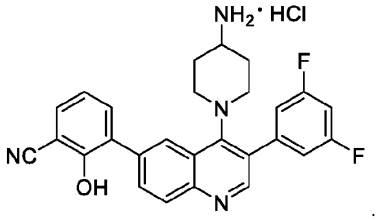
CLAIMS

WHAT IS CLAIMED IS:

1. 3-[4-(4-Amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, having the following structure:



2. Crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof.

3. The crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, of claim 2, having:
   - an X-ray powder diffraction (XRPD) pattern with peaks at 4.5° 2-Theta, 9.1° 2-Theta, 10.2° 2-Theta, 16.3° 2-Theta, 18.4° 2-Theta, and 19.1° 2-Theta;
   - an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 1**;
   - a Differential Scanning Calorimetry (DSC) thermogram with an endotherm having an onset at about 207 °C and a peak at about 220 °C;
   - a Differential Scanning Calorimetry (DSC) thermogram substantially the same as shown in **Figure 2(a)**;
   - a Thermogravimetric Analysis (TGA) thermogram substantially the same as shown in **Figure 2(b)**;
   - an infrared (IR) spectrum with peaks at 2223 cm^{-1}, 1620 cm^{-1}, 1595 cm^{-1}, 1457 cm^{-1}, 1238 cm^{-1}, 1220 cm^{-1}, and 1117 cm^{-1};
   - an infrared (IR) spectrum substantially the same as shown in **Figure 3**;
   - an unchanged XRPD when heated up to about 200° C, upon exposure to more than 90% relative humidity for about 24 hours, or upon exposure to about 75% RH and 40 °C over one week, or combinations thereof;

   or

   - combinations thereof.

4. The crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, of claim 2, having an X-ray powder diffraction (XRPD) pattern with peaks at 4.5° 2-Theta, 9.1° 2-Theta, 10.2° 2-Theta, 16.3° 2-Theta, 18.4° 2-Theta, and 19.1° 2-Theta.

5. The crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, of claim 2, having an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 1**.
6. The crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, of any one of claims 2-5 having a Differential Scanning Calorimetry (DSC) thermogram with an endotherm having an onset at about 207° C and a peak at about 220° C.
7. The crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, of any one of claims 2-5 having a Differential Scanning Calorimetry (DSC) thermogram substantially the same as shown in **Figure 2(a)**.
8. The crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, of any one of claims 2-7 having an unchanged XRPD when heated up to about 200° C.
9. The crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, of any one of claims 2-8 having an unchanged XRPD upon exposure to more than 90% relative humidity for 24 hours and upon exposure to about 75% RH and 40 °C over one week.
10. The crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, of any one of claims 2-9 having an infrared (IR) spectrum with characteristic peaks at 2223 cm^{-1}, 1620 cm^{-1}, 1595 cm^{-1}, 1457 cm^{-1}, 1238 cm^{-1}, 1220 cm^{-1}, and 1117 cm^{-1}.
11. The crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, of any one of claims 2-9 having an infrared (IR) spectrum substantially the same as the IR spectrum shown in Figure 3.
12. A pharmaceutical composition comprising crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, of any one of claims 2-11 and at least one pharmaceutically acceptable excipient.
13. The pharmaceutical composition of claim 12, wherein the pharmaceutical composition is formulated for administration to a mammal by oral administration.
14. The pharmaceutical composition of claim 12 or claim 13, wherein the pharmaceutical composition is in the form of a solid form pharmaceutical composition.

15. The pharmaceutical composition of any one of claims 12-14, wherein the pharmaceutical composition is in the form of a tablet, a pill, or a capsule.

