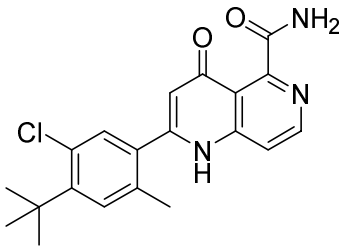
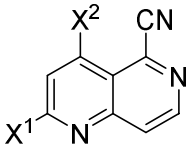
CLAIMS

1. A process for preparing Compound **I**:



I

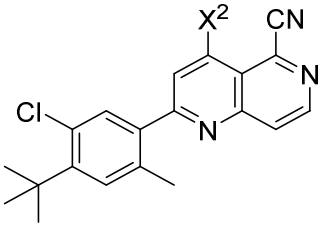
comprising transforming a compound of formula (A_1):



(A_1)

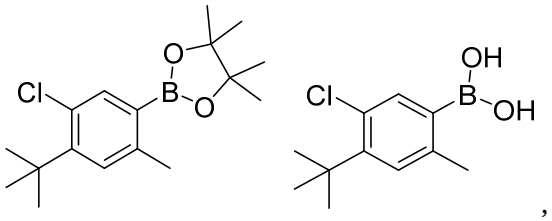
to Compound **I**;

wherein each of X^1 and X^2 are independently selected from halogen, optionally wherein X_1 and X_2 are both chloro, optionally wherein transforming the compound of formula (A_1) to Compound **I** comprises transforming the compound of formula (A_1) to a compound of formula (C_1):



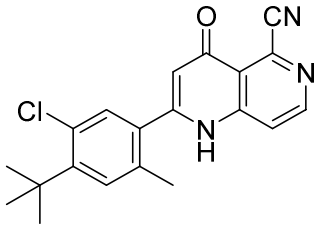
(C_1)

and transforming the compound of formula (C_1) to Compound **I**, optionally wherein transforming the compound of formula (A_1) to the compound of formula (C_1) comprises contacting the compound of formula (A_1) with a compound of formula (B_1) or (B_2):



(B_1) (B_2)

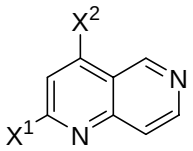
optionally wherein transforming the compound of formula (C_1) to Compound **I** comprises transforming the compound of formula (C_1) to a compound of formula (C_4):



(C_4) ; and

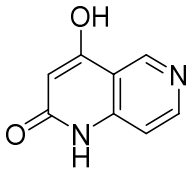
transforming the compound of formula (C_4) to Compound **I**.

2. The process of claim 1, further comprising transforming a compound of formula ($A_{1\text{-}1}$):



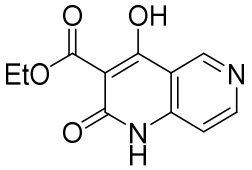
($A_{1\text{-}1}$)

to the compound of formula (A_1), optionally further comprising transforming a compound of formula ($A_{1\text{-}2}$):



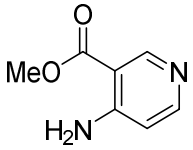
($A_{1\text{-}2}$)

to the compound of formula ($A_{1\text{-}1}$), optionally further comprising transforming a compound of formula ($A_{1\text{-}3}$):



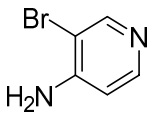
($A_{1\text{-}3}$)

to the compound of formula ($A_{1\text{-}2}$), optionally further comprising transforming a compound of formula ($A_{1\text{-}4}$):



($A_{1\text{-}4}$)

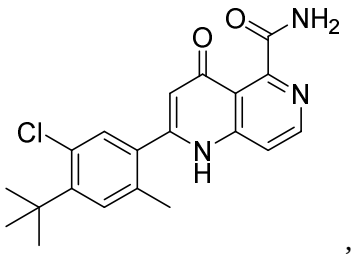
to the compound of formula ($A_{1\text{-}3}$), optionally further comprising transforming a compound of formula ($A_{1\text{-}5}$):



($A_{1\text{-}5}$)

to the compound of formula ($A_{1\text{-}4}$).

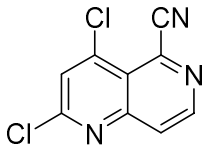
3. A process for preparing Compound **I**:



,

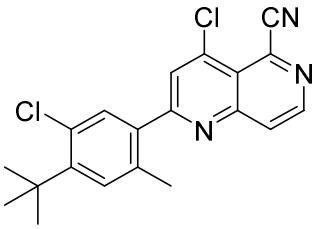
I

comprising transforming a compound of formula (A_2):



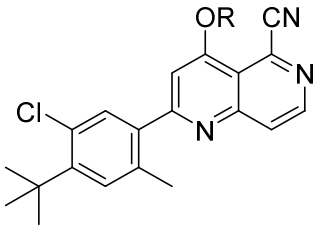
(A_2)

to Compound **I**, optionally wherein the step of transforming the compound of formula (A_2) to Compound **I** comprises transforming the compound of formula (A_2) to a compound of formula (C_2):



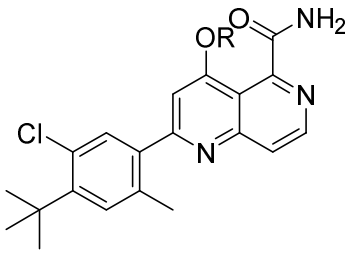
(C_2) ; and

transforming the compound of formula (C_2) to Compound **I**, optionally wherein the step of transforming the compound of formula (C_2) to Compound **I** comprises transforming the compound of formula (C_2) to a compound of formula (C_{3a}):



(C_{3a}) ;

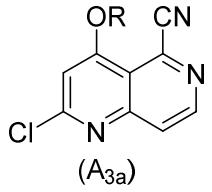
wherein R is C_1-C_6 alkyl; and transforming the compound of formula (C_{3a}) to Compound **I**, optionally wherein the step of transforming the compound of formula (C_{3a}) to Compound **I** comprises transforming the compound of formula (C_{3a}) to a compound of formula (C_{8a}):



(C_{8a}) ;

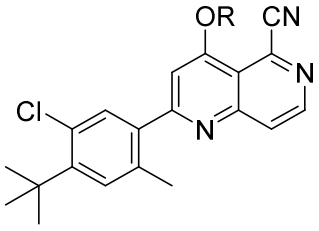
wherein R is C_1-C_6 alkyl; and transforming the compound of formula (C_{8a}) to Compound **I**.

