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(54) **Title**: 4 -OXO- IH -QUINOLINE- 3 - CARBOXAMIDES AS MODULATORS OF ATP -BINDING CASSETTE TRANSPORTERS

(57) **Abstract**: The present invention relates to 4 -oxo- lH-quinoline- 3 carboxamides as modulators of ATP -Binding Cassette ("ABC") transporters or fragments thereof, including Cystic Fibrosis Transmembrane Conductance Regulator, compositions thereof, and methods therewith. The present Invention also relates to methods of treating ABC transporter mediated diseases using such modulators.

4 -OXO- IH -QUINOLINE- 3 - CARBOXAMIDES AS MODULATORS OF ATP -BINDING CASSETTE TRANSPORTERS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to utility application U.S. Serial No. 12/635,927, filed on December 11, 2009. The contents of which is incorporated herein by reference in its entirety.

TECHNICAL FIELD OF THE INVENTION

[001] The present invention relates to modulators of ATP-Binding Cassette ("ABC") transporters or fragments thereof, including cystic fibrosis transmembrane conductance regulator ("CFTR"), compositions thereof, and methods therewith. The present invention also relates to methods of treating ABC transporter mediated diseases using such modulators.

BACKGROUND OF THE INVENTION

[002] ABC transporters are a family of membrane transporter proteins that regulate the transport of a wide variety of pharmacological agents, potentially toxic drugs, and xenobiotics, as well as anions. ABC transporters are homologous membrane proteins that bind and use cellular adenosine triphosphate (ATP) for their specific activities. Some of these transporters were discovered as multidrug resistance proteins (like the MDR1-P glycoprotein, or the multidrug resistance protein, MRP1), defending malignant cancer cells against chemotherapeutic agents. To date, 48 ABC Transporters have been identified and grouped into 7 families based on their sequence identity and function.

[003] ABC transporters regulate a variety of important physiological roles within the body and provide defense against harmful environmental compounds. Because of this, they represent important potential drug targets for the treatment of diseases associated with defects in the transporter, prevention of drug transport out of the target cell, and intervention in other diseases in which modulation of ABC transporter activity may be beneficial.

[004] One member of the ABC transporter family commonly associated with disease is the cAMP/ATP-mediated anion channel, CFTR. CFTR is expressed in a variety of cells types, including absorptive and secretory epithelia cells, where it regulates anion flux across the membrane, as well as the activity of other ion channels and proteins. In epithelia cells, normal functioning of CFTR is critical for the maintenance of electrolyte transport throughout the body, including respiratory and digestive tissue. CFTR is composed of approximately 1480 amino acids that encode a protein made up of a tandem repeat of transmembrane domains, each containing six transmembrane helices and a nucleotide binding domain. The

two transmembrane domains are linked by a large, polar, regulatory (R)-domain with multiple phosphorylation sites that regulate channel activity and cellular trafficking.

[005] The gene encoding CFTR has been identified and sequenced (See Gregory, R. J. et al. (1990) Nature 347:382-386; Rich, D. P. et al. (1990) Nature 347:358-362), (Riordan, J. R. et al. (1989) Science 245:1066-1073). A defect in this gene causes mutations in CFTR resulting in cystic fibrosis ("CF"), the most common fatal genetic disease in humans. Cystic fibrosis affects approximately one in every 2,500 infants in the United States. Within the general United States population, up to 10 million people carry a single copy of the defective gene without apparent ill effects. In contrast, individuals with two copies of the CF associated gene suffer from the debilitating and fatal effects of CF, including chronic lung disease.

[006] In patients with cystic fibrosis, mutations in CFTR endogenously expressed in respiratory epithelia leads to reduced apical anion secretion causing an imbalance in ion and fluid transport. The resulting decrease in anion transport contributes to enhanced mucus accumulation in the lung and the accompanying microbial infections that ultimately cause death in CF patients. In addition to respiratory disease, CF patients typically suffer from gastrointestinal problems and pancreatic insufficiency that, if left untreated, results in death. In addition, the majority of males with cystic fibrosis are infertile and fertility is decreased among females with cystic fibrosis. In contrast to the severe effects of two copies of the CF associated gene, individuals with a single copy of the CF associated gene exhibit increased resistance to cholera and to dehydration resulting from diarrhea – perhaps explaining the relatively high frequency of the CF gene within the population.

[007] Sequence analysis of the CFTR gene of CF chromosomes has revealed a variety of disease causing mutations (Cutting, G. R. et al. (1990) Nature 346:366-369; Dean, M. et al. (1990) Cell 61:863:870; and Kerem, B-S. et al. (1989) Science 245:1073-1080; Kerem, B-S et al. (1990) Proc. Natl. Acad. Sci. USA 87:8447-8451). To date, > 1000 disease causing mutations in the CF gene have been identified (http://www.genet.sickkids.on.ca/cftr/). The most prevalent mutation is a deletion of phenylalanine at position 508 of the CFTR amino acid sequence, and is commonly referred to as ΔF508-CFTR. This mutation occurs in approximately 70% of the cases of cystic fibrosis and is associated with a severe disease.

[008] The deletion of residue 508 in ΔF508-CFTR prevents the nascent protein from folding correctly. This results in the inability of the mutant protein to exit the ER, and traffic to the plasma membrane. As a result, the number of channels present in the membrane is far less than observed in cells expressing wild-type CFTR. In addition to impaired trafficking, the mutation results in defective channel gating. Together, the reduced number of

channels in the membrane and the defective gating lead to reduced anion transport across epithelia leading to defective ion and fluid transport. (Quinton, P. M. (1990), FASEB J. 4: 2709-2727). Studies have shown, however, that the reduced numbers of ΔF508-CFTR in the membrane are functional, albeit less than wild-type CFTR. (Dolmans et al. (1991), Nature Lond. 354: 526-528; Denning et al., supra; Pasyk and Foskett (1995), J. Cell. Biochem. 270: 12347-50). In addition to ΔF508-CFTR, R117H-CFTR and G551D-CFTR other disease causing mutations in CFTR that result in defective trafficking, synthesis, and/or channel gating could be up- or down-regulated to alter anion secretion and modify disease progression and/or severity.

[009] Although CFTR transports a variety of molecules in addition to anions, it is clear that this role (the transport of anions, chloride and bicarbonate) represents one element in an important mechanism of transporting ions and water across the epithelium. The other elements include the epithelial Na^+ channel, ENaC, $Na^+/2Cl^-/K^+$ co-transporter, Na^+-K^+-ATPase pump and the basolateral membrane K^+ channels, that are responsible for the uptake of chloride into the cell.

[010] These elements work together to achieve directional transport across the epithelium via their selective expression and localization within the cell. Chloride absorption takes place by the coordinated activity of ENaC and CFTR present on the apical membrane and the Na^+-K^+-ATPase pump and Cl- ion channels expressed on the basolateral surface of the cell. Secondary active transport of chloride from the luminal side leads to the accumulation of intracellular chloride, which can then passively leave the cell via Cl^- channels, resulting in a vectorial transport. Arrangement of $Na^+/2Cl^-/K^+$ co-transporter, Na^+-K^+-ATPase pump and the basolateral membrane K^+ channels on the basolateral surface and CFTR on the luminal side coordinate the secretion of chloride via CFTR on the luminal side. Because water is probably never actively transported itself, its flow across epithelia depends on tiny transepithelial osmotic gradients generated by the bulk flow of sodium and chloride.

[011] Defective bicarbonate transport due to mutations in CFTR is hypothesized to cause defects in certain secretory functions. See, e.g., "Cystic fibrosis: impaired bicarbonate secretion and mucoviscidosis," Paul M. Quinton, Lancet 2008; *372*: 415-417.

[012] Mutations in CFTR that are associated with moderate CFTR dysfunction are also evident in patients with conditions that share certain disease manifestations with CF but do not meet the diagnostic criteria for CF. These include congenital bilateral absence of the vas deferens, idiopathic chronic pancreatitis, chronic bronchitis, and chronic rhinosinusitis. Other diseases in which mutant CFTR is believed to be a risk factor along with modifier genes

or environmental factors include primary sclerosing cholangitis, allergic bronchopulmonary aspergillosis, and asthma.

[013] Cigarette smoke, hypoxia, and environmental factors that induce hypoxic signaling have also been demonstrated to impair CFTR function and may contribute to certain forms of respiratory disease, such as chronic bronchitis. Diseases that may be due to defective CFTR function but do not meet the diagnostic criteria for CF are characterized as CFTR-related diseases.

[014] In addition to cystic fibrosis, modulation of CFTR activity may be beneficial for other diseases not directly caused by mutations in CFTR, such as secretory diseases and other protein folding diseases mediated by CFTR. CFTR regulates chloride and bicarbonate flux across the epithelia of many cells to control fluid movement, protein solubilization, mucus viscosity, and enzyme activity. Defects in CFTR can cause blockage of the airway or ducts in many organs, including the liver and pancreas. Potentiators are compounds that enhance the gating activity of CFTR present in the cell membrane. Any disease which involves thickening of the mucus, impaired fluid regulation, impaired mucus clearance, or blocked ducts leading to inflammation and tissue destruction could be a candidate for potentiators.

[015] These include, but are not limited to, chronic obstructive pulmonary disease (COPD), asthma, smoke induced COPD, chronic bronchitis, rhinosinusitis, constipation, dry eye disease, and Sjögren's Syndrome, gastro-esophageal reflux disease, gallstones, rectal prolapse, and inflammatory bowel disease. COPD is characterized by airflow limitation that is progressive and not fully reversible. The airflow limitation is due to mucus hypersecretion, emphysema, and bronchiolitis. Activators of mutant or wild-type CFTR offer a potential treatment of mucus hypersecretion and impaired mucociliary clearance that is common in COPD. Specifically, increasing anion secretion across CFTR may facilitate fluid transport into the airway surface liquid to hydrate the mucus and optimized periciliary fluid viscosity. This would lead to enhanced mucociliary clearance and a reduction in the symptoms associated with COPD. In addition, by preventing ongoing infection and inflammation due to improved airway clearance, CFTR modulators may prevent or slow the parenchimal destruction of the airway that characterizes emphysema and reduce or reverse the increase in mucus secreting cell number and size that underlyses mucus hypersecretion in airway diseases. Dry eye disease is characterized by a decrease in tear aqueous production and abnormal tear film lipid, protein and mucin profiles. There are many causes of dry eye, some of which include age, Lasik eye surgery, arthritis, medications, chemical/thermal burns, allergies, and diseases, such as cystic fibrosis and Sjögrens's syndrome. Increasing anion secretion via

CFTR would enhance fluid transport from the corneal endothelial cells and secretory glands surrounding the eye to increase corneal hydration. This would help to alleviate the symptoms associated with dry eye disease. Sjögrens's syndrome is an autoimmune disease in which the immune system attacks moisture-producing glands throughout the body, including the eye, mouth, skin, respiratory tissue, liver, vagina, and gut. Symptoms, include, dry eye, mouth, and vagina, as well as lung disease. The disease is also associated with rheumatoid arthritis, systemic lupus, systemic sclerosis, and polymypositis/dermatomyositis. Defective protein trafficking is believed to cause the disease, for which treatment options are limited. Modulators of CFTR activity may hydrate the various organs afflicted by the disease and may help to alleviate the associated symptoms. Individuals with cystic fibrosis have recurrent episodes of intestinal obstruction and higher incidences of rectal polapse, gallstones, gastro-esophageal reflux disease, GI malignancies, and inflammatory bowel disease, indicating that CFTR function may play an important role in preventing such diseases.

[016] As discussed above, it is believed that the deletion of residue 508 in ΔF508-CFTR prevents the nascent protein from folding correctly, resulting in the inability of this mutant protein to exit the ER, and traffic to the plasma membrane. As a result, insufficient amounts of the mature protein are present at the plasma membrane and chloride transport within epithelial tissues is significantly reduced. In fact, this cellular phenomenon of defective ER processing of CFTR by the ER machinery, has been shown to be the underlying basis not only for CF disease, but for a wide range of other isolated and inherited diseases. The two ways that the ER machinery can malfunction is either by loss of coupling to ER export of the proteins leading to degradation, or by the ER accumulation of these defective/misfolded proteins [Aridor M, *et al.*, Nature Med., *5*(7), pp 745- 751 (1999); Shastry, B.S., *et al.*, Neurochem. International, *43*, pp 1-7 (2003); Rutishauser, J., *et al.*, Swiss Med Wkly, *132*, pp 211-222 (2002); Morello, JP *et al.*, TIPS, *21*, pp. 466- 469 (2000); Bross P., *et al.*, Human Mut., *14*, pp. 186-198 (1999)]. The diseases associated with the first class of ER malfunction are cystic fibrosis (due to misfolded ΔF508-CFTR as discussed above), hereditary emphysema (due to a1-antitrypsin; non Piz variants), 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 (due to lysosomal processing enzymes), Sandhof/Tay-Sachs (due to β-hexosaminidase), Crigler-Najjar type II (due to UDP-glucuronyl-sialyc-transferase), polyendocrinopathy/hyperinsulemia, Diabetes mellitus (due to insulin receptor), Laron

dwarfism (due to growth hormone receptor), myleoperoxidase deficiency, primary hypoparathyroidism (due to preproparathyroid hormone), melanoma (due to tyrosinase). The diseases associated with the latter class of ER malfunction are Glycanosis CDG type 1, hereditary emphysema (due to α1-Antitrypsin (PiZ variant), congenital hyperthyroidism, osteogenesis imperfecta (due to Type I, II, IV procollagen), hereditary hypofibrinogenemia (due to fibrinogen), ACT deficiency (due to α1-antichymotrypsin), Diabetes insipidus (DI), neurophyseal DI (due to vasopvessin hormone/V2-receptor), neprogenic DI (due to aquaporin II), Charcot-Marie Tooth syndrome (due to peripheral myelin protein 22), Perlizaeus-Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease (due to βAPP and presenilins), Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, 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 (due to lysosomal α-galactosidase A), Straussler-Scheinker syndrome (due to Prp processing defect), infertility pancreatitis, pancreatic insufficiency, osteoporosis, osteopenia, Gorham's Syndrome, chloride channelopathies, myotonia congenita (Thomson and Becker forms), Bartter's syndrome type III, Dent's disease, hyperekplexia, epilepsy, hyperekplexia, lysosomal storage disease, Angelman syndrome, Primary Ciliary Dyskinesia (PCD), PCD with situs inversus (also known as Kartagener syndrome), PCD without situs inversus and ciliary aplasia, and liver disease.

[017] Other diseases implicated by a mutation in CFTR include male infertility caused by congenital bilateral absence of the vas deferens (CBAVD), mild pulmonary disease, idiopathic pancreatitis, and allergic bronchopulmonary aspergillosis (ABPA). See, "CFTR-opathies: disease phenotypes associated with cystic fibrosis transmembrane regulator gene mutations," Peader G. Noone and Michael R. Knowles, Respir. Res. 2001, 2: 328-332 (incorporated herein by reference).

[018] In addition to up-regulation of CFTR activity, reducing anion secretion by CFTR modulators may be beneficial for the treatment of secretory diarrheas, in which epithelial water transport is dramatically increased as a result of secretagogue activated chloride transport. The mechanism involves elevation of cAMP and stimulation of CFTR.

[019] Although there are numerous causes of diarrhea, the major consequences of diarrheal diseases, resulting from excessive chloride transport are common to all, and include dehydration, acidosis, impaired growth and death. Acute and chronic diarrheas represent a

major medical problem in many areas of the world. Diarrhea is both a significant factor in malnutrition and the leading cause of death (5,000,000 deaths/year) in children less than five years old.

[020] Secretory diarrheas are also a dangerous condition in patients of acquired immunodeficiency syndrome (AIDS) and chronic inflammatory bowel disease (IBD). 16 million travelers to developing countries from industrialized nations every year develop diarrhea, with the severity and number of cases of diarrhea varying depending on the country and area of travel.

[021] Diarrhea in barn animals and pets such as cows, pigs and horses, sheep, goats, cats and dogs, also known as scours, is a major cause of death in these animals. Diarrhea can result from any major transition, such as weaning or physical movement, as well as in response to a variety of bacterial or viral infections and generally occurs within the first few hours of the animal's life.

[022] The most common diarrheal causing bacteria is enterotoxogenic E.coli (ETEC) having the K99 pilus antigen. Common viral causes of diarrhea include rotavirus and coronavirus. Other infectious agents include cryptosporidium, giardia lamblia, and salmonella, among others.

[023] Symptoms of rotaviral infection include excretion of watery feces, dehydration and weakness. Coronavirus causes a more severe illness in the newborn animals, and has a higher mortality rate than rotaviral infection. Often, however, a young animal may be infected with more than one virus or with a combination of viral and bacterial microorganisms at one time. This dramatically increases the severity of the disease.

[024] Accordingly, there is a need for modulators of an ABC transporter activity, and compositions thereof, that can be used to modulate the activity of the ABC transporter in the cell membrane of a mammal.

[025] There is a need for methods of treating ABC transporter mediated diseases using such modulators of ABC transporter activity.

[026] There is a need for methods of modulating an ABC transporter activity in an *ex vivo* cell membrane of a mammal.

[027] There is a need for modulators of CFTR activity that can be used to modulate the activity of CFTR in the cell membrane of a mammal.

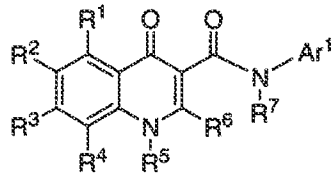
[028] There is also a need for potent and selective CFTR potentiators of wild-type and mutant forms of human CFTR. These mutant CFTR forms include, but are not limited to, ΔF508del, G551D, R117H, 2789+5G->A.

[029] There is a need for methods of treating CFTR-mediated diseases using such modulators of CFTR activity.

[030] There is a need for methods of modulating CFTR activity in an *ex vivo* cell membrane of a mammal.

SUMMARY OF THE INVENTION

[031] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are useful as modulators of ABC transporter activity. These compounds have the general formula **I:**



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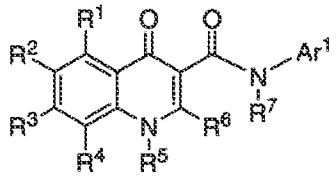
or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, and Ar^1 are described generally and in classes and subclasses below.

[032] These compounds and pharmaceutically acceptable compositions are useful for treating or lessening the severity of a variety of diseases, disorders, or conditions, including, but not limited to, cystic fibrosis, 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, Hereditary emphysema, 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 asuch 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, Fabry disease, Straussler-Scheinker syndrome, COPD, dry-eye disease, and Sjogren's disease.

DETAILED DESCRIPTION OF THE INVENTION

[033] *I. General Description of Compounds of the Invention:*

[034] The present invention relates to compounds of formula I useful as modulators of ABC transporter activity:



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or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is a 5-6 membered aromatic monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is optionally fused to a 5-12 membered monocyclic or bicyclic, aromatic, partially unsaturated, or saturated ring, wherein each ring contains 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein Ar^1 has m substituents, each independently selected from $-WR^W$;

W is a bond or is an optionally substituted C_1-C_6 alkylidene chain wherein up to two methylene units of W 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'-;

R^W is independently R', halo, NO_2, CN, CF_3, or OCF_3;

m is 0-5;

each of R^1, R^2, R^3, R^4, and R^5 is indendently $-X-R^X$;

X is a bond or is an optionally substituted C_1-C_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'-;

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

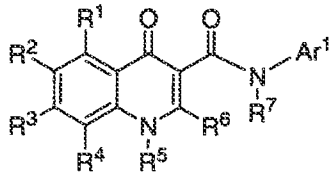
R^6 is hydrogen, CF_3, -OR', -SR', or an optionally substituted C_{1-6} aliphatic group;

R^7 is hydrogen or a C_{1-6} aliphatic group optionally substituted with $-X-R^X$;

R' is independently selected from hydrogen or an optionally substituted group selected from a C_1-C_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 nitrogen, oxygen, or sulfur.

[035] In certain other embodiments, compounds of formula I are provided:



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or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is a 5-6 membered aromatic monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is optionally fused to a 5-12 membered monocyclic or bicyclic, aromatic, partially unsaturated, or saturated ring, wherein each ring contains 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein Ar^1 has m substituents each independently selected from $-WR^W$;

W is a bond or is an optionally substituted C_1-C_6 alkylidene chain wherein up to two methylene units of W 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'-, $-SO_2NR'$-, $NR'SO_2$-, $-NR'SO_2NR'$-;

R^W is independently R', halo, NO_2, CN, CF_3, or OCF_3;

m is 0-5;

each of R^1, R^2, R^3, R^4, and R^5 is independently $-X-R^X$;

X is a bond or is an optionally substituted C_1-C_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 $-NR'SO_2NR'$-;

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

R^6 is hydrogen, CF_3, -OR', -SR', or an optionally substituted C1-C8 aliphatic group;

R^7 is hydrogen or a C1-C6 aliphatic group optionally substituted with $-X-R^X$;

R' is independently selected from hydrogen or an optionally substituted group selected from a C_1-C_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 nitrogen, oxygen, or sulfur;

provided that:

i) when R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are hydrogen, then Ar^1 is not phenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 2,6-dichlorophenyl, 2,4-dichlorophenyl, 2-bromophenyl, 4-bromophenyl, 4-hydroxyphenyl, 2,4-dinitrophenyl, 3,5-dicarboxylic acid phenyl, 2,4-dimethylphenyl, 2,6-dimethylphenyl, 2-ethylphenyl, 3-nitro-4-methylphenyl, 3-carboxylic-acid phenyl, 2-fluorophenyl, 3-fluorophenyl, 3-trifluoromethylphenyl, 3-ethoxyphenyl, 4-chlorophenyl, 3-methoxyphenyl, 4-dimethylaminophenyl, 3,4-dimethylphenyl, 2-ethylphenyl, or 4-ethoxycarbonylphenyl;

ii) when R^1, R^2, R^3, R^5, R^6 and R^7 are hydrogen, and R^4 is methoxy, then Ar^1 is not 2-fluorophenyl or 3-fluorophenyl;

iii) when R^1, R^3, R^4, R^5, R^6 and R^7 are hydrogen, R^2 is 1,2,3,4-tetrahydroisoquinolin-1-yl-sulfonyl, then Ar^1 is not 3-trifluoromethylphenyl;

iv) when R^1, R^2, R^3, R^4, R^5 and R^7 are hydrogen, R^6 is methyl, then Ar^1 is not phenyl;

v) when R^1, R^4, R^5, R^6 and R^7 are hydrogen, R^2 and R^3, taken together, are methylenedioxy, then Ar^1 is not 4-chlorophenyl, 4-bromophenyl, 4-nitrophenyl, 4-carboethoxyphenyl, 6-ethoxy-benzothiazol-2-yl, 6-carboethoxy-benzothiazol-2-yl, 6-halo-benzothiazol-2-yl, 6-nitro-benzothiazol-2-yl, or 6-thiocyano-benzothiazol-2-yl.

vi) when R^1, R^4, R^5, R^6 and R^7 are hydrogen, R^2 and R^3, taken together, are methylenedioxy, then Ar^1 is not 4-substituted phenyl wherein said substituent is $-SO_2NHR^{xx}$, wherein R^{xx} is 2-pyridinyl, 4-methyl-2-pyrimidinyl, 3,4-dimethyl-5-isoxazolyl;

vii) when R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are hydrogen, then Ar^1 is not thiazol-2-yl, 1*H*-1,2,4-triazol-3-yl, or 1*H*-1,3,4-triazol-2-yl;

viii) when R^1, R^2, R^3, R^5, R^6, and R^7 are hydrogen, and R^4 is CF_3, OMe, chloro, SCF_3, or OCF_3, then Ar^1 is not 5-methyl-1,2-oxazol-3-yl, thiazol-2-yl, 4-fluorophenyl, pyrimidin-2-yl, 1-methyl-1,2-(*1H*)-pyrazol-5-yl, pyridine-2-yl, phenyl, N-methyl-imidazol-2-yl, imidazol-2-yl, 5-methyl-imidazol-2-yl, 1,3-oxazol-2-yl, or 1,3,5-(*1H*)-triazol-2-yl;

ix) when R^1, R^2, R^3, R^4, R^5, R^6, and R^7 each is hydrogen, then Ar^1 is not pyrimidin-2-yl, 4,6-dimethyl-pyrimidin-2-yl, 4-methoxy-6-methyl-1,3,5-triazin-2-yl; 5-bromo-pyridin-2-yl, pyridin-2-yl, or 3,5-dichloro-pyridin-2-yl;

x) when R^1, R^2, R^3, R^4, R^5 and R^7 each is hydrogen, R^6 is hydroxy, then Ar^1 is not 2,6-dichloro-4-aminosulfonyl-phenyl;

xi) when R^2 or R^3 is an optionally substituted N-piperazyl, N-piperidyl, or N-morpholinyl, then Ar^1 is not an optionally substituted ring selected from thiazol-2-yl, pyridyl, phenyl, thiadiazolyl, benzothiazol-2-yl, or indazolyl;

xii) when R^2 is optionally substituted cyclohexylamino, then Ar^1 is not optionally substituted phenyl, pyridyl, or thiadiazolyl;

xiii) Ar^1 is not optionally substituted tetrazolyl;

xiv) when R^2, R^4, R^5, R^6, and R^7 each is hydrogen, and R^1 and R^3 both are simultaneously CF_3, chloro, methyl, or methoxy, then Ar^1 is not 4,5-dihydro-1,3-thiazol-2-yl, thiazol-2-yl, or [3,5-bis(trifluoromethyl)-*1H*-pyrazol-1-yl]phenyl;

xv) when R^1, R^4, R^5, R^6, and R^7 each is hydrogen, and Ar^1 is thiazol-2-yl, then neither R^2 nor R^3 is isopropyl, chloro, or CF_3;

xvi) when Ar^1 is 4-methoxyphenyl, 4-trifluoromethylphenyl, 2-fluorophenyl, phenyl, or 3-chlorophenyl, then:

a) when R^1, R^2, R^4, R^5, R^6, and R^7 each is hydrogen, then R^3 is not methoxy; or

b) when R^1, R^3, R^4, R^5, R^6, and R^7 each is hydrogen, then R^2 is not chloro; or

c) when R^1, R^2, R^3, R^5, R^6, and R^7 each is hydrogen, then R^4 is not methoxy; or

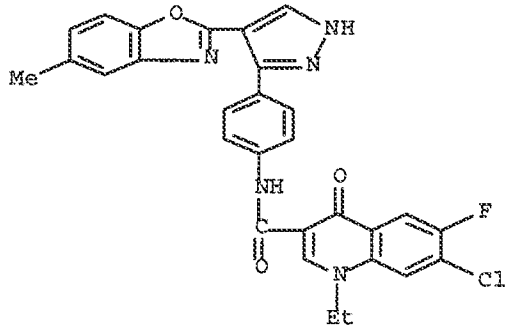
d) when when R^1, R^3, R^4, R^6, and R^7 each is hydrogen, and R^5 is ethyl, then R^2 is not chloro;

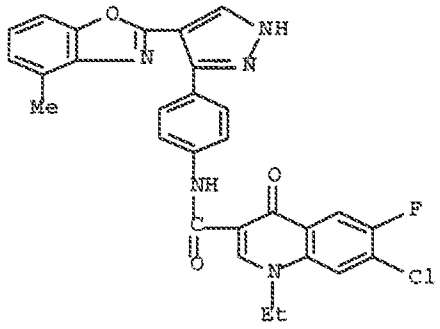
e) when R^1, R^2, R^4, R^5, R^6, and R^7 each is hydrogen, then R^3 is not chloro;

xvi) when R^1, R^3, R^4, R^5, R^6, and R^7 each is hydrogen, and R^2 is CF_3 or OCF_3, then Ar^1 is not [3,5-bis(trifluoromethyl)-*1H*-pyrazol-1-yl]phenyl;

xvii) when R^1, R^2, R^4, R^5, R^6, and R^7 each is hydrogen, and R3 is hydrogen or CF3, then Ar1 is not a phenyl substituted with $-OCH_2CH_2Ph$, $-OCH_2CH_2$(2-trifluoromethyl-phenyl), $-OCH_2CH_2$-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl), or substituted 1*H*-pyrazol-3-yl; and

xviii) the following two compounds are excluded:





and

[036] *2. Compounds and Definitions:*

[037] Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated.

[038] 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.

[039] The term "CFTR" as used herein means cystic fibrosis transmembrane conductance regulator or a mutation thereof capable of regulator activity, including, but not limited to, ΔF508 CFTR and G551D CFTR (see, e.g., http://www.genet.sickkids.on.ca/cftr/, for CFTR mutations).

[040] The term "modulating" as used herein means increasing or decreasing by a measurable amount.

[041] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[042] As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by

particular classes, subclasses, and species of the invention. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." In general, the term "substituted", whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[043] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle" "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-20 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-10 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-8 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms, and in yet other embodiments aliphatic groups contain 1-4 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C_3-C_8 hydrocarbon or bicyclic or tricyclic C_8-C_{14} hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule wherein any individual ring in said bicyclic ring system has 3-7 members. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl. Suitable cycloaliphatic groups include cycloalkyl,

bicyclic cycloalkyl (e.g., decalin), bridged bicycloalkyl such as norbornyl or [2.2.2]bicyclo-octyl, or bridged tricyclic such as adamantyl.

[044] The term "heteroaliphatic", as used herein, means aliphatic groups wherein one or two carbon atoms are independently replaced by one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon. Heteroaliphatic groups may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and include "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" groups.

[045] The term "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" as used herein means non-aromatic, monocyclic, bicyclic, or tricyclic ring systems in which one or more ring members is an independently selected heteroatom. In some embodiments, the "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" group has three to fourteen ring members in which one or more ring members is a heteroatom independently selected from oxygen, sulfur, nitrogen, or phosphorus, and each ring in the system contains 3 to 7 ring members.

[046] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[047] The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation.

[048] The term "alkoxy", or "thioalkyl", as used herein, refers to an alkyl group, as previously defined, attached to the principal carbon chain through an oxygen ("alkoxy") or sulfur ("thioalkyl") atom.

[049] The terms "haloaliphatic" and "haloalkoxy" means aliphatic or alkoxy, as the case may be, substituted with one or more halo atoms. The term "halogen" or "halo" means F, Cl, Br, or I. Examples of haloaliphatic incude $-CHF_2$, $-CH_2F$, $-CF_3$, $-CF_2-$, or perhaloalkyl, such as, $-CF_2CF_3$.

[050] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring". The term "aryl" also refers to heteroaryl ring systems as defined hereinbelow.

[051] The term "heteroaryl", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system contains 3 to 7 ring members. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic".

[052] An aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents. Suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group are selected from halo; -R°; -OR°; -SR°; 1,2-methylene-dioxy; 1,2-ethylenedioxy; phenyl (Ph) optionally substituted with R°; -O(Ph) optionally substituted with R°; -$(CH_2)_{1-2}$(Ph), optionally substituted with R°; -CH=CH(Ph), optionally substituted with R°; -NO_2; -CN; -$N(R°)_2$; -NR°C(O)R°; -NR°C(O)$N(R°)_2$; -NR°CO_2R°; -NR°NR°C(O)R°; -NR°NR°C(O)$N(R°)_2$; -NR°NR°CO_2R°; -C(O)C(O)R°; -C(O)CH_2C(O)R°; -CO_2R°; -C(O)R°; -C(O)$N(R°)_2$; -OC(O)$N(R°)_2$; -$S(O)_2$R°; -$SO_2N(R°)_2$; -S(O)R°; -NR°$SO_2N(R°)_2$; -NR°SO_2R°; -C(=S)$N(R°)_2$; -C(=NH)-$N(R°)_2$; or –$(CH_2)_{0-2}$NHC(O)R° wherein each independent occurrence of R° is selected from hydrogen, optionally substituted C_{1-6} aliphatic, an unsubstituted 5-6 membered heteroaryl or heterocyclic ring, phenyl, -O(Ph), or -CH_2(Ph), or, notwithstanding the definition above, two independent occurrences of R°, on the same substituent or different substituents, taken together with the atom(s) to which each R° group is bound, form a 3-8-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Optional substituents on the aliphatic group of R° are selected from NH_2, NH(C_{1-4}aliphatic), N(C_{1-4}aliphatic)$_2$, halo, C_{1-4}aliphatic, OH, O(C_{1-4}aliphatic), NO_2, CN, CO_2H, CO_2(C_{1-4}aliphatic), O(haloC_{1-4} aliphatic), or haloC_{1-4}aliphatic, wherein each of the foregoing C_{1-4}aliphatic groups of R° is unsubstituted.

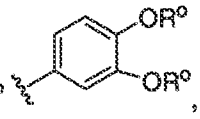
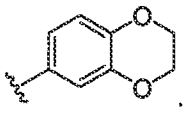
[053] An aliphatic or heteroaliphatic group, or a non-aromatic heterocyclic ring may contain one or more substituents. Suitable substituents on the saturated carbon of an aliphatic or heteroaliphatic group, or of a non-aromatic heterocyclic ring are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and additionally include the following: =O, =S, =NNHR*, =N$N(R^*)_2$, =NNHC(O)R*, =NNHCO_2(alkyl), =NNHSO_2(alkyl), or =NR*, where each R* is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic. Optional substituents on the aliphatic group of R* are selected from NH_2, NH(C_{1-4} aliphatic), N(C_{1-4} aliphatic)$_2$, halo, C_{1-4} aliphatic, OH, O(C_{1-4} aliphatic), NO_2, CN,

CO_2H, $CO_2(C_{1-4}$ aliphatic), O(halo C_{1-4} aliphatic), or halo(C_{1-4} aliphatic), wherein each of the foregoing C_{1-4}aliphatic groups of R^* is unsubstituted.

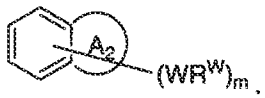
[054] Optional substituents on the nitrogen of a non-aromatic heterocyclic ring are selected from $-R^+$, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$, $-C(=S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$, or $-NR^+SO_2R^+$; wherein R^+ is hydrogen, an optionally substituted C_{1-6} aliphatic, optionally substituted phenyl, optionally substituted -O(Ph), optionally substituted $-CH_2$(Ph), optionally substituted $-(CH_2)_{1-2}$(Ph); optionally substituted -CH=CH(Ph); or an unsubstituted 5-6 membered heteroaryl or heterocyclic ring having one to four heteroatoms independently selected from oxygen, nitrogen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R^+, on the same substituent or different substituents, taken together with the atom(s) to which each R^+ group is bound, form a 3-8-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Optional substituents on the aliphatic group or the phenyl ring of R^+ are selected from NH_2, $NH(C_{1-4}$ aliphatic), $N(C_{1-4}$ aliphatic)$_2$, halo, C_{1-4} aliphatic, OH, $O(C_{1-4}$ aliphatic), NO_2, CN, CO_2H, $CO_2(C_{1-4}$ aliphatic), O(halo C_{1-4} aliphatic), or halo(C_{1-4} aliphatic), wherein each of the foregoing C_{1-4}aliphatic groups of R^+ is unsubstituted.

[055] The term "alkylidene chain" refers to a straight or branched carbon chain that may be fully saturated or have one or more units of unsaturation and has two points of attachment to the rest of the molecule. The term "spirocycloalkylidene" refers to a carbocyclic ring that may be fully saturated or have one or more units of unsaturation and has two points of attachment from the same ring carbon atom to the rest of the molecule.

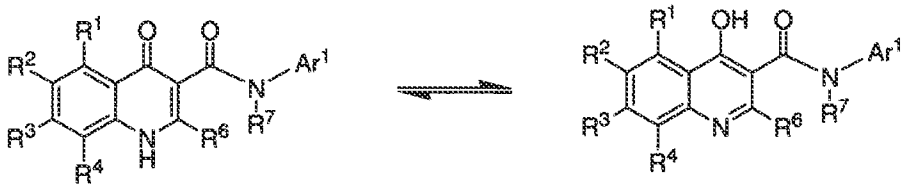
[056] As detailed above, in some embodiments, two independent occurrences of R° (or R^+, or any other variable similarly defined herein), are taken together together with the atom(s) to which each variable is bound to form a 3-8-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Exemplary rings that are formed when two independent occurrences of R° (or R^+, or any other variable similarly defined herein) are taken together with the atom(s) to which each variable is bound include, but are not limited to the following: a) two independent occurrences of R° (or R^+, or any other variable similarly defined herein) that are bound to the same atom and are taken together with that atom to form a ring, for example, $N(R^\circ)_2$, where both occurrences of R° are taken together with the nitrogen atom to form a piperidin-1-yl, piperazin-1-yl, or morpholin-4-yl group; and b) two independent occurrences of R° (or R^+, or any other variable similarly defined herein) that are bound to different atoms and are taken

together with both of those atoms to form a ring, for example where a phenyl group is substituted with two occurrences of OR^o  , these two occurrences of R^o are taken together with the oxygen atoms to which they are bound to form a fused 6-membered oxygen containing ring:  . It will be appreciated that a variety of other rings can be formed when two independent occurrences of R^o (or R^+, or any other variable similarly defined herein) are taken together with the atom(s) to which each variable is bound and that the examples detailed above are not intended to be limiting.

[057] A substituent bond in, e.g., a bicyclic ring system, as shown below, means that the substituent can be attached to any substitutable ring atom on either ring of the bicyclic ring system:



[058] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. E.g., when R^5 in compounds of formula I is hydrogen, compounds of formula I may exist as tautomers:



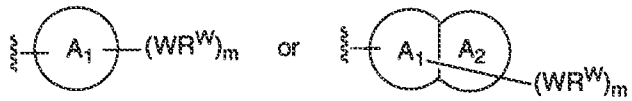
I I

Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within

the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

[059] *3. Description of Exemplary Compounds:*

[060] In some embodiments of the present invention, Ar^1 is selected from:



a-i **a-ii;**

wherein ring A_1 5-6 membered aromatic monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

A_1 and A_2, together, is an 8-14 aromatic, bicyclic or tricyclic aryl ring, wherein each ring contains 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[061] In some embodiments, A_1 is an optionally substituted 6 membered aromatic ring having 0-4 heteroatoms, wherein said heteroatom is nitrogen. In some embodiments, A_1 is an optionally substituted phenyl. Or, A_1 is an optionally substituted pyridyl, pyrimidinyl, pyrazinyl or triazinyl. Or, A_1 is an optionally substituted pyrazinyl or triazinyl. Or, A_1 is an optionally substituted pyridyl.

[062] In some embodiments, A_1 is an optionally substituted 5-membered aromatic ring having 0-3 heteroatoms, wherein said heteroatom is nitrogen, oxygen, or sulfur. In some embodiments, A_1 is an optionally substituted 5-membered aromatic ring having 1-2 nitrogen atoms. In one embodiment, A_1 is an optionally substituted 5-membered aromatic ring other than thiazolyl.

[063] In some embodiments, A_2 is an optionally substituted 6 membered aromatic ring having 0-4 heteroatoms, wherein said heteroatom is nitrogen. In some embodiments, A_2 is an optionally substituted phenyl. Or, A_2 is an optionally substituted pyridyl, pyrimidinyl, pyrazinyl, or triazinyl.

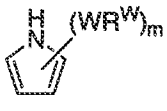
[064] In some embodiments, A_2 is an optionally substituted 5-membered aromatic ring having 0-3 heteroatoms, wherein said heteroatom is nitrogen, oxygen, or sulfur. In some embodiments, A_2 is an optionally substituted 5-membered aromatic ring having 1-2 nitrogen atoms. In certain embodiments, A_2 is an optionally substituted pyrrolyl.

[065] In some embodiments, A_2 is an optionally substituted 5-7 membered saturated or unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen,

sulfur, or oxygen. Exemplary such rings include piperidyl, piperazyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, tetrahydrofuranyl, etc.

[066] In some embodiments, A_2 is an optionally substituted 5-10 membered saturated or unsaturated carbocyclic ring. In one embodiment, A_2 is an optionally substituted 5-10 membered saturated carbocyclic ring. Exemplary such rings include cyclohexyl, cyclopentyl, etc.

[067] In some embodiments, ring A_2 is selected from:



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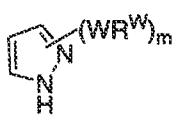

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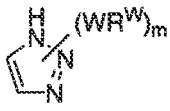

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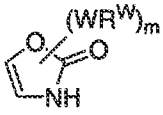

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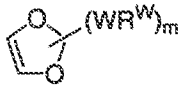

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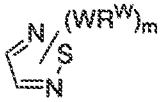

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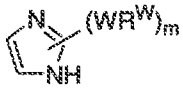

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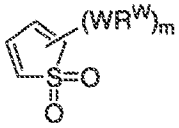

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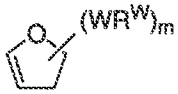

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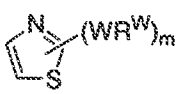

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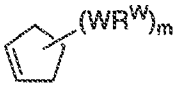

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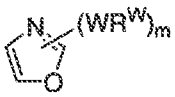

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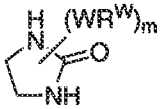

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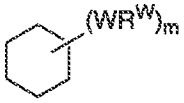

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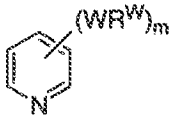

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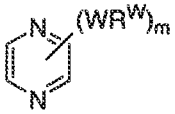

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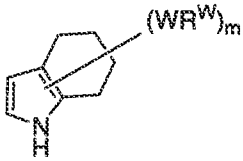

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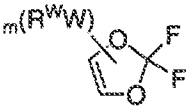

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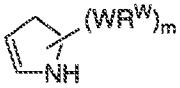

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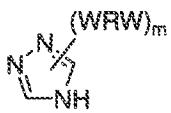

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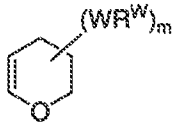

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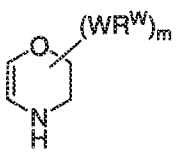
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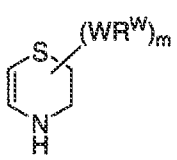
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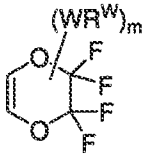
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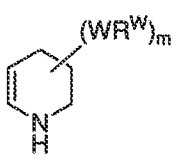
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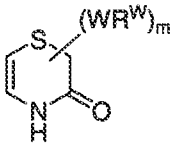
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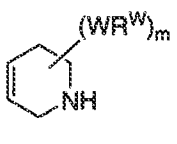
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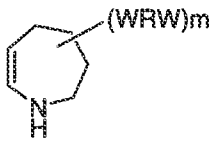
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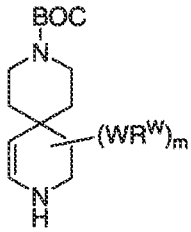
xxxii;

wherein ring A_2 is fused to ring A_1 through two adjacent ring atoms.

[068] In other embodiments, W is a bond or is an optionally substituted C_{1-6} alkylidene chain wherein one or two methylene units are optionally and independently replaced by O, NR', S, SO, SO_2, or COO, CO, SO_2NR', NR'SO_2, C(O)NR', NR'C(O), OC(O), OC(O)NR', and R^W is R' or halo. In still other embodiments, each occurrence of WR^W is independently -C1-C3 alkyl, C1-C3 perhaloalkyl, -O(C1-C3alkyl), -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 -$(CH_2)N(R')(R')$.

[069] In some embodiments, m is 0. Or, m is 1. Or, m is 2. In some embodiments, m is 3. In yet other embodiments, m is 4.

[070] In one embodiment, R^5 is X-R^X. In some embodiments R^5 is hydrogen. Or, R^5 is an optionally substituted C_{1-8} aliphatic group. In some embodiments, R^5 is optionally substituted C_{1-4} aliphatic. Or, R^5 is benzyl.

[071] In some embodiments R^6 is hydrogen. Or, R^6 is an optionally substituted C_{1-8} aliphatic group. In some embodiments, R^6 is optionally substituted C_{1-4} aliphatic. In certain other embodiments, R^6 is -(O-C_{1-4} aliphatic) or -(S-C_{1-4} aliphatic). Preferably, R^6 is -OMe or -SMe. In certain other embodiments, R_6 is CF_3.

[072] In one embodiment of the present invention, R^1, R^2, R^3, and R^4 are simultaneously hydrogen. In another embodiment, R^6 and R^7 are both simultaneously hydrogen.

[073] In another embodiment of the present invention, R^1, R^2, R^3, R^4, and R^5 are simultaneously hydrogen. In another embodiment of the present invention, R^1, R^2, R^3, R^4, R^5 and R^6 are simultaneously hydrogen.

[074] In another embodiment of the present invention, R^2 is $X\text{-}R^X$, wherein X is -SO_2NR'-, and R^X is R'; i.e., R^2 is -$SO_2N(R')_2$. In one embodiment, the two R' therein taken together form an optionally substituted 5-7 membered ring with 0-3 additional heteroatoms selected from nitrogen, oxygen, or sulfur. Or, R^1, R^3, R^4, R^5 and R^6 are simultaneously hydrogen, and R^2 is $SO_2N(R')_2$.

[075] In some embodiments, X is a bond or is an optionally substituted C_{1-6} alkylidene chain wherein one or two non-adjacent methylene units are optionally and independently replaced by O, NR', S, SO_2, or COO, CO, and R^X is R' or halo. In still other embodiments, each occurrence of XR^X is independently -C_{1-3}alkyl, -O(C_{1-3}alkyl), -CF_3, -OCF_3, -SCF_3, -F, -Cl, -Br, OH, -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 phenyl, -N(R')(R'), -$(CH_2)_2$N(R')(R'), or -(CH_2)N(R')(R').

[076] In some embodiments, R^7 is hydrogen. In certain other embodiment, R^7 is C_{1-4} straight or branched aliphatic.

[077] In some embodiments, R^W is selected from halo, cyano, CF_3, CHF_2, $OCHF_2$, Me, Et, $CH(Me)_2$, CHMeEt, n-propyl, t-butyl, OMe, OEt, OPh, O-fluorophenyl, O-difluorophenyl, O-methoxyphenyl, O-tolyl, O-benzyl, SMe, SCF_3, $SCHF_2$, SEt, CH_2CN, NH_2, NHMe, $N(Me)_2$, NHEt, $N(Et)_2$, $C(O)CH_3$, C(O)Ph, $C(O)NH_2$, SPh, SO_2-(amino-pyridyl), SO_2NH_2, SO_2Ph, SO_2NHPh, SO_2-N-morpholino, SO_2-N-pyrrolidyl, N-pyrrolyl, N-morpholino, 1-piperidyl, phenyl, benzyl, (cyclohexyl-methylamino)methyl, 4-Methyl-2,4-dihydro-pyrazol-3-one-2-yl, benzimidazol-2yl, furan-2-yl, 4-methyl-4H-[1,2,4]triazol-3-yl, 3-(4'-chlorophenyl)-[1,2,4]oxadiazol-5-yl, NHC(O)Me, NHC(O)Et, NHC(O)Ph, $NHSO_2Me$, 2-indolyl, 5-indolyl, $-CH_2CH_2OH$, $-OCF_3$, O-(2,3-dimethylphenyl), 5-methylfuryl, $-SO_2$-N-piperidyl, 2-tolyl, 3-tolyl, 4-tolyl, O-butyl, $NHCO_2C(Me)_3$, $CO_2C(Me)_3$, isopropenyl, n-butyl, O-(2,4-dichlorophenyl), $NHSO_2PhMe$, O-(3-chloro-5-trifluoromethyl-2-pyridyl), phenylhydroxymethyl, 2,5-dimethylpyrrolyl, $NHCOCH_2C(Me)_3$, O-(2-*tert*-butyl)phenyl, 2,3-dimethylphenyl, 3,4-dimethylphenyl, 4-hydroxymethyl phenyl, 4-dimethylaminophenyl, 2-trifluoromethylphenyl, 3- trifluoromethylphenyl, 4- trifluoromethylphenyl, 4-cyanomethylphenyl, 4-isobutylphenyl, 3-pyridyl, 4-pyridyl, 4-isopropylphenyl, 3-isopropylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-methylenedioxyphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-

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[078] In one embodiment, R' is hydrogen.

[079] In one embodiment, R' is a C1-C8 aliphatic group, optionally substituted with up to 3 substituents selected from halo, CN, CF_3, CHF_2, OCF_3, or $OCHF_2$, wherein up to two methylene units of said C1-C8 aliphatic is optionally replaced with –CO-, -CONH(C1-C4 alkyl)-, -CO_2-, -OCO-, -N(C1-C4 alkyl)CO_2-, -O-, -N(C1-C4 alkyl)CON(C1-C4 alkyl)-, -OCON(C1-C4 alkyl)-, -N(C1-C4 alkyl)CO-, -S-, -N(C1-C4 alkyl)-, -SO_2N(C1-C4 alkyl)-, N(C1-C4 alkyl)SO_2-, or -N(C1-C4 alkyl)SO_2N(C1-C4 alkyl)-.

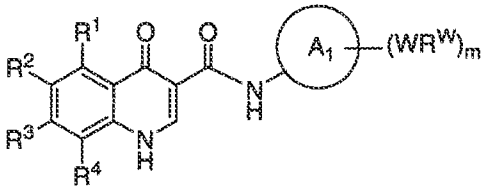
[080] In one embodiment, R' is a 3-8 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from

nitrogen, oxygen, or sulfur, wherein R' is optionally substituted with up to 3 substituents selected from halo, CN, CF_3, CHF_2, OCF_3, $OCHF_2$, or C1-C6 alkyl, wherein up to two methylene units of said C1-C6 alkyl is optionally replaced with -CO-, -CONH(C1-C4 alkyl)-, -CO_2-, -OCO-, -N(C1-C4 alkyl)CO_2-, -O-, -N(C1-C4 alkyl)CON(C1-C4 alkyl)-, -OCON(C1-C4 alkyl)-, -N(C1-C4 alkyl)CO-, -S-, -N(C1-C4 alkyl)-, -SO_2N(C1-C4 alkyl)-, N(C1-C4 alkyl)SO_2-, or -N(C1-C4 alkyl)SO_2N(C1-C4 alkyl)-.

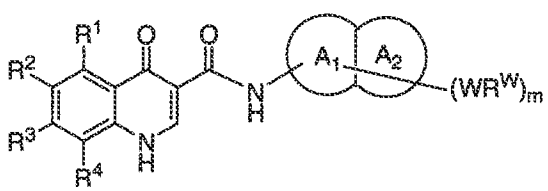
[081] In one embodiment, R' is an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein R' is optionally substituted with up to 3 substituents selected from halo, CN, CF_3, CHF_2, OCF_3, $OCHF_2$, or C1-C6 alkyl, wherein up to two methylene units of said C1-C6 alkyl is optionally replaced with –CO-, -CONH(C1-C4 alkyl)-, -CO_2-, -OCO-, -N(C1-C4 alkyl)CO_2-, -O-, -N(C1-C4 alkyl)CON(C1-C4 alkyl)-, -OCON(C1-C4 alkyl)-, -N(C1-C4 alkyl)CO-, -S-, -N(C1-C4 alkyl)-, -SO_2N(C1-C4 alkyl)-, N(C1-C4 alkyl)SO_2-, or -N(C1-C4 alkyl)SO_2N(C1-C4 alkyl)-.

[082] In one embodiment, 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 nitrogen, oxygen, or sulfur, wherein R' is optionally substituted with up to 3 substituents selected from halo, CN, CF_3, CHF_2, OCF_3, $OCHF_2$, or C1-C6 alkyl, wherein up to two methylene units of said C1-C6 alkyl is optionally replaced with –CO-, -CONH(C1-C4 alkyl)-, -CO_2-, -OCO-, -N(C1-C4 alkyl)CO_2-, -O-, -N(C1-C4 alkyl)CON(C1-C4 alkyl)-, -OCON(C1-C4 alkyl)-, -N(C1-C4 alkyl)CO-, -S-, -N(C1-C4 alkyl)-, -SO_2N(C1-C4 alkyl)-, N(C1-C4 alkyl)SO_2-, or -N(C1-C4 alkyl)SO_2N(C1-C4 alkyl)-.

[083] According to one embodiment, the present invention provides compounds of formula **IIA** or formula **IIB**:

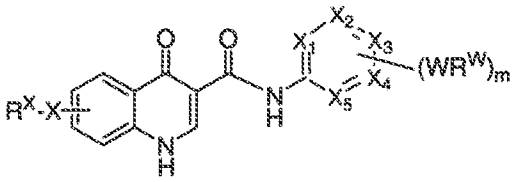


IIA

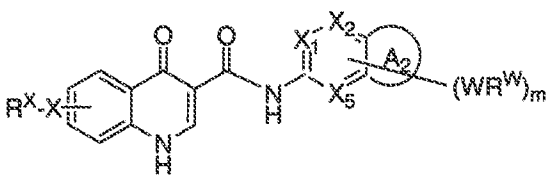


IIB

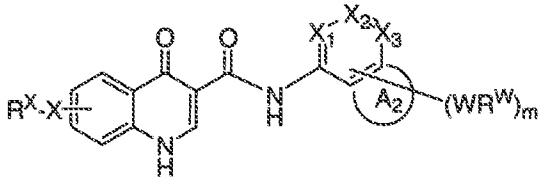
[084] According to another embodiment, the present invention provides compounds of formula **IIIA**, formula **IIIB**, formula **IIIC**, formula **IIID**, or formula **IIIE**:



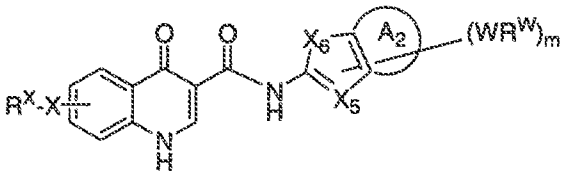
IIIA



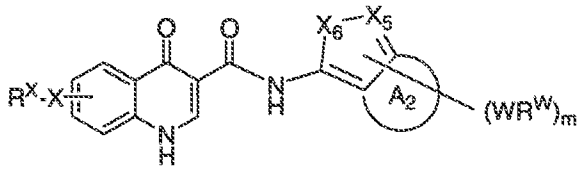
IIIB



IIIC



IIID



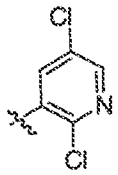
IIIE

wherein each of X_1, X_2, X_3, X_4, and X_5 is independently selected from CH or N; and X_6 is O, S, or NR'.

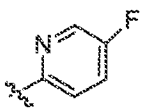
[085] In one embodiment, compounds of formula **IIIA**, formula **IIIB**, formula **IIIC**, formula **IIID**, or formula **IIIE** have y occurrences of substituent X-R^X, wherein y is 0-4. Or, y is 1. Or, y is 2.

[086] In some embodiments of formula **IIIA**, X_1, X_2, X_3, X_4, and X_5 taken together with WR^W and m is optionally substituted phenyl.

