PROCESS OF MAKING SOMATOSTATIN MODULATORS

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/618,538 filed on January 17, 2018, which is herein incoporated by reference in its entirety.

FIELD OF THE INVENTION

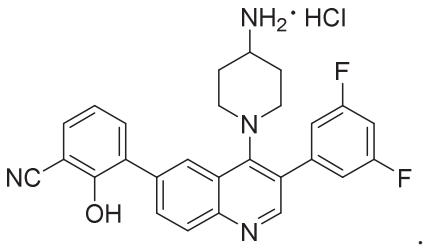
[0002] Described herein are compounds that are somatostatin modulators, methods of making such compounds, pharmaceutical compositions and medicaments comprising such compounds, and methods of using such compounds in the treatment of conditions, diseases, or disorders that would benefit from modulating somatostatin activity.

BACKGROUND OF THE INVENTION

[0003] Somatostatin is a peptide hormone that regulates the endocrine system and affects neurotransmission and cell proliferation via interaction with G-protein-coupled somatostatin receptors and inhibition of the release of numerous secondary hormones. Six subtype somatostatin receptor proteins have been identified (SSTR1, SSTR2a, SSTR2b, SSTR3, SSTR4, SSTR5) and are encoded by five different somatostatin receptor genes. Modulation of a particular subtype somatostatin receptor, or combination thereof, is attractive for the treatment of conditions, diseases, or disorders that would benefit from modulating somatostatin activity.

SUMMARY OF THE ~~INVENTION~~DISCLOSURE

[0004] In one aspect, described herein the compound 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:



[0004a] In another aspect, described herein is a pharmaceutical composition comprising the compound as described herein and at least one pharmaceutically acceptable excipient, optionally wherein the pharmaceutical composition is formulated for administration to a mammal by oral administration.

[0004b] In another aspect, described herein is a use of the compound or the pharmaceutical composition as described herein in the manufacture of a medicament for treating acromegaly or a neuroendocrine tumor, or combinations thereof.

[0004c] In one aspect, described herein is 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 45° C;

(ii) adding 0.5 to 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 4.0-6.0;

(iii) adding water over 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 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 20 volumes to 50 volumes of water; and

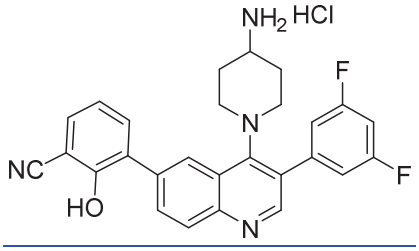
(i) filtering the solids of step (c) to provide 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof;

optionally wherein:

ammonium hydroxide solution used in (a)(ii); and

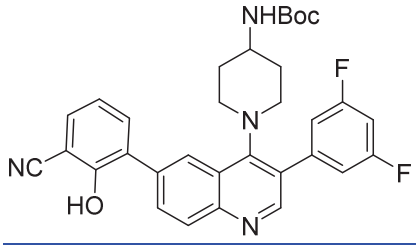
the suitable solvent in (b) is methanol, ethanol, isopropyl alcohol, acetone, methyl acetate, ethyl acetate, tetrahydrofuran, tetrahydropyran, water, or combinations thereof.

[0004d] In one aspect, described herein is 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;

optionally wherein the suitable solvent is isopropyl alcohol, ethyl acetate, or isopropyl acetate.

[0004e] In one aspect, described herein is the compound or the pharmaceutical composition as described herein for use in therapy.

[0005] In another ~~aspect~~example, described herein is crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof. In some ~~embodiment~~examples, the crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, has: 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.

