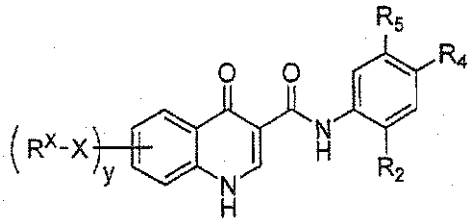
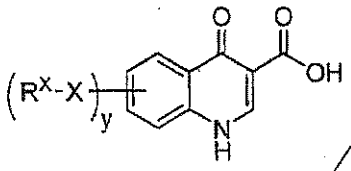
WHAT IS CLAIMED IS:

1. A process for the preparation of a compound of Formula **1**,



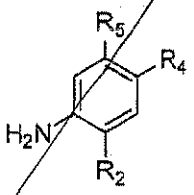
Formula 1

comprising coupling a carboxylic acid of Formula **2**



Formula 2

with an aniline of Formula **3**



Formula 3

in the presence of a coupling agent 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®; wherein

each R_2 and R_4 is independently selected from hydrogen, CN, CF_3, halo, C_{1-6} straight or branched alkyl, 3-12 membered cycloaliphatic, phenyl, C_{5-10} heteroaryl or C_{3-7} heterocyclic, wherein said heteroaryl or heterocyclic has up to 3 heteroatoms selected from O, S, or N, and each C_{1-6} straight or branched alkyl, 3-12 membered cycloaliphatic, phenyl, C_{5-10} heteroaryl or C_{3-7} heterocyclic is independently and optionally substituted with up to three substituents selected from —OR′, —CF_3, —OCF_3, SR′, S(O)R′, SO_2R′, —SCF_3, halo, CN, —COOR′, —COR′, —$O(CH_2)_2N(R')(R')$, —$O(CH_2)N(R')(R')$, —$CON(R')(R')$, —$(CH_2)_2OR'$, —$(CH_2)OR'$, CH_2CN, optionally substituted phenyl or phenoxy, —$N(R')(R')$, —$NR'C(O)OR'$, —$NR'C(O)R'$, —$(CH_2)_2N(R')(R')$, or —$(CH_2)N(R')(R')$;

each R_5 is independently selected from hydrogen, —OH, NH_2, CN, CHF_2, NHR′, $N(R')_2$,

—NHC(O)R′, NHC(O)OR′, $NHSO_2R'$, —OR′, OC(O)OR′, OC(O)NHR′, $OC(O)NR'_2$, CH_2OH, $CH_2N(R')_2$, C(O)OR′, SO_2NHR', $SO_2N(R')_2$, or $CH_2NHC(O)OR'$, or

R_4 and R_5 are taken together form a 5-7 membered ring containing 0-3 three heteroatoms selected from N, O, or S, wherein said ring is optionally substituted with up to three R_3 substituents;

each X is independently a bond or is an optionally substituted C_{1-6} alkylidene chain wherein up to two methylene units of X are optionally and independently replaced by —CO—, —CS—, —COCO—, —CONR′—, —CONR′NR′—, $—CO_2—$, —OCO—, $—NR'CO_2—$, —O—, —NR′CONR′—, —OCONR′—, —NR′NR′, —NR′NR′CO—, —NR′CO—, —S—, —SO, $—SO_2—$, —NR′—, $—SO_2NR'—$, $NR'SO_2—$, or $—NR'SO_2NR'—$;

each R^X is independently R′, halo, NO_2, CN, CF_3, or OCF_3;

y is an integer from 0-4;

each R′ is independently selected from hydrogen or an optionally substituted group selected from a C_{1-8} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or two occurrences of R′ are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from N, O, or S; and

each R_3 is independently —C_{1-3} alkyl, C_{1-3} perhaloalkyl, —O(C_{1-3} alkyl), $—CF_3$, $—OCF_3$, $—SCF_3$, —F, —Cl, —Br, or —COOR′, —COR′, $—O(CH_2)_2N(R')(R')$, $—O(CH_2)N(R')(R')$, —CON(R′)(R′), $—(CH_2)_2OR'$, $—(CH_2)OR'$, optionally substituted monocyclic or bicyclic aromatic ring, optionally substituted arylsulfone, optionally substituted 5-membered heteroaryl ring, —N(R′)(R′), $—(CH_2)_2N(R')(R')$, or $—(CH_2)N(R')(R')$.

2. The process of claim 1, wherein R_5 is independently —OC(O)OR′, —OC(O)NHR′, or $—OC(O)N(R')_2$, wherein R′ is not hydrogen.

