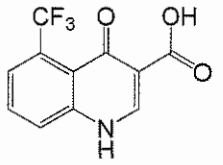
[0016] In addition, there is a need for stable solid forms of said compound that can be used readily in pharmaceutical compositions suitable for use as therapeutics.

SUMMARY ~~OF THE INVENTION~~

[0017] The present ~~invention~~disclosure relates to processes for the synthesis of compounds useful as modulators of CFTR.

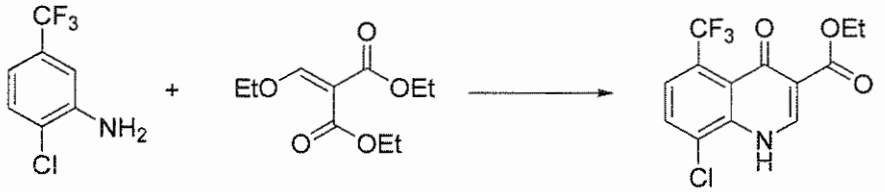
[0017a] In a first aspect, there is provided a process for preparing Compound 2



2

comprising:

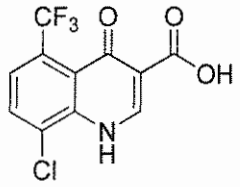
(a) reacting Compound 4 with diethyl 2-(ethoxymethylene)malonate 5 to generate ester 6A



4 **5** **6A**

;

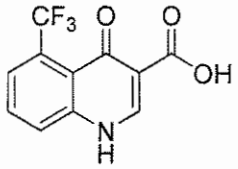
(b) treating ester 6A with a base selected from aqueous sodium hydroxide and aqueous potassium hydroxide to generate Compound 6D



6D

; and

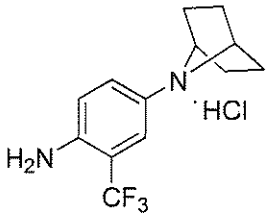
(c) treating Compound 6D with hydrogen gas or formate in the presence of a palladium catalyst to produce compound 2



2

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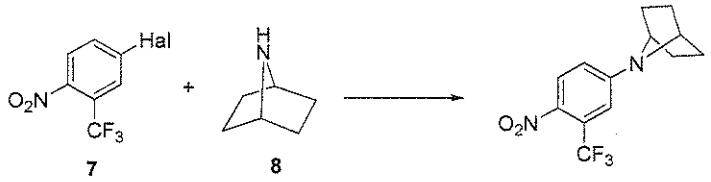
[0017b] In a second aspect, there is provided a process for preparing Compound 3-HCl



3-HCl

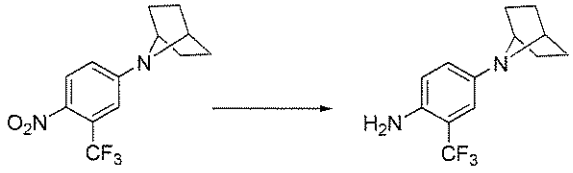
comprising:

(a) reacting compound 7 with compound 8, or a salt thereof, in the presence of a base and a polar aprotic solvent, wherein Hal is F, Cl, Br or I, to generate compound 9



7 **8** **9**

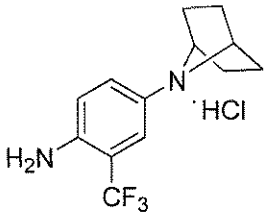
(b) reducing the nitro moiety in compound 9 with hydrogen gas in the presence of a catalyst and a solvent to provide aniline 3; wherein the catalyst comprises Pd, Ni, or Pt; and wherein the solvent comprises isopropanol, ethanol, or methanol



9 **3**

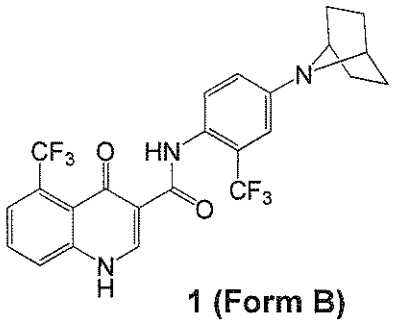
;and

(c) contacting Compound 3 with HCl to provide the hydrochloride salt 3-HCl



3-HCl

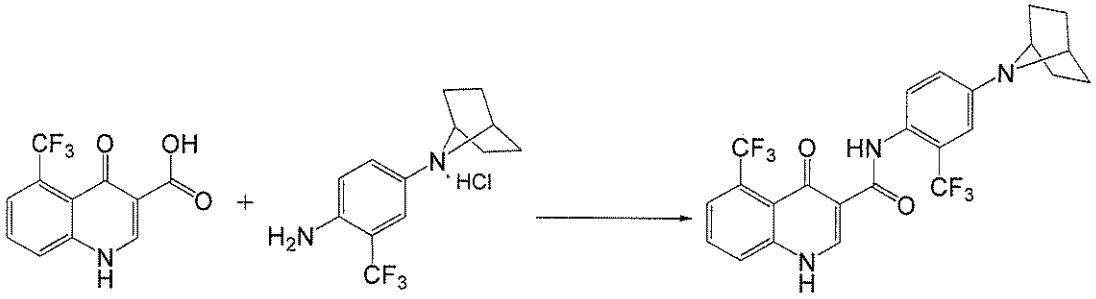
[0017c] In a third aspect, there is provided a process for producing Compound 1 having solid Form B