[087] In some embodiments of formula **IIIA**, X_1, X_2, X_3, X_4, and X_5 taken together is an optionally substituted ring selected from:



a-i



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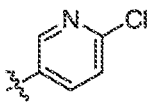

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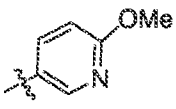

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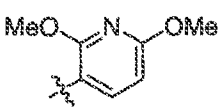

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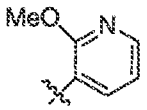

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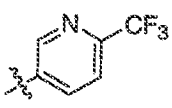

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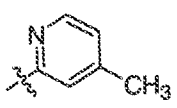

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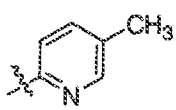

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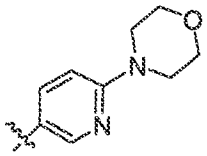

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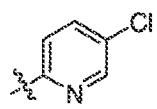
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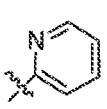
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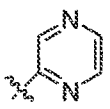
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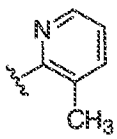
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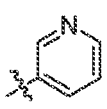
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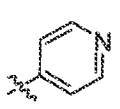
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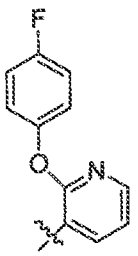
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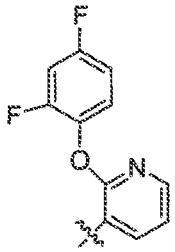
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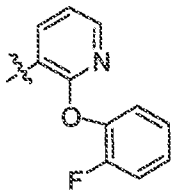
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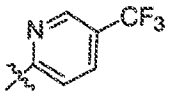
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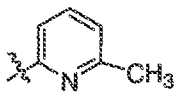
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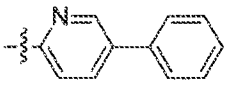
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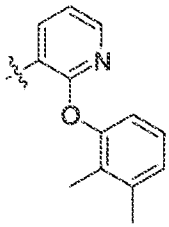
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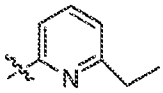
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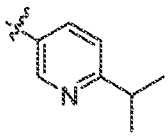
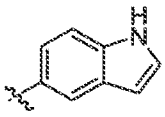

a-xxv

[088] In some embodiments of formula **IIIB**, formula **IIIC**, formula **IIID**, or formula **IIIE**, X_1, X_2, X_3, X_4, X_5, or X_6, taken together with ring A_2 is an optionally substituted ring selected from: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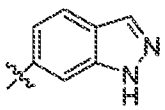
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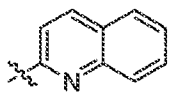
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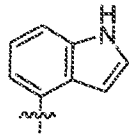
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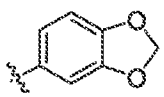
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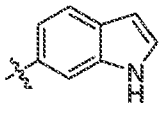
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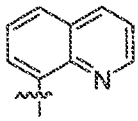
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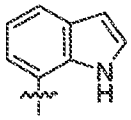
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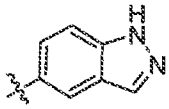
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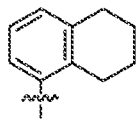
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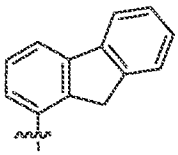
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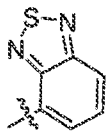
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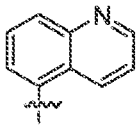
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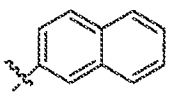
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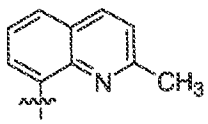
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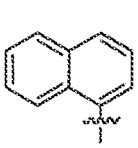

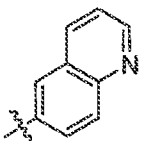

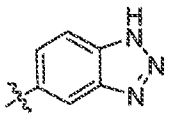

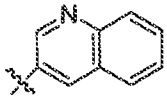

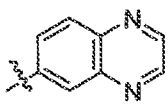

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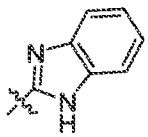
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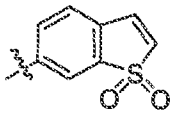
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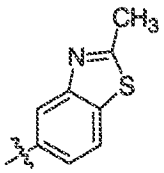
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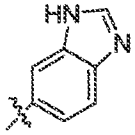
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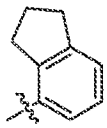
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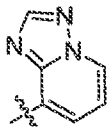
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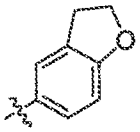
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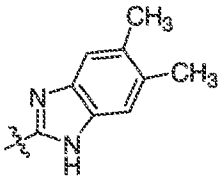
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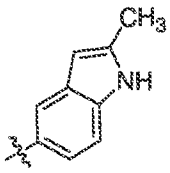
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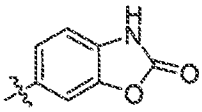
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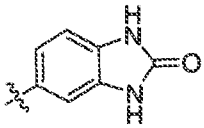
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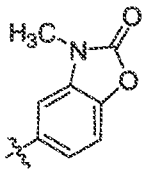
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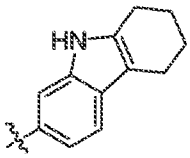
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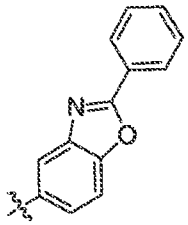
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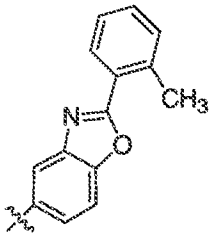
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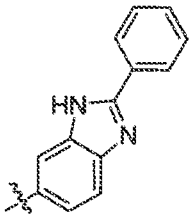
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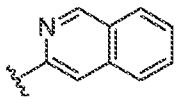
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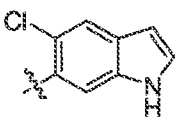
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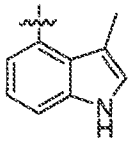
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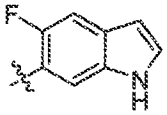
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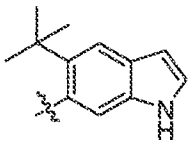
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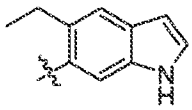
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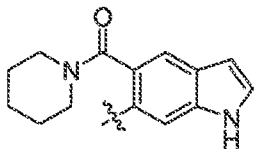
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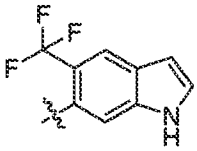
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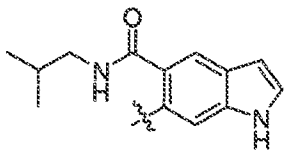
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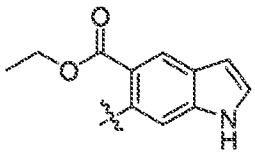
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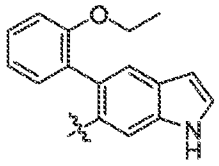

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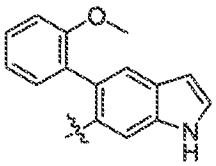

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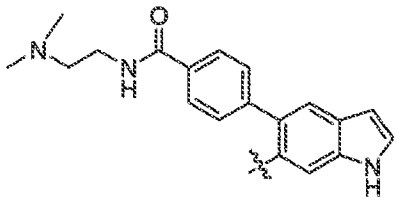

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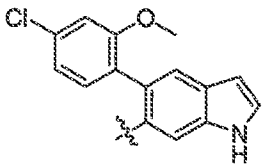

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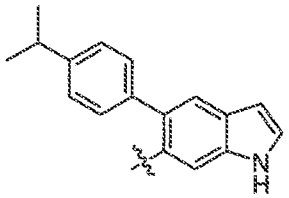

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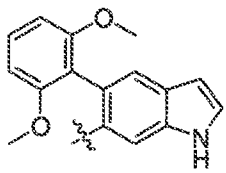

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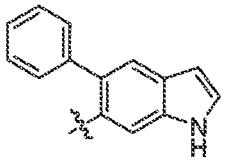

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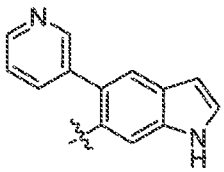

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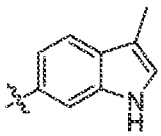

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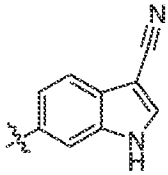

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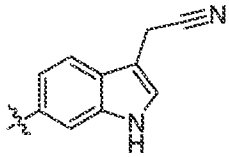

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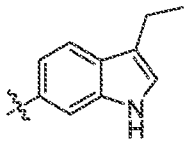

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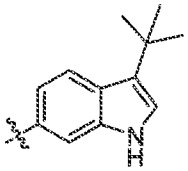

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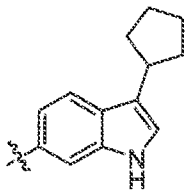

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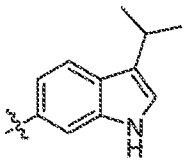
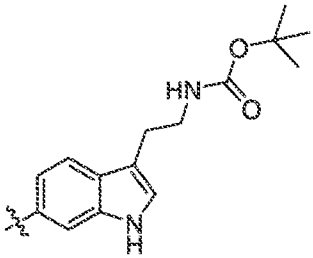


b-Lxi



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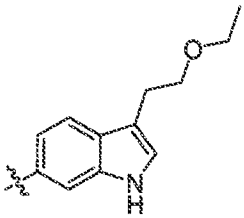
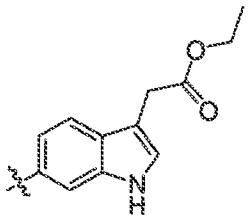


b-Lxiii



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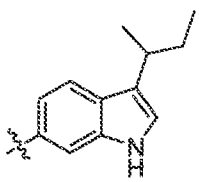

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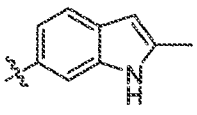
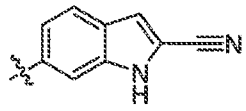
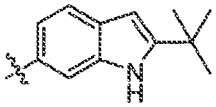


b-Lxvi



b-Lxvii



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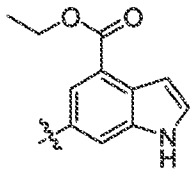
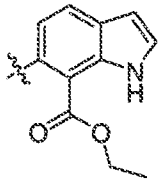
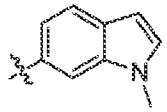


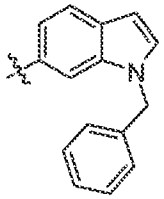
b-Lxix



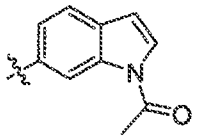
b-Lxx



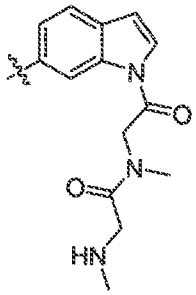
b-Lxxi



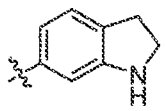
b-Lxxii



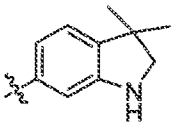
b-Lxxiii



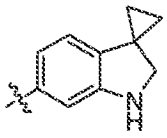
b-Lxxiv



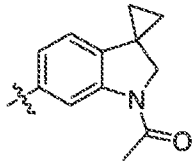
b-Lxxv



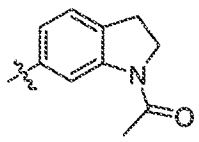
b-Lxxvi



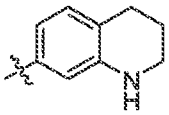
b-Lxxvii



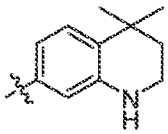
b-Lxxviii



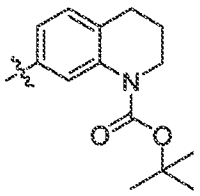
b-Lxxix



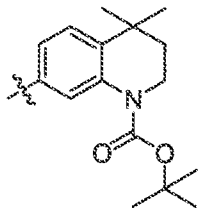
b-Lxxx



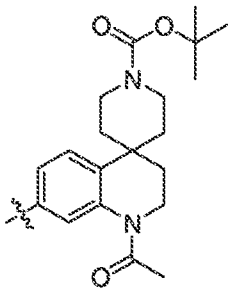
b-Lxxxi



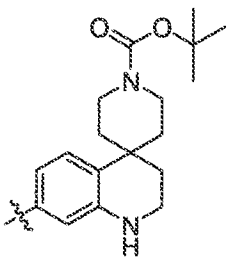
b-Lxxxii



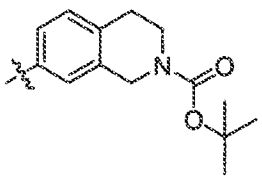
b-Lxxxiii



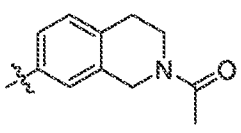
b-Lxxxiv

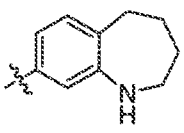


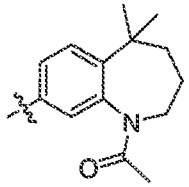
b-Lxxxv

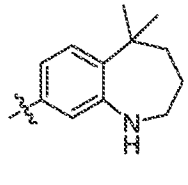


b-Lxxxvi

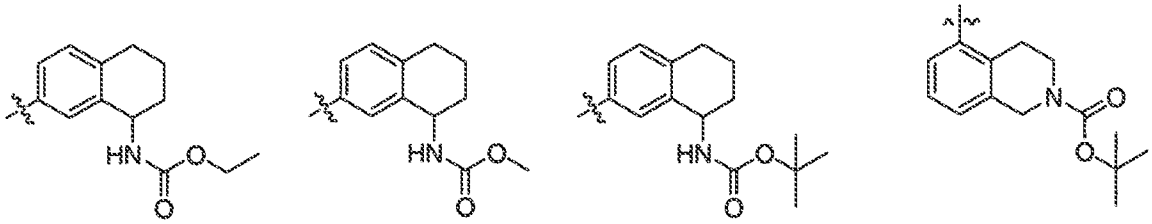




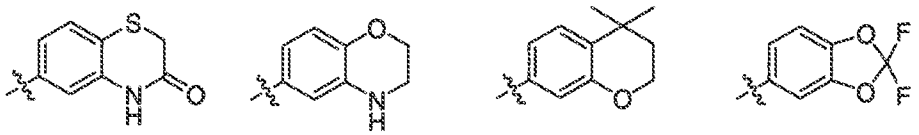




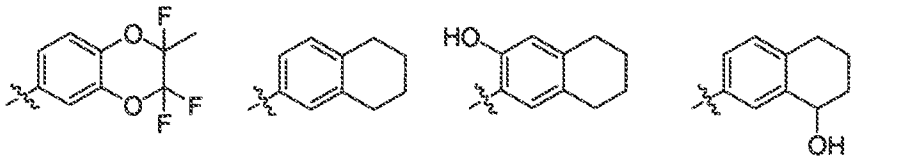
b-Lxxxviii b-Lxxxix b-xC b-xCi



b-xCi b-xCii b-xCiii b-xCiv



b-xCv b-xCvi b-xCvii b-xCviii

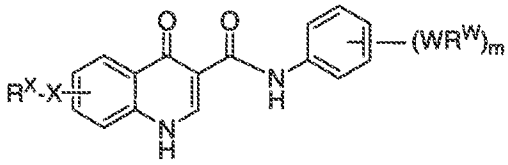


b-xCix b-C b-Ci b-Cii.

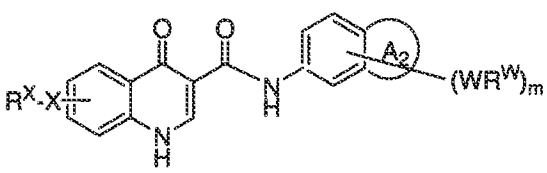
[089] In some embodiments, R^W is selected from halo, cyano, CF_3, CHF_2, $OCHF_2$, Me, Et, $CH(Me)_2$, CHMeEt, n-propyl, t-butyl, OMe, OEt, OPh, O-fluorophenyl, O-difluorophenyl, O-methoxyphenyl, O-tolyl, O-benzyl, SMe, SCF_3, $SCHF_2$, SEt, CH_2CN, NH_2, NHMe, $N(Me)_2$, NHEt, $N(Et)_2$, $C(O)CH_3$, C(O)Ph, $C(O)NH_2$, SPh, SO_2-(amino-pyridyl), SO_2NH_2, SO_2Ph, SO_2NHPh, SO_2-N-morpholino, SO_2-N-pyrrolidyl, N-pyrrolyl, N-morpholino, 1-piperidyl, phenyl, benzyl, (cyclohexyl-methylamino)methyl, 4-Methyl-2,4-dihydro-pyrazol-3-one-2-yl, benzimidazol-2yl, furan-2-yl, 4-methyl-4H-[1,2,4]triazol-3-yl, 3-(4'-chlorophenyl)-[1,2,4]oxadiazol-5-yl, NHC(O)Me, NHC(O)Et, NHC(O)Ph, or $NHSO_2Me$

[090] In some embodiments, X and R^X, taken together, is Me, Et, halo, CN, CF_3, OH, OMe, OEt, $SO_2N(Me)$(fluorophenyl), SO_2-(4-methyl-piperidin-1-yl, or SO_2-N-pyrrolidinyl.

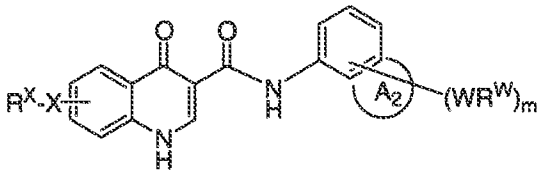
[091] According to another embodiment, the present invention provides compounds of formula **IVA**, formula **IVB**, or formula **IVC**:



IVA



IVB



IVC

[092] In one embodiment compounds of formula **IVA**, formula **IVB**, and formula **IVC** have y occurrences of substituent $X\text{-}R^X$, wherein y is 0-4. Or, y is 1. Or, y is 2.

[093] In one embodiment, the present invention provides compounds of formula **IVA**, formula **IVB**, and formula **IVC**, wherein X is a bond and R^X is hydrogen.

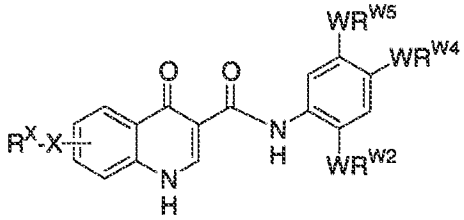
[094] In one embodiment, the present invention provides compounds of formula formula **IVB**, and formula **IVC**, wherein ring A_2 is an optionally substituted, saturated, unsaturated, or aromatic seven membered ring with 0-3 heteroatoms selected from O, S, or N. Exemplary rings include azepanyl, 5,5-dimethyl azepanyl, etc.

[095] In one embodiment, the present invention provides compounds of formula **IVB** and **IVC**, wherein ring A_2 is an optionally substituted, saturated, unsaturated, or aromatic six membered ring with 0-3 heteroatoms selected from O, S, or N. Exemplary rings include piperidinyl, 4,4-dimethylpiperidinyl, etc.

[096] In one embodiment, the present invention provides compounds of formula **IVB** and **IVC**, wherein ring A_2 is an optionally substituted, saturated, unsaturated, or aromatic five membered ring with 0-3 heteroatoms selected from O, S, or N.

[097] In one embodiment, the present invention provides compounds of formula **IVB** and **IVC**, wherein ring A_2 is an optionally substituted five membered ring with one nitrogen atom, e.g., pyrrolyl or pyrrolidinyl.

[098] According to one embodiment of formula **IVA**, the following compound of formula **VA-1** is provided:



VA-1

wherein each of WR^{W2} and WR^{W4} is independently selected from hydrogen, CN, CF_3, halo, C1-C6 straight or branched alkyl, 3-12 membered cycloaliphatic, phenyl, C5-C10 heteroaryl or C3-C7 heterocyclic, wherein said heteroaryl or heterocyclic has up to 3 heteroatoms selected from O, S, or N, wherein said WR^{W2} and WR^{W4} 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

WR^{W5} is selected from hydrogen, -OH, NH_2, CN, CHF_2, NHR', $N(R')_2$, -NHC(O)R', -NHC(O)OR', $NHSO_2$R', -OR', CH_2OH, CH2$N(R')_2$, C(O)OR', SO_2NHR', $SO_2N(R')_2$, or $CH_2NHC(O)OR'$. Or, WR^{W4} and WR^{W5} 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 WR^W substituents.

[0099] In one embodiment, compounds of formula **VA-1** have y occurrences of X-R^X, wherein y is 0-4. In one embodiment, y is 0.

[0100] In one embodiment, the present invention provides compounds of formula **VA-1**, wherein X is a bond and R^X is hydrogen.

[0101] In one embodiment, the present invention provides compounds of formula **VA-1**, wherein:

each of WR^{W2} and WR^{W4} is independently selected from hydrogen, CN, CF_3, halo, C1-C6 straight or branched alkyl, 3-12 membered cycloaliphatic, or phenyl, wherein said WR^{W2} and WR^{W4} is independently and optionally substituted with up to three substituents selected from –OR', -CF_3, -OCF_3, -SCF_3, halo, -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 phenyl, -$N(R')(R')$, -NC(O)OR', -NC(O)R', -$(CH_2)_2N(R')(R')$, or -$(CH_2)N(R')(R')$; and

WR^{W5} is selected from hydrogen, -OH, NH_2, CN, NHR', $N(R')_2$, -NHC(O)R', -NHC(O)OR', $NHSO_2$R', -OR', CH_2OH, C(O)OR', SO_2NHR', or $CH_2NHC(O)O$-(R').

[0102] In one embodiment, the present invention provides compounds of formula **VA-1**, wherein:

WR^{W2} is a pheny ring 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 -$(CH_2)N(R')(R')$;

WR^{W4} is C1-C6 straight or branched alkyl; and

WR^{W5} is OH.

[0103] In one embodiment, each of WR^{W2} and WR^{W4} is independently selected from CF_3 or halo. In one embodiment, each of WR^{W2} and WR^{W4} is independently selected from

optionally substituted hydrogen, C1-C6 straight or branched alkyl. In certain embodiments, each of of WR^{W2} and WR^{W4} is independently selected from optionally substituted n-propyl, isopropyl, n-butyl, sec-butyl, t-butyl, 1,1-dimethyl-2-hydroxyethyl, 1,1-dimethyl-2-(ethoxycarbonyl)-ethyl, 1,1-dimethyl-3-(t-butoxycarbonyl-amino) propyl, or n-pentyl.

[0104] In one embodiment, each of WR^{W2} and WR^{W4} is independently selected from optionally substituted 3-12 membered cycloaliphatic. Exemplary embodiments of such cycloaliphatic include cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl, [2.2.2.]bicyclo-octyl, [2.3.1.] bicyclo-octyl, or [3.3.1]bicyclo-nonyl.

[0105] In certain embodiments WR^{W2} is hydrogen and WR^{W4} is C1-C6 straight or branched alkyl. In certain embodiments, WR^{W4} is selected from methyl, ethyl, propyl, n-butyl, sec-butyl, or t-butyl.

[0106] In certain embodiments WR^{W4} is hydrogen and WR^{W2} is C1-C6 straight or branched alkyl. In certain embodiments, WR^{W2} is selected from methyl, ethyl, propyl, n-butyl, sec-butyl, t-butyl, or n-pentyl.

[0107] In certain embodiments each of WR^{W2} and WR^{W4} is C1-C6 straight or branched alkyl. In certain embodiments, each of WR^{W2} and WR^{W4} is selected from methyl, ethyl, propyl, n-butyl, sec-butyl, t-butyl, or pentyl.

[0108] In one embodiment, WR^{W5} is selected from hydrogen, CHF_2, NH_2, CN, NHR', $N(R')_2$, $CH_2N(R')_2$, -NHC(O)R', -NHC(O)OR', -OR', C(O)OR', or SO_2NHR'. Or, WR^{W5} is -OR', e.g., OH.

[0109] In certain embodiments, WR^{W5} is selected from hydrogen, NH_2, CN, CHF_2, NH(C1-C6 alkyl), N(C1-C6 alkyl)$_2$, -NHC(O)(C1-C6 alkyl), -CH_2NHC(O)O(C1-C6 alkyl), -NHC(O)O(C1-C6 alkyl), -OH, -O(C1-C6 alkyl), C(O)O(C1-C6 alkyl), CH_2O(C1-C6 alkyl), or SO_2NH_2. In another embodiment, WR^{W5} is selected from –OH, OMe, NH_2, -NHMe, -N(Me)$_2$, -CH_2NH_2, CH_2OH, NHC(O)OMe, NHC(O)OEt, CN, CHF_2, -CH_2NHC(O)O(t-butyl), -O-(ethoxyethyl), -O-(hydroxyethyl), -C(O)OMe, or –SO_2NH_2.

[0110] In one embodiment, compound of formula **VA-1** has one, preferably more, or more preferably all, of the following features:

i) WR^{W2} is hydrogen;

ii) WR^{W4} is C1-C6 straight or branched alkyl or monocyclic or bicyclic aliphatic; and

iii) WR^{W5} is selected from hydrogen, CN, CHF_2, NH_2, NH(C1-C6 alkyl), N(C1-C6 alkyl)$_2$, -NHC(O)(C1-C6 alkyl), -NHC(O)O(C1-C6 alkyl), -CH_2C(O)O(C1-C6 alkyl), -OH, -O(C1-C6 alkyl), C(O)O(C1-C6 alkyl), or SO_2NH_2.

[0111] In one embodiment, compound of formula **VA-1** has one, preferably more, or more preferably all, of the following features:

i) WR^{W2} is halo, C1-C6 alkyl, CF_3, CN, or phenyl optionally substituted with up to 3 substituents selected from C1-C4 alkyl, -O(C1-C4 alkyl), or halo;

ii) WR^{W4} is CF_3, halo, C1-C6 alkyl, or C6-C10 cycloaliphatic; and

iii) WR^{W5} is OH, NH_2, NH(C1-C6 alkyl), or N(C1-C6 alkyl).

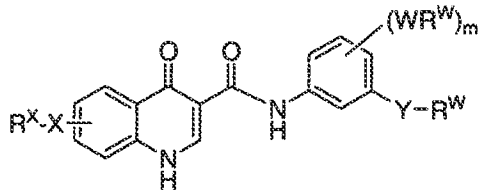
[0112] In one embodiment, $X\text{-}R^X$ is at the 6-position of the quinolinyl ring. In certain embodiments, $X\text{-}R^X$ taken together is C1-C6 alkyl, -O-(C1-C6 alkyl), or halo.

[0113] In one embodiment, $X\text{-}R^X$ is at the 5-position of the quinolinyl ring. In certain embodiments, $X\text{-}R^X$ taken together is -OH.

[0114] In another embodiment, the present invention provides compounds of formula **VA-1**, wherein WR^{W4} and WR^{W5} 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 WR^W substituents.

[0115] In certain embodiments, WR^{W4} and WR^{W5} taken together form an optionally substituted 5-7 membered saturated, unsaturated, or aromatic ring containing 0 heteroatoms. In other embodiments, WR^{W4} and WR^{W5} taken together form an optionally substituted 5-7 membered ring containing 1-3 heteroatoms selected from N, O, or S. In certain other embodiments, WR^{W4} and WR^{W5} taken together form an optionally substituted saturated, unsaturated, or aromatic 5-7 membered ring containing 1 nitrogen heteroatom. In certain other embodiments, WR^{W4} and WR^{W5} taken together form an optionally substituted 5-7 membered ring containing 1 oxygen heteroatom.

[0116] In another embodiment, the present invention provides compounds of formula **V-A-2**:



V-A-2

wherein:

Y is CH_2, C(O)O, C(O), or $S(O)_2$;

m is 0-4; and

X, R^X, W, and R^W are as defined above.

[0117] In one embodiment, compounds of formula **VA-2** have y occurrences of $X\text{-}R^X$, wherein y is 0-4. In one embodiment, y is 0. Or, y is 1. Or, y is 2.

[0118] In one embodiment, Y is C(O). In another embodiment, Y is C(O)O. Or, Y is $S(O)_2$. Or, Y is CH_2.

[0119] In one embodiment, m is 1 or 2. Or, m is 1. Or, m is 0.

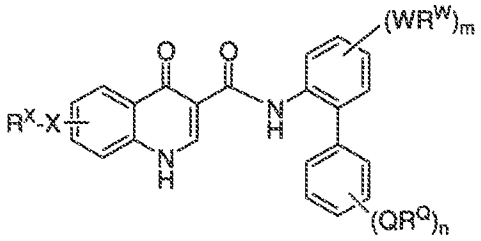
[0120] In one embodiment, W is a bond.

[0121] In another embodiment, R^W is C1-C6 aliphatic, halo, CF_3, or phenyl optionally substituted with C1-C6 alkyl, halo, cyano, or CF_3, wherein up to two methylene units of said C1-C6 aliphatic or C1-C6 alkyl is optionally replaced with –CO-, -CONR'-, $-CO_2-$, -OCO-, $-NR'CO_2-$, -O-, -NR'CONR'-, -OCONR'-, -NR'CO-, -S-, -NR'-, $-SO_2NR'-$, $NR'SO_2-$, or $-NR'SO_2NR'-$. In another embodiment, R' above is C1-C4 alkyl.

Exemplary embodiments of WR^W include methyl, ethyl, propyl, tert-butyl, or 2-ethoxyphenyl.

[0122] In another embodiment, R^W in $Y\text{-}R^W$ is C1-C6 aliphatic optionally substituted with $N(R'')_2$, wherein R" is hydrogen, C1-C6 alkyl, or two R" taken together form a 5-7 membered heterocyclic ring with up to 2 additional heteroatoms selected from O, S, or NR'. Exemplary such heterocyclic rings include pyrrolidinyl, piperidyl, morpholinyl, or thiomorpholinyl.

[0123] In another embodiment, the present invention provides compounds of formula **V-A-3**:



V-A-3

wherein:

Q is W;

R^Q is R^W;

m is 0-4;

n is 0-4; and

X, R^X, W, and R^W are as defined above.

[0124] In one embodiment, compounds of formula **VA-3** have y occurrences of $X\text{-}R^X$, wherein y is 0-4. In one embodiment, y is 0. Or, y is 1. Or, y is 2.

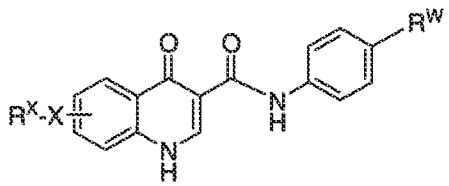
[0125] In one embodiment, n is 0-2.

[0126] In another embodiment, m is 0-2. In one embodiment, m is 0. In one embodiment, m is 1. Or, m is 2.

[0127] In one embodiment, QR^Q taken together is halo, CF_3, OCF_3, CN, C1-C6 aliphatic, O-C1-C6 aliphatic, O-phenyl, NH(C1-C6 aliphatic), or N(C1-C6 aliphatic)$_2$, wherein said aliphatic and phenyl are optionally substituted with up to three substituents selected from C1-C6 alkyl, O-C1-C6 alkyl, halo, cyano, OH, or CF_3, wherein up to two methylene units of said C1-C6 aliphatic or C1-C6 alkyl is optionally replaced with –CO-, -CONR'-, -CO_2-, -OCO-, -NR'CO_2-, -O-, -NR'CONR'-, -OCONR'-, -NR'CO-, -S-, -NR'-, SOR', SO_2R', -SO_2NR'-, NR'SO_2-, or -NR'SO_2NR'-. In another embodiment, R' above is C1-C4 alkyl.

[0128] Exemplary QR^Q include methyl, isopropyl, sec-butyl, hydroxymethyl, CF_3, NMe_2, CN, CH_2CN, fluoro, chloro, OEt, OMe, SMe, OCF_3, OPh, C(O)OMe, C(O)O-iPr, S(O)Me, NHC(O)Me, or S(O)$_2$Me.

[0129] In another embodiment, the present invention provides compounds of formula **V-A-4**:



V-A-4

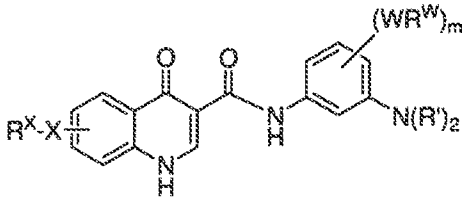
wherein X, R^X, and R^W are as defined above.

[0130] In one embodiment, compounds of formula **VA-4** have y occurrences of X-R^X, wherein y is 0-4. In one embodiment, y is 0. Or, y is 1. Or, y is 2.

[0131] In one embodiment, R^W is C1-C12 aliphatic, C5-C10 cycloaliphatic, or C5-C7 heterocyclic ring, wherein said aliphatic, cycloaliphatic, or heterocyclic ring is optionally substituted with up to three substituents selected from C1-C6 alkyl, halo, cyano, oxo, OH, or CF_3, wherein up to two methylene units of said C1-C6 aliphatic or C1-C6 alkyl is optionally replaced with –CO-, -CONR'-, -CO_2-, -OCO-, -NR'CO_2-, -O-, -NR'CONR'-, -OCONR'-, -NR'CO-, -S-, -NR'-, -SO_2NR'-, NR'SO_2-, or -NR'SO_2NR'-. In another embodiment, R' above is C1-C4 alkyl.

[0132] Exemplary R^W includes methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, t-butyl, n-pentyl, vinyl, cyanomethyl, hydroxymethyl, hydroxyethyl, hydroxybutyl, cyclohexyl, adamantyl, or -C(CH_3)$_2$-NHC(O)O-T, wherein T is C1-C4 alkyl, methoxyethyl, or tetrahydrofuranylmethyl.

[0133] In another embodiment, the present invention provides compounds of formula **V-A-5**:



V-A-5

wherein:

m is 0-4; and

X, R^X, W, R^W, and R' are as defined above.

[0134] In one embodiment, compounds of formula **VA-5** have y occurrences of $X\text{-}R^X$, wherein y is 0-4. In one embodiment, y is 0. Or, y is 1. Or, y is 2.

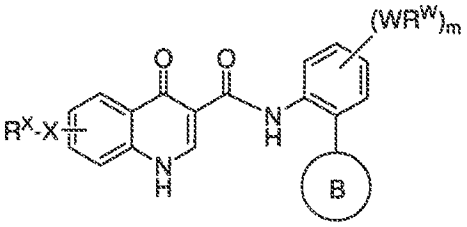
[0135] In one embodiment, m is 0-2. Or, m is 1. Or, m is 2.

[0136] In another embodiment, both R' are hydrogen. Or, one R' is hydrogen and the other R' is C1-C4 alkyl, e.g., methyl. Or, both R' are C1-C4 alkyl, e.g., methyl.

[0137] In another embodiment, m is 1 or 2, and R^W is halo, CF_3, CN, C1-C6 aliphatic, O-C1-C6 aliphatic, or phenyl, wherein said aliphatic and phenyl are optionally substituted with up to three substituents selected from C1-C6 alkyl, O-C1-C6 alkyl, halo, cyano, OH, or CF_3, wherein up to two methylene units of said C1-C6 aliphatic or C1-C6 alkyl is optionally replaced with –CO-, -CONR'-, $-CO_2-$, -OCO-, $-NR'CO_2-$, -O-, -NR'CONR'-, -OCONR'-, -NR'CO-, -S-, -NR'-, $-SO_2NR'-$, $NR'SO_2-$, or $-NR'SO_2NR'-$. In another embodiment, R' above is C1-C4 alkyl.

[0138] Exemplary embodiments of R^W include chloro, CF_3, OCF_3, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, methoxy, ethoxy, propyloxy, or 2-ethoxyphenyl.

[0139] In another embodiment, the present invention provides compounds of formula **V-A-6**:



V-A-6

wherein:

ring B is a 5-7 membered monocyclic or bicyclic, heterocyclic or heteroaryl ring optionally substituted with up to n occurrences of -Q-R^Q, wherein n is 0-4, and Q and R^Q are as defined above; and

Q, R^Q, X, R^X, W, and R^W are as defined above.

[0140] In one embodiment, compounds of formula **VA-6** have y occurrences of X-R^X, wherein y is 0-4. In one embodiment, y is 0. Or, y is 1. Or, y is 2.

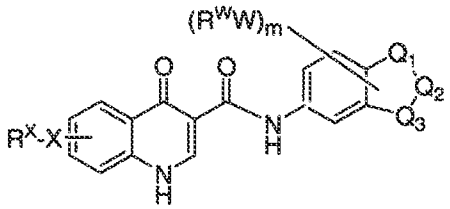
[0141] In one embodiment, m is 0-2. Or, m is 0. Or m is 1.

[0142] In one embodiment, n is 0-2. Or, n is 0. Or, n is 1.

[0143] In another embodiment, ring B is a 5-7 membered monocyclic, heterocyclic ring having up to 2 heteroatoms selected from O, S, or N, optionally substituted with up to n occurrences of -Q-R^Q. Exemplary heterocyclic rings include N-morpholinyl, N-piperidinyl, 4-benzoyl-piperazin-1-yl, pyrrolidin-1-yl, or 4-methyl-piperidin-1-yl.

[0144] In another embodiment, ring B is a 5-6 membered monocyclic, heteroaryl ring having up to 2 heteroatoms selected from O, S, or N, optionally substituted with up to n occurrences of -Q-R^Q. Exemplary such rings include benzimidazol-2-yl, 5-methyl-furan-2-yl, 2,5-dimethyl-pyrrol-1-yl, pyridine-4-yl, indol-5-yl, indol-2-yl, 2,4-dimethoxy-pyrimidin-5-yl, furan-2-yl, furan-3-yl, 2-acyl-thien-2-yl, benzothiophen-2-yl, 4-methyl-thien-2-yl, 5-cyano-thien-2-yl, 3-chloro-5-trifluoromethyl-pyridin-2-yl.

[0145] In another embodiment, the present invention provides compounds of formula **V-B-1**:



V-B-1

wherein:

one of Q_1 and Q_3 is N(WR^W) and the other of Q_1 and Q_3 is selected from O, S, or N(WR^W);

Q_2 is C(O), CH_2-C(O), C(O)-CH_2, CH_2, CH_2-CH_2, CF_2, or CF_2-CF_2;

m is 0-3; and

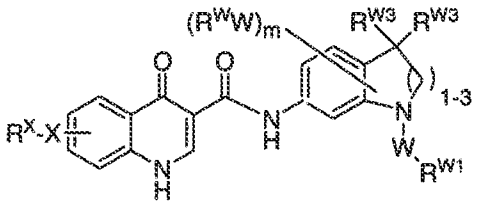
X, W, R^X, and R^W are as defined above.

[0146] In one embodiment, compounds of formula **V-B-1** have y occurrences of X-R^X, wherein y is 0-4. In one embodiment, y is 0. Or, y is 1. Or, y is 2.

[0147] In one embodiment, Q_3 is $N(WR^W)$; exemplary WR^W include hydrogen, C1-C6 aliphatic, C(O)C1-C6 aliphatic, or C(O)OC1-C6 aliphatic.

[0148] In another embodiment, Q_3 is $N(WR^W)$, Q_2 is C(O), CH_2, CH_2-CH_2, and Q_1 is O.

[0149] In another embodiment, the present invention provides compounds of formula **V-B-2**:



V-B-2

wherein:

R^{W1} is hydrogen or C1-C6 aliphatic;

each of R^{W3} is hydrogen or C1-C6 aliphatic; or

both R^{W3} taken together form a C3-C6 cycloalkyl or heterocyclic ring having up to two heteroatoms selected from O, S, or NR', wherein said ring is optionally substituted with up to two WR^W substituents;

m is 0-4; and

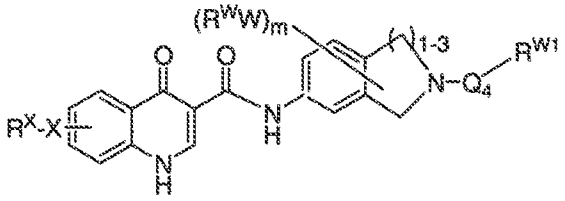
X, R^X, W, and R^W are as defined above.

[0150] In one embodiment, compounds of formula **V-B-2** have y occurrences of $X\text{-}R^X$, wherein y is 0-4. In one embodiment, y is 0. Or, y is 1. Or, y is 2.

[0151] In one embodiment, WR^{W1} is hydrogen, C1-C6 aliphatic, C(O)C1-C6 aliphatic, or C(O)OC1-C6 aliphatic.

[0152] In another embodiment, each R^{W3} is hydrogen, C1-C4 alkyl. Or, both R^{W3} taken together form a C3-C6 cycloaliphatic ring or 5-7 membered heterocyclic ring having up to two heteroatoms selected from O, S, or N, wherein said cycloaliphatic or heterocyclic ring is optionally substituted with up to three substitutents selected from WR^{W1}. Exemplary such rings include cyclopropyl, cyclopentyl, optionally substituted piperidyl, etc.

[0153] In another embodiment, the present invention provides compounds of formula **V-B-3**:



V-B-3

wherein:

Q_4 is a bond, C(O), C(O)O, or $S(O)_2$;

R^{W1} is hydrogen or C1-C6 aliphatic;

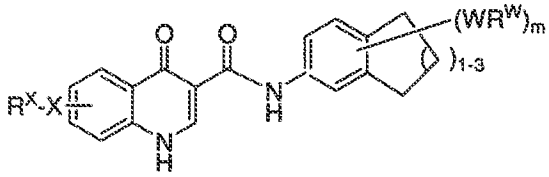
m is 0-4; and

X, W, R^W, and R^X are as defined above.

[0154] In one embodiment, compounds of formula **V-B-3** have y occurrences of $X\text{-}R^X$, wherein y is 0-4. In one embodiment, y is 0.

[0155] In one embodiment, Q_4 is C(O). Or Q_4 is C(O)O. In another embodiment, R^{W1} is C1-C6 alkyl. Exemplary R^{W1} include methyl, ethyl, or t-butyl.

[0156] In another embodiment, the present invention provides compounds of formula **V-B-4**:



V-B-4

wherein:

m is 0-4; and

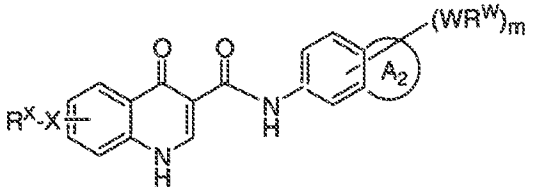
X, R^X, W, and R^W are as defined above.

[0157] In one embodiment, compounds of formula **V-B-4** have y occurrences of $X\text{-}R^X$, wherein y is 0-4. In one embodiment, y is 0. Or, y is 1. Or, y is 2.

[0158] In one embodiment, m is 0-2. Or, m is 0. Or, m is 1.

[0159] In another embodiment, said cycloaliphatic ring is a 5-membered ring. Or, said ring is a six-membered ring.

[0160] In another embodiment, the present invention provides compounds of formula **V-B-5**:



V-B-5

wherein:

ring A_2 is a phenyl or a 5-6 membered heteroaryl ring, wherein ring A_2 and the phenyl ring fused thereto together have up 4 substituents independently selected from WR^W;

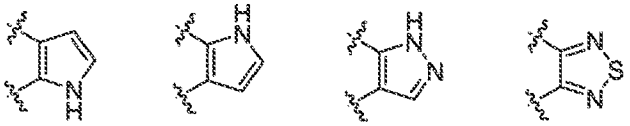
m is 0-4; and

X, W, R^W and R^X are as defined above.

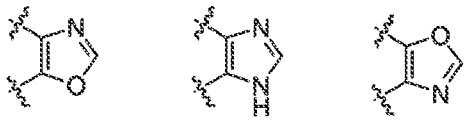
[0161] In one embodiment, compounds of formula **V-B-5** have y occurrences of $X\text{-}R^X$, wherein y is 0-4. In one embodiment, y is 0. Or, y is 1. Or, y is 2.

[0162] In one embodiment, ring A_2 is an optionally substituted 5-membered ring selected from pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, or triazolyl.

[0163] In one embodiment, ring A_2 is an optionally substituted 5-membered ring selected from pyrrolyl, pyrazolyl, thiadiazolyl, imidazolyl, oxazolyl, or triazolyl. Exemplary such rings include:



aa **bb** **cc** **dd**



ee **ff** **gg;**

wherein said ring is optionally substituted as set forth above.

[0164] In another embodiment, ring A_2 is an optionally substituted 6-membered ring. Exemplary such rings include pyridyl, pyrazinyl, or triazinyl. In another embodiment, said ring is an optionally pyridyl.

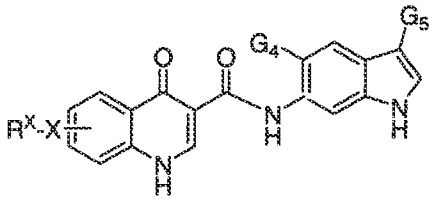
[0165] In one embodiment, ring A_2 is phenyl.

[0166] In another embodiment, ring A_2 is pyrrolyl, pyrazolyl, pyridyl, or thiadiazolyl.

[0167] Examplary W in formula **V-B-5** includes a bond, C(O), C(O)O or C1-C6 alkylene.

[0168] Exemplary R^W in formula **V-B-5** include cyano, halo, C1-C6 aliphatic, C3-C6 cycloaliphatic, aryl, 5-7 membered heterocyclic ring having up to two heteroatoms selected from O, S, or N, wherein said aliphatic, phenyl, and heterocyclic are independently and optionally substituted with up to three substituents selected from C1-C6 alkyl, O-C1-C6 alkyl, halo, cyano, OH, or CF_3, wherein up to two methylene units of said C1-C6 aliphatic or C1-C6 alkyl is optionally replaced with –CO-, -CONR'-, -CO_2-, -OCO-, -NR'CO_2-, -O-, -NR'CONR'-, -OCONR'-, -NR'CO-, -S-, -NR'-, -SO_2NR'-, NR'SO_2-, or -NR'SO_2NR'-. In another embodiment, R' above is C1-C4 alkyl.

[0169] In one embodiment, the present invention provides compounds of formula **V-B-5-a**:



V-B-5-a

wherein:

G_4 is hydrogen, halo, CN, CF_3, CHF_2, CH_2F, optionally substituted C1-C6 aliphatic, aryl-C1-C6 alkyl, or a phenyl, wherein G_4 is optionally substituted with up to 4 WR^W substituents; wherein up to two methylene units of said C1-C6 aliphatic or C1-C6 alkyl is optionally replaced with -CO-, -CONR'-, -CO_2-, -OCO-, -NR'CO_2-, -O-, -NR'CONR'-, -OCONR'-, -NR'CO-, -S-, -NR'-, -SO_2NR'-, NR'SO_2-, or -NR'SO_2NR'-. ;

G_5 is hydrogen or an optionally substituted C1-C6 aliphatic;

wherein said indole ring system is further optionally substituted with up to 3 substituents independently selected from WR^W.

[0170] In one embodiment, compounds of formula **V-B-5-a** have y occurrences of X-R^X, wherein y is 0-4. In one embodiment, y is 0. Or, y is 1. Or, y is 2.

[0171] In one embodiment, G_4 is hydrogen. Or, G_5 is hydrogen.

[0172] In another embodiment, G_4 is hydrogen, and G_5 is C1-C6 aliphatic, wherein said aliphatic is optionally substituted with C1-C6 alkyl, halo, cyano, or CF_3, and wherein up to two methylene units of said C1-C6 aliphatic or C1-C6 alkyl is optionally replaced with -CO-, -CONR'-, -CO_2-, -OCO-, -NR'CO_2-, -O-, -NR'CONR'-, -OCONR'-, -NR'CO-, -S-, -NR'-, -SO_2NR'-, NR'SO_2-, or -NR'SO_2NR'-. In another embodiment, R' above is C1-C4 alkyl.

[0173] In another embodiment, G_4 is hydrogen, and G_5 is cyano, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl, cyanomethyl, methoxyethyl, $CH_2C(O)OMe$, $(CH_2)_2$-NHC(O)O-*tert*-butyl, or cyclopentyl.

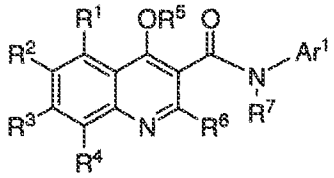
[0174] In another embodiment, G_5 is hydrogen, and G_4 is halo, C1-C6 aliphatic or phenyl, wherein said aliphatic or phenyl is optionally substituted with C1-C6 alkyl, halo, cyano, or CF_3, wherein up to two methylene units of said C1-C6 aliphatic or C1-C6 alkyl is optionally replaced with –CO-, -CONR'-, $-CO_2-$, -OCO-, $-NR'CO_2-$, -O-, -NR'CONR'-, -OCONR'-, -NR'CO-, -S-, -NR'-, $-SO_2NR'-$, $NR'SO_2-$, or $-NR'SO_2NR'-$. In another embodiment, R' above is C1-C4 alkyl.

[0175] In another embodiment, G_5 is hydrogen, and G_4 is halo, CF_3, ethoxycarbonyl, t-butyl, 2-methoxyphenyl, 2-ethoxyphenyl, (4-$C(O)NH(CH_2)_2$-NMe_2)-phenyl, 2-methoxy-4-chloro-phenyl, pyridine-3-yl, 4-isopropylphenyl, 2,6-dimethoxyphenyl, sec-butylaminocarbonyl, ethyl, t-butyl, or piperidin-1-ylcarbonyl.

[0176] In another embodiment, G_4 and G_5 are both hydrogen, and the nitrogen ring atom of said indole ring is substituted with C1-C6 aliphatic, C(O)(C1-C6 aliphatic), or benzyl, wherein said aliphatic or benzyl is optionally substituted with C1-C6 alkyl, halo, cyano, or CF_3, wherein up to two methylene units of said C1-C6 aliphatic or C1-C6 alkyl is optionally replaced with –CO-, -CONR'-, $-CO_2-$, -OCO-, $-NR'CO_2-$, -O-, -NR'CONR'-, -OCONR'-, -NR'CO-, -S-, -NR'-, $-SO_2NR'-$, $NR'SO_2-$, or $-NR'SO_2NR'-$. In another embodiment, R' above is C1-C4 alkyl.

[0177] In another embodiment, G_4 and G_5 are both hydrogen, and the nitrogen ring atom of said indole ring is substituted with acyl, benzyl, $C(O)CH_2N(Me)C(O)CH_2NHMe$, or ethoxycarbonyl.

[0178] In another embodiment, the present invention provides compounds of formula I':



I'

or pharmaceutically acceptable salts thereof,

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, and Ar^1 is as defined above for compounds of formula I'.

[0179] In one embodiment, each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, and Ar^1 in compounds of formula I' is independently as defined above for any of the embodiments of compounds of formula I.

[0180] Representative compounds of the present invention are set forth below in Table 1 below.

[0181] Table 1

Cmpd No.	Name
1	N-[5-(5-chloro-2-methoxy-phenyl)-1H-indol-6-yl]-4-oxo-1H-quinoline-3-carboxamide
2	N-(3-methoxy-4-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
3	N-[2-(2-methoxyphenoxy)-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
4	N-(2-morpholinophenyl)-4-oxo-1H-quinoline-3-carboxamide
5	N-[4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
6	N-[3-(hydroxymethyl)-4-*tert*-butyl-phenyl]-4-oxo-1H-quinoline-3-carboxamide
7	N-(4-benzoylamino-2,5-diethoxy-phenyl)-4-oxo-1H-quinoline-3-carboxamide
8	N-(3-amino-4-ethyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
9	4-oxo-N-(3-sulfamoylphenyl)-1H-quinoline-3-carboxamide
10	1,4-dihydro-N-(2,3,4,5-tetrahydro-1H-benzo[b]azepin-8-yl)-4-oxoquinoline-3-carboxamide
11	4-oxo-N-[2-[2-(trifluoromethyl)phenyl]phenyl]-1H-quinoline-3-carboxamide
12	N-[2-(4-dimethylaminophenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
13	N-(3-cyano-4-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
14	[5-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-2-*tert*-butyl-phenyl]aminoformic acid methyl ester
15	N-(2-methoxy-3-pyridyl)-4-oxo-1H-quinoline-3-carboxamide
16	4-oxo-N-(2-propylphenyl)-1H-quinoline-3-carboxamide
17	N-(5-amino-2-propoxy-phenyl)-4-oxo-1H-quinoline-3-carboxamide
18	N-(9H-fluoren-1-yl)-4-oxo-1H-quinoline-3-carboxamide
19	4-oxo-N-(2-quinolyl)-1H-quinoline-3-carboxamide
20	N-[2-(2-methylphenoxy)phenyl]-4-oxo-1H-quinoline-3-carboxamide
21	4-oxo-N-[4-(2-pyridylsulfamoyl)phenyl]-1H-quinoline-3-carboxamide

22	4-Oxo-1,4-dihydro-quinoline-3-carboxylic acid N-(1',2'-dihydrospiro[cyclopropane-1,3'-[3H]indol]-6'-yl)-amide
23	N-[2-(2-ethoxyphenyl)-5-hydroxy-4-*tert*-butyl-phenyl]-4-oxo-1H-quinoline-3-carboxamide
24	4-oxo-N-(3-pyrrolidin-1-ylsulfonylphenyl)-1H-quinoline-3-carboxamide
25	N-[2-(3-acetylaminophenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
26	4-oxo-N-[2-(1-piperidyl)phenyl]-1H-quinoline-3-carboxamide
27	N-[1-[2-[methyl-(2-methylaminoacetyl)-amino]acetyl]-1H-indol-6-yl]-4-oxo-1H-quinoline-3-carboxamide
28	[2-methyl-2-[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]-propyl]aminoformic acid 2-methoxyethyl ester
29	1-isopropyl-4-oxo-N-phenyl-1H-quinoline-3-carboxamide
30	[2-isopropyl-5-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]aminoformic acid methyl ester
31	4-oxo-N-(p-tolyl)-1H-quinoline-3-carboxamide
32	N-(5-chloro-1H-indol-6-yl)-4-oxo-1H-quinoline-3-carboxamide
33	N-(1H-indol-6-yl)-4-oxo-1H-quinoline-3-carboxamide
34	N-[4-(1,1-diethylpropyl)-2-fluoro-5-hydroxy-phenyl]-4-hydroxy-quinoline-3-carboxamide
35	1,4-dihydro-N-(2,3,4,5-tetrahydro-5,5-dimethyl-1H-benzo[b]azepin-8-yl)-4-oxoquinoline-3-carboxamide
36	N-(2-isopropylphenyl)-4-oxo-1H-quinoline-3-carboxamide
37	N-(1H-indol-7-yl)-4-oxo-1H-quinoline-3-carboxamide
38	N-[2-(1H-indol-2-yl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
39	[3-[(2,4-dimethoxy-3-quinolyl)carbonylamino]-4-*tert*-butyl-phenyl]aminoformic acid tert-butyl ester
40	N-[2-(2-hydroxyethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
41	N-(5-amino-2-propyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
42	N-[2-[[3-chloro-5-(trifluoromethyl)-2-pyridyl]oxy]phenyl]-4-oxo-1H-quinoline-3-carboxamide
43	N-[2-(3-ethoxyphenyl)-5-hydroxy-4-*tert*-butyl-phenyl]-4-oxo-1H-quinoline-3-carboxamide
44	N-(2-methylbenzothiazol-5-yl)-4-oxo-1H-quinoline-3-carboxamide
45	N-(2-cyano-3-fluoro-phenyl)-4-oxo-1H-quinoline-3-carboxamide
46	N-[3-chloro-5-(2-morpholinoethylsulfonylamino)phenyl]-4-oxo-1H-quinoline-3-carboxamide
47	N-[4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
48	N-(5-chloro-2-fluoro-phenyl)-4-oxo-1H-quinoline-3-carboxamide

49	N-[2-(2,6-dimethoxyphenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
50	4-oxo-N-(2,4,6-trimethylphenyl)-1H-quinoline-3-carboxamide
51	6-[(4-methyl-1-piperidyl)sulfonyl]-4-oxo-N-(5-*tert*-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
52	N-[2-(m-tolyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
53	4-oxo-N-(4-pyridyl)-1H-quinoline-3-carboxamide
54	4-oxo-N-(8-thia-7,9-diazabicyclo[4.3.0]nona-2,4,6,9-tetraen-5-yl)-1H-quinoline-3-carboxamide
55	N-(3-amino-2-methoxy-5-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
56	1,4-dihydro-N-(1,2,3,4-tetrahydro-6-hydroxynaphthalen-7-yl)-4-oxoquinoline-3-carboxamide
57	N-[4-(3-ethyl-2,6-dioxo-3-piperidyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
58	N-[3-amino-4-(trifluoromethoxy)phenyl]-4-oxo-1H-quinoline-3-carboxamide
59	N-[2-(5-isopropyl-2-methoxy-phenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
60	[4-isopropyl-3-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]aminoformic acid tert-butyl ester
61	N-(2,3-dimethylphenyl)-4-oxo-1H-quinoline-3-carboxamide
62	4-oxo-N-[3-(trifluoromethoxy)phenyl]-1H-quinoline-3-carboxamide
63	N-[2-(2,4-difluorophenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
64	4-oxo-N-(2-oxo-1,3-dihydrobenzoimidazol-5-yl)-1H-quinoline-3-carboxamide
65	4-oxo-N-[5-(3-pyridyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide
66	N-(2,2-difluorobenzo[1,3]dioxol-5-yl)-4-oxo-1H-quinoline-3-carboxamide
67	6-ethyl-4-hydroxy-N-(1H-indol-6-yl)quinoline-3-carboxamide
68	3-[2-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]benzoic acid methyl ester
69	N-(3-amino-4-isopropyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
70	4-oxo-N-[2-(4-pyridyl)phenyl]-1H-quinoline-3-carboxamide
71	3-[2-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]benzoic acid isopropyl ester
72	N-(2-ethylphenyl)-4-oxo-1H-quinoline-3-carboxamide
73	4-oxo-N-(2-phenyl-3H-benzoimidazol-5-yl)-1H-quinoline-3-carboxamide
74	4-oxo-N-[5-(trifluoromethyl)-2-pyridyl]-1H-quinoline-3-carboxamide
75	4-oxo-N-(3-quinolyl)-1H-quinoline-3-carboxamide

76	N-[2-(3,4-difluorophenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
77	N-(5-fluoro-1H-indol-6-yl)-4-oxo-1H-quinoline-3-carboxamide
78	4-oxo-N-(2-sulfamoylphenyl)-1H-quinoline-3-carboxamide
79	N-[2-(4-fluoro-3-methyl-phenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
80	N-(2-methoxyphenyl)-4-oxo-1H-quinoline-3-carboxamide
81	4-oxo-N-(3-propionylaminophenyl)-1H-quinoline-3-carboxamide
82	N-(4-diethylamino-2-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
83	N-[2-(3-cyanophenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
84	N-(4-methyl-2-pyridyl)-4-oxo-1H-quinoline-3-carboxamide
85	N-[2-(3,4-dichlorophenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
86	N-[4-[2-(aminomethyl)phenyl]phenyl]-4-oxo-1H-quinoline-3-carboxamide
87	4-oxo-N-(3-phenoxyphenyl)-1H-quinoline-3-carboxamide
88	[2-methyl-2-[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]-propyl]aminoformic acid tert-butyl ester
89	N-(2-cyano-5-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
90	4-oxo-N-(2-*tert*-butylphenyl)-1H-quinoline-3-carboxamide
91	N-(3-chloro-2,6-diethyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
92	N-[2-fluoro-5-hydroxy-4-(1-methylcyclohexyl)-phenyl]-4-oxo-1H-quinoline-3-carboxamide
93	N-[2-(5-cyano-2-thienyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
94	N-(5-amino-2-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
95	N-(2-cyanophenyl)-4-oxo-1H-quinoline-3-carboxamide
96	N-[3-(cyanomethyl)-1H-indol-6-yl]-4-oxo-1H-quinoline-3-carboxamide
97	N-[2-(2,4-dimethoxypyrimidin-5-yl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
98	N-(5-dimethylamino-2-propyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
99	4-oxo-N-(4-pentylphenyl)-1H-quinoline-3-carboxamide
100	N-(1H-indol-4-yl)-4-oxo-1H-quinoline-3-carboxamide
101	N-(5-amino-2-isopropyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
102	N-[2-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]phenyl]-4-oxo-1H-quinoline-3-carboxamide

103	6-fluoro-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
104	N-(2-methyl-1H-indol-6-yl)-4-oxo-1H-quinoline-3-carboxamide
105	1,4-dihydro-N-(3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-4-oxoquinoline-3-carboxamide
106	N-(2-cyano-4,5-dimethoxy-phenyl)-4-oxo-1H-quinoline-3-carboxamide
107	7-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-1,2,3,4-tetrahydroisoquinoline-2-carboxylic acid tert-butyl ester
108	4,4-dimethyl-7-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-1,2,3,4-tetrahydroquinoline-1-carboxylic acid tert-butyl ester
109	N-(1-acetyl-2,3,4,5-tetrahydro-5,5-dimethyl-1H-benzo[b]azepin-8-yl)-1,4-dihydro-4-oxoquinoline-3-carboxamide
110	N-[4-(cyanomethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
111	4-oxo-N-[2-(trifluoromethyl)phenyl]-1H-quinoline-3-carboxamide
112	6-ethoxy-4-hydroxy-N-(1H-indol-6-yl)quinoline-3-carboxamide
113	N-(3-methyl-1H-indol-6-yl)-4-oxo-1H-quinoline-3-carboxamide
114	[4-(2-ethoxyphenyl)-3-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]aminoformic acid tert-butyl ester
115	N-[2-(2-furyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
116	5-hydroxy-N-(1H-indol-6-yl)-4-oxo-1H-quinoline-3-carboxamide
117	N-(3-dimethylamino-4-isopropyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
118	N-[2-(1H-indol-5-yl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
119	[2-methyl-2-[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]-propyl]aminoformic acid ethyl ester
120	N-(2-methoxy-5-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
121	N-(3,4-dichlorophenyl)-4-oxo-1H-quinoline-3-carboxamide
122	N-(3,4-dimethoxyphenyl)-4-oxo-1H-quinoline-3-carboxamide
123	N-[2-(3-furyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
124	6-fluoro-4-oxo-N-(5-*tert*-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
125	N-(6-ethyl-2-pyridyl)-4-oxo-1H-quinoline-3-carboxamide
126	N-[3-hydroxy-4-[2-(2-methoxyethoxy)-1,1-dimethyl-ethyl]-phenyl]-4-oxo-1H-quinoline-3-carboxamide
127	[5-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-2-*tert*-butyl-phenyl]aminoformic acid ethyl ester
128	1,6-dimethyl-4-oxo-N-(2-phenylphenyl)-1H-quinoline-3-carboxamide
129	[2-ethyl-5-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]aminoformic acid methyl ester

130	4-hydroxy-N-(1H-indol-6-yl)-5,7-bis(trifluoromethyl)quinoline-3-carboxamide
131	N-(3-amino-5-chloro-phenyl)-4-oxo-1H-quinoline-3-carboxamide
132	N-(5-acetylamino-2-ethoxy-phenyl)-4-oxo-1H-quinoline-3-carboxamide
133	N-[3-chloro-5-[2-(1-piperidyl)ethylsulfonylamino]phenyl]-4-oxo-1H-quinoline-3-carboxamide
134	N-[2-(4-methylsulfinylphenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
135	N-(2-benzo[1,3]dioxol-5-ylphenyl)-4-oxo-1H-quinoline-3-carboxamide
136	N-(2-hydroxy-3,5-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
137	6-[(4-fluorophenyl)-methyl-sulfamoyl]-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
138	N-[2-(3,5-difluorophenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
139	N-[2-(2,4-dichlorophenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
140	N-(4-cyclohexylphenyl)-4-oxo-1H-quinoline-3-carboxamide
141	[2-methyl-5-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]aminoformic acid ethyl ester
142	4-oxo-N-(2-sec-butylphenyl)-1H-quinoline-3-carboxamide
143	N-(2-fluoro-5-hydroxy-4-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
144	N-(3-hydroxyphenyl)-4-oxo-1H-quinoline-3-carboxamide
145	6-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-1H-indole-4-carboxylic acid ethyl ester
146	4-oxo-N-(1,7,9-triazabicyclo[4.3.0]nona-2,4,6,8-tetraen-5-yl)-1H-quinoline-3-carboxamide
147	N-[2-(4-fluorophenoxy)-3-pyridyl]-4-oxo-1H-quinoline-3-carboxamide
148	4-oxo-N-[5-(1-piperidylcarbonyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide
149	N-(3-acetylamino-4-ethyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
150	4-oxo-N-[4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]-1H-quinoline-3-carboxamide
151	N-[2-(4-methyl-2-thienyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
152	4-oxo-N-(2-oxo-3H-benzooxazol-6-yl)-1H-quinoline-3-carboxamide
153	N-[4-(1,1-diethyl-2,2-dimethyl-propyl)-2-fluoro-5-hydroxy-phenyl]-4-hydroxy-quinoline-3-carboxamide
154	N-[3,5-bis(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
155	4-oxo-N-(2-pyridyl)-1H-quinoline-3-carboxamide
156	4-oxo-N-[2-[2-(trifluoromethoxy)phenyl]phenyl]-1H-quinoline-3-carboxamide

157	N-(2-ethyl-5-methylamino-phenyl)-4-oxo-1H-quinoline-3-carboxamide
158	4-oxo-N-(5-phenyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
159	[7-[(4-oxo-1H-quinolin-3-yl)carbonylamino]tetralin-1-yl]aminoformic acid methyl ester
160	N-(3-amino-4-propyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
161	N-[3-(2-ethoxyethoxy)-4-*tert*-butyl-phenyl]-4-oxo-1H-quinoline-3-carboxamide
162	N-(6-methoxy-3-pyridyl)-4-oxo-1H-quinoline-3-carboxamide
163	N-[5-(aminomethyl)-2-(2-ethoxyphenyl)-phenyl]-4-oxo-1H-quinoline-3-carboxamide
164	4-oxo-N-[3-(trifluoromethyl)phenyl]-1H-quinoline-3-carboxamide
165	4-oxo-N-(4-sulfamoylphenyl)-1H-quinoline-3-carboxamide
166	4-[2-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]benzoic acid methyl ester
167	N-(3-amino-4-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
168	4-oxo-N-(3-pyridyl)-1H-quinoline-3-carboxamide
169	N-(1-methyl-1H-indol-6-yl)-4-oxo-1H-quinoline-3-carboxamide
170	N-(5-chloro-2-pyridyl)-4-oxo-1H-quinoline-3-carboxamide
171	N-[2-(2,3-dichlorophenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
172	N-(2-(benzo[b]thiophen-2-yl)phenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide
173	N-(6-methyl-2-pyridyl)-4-oxo-1H-quinoline-3-carboxamide
174	N-[2-(5-acetyl-2-thienyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
175	4-Oxo-1,4-dihydro-quinoline-3-carboxylic acid N-(1'-Acetyl-1',2'-dihydrospiro[cyclopropane-1,3'-3H-indol]-6'-yl)-amide
176	4-oxo-N-[4-(trifluoromethoxy)phenyl]-1H-quinoline-3-carboxamide
177	N-(2-butoxyphenyl)-4-oxo-1H-quinoline-3-carboxamide
178	4-oxo-N-[2-(2-*tert*-butylphenoxy)phenyl]-1H-quinoline-3-carboxamide
179	N-(3-carbamoylphenyl)-4-oxo-1H-quinoline-3-carboxamide
180	N-(2-ethyl-6-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
181	4-oxo-N-[2-(p-tolyl)phenyl]-1H-quinoline-3-carboxamide
182	N-[2-(4-fluorophenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
183	7-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-1,2,3,4-tetrahydroquinoline-1-carboxylic acid tert-butyl ester

184	N-(1H-indol-6-yl)-4-oxo-2-(trifluoromethyl)-1H-quinoline-3-carboxamide
185	N-(3-morpholinosulfonylphenyl)-4-oxo-1H-quinoline-3-carboxamide
186	N-(3-cyclopentyl-1H-indol-6-yl)-4-oxo-1H-quinoline-3-carboxamide
187	N-(1-acetyl-1H-indol-6-yl)-4-oxo-1H-quinoline-3-carboxamide
188	6-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-1H-indole-5-carboxylic acid ethyl ester
189	N-(4-benzyloxyphenyl)-4-oxo-1H-quinoline-3-carboxamide
190	N-[2-(3-chloro-4-fluoro-phenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
191	4-oxo-N-(5-quinolyl)-1H-quinoline-3-carboxamide
192	N-(3-methyl-2-pyridyl)-4-oxo-1H-quinoline-3-carboxamide
193	N-(2,6-dimethoxy-3-pyridyl)-4-oxo-1H-quinoline-3-carboxamide
194	N-(4-cyanophenyl)-4-oxo-1H-quinoline-3-carboxamide
195	N-(5-methyl-2-pyridyl)-4-oxo-1H-quinoline-3-carboxamide
196	N-[5-(3,3-dimethylbutanoylamino)-2-*tert*-butyl-phenyl]-4-oxo-1H-quinoline-3-carboxamide
197	4-oxo-N-[6-(trifluoromethyl)-3-pyridyl]-1H-quinoline-3-carboxamide
198	N-(4-fluorophenyl)-4-oxo-1H-quinoline-3-carboxamide
199	N-[2-(o-tolyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
200	1,4-dihydro-N-(1,2,3,4-tetrahydro-1-hydroxynaphthalen-7-yl)-4-oxoquinoline-3-carboxamide
201	N-(2-cyano-3-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
202	N-[2-(5-chloro-2-methoxy-phenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
203	N-(1-benzyl-1H-indol-6-yl)-4-oxo-1H-quinoline-3-carboxamide
204	N-(4,4-dimethylchroman-7-yl)-4-oxo-1H-quinoline-3-carboxamide
205	N-[2-(4-methoxyphenoxy)-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
206	N-[2-(2,3-dimethylphenoxy)-3-pyridyl]-4-oxo-1H-quinoline-3-carboxamide
207	2-[6-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-1H-indol-3-yl]acetic acid ethyl ester
208	N-[4-(2-adamantyl)-5-hydroxy-2-methyl-phenyl]-4-oxo-1H-quinoline-3-carboxamide
209	N-[4-(hydroxymethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
210	2,4-dimethoxy-N-(2-phenylphenyl)-quinoline-3-carboxamide