[0006] In some ~~embodiment~~examples, the crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, has 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. In some ~~embodiment~~examples, the crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, has an XRPD pattern further comprises peaks at 20.7° 2-Theta, 23.3° 2-Theta, 23.4° 2-Theta, 23.6° 2-Theta, 27.1° 2-Theta, and 28.0° 2-Theta. In some ~~embodiment~~examples, the crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, has an X-ray powder diffraction (XRPD) pattern substantially the same as shown in Figure 1. In some ~~embodiment~~examples, the crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, has a Differential Scanning Calorimetry (DSC) thermogram with an endotherm having an onset at about 207° C and a peak at about 220° C. In some ~~embodiment~~examples, the crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, has a Differential Scanning Calorimetry (DSC) thermogram substantially the same as shown in Figure 2(a). In some ~~embodiment~~examples, the crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, has an unchanged XRPD when heated up to about 200° C. In some ~~embodiment~~examples, the crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, has 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. In some ~~embodiment~~examples, the crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, has 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}. In some ~~embodiment~~examples, the crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile

monohydrochloride, or solvate thereof, has an infrared (IR) spectrum substantially the same as the IR spectrum shown in Figure 3.

[0007] In another ~~aspect~~example, described herein is 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, and at least one pharmaceutically acceptable excipient. In some ~~embodiment~~examples, the pharmaceutical composition is formulated for administration to a mammal by oral administration. In some ~~embodiment~~examples, the pharmaceutical composition is in the form of a solid form pharmaceutical composition. In some ~~embodiment~~examples, the pharmaceutical composition is in the form of a tablet, a pill, or a capsule.

[0008] In another ~~aspect~~example, described herein is 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

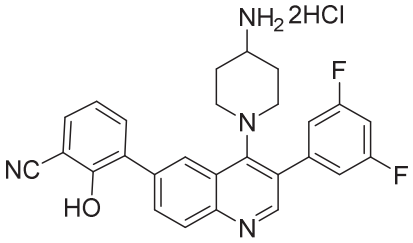
(c) stirring 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile dihydrochloride in about 20 volumes to about 50 volumes of water; and

(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.

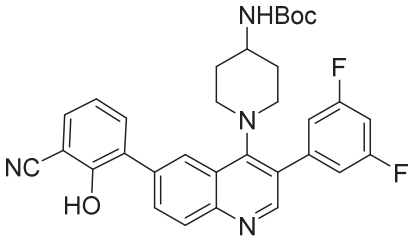
[0009] In some ~~embodiment~~examples, ammonium hydroxide solution is used in (a)(ii). In some ~~embodiment~~examples, the amount of ammonium hydroxide solution used in (a)(ii) is about 0.8 equivalents and the pH achieved is about 4.5-4.7.

[0010] In some ~~embodiment~~examples, the suitable solvent in (b) is methanol, ethanol, isopropyl alcohol, acetone, methyl acetate, ethyl acetate, tetrahydrofuran, tetrahydropyran, water, or combinations thereof.

[0011] In another ~~aspect~~example, described herein is 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:



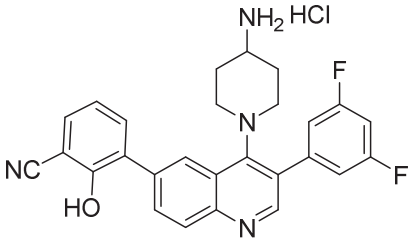
comprising the step of treating Compound **A-VI**:



Compound **A-VI**

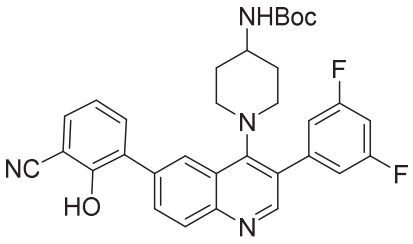
with hydrochloric acid in a suitable solvent.

[0012] In another ~~aspect~~example, described herein is 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**:



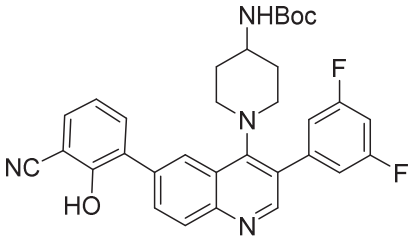
Compound **A-VI**

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.

[0013] In some ~~embodiment~~examples, the suitable solvent is isopropyl alcohol, ethyl acetate, or isopropyl acetate. In some ~~embodiment~~examples, the suitable solvent is isopropyl alcohol.