1 (Form B)

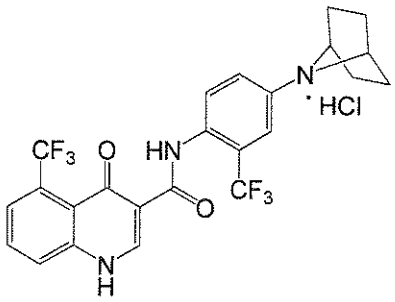
comprising:

reacting Compound 2 with the hydrochloride salt of Compound 3 (3-HCl) in the presence of a coupling agent, a base, and a solvent; wherein the coupling agent is selected from the group consisting of 2-chloro-1,3-dimethyl-2-imidazolium tetrafluoroborate, HBTU, HCTU, 2-chloro-4,6-dimethoxy-1,3,5-triazine, HATU, HOBT/EDC, and propane phosphonic anhydride; wherein the base is selected from the group consisting of K_2CO_3, Et_3N, N-methylmorpholine (NMM), pyridine, and DIEA; and wherein the solvent is selected from the group consisting of EtOAc, IPAc, THF, MEK, NMP, acetonitrile, DMF, and 2-methyltetrahydrofuran



2 **3-HCl** **1 (Form B)**

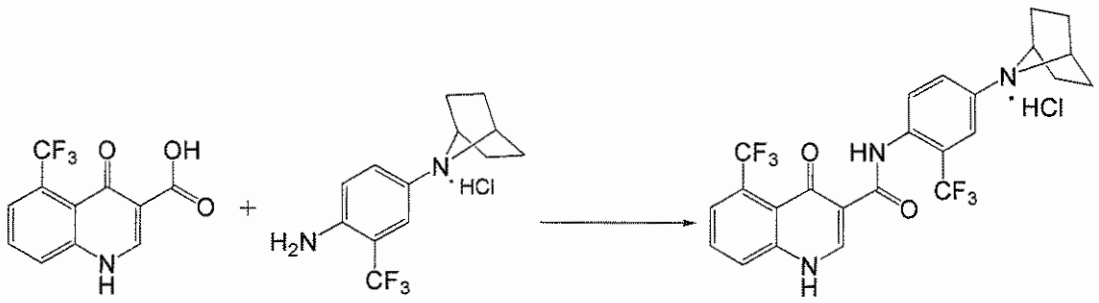
[0017d] In a fourth aspect, there is provided a process for producing the hydrochloride salt of Compound 1 having solid Form A-HCl



1 (Form A-HCl)

comprising:

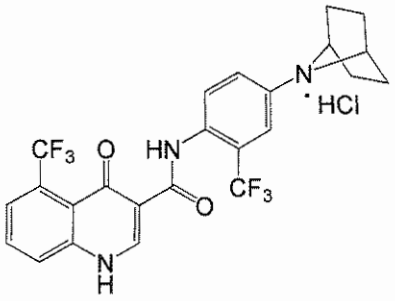
(a) reacting Compound 2 with the hydrochloride salt of Formula 3 (3-HCl) in the presence of a coupling agent, a base, and a polar aprotic solvent; wherein the coupling agent is selected from the group consisting of 2-chloro-1,3-dimethyl-2-imidazolium tetrafluoroborate, HBTU, HCTU, 2-chloro-4,6-dimethoxy-1,3,5-triazine, HATU, HOBT/EDC, and propane phosphonic anhydride; wherein the base is selected from the group consisting of K_2CO_3, Et_3N, N-methylmorpholine (NMM), pyridine, and DIEA; and wherein the polar aprotic solvent is selected from the group consisting of ethyl acetate, isopropyl acetate, tetrahydrofuran, methylethyl ketone, N-Methyl-2-pyrrolidone, acetonitrile, N,N-dimethyl formamide, and 2-methyltetrahydrofuran



2 **3-HCl** **1 (Form A-HCl)** ; and

(b) treating a mixture comprising the product of step (a) with HCl.

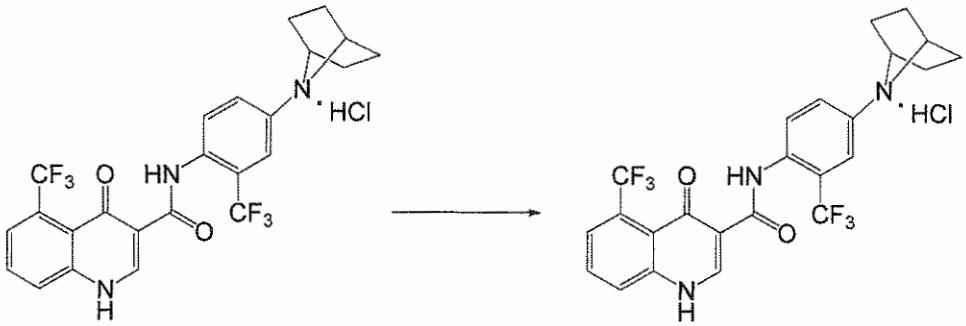
[0017e] In a fifth aspect, there is provided a process for producing a hydrochloride salt of Compound 1 having the solid Form B-HCl



