ray diffraction pattern of the obtained compound is matching with PXRD of crystalline form-C disclosed in US20130338172.

5 **Example-25: Preparation of amorphous form of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (Formula-1)**

Crystalline form-C of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (100 gm) was dissolved in DMSO (300 ml) at 25-30°C and stirred the reaction mixture for 15 minutes. The above reaction mixture was
10 added to pre-cooled water (3000 ml) at 0-5° over a period of 60 minutes and stirred the reaction mixture for 2 hrs at the same temperature. Filtered the obtained solid and washed with water. Water (1500 ml) was added to the obtained compound at 0-5°C and stirred for 2 hrs at the same temperature. Filtered the solid, washed with water and dried to get the title compound. Yield: 96 gm;

15 The Powder X-ray diffraction pattern of the obtained compound is shown in figure-4.

Example-26: Preparation of amorphous form of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (Formula-1)

Crystalline form-C of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (50 gm) was dissolved in dichloromethane
20 (200 ml) at 25-30°C and distilled off the solvent from the reaction mixture under reduced pressure. Dichloromethane (100 ml) was added to the obtained compound and stirred for 15 minutes at 25-30°C. Filtered the reaction mixture and filtrate was slowly added to pre-cooled n-pentane (2500 ml) at -40 to -35°C. Stirred the reaction mixture for 2 hrs at -40 to -35°C. Filtered the obtained solid, washed with n-pentane and dried to get the title compound.

25 Yield: 42 gm;

The Powder X-ray diffraction pattern of the obtained compound is shown in figure-4.

Example-27: Preparation of amorphous form of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (Formula-1)

Crystalline form-C of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (100 gm) was dissolved in Dimethyl
30

acetamide (200 ml) at 25-30°C and stirred the reaction mixture for 15 minutes. Filtered the reaction mixture. The filtrate was added to pre-cooled water (3000 ml) at 15-20° over a period of 60 minutes and stirred the reaction mixture for 2 hrs at the same temperature. Filtered the obtained solid and washed with water. Water (1500 ml) was added to the
5 obtained compound at 15-20°C and stirred for 2 hrs at the same temperature. Filtered the solid, washed with water and dried to get the title compound to get the title compound.

Yield: 88 gm.

The Powder X-ray diffraction pattern of the obtained compound is shown in figure-4.

Example-28: Preparation of amorphous form of 1-[(3R)-3-[4-amino-3-(4-phenoxy phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (Formula-1)

Crystalline form-C of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (100 gm) was dissolved in Dimethyl formamide (200 ml) at 25-30°C and stirred the reaction mixture for 15 minutes. Filtered the reaction mixture. The filtrate was added to pre-cooled water (3000 ml) at 15-20° over a
15 period of 45 minutes and stirred the reaction mixture for 2 hrs at the same temperature. Filtered the obtained solid and washed with water. Water (1500 ml) was added to the obtained compound at 15-20°C and stirred for 2 hrs at the same temperature. Filtered the solid, washed with water and dried to get the title compound to get the title compound.

Yield: 87 gm.

Particle size distribution after micronisation: D₉₀: 58.817 µm.

The Powder X-ray diffraction pattern of the obtained compound is shown in figure-4.

Example-29: Preparation of amorphous form of 1-[(3R)-3-[4-amino-3-(4-phenoxy phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (Formula-1)

Crystalline form-C of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (100 gm) was dissolved in Dimethyl formamide (200 ml) at 25-30°C and stirred the reaction mixture for 15 minutes. Filtered the reaction mixture. The filtrate was added to pre-cooled water (3000 ml) at 0-5° over a period of 60 minutes and stirred the reaction mixture for 15 minutes at the same temperature. Raised temperature of the reaction mixture to 25-30°C minutes and stirred for 1 hr 30 minutes at the
30 same temperature. Filtered the obtained solid and washed with water. Slurrying the obtained

compound with water. Filtered the solid, washed with water and dried to get the title compound.

Yield: 87 gm.

The Powder X-ray diffraction pattern of the obtained compound is shown in figure-4.

5 **Example-30: Preparation of amorphous form of 1-[(3R)-3-[4-amino-3-(4-phenoxy phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (Formula-1)**

The mixture of dichloromethane (3 ml) and crystalline form-C of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1 (0.5 gm) was stirred for 30 minutes at 25-30°C. Filtered the reaction
10 mixture and washed with dichloromethane. Distilled off the solvent completely from the reaction mixture under reduced pressure, unload the compound and dried to get amorphous form of compound of formula-1. Yield: 0.3 gm.

The Powder X-ray diffraction pattern of the obtained compound is shown in figure-4.

15 **Example-31: Preparation of crystalline form-A of 1-[(3R)-3-[4-amino-3-(4-phenoxy phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (Formula-1)**

(R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13 (100 gm) was added to a mixture of dichloromethane (3000 ml) and N,N-diisopropylethylamine (84.5 gm) at 25-30°C and stirred for 10 minutes under nitrogen atmosphere. Cooled the reaction mixture to -45 to -40°C. A
20 mixture of acryloyl chloride (19 gm) and dichloromethane (200 ml) was added to the reaction mixture at -45 to -40°C and stirred the reaction mixture for 60 minutes at the same temperature. Quenched the reaction mixture with water at below -15°C and stirred the reaction mixture for 20 minutes at the same temperature. Raised the temperature of the reaction mixture to 0-5°C. Both the organic and aqueous layers were separated and extracted
25 the aqueous layer with dichloromethane. Combined the organic layers and washed with dilute sulfuric acid, followed by aqueous sodium bicarbonate solution. The organic layer was washed with water followed by aqueous sodium chloride solution. Distilled off the solvent from the organic layer completely under reduced pressure. Ethanol (720 ml) and dichloromethane (80 ml) was added to the above obtained compound and stirred the reaction
30 mixture for 30 minutes at 25-30°C. Carbon (10 gm) was added to the reaction mixture at 25-