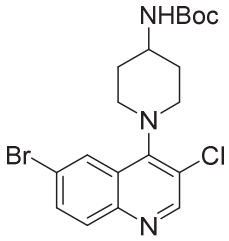
[0014] In another ~~aspect~~example, described herein is a process for the preparation of Compound **A-VI**:



Compound **A-VI**

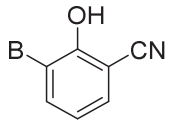
comprising the steps of:

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



Compound **A-IV**

with Compound **1**:

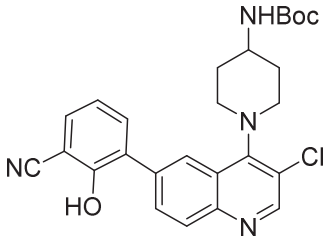


Compound **1**

wherein,

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

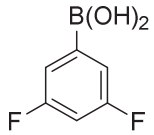
in the presence of a coupling catalyst, a suitable base, and in a suitable solvent, to provide Compound **A-V**:



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**.

[0015] In some ~~embodiment~~examples, B is a boronic acid or trifluoroborate.

[0016] In some ~~embodiment~~examples, B is a boronic acid. In some ~~embodiment~~examples, B is trifluoroborate.

[0017] In some ~~embodiment~~examples, 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. In some ~~embodiment~~examples, Step (1) is performed at a temperature of about 80 °C. In some ~~embodiment~~examples, Step (1) is performed at a temperature of about 80-85 °C.

[0018] In some ~~embodiment~~examples, 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.

[0019] In some ~~embodiment~~examples, 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. In some ~~embodiment~~examples, Step (2) is performed at a temperature of about 90 °C to about 100 °C. In some ~~embodiment~~examples, 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.

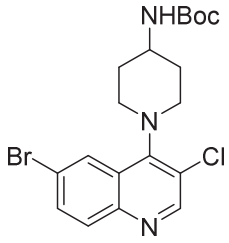
[0020] In some ~~embodiment~~examples, Compound **A-V** is isolated prior to step (2).

[0021] In some ~~embodiment~~examples, Compound **A-V** is not isolated prior to step (2).

[0022] In some ~~embodiment~~examples, the process further comprises recrystallizing Compound **A-VI** from a suitable solvent. In some ~~embodiment~~examples, 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. In some ~~embodiment~~examples, the suitable solvent is ethyl acetate or isopropyl acetate.

[0023] In some ~~embodiment~~examples, the process further comprises treatment of the recrystallized Compound **A-VI** with a metal scavenger. In some ~~embodiment~~examples, the metal scavenger comprises SiO_2, charcoal, aqueous solution of L-cysteine, a Silicycle metal scavenger, Si-thiol, SiliaBond DMT or SiliaBond Cysteine.

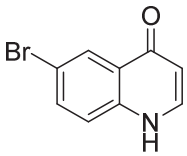
[0024] In another ~~aspect~~example, described herein is a process for the preparation of Compound **A-IV**:



Compound **A-IV**

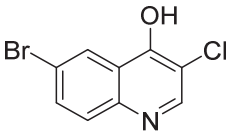
comprising the steps of:

(1) chlorinating Compound **A-I**:



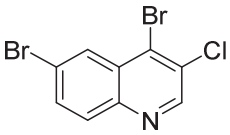
Compound **A-I**

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**:



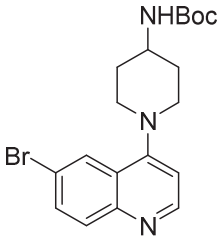
Compound **A-III**;

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**.

[0025] In some ~~embodiment~~examples, 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.

[0026] In some ~~embodiment~~examples, the chlorinating agent of step (1) is *N*-chlorosuccinimide; and the suitable solvent of step (1) is acetic acid.

[0027] In some ~~embodiment~~examples, 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.

