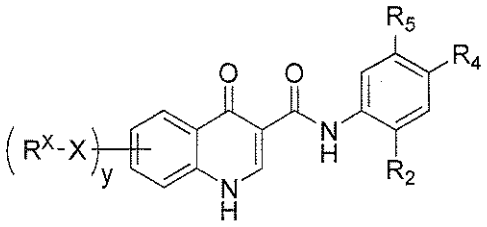
[0016] There is also a need for processes for the preparation of compounds which modulate CFTR activity.

SUMMARY ~~OF THE INVENTION~~

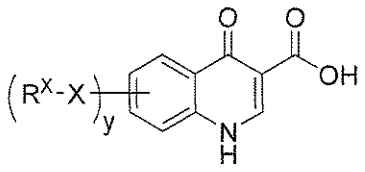
[0017] In general, the disclosure~~invention~~ provides processes for the preparation of compounds useful as modulators of CFTR.

[0017a] In one aspect, there is provided a process for the preparation of a compound of Formula **1**,



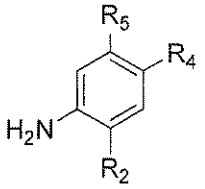
Formula 1

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



Formula 2

with an aniline of Formula **3**



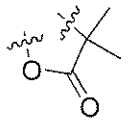
Formula 3

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 propane phosphonic anhydride; 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$(CH_2)_2$N(R′)(R′), —O(CH_2)N(R′)(R′), —CON(R′)(R′), —$(CH_2)_2$OR′, —(CH_2)OR′, CH_2CN, optionally substituted phenyl or phenoxy, —N(R′)(R′), —NR′C(O)OR′, —NR′C(O)R′, —$(CH_2)_2$N(R′)(R′), or —(CH_2)N(R′)(R′);

R_5 is —OC(O)OR′, —OC(O)NHR′, —OC(O)N$(R')_2$, wherein R′ is not hydrogen, or

R_4 and R_5 are taken together form the moiety,  ;

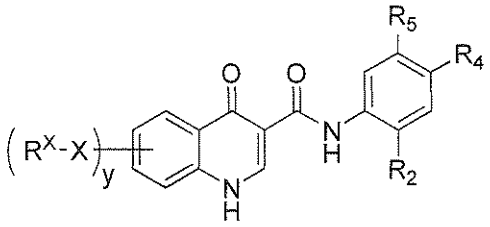
each X is independently a bond or is an optionally substituted C_{1-6} alkylidene chain wherein up to two methylene units of X are optionally and independently replaced by —CO—, —CS—, —COCO—, —CONR′—, —CONR′NR′—, —CO_2—, —OCO—, —NR′CO_2—, —O—, —NR′CONR′—, —OCONR′—, —NR′NR′, —NR′NR′CO—, —NR′CO—, —S—,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

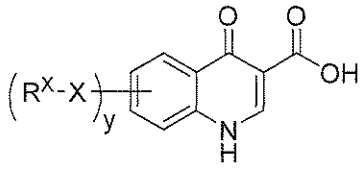
each R′ is independently selected from hydrogen or an optionally substituted group selected from a C_{1-8} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 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.

[0018] In one embodiment~~aspect~~, the disclosure~~invention~~ provides a process for the preparation of a compound of Formula **1**,



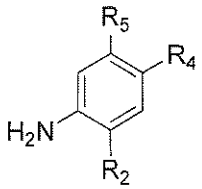
Formula 1

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®.

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.

Each R_3 is independently —C_1-C_3 alkyl, C_1-C_3 perhaloalkyl, —O(C_1-C_3 alkyl), —CF_3, —OCF_3, —SCF_3, —F, —Cl, —Br, —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 —$(CH_2)N(R')(R')$.