4. The process of claim 3, wherein the step of the step of transforming the compound of formula (A_2) to Compound **I** comprises transforming the compound of formula (A_2) to a compound of formula (A_{3a}):



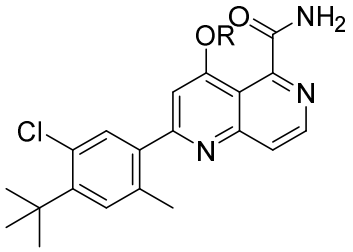
(A_{3a}) ;

wherein R is C_1-C_6 alkyl; and transforming the compound of formula (A_{3a}) to Compound **I**, optionally wherein the step of transforming the compound of formula (A_{3a}) to Compound **I** comprises transforming the compound of formula (A_{3a}) to a compound of formula (C_{3a}):



(C_{3a}) ;

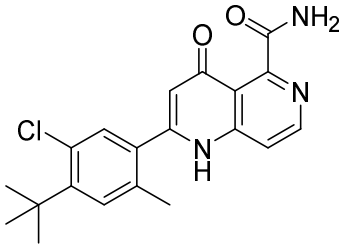
wherein R is C_1-C_6 alkyl; and transforming the compound of formula (C_{3a}) to Compound **I**, optionally wherein the step of transforming the compound of formula (C_{3a}) to Compound **I** comprises transforming the compound of formula (C_{3a}) to a compound of formula (C_{8a}):



(C_{8a}) ;

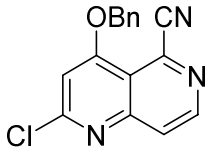
wherein R is C_1-C_6 alkyl; and transforming the compound of formula (C_{8a}) to Compound **I**.

5. A process for preparing Compound **I**:



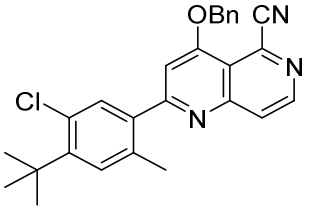
I

comprising transforming a compound of formula (A_3):



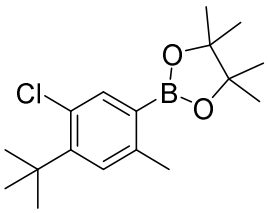
(A_3)

to Compound **I**, optionally wherein transforming the compound of formula (A_3) to Compound **I** comprises transforming the compound of formula (A_3) to a compound of formula (C_3):

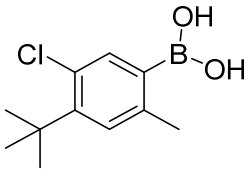


(C_3)

and transforming the compound of formula (C_3) to Compound **I**, optionally wherein transforming the compound of formula (A_3) to the compound of formula (C_3) comprises contacting the compound of formula (A_3) with a compound of formula (B_1) or (B_2):

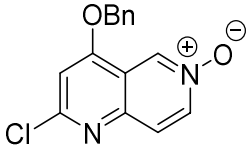


(B_1)



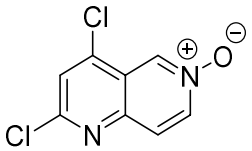
(B_2)

6. The process of claim 5, further comprising transforming a compound of formula (A_{3-1}):



(A_{3-1})

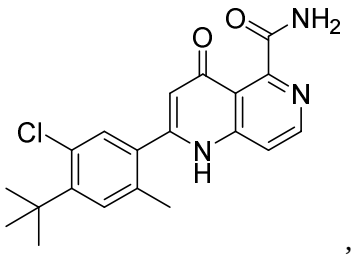
to the compound of formula (A_3), optionally further comprising transforming a compound of formula (A_{3-2}):



(A_{3-2})

to the compound of formula (A_{3-1}).

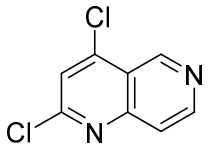
7. A process for preparing Compound **I**:



,

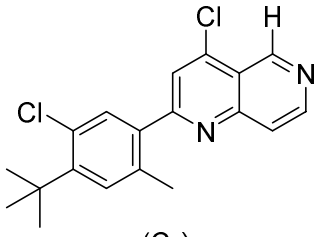
I

comprising transforming a compound of formula (A_{2-1}):



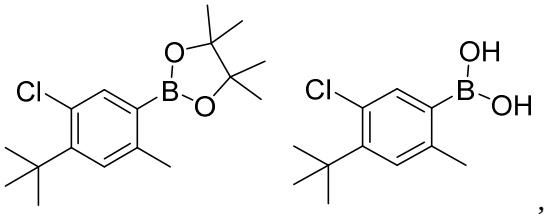
(A_{2-1})

to Compound **I**, optionally wherein the step of transforming the compound of formula (A_{2-1}) to Compound **I** comprises transforming the compound of formula (A_{2-1}) to a compound of formula (C_5):



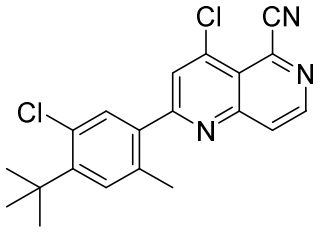
(C_5) ; and

transforming the compound of formula (C_5) to Compound **I**, optionally wherein transforming the compound of formula ($A_{2\text{-}1}$) to the compound of formula (C_5) comprises treating the compound of formula ($A_{2\text{-}1}$) with a compound of formula (B_1) or (B_2):



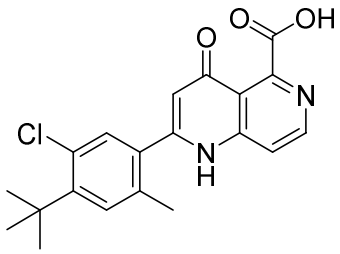
(B_1) (B_2)

8. The process of claim 7, wherein the step of transforming the compound of formula (C_5) to Compound **I** comprises transforming the compound of formula (C_5) to a compound of formula (C_2):



(C_2) ; and

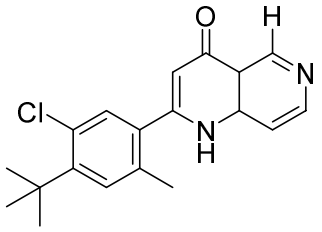
transforming the compound of formula (C_2) to Compound **I**, optionally wherein the step of transforming the compound of formula (C_2) to Compound **I** comprises transforming the compound of formula (C_2) to a compound of formula (C_7):



(C_7) ; and

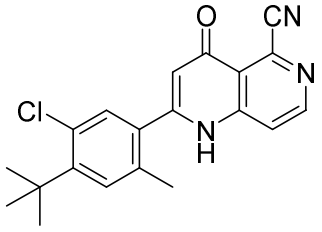
transforming the compound of formula (C_7) to Compound **I**.

