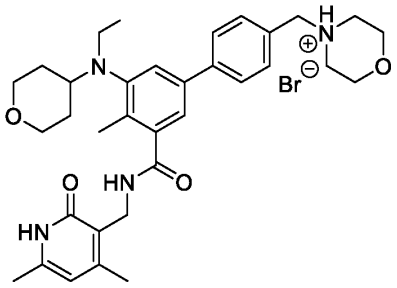
CLAIMS

1. A method of making a crystalline form of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide hydrobromide (Compound I hydrobromide):



(Compound I hydrobromide),

comprising:

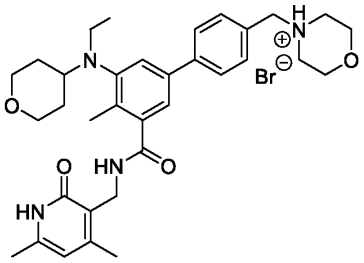
step a) mixing Compound I hydrobromide, ethanol, and water, wherein the vol/vol ratio of ethanol:water is from about 92:8 to about 87:13, to form a first mixture.

2. The method of claim 1, wherein the method further comprises before step a):

step 1) mixing N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide (Compound I), ethanol, and toluene to form mixture A; and after step 1):

step 2) adding hydrobromic acid to mixture A to form a mixture B, wherein Compound I hydrobromide is formed.

3. A method of making N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide hydrobromide (Compound I hydrobromide):



(Compound I hydrobromide),

wherein the method comprises:

step 1) mixing N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide (Compound I), ethanol, and toluene to form mixture A; and after step 1):

step 2) adding hydrobromic acid to mixture A to form a mixture B, wherein Compound I hydrobromide is formed.

4. The method of any one of the preceding claims, wherein the vol/vol ratio of ethanol:water is selected from the group consisting of about 92:8, about 91.5:8.5, about 91:9, about 90.5:9.5, about 90:10, about 89.5:10.5, about 89:11, about 88.5:11.5, about 88:12, and about 87.5:12.5.

5. The method of any one of the preceding claims, further comprising after step a): step b) adding a seed to the first mixture to form a second mixture.

6. The method of any one of the preceding claims, wherein the seed is Compound I hydrobromide.

7. The method of any one of the preceding claims, wherein the seed is crystalline Compound I hydrobromide and wherein the seed exhibits an X-ray powder diffraction pattern having one or two characteristic peaks expressed in degrees 2-theta, selected from the group consisting of 17.5 +/- 0.3 and 22.0 +/- 0.3.

8. The method of any one of the preceding claims, wherein in step b) the amount of seed in the second mixture is from about 1.0 wt. % to about 3.0 wt. %, relative to the crystalline form of Compound I hydrobromide.

9. The method of any one of the preceding claims, wherein the seed in step b) has a D90 particle size of from about 4 μm to about 6 μm.

10. The method of any one of the preceding claims, further comprising after step a) and before step b): step a-1) heating the first mixture.

11. The method of any one of the preceding claims, wherein in step a-1) the first mixture is heated to a temperature of from about 70°C to about 75°C.

12. The method of any one of the preceding claims, further comprising after step a-1) and before step b): step a-2) cooling the first mixture.

13. The method of any one of the preceding claims, wherein in step a-2) the first mixture is cooled to a temperature of from about 50 °C to about 55 °C.

14. The method of any one of the preceding claims, further comprising after step b): step b-1) stirring the second mixture.

15. The method of any one of the preceding claims, wherein the second mixture is stirred for at least 6 h.

16. The method of any one of the preceding claims, further comprising after step b-1): step b-2) cooling the second mixture.

17. The method of any one of the preceding claims, wherein in step b-2) the second mixture is cooled at a cooling rate of from about 2 °C/h to about 9 °C/h.

18. The method of any one of the preceding claims, wherein in step b-2) the second mixture is cooled to a temperature of from about 18 °C to about 30 °C.

19. The method of any one of the preceding claims, further comprising after step b-2): step b-3) stirring the second mixture.

20. The method of any one of the preceding claims, wherein in step b-3) the second mixture is stirred for at least about 3h.

21. The method of any one of the preceding claims, further comprising after step b-3): step c) adding an anti-solvent to the second mixture to form a third mixture, wherein the anti-solvent is selected from the group consisting of ethyl acetate, methyl tert-butyl ether, tetrahydrofuran, and acetone.

22. The method of any one of the preceding claims, further comprising after step c): step d) isolating the crystalline form of Compound I hydrobromide from the third mixture.

23. The method of any one of the preceding claims, wherein in step 1) the vol/vol ratio of ethanol:toluene is about 25:75 to about 45:55.

24. The method of any one of the preceding claims, wherein in step 2) hydrobromic acid is added to mixture B at a temperature of from about 10 °C to about 50 °C.

25. The method of any one of the preceding claims, wherein in step 2) hydrobromic acid is added in an amount of about 0.9 mol eq. to about 1.1 mol eq. with respect to Compound I.

26. A crystalline form of Compound I hydrobromide, prepared by a method of any one of the preceding claims.

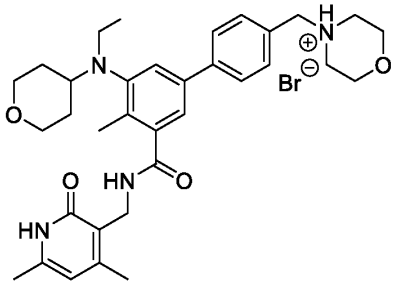
27. The crystalline form of any one of the preceding claims, wherein the crystalline form forms particles having a D90 particle size of from about 15 μm to about 50 μm.

28. The crystalline form of any one of the preceding claims, wherein the crystalline form forms particles wherein at least about 90 % of the particles have a particle size of from about 6 μm to about 40 μm.

29. The crystalline form of any one of the preceding claims, wherein the crystalline form exhibits an X-ray powder diffraction pattern having one or two characteristic peaks expressed in degrees 2-theta, selected from the group consisting of 17.5 +/- 0.3 and 22.0 +/- 0.3.

30. The crystalline form of any one of the preceding claims, wherein the crystalline form has a purity of at least 99.8%.

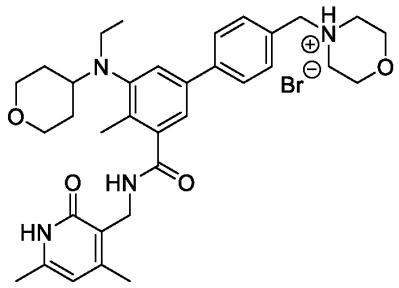
31. A crystalline form of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide hydrobromide (Compound I hydrobromide):



(Compound I hydrobromide), wherein the crystalline form forms particles wherein at least about 90% of the microparticles have a diameter of from about 6 μm to about 40 μm.

32. A plurality of microparticles of a crystalline form of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-

(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide hydrobromide (Compound I hydrobromide):



(Compound I hydrobromide),

wherein at least about 90% of the microparticles have a diameter of from about 6 μm to about 40 μm.

33. The crystalline form of any one of the preceding claims, wherein the crystalline form forms particles having a D90 particle size of from about 15 μm to about 50 μm.

34. The plurality of microparticles of any one of the preceding claims, wherein the D90 particle size of the microparticles is from about 15 μm to about 50 μm.

35. A pharmaceutical composition comprising a plurality of microparticles or a crystalline form of any one of the preceding claims.

36. The pharmaceutical composition of any one of the preceding claims, further comprising:
lactose monohydrate;
low-substituted hydroxypropyl cellulose;
sodium starch glycolate;
hydroxypropyl cellulose; and/or
magnesium stearate.