3. The process of claim 2, further comprising cleaving the —OC(O)OR′, —OC(O)NHR′, or $—OC(O)N(R')_2$ to form —OH.

4. The process of claim 3, wherein the cleavage is performed by treating a compound of Formula **1** with an alcoholic solvent in the presence of NaOH, KOH or sodium methoxide.

5. The process of claim 4, wherein the alcoholic solvent is methanol.

6. The process of claim 1, wherein at least one of R_4 or R_2 is independently a C_{1-6} straight or branched alkyl which is substituted with —COOR′ or —CON(R′)$_2$, wherein R′ is not hydrogen.

7. The process of claim 6, further comprising hydrolyzing each —COOR′, or —CON(R′)$_2$ to form —COOH.

8. The process of claim 7, wherein the hydrolysis is performed by treating a compound of Formula **1** with an alcoholic solvent in the presence of NaOH, KOH or sodium methoxide.

9. The process of claim 8, wherein the alcoholic solvent is methanol.

10. The process of claim 6, wherein R_5 is independently —OC(O)OR′, —OC(O)NHR′, or —OC(O)N(R′)$_2$, wherein R′ is not hydrogen.

11. The process of claim 10, further comprising cleaving the —OC(O)OR′, —OC(O)NHR′, or —OC(O)N(R′)$_2$ to form —OH.

12. The process of claim 11, wherein the cleavage is performed by treating a compound of Formula **1** with an alcoholic solvent in the presence of NaOH, KOH or sodium methoxide.

13. The process of claim 12, wherein the alcoholic solvent is methanol.

14. The process of any of claims 1-13, wherein the coupling is performed in the presence of a base.

15. The process of claim 14, wherein the base is K_2CO_3, Et_3N, NMM, pyridine or DIEA.

16. The process of any of claims 1-15, wherein the coupling is performed in the presence of a solvent.

17. The process of claim 16, wherein the solvent is acetonitrile.

18. The process of claim 16, wherein the solvent is DMF.

19. The process of claim 16, wherein the solvent is 2-methyltetrahydrofuran.

20. The process of any of claims 1-19, wherein the coupling is performed at a reaction temperature which is maintained between about 10 °C and 78 °C.

21. The process of claim 20, wherein the coupling is performed at a reaction temperature which is maintained between about 20 °C and 30 °C.

22. The process of claim 20, wherein the coupling is performed at a reaction temperature which is maintained between about 40 °C and 50 °C.

23. The process of claim 20, wherein the coupling is performed at a reaction temperature which is maintained between about 42 °C and 53 °C.

24. The process of any of claims claim 1-23, wherein the coupling reaction is stirred for at least 2 hours.

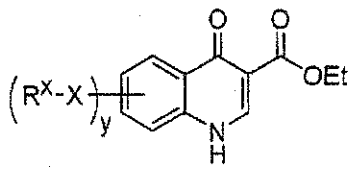
25. The process of claim 24, wherein the coupling reaction is stirred for at least 70 hours.

26. The process of claim 24, wherein the coupling reaction is stirred for at least 3 days.

27. The process of any of claims 1-26, wherein y is 0.

28. The process of any of claims 1-27, wherein R_2 is *tert*-butyl.

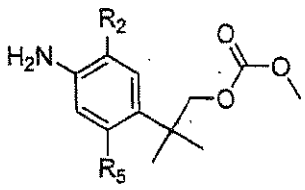
29. The process according to any of claims 1-28 further comprising the step of contacting a compound of Formula 4



Formula 4

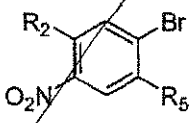
with an aqueous acid to produce a compound of Formula 2.

30. The process of any of claims 1-29, wherein the compound of Formula 3 is a compound of Formula 40



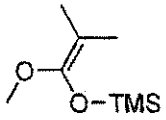
Formula 40

31. The process of claim 30 further comprising the step of contacting a compound of Formula 41



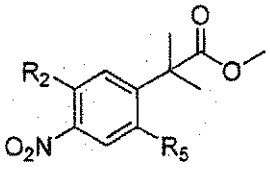
Formula 41

with methyl trimethylsilyl dimethylketene acetal (MTDA)



MTDA

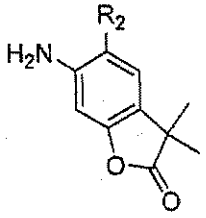
to produce a compound of Formula 42



Formula 42

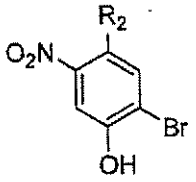
32. The process of claim 31 further comprising the step of reducing a compound of Formula 42 to produce a compound of Formula 40.