211	N-(2-methoxy-5-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
212	N-[3-(3-methyl-5-oxo-1,4-dihydropyrazol-1-yl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
213	N-[2-(2,5-dichlorophenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
214	N-(3-methylsulfonylaminophenyl)-4-oxo-1H-quinoline-3-carboxamide
215	4-oxo-N-phenyl-1H-quinoline-3-carboxamide
216	N-(3H-benzoimidazol-2-yl)-4-oxo-1H-quinoline-3-carboxamide
217	N-(1H-indazol-5-yl)-4-oxo-1H-quinoline-3-carboxamide
218	6-fluoro-N-[2-fluoro-5-hydroxy-4-(1-methylcyclohexyl)-phenyl]-4-oxo-1H-quinoline-3-carboxamide
219	4-oxo-N-pyrazin-2-yl-1H-quinoline-3-carboxamide
220	N-(2,3-dihydroxy-4,6-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
221	[5-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-2-propyl-phenyl]aminoformic acid methyl ester
222	N-(3-chloro-2-cyano-phenyl)-4-oxo-1H-quinoline-3-carboxamide
223	N-[2-(4-methylsulfanylphenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
224	4-oxo-N-[4-[2-[(2,2,2-trifluoroacetyl)aminomethyl]phenyl]phenyl]-1H-quinoline-3-carboxamide
225	[2-isopropyl-5-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]aminoformic acid ethyl ester
226	4-oxo-N-(4-propylphenyl)-1H-quinoline-3-carboxamide
227	N-[2-(3H-benzoimidazol-2-yl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
228	N-[2-(hydroxy-phenyl-methyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
229	N-(2-methylsulfanylphenyl)-4-oxo-1H-quinoline-3-carboxamide
230	N-(2-methyl-1H-indol-5-yl)-4-oxo-1H-quinoline-3-carboxamide
231	3-[4-hydroxy-2-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-5-*tert*-butyl-phenyl]benzoic acid methyl ester
232	N-(5-acetylamino-2-propyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
233	N-(1-acetylindolin-6-yl)-4-oxo-1H-quinoline-3-carboxamide
234	4-oxo-N-[5-(trifluoromethyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide
235	N-(6-isopropyl-3-pyridyl)-4-oxo-1H-quinoline-3-carboxamide
236	4-oxo-N-[4-(trifluoromethyl)phenyl]-1H-quinoline-3-carboxamide
237	N-[5-(2-methoxyphenyl)-1H-indol-6-yl]-4-oxo-1H-quinoline-3-carboxamide

238	7'-[(4-oxo-1H-quinolin-3-ylcarbonyl)amino]-spiro[piperidine-4,4'(1'H)-quinoline], 2',3'-dihydro-carboxylic acid tert-butyl ester
239	[4-isopropyl-3-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]aminoformic acid methyl ester
240	N-(2-benzyloxyphenyl)-4-oxo-1H-quinoline-3-carboxamide
241	4-oxo-N-(8-quinolyl)-1H-quinoline-3-carboxamide
242	N-(5-amino-2,4-dichloro-phenyl)-4-oxo-1H-quinoline-3-carboxamide
243	N-(5-acetylamino-2-isopropyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
244	4-oxo-N-(6,7,8,9-tetrahydro-5H-carbazol-2-yl)-1H-quinoline-3-carboxamide
245	N-[2-(2,4-dichlorophenoxy)phenyl]-4-oxo-1H-quinoline-3-carboxamide
246	N-(3,4-dimethylphenyl)-4-oxo-1H-quinoline-3-carboxamide
247	4-oxo-N-[2-(2-phenoxyphenyl)phenyl]-1H-quinoline-3-carboxamide
248	N-(3-acetylamino-4-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
249	[4-ethyl-3-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]aminoformic acid methyl ester
250	N-(5-acetylamino-2-methoxy-phenyl)-4-oxo-1H-quinoline-3-carboxamide
251	[2-methyl-2-[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]-propyl]aminoformic acid isobutyl ester
252	N-(2-benzoylphenyl)-4-oxo-1H-quinoline-3-carboxamide
253	4-oxo-N-[2-[3-(trifluoromethoxy)phenyl]phenyl]-1H-quinoline-3-carboxamide
254	6-fluoro-N-(5-fluoro-1H-indol-6-yl)-4-oxo-1H-quinoline-3-carboxamide
255	N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-6-pyrrolidin-1-ylsulfonyl-1H-quinoline-3-carboxamide
256	N-(1H-benzotriazol-5-yl)-4-oxo-1H-quinoline-3-carboxamide
257	N-(4-fluoro-3-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
258	N-indolin-6-yl-4-oxo-1H-quinoline-3-carboxamide
259	4-oxo-N-(3-sec-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
260	N-(5-amino-2-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
261	N-[2-(3,4-dimethylphenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
262	1,4-dihydro-N-(3,4-dihydro-3-oxo-2H-benzo[b][1,4]thiazin-6-yl)-4-oxoquinoline-3-carboxamide
263	N-(4-bromo-2-ethyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
264	N-(2,5-diethoxyphenyl)-4-oxo-1H-quinoline-3-carboxamide

265	N-(2-benzylphenyl)-4-oxo-1H-quinoline-3-carboxamide
266	N-[5-hydroxy-4-*tert*-butyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
267	4-oxo-N-(4-phenoxyphenyl)-1H-quinoline-3-carboxamide
268	4-oxo-N-(3-sulfamoyl-4-*tert*-butyl-phenyl)-1H-quinoline-3-carboxamide
269	[4-isopropyl-3-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]aminoformic acid ethyl ester
270	N-(2-cyano-1H-indol-6-yl)-4-oxo-1H-quinoline-3-carboxamide
271	N-(3-amino-4-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
272	N-[3-(2-morpholinoethylsulfonylamino)-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
273	[7-[(4-oxo-1H-quinolin-3-yl)carbonylamino]tetralin-1-yl]aminoformic acid tert-butyl ester
274	4-oxo-6-pyrrolidin-1-ylsulfonyl-N-(5-*tert*-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
275	4-benzyloxy-N-(3-hydroxy-4-*tert*-butyl-phenyl)-quinoline-3-carboxamide
276	N-(4-morpholinosulfonylphenyl)-4-oxo-1H-quinoline-3-carboxamide
277	N-[2-(3-fluorophenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
278	4-oxo-N-[2-[3-(trifluoromethyl)phenyl]phenyl]-1H-quinoline-3-carboxamide
279	N-[2-(2-methylsulfanylphenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
280	4-oxo-N-(6-quinolyl)-1H-quinoline-3-carboxamide
281	N-(2,4-dimethylphenyl)-4-oxo-1H-quinoline-3-carboxamide
282	N-(5-amino-2-ethyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
283	N-[2-(3-methoxyphenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
284	N-(1H-indazol-6-yl)-4-oxo-1H-quinoline-3-carboxamide
285	N-[2-(2,3-difluorophenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
286	1,4-dihydro-N-(1,2,3,4-tetrahydronaphthalen-5-yl)-4-oxoquinoline-3-carboxamide
287	N-[2-fluoro-5-hydroxy-4-(1-methylcyclohexyl)-phenyl]-5-hydroxy-4-oxo-1H-quinoline-3-carboxamide
288	N-(5-fluoro-2-methoxycarbonyloxy-3-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
289	N-(2-fluoro-4-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
290	N-[2-(3-isopropylphenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
291	N-(2-chloro-5-hydroxy-4-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide

292	N-(5-chloro-2-phenoxy-phenyl)-4-oxo-1H-quinoline-3-carboxamide
293	4-oxo-N-[2-(1H-pyrrol-1-yl)phenyl]-1H-quinoline-3-carboxamide
294	N-(1H-indol-5-yl)-4-oxo-1H-quinoline-3-carboxamide
295	4-oxo-N-(2-pyrrolidin-1-ylphenyl)-1H-quinoline-3-carboxamide
296	2,4-dimethoxy-N-(2-*tert*-butylphenyl)-quinoline-3-carboxamide
297	N-[2-(2,5-dimethyl-1H-pyrrol-1-yl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
298	[2-ethyl-5-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]aminoformic acid ethyl ester
299	4-oxo-N-(1,2,3,4-tetrahydroquinolin-7-yl)-1H-quinoline-3-carboxamide
300	N-(4,4-dimethyl-1,2,3,4-tetrahydroquinolin-7-yl)-4-oxo-1H-quinoline-3-carboxamide
301	N-[4-(4-methyl-4H-1,2,4-triazol-3-yl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
302	N-[2-[4-(hydroxymethyl)phenyl]phenyl]-4-oxo-1H-quinoline-3-carboxamide
303	N-(2-acetyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-oxo-1H-quinoline-3-carboxamide
304	[4-(2-ethoxyphenyl)-3-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenylmethyl]aminoformic acid tert-butyl ester
305	N-[2-(4-methoxyphenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
306	N-[2-(3-ethoxyphenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
307	N-[2-(3-chlorophenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
308	N-[2-(cyanomethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
309	N-(3-isoquinolyl)-4-oxo-1H-quinoline-3-carboxamide
310	4-oxo-N-(4-sec-butylphenyl)-1H-quinoline-3-carboxamide
311	N-[2-(5-methyl-2-furyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
312	N-[2-(2,4-dimethoxyphenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
313	N-[2-(2-fluorophenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
314	N-(2-ethyl-6-isopropyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
315	N-(2,6-dimethylphenyl)-4-oxo-1H-quinoline-3-carboxamide
316	N-(5-acetylamino-2-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
317	N-(2,6-dichlorophenyl)-4-oxo-1H-quinoline-3-carboxamide
318	4-oxo-N-[3-[2-(1-piperidyl)ethylsulfonylamino]-5-(trifluoromethyl)phenyl]-1H-quinoline-3-carboxamide

319	6-fluoro-N-(2-fluoro-5-hydroxy-4-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
320	4-oxo-N-(2-*tert*-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
321	N-[2-(4-benzoylpiperazin-1-yl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
322	N-(2-ethyl-6-sec-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
323	[2-methyl-2-[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]-propyl]aminoformic acid methyl ester
324	N-(4-butylphenyl)-4-oxo-1H-quinoline-3-carboxamide
325	N-(2,6-diethylphenyl)-4-oxo-1H-quinoline-3-carboxamide
326	N-[2-(4-methylsulfonylphenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
327	N-[5-(2-ethoxyphenyl)-1H-indol-6-yl]-4-oxo-1H-quinoline-3-carboxamide
328	N-(3-acetylphenyl)-4-oxo-1H-quinoline-3-carboxamide
329	N-[2-(o-tolyl)benzooxazol-5-yl]-4-oxo-1H-quinoline-3-carboxamide
330	N-(2-chlorophenyl)-4-oxo-1H-quinoline-3-carboxamide
331	N-(2-carbamoylphenyl)-4-oxo-1H-quinoline-3-carboxamide
332	N-(4-ethynylphenyl)-4-oxo-1H-quinoline-3-carboxamide
333	N-[2-[4-(cyanomethyl)phenyl]phenyl]-4-oxo-1H-quinoline-3-carboxamide
334	7'-[(4-oxo-1H-quinolin-3-ylcarbonyl)amino]-spiro[piperidine-4,4'(1'H)-1-acetyl-quinoline], 2',3'-dihydro- carboxylic acid tert-butyl ester
335	N-(2-carbamoyl-5-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
336	N-(2-butylphenyl)-4-oxo-1H-quinoline-3-carboxamide
337	N-(5-hydroxy-2,4-ditert-butyl-phenyl)-N-methyl-4-oxo-1H-quinoline-3-carboxamide
338	N-(3-methyl-1H-indol-4-yl)-4-oxo-1H-quinoline-3-carboxamide
339	N-(3-cyano-1H-indol-6-yl)-4-oxo-1H-quinoline-3-carboxamide
340	N-(3-methylsulfonylamino-4-propyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
341	[2-methyl-2-[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]-propyl]aminoformic acid neopentyl ester
342	N-[5-(4-isopropylphenyl)-1H-indol-6-yl]-4-oxo-1H-quinoline-3-carboxamide
343	N-[5-(isobutylcarbamoyl)-1H-indol-6-yl]-4-oxo-1H-quinoline-3-carboxamide
344	N-[2-(2-ethoxyphenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
345	6-fluoro-4-hydroxy-N-(1H-indol-6-yl)quinoline-3-carboxamide

346	4-oxo-N-phenyl-7-(trifluoromethyl)-1H-quinoline-3-carboxamide
347	N-[5-[4-(2-dimethylaminoethylcarbamoyl)phenyl]-1H-indol-6-yl]-4-oxo-1H-quinoline-3-carboxamide
348	N-[2-(4-ethoxyphenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
349	4-oxo-N-(2-phenylsulfonylphenyl)-1H-quinoline-3-carboxamide
350	N-(1-naphthyl)-4-oxo-1H-quinoline-3-carboxamide
351	N-(5-ethyl-1H-indol-6-yl)-4-oxo-1H-quinoline-3-carboxamide
352	2-[6-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-1H-indol-3-yl]ethylaminoformic acid tert-butyl ester
353	[3-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-4-*tert*-butyl-phenyl]aminoformic acid tert-butyl ester
354	N-[2-[(cyclohexyl-methyl-amino)methyl]phenyl]-4-oxo-1H-quinoline-3-carboxamide
355	N-[2-(2-methoxyphenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
356	N-(5-methylamino-2-propyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
357	N-(3-isopropyl-1H-indol-6-yl)-4-oxo-1H-quinoline-3-carboxamide
358	6-chloro-4-hydroxy-N-(1H-indol-6-yl)quinoline-3-carboxamide
359	N-[3-(2-dimethylaminoethylsulfonylamino)-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
360	N-[4-(difluoromethoxy)phenyl]-4-oxo-1H-quinoline-3-carboxamide
361	N-[2-(2,5-dimethoxyphenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
362	N-(2-chloro-4-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
363	N-[2-(2-fluoro-3-methoxy-phenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
364	N-(2-methyl-8-quinolyl)-4-oxo-1H-quinoline-3-carboxamide
365	N-(2-acetylphenyl)-4-oxo-1H-quinoline-3-carboxamide
366	4-oxo-N-[2-[4-(trifluoromethyl)phenyl]phenyl]-1H-quinoline-3-carboxamide
367	N-[2-(3,5-dichlorophenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
368	N-(3-amino-4-propoxy-phenyl)-4-oxo-1H-quinoline-3-carboxamide
369	N-(2,4-dichloro-6-cyano-phenyl)-4-oxo-1H-quinoline-3-carboxamide
370	N-(3-chlorophenyl)-4-oxo-1H-quinoline-3-carboxamide
371	4-oxo-N-[2-(trifluoromethylsulfanyl)phenyl]-1H-quinoline-3-carboxamide
372	N-[2-(4-methyl-1-piperidyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide

373	N-indan-4-yl-4-oxo-1H-quinoline-3-carboxamide
374	4-hydroxy-N-(1H-indol-6-yl)-2-methylsulfanyl-quinoline-3-carboxamide
375	1,4-dihydro-N-(1,2,3,4-tetrahydronaphthalen-6-yl)-4-oxoquinoline-3-carboxamide
376	4-oxo-N-(2-phenylbenzooxazol-5-yl)-1H-quinoline-3-carboxamide
377	6,8-difluoro-4-hydroxy-N-(1H-indol-6-yl)quinoline-3-carboxamide
378	N-(3-amino-4-methoxy-phenyl)-4-oxo-1H-quinoline-3-carboxamide
379	N-[3-acetylamino-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
380	N-(2-ethoxyphenyl)-4-oxo-1H-quinoline-3-carboxamide
381	4-oxo-N-(5-*tert*-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
382	[5-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-2-propyl-phenyl]aminoformic acid ethyl ester
383	N-(3-ethyl-1H-indol-6-yl)-4-oxo-1H-quinoline-3-carboxamide
384	N-[2-(2,5-difluorophenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
385	N-[2-(2,4-difluorophenoxy)-3-pyridyl]-4-oxo-1H-quinoline-3-carboxamide
386	N-(3,3-dimethylindolin-6-yl)-4-oxo-1H-quinoline-3-carboxamide
387	N-[2-methyl-3-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
388	4-oxo-N-[2-[4-(trifluoromethoxy)phenyl]phenyl]-1H-quinoline-3-carboxamide
389	N-(3-benzylphenyl)-4-oxo-1H-quinoline-3-carboxamide
390	N-[3-(aminomethyl)-4-*tert*-butyl-phenyl]-4-oxo-1H-quinoline-3-carboxamide
391	N-[2-(4-isobutylphenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
392	N-(6-chloro-3-pyridyl)-4-oxo-1H-quinoline-3-carboxamide
393	N-[5-amino-2-(2-ethoxyphenyl)-phenyl]-4-oxo-1H-quinoline-3-carboxamide
394	1,6-dimethyl-4-oxo-N-phenyl-1H-quinoline-3-carboxamide
395	N-[4-(1-adamantyl)-2-fluoro-5-hydroxy-phenyl]-4-hydroxy-quinoline-3-carboxamide
396	[2-methyl-2-[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]-propyl]aminoformic acid tetrahydrofuran-3-ylmethyl ester
397	4-oxo-N-(4-phenylphenyl)-1H-quinoline-3-carboxamide
398	4-oxo-N-[2-(p-tolylsulfonylamino)phenyl]-1H-quinoline-3-carboxamide
399	N-(2-isopropyl-5-methylamino-phenyl)-4-oxo-1H-quinoline-3-carboxamide

400	N-(6-morpholino-3-pyridyl)-4-oxo-1H-quinoline-3-carboxamide
401	N-[2-(2,3-dimethylphenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
402	4-oxo-N-(5-phenyl-2-pyridyl)-1H-quinoline-3-carboxamide
403	N-[2-fluoro-5-hydroxy-4-(1-methylcyclooctyl)-phenyl]-4-hydroxy-quinoline-3-carboxamide
404	N-[5-(2,6-dimethoxyphenyl)-1H-indol-6-yl]-4-oxo-1H-quinoline-3-carboxamide
405	N-(4-chlorophenyl)-4-oxo-1H-quinoline-3-carboxamide
406	6-[(4-fluorophenyl)-methyl-sulfamoyl]-4-oxo-N-(5-*tert*-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
407	N-(2-fluoro-5-hydroxy-4-*tert*-butyl-phenyl)-5-hydroxy-4-oxo-1H-quinoline-3-carboxamide
408	N-(3-methoxyphenyl)-4-oxo-1H-quinoline-3-carboxamide
409	N-(5-dimethylamino-2-ethyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
410	4-oxo-N-[2-(4-phenoxyphenyl)phenyl]-1H-quinoline-3-carboxamide
411	7-chloro-4-oxo-N-phenyl-1H-quinoline-3-carboxamide
412	6-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-1H-indole-7-carboxylic acid ethyl ester
413	4-oxo-N-(2-phenoxyphenyl)-1H-quinoline-3-carboxamide
414	N-(3H-benzoimidazol-5-yl)-4-oxo-1H-quinoline-3-carboxamide
415	N-(3-hydroxy-4-*tert*-butyl-phenyl)-4-methoxy-quinoline-3-carboxamide
416	[2-methyl-2-[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]-propyl]aminoformic acid propyl ester
417	N-(2-(benzo[b]thiophen-3-yl)phenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide
418	N-(3-dimethylaminophenyl)-4-oxo-1H-quinoline-3-carboxamide
419	N-(3-acetylaminophenyl)-4-oxo-1H-quinoline-3-carboxamide
420	2-methyl-2-[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]-propanoic acid ethyl ester
421	N-[5-methoxy-4-*tert*-butyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
422	N-(5,6-dimethyl-3H-benzoimidazol-2-yl)-4-oxo-1H-quinoline-3-carboxamide
423	N-[3-(2-ethoxyethyl)-1H-indol-6-yl]-4-oxo-1H-quinoline-3-carboxamide
424	N-[2-(4-chlorophenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
425	N-(4-isopropylphenyl)-4-oxo-1H-quinoline-3-carboxamide
426	N-(4-chloro-5-hydroxy-2-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide

427	5-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-1,2,3,4-tetrahydroisoquinoline-2-carboxylic acid tert-butyl ester
428	N-(3-hydroxy-4-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
429	N-[3-amino-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
430	N-(2-isopropyl-6-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
431	N-(3-aminophenyl)-4-oxo-1H-quinoline-3-carboxamide
432	N-[2-(4-isopropylphenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
433	N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
434	N-(2,5-dimethylphenyl)-4-oxo-1H-quinoline-3-carboxamide
435	N-[2-(2-fluorophenoxy)-3-pyridyl]-4-oxo-1H-quinoline-3-carboxamide
436	N-[2-(3,4-dimethoxyphenyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
437	N-benzo[1,3]dioxol-5-yl-4-oxo-1H-quinoline-3-carboxamide
438	N-[5-(difluoromethyl)-2,4-ditert-butyl-phenyl]-4-oxo-1H-quinoline-3-carboxamide
439	N-(4-methoxyphenyl)-4-oxo-1H-quinoline-3-carboxamide
440	N-(2,2,3,3-tetrafluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1,4-dihydro-4-oxoquinoline-3-carboxamide
441	N-[3-methylsulfonylamino-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
442	4-oxo-N-[3-(1-piperidylsulfonyl)phenyl]-1H-quinoline-3-carboxamide
443	4-oxo-N-quinoxalin-6-yl-1H-quinoline-3-carboxamide
444	5-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-2-*tert*-butyl-benzoic acid methyl ester
445	N-(2-isopropenylphenyl)-4-oxo-1H-quinoline-3-carboxamide
446	N-(1,1-dioxobenzothiophen-6-yl)-4-oxo-1H-quinoline-3-carboxamide
447	N-(3-cyanophenyl)-4-oxo-1H-quinoline-3-carboxamide
448	4-oxo-N-(4-*tert*-butylphenyl)-1H-quinoline-3-carboxamide
449	N-(m-tolyl)-4-oxo-1H-quinoline-3-carboxamide
450	N-[4-(1-hydroxyethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
451	N-(4-cyano-2-ethyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
452	4-oxo-N-(4-vinylphenyl)-1H-quinoline-3-carboxamide
453	N-(3-amino-4-chloro-phenyl)-4-oxo-1H-quinoline-3-carboxamide

454	N-(2-methyl-5-phenyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
455	N-[4-(1-adamantyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
456	4-oxo-N-[3-(trifluoromethylsulfanyl)phenyl]-1H-quinoline-3-carboxamide
457	N-(4-morpholinophenyl)-4-oxo-1H-quinoline-3-carboxamide
458	N-[3-(2-hydroxyethoxy)-4-*tert*-butyl-phenyl]-4-oxo-1H-quinoline-3-carboxamide
459	N-(o-tolyl)-4-oxo-1H-quinoline-3-carboxamide
460	[2-methyl-2-[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]-propyl]aminoformic acid butyl ester
461	4-oxo-N-(2-phenylphenyl)-1H-quinoline-3-carboxamide
462	N-(3-dimethylamino-4-propyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
463	N-(4-ethylphenyl)-4-oxo-1H-quinoline-3-carboxamide
464	5-hydroxy-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
465	[5-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-2-*tert*-butyl-phenylmethyl]aminoformic acid tert-butyl ester
466	N-(2,6-diisopropylphenyl)-4-oxo-1H-quinoline-3-carboxamide
467	N-(2,3-dihydrobenzofuran-5-yl)-4-oxo-1H-quinoline-3-carboxamide
468	1-methyl-4-oxo-N-phenyl-1H-quinoline-3-carboxamide
469	4-oxo-N-(2-phenylphenyl)-7-(trifluoromethyl)-1H-quinoline-3-carboxamide
470	4-oxo-N-(4-phenylsulfanylphenyl)-1H-quinoline-3-carboxamide
471	[3-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-4-propyl-phenyl]aminoformic acid methyl ester
472	[4-ethyl-3-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]aminoformic acid ethyl ester
473	1-isopropyl-4-oxo-N-(2-*tert*-butylphenyl)-1H-quinoline-3-carboxamide
474	N-(3-methyl-2-oxo-3H-benzooxazol-5-yl)-4-oxo-1H-quinoline-3-carboxamide
475	N-(2,5-dichloro-3-pyridyl)-4-oxo-1H-quinoline-3-carboxamide
476	N-(2-cyano-5-hydroxy-4-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
477	N-(5-fluoro-2-pyridyl)-4-oxo-1H-quinoline-3-carboxamide
478	4-oxo-N-(3-*tert*-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
479	N-(1H-indol-6-yl)-5-methoxy-4-oxo-1H-quinoline-3-carboxamide
480	1-ethyl-6-methoxy-4-oxo-N-phenyl-1H-quinoline-3-carboxamide

481	N-(2-naphthyl)-4-oxo-1H-quinoline-3-carboxamide
482	[7-[(4-oxo-1H-quinolin-3-yl)carbonylamino]tetralin-1-yl]aminoformic acid ethyl ester
483	N-[2-fluoro-5-hydroxy-4-(1-methylcycloheptyl)-phenyl]-4-hydroxy-quinoline-3-carboxamide
484	N-(3-methylamino-4-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
485	N-(3-dimethylamino-4-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
486	6,7-difluoro-N-(2-fluoro-5-hydroxy-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
487	5-hydroxy-N-[5-hydroxy-4-tert-butyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
488	4-oxo-N-[3-(1-piperidyl)-5-(trifluoromethyl)phenyl]-1H-quinoline-3-carboxamide
489	N-[4-(3,3-dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl]-6-methyl-4-oxo-1H-quinoline-3-carboxamide
490	6-fluoro-N-(3-hydroxy-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
491	N-(3-fluoro-4-tert-butyl-phenyl)-5-hydroxy-4-oxo-1H-quinoline-3-carboxamide
492	methyl 1-[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-3-(trifluoromethyl)phenyl]piperidine-2-carboxylate
493	5-hydroxy-N-[4-[2-hydroxy-1-(hydroxymethyl)-1-methyl-ethyl]phenyl]-4-oxo-1H-quinoline-3-carboxamide
494	5-hydroxy-4-oxo-N-[5-(trifluoromethyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide
495	6-fluoro-4-oxo-N-[2-(trifluoromethyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide
496	N-(5-hydroxy-2,4-ditert-butyl-phenyl)-6-methoxy-4-oxo-1H-quinoline-3-carboxamide
497	N-[5-hydroxy-4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
498	N-[2-fluoro-5-hydroxy-4-(1-methylcyclohexyl)-phenyl]-5-methyl-4-oxo-1H-quinoline-3-carboxamide
499	N-[2-fluoro-5-hydroxy-4-(1-methylcyclohexyl)-phenyl]-7-methyl-4-oxo-1H-quinoline-3-carboxamide
500	5-hydroxy-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
501	N-[2-fluoro-5-hydroxy-4-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
502	5-hydroxy-N-[3-methoxy-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
503	6-methyl-N-[4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
504	N-[4-(3,3-dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl]-6-methoxy-4-oxo-1H-quinoline-3-carboxamide
505	8-cyano-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
506	N-[3-hydroxy-4-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
507	N-(2-ethyl-5-hydroxy-4-tert-butyl-phenyl)-5-hydroxy-4-oxo-1H-quinoline-3-carboxamide

508	4-oxo-N-[3-tert-butyl-5-(trifluoromethyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide
509	6-fluoro-N-[5-hydroxy-4-tert-butyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
510	4-oxo-N-[3-(1-piperidyl)-4-tert-butyl-phenyl]-1H-quinoline-3-carboxamide
511	(S)-5-methyl-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
512	N-[4-cyclopentyl-5-hydroxy-2-(3-hydroxyprop-1-ynyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
513	(S)-N-(4-(3-(dimethylamino)pyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
514	4-oxo-N-[2-(1-piperidyl)-4-(trifluoromethyl)phenyl]-1H-quinoline-3-carboxamide
515	N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-6-(trifluoromethyl)-1H-quinoline-3-carboxamide
516	N-(4-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-5-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide
517	8-ethoxy-N-[4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
518	N-(5-hydroxy-2-methyl-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
519	8-cyano-N-(2-fluoro-5-hydroxy-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
520	N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-5-(trifluoromethyl)-1H-quinoline-3-carboxamide
521	6-fluoro-N-[4-(3-methyloxetan-3-yl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
522	N-(4-cyclohexyl-3-hydroxy-phenyl)-5-hydroxy-4-oxo-1H-quinoline-3-carboxamide
523	N-[4-(3-methyloxetan-3-yl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
524	6-ethoxy-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
525	6-cyano-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
526	8-ethoxy-N-(2-fluoro-5-hydroxy-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
527	6-fluoro-N-(3-fluoro-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
528	N-[4-(3,3-difluoropyrrolidin-1-yl)-2-(trifluoromethyl)phenyl]-5-methyl-4-oxo-1H-quinoline-3-carboxamide
529	5-hydroxy-N-[4-(3-methyloxetan-3-yl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
530	(2S,3S)-methyl 3-methyl-1-(4-(4-oxo-1,4-dihydroquinoline-3-carboxamido)-3-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate
531	(1S,2S,5R)-methyl 3-(4-(4-oxo-1,4-dihydroquinoline-3-carboxamido)-3-(trifluoromethyl)phenyl)-3-azabicyclo[3.1.0]hexane-2-carboxylate
532	N-[2-chloro-4-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
533	6-methoxy-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
534	(R)-N-(4-(3-(dimethylamino)pyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide

535	5-hydroxy-4-oxo-N-(3-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
536	N-[4-(3,3-dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
537	4-oxo-N-[2-(trifluoromethyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide
538	N-[2-methyl-4-(trifluoromethoxy)phenyl]-4-oxo-1H-quinoline-3-carboxamide
539	N-(4-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-5-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide
540	(R)-tert-butyl 1-(4-(4-oxo-1,4-dihydroquinoline-3-carboxamido)-3-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate
541	(R)-N-(4-(3-fluoropyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-5-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide
542	N-(5-hydroxy-2,4-ditert-butyl-phenyl)-5-methylamino-4-oxo-1H-quinoline-3-carboxamide
543	4-oxo-N-[4-(1-piperidyl)phenyl]-1H-quinoline-3-carboxamide
544	6-dimethylamino-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
545	4-oxo-N-[3-(trifluoromethyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide
546	5-methyl-N-[4-(3-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
547	N-[4-isopropoxy-2-(trifluoromethyl)phenyl]-5-methyl-4-oxo-1H-quinoline-3-carboxamide
548	7-cyano-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
549	4-oxo-N-[3-(2-thienyl)phenyl]-1H-quinoline-3-carboxamide
550	(2S,4R)-methyl 4-tert-butoxy-1-(4-(4-oxo-1,4-dihydroquinoline-3-carboxamido)-3-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate
551	N-(4-hydroxy-2-naphthyl)-4-oxo-1H-quinoline-3-carboxamide
552	5-fluoro-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
553	6-bromo-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
554	6-fluoro-4-oxo-N-(3-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
555	N-[4-(3-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
556	N-[4-(2,2-dimethylpropanoylamino)-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
557	6-fluoro-N-[4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
558	7-cyano-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
559	4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-8-(trifluoromethyl)-1H-quinoline-3-carboxamide
560	N-[4-(2,5-dimethylpyrrol-1-yl)-3-methoxy-phenyl]-4-oxo-1H-quinoline-3-carboxamide
561	6-chloro-N-(2-fluoro-5-hydroxy-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide

562	6-fluoro-4-oxo-N-[4-pyrrolidin-1-yl-2-(trifluoromethyl)phenyl]-1H-quinoline-3-carboxamide
563	N-[3-hydroxy-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
564	N-(4-cyclohexyl-3-hydroxy-phenyl)-4-oxo-1H-quinoline-3-carboxamide
565	5-methyl-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
566	6-fluoro-N-[1-(2-methoxyethyl)-5-(trifluoromethyl)indol-6-yl]-4-oxo-1H-quinoline-3-carboxamide
567	(S)-1-[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-3-(trifluoromethyl)phenyl]pyrrolidine-2-carboxylic acid
568	N-(5-hydroxy-2,4-ditert-butyl-phenyl)-5-methyl-4-oxo-1H-quinoline-3-carboxamide
569	N-(4-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-6-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide
570	N-[5-benzyloxy-4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
571	N-[6-methoxy-5-(trifluoromethyl)-2-pyridyl]-4-oxo-1H-quinoline-3-carboxamide
572	(R)-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
573	8-fluoro-N-[4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
574	6-fluoro-N-[3-hydroxy-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
575	N-(3-hydroxy-4-isopropyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
576	7-methyl-4-oxo-N-[5-(trifluoromethyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide
577	N-[2-methyl-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
578	N-[4-(3,3-dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl]-5-methyl-4-oxo-1H-quinoline-3-carboxamide
579	4-oxo-N-[3-pyrrolidin-1-yl-4-(trifluoromethoxy)phenyl]-1H-quinoline-3-carboxamide
580	N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-8-(trifluoromethyl)-1H-quinoline-3-carboxamide
581	(S)-5-methyl-N-(6-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
582	N-(4-((1S,4R)-2-azabicyclo[2.2.1]heptan-2-yl)-2-(trifluoromethyl)phenyl)-5-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide
583	N-(5-hydroxy-2,4-ditert-butyl-phenyl)-7-methoxy-4-oxo-1H-quinoline-3-carboxamide
584	N-[2-fluoro-5-hydroxy-4-(1-methylcyclohexyl)-phenyl]-6-methoxy-4-oxo-1H-quinoline-3-carboxamide
585	5-amino-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
586	(R)-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-5-(trifluoromethyl)-1,4-dihydroquinoline-3-carboxamide
587	5-hydroxy-N-(3-hydroxy-4-isopropyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
588	5-hydroxy-N-(5-hydroxy-2-methyl-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide

589	6,7-difluoro-N-[4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
590	N-[4-[2-hydroxy-1-(hydroxymethyl)-1-methyl-ethyl]phenyl]-4-oxo-1H-quinoline-3-carboxamide
591	N-(5-ethyl-1H-indol-6-yl)-5-hydroxy-4-oxo-1H-quinoline-3-carboxamide
592	N-(4-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-5-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide
593	4-oxo-N-[3-pyrrolidin-1-yl-5-(trifluoromethyl)phenyl]-1H-quinoline-3-carboxamide
594	N-(3-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
595	N-[4-cyclopentoxy-2-(trifluoromethyl)phenyl]-5-methyl-4-oxo-1H-quinoline-3-carboxamide
596	N-(5-fluoro-1H-indol-6-yl)-5-hydroxy-4-oxo-1H-quinoline-3-carboxamide
597	6-fluoro-N-(3-hydroxy-4-isopropyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
598	N-[4-morpholino-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
599	5-hydroxy-N-[3-hydroxy-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
600	tert-butyl [[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-3-(trifluoromethyl)phenyl]amino]formate
601	(S)-6-methoxy-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
602	4-oxo-N-(3-tert-butylphenyl)-1H-quinoline-3-carboxamide
603	6-chloro-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
604	7-acetyl-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
605	8-ethyl-N-(2-fluoro-5-hydroxy-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
606	5-hydroxy-N-[3-hydroxy-4-(1-methylcyclohexyl)-phenyl]-4-oxo-1H-quinoline-3-carboxamide
607	(S)-7-methyl-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
608	N-(2,4-dichloro-5-hydroxy-phenyl)-4-oxo-1H-quinoline-3-carboxamide
609	5-hydroxy-N-(5-hydroxy-2-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
610	5-fluoro-N-(2-fluoro-5-hydroxy-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
611	7-fluoro-6-methoxy-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
612	N-[4-(3,3-dimethyl-1-piperidyl)-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
613	(R)-5-methyl-N-(4-(3-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
614	4-oxo-N-[4-(3-pyridyloxy)phenyl]-1H-quinoline-3-carboxamide
615	N-(2-methyl-4-pyrrolidin-1-yl-phenyl)-4-oxo-1H-quinoline-3-carboxamide

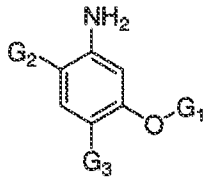
616	8-ethoxy-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
617	6-fluoro-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-7-methoxy-4-oxo-1H-quinoline-3-carboxamide
618	(S)-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
619	N-[4-cyclohexyl-5-hydroxy-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
620	5-hydroxy-4-oxo-N-(3-tert-butylphenyl)-1H-quinoline-3-carboxamide
621	N-(5-hydroxy-2,4-ditert-butyl-phenyl)-8-methyl-4-oxo-1H-quinoline-3-carboxamide
622	N-(2-cyano-4-pyrrolidin-1-yl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
623	6-chloro-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
624	N-[2-fluoro-5-hydroxy-4-(1-methylcyclohexyl)-phenyl]-6-methyl-4-oxo-1H-quinoline-3-carboxamide
625	N-(2-fluoro-5-hydroxy-4-tert-butyl-phenyl)-8-methyl-4-oxo-1H-quinoline-3-carboxamide
626	(S)-N-(4-(3-fluoropyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-5-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide
627	6-fluoro-N-[4-[2-hydroxy-1-(hydroxymethyl)-1-methyl-ethyl]phenyl]-4-oxo-1H-quinoline-3-carboxamide
628	N-[2-chloro-4-(trifluoromethoxy)phenyl]-4-oxo-1H-quinoline-3-carboxamide
629	(S)-tert-butyl 1-(4-(4-oxo-1,4-dihydroquinoline-3-carboxamido)-3-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate
630	N-[2,5-bis(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
631	(S)-methyl 2-methyl-1-(4-(4-oxo-1,4-dihydroquinoline-3-carboxamido)-3-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate
632	4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-7-(trifluoromethoxy)-1H-quinoline-3-carboxamide
633	5-hydroxy-N-(3-hydroxy-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
634	(S)-N-(4-(2-(hydroxymethyl)pyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
635	N-[2-chloro-4-(trifluoromethyl)phenyl]-5-hydroxy-4-oxo-1H-quinoline-3-carboxamide
636	N-[2-chloro-4-(trifluoromethyl)phenyl]-6-fluoro-4-oxo-1H-quinoline-3-carboxamide
637	N-[4-isopropyl-2-(trifluoromethyl)phenyl]-8-methyl-4-oxo-1H-quinoline-3-carboxamide
638	N-(2-fluoro-5-hydroxy-4-tert-butyl-phenyl)-4-oxo-8-(trifluoromethyl)-1H-quinoline-3-carboxamide
639	N-[4-(4-isopropylpiperazin-1-yl)-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
640	N-(5-hydroxy-2,4-ditert-butyl-phenyl)-7-methyl-4-oxo-1H-quinoline-3-carboxamide
641	8-ethoxy-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
642	(S)-7-methoxy-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide

643	5-methyl-N-[4-(3-methyl-1-piperidyl)-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
644	8-methyl-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
645	N-(3-fluoro-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
646	6,7-difluoro-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
647	N-(4-cyclohexyl-2-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
648	5-hydroxy-N-[4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
649	N-(2-ethyl-5-hydroxy-4-tert-butyl-phenyl)-6-fluoro-4-oxo-1H-quinoline-3-carboxamide
650	6-fluoro-N-[3-hydroxy-4-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
651	N-(4-cyclohexyl-3-hydroxy-phenyl)-6-fluoro-4-oxo-1H-quinoline-3-carboxamide
652	7-hydroxy-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
653	8-ethyl-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
654	N-[5-benzyloxy-4-cyclohexyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
655	(S)-N-(4-(3-hydroxypyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
656	5-fluoro-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
657	6-chloro-N-[4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
658	4-oxo-N-[4-pyrrolidin-1-yl-2-(trifluoromethyl)phenyl]-1H-quinoline-3-carboxamide
659	N-(2-ethyl-5-hydroxy-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
660	(S)-ethyl 1-(4-(4-oxo-1,4-dihydroquinoline-3-carboxamido)-3-(trifluoromethyl)phenyl)piperidine-3-carboxylate
661	5-methyl-4-oxo-N-[5-(trifluoromethyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide
662	N-(5-hydroxy-2-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
663	8-chloro-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
664	6-fluoro-4-oxo-N-(3-tert-butylphenyl)-1H-quinoline-3-carboxamide
665	6-fluoro-N-(5-hydroxy-2-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
666	6-fluoro-N-[3-methoxy-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
667	(R)-N-(4-(4,4-difluoro-2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-5-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide
668	N-[4-[4-(hydroxymethyl)-1-piperidyl]-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
669	(S)-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-5-(trifluoromethyl)-1,4-dihydroquinoline-3-carboxamide

670	(R)-N-(4-(2-(hydroxymethyl)pyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
671	N-(2-aminobenzothiazol-6-yl)-4-oxo-1H-quinoline-3-carboxamide
672	6,7-difluoro-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
673	N-[4-[4-(2-hydroxyethyl)piperazin-1-yl]-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
674	4-oxo-N-(4-pyrrolidin-1-ylphenyl)-1H-quinoline-3-carboxamide
675	N-(2-methoxy-4-pyrrolidin-1-yl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
676	5-hydroxy-N-[2-methyl-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
677	7-cyano-N-(2-fluoro-5-hydroxy-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
678	6-fluoro-N-[2-methyl-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
679	6-hydroxy-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
680	8-fluoro-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
681	6-ethoxy-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
682	8-ethyl-N-[4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
683	6-fluoro-N-(5-hydroxy-2-methyl-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
684	(R)-6-fluoro-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
685	N-(4-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxamide
686	4-oxo-N-[4-(1-piperidyl)-2-(trifluoromethyl)phenyl]-1H-quinoline-3-carboxamide
687	8-fluoro-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
688	N-(5-hydroxy-2,4-ditert-butyl-phenyl)-6-methyl-4-oxo-1H-quinoline-3-carboxamide
689	N-[4-azetidin-1-yl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
690	methyl 4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-2-tert-butyl-thiophene-3-carboxylate
691	N-[3-methoxy-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
692	4-oxo-N-[2-(2-pyridyl)phenyl]-1H-quinoline-3-carboxamide
693	5-hydroxy-4-oxo-N-[2-(trifluoromethyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide
694	N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-7-(trifluoromethoxy)-1H-quinoline-3-carboxamide
695	N-(4-chloro-2-fluoro-5-hydroxy-phenyl)-4-oxo-1H-quinoline-3-carboxamide
696	4-oxo-N-[3-(1-piperidyl)-4-(trifluoromethoxy)phenyl]-1H-quinoline-3-carboxamide

697	(R)-5-methyl-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
698	(R)-1-[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-3-(trifluoromethyl)phenyl]pyrrolidine-2-carboxylic acid
699	5-fluoro-N-[4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
700	5-hydroxy-N-[3-hydroxy-4-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
701	N-(3-hydroxy-4-isopropoxy-phenyl)-5-methyl-4-oxo-1H-quinoline-3-carboxamide
702	6-hydroxy-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide
703	6-fluoro-4-oxo-N-[5-(trifluoromethyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide
704	7-methyl-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide
705	(R)-N-(4-(3-hydroxypyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
706	N-[2-fluoro-5-hydroxy-4-(1-methylcyclohexyl)-phenyl]-4-oxo-5-(trifluoromethyl)-1H-quinoline-3-carboxamide
707	4-oxo-N-(3-pyrrolidin-1-yl-4-tert-butyl-phenyl)-1H-quinoline-3-carboxamide
708	4-oxo-N-[4-phenyl-5-(trifluoromethyl)-3-thienyl]-1H-quinoline-3-carboxamide
709	7-fluoro-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-6-methoxy-4-oxo-1H-quinoline-3-carboxamide
710	4-oxo-N-(1,4,4-trimethyl-2,3-dihydroquinolin-7-yl)-1H-quinoline-3-carboxamide
711	6-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-1H-indole-4-carboxylic acid
712	N-[3-fluoro-4-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
713	(S)-N-(4-(2-methylpiperidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
714	(S)-6-fluoro-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
715	(S)-methyl 1-(4-(4-oxo-1,4-dihydroquinoline-3-carboxamido)-3-(trifluoromethyl)phenyl)piperidine-2-carboxylate
716	8-chloro-N-[3-hydroxy-4-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide
717	N-(4-methoxy-2-naphthyl)-4-oxo-1H-quinoline-3-carboxamide
718	5,8-difluoro-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide

[0182] In another embodiment, the present invention provides compounds useful as intermediates in the synthesis of compounds of formula I. In one embodiment, such compounds have formula **A-I**:



A-I;

or a salt thereof;

wherein:

G_1 is hydrogen, R', C(O)R', C(S)R', S(O)R', $S(O)_2R'$, $Si(CH_3)_2R'$, $P(O)(OR')_3$, $P(S)(OR')_3$, or $B(OR')_2$;

G_2 is halo, CN, CF_3, isopropyl, or phenyl wherein said isopropyl or phenyl is optionally substituted with up to 3 substituents independently selected from WR^W, wherein W and R^W are as defined above for formula I and embodiments thereof;

G_3 is an isopropyl or a C3-C10 cycloaliphatic ring, wherein said G_3 is optionally substituted with up to 3 substituents independently selected from WR^W, wherein W and R^W are as defined above for formula I and embodiments thereof;

provided that when G_1 is methoxy, G_3 is tert-butyl, then G_2 is not 2-amino-4-methoxy-5-*tert*-butyl-phenyl.

[0183] In one embodiment, the present invention provides compounds of formula A-I, provided that when G_2 and G_3 each is t-butyl, then G_1 is not hydrogen.

[0184] In another embodiment:

G_1 is hydrogen;

G_2 is halo or isopropyl, wherein said isopropyl is optionally substituted with up to 3 substituents independently selected from R'; and

G_3 is an isopropyl or a C3-C10 cycloaliphatic ring, wherein said G_3 is optionally substituted with up to 3 substituents independently selected from R'.

[0185] In another embodiment:

G_1 is hydrogen;

G_2 is halo, preferably fluoro; and

G_3 is a C3-C10 cycloaliphatic ring, wherein said G_3 is optionally substituted with up to 3 substituents independently selected from methyl, ethyl, propyl, or butyl.

[0186] In another embodiment:

G_1 is hydrogen;

G_2 is CN, halo, or CF_3; and

G_3 is an isopropyl or a C3-C10 cycloaliphatic ring, wherein said G_3 is optionally substituted with up to 3 substituents independently selected from R'.

[0187] In another embodiment:

G_1 is hydrogen;

G_2 is phenyl is optionally substituted with up to 3 substituents independently selected from -OC1-C4 alkyl, CF_3, halo, or CN; and

G_3 is an isopropyl or a C3-C10 cycloaliphatic ring, wherein said G_3 is optionally substituted with up to 3 substituents independently selected from R'.

[0188] Exemplary G_3 include optionally substituted cyclopentyl, cyclohexyl, cycloheptyl, or adamantyl. Or, G3 is C3-C8 branched aliphatic chain. Exemplary G3 include isopropyl, t-butyl, 3,3-diethyl-prop-3-yl, or 3,3-diethyl-2,2-dimethyl-prop-3-yl.

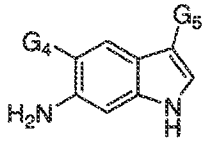
[0189] In another embodiment:

G_1 is hydrogen;

G_2 is t-butyl; and

G_3 is a t-butyl.

[0190] In another embodiment, the present invention provides a compound of formula **A-II**:



A-II;

or a salt thereof, wherein:

G_4 is hydrogen, halo, CN, CF_3, CHF_2, CH_2F, optionally substituted C1-C6 aliphatic, aralkyl, or a phenyl ring optionally substituted with up to 4 WR^W substituents;

G_5 is hydrogen or an optionally substituted C1-C6 aliphatic;

provided that both, G_4 and G_5, are not simultaneously hydrogen;

wherein said indole ring system is further optionally substituted with up to 3 substituents independently selected from WR^W.

[0191] In one embodiment, G_4 is hydrogen. Or, G_5 is hydrogen.

[0192] In another embodiment, G_4 is hydrogen, and G_5 is C1-C6 aliphatic, wherein said aliphatic is optionally substituted with C1-C6 alkyl, halo, cyano, or CF_3, and wherein up to two methylene units of said C1-C6 aliphatic or C1-C6 alkyl is optionally replaced with -CO-, -CONR'-, -CO_2-, -OCO-, -NR'CO_2-, -O-, -NR'CONR'-, -OCONR'-, -NR'CO-, -S-, -

NR'-, -SO_2NR'-, NR'SO_2-, or -NR'SO_2NR'-. In another embodiment, R' above is C1-C4 alkyl.

[0193] In another embodiment, G_4 is hydrogen, and G_5 is cyano, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl, cyanomethyl, methoxyethyl, $CH_2C(O)OMe$, $(CH_2)_2$-NHC(O)O-*tert*-But, or cyclopentyl.

[0194] In another embodiment, G_5 is hydrogen, and G_4 is halo, C1-C6 aliphatic or phenyl, wherein said aliphatic or phenyl is optionally substituted with C1-C6 alkyl, halo, cyano, or CF_3, wherein up to two methylene units of said C1-C6 aliphatic or C1-C6 alkyl is optionally replaced with –CO-, -CONR'-, -CO_2-, -OCO-, -NR'CO_2-, -O-, -NR'CONR'-, -OCONR'-, -NR'CO-, -S-, -NR'-, -SO_2NR'-, NR'SO_2-, or -NR'SO_2NR'-. In another embodiment, R' above is C1-C4 alkyl.

[0195] In another embodiment, G_5 is hydrogen, and G_4 is halo, ethoxycarbonyl, t-butyl, 2-methoxyphenyl, 2-ethoxyphenyl, 4-$C(O)NH(CH_2)_2$-NMe_2, 2-methoxy-4-chloro-phenyl, pyridine-3-yl, 4-isopropylphenyl, 2,6-dimethoxyphenyl, sec-butylaminocarbonyl, ethyl, t-butyl, or piperidin-1-ylcarbonyl.

[0196] In a related embodiment of formula A-II, the nitrogen ring atom of said indole ring is substituted with C1-C6 aliphatic, C(O)(C1-C6 aliphatic), or benzyl, wherein said aliphatic or benzyl is optionally substituted with C1-C6 alkyl, halo, cyano, or CF_3, wherein up to two methylene units of said C1-C6 aliphatic or C1-C6 alkyl is optionally replaced with –CO-, -CONR'-, -CO_2-, -OCO-, -NR'CO_2-, -O-, -NR'CONR'-, -OCONR'-, -NR'CO-, -S-, -NR'-, -SO_2NR'-, NR'SO_2-, or -NR'SO_2NR'-. In another embodiment, R' above is C1-C4 alkyl.

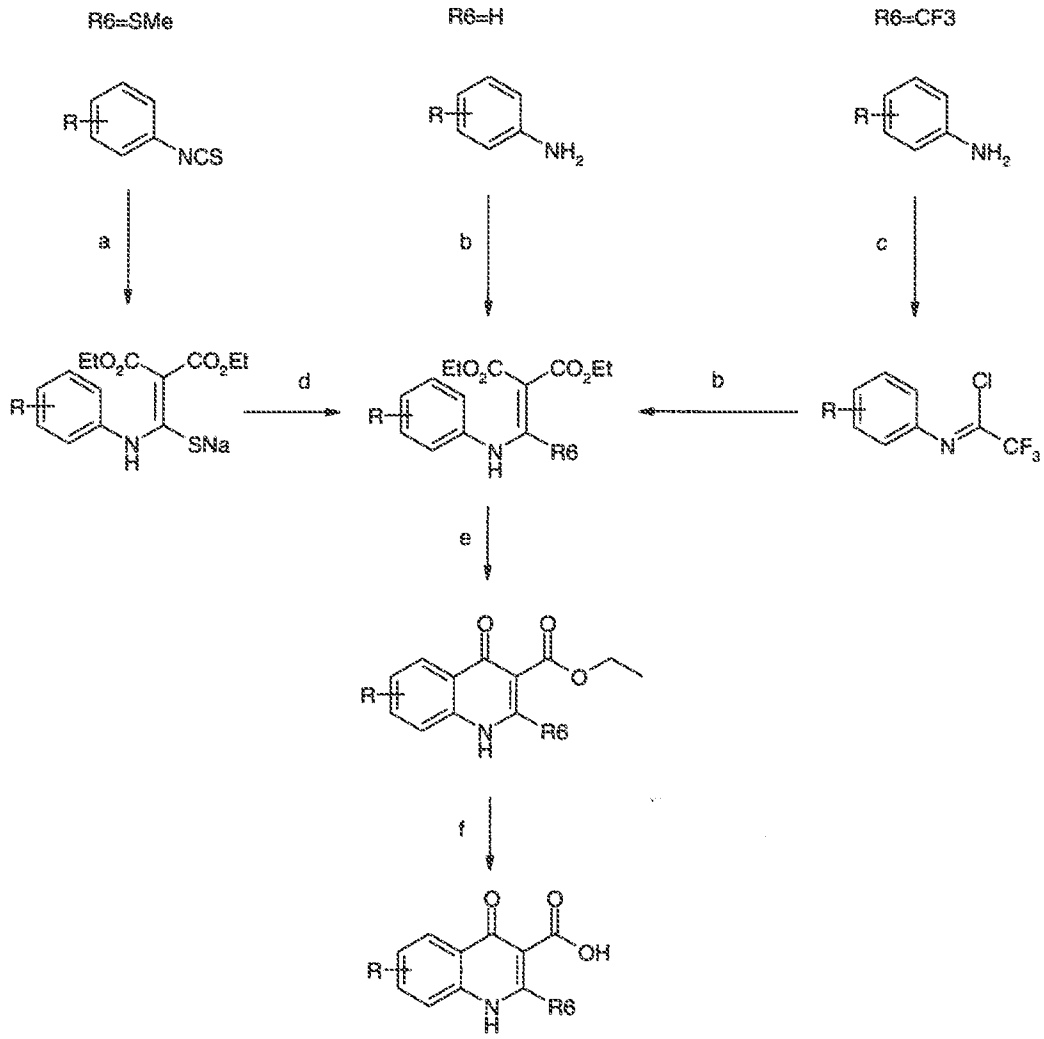
[0197] In another embodiment the nitrogen ring atom of said indole ring is substituted with acyl, benzyl, $C(O)CH_2N(Me)C(O)CH_2NHMe$, or ethoxycarbonyl.

[0198] *4. General Synthetic Schemes*

[0199] Compounds of the present invention are readily prepared by methods known in the art. Illustrated below are exemplary methods for the preparation of compounds of the present invention.

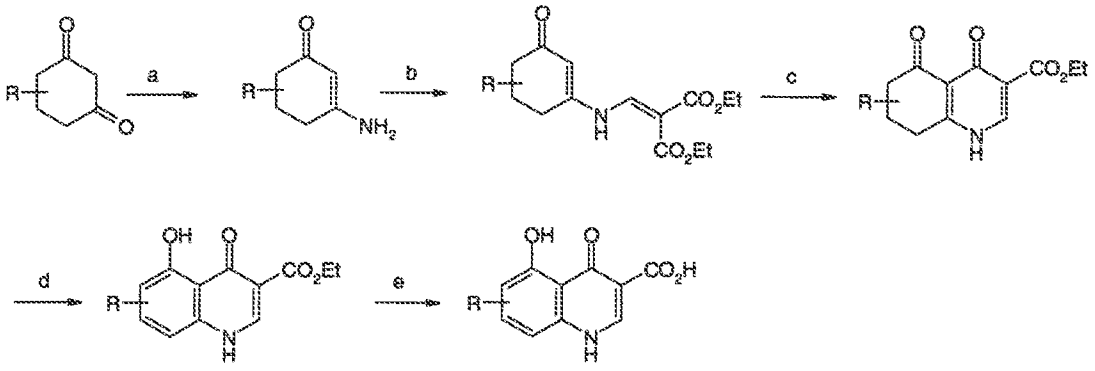
[0200] The scheme below illustrates the synthesis of acid precursors of the compounds of the present invention.

[0201] Synthesis of Acid Precursors **P-IV-A, P-IV-B or P-IV-C:**



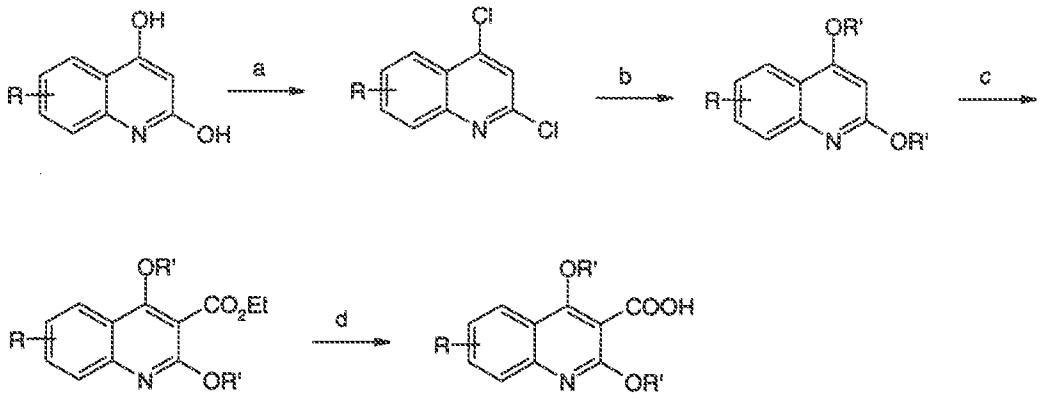
a) $(CO_2Et)_2CH_2$; b) $(CO_2Et)_2CH{=}CH(OEt)$; c) CF_3CO_2H, PPh_3, CCl_4, Et_3N; d) MeI; e) PPA or diphenylether; f) NaOH.

[0202] Synthesis of Acid Precursors **P-IV-A, P-IV-B or P-IV-C:**



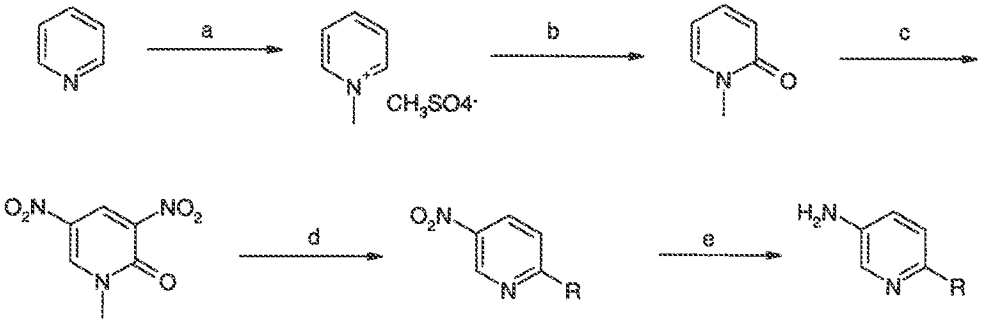
a) $AcONH_4$; b) $EtOCHC(CO_2Et)_2$, 130°C; c) Ph_2O, ΔT; d) I_2, EtOH; e) NaOH.