[0028] In some ~~embodiment~~examples, the brominating agent of step (2) is phosphorus tribromide; and the suitable solvent of step (2) is *N,N*-dimethylformamide.

[0029] In some ~~embodiment~~examples, 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.

[0030] In some ~~embodiment~~examples, the base of step (3) is diisopropylethylamine; and the suitable solvent of step (3) is dimethylsulfoxide.

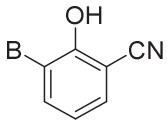
[0031] In some ~~embodiment~~examples, the suitable base of step (i) is triethylamine, diisopropylethylamine, 1,8-diazabicycloundec-7-ene, 1,2,2,6,6-pentamethylpiperidine, tributylamine, sodium bicarbonate, Na_2CO_3, K_2CO_3, or Cs_2CO_3; and the suitable solvent of step (i) is *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethylsulfoxide, dichlormethane, chloroform, carbon tetrachloride, dioxane, tetrahydrofuran, toluene, acetonitrile, ethanol, or isopropanol.

[0032] In some ~~embodiment~~examples, the base of step (i) is K_2CO_3; and the suitable solvent of step (i) is *N,N*-dimethylformamide.

[0033] In some ~~embodiment~~examples, 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.

[0034] In some ~~embodiment~~examples, the chlorinating agent of step (ii) is *N*-chlorosuccinimide; and the suitable solvent of step (ii) is toluene.

[0035] In another ~~aspect~~example, described herein is a process for the preparation of Compound **1**:



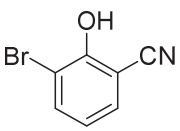
Compound **1**

wherein,

B is a boronic acid or boronate ester;

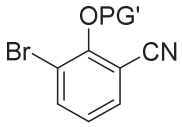
comprising the steps of:

(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**.

[0036] In some ~~embodiment~~examples, B is a boronic acid.

[0037] In some ~~embodiment~~examples, the process further comprises converting B to a trifluoroborate.

[0038] In some ~~embodiment~~examples, 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.

[0039] In some ~~embodiment~~examples, the suitable reaction conditions of (2) comprise the use of metal halogen exchange reagents. In some ~~embodiment~~examples, the suitable reaction conditions of (2) comprise the use of metal halogen exchange reagents selected from Grignard reagents and alkyl lithium reagents. In some ~~embodiment~~examples, the suitable reaction conditions of (2) comprise the use of isopropyl magnesium chloride in tetrahydrofuran.

[0040] In some ~~embodiment~~examples, the borylation agent is triisopropyl borate and the suitable reaction conditions of (2) comprise the use of isopropyl magnesium chloride in tetrahydrofuran.

[0041] In some ~~embodiment~~examples, the suitable reaction conditions of (2) comprise the use of transition metal mediated reaction conditions.

[0042] In some ~~embodiment~~examples, the suitable reaction conditions of (2) comprise the use of palladium metal mediated reaction conditions.

[0043] In some ~~embodiment~~examples, 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.

[0044] In some ~~embodiment~~examples, the suitable protecting group (PG′) is methoxymethyl, 2-methoxyethoxymethyl, benzyl, *para*-methoxybenzyl, methyl, allyl, tetrahydropyran-2-yl, [2-(trimethylsilyl)ethoxy]methyl, trimethylsilyl, triethylsilyl, triisopropyl silyl, *tert*-butyldimethylsilyl, or *tert*-butyldiphenylsilyl.

[0045] In some ~~embodiment~~examples, the suitable protecting group (PG′) is methoxymethyl, ethoxyethyl, methoxypropyl, benzyloxymethyl, 2-methoxyethoxymethyl, benzyl, *para*-methoxybenzyl, 2-naphthylmethyl, methyl, allyl, or tetrahydropyranyl. In some ~~embodiment~~examples, the suitable protecting group (PG′) is methoxymethyl, ethoxyethyl, or 2-methoxyethoxymethyl. In some ~~embodiment~~examples, the suitable protecting group (PG′) is methoxymethyl.