9. The process of claim 7, wherein the step of transforming the compound of formula (C_5) to Compound **I** comprises transforming the compound of formula (C_5) to a compound of formula (C_6):



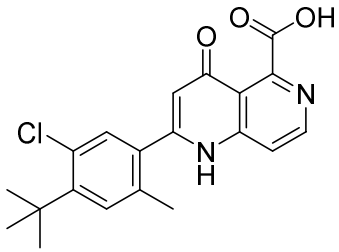
(C_6) ; and

transforming the compound of formula (C_6) to Compound **I**, optionally wherein the step of transforming the compound of formula (C_6) to Compound **I** comprises transforming the compound of formula (C_6) to a compound of formula (C_4):



(C_4) ; and

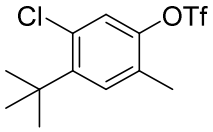
transforming the compound of formula (C_4) to Compound **I**, optionally wherein the step of transforming the compound of formula (C_4) to Compound **I** comprises transforming the compound of formula (C_4) to a compound of formula (C_7):



(C_7) ; and

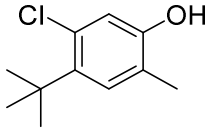
transforming the compound of formula (C_7) to Compound **I**.

10. The process of any one of claims 1, 2, and 5 to 9, further comprising transforming a compound of formula ($B_{1\text{-}1}$):



($B_{1\text{-}1}$)

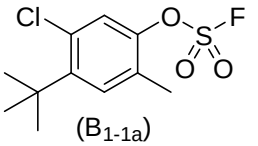
to the compound of formula (B_1), optionally further comprising transforming a compound of formula ($B_{1\text{-}2}$):



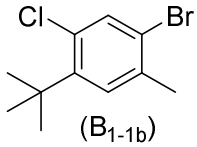
($B_{1\text{-}2}$)

to the compound of formula ($B_{1\text{-}1}$).

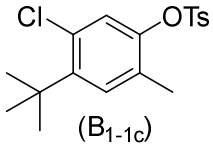
11. The process of any one of claims 1, 2, and 5 to 9, further comprising transforming a compound of formula ($B_{1\text{-}1a}$), ($B_{1\text{-}1b}$), ($B_{1\text{-}1c}$), ($B_{1\text{-}1d}$), ($B_{1\text{-}1e}$), ($B_{1\text{-}1f}$), or ($B_{1\text{-}1g}$):



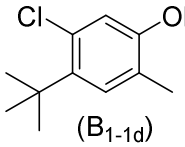
($B_{1\text{-}1a}$),



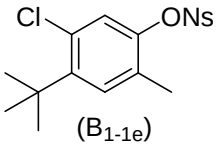
($B_{1\text{-}1b}$),



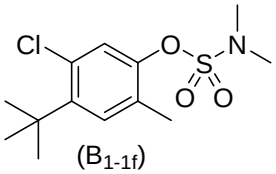
($B_{1\text{-}1c}$),



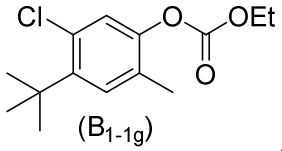
($B_{1\text{-}1d}$),



($B_{1\text{-}1e}$),

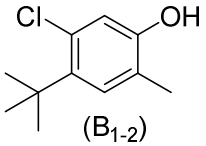


($B_{1\text{-}1f}$), or



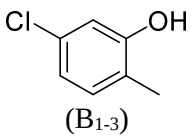
($B_{1\text{-}1g}$).

to the compound of formula (B_1), optionally further comprising transforming a compound of formula ($B_{1\text{-}2}$):



($B_{1\text{-}2}$)

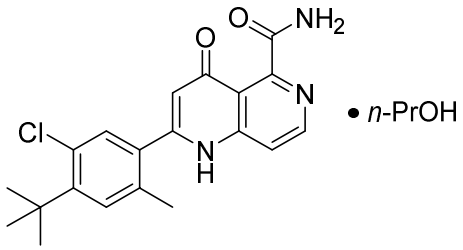
to the compound of formula ($B_{1\text{-}1a}$), ($B_{1\text{-}1b}$), ($B_{1\text{-}1c}$), ($B_{1\text{-}1d}$), ($B_{1\text{-}1e}$), ($B_{1\text{-}1f}$), or ($B_{1\text{-}1g}$), optionally further comprising transforming a compound of formula ($B_{1\text{-}3}$):



($B_{1\text{-}3}$)

to the compound of formula ($B_{1\text{-}2}$).

12. The process of any one of claims 1 to 11, further comprising transforming Compound **I** to a solvate of Compound **I**, optionally wherein the solvate of the compound of formula (I) is a compound of formula (D):

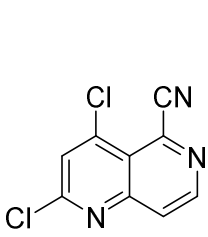


,

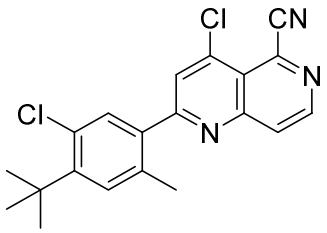
(D)

optionally further comprising transforming the solvate of Compound **I** to Form A of Compound **I**.

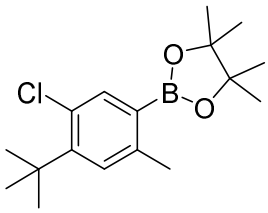
13. A compound selected from:



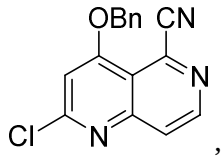
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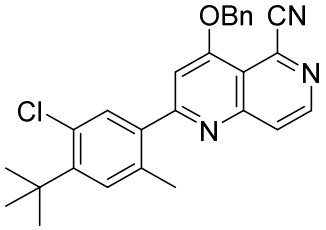
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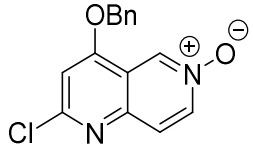
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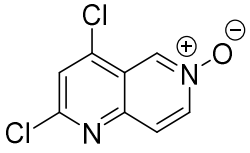
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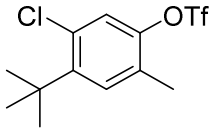
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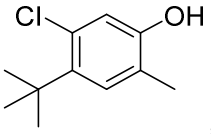
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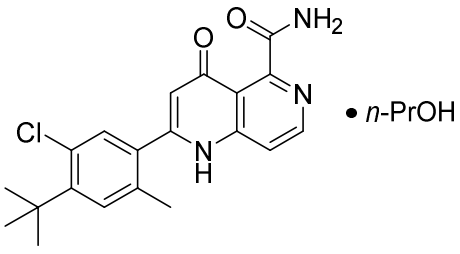


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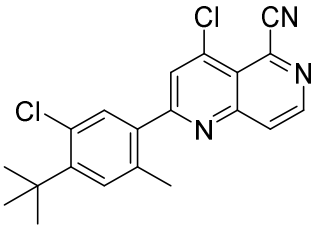
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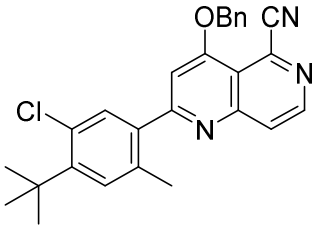
and

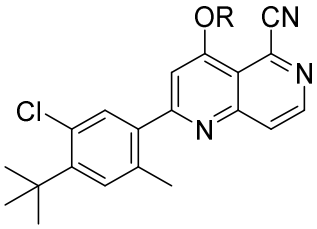


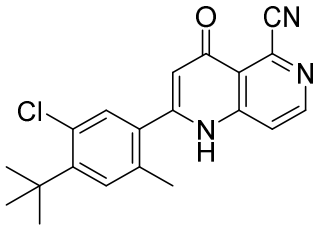
.