16. A method of making crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, comprising the steps of:

(a) slurrying 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile dihydrochloride in 5 volumes of isopropanol:water (1:1) mixture;

(i) heating the slurry of (a) to about 45° C;

(ii) adding about 0.5 to about 1.2 equivalents of ammonium hydroxide solution, sodium bicarbonate solution, or sodium hydroxide solution to the heated slurry of step (a)(i) to achieve a pH of about 4.0-6.0;

(iii) adding water over about 2 hours to the mixture of step (a)(ii); and

(iv) filtering the slurry of step (a)(iii) to provide 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof;

or

(b) adding a suitable solvent to 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile;

(i) adding about 1 equivalent of hydrochloric acid to the mixture of solvent and 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile of (b); and

(ii) filtering the solids resulting from step (b)(ii) to provide 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof;

or

(c) stirring 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile dihydrochloride in about 20 volumes to about 50 volumes of water; and

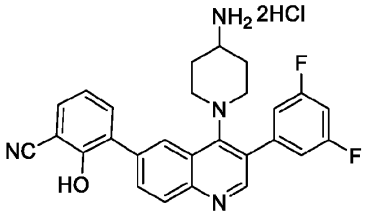
(i) filtering the solids of step (c) to provide 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof.

17. The method of claim 16, wherein ammonium hydroxide solution used in (a)(ii).

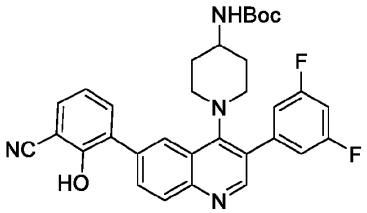
18. The method of claim 16 or claim 17, wherein the amount of ammonium hydroxide solution used in (a)(ii) is about 0.8 equivalents and the pH achieved is about 4.5-4.7.

19. The method of making of claim 16, wherein the suitable solvent in (b) is methanol, ethanol, isopropyl alcohol, acetone, methyl acetate, ethyl acetate, tetrahydrofuran, tetrahydropyran, water, or combinations thereof.

20. A process for the synthesis of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile dihydrochloride:



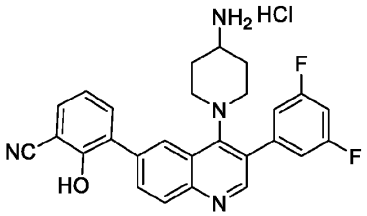
comprising the step of treating Compound **A-VI**:



Compound **A-VI**

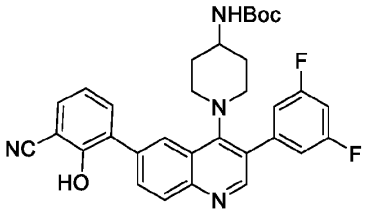
with hydrochloric acid in a suitable solvent.

21. A process for the synthesis of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride:



comprising the steps of:

(1) treating Compound **A-VI**:



Compound **A-VI**

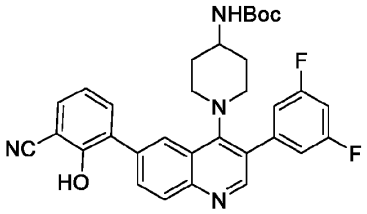
with hydrochloric acid in a suitable solvent to provide 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile dihydrochloride; and

(2) treating 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile dihydrochloride with acqueous ammonia to provide 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride.

22. The process of claim 20 or claim 21, wherein the suitable solvent is isopropyl alcohol, ethyl acetate, or isopropyl acetate.

23. The process of any one of claims 20-21, wherein the suitable solvent is isopropyl alcohol.

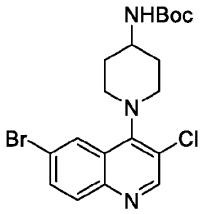
24. A process for the preparation of Compound **A-VI**:



Compound **A-VI**

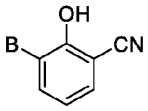
comprising the steps of:

(1) reacting Compound **A-IV**:



Compound **A-IV**

with Compound **1**:

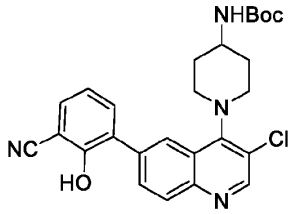


Compound **1**

wherein,

B is a boronic acid, bononate ester, or trifluoroborate;

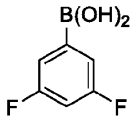
in the presence of a coupling catalyst, a suitable base, and in a suitable solvent, to provide Compound **A-V**:



Compound **A-V**

and

(2) reacting Compound **A-V** with 3,5-difluorophenylboronic acid:



in the presence of a coupling catalyst, a suitable base, and in a suitable solvent, to provide Compound **A-VI**.