[0046] In some ~~embodiment~~examples, the suitable protecting group (PG′) is acetyl, benzoyl, or 2,2,2-trichloroethyl carbonyl. In some ~~embodiment~~examples, the suitable protecting group (PG′) is acetyl.

[0047] In some ~~embodiment~~examples, 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.

[0048] In some ~~embodiment~~examples, the suitable protecting group (PG′) is methoxymethyl; and removal of the protecting group in step (3) is accomplished by treatment with hydrochloric acid.

[0049] Articles of manufacture, which include packaging material, a somatostatin modulator, or a pharmaceutically acceptable salt or solvate thereof, as described herein, within the packaging material, and a label that indicates that the somatostatin modulator, or pharmaceutically acceptable salt, or solvate thereof, is used for modulating one or more subtype somatostatin receptor proteins, or for the treatment, prevention or amelioration of one or more symptoms of a disease or condition that would benefit from modulating one or more subtype somatostatin receptor proteins, are provided.

[0050] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific ~~embodiment~~examples, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

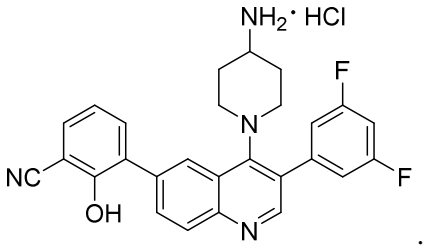
[0051] **Figure 1.** X-ray powder diffraction (XRPD) pattern of Compound A, mono-HCl salt.

[0052] **Figure 2(a).** Differential Scanning Calorimetry (DSC) thermogram.

CLAIMS

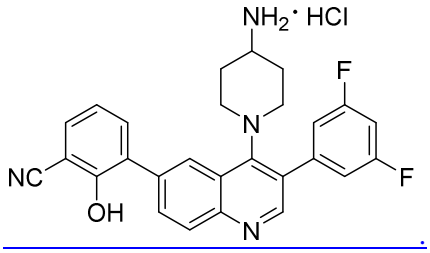
WHAT IS CLAIMED IS:

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



.

2. The compound of claim 1, or solvate thereof, wherein the compound is ~~C~~crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrilemonohydrochloride, or solvate thereof~~.~~, having the following structure:



.