1 (Form B-HCl) ,

comprising:

(a) mixing a hydrochloride salt of Compound 1 Form A-HCl with an organic solvent and water, wherein the organic solvent comprises dimethyl sulfoxide, dimethylformamide, dioxane, hexamethylphosphorotriamide, tetrahydrofuran, EtOAc, IPAc, THF, MEK, NMP, acetonitrile, DMF, EtOH, MeOH, isopropyl alcohol, or 2-methyltetrahydrofuran, to generate a mixture

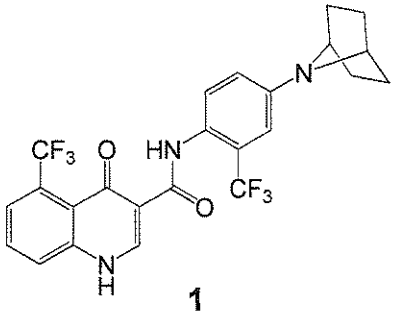


I (FORM A-HCl) **I (FORM B-HCl)** ;

and

(b) heating the mixture.

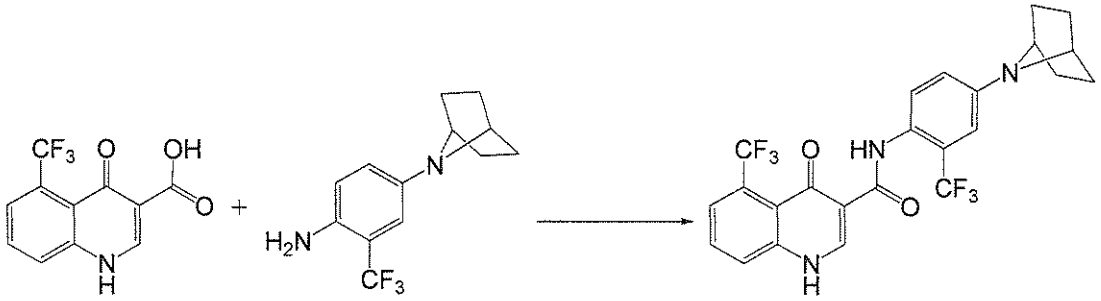
[0018] ~~In one aspect, t~~The present disclosure discloses a~~invention provides A~~ process for making a crystalline form of Compound 1:



1

comprising:

(a) reacting Compound 2 with Compound 3 in the presence of a coupling agent:



2 3 1

wherein the coupling agent is selected from the group consisting of 2-chloro-1,3-dimethyl-2-imidazolium tetrafluoroborate, HBTU, HCTU, 2-chloro-4,6-dimethoxy-1,3,5-triazine, HATU, HOBT/EDC, and T3P®.

[0019] Compounds of Formula I and pharmaceutically acceptable compositions thereof are useful for treating or lessening the severity of a variety of diseases, disorders, or conditions, including, but not limited to, cystic fibrosis, asthma, smoke induced COPD, chronic bronchitis, rhinosinusitis, constipation, pancreatitis, pancreatic insufficiency, male infertility caused by congenital bilateral absence of the vas deferens (CBAVD), mild pulmonary disease, idiopathic pancreatitis, allergic bronchopulmonary aspergillosis (ABPA), liver disease, hereditary emphysema, hereditary hemochromatosis, coagulation-fibrinolysis

deficiencies, such as protein C deficiency, Type 1 hereditary angioedema, lipid processing deficiencies, such as familial hypercholesterolemia, Type 1 chylomicronemia, abetalipoproteinemia, lysosomal storage diseases, such as I-cell disease/pseudo-Hurler, mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, polyendocrinopathy/hyperinsulemia, Diabetes mellitus, Laron dwarfism, myleoperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type 1, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), neurophyseal DI, neprogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear plasy, Pick's disease, several polyglutamine neurological disorders such as Huntington's, spinocerebullar ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidoluysian, and myotonic dystrophy, as well as spongiform encephalopathies, such as hereditary Creutzfeldt-Jakob disease (due to prion protein processing defect), Fabry disease, Straussler-Scheinker syndrome, COPD, dry-eye disease, or Sjogren's disease, Osteoporosis, Osteopenia, bone healing and bone growth (including bone repair, bone regeneration, reducing bone resorption and increasing bone deposition), Gorham's Syndrome, chloride channelopathies such as myotonia congenita (Thomson and Becker forms), Bartter's syndrome type III, Dent's disease, hyperekplexia, epilepsy, hyperekplexia, lysosomal storage disease, Angelman syndrome, and Primary Ciliary Dyskinesia (PCD), a term for inherited disorders of the structure and/or function of cilia, including PCD with situs inversus (also known as Kartagener syndrome), PCD without situs inversus and ciliary aplasia.

[0020] In one ~~aspect~~embodiment, Compound 1 is in a crystalline form referred to as Form A.

