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

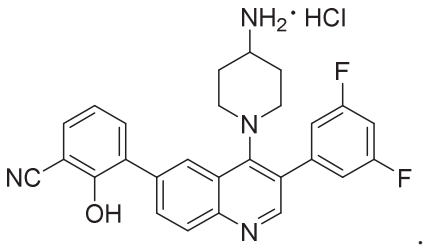
[0002] Described herein are compounds that are somatostatin modulators, methods of making such compounds, pharmaceutical compositions and medicaments comprising such compounds, and methods of using such compounds in the treatment of conditions, diseases, or disorders that would benefit from modulating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



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[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

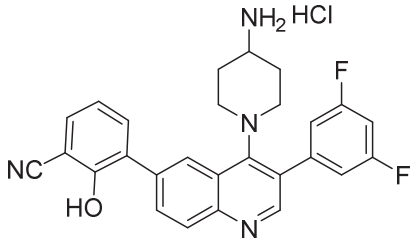
(i) filtering the solids of step (c) to provide 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof;

optionally wherein:

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

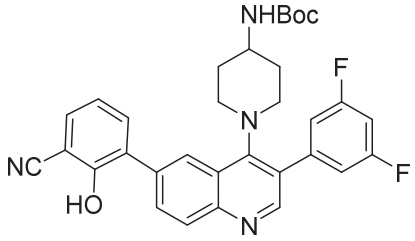
the suitable solvent in (b) is methanol, ethanol, isopropyl alcohol, acetone, methyl acetate, ethyl acetate, tetrahydrofuran, tetrahydropyran, water, or combinations thereof.

[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 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 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 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 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 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 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 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 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 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 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 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 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 examples, the pharmaceutical composition is formulated for administration to a mammal by oral administration. In some examples, the pharmaceutical composition is in the form of a solid form pharmaceutical composition. In some examples, the pharmaceutical composition is in the form of a tablet, a pill, or a capsule.

[0008] In another 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

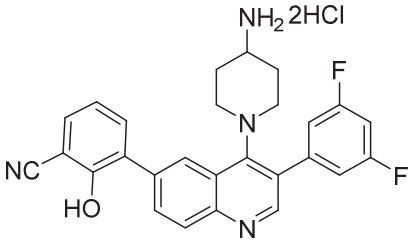
(c) stirring 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile dihydrochloride in about 20 volumes to about 50 volumes of water; and

(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.

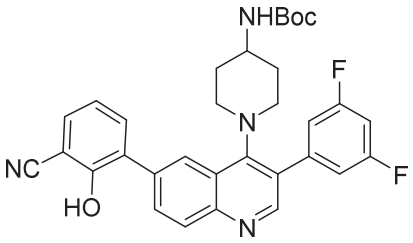
[0009] In some examples, ammonium hydroxide solution is used in (a)(ii). In some examples, the amount of ammonium hydroxide solution used in (a)(ii) is about 0.8 equivalents and the pH achieved is about 4.5-4.7.

[0010] In some 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 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:



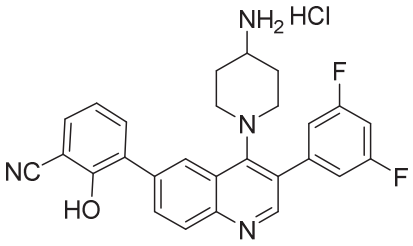
comprising the step of treating Compound **A-VI**:



Compound **A-VI**

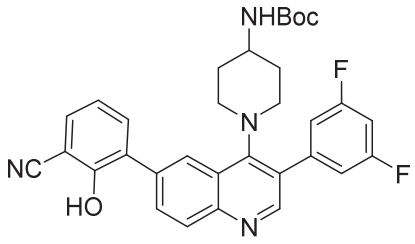
with hydrochloric acid in a suitable solvent.

[0012] In another 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**:



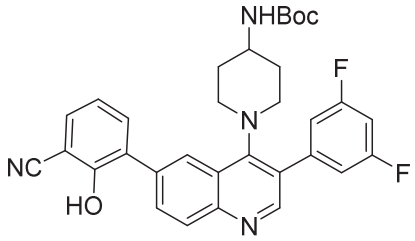
Compound **A-VI**

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 examples, the suitable solvent is isopropyl alcohol, ethyl acetate, or isopropyl acetate. In some examples, the suitable solvent is isopropyl alcohol.

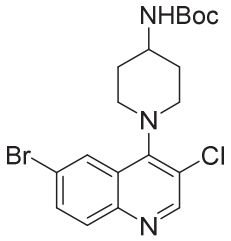
[0014] In another example, described herein is a process for the preparation of Compound **A-VI**:



Compound **A-VI**

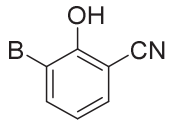
comprising the steps of:

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



Compound **A-IV**

with Compound **1**:

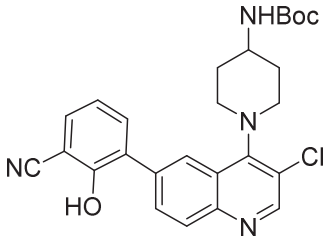


Compound **1**

wherein,

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

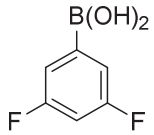
in the presence of a coupling catalyst, a suitable base, and in a suitable solvent, to provide Compound **A-V**:



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 examples, B is a boronic acid or trifluoroborate.