33. The process of any of claims 1-29, wherein the compound of Formula 3 is a compound of Formula 43



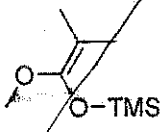
Formula 43

34. The process of claim 33, comprising the step of contacting a compound of Formula 44



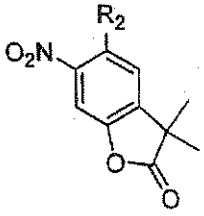
Formula 44

with methyl trimethylsilyl dimethylketene acetal (MTDA)



MTDA

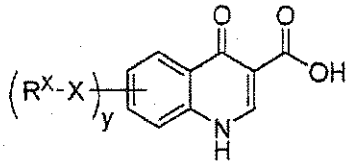
to produce a compound of Formula 45



Formula 45

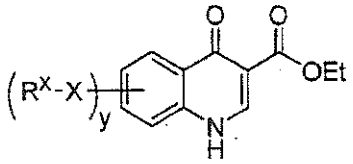
35. The process of claim 34 further comprising the step of reducing a compound of Formula 45 to produce a compound of Formula 43.

36. A process for the preparation of a compound of Formula 2



Formula 2

comprising contacting a compound of Formula 4



Formula 4

with an aqueous acid, wherein

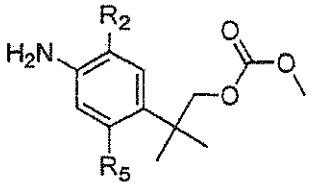
each X is independently a bond or is an optionally substituted C_{1-6} alkylidene chain wherein up to two methylene units of X are optionally and independently replaced by —CO—, —CS—, —COCO—, —CONR′—, —CONR′NR′—, —CO_2—, —OCO—, —NR′CO_2—, —O—, —NR′CONR′—, —OCONR′—, —NR′NR′, —NR′NR′CO—, —NR′CO—, —S—, —SO, —SO_2—, —NR′—, —SO_2NR′—, NR′SO_2—, or —NR′SO_2NR′—;

each R^X is independently R′, halo, NO_2, CN, CF_3, or OCF_3;

y is an integer from 0-4; and

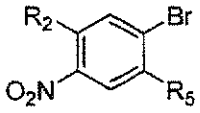
each R′ is independently selected from hydrogen or an optionally substituted group selected from a C_{1-8} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or two occurrences of R′ are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from N, O, or S.

37. A process for the preparation of a compound of Formula 40



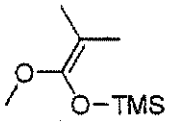
Formula 40

comprising the step of contacting a compound of Formula 41



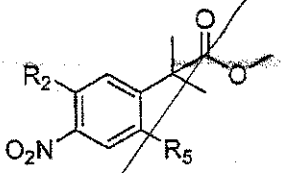
Formula 41

with methyl trimethylsilyl dimethylketene acetal (MTDA)



MTDA

to produce a compound of Formula 42



Formula 42 , wherein

each R_2 is independently selected from hydrogen, CN, CF_3, halo, $C_{1\text{-}6}$ straight or branched alkyl, 3-12 membered cycloaliphatic, phenyl, $C_{5\text{-}10}$ heteroaryl or $C_{3\text{-}7}$ heterocyclic, wherein said heteroaryl or heterocyclic has up to 3 heteroatoms selected from O, S, or N, and each $C_{1\text{-}6}$ straight or branched alkyl, 3-12 membered cycloaliphatic, phenyl, $C_{5\text{-}10}$ heteroaryl or $C_{3\text{-}7}$ heterocyclic is independently and optionally substituted with up to three substituents selected from —OR′, —CF_3, —OCF_3, SR′, S(O)R′, SO_2R′, —SCF_3, halo, CN, —COOR′, —COR—, —$O(CH_2)_2N(R')(R')$, —$O(CH_2)N(R')(R')$, —$CON(R')(R')$, —$(CH_2)_2OR'$, —$(CH_2)OR'$, CH_2CN, optionally substituted phenyl or phenoxy, —$N(R')(R')$, —$NR'C(O)OR'$, —$NR'C(O)R'$, —$(CH_2)_2N(R')(R')$, or —$(CH_2)N(R')(R')$;