30°C and stirred it for 30 minutes at the same temperature. Filtered the reaction mixture through hyflow bed and washed with the mixture of ethanol and dichloromethane. Cooled the filtrate to 0-5°C and stirred it for 3 hours at the same temperature. Filtered the precipitated solid, washed with methanol and dried to get the title compound. Yield: 47.0 gm;

5 The Powder X-ray diffraction pattern of the obtained compound is matching with PXRD of crystalline form-A disclosed in US20130338172.

Example-32: Preparation of crystalline form-A of 1-[(3R)-3-[4-amino-3-(4-phenoxy phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (Formula-1)

(R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine
10 dihydrochloride compound of formula-13 (100 gm) was added to a mixture of dichloromethane (3000 ml) and N,N-diisopropyl ethylamine (84.5 gm) at 25-30°C and stirred for 10 minutes under nitrogen atmosphere. Cooled the reaction mixture to -45 to -40°C. A mixture of acryloyl chloride (19 gm) and dichloromethane (200 ml) was added to the reaction mixture at -45 to -40°C and stirred the reaction mixture for 60 minutes at the same
15 temperature. Quenched the reaction mixture with water at below -15°C and stirred the reaction mixture for 20 minutes at the same temperature. Raised the temperature of the reaction mixture to 0-5°C. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Combined the organic layers and washed with dilute sulfuric acid, followed by aqueous sodium bicarbonate solution. The organic layer was
20 washed with water followed by aqueous sodium chloride solution. Distilled off the solvent from the organic layer completely under reduced pressure. Isopropanol (300 ml) was added to the above obtained compound and stirred the reaction mixture for 30 minutes at 25-30°C. Cooled the reaction mixture to 0-5°C and stirred for 2 hours. Filtered the solid and washed with isopropanol and dried to get the title compound. Yield: 68.0 gm;

25 The Powder X-ray diffraction pattern of the obtained compound is matching with PXRD of crystalline form-C disclosed in US20130338172.

Example-33: Preparation of crystalline form-A of 1-[(3R)-3-[4-amino-3-(4-phenoxy phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (Formula-1)

(R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine
30 dihydrochloride compound of formula-13 (100 gm) was added to a mixture of

dichloromethane (3000 ml) and N,N-diisopropyl ethylamine (84.5 gm) at 25-30°C and stirred for 10 minutes at the same temperature. Cooled the reaction mixture to -45 to -40°C. A mixture of acryloyl chloride (19 gm) and dichloromethane (200 ml) was added to the reaction mixture at -45 to -40°C and stirred the reaction mixture for 60 minutes at the same temperature. Quenched the reaction mixture with water at below -15°C and stirred the reaction mixture for 20 minutes at the same temperature. Raised the temperature of the reaction mixture to 0-5°C. Both the organic and aqueous layers were separated and extracted the aqueous layer with dichloromethane. Combined the organic layers and washed with aqueous sulfuric acid, followed by aqueous sodium bicarbonate solution. The organic layer was washed with water followed by aqueous sodium chloride solution. Distilled off the solvent from the organic layer completely under reduced pressure. Methanol (720 ml) and dichloromethane (80 ml) was added to the above obtained compound and stirred the reaction mixture for 30 minutes at 25-30°C. Carbon (10 gm) was added to the reaction mixture at 25-30°C and stirred it for 30 minutes at the same temperature. Filtered the reaction mixture through hyflow bed and washed with the mixture of methanol and dichloromethane. Cooled the filtrate to 0-5°C and stirred it for 3 hours at the same temperature. Filtered the precipitated solid, washed with methanol at 0-5°C. Isopropanol (290 ml) was added to the obtained compound at 25-30°C and stirred for 2 hours at the same temperature. Water (580 ml) was slowly added to the reaction mixture at 25-30°C and stirred for 1 hour at the same temperature. Cooled the reaction mixture to 0-5°C and stirred for 1 hour at the same temperature. Filtered the precipitated solid, washed with water and dried to get the title compound. Yield: 49.8 gms.

The Powder X-ray diffraction pattern of the obtained compound is matching with PXRD of crystalline form-C disclosed in US20130338172.

We claim:

1. A process for the preparation of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1,
5 comprising of:
 - a) Reacting 4-fluorobenzaldehyde compound of formula-2 with phenol compound of formula-3 in presence of a base in a suitable solvent to provide 4-phenoxy benzaldehyde compound of formula-4,
 - b) oxidizing compound of formula-4 in-situ with a suitable oxidizing agent in a suitable
10 solvent to provide 4-phenoxybenzoic acid compound of formula-5,
 - c) converting the compound of formula-5 into its acid chloride by using a suitable chlorinating agent in presence or absence of a solvent,
 - d) reacting the compound obtained in step-(c) with malononitrile in presence of a base in a suitable solvent provides 2-(hydroxy(4-phenoxyphenyl)methylene) malononitrile
15 compound of formula-6,
 - e) methylating the compound of formula-6 in-situ with a suitable methylating agent optionally in presence of a base in a suitable solvent provides 2-(methoxy(4-phenoxyphenyl) methylene)malononitrile compound of formula-7,
 - f) reacting the compound of formula-7 with hydrazine hydrate in a suitable solvent
20 provides 3-amino-5-(4-phenoxyphenyl)-1H-pyrazole-4-carbonitrile compound of formula-8,
 - g) reacting the compound of formula-8 with formamide in presence of a suitable catalyst at a suitable temperature in a suitable solvent provides 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine compound of formula-9,
 - 25 h) optionally, purifying the compound obtained in step-g) in a suitable solvent provides pure compound of formula-9,
 - i) reacting 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine compound of formula-9 with (S)-tert-butyl 3-hydroxypiperidine-1-carboxylate compound of formula-17 in presence of diisopropylazodicarboxylate and triphenylphosphine in