25. The process of claim 24, wherein B is a boronic acid or trifluoroborate.

26. The process of claim 24 or claim 25, wherein:

the coupling catalyst of step (1) is a palladium catalyst;

the suitable base of step (1) is triethylamine, diisopropylethylamine, 1,2,2,6,6-pentamethylpiperidine, tributylamine, sodium bicarbonate, Na_2CO_3, K_2CO_3, Cs_2CO_3, NaOAc, KOAc, $Ba(OH)_2$, Na_3PO_4 or K_3PO_4; and

the suitable solvent of step (1) is acetonitrile, dimethylformamide, ethanol, tetrahydrofuran, isopropyl alcohol, 1,4-dioxane, water, or combinations thereof.

27. The process of claim 26, wherein:

Step (1) is performed at a temperature of about 80-85 °C.

28. The process of any one of claims 24-27, wherein:

the coupling catalyst of step (1) is a palladium catalyst;

the suitable base of step (1) is K_2CO_3; and

the suitable solvent of step (1) is a mixture of 1,4-dioxane and water.

29. The process of any one of claims 24-28, wherein:

the coupling catalyst of step (2) is a palladium catalyst;

the suitable base of step (2) is triethylamine, diisopropylethylamine, 1,2,2,6,6-pentamethylpiperidine, tributylamine, sodium bicarbonate, Na_2CO_3, K_2CO_3, Cs_2CO_3, NaOAc, KOAc, $Ba(OH)_2$, Na_3PO_4 or K_3PO_4; and

the suitable solvent of step (2) is acetonitrile, dimethylformamide, ethanol, tetrahydrofuran, isopropyl alcohol, 1,4-dioxane, water, or combinations thereof.

30. The process of any one of claims 24-29, wherein:

Step (2) is performed at a temperature of about 90 °C to about 100 °C.

31. The process of any one of claims 24-30, wherein:
the coupling catalyst of step (2) is a palladium catalyst;
the suitable base of step (2) is K_2CO_3; and
the suitable solvent of step (2) is a mixture of 1,4-dioxane and water.

32. The process of any one of claims 24-31, wherein:
Compound **A-V** is isolated prior to step (2).

33. The process of any one of claims 24-31, wherein:
Compound **A-V** is not isolated prior to step (2).

34. The process of any one of claims 24-33, further comprising recrystallizing Compound **A-VI** from a suitable solvent.

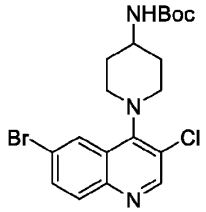
35. The process of claim 34, wherein:
the suitable solvent is methyl acetate, ethyl acetate, isopropyl acetate, methanol, ethanol, isopropyl alcohol, dichloromethane/petroleum ether, acetonitrile, tetrahydrofuran/water, tetrahydrofuran/petroleum ether, dimethylformamide/water, dichloromethane/methyl tert-butyl ether, methanol/ methyl tert-butyl ether, methyl tert-butyl ether, or toluene.

36. The process of claim 34, wherein:
the suitable solvent is ethyl acetate or isopropyl acetate.

37. The process of any one of claims 34-36, further comprising treatment of the recrystallized Compound **A-VI** with a metal scavenger.

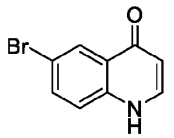
38. The process of claim 37, wherein:
the metal scavenger comprises SiO_2, charcoal, aqueous solution of L-cysteine, a Silicycle metal scavenger, Si-thiol, SiliaBond DMT or SiliaBond Cysteine.