[0021] In another ~~aspect~~embodiment, Compound 1 is in a crystalline form referred to as Form B.

[0022] In a further ~~aspect~~embodiment, Compound 1 is in a crystalline form referred to as Form A-HCl.

[0023] In an additional ~~aspect~~embodiment, Compound 1 is in a crystalline form referred to as Form B-HCl.

[0024] Processes described herein can be used to prepare the compositions of this ~~invention~~disclosure comprising Form A, Form A-HCl, Form B, Form B-HCl, or any combination of these forms.

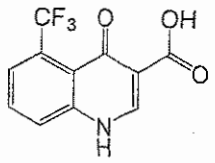
BRIEF DESCRIPTION OF THE DRAWINGS

[0025] **Figure 1** is an X-ray powder diffraction pattern of a representative sample of Compound 1 Form A.

[0026] **Figure 2** is an FTIR spectrum of a representative sample of Compound 1 Form A.

WHAT IS CLAIMED IS:

1. A process for preparing Compound 2

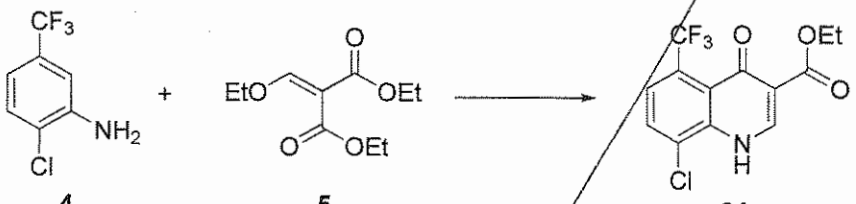


2

,

comprising:

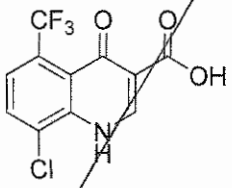
(a) reacting Compound 4 with diethyl 2-(ethoxymethylene)malonate 5 to generate ester 6A



4 5 6A

;

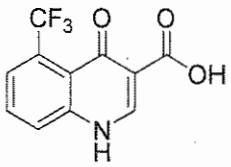
(b) treating ester 6A with a base selected from aqueous sodium hydroxide and aqueous potassium hydroxide to generate Compound 6D



6D

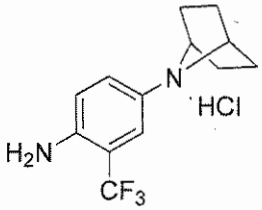
; and

(c) treating Compound 6D with hydrogen gas or formate in the presence of a palladium catalyst to produce compound 2



2

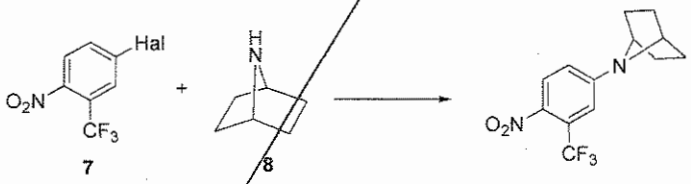
2. A process for preparing Compound 3-HCl



3-HCl

comprising:

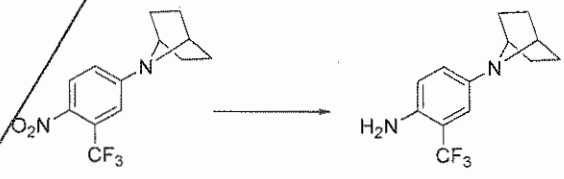
(a) reacting compound 7 with compound 8, or a salt thereof, in the presence of a base and a polar aprotic solvent, wherein Hal is F, Cl, Br or I, to generate compound 9



7 **8** **9**

;

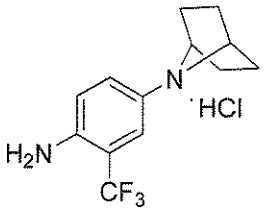
(b) reducing the nitro moiety in compound 9 with hydrogen gas in the presence of a catalyst and a solvent to provide aniline 3; wherein the catalyst comprises Pd, Ni, or Pt; and wherein the solvent comprises isopropanol, ethanol, or methanol



9 **3**

;and

(c) contacting Compound 3 with HCl to provide the hydrochloride salt 3-HCl



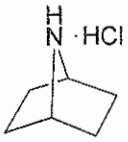
3-HCl

3. The process of claim 2, wherein the base in step (a) is triethyl amine or diisopropylethyl amine, and the solvent in step (a) is acetonitrile.

4. The process of claims 2 or 3, wherein the catalyst comprises Pd.

5. The process of any of claims 2-4, wherein the solvent in step (b) comprises ethanol.

6. The process of any of claims 2-5, wherein compound 8 is in the salt form, Compound 8-HCl

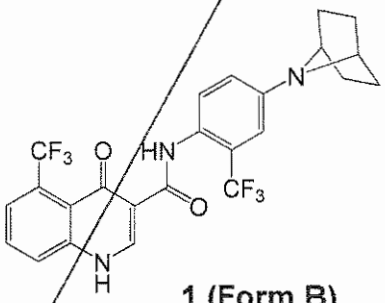


8-HCl

7. The process of any of claims 2-6, wherein the base in step (a) is sodium carbonate and the polar aprotic solvent in step (a) is DMSO.

