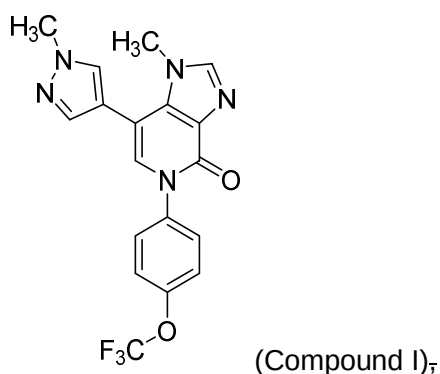


What is claimed is: Claims

1. A compound which is a mono-tosylate salt of 1-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)-5-(4-(trifluoromethoxy)phenyl)-1,5-dihydro-4*H*-imidazo[4,5-*c*]pyridin-4-one (Compound I):



~~with the proviso that the salt is not a hydrochloride salt of Compound I.~~

- ~~2. The compound of claim 1, selected from the group consisting of besylate, citrate, fumarate, hemi-edisylate, hemi-napadisylate, hydrobromide, maleate, nicotinate, nitrate, oxalate, phosphate, saccharinate, sulfate, L-tartrate, and tosylate salts of Compound I.~~
- ~~3. The compound of claim 2, selected from the group consisting of besylate, hemi-edisylate, hemi-napadisylate, hydrobromide, nitrate, phosphate, sulfate, and tosylate salts of Compound I.~~
- ~~4. The compound of claim 3, wherein the salt is a tosylate.~~
- ~~5. The compound of claim 4, wherein the salt is a mono-tosylate or a di-tosylate.~~
- ~~6. The compound of claim 5, wherein the salt is a mono-tosylate.~~
- ~~7.2. The compound of claim 61, wherein the mono-tosylate salt is characterized by an X-ray diffraction pattern substantially similar to that set forth in FIG 8.~~
- ~~8.3. The compound of claim 61, wherein the mono-tosylate salt is characterized by an X-ray diffraction pattern having three or more peaks selected from those at diffraction angle 2θ values of 10.92°± 0.2°, 13.28°± 0.2°, 15.36°± 0.2°, 16.94°± 0.2°, 17.74°± 0.2°, 18.20°± 0.2°,~~

20.51°± 0.2°, 23.21°± 0.2°, 23.86°± 0.2°, 24.73°± 0.2°, 25.69°± 0.2°, 26.68°± 0.2°, 27.63°± 0.2°, 29.12°± 0.2°, and 30.532°± 0.2°, when irradiated with a Cu-K α light source.

~~9.4.~~ The compound of claim ~~6~~1, wherein the mono-tosylate salt is characterized by an X-ray diffraction pattern having three or more peaks selected from those at diffraction angle 2 θ values of 10.92°± 0.2°, 15.36°± 0.2°, 16.94°± 0.2°, 17.74°± 0.2°, 23.21°± 0.2°, 23.86°± 0.2°, 24.73°± 0.2°, 25.69°± 0.2°, 27.63°± 0.2°, and 29.12°± 0.2°, when irradiated with a Cu-K α light source.

~~10.5.~~ The compound of claim ~~6~~1, wherein the mono-tosylate salt is characterized by an X-ray diffraction pattern having three or more peaks selected from those at diffraction angle 2 θ values of 15.36°± 0.2°, 17.74°± 0.2°, 23.21°± 0.2°, 23.86°± 0.2°, and 24.73°± 0.2°, when irradiated with a Cu-K α light source.

~~11.6.~~ The compound of claim any one of claims ~~6 to 10~~1 to 5, wherein the mono-tosylate salt is further characterized by a melt onset in a range of ~~about~~ 204 °C to ~~about~~ 207 °C.

~~12.~~ The compound of any one of claims 1 to 6, wherein the compound is amorphous.

~~13.~~ The compound of any one of claims 1 to 6, wherein the compound is crystalline.

~~14.~~ The compound of claim 1, characterized by an X-ray diffraction pattern substantially similar to that set forth in any one of FIG. 1 to FIG. 12.