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, measured using Cu Kα1 radiation;
- ~~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~~;~~
- ~~~~, measured with a ~~Differential Scanning Calorimetry (DSC) thermogram substantially the same as shown in **Figure 2(a)**;~~heating rate of 10.0 °C/min;
- ~~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 or claim 3, 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, measured using Cu Kα1 radiation.

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,~~any one of claims2 - 4 having a Differential Scanning Calorimetry (DSC) thermogram with an ~~X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 1**~~endotherm having an onset at 207° C and a peak at 220° C, measured with a heating rate of 10.0 °C/min.

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~~ having an unchanged XRPD when heated up to 200° C.

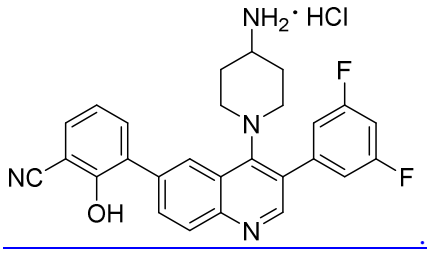
7. The crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, of any one of claims 2-~~5 having a Differential Scanning Calorimetry (DSC) thermogram substantially the same as shown in **Figure 2(a)**.~~6 having an unchanged XRPD upon exposure to more than 90% relative humidity for 24 hours and upon exposure to 75% RH and 40 °C over one week.

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.~~9 The ~~crystalline~~compound of claim 1, wherein the compound is amorphous 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~~having the ~~IR spectrum shown in Figure 3.~~following structure:



~~12.~~10. 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~~the compound of any one of claims 1-9 and at least one pharmaceutically acceptable excipient~~.~~;

~~13. The pharmaceutical composition of claim 12,~~optionally wherein the pharmaceutical composition is formulated for administration to a mammal by oral administration.

~~14.~~11. The pharmaceutical composition of claim ~~12 or claim 13,~~10 wherein the pharmaceutical composition is in the form of a solid form pharmaceutical composition.

~~15.~~12. The pharmaceutical composition of ~~any one of claims 12-14~~claim 10 or claim 11, wherein the pharmaceutical composition is in the form of a tablet, a pill, or a capsule.

13. Use of the compound of any one of claims 1 to 9, or the pharmaceutical composition of any one of claims 10-12, in the manufacture of a medicament for treating acromegaly or a neuroendocrine tumor, or combinations thereof.

~~16.~~14. 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

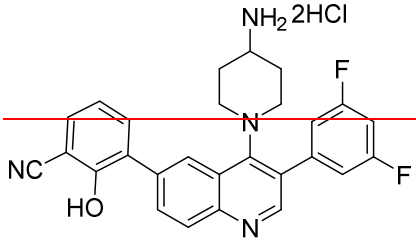
(i) filtering the solids of step (c) to provide 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof~~.~~;

~~17. The method of claim 16,~~optionally wherein~~-~~: ammonium hydroxide solution used in (a)(ii~~)~~.); and

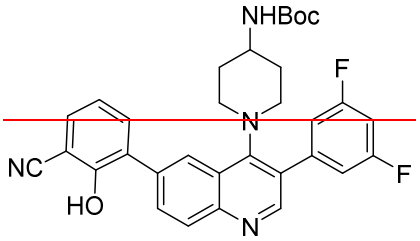
~~18. The method of claim 16 or claim 17, wherein the amount of ammonium hydroxide solution used in (a)(ii) is about 0.8 equivalents and the pH achieved is about 4.5-4.7.~~

~~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:~~



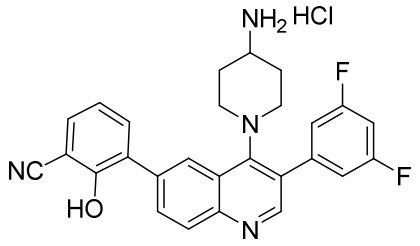
~~comprising the step of treating Compound **A-VI**:~~



~~Compound **A-VI**~~

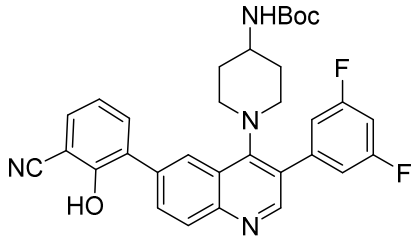
~~with hydrochloric acid in a suitable solvent.~~

~~21.~~15. 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**

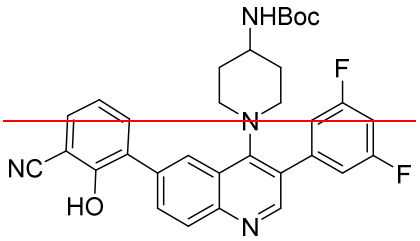