[0203] Synthesis of Acid Precursors **P-IV-A, P-IV-B or P-IV-C**



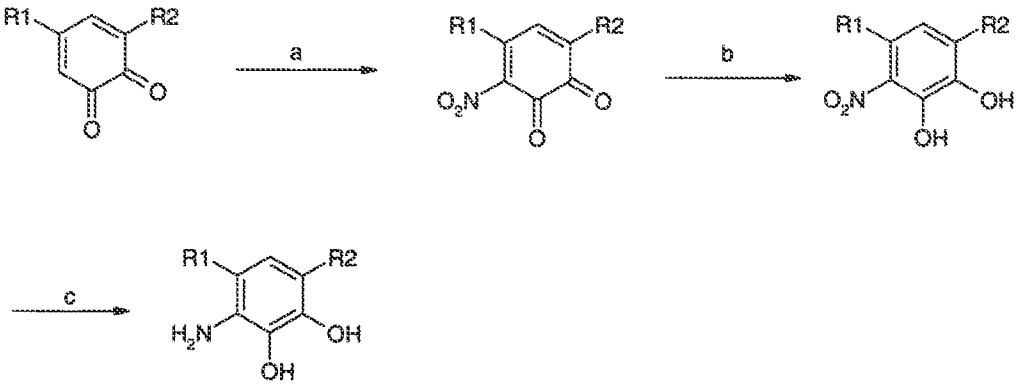
[0204] $POCl_3$; b) R'ONa; c) n-BuLi, $ClCO_2Et$; d) NaOH

[0205] Synthesis of Amine Precursor **P-III-A:**



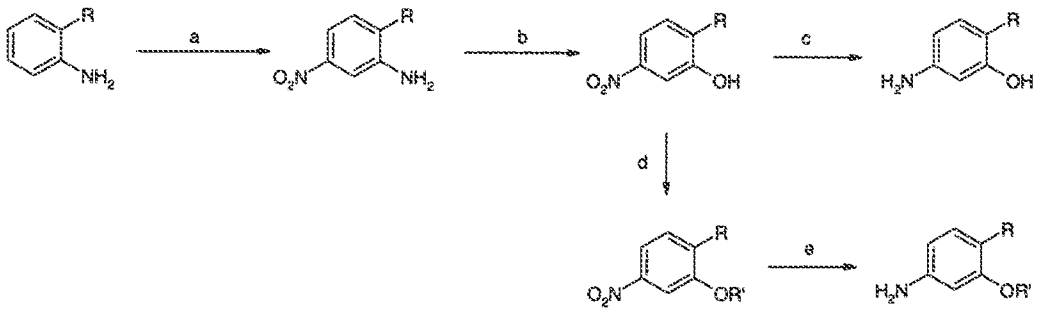
$(CH_3)_2SO_4$; b) $K_3Fe(CN)_6$, NaOH, H_2O; c) HNO_3, H_2SO_4; d) $RCOCH_3$, MeOH, NH_3; e) H_2, Raney Ni

[0206] Synthesis of Amine Precursor **P-IV-A:**



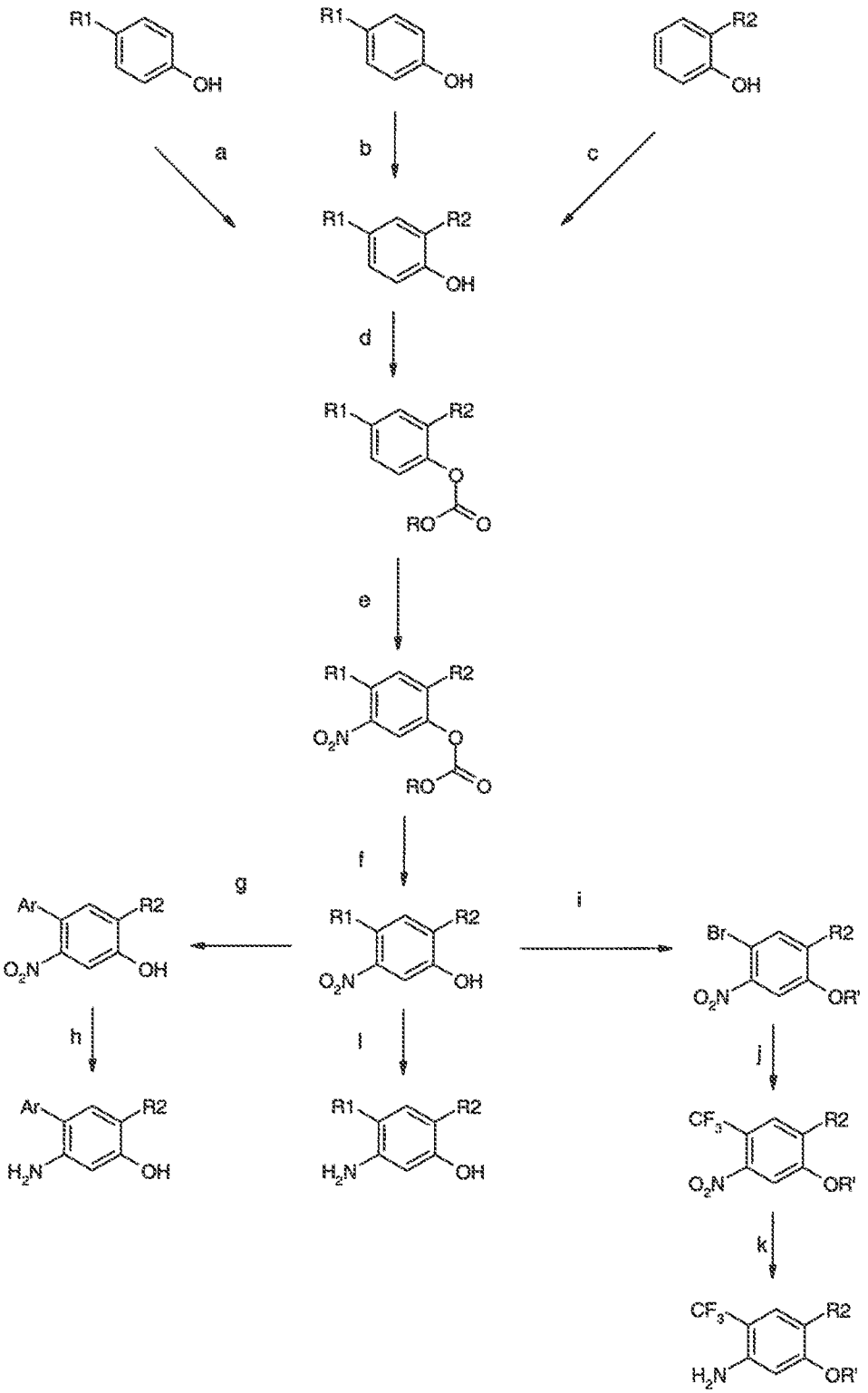
[0207] HNO_3, HOAc; b) $Na_2S_2O_4$, THF/H_2O; c) H_2, Pd/C.

[0208] Synthesis of Amine Precursor **P-V-A-1:**



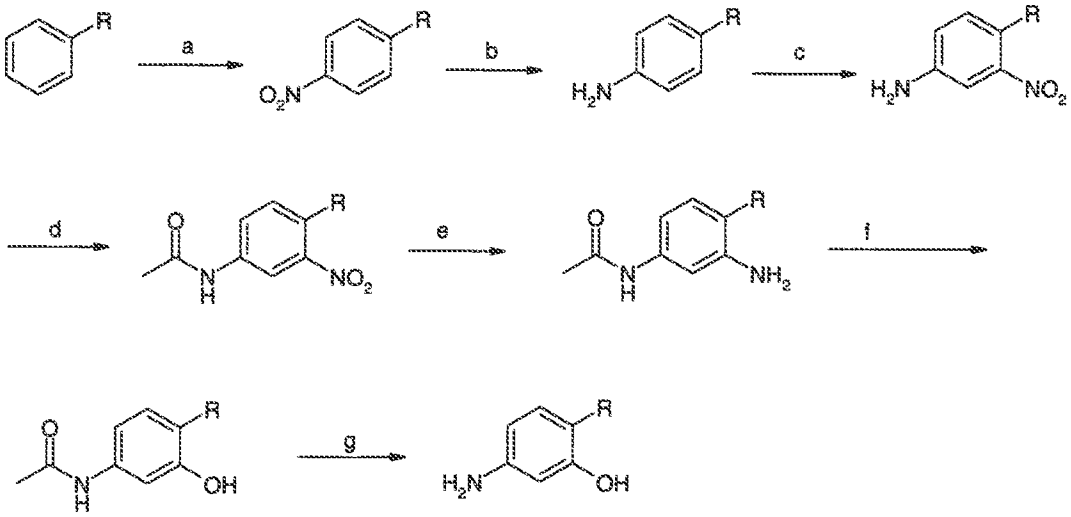
[0209] KNO_3, H_2SO_4; b) $NaNO_2$, H_2SO_4- H_2O; c) NH_4CO_2H, Pd-C; d) R'X; e) NH_4CO_2H, Pd-C

[0210] Synthesis of Amine Precursor **P-V-A-1**:



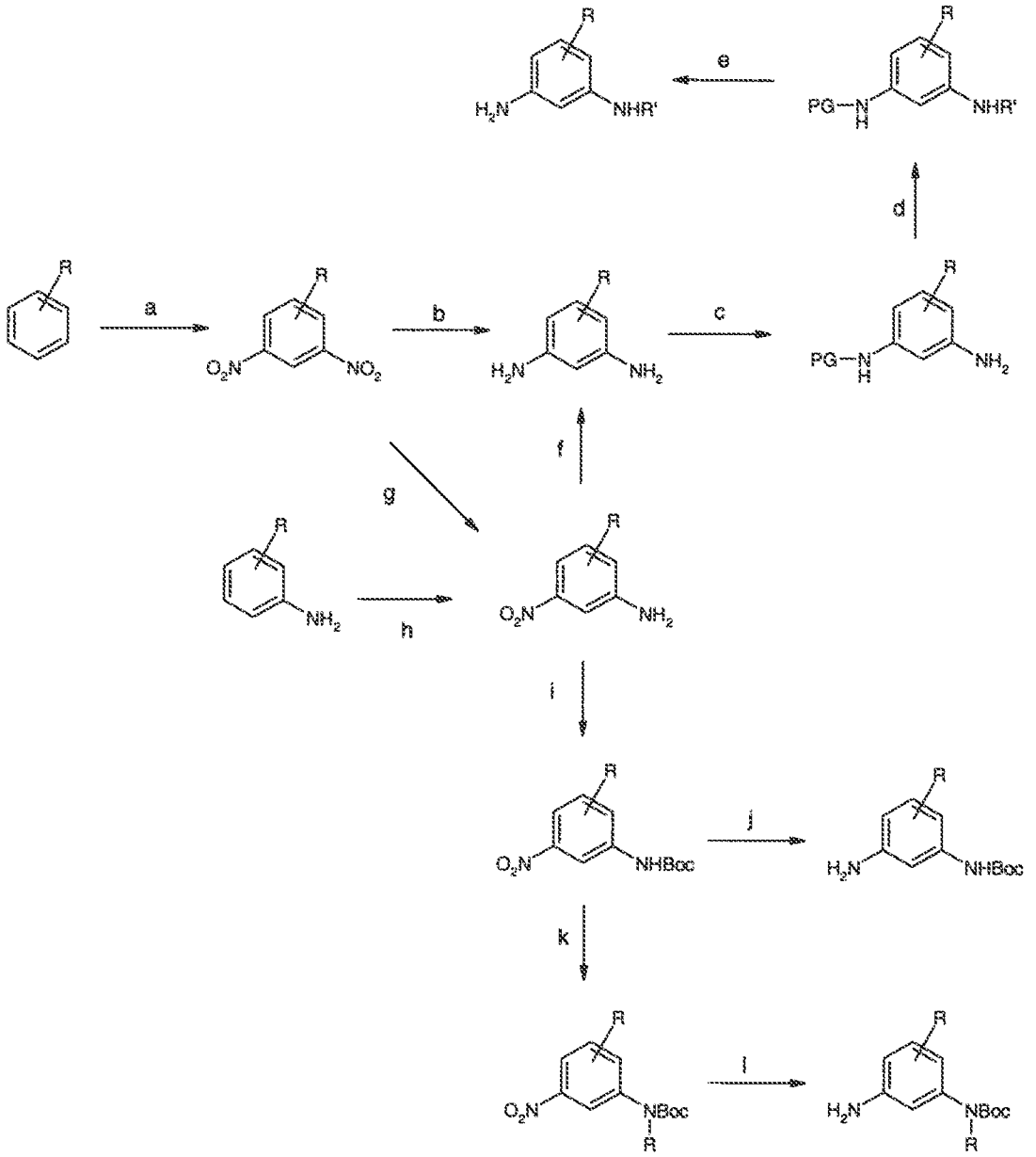
a) SO_2Cl_2, R2= Cl; b) R2OH, R2=alkyl; c) NBS, R1=Br; d) $ClCO_2R$, TEA; e) HNO_3, H_2SO_4; f) base; g) $ArB(OH)_2$, R1=Br; h) [H]; I) R'X, R1= Br; j) $ClCF_2CO_2Me$; k) [H]; l) [H].

[0211] Synthesis of Amine Precursor **P-V-A-1**:



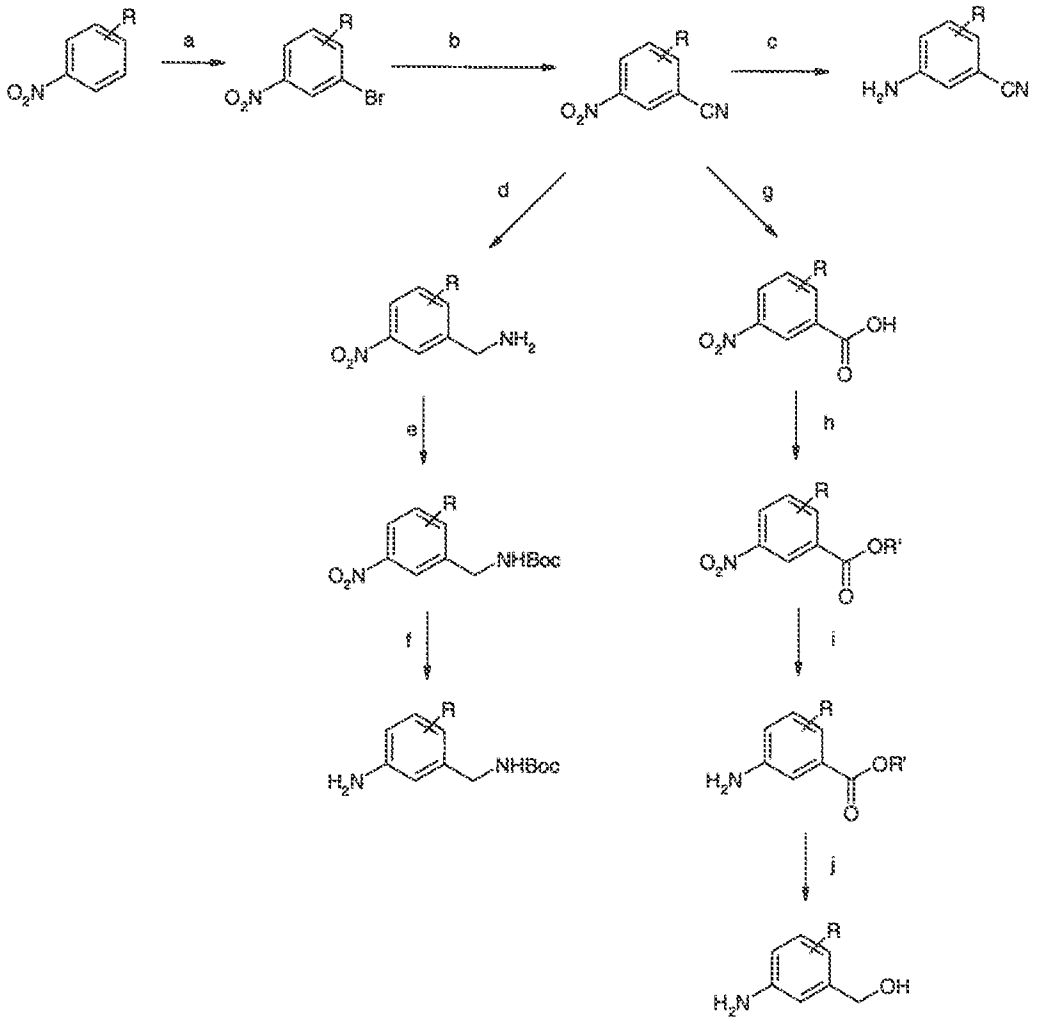
[0212] KNO_3; b) [H]; c) KNO_3; d) AcCl; e) [H]; f) i) $NaNO_2$; ii) H_2O; g) HCl

[0213] Synthesis of Amine Precursor **P-V-A-1**:



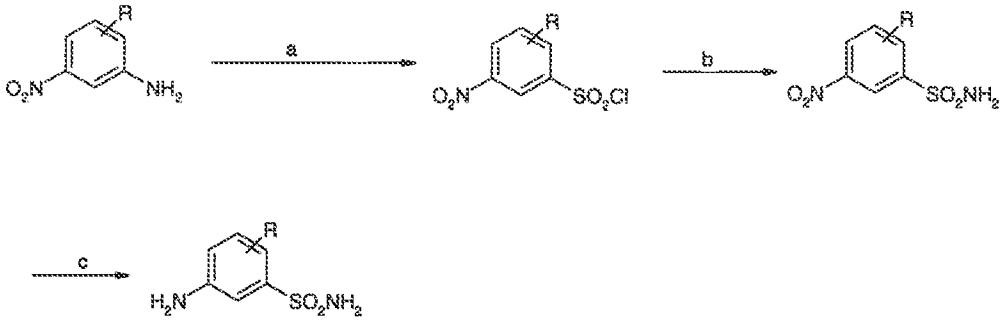
[0214] HNO_3, H_2SO_4; b) [H]; c) protection; d) R'CHO; e) deprotection; f) [H]; g) Na_2S, S, H_2O; h) nitration; i) $(BOC)_2O$; j) [H]; k) RX; l) [H]; PG= protecting group

[0215] Synthesis of Amine Precursors **P-V-A-1** or **P-V-A-2:**



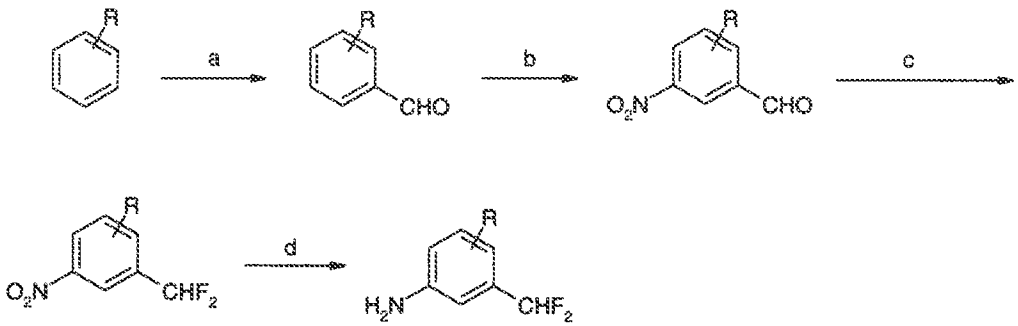
[0216] a) Br_2; b) $Zn(CN)_2$, $Pd(PPh)_3$; c) [H]; d) BH_3; e) $(BOC)_2O$; f) [H]; g) H_2SO_4, H_2O; h) R'X; i) [H]; j) $LiAlH_4$

[0217] Synthesis of Amine Precursors **P-V-A-1** or **P-V-A-2:**



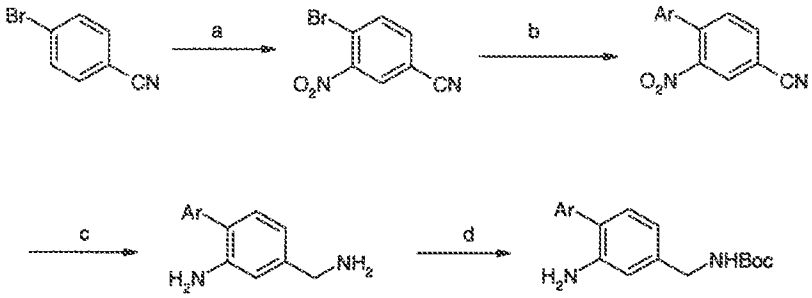
(i)$NaNO_2$, HCl; ii) Na_2SO_3, $CuSO_4$, HCl; b) NH_4Cl; c) [H]

[0218] Synthesis of Amine Precursors **P-V-A-1:**



a) $CHCl_2OMe$; b) KNO_3, H_2SO_4; c) Deoxo-Fluor; d) Fe

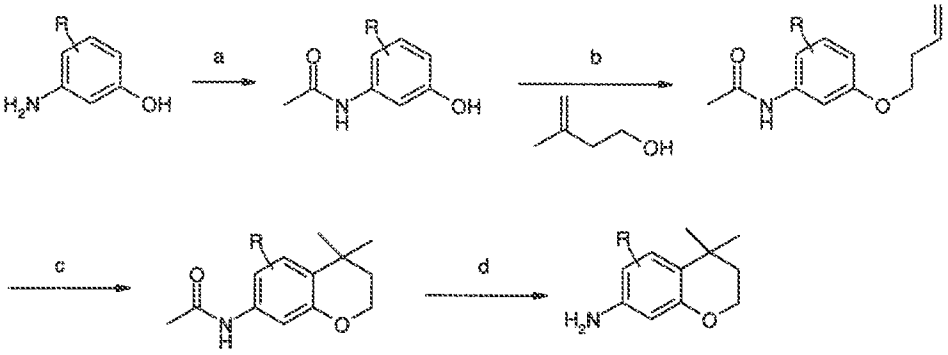
[0219] Synthesis of Amine Precursors **P-V-A-3:**



Ar = Aryl or Heteroaryl

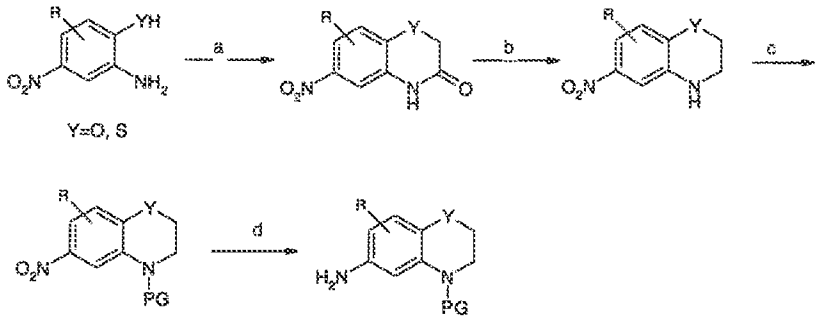
a) Nitration; b) $ArB(OH)_2$, Pd; c) BH_3; d) $(BOC)_2O$

[0220] Synthesis of Amine Precursors **P-V-B-1:**



a) AcCl; b) DEAD; c) $AlCl_3$; d) NaOH

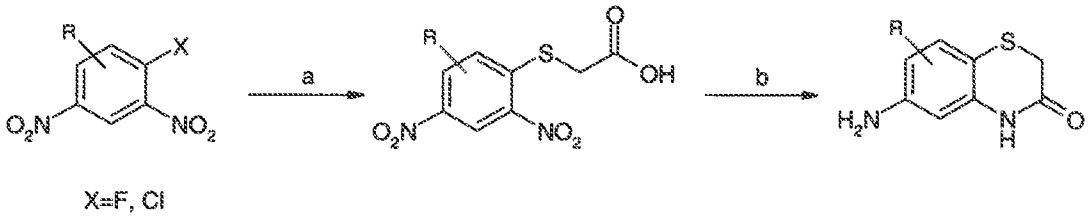
[0221] Synthesis of Amine Precursors **P-V-B-1:**



a) $ClCH_2COCl$; b) [H]; c) protection; d) [H]

PG= protecting group

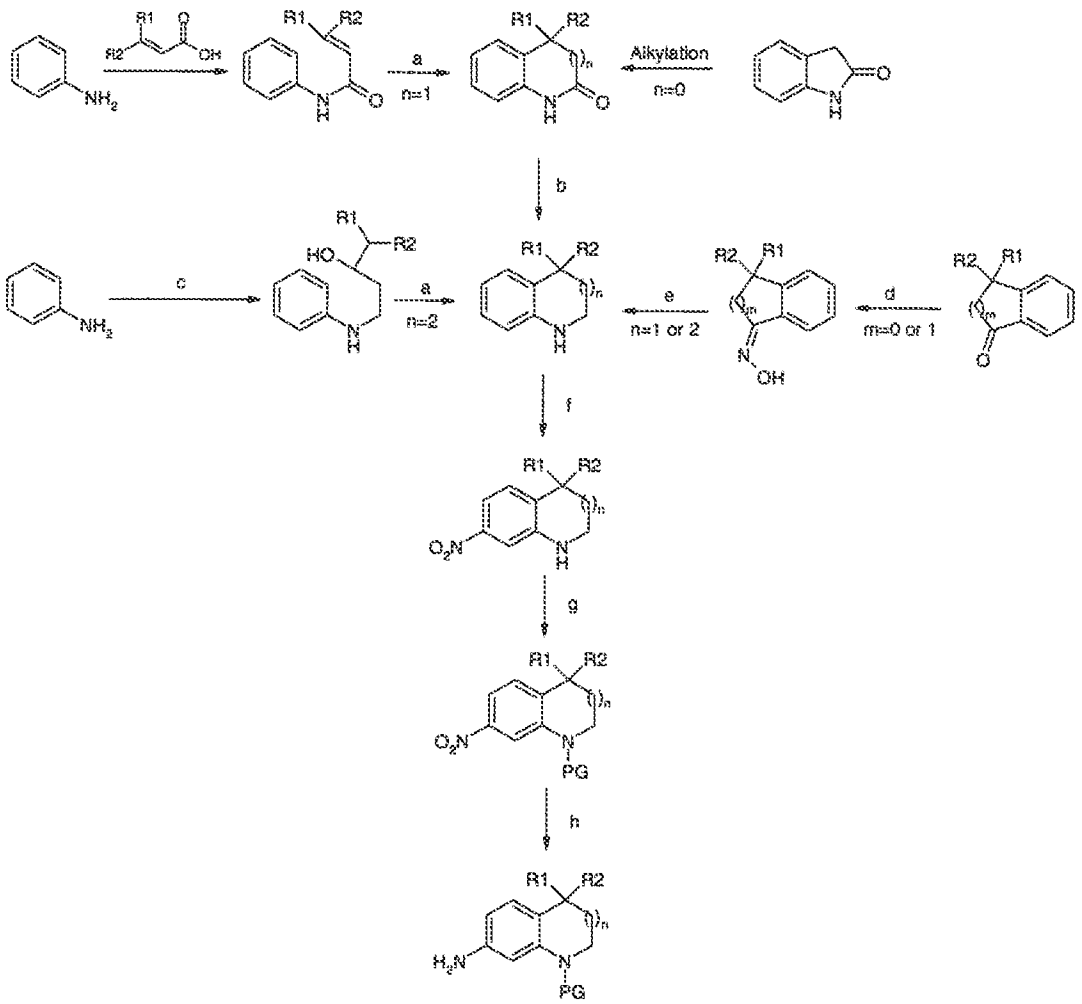
[0222] Synthesis of Amine Precursors **P-V-B-1**:



X=F, Cl

a) $HSCH_2CO_2H$; b) [H]

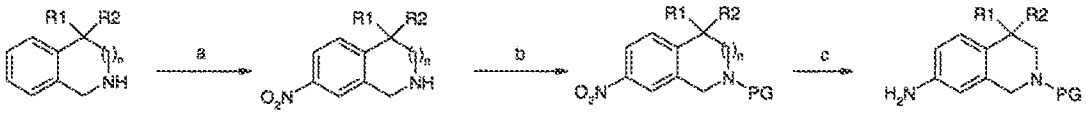
[0223] Synthesis of Amine Precursors **P-V-B-2**:



a) $AlCl_3$; b) [H]; c) i) R1R2CHCOCH$_2$CH$_2$Cl; ii) $NaBH_4$; d) NH_2OH; e) DIBAL-H; f) nitration; g) protection; h) [H]

PG= protecting group

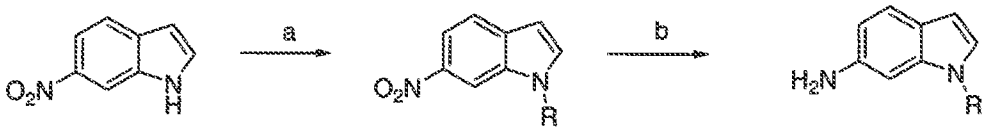
[0224] Synthesis of Amine Precursors **P-V-B-3**:



a) Nitration; b) Protection; c) [H]

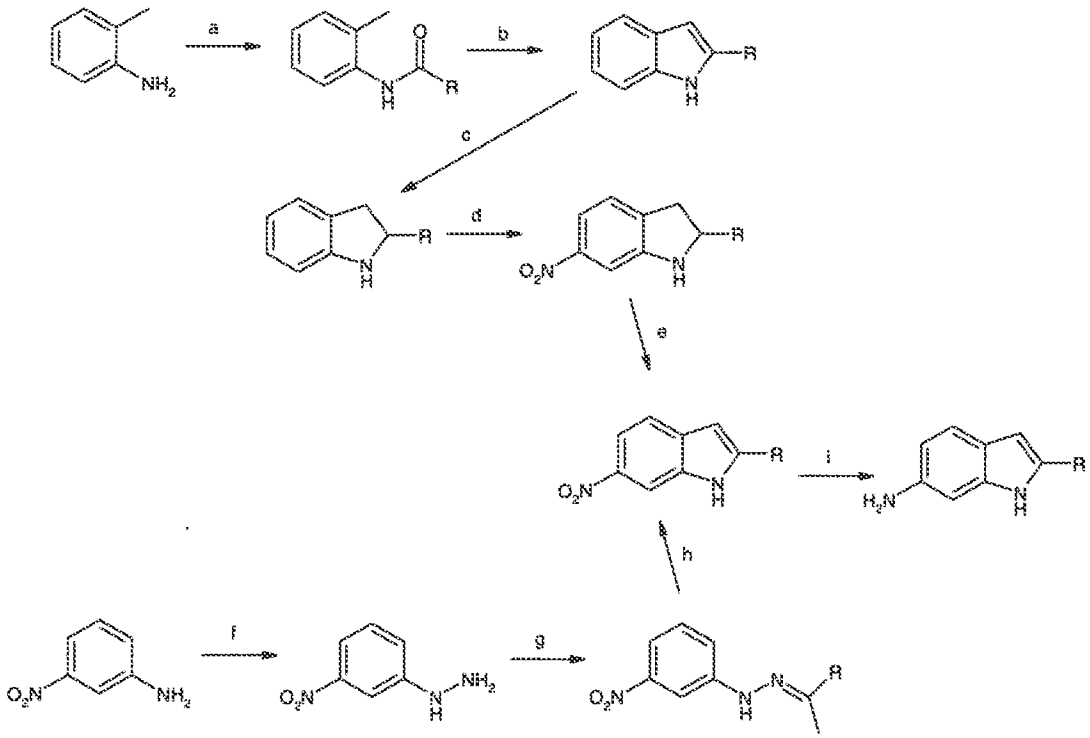
PG= protecting group

[0225] Synthesis of Amine Precursors **P-V-B-5**:



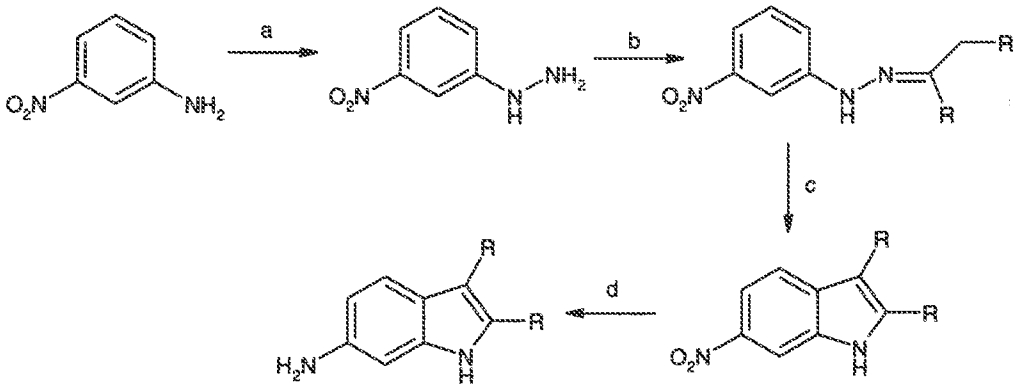
a) when X=Cl, Br, I: RX, K_2CO_3, DMF or CH_3CN; when X=OH: RX, TFFH, DIEA, THF b) H_2, Pd-C, EtOH or $SnCl_2.2H_2O$, EtOH or $SnCl_2.2H_2O$, DIEA, EtOH.

[0226] Synthesis of Amine Precursors **P-V-B-5**:



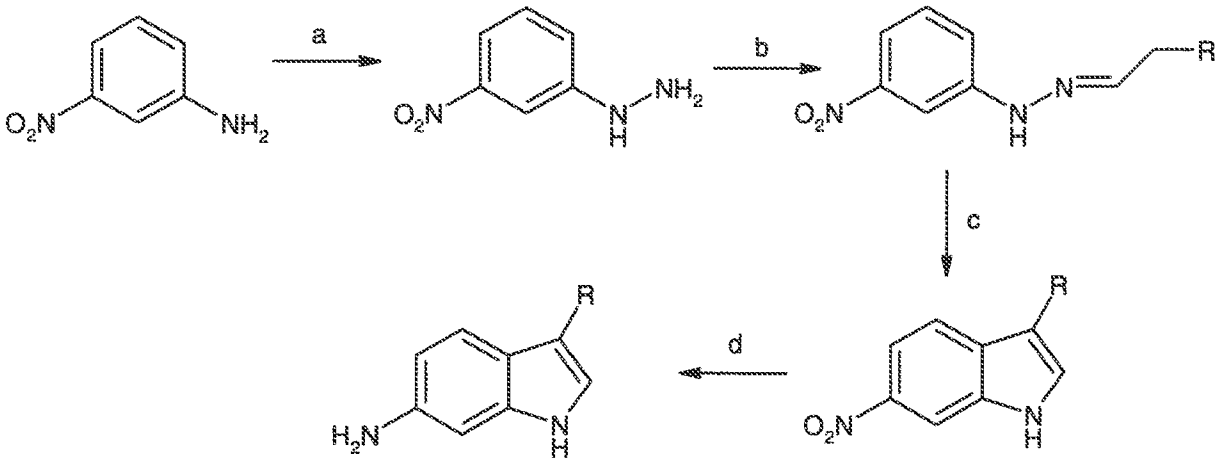
a) RCOCl, Et_3N, CH_2Cl_2; b) n-BuLi, THF; c) $NaBH_4$, AcOH; d) KNO_3, H_2SO_4; e) DDQ, 1,4-dioxane; f) $NaNO_2$, HCl, $SnCl_2.2H_2O$, H_2O; g) MeCOR, EtOH; h) PPA; i) $LiAlH_4$, THF or H_2, Raney Ni, EtOH or MeOH

[0227] Synthesis of Amine Precursors V-B-5:



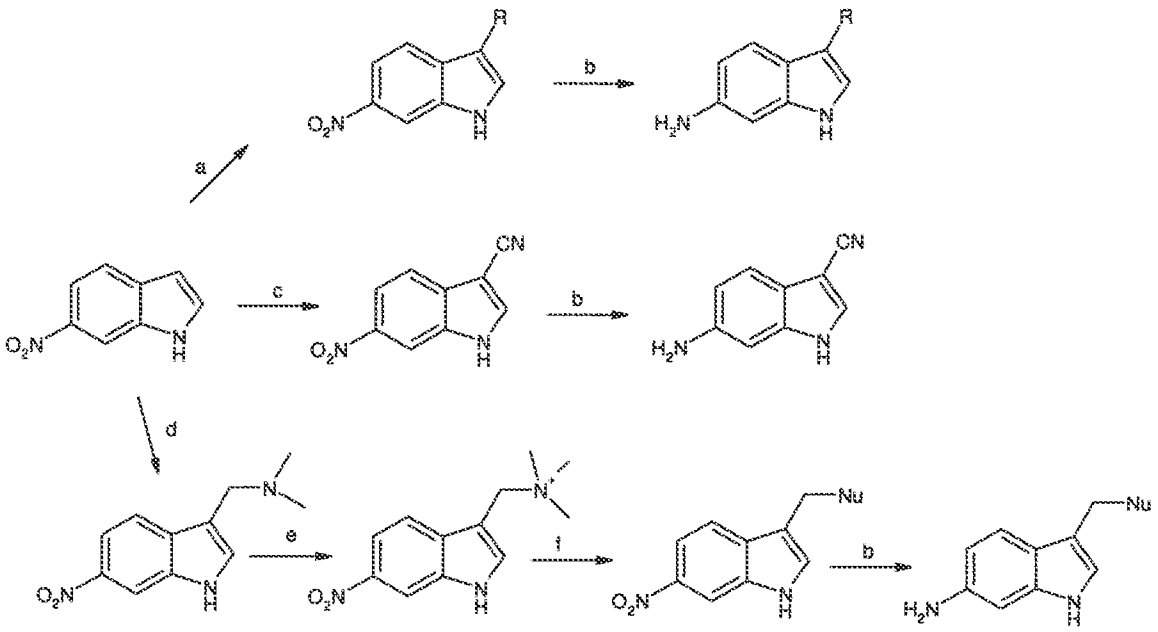
a) $NaNO_2$, HCl, $SnCl_2.2H_2O$, H_2O; b) RCH_2COR, AcOH, EtOH; c) H_3PO_4, toluene; d) H_2, Pd-C, EtOH

[0228] Synthesis of Amine Precursors P-V-B-5:



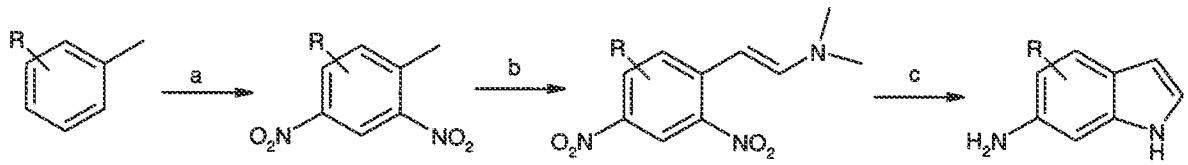
a) $NaNO_2$, HCl, $SnCl_2.2H_2O$, H_2O; b) RCH_2COH, AcOH, EtOH; c) H_3PO_4, toluene; d) H_2, Pd-C, EtOH

[0229] Synthesis of Amine Precursors **P-V-B-5**:



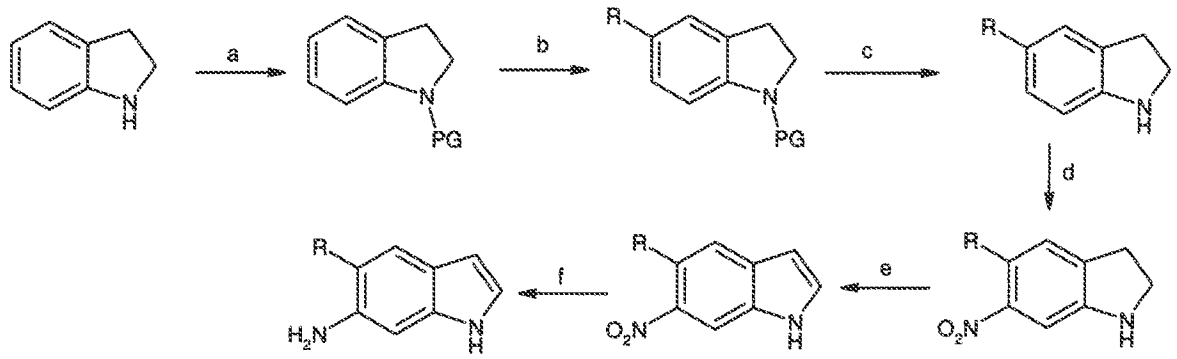
a) RX (X=Br, I), zinc triflate, TBAI, DIEA, toluene; b) H_2, Raney Ni, EtOH or H_2, Pd-C, EtOH or $SnCl_2.2H_2O$, EtOH; c) $ClSO_2NCO$, DMF, CH_3CN; d) Me_2NH, H_2CO, AcOH; e) MeI, DMF, THF, H_2O; f) MNu (M= Na, K, Li; Nu= nucleophile)

[0230] Synthesis of Amine Precursors **P-V-B-5**:



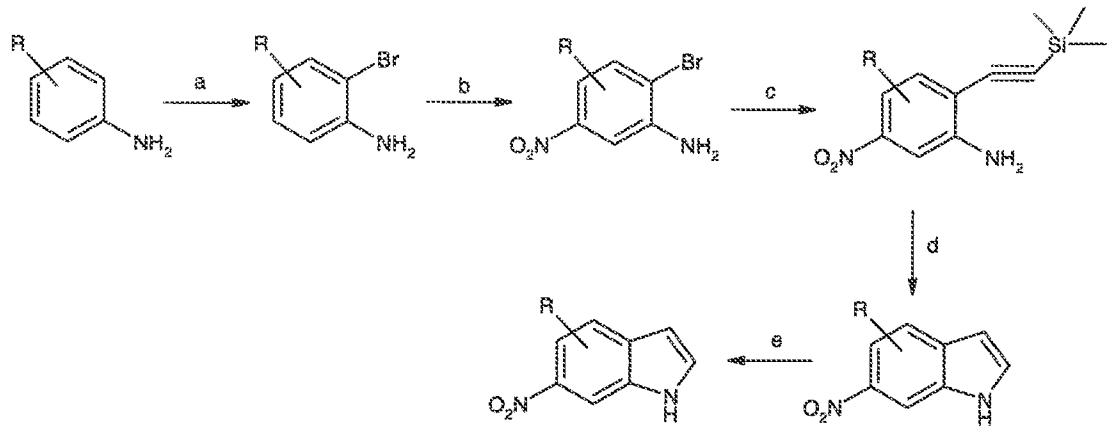
a) HNO_3, H_2SO_4; b) $Me_2NCH(OMe)_2$, DMF; c) H_2, Raney Ni, EtOH

[0231] Synthesis of Amine Precursors **P-V-B-5:**



a) When PG= SO_2Ph: $PhSO_2Cl$, Et_3N, DMAP, CH_2Cl_2; When PG= Ac: AcCl, $NaHCO_3$, CH_2Cl_2; b) When R= RCO: $(RCO)_2O$, $AlCl_3$, CH_2Cl_2; When R=Br: Br_2, AcOH; c) HBr or HCl; d) KNO_3, H_2SO_4; e) MnO_2, CH_2Cl_2 or DDQ, 1,4-dioxane; f) H_2, Raney Ni, EtOH.

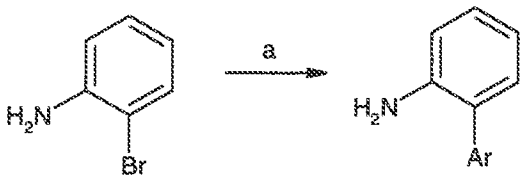
[0232] Synthesis of Amine Precursors **P-V-B-5:**



a) NBS, DMF; b) KNO_3, H_2SO_4; c) $HC{\equiv}CSiMe_3$, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, Toluene, H_2O; d) CuI, DMF; e) H_2, Raney Ni, MeOH

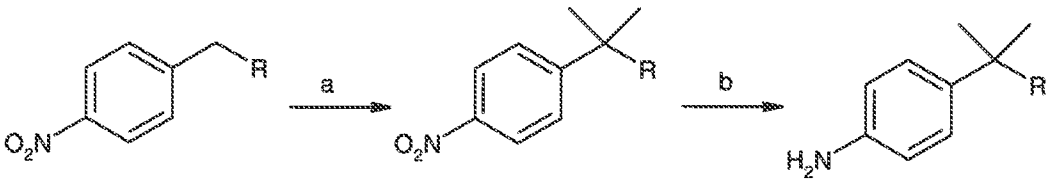
[0233] Synthesis of Amine Precursors **P-V-A-3** and **P-V-A-6:**

Ar= Aryl or heteroaryl



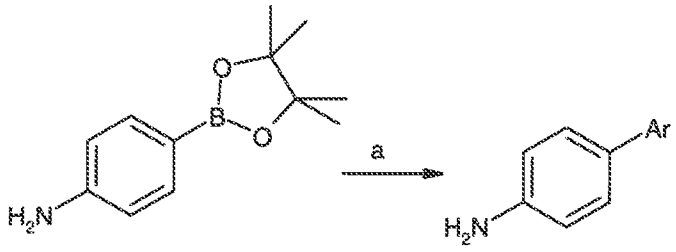
a) $ArB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, H_2O, THF or $ArB(OH)_2$, $Pd_2(dba)_3$, $P(tBu)_3$, KF, THF

[0234] Synthesis of Amine Precursors **P-V-A-4:**



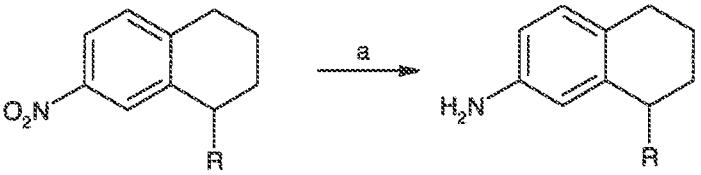
R= CN, CO_2Et; a) MeI, NaOtBu, DMF; b) HCO_2K, Pd-C, EtOH or HCO_2NH_4, Pd-C, EtOH

[0235] Synthesis of Amine Precursors **P-V-A-4:**



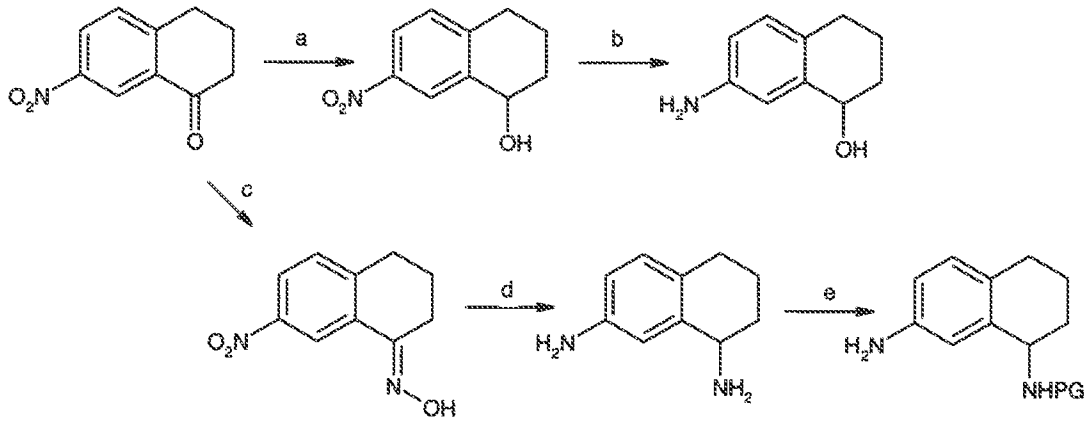
a) ArBr, $Pd(OAc)_2$, PS-PPh_3, K_2CO_3, DMF

[0236] Synthesis of Amine Precursors **P-V-B-4:**



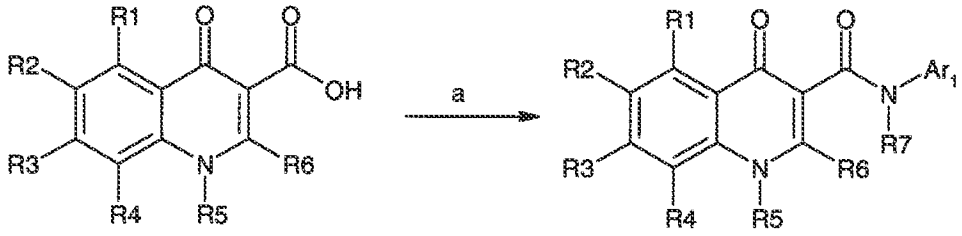
a) H_2, Pd-C, MeOH

[0237] Synthesis of Amine Precursors **P-V-B-4:**



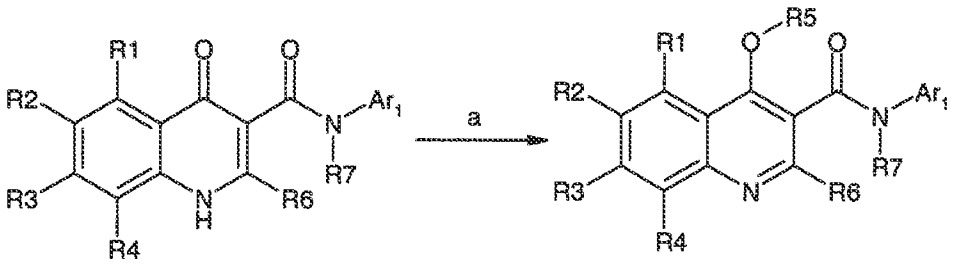
a) $NaBH_4$, MeOH; b) H_2, Pd-C, MeOH; c) NH_2OH, Pyridine; d) H_2, Pd-C, MeOH; e) Boc_2O, Et_3N, MeOH

[0238] Synthesis of Compounds of Formula I:



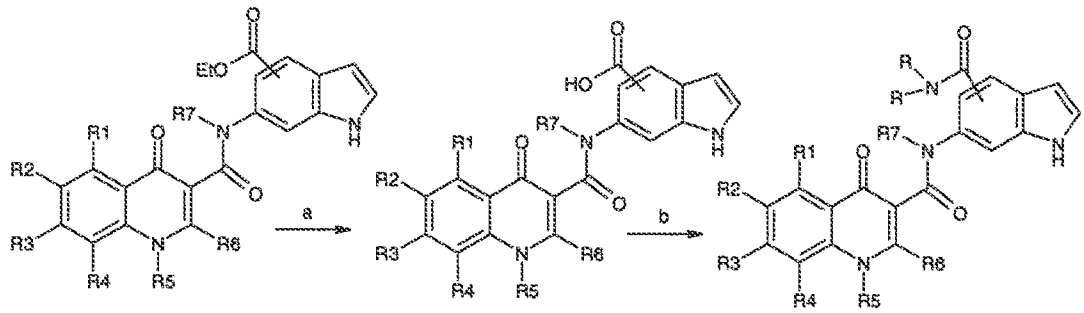
a) Ar_1R7NH, coupling reagent, base, solvent. Examples of conditions used: HATU, DIEA; BOP, DIEA, DMF; HBTU, Et_3N, CH_2Cl_2; PFPTFA, pyridine.

[0239] Synthesis of Compounds of Formula I':



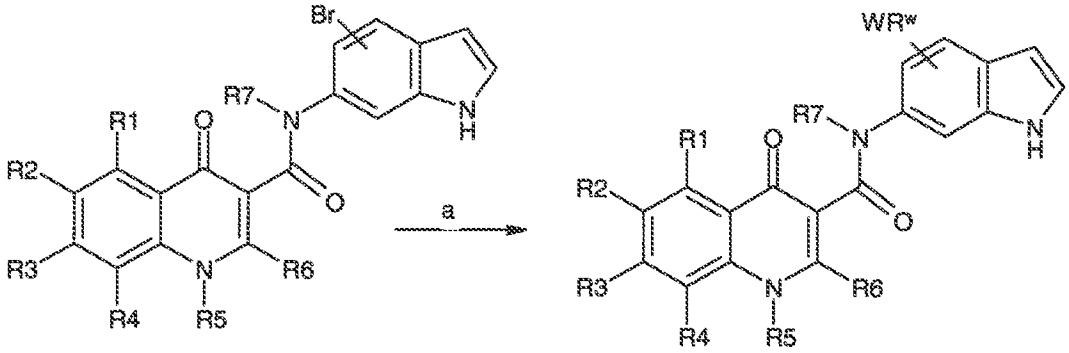
R^5 = aliphatic: a) R^5X (X= Br, I), Cs_2CO_3, DMF

[0240] Syntheis of Compounds of formula V-B-5:



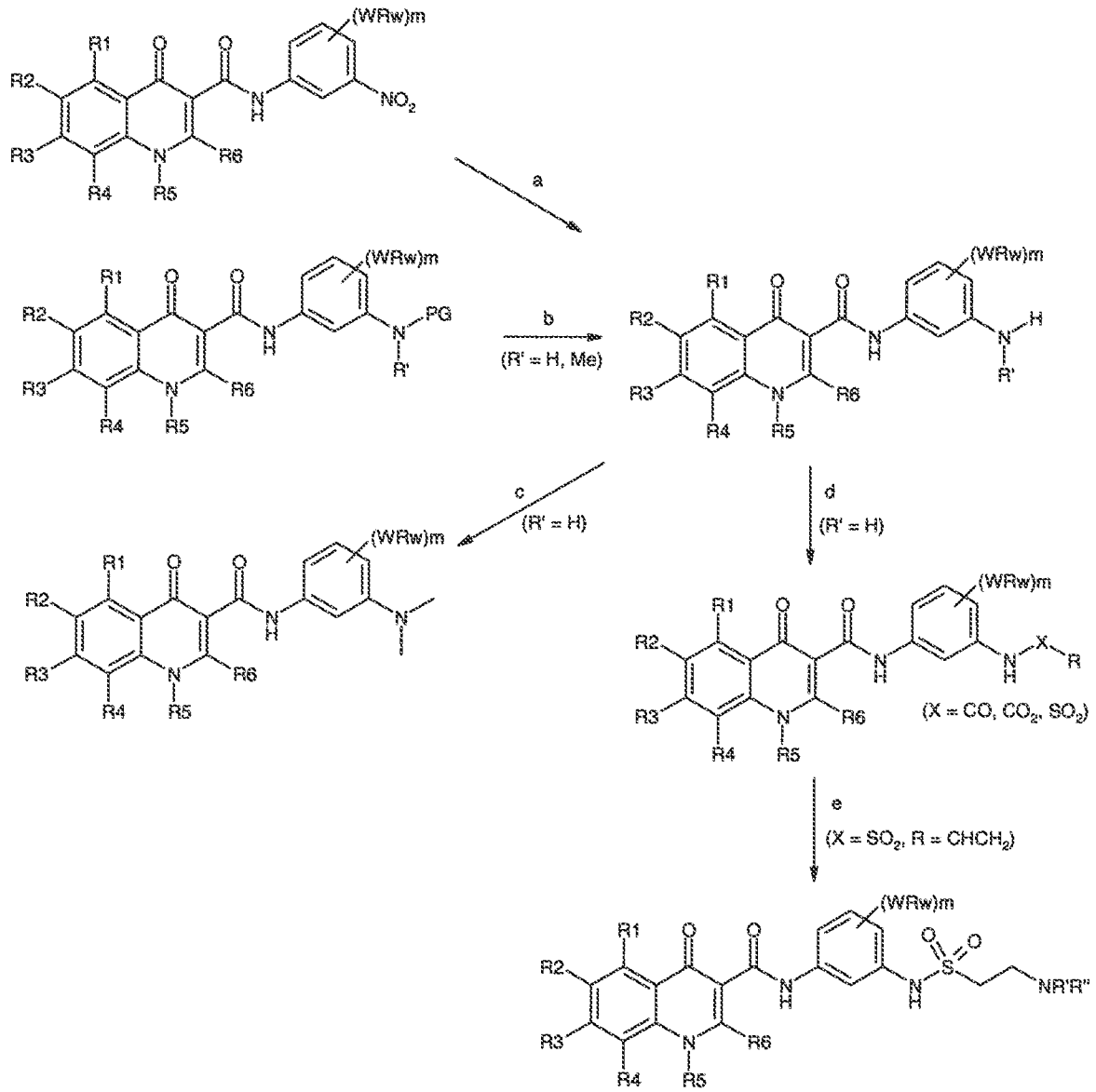
a) NaOH, THF; b) HNR_2, HATU, DIEA, DMF

[0241] Syntheis of Compounds of formula V-B-5:



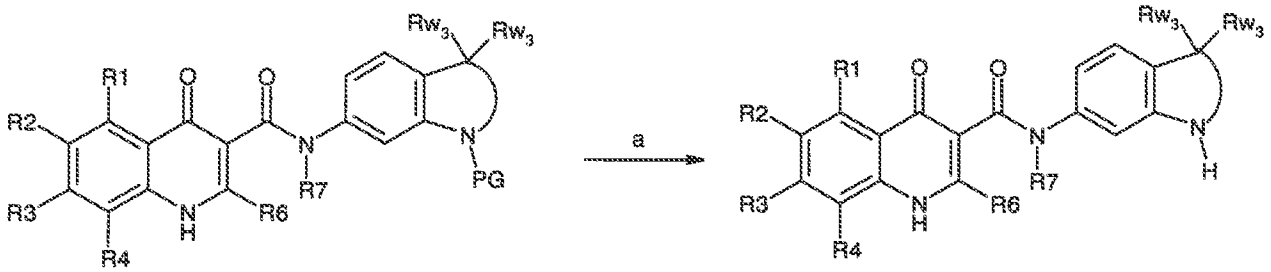
WR^w = aryl or heteroaryl: a) $ArB(OH)_2$, $(dppf)PdCl_2$, K_2CO_3, DMF

[0242] Synthesis of Compounds of Formula V-A-2 & V-A-5:



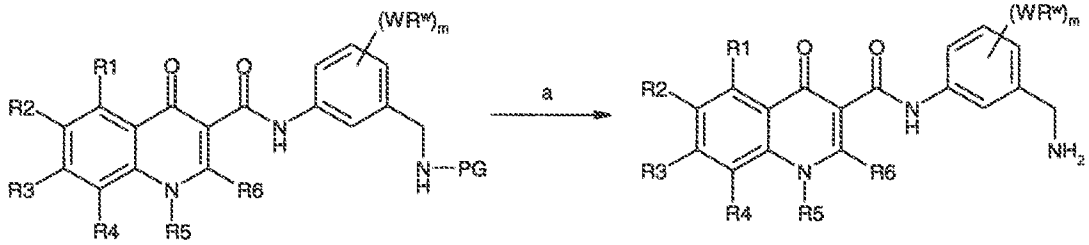
a) $SnCl_2.2H_2O$, EtOH; b) PG= BOC: TFA, CH_2Cl_2; c) CH_2O, $NaBH_3CN$, CH_2Cl_2, MeOH; d) RXCl, DIEA, THF or RXCl, NMM, 1,4-dioxane or RXCl, CH_2Cl_2, DMF; e) R'R''NH, $LiClO_4$, CH_2Cl_2, iPrOH

[0243] Synthesis of compounds of formula V-B-2:

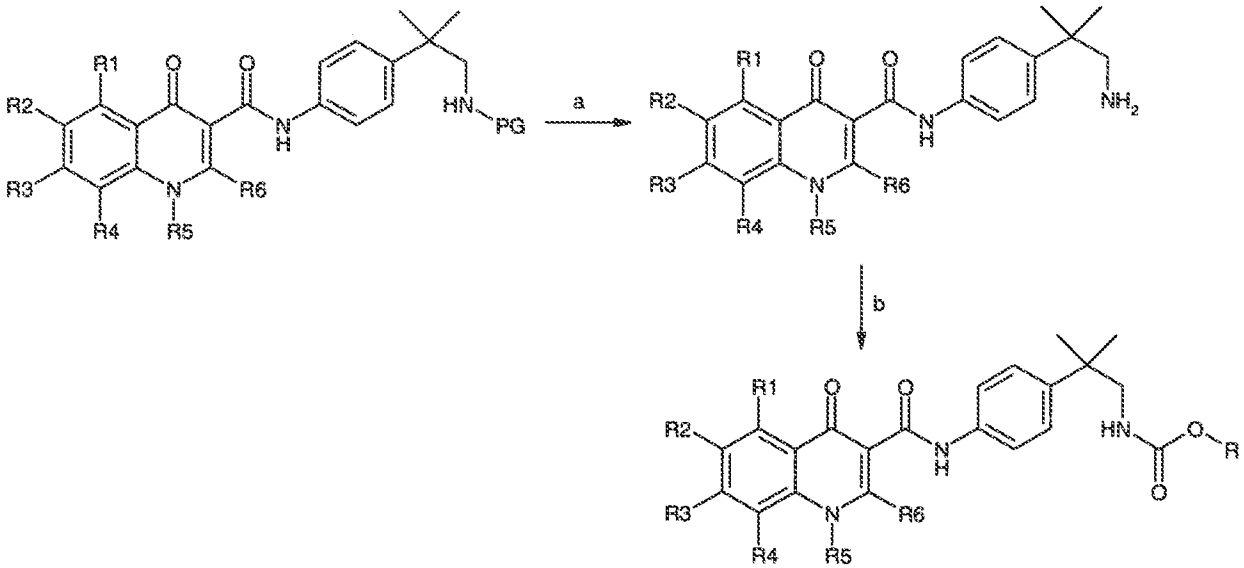


a) When PG = BOC: TFA, CH_2Cl_2; When PG = Ac: NaOH or HCl, EtOH or THF

[0244] Synthesis of compounds of formula V-A-2:

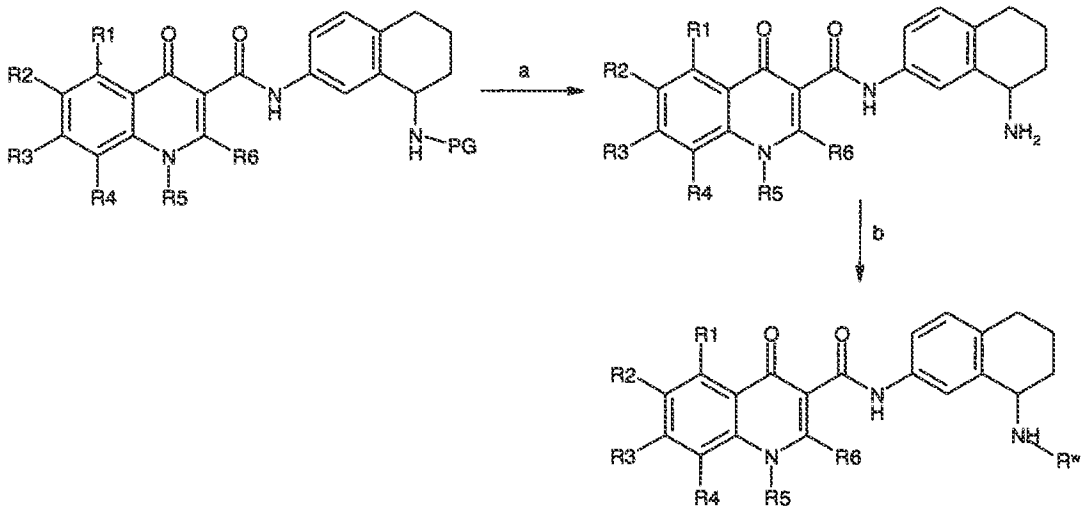


a) When PG = BOC: TFA, CH_2Cl_2



a) When PG = BOC: TFA, CH_2Cl_2; b) ROCOCl, Et_3N, DMF

[0245] Synthesis of compounds of formula V-A-4:



a)When PG = BOC: TFA, CH_2Cl_2; b) When $R^w = CO_2R$: ROCOCl, DIEA, MeOH

[0246] In the schemes above, the radical R employed therein is a substituent, e.g., R^W as defined hereinabove. One of skill in the art will readily appreciate that synthetic routes suitable for various substituents of the present invention are such that the reaction conditions and steps employed do not modify the intended substituents.

[0247] *5. Uses, Formulation and Administration*

[0248] *Pharmaceutically acceptable compositions*

[0249] As discussed above, the present invention provides compounds that are useful as modulators of ABC transporters and thus are useful in the treatment of disease, disorders or conditions such as cystic fibrosis, 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 asuch 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.

[0250] Accordingly, in another aspect of the present invention, pharmaceutically acceptable compositions are provided, wherein these compositions comprise any of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

[0251] It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative or a prodrug thereof. According to the present invention, a pharmaceutically acceptable derivative or a prodrug includes, but is not limited to, pharmaceutically acceptable salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need thereof is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[0252] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt or salt of an ester of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof.

[0253] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, **1977**, *66*, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate,

gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersable products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[0254] As described above, the pharmaceutically acceptable compositions of the present invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and

cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; RingeR's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[0255] *Uses of Compounds and Pharmaceutically Acceptable Compositions*

[0256] In yet another aspect, the present invention provides a method of treating or lessening the severity of a condition, disease, or disorder implicated by CFTR mutation. In certain embodiments, the present invention provides a method of treating a condition, disease, or disorder implicated by a deficiency of the CFTR activity, the method comprising administering a composition comprising a compound of Formula (I) to a subject, preferably a mammal, in need thereof.