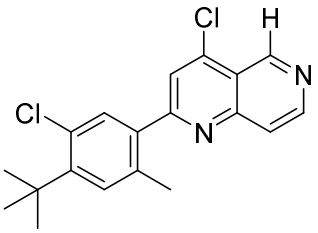
14. A compound selected from:

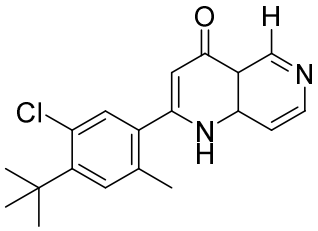


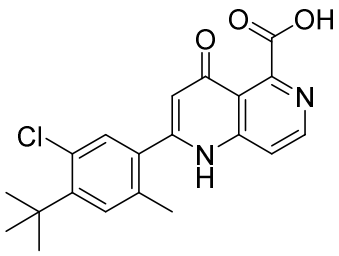
(C_2) ,


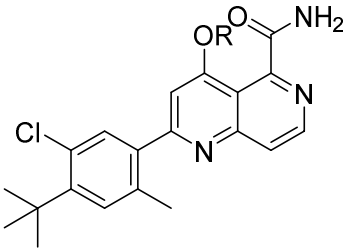
(C_3) ,


(C_{3a}) ,


(C_4) ,


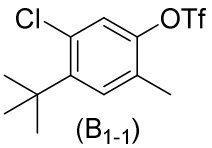
(C_5) ,


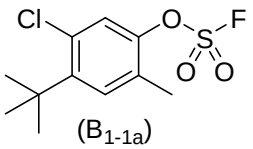
(C_6) ,


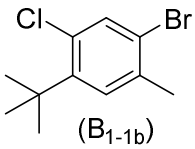
(C_7) , and


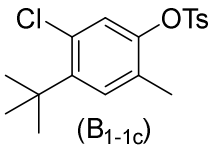
(C_{8a}) , wherein R is C_1-C_6 alkyl.

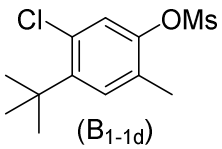
15. A compound selected from:

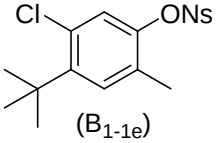


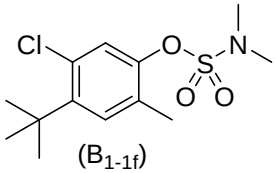
($B_{1\text{-}1}$) ,


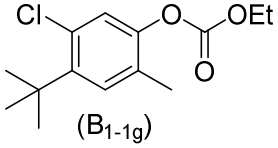
($B_{1\text{-}1a}$) ,


($B_{1\text{-}1b}$) ,


($B_{1\text{-}1c}$) ,


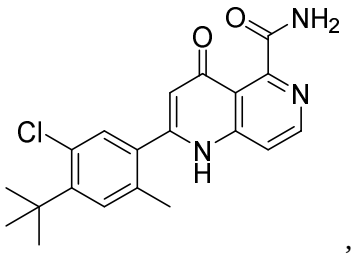
($B_{1\text{-}1d}$) ,


($B_{1\text{-}1e}$) ,


($B_{1\text{-}1f}$) , and


($B_{1\text{-}1g}$) .

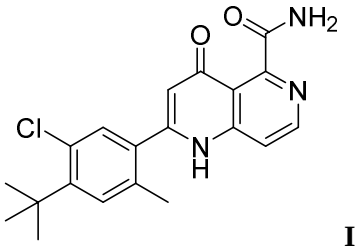
16. Compound **I**:



I

prepared by the process of any one of claims 1 to 12.

17. A substantially crystalline Compound I



I

wherein the substantially crystalline Compound **I** is selected from Compound **I** Neat Form A, Compound **I** Neat Form B, Compound **I** Neat Form C, Compound **I** hemi-hydrate, Compound **I** monohydrate, Compound **I** methanol solvate, Compound **I** nPA solvate mixture A, Compound **I** nPA solvate B, Compound **I** nPA solvate C, Compound **I** Na hemi salt nPA solvate, Compound **I** nPA solvate J, Compound **I** 2-Me THF Solvate A, Compound **I** 2-Me THF Solvate Mixture A, Compound **I** 2-Me THF Mixture C, Compound **I** mandelic acid cocrystal, Compound **I** DL-oxalic acid cocrystal, and Compound **I** TFA Salt A.

18. The substantially crystalline Compound according to claim 17, where the substantially crystalline Compound **I** is Compound **I** Neat Form A, optionally wherein Compound **I** Neat Form A is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 5.5 ± 0.2 degrees two-theta, 9.0 ± 0.2 degrees two-theta, and 10.4 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 8**; and/or

(c) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 179.6 ± 0.2 ppm, 178.7 ± 0.2 ppm, 177.5 ± 0.2 ppm, 174.6 ± 0.2 ppm, 169.7 ± 0.2 ppm, 168.2 ± 0.2 ppm, 155.9 ± 0.2 ppm, 154.8 ± 0.2 ppm, 153.0 ± 0.2 ppm, 152.3 ± 0.2 ppm, 150.9 ± 0.2 ppm, 149.1 ± 0.2 ppm, 147.7 ± 0.2 ppm, 146.7 ± 0.2 ppm, 145.6 ± 0.2 ppm, 144.7 ± 0.2 ppm, 135.6 ± 0.2 ppm, 134.7 ± 0.2 ppm, 132.8 ± 0.2 ppm, 131.0 ± 0.2 ppm, 129.7 ± 0.2 ppm, 116.3 ± 0.2 ppm, 115.0 ± 0.2 ppm, 113.6 ± 0.2 ppm, 113.3 ± 0.2 ppm, 111.4 ± 0.2 ppm, 36.5 ± 0.2 ppm, 36.2 ± 0.2 ppm, 30.3 ± 0.2 ppm, 29.5 ± 0.2 ppm, and 20.4 ± 0.2 ppm; and/or