tetrahydrofuran provides (R)-tert-butyl-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate compound of formula-12,

j) treating the compound of formula-12 in-situ with a suitable hydrochloric acid source in a suitable solvent provides (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13,

k) optionally purifying the obtained compound from a suitable solvent or mixture thereof,

l) reacting the compound of formula-13 with acryloyl chloride in presence of a suitable base in a suitable solvent provides compound of formula-1,

m) optionally, purifying the obtained compound of formula-1 with a suitable solvent or mixtures thereof provides pure compound of formula-1.

2. The process according to claim-1, wherein,

in step-a) the suitable base is inorganic base or organic base,

in step-d) & step-l) the base is organic base,

in step-e) the base is inorganic base,

in step-j) the suitable hydrochloric acid source is selected from HCl gas, aqueous HCl, dry HCl, ethylacetate-HCl, IPA-HCl, ethanol-HCl, methanol-HCl;

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

3. A process for the preparation of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, comprising of:

a) Reacting 4-fluorobenzaldehyde compound of formula-2 with phenol compound of formula-3 in presence of potassium carbonate in dimethylformamide provides 4-phenoxybenzaldehyde compound of formula-4,

b) oxidizing the compound of formula-4 in-situ with potassium permanganate in water to provide 4-phenoxybenzoic acid compound of formula-5,

- c) converting the compound of formula-5 into its acid chloride derivative by treating it with thionyl chloride,
- d) reacting the compound obtained in step-(c) in-situ with malononitrile in presence of diisopropylethylamine in toluene provides 2-(hydroxy(4-phenoxyphenyl)methylene) malononitrile compound of formula-6,
- e) methylating compound of formula-6 in-situ with dimethyl sulfate in presence of sodium bicarbonate in acetone provides 2-(methoxy(4-phenoxyphenyl)methylene) malononitrile compound of formula-7,
- f) reacting compound of formula-7 with hydrazine hydrate in methanol provides 3-amino-5-(4-phenoxyphenyl)-1H-pyrazole-4-carbonitrile compound of formula-8,
- g) reacting compound of formula-8 with formamide in presence of zinc chloride in O-xylene at a temperature ranging from 110°C to 120°C provides 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine compound of formula-9,
- h) purifying the compound obtained in step-g) in water provides pure compound of formula-9,
- i) reacting 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine compound of formula-9 with (S)-tert-butyl 3-hydroxypiperidine-1-carboxylate compound of formula-17 in presence of diisopropylazodicarboxylate and triphenylphosphine in tetrahydrofuran provides (R)-tert-butyl-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate compound of formula-12,
- j) treating the compound of formula-12 in-situ with methanolic HCl in ethylacetate provides (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13,
- k) purifying the obtained compound from aqueous isopropanol provides pure compound of formula-13,
- l) reacting the compound of formula-13 with acryloyl chloride in presence of diisopropylethylamine in dichloromethane provides compound of formula-1,
- m) purifying the obtained compound of formula-1 with a mixture of dichloromethane and methanol provides pure compound of formula-1.

4. A process for the preparation of 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine compound of formula-9, comprising of :

- a) Reacting 4-fluorobenzaldehyde compound of formula-2 with phenol compound of formula-3 in presence of potassium carbonate in dimethylformamide provides 4-phenoxybenzaldehyde compound of formula-4,
- b) oxidizing compound of formula-4 in-situ with potassium permanganate in water to provide 4-phenoxybenzoic acid compound of formula-5,
- c) converting the compound of formula-5 into its acid chloride derivative by treating it with thionyl chloride,
- d) reacting the compound obtained in step-(c) with malononitrile in presence of diisopropylethylamine in toluene provides 2-(hydroxy(4-phenoxyphenyl)methylene) malononitrile compound of formula-6,
- e) methylating compound of formula-6 in-situ with dimethyl sulfate in presence of sodium bicarbonate in acetone provides 2-(methoxy(4-phenoxyphenyl)methylene) malononitrile compound of formula-7,
- f) reacting compound of formula-7 with hydrazine hydrate in methanol provides 3-amino-5-(4-phenoxyphenyl)-1H-pyrazole-4-carbonitrile compound of formula-8,
- g) reacting compound of formula-8 with formamide in presence of zinc chloride in O-xylene at a temperature ranging from 110°C to 120°C provides 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine compound of formula-9,
- h) purifying the compound obtained in step-g) in water provides pure compound of formula-9.