with hydrochloric acid in a suitable solvent to provide 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile dihydrochloride; and

(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,~~optionally wherein the suitable solvent is isopropyl alcohol, ethyl acetate, or isopropyl acetate.

~~23.~~16. The process of ~~any one of claims 20-21~~claim 15, wherein ~~the suitable solvent is isopropyl alcohol.~~

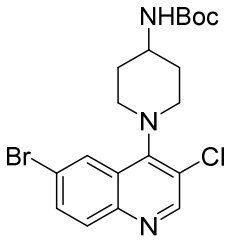
~~24. A process for the preparation of~~ Compound **A-VI**~~:~~



~~Compound A-VI~~

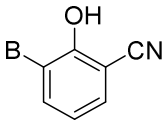
~~comprising the steps of~~ is prepared by:

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



Compound **A-IV**

~~———~~with Compound **1**:

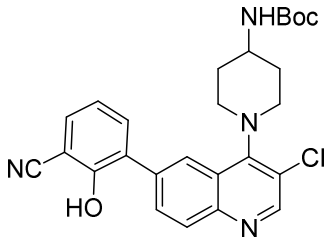


Compound **1**

~~———~~wherein,

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

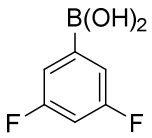
in the presence of a coupling catalyst, a suitable base, and in a suitable solvent, to provide Compound **A-V**:



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,~~optionally 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:~~

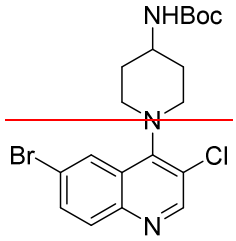
~~the suitable solvent is ethyl acetate or isopropyl acetate.~~

~~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.~~

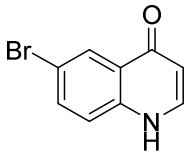
~~39.~~ 17. ~~A process for the preparation of~~ The process of claim 16, wherein Compound **A-IV**~~:~~



~~Compound A-IV~~

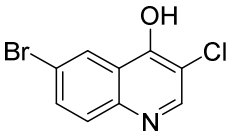
~~comprising the steps of~~ is prepared by:

(1) chlorinating Compound **A-I**



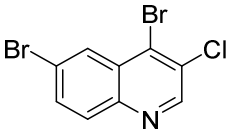
Compound **A-I**;

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**:



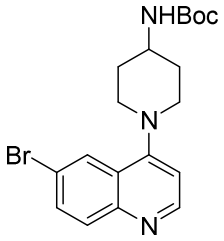
Compound **A-III**;

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,optionally 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; anddibromotriphenylphosphorane;

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.; and/or

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.

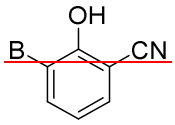
18. The compound of any one of claims 1 to 9, or the pharmaceutical composition of any one of claims 10-12, for use in therapy.

~~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**:~~



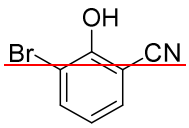
~~Compound **1**~~

~~wherein,~~

~~B is a boronic acid or boronate ester;~~

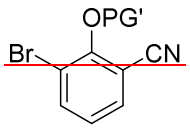
~~comprising the steps of:~~

~~(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:

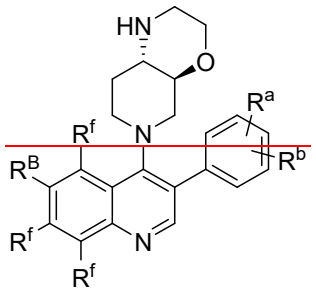
removal of the protecting group in step (3) is accomplished by treatment with hydrochloric acid, hydrobromic acid, acetic acid, trifluoroacetic acid, para-toluenesulfonic acid, $ZnBr_2$, hydrogen over Pd/C, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), boron tribromide, boron trichloride, trimethylsilyl 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^e and R^d;

R^e 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;

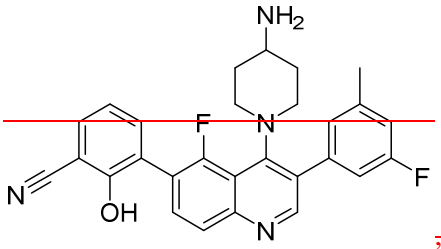
2-{4-[(4aS,8aS)-octahydro-1H-pyrido[3,4-b][1,4]oxazin-6-yl]-3-(3-chloro-5-fluorophenyl)quinolin-6-yl}-3-aminopyridine-4-carbonitrile;

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;

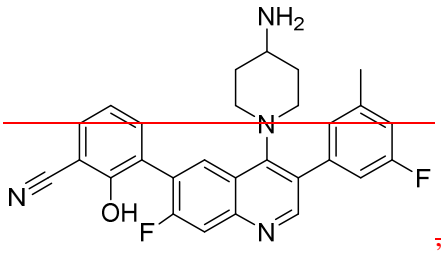
2-{4-[(4aS,8aS)-octahydro-1H-pyrido[3,4-b][1,4]oxazin-6-yl]-3-(3-fluorophenyl)quinolin-6-yl}-4-methylpyridin-3-amine.

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.