[0019] Embodiments ~~of this aspect~~ include one or more of the following features. R_5 is independently —$OC(O)OR'$, —$OC(O)NHR'$, or —$OC(O)N(R')_2$, and R′ is not hydrogen; at least one of R_4 or R_2 is independently a C_{1-6} straight or branched alkyl which is substituted

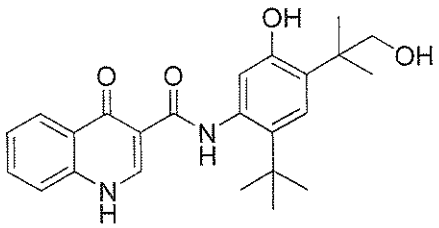
with -COOR′ or —CON(R′)(R′), and R′ is not hydrogen. The process further comprises cleaving the —OC(O)OR′, —OC(O)NHR′, or —OC(O)N(R′)$_2$ group to form —OH. The process further comprises hydrolyzing each —COOR′, or —CON(R′)$_2$ group to form —COOH. The hydrolysis is performed by treating a compound of Formula **1** with an alcoholic solvent in the presence of base such as NaOH, KOH or sodium methoxide. The alcoholic solvent used in the hydrolysis is methanol. The coupling a compound of Formula **2** and a compound of Formula **3** to produce a compound of Formula **1** is performed in the presence of a base such as K_2CO_3, Et_3N, NMM, pyridine or DIEA. The coupling a compound of Formula **2** and a compound of Formula **3** to produce a compound of Formula **1** is performed in the presence of a solvent such as EtOAc, IPAc, THF, MEK, NMP, acetonitrile, DMF, or 2-methyltetrahydrofuran. The coupling a compound of Formula **2** and a compound of Formula **3** to produce a compound of Formula **1** is performed at a reaction temperature which is maintained between about 10 °C and 78 °C such as between about 20 °C and 30 °C, between about 40 °C and 50 °C, and between about 42 °C and 53 °C. The coupling reaction is stirred for at least 2 hours such as for at least 70 hours or for at least 3 days.

[0020] In some embodiments, R_5 is independently —OC(O)OR′, —OC(O)NHR′, or —OC(O)N(R′)$_2$, and R′ is not hydrogen; and each of R_2 and R_4 is independently selected from hydrogen, CF_3, C_1-C_6 straight or branched alkyl, 3-12 membered cycloaliphatic or phenyl.

[0021] In some further embodiments, R_5 is independently —OC(O)OR′, and R′ is not hydrogen; and each of R_2 and R_4 is independently C_1-C_6 straight or branched alkyl or 3-12 membered cycloaliphatic.

[0022] In some embodiments, R_2 and R_4 are *t*-butyl.

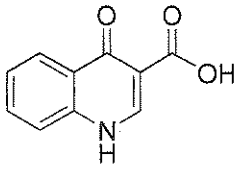
[0023] In another embodiment~~aspect~~, the disclosure~~invention~~ provides a process for the preparation of compound **27**



Compound 27

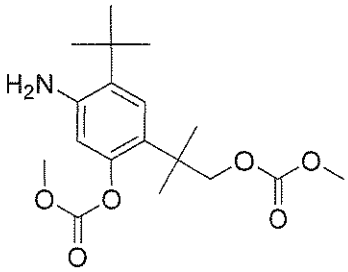
comprising:

(a) coupling compound **26**



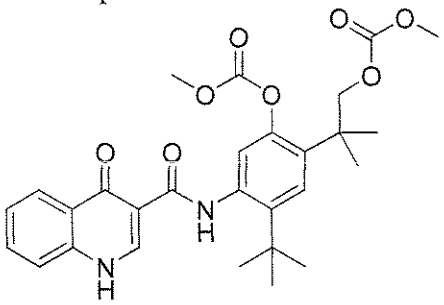
Compound 26

with compound **13**



Compound 13

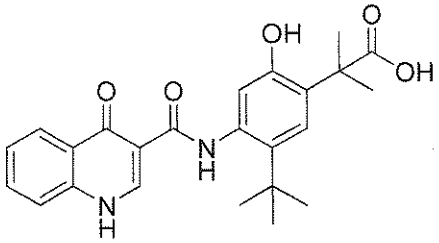
in the presence of EDCI, HOBT and DIEA using DMF as the solvent, wherein the reaction temperature is maintained between about 20 °C and 30 °C, and the reaction is allowed proceed for at least 70 hours, to produce compound **14**



Compound 14 ; and

(b) treating compound **14** with KOH in methanol.