~~15.~~ A process for preparing Compound I comprising the steps of:

(1) reacting 2,4-dichloro-3-nitropyridine with methylamine to yield 2-chloro-*N*-methyl-3-nitropyridin-4-amine;

(2) reducing 2-chloro-*N*-methyl-3-nitropyridin-4-amine to yield 2-chloro-*N*⁴-methylpyridine-3,4-diamine;

(3) condensing 2-chloro-*N*⁴-methylpyridine-3,4-diamine with formic acid to yield 1-methyl-1,5-dihydro-4H-imidazo[4,5-*c*]pyridin-4-one;

~~(4) coupling 1-methyl-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one with 1-bromo-4-(trifluoromethoxy)benzene to yield 1-methyl-5-(4-(trifluoromethoxy)phenyl)-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one;~~

~~(5) brominating 1-methyl-5-(4-(trifluoromethoxy)phenyl)-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one to yield 7-bromo-1-methyl-5-(4-(trifluoromethoxy)phenyl)-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one; and~~

~~(6) coupling 7-bromo-1-methyl-5-(4-(trifluoromethoxy)phenyl)-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole to yield Compound I.~~

~~16. The process of claim 15, further comprising a step (7) recrystallizing Compound I.~~

~~17. The process of claim 16, wherein Compound I is recrystallized in a two-solvent system.~~

~~18. The process of claim 17, wherein the two-solvent system comprises acetic acid and ethanol.~~

~~19. The process of claim 18, wherein ethanol is present in the two-solvent system in a volumetric excess compared to acetic acid.~~

~~20. The process of claim 19, wherein acetic acid and ethanol are present in a v/v ratio of about 1:1 to about 1:15, or about 1:1 to about 1:10, or about 1:4 to about 1:10, or about 1:6 to about 1:8 acetic acid:ethanol.~~

~~21.7. A process for preparing 1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-5-(4-(trifluoromethoxy)phenyl)-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one mono-tosylate (Compound I mono-tosylate) comprising the steps of:~~

~~(1) reacting 2,4-dichloro-3-nitropyridine with methylamine to yield 2-chloro-N-methyl-3-nitropyridin-4-amine;~~

~~(2) reducing 2-chloro-N-methyl-3-nitropyridin-4-amine to yield 2-chloro-N⁴-methylpyridine-3,4-diamine;~~

(3) condensing 2-chloro-*N*⁴-methylpyridine-3,4-diamine with formic acid to yield 1-methyl-1,5-dihydro-4H-imidazo[4,5-*c*]pyridin-4-one;

(4) coupling 1-methyl-1,5-dihydro-4H-imidazo[4,5-*c*]pyridin-4-one with 1-bromo-4-(trifluoromethoxy)benzene to yield 1-methyl-5-(4-(trifluoromethoxy)phenyl)-1,5-dihydro-4H-imidazo[4,5-*c*]pyridin-4-one;

(5) brominating 1-methyl-5-(4-(trifluoromethoxy)phenyl)-1,5-dihydro-4H-imidazo[4,5-*c*]pyridin-4-one to yield 7-bromo-1-methyl-5-(4-(trifluoromethoxy)phenyl)-1,5-dihydro-4H-imidazo[4,5-*c*]pyridin-4-one;

(6) coupling 7-bromo-1-methyl-5-(4-(trifluoromethoxy)phenyl)-1,5-dihydro-4H-imidazo[4,5-*c*]pyridin-4-one with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole to yield Compound I;

(7) recrystallizing Compound I in a two-solvent system; and

(8) contacting Compound I with *p*-toluenesulfonic acid to yield Compound I mono-tosylate.

22. A process for preparing Compound I tosylate comprising the step of contacting Compound I with *p*-toluenesulfonic acid to yield Compound I tosylate.

23. The process of claim 21 or 22, wherein the Compound I tosylate is a mono-tosylate.

24. A process for preparing Compound I comprising the step of coupling 7-bromo-1-methyl-5-(4-(trifluoromethoxy)phenyl)-1,5-dihydro-4H-imidazo[4,5-*c*]pyridin-4-one with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole to yield Compound I.

25. A process for preparing 7-bromo-1-methyl-5-(4-(trifluoromethoxy)phenyl)-1,5-dihydro-4H-imidazo[4,5-*c*]pyridin-4-one comprising the step of brominating 1-methyl-5-(4-(trifluoromethoxy)phenyl)-1,5-dihydro-4H-imidazo[4,5-*c*]pyridin-4-one to yield 7-bromo-1-methyl-5-(4-(trifluoromethoxy)phenyl)-1,5-dihydro-4H-imidazo[4,5-*c*]pyridin-4-one.