[0257] In certain embodiments, the present invention provides a method of treating diseases associated with reduced CFTR function due to mutations in the gene encoding CFTR or environmental factors (e.g., smoke). These diseases include, cystic fibrosis, chronic bronchitis, recurrent bronchitis, acute bronchitis, male infertility caused by congenital bilateral absence of the vas deferens (CBAVD), female infertility caused by congenital absence of the uterus and vagina (CAUV), idiopathic chronic pancreatitis (ICP), idiopathic recurrent pancreatitis, idiopathic acute pancreatitis, chronic rhinosinusitis, primary sclerosing cholangitis, allergic bronchopulmonary aspergillosis, diabetes, dry eye, constipation, allergic bronchopulmonary aspergillosis (ABPA), bone diseases (e.g., osteoporosis), and asthma.

[0258] In certain embodiments, the present invention provides a method for treating diseases associated with normal CFTR function. These diseases include, chronic obstructive pulmonary disease (COPD), chronic bronchitis, recurrent bronchitis, acute bronchitis, rhinosinusitis, constipation, pancreatitis including chronic pancreatitis, recurrent pancreatitis, and acute pancreatitis, pancreatic insufficiency, male infertility caused by congenital bilateral absence of the vas deferens (CBAVD), mild pulmonary disease, idiopathic pancreatitis, liver disease, hereditary emphysema, gallstones, gasgtro-esophageal reflux disease, gastrointestinal

malignancies, inflammatory bowel disease, constipation, diabetes, arthritis, osteoporosis, and osteopenia.

[0259] In certain embodiments, the present invention provides a method for treating diseases associated with normal CFTR function including 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 palsy, 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, Gorham's Syndrome, chloride channelopathies, myotonia congenita (Thomson and Becker forms), Bartter's syndrome type III, Dent's disease, hyperekplexia, epilepsy, hyperekplexia, lysosomal storage disease, Angelman syndrome, Primary Ciliary Dyskinesia (PCD), PCD with situs inversus (also known as Kartagener syndrome), PCD without situs inversus and ciliary aplasia, or Sjogren's disease, comprising the step of administering to said mammal an effective amount of a composition comprising a compound of the present invention.

[0260] According to an alternative preferred embodiment, the present invention provides a method of treating cystic fibrosis comprising the step of administering to said mammal a composition comprising the step of administering to said mammal an effective amount of a composition comprising a compound of the present invention.

[0261] According to the invention an "effective amount" of the compound or pharmaceutically acceptable composition is that amount effective for treating or lessening the severity of one or more of the diseases, disorders or conditions as recited above.

[0262] The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for

treating or lessening the severity of one or more of the diseases, disorders or conditions as recited above.

[0263] In certain embodiments, the compounds and compositions of the present invention are useful for treating or lessening the severity of cystic fibrosis in patients who exhibit residual CFTR activity in the apical membrane of respiratory and non-respiratory epithelia. The presence of residual CFTR activity at the epithelial surface can be readily detected using methods known in the art, e.g., standard electrophysiological, biochemical, or histochemical techniques. Such methods identify CFTR activity using *in vivo* or *ex vivo* electrophysiological techniques, measurement of sweat or salivary Cl^- concentrations, or *ex vivo* biochemical or histochemical techniques to monitor cell surface density. Using such methods, residual CFTR activity can be readily detected in patients heterozygous or homozygous for a variety of different mutations, including patients homozygous or heterozygous for the most common mutation, ΔF508.

[0264] In another embodiment, the compounds and compositions of the present invention are useful for treating or lessening the severity of cystic fibrosis in patients who have residual CFTR activity induced or augmented using pharmacological methods or gene therapy. Such methods increase the amount of CFTR present at the cell surface, thereby inducing a hitherto absent CFTR activity in a patient or augmenting the existing level of residual CFTR activity in a patient.

[0265] In one embodiment, the compounds and compositions of the present invention are useful for treating or lessening the severity of cystic fibrosis in patients within certain genotypes exhibiting residual CFTR activity, e.g., class III mutations (impaired regulation or gating), class IV mutations (altered conductance), or class V mutations (reduced synthesis) (Lee R. Choo-Kang, Pamela L., Zeitlin, *Type I, II, III, IV, and V cystic fibrosis Tansmembrane Conductance Regulator Defects and Opportunities of Therapy*; Current Opinion in Pulmonary Medicine 6:521 – 529, 2000). Other patient genotypes that exhibit residual CFTR activity include patients homozygous for one of these classes or heterozygous with any other class of mutations, including class I mutations, class II mutations, or a mutation that lacks classification.

[0266] In one embodiment, the compounds and compositions of the present invention are useful for treating or lessening the severity of cystic fibrosis in patients within certain clinical phenotypes, e.g., a moderate to mild clinical phenotype that typically correlates with the amount of residual CFTR activity in the apical membrane of epithelia. Such phenotypes

include patients exhibiting pancreatic insufficiency or patients diagnosed with idiopathic pancreatitis and congenital bilateral absence of the vas deferens, or mild lung disease.

[0267] The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[0268] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops or patch), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[0269] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures

thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0270] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0271] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0272] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[0273] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are

solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0274] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0275] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[0276] The active compounds can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and

pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0277] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms are prepared by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[0278] As described generally above, the compounds of the invention are useful as modulators of ABC transporters. Thus, without wishing to be bound by any particular theory, the compounds and compositions are particularly useful for treating or lessening the severity of a disease, condition, or disorder where hyperactivity or inactivity of ABC transporters is implicated in the disease, condition, or disorder. When hyperactivity or inactivity of an ABC transporter is implicated in a particular disease, condition, or disorder, the disease, condition, or disorder may also be referred to as a "ABC transporter-mediated disease, condition or disorder". Accordingly, in another aspect, the present invention provides a method for treating or lessening the severity of a disease, condition, or disorder where hyperactivity or inactivity of an ABC transporter is implicated in the disease state.

[0279] The activity of a compound utilized in this invention as a modulator of an ABC transporter may be assayed according to methods described generally in the art and in the Examples herein.

[0280] It will also be appreciated that the compounds and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the compounds and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a

combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated".

[0281] In one embodiment, the additional agent is selected from a mucolytic agent, bronchodialator, an anti-biotic, an anti-infective agent, an anti-inflammatory agent, a CFTR modulator other than a compound of the present invention, or a nutritional agent. In a further embodiment, the additional agent is a CFTR modulator other than a compound of the present invention.

[0282] In one embodiment, the additional agent is an antibiotic. Exemplary antibiotics useful herein include tobramycin, including tobramycin inhaled powder (TIP), azithromycin, aztreonam, including the aerosolized form of aztreonam, amikacin, including liposomal formulations thereof, ciprofloxacin, including formulations thereof suitable for administration by inhalation, levoflaxacin, including aerosolized formulations thereof, and combinations of two antibiotics, e.g., fosfomycin and tobramycin.

[0283] In another embodiment, the additional agent is a mucolyte. Exemplary mucolytes useful herein includes Pulmozyme®.

[0284] In another embodiment, the additional agent is a bronchodialator. Exemplary bronchodialtors include albuterol, metaprotenerol sulfate, pirbuterol acetate, salmeterol, or tetrabuline sulfate.

[0285] In another embodiment, the additional agent is effective in restoring lung airway surface liquid. Such agents improve the movement of salt in and out of cells, allowing mucus in the lung airway to be more hydrated and, therefore, cleared more easily. Exemplary such agents include hypertonic saline, denufosol tetrasodium ([[(3S,5R)-5-(4-amino-2-oxopyrimidin-1-yl)-3-hydroxyoxolan-2-yl]methoxy-hydroxyphosphoryl] [[[(2R,3S,4R,5R)-5-(2,4-dioxopyrimidin-1-yl)-3, 4-dihydroxyoxolan-2-yl]methoxy-hydroxyphosphoryl]oxy-hydroxyphosphoryl] hydrogen phosphate), or bronchitol (inhaled formulation of mannitol).

[0286] In another embodiment, the additional agent is an anti-inflammatory agent, i.e., an agent that can reduce the inflammation in the lungs. Exemplary such agents useful herein

include ibuprofen, docosahexanoic acid (DHA), sildenafil, inhaled glutathione, pioglitazone, hydroxychloroquine, or simavastatin.

[0287] In another embodiment, the additional agent reduces the activity of the epithelial sodium channel blocker (ENaC) either directly by blocking the channel or indirectly by modulation of proteases that lead to an increase in ENaC activity (e.g., seine proteases, channel-activating proteases). Exemplary such agents include camostat (a trypsin-like protease inhibitor), QAU145, 552-02, GS-9411, INO-4995, Aerolytic, and amiloride. Additional agents that reduce the activity of the epithelial sodium channel blocker (ENaC) can be found, for example in PCT Publication No. WO2009/074575, the entire contents of which are incorporated herein in their entirety.

[0288] Amongst other diseases described herein, combinations of CFTR modulators, such as compounds of Formula I, and agents that reduce the activity of ENaC are use for treating Liddle's syndrome, an inflammatory or allergic condition including cystic fibrosis, primary ciliary dyskinesia, chronic bronchitis, chronic obstructive pulmonary disease, asthma, respiratory tract infections, lung carcinoma, xerostomia and keratoconjunctivitis sire, respiratory tract infections (acute and chronic; viral and bacterial) and lung carcinoma.

[0289] Combinations of CFTR modulators, such as compounds of Formula I, and agents that reduce the activity of ENaC are also useful for treating diseases mediated by blockade of the epithelial sodium channel also include diseases other than respiratory diseases that are associated with abnormal fluid regulation across an epithelium, perhaps involving abnormal physiology of the protective surface liquids on their surface, e.g., xerostomia (dry mouth) or keratoconjunctivitis sire (dry eye). Furthermore, blockade of the epithelial sodium channel in the kidney could be used to promote diuresis and thereby induce a hypotensive effect.

[0290] Asthma includes both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial infection. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g., of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome" .) Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g., of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways

hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e., therapy for or intended to restrict or abort symptomatic attack when it occurs, e.g., anti-inflammatory (e.g., cortico-steroid) or bronchodilatory. Prophylactic benefit in asthma may, in particular, be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognized asthmatic syndrome, common to a substantial percentage of asthmatics and characterized by asthma attack, e.g., between the hours of about 4-6 am, i.e., at a time normally substantially distant from any previously administered symptomatic asthma therapy.

[0291] Chronic obstructive pulmonary disease includes chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular, other inhaled drug therapy. In some embodiments, the combinations of CFTR modulators, such as compounds of Formula I, and agents that reduce the activity of ENaC are useful for the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis.

[0292] In another embodiment, the additional agent is a CFTR modulator other than a compound of formula I, i.e., an agent that has the effect of modulating CFTR activity. Exemplary such agents include ataluren ("PTC124®"; 3-[5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl]benzoic acid), sinapultide, lancovutide, depelestat (a human recombinant neutrophil elastase inhibitor), cobiprostone (7-{(2R, 4aR, 5R, 7aR)-2-[(3S)-1,1-difluoro-3-methylpentyl]-2-hydroxy-6-oxooctahydrocyclopenta[b]pyran-5-yl}heptanoic acid), or (3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid. In another embodiment, the additional agent is (3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid.

[0293] In another embodiment, the additional agent is a nutritional agent. Exemplary such agents include pancrelipase (pancreating enzyme replacement), including Pancrease®, Pancreacarb®, Ultrase®, or Creon®, Liprotomase® (formerly Trizytek®), Aquadeks®, or glutathione inhalation. In one embodiment, the additional nutritional agent is pancrelipase.

[0294] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[0295] The compounds of this invention or pharmaceutically acceptable compositions thereof may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Accordingly, the present invention, in another aspect, includes a composition for coating an implantable device comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. In still another aspect, the present invention includes an implantable device coated with a composition comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. Suitable coatings and the general preparation of coated implantable devices are described in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccarides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

[0296] Another aspect of the invention relates to modulating ABC transporter activity in a biological sample or a patient (e.g., *in vitro* or *in vivo*), which method comprises administering to the patient, or contacting said biological sample with a compound of formula I or a composition comprising said compound. The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[0297] Modulation of ABC transporter activity, e.g., CFTR, in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, the study of ABC transporters in biological and pathological phenomena; and the comparative evaluation of new modulators of ABC transporters.

[0298] In yet another embodiment, a method of modulating activity of an anion channel *in vitro* or *in vivo*, is provided comprising the step of contacting said channel with a compound of formula (I). In preferred embodiments, the anion channel is a chloride channel or a bicarbonate channel. In other preferred embodiments, the anion channel is a chloride channel.

[0299] According to an alternative embodiment, the present invention provides a method of increasing the number of functional ABC transporters in a membrane of a cell, comprising the step of contacting said cell with a compound of formula (**I**). The term "functional ABC transporter" as used herein means an ABC transporter that is capable of transport activity. In preferred embodiments, said functional ABC transporter is CFTR.

[0300] According to another preferred embodiment, the activity of the ABC transporter is measured by measuring the transmembrane voltage potential. Means for measuring the voltage potential across a membrane in the biological sample may employ any of the known methods in the art, such as optical membrane potential assay or other electrophysiological methods.

[0301] The optical membrane potential assay utilizes voltage-sensitive FRET sensors described by Gonzalez and Tsien (See, Gonzalez, J. E. and R. Y. Tsien (1995) "Voltage sensing by fluorescence resonance energy transfer in single cells" Biophys J **69**(4): 1272-80, and Gonzalez, J. E. and R. Y. Tsien (1997) "Improved indicators of cell membrane potential that use fluorescence resonance energy transfer" Chem Biol **4**(4): 269-77) in combination with instrumentation for measuring fluorescence changes such as the Voltage/Ion Probe Reader (VIPR) (See, Gonzalez, J. E., K. Oades, et al. (1999) "Cell-based assays and instrumentation for screening ion-channel targets" Drug Discov Today **4**(9): 431-439).

[0302] These voltage sensitive assays are based on the change in fluorescence resonant energy transfer (FRET) between the membrane-soluble, voltage-sensitive dye, $DiSBAC_2(3)$, and a fluorescent phospholipid, CC2-DMPE, which is attached to the outer leaflet of the plasma membrane and acts as a FRET donor. Changes in membrane potential (V_m) cause the negatively charged $DiSBAC_2(3)$ to redistribute across the plasma membrane and the amount of energy transfer from CC2-DMPE changes accordingly. The changes in fluorescence emission can be monitored using VIPR™ II, which is an integrated liquid handler and fluorescent detector designed to conduct cell-based screens in 96- or 384-well microtiter plates.

[0303] In another aspect the present invention provides a kit for use in measuring the activity of a ABC transporter or a fragment thereof in a biological sample *in vitro* or *in vivo* comprising (i) a composition comprising a compound of formula (**I**) or any of the above embodiments; and (ii) instructions for a) contacting the composition with the biological sample and b) measuring activity of said ABC transporter or a fragment thereof. In one embodiment, the kit further comprises instructions for a) contacting an additional composition with the biological sample; b) measuring the activity of said ABC transporter or a fragment thereof in the presence of said additional compound, and c) comparing the activity of the ABC

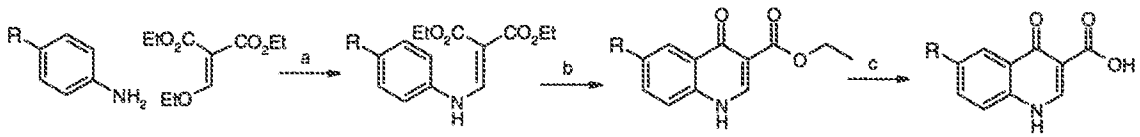
transporter in the presence of the additional compound with the density of the ABC transporter in the presence of a composition of formula (**I**). In preferred embodiments, the kit is used to measure the density of CFTR.

[0304] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

EXAMPLES

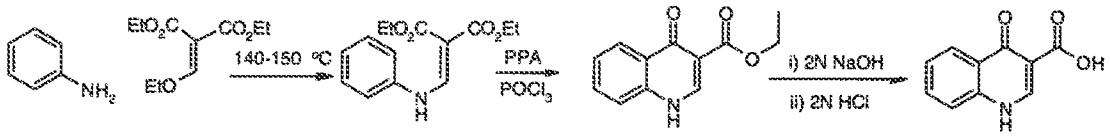
[0305] Example 1:

[0306] General scheme to prepare Acid Moities:



a) 140-150 °C; b) PPA, $POCl_3$, 70 °C or diphenyl ether, 220 °C; c) i) 2N NaOH ii) 2N HCl

[0307] Specific example: **2-Phenylaminomethylene-malonic acid diethyl ester**



A-1

A mixture of aniline (25.6 g, 0.28 mol) and diethyl 2-(ethoxymethylene)malonate (62.4 g, 0.29 mol) was heated at 140-150 °C for 2 h. The mixture was cooled to room temperature and dried under reduced pressure to afford 2-phenylaminomethylene-malonic acid diethyl ester as a solid, which was used in the next step without further purification. ^{1}H NMR (*d*-DMSO) δ 11.00 (d, 1H), 8.54 (d, *J* = 13.6 Hz, 1H), 7.36-7.39 (m, 2H), 7.13-7.17 (m, 3 H), 4.17-4.33 (m, 4H), 1.18-1.40 (m, 6H).

[0308] 4-Hydroxyquinoline-3-carboxylic acid ethyl ester

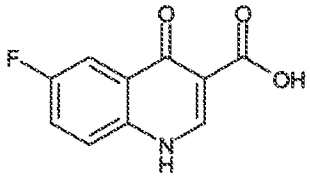
A 1 L three-necked flask fitted with a mechanical stirrer was charged with 2-phenylaminomethylene-malonic acid diethyl ester (26.3 g, 0.1 mol), polyphosphoric acid (270 g) and phosphoryl chloride (750 g). The mixture was heated to about 70 °C and stirred for 4 h. The mixture was cooled to room temperature, and filtered. The residue was treated with aqueous Na_2CO_3 solution, filtered, washed with water and dried. 4-Hydroxyquinoline-3-carboxylic acid

ethyl ester was obtained as a pale brown solid (15.2 g, 70 %). The crude product was used in next step without further purification.

[0309] A-1; 4-Oxo-1,4-dihydroquinoline-3-carboxylic acid

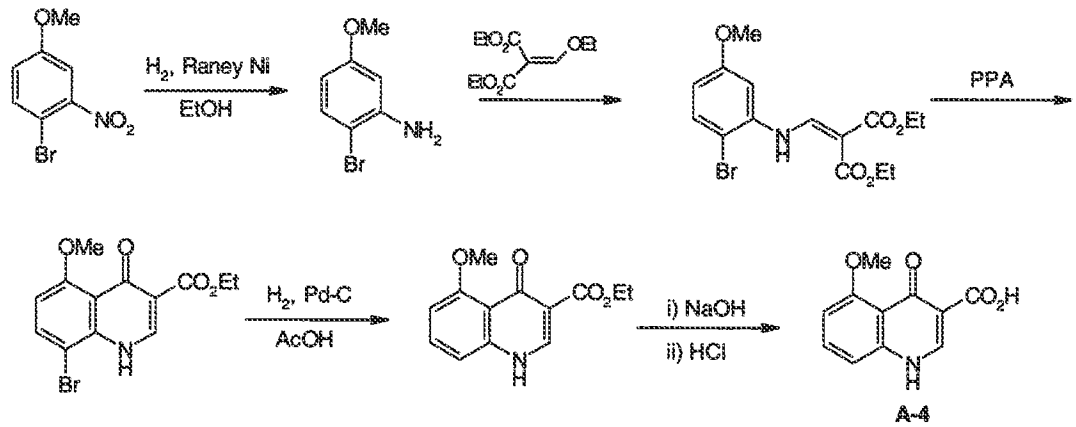
4-Hydroxyquinoline-3-carboxylic acid ethyl ester (15 g, 69 mmol) was suspended in sodium hydroxide solution (2N, 150 mL) and stirred for 2 h under reflux. After cooling, the mixture was filtered, and the filtrate was acidified to pH 4 with 2N HCl. The resulting precipitate was collected via filtration, washed with water and dried under vacuum to give 4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**A-1**) as a pale white solid (10.5 g, 92 %). ^{1}H NMR (*d*-DMSO) δ15.34 (s, 1 H), 13.42 (s, 1 H), 8.89 (s, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 7.88 (m, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.60 (m, 1H).

[0310] Specific Example: **A-2; 6-Fluoro-4-hydroxy-quinoline-3-carboxylic acid**



6-Fluoro-4-hydroxy-quinoline-3-carboxylic acid (**A-2**) was synthesized following the general scheme above starting from 4-fluoro-phenylamine. Overall yield (53 %). ^{1}H NMR (DMSO-d_6) δ 15.2 (br s, 1 H), 8.89 (s, 1 H), 7.93-7.85 (m, 2 H), 7.80-7.74 (m, 1 H); ESI-MS 207.9 m/z (MH^+).

[0311] Example 2:



[0312] 2-Bromo-5-methoxy-phenylamine

A mixture of 1-bromo-4-methoxy-2-nitro-benzene (10 g, 43 mmol) and Raney Ni (5 g) in ethanol (100 mL) was stirred under H_2 (1 atm) for 4 h at room temperature. Raney Ni was filtered off and the filtrate was concentrated under reduced pressure. The resulting solid was purified by column chromatography to give 2-bromo-5-methoxy-phenylamine (7.5 g, 86 %).

[0313] 2-[(2-Bromo-5-methoxy-phenylamino)-methylene]-malonic acid diethyl ester

A mixture of 2-bromo-5-methoxy-phenylamine (540 mg, 2.64 mmol) and diethyl 2-(ethoxymethylene)malonate (600 mg, 2.7 mmol) was stirred at 100 °C for 2 h. After cooling, the reaction mixture was recrystallized from methanol (10 mL) to give 2-[(2-bromo-5-methoxy-phenylamino)-methylene]-malonic acid diethyl ester as a yellow solid (0.8 g, 81 %).

[0314] 8-Bromo-5-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester

2-[(2-Bromo-5-methoxy-phenylamino)-methylene]-malonic acid diethyl ester (9 g, 24.2 mmol) was slowly added to polyphosphoric acid (30 g) at 120 °C. The mixture was stirred at this temperature for additional 30 min and then cooled to room temperature. Absolute ethanol (30 mL) was added and the resulting mixture was refluxed for 30 min. The mixture was basified with aqueous sodium bicarbonate at 25 °C and extracted with EtOAc (4 x 100 mL). The organic layers were combined, dried and the solvent evaporated to give 8-bromo-5-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (2.3 g, 30 %).

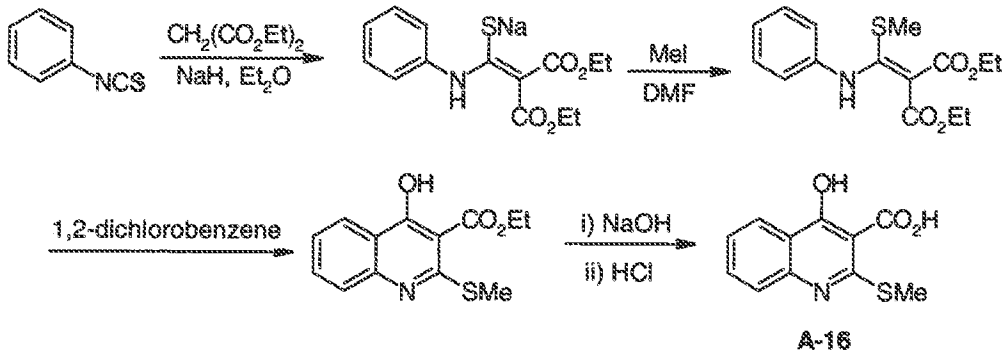
[0315] 5-Methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester

A mixture of 8-bromo-5-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (2.3 g, 7.1 mmol), sodium acetate (580 mg, 7.1 mmol) and 10 % Pd/C (100 mg) in glacial acetic acid (50 mL) was stirred under H_2 (2.5 atm) overnight. The catalyst was removed via filtration, and the reaction mixture was concentrated under reduced pressure. The resulting oil was dissolved in CH_2Cl_2 (100 mL) and washed with aqueous sodium bicarbonate solution and water. The organic layer was dried, filtered and concentrated. The crude product was purified by column chromatography to afford 5-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester as a yellow solid (1 g, 57 %).

[0316] A-4; 5-Methoxy-4-oxo-1, 4-dihydro-quinoline-3-carboxylic acid

A mixture of 5-methoxy-4-oxo-1, 4-dihydro-quinoline-3-carboxylic acid ethyl ester (1 g, 7.1 mmol) in 10% NaOH solution (50 mL) was heated to reflux overnight and then cooled to room temperature. The mixture was extracted with ether. The aqueous phase was separated and acidified with conc. HCl solution to pH 1-2. The resulting precipitate was collected by filtration to give 5-methoxy-4-oxo-1, 4-dihydro-quinoline-3-carboxylic acid (**A-4**) (530 mg, 52 %). ^{1}H NMR (DMSO) δ: 15.9 (s, 1 H), 13.2 (br, 1 H), 8.71 (s, 1 H), 7.71 (t, J = 8.1 Hz, 1 H), 7.18 (d, J = 8.4 Hz, 1 H), 6.82 (d, J = 8.4 Hz, 1 H), 3.86 (s, 3 H); ESI-MS 219.9 m/z (MH^+).

[0317] Example 3:



A-16

[0318] Sodium 2-(mercapto-phenylamino-methylene)-malonic acid diethyl ester

To a suspension of NaH (60% in mineral oil, 6 g, 0.15 mol) in Et_2O at room temperature was added dropwise, over a 30 minutes period, ethyl malonate (24 g, 0.15 mol). Phenyl isothiocyanate (20.3 g, 0.15 mol) was then added dropwise with stirring over 30 min. The mixture was refluxed for 1 h and then stirred overnight at room temperature. The solid was separated, washed with anhydrous ether (200 mL), and dried under *vacuum* to yield sodium 2-(mercapto-phenylamino-methylene)-malonic acid diethyl ester as a pale yellow powder (46 g, 97 %).

[0319] 2-(Methylsulfanyl-phenylamino-methylene)-malonic acid diethyl ester

Over a 30 min period, methyl iodide (17.7 g, 125 mmol) was added dropwise to a solution of sodium 2-(mercapto-phenylamino-methylene)-malonic acid diethyl ester (33 g, 104 mmol) in DMF (100 mL) cooled in an ice bath. The mixture was stirred at room temperature for 1 h, and then poured into ice water (300 mL). The resulting solid was collected via filtration, washed

with water and dried to give 2-(methylsulfanyl-phenylamino-methylene)-malonic acid diethyl ester as a pale yellow solid (27 g, 84 %).

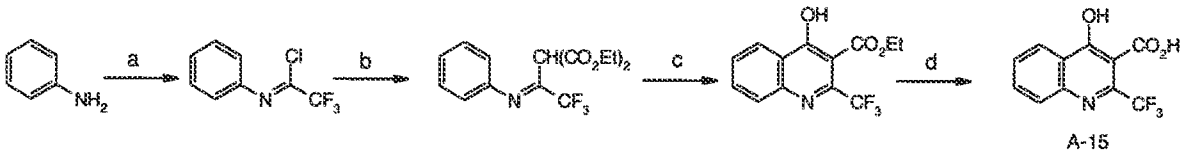
[0320] 4-Hydroxy-2-methylsulfanyl-quinoline-3-carboxylic acid ethyl ester

A mixture of 2-(methylsulfanyl-phenylamino-methylene)-malonic acid diethyl ester (27 g, 87 mmol) in 1,2-dichlorobenzene (100 mL) was heated to reflux for 1.5 h. The solvent was removed under reduced pressure and the oily residue was triturated with hexane to afford a pale yellow solid that was purified by preparative HPLC to yield 4-hydroxy-2-methylsulfanyl-quinoline-3-carboxylic acid ethyl ester (8 g, 35 %).

[0321] A-16; 2-Methylsulfanyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

4-Hydroxy-2-methylsulfanyl-quinoline-3-carboxylic acid ethyl ester (8 g, 30 mmol) was heated under reflux in NaOH solution (10%, 100 mL) for 1.5 h. After cooling, the mixture was acidified with concentrated HCl to pH 4. The resulting solid was collected via filtration, washed with water (100 mL) and MeOH (100 mL) to give 2-methylsulfanyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**A-16**) as a white solid (6 g, 85 %). ^{1}H NMR ($CDCl_3$) δ 16.4 (br s, 1 H), 11.1 (br s, 1 H), 8.19 (d, J = 8 Hz, 1H), 8.05 (d, J = 8 Hz, 1H), 7.84 (t, J = 8, 8 Hz, 1H), 7.52 (t, J = 8 Hz, 1H), 2.74 (s, 3H); ESI-MS 235.9 m/z (MH^+).

[0322] Example 4:



A-15

a) PPh_3, Et_3N, CCl_4, CF_3CO_2H; b) diethyl malonate; c) T~ 200°C; d) 10% NaOH

[0323] 2,2,2-Trifluoro-N-phenyl-acetimidoyl chloride

A mixture of Ph_3P (138.0 g, 526 mmol), Et_3N (21.3 g, 211 mmol), CCl_4 (170 mL) and TFA (20 g, 175 mmol) was stirred for 10 min in an ice-bath. Aniline (19.6 g, 211 mmol) was dissolved in CCl_4 (20 mL) was added. The mixture was stirred at reflux for 3 h. The solvent was removed under vacuum and hexane was added. The precipitates (Ph_3PO and Ph_3P) were filtered off and washed with hexane. The filtrate was distilled under reduced pressure to yield 2,2,2-trifluoro-*N*-phenyl-acetimidoyl chloride (19 g), which was used in the next step without further purification.

[0324] 2-(2,2,2-Trifluoro-1-phenylimino-ethyl)-malonic acid diethyl ester

To a suspension of NaH (3.47 g, 145 mmol, 60 % in mineral oil) in THF (200 mL) was added diethyl malonate (18.5 g, 116 mmol) at 0 °C. The mixture was stirred for 30 min at this temperature and 2,2,2-trifluoro-N-phenyl-acetimidoyl chloride (19 g, 92 mmol) was added at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was diluted with CH_2Cl_2, washed with saturated sodium bicarbonate solution and brine. The combined organic layers were dried over Na_2SO_4, filtered and concentrated to provide 2-(2,2,2-trifluoro-1-phenylimino-ethyl)-malonic acid diethyl ester, which was used directly in the next step without further purification.

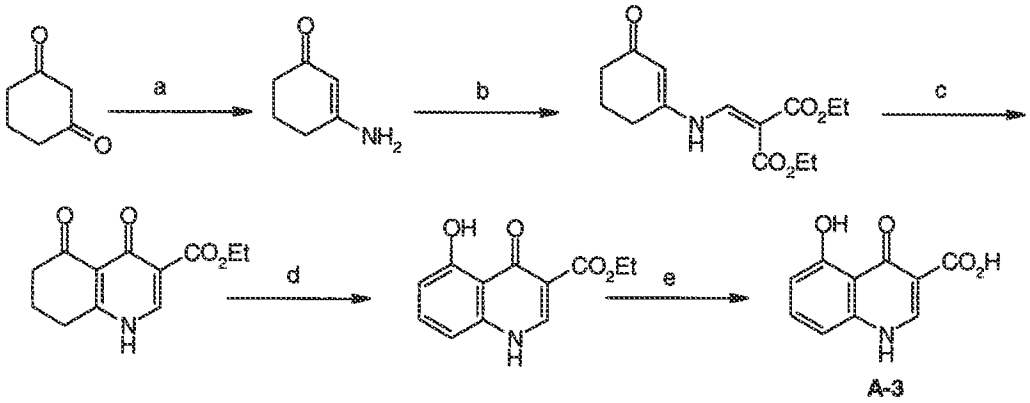
[0325] 4-Hydroxy-2-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester

2-(2,2,2-Trifluoro-1-phenylimino-ethyl)-malonic acid diethyl ester was heated at 210 °C for 1 h with continuous stirring. The mixture was purified by column chromatography (petroleum ether) to yield 4-hydroxy-2-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (12 g, 24 % over 3 steps).

[0326] A-15; 4-Hydroxy-2-trifluoromethyl-quinoline-3-carboxylic acid

A suspension of 4-hydroxy-2-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester (5 g, 17.5 mmol) in 10% aqueous NaOH solution was heated at reflux for 2 h. After cooling, dichloromethane was added and the aqueous phase was separated and acidified with concentrated HCl to pH 4. The resulting precipitate was collected via filtration, washed with water and Et_2O to provide 4-hydroxy-2-trifluoromethyl-quinoline-3-carboxylic acid (**A-15**) (3.6 g, 80 %). ^{1}H NMR (DMSO-d_6) δ 8.18-8.21 (d, J = 7.8 Hz, 1 H), 7.92-7.94 (d, J = 8.4 Hz, 1 H), 7.79-7.83 (t, J = 14.4 Hz, 1 H), 7.50-7.53 (t, J = 15 Hz, 1 H); ESI-MS 257.0 m/z (MH^+).

[0327] Example 5:



a) $CH_3C(O)ONH_4$, toluene; b) $EtOCHC(CO_2Et)_2$, 130 °C; c) Ph_2O; d) I_2, EtOH; e) NaOH

[0328] 3-Amino-cyclohex-2-enone

A mixture of cyclohexane-1,3-dione (56.1 g, 0.5 mol) and $AcONH_4$ (38.5 g, 0.5 mol) in toluene was heated at reflux for 5 h with a Dean-stark apparatus. The resulting oily layer was separated and concentrated under reduced pressure to give 3-amino-cyclohex-2-enone (49.9 g, 90 %), which was used directly in the next step without further purification.

[0329] 2-[(3-Oxo-cyclohex-1-enylamino)-methylene]-malonic acid diethyl ester

A mixture of 3-amino-cyclohex-2-enone (3.3 g, 29.7 mmol) and diethyl 2-(ethoxymethylene)malonate (6.7 g, 31.2 mmol) was stirred at 130 °C for 4 h. The reaction mixture was concentrated under reduced pressure and the resulting oil was purified by column chromatography (silica gel, ethyl acetate) to give 2-[(3-oxo-cyclohex-1-enylamino)-methylene]-malonic acid diethyl ester (7.5 g, 90 %).

[0330] 4,5-Dioxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid ethyl ester

A mixture of 2-[(3-oxo-cyclohex-1-enylamino)-methylene]-malonic acid diethyl ester (2.8 g, 1 mmol) and diphenylether (20 mL) was refluxed for 15 min. After cooling, *n*-hexane (80 mL) was added. The resulting solid was isolated via filtration and recrystallized from methanol to give 4,5-dioxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid ethyl ester (1.7 g 72 %).

[0331] 5-Hydroxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester

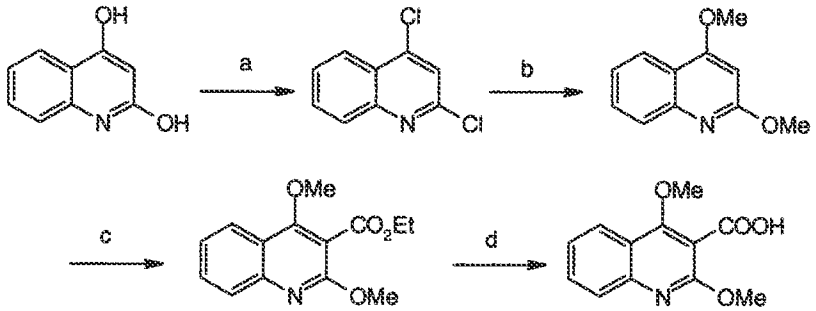
To a solution of 4,5-dioxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid ethyl ester (1.6 g, 6.8 mmol) in ethanol (100 mL) was added iodine (4.8 g, 19 mmol). The mixture was refluxed for 19 h and then concentrated under reduced pressure. The resulting solid was washed with ethyl acetate, water and acetone, and then recrystallized from DMF to give 5-hydroxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (700 mg, 43 %).

[0332] A-3; 5-Hydroxy-4-oxo-1, 4-dihydro-quinoline-3-carboxylic acid

A mixture of 5-hydroxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (700 mg, 3 mmol) in 10% NaOH (20 mL) was heated at reflux overnight. After cooling, the mixture was extracted with ether. The aqueous phase was separated and acidified with conc. HCl to pH 1-2. The resulting precipitate was collected via filtration to give 5-hydroxy-4-oxo-1, 4-dihydro-quinoline-3-carboxylic acid (**A-3**) (540 mg, 87 %). ^1H NMR (DMSO-d_6) δ 13.7 (br, 1 H), 13.5

(br, 1 H), 12.6 (s, 1 H), 8.82 (s, 1 H), 7.68 (t, J = 8.1 Hz, 1 H), 7.18 (d, J = 8.4 Hz, 1 H), 6.82 (d, J = 8.4 Hz, 1 H); ESI-MS 205.9 m/z (MH^+).

[0333] Example 6:



A-17

a) $POCl_3$; b) MeONa; c) *n*-BuLi, $ClCO_2Et$; d) NaOH

2,4-Dichloroquinoline

A suspension of quinoline-2,4-diol (15 g, 92.6 mmol) in $POCl_3$ was heated at reflux for 2 h. After cooling, the solvent was removed under reduced pressure to yield 2,4-dichloroquinoline, which was used without further purification.

[0334] 2,4-Dimethoxyquinoline

To a suspension of 2,4-dichloroquinoline in MeOH (100 mL) was added sodium methoxide (50 g). The mixture was heated at reflux for 2 days. After cooling, the mixture was filtered. The filtrate was concentrated under reduced pressure to yield a residue that was dissolved in water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give 2,4-dimethoxyquinoline as a white solid (13 g, 74 % over 2 steps).

[0335] Ethyl 2,4-dimethoxyquinoline-3-carboxylate

To a solution of 2,4-dimethoxyquinoline (11.5 g, 60.8 mmol) in anhydrous THF was added dropwise *n*-BuLi (2.5 M in hexane, 48.6 mL, 122 mmol) at 0 °C. After stirring for 1.5 h at 0 °C, the mixture was added to a solution of ethyl chloroformate in anhydrous THF and stirred at 0 °C for additional 30 min and then at room temperature overnight. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The resulting residue was purified by column chromatography

(petroleum ether / EtOAc = 50 / 1) to give ethyl 2, 4-dimethoxyquinoline-3-carboxylate (9.6 g, 60 %).

[0336] A-17; 2,4-Dimethoxyquinoline-3-carboxylic acid

Ethyl 2,4-dimethoxyquinoline-3-carboxylate (1.5 g, 5.7 mmol) was heated at reflux in NaOH solution (10 %, 100 mL) for 1 h. After cooling, the mixture was acidified with concentrated HCl to pH 4. The resulting precipitate was collected via filtration and washed with water and ether to give 2,4-dimethoxyquinoline-3-carboxylic acid (A-17) as a white solid (670 mg, 50 %). ^{1}H NMR ($CDCl_3$) δ 8.01-8.04 (d, *J* =12 Hz, 1 H), 7.66-7.76 (m, 2 H), 7.42-7.47 (t, *J* = 22 Hz, 2 H), 4.09 (s, 3 H). 3.97 (s, 3 H); ESI-MS 234.1 m/z (MH^+).

[0337] Commercially available acids

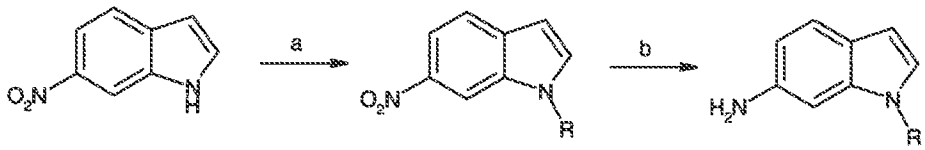
Acid	Name
A-5	6,8-Difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
A-6	6-[(4-Fluoro-phenyl)-methyl-sulfamoyl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
A-7	6-(4-Methyl-piperidine-1-sulfonyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
A-8	4-Oxo-6-(pyrrolidine-1-sulfonyl)-1,4-dihydro-quinoline-3-carboxylic acid
A-10	6-Ethyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
A-11	6-Ethoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
A-12	4-Oxo-7-trifluoromethyl-1,4-dihydro-quinoline-3-carboxylic acid
A-13	7-Chloro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
A-14	4-Oxo-5,7-bis-trifluoromethyl-1,4-dihydro-quinoline-3-carboxylic acid
A-20	1-Methyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
A-21	1-Isopropyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
A-22	1,6-Dimethyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
A-23	1-Ethyl-6-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
A-24	6-Chloro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

[0338] Amine Moieties

[0339] N-1 Substituted 6-aminoindoles

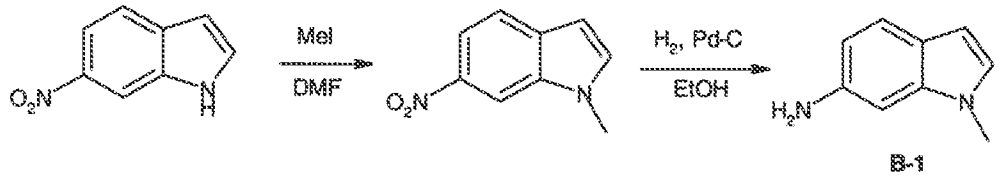
[0340] Example 1:

[0341] General Scheme:



a) RX (X = Cl, Br, I), K_2CO_3, DMF or CH_3CN; b) H_2, Pd-C, EtOH or $SnCl_2 \cdot 2H_2O$, EtOH.

[0342] Specific example:



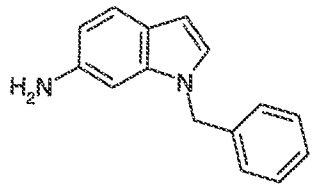
[0343] 1-Methyl-6-nitro-1H-indole

To a solution of 6-nitroindole (4.05g 25 mmol) in DMF (50 mL) was added K_2CO_3 (8.63 g, 62.5 mmol) and MeI (5.33 g, 37.5 mmol). After stirring at room temperature overnight, the mixture was poured into water and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated under *vacuum* to give the product 1-methyl-6-nitro-1H-indole (4.3 g, 98 %).

[0344] B-1; 1-Methyl-1H-indol-6-ylamine

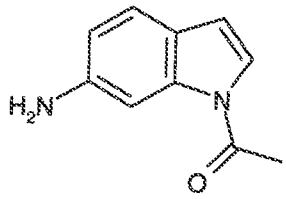
A suspension of 1-methyl-6-nitro-1H-indole (4.3 g, 24.4 mmol) and 10% Pd-C (0.43 g) in EtOH (50 mL) was stirred under H_2 (1 atm) at room temperature overnight. After filtration, the filtrate was concentrated and acidified with HCl-MeOH (4 mol/L) to give 1-methyl-1H-indol-6-ylamine hydrochloride salt (**B-1**) (1.74 g, 49 %) as a grey powder. ^{1}H NMR (DMSO-d_6): δ 9.10 (s, 2 H), 7.49 (d, J = 8.4 Hz, 1 H), 7.28 (d, J = 2.0 Hz, 1H), 7.15(s, 1 H), 6.84 (d, J = 8.4 Hz, 1 H), 6.38 (d, J = 2.8 Hz, 1H), 3.72 (s, 3 H); ESI-MS 146.08 m/z (MH^+).

[0345] Other examples:



[0346] B-2; 1-Benzyl-1H-indol-6-ylamine

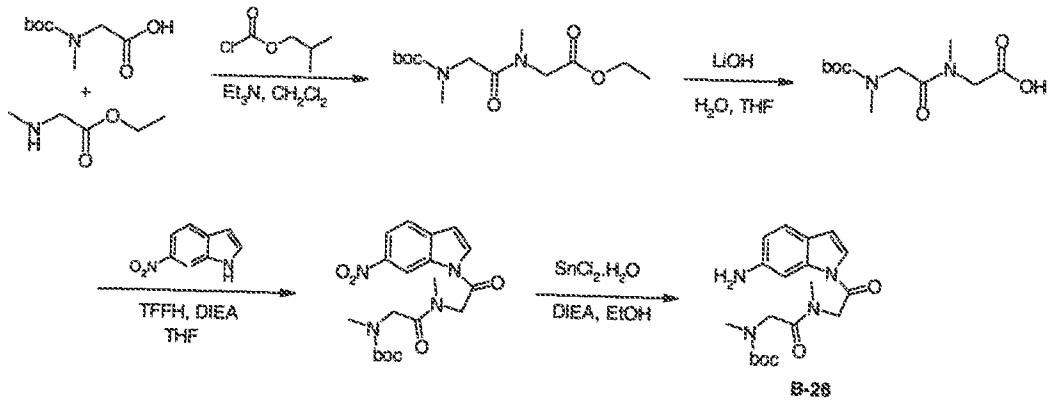
1-Benzyl-1H-indol-6-ylamine **(B-2)** was synthesized following the general scheme above starting from 6-nitroindole and benzyl bromide. Overall yield (~ 40 %). HPLC ret. time 2.19 min, 10–99 % CH_3CN, 5 min run; ESI-MS 223.3 m/z (MH^+).



[0347] B-3; 1-(6-Amino-indol-1-yl)-ethanone

1-(6-Amino-indol-1-yl)-ethanone **(B-3)** was synthesized following the general scheme above starting from 6-nitroindole and acetyl chloride. Overall yield (~ 40 %). HPLC ret. time 0.54 min, 10–99 % CH_3CN, 5 min run; ESI-MS 175.1 m/z (MH+).

[0348] Example 2:



[0349] {[2-(*tert*-Butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetic acid ethyl ester

To a stirred solution of (tert-butoxycarbonyl-methyl-amino)-acetic acid (37 g, 0.2 mol) and Et_3N (60.6 g, 0.6 mol) in CH_2Cl_2 (300 mL) was added isobutyl chloroformate (27.3 g, 0.2 mmol) dropwise at –20 °C under argon. After stirring for 0.5 h, methylamino-acetic acid ethyl ester hydrochloride (30.5 g, 129 mmol) was added dropwise at –20 °C. The mixture was allowed to warm to room temperature (c.a. 1 h) and quenched with water (500 mL). The organic layer was separated, washed with 10 % citric acid solution, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (petroleum ether / EtOAc 1:1) to give {[2-(tert-butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}- acetic acid ethyl ester (12.5 g, 22 %).

[0350] {[2-(*tert*-Butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetic acid

A suspension of {[2-(*tert*-butoxycarbonyl-methyl-amino)-acetyl]- methyl-amino}-acetic acid ethyl ester (12.3 g, 42.7 mmol) and LiOH (8.9 g, 214 mmol) in H_2O (20 mL) and THF (100 mL) was stirred overnight. Volatile solvent was removed under *vacuum* and the residue was extracted with ether (2 x 100 mL). The aqueous phase was acidified to pH 3 with dilute HCl solution, and then extracted with CH_2Cl_2 (2 x 300 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under *vacuum* to give {[2-(tert-butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetic acid as a colorless oil (10 g, 90 %). ^1H NMR ($CDCl_3$) δ 7.17 (br s, 1 H), 4.14-4.04 (m, 4 H), 3.04-2.88 (m, 6 H), 1.45-1.41 (m, 9 H); ESI-MS 282.9 m/z ($M+Na^+$).

[0351] Methyl-({methyl-[2-(6-nitro-indol-1-yl)-2-oxo-ethyl]-carbamoyl}-methyl)-carbamic acid *tert*-butyl ester

To a mixture of {[2-(tert-butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetic acid (13.8g, 53 mmol) and TFFH (21.0g, 79.5 mmol) in anhydrous THF (125 mL) was added DIEA (27.7 mL, 159 mmol) at room temperature under nitrogen. The solution was stirred at room temperature for 20 min. A solution of 6-nitroindole (8.6g, 53 mmol) in THF (75 mL) was added and the reaction mixture was heated at 60 °C for 18 h. The solvent was evaporated and the crude mixture was re-partitioned between EtOAc and water. The organic layer was separated, washed with water (x 3), dried over Na_2SO_4 and concentrated. Diethyl ether followed by EtOAc was added. The resulting solid was collected via filtration, washed with diethyl ether and air dried to yield methyl-({methyl-[2-(6-nitro-indol-1-yl)-2-oxo-ethyl]-carbamoyl}-methyl)-

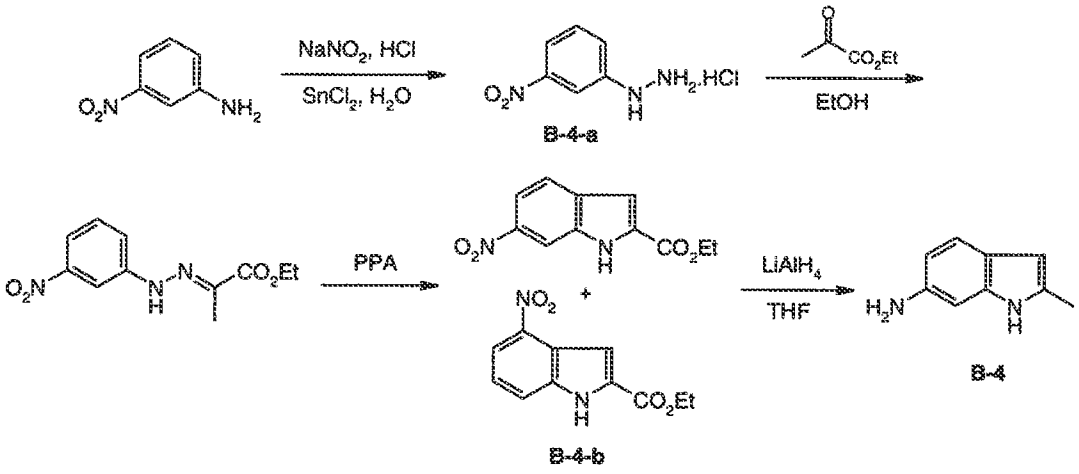
carbamic acid *tert*-butyl ester (6.42 g, 30 %). ^{1}H NMR (400 MHz, DMSO-d6) δ 1.37 (m, 9H), 2.78 (m, 3H), 2.95 (d, J = 1.5 Hz, 1H), 3.12 (d, J = 2.1 Hz, 2H), 4.01 (d, J = 13.8 Hz, 0.6H), 4.18 (d, J = 12.0 Hz, 1.4H), 4.92 (d, J = 3.4 Hz, 1.4H), 5.08 (d, J = 11.4 Hz, 0.6H), 7.03 (m, 1H), 7.90 (m, 1H), 8.21 (m, 1H), 8.35 (d, J = 3.8 Hz, 1H), 9.18 (m, 1H); HPLC ret. time 3.12 min, 10-99 % CH_3CN, 5 min run; ESI-MS 405.5 m/z (MH^+).

[0352] B-26; ({[2-(6-Amino-indol-1-yl)-2-oxo-ethyl]-methyl-carbamoyl}-methyl)-methyl-carbamic acid *tert*-butyl ester

A mixture of methyl-({methyl-[2-(6-nitro-indol-1-yl)-2-oxo-ethyl]-carbamoyl}-methyl)-carbamic acid *tert*-butyl ester (12.4 g, 30.6 mmol), $SnCl_2{\cdot}2H_2O$ (34.5g, 153.2 mmol) and DIEA (74.8 mL, 429 mmol) in ethanol (112 mL) was heated to 70 °C for 3 h. Water and EtOAc were added and the mixture was filtered through a short plug of Celite. The organic layer was separated, dried over Na_2SO_4 and concentrated to yield ({[2-(6-Amino-indol-1-yl)-2-oxo-ethyl]-methyl-carbamoyl}-methyl)-methyl-carbamic acid *tert*-butyl ester **(B-26)** (11.4 g, quant.). HPLC ret. time 2.11 min, 10-99 % CH_3CN, 5 min run; ESI-MS 375.3 m/z (MH^+).

[0353] 2-Substituted 6-aminoindoles

[0354] Example 1:



[0355] B-4-a; (3-Nitro-phenyl)-hydrazine hydrochloride salt

3-Nitro-phenylamine (27.6 g, 0.2 mol) was dissolved in a mixture of H_2O (40 mL) and 37% HCl (40 mL). A solution of $NaNO_2$ (13.8 g, 0.2 mol) in H_2O (60 mL) was added at 0 °C, followed by the addition of $SnCl_2{\cdot}H_2O$ (135.5 g, 0.6 mol) in 37% HCl (100 mL) at that temperature. After

stirring at 0 °C for 0.5 h, the solid was isolated via filtration and washed with water to give (3-nitro-phenyl)-hydrazine hydrochloride salt (**B-4-a**) (27.6 g, 73 %).

[0356] 2-[(3-Nitro-phenyl)-hydrazono]-propionic acid ethyl ester

(3-Nitro-phenyl)-hydrazine hydrochloride salt (**B-4-a**) (30.2 g, 0.16 mol) and 2-oxo-propionic acid ethyl ester (22.3 g, 0.19 mol) was dissolved in ethanol (300 mL). The mixture was stirred at room temperature for 4 h. The solvent was evaporated under reduced pressure to give 2-[(3-nitro-phenyl)-hydrazono]-propionic acid ethyl ester, which was used directly in the next step.

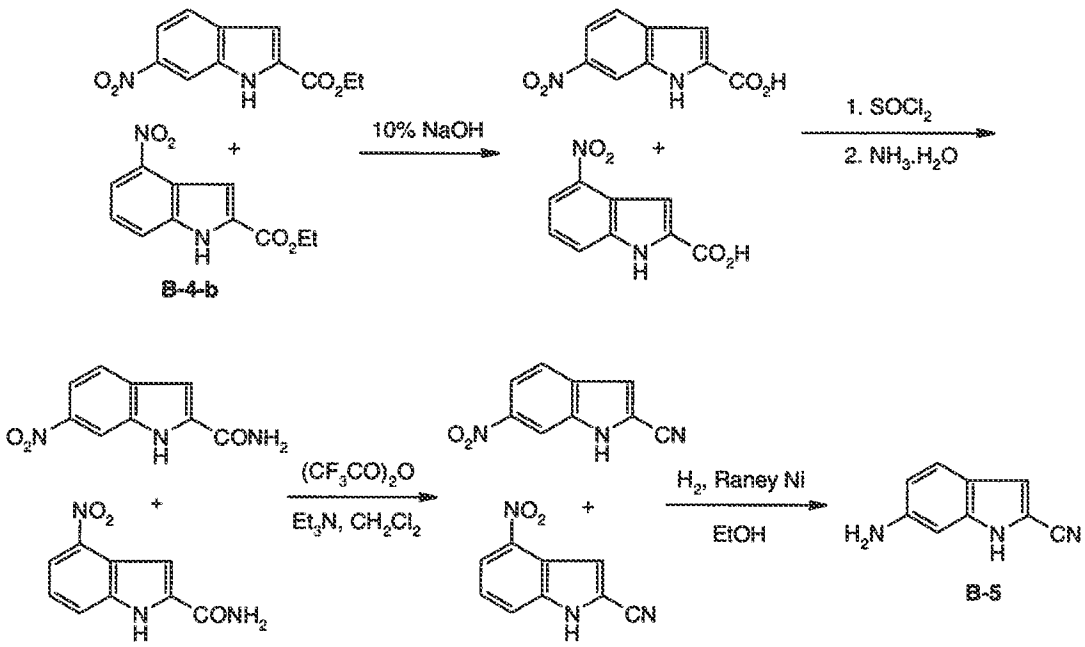
[0357] B-4-b; 4-Nitro-1H-indole-2-carboxylic acid ethyl ester and 6-Nitro-1H-indole -2-carboxylic acid ethyl ester

2-[(3-Nitro-phenyl)-hydrazono]-propionic acid ethyl ester from the preceding step was dissolved in toluene (300 mL). PPA (30 g) was added. The mixture was heated at reflux overnight and then cooled to room temperature. The solvent was removed to give a mixture of 4-nitro-1H-indole-2-carboxylic acid ethyl ester and 6-nitro-1H-indole -2-carboxylic acid ethyl ester (**B-4-b**) (15 g, 40 %).

[0358] B-4; 2-Methyl-1H-indol-6-ylamine

To a suspension of $LiAlH_4$ (7.8 g, 0.21 mol) in THF (300 mL) was added dropwise a mixture of 4-nitro-1H-indole-2-carboxylic acid ethyl ester and 6-nitro-1H-indole -2-carboxylic acid ethyl ester (**B-4-b**) (6g, 25.7 mmol) in THF (50 mL) at 0 °C under N_2. The mixture was heated at reflux overnight and then cooled to 0 °C. H_2O (7.8 mL) and 10 % NaOH (7.8 mL) were added to the mixture at 0 °C. The insoluble solid was removed via filtration. The filtrate was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography to afford 2-methyl-1H-indol-6-ylamine (**B-4**) (0.3 g, 8 %). ^1H NMR ($CDCl_3$) δ 7.57 (br s, 1 H), 7.27 (d, J = 8.8 Hz, 1 H), 6.62 (s, 1 H), 6.51-6.53 (m, 1 H), 6.07 (s, 1 H), 3.59-3.25 (br s, 2 H), 2.37 (s, 3H); ESI-MS 147.2 m/z (MH^+).

[0359] Example 2:



[0360] 6-Nitro-1H-indole-2-carboxylic acid and 4-Nitro-1H- indole-2-carboxylic acid

A mixture of 4-nitro-1H-indole-2-carboxylic acid ethyl ester and 6-nitro-1H-indole -2-carboxylic acid ethyl ester **(B-4-b)** (0.5 g, 2.13 mmol) in 10 % NaOH (20 mL) was heated at reflux overnight and then cooled to room temperature. The mixture was extracted with ether. The aqueous phase was separated and acidified with HCl to pH 1-2. The resulting solid was isolated via filtration to give a mixture of 6-nitro-1H-indole-2-carboxylic acid and 4-nitro-1H-indole-2-carboxylic acid (0.3 g, 68 %).

[0361] 6-Nitro-1H-indole-2-carboxylic acid amide and 4-Nitro-1H- indole-2-carboxylic acid amide

A mixture of 6-nitro-1H-indole-2-carboxylic acid and 4-nitro-1H- indole-2-carboxylic acid (12 g, 58 mmol) and $SOCl_2$ (50 mL, 64 mmol) in benzene (150 mL) was refluxed for 2 h. The benzene and excessive $SOCl_2$ was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (250 mL). NH_4OH (21.76 g, 0.32 mol) was added dropwise at 0 °C. The mixture was stirred at room temperature for 1 h. The resulting solid was isolated via filtration to give a crude mixture of 6-nitro-1H-indole-2-carboxylic acid amide and 4-nitro-1H- indole-2-carboxylic acid amide (9 g, 68 %), which was used directly in the next step.

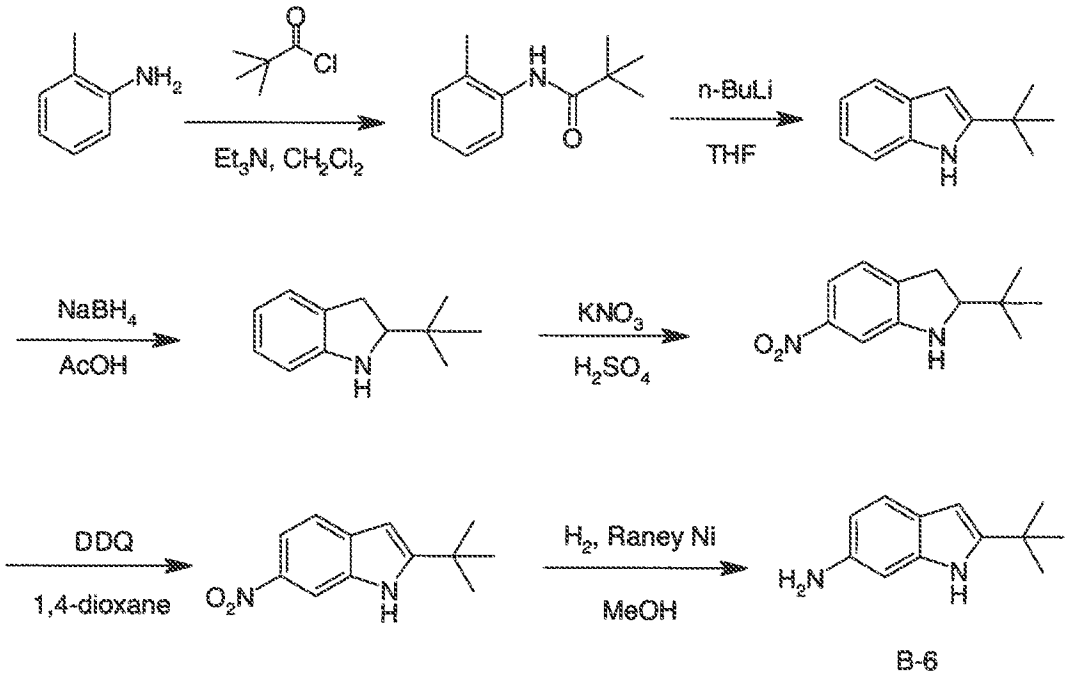
[0362] 6-Nitro-1H-indole-2-carbonitrile and 4-Nitro-1H- indole-2-carbonitrile

A mixture of 6-nitro-1H-indole-2-carboxylic acid amide and 4-nitro-1H- indole-2-carboxylic acid amide (5 g, 24 mmol) was dissolved in CH_2Cl_2 (200 mL). Et_3N (24.24 g, 0.24 mol) was added, followed by the addition of $(CF_3CO)_2O$ (51.24 g, 0.24 mol) at room temperature. The mixture was stirred for 1 h and poured into water (100 mL). The organic layer was separated. The aqueous layer was extracted with EtOAc (100 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography to give a mixture of 6-nitro-1H-indole-2-carbonitrile and 4-nitro-1H- indole-2-carbonitrile (2.5 g, 55 %).

[0363] B-5; 6-Amino-1H-indole-2-carbonitrile

A mixture of 6-nitro-1H-indole-2-carbonitrile and 4-nitro-1H- indole-2-carbonitrile (2.5 g, 13.4 mmol) and Raney Ni (500 mg) in EtOH (50 mL) was stirred at room temperature under H_2 (1 atm) for 1 h. Raney Ni was filtered off. The filtrate was evaporated under reduced pressure and purified by column chromatography to give 6-amino-1H-indole-2-carbonitrile (**B-5**) (1 g, 49 %). ^{1}H NMR (DMSO-d_6) δ 12.75 (br s, 1 H), 7.82 (d, J = 8 Hz, 1 H), 7.57 (s, 1 H), 7.42 (s, 1 H), 7.15 (d, J = 8 Hz, 1 H); ESI-MS 158.2 m/z (MH^+).