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

[0017] In some 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 examples, Step (1) is performed at a temperature of about 80 ^oC. In some examples, Step (1) is performed at a temperature of about 80-85 ^oC.

[0018] In some 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 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 examples, Step (2) is performed at a temperature of about 90 °C to about 100 °C. In some 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.

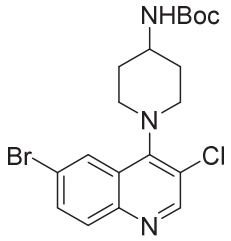
[0020] In some examples, Compound **A-V** is isolated prior to step (2).

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

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

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

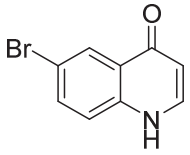
[0024] In another example, described herein is a process for the preparation of Compound **A-IV**:



Compound **A-IV**

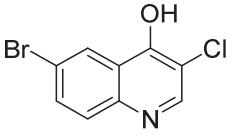
comprising the steps of:

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



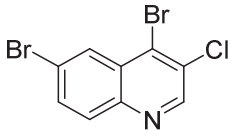
Compound **A-I**

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**:



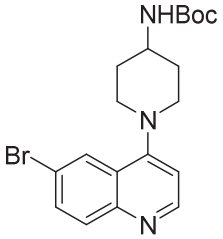
Compound **A-III**;

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 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 examples, the chlorinating agent of step (1) is *N*-chlorosuccinimide; and the suitable solvent of step (1) is acetic acid.

[0027] In some 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 examples, the brominating agent of step (2) is phosphorus tribromide; and the suitable solvent of step (2) is *N,N*-dimethylformamide.

[0029] In some 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 examples, the base of step (3) is diisopropylethylamine; and the suitable solvent of step (3) is dimethylsulfoxide.

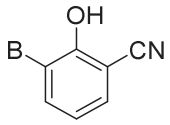
[0031] In some examples, the suitable base of step (i) is triethylamine, diisopropylethylamine, 1,8-diazabicycloundec-7-ene, 1,2,2,6,6-pentamethylpiperidine, tributylamine, sodium bicarbonate, Na_2CO_3, K_2CO_3, or Cs_2CO_3; and the suitable solvent of step (i) is *N,N*-dimethylformamide, *N,N*-dimethylacetamide,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

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

[0033] In some 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 examples, the chlorinating agent of step (ii) is *N*-chlorosuccinimide; and the suitable solvent of step (ii) is toluene.

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



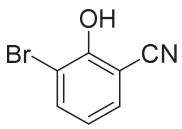
Compound **1**

wherein,

B is a boronic acid or boronate ester;

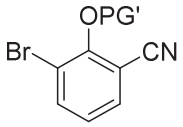
comprising the steps of:

(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 examples, B is a boronic acid.

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

[0038] In some 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 examples, the suitable reaction conditions of (2) comprise the use of metal halogen exchange reagents. In some 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 examples, the suitable reaction conditions of (2) comprise the use of isopropyl magnesium chloride in tetrahydrofuran.

[0040] In some 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 examples, the suitable reaction conditions of (2) comprise the use of transition metal mediated reaction conditions.

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

[0043] In some 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 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 examples, the suitable protecting group (PG′) is methoxymethyl, ethoxyethyl, methoxypropyl, benzyloxymethyl, 2-methoxyethoxymethyl, benzyl, *para*-methoxybenzyl, 2-naphthylmethyl, methyl, allyl, or tetrahydropyranyl. In some examples, the suitable protecting group (PG′) is methoxymethyl, ethoxyethyl, or 2-methoxyethoxymethyl. In some examples, the suitable protecting group (PG′) is methoxymethyl.

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

[0047] In some 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 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 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

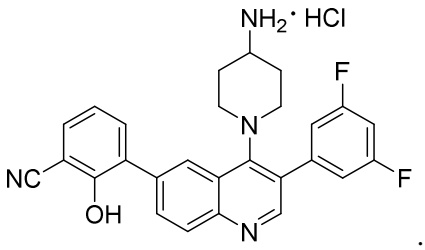
[0051] **Figure 1.** X-ray powder diffraction (XRPD) pattern of Compound A, mono-HCl salt.