26. A process for preparing 1-methyl-5-(4-(trifluoromethoxy)phenyl)-1,5-dihydro-4H-imidazo[4,5-*c*]pyridin-4-one comprising the step of coupling 1-methyl-1,5-dihydro-4H-imidazo[4,5-

~~c]pyridin-4-one with 1-bromo-4-(trifluoromethoxy)benzene to yield 1-methyl-5-(4-(trifluoromethoxy)phenyl)-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one.~~

27. ~~A process for preparing 1-methyl-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one comprising the step of condensing 2-chloro-N⁴-methylpyridine-3,4-diamine with formic acid to yield 1-methyl-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one.~~

28. ~~A process for preparing 2-chloro-N⁴-methylpyridine-3,4-diamine comprising the step of reducing 2-chloro-N-methyl-3-nitropyridin-4-amine to yield 2-chloro-N⁴-methylpyridine-3,4-diamine.~~

29. ~~A process for preparing 2-chloro-N-methyl-3-nitropyridin-4-amine comprising the step of reacting 2,4-dichloro-3-nitropyridine with methylamine to yield 2-chloro-N-methyl-3-nitropyridin-4-amine.~~

~~30.8.~~ 8. A pharmaceutical composition comprising particles of ~~a~~ the mono-tosylate salt of Compound I, wherein the particles have a size distribution characterized by a D50 in a range of ~~about~~ 10 µm to ~~about~~ 60 µm.

~~31.9.~~ 9. The pharmaceutical composition of claim ~~30~~ 8, wherein the D50 is in a range of ~~about~~ 25 µm to ~~about~~ 30 µm.

~~32.10.~~ 10. A pharmaceutical composition comprising particles of ~~a~~ the mono-tosylate salt of Compound I, wherein the particles have a size distribution characterized by a volume mean diameter D[4,3] in a range of ~~about~~ 25 µm to ~~about~~ 45 µm.

~~33.11.~~ 11. The pharmaceutical composition of claim ~~32~~ 10, wherein the D[4,3] is in a range of ~~about~~ 30 µm to ~~about~~ 40 µm.

~~34.12.~~ 12. The pharmaceutical composition of any one of claims ~~30 to 33~~ 8 to 11, wherein the particles are further characterized by D10 in a range of ~~about~~ 1 µm to ~~about~~ 20 µm.

~~35.13.~~ 13. The pharmaceutical composition of any one of claims ~~30 to 33~~ 8 to 11, wherein the particles are further characterized by D90 in a range of ~~about~~ 50 µm to ~~about~~ 100 µm.

~~36. The pharmaceutical composition of any one of claims 30 to 35, wherein the salt is Compound I tosylate.~~

~~37. The pharmaceutical composition of claim 36, wherein the Compound I tosylate is a mono-tosylate.~~

~~38.14.~~ A pharmaceutical composition comprising a the mono-tosylate salt of Compound I salt compound of any one of claims 1 to ~~14~~6 or composition thereof, or a the pharmaceutical composition of any one of claims ~~30 to 37~~8 to 13, each further comprising a pharmaceutically acceptable excipient.

~~39.15.~~ A granulate comprising the pharmaceutical composition of claim ~~38~~14, wherein the excipient comprises a binder.

~~40.16.~~ The granulate of claim ~~39~~15, wherein the binder comprising a sugar, a starch, a sugar alcohol, a protein, a polymer, or any combination thereof.

~~41.17.~~ The granulate of claim ~~40~~16, wherein the binder comprises sucrose, glucose, lactose, starch, cellulose, microcrystalline cellulose, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose (hypromellose), sodium carboxymethyl cellulose (croscarmellose sodium), xylitol, sorbitol, mannitol, maltitol, acacia, tragacanth, alginic acid, gelatin, polyvinyl alcohols, polymethacrylates, polyvinylpyrrolidone (PVP), and polyethylene glycol (PEG), or any combination thereof.

~~42.18.~~ The granulate of any one of claims ~~39 to 41~~15 to 17, further comprising a filler.

~~43.19.~~ The granulate of claim ~~42~~18, wherein the filler comprises a sugar, a starch, a sugar alcohol, an inorganic salt, or any combination thereof.