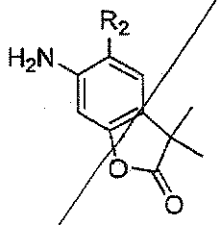
each R_5 is independently selected from hydrogen, —OH, NH_2, CN, CHF_2, NHR′, $N(R')_2$, —NHC(O)R′, NHC(O)OR′, $NHSO_2R'$, —OR′, OC(O)OR′, OC(O)NHR′, $OC(O)NR'_2$, CH_2OH, $CH_2N(R')_2$, C(O)OR′, SO_2NHR', $SO_2N(R')_2$, or $CH_2NHC(O)OR'$; and

2

each R' is independently selected from hydrogen or an optionally substituted group selected from a C_{1-8} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from N, O, or S.

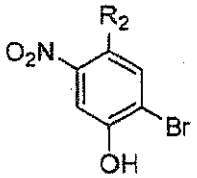
38. The process of claim 37 further comprising the step of reducing a compound of Formula 42 to produce a compound of Formula 40.

39. A process for the preparation of a compound of Formula 43



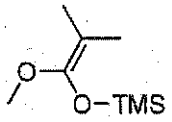
Formula 43

comprising the step of contacting a compound having the Formula 44



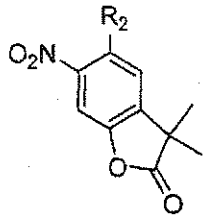
Formula 44

with methyl trimethylsilyl dimethylketene acetal (MTDA)



MTDA

to produce a compound of Formula 45



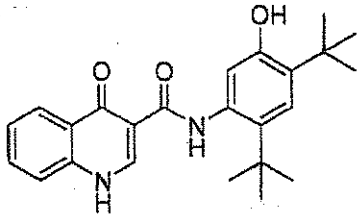
Formula 45 , wherein

each R_2 is independently selected from hydrogen, CN, CF_3, halo, C_{1-6} straight or branched alkyl, 3-12 membered cycloaliphatic, phenyl, C_{5-10} heteroaryl or C_{3-7} heterocyclic, wherein said heteroaryl or heterocyclic has up to 3 heteroatoms selected from O, S, or N, and each C_{1-6} straight or branched alkyl, 3-12 membered cycloaliphatic, phenyl, C_{5-10} heteroaryl or C_{3-7} heterocyclic is independently and optionally substituted with up to three substituents selected from —OR′, —CF_3, —OCF_3, SR′, S(O)R′, SO_2R′, —SCF_3, halo, CN, —COOR′, —COR—, —$O(CH_2)_2N(R')(R')$, —$O(CH_2)N(R')(R')$, —$CON(R')(R')$, —$(CH_2)_2OR'$, —$(CH_2)OR'$, CH_2CN, optionally substituted phenyl or phenoxy, —$N(R')(R')$, —$NR'C(O)OR'$, —$NR'C(O)R'$, —$(CH_2)_2N(R')(R')$, or —$(CH_2)N(R')(R')$; and

each R′ is independently selected from hydrogen or an optionally substituted group selected from a C_{1-8} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or two occurrences of R′ are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from N, O, or S.

40. The process of claim 39 further comprising the step of reducing a compound of Formula 45 to produce a compound of Formula 43.

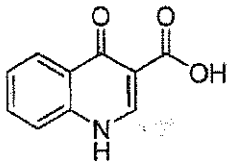
41. A process for the preparation of a compound **34**



Compound 34

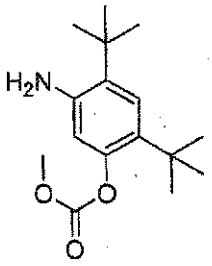
comprising:

(a) reacting compound **26**



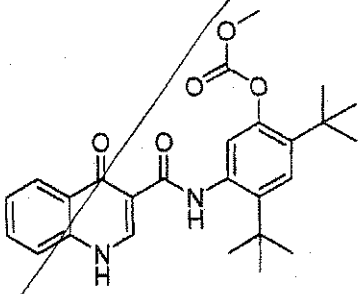
Compound 26

with compound **32**



Compound 32

in the presence of T3P® and pyridine using 2-methyl tetrahydrofuran as the solvent, wherein the reaction temperature is maintained between about 42 °C and 53 °C, and wherein the reaction is allowed proceed for at least 2 hours, to produce compound **33**



Compound 33 ; and

(b) treating compound **33** with NaOMe/MeOH in 2-methyl tetrahydrofuran.