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

CLAIMS

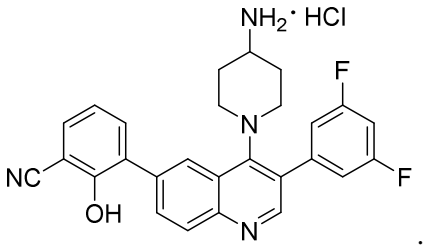
WHAT IS CLAIMED IS:

1. The compound 3-[4-(4-amino-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 crystalline 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:



.

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;
   - a Differential Scanning Calorimetry (DSC) thermogram with an endotherm having an onset at 207 °C and a peak at 220 °C, measured with a heating rate of 10.0 °C/min;
   - 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 unchanged XRPD when heated up to 200° C, upon exposure to more than 90% relative humidity for 24 hours, or upon exposure to 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.

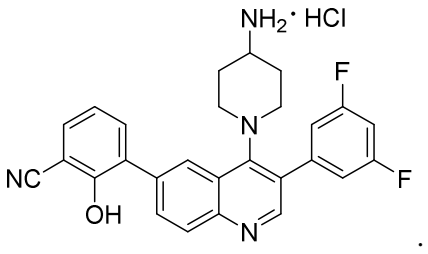
5. The crystalline 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, of any one of claims2 - 4 having a Differential Scanning Calorimetry (DSC) thermogram with an endotherm having an onset at 207° C and a peak at 220° C, 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 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 2-6 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 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}.

9 The 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, having the following structure:



.

10. A pharmaceutical composition comprising the compound of any one of claims 1-9 and at least one pharmaceutically acceptable excipient;

optionally wherein the pharmaceutical composition is formulated for administration to a mammal by oral administration.

11. The pharmaceutical composition of claim 10 wherein the pharmaceutical composition is in the form of a solid form pharmaceutical composition.

12. The pharmaceutical composition of 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.

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 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

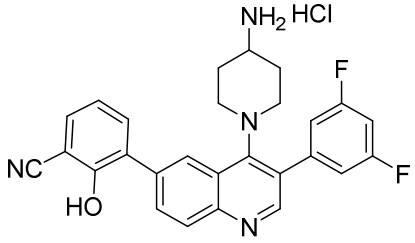
(i) filtering the solids of step (c) to provide 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof;

optionally wherein:

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

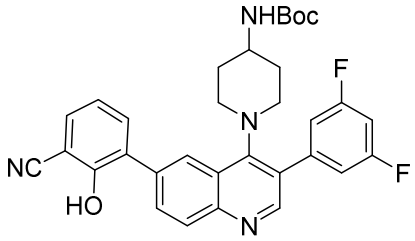
the suitable solvent in (b) is methanol, ethanol, isopropyl alcohol, acetone, methyl acetate, ethyl acetate, tetrahydrofuran, tetrahydropyran, water, or combinations thereof.

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**

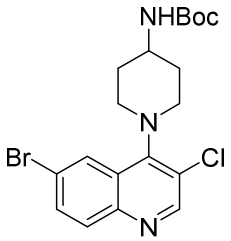
with hydrochloric acid in a suitable solvent to provide 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile dihydrochloride; and

(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;

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

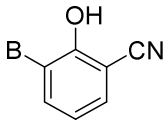
16. The process of claim 15, wherein Compound **A-VI** is prepared by:

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



Compound **A-IV**

with Compound **1**:

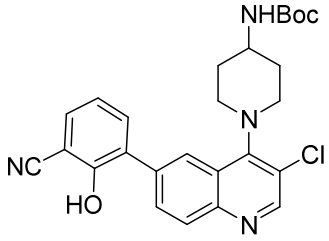


Compound **1**

wherein,

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

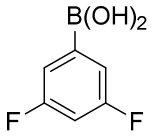
in the presence of a coupling catalyst, a suitable base, and in a suitable solvent, to provide Compound **A-V**:



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**;

optionally wherein:

B is a boronic acid or trifluoroborate;

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;

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

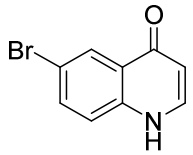
the coupling catalyst of step (2) is a palladium catalyst;

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.

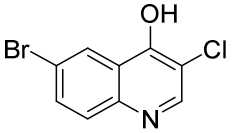
17. The process of claim 16, wherein Compound **A-IV** is prepared by:

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



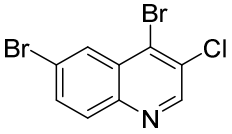
Compound **A-I**;

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**:



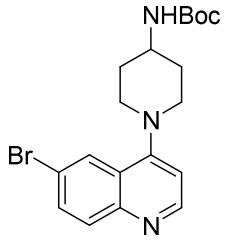
Compound **A-III**;

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**;

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,

the brominating agent of step (2) is phosphorus tribromide, phosphorus oxybromide, hydrobromic acid, bromine, or dibromotriphenylphosphorane;

the suitable solvent of step (2) is acetonitrile, water, ethanol, isopropanol, dichloromethane, toluene, *N,N*-dimethylformamide, acetic acid, or acetone,

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

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.