5. A process for the preparation of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, comprising of:

- a) Reacting 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine compound of formula-9 with (S)-tert-butyl 3-hydroxypiperidine-1-carboxylate compound of formula-17 in presence of diisopropylazodicarboxylate and triphenylphospine in

tetrahydrofuran provides (R)-tert-butyl-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate compound of formula-12,

b) treating the compound of formula-12 in-situ with methanolic HCl in ethylacetate provides (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13,

c) purifying the obtained compound from aqueous isopropanol provides pure compound of formula-13,

d) reacting the compound of formula-13 with acryloyl chloride in presence of diisopropylethylamine in dichloromethane provides compound of formula-1,

e) purifying the obtained compound of formula-1 with a mixture of dichloromethane and methanol provides pure compound of formula-1.

6. The crystalline form-M of (S)-tert-butyl-3-(tosyloxy)piperidine-1-carboxylate compound of formula-11a is characterized by:

a) its powder X-ray diffraction pattern having peaks at 11.0, 18.8, 19.3, 20.3, 20.9 and 21.3 ± 0.2 degrees of two-theta,

b) further characterized by its powder X-ray diffraction pattern having peaks at 7.9, 8.4, 13.7, 14.9 and 16.7 ± 0.2 degrees of two-theta; and

c) its powder X-ray diffraction pattern as shown in figure-1.

7. The crystalline form-S of (S)-tert-butyl-3-((methylsulfonyl)oxy)piperidine-1-carboxylate compound of formula-11b is characterized by:

a) its powder X-ray diffraction pattern having peaks at 8.2, 13.6, 18.7 and 20.0 ± 0.2 degrees of two-theta,

b) further characterized by its powder X-ray diffraction pattern having peaks at 9.3, 11.5, 14.4, 15.3, 15.6, 16.8, 21.0, 22.2, 22.6, 23.3 and 24.9 ± 0.2 degrees of two-theta; and

c) its powder X-ray diffraction pattern as shown in figure-2.

8. The crystalline form-N of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13, is characterized by:

- a) its powder X-ray diffraction pattern having peaks at 3.7, 7.4, 9.0, 14.2 and 22.3 ± 0.2 degrees of two-theta ,
- b) its powder X-ray diffraction pattern as shown in figure-3.

9. A process for the preparation of crystalline form-M of (S)-tert-butyl-3-(tosyloxy)piperidine-1-carboxylate compound of formula-11a, comprising of;

- a) Adding a suitable solvent to (S)-tert-butyl-3-(tosyloxy)piperidine-1-carboxylate compound of formula-11a at a suitable temperature,
- b) stirring the reaction mixture,
- c) cooling the reaction mixture to a suitable temperature,
- d) stirring the reaction mixture,
- e) filtering the solid, washing with suitable solvent and then drying to get crystalline form-M of compound of formula-11a.

10. A process for the preparation of crystalline form-S of (S)-tert-butyl-3-((methylsulfonyl)oxy)piperidine-1-carboxylate compound of formula-11b, comprising of;

- a) Adding a suitable solvent to (S)-tert-butyl-3-((methylsulfonyl)oxy)piperidine-1-carboxylate compound of formula-11b at a suitable temperature,
- b) stirring the reaction mixture,
- c) cooling the reaction mixture to a suitable temperature,
- d) stirring the reaction mixture,
- e) filtering the solid, washing with suitable solvent and then drying to get crystalline form-S of compound of formula-11b.

11. The process according to claims 9 or 10, wherein,

in step-a) & e) the suitable solvent is selected from hydrocarbon solvents, ether solvents, ester solvents, chloro solvents, alcoholic solvents, polar aprotic solvents, ketone solvents, nitrile solvents, polar solvents or mixtures thereof, preferably the suitable solvent is selected from hydrocarbon solvents;

in step-a) the suitable temperature is ranging from 25-30°C;

in step-c) the suitable temperature is below 15°C.

12. A process for the preparation of crystalline form-N of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13, comprising of:

- a) Dissolving the (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13 in a suitable solvent or in a mixture of solvents by heating to a suitable temperature,
- b) cooling the reaction mixture to a suitable temperature,
- c) stirring the reaction mixture,
- d) filtering the solid, washing with suitable solvent and then drying to provide crystalline form-N of compound of formula-13.

13. A process for the preparation of crystalline form-N of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13, comprising of:

- a) Dissolving the (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13 in aqueous isopropyl alcohol by heating to 75-80°C,
- b) cooling the reaction mixture to 0-5°C,
- c) stirring the reaction mixture,
- d) filtering the solid, washing with isopropyl alcohol and then drying to get crystalline form-N of compound of formula-13.

14. A process for the preparation of amorphous 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, comprising of:

- a) Dissolving 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1 in a suitable first solvent,
- b) adding the solution obtained in step-a) to a suitable second solvent,
- c) filtering the obtained solid,

- d) optionally, slurring the solid obtained in step-c) in a suitable third solvent provides amorphous form of the compound of formula-1.

15. The process according to claim-14, wherein,

- 5 In step-a) the suitable solvent used is selected from polar aprotic solvents, nitrile solvents, alcohol solvents, ketone solvents, chloro solvents or mixtures thereof;
in step-b) the suitable second solvent used is selected from polar solvents, hydrocarbon solvents or mixtures thereof.
in step-c) the suitable third solvent used is selected from polar solvents.

10

16. A process for the preparation of amorphous 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d] pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, comprising of:

15

- a) Dissolving crystalline Form-C of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1 in dimethylformamide,
b) adding the solution obtained in step-a) to water,
c) filtering the obtained solid,
d) slurring the solid obtained in step-c) in water provides amorphous form of the compound of formula-1.