8. The process of any of claims 2-7, wherein the catalyst in step (b) comprises Pd and the solvent in step (b) comprises ethanol.

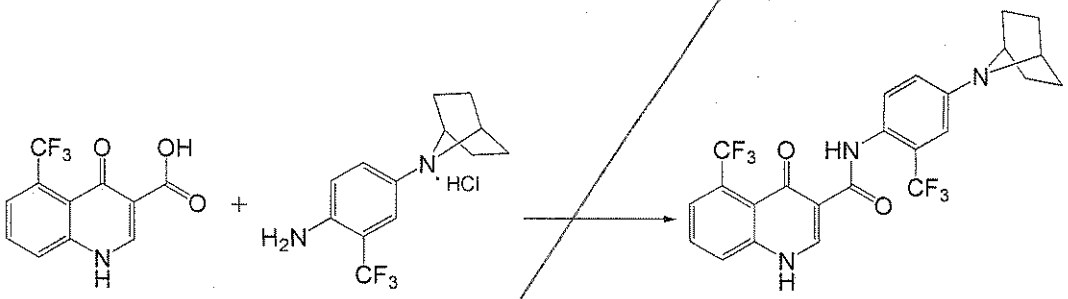
9. A process for producing Compound 1 having solid Form B



1 (Form B)

comprising:

reacting Compound 2 with the hydrochloride salt of Compound 3 **(3-HCl)** in the presence of a coupling agent, a base, and a solvent; wherein the coupling agent is selected from the group consisting of 2-chloro-1,3-dimethyl-2-imidazolium tetrafluoroborate, HBTU, HCTU, 2-chloro-4,6-dimethoxy-1,3,5-triazine, HATU, HOBT/EDC, and propane phosphonic anhydride; wherein the base is selected from the group consisting of K_2CO_3, Et_3N, N-methylmorpholine (NMM), pyridine, and DIEA; and wherein the solvent is selected from the group consisting of EtOAc, IPAc, THF, MEK, NMP, acetonitrile, DMF, and 2-methyltetrahydrofuran



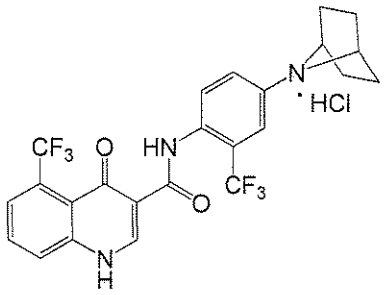
2 **3-HCl** **1 (Form B)**

10. The process of claim 9, wherein the base is pyridine.

11. The process of any of claims 9-10, wherein the solvent is 2-methyltetrahydrofuran.

12. The process of any of claims 9-11, wherein the coupling of Compound 2 and the hydrochloride salt **3-HCl** is performed at a reaction temperature that is maintained between 15 °C and 70 °C.

13. A process for producing the hydrochloride salt of Compound 1 having solid Form A-HCl

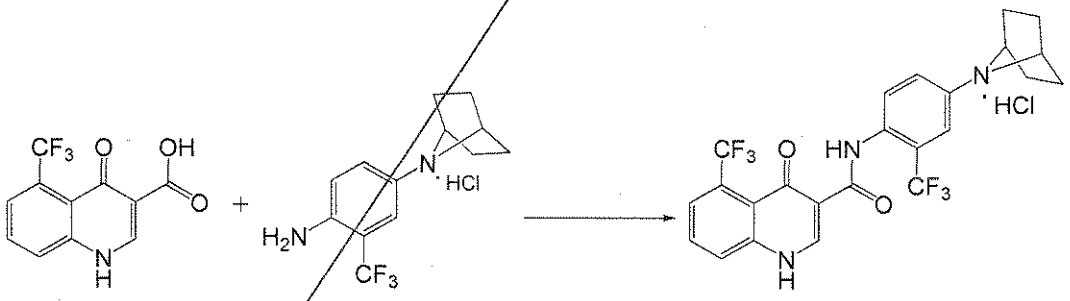


1 (Form A-HCl)

,

comprising:

(a) reacting Compound 2 with the hydrochloride salt of Formula **3 (3-HCl)** in the presence of a coupling agent, a base, and a polar aprotic solvent; wherein the coupling agent is selected from the group consisting of 2-chloro-1,3-dimethyl-2-imidazolium tetrafluoroborate, HBTU, HCTU, 2-chloro-4,6-dimethoxy-1,3,5-triazine, HATU, HOBT/EDC, and propane phosphonic anhydride; wherein the base is selected from the group consisting of K_2CO_3, Et_3N, N-methylmorpholine (NMM), pyridine, and DIEA; and wherein the polar aprotic solvent is selected from the group consisting of ethyl acetate, isopropyl acetate, tetrahydrofuran, methylethyl ketone, N-Methyl-2-pyrrolidone, acetonitrile, N,N-dimethyl formamide, and 2-methyltetrahydrofuran



2 **3-HCl** **1 (Form A-HCl)**

; and

(b) treating a mixture comprising the product of step (a) with HCl.