[0364] Example 3:



B-6

[0365] 2,2-Dimethyl-N-*o*-tolyl-propionamide

To a solution of *o*-tolylamine (21.4 g, 0.20 mol) and Et_3N (22.3 g, 0.22 mol) in CH_2Cl_2 was added 2,2-dimethyl-propionyl chloride (25.3 g, 0.21 mol) at 10 °C. The mixture was stirred overnight at room temperature, washed with aq. HCl (5%, 80 mL), saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated under *vacuum* to give 2,2-dimethyl-N-*o*-tolyl-propionamide (35.0 g, 92 %).

[0366] 2-*tert*-Butyl-1H-indole

To a solution of 2,2-dimethyl-N-o-tolyl- propionamide (30.0 g, 159 mmol) in dry THF (100 mL) was added dropwise *n*-BuLi (2.5 M, in hexane, 190 mL) at 15 °C. The mixture was stirred overnight at 15 °C, cooled in an ice-water bath and treated with saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuum*. The residue was purified by column chromatography to give 2-*tert*-butyl-1H-indole (23.8 g, 88 %).

[0367] 2-*tert*-Butyl-2,3-dihydro-1H-indole

To a solution of 2-*tert*-butyl-1H-indole (5.0 g, 29 mmol) in AcOH (20 mL) was added $NaBH_4$ at 10 °C. The mixture was stirred for 20 min at 10 °C, treated dropwise with H_2O under ice cooling, and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under *vacuum* to give a mixture of starting material and 2-*tert*-butyl-2,3-dihydro-1H-indole (4.9 g), which was used directly in the next step.

[0368] 2-*tert*-Butyl-6-nitro-2,3-dihydro-1H-indole

To a solution of the mixture of 2-*tert*-butyl-2,3-dihydro-1H-indole and 2-*tert*-butyl-1H-indole (9.7 g) in H_2SO_4 (98%, 80 mL) was slowly added KNO_3 (5.6 g, 55.7 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, carefully poured into cracked ice, basified with Na_2CO_3 to pH~8 and extracted with ethyl acetate. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under *vacuum*. The residue was purified by column chromatography to give 2-*tert*-butyl-6-nitro-2,3-dihydro-1H-indole (4.0 g, 32 % over 2 steps).

[0369] 2-*tert*-Butyl-6-nitro-1H-indole

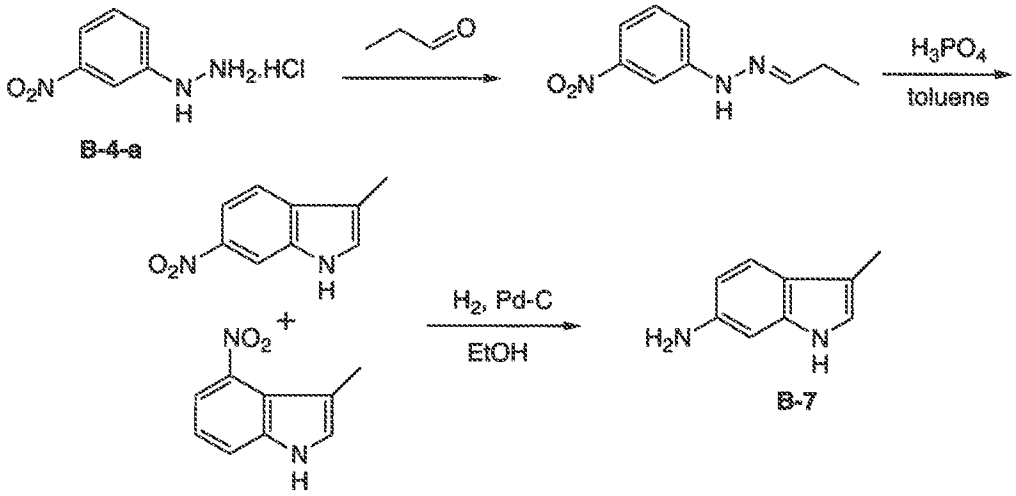
To a solution of 2-*tert*-butyl-6-nitro-2,3-dihydro-1H-indole (2.0 g, 9.1 mmol) in 1,4-dioxane (20 mL) was added DDQ at room temperature. After refluxing for 2.5 h, the mixture was filtered and the filtrate was concentrated under *vacuum*. The residue was purified by column chromatography to give 2-*tert*-butyl-6-nitro-1H-indole (1.6 g, 80 %).

[0370] B-6; 2-*tert*-Butyl-1H-indol-6-ylamine

To a solution of 2-*tert*-butyl-6-nitro-1H-indole (1.3 g, 6.0 mmol) in MeOH (10 mL) was added Raney Ni (0.2 g). The mixture was stirred at room temperature under H_2 (1 atm) for 3 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was washed with petroleum ether to give 2-*tert*-butyl-1H-indol-6-ylamine **(B-6)** (1.0 g, 89 %). ^{1}H NMR (DMSO-d_6) δ 10.19 (s, 1 H), 6.99 (d, J = 8.1 Hz, 1 H), 6.46 (s, 1 H), 6.25 (dd, J = 1.8, 8.1 Hz, 1 H), 5.79 (d, J = 1.8 Hz, 1 H), 4.52 (s, 2 H), 1.24 (s, 9 H); ESI-MS 189.1 m/z (MH^+).

[0371] <u>3-Substituted 6-aminoindoles</u>

[0372] Example 1:



[0373] N-(3-Nitro-phenyl)-N'-propylidene-hydrazine

Sodium hydroxide solution (10 %, 15 mL) was added slowly to a stirred suspension of (3-nitro-phenyl)-hydrazine hydrochloride salt **(B-4-a)** (1.89 g, 10 mmol) in ethanol (20 mL) until pH 6. Acetic acid (5 mL) was added to the mixture followed by propionaldehyde (0.7 g, 12 mmol). After stirring for 3 h at room temperature, the mixture was poured into ice-water and the

resulting precipitate was isolated via filtration, washed with water and dried in air to obtain N-(3-nitro-phenyl)-N'-propylidene-hydrazine, which was used directly in the next step.

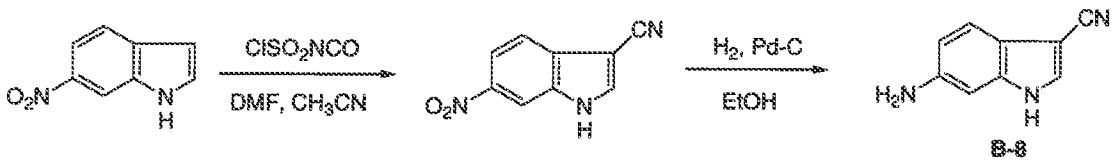
[0374] 3-Methyl-4-nitro-1H-indole and 3-Methyl-6-nitro-1H-indole

A mixture of N-(3-nitro-phenyl)-N'-propylidene-hydrazine dissolved in 85 % H_3PO_4 (20 mL) and toluene (20 mL) was heated at 90-100 °C for 2 h. After cooling, toluene was removed under reduced pressure. The resultant oil was basified with 10 % NaOH to pH 8. The aqueous layer was extracted with EtOAc (100 mL x 3). The combined organic layers were dried, filtered and concentrated under reduced pressure to afford a mixture of 3-methyl-4-nitro-1H-indole and 3-methyl-6-nitro-1H-indole (1.5 g, 86 % over two steps), which was used directly in the next step.

[0375] B-7; 3-Methyl-1H-indol-6-ylamine

A mixture of 3-methyl-4-nitro-1H-indole and 3-methyl-6-nitro-1H-indole (3 g, 17 mol) and 10 % Pd-C (0.5 g) in ethanol (30 mL) was stirred overnight under H_2 (1 atm) at room temperature. Pd-C was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography to give 3-methyl-1H-indol-6-ylamine (**B-7**) (0.6 g, 24 %). ^{1}H NMR ($CDCl_3$) δ 7.59 (br s, 1 H), 7.34 (d, J = 8.0 Hz, 1 H), 6.77 (s, 1H), 6.64 (s, 1 H), 6.57 (m, 1 H), 3.57 (br s, 2 H), 2.28 (s, 3H); ESI-MS 147.2 m/z (MH^+).

[0376] Example 2:



B-8

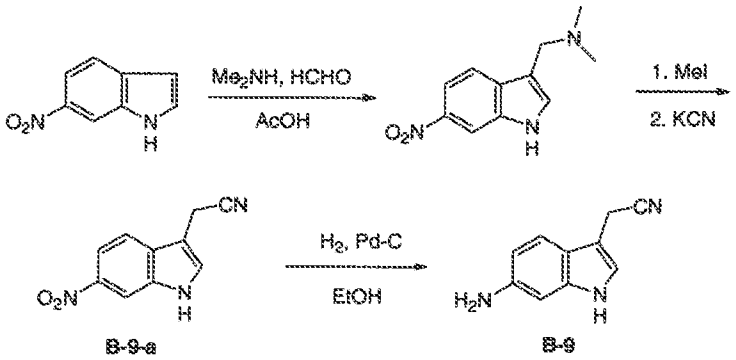
[0377] 6-Nitro-1H-indole-3-carbonitrile

To a solution of 6-nitroindole (4.86 g 30 mmol) in DMF (24.3 mL) and CH_3CN (243 mL) was added dropwise a solution of $ClSO_2NCO$ (5 mL, 57 mmol) in CH_3CN (39 mL) at 0 °C . After addition, the reaction was allowed to warm to room temperature and stirred for 2 h. The mixture was poured into ice-water, basified with sat. $NaHCO_3$ solution to pH 7-8 and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give 6-nitro-1H-indole-3-carbonitrile (4.6 g, 82 %).

[0378] B-8; 6-Amino-1H-indole-3-carbonitrile

A suspension of 6-nitro-1H-indole-3-carbonitrile (4.6 g, 24.6 mmol) and 10% Pd-C (0.46 g) in EtOH (50 mL) was stirred under H_2 (1 atm) at room temperature overnight. After filtration, the filtrate was concentrated and the residue was purified by column chromatography (Pet. Ether / EtOAc = 3 / 1) to give 6-amino-1H-indole-3-carbonitrile (**B-8**) (1 g, 99 %) as a pink powder. ^{1}H NMR (DMSO-d_6) δ 11.51 (s, 1 H), 7.84 (d, J = 2.4 Hz, 1 H), 7.22 (d, J = 8.4 Hz, 1 H), 6.62 (s, 1H), 6.56 (d, J = 8.4 Hz, 1 H), 5.0 (s, 2H); ESI-MS 157.1 m/z (MH^+).

[0379] Example 3:



[0380] Dimethyl-(6-nitro-1H-indol-3-ylmethyl)-amine

A solution of dimethylamine (25 g, 0.17 mol) and formaldehyde (14.4 mL, 0.15 mol) in acetic acid (100 mL) was stirred at 0 °C for 30 min. To this solution was added 6-nitro-1H-indole (20 g, 0.12 mol). After stirring for 3 days at room temperature, the mixture was poured into 15% aq. NaOH solution (500 mL) at 0 °C. The precipitate was collected via filtration and washed with water to give dimethyl-(6-nitro-1H-indol-3-ylmethyl)-amine (23 g, 87 %).

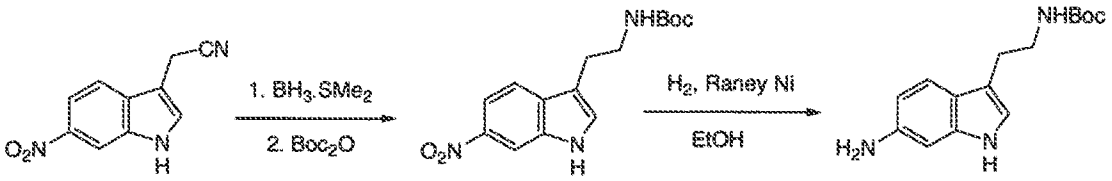
[0381] B-9-a; (6-Nitro-1H-indol-3-yl)-acetonitrile

To a mixture of DMF (35 mL) and MeI (74.6 g, 0.53 mol) in water (35 mL) and THF (400 mL) was added dimethyl-(6-nitro-1H-indol-3-ylmethyl)-amine (23 g, 0.105 mol). After the reaction mixture was refluxed for 10 min, potassium cyanide (54.6 g, 0.84 mol) was added and the mixture was kept refluxing overnight. The mixture was then cooled to room temperature and filtered. The filtrate was washed with brine (300 mL x 3), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography to give (6-nitro-1H-indol-3-yl)-acetonitrile (**B-9-a**) (7.5 g, 36 %).

[0382] B-9; (6-Amino-1H-indol-3-yl)-acetonitrile

A mixture of (6-nitro-1H-indol-3-yl)-acetonitrile **(B-9-a)** (1.5 g, 74.5 mmL) and 10 % Pd-C (300 mg) in EtOH (50 mL) was stirred at room temperature under H_2 (1 atm) for 5 h. Pd-C was removed via filtration and the filtrate was evaporated to give (6-amino-1H-indol-3-yl)-acetonitrile **(B-9)** (1.1 g, 90 %). ^{1}H NMR (DMSO-d_6) δ 10.4 (br s, 1 H), 7.18 (d, J = 8.4 Hz, 1 H), 6.94 (s, 1H), 6.52 (s, 1 H), 6.42 (dd, J = 8.4, 1.8 Hz, 1 H), 4.76(s, 2 H), 3.88 (s, 2 H); ESI-MS 172.1 m/z (MH^+).

[0383] Example 4:



B-9-a **B-10**

[0384] [2-(6-Nitro-1H- indol-3-yl)-ethyl]-carbamic acid *tert*-butyl ester

To a solution of (6-nitro-1H-indol-3-yl)-acetonitrile **(B-9-a)** (8.6 g, 42.8 mmol) in dry THF (200 mL) was added a solution of 2 M borane-dimethyl sulfide complex in THF (214 mL. 0.43 mol) at 0 °C. The mixture was heated at reflux overnight under nitrogen. The mixture was then cooled to room temperature and a solution of $(Boc)_2O$ (14 g, 64.2 mmol) and Et_3N (89.0 mL, 0.64 mol) in THF was added. The reaction mixture was kept stirring overnight and then poured into ice-water. The organic layer was separated and the aqueous phase was extracted with EtOAc (200 x 3 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by column chromatography to give [2-(6-nitro-1H- indol-3-yl)-ethyl]-carbamic acid *tert*-butyl ester (5 g, 38 %).

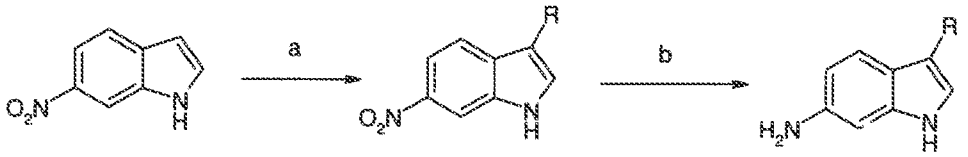
[0385] B-10; [2-(6-Amino-1H-indol-3-yl)-ethyl]-carbamic acid *tert*-butyl ester

A mixture of [2-(6-nitro-1H- indol-3-yl)-ethyl]-carbamic acid *tert*-butyl ester (5 g, 16.4 mmol) and Raney Ni (1 g) in EtOH (100 mL) was stirred at room temperature under H_2 (1 atm) for 5 h. Raney Ni was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography to give [2-(6-amino-1H-indol-3-yl)-ethyl]-carbamic acid *tert*-butyl ester **(B-10)** (3 g, 67 %). ^{1}H NMR (DMSO-d_6) δ 10.1 (br s, 1 H), 7.11 (d, J = 8.4 Hz, 1 H), 6.77-6.73 (m, 2 H), 6.46 (d, J = 1.5 Hz, 1 H), 6.32 (dd, J = 8.4, 2.1 Hz, 1

H), 4.62 (s, 2 H), 3.14-3.08 (m, 2 H), 2.67-2.62 (m, 2 H), 1.35 (s, 9H); ESI-MS 275.8 m/z (MH^+).

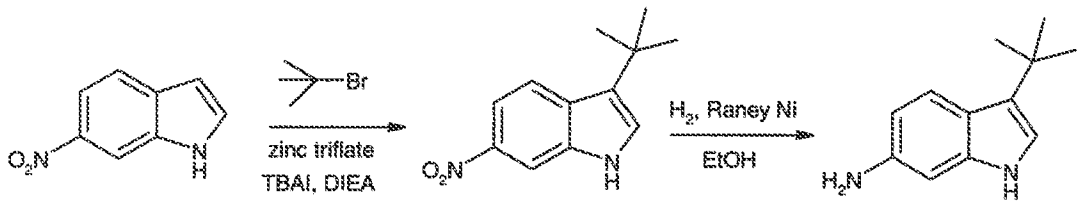
[0386] Example 5:

[0387] General Scheme:



a) RX (X=Br,I), zinc triflate, TBAI, DIEA, toluene; b) H_2, Raney Ni, EtOH or $SnCl_2 \cdot 2H_2O$, EtOH.

[0388] Specific example:



B-11

[0389] 3-*tert*-Butyl-6-nitro-1H-indole

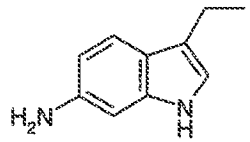
To a mixture of 6-nitroindole (1 g, 6.2 mmol), zinc triflate (2.06 g, 5.7 mmol) and TBAI (1.7 g, 5.16 mmol) in anhydrous toluene (11 mL) was added DIEA (1.47 g, 11.4 mmol) at room temperature under nitrogen. The reaction mixture was stirred for 10 min at 120 °C, followed by addition of *t*-butyl bromide (0.707 g, 5.16 mmol). The resulting mixture was stirred for 45 min at 120 °C. The solid was filtered off and the filtrate was concentrated to dryness and purified by column chromatography on silica gel (Pet.Ether./EtOAc 20:1) to give 3-*tert*-butyl-6-nitro-1H-indole as a yellow solid (0.25 g, 19 %). ^{1}H NMR ($CDCl_3$) δ 8.32 (d, J = 2.1 Hz, 1H), 8.00 (dd, J = 2.1, 14.4 Hz, 1H), 7.85 (d, J = 8.7 Hz, 1H), 7.25 (s, 1H), 1.46 (s, 9H).

[0390] B-11; 3-*tert*-Butyl-1H-indol-6-ylamine

A suspension of 3-*tert*-butyl-6-nitro-1H-indole (3.0 g, 13.7mmol) and Raney Ni (0.5g) in ethanol was stirred at room temperature under H_2 (1 atm) for 3 h. The catalyst was filtered off and the filtrate was concentrated to dryness. The residue was purified by column

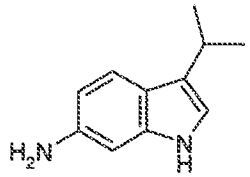
chromatography on silica gel (Pet.Ether. / EtOAc 4 : 1) to give 3-*tert*-butyl-1H-indol-6-ylamine (**B-11**) (2.0 g, 77.3%) as a gray solid. ^{1}H NMR ($CDCl_3$): δ 7.58 (m, 2H), 6.73 (d, J = 1.2 Hz, 1H), 6.66 (s, 1H), 6.57(dd, J = 0.8, 8.6 Hz, 1H), 3.60 (br s, 2H), 1.42 (s, 9H).

[0391] Other examples:



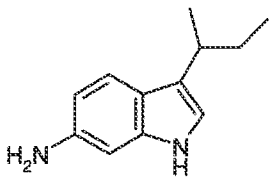
[0392] B-12; 3-Ethyl-1H-indol-6-ylamine

3-Ethyl-1H-indol-6-ylamine (**B-12**) was synthesized following the general scheme above starting from 6-nitroindole and ethyl bromide. Overall yield (42 %). HPLC ret. time 1.95 min, 10–99 % CH_3CN, 5 min run; ESI-MS 161.3 m/z (MH^+).



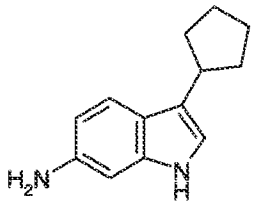
[0393] B-13; 3-Isopropyl-1H-indol-6-ylamine

3-Isopropyl-1H-indol-6-ylamine (**B-13**) was synthesized following the general scheme above starting from 6-nitroindole and isopropyl iodide. Overall yield (17 %). HPLC ret. time 2.06 min, 10–99 % CH_3CN, 5 min run; ESI-MS 175.2 m/z (MH^+).



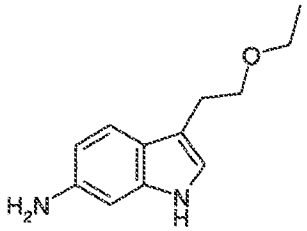
[0394] B-14; 3-sec-Butyl-1H-indol-6-ylamine

3-*sec*-Butyl-1H-indol-6-ylamine (**B-14**) was synthesized following the general scheme above starting from 6-nitroindole and 2-bromobutane. Overall yield (20 %). HPLC ret. time 2.32 min, 10–99 % CH_3CN, 5 min run; ESI-MS 189.5 m/z (MH^+).



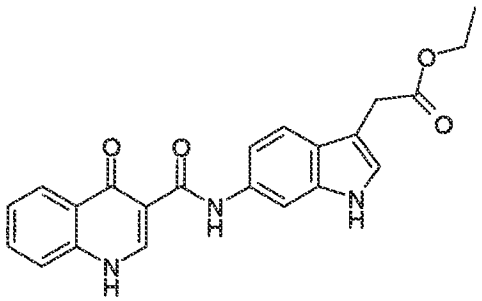
[0395] B-15; 3-Cyclopentyl-1H-indol-6-ylamine

3- Cyclopentyl -1H-indol-6-ylamine **(B-15)** was synthesized following the general scheme above starting from 6-nitroindole and iodo-cyclopentane. Overall yield (16 %). HPLC ret. time 2.39 min, 10–99 % CH_3CN, 5 min run; ESI-MS 201.5 m/z (MH^+).



[0396] B-16; 3-(2-Ethoxy-ethyl)-1H-indol-6-ylamine

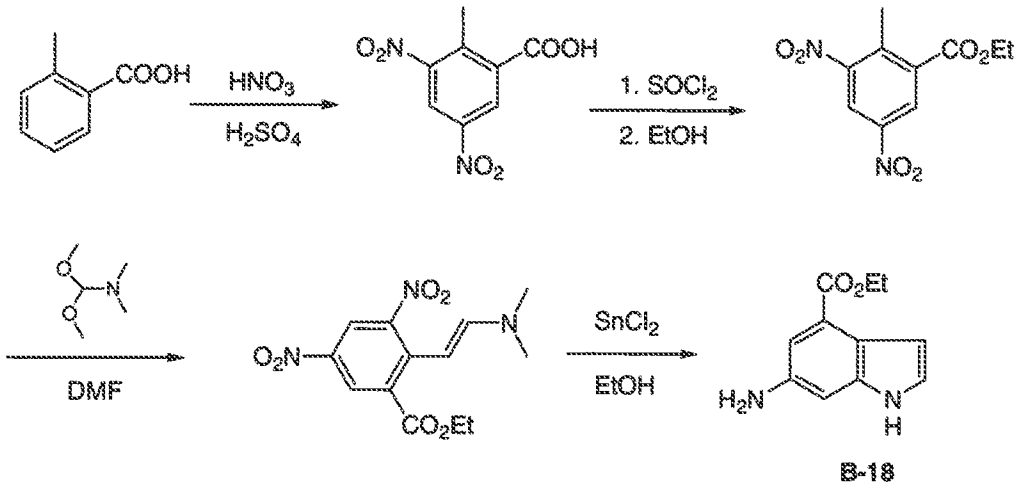
3-(2-Ethoxy-ethyl)-1H-indol-6-ylamine **(B-16)** was synthesized following the general scheme above starting from 6-nitroindole and 1-bromo-2-ethoxy-ethane. Overall yield (15 %). HPLC ret. time 1.56 min, 10–99 % CH_3CN, 5 min run; ESI-MS 205.1 m/z (MH^+).



[0397] B-17; (6-Amino-1H-indol-3-yl)-acetic acid ethyl ester

(6-Amino-1H-indol-3-yl)-acetic acid ethyl ester **(B-17)** was synthesized following the general scheme above starting from 6-nitroindole and iodo-acetic acid ethyl ester. Overall yield (24 %). HPLC ret. time 0.95 min, 10–99 % CH_3CN, 5 min run; ESI-MS 219.2 m/z (MH^+).

[0398] 4-Substituted 6-aminoindole



B-18

[0399] 2-Methyl-3,5-dinitro-benzoic acid

To a mixture of HNO_3 (95%, 80 mL) and H_2SO_4 (98%, 80 mL) was slowly added 2-methylbenzoic acid (50 g, 0.37 mol) at 0 °C. After addition, the reaction mixture was stirred for 1.5 h while keeping the temperature below 30 °C, poured into ice-water and stirred for 15 min. The resulting precipitate was collected via filtration and washed with water to give 2-methyl-3,5-dinitro-benzoic acid (70 g, 84 %).

[0400] 2-Methyl-3,5-dinitro-benzoic acid ethyl ester

A mixture of 2-methyl-3,5-dinitro-benzoic acid (50 g, 0.22 mol) in $SOCl_2$ (80 mL) was heated at reflux for 4 h and then was concentrated to dryness. CH_2Cl_2 (50 mL) and EtOH (80 mL) were added. The mixture was stirred at room temperature for 1 h, poured into ice-water and extracted with EtOAc (3 x 100 mL). The combined extracts were washed with sat. Na_2CO_3 (80 mL), water (2 x 100 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated to dryness to give 2-methyl-3,5-dinitro-benzoic acid ethyl ester (50 g, 88 %).

[0401] 2-(2-Dimethylamino-vinyl)-3,5-dinitro-benzoic acid ethyl ester

A mixture of 2-methyl-3,5-dinitro-benzoic acid ethyl ester (35 g, 0.14 mol) and dimethoxymethyl-dimethyl-amine (32 g, 0.27 mol) in DMF (200 mL) was heated at 100 °C for 5 h. The mixture was poured into ice-water. The precipitate was collected via filtration and washed with water to give 2-(2-dimethylamino-vinyl)-3,5-dinitro-benzoic acid ethyl ester (11.3 g, 48 %).

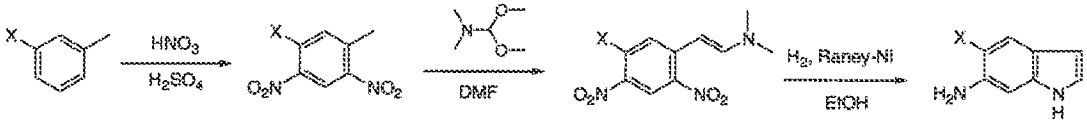
[0402] B-18; 6-Amino-1H-indole-4-carboxylic acid ethyl ester

A mixture of 2-(2-dimethylamino-vinyl)-3,5-dinitro- benzoic acid ethyl ester (11.3 g, 0.037 mol) and $SnCl_2$ (83 g. 0.37 mol) in ethanol was heated at reflux for 4 h. The mixture was concentrated to dryness and the residue was poured into water and basified with sat. Na_2CO_3 solution to pH 8. The precipitate was filtered off and the filtrate was extracted with ethyl acetate (3 x 100 mL). The combined extracts were washed with water (2 x 100 mL) and brine (150 mL), dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography on silica gel to give 6-amino-1H-indole-4-carboxylic acid ethyl ester (**B-18**) (3 g, 40 %). ^{1}H NMR (DMSO-d_6) δ 10.76 (br s, 1 H), 7.11-7.14 (m, 2 H), 6.81-6.82 (m, 1 H), 6.67-6.68 (m, 1 H), 4.94 (br s, 2 H), 4.32-4.25 (q, J = 7.2 Hz, 2 H), 1.35-1.31 (t, J = 7.2, 3 H). ESI-MS 205.0 m/z (MH^+).

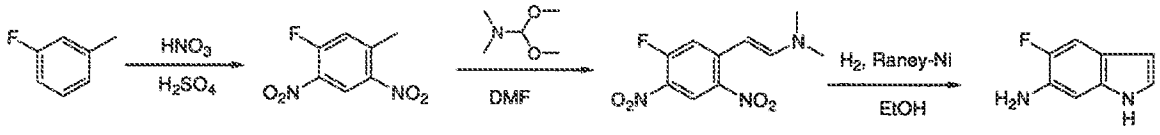
[0403] <u>5-Substituted 6-aminoindoles</u>

[0404] Example 1:

[0405] General Scheme:



[0406] Specific example:



B-20

1-Fluoro-5-methyl-2,4-dinitro-benzene

To a stirred solution of HNO_3 (60 mL) and H_2SO_4 (80 mL), cooled in an ice bath, was added 1-fluoro-3-methyl-benzene (27.5g, 25 mmol) at such a rate that the temperature did not rise over 35 °C. The mixture was allowed to stir for 30 min at room temperature and poured into ice water (500 mL). The resulting precipitate (a mixture of the desired product and 1-fluoro-3-methyl-2,4-dinitro-benzene, approx. 7:3) was collected via filtration and purified by recrystallization from 50 mL isopropyl ether to give 1-fluoro-5-methyl-2,4-dinitro-benzene as a white solid (18 g, 36 %).

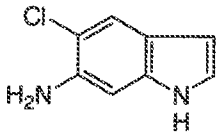
[0407] [2-(5-Fluoro-2,4-dinitro-phenyl)-vinyl]-dimethyl-amine

A mixture of 1-fluoro-5-methyl-2,4-dinitro-benzene (10 g, 50 mmol), dimethoxymethyl-dimethylamine (11.9 g, 100 mmol) and DMF (50 mL) was heated at 100 °C for 4 h. The solution was cooled and poured into water. The red precipitate was collected via filtration, washed with water adequately and dried to give [2-(5-fluoro-2,4-dinitro-phenyl)-vinyl]-dimethyl-amine (8 g, 63 %).

[0408] B-20; 5-Fluoro-1H-indol-6-ylamine

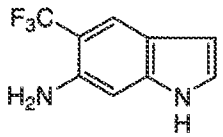
A suspension of [2-(5-fluoro-2,4-dinitro-phenyl)-vinyl]-dimethyl-amine (8 g, 31.4 mmol) and Raney Ni (8 g) in EtOH (80 mL) was stirred under H_2 (40 psi) at room temperature for 1 h. After filtration, the filtrate was concentrated and the residue was purified by chromatography (Pet.Ether/ EtOAc = 5 / 1) to give 5-fluoro-1H-indol-6-ylamine (**B-20**) as a brown solid (1 g, 16 %). ^{1}H NMR (DMSO-d_6) δ 10.56 (br s, 1 H), 7.07 (d, J = 12 Hz, 1 H), 7.02 (m, 1H), 6.71 (d, J = 8 Hz, 1H), 6.17 (s, 1H), 3.91 (br s , 2H); ESI-MS 150.1 m/z (MH^+).

[0409] Other examples:



[0410] B-21; 5-Chloro-1H-indol-6-ylamine

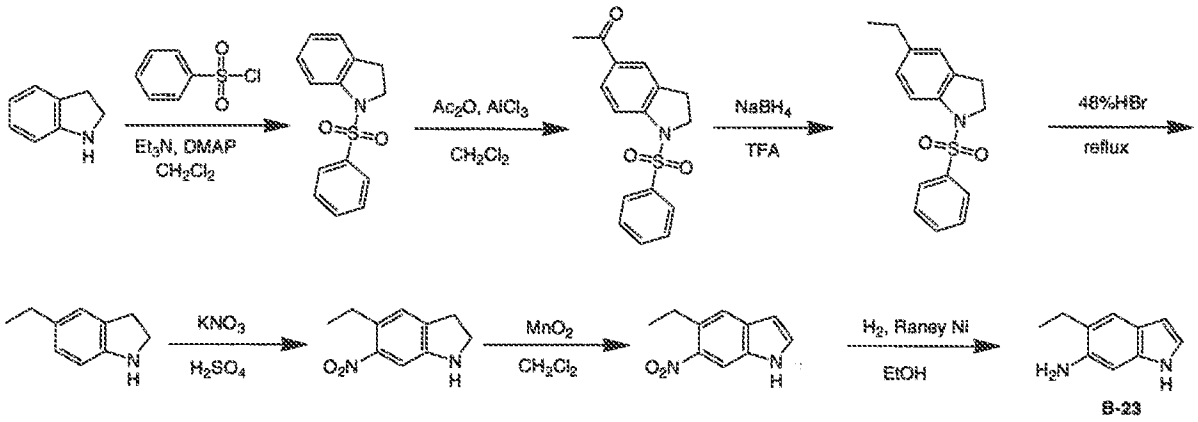
5-Chloro-1H-indol-6-ylamine (**B-21**) was synthesized following the general scheme above starting from 1-chloro-3-methyl-benzene. Overall yield (7 %). ^{1}H NMR ($CDCl_3$) δ.7.85 (br s, 1 H), 7.52 (s, 1 H), 7.03 (s, 1H), 6.79 (s, 1H), 6.34 (s, 1H), 3.91 (br s, 2H); ESI-MS 166.0 m/z (MH^+).



[0411] B-22; 5-Trifluoromethyl-1H-indol-6-ylamine

5-Trifluoromethyl-1H-indol-6-ylamine (**B-22**) was synthesized following the general scheme above starting from 1-methyl-3-trifluoromethyl-benzene. Overall yield (2 %). ^{1}H NMR (DMSO-d_6) 10.79 (br s, 1 H), 7.55 (s, 1 H), 7.12 (s, 1 H), 6.78 (s, 1 H), 6.27(s, 1 H), 4.92 (s, 2 H); ESI-MS 200.8 m/z (MH^+).

[0412] Example 2:



[0413] 1-Benzenesulfonyl-2,3-dihydro-1H-indole

To a mixture of DMAP (1.5 g), benzenesulfonyl chloride (24 g, 136 mmol) and 2,3-dihydro-1H-indole (14.7 g, 124 mmol) in CH_2Cl_2 (200 mL) was added dropwise Et_3N (19 g, 186 mmol) in an ice-water bath. After addition, the mixture was stirred at room temperature overnight, washed with water, dried over Na_2SO_4 and concentrated to dryness under reduced pressure to provide 1-benzenesulfonyl-2,3-dihydro-1H-indole (30.9 g, 96 %).

[0414] 1-(1-Benzenesulfonyl-2,3-dihydro-1H-indol-5-yl)-ethanone

To a stirring suspension of $AlCl_3$ (144 g, 1.08 mol) in CH_2Cl_2 (1070 mL) was added acetic anhydride (54 mL). The mixture was stirred for 15 minutes. A solution of 1-benzenesulfonyl-2,3-dihydro-1H-indole (46.9 g, 0.18 mol) in CH_2Cl_2 (1070 mL) was added dropwise. The mixture was stirred for 5 h and quenched by the slow addition of crushed ice. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated under *vacuum* to yield 1-(1-benzenesulfonyl-2,3-dihydro-1H-indol-5-yl)-ethanone (42.6 g, 79 %).

[0415] 1-Benzenesulfonyl-5-ethyl-2,3-dihydro-1H-indole

To magnetically stirred TFA (1600 mL) was added at 0 °C sodium borohydride (64 g, 1.69 mol) over 1 h. To this mixture was added dropwise a solution of 1-(1-benzenesulfonyl-2,3-dihydro-1H-indol-5-yl)-ethanone (40 g, 0.13 mol) in TFA (700 mL) over 1 h. The mixture was stirred overnight at 25 °C, diluted with H_2O (1600 mL), and basified with sodium hydroxide pellets at 0 °C. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under

reduced pressure. The residue was purified by column chromatography on silica gel to give 1-benzenesulfonyl-5-ethyl-2,3-dihydro-1H-indole (16.2 g, 43 %).

[0416] 5-Ethyl-2,3-dihydro-1H-indole

A mixture of 1-benzenesulfonyl-5-ethyl-2,3-dihydro-1H-indole (15 g, 0.05 mol) in HBr (48%, 162 mL) was heated at reflux for 6 h. The mixture was basified with sat. NaOH solution to pH 9 and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give 5-ethyl-2,3-dihydro-1H-indole (2.5 g, 32 %).

[0417] 5-Ethyl-6-nitro-2,3-dihydro-1H-indole

To a solution of 5-ethyl-2,3-dihydro-1H-indole (2.5 g, 17 mmol) in H_2SO_4 (98%, 20 mL) was slowly added KNO_3 (1.7 g, 17 mmol) at 0 °C. After addition, the mixture was stirred at 0 - 10 °C for 10 min, carefully poured into ice, basified with NaOH solution to pH 9 and extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography on silica gel to give 5-ethyl-6-nitro-2,3-dihydro-1H-indole (1.9 g, 58 %).

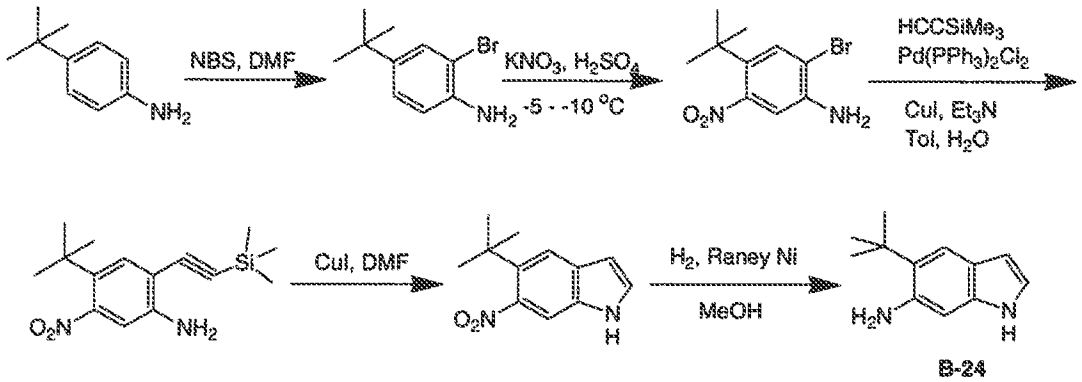
[0418] 5-Ethyl-6-nitro-1H-indole

To a solution of 5-ethyl-6-nitro-2,3-dihydro-1H-indole (1.9 g, 9.9 mmol) in CH_2Cl_2 (30 mL) was added MnO_2 (4 g, 46 mmol). The mixture was stirred at room temperature for 8 h. The solid was filtered off and the filtrate was concentrated to dryness to give crude 5-ethyl-6-nitro-1H-indole (1.9 g, quant.).

[0419] B-23; 5-Ethyl-1H-indol-6-ylamine

A suspension of 5-ethyl-6-nitro-1H-indole (1.9 g, 10 mmol) and Raney Ni (1 g) was stirred under H_2 (1 atm) at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated to dryness. The residue was purified by column chromatography on silica gel to give 5-ethyl-1H-indol-6-ylamine (**B-23**) (760 mg, 48 %). ^{1}H NMR ($CDCl_3$)δ 7.90 (br s, 1H), 7.41 (s, 1H), 7.00 (s, 1H), 6.78 (s, 2H), 6.39 (s, 1H), 3.39 (br s, 2H), 2.63 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 6.9 Hz, 3H); ESI-MS 161.1 m/z (MH^+).

[0420] Example 3:



[0421] 2-Bromo-4-*tert*-butyl-phenylamine

To a solution of 4-*tert*-butyl-phenylamine (447 g, 3 mol) in DMF (500 mL) was added dropwise NBS (531 g, 3 mol) in DMF (500 mL) at room temperature. Upon completion, the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated. The crude product was directly used in the next step without further purification.

[0422] 2-Bromo-4-*tert*-butyl-5-nitro-phenylamine

2-Bromo-4-*tert*-butyl-phenylamine (162 g, 0.71 mol) was added dropwise to H_2SO_4 (410 mL) at room temperature to yield a clear solution. This clear solution was then cooled down to –5 to –10 °C. A solution of KNO_3 (82.5 g, 0.82 mol) in H_2SO_4 (410 mL) was added dropwise while the temperature was maintained between –5 to –10 °C. Upon completion, the reaction mixture was poured into ice / water and extracted with EtOAc. The combined organic layers were washed with 5% Na_2CO_3 and brine, dried over Na_2SO_4 and concentrated. The residue was purified by a column chromatography (EtOAc / petroleum ether 1 / 10) to give 2-bromo-4-*tert*-butyl-5-nitro-phenylamine as a yellow solid (152 g, 78 %).

[0423] 4-*tert*-Butyl-5-nitro-2-trimethylsilanylethynyl-phenylamine

To a mixture of 2-bromo-4-*tert*-butyl-5-nitro-phenylamine (27.3 g, 100 mmol) in toluene (200 mL) and water (100 mL) was added Et_3N (27.9 mL, 200 mmol), $Pd(PPh_3)_2Cl_2$ (2.11 g, 3 mmol), CuI (950 mg, 0.5 mmol) and trimethylsilyl acetylene (21.2 mL, 150 mmol) under a nitrogen atmosphere. The reaction mixture was heated at 70 °C in a sealed pressure flask for 2.5 h., cooled down to room temperature and filtered through a short plug of Celite. The filter cake was washed with EtOAc. The combined filtrate was washed with 5% NH_4OH solution and water,

dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (0 – 10 % EtOAc / petroleum ether) to provide 4-*tert*-butyl-5-nitro-2-trimethylsilanylethynyl-phenylamine as a brown viscous liquid (25 g, 81 %).

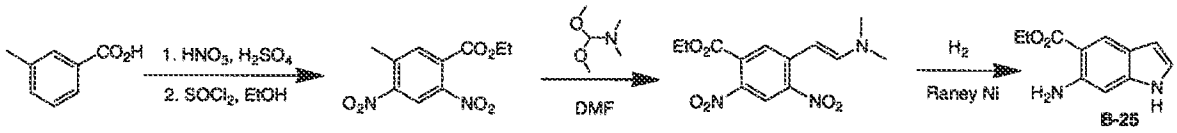
[0424] 5-*tert*-Butyl-6-nitro-1H-indole

To a solution of 4-*tert*-butyl-5-nitro-2-trimethylsilanylethynyl-phenylamine (25 g, 86 mmol) in DMF (100 mL) was added CuI (8.2 g, 43 mmol) under a nitrogen atmosphere. The mixture was heated at 135 °C in a sealed pressure flask overnight, cooled down to room temperature and filtered through a short plug of Celite. The filter cake was washed with EtOAc. The combined filtrate was washed with water, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (10 – 20 % EtOAc / Hexane) to provide 5-*tert*-butyl-6-nitro-1H-indole as a yellow solid (12.9 g, 69 %).

[0425] B-24; 5-*tert*-Butyl-1H-indol-6-ylamine

Raney Ni (3 g) was added to 5-*tert*-butyl-6-nitro-1H-indole (14.7 g, 67 mmol) in methanol (100 mL). The mixture was stirred under hydrogen (1 atm) at 30 °C for 3 h. The catalyst was filtered off. The filtrate was dried over Na_2SO_4 and concentrated. The crude dark brown viscous oil was purified by column chromatography (10 – 20 % EtOAc / petroleum ether) to give 5-*tert*-butyl-1H-indol-6-ylamine (**B-24**) as a gray solid (11 g, 87 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.3 (br s, 1H), 7.2 (s, 1H), 6.9 (m, 1H), 6.6 (s, 1H), 6.1 (m, 1H), 4.4 (br s, 2H), 1.3 (s, 9H).

[0426] Example 4:



[0427] 5-Methyl-2,4-dinitro-benzoic acid

To a mixture of HNO_3 (95 %, 80 mL) and H_2SO_4 (98 %, 80 mL) was slowly added 3-methylbenzoic acid (50 g, 0.37 mol) at 0 °C. After addition, the mixture was stirred for 1.5 h while maintaining the temperature below 30 °C. The mixture was poured into ice-water and stirred for 15 min. The precipitate was collected via filtration and washed with water to give a mixture of 3-methyl-2,6-dinitro-benzoic acid and 5-methyl-2,4-dinitro-benzoic acid (70 g, 84 %). To a solution of this mixture in EtOH (150 mL) was added dropwise $SOCl_2$ (53.5 g, 0.45

mol). The mixture was heated at reflux for 2 h and concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc (100 mL) and extracted with 10% Na_2CO_3 solution (120 mL). The organic layer was found to contain 5-methyl-2,4-dinitro-benzoic acid ethyl ester while the aqueous layer contained 3-methyl-2,6-dinitro-benzoic acid. The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated to dryness to provide 5-methyl-2,4-dinitro-benzoic acid ethyl ester (20 g, 20 %).

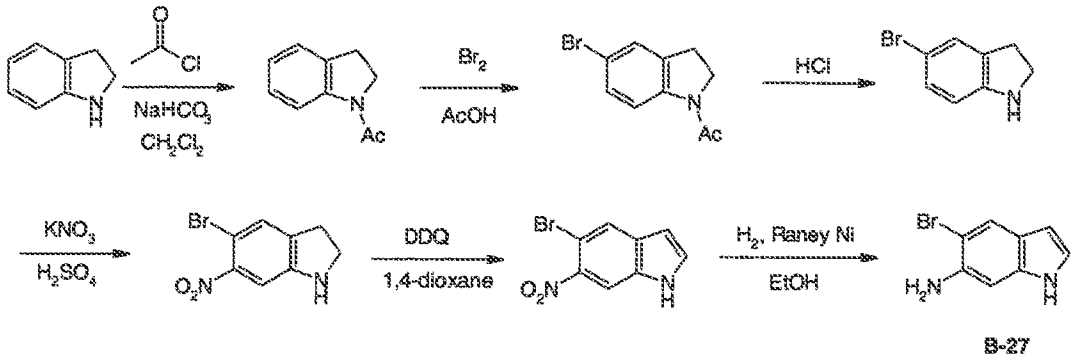
[0428] 5-(2-Dimethylamino-vinyl)-2,4-dinitro-benzoic acid ethyl ester

A mixture of 5-methyl-2,4-dinitro-benzoic acid ethyl ester (39 g, 0.15 mol) and dimethoxymethyl-dimethylamine (32 g, 0.27 mol) in DMF (200 mL) was heated at 100 °C for 5 h. The mixture was poured into ice water. The precipitate was collected via filtration and washed with water to afford 5-(2-dimethylamino-vinyl)-2,4-dinitro-benzoic acid ethyl ester (15 g, 28 %).

[0429] B-25; 6-Amino-1H-indole-5-carboxylic acid ethyl ester

A mixture of 5-(2-dimethylamino-vinyl)-2,4-dinitro-benzoic acid ethyl ester (15 g, 0.05 mol) and Raney Ni (5 g) in EtOH (500 mL) was stirred under H_2 (50 psi) at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated to dryness. The residue was purified by column chromatography on silica gel to give 6-amino-1H-indole-5-carboxylic acid ethyl ester **(B-25)** (3 g, 30 %). ^{1}H NMR (DMSO-d_6) δ 10.68 (s, 1 H), 7.99 (s, 1 H), 7.01-7.06 (m, 1 H), 6.62 (s, 1 H), 6.27-6.28 (m, 1 H), 6.16 (s, 2 H), 4.22 (q, J = 7.2 Hz, 2 H), 1.32-1.27 (t, J = 7.2 Hz, 3 H).

[0430] Example 5:



B-27

1-(2,3-Dihydro-indol-1-yl)-ethanone

To a suspension of $NaHCO_3$ (504 g, 6.0 mol) and 2,3-dihydro-1H-indole (60 g, 0.5 mol) in CH_2Cl_2 (600 mL) cooled in an ice-water bath, was added dropwise acetyl chloride (78.5 g, 1.0 mol). The mixture was stirred at room temperature for 2 h. The solid was filtered off and the filtrate was concentrated to give 1-(2,3-dihydro-indol-1-yl)-ethanone (82 g, 100 %).

[0431] 1-(5-Bromo-2,3-dihydro-indol-1-yl)-ethanone

To a solution of 1-(2,3-dihydro-indol-1-yl)-ethanone (58.0 g, 0.36 mol) in acetic acid (3000 mL) was added Br_2 (87.0 g, 0.54 mol) at 10 °C. The mixture was stirred at room temperature for 4 h. The precipitate was collected via filtration to give crude 1-(5-bromo-2,3-dihydro-indol-1-yl)-ethanone (100 g, 96 %), which was used directly in the next step.

[0432] 5-Bromo-2,3-dihydro-1H-indole

A mixture of crude 1-(5-bromo-2,3-dihydro-indol-1-yl)-ethanone (100 g, 0.34 mol) in HCl (20 %, 1200 mL) was heated at reflux for 6 h. The mixture was basified with Na_2CO_3 to pH 8.5-10 and then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give 5-bromo-2,3-dihydro-1H-indole (37 g, 55 %).

[0433] 5-Bromo-6-nitro-2,3-dihydro-1H-indole

To a solution of 5-bromo-2,3-dihydro-1H-indole (45 g, 0.227 mol) in H_2SO_4 (98 %, 200 mL) was slowly added KNO_3 (23.5 g, 0.23 mol) at 0 °C. After addition, the mixture was stirred at 0 – 10 °C for 4 h, carefully poured into ice, basified with Na_2CO_3 to pH 8 and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography on silica gel to give 5-bromo-6-nitro-2,3-dihydro-1H-indole (42 g, 76 %).

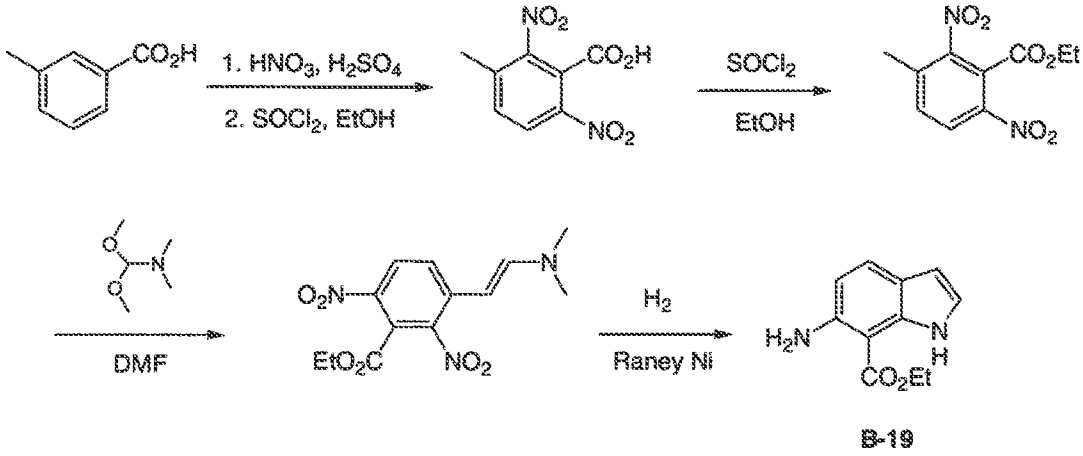
[0434] 5-Bromo-6-nitro-1H-indole

To a solution of 5-bromo-6-nitro-2,3-dihydro-1H-indole (20 g, 82.3 mmol) in 1,4-dioxane (400 mL) was added DDQ (30 g, 0.13 mol). The mixture was stirred at 80 °C for 2 h. The solid was filtered off and the filtrate was concentrated to dryness. The residue was purified by column chromatography on silica gel to afford 5-bromo-6-nitro-1H-indole (7.5 g, 38 %).

[0435] B-27; 5-Bromo-1H-indol-6-ylamine

A mixture of 5-bromo-6-nitro-1H-indole (7.5 g, 31.1 mmol) and Raney Ni (1 g) in ethanol was stirred under H_2 (1 atm) at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated to dryness. The residue was purified by column chromatography on silica gel to give 5-bromo-1H-indol-6-ylamine (**B-27**) (2 g, 30 %). ^{1}H NMR (DMSO-d_6) δ 10.6 (s, 1 H), 7.49 (s, 1 H), 6.79-7.02 (m, 1 H), 6.79 (s, 1 H), 6.14-6.16 (m, 1 H), 4.81 (s, 2 H).

[0436] 7-Substituted 6-aminoindole



B-19

[0437] 3-Methyl-2,6-dinitro-benzoic acid

To a mixture of HNO_3 (95 %, 80 mL) and H_2SO_4 (98 %, 80 mL) was slowly added 3-methylbenzoic acid (50 g, 0.37 mol) at 0 °C. After addition, the mixture was stirred for 1.5 h while maintaining the temperature below 30 °C. The mixture was poured into ice-water and stirred for 15 min. The precipitate was collected via filtration and washed with water to give a mixture of 3-methyl-2,6-dinitro-benzoic acid and 5-methyl-2,4-dinitro-benzoic acid (70 g, 84 %). To a solution of this mixture in EtOH (150 mL) was added dropwise $SOCl_2$ (53.5 g, 0.45 mol). The mixture was heated to reflux for 2 h and concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc (100 mL) and extracted with 10% Na_2CO_3 solution (120 mL). The organic layer was found to contain 5-methyl-2,4-dinitro-benzoic acid ethyl ester. The aqueous layer was acidified with HCl to pH 2 ~ 3 and the resulting precipitate was collected via filtration, washed with water and dried in air to give 3-methyl-2,6-dinitro-benzoic acid (39 g, 47 %).

[0438] 3-Methyl-2,6-dinitro-benzoic acid ethyl ester

A mixture of 3-methyl-2,6-dinitro-benzoic acid (39 g, 0.15 mol) and $SOCl_2$ (80 mL) was heated at reflux for 4 h. The excess $SOCl_2$ was removed under reduced pressure and the residue was added dropwise to a solution of EtOH (100 mL) and Et_3N (50 mL). The mixture was stirred at 20 °C for 1 h and concentrated to dryness. The residue was dissolved in EtOAc (100 mL), washed with Na_2CO_3 (10 %, 40 mL x 2), water (50 mL x 2) and brine (50 mL), dried over Na_2SO_4 and concentrated to give 3-methyl-2,6-dinitro-benzoic acid ethyl ester (20 g, 53 %).

[0439] 3-(2-Dimethylamino-vinyl)-2,6-dinitro-benzoic acid ethyl ester

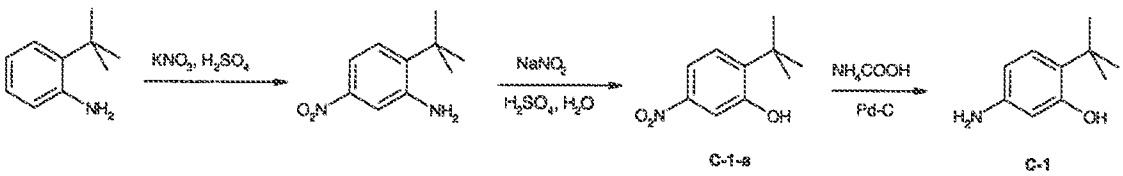
A mixture of 3-methyl-2,6-dinitro-benzoic acid ethyl ester (35 g, 0.14 mol) and dimethoxymethyl-dimethylamine (32 g, 0.27 mol) in DMF (200 mL) was heated at 100 °C for 5 h. The mixture was poured into ice water and the precipitate was collected via filtration and washed with water to give 3-(2-dimethylamino-vinyl)-2,6-dinitro-benzoic acid ethyl ester (25 g, 58 %).

[0440] B-19; 6-Amino-1H-indole-7-carboxylic acid ethyl ester

A mixture of 3-(2-dimethylamino-vinyl)-2, 6-dinitro-benzoic acid ethyl ester (30 g, 0.097 mol) and Raney Ni (10 g) in EtOH (1000 mL) was stirred under H_2 (50 psi) for 2 h. The catalyst was filtered off, and the filtrate was concentrated to dryness. The residue was purified by column chromatography on silica gel to give 6-amino-1H-indole-7-carboxylic acid ethyl ester (**B-19**) as an off-white solid (3.2 g, 16 %). ^{1}H NMR (DMSO-d_6) δ 10.38 (s, 1 H), 7.44-7.41 (d, J = 8.7 Hz, 1 H), 6.98 (t, 1 H), 6.65 (s, 2 H), 6.50-6.46 (m, 1 H), 6.27-6.26 (m, 1 H), 4.43-4.36 (q, J = 7.2 Hz, 2 H), 1.35 (t, J = 7.2 Hz, 3 H).

[0441] Phenols

[0442] Example 1:



[0443] 2-*tert*-Butyl-5-nitroaniline

To a cooled solution of sulfuric acid (90 %, 50 mL) was added dropwise 2-*tert*-butyl-phenylamine (4.5 g, 30 mmol) at 0 °C. Potassium nitrate (4.5 g, 45 mmol) was added in portions at 0 °C. The reaction mixture was stirred at 0-5 °C for 5 min, poured into ice-water and then

extracted with EtOAc three times. The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of solvent, the residue was purified by recrystallization using 70 % EtOH - H_2O to give 2-*tert*-butyl-5-nitroaniline (3.7 g, 64 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 8.7, 2.4 Hz, 1H), 7.48 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.7 Hz, 1H), 4.17 (s, 2H), 1.46 (s, 9H); HPLC ret. time 3.27 min, 10-99 % CH_3CN, 5 min run; ESI-MS 195.3 m/z (MH^+).

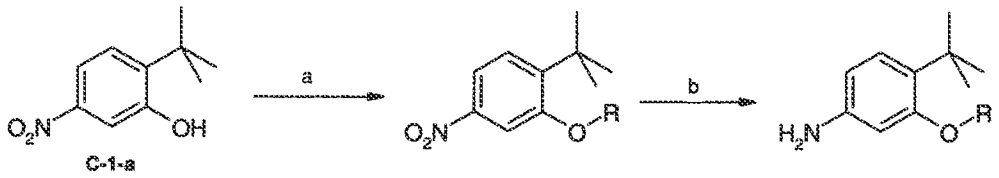
[0444] C-1-a; 2-*tert*-Butyl-5-nitrophenol

To a mixture of 2-*tert*-butyl-5-nitroaniline (1.94 g, 10 mmol) in 40 mL of 15 % H_2SO_4 was added dropwise a solution of $NaNO_2$ (763 mg, 11.0 mmol) in water (3 mL) at 0 °C. The resulting mixture was stirred at 0-5 °C for 5 min. Excess $NaNO_2$ was neutralized with urea, then 5 mL of H_2SO_4-H_2O (v/v 1:2) was added and the mixture was refluxed for 5 min. Three additional 5 mL aliquots of H_2SO_4-H_2O (v/v 1:2) were added while heating at reflux. The reaction mixture was cooled to room temperature and extracted with EtOAc twice. The combined organic layers were washed with brine and dried over $MgSO_4$. After removal of solvent, the residue was purified by column chromatography (0-10 % EtOAc – Hexane) to give 2-*tert*-butyl-5-nitrophenol (**C-1-a**) (1.2 g, 62 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, J = 8.6, 2.2 Hz, 1H), 7.58 (d, J = 2.1 Hz, 1H), 7.43 (d, J = 8.6 Hz, 1H), 5.41 (s, 1H), 1.45 (s, 9H); HPLC ret. time 3.46 min, 10-99 % CH_3CN, 5 min run.

[0445] C-1; 2-*tert*-Butyl-5-aminophenol. To a refluxing solution of 2-*tert*-butyl-5-nitrophenol (**C-1-a**) (196 mg, 1.0 mmol) in EtOH (10 mL) was added ammonium formate (200 mg, 3.1 mmol), followed by 140 mg of 10% Pd-C. The reaction mixture was refluxed for additional 30 min, cooled to room temperature and filtered through a plug of Celite. The filtrate was concentrated to dryness and purified by column chromatography (20-30% EtOAc-Hexane) to give 2-*tert*-butyl-5-aminophenol (**C-1**) (144 mg, 87 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H), 6.74 (d, J = 8.3 Hz, 1H), 6.04 (d, J = 2.3 Hz, 1H), 5.93 (dd, J = 8.2, 2.3 Hz, 1H), 4.67 (s, 2H), 1.26 (s, 9H); HPLC ret. time 2.26 min, 10-99 % CH_3CN, 5 min run; ESI-MS 166.1 m/z (MH^+).

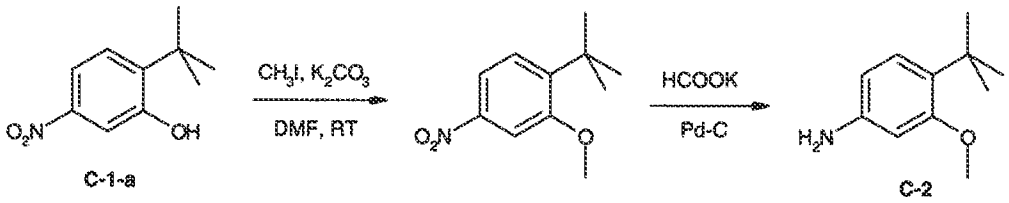
[0446] Example 2:

[0447] General scheme:



a) RX (X = Br, I), K_2CO_3 or Cs_2CO_3, DMF; b) HCO_2NH_4 or HCO_2K, Pd-C, EtOH

[0448] Specific example:



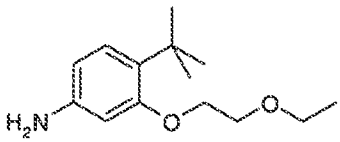
[0449] **1-*tert*-Butyl-2-methoxy-4-nitrobenzene**

To a mixture of 2-*tert*-butyl-5-nitrophenol (**C-1-a**) (100 mg, 0.52 mmol) and K_2CO_3 (86 mg, 0.62 mmol) in DMF (2 mL) was added CH_3I (40 uL, 0.62 mmol). The reaction mixture was stirred at room temperature for 2 h, diluted with water and extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. After filtration, the filtrate was evaporated to dryness to give 1-*tert*-butyl-2-methoxy-4-nitrobenzene (82 mg, 76 %) that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (t, J = 4.3 Hz, 1H), 7.70 (d, J = 2.3 Hz, 1H), 7.40 (d, J = 8.6 Hz, 1H), 3.94 (s, 3H), 1.39 (s, 9H).