39. A process for the preparation of Compound **A-IV**:



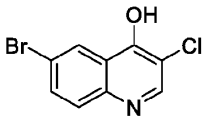
Compound **A-IV**

comprising the steps of:
(1) chlorinating Compound **A-I**



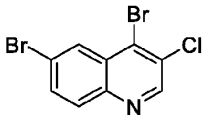
Compound **A-I**;

with a suitable chlorinating agent in a suitable solvent to provide Compound **A-II**



Compound **A-II**;

(2) brominating Compound **A-II** with a suitable brominating agent in a suitable solvent to provide Compound **A-III**:



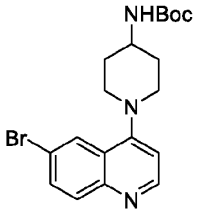
Compound **A-III**;

and

(3) coupling 4-(*N*-Boc amino)piperidine with Compound **A-III** in the presence of a suitable base and in a suitable solvent to provide Compound **A-IV**;

or

(i) coupling 4-(*N*-Boc amino)piperidine with 6-bromo-4-chloro-quinoline in the presence of a suitable base and in a suitable solvent to provide Compound **4**;



Compound **4**;

and

(ii) chlorinating Compound **4** with a suitable chlorinating agent in a suitable solvent to provide Compound **A-IV**.

40. The process of claim 39, wherein:

the chlorinating agent of step (1) is *N*-chlorosuccinimide, trichloroisocyanuric acid, sulfuryl chloride, chlorine, sodium hypochlorite, calcium hypochlorite, hypochlorous acid, or 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one; and

the suitable solvent of step (1) is acetic acid, water, ethanol, methanol, toluene, dichloromethane, tetrahydrofuran, dioxane, or *N,N*-dimethylformamide.

41. The process of claim 39 or claim 40, wherein:
the chlorinating agent of step (1) is *N*-chlorosuccinimide; and
the suitable solvent of step (1) is acetic acid.

42. The process of any one of claims 39-41, wherein:
the brominating agent of step (2) is phosphorus tribromide, phosphorus oxybromide, hydrobromic acid, bromine, or dibromotriphenylphosphorane; and
the suitable solvent of step (2) is acetonitrile, water, ethanol, isopropanol, dichloromethane, toluene, *N,N*-dimethylformamide, acetic acid, or acetone.

43. The process of any one of claims 39-42, wherein:
the brominating agent of step (2) is phosphorus tribromide; and
the suitable solvent of step (2) is *N,N*-dimethylformamide.

44. The process of any one of claims 39-43, wherein:
the suitable base of step (3) is triethylamine, diisopropylethylamine, 1,8-diazabicycloundec-7-ene, 1,2,2,6,6-pentamethylpiperidine, tributylamine, sodium bicarbonate, Na_2CO_3, K_2CO_3, or Cs_2CO_3; and
the suitable solvent of step (3) is *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethylsulfoxide, dichlormethane, chloroform, carbon tetrachloride, dioxane, tetrahydrofuran, toluene, acetonitrile, ethanol, or isopropanol.

45. The process of any one of claims 39-44, wherein:
the base of step (3) is diisopropylethylamine; and
the suitable solvent of step (3) is dimethylsulfoxide.

46. The process of any one of claims 39-45, wherein:
the suitable base of step (i) is triethylamine, diisopropylethylamine, 1,8-diazabicycloundec-7-ene, 1,2,2,6,6-pentamethylpiperidine, tributylamine, sodium bicarbonate, Na_2CO_3, K_2CO_3, or Cs_2CO_3; and
the suitable solvent of step (i) is *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethylsulfoxide, dichlormethane, chloroform, carbon tetrachloride, dioxane, tetrahydrofuran, toluene, acetonitrile, ethanol, or isopropanol.

47. The process of any one of claims 39-45, wherein:
the base of step (i) is K_2CO_3; and
the suitable solvent of step (i) is *N,N*-dimethylformamide.