(d) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 178.8 ± 0.2 ppm, 177.5 ± 0.2 ppm, 174.7 ± 0.2 ppm, 168.3 ± 0.2 ppm, 156.0 ± 0.2 ppm, 153.1 ± 0.2 ppm, 152.4 ± 0.2 ppm, 150.9 ± 0.2 ppm, 149.4 ± 0.2 ppm, 148.3 ± 0.2 ppm, 146.8 ± 0.2 ppm, 145.6 ± 0.2 ppm, 144.8 ± 0.2 ppm, 135.7 ± 0.2 ppm, 134.6 ± 0.2 ppm, 132.8 ± 0.2 ppm, 130.9 ± 0.2 ppm, 129.6 ± 0.2 ppm, 116.3 ± 0.2 ppm, 115.1 ± 0.2 ppm, 113.5 ± 0.2 ppm, 111.5 ± 0.2 ppm, 36.4 ± 0.2 ppm, 30.3 ± 0.2 ppm, 29.7 ± 0.2 ppm, and 20.5 ± 0.2 ppm; and/or

(e) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 179.7 ± 0.2 ppm, 178.8 ± 0.2 ppm, 177.6 ± 0.2 ppm, 174.8 ± 0.2 ppm, 169.8 ± 0.2 ppm, 168.3 ± 0.2 ppm, 155.9 ± 0.2 ppm, 154.9 ± 0.2 ppm, 153.0 ± 0.2 ppm, 152.4 ± 0.2 ppm, 151.1 ± 0.2 ppm, 149.2 ± 0.2 ppm, 147.8 ± 0.2 ppm, 146.8 ± 0.2 ppm, 145.7 ± 0.2 ppm, 144.7 ± 0.2 ppm, 135.6 ± 0.2 ppm, 135.0 ± 0.2 ppm, 132.8 ± 0.2 ppm, 131.0 ± 0.2 ppm, 116.3 ± 0.2 ppm, 115.1 ± 0.2 ppm, 113.5 ± 0.2 ppm, 111.4, 36.3 ± 0.2 ppm, 30.3 ± 0.2 ppm, 29.6 ± 0.2 ppm, and 20.5 ± 0.2 ppm; and/or

(f) a ^{13}C SSNMR spectrum substantially similar to **FIG. 9A**; and/or

(g) a ^{13}C SSNMR spectrum substantially similar to **FIG. 9B** (bottom trace); and/or

(h) a ^{13}C SSNMR spectrum substantially similar to **FIG. 9B** (middle trace); and/or

(i) a ^{13}C SSNMR spectrum substantially similar to **FIG. 9B** (top trace); and/or

(j) a triclinic crystal system, P-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K_α radiation (λ=1.54178 Å) of:

a	11.0 ± 0.1 Å	α	98.0 ± 0.1°
b	11.2 ± 0.1 Å	β	93.1 ± 0.1°
c	15.9 ± 0.1 Å	γ	95.8 ± 0.1°

19. The substantially crystalline Compound according to claim 17, where the substantially crystalline Compound **I** is Compound **I** Neat Form B, optionally wherein Compound **I** Neat Form B is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 5.8 ± 0.2 degrees two-theta, 9.5 ± 0.2 degrees two-theta, and 9.8 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 10**; and/or

(c) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 177.9 ± 0.2 ppm, 176.6 ± 0.2 ppm, 174.4 ± 0.2 ppm, 169.7 ± 0.2 ppm, 157.5 ± 0.2 ppm, 152.8 ± 0.2 ppm,

151.6 ± 0.2 ppm, 150.2 ± 0.2 ppm, 149.4 ± 0.2 ppm, 147.5 ± 0.2 ppm, 145.2 ± 0.2 ppm, 134.5 ± 0.2 ppm, 133.8 ± 0.2 ppm, 133.4 ± 0.2 ppm, 132.4 ± 0.2 ppm, 131.1 ± 0.2 ppm, 130.6 ± 0.2 ppm, 115.5 ± 0.2 ppm, 114.2 ± 0.2 ppm, 113.9 ± 0.2 ppm, 111.4 ± 0.2 ppm, 36.3 ± 0.2 ppm, 30.9 ± 0.2 ppm, 29.1 ± 0.2 ppm, 19.8 ± 0.2 ppm, and 18.1 ± 0.2 ppm; and/or

(d) a ^{13}C SSNMR spectrum substantially similar to **FIG. 11**; and/or

(e) a triclinic crystal system, a P-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K_α radiation (λ=1.54178 Å) of:

a	11.1 ± 0.1 Å	α	87.6 ± 0.1°
b	11.5 ± 0.1 Å	β	88.2 ± 0.1°
c	15.0 ± 0.1 Å	γ	88.9 ± 0.1°

20. The substantially crystalline Compound according to claim 17, where the substantially crystalline Compound **I** is Compound **I** Neat Form C, optionally wherein Compound **I** Neat Form C is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 6.0 ± 0.2 degrees two-theta, 13.9 ± 0.2 degrees two-theta, and 19.7 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 12**; and/or

(c) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 177.9 ± 0.2 ppm, 176.5 ± 0.2 ppm, 173.9 ± 0.2 ppm, 169.3 ± 0.2 ppm, 157.8 ± 0.2 ppm, 153.9 ± 0.2 ppm, 151.5 ± 0.2 ppm, 149.8 ± 0.2 ppm, 148.4 ± 0.2 ppm, 147.8 ± 0.2 ppm, 145.6 ± 0.2 ppm, 135.4 ± 0.2 ppm, 134.5 ± 0.2 ppm, 133.0 ± 0.2 ppm, 131.3 ± 0.2 ppm, 130.4 ± 0.2 ppm, 115.6 ± 0.2 ppm, 115.4 ± 0.2 ppm, 114.5 ± 0.2 ppm, 114.1 ± 0.2 ppm, 111.4 ± 0.2 ppm, 36.5 ± 0.2 ppm, 36.3 ± 0.2 ppm, 31.3 ± 0.2 ppm, 30.2 ± 0.2 ppm, 20.9 ± 0.2 ppm, and 17.9 ± 0.2 ppm; and/or

(d) a ^{13}C SSNMR spectrum substantially similar to **FIG. 13**; and/or

(e) a triclinic crystal system, a P-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K_α radiation (λ=1.54178 Å) of:

a	11.3 ± 0.1 Å	α	84.3 ± 0.1°
b	11.5 ± 0.1 Å	β	68.8 ± 0.1°
c	15.2 ± 0.1 Å	γ	89.0 ± 0.1°

and/or

(f) a triclinic crystal system, a P-1 space group, and unit cell dimensions measured at 298K on a diffractometer utilizing Cu K_α radiation (λ=1.54178 Å) of:

a	11.4 ± 0.1 Å	α	84.2 ± 0.1°
b	11.6 ± 0.1 Å	β	69.6 ± 0.1°
c	15.3 ± 0.1 Å	γ	88.9 ± 0.1°