20

17. A process for the preparation of crystalline form-C of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, comprising of:

25

- a) Reacting the (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13 with acryloyl chloride in presence of a suitable base in a suitable solvent provides 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1,

30

- b) purifying the compound of formula-1 obtained in step-a) in a suitable solvent provides pure crystalline form-C of the compound of formula-1.

18. The process according to claim-17, wherein,

in step-a) the suitable base is organic base;

in step-a) & b) the suitable solvent used is selected from hydrocarbon solvents, ether

5 solvents, ester solvents, chloro solvents, alcoholic solvents, polar aprotic solvents, ketone solvents, nitrile solvents, polar solvents or mixtures thereof.

19. A process for the preparation of crystalline form-C of 1-[(3R)-3-[4-amino-3-(4-

phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one

10 compound of formula-1, comprising of :

a) Reacting the (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13 with acryloyl chloride in presence of diisopropyl ethylamine in dichloromethane provides 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1,

b) dissolving the compound of formula-1 obtained in step-a) in a mixture of methanol and dichloromethane,

c) treating the reaction mixture with carbon,

d) cooling the reaction mixture,

20 e) filtering the solid obtained in step-d) to get pure crystalline form-C of the compound of formula-1.

20. A process for the preparation of crystalline from-A of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one

25 compound of formula-1, comprising of:

a) Treating the (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13 with acryloyl chloride in presence of a base in a suitable solvent provides 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1,

- b) purifying the compound of formula-1 obtained in step-a) in a suitable solvent provides pure crystalline form-A of the compound of formula-1.

21. The process according to claim-20, wherein,

5 In step-a) the suitable base used is organic base;

in step-a) & b) the suitable solvent used is selected from hydrocarbon solvents, ether solvents, ester solvents, chloro solvents, alcoholic solvents, polar aprotic solvents, ketone solvents, nitrile solvents, polar solvents or mixtures thereof,

10 22. A process for the preparation of crystalline form-A of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, comprising of :

a) Reacting the (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13 with acryloyl chloride
15 in presence of diisopropylethylamine in dichloromethane provides 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1,

b) dissolving the compound of formula-1 obtained in step-a) in a mixture of methanol and dichloromethane,

20 c) treating the reaction mixture with carbon,

d) cooling the reaction mixture,

e) filtering the obtained solid,

f) slurrying the solid in a mixture of isopropanol and water,

25 g) filtering the obtained solid and drying to get pure crystalline form-C of the compound of formula-1.

23. A process for the preparation of crystalline form-A of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1, comprising of :

30 a) Reacting the (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13 with acryloyl chloride

in presence of diisopropylethylamine in dichloromethane provides 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1,

- 5 b) dissolving the compound of formula-1 obtained in step-a) in the mixture of ethanol and dichloromethane,
- c) treating the reaction mixture with carbon,
- d) cooling the reaction mixture,
- e) filtering the solid obtained in step-d) to get pure crystalline form-A of the compound of formula-1.

10

24. A process for the preparation of crystalline form-A of compound of formula-1 from the crystalline form-C of compound of formula-1.

15

25. A process for the preparation of amorphous compound of formula-1 from the crystalline form-C of compound of formula-1.

20

26. Use of crystalline Form-M of compound of formula-11a (or) crystalline Form-S of compound of formula-11b for the preparation of pure (R)-tert-butyl 3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate compound of formula-12.

25

27. Use of crystalline Form-N of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine dihydrochloride compound of formula-13 for the preparation of pure 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1.

30

28. Particle size distribution of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1 having d(0.9) less than 200 µm, preferably less than 100 µm, more preferably less than 50 µm.

29. The 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1 obtained according to any of the preceding claims is substantially free of chloro impurity by HPLC.

5 30. The 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1 obtained according to any of the preceding claims is substantially free of N-oxide impurity and diamide impurity by HPLC.

10 31. The 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1 obtained according to any of the preceding claims having purity greater than 99% by HPLC, preferably greater than 99.6 % purity by HPLC.