~~44.20.~~ The granulate of claim ~~43~~19, wherein the filler comprises sucrose, lactose, dextrose, starch, sorbitol, mannitol, calcium phosphate, calcium sulfate, calcium carbonate, or any combination thereof.

~~45.21.~~ The granulate of any one of claims ~~39 to 44~~15 to 20, further comprising a disintegrant.

~~46-22.~~ 4521. The granulate of claim ~~4521~~, wherein the disintegrant comprises a sugar, a crosslinked polymer, a modified starch, or any combination thereof.

~~47-23.~~ 4622. The granulate of claim ~~4622~~, wherein the disintegrant comprises alginic acid, sodium starch glycolate, sodium carboxymethyl cellulose (croscarmellose sodium), polyvinylpovidone, or any combination thereof.

~~48-24.~~ 4715 to 23. The granulate of any one of claims ~~39 to 47~~ 15 to 23, further comprising a lubricant.

~~49-25.~~ 4824. The granulate of claim ~~4824~~, wherein the lubricant is present in an amount of ~~about~~ 0.5 wt% to 5 wt%.

~~50-26.~~ 4924 or 25. The granulate of claim ~~48 or 49~~ 24 or 25, wherein the lubricant is selected from the group consisting of stearic acid, magnesium stearate, calcium stearate, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium lauryl sulfate, glyceryl palmitostearate, glyceryl behenate, sodium benzoate, sodium stearyl fumarate, talc, and fumed silica.

~~51-27.~~ 5015 to 26. A pharmaceutical composition comprising the granulate of any one of claims ~~39 to 50~~ 15 to 26 and further comprising an extragranular excipient.

~~52-28.~~ 5127. The pharmaceutical composition of claim ~~5127~~, wherein the extragranular excipient comprises an extragranular disintegrant, extragranular lubricant, extragranular binder, or any combination thereof.

~~53-29.~~ 5227. The pharmaceutical composition of claim ~~5227~~, wherein the extragranular excipient comprises an extragranular disintegrant and an extragranular binder.

~~54-30.~~ 5328 or 29. The pharmaceutical composition of claim ~~52 or 53~~ 28 or 29, wherein the extragranular binder comprises a sugar, a starch, a sugar alcohol, a protein, a polymer, or any combination thereof.

~~55-31.~~ 5430. The pharmaceutical composition of claim ~~5430~~, wherein the extragranular binder comprises sucrose, glucose, lactose, starch, cellulose, microcrystalline cellulose, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose (hypromellose), sodium carboxymethyl cellulose (croscarmellose sodium), xylitol, sorbitol,

mannitol, maltitol, acacia, tragacanth, alginic acid, gelatin, polyvinyl alcohols, polymethacrylates, polyvinylpyrrolidone (PVP), and polyethylene glycol (PEG), or any combination thereof.

~~56-32.~~ 56-32. The pharmaceutical composition of any one of claims ~~53 to 55~~ 29 to 31, wherein the extragranular disintegrant comprises a sugar, a crosslinked polymer, a modified starch, or any combination thereof.

~~57-33.~~ 57-33. The pharmaceutical composition of claim ~~56~~ 32, wherein the extragranular disintegrant comprises alginic acid, sodium starch glycolate, sodium carboxymethyl cellulose (croscarmellose sodium), polyvinylpovidone, or any combination thereof.

~~58-34.~~ 58-34. The pharmaceutical composition of any one of claims ~~53 to 57~~ 29 to 33, wherein the extragranular excipient further comprises an extragranular lubricant.

~~59-35.~~ 59-35. The pharmaceutical composition or granulate of any one of claims ~~38 to 58~~ 14 to 34, wherein the excipient comprises a polymeric precipitation inhibitor.

~~60-36.~~ 60-36. The pharmaceutical composition or granulate of claim ~~59~~ 35, wherein the polymeric precipitation inhibitor comprises cellulose acetate phthalate, carbomer, ethyl cellulose, Eudragit®, alginic acid, gum Arabic, locust bean xanthan, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate succinate, hydroxypropyl methylcellulose phthalate, methyl cellulose, methyl 2-hydroxyethyl cellulose, poly(acrylic acid), polyallylamine hydrogen chloride, poly(acrylamide-co-acrylic acid), polydiallyldimethyl ammonium chloride, polyethylene imine, P-EPE, poly(2-ethyl 2-oxazoline), polyvinyl alcohol, polyvinyl pyrrolidone, sodium carboxymethyl cellulose, or any combination thereof.