21. The substantially crystalline Compound according to claim 17, where the substantially crystalline Compound **I** is Compound **I** hemi-hydrate, optionally wherein Compound **I** hemi-hydrate is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 5.1 ± 0.2 degrees two-theta, 10.2 ± 0.2 degrees two-theta, and 12.3 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 14**; and/or

(c) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 178.1 ± 0.2 ppm, 169.2 ± 0.2 ppm, 155.4 ± 0.2 ppm, 154.0 ± 0.2 ppm, 147.7 ± 0.2 ppm, 146.4 ± 0.2 ppm, 137.6 ± 0.2 ppm, 137.0 ± 0.2 ppm, 133.4 ± 0.2 ppm, 129.0 ± 0.2 ppm, 127.2 ± 0.2 ppm, 116.7 ± 0.2 ppm, 115.6 ± 0.2 ppm, 113.0 ± 0.2 ppm, 35.4 ± 0.2 ppm, 29.6 ± 0.2 ppm, and 21.1 ± 0.2 ppm; and/or

(d) a ^{13}C SSNMR spectrum substantially similar to **FIG. 15**.

22. The substantially crystalline Compound according to claim 17, where the substantially crystalline Compound **I** is Compound **I** monohydrate, optionally wherein Compound **I** monohydrate is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 5.0 ± 0.2 degrees two-theta, 10.2 ± 0.2 degrees two-theta, and 14.2 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 16**.

23. The substantially crystalline Compound according to claim 17, where the substantially crystalline Compound **I** is Compound **I** methanol solvate, optionally wherein Compound **I** methanol solvate is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 6.6 ± 0.2 degrees two-theta, 8.4 ± 0.2 degrees two-theta, and 10.6 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 17**; and/or

(c) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 178.3 ± 0.2 ppm, 177.4 ± 0.2 ppm, 172.8 ± 0.2 ppm, 170.3 ± 0.2 ppm, 156.9 ± 0.2 ppm, 154.1 ± 0.2 ppm, 151.9 ± 0.2 ppm, 150.0 ± 0.2 ppm, 149.2 ± 0.2 ppm, 147.8 ± 0.2 ppm, 146.4 ± 0.2 ppm, 135.0 ± 0.2 ppm, 134.0 ± 0.2 ppm, 132.9 ± 0.2 ppm, 131.5 ± 0.2 ppm, 129.6 ± 0.2 ppm, 116.2 ± 0.2 ppm, 115.0 ± 0.2 ppm, 114.6 ± 0.2 ppm, 112.0 ± 0.2 ppm, 49.5 ± 0.2 ppm, 49.3 ± 0.2 ppm, 49.0 ± 0.2 ppm, 36.4 ± 0.2 ppm, 35.3 ± 0.2 ppm, 30.2 ± 0.2 ppm, 28.2 ± 0.2 ppm, 19.1 ± 0.2 ppm, and 18.8 ± 0.2 ppm; and/or

(d) a ^{13}C SSNMR spectrum substantially similar to **FIG. 18**; and/or

(e) a triclinic crystal system, P-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K_α radiation (λ=1.54178 Å) of:

a	12.3 ± 0.1 Å	α	100.4 ± 0.1°
b	14.1 ± 0.1 Å	β	105.3 ± 0.1°
c	14.4 ± 0.1 Å	γ	107.5 ± 0.1°

24. The substantially crystalline Compound according to claim 17, where the substantially crystalline Compound **I** is Compound **I** nPA solvate mixture A, optionally wherein Compound **I** nPA solvate mixture A is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 5.3 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, and 10.6 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 19**; and/or

(c) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 175.2 ± 0.2 ppm, 172.3 ± 0.2 ppm, 155.1 ± 0.2 ppm, 149.7 ± 0.2 ppm, 147.2 ± 0.2 ppm, 145.3 ± 0.2 ppm, 143.5 ± 0.2 ppm, 135.3 ± 0.2 ppm, 134.7 ± 0.2 ppm, 132.6 ± 0.2 ppm, 130.9 ± 0.2 ppm, 117.1 ± 0.2 ppm, 112.9 ± 0.2 ppm, 64.3 ± 0.2 ppm, 36.5 ± 0.2 ppm, 30.4 ± 0.2 ppm, 24.8 ± 0.2 ppm, 20.7 ± 0.2 ppm, and 11.9 ± 0.2 ppm; and/or

(d) a ^{13}C SSNMR spectrum substantially similar to **FIG. 20**; and/or

(e) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 176.5 ± 0.2 ppm, 175.2 ± 0.2 ppm, 171.8 ± 0.2 ppm, 154.3 ± 0.2 ppm, 153.2 ± 0.2 ppm, 150.1 ± 0.2 ppm, 147.6 ± 0.2 ppm, 144.9 ± 0.2 ppm, 143.5 ± 0.2 ppm, 142.2 ± 0.2 ppm, 135.5 ± 0.2 ppm, 134.5 ± 0.2 ppm, 132.6 ± 0.2 ppm, 131.1 ± 0.2 ppm, 117.0 ± 0.2 ppm, 113.6 ± 0.2 ppm, 112.1 ± 0.2 ppm, 64.3 ± 0.2 ppm, 63.9 ± 0.2 ppm,

36.5 ± 0.2 ppm, 29.9 ± 0.2 ppm, 25.9 ± 0.2 ppm, 24.9 ± 0.2 ppm, 20.9 ± 0.2 ppm, 13.4 ± 0.2 ppm, and 11.7 ± 0.2 ppm; and/or

(f) a ^{13}C SSNMR spectrum substantially similar to **FIG. 21**; and/or

(g) a monoclinic crystal system, *C2/c* space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K_α radiation (λ=1.54178 Å) of:

a	19.9 ± 0.1 Å	α	90
b	6.9 ± 0.1 Å	β	93.9 ± 0.1°
c	32.6 ± 0.1 Å	γ	90

25. The substantially crystalline Compound according to claim 17, where the substantially crystalline Compound **I** is Compound **I** nPA solvate B, optionally wherein Compound **I** nPA solvate B is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 5.3 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, and 10.6 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 22**; and/or