42. The process of claim 41, wherein the reaction is allowed to proceed for at least 6 hours.

43. The process of claim 41, further comprising forming a slurry of compound **34** in a mixture of acetonitrile and water.

44. The process of claim 43, wherein the ratio of acetonitrile to water is about 9:1.

45. The process of claim 43, wherein the slurry is heated to a temperature between about 73 °C and 83 °C.

46. The process of claim 43, wherein compound **34** is in the slurry for at least about 3 hours.

47. The process of claim 43, further comprising forming a slurry of compound **34** in Isopropyl acetate.

48. The process of either of claims 46 or 47, wherein the slurry is heated to reflux temperature.

49. The process of claim 41, further comprising dissolving compound **34** in a biphasic solution of 2-methyltetrahydrofuran and 0.1N HCl; stirring said biphasic solution; separating the organic phase from said biphasic solution; filtering and removing solid matter from said organic phase; reducing the volume of said organic phase by approximately 50% using distillation; performing thrice the procedure of: adding MeOAc, EtOAc, IPAc, *t*-BuOAc, tetrahydrofuran (THF), Et_2O or methyl-*t*-butyl ether (MTBE) to the organic phase until the volume of said organic phase increases by 100% and reducing the volume of the organic phase by 50% using distillation; adding MeOAc, EtOAc, IPAc, *t*-BuOAc, tetrahydrofuran (THF), Et_2O or methyl-*t*-butyl ether (MTBE) to the organic phase until the volume of said organic phase increases by 100%; heating the organic phase to reflux temperature, and maintaining said reflux temperature for a time at least about 5 hours; and cooling the organic phase to a temperature between about
-5 °C and 5 °C over a time period of about 4.5 hours to 5.5 hours.

50. The process of claim 41, further comprising quenching the reaction mixture with 1.2 N HCl; thereby creating a biphasic mixture; agitating said biphasic mixture; separating the organic phase from said biphasic mixture; adding 0.1N HCl to the organic layer thereby creating a biphasic mixture; agitating said biphasic mixture; separating the organic phase; filtering and removing solid matter from said organic phase; reducing the volume of the organic phase by approximately 50% using distillation; performing thrice the steps of: adding acetonitrile to the organic phase until the volume of said organic phase increases by 100% and reducing the volume of the organic phase by approximately 50%; increasing the volume of the organic phase by approximately 100% by adding acetonitrile and then adding water, to

form a slurry wherein the final solvent ratio is 9:1 acetonitrile/water; heating said slurry to a temperature between about 73 °C and 83 °C; stirring said slurry for at least 5 hours; and cooling said slurry to a temperature between about 20 °C and 25 °C; filtering and removing solid matter from said slurry; washing the solid matter with acetonitrile having a temperature of between about 20 °C and 25 °C four times; and drying the solid material under vacuum at a temperature of from about 45 °C to about 55 °C.

51. A compound produced by the process of any of claims 1-50.

52. A pharmaceutical composition comprising a compound produced by the process of any of claims 1-50.

53. A method of modulating CFTR activity in a biological sample comprising the step of contacting said biological sample with a compound produced by the process of any of claims 1-50.

54. A method of treating or lessening the severity of a disease in a patient comprising administering to said patient an effective amount of a compound compound produced by the process of any of claims 1-50, wherein said disease is selected from 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, 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.

55. The method of claim 54, wherein said disease is cystic fibrosis.

56. A kit for use in measuring the activity of CFTR or a fragment thereof in a biological sample *in vitro* or *in vivo*, comprising:

i. a composition comprising a compound produced by the process of any of claims 1-50; and

ii. instructions for:

a. contacting the composition with the biological sample; and

b. measuring the activity of said CFTR or a fragment thereof.

57. The kit of claim 56, further comprising instructions for:

i. contacting an additional compound with the biological sample;

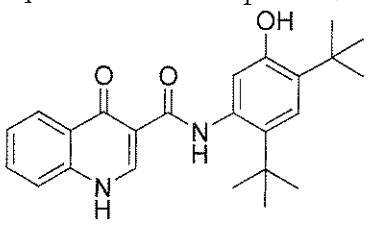
ii. measuring the activity of said CFTR or a fragment thereof in the presence of said additional compound; and

iii. comparing the activity of the CFTR or a fragment thereof in the presence of the additional compound with the activity of the CFTR or a fragment thereof in the presence of a composition comprising a compound of Formula **1**.

58. The kit according to claim 57, wherein the step of comparing the activity of said CFTR or a fragment thereof provides a measure of the density of said CFTR or a fragment thereof.

