

Claims

1. A process for the manufacture of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate comprising the steps of:
 - 5 a) reacting tert-butyl piperazine-1-carboxylate (A1) with hexafluoropropan-2-ol in the presence of an acyl transfer agent to form 1-(tert-butyl) 4-(1,1,1,3,3,3-hexafluoropropan-2-yl) piperazine-1,4-dicarboxylate (A2), wherein step a) is carried out in a first solvent;
 - b) reacting 1-(tert-butyl) 4-(1,1,1,3,3,3-hexafluoropropan-2-yl) piperazine-1,4-dicarboxylate (A2) obtained in step a) with a strong acid to form 1,1,1,3,3,3-hexafluoropropan-2-yl
10 piperazine-1-carboxylate (A3), or a pharmaceutically acceptable salt thereof, wherein step b) is optionally carried out in a second solvent;
 - c) reacting 1,1,1,3,3,3-hexafluoropropan-2-yl piperazine-1-carboxylate (A3), or a pharmaceutically acceptable salt thereof obtained in step b) with 2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzaldehyde in the presence of a reducing agent and an organic base to
15 form a reaction mixture comprising 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, wherein the reaction in step c) is carried out in a third solvent.
2. The process according to claim 1, wherein step a) is carried out under pressure of 2 bar to 6 bar.
3. The process according to any one of claims 1-2, wherein the ingredients in step a) are added in
20 the consecutive order of the acyl transfer agent, the first solvent, tert-butyl piperazine-1-carboxylate (A1), and hexafluoropropan-2-ol as the last ingredient.
4. The process according to any one of claims 1-3, wherein the strong acid in step b) is HCl; and wherein the step b) is carried out in a second solvent.
5. The process according to claim 4, wherein the second solvent is selected from the group
25 consisting of toluene, isopropyl acetate, dichloromethane, acetonitrile, ethers and esters.
6. The process according to any one of claims 1-5, wherein the third solvent in step c) is ethyl acetate.
7. The process according to any one of claims 1-6, wherein step c) comprises the steps of:
 - i) providing a mixture comprising 1,1,1,3,3,3-hexafluoropropan-2-yl piperazine-1-carboxylate
30 (A3), or a pharmaceutically acceptable salt thereof obtained in step b), 2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzaldehyde, the organic base, and the third solvent;

ii) adding the reducing agent to the mixture obtained from step i) to provide a reaction mixture comprising 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate.

8. The process according to any one of claims 1-7, wherein step c) further comprises the step of:

5 iii) adding water to the reaction mixture comprising 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate to form a phase separation having an organic phase comprising 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, followed by diluting the organic phase with the third solvent.

10 9. The process according to claim 8, wherein step c) further comprises the steps of:

iv) adding an C₁-C₄ alcohol to the organic phase comprising 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate to provide a solution comprising 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, optionally concentrating the solution.

15 v) adding water to the solution comprising 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate to form a suspension comprising 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate.

10. The process according to claim 9, wherein step c) further comprises the step of:

20 vi) isolating 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate from the suspension comprising 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate obtained in claim 9.

11. The process according to any one of claims 1-10, wherein 2-(pyrrolidin-1-yl)-4-

25 (trifluoromethyl)benzaldehyde is obtained in step c0) prior to step c), wherein step c0) comprises the step of; reacting 2-fluoro-4-(trifluoromethyl)benzaldehyde with pyrrolidine in the presence of an inorganic base to form 2-(pyrrolidine-1-yl)-4-(trifluoromethyl)benzaldehyde, wherein the reaction in step c0) is carried out in the fourth solvent.

12. The process according to claim 11, wherein the inorganic base and the fourth solvent in step c0)

30 is Na₂CO₃ and ethyl acetate.

13. The process according to any one of claims 11-12, wherein step c0) further comprises adding around 1-2% w/w of water to the mixture comprising ethyl acetate and 2-(pyrrolidine-1-yl)-4-(trifluoromethyl)benzaldehyde.

14. A process for the manufacture of crystalline 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate mono-hydrochloride salt form 2 comprising the steps of:

manufacturing 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate by the process according to any one of claims 1-13, and

d) converting 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate to crystalline 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate mono-hydrochloride salt form 2.

15. A process for the manufacture of crystalline 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate mono-hydrochloride salt form 2 comprising the steps of:

D1) dissolving 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, or a pharmaceutically acceptable salt thereof in a sixth solvent at a temperature of 38 – 70 °C, preferably at a temperature of 38-42 °C, optionally under stirring;

D2) converting the 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, or a pharmaceutically acceptable salt thereof into 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate mono-hydrochloride salt by addition of HCl, optionally under stirring at a temperature of 70-76 °C, more preferably at a temperature of 74-76 °C;

D3) optionally filtering the solution obtained in step D2)

D4) cooling the solution to 63-69 °C, preferably to 65-68 °C, and adding seed crystals of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate mono-hydrochloride salt form 2;

D5) optionally, stirring the suspension for at least 1 hour;

D6) cooling the suspension from 63-69 °C to a temperature of 10-40 °C, preferably at a temperature of 16-23 °C during a period between 12 -20 hours under stirring.

16. The process according to claim 15, wherein the process further comprises a step of milling crystalline 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate mono-hydrochloride salt form 2.
17. The process according to any one of claims 15-16, wherein the obtained crystalline 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate mono-hydrochloride salt form 2 is characterized by having a d10 particle size of 10-30 μm ; a d90 particle size below 200 μm , optionally a d50 particle size ranging of 60-80 μm .
18. The process according to any one of claims 14-17, wherein the obtained crystalline 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate mono-hydrochloride salt form 2 is formulated into a tablet together with at least one excipient.
19. The process according to any one of claims 14-18, wherein the obtained crystalline 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate mono-hydrochloride salt form 2 is characterized by having an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 8.6° 2-Theta, 14.3° 2-Theta, 15.6° 2-Theta, 19.0° 2-Theta, 19.8° 2-Theta, and 20.7° 2-Theta.