(c) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 175.2 ± 0.2 ppm, 172.3 ± 0.2 ppm, 155.1 ± 0.2 ppm, 149.7 ± 0.2 ppm, 147.2 ± 0.2 ppm, 145.3 ± 0.2 ppm, 143.5 ± 0.2 ppm, 135.3 ± 0.2 ppm, 134.7 ± 0.2 ppm, 132.6 ± 0.2 ppm, 130.9 ± 0.2 ppm, 117.1 ± 0.2 ppm, 112.9 ± 0.2 ppm, 64.3 ± 0.2 ppm, 36.5 ± 0.2 ppm, 30.4 ± 0.2 ppm, 24.8 ± 0.2 ppm, and 20.7 ± 0.2 ppm; and/or

(d) a ^{13}C SSNMR spectrum substantially similar to **FIG. 23**; and/or

(e) a triclinic crystal system, *P*-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K_α radiation (λ=1.54178 Å) of:

a	6.8 ± 0.1 Å	α	93.8 ± 0.1°
b	10.5 ± 0.1 Å	β	92.9 ± 0.1°
c	16.4 ± 0.1 Å	γ	105.8 ± 0.1°

26. The substantially crystalline Compound according to claim 17, where the substantially crystalline Compound **I** is Compound **I** nPA solvate C, optionally wherein Compound **I** nPA solvate C is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 6.1 ± 0.2 degrees two-theta, 11.8 ± 0.2 degrees two-theta, and 12.2 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 24**.

27. The substantially crystalline Compound according to claim 17, where the substantially crystalline Compound **I** is Compound **I** Na hemi salt nPA solvate, optionally wherein Compound **I** Na hemi salt nPA solvate is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 6.7 ± 0.2 degrees two-theta, 14.1 ± 0.2 degrees two-theta, and 14.9 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 25**; and/or

(c) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 178.0 ± 0.2 ppm, 176.8 ± 0.2 ppm, 175.7 ± 0.2 ppm, 174.2 ± 0.2 ppm, 161.9 ± 0.2 ppm, 152.1 ± 0.2 ppm, 151.1 ± 0.2 ppm, 150.4 ± 0.2 ppm, 147.4 ± 0.2 ppm, 146.1 ± 0.2 ppm, 144.6 ± 0.2 ppm, 142.6 ± 0.2 ppm, 135.4 ± 0.2 ppm, 134.4 ± 0.2 ppm, 133.0 ± 0.2 ppm, 132.0 ± 0.2 ppm, 130.5 ± 0.2 ppm, 119.6 ± 0.2 ppm, 118.8 ± 0.2 ppm, 115.9 ± 0.2 ppm, 114.4 ± 0.2 ppm, 114.0 ± 0.2 ppm, 111.6 ± 0.2 ppm, 65.1 ± 0.2 ppm, 62.6 ± 0.2 ppm, 36.5 ± 0.2 ppm, 30.7 ± 0.2 ppm, 26.2 ± 0.2 ppm, 24.8 ± 0.2 ppm, 21.4 ± 0.2 ppm, and 20.8 ± 0.2 ppm; and/or

(d) a ^{13}C SSNMR spectrum substantially similar to **FIG. 26**; and/or

(e) triclinic crystal system, *P*-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K_α radiation (λ=1.54178 Å) of:

a	10.3 ± 0.1 Å	α	94.2 ± 0.1°
b	13.3 ± 0.1 Å	β	91.0 ± 0.1°
c	16.7 ± 0.1 Å	γ	104.0 ± 0.1°

28. The substantially crystalline Compound according to claim 17, where the substantially crystalline Compound **I** is Compound **I** nPA solvate J, optionally wherein Compound **I** nPA solvate J is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 5.3 ± 0.2 degrees two-theta, 10.4 ± 0.2 degrees two-theta, and 19.0 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 27**.

29. The substantially crystalline Compound according to claim 17, where the substantially crystalline Compound **I** is Compound **I** 2-Me THF Solvate A, optionally wherein Compound **I** 2-Me THF Solvate A is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 5.8 ± 0.2 degrees two-theta, 9.4 ± 0.2 degrees two-theta, and 14.0 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 28**.

30. The substantially crystalline Compound according to claim 17, where the substantially crystalline Compound **I** is Compound **I** 2-Me THF Solvate Mixture A, optionally wherein Compound **I** 2-Me THF Solvate Mixture A is characterized by:

(a) an X-ray powder diffractogram having a signal at 4.6 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 29**.

31. The substantially crystalline Compound according to claim 17, where the substantially crystalline Compound **I** is Compound **I** 2-Me THF Mixture C, optionally wherein Compound **I** 2-Me THF Mixture C is characterized by:

(a) an X-ray powder diffractogram having a signal at 4.9 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 30**.

32. The substantially crystalline Compound according to claim 17, where the substantially crystalline Compound **I** is Compound **I** mandelic acid cocrystal, optionally wherein Compound **I** mandelic acid cocrystal is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 6.6 ± 0.2 degrees two-theta, 10.6 ± 0.2 degrees two-theta, and 21.1 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 31**.

33. The substantially crystalline Compound according to claim 17, where the substantially crystalline Compound **I** is Compound **I** DL-oxalic acid cocrystal, optionally wherein Compound **I** DL-oxalic acid cocrystal is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 8.9 ± 0.2 degrees two-theta, 11.6 ± 0.2 degrees two-theta, and 14.5 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 32**; and/or

(c) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 177.5 ± 0.2 ppm, 169.8 ± 0.2 ppm, 169.5 ± 0.2 ppm, 162.4 ± 0.2 ppm, 161.5 ± 0.2 ppm, 154.3 ± 0.2 ppm, 153.7 ± 0.2 ppm, 149.3 ± 0.2 ppm, 148.0 ± 0.2 ppm, 146.4 ± 0.2 ppm, 146.1 ± 0.2 ppm, 134.9 ± 0.2 ppm, 133.0 ±

0.2 ppm, 132.0 ± 0.2 ppm, 130.9 ± 0.2 ppm, 130.0 ± 0.2 ppm, 128.1 ± 0.2 ppm, 117.7 ± 0.2 ppm, 114.6 ± 0.2 ppm, 112.4 ± 0.2 ppm, 36.3 ± 0.2 ppm, 29.3 ± 0.2 ppm, and 17.9 ± 0.2 ppm; and/or

(d) a ^{13}C SSNMR spectrum substantially similar to **FIG. 33**.