~~61-37.~~ 61-37. The pharmaceutical composition or granulate of claim ~~60~~ 36, wherein the polymeric precipitation inhibitor comprises one or more cellulosic materials.

~~62-38.~~ 62-38. The pharmaceutical composition or granulate of claim ~~61~~ 37, wherein the polymeric precipitation inhibitor comprises hydroxypropyl methylcellulose.

~~63-39.~~ The pharmaceutical composition or granulate of claim ~~6238~~, wherein the polymeric precipitation inhibitor is present in a concentration of about 0.5 wt.%.

~~64-40.~~ A pharmaceutical composition comprising ~~about 30 wt% to about 40 wt%~~ of the mono-tosylate salt of Compound I ~~mono-tosylate, about 40 wt% to about 45 wt% binder, about 10 wt% to about 20 wt% filler, and about 0.5 wt% to about 5 wt% disintegrant.~~

~~65-41.~~ An oral dosage form comprising the pharmaceutical composition or granulate of any one of claims ~~38 to 64~~ 15 to 40.

~~66-42.~~ The oral dosage form of claim ~~65-41~~ in the form of a pill, tablet, core, capsule, caplet, or suspension.

~~67-43.~~ A granulate comprising a mono-tosylate salt of Compound I, microcrystalline cellulose, lactose, sodium carboxymethyl cellulose, and magnesium stearate.

~~68-44.~~ The granulate of claim ~~6743~~, further comprising extragranular sodium starch glycolate and hydroxypropyl methylcellulose.

~~69-45.~~ The granulate of claim ~~6844~~, further comprising extragranular magnesium stearate.

~~70.~~ The granulate of any one of claims 67 to 69, wherein the salt is a mono-tosylate.

~~71-46.~~ A process for producing a pharmaceutical composition comprising ~~a~~ the mono-tosylate salt of Compound I, the process comprising the steps of:

- (a) sieving a Compound I salt, a binder, a filler, and a disintegrant;
- (b) blending the sieved components to form a first mixture;
- (c) further blending said first mixture with a lubricant to form a second mixture;
- (d) compressing the second mixture;
- (e) grinding the compressed second mixture;

- (e) blending the ground second mixture with an extragranular disintegrant and an extragranular binder to form a third mixture;
- (f) blending said third mixture with an extragranular lubricant to form a fourth mixture; and
- (g) compressing said fourth mixture to form a tablet.

~~72. The process of claim 71, wherein the Compound I salt is a tosylate salt.~~

~~73. The process of claim 72, wherein the Compound I tosylate salt is a mono-tosylate salt.~~

~~74. A nanosuspension comprising Compound I free base.~~

~~75. The nanosuspension of claim 74, further comprising water, HPMC, and SDS.~~

~~76. An oral dosage form comprising the nanosuspension of claim 74 or 75.~~

~~77. A solid oral dosage form produced by a process comprising drying the nanosuspension of claim 74 or 75.~~

~~78. A process for preparing a solid oral dosage form comprising the steps of:~~

- ~~(a) granulating the nanosuspension of claim 74 or 75 to produce a granulated nanosuspension;~~
- ~~(b) adding mannitol to the granulated nanosuspension prepared in step (a) to produce a nanosuspension mixture;~~
- ~~(c) spraying the nanosuspension mixture prepared in step (b) onto a fluid bed charged with microcrystalline cellulose to produce a nanosuspension wet blend;~~
- ~~(d) raising the temperature of the fluid bed to above 40 °C to dry the nanosuspension wet blend to produce a nanosuspension dry blend; and~~
- ~~(e) milling the nanosuspension dry blend to produce nanosuspension granules.~~

~~79. The process of claim 78 further comprising pressing the nanosuspension granules into a tablet.~~

~~80. The process of claim 78 or 79, wherein the granules having a particle size D_{50} of about 100 μm to about 170 μm .~~

~~81. The process of claim 78 or 79, wherein the granules having a particle size D_{50} of about 135 μm .~~

~~82. A solid oral dosage form produced by the process of any one of claims 78 to 81.~~