15

20

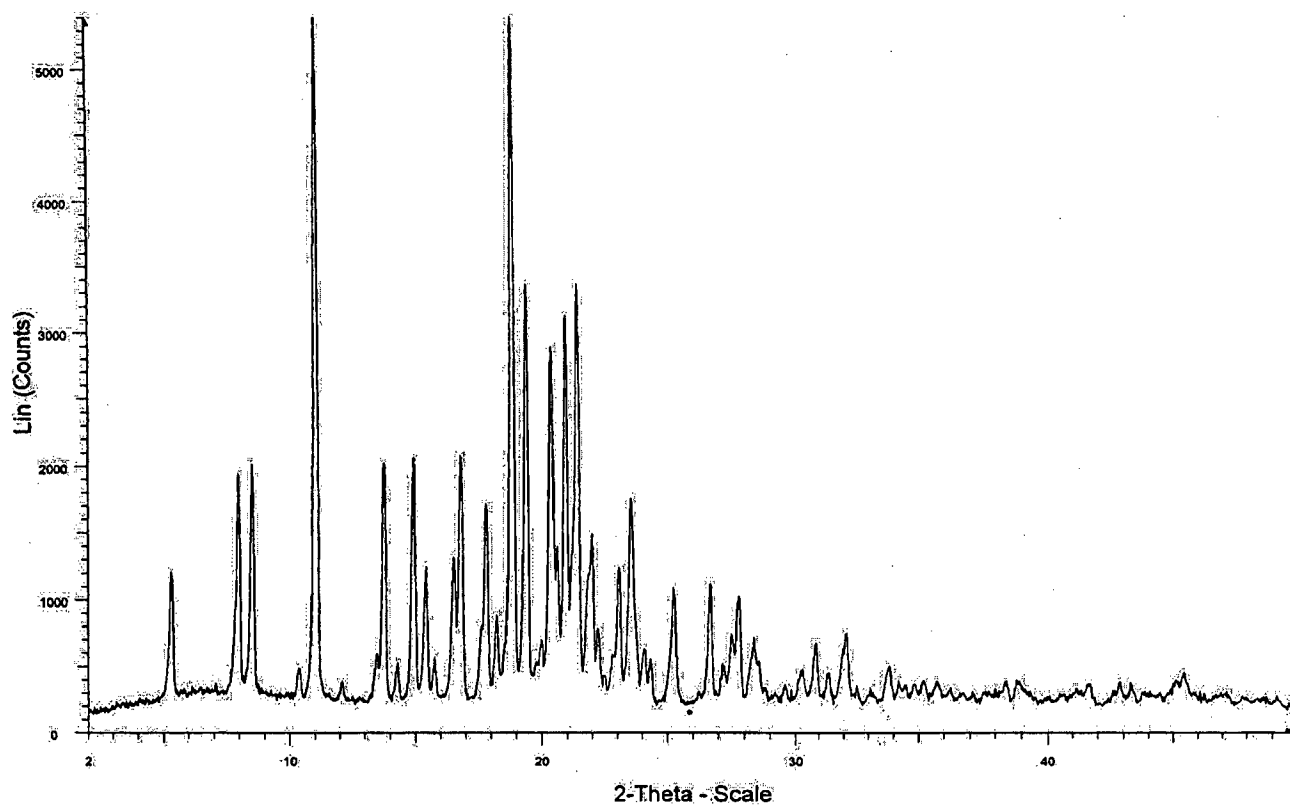


Figure-1

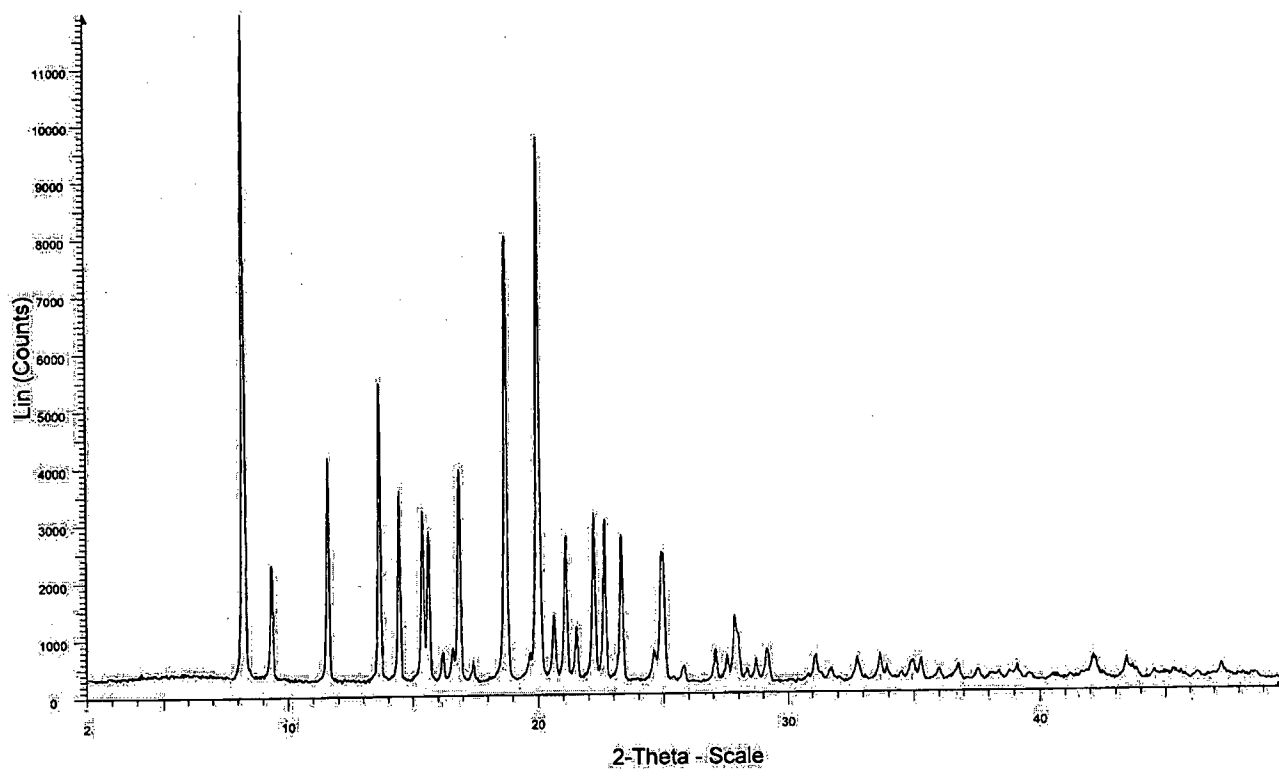


Figure-2

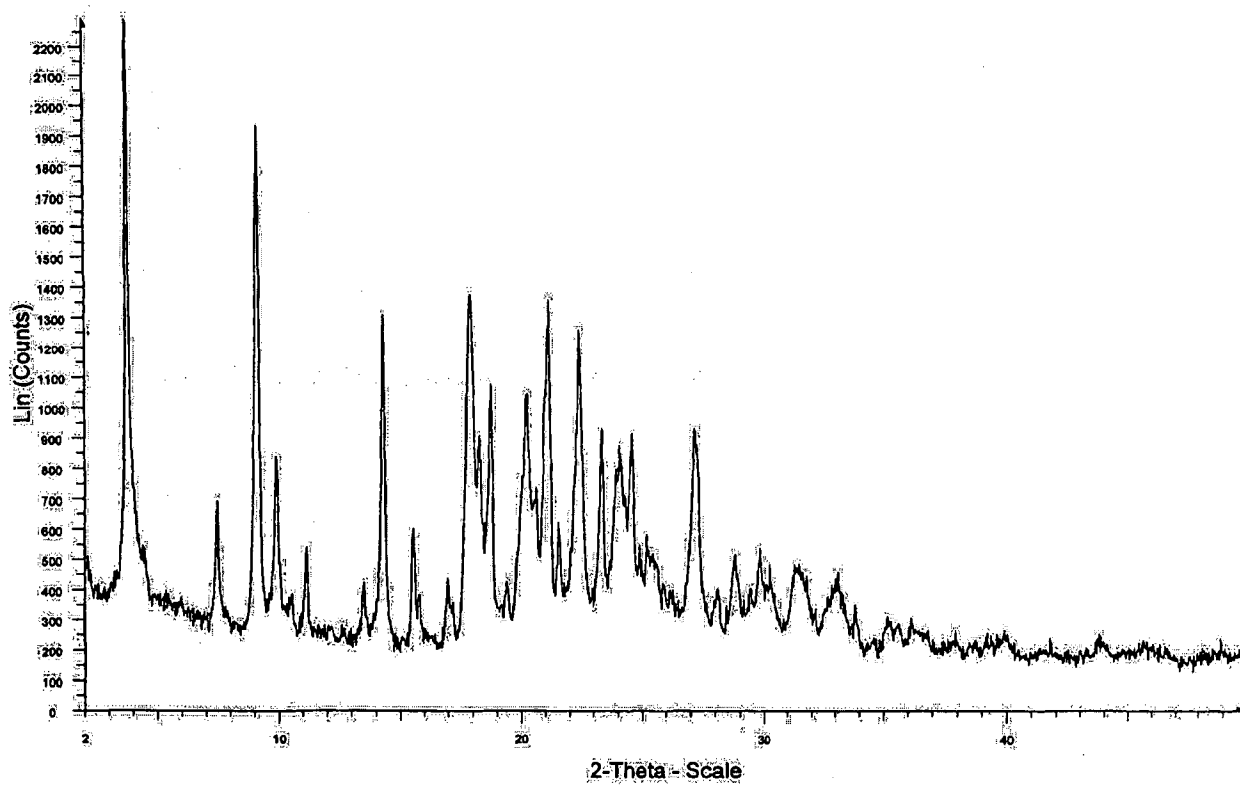


Figure-3

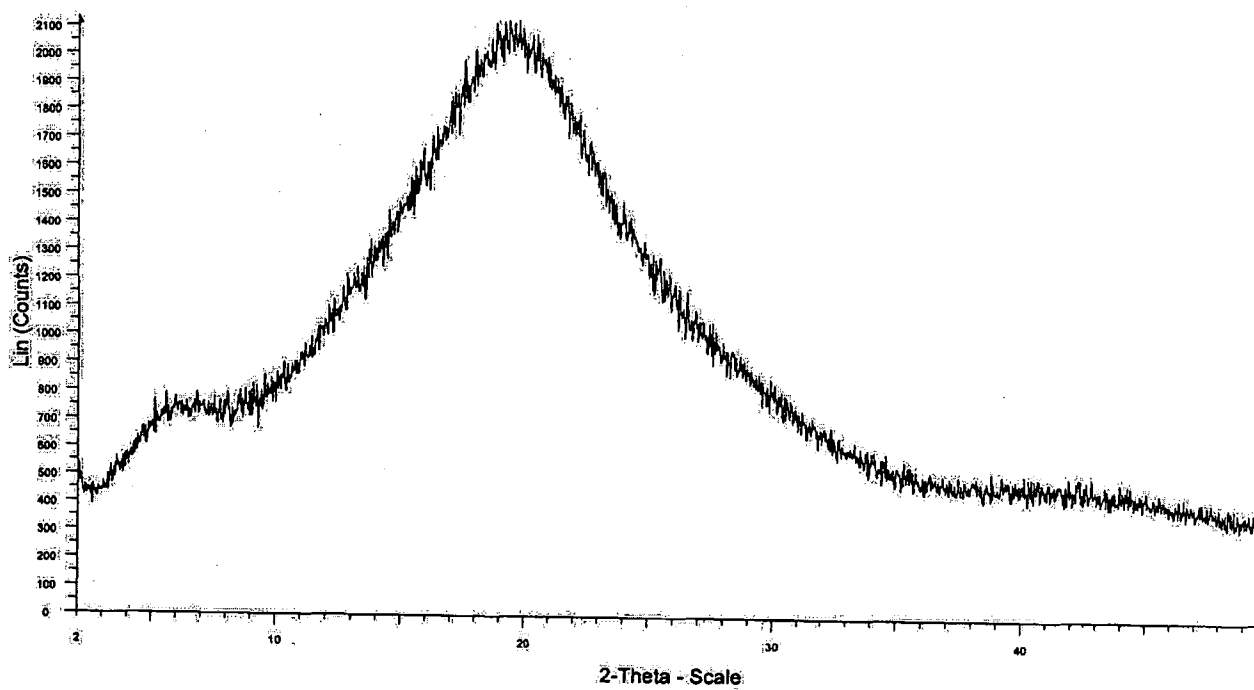


Figure-4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2016/000106

A. CLASSIFICATION OF SUBJECT MATTER

A61K31/519, C07D401/04, C07D487/04, C07D211/56 Version=2016.01

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)