48. The process of any one of claims 39-47, wherein:

the chlorinating agent of step (ii) is *N*-chlorosuccinimide, trichloroisocyanuric acid, sulfuryl chloride, chlorine, sodium hypochlorite, calcium hypochlorite, hypochlorous acid, or 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one; and

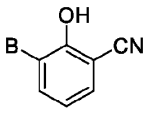
the suitable solvent of step (ii) is acetic acid, water, ethanol, methanol, toluene, dichloromethane, tetrahydrofuran, dioxane, or *N*,*N*-dimethylformamide.

49. The process of any one of claims 39-47, wherein:

the chlorinating agent of step (ii) is *N*-chlorosuccinimide; and

the suitable solvent of step (ii) is toluene.

50. A process for the preparation of Compound **1**:



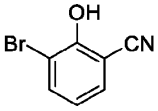
Compound **1**

wherein,

B is a boronic acid or boronate ester;

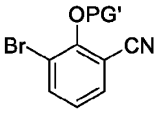
comprising the steps of:

(1) protecting the hydroxyl group of Compound **2**:



Compound **2**;

with a suitable protecting group (PG′) to provide compound **2a**:



Compound **2a**;

(2) reacting Compound **2a** with a borylation agent under suitable reaction conditions; and

(3) removal of the protecting group (PG′) to provide Compound **1**.

51. The process of claim 50, wherein B is a boronic acid.

52. The process of claim 50, further comprising the step of

(4) converting B to a trifluoroborate.

53. The process of any one of claims 50-52, wherein:

the borylation agent is triisopropyl borate, trimethyl borate, tetrahydroxydiboron, pinacolborane, catecholborane, bis(neopentyl glycolato)diboron, bis(pinacolato)diboron, bis(hexylene glycolato)diboron, bis(catecholato)diboron, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 4,6,6-trimethyl-1,3,2-dioxaborinane,

diisopropylamine borane, bis(neopentyl glycolato)diboron, bis(catecholato)diboron, or bis(pinacolato)diboron.

54. The process of any one of claims 50-53, wherein:
the suitable reaction conditions of (2) comprise the use of metal halogen exchange reagents.

55. The process of any one of claims 50-54, wherein:
the suitable reaction conditions of (2) comprise the use of metal halogen exchange reagents selected from Grignard reagents and alkyl lithium reagents.

56. The process of any one of claims 50-55, wherein:
the suitable reaction conditions of (2) comprise the use of isopropyl magnesium chloride in tetrahydrofuran.

57. The process of any one of claims 50-56, wherein:
the borylation agent is triisopropyl borate and the suitable reaction conditions of (2) comprise the use of isopropyl magnesium chloride in tetrahydrofuran.

58. The process of claim 50, wherein:
the suitable reaction conditions of (2) comprise the use of transition metal mediated reaction conditions.

59. The process of claim 50, wherein:
the suitable reaction conditions of (2) comprise the use of palladium metal mediated reaction conditions.

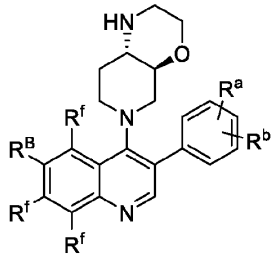
60. The process of any one of claims 50-59, wherein:
the suitable protecting group (PG′) is methoxymethyl, ethoxyethyl, methoxypropyl, benzyloxymethyl, 2-methoxyethoxymethyl, benzyl, *para*-methoxybenzyl, 2-naphthylmethyl, methyl, allyl, tetrahydropyranyl, acetyl, benzoyl, 2,2,2-trichloroethyl carbonyl, trimethylsilyl, triethylsilyl, triisopropyl silyl, *tert*-butyldimethylsilyl, or *tert*-butyldiphenylsilyl.

61. The process of claim 55, wherein:
removal of the protecting group in step (3) is accomplished by treatment with hydrochloric acid, hydrobromic acid, acetic acid, trifluoroacetic acid, para-toluenesulfonic acid, $ZnBr_2$, hydrogen over Pd/C, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), boron tribromide, boron trichloride, trimethylsilyl iodide, $Pd(PPh_3)_4$, tetra-*n*-butylammonium fluoride (TBAF), or HF-pyridine.