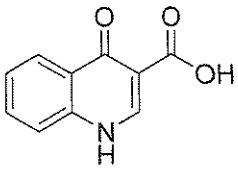
[0024] In still another ~~embodiment~~aspect, the ~~disclosure~~invention provides a process for the preparation of compound **28**



Compound 28

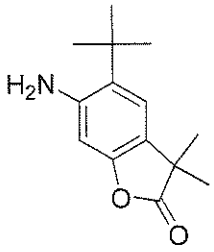
comprising:

(a) coupling compound **26**



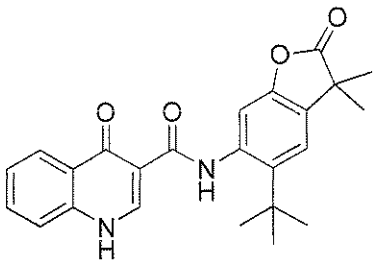
Compound 26

with compound **20**



Compound 20

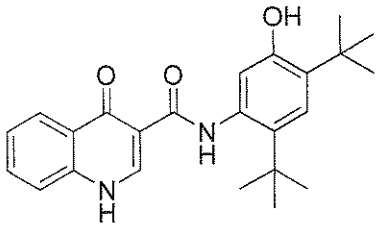
in the presence of HATU and DIEA using acetonitrile as the solvent, wherein the reaction temperature is maintained between about 40 °C and 50 °C, and wherein the reaction is allowed proceed for at least 3 days, to produce compound **21**



Compound 21 ; and

(b) treating compound **21** with NaOH in methanol.

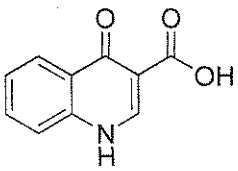
[0025] In yet another embodiment~~aspect~~, the disclosure~~invention~~ provides a process for the preparation of compound **34**



Compound 34

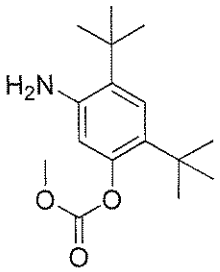
comprising:

(a) coupling compound **26**



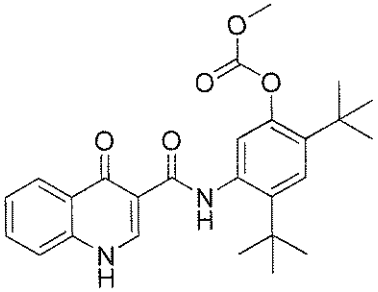
Compound 26

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 ;

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

[0026] In one embodiment, the method further includes the step of forming a slurry of compound **34** in a mixture of acetonitrile and water, wherein the solid form of compound **34** is converted to Compound **34**.

[0027] Embodiments ~~of the forgoing aspect~~ include one or more of the following features. The process further comprises dissolving Compound **34** in a biphasic solution of 2-methyltetrahydrofuran and 0.1N HCl, which is stirred. The process further comprises separating the organic phase from the biphasic solution. The process further comprises filtering and removing solid matter from the organic phase. The process further comprises reducing the volume of the organic phase by approximately 50% using distillation. The process further comprises 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. The process further comprises 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%. The process further comprises heating the organic phase to reflux temperature, and maintaining said reflux temperature for a time at least about 5 hours. The process further comprises cooling the organic phase to a temperature between -5 °C and 5 °C over a time period of 4.5 hours to 5.5 hours.

[0028] In still another embodimentaspect, the disclosureinvention provides compounds produced by any process described herein.

[0029] In a further embodimentaspect, the disclosureinvention provides a pharmaceutical composition comprising a compound produced by any process described herein.

[0030] In still a further embodimentaspect, the disclosureinvention provides a method of modulating CFTR activity in a biological sample comprising the step of contacting said biological sample with a compound produced by any process described herein.

[0031] In another embodimentaspect, the disclosureinvention also provides a method of treating or lessening the severity of a disease in a patient comprising administering to said patient one of the compositions as defined herein, and 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'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.

[0032] In certain embodiments, the disease is cystic fibrosis.

[0033] In another embodiment~~aspect~~, the disclosure~~invention~~ provides 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 any process described herein; and

ii. instructions for:

a. contacting the composition with the biological sample; and

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

[0034] In certain embodiments, the kit further comprises 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 in the presence of the additional compound with the density of the CFTR in the presence of a composition of Formula **1**.

[0035] Advantageously, the disclosure~~invention~~ provides processes for the synthesis of compounds useful as modulators of CFTR in higher yield and in higher purity relative to known processes.