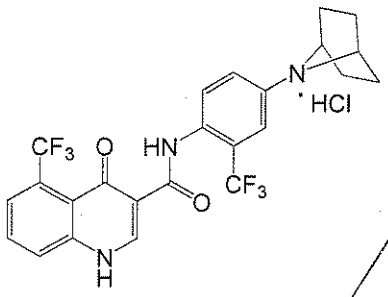
14. The process of claim 13, wherein the base is pyridine.

15. The process of any of claims 13-14, wherein the solvent is 2-methyltetrahydrofuran.

16. The process of any of claims 13-15, wherein step (a) is performed at a reaction temperature that is maintained between 15 °C and 70 °C.

17. The process of any of claims 13-16, wherein, in step (b), HCl gas is bubbled into a mixture comprising the product of step (a) and 2-Methyltetrahydrofuran.

18. A process for producing a hydrochloride salt of Compound 1 having the solid Form B-HCl

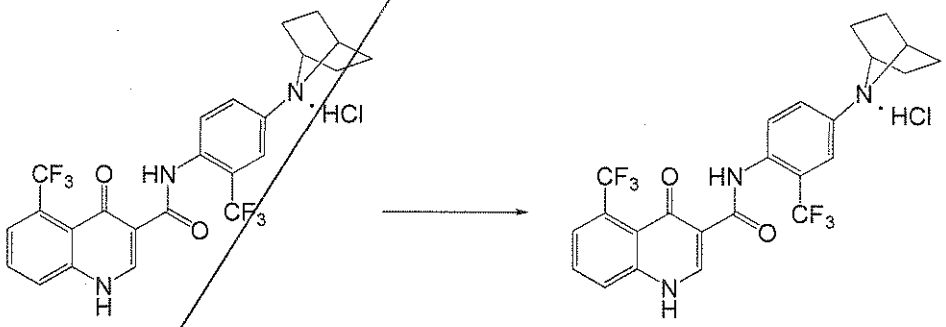


1 (Form B-HCl)

,

comprising:

(a) mixing a hydrochloride salt of Compound 1 Form A-HCl with an organic solvent and water, wherein the organic solvent comprises dimethyl sulfoxide, dimethylformamide, dioxane, hexamethylphosphorotriamide, tetrahydrofuran, EtOAc, IPAc, THF, MEK, NMP, acetonitrile, DMF, EtOH, MeOH, isopropyl alcohol, or 2-methyltetrahydrofuran, to generate a mixture



I (FORM A-HCl) **I (FORM B-HCl)**

;

and

(b) heating the mixture.

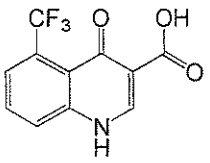
19. The process of claim 18, wherein the aprotic solvent comprises 2-methyltetrahydrofuran.

20. The process of claims 18 or 19, wherein the mixture is maintained at a temperature of about 30 °C to about 80 °C for a period of from about 12 hours to about 72 hours.

21. The process of any of claims 18-20, wherein the mixture is filtered to generate a filter cake, and the cake is further washed with an aprotic solvent.

WHAT IS CLAIMED IS:

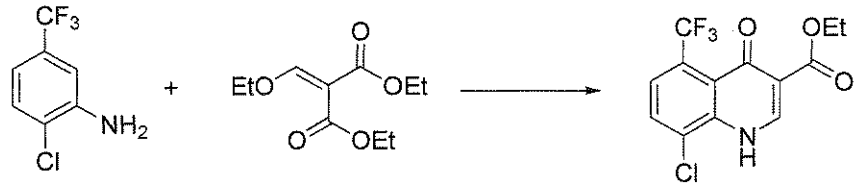
1. A process for preparing Compound 2



2 ,

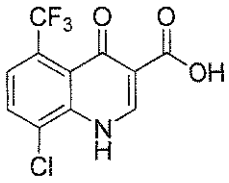
comprising:

(a) reacting Compound 4 with diethyl 2-(ethoxymethylene)malonate 5 to generate ester 6A



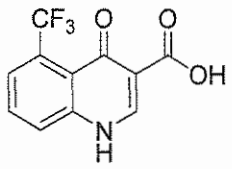
4 **5** **6A** ;

(b) treating ester 6A with a base selected from aqueous sodium hydroxide and aqueous potassium hydroxide to generate Compound 6D



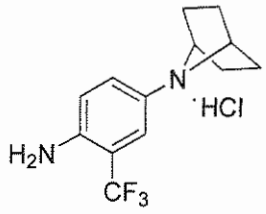
6D ; and

(c) treating Compound 6D with hydrogen gas or formate in the presence of a palladium catalyst to produce compound 2



2

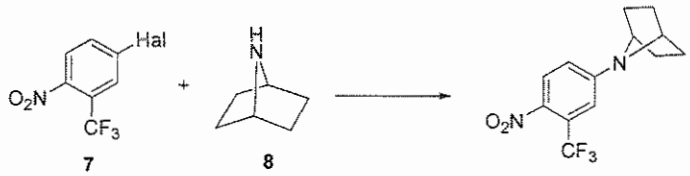
2. A process for preparing Compound 3-HCl



