

CLAIMS

1. Amorphous (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride.
2. A pharmaceutical formulation comprising amorphous (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride.
3. The formulation of claim 2, further comprising precipitated silica, fumed silica or amorphous silica.
4. The formulation of claim 3, further comprising microcrystalline cellulose.
5. The formulation of claim 4, further comprising antioxidant selected from BHA, BHT or propyl gallate.
6. The formulation of claim 5, further comprising polyvinylpyrrolidone.
7. The formulation of claim 2, comprising 100 to 400 mg of (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one.
8. The formulation of claim 2, wherein the formulation is a tablet for oral delivery.
9. The formulation of claim 2, further comprising Polyvinyl pyrrolidone, Butylated hydroxyl anisole, Croscarmellose sodium, Fumed silica, Microcrystalline cellulose and Stearic acid.
10. A process of producing amorphous (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride, comprising spray drying a mixture comprising (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride or a solvate thereof and solvent.

11. A process of producing amorphous (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride, comprising contacting a mixture comprising (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride or a solvate thereof with a gas.

12. The process of claim 11, wherein the gas comprises nitrogen and water.

13. A tablet for oral delivery comprising amorphous (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride.

14. The tablet of claim 13, comprising 100 mg (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride.

15. The tablet of claim 13, comprising 400 mg (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride.

16. The amorphous (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride of claim 2, comprising onset T_g in the range of about 124-130 °C.

17. The amorphous (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride of claim 16, wherein said onset T_g is stable for at least about 12 weeks.

18. The amorphous (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride of claim 2, comprising water content between about 3.5-4.0 %.

19. The amorphous (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride of claim 2, further comprising water, wherein said water content remains between about 3.5-4.5 % for at least 12 weeks.

20. The amorphous (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride of claim 1, which shows a glass transition in a differential scanning calorimetry (DSC) spectrum, wherein the glass transition is evident in a second heating cycle

wherein the glass transition onset temperature is about 114 °C.

21. The amorphous (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride of claim 1, which shows a glass transition in a modulated differential scanning calorimetry (DSC) spectrum wherein the glass transition onset temperature is about 124-134 °C and the modulated differential scanning calorimetry (DSC) has a rate of about 2 °C/minute with modulation of about ± 1 °C every 60 seconds.

22. A composition consisting essentially of amorphous (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride.

23. The process of claim 10, wherein said solvent is water or ethanol.

24. The process of claim 10, wherein said spray dried amorphous (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride comprises about 0.01 to about 2.5 % residual solvent.

25. The process of claim 10, wherein said solvate is an ethyl acetate solvate, said solvent is water, and said spray dried amorphous (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride comprises less than about 1.0 %w/w water and about 0.25 %w/w or less ethyl acetate.

26. The process of claim 10, further comprising drying the spray-dried amorphous (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride.

27. The process of claim 26, wherein said spray dried amorphous (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride comprises less than about 0.5% solvent after said drying.

28. A crystalline form of (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride having X-ray diffraction pattern that includes a characteristic peak at about 7.1.

29. The crystalline form of claim 28, further comprising one or more characteristic peaks selected from 8.4, 8.8, 10.5, 12.7, 13.7, 13.9, 17.4, 21.1 and 22.3.

30. A liquid fill capsule comprising (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride and a solvent selected from mono-esters, di-esters, tri-esters and combinations thereof, of fatty acids (C₃₋₂₀ alkyl or C₈₋₁₈ alkyl) and glycerol, ethylene glycol, propylene glycol or polyethylene glycol.

31. The capsule of claim 30, wherein the solvent is selected from glyceryl stearate, esters of natural fatty, stearic and palmitic acids with glycerin, alkylglycol caprylates, propylene glycol monocaprylate, polyethyleneglycol glyceryl laurate, polyethyleneglycol glyceryl oleate, polyethyleneglycol glyceryl linoleate, propylene glycol monolaurate, poloxamer, polyethyleneglycol, propylene glycol, glycerol, d-alpha tocopheryl polyethyleneglycol succinate, polyethyleneglycol caprylic or capric glyceride, and esters of caprylic or capric fatty acids with glycerin or propylene glycol.

32. The capsule of claim 30, wherein the solvent is propylene glycol caprylate or propylene glycol monolaurate.

33. A crystalline composition comprising (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride and solvent selected from the group consisting of capryol glycol, lauryl glycol, MEK, MIBK, MTBK, chloroform, dichloromethane, ethyl acetate, toluene, chlorobenzene, ethylbenzene, THF, 2-methylTHF, 1,2-dichloroethane, ortho-xylene, meta-xylene, para-xylene, anisole, methyl acetate, cumene, tetralin, propyl acetate, isopropyl acetate, diisobutyl ketone, isobutyl acetate, t-butyl acetate,

amyl acetate, glycerol triacetate, 1,2-dimethoxyethane, 1,2-diethoxyethane, 2,2-dimethoxypropane, ethyl ether, t-butyl methyl ether, water and mixtures thereof.

34. The composition of claim 33, further comprising said solvent solvated to said (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride.

35. The composition of claim 34, further comprising said (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride solvated in a 1:1 molar ratio with said solvent.

36. The composition of claim 34, further comprising said (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride solvated in a w/w% (solvent:compound) in the range of about 0.1% to about 20%.

37. Mesomorphous (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride.

38. A process of producing mesomorphous (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride, comprising contacting (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride with a solvent comprising antisolvent, and removing said solvent.

39. The process of claim 38, wherein said solvent has solubility greater than about 20 mg/mL for (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride.

40. The process of claim 39, wherein said solvent comprises water, ethyl acetate, methanol, ethanol, isopropanol, 2-butanol, t-butanol and 2-methoxy ethanol, tetrahydrofuran, 2-methyltetrahydrofuran, toluene, chloroform, dichloromethane, 1,2-dichloroethane or acetone.

41. The process of claim 39, wherein said solvent comprises ethyl acetate.
42. The process of claim 41, wherein said solvent comprises ethyl acetate:isopropanol in 1:1 mixture.
43. The process of claim 38, wherein said antisolvent has solubility less than about 20 mg/mL for (S)-2-(4-chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one monohydrochloride.
44. The process of claim 43, wherein said antisolvent comprises pentane, hexane, cyclohexane, heptane, ethyl acetate, iso-propyl acetate, methyl t-butyl ether (MTBE) or methyl iso-butyl ketone.