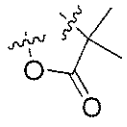
DETAILED DESCRIPTION

[0036] I. DEFINITIONS

[0037] As used herein, the following definitions shall apply unless otherwise indicated.

[0038] The term "ABC-transporter" as used herein means an ABC-transporter protein or a fragment thereof comprising at least one binding domain, wherein said protein or fragment thereof is present in vivo or in vitro. The term "binding domain" as used herein means a domain on the ABC-transporter that can bind to a modulator. See, e.g., Hwang, T. C. et al., J. Gen. Physiol. (1998): 111(3), 477-90.

R_5 is —OC(O)OR′, —OC(O)NHR′, —OC(O)N(R′)$_2$, wherein R′ is not hydrogen, or

R_4 and R_5 are taken together form the moiety,  ~~, or 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; 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~~; 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$(CH_2)_2$N(R′)(R′), —O(CH_2)N(R′)(R′), —CON(R′)(R′), —$(CH_2)_2$OR′, —(CH_2)OR′, optionally substituted monocyclic or bicyclic aromatic ring, optionally substituted arylsulfone, optionally substituted 5-membered heteroaryl ring, —N(R′)(R′), —$(CH_2)_2$N(R′)(R′), or —(CH_2)N(R′)(R′)~~.

2. The process of claim 1, further comprising cleaving the —OC(O)OR′, —OC(O)NHR′, or —OC(O)N(R′)$_2$ to form —OH.

3. The process of claim 2, 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.

4. The process of claim 3, wherein the alcoholic solvent is methanol.

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

6. The process of claim 5, further comprising hydrolyzing each —COOR′, or —CON(R′)$_2$ to form —COOH.

7. The process of claim 6, 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.

8. The process of claim 7, wherein the alcoholic solvent is methanol.

~~9. The process of claim 5, wherein R_5 is independently —OC(O)OR′, —OC(O)NHR′, or —OC(O)N(R′)$_2$, wherein R′ is not hydrogen.~~

9~~10~~. The process of claim 5~~9~~, further comprising cleaving the —OC(O)OR′, —OC(O)NHR′, or —OC(O)N(R′)$_2$ to form —OH.

10~~11~~. The process of claim 9~~10~~, 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.

11~~12~~. The process of claim 10~~11~~, wherein the alcoholic solvent is methanol.

123. The process of any of claims 1-112, wherein the coupling is performed in the presence of a base.

134. The process of claim 123, wherein the base is K_2CO_3, Et_3N, NMM, pyridine or DIEA.

145. The process of any of claims 1-134, wherein the coupling is performed in the presence of a solvent.

156. The process of claim 145, wherein the solvent is acetonitrile.

167. The process of claim 145, wherein the solvent is DMF.

178. The process of claim 145, wherein the solvent is 2-methyltetrahydrofuran.

189. The process of any of claims 1-178, wherein the coupling is performed at a reaction temperature which is maintained between about 10 °C and 78 °C.

1920. The process of claim 189, wherein the coupling is performed at a reaction temperature which is maintained between about 20 °C and 30 °C.

201. The process of claim 189, wherein the coupling is performed at a reaction temperature which is maintained between about 40 °C and 50 °C.

212. The process of claim 189, wherein the coupling is performed at a reaction temperature which is maintained between about 42 °C and 53 °C.

223. The process of any of claims 1-212, wherein the coupling reaction is stirred for at least 2 hours.

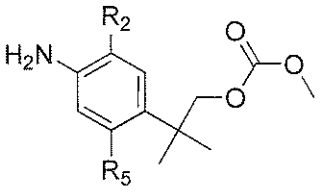
234. The process of claim 223, wherein the coupling reaction is stirred for at least 70 hours.

245. The process of claim 223, wherein the coupling reaction is stirred for at least 3 days.

256. The process of any of claims 1-241, ~~or 2-25~~, wherein y is 0.

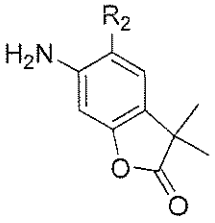
267. The process of any of claims 1-25, ~~or 2-26~~, wherein R_2 is *tert*-butyl.

278. The process of any of claims 1-26, ~~or 2-27~~, wherein the compound of Formula 3 is a compound of Formula 40.



Formula 40

289. The process of any of claims 1-278, wherein the compound of Formula 3 is a compound of Formula 43



Formula 43