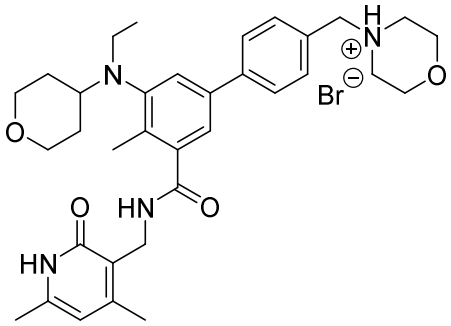
CLAIMS

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:

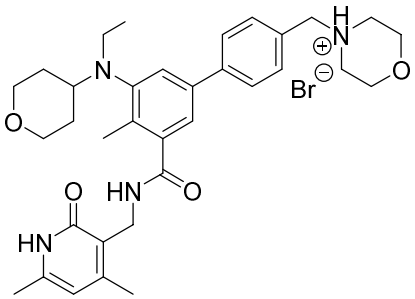
step a) mixing Compound I hydrobromide, ethanol, and water, wherein the vol/vol ratio of ethanol:water is from about 92:8 to about 87:13, to form a first mixture.

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~~, optionally 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~~, further optionally wherein the seed is Compound I hydrobromide~~.~~

~~7.~~4. ~~The method of any one of the preceding claims~~, further optionally 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.~~5. ~~The method of any one of the preceding claims~~, optionally 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~~, optionally 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 optionally comprising after step a-1) and before step b): step a-2) cooling the first mixture~~.~~

~~13.~~6. ~~The method of any one of the preceding claims~~, optionally 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~~, optionally wherein the second mixture is stirred for at least 6 h~~.~~

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

~~17.~~7. ~~The method of any one of the preceding claims~~, optionally 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.~~8. 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~~, optionally 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 optionally 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.~~9. ~~The method of any one of the preceding claims~~, further optionally comprising after step c): step d) isolating the crystalline form of Compound I hydrobromide from the third mixture.

~~23.~~10. The method of any one of the preceding claims, wherein at least one of,

i) 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~~ ii) 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~~ iii) 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.~~11. A crystalline form of Compound I hydrobromide, prepared by a method of any one of the preceding claims.

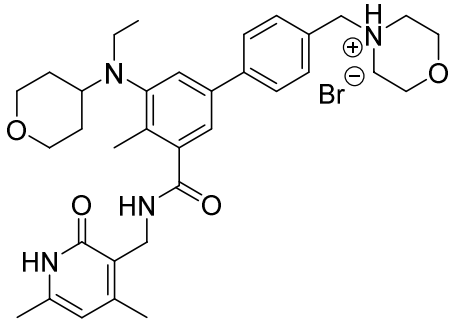
~~27.~~ The crystalline form of any one of the preceding claims, wherein the crystalline form forms particles having a D90 particle size of from about 15 μm to about 50 μm~~.~~

~~28. The crystalline form of any one of the preceding claims~~, further comprising at least one of i) 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~~, ii) 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~~.~~

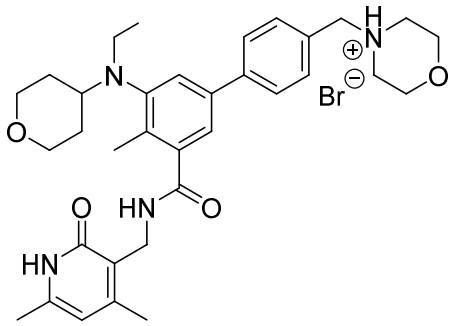
~~30.~~12. ~~The crystalline form of any one of the preceding claims~~, iii) wherein the crystalline form has a purity of at least 99.8%.

~~31.~~13. 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.~~14. 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.~~15. 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.~~16. 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.~~17. ~~The pharmaceutical composition of any one of the preceding claims~~, optionally further comprising:

lactose monohydrate;

low-substituted hydroxypropyl cellulose;

sodium starch glycolate;

hydroxypropyl cellulose; and/or

magnesium stearate.