3-HCl ,

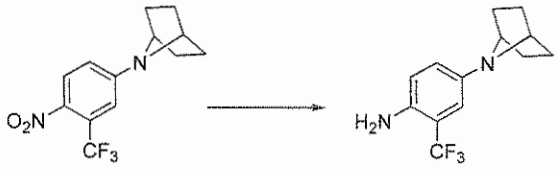
comprising:

(a) reacting compound 7 with compound 8, or a salt thereof, in the presence of a base and a polar aprotic solvent, wherein Hal is F, Cl, Br or I, to generate compound 9



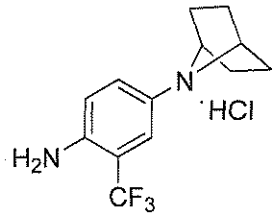
7 8 9 ;

(b) reducing the nitro moiety in compound 9 with hydrogen gas in the presence of a catalyst and a solvent to provide aniline 3; wherein the catalyst comprises Pd, Ni, or Pt; and wherein the solvent comprises isopropanol, ethanol, or methanol



9 3 ;and

(c) contacting Compound 3 with HCl to provide the hydrochloride salt 3-HCl



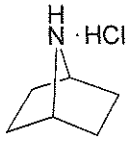
3-HCl

3. The process of claim 2, wherein the base in step (a) is triethyl amine or diisopropylethyl amine, and the solvent in step (a) is acetonitrile.

4. The process of claims 2 or 3, wherein the catalyst comprises Pd.

5. The process of any of claims 2-4, wherein the solvent in step (b) comprises ethanol.

6. The process of any of claims 2-5, wherein compound 8 is in the salt form, Compound 8-HCl

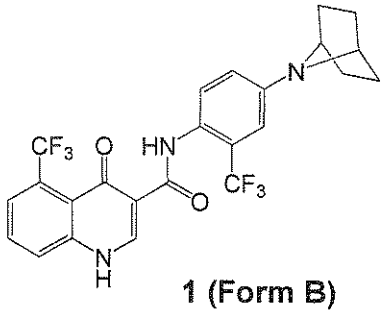


8-HCl .

7. The process of any of claims 2-6, wherein the base in step (a) is sodium carbonate and the polar aprotic solvent in step (a) is DMSO.

8. The process of any of claims 2-7, wherein the catalyst in step (b) comprises Pd and the solvent in step (b) comprises ethanol.

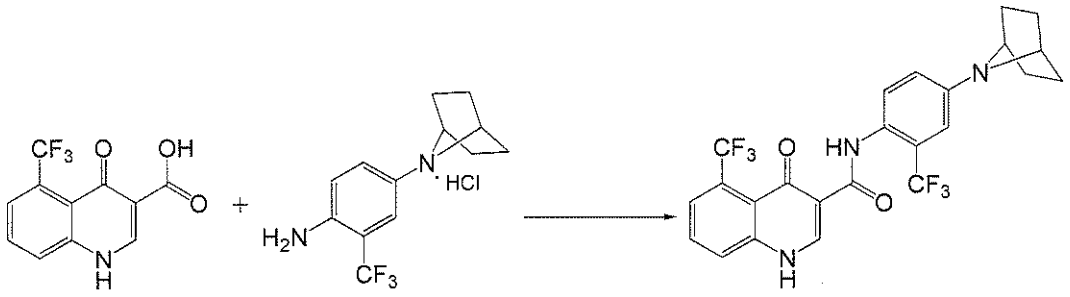
9. A process for producing Compound 1 having solid Form B



1 (Form B) ,

comprising:

reacting Compound 2 with the hydrochloride salt of Compound 3 (**3-HCl**) in the presence of a coupling agent, a base, and a solvent; wherein the coupling agent is selected from the group consisting of 2-chloro-1,3-dimethyl-2-imidazolium tetrafluoroborate, HBTU, HCTU, 2-chloro-4,6-dimethoxy-1,3,5-triazine, HATU, HOBT/EDC, and propane phosphonic anhydride; wherein the base is selected from the group consisting of K_2CO_3, Et_3N, N-methylmorpholine (NMM), pyridine, and DIEA; and wherein the solvent is selected from the group consisting of EtOAc, IPAc, THF, MEK, NMP, acetonitrile, DMF, and 2-methyltetrahydrofuran



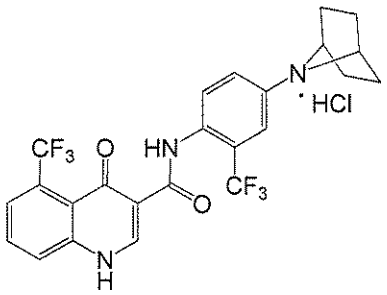
2 **3-HCl** **1 (Form B)**

10. The process of claim 9, wherein the base is pyridine.

11. The process of any of claims 9-10, wherein the solvent is 2-methyltetrahydrofuran.

12. The process of any of claims 9-11, wherein the coupling of Compound 2 and the hydrochloride salt **3-HCl** is performed at a reaction temperature that is maintained between 15 °C and 70 °C.