A61K, C07D

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: process, preparation, Ibrutinib, formamide, hydrazine, acryloyl chloride

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/039218 A2, (PHARMACYCLICS, INC. [US]) 3 April 2008 (03.04.2008) See Example 1, scheme 1, page 70	5 (fully) & 28-31 (partially)
Y	See Example 1, scheme 1, page 70 -----	1-3 (fully)
X	CN 103626774 A, (SUZHOU MINGRUI PHARMACEUTICAL CO LTD [CN]; XU XUENONG [CN]), 12 March 2014 (12.03.2014) See description para [0006] to [0015]	5 (fully) & 28-31 (partially)
Y	See description para [0006] to [0015] -----	1-3 (fully)
Y	US 2014/0275126 A1, (JANSSEN PHARMACEUTICA NV[BE]), 18 September 2014 (18.09.2014) See description para [0006] to [0007] & para [0099] to [0110] -----	1-3, 5 (fully) & 28-31 (partially)
Y	Tsuyoshi Nakamura et al., "Discovery of CS-2100, a potent, orally active and S1P3-sparing S1P1 agonist", Bioorganic and Medicinal Chemistry Letters, vol. 22, issue 4, pages 1788 - 1792,	1-3 (fully)



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

14-09-2016

Date of mailing of the international search report

14-09-2016

Name and mailing address of the ISA/

Indian Patent Office
Plot No.32, Sector 14, Dwarka, New Delhi-110075
Facsimile No.

Authorized officer

Arup Garu

Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN2016/000106

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Published on: 15 February 2012 (15/02/2012) See figure 6	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2016/000106

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:
Group 1. Claims 1-3, 5 (fully) & 28-31 (partially)

The subject matter of these claims relates a process for the preparation of
1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one
compound
of formula-1 which is commonly known as Ibrutinib and its purity & particle size.
Group 2. Claim 4 (fully)

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.:
1-3, 5 (fully) & 28-31 (partially)

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)

The subject matter of this claim relates to a process for the preparation of 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine compound of formula-9. It is an intermediate of the Ibrutinib.
Group 3. Claims 6, 9 (fully) & 11, 26 (partially)

The subject matter of these claims relates to the crystalline form-M of (S)-tert-butyl-3-(tosyloxy)piperidine-1-carboxylate compound of formula-11a, process for preparation thereof and its use. It is an intermediate of the Ibrutinib.
Group 4. Claims 7, 10 (fully) & 11, 26 (partially)

The subject matter of these claims relates to the crystalline form-S of (S)-tert-butyl-3-((methylsulfonyl)oxy)piperidine-1-carboxylate compound of formula-11b, process for preparation thereof and its use. It is an intermediate of the Ibrutinib.
Group 5. Claims 8, 12, 13 & 27 (fully)

The subject matter of these claims relates to the crystalline form-N of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1 H-pyrazolo [3,4-d] pyrimidin-4-amine dihydrochloride compound of formula-13, process for preparation thereof and its use. It is an intermediate of the Ibrutinib.
Group 6. Claims 14-16 & 25 (fully) & 28-31 (partially)

The subject matter of these claims relates a process for the preparation of amorphous form of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1 which is commonly known as Ibrutinib and its purity & particle size.
Group 7. Claims 17-19 (fully) & 28-31 (partially)

The subject matter of these claims relates a process for the preparation of crystalline form C of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1 which is commonly known as Ibrutinib and its purity & particle size.
Group 8. Claims 20-24 (fully) & 28-31 (partially)

The subject matter of these claims relates a process for the preparation of crystalline form A of 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one compound of formula-1 which is commonly known as Ibrutinib and its purity & particle size.

Reason:

The 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one

compound
of formula-1 i.e. Ibrutinib is the only common technical features connecting these eight groups of invention. However, there are several prior art which disclose Ibrutinib and its pharmaceutical application. The document WO 2013184572 A1 discloses the various crystalline forms of Ibrutinib and its pharmaceutical composition. The document US 2014/0275126 A1 (D3) discloses the several process for synthesising Ibrutinib. Therefore, the common technical features Ibrutinib of these eight groups could not serve as a special technical feature connecting these groups of inventions.

Further, there is no other special technical feature which correlates these eight 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/IN2016/000106

Citation	Pub.Date	Family	Pub.Date
WO 2008039218 A2	03-04-2008	WO 2008039218 A3	29-05-2008
		AU 2006348662 A1	03-04-2008
		CA 2663116 A1	03-04-2008
		CN 101610676 A	23-12-2009
		EP 2081435 A2	29-07-2009
		JP 2010504324 A	12-02-2010
		US 2008108636 A1	08-05-2008
CN 103626774 A	12-03-2014	WO 2015074464 A1	28-05-2015
US 2014275126 A1	18-09-2014	AU 2014230935 A1	03-09-2015
		CA 2901510 A1	18-09-2014
		EP 2970291 A1	20-01-2016
		JP 2016510779 A	11-04-2016