WHAT IS CLAIMED IS:

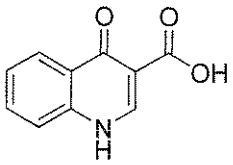
1. A process for the preparation of a compound **34**



Compound 34

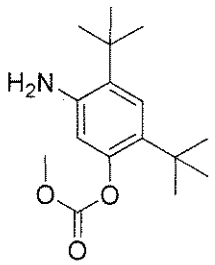
comprising:

(a) reacting compound **26**



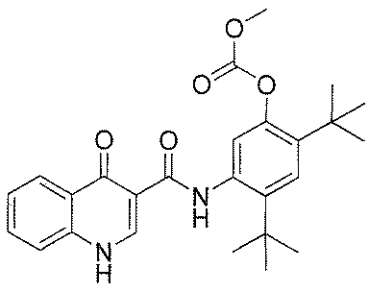
Compound 26

with compound **32**



Compound 32

in the presence of T3P® and pyridine using 2-methyl tetrahydrofuran as the solvent, wherein the reaction temperature is maintained between about 42 °C and 53 °C, and wherein the reaction is allowed proceed for at least 2 hours, to produce compound **33**



Compound 33 ; and

(b) treating compound **33** with NaOMe/MeOH in 2-methyl tetrahydrofuran.

2. The process of claim 1, wherein the reaction is allowed to proceed for at least 6 hours.

3. The process of claim 1, further comprising forming a slurry of compound **34** in a mixture of acetonitrile and water.

4. The process of claim 3, wherein the ratio of acetonitrile to water is about 9:1.

5. The process of claim 3, wherein the slurry is heated to a temperature between about 73 °C and 83 °C.

6. The process of claim 3, wherein compound **34** is in the slurry for at least about 3 hours.

7. The process of claim 3, further comprising forming a slurry of compound **34** in Isopropyl acetate.

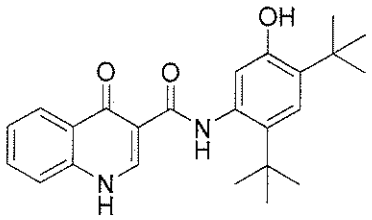
8. The process of either of claims 6 or 7, wherein the slurry is heated to reflux temperature.

9. The process of claim 1, further comprising dissolving compound **34** in a biphasic solution of 2-methyltetrahydrofuran and 0.1N HCl; stirring said biphasic solution; separating the organic phase from said biphasic solution; filtering and removing solid matter from said organic

phase; reducing the volume of said organic phase by approximately 50% using distillation; performing thrice the procedure of: adding MeOAc, EtOAc, IPAc, *t*-BuOAc, tetrahydrofuran (THF), Et_2O or methyl-*t*-butyl ether (MTBE) to the organic phase until the volume of said organic phase increases by 100% and reducing the volume of the organic phase by 50% using distillation; adding MeOAc, EtOAc, IPAc, *t*-BuOAc, tetrahydrofuran (THF), Et_2O or methyl-*t*-butyl ether (MTBE) to the organic phase until the volume of said organic phase increases by 100%; heating the organic phase to reflux temperature, and maintaining said reflux temperature for a time at least about 5 hours; and cooling the organic phase to a temperature between about -5 °C and 5 °C over a time period of about 4.5 hours to 5.5 hours.

10. The process of claim 1, further comprising quenching the reaction mixture with 1.2 N HCl; thereby creating a biphasic mixture; agitating said biphasic mixture; separating the organic phase from said biphasic mixture; adding 0.1N HCl to the organic layer thereby creating a biphasic mixture; agitating said biphasic mixture; separating the organic phase; filtering and removing solid matter from said organic phase; reducing the volume of the organic phase by approximately 50% using distillation; performing thrice the steps of: adding acetonitrile to the organic phase until the volume of said organic phase increases by 100% and reducing the volume of the organic phase by approximately 50%; increasing the volume of the organic phase by approximately 100% by adding acetonitrile and then adding water, to form a slurry wherein the final solvent ratio is 9:1 acetonitrile/water; heating said slurry to a temperature between about 73 °C and 83 °C; stirring said slurry for at least 5 hours; and cooling said slurry to a temperature between about 20 °C and 25 °C; filtering and removing solid matter from said slurry; washing the solid matter with acetonitrile having a temperature of between about 20 °C and 25 °C four times; and drying the solid material under vacuum at a temperature of from about 45 °C to about 55 °C.