13. A process for producing the hydrochloride salt of Compound 1 having solid Form A-HCl

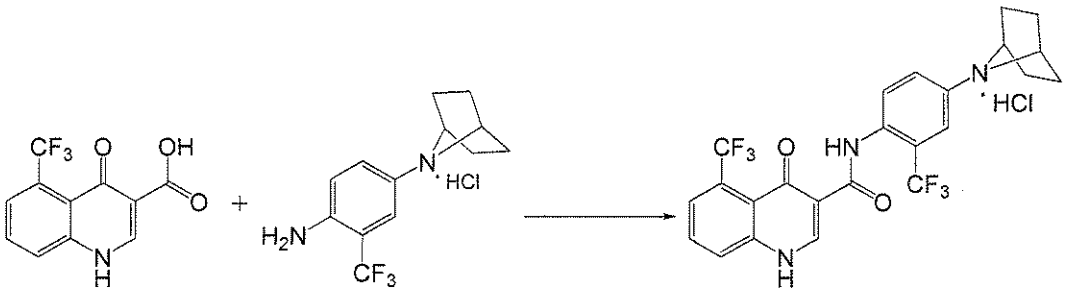


1 (Form A-HCl)

,

comprising:

(a) reacting Compound 2 with the hydrochloride salt of Formula **3 (3-HCl)** in the presence of a coupling agent, a base, and a polar aprotic solvent; wherein the coupling agent is selected from the group consisting of 2-chloro-1,3-dimethyl-2-imidazolium tetrafluoroborate, HBTU, HCTU, 2-chloro-4,6-dimethoxy-1,3,5-triazine, HATU, HOBT/EDC, and propane phosphonic anhydride; wherein the base is selected from the group consisting of K_2CO_3, Et_3N, N-methylmorpholine (NMM), pyridine, and DIEA; and wherein the polar aprotic solvent is selected from the group consisting of ethyl acetate, isopropyl acetate, tetrahydrofuran, methylethyl ketone, N-Methyl-2-pyrrolidone, acetonitrile, N,N-dimethyl formamide, and 2-methyltetrahydrofuran



2 **3-HCl** **1 (Form A-HCl)**

; and

(b) treating a mixture comprising the product of step (a) with HCl.

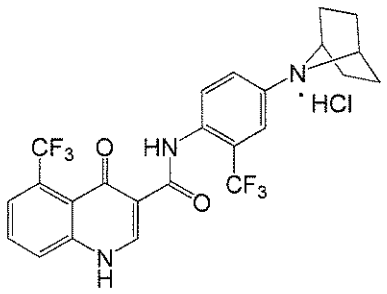
14. The process of claim 13, wherein the base is pyridine.

15. The process of any of claims 13-14, wherein the solvent is 2-methyltetrahydrofuran.

16. The process of any of claims 13-15, wherein step (a) is performed at a reaction temperature that is maintained between 15 °C and 70 °C.

17. The process of any of claims 13-16, wherein, in step (b), HCl gas is bubbled into a mixture comprising the product of step (a) and 2-Methyltetrahydrofuran.

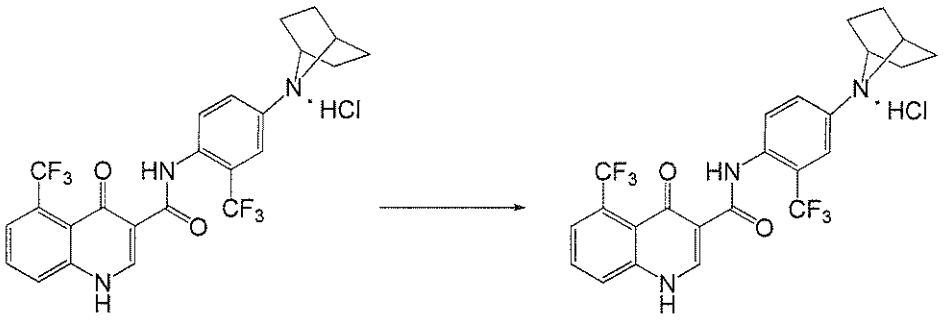
18. A process for producing a hydrochloride salt of Compound 1 having the solid Form B-HCl



1 (Form B-HCl)

comprising:

(a) mixing a hydrochloride salt of Compound 1 Form A-HCl with an organic solvent and water, wherein the organic solvent comprises dimethyl sulfoxide, dimethylformamide, dioxane, hexamethylphosphorotriamide, tetrahydrofuran, EtOAc, IPAc, THF, MEK, NMP, acetonitrile, DMF, EtOH, MeOH, isopropyl alcohol, or 2-methyltetrahydrofuran, to generate a mixture



I (FORM A-HCl) **I (FORM B-HCl)**

;

and

(b) heating the mixture.

19. The process of claim 18, wherein the aprotic solvent comprises 2-methyltetrahydrofuran.

20. The process of claims 18 or 19, wherein the mixture is maintained at a temperature of about 30 °C to about 80 °C for a period of from about 12 hours to about 72 hours.

21. The process of any of claims 18-20, wherein the mixture is filtered to generate a filter cake, and the cake is further washed with an aprotic solvent.