34. The substantially crystalline Compound according to claim 17, where the substantially crystalline Compound **I** is Compound **I** TFA Salt A, optionally wherein Compound **I** TFA Salt A is characterized by:

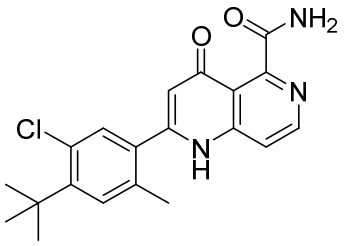
(a) an X-ray powder diffractogram having one, two, or three signals selected from 8.4 ± 0.2 degrees two-theta, 15.1 ± 0.2 degrees two-theta, and 19.7 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 34**; and/or

(c) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 171.9 ± 0.2 ppm, 169.2 ± 0.2 ppm, 160.7 ± 0.2 ppm, 159.5 ± 0.2 ppm, 149.1 ± 0.2 ppm, 147.4 ± 0.2 ppm, 146.8 ± 0.2 ppm, 136.1 ± 0.2 ppm, 133.7 ± 0.2 ppm, 132.1 ± 0.2 ppm, 131.0 ± 0.2 ppm, 118.1 ± 0.2 ppm, 116.0 ± 0.2 ppm, 113.0 ± 0.2 ppm, 36.6 ± 0.2 ppm, 31.3 ± 0.2 ppm, and 18.4 ± 0.2 ppm; and/or

(d) a ^{13}C SSNMR spectrum substantially similar to **FIG. 35**.

35. An amorphous Compound I



I.

36. A pharmaceutical composition comprising the substantially crystalline Compound I according to any one of claims 17 to 34 or the amorphous Compound I according to claim 35.

37. Use of the substantially crystalline Compound I according to any one of claims 17 to 34, the amorphous Compound I according to claim 35, or the pharmaceutical composition according to claim 36, in the manufacture of a medicament for treating or lessening the severity in a subject of pain, optionally wherein the pain comprises chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain, visceral pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or cardiac arrhythmia.

38. A method of preparing a solid form of Compound **I**, comprising:

(a) (i) suspending Compound **I** amorphous material in methanol, (ii) shaking at room temperature for 1 hour, (iii) collecting the solids, and (iv) drying under vacuum at 40 °C to afford Compound **I** Neat Form A;

(b) (i) suspending Amorphous Compound **I** in nitromethane to form a mixture, (ii) agitating the mixture at room temperature for about 1 hour, (iii) isolating the solids from the mixture, and (iv) drying the solids in an oven for about 72 hours to afford Compound **I** Neat Form B;

(c) (i) suspending Compound **I** Neat Form A in 2-MeTHF to form a mixture, (ii) stirring the mixture at about 20 °C for about 1 hour, (iii) isolating the solids from the mixture, and (iv) drying the solids in an oven for about 72 hours to afford Compound **I** Neat Form C;

(d) (i) suspending Compound **I** in water, (ii) shaking at 40 °C for at least 1 week, at least 2 weeks, at least three weeks, or at least 4 weeks, (iii) collecting the solids, and (iv) drying under vacuum at 40 °C to afford Compound **I** Hemi-Hydrate;

(e) (i) suspending Compound **I** in water, (ii) shaking at 40 °C for no more than 48 hours, (iii) collecting the solids, and (iv) drying under vacuum at 40 °C to afford Compound **I** Monohydrate;

(f) (i) suspending Compound **I** amorphous material in methanol, (ii) shaking at 40 °C for 1 hour, and (iii) collecting the solids to afford Compound **I** Methanol Solvate;

(g) (i) suspending Compound **I** nPA Solvate B and NaTFA in nPA, (ii) mixing at room temperature for 6-18 hours, (iii) collecting the solids, and (iv) air-drying for 15-45 minutes to afford Compound **I** nPA Solvate Mixture A;

(h) (i) suspending Compound **I** nPA amorphous material in nPA, (ii) mixing at room temperature for 18-30 hours, (iii) collecting the solids, and (iv) drying under vacuum at 40 °C to afford Compound **I** nPA Solvate B;

(i) (i) dissolving Compound **I** in nPA, (ii) mixing at 90-100 °C for 1-2 hours, (iii) mixing at room temperature for 6-30 hours, and (iv) collecting the solids to afford Compound **I** nPA Solvate C;

(j) (i) treating 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-chloro-1,6-naphthyridine-5-carbonitrile with water and TFA, (ii) mixing at 60 °C for 18-30 hours, (iii) treating the mixture with water and sodium hydroxide at room temperature, (iv) washing the mixture with aqueous sodium chloride, (v) diluting the mixture with 2-MeTHF and subsequently concentrating, (vi) treating the mixture with nPA and subsequently concentrating, (vii) heating the mixture to 90 °C and subsequently holding the mixture at 50 °C for 6-18 hours, (viii) cooling the mixture to room temperature, (ix) collecting the solids, and (s) drying under vacuum at 40 °C for 6-18 hours to afford Compound **I** Na Hemi Salt nPA Solvate;

(k) (i) treating a mixture of Compound **I** and 2-MeTHF with nPA, (ii) concentrating the mixture at 20-30 °C, (iii) treating the mixture with nPA and subsequently concentrating the mixture at 20-30 °C, (iv) heating the mixture to 80-100 °, (v) cooling the mixture to room temperature over 8-16 hours, (v) collecting the solids, and (vi) drying under vacuum at 45 °C to afford Compound **I** nPA Solvate J;

(l) (i) treating Compound **I** Form A with 2-MeTHF, (ii) agitating the mixture for 24 hours at about 22 °C, and (iii) isolating the solids to afford Compound **I** 2-MeTHF Solvate A;

(m) (i) obtaining a solution of Compound **I** in 2-MeTHF, (ii) concentrating the solution to obtain a slurry, (iii) collecting the solids, and (iv) drying under vacuum at 50 °C to afford Compound **I** 2-MeTHF Solvate Mixture A;

(n) (i) obtaining a solution of Compound **I** in 2-MeTHF, (ii) concentrating the solution to obtain a slurry, (iii) warming the slurry to 90 °C to dissolve solids, (iv) cooling to 25 °C, (v) collecting the solids, and (iv) drying at 50 °C to afford Compound **I** 2-MeTHF Solvate Mixture C;

(o) (i) combining Compound **I** and Mandelic acid, (ii) diluting the mixture in DCM, (iii) agitating the mixture for at least 1 hour, (iv) collecting the resulting solid material, and (v) drying the collected solid material in a vacuum oven at 50 °C to afford Compound **I** Mandelic Acid Cocrystal;

(p) (i) suspending Compound **I** and oxalic acid (1:1) in DCM, (ii) stirring the resulting slurry at room temperature, (iii) collecting the solids, and (iv) drying under vacuum at 50 °C to afford Compound **I** Oxalic Acid Cocrystal;

(q) (i) suspending Compound **I** in DCM, (ii) treating the suspension with TFA, (iii) stirring at room temperature for 15-45 minutes, (iv) collecting the solids, and (v) drying at room temperature to afford Compound **I** TFA Salt A; or

(r) (i) combining Compound **I** and t-butanol to form a mixture, (ii) stirring the mixture at about 70 °C for about 1 hour, (iii) adding water to the mixture, (iv) freezing the mixture, and (v) isolating the solid material to afford Amorphous Compound **I**.