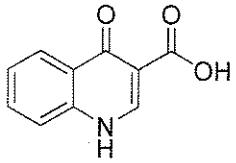
11. A process for the preparation of a compound **34**



Compound 34

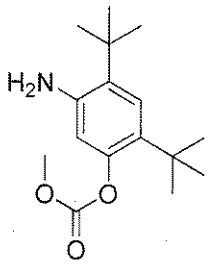
comprising the steps of:

(a) reacting compound **26**



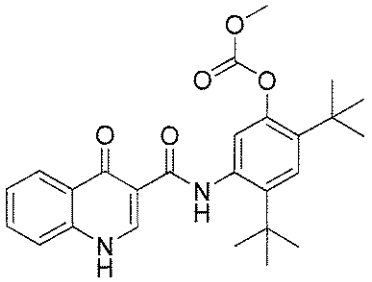
Compound 26

with compound **32**



Compound 32

in the presence of 2-propane phosphonic anhydride and pyridine using 2-methyl tetrahydrofuran as a solvent, wherein the reaction temperature is maintained between about 42 °C and 53 °C, and wherein the reaction is allowed proceed for at least 6 hours, to produce compound **33**



Compound 33 ;

(b) treating compound **33** with NaOMe/MeOH in 2-methyl tetrahydrofuran;

(c) adding a solution of 1.2 M HCl to the reaction mixture, thereby forming a first biphasic mixture;

(d) separating the organic layer from the first biphasic mixture;

(e) adding a solution of 0.1 M HCl to the organic layer of the first biphasic mixture, thereby forming a second biphasic mixture;

(f) separating the organic layer from the second biphasic mixture;

(g) reducing the amount of solvent in the organic layer of the second biphasic mixture by 50% using distillation;

(h) increasing the volume of the organic layer of the second biphasic mixture by 100% by adding acetonitrile;

(i) performing step (g) through step (h) two additional times;

(j) adding water to the organic layer of the second biphasic mixture to form a slurry of compound 34 in acetonitrile and water, wherein the slurry has a ratio of 9:1 of acetonitrile to water;

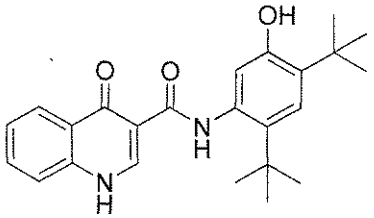
(k) heating the slurry to a temperature between 73 °C and 83 °C for at least 3 hours;

(l) cooling the slurry to a temperature between 20 °C and 25 °C; and

(m) filtering and removing solid matter from the slurry.

12. The process of claim 11, further comprising dissolving compound **34** in a biphasic solution of 2-methyltetrahydrofuran and 0.1N HCl; stirring the biphasic solution; separating the organic phase from the biphasic solution; filtering and removing solid matter from the organic phase; reducing the volume of the organic phase by approximately 50% using distillation; performing thrice the procedure of adding MeOAc, EtOAc, IPAc, *t*-BuOAc, tetrahydrofuran (THF), Et_2O or methyl-*t*-butyl ether (MTBE) to the organic phase until the volume of the organic phase increases by 100% and reducing the volume of the organic phase by 50% using distillation; adding MeOAc, EtOAc, IPAc, *t*-BuOAc, tetrahydrofuran (THF), Et_2O or methyl-*t*-butyl ether (MTBE) to the organic phase until the volume of the organic phase increases by 100%; heating the organic phase to reflux temperature, and maintaining the reflux temperature for a time of at least about 5 hours; and cooling the organic phase to a temperature between about -5 °C and 5 °C over a time period of about 4.5 hours to 5.5 hours.

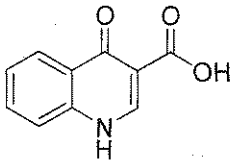
13. A process for the preparation of a compound **34**



Compound 34

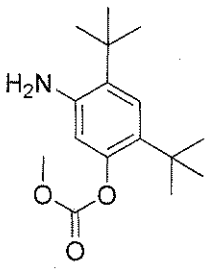
comprising:

(a) reacting compound **26**



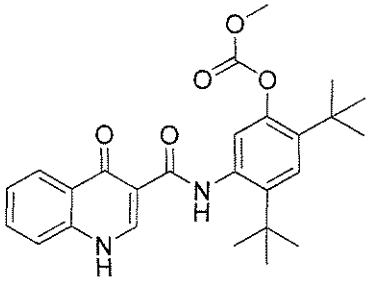
Compound 26

with compound **32**



Compound 32

in the presence of propane phosphonic anhydride and pyridine using 2-methyl tetrahydrofuran as a solvent, wherein the reaction temperature is maintained between about 42 °C and 53 °C, and wherein the reaction is allowed proceed for at least 2 hours, to produce compound **33**