62. The process of claim 50, wherein:
the suitable protecting group (PG′) is methoxymethyl; and

removal of the protecting group in step (3) is accomplished by treatment with hydrochloric acid.

63. A compound of Formula (I), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, or enantiomer thereof:



Formula (I)

wherein:

R^a is F, Cl, or $-CH_3$;

R^b is hydrogen, F, Cl, $-CH_3$, -CN, -OH, or $-OCH_3$;

R^B is an unsubstituted or substituted phenyl or an unsubstituted or substituted pyridinyl, wherein if R^B is substituted then R^B is substituted with R^c and R^d;

R^c is hydrogen, F, Cl, Br, $-CH_3$, -CN, -OH, $-OCH_3$, $-C(=NOCH_3)H$, or $-C(=NOH)H$;

R^d is -OH, or $-NH_2$; and

each R^f is hydrogen or F.

64. The compound of claim 63, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, diastereomeric mixture, or enantiomer thereof, wherein the compound is:

2-{4-[(4aS,8aS)-octahydro-1H-pyrido[3,4-b][1,4]oxazin-6-yl]-3-(3,5-difluorophenyl)quinolin-6-yl}-6-[(1E)-(hydroxyimino)methyl]phenol;

2-{4-[(4aS,8aS)-octahydro-1H-pyrido[3,4-b][1,4]oxazin-6-yl]-3-(3-fluoro-5-methylphenyl)quinolin-6-yl}-4-[(1E)-(methoxyimino)methyl]pyridin-3-amine;

2-{4-[(4aS,8aS)-octahydro-1H-pyrido[3,4-b][1,4]oxazin-6-yl]-3-(3-chloro-5-fluorophenyl)quinolin-6-yl}-4-[(1E)-(methoxyimino)methyl]pyridin-3-amine;

2-{4-[(4aS,8aS)-octahydro-1H-pyrido[3,4-b][1,4]oxazin-6-yl]-3-(3-fluoro-5-methylphenyl)quinolin-6-yl}-3-aminopyridine-4-carbonitrile;

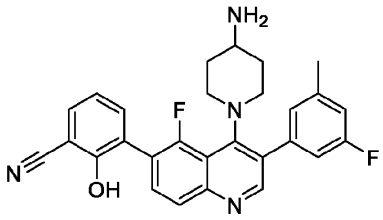
2-{4-[(4aS,8aS)-octahydro-1H-pyrido[3,4-b][1,4]oxazin-6-yl]-3-(3-chloro-5-fluorophenyl)quinolin-6-yl}-3-aminopyridine-4-carbonitrile;

2-{4-[(4aS,8aS)-octahydro-1H-pyrido[3,4-b][1,4]oxazin-6-yl]-3-(3,5-difluorophenyl)quinolin-6-yl}-4-[(1E)-(hydroxyimino)methyl]pyridin-3-amine;

2-{4-[(4aS,8aS)-octahydro-1H-pyrido[3,4-b][1,4]oxazin-6-yl]-3-(3-fluorophenyl)quinolin-6-yl}-3-aminopyridine-4-carbonitrile;

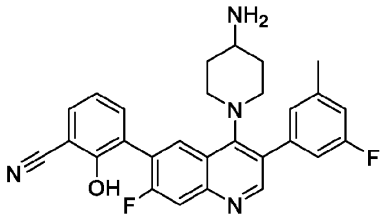
2-{4-[(4aS,8aS)-octahydro-1H-pyrido[3,4-b][1,4]oxazin-6-yl]-3-(3-fluorophenyl)quinolin-6-yl}-4-methylpyridin-3-amine.

65. The compound 3-[4-(4-aminopiperidin-1-yl)-5-fluoro-3-(3-fluoro-5-methylphenyl)quinolin-6-yl]-2-hydroxybenzonitrile:



, or a pharmaceutically acceptable salt thereof.

66. The compound 3-[4-(4-aminopiperidin-1-yl)-7-fluoro-3-(3-fluoro-5-methylphenyl)quinolin-6-yl]-2-hydroxybenzonitrile:



, or a pharmaceutically acceptable salt thereof.