[0450] **C-2; 4-*tert*-Butyl-3-methoxyaniline**

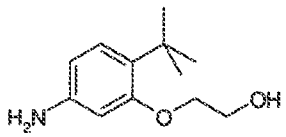
To a refluxing solution of 1-*tert*-butyl-2-methoxy-4-nitrobenzene (82 mg, 0.4 mmol) in EtOH (2 mL) was added potassium formate (300 mg, 3.6 mmol) in water (1 mL), followed by 10% Pd-C (15 mg). The reaction mixture was refluxed for additional 60 min, cooled to room temperature and filtered through Celite. The filtrate was concentrated to dryness to give 4-*tert*-butyl-3-methoxyaniline (**C-2**) (52 mg, 72 %) that was used without further purification. HPLC ret. time 2.29 min, 10-99 % CH_3CN, 5 min run; ESI-MS 180.0 m/z (MH^+).

[0451] Other examples:



[0452] C-3; 3-(2-Ethoxyethoxy)-4-*tert*-butylbenzenamine

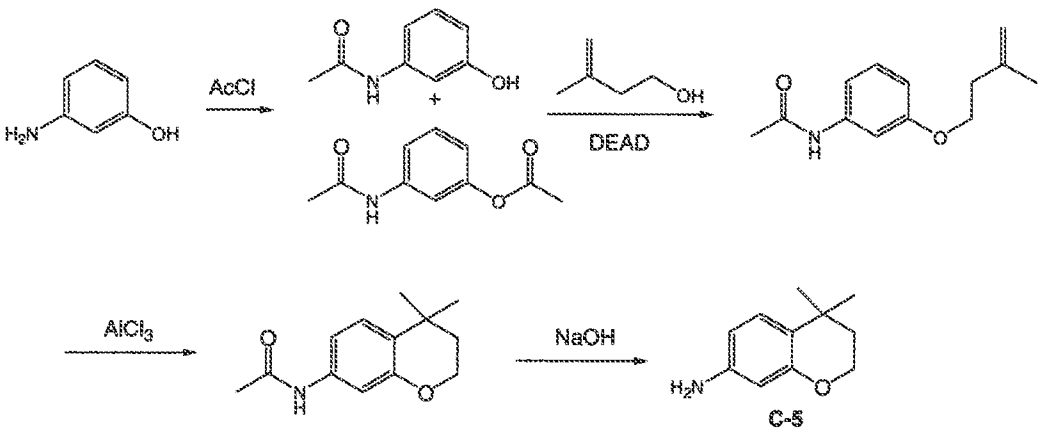
3-(2-Ethoxyethoxy)-4-*tert*-butylbenzenamine (**C-3**) was synthesized following the general scheme above starting from 2-*tert*-butyl-5-nitrophenol (**C-1-a**) and 1-bromo-2-ethoxyethane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, J = 7.9 Hz, 1H), 6.17 (s, 1H), 6.14 (d, J = 2.3 Hz, 1H), 4.00 (t, J = 5.2 Hz, 2H), 3.76 (t, J = 5.2 Hz, 2H), 3.53 (q, J = 7.0 Hz, 2H), 1.27 (s, 9H), 1.16 (t, J = 7.0 Hz, 3H); HPLC ret. time 2.55 min, 10-99 % CH_3CN, 5 min run; ESI-MS 238.3 m/z (MH^+).



[0453] C-4; 2-(2-*tert*-Butyl-5-aminophenoxy)ethanol

2-(2-*tert*-Butyl-5-aminophenoxy)ethanol (**C-4**) was synthesized following the general scheme above starting from 2-*tert*-butyl-5-nitrophenol (**C-1-a**) and 2-bromoethanol. HPLC ret. time 2.08 min, 10-99 % CH_3CN, 5 min run; ESI-MS 210.3 m/z (MH^+).

[0454] Example 3:



[0455] N-(3-Hydroxy-phenyl)-acetamide and acetic acid 3-formylamino-phenyl ester

To a well stirred suspension of 3-amino-phenol (50 g, 0.46 mol) and $NaHCO_3$ (193.2 g, 2.3 mol) in chloroform (1 L) was added dropwise chloroacetyl chloride (46.9 g, 0.6 mol) over a period of 30 min at 0 °C. After the addition was complete, the reaction mixture was refluxed overnight and then cooled to room temperature. The excess $NaHCO_3$ was removed via filtration. The filtrate was poured into water and extracted with EtOAc (300 x 3 mL). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a mixture of N-(3-hydroxy-phenyl)-acetamide and acetic acid 3-formylamino-phenyl ester (35 g, 4:1 by NMR analysis). The mixture was used directly in the next step.

[0456] N-[3-(3-Methyl-but-3-enyloxy)-phenyl]-acetamide

A suspension of the mixture of N-(3-hydroxy-phenyl)-acetamide and acetic acid 3-formylamino-phenyl ester (18.12 g, 0.12 mol), 3-methyl-but-3-en-1-ol (8.6 g, 0.1 mol), DEAD (87 g, 0.2 mol) and Ph_3P (31.44 g, 0.12 mol) in benzene (250 mL) was heated at reflux overnight and then cooled to room temperature. The reaction mixture was poured into water and the organic layer was separated. The aqueous phase was extracted with EtOAc (300 x 3 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography to give N-[3-(3-methyl-but-3-enyloxy)-phenyl]-acetamide (11 g, 52 %).

[0457] N-(4,4-Dimethyl-chroman-7-yl)-acetamide

A mixture of N-[3-(3-methyl-but-3-enyloxy)-phenyl]-acetamide (2.5 g, 11.4 mmol) and $AlCl_3$ (4.52 g, 34.3 mmol) in fluoro-benzene (50 mL) was heated at reflux overnight. After cooling, the reaction mixture was poured into water. The organic layer was separated and the aqueous phase was extracted with EtOAc (40 x 3 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under *vacuum*. The residue was purified by column chromatography to give N-(4,4-dimethyl-chroman-7-yl)-acetamide (1.35 g, 54 %).

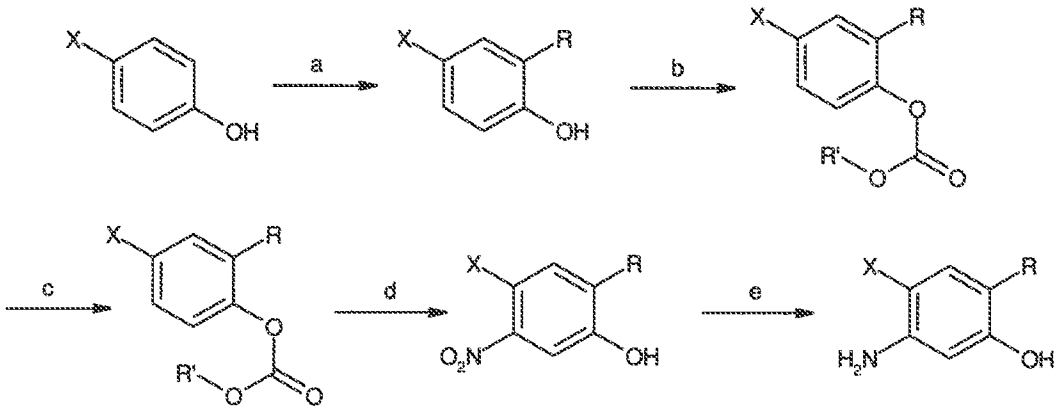
[0458] C-5; 3,4-Dihydro-4,4-dimethyl-2H-chromen-7-amine

A mixture of N-(4,4-dimethyl-chroman-7-yl)-acetamide (1.35 g, 6.2 mmol) in 20 % HCl solution (30 mL) was heated at reflux for 3 h and then cooled to room temperature. The reaction mixture was basified with 10 % aq. NaOH to pH 8 and extracted with EtOAc (30 x 3 mL). The

combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give 3,4-dihydro-4,4-dimethyl-2H-chromen-7-amine (**C-5**) (1 g, 92 %). ^{1}H NMR (DMSO-d_6) δ 6.87 (d, J = 8.4 Hz, 1 H), 6.07 (dd, J = 8.4, 2.4 Hz, 1 H), 5.87 (d, J = 2.4 Hz, 1 H), 4.75 (s, 2 H), 3.99 (t, J = 5.4 Hz, 2 H), 1.64 (t, J = 5.1 Hz, 2 H), 1.15 (s, 6 H); ESI-MS 178.1 m/z (MH^+).

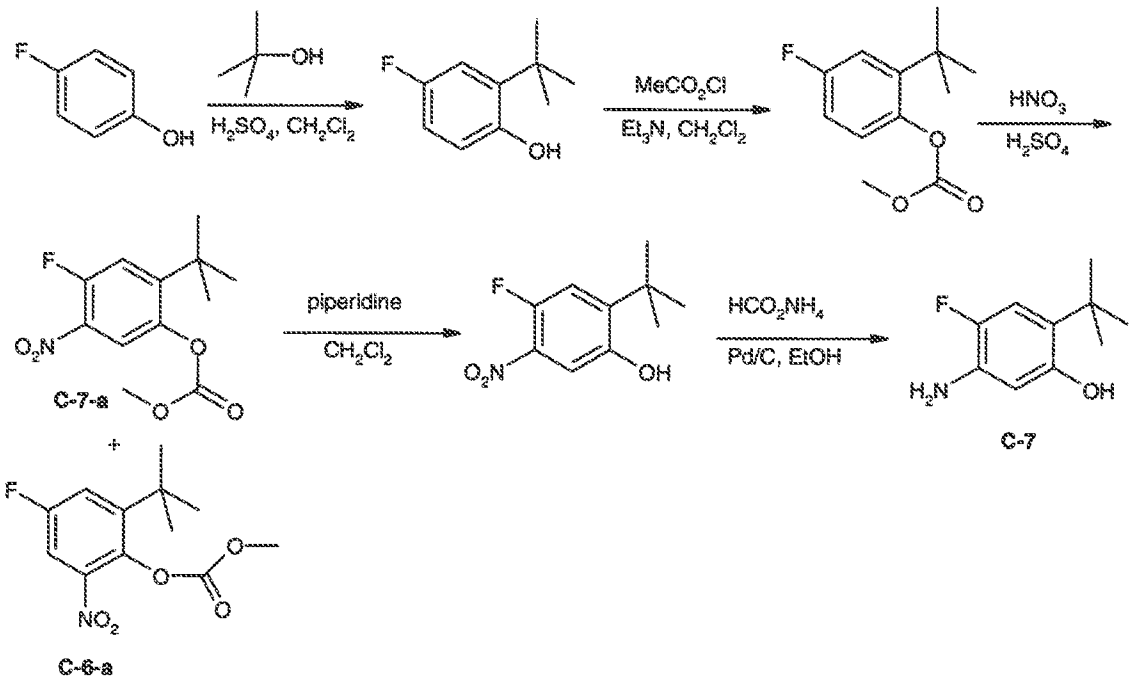
[0459] Example 4:

[0460] General scheme:



X = F, Cl; a) ROH, H_2SO_4 or $MeSO_3H$, CH_2Cl_2; b) $R'CO_2Cl$, Et_3N, 1,4-dioxane or $CHCl_3$; c) HNO_3, H_2SO_4 or KNO_3, H_2SO_4 or HNO_3, AcOH; d) piperidine, CH_2Cl_2; e) HCO_2NH_4, Pd-C, EtOH or $SnCl_2.2H_2O$, EtOH or H_2, Pd-C, MeOH.

[0461] Specific example



[0462] **2-*tert*-Butyl-4-fluorophenol**

4-Fluorophenol (5g, 45 mmol) and *tert*-butanol (5.9 mL, 63 mmol) were dissolved in CH_2Cl_2 (80 mL) and treated with concentrated sulfuric acid (98 %, 3 mL). The mixture was stirred at room temperature overnight. The organic layer was washed with water, neutralized with $NaHCO_3$, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (5-15 % EtOAc - Hexane) to give 2-*tert*-butyl-4-fluorophenol (3.12 g, 42 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.32 (s, 1H), 6.89 (dd, J = 11.1, 3.1 Hz, 1H), 6.84-6.79 (m, 1H), 6.74 (dd, J = 8.7, 5.3 Hz, 1H), 1.33 (s, 9H).

[0463] **2-*tert*-Butyl-4-fluorophenyl methyl carbonate**

To a solution of 2-*tert*-butyl-4-fluorophenol (2.63g, 15.7 mmol) and NEt_3 (3.13 mL, 22.5 mmol) in dioxane (45 mL) was added methyl chloroformate (1.27 mL, 16.5 mmol). The mixture was stirred at room temperature for 1 h. The precipitate was removed via filtration. The filtrate was then diluted with water and extracted with ether. The ether extract was washed with water and dried over $MgSO_4$. After removal of solvent, the residue was purified by column chromatography to give 2-*tert*-butyl-4-fluorophenyl methyl carbonate (2.08g, 59 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24 (dd, J = 8.8, 5.4 Hz, 1H), 7.17-7.10 (m, 2H), 3.86 (s, 3H), 1.29 (s, 9H).

[0464] 2-*tert*-Butyl-4-fluoro-5-nitrophenyl methyl carbonate (C-7-a) and 2-*tert*-butyl-4-fluoro-6-nitrophenyl methyl carbonate (C-6-a)

To a solution of 2-*tert*-butyl-4-fluorophenyl methyl carbonate (1.81g, 8 mmol) in H_2SO_4 (98 %, 1 mL) was added slowly a cooled mixture of H_2SO_4 (1 mL) and HNO_3 (1 mL) at 0 °C. The mixture was stirred for 2 h while warming to room temperature, poured into ice and extracted with diethyl ether. The ether extract was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (0-10 % EtOAc - Hexane) to give 2-*tert*-butyl-4-fluoro-5-nitrophenyl methyl carbonate (**C-7-a**) (1.2 g, 55 %) and 2-*tert*-butyl-4-fluoro-6-nitrophenyl methyl carbonate (**C-6-a**) (270 mg, 12 %). 2-*tert*-Butyl-4-fluoro-5-nitrophenyl methyl carbonate (**C-7-a**): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (d, J = 7.1 Hz, 1H), 7.55 (d, J = 13.4 Hz, 1H), 3.90 (s, 3H), 1.32 (s, 9H). 2-*tert*-butyl-4-fluoro-6-nitrophenyl methyl carbonate (**C-6-a**): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (dd, J = 7.6, 3.1 Hz, 1H), 7.69 (dd, J = 10.1, 3.1 Hz, 1H), 3.91 (s, 3H), 1.35 (s, 9H).

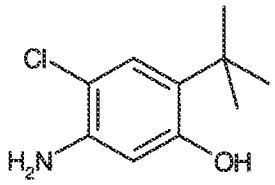
[0465] 2-*tert*-Butyl-4-fluoro-5-nitrophenol

To a solution of 2-*tert*-butyl-4-fluoro-5-nitrophenyl methyl carbonate (**C-7-a**) (1.08 g, 4 mmol) in CH_2Cl_2 (40 mL) was added piperidine (3.94 mL, 10 mmol). The mixture was stirred at room temperature for 1 h and extracted with 1N NaOH (3x). The aqueous layer was acidified with 1N HCl and extracted with diethyl ether. The ether extract was washed with brine, dried ($MgSO_4$) and concentrated to give 2-*tert*-butyl-4-fluoro-5-nitrophenol (530 mg, 62 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 1H), 7.49 (d, J = 6.8 Hz, 1H), 7.25 (d, J = 13.7 Hz, 1H), 1.36 (s, 9H).

[0466] C-7; 2-*tert*-Butyl-5-amino-4-fluorophenol

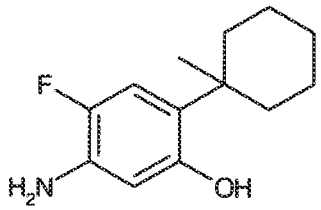
To a refluxing solution of 2-*tert*-butyl-4-fluoro-5-nitrophenol (400 mg, 1.88 mmol) and ammonium formate (400 mg, 6.1 mmol) in EtOH (20 mL) was added 5 % Pd-C (260 mg). The mixture was refluxed for additional 1 h, cooled and filtered through Celite. The solvent was removed by evaporation to give 2-*tert*-butyl-5-amino-4-fluorophenol (**C-7**) (550 mg, 83 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (br s, 1H), 6.66 (d, J = 13.7 Hz, 1H), 6.22 (d, J = 8.5 Hz, 1H), 4.74 (br s, 2H), 1.26 (s, 9H); HPLC ret. time 2.58 min, 10-99 % CH_3CN, 5 min run; ESI-MS 184.0 m/z (MH^+).

[0467] Other examples:



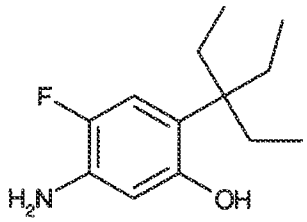
[0468] C-10; 2-*tert*-Butyl-5-amino-4-chlorophenol

2-*tert*-Butyl-5-amino-4-chlorophenol (**C-10**) was synthesized following the general scheme above starting from 4-chlorophenol and *tert*-butanol. Overall yield (6 %). HPLC ret. time 3.07 min, 10-99 % CH_3CN, 5 min run; ESI-MS 200.2 m/z (MH^+).



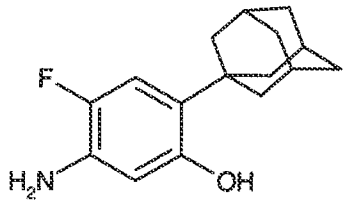
[0469] C-13; 5-Amino-4-fluoro-2-(1-methylcyclohexyl)phenol

5-Amino-4-fluoro-2-(1-methylcyclohexyl)phenol (**C-13**) was synthesized following the general scheme above starting from 4-fluorophenol and 1-methylcyclohexanol. Overall yield (3 %). HPLC ret. time 3.00 min, 10-99 % CH_3CN, 5 min run; ESI-MS 224.2 m/z (MH^+).



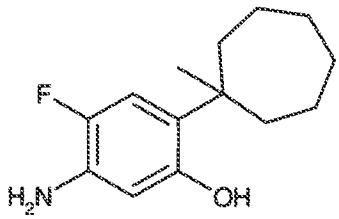
[0470] C-19; 5-Amino-2-(3-ethylpentan-3-yl)-4-fluoro-phenol

5-Amino-2-(3-ethylpentan-3-yl)-4-fluoro-phenol (**C-19**) was synthesized following the general scheme above starting from 4-fluorophenol and 3-ethyl-3-pentanol. Overall yield (1 %).



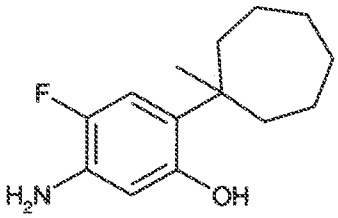
[0471] C-20; 2-Admantyl-5-amino-4-fluoro-phenol

2-Admantyl-5-amino-4-fluoro-phenol (**C-20**) was synthesized following the general scheme above starting from 4-fluorophenol and adamantan-1-ol.



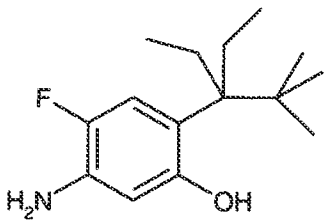
[0472] C-21; 5-Amino-4-fluoro-2-(1-methylcycloheptyl)phenol

5-Amino-4-fluoro-2-(1-methylcycloheptyl)phenol (**C-21**) was synthesized following the general scheme above starting from 4-fluorophenol and 1-methyl-cycloheptanol.



[0473] C-22; 5-Amino-4-fluoro-2-(1-methylcyclooctyl)phenol

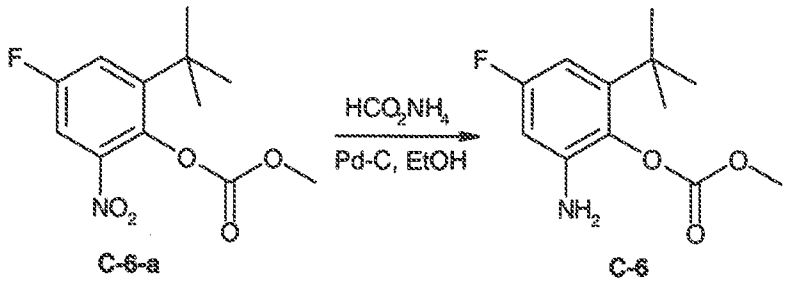
5-Amino-4-fluoro-2-(1-methylcyclooctyl)phenol (**C-22**) was synthesized following the general scheme above starting from 4-fluorophenol and 1-methyl-cyclooctanol.



[0474] C-23; 5-Amino-2-(3-ethyl-2,2-dimethylpentan-3-yl)-4-fluoro-phenol

5-Amino-2-(3-ethyl-2,2-dimethylpentan-3-yl)-4-fluoro-phenol (**C-23**) was synthesized following the general scheme above starting from 4-fluorophenol and 3-ethyl-2,2-dimethyl-pentan-3-ol.

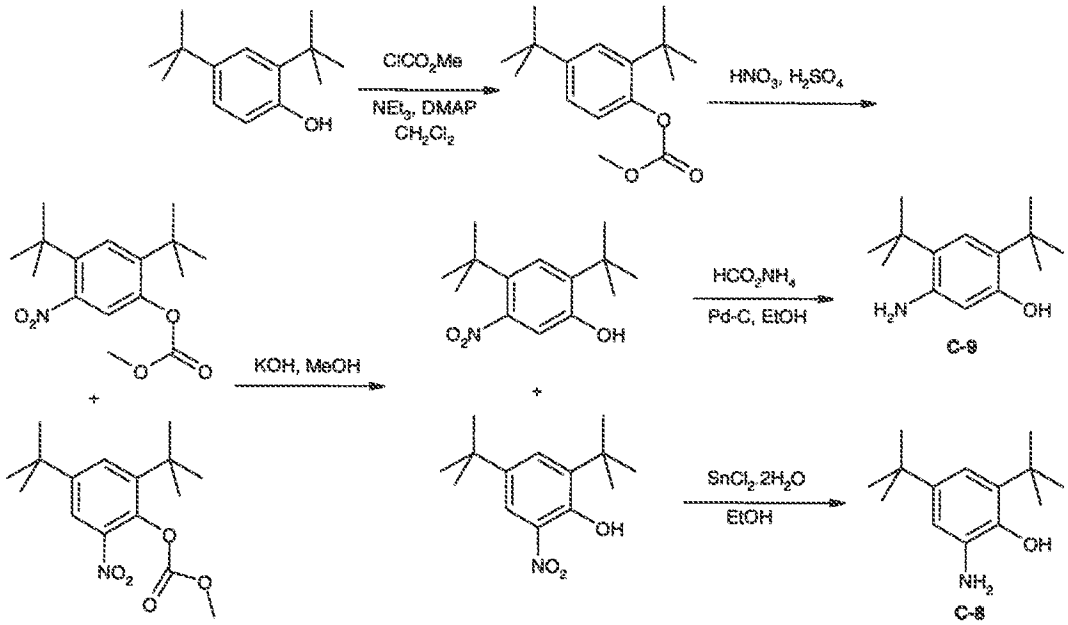
[0475] Example 5:



[0476] C-6; 2-*tert*-Butyl-4-fluoro-6-aminophenyl methyl carbonate

To a refluxing solution of 2-*tert*-butyl-4-fluoro-6-nitrophenyl methyl carbonate (250 mg, 0.92 mmol) and ammonium formate (250 mg, 4 mmol) in EtOH (10 mL) was added 5 % Pd-C (170 mg). The mixture was refluxed for additional 1 h, cooled and filtered through Celite. The solvent was removed by evaporation and the residue was purified by column chromatography (0-15 %, EtOAc – Hexane) to give 2-*tert*-butyl-4-fluoro-6-aminophenyl methyl carbonate (**C-6**) (60 mg, 27 %). HPLC ret. time 3.35 min, 10-99 % CH_3CN, 5 min run; ESI-MS 242.0 m/z (MH^+).

[0477] Example 6:



[0478] Carbonic acid 2,4-di-*tert*-butyl-phenyl ester methyl ester

Methyl chloroformate (58 mL, 750 mmol) was added dropwise to a solution of 2,4-di-*tert*-butyl-phenol (103.2g, 500 mmol), Et_3N (139 mL, 1000 mmol) and DMAP (3.05g, 25 mmol) in dichloromethane (400 mL) cooled in an ice-water bath to 0 °C. The mixture was allowed to

warm to room temperature while stirring overnight, then filtered through silica gel (approx. 1L) using 10% ethyl acetate – hexanes (~ 4 L) as the eluent. The combined filtrates were concentrated to yield carbonic acid 2,4-di-*tert*-butyl-phenyl ester methyl ester as a yellow oil (132 g, quant.). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 (d, J = 2.4 Hz, 1H), 7.29 (dd, J = 8.5, 2.4 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 3.85 (s, 3H), 1.30 (s, 9H), 1.29 (s, 9H).

[0479] Carbonic acid 2,4-di-*tert*-butyl-5-nitro-phenyl ester methyl ester and Carbonic acid 2,4-di-*tert*-butyl-6-nitro-phenyl ester methyl ester

To a stirring mixture of carbonic acid 2,4-di-*tert*-butyl-phenyl ester methyl ester (4.76 g, 18 mmol) in conc. sulfuric acid (2 mL), cooled in an ice-water bath, was added a cooled mixture of sulfuric acid (2 mL) and nitric acid (2 mL). The addition was done slowly so that the reaction temperature did not exceed 50 °C. The reaction was allowed to stir for 2 h while warming to room temperature. The reaction mixture was then added to ice-water and extracted into diethyl ether. The ether layer was dried ($MgSO_4$), concentrated and purified by column chromatography (0 – 10% ethyl acetate – hexanes) to yield a mixture of carbonic acid 2,4-di-*tert*-butyl-5-nitro-phenyl ester methyl ester and carbonic acid 2,4-di-*tert*-butyl-6-nitro-phenyl ester methyl ester as a pale yellow solid (4.28 g), which was used directly in the next step.

[0480] 2,4-Di-*tert*-butyl-5-nitro-phenol and 2,4-Di-*tert*-butyl-6-nitro-phenol

The mixture of carbonic acid 2,4-di-*tert*-butyl-5-nitro-phenyl ester methyl ester and carbonic acid 2,4-di-*tert*-butyl-6-nitro-phenyl ester methyl ester (4.2 g, 12.9 mmol) was dissolved in MeOH (65 mL) and KOH (2.0g, 36 mmol) was added. The mixture was stirred at room temperature for 2 h. The reaction mixture was then made acidic (pH 2-3) by adding conc. HCl and partitioned between water and diethyl ether. The ether layer was dried ($MgSO_4$), concentrated and purified by column chromatography (0 – 5 % ethyl acetate – hexanes) to provide 2,4-di-*tert*-butyl-5-nitro-phenol (1.31 g, 29 % over 2 steps) and 2,4-di-*tert*-butyl-6-nitro-phenol. 2,4-Di-*tert*-butyl-5-nitro-phenol: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H, OH), 7.34 (s, 1H), 6.83 (s, 1H), 1.36 (s, 9H), 1.30 (s, 9H). 2,4-Di-*tert*-butyl-6-nitro-phenol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.48 (s, 1H), 7.98 (d, J = 2.5 Hz, 1H), 7.66 (d, J = 2.4 Hz, 1H), 1.47 (s, 9H), 1.34 (s, 9H).

[0481] C-9; 5-Amino-2,4-di-*tert*-butyl-phenol

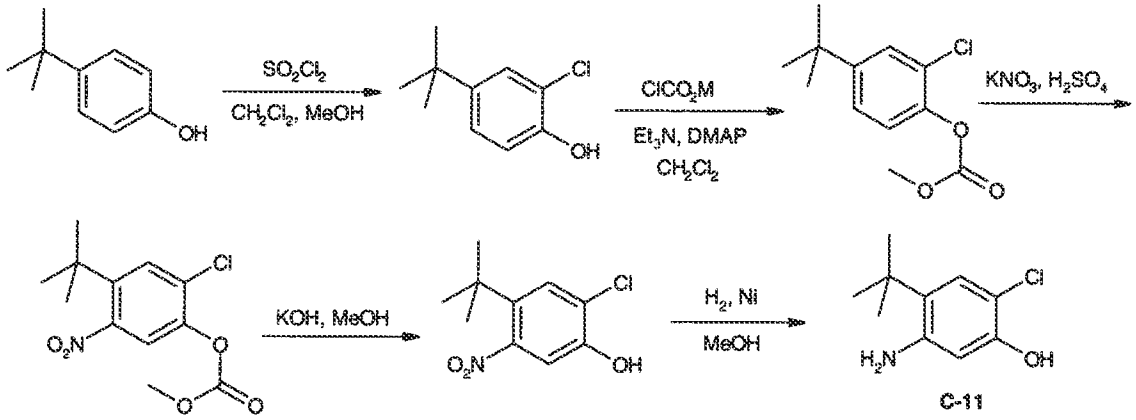
To a reluxing solution of 2,4-di-*tert*-butyl-5-nitro-phenol (1.86 g, 7.4 mmol) and ammonium formate (1.86 g) in ethanol (75 mL) was added Pd-5% wt. on activated carbon (900 mg). The

reaction mixture was stirred at reflux for 2 h, cooled to room temperature and filtered through Celite. The Celite was washed with methanol and the combined filtrates were concentrated to yield 5-amino-2,4-di-*tert*-butyl-phenol as a grey solid (1.66 g, quant.). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H, OH), 6.84 (s, 1H), 6.08 (s, 1H), 4.39 (s, 2H, NH_2), 1.27 (m, 18H); HPLC ret. time 2.72 min, 10-99 % CH_3CN, 5 min run; ESI-MS 222.4 m/z (MH^+).

[0482] C-8; 6-Amino-2,4-di-*tert*-butyl-phenol

A solution.of 2,4-di-*tert*-butyl-6-nitro-phenol (27 mg, 0.11 mmol) and $SnCl_2.2H_2O$ (121 mg, 0.54 mmol) in EtOH (1.0 mL) was heated in microwave oven at 100 °C for 30 min. The mixture was diluted with EtOAc and water, basified with sat. $NaHCO_3$ and filtered through Celite. The organic layer was separated and dried over Na_2SO_4. Solvent was removed by evaporation to provide 6-amino-2,4-di-*tert*-butyl-phenol (**C-8**), which was used without further purification. HPLC ret. time 2.74 min, 10-99 % CH_3CN, 5 min run; ESI-MS 222.5 m/z (MH^+).

[0483] Example 7:



[0484] 4-*tert*-butyl-2-chloro-phenol

To a solution of 4-*tert*-butyl-phenol (40.0 g, 0.27 mol) and SO_2Cl_2 (37.5 g, 0.28 mol) in CH_2Cl_2 was added MeOH (9.0 g, 0.28 mol) at 0 °C. After addition was complete, the mixture was stirred overnight at room temperature and then water (200 mL) was added. The resulting solution was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under *vacuum*. The residue was purified by column chromatography (Pet. Ether / EtOAc, 50:1) to give 4-*tert*-butyl-2-chloro-phenol (47.0 g, 95 %).

[0485] 4-*tert*-Butyl-2-chlorophenyl methyl carbonate

To a solution of 4-*tert*-butyl-2-chlorophenol (47.0 g, 0.25 mol) in dichloromethane (200 mL) was added Et_3N (50.5 g, 0.50 mol), DMAP (1 g) and methyl chloroformate (35.4 g, 0.38 mol) at 0 °C. The reaction was allowed to warm to room temperature and stirred for additional 30 min. The reaction mixture was washed with H_2O and the organic layer was dried over Na_2SO_4 and concentrated to give 4-*tert*-butyl-2-chlorophenyl methyl carbonate (56.6 g, 92 %), which was used directly in the next step.

[0486] 4-*tert*-Butyl-2-chloro-5-nitrophenyl methyl carbonate

4-*tert*-Butyl-2-chlorophenyl methyl carbonate (36.0 g, 0.15 mol) was dissolved in conc. H_2SO_4 (100 mL) at 0 °C. KNO_3 (0.53 g, 5.2 mmol) was added in portions over 25 min. The reaction was stirred for 1.5 h and poured into ice (200 g). The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with aq. $NaHCO_3$, dried over Na_2SO_4 and concentrated under *vacuum* to give 4-*tert*-butyl-2-chloro-5-nitrophenyl methyl carbonate (41.0 g), which was used without further purification.

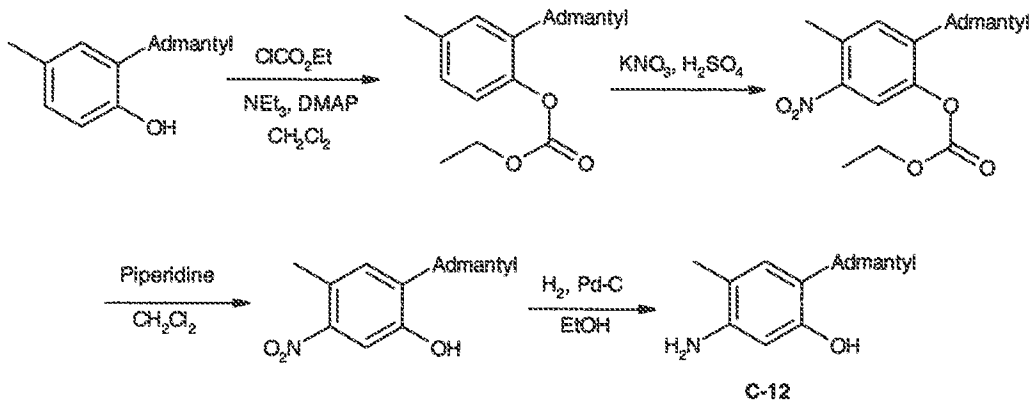
[0487] 4-*tert*-Butyl-2-chloro-5-nitro-phenol

Potassium hydroxide (10.1 g, 181 mmol) was added to 4-*tert*-butyl-2-chloro-5-nitrophenyl methyl carbonate (40.0 g, 139 mmol) in MeOH (100 mL). After 30 min, the reaction was acidified with 1N HCl and extracted with dichloromethane. The combined organic layers were combined, dried over Na_2SO_4 and concentrated under *vacuum*. The crude residue was purified by column chromatography (Pet. Ether / EtOAc, 30:1) to give 4-*tert*-butyl-2-chloro-5-nitro-phenol (23.0 g, 68 % over 2 steps).

[0488] C-11; 4-*tert*-Butyl-2-chloro-5-amino-phenol

To a solution of 4-*tert*-butyl-2-chloro-5-nitro-phenol (12.6 g, 54.9 mmol) in MeOH (50 mL) was added Ni (1.2 g). The reaction was shaken under H_2 (1 atm) for 4 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography (P.E. / EtOAc, 20:1) to give 4-*tert*-butyl-2-chloro-5-amino-phenol (**C-11**) (8.5 g, 78 %). ^1H NMR (DMSO-d_6) δ 9.33 (s, 1 H), 6.80 (s, 1 H), 6.22 (s, 1 H), 4.76 (s, 1 H), 1.23 (s, 9 H); ESI-MS 200.1 m/z (MH^+).

[0489] Example 8:



C-12

2-Admantyl-4-methyl-phenyl ethyl carbonate

Ethyl chloroformate (0.64 mL, 6.7 mmol) was added dropwise to a solution of 2-admantyl-4-methylphenol (1.09 g, 4.5 mmol), Et_3N (1.25 mL, 9 mmol) and DMAP (catalytic amount) in dichloromethane (8 mL) cooled in an ice-water bath to 0 °C. The mixture was allowed to warm to room temperature while stirring overnight, then filtered and the filtrate was concentrated. The residue was purified by column chromatography (10-20 % ethyl acetate – hexanes) to yield 2-admantyl-4-methyl-phenyl ethyl carbonate as a yellow oil (1.32 g, 94 %).

[0490] 2-Admantyl-4-methyl-5-nitrophenyl ethyl carbonate

To a cooled solution of 2-admantyl-4-methyl-phenyl ethyl carbonate (1.32 g, 4.2 mmol) in H_2SO_4 (98 %, 10 mL) was added KNO_3 (510 mg, 5.0 mmol) in small portions at 0 °C. The mixture was stirred for 3 h while warming to room temperature, poured into ice and then extracted with dichloromethane. The combined organic layers were washed with $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated to dryness. The residue was purified by column chromatography (0-10 % EtOAc - Hexane) to yield 2-admantyl-4-methyl-5-nitrophenyl ethyl carbonate (378 mg, 25 %).

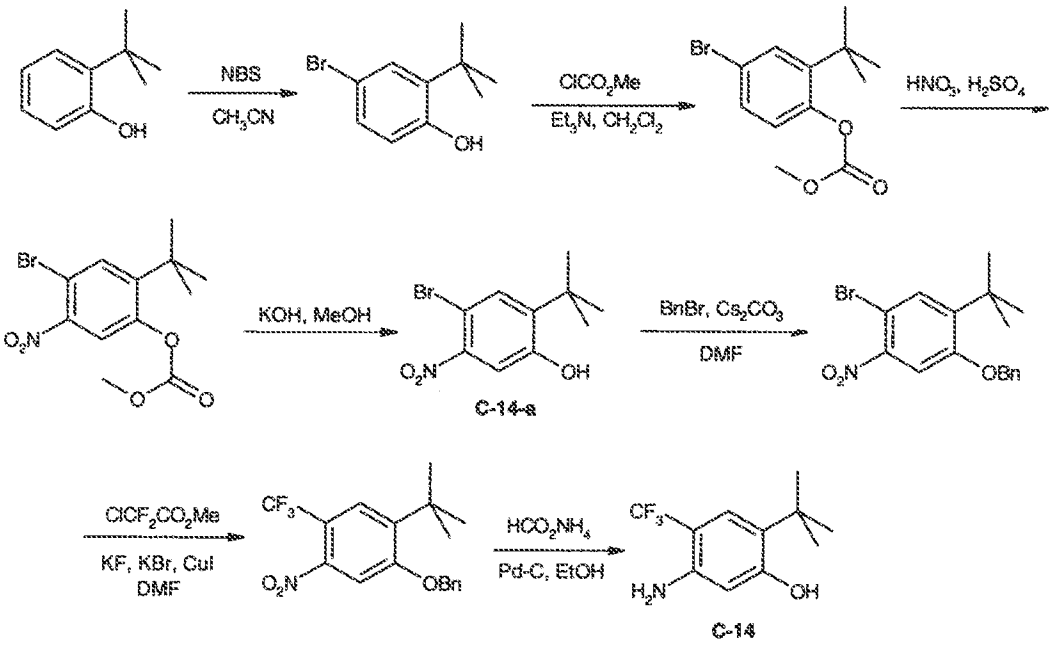
[0491] 2-Admantyl-4-methyl-5-nitrophenol

To a solution of 2-admantyl-4-methyl-5-nitrophenyl ethyl carbonate (378 mg, 1.05 mmol) in CH_2Cl_2 (5 mL) was added piperidine (1.0 mL). The solution was stirred at room temperature for 1 h, adsorbed onto silica gel under reduced pressure and purified by flash chromatography on silica gel (0-15 %, EtOAc - Hexanes) to provide 2-admantyl-4-methyl-5-nitrophenol (231 mg, 77 %).

[0492] C-12; 2-Admantyl-4-methyl-5-aminophenol

To a solution of 2-admantyl-4-methyl-5-nitrophenol (231 mg, 1.6 mmol) in EtOH (2 mL) was added Pd- 5% wt on carbon (10 mg). The mixture was stirred under H_2 (1 atm) overnight and then filtered through Celite. The filtrate was evaporated to dryness to provide 2-admantyl-4-methyl-5-aminophenol (**C-12**), which was used without further purification. HPLC ret. time 2.52 min, 10-99 % CH_3CN, 5 min run; ESI-MS 258.3 m/z (MH^+).

[0493] Example 9:



2-*tert*-Butyl-4-bromophenol

To a solution of 2-*tert*-butylphenol (250g, 1.67 mol) in CH_3CN (1500 mL) was added NBS (300 g, 1.67 mol) at room temperature. After addition, the mixture was stirred at room temperature overnight and then the solvent was removed. Petroleum ether (1000 mL) was added, and the resulting white precipitate was filtered off. The filtrate was concentrated under reduced pressure to give the crude 2-*tert*-butyl-4-bromophenol (380 g), which was used without further purification.

[0494] Methyl (2-*tert*-butyl-4-bromophenyl) carbonate

To a solution of 2-*t*-butyl-4-bromophenol (380 g, 1.67 mol) in dichloromethane (1000 mL) was added Et_3N (202 g, 2 mol) at room temperature. Methyl chloroformate (155 mL) was added

dropwise to the above solution at 0 °C. After addition, the mixture was stirred at 0 °C for 2 h., quenched with saturated ammonium chloride solution and diluted with water. The organic layer was separated and washed with water and brine, dried over Na_2SO_4, and concentrated to provide the crude methyl (2-*tert*-butyl-4-bromophenyl) carbonate (470 g), which was used without further purification.

[0495] Methyl (2-*tert*-butyl-4-bromo-5-nitrophenyl) carbonate

Methyl (2-*tert*-butyl-4-bromophenyl) carbonate (470 g, 1.67 mol) was dissolved in conc. H_2SO_4 (1000 mL) at 0 °C. KNO_3 (253 g, 2.5 mol) was added in portions over 90 min. The reaction mixture was stirred at 0 °C for 2 h and poured into ice-water (20 L). The resulting precipitate was collected via filtration and washed with water thoroughly, dried and recrystallized from ether to give methyl (2-*tert*-butyl-4-bromo-5-nitrophenyl) carbonate (332 g, 60 % over 3 steps).

[0496] C-14-a; 2-*tert*-Butyl-4-bromo-5-nitro-phenol

To a solution of methyl (2-*tert*-butyl-4-bromo-5-nitrophenyl) carbonate (121.5 g, 0.366 mol) in methanol (1000 mL) was added potassium hydroxide (30.75 g, 0.549 mol) in portions. After addition, the mixture was stirred at room temperature for 3 h and acidified with 1N HCl to pH 7. Methanol was removed and water was added. The mixture was extracted with ethyl acetate and the organic layer was separated, dried over Na_2SO_4 and concentrated to give 2-*tert*-butyl-4-bromo-5-nitro-phenol (**C-14-a**) (100 g, 99 %).

[0497] 1-*tert*-Butyl-2-(benzyloxy)-5-bromo-4-nitrobenzene

To a mixture of 2-*tert*-butyl-4-bromo-5-nitrophenol (**C-14-a**) (1.1 g, 4 mmol) and Cs_2CO_3 (1.56 g, 4.8 mmol) in DMF (8 mL) was added benzyl bromide (500 µL, 4.2 mmol). The mixture was stirred at room temperature for 4 h, diluted with H_2O and extracted twice with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. After removal of solvent, the residue was purified by column chloromatography (0-5 % EtOAc - Hexane) to yield 1-*tert*-butyl-2-(benzyloxy)-5-bromo-4-nitrobenzene (1.37 g, 94 %). ^1H NMR (400 MHz, $CDCl_3$) 7.62 (s, 1H), 7.53 (s, 1H), 7.43 (m, 5H), 5.22 (s, 2H), 1.42 (s, 9H).

[0498] 1-*tert*-Butyl-2-(benzyloxy)-5-(trifluoromethyl)-4-nitrobenzene

A mixture of 1-*tert*-butyl-2-(benzyloxy)-5-bromo-4-nitrobenzene (913 mg, 2.5 mmol), KF (291 mg, 5 mmol), KBr (595 mg, 5 mmol), CuI (570 mg, 3 mmol), methyl chlorodifluoroacetate (1.6 mL, 15 mmol) and DMF (5 mL) was stirred at 125 °C in a sealed tube overnight, cooled to room

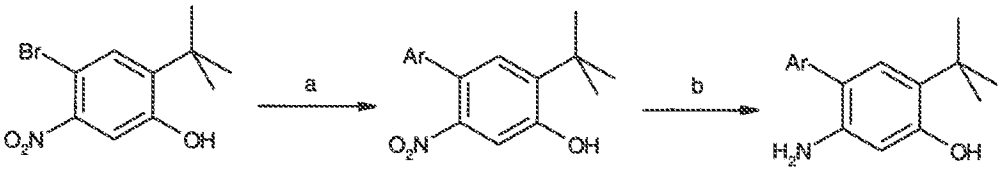
temperature, diluted with water and extracted three times with EtOAc. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (0-5 % EtOAc - Hexane) to yield 1-*tert*-butyl-2-(benzyloxy)-5-(trifluoromethyl)-4-nitrobenzene (591 mg, 67 %). ^{1}H NMR (400 MHz, $CDCl_3$) 7.66 (s, 1H), 7.37 (m, 5H), 7.19 (s, 1H), 5.21 (s, 2H), 1.32 (s, 9H).

[0499] C-14; 5-Amino-2-*tert*-butyl-4-trifluoromethyl-phenol

To a refluxing solution of 1-*tert*-butyl-2-(benzyloxy)-5-(trifluoromethyl)-4-nitrobenzene (353 mg, 1.0 mmol) and ammonium formate (350 mg, 5.4 mmol) in EtOH (10 mL) was added 10% Pd-C (245 mg). The mixture was refluxed for additional 2 h, cooled to room temperature and filtered through Celite. After removal of solvent, the residue was purified by column chromatography to give 5-Amino-2-*tert*-butyl-4-trifluoromethyl-phenol (**C-14**) (120 mg, 52 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1H), 6.05 (s, 1H), 1.28 (s, 9H); HPLC ret. time 3.46 min, 10-99 % CH_3CN, 5 min run; ESI-MS 234.1 m/z (MH^+).

[0500] Example 10:

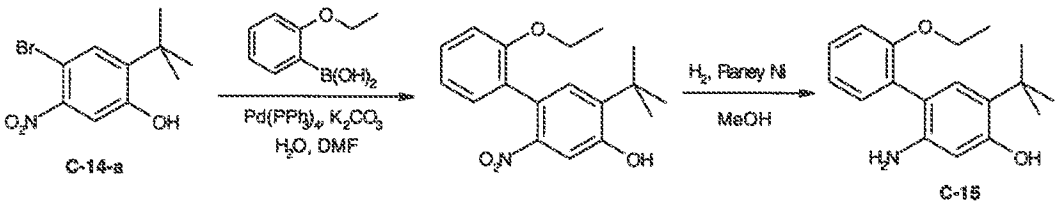
[0501] General scheme:



C-14-a

a) $ArB(OH)_2$, K_2CO_3, $Pd(PPh_3)_4$, H_2O, DMF or $ArB(OH)_2$, $(dppf)PdCl_2$, K_2CO_3, EtOH; b) H_2, Raney Ni, MeOH or HCO_2NH_4, Pd-C, EtOH or $SnCl_2.2H_2O$.

[0502] Specific example:



C-14-a C-15

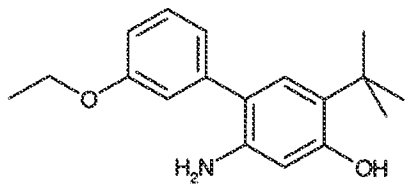
[0503] 2-*tert*-Butyl-4-(2-ethoxyphenyl)-5-nitrophenol

To a solution of 2-*tert*-butyl-4-bromo-5-nitrophenol (**C-14-a**) (8.22 g, 30 mmol) in DMF (90 mL) was added 2-ethoxyphenyl boronic acid (5.48 g, 33 mmol), potassium carbonate (4.56 g, 33 mmol), water (10 mL) and $Pd(PPh_3)_4$ (1.73 g, 1.5 mmol). The mixture was heated at 90 °C for 3 h under nitrogen. The solvent was removed under reduced pressure. The residue was partitioned between water and ethyl acetate. The combined organic layers were washed with water and brine, dried and purified by column chromatography (petroleum ether - ethyl acetate, 10:1) to afford 2-*tert*-butyl-4-(2-ethoxyphenyl)-5-nitrophenol (9.2 g, 92 %). ^{1}HNMR (DMSO-d_6) δ 10.38 (s, 1 H), 7.36 (s, 1 H), 7.28 (m, 2 H), 7.08 (s, 1 H), 6.99 (t, 1 H, J = 7.35 Hz), 6.92 (d, 1 H, J = 8.1 Hz), 3.84 (q, 2 H, J = 6.6 Hz), 1.35 (s, 9 H), 1.09 (t, 3 H, J = 6.6 Hz); ESI-MS 314.3 m/z (MH^+).

[0504] C-15; 2-*tert*-Butyl-4-(2-ethoxyphenyl)-5-aminophenol

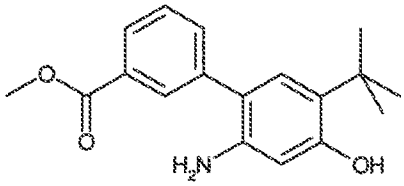
To a solution of 2-*tert*-butyl-4-(2-ethoxyphenyl)-5-nitrophenol (3.0 g, 9.5 mmol) in methanol (30 mL) was added Raney Ni (300 mg). The mixture was stirred under H_2 (1 atm) at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated. The residue was purified by column chromatography (petroleum ether – ethyl acetate, 6:1) to afford 2-*tert*-butyl-4-(2-ethoxyphenyl)-5-aminophenol (**C-15**) (2.35 g, 92 %). ^{1}HNMR (DMSO-d_6) δ 8.89 (s, 1H), 7.19 (t, 1H, J = 4.2 Hz), 7.10 (d, 1H, J = 1.8 Hz), 7.08 (d, 1H, J = 1.8 Hz), 6.94 (t, 1H, J = 3.6 Hz), 6.67 (s, 1 H), 6.16 (s, 1 H), 4.25 (s, 1 H), 4.00 (q, 2H, J = 6.9 Hz), 1.26 (s, 9H), 1.21 (t, 3 H, J = 6.9 Hz); ESI-MS 286.0 m/z (MH^+).

[0505] Other examples:



[0506] C-16; 2-*tert*-Butyl-4-(3-ethoxyphenyl)-5-aminophenol

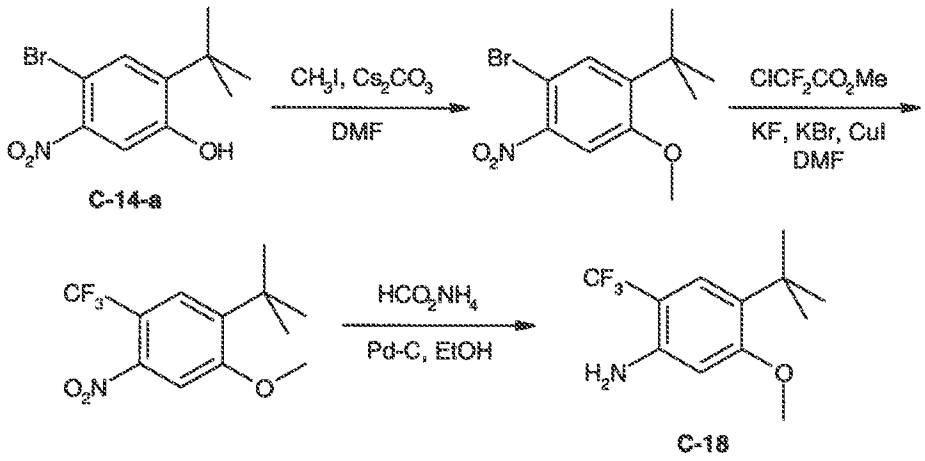
2-*tert*-Butyl-4-(3-ethoxyphenyl)-5-aminophenol (**C-16**) was synthesized following the general scheme above starting from 2-*tert*-butyl-4-bromo-5-nitrophenol (**C-14-a**) and 3-ethoxyphenyl boronic acid. HPLC ret. time 2.77 min, 10-99 % CH_3CN, 5 min run; ESI-MS 286.1 m/z (MH^+).



[0507] C-17; 2-*tert*-Butyl-4-(3-methoxycarbonylphenyl)-5-aminophenol (C-17)

2-*tert*-Butyl-4-(3-methoxycarbonylphenyl)-5-aminophenol (**C-17**) was synthesized following the general scheme above starting from 2-*tert*-butyl-4-bromo-5-nitrophenol (**C-14-a**) and 3-(methoxycarbonyl)phenylboronic acid. HPLC ret. time 2.70 min, 10-99 % CH_3CN, 5 min run; ESI-MS 300.5 m/z (MH^+).

[0508] Example 11;



[0509] 1-*tert*-Butyl-2-methoxy-5-bromo-4-nitrobenzene

To a mixture of 2-*tert*-butyl-4-bromo-5-nitrophenol (**C-14-a**) (1.5 g, 5.5 mmol) and Cs_2CO_3 (2.2 g, 6.6 mmol) in DMF (6 mL) was added methyl iodide (5150 µL, 8.3 mmol). The mixture was stirred at room temperature for 4 h, diluted with H_2O and extracted twice with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. After removal of solvent, the residue was washed with hexane to yield 1-*tert*-butyl-2-methoxy-5-bromo-4-nitrobenzene (1.1 g, 69 %). ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.44 (s, 1H), 3.92 (s, 3H), 1.39 (s, 9H).

[0510] 1-*tert*-Butyl-2-methoxy-5-(trifluoromethyl)-4-nitrobenzene

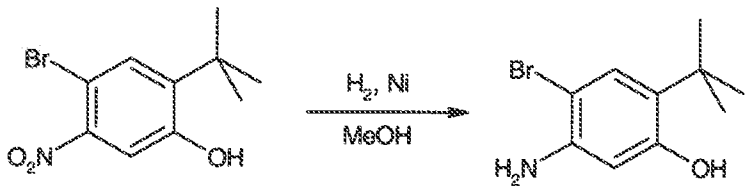
A mixture of 1-*tert*-butyl-2-methoxy-5-bromo-4-nitrobenzene (867 mg, 3.0 mmol), KF (348 mg, 6 mmol), KBr (714 mg, 6 mmol), CuI (684 mg, 3.6 mmol), methyl chlorodifluoroacetate (2.2

mL, 21.0 mmol) in DMF (5 mL) was stirred at 125 °C in a sealed tube overnight, cooled to room temperature, diluted with water and extracted three times with EtOAc. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (0-5 % EtOAc - Hexane) to yield 1-*tert*-butyl-2-methoxy-5-(trifluoromethyl)-4-nitrobenzene (512 mg, 61 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.29 (s, 1H), 3.90 (s, 3H), 1.33 (s, 9H).

[0511] C-18; 1-*tert*-Butyl-2-methoxy-5-(trifluoromethyl)-4-aminobenzene

To a refluxing solution of 1-*tert*-butyl-2-methoxy-5-(trifluoromethyl)-4-nitrobenzene (473 mg, 1.7 mmol) and ammonium formate (473 mg, 7.3 mmol) in EtOH (10 mL) was added 10% Pd-C (200 mg). The mixture was refluxed for 1 h, cooled and filtered through Celite. The solvent was removed by evaporation to give 1-*tert*-butyl-2-methoxy-5-(trifluoromethyl)-4-aminobenzene (**C-18**) (403 mg, 95 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 1H), 6.14 (s, 1H), 4.02 (bs, 2H), 3.74 (s, 3H), 1.24 (s, 9H).

[0512] Example 12:

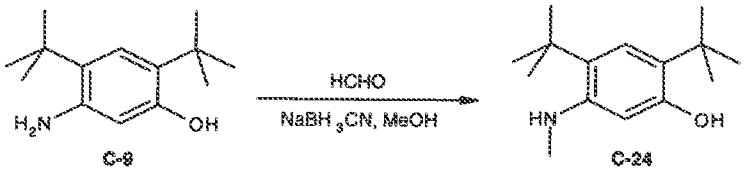


C-14-a **C-27**

[0513] C-27; 2-*tert*-Butyl-4-bromo-5-amino-phenol

To a solution of 2-*tert*-butyl-4-bromo-5-nitrophenol (**C-14-a**) (12 g, 43.8 mmol) in MeOH (90 mL) was added Ni (2.4 g). The reaction mixture was stirred under H_2 (1 atm) for 4 h. The mixture was filtered and the filtrate was concentrated. The crude product was recrystallized from ethyl acetate and petroleum ether to give 2-*tert*-butyl-4-bromo-5-amino-phenol (**C-27**) (7.2 g, 70 %). ^{1}H NMR (DMSO-d_6) δ 9.15 (s, 1 H), 6.91 (s, 1 H), 6.24 (s, 1 H), 4.90 (br s, 2 H), 1.22 (s, 9 H); ESI-MS 244.0 m/z (MH^+).

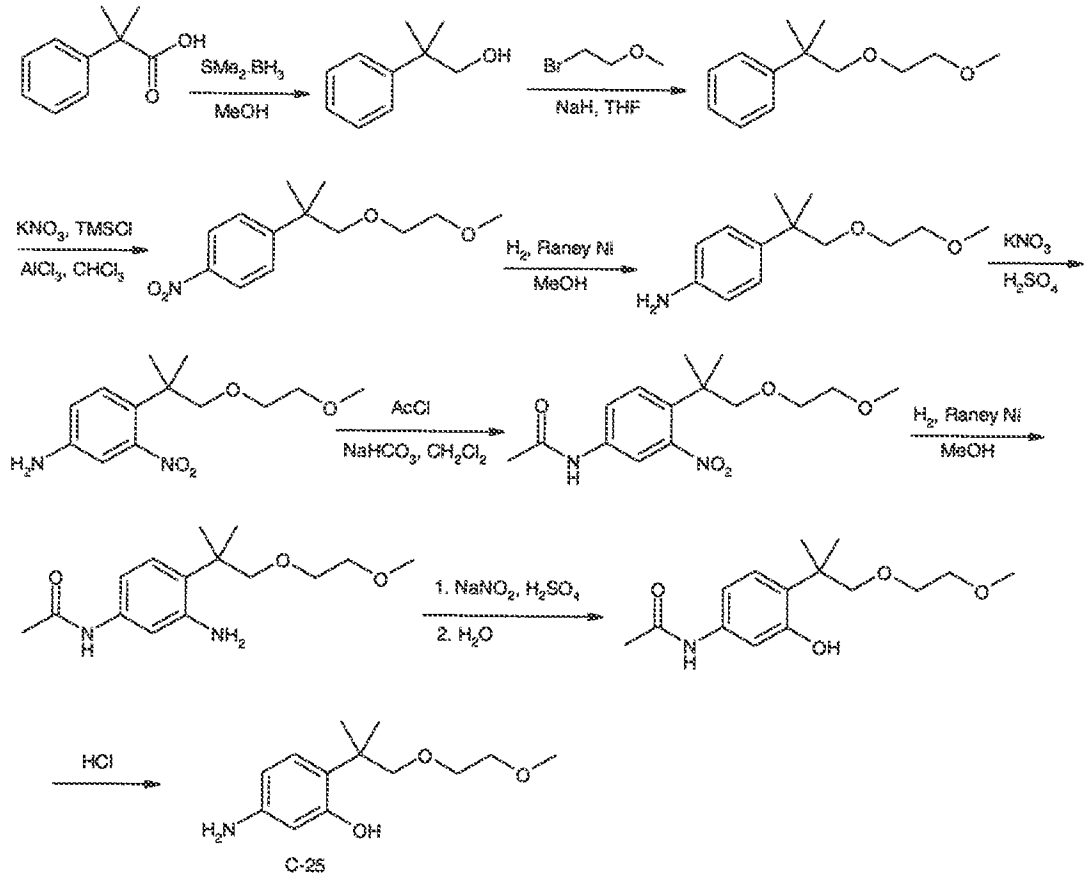
[0514] Example 13:



[0515] C-24; 2,4-Di-*tert*-butyl-6-(N-methylamino)phenol

A mixture of 2,4-di-*tert*-butyl-6-amino-phenol (**C-9**) (5.08 g, 23 mmol), $NaBH_3CN$ (4.41 g, 70 mmol) and paraformaldehyde (2.1 g, 70 mmol) in methanol (50 mL) was stirred at reflux for 3 h. After removal of the solvent, the residue was purified by column chromatography (petroleum ether – EtOAc, 30:1) to give 2,4-di-*tert*-butyl-6-(N-methylamino)phenol (**C-24**) (800 mg, 15 %). ^{1}HNMR (DMSO-d_6) δ 8.67 (s, 1 H), 6.84 (s, 1 H), 5.99 (s, 1 H), 4.36 (q, J = 4.8 Hz, 1H), 2.65 (d, J = 4.8 Hz, 3 H), 1.23 (s, 18 H); ESI-MS 236.2 m/z (MH^+).

[0516] Example 14:



[0517] 2-Methyl-2-phenyl-propan-1-ol

To a solution of 2-methyl-2-phenyl- propionic acid (82 g, 0.5 mol) in THF (200 mL) was added dropwise borane-dimethyl sulfide (2M, 100 mL) at 0-5 °C. The mixture was stirred at this temperature for 30 min and then heated at reflux for 1 h. After cooling, methanol (150 mL) and water (50 mL) were added. The mixture was extracted with EtOAc (100 mL × 3), and the combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated to give 2-methyl-2-phenyl-propan-1-ol as an oil (70 g, 77 %).

[0518] 2-(2-Methoxy-ethoxy)-1,1-dimethyl-ethyl]-benzene

To a suspension of NaH (29 g, 0.75 mol) in THF (200 mL) was added dropwise a solution of 2-methyl-2-phenyl-propan-1-ol (75 g, 0.5 mol) in THF (50 mL) at 0 °C. The mixture was stirred at 20 °C for 30 min and then a solution of 1-bromo-2-methoxy-ethane (104 g, 0.75 mol) in THF (100 mL) was added dropwise at 0 °C. The mixture was stirred at 20 °C overnight, poured into water (200 mL) and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, petroleum ether) to give 2-(2-Methoxy-ethoxy)-1,1-dimethyl-ethyl]-benzene as an oil (28 g, 27 %).

[0519] 1-[2-(2-Methoxy-ethoxy)-1,1-dimethyl-ethyl]-4-nitro-benzene

To a solution of 2-(2-methoxy-ethoxy)-1,1-dimethyl-ethyl]-benzene (52 g, 0.25 mol) in $CHCl_3$ (200 mL) was added KNO_3 (50.5 g, 0.5 mol) and TMSCl (54 g, 0.5 mol). The mixture was stirred at 20 °C for 30 min and then $AlCl_3$ (95 g, 0.7 mol) was added. The reaction mixture was stirred at 20 °C for 1 h and poured into ice-water. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (50 mL × 3). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, petroleum ether) to obtain 1-[2-(2-methoxy-ethoxy)-1,1-dimethyl-ethyl]-4-nitro-benzene (6 g, 10 %).

[0520] 4-[2-(2-Methoxy-ethoxy)-1,1-dimethyl-ethyl]-phenylamine

A suspension of 1-[2-(2-methoxy-ethoxy)-1,1-dimethyl-ethyl]-4-nitro-benzene (8.1 g, 32 mmol) and Raney Ni (1 g) in MeOH (50 mL) was stirred under H_2 (1 atm) at room temperature for 1 h. The catalyst was filtered off and the filtrate was concentrated to obtain 4-[2-(2-methoxy-ethoxy)-1,1-dimethyl-ethyl]-phenylamine (5.5 g, 77 %).

[0521] 4-[2-(2-Methoxy-ethoxy)-1,1-dimethyl-ethyl]-3-nitro-phenylamine

To a solution of 4-[2-(2-methoxy-ethoxy)-1,1-dimethyl-ethyl]-phenylamine (5.8 g, 26 mmol) in H_2SO_4 (20 mL) was added KNO_3 (2.63 g, 26 mmol) at 0 °C. After addition was complete, the mixture was stirred at this temperature for 20 min and then poured into ice-water. The mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (petroleum ether – EtOAc, 100:1) to give 4-[2-(2-methoxy-ethoxy)-1,1-dimethyl-ethyl]-3-nitro-phenylamine (5 g, 71 %).

[0522] N-{4-[2-(2-Methoxy-ethoxy)-1,1-dimethyl-ethyl]-3-nitro-phenyl}-acetamide

To a suspension of $NaHCO_3$ (10 g, 0.1 mol) in dichloromethane (50 mL) was added 4-[2-(2-methoxy-ethoxy)-1,1-dimethyl-ethyl]-3-nitro-phenylamine (5 g, 30 mmol) and acetyl chloride (3 mL, 20 mmol) at 0-5 °C. The mixture was stirred overnight at 15 °C and then poured into water (200 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (50 mL × 2). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated to dryness to give N-{4-[2-(2-methoxy-ethoxy)-1,1-dimethyl-ethyl]-3-nitro-phenyl}-acetamide (5.0 g, 87 %).

[0523] N-{3-Amino-4-[2-(2-methoxy-ethoxy)-1,1-dimethyl-ethyl]-phenyl}-acetamide

A mixture of N-{4-[2-(2-methoxy-ethoxy)-1,1-dimethyl-ethyl]-3-nitro-phenyl}-acetamide (5 g, 16 mmol) and Raney Ni (1 g) in MeOH (50 mL) was stirred under H_2 (1 atm) at room temperature 1 h. The catalyst was filtered off and the filtrate was concentrated. The residue was purified by column chromatography (petroleum ether – EtOAc, 100:1) to give N-{3-amino-4-[2-(2-methoxy-ethoxy)-1,1-dimethyl-ethyl]-phenyl}-acetamide (1.6 g, 35 %).

[0524] N-{3-Hydroxy-4-[2-(2-methoxy-ethoxy)-1,1-dimethyl-ethyl]-phenyl}-acetamide

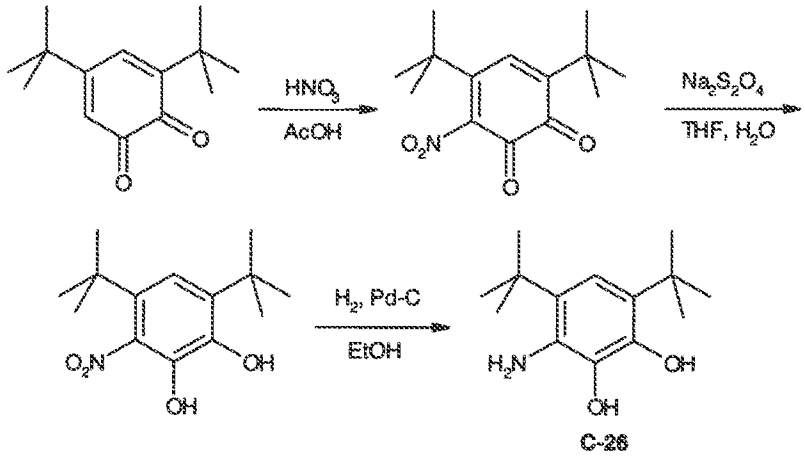
To a solution of N-{3-amino-4-[2- (2-methoxy- ethoxy)-1,1-dimethyl-ethyl]-phenyl}- acetamide (1.6 g, 5.7 mmol) in H_2SO_4 (15 %, 6 mL) was added $NaNO_2$ at 0-5 °C. The mixture was stirred at this temperature for 20 min and then poured into ice water. The mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (petroleum

ether – EtOAc, 100:1) to give N-{3-hydroxy-4-[2-(2-methoxy-ethoxy)-1,1-dimethyl-ethyl]-phenyl}- acetamide (0.7 g, 38 %).

[0525] C-25; 2-(1-(2-Methoxyethoxy)-2-methylpropan-2-yl)-5-aminophenol

A mixture of N-{3-hydroxy-4-[2-(2-methoxy-ethoxy)-1,1-dimethyl-ethyl]-phenyl}- acetamide (1 g, 3.5 mmol) and HCl (5 mL) was heated at reflux for 1 h. The mixture was basified with Na_2CO_3 solution to pH 9 and then extracted with EtOAc (20 mL × 3). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (petroleum ether – EtOAc, 100:1) to obtain 2-(1-(2-methoxyethoxy)-2-methylpropan-2-yl)-5-aminophenol (**C-25**) (61 mg, 6 %). ^{1}HNMR ($CDCl_3$) δ 9.11 (br s, 1 H), 6.96-6.98 (d, J = 8 Hz, 1 H), 6.26-6.27 (d, J = 4 Hz, 1 H), 6.17-6.19 (m, 1 H), 3.68-3.69 (m, 2 H), 3.56-3.59 (m, 4 H), 3.39 (s, 3 H), 1.37 (s, 6 H); ESI-MS 239.9 m/z (MH^+).

[0526] Example 15:



C-26

[0527] 4,6-di-*tert*-Butyl-3-nitrocyclohexa-3,5-diene-1,2-dione

To a solution of 3,5-di-*tert*-butylcyclohexa-3,5-diene-1,2-dione (4.20 g, 19.1 mmol) in acetic acid (115 mL) was slowly added HNO_3 (15 mL). The mixture was heated at 60 °C for 40 min before it was poured into H_2O (50 mL). The mixture was allowed to stand at room temperature for 2 h, then was placed in an ice bath for 1 h. The solid was collected and washed with water to provide 4,6-di-*tert*-butyl-3-nitrocyclohexa-3,5-diene-1,2-dione (1.2 g, 24 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.89 (s, 1H), 1.27 (s, 9H), 1.24 (s, 9H).

[0528] 4,6-Di-*tert*-butyl-3-nitrobenzene-1,2-diol

In a separatory funnel was placed THF/H_2O (1:1, 400 mL), 4,6-di-*tert*-butyl-3-nitrocyclohexa-3,5-diene-1,2-dione (4.59 g, 17.3 mmol) and $Na_2S_2O_4$ (3 g, 17.3 mmol). The separatory funnel was stoppered and was shaken for 2 min. The mixture was diluted with EtOAc (20 mL). The layers were separated and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated to provide 4,6-di-*tert*-butyl-3-nitrobenzene-1,2-diol (3.4 g, 74 %), which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (s, 1H), 8.76 (s, 1H), 6.87 (s, 1H), 1.35 (s, 9H), 1.25 (s, 9H).

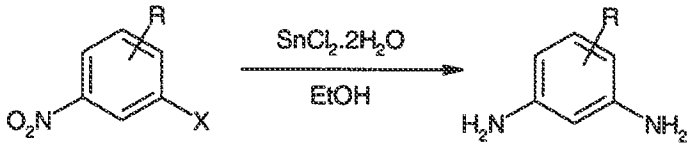
[0529] C-26; 4,6-Di-*tert*-butyl-3-aminobenzene-1,2-diol

To a solution of 4,6-di-*tert*-butyl-3-nitrobenzene-1,2-diol (1.92 g, 7.2 mmol) in EtOH (70 mL) was added Pd-5% wt. on carbon (200 mg). The mixture was stirred under H_2 (1 atm) for 2 h. The reaction was recharged with Pd-5% wt. on carbon (200 mg) and stirred under H_2 (1 atm) for another 2 h. The mixture was filtered through Celite and the filtrate was concentrated and purified by column chromatography (10-40 % ethyl acetate – hexanes) to give 4,6-di-*tert*-butyl-3-aminobenzene-1,2-diol (**C-26**) (560 mg, 33 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 1H), 1.42 (s, 9H), 1.38 (s, 9H).

[0530] Anilines

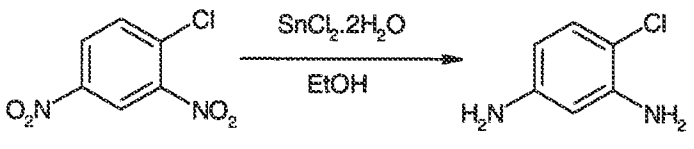
[0531] Example 1:

[0532] General scheme



X = NO_2 or NH_2

[0533] Specific example:

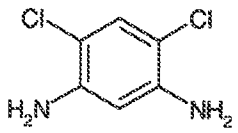


D-1

[0534] ***D-1; 4-Chloro-benzene-1,3-diamine***

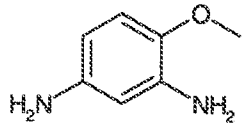
A mixture of 1-chloro-2,4-dinitro-benzene (100 mg, 0.5 mmol) and $SnCl_2 \cdot 2H_2O$ (1.12 g, 5 mmol) in ethanol (2.5 mL) was stirred at room temperature overnight. Water was added and then the mixture was basified to pH 7-8 with saturated $NaHCO_3$ solution. The solution was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to yield 4-chloro-benzene-1,3-diamine (**D-1**) (79 mg, quant.). HPLC ret. time 0.38 min, 10-99 % CH_3CN, 5 min run; ESI-MS 143.1 m/z (MH^+)

[0535] Other examples:



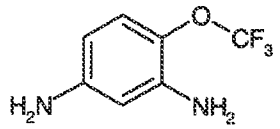
[0536] D-2; 4,6-Dichloro-benzene-1,3-diamine

4,6-Dichloro-benzene-1,3-diamine (**D-2**) was synthesized following the general scheme above starting from 1,5-dichloro-2,4-dinitro-benzene. Yield (95 %). HPLC ret. time 1.88 min, 10-99 % CH_3CN, 5 min run; ESI-MS 177.1 m/z (MH^+).



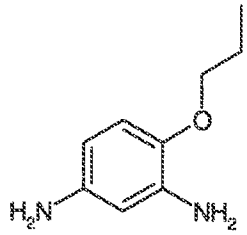
[0537] D-3; 4-Methoxy-benzene-1,3-diamine

4-Methoxy-benzene-1,3-diamine (**D-3**) was synthesized following the general scheme above starting from 1-methoxy-2,4-dinitro-benzene. Yield (quant.). HPLC ret. time 0.31 min, 10-99 % CH_3CN, 5 min run.



[0538] D-4; 4-Trifluoromethoxy-benzene-1,3-diamine

4-Trifluoromethoxy-benzene-1,3-diamine (**D-4**) was synthesized following the general scheme above starting from 2,4-dinitro-1-trifluoromethoxy-benzene. Yield (89 %). HPLC ret. time 0.91 min, 10-99 % CH_3CN, 5 min run; ESI-MS 193.3 m/z (MH^+).

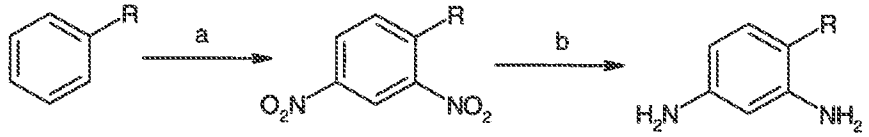


[0539] D-5; 4-Propoxybenzene-1,3-diamine

4-Propoxybenzene-1,3-diamine (**D-5**) was synthesized following the general scheme above starting from 5-nitro-2-propoxy-phenylamine. Yield (79 %). HPLC ret. time 0.54 min, 10-99 % CH_3CN, 5 min run; ESI-MS 167.5 m/z (MH^+).

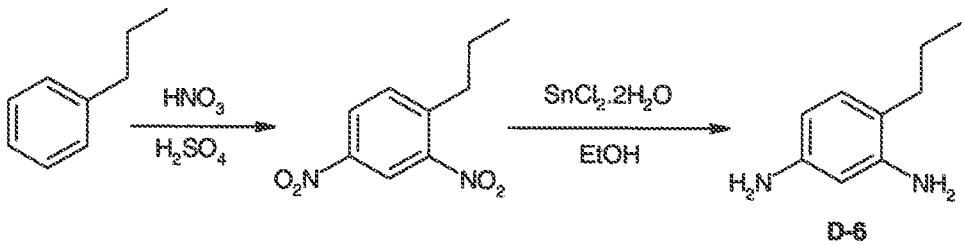
[0540] Example 2:

[0541] General scheme



a) HNO_3, H_2SO_4; b) $SnCl_2 \cdot 2H_2O$, EtOH or H_2, Pd-C, MeOH

[0542] Specific example:



D-6

[0543] 2,4-Dinitro-propylbenzene

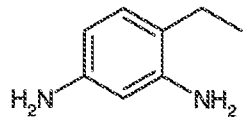
A solution of propylbenzene (10 g, 83 mmol) in conc. H_2SO_4 (50 mL) was cooled at 0 °C for 30 min, and a solution of conc. H_2SO_4 (50 mL) and fuming HNO_3 (25 mL), previously cooled to 0 °C, was added in portions over 15 min. The mixture was stirred at 0 °C for additional 30 min, and then allowed to warm to room temperature. The mixture was poured into ice (200 g) - water (100 mL) and extracted with ether (2 x 100 mL). The combined extracts were washed with H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated to afford 2,4-dinitro-propylbenzene (15.6 g, 89 %). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.73 (d, J = 2.2 Hz, 1H), 8.38 (dd,

J = 8.3, J = 2.2, 1H), 7.6 (d, J = 8.5 Hz, 1H), 2.96 (dd, 2H), 1.73 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H).

[0544] D-6; 4-Propyl-benzene-1,3-diamine

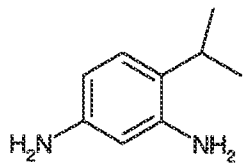
To a solution of 2,4-dinitro-propylbenzene (2.02 g, 9.6 mmol) in ethanol (100 mL) was added $SnCl_2$ (9.9 g, 52 mmol) followed by conc. HCl (10 mL). The mixture was refluxed for 2 h, poured into ice-water (100 mL), and neutralized with solid sodium bicarbonate. The solution was further basified with 10% NaOH solution to pH ~ 10 and extracted with ether (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated to provide 4-propyl-benzene-1,3-diamine **(D-6)** (1.2 g, 83 %). No further purification was necessary for use in the next step; however, the product was not stable for an extended period of time. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.82 (d, J = 7.9 Hz, 1H), 6.11 (dd, J = 7.5, J = 2.2 Hz, 1H), 6.06 (d, J = 2.2 Hz, 1H), 3.49 (br s, 4H, NH_2), 2.38 (t, J = 7.4 Hz, 2H), 1.58 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H); ESI-MS 151.5 m/z (MH^+).

[0545] Other examples:



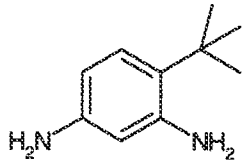
[0546] D-7; 4-Ethylbenzene-1,3-diamine

4-Ethylbenzene-1,3-diamine **(D-7)** was synthesized following the general scheme above starting from ethylbenezene. Overall yield (76 %).



[0547] D-8; 4-Isopropylbenzene-1,3-diamine

4-Isopropylbenzene-1,3-diamine **(D-8)** was synthesized following the general scheme above starting from isopropylbenezene. Overall yield (78 %).

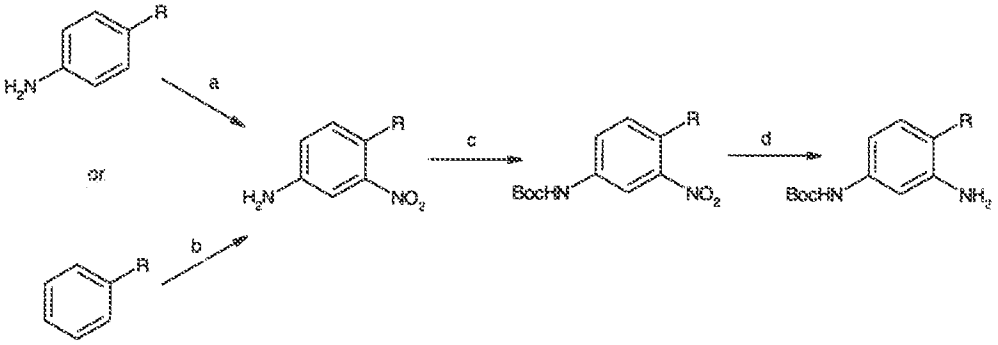


[0548] D-9; 4-*tert*-Butylbenzene-1,3-diamine

4-*tert*-Butylbenzene-1,3-diamine **(D-9)** was synthesized following the general scheme above starting from *tert*-butylbenzene. Overall yield (48 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 8.3 Hz, 1H), 6.10 (dd, J= 2.4, 8.3 Hz, 1H), 6.01 (d, J = 2.4 Hz, 1H), 3.59 (br, 4H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 145.3, 127.6, 124.9, 105.9, 104.5, 33.6, 30.1; ESI-MS 164.9 m/z (MH^+).

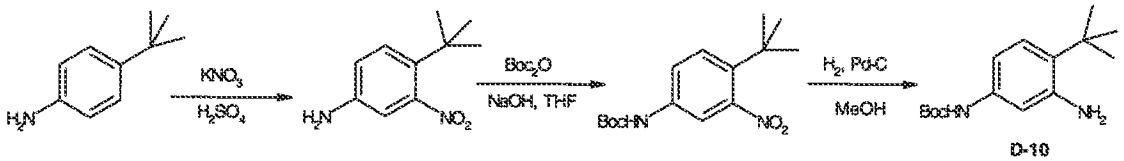
[0549] Example 3:

[0550] General scheme



a) KNO_3, H_2SO_4; b) (i) HNO_3, H_2SO_4; (ii) Na_2S, S, H_2O; c) Boc_2O, NaOH, THF; d) H_2, Pd-C, MeOH

[0551] Specific example:



[0552] 4-*tert*-Butyl-3-nitro-phenylamine

To a mixture of 4-*tert*-butyl-phenylamine (10.0 g, 67.01 mmol) dissolved in H_2SO_4 (98 %, 60 mL) was slowly added KNO_3 (8.1 g, 80.41 mmol) at 0 °C. After addition, the reaction was allowed to warm to room temperature and stirred overnight. The mixture was then poured into ice-water and basified with sat. $NaHCO_3$ solution to pH 8. The mixture was extracted several

times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (petroleum ether - EtOAc, 10:1) to give 4-*tert*-butyl-3-nitro-phenylamine (10 g, 77 %).

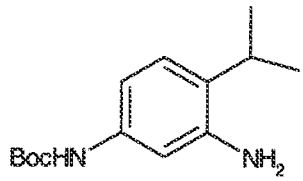
[0553] (4-*tert*-Butyl-3-nitro-phenyl)-carbamic acid *tert*-butyl ester

A mixture of 4-*tert*-butyl-3-nitro-phenylamine (4.0 g, 20.6 mmol) and Boc_2O (4.72 g, 21.6 mmol) in NaOH (2N, 20 mL) and THF (20 mL) was stirred at room temperature overnight. THF was removed under reduced pressure. The residue was dissolved in water and extracted with CH_2Cl_2. The organic layer was washed with $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated to afford (4-*tert*-butyl-3-nitro-phenyl)-carbamic acid *tert*-butyl ester (4.5 g, 74 %).

[0554] *D-10; (3-Amino-4-tert-butyl-phenyl)-carbamic acid* tert-*butyl* ester

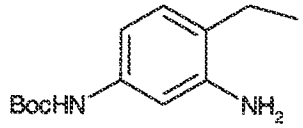
A suspension of (4-*tert*-butyl-3-nitro-phenyl)-carbamic acid *tert*-butyl ester (3.0 g, 10.19 mol) and 10% Pd-C (1 g) in MeOH (40 mL) was stirred under H_2 (1 atm) at room temperature overnight. After filtration, the filtrate was concentrated and the residue was purified by column chromatograph (petroleum ether - EtOAc, 5:1) to give (3-amino-4-*tert*-butyl-phenyl)-carbamic acid *tert*-butyl ester **(D-10)** as a brown oil (2.5 g, 93 %). ^{1}H NMR ($CDCl_3$) δ 7.10 (d, J = 8.4 Hz, 1 H), 6.92 (s, 1 H), 6.50-6.53 (m, 1 H), 6.36 (s, 1 H), 3.62 (br s, 2 H), 1.50 (s, 9 H), 1.38 (s, 9 H); ESI-MS 528.9 m/z ($2M+H^+$).

[0555] Other examples:



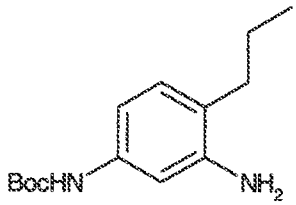
[0556] D-11; (3-Amino-4-isopropyl-phenyl)-carbamic acid *tert*-butyl ester

(3-Amino-4-isopropyl-phenyl)-carbamic acid *tert*-butyl ester **(D-11)** was synthesized following the general scheme above starting from isopropylbenezene. Overall yield (56 %).



[0557] D-12; (3-Amino-4-ethyl-phenyl)-carbamic acid *tert*-butyl ester

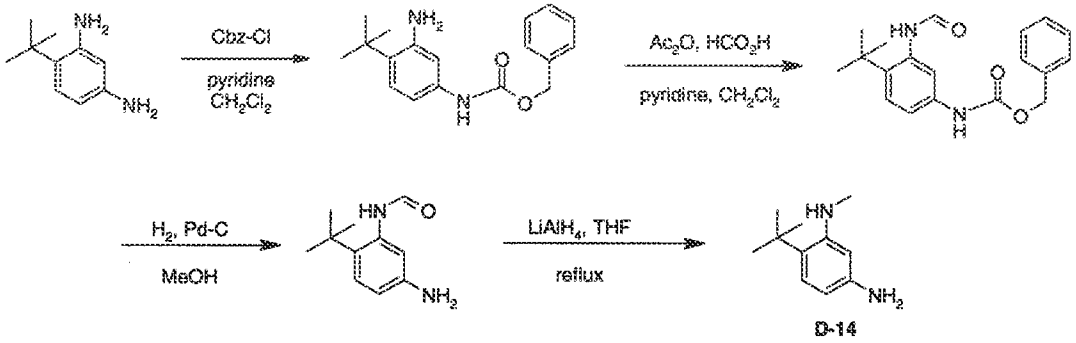
(3-Amino-4-ethyl-phenyl)-carbamic acid *tert*-butyl ester (**D-12**) was synthesized following the general scheme above starting from ethylbenezene. Overall yield (64 %). ^{1}H NMR (CD_3OD, 300 MHz) δ 6.87 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 2.2 Hz, 1H), 6.63 (dd, J = 8.1, J = 2.2, 1H), 2.47 (q, J = 7.4 Hz, 2H), 1.50 (s, 9H), 1.19 (t, J = 7.4 Hz, 3H); ESI-MS 237.1 m/z (MH^+).



[0558] D-13; (3-Amino-4-propyl-phenyl)-carbamic acid *tert*-butyl ester

(3-Amino-4-propyl-phenyl)-carbamic acid *tert*-butyl ester (**D-13**) was synthesized following the general scheme above starting from propylbenezene. Overall yield (48 %).

[0559] Example 4:



D-14

[0560] (3-Amino-4-*tert*-butyl-phenyl)-carbamic acid benzyl ester

A solution of 4-*tert*-butylbenzene-1,3-diamine (**D-9**) (657 mg, 4 mmol) and pyridine (0.39 mL, 4.8 mmol) in CH_2Cl_2 / MeOH (12 / 1, 8 mL) was cooled to 0 °C, and a solution of benzyl chloroformate (0.51 mL, 3.6 mmol) in CH_2Cl_2 (8 mL) was added dropwise over 10 min. The mixture was stirred at 0 °C for 15 min, then warmed to room temperature. After 1 h, the mixture was washed with 1M citric acid (2 x 20 mL), saturated aqueous sodium bicarbonate (20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to afford the crude (3-amino-4-*tert*-butyl-phenyl)-carbamic acid benzyl ester as a brown viscous gum (0.97 g), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.32 (m, 6H,), 7.12 (d, J = 8.5 Hz, 1H), 6.89 (br s, 1H), 6.57 (dd, J = 2.3, 8.5 Hz, 1H), 5.17 (s, 2H), 3.85 (br s, 2H), 1.38 (s, 9H); ^{13}C

NMR (100 MHz, $CDCl_3$, rotameric) δ 153.3 (br), 145.3, 136.56, 136.18, 129.2, 128.73, 128.59, 128.29, 128.25, 127.14, 108.63 (br), 107.61 (br), 66.86, 33.9, 29.7; ESI-MS 299.1 m/z (MH^+).

[0561] (4-*tert*-Butyl-3-formylamino-phenyl)-carbamic acid benzyl ester

A solution of (3-amino-4-*tert*-butyl-phenyl)-carbamic acid benzyl ester (0.97 g, 3.25 mmol) and pyridine (0.43 mL, 5.25 mmol) in CH_2Cl_2 (7.5 mL) was cooled to 0 °C, and a solution of formic-acetic anhydride (3.5 mmol, prepared by mixing formic acid (158 µL, 4.2 mmol, 1.3 equiv) and acetic anhydride (0.32 mL, 3.5 mmol, 1.1 eq.) neat and ageing for 1 hour) in CH_2Cl_2 (2.5 mL) was added dropwise over 2 min. After the addition was complete, the mixture was allowed to warm to room temperature, whereupon it deposited a precipitate, and the resulting slurry was stirred overnight. The mixture was washed with 1 M citric acid (2 x 20 mL), saturated aqueous sodium bicarbonate (20 mL), dried (Na_2SO_4), and filtered. The cloudy mixture deposited a thin bed of solid above the drying agent, HPLC analysis showed this to be the desired formamide. The filtrate was concentrated to approximately 5 mL, and diluted with hexane (15 mL) to precipitate further formamide. The drying agent (Na_2SO_4) was slurried with methanol (50 mL), filtered, and the filtrate combined with material from the CH_2Cl_2 / hexane recrystallisation. The resultant mixture was concentrated to afford (4-*tert*-butyl-3-formylamino-phenyl)-carbamic acid benzyl ester as an off-white solid (650 mg, 50 % over 2 steps). ^1H and ^{13}C NMR (CD_3OD) show the product as a rotameric mixture. ^1H NMR (400 MHz, CD_3OD, rotameric) δ 8.27 (s, 1H-a), 8.17 (s, 1H-b), 7.42-7.26 (m, 8H), 5.17 (s, 1H-a), 5.15 (s, 1H-b), 4.86 (s, 2H), 1.37 (s, 9H-a), 1.36 (s, 9H-b); ^{13}C NMR (100 MHz, CD_3OD, rotameric) δ 1636.9, 163.5, 155.8, 141.40, 141.32, 139.37, 138.88, 138.22, 138.14, 136.4, 135.3, 129.68, 129.65, 129.31, 129.24, 129.19, 129.13, 128.94, 128.50, 121.4 (br), 118.7 (br), 67.80, 67.67, 35.78, 35.52, 31.65, 31.34; ESI-MS 327.5 m/z (MH^+).

[0562] *N*-(5-Amino-2-*tert*-butyl-phenyl)-formamide

A 100 mL flask was charged with (4-*tert*-butyl-3-formylamino-phenyl)-carbamic acid benzyl ester (650 mg, 1.99 mmol), methanol (30 mL) and 10% Pd-C (50 mg), and stirred under H_2 (1 atm) for 20 h. CH_2Cl_2 (5 mL) was added to quench the catalyst, and the mixture then filtered through Celite, and concentrated to afford *N*-(5-amino-2-*tert*-butyl-phenyl)-formamide as an off-white solid (366 mg, 96 %). Rotameric by ^1H and ^{13}C NMR (DMSO-d_6). ^1H NMR (400 MHz, DMSO-d_6, rotameric) δ 9.24 (d, J = 10.4 Hz, 1H), 9.15 (s, 1H), 8.23 (d, J = 1.5 Hz, 1H), 8.06 (d, J = 10.4 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 6.51 (d, J = 2.5 Hz, 1H), 6.46 (dd, J = 2.5, 8.5 Hz, 1H), 6.39 (dd, J = 2.5, 8.5 Hz, 1H), 6.29 (d, J = 2.5Hz, 1H), 5.05 (s, 2H), 4.93 (s, 2H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, rotameric) δ 164.0, 160.4,

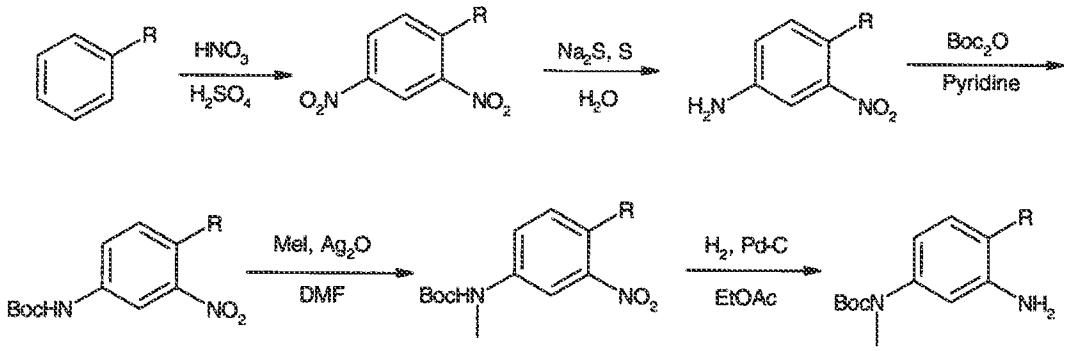
147.37, 146.74, 135.38, 135.72, 132.48, 131.59, 127.31, 126.69, 115.15, 115.01, 112.43, 112.00, 33.92, 33.57, 31.33, 30.92; ESI-MS 193.1 m/z (MH^+).

[0563] D-14; 4-*tert*-butyl-N^3-methyl-benzene-1,3-diamine

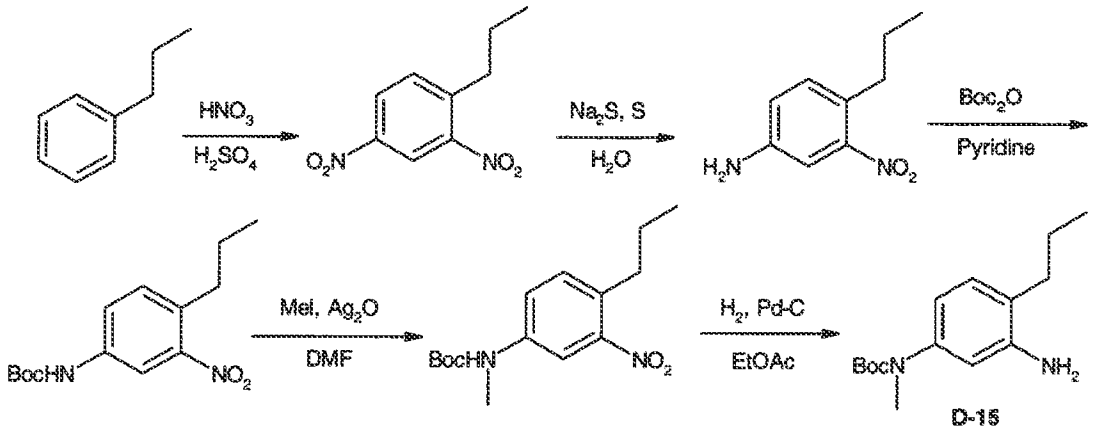
A 100 mL flask was charged with *N*-(5-amino-2-*tert*-butyl-phenyl)-formamide (340 mg, 1.77 mmol) and purged with nitrogen. THF (10 mL) was added, and the solution was cooled to 0 °C. A solution of lithium aluminum hydride in THF (4.4 mL, 1M solution) was added over 2 min. The mixture was then allowed to warm to room temperature. After refluxing for 15 h, the yellow suspension was cooled to 0 °C, quenched with water (170 µL), 15 % aqueous NaOH (170 µL), and water (510 µL) which were added sequentially and stirred at room temperature for 30 min. The mixture was filtered through Celite, and the filter cake washed with methanol (50 mL). The combined filtrates were concentrated in *vacuo* to give a gray-brown solid, which was partitioned between chloroform (75 mL) and water (50 mL). The organic layer was separated, washed with water (50 mL), dried (Na_2SO_4), filtered, and concentrated to afford 4-*tert*-butyl-N^3-methyl-benzene-1,3-diamine **(D-14)** as a brown oil which solidified on standing (313 mg, 98 %). ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 8.1 Hz, 1H), 6.05 (dd, J = 2.4, 8.1 Hz, 1H), 6.03 (d, J = 2.4 Hz, 1H), 3.91 (br s, 1H), 3.52 (br s, 2H), 2.86 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 145.7, 127.0, 124.3, 103.6, 98.9, 33.5, 31.15, 30.31; ESI-MS 179.1 m/z (MH^+).

[0564] Example 5:

[0565] General scheme:



[0566] Specific example:



[0567] 2,4-Dinitro-propylbenzene

A solution of propylbenzene (10 g, 83 mmol) in conc. H_2SO_4 (50 mL) was cooled at 0 °C for 30 mins, and a solution of conc. H_2SO_4 (50 mL) and fuming HNO_3 (25 mL), previously cooled to 0 °C, was added in portions over 15 min. The mixture was stirred at 0 °C for additional 30 min. and then allowed to warm to room temperature. The mixture was poured into ice (200 g) -water (100 mL) and extracted with ether (2 x 100 mL). The combined extracts were washed with H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated to afford 2,4-dinitro-propylbenzene (15.6 g, 89 %). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.73 (d, J = 2.2 Hz, 1H), 8.38 (dd, J = 8.3, 2.2 Hz, 1H), 7.6 (d, J = 8.5 Hz, 1H), 2.96 (m, 2H), 1.73 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H).

[0568] 4-Propyl-3-nitroaniline

A suspension of 2,4-dinitro-propylbenzene (2 g, 9.5 mmol) in H_2O (100 mL) was heated near reflux and stirred vigorously. A clear orange-red solution of polysulfide (300 mL (10 eq.), previously prepared by heating sodium sulfide nanohydrate (10.0 g), sulfur powder (2.60 g) and H_2O (400 mL), was added dropwise over 45 mins. The red-brown solution was heated at reflux for 1.5 h. The mixture was cooled to 0 °C and then extracted with ether (2 x 200 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 4-propyl-3-nitroaniline (1.6 g, 93 %), which was used without further purification.

[0569] (3-Nitro-4-propyl-phenyl)-carbamic acid *tert*-butyl ester

4-Propyl-3-nitroaniline (1.69 g, 9.4 mmol) was dissolved in pyridine (30 mL) with stirring. Boc anhydride (2.05 g, 9.4 mmol) was added. The mixture was stirred and heated at reflux for 1 h

before the solvent was removed *in vacuo*. The oil obtained was re-dissolved in CH_2Cl_2 (300 mL) and washed with water (300 mL) and brine (300 mL), dried over Na_2SO_4, filtered, and concentrated. The crude oil that contained both mono- and *bis*-acylated nitro products was purified by column chromatography (0–10 % CH_2Cl_2 - MeOH) to afford (3-nitro-4-propyl-phenyl)-carbamic acid tert-butyl ester (2.3 g, 87 %).

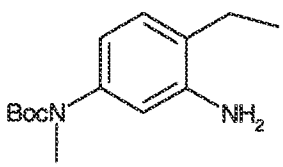
[0570] Methyl-(3-nitro-4-propyl-phenyl)-carbamic acid *tert*-butyl ester

To a solution of (3-nitro-4-propyl-phenyl)-carbamic acid *tert*-butyl ester (200 mg, 0.71 mmol) in DMF (5 mL) was added Ag_2O (1.0 g, 6.0 mmol) followed by methyl iodide (0.20 mL, 3.2 mmol). The resulting suspension was stirred at room temperature for 18 h and filtered through a pad of Celite. The filter cake was washed with CH_2Cl_2 (10 mL). The filtrate was concentrated *in vacuo*. The crude oil was purified by column chromatography (0–10 % CH_2Cl_2 - MeOH) to afford methyl-(3-nitro-4-propyl-phenyl)-carbamic acid *tert*-butyl ester as a yellow oil (110 mg, 52 %). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.78 (d, J = 2.2 Hz, 1H), 7.42 (dd, J = 8.2, 2.2 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 3.27 (s, 3H), 2.81 (t, J = 7.7 Hz, 2H), 1.66 (m, 2H), 1.61 (s, 9H), 0.97 (t, J = 7.4 Hz, 3H).

[0571] D-15; (3-Amino-4-propyl-phenyl)-methyl-carbamic acid *tert*-butyl ester

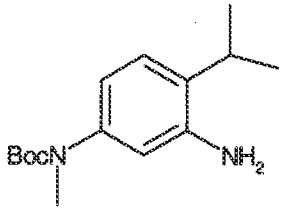
To a solution of methyl-(3-nitro-4-propyl-phenyl)-carbamic acid *tert*-butyl ester (110 mg, 0.37 mmol) in EtOAc (10 mL) was added 10% Pd-C (100 mg). The resulting suspension was stirred at room temperature under H_2 (1 atm) for 2 days. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to afford (3-Amino-4-propyl-phenyl)-methyl-carbamic acid *tert*-butyl ester (**D-15**) as a colorless crystalline compound (80 mg, 81 %). ESI-MS 265.3 m/z (MH^+).

[0572] Other examples:



[0573] D-16; (3-Amino-4-ethyl-phenyl)-methyl-carbamic acid *tert*-butyl ester

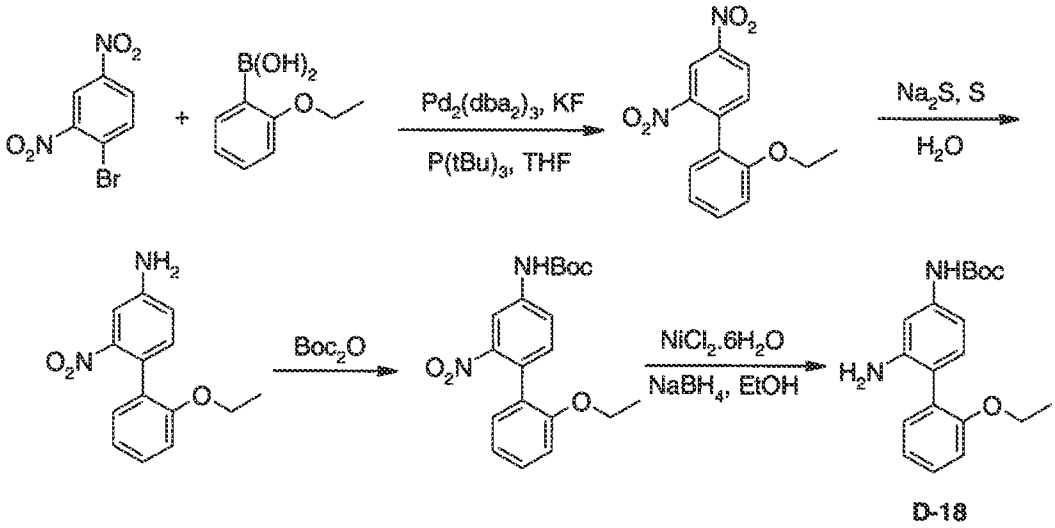
(3-Amino-4-ethyl-phenyl)-methyl-carbamic acid *tert*-butyl ester (**D-16**) was synthesized following the general scheme above starting from ethylbenezene. Overall yield (57 %).



[0574] D-17; (3-Amino-4-isopropyl-phenyl)-methyl-carbamic acid *tert*-butyl ester

(3-Amino-4-isopropyl-phenyl)-methyl-carbamic acid *tert*-butyl ester **(D-17)** was synthesized following the general scheme above starting from isopropylbenezene. Overall yield (38 %).

[0575] Example 6:



[0576] 2'-Ethoxy-2,4-dinitro-biphenyl

A pressure flask was charged with 2-ethoxyphenylboronic acid (0.66 g, 4.0 mmol), KF (0.77 g, 13 mmol), $Pd_2(dba)_3$ (16 mg, 0.02 mmol), and 2,4-dinitro-bromobenzene (0.99 g, 4.0 mmol) in THF (5 mL). The vessel was purged with argon for 1 min followed by the addition of tri-*tert*-butylphosphine (0.15 mL, 0.48 mmol, 10 % solution in hexanes). The reaction vessel was purged with argon for additional 1 min., sealed and heated at 80 °C overnight. After cooling to room temperature, the solution was filtered through a plug of Celite. The filter cake was rinsed with CH_2Cl_2 (10 mL), and the combined organic extracts were concentrated under reduced pressure to provide the crude product 2'-ethoxy-2,4-dinitro-biphenyl (0.95 g, 82%). No further purification was performed. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.43 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 3.44 (q, J = 6.6 Hz, 2H), 1.24 (t, J = 6.6 Hz, 3H); HPLC ret. time 3.14 min, 10-100 % CH_3CN, 5 min gradient.

[0577] 2'-Ethoxy-2-nitrobiphenyl-4-yl amine

A clear orange-red solution of polysulfide (120 mL, 7.5 eq.), previously prepared by heating sodium sulfide monohydrate (10 g), sulfur (1.04 g) and water (160 mL), was added dropwise at 90 °C over 45 minutes to a suspension of 2'-ethoxy-2,4-dinitro-biphenyl (1.2 g, 4.0 mmol) in water (40 mL). The red-brown solution was heated at reflux for 1.5 h. The mixture was cooled to room temperature, and solid NaCl (5 g) was added. The solution was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic extracts was concentrated to provide 2'-ethoxy-2-nitrobiphenyl-4-yl amine (0.98 g, 95 %) that was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 2H), 7.17 (d, J = 2.7 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H), 7.00 (t, J = 6.9 Hz, 1H), 6.83 (m, 2H), 3.91 (q, J = 6.9 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H); HPLC ret. time 2.81 min, 10-100 % CH_3CN, 5 min gradient; ESI-MS 259.1 m/z (MH^+).

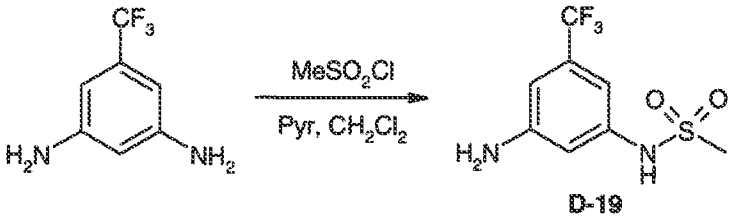
[0578] (2'-Ethoxy-2-nitrobiphenyl-4-yl)-carbamic acid *tert*-butyl ester

A mixture of 2'-ethoxy-2-nitrobipenyl-4-yl amine (0.98 g, 4.0 mmol) and Boc_2O (2.6g, 12 mmol) was heated with a heat gun. Upon the consumption of the starting material as indicated by TLC, the crude mixture was purified by flash chromatography (silica gel, CH_2Cl_2) to provide (2'-ethoxy-2-nitrobiphenyl-4-yl)-carbamic acid *tert*-butyl ester (1.5 g, 83 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.25 (m, 3H), 6.99 (t, J = 7.5 Hz, 1H), 6.82 (m, 2H), 3.88 (q, J = 6.9 Hz, 2H), 1.50 (s, 9 H), 1.18 (t, J = 6.9 Hz, 3H); HPLC ret. time 3.30 min, 10-100 % CH_3CN, 5 min gradient.

[0579] D-18; (2'-ethoxy-2-aminobiphenyl-4-yl)-carbamic acid *tert*-butyl ester

To a soloution of $NiCl_2.6H_2O$ (0.26 g, 1.1 mmol) in EtOH (5 mL) was added $NaBH_4$ (40 mg, 1.1 mmol) at -10 °C. Gas evolution was observed and a black precipitate was formed. After stirring for 5 min, a solution of 2'-ethoxy-2-nitrobiphenyl-4-yl)carbamic acid *tert*-butyl ester (0.50 g, 1.1 mmol) in EtOH (2 mL) was added. Additional $NaBH_4$ (80 mg, 60 mmol) was added in 3 portions over 20 min. The reaction was stirred at 0 °C for 20 min followed by the addition of NH_4OH (4 mL, 25% aq. solution). The resulting solution was stirred for 20 min. The crude mixture was filtered through a short plug of silica. The silica cake was flushed with 5% MeOH in CH_2Cl_2 (10 mL), and the combined organic extracts was concentrated under reduced pressure to provide (2'-ethoxy-2-aminobiphenyl-4-yl)-carbamic acid *tert*-butyl ester (**D-18**) (0.36 g, quant.), which was used without further purification. HPLC ret. time 2.41 min, 10-100 % CH_3CN, 5 min gradient; ESI-MS 329.3 m/z (MH^+).

[0580] Example 7:



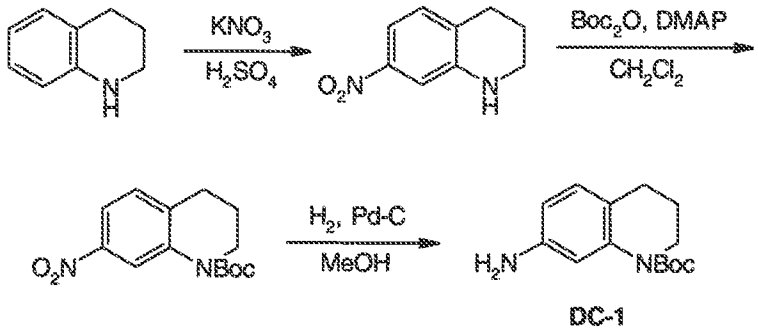
D-19

[0581] ***D-19; N-(3-Amino-5-trifluoromethyl-phenyl)-methanesulfonamide***

A solution of 5-trifluoromethyl-benzene-1,3-diamine (250 mg, 1.42 mmol) in pyridine (0.52 mL) and CH_2Cl_2 (6.5 mL) was cooled to 0 °C. Methanesulfonyl chloride (171 mg, 1.49 mmol) was slowly added at such a rate that the temperature of the solution remained below 10 °C. The mixture was stirred at ~ 8 °C and then allowed to warm to room temperature after 30 min. After stiring at room temperature for 4 h, reaction was almost complete as indicated by LCMS analysis. The reaction mixture was quenched with sat. aq. NH_4Cl (10 mL) solution, extracted with CH_2Cl_2 (4 x 10 mL), dried over Na_2SO_4, filtered, and concentrated to yield N-(3-amino-5-trifluoromethyl-phenyl)-methanesulfonamide (**D-19**) as a reddish semisolid (0.35 g, 97 %), which was used without further purification. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.76 (m, 1H), 6.70 (m, 1H), 6.66 (s, 1H), 3.02 (s, 3H); ESI-MS 255.3 m/z (MH^+).

[0582] Cyclic amines

[0583] Example 1:



DC-1

[0584] 7-Nitro-1,2,3,4-tetrahydro-quinoline

To a mixture of 1,2,3,4-tetrahydro-quinoline (20.0 g, 0.15 mol) dissolved in H_2SO_4 (98 %, 150 mL), KNO_3 (18.2 g, 0.18 mol) was slowly added at 0 °C. The reaction was allowed to warm to

room temperature and stirred over night. The mixture was then poured into ice-water and basified with sat. $NaHCO_3$ solution to pH 8. After extraction with CH_2Cl_2, the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (petroleum ether – EtOAc, 10:1) to give 7-nitro-1,2,3,4-tetrahydro-quinoline (6.6 g, 25 %).

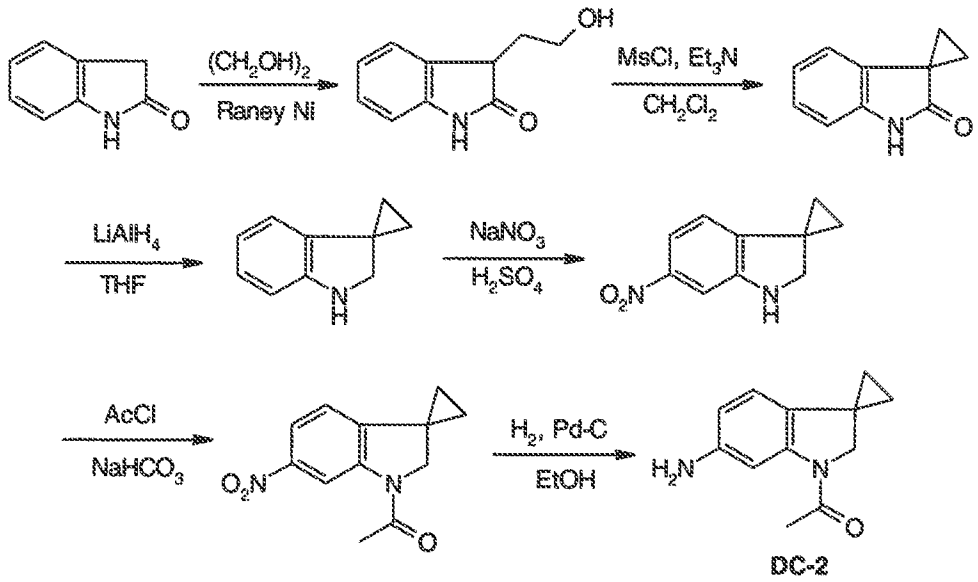
[0585] 7-Nitro-3,4-dihydro-2H-quinoline-1-carboxylic acid *tert*-butyl ester

A mixture of 7-nitro-1,2,3,4-tetrahydro-quinoline (4.0 g, 5.61 mmol), Boc_2O (1.29 g, 5.89 mmol) and DMAP (0.4 g) in CH_2Cl_2 was stirred at room temperature overnight. After diluted with water, the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated to provide crude 7-nitro-3,4-dihydro-2H-quinoline-1-carboxylic acid *tert*-butyl ester that was used in the next step without further purification.

[0586] *DC-1;* tert-*Butyl* 7-amino-*3,4-dihydroquinoline-1(2H)-carboxylate*

A suspension of the crude 7-nitro-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester (4.5 g, 16.2 mol) and 10% Pd-C (0.45 g) in MeOH (40 mL) was stirred under H_2 (1 atm) at room temperature overnight. After filtration, the filtrate was concentrated and the residue was purified by column chromatography (petroleum ether – EtOAc, 5:1) to give tert-butyl 7-amino-3,4-dihydroquinoline-1(2H)-carboxylate **(DC-1)** as a brown solid (1.2 g, 22 % over 2 steps). ^1H NMR ($CDCl_3$) δ 7.15 (d, J = 2 Hz, 1 H), 6.84 (d, J = 8 Hz, 1 H), 6.36-6.38 (m, 1 H), 3.65-3.68 (m, 2 H), 3.10 (br s, 2 H), 2.66 (t, J = 6.4 Hz, 2 H), 1.84-1.90 (m, 2 H), 1.52 (s, 9 H); ESI-MS 496.8 m/z ($2M+H^+$).

[0587] Example 2:



DC-2

[0588] 3-(2-Hydroxy-ethyl)-1,3-dihydro-indol-2-one

A stirring mixture of oxindole (5.7 g, 43 mmol) and Raney nickel (10 g) in ethane-1,2-diol (100 mL) was heated in an autoclave. After the reaction was complete, the mixture was filtered and the excess of diol was removed under *vacuum*. The residual oil was triturated with hexane to give 3-(2-hydroxy-ethyl)-1,3-dihydro-indol-2-one as a colorless crystalline solid (4.6 g, 70 %).

[0589] 1,2-Dihydro-3-spiro-1'-cyclopropyl-1*H*-indole-2-one

To a solution of 3-(2-hydroxy-ethyl)-1,3-dihydro-indol-2-one (4.6 g, 26 mmol) and triethylamine (10 mL) in CH_2Cl_2 (100 mL) was added MsCl (3.4 g, 30 mmol) dropwise at -20 °C. The mixture was then allowed to warm up to room temperature and stirred overnight. The mixture was filtered and the filtrate was concentrated under *vacuum*. The residue was purified by column chromatography to give crude 1,2-dihydro-3-spiro-1'-cyclopropyl-1*H*-indole-2-one as a yellow solid (2.5 g), which was used directly in the next step.

[0590] 1,2-Dihydro-3-spiro-1'-cyclopropyl-1*H*-indole

To a solution of 1,2-dihydro-3-spiro-1'-cyclopropyl-1*H*-indole-2-one (2.5 g crude) in THF (50 mL) was added $LiAlH_4$ (2 g, 52 mmol) portionwise. After heating the mixture to reflux, it was poured into crushed ice, basified with aqueous ammonia to pH 8 and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give

the crude 1,2-dihydro-3-spiro-1'-cyclopropyl-1*H*-indole as a yellow solid (about 2 g), which was used directly in the next step.

[0591] 6-Nitro-1,2-dihydro-3-spiro-1'-cyclopropyl-1*H*-indole

To a cooled solution (-5 °C to -10 °C) of $NaNO_3$ (1.3 g, 15.3 mmol) in H_2SO_4 (98 %, 30 mL) was added 1,2-dihydro- 3-spiro-1'-cyclopropyl-1*H*-indole (2 g, crude) dropwise over a period of 20 min. After addition, the reaction mixture was stirred for another 40 min and poured over crushed ice (20 g). The cooled mixture was then basified with NH_4OH and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to yield 6-nitro-1,2-dihydro-3-spiro-1'-cyclopropyl- 1*H*-indole as a dark gray solid (1.3 g)

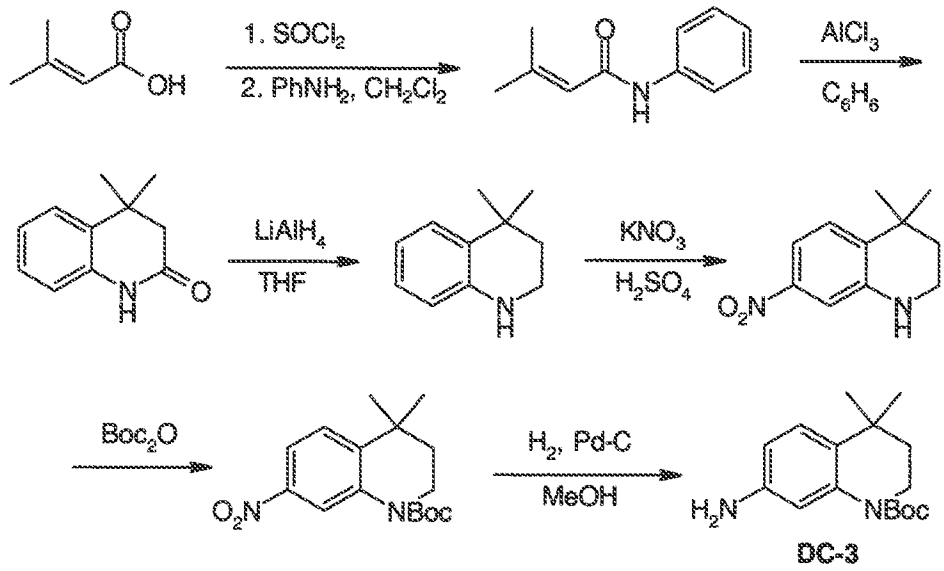
[0592] 1-Acetyl-6-nitro-1,2-dihydro-3-spiro-1'-cyclopropyl-1*H*-indole

$NaHCO_3$ (5 g) was suspended in a solution of 6-nitro-1,2-dihydro-3-spiro-1'-cyclopropyl-1*H*-indole (1.3 g, crude) in CH_2Cl_2 (50 mL). While stirring vigorously, acetyl chloride (720 mg) was added dropwise. The mixture was stirred for 1 h and filtered. The filtrate was concentrated under *vacuum*. The residue was purified by flash column chromatography on silica gel to give 1-acetyl-6-nitro-1,2-dihydro-3-spiro-1'-cyclopropyl-1*H*-indole (0.9 g, 15 % over 4 steps).

[0593] DC-2; 1-Acetyl-6-amino-1,2-dihydro-3-spiro-1'-cyclopropyl-1*H*-indole

A mixture of 1-acetyl-6-nitro-1,2-dihydro-3-spiro-1'-cyclopropyl- 1*H*-indole (383 mg, 2 mmol) and Pd-C (10 %, 100 mg) in EtOH (50 mL) was stirred at room temperature under H_2 (1 atm) for 1.5 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was treated with HCl / MeOH to give 1-acetyl-6-amino-1,2-dihydro-3-spiro-1'-cyclopropyl-1*H*-indole **(DC-2)** (300 mg, 90 %) as a hydrochloride salt.

[0594] Example 3:



[0595] 3-Methyl-but-2-enoic acid phenylamide

A mixture of 3-methyl-but-2- enoic acid (100 g, 1 mol) and $SOCl_2$ (119 g, 1 mol) was heated at reflux for 3 h. The excess $SOCl_2$ was removed under reduced pressure. CH_2Cl_2 (200 mL) was added followed by the addition of aniline (93 g, 1.0 mol) in Et_3N (101 g, 1 mol) at 0 °C. The mixture was stirred at room temperature for 1 h and quenched with HCl (5%, 150 mL). The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were washed with water (2x100 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated to give 3-methyl-but-2-enoic acid phenylamide (120 g, 80 %).

[0596] 4,4-Dimethyl-3,4-dihydro-1H-quinolin-2-one

$AlCl_3$ (500 g, 3.8 mol) was carefully added to a suspension of 3-methyl-but-2-enoic acid phenylamide (105 g, 0.6 mol) in benzene (1000 mL). The reaction mixture was stirred at 80 °C overnight and poured into ice-water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (250 mL x 3). The combined organic layers were washed with water (200 mL x 2) and brine (200 mL), dried over Na_2SO_4 and concentrated to give 4,4-dimethyl-3,4-dihydro-1H-quinolin-2-one (90 g, 86 %).

[0597] 4,4-Dimethyl-1,2,3,4-tetrahydro-quinoline

A solution of 4,4-dimethyl-3,4-dihydro-1H-quinolin-2-one (35 g, 0.2 mol) in THF (100 mL) was added dropwise to a suspension of $LiAlH_4$ (18 g, 0.47 mol) in THF (200 mL) at 0 °C. After

addition, the mixture was stirred at room temperature for 30 min and then slowly heated to reflux for 1 h. The mixture was then cooled to 0 °C. Water (18 mL) and NaOH solution (10 %, 100 mL) were carefully added to quench the reaction. The solid was filtered off and the filtrate was concentrated to give 4,4-dimethyl-1,2,3,4-tetrahydro-quinoline.

[0598] 4,4-Dimethyl-7-nitro-1,2,3,4-tetrahydro-quinoline

To a mixture of 4,4-dimethyl-1,2,3,4-tetrahydro-quinoline (33 g, 0.2 mol) in H_2SO_4 (120 mL) was slowly added KNO_3 (20.7 g, 0.2 mol) at 0 °C. After addition, the mixture was stirred at room temperature for 2 h, carefully poured into ice water and basified with Na_2CO_3 to pH 8. The mixture was extracted with ethyl acetate (3 x 200 mL). The combined extracts were washed with water and brine, dried over Na_2SO_4 and concentrated to give 4, 4-dimethyl-7-nitro-1, 2, 3, 4-tetrahydro-quinoline (21 g, 50 %).

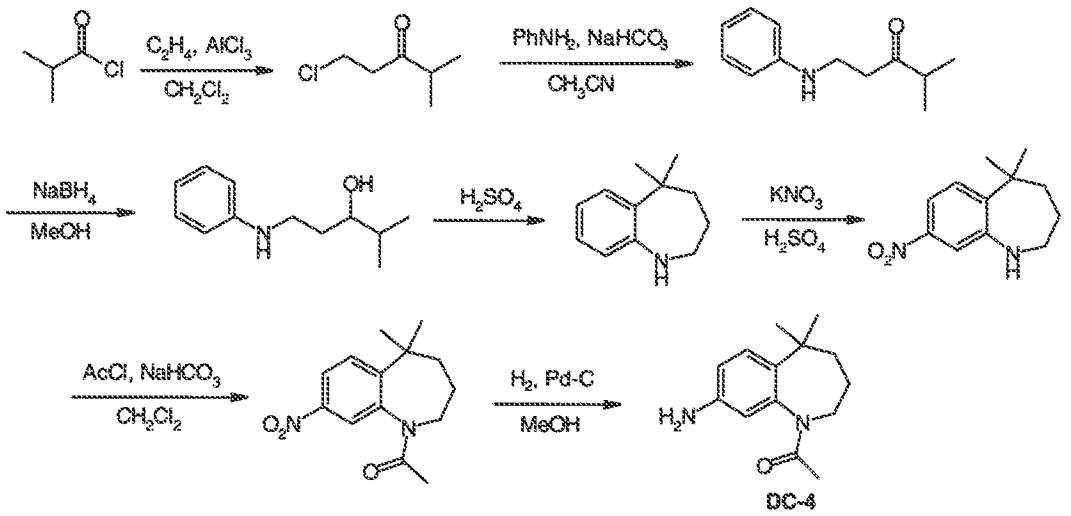
[0599] 4,4-Dimethyl-7-nitro-3,4-dihydro-2H-quinoline-1-carboxylic acid *tert*-butyl ester

A mixture of 4,4-dimethyl-7-nitro-1,2,3,4-tetrahydro-quinoline (25 g, 0.12 mol) and Boc_2O (55 g, 0.25 mol) was stirred at 80 °C for 2 days. The mixture was purified by silica gel chromatography to give 4,4-dimethyl-7-nitro-3,4-dihydro-2H-quinoline-1-carboxylic acid *tert*-butyl ester(8 g, 22 %).

[0600] DC-3; *tert*-Butyl 7-amino-3,4-dihydro-4,4-dimethylquinoline-1(2H)-carboxylate

A mixture of 4,4-dimethyl-7-nitro-3,4-dihydro-2H-quinoline-1 carboxylic acid *tert*-butyl ester (8.3 g, 0.03 mol) and Pd-C (0.5 g) in methanol (100 mL) was stirred under H_