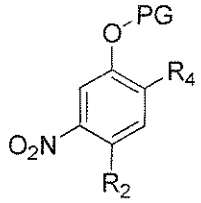


Compound 33 ;

(b) hydrolyzing the methoxycarbonyl protecting group from the phenolic oxygen atom of Compound **33** by treating compound **33** with NaOMe/MeOH in 2-methyl tetrahydrofuran to provide Compound **34**; and

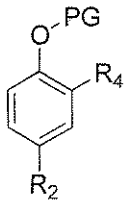
(c) forming a slurry of compound **34** in acetonitrile and water to provide Compound **34** in a pure form.

14. A process for the preparation of a compound of Formula **8**



Formula 8

comprising nitrating a compound of Formula **7** using a mixture of sulfuric acid and nitric acid in the presence of dichloromethane



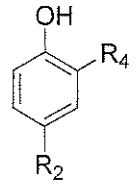
Formula 7

wherein PG is a protecting group and R_4 and R_5 are *tert*-butyl, and wherein the nitro compound of Formula **8** is purified by crystallization.

15. The process of claim 14, wherein PG is propoxy formyl, methanesulfonyl, 4-nitro-benzoyl, ethoxy formyl, butoxy formyl, *t*-butoxy formyl, *i*-propoxy formyl or methoxy formyl.

16. The process of claim 15, wherein PG is methoxy formyl.

17. The process of claim 14, further comprising producing a compound of formula **7** by reacting a compound of Formula **6**



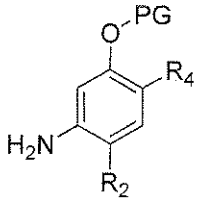
Formula 6

with a reagent capable of causing a protecting group to be attached to the phenolic oxygen of a compound of Formula **6** in the presence of a solvent.

18. The process of claim 17, wherein the solvent is diethyl ether, or methylene chloride.

19. The process of claim 18, wherein the solvent is methylene chloride.

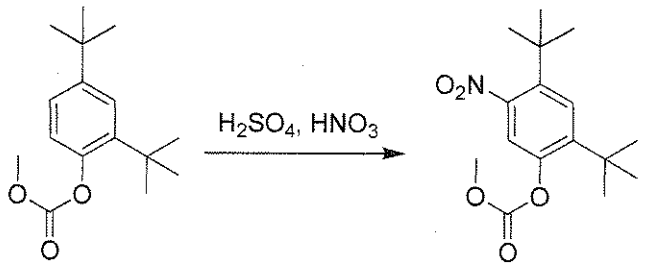
20. The process of claim 14, further comprising producing a compound of Formula **5**



Formula 5

by reducing a compound of formula **8**.

21. A process for the preparation of Compound 31, comprising contacting Compound 30 with a mixture of nitric acid and sulfuric acid in the presence of dichloromethane



30 **31**

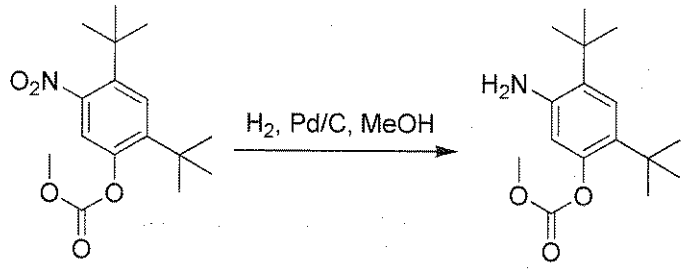
22. The process of claim 21, wherein the reaction is quenched by adding the reaction mixture to cold water.

23. The process of claim 21, wherein the aqueous layer is extracted with dichloromethane.

24. The process of claim 23, wherein the dichloromethane is further washed with water.

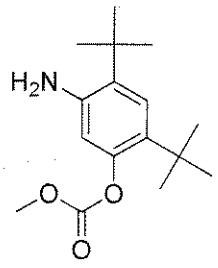
25. The process of claim 21, wherein the product is isolated by crystallization with hexane.

26. The process of claim 21, further comprising contacting Compound 31 in the presence of hydrogen gas, palladium on carbon, and methanol to provide Compound 32



31 **32**

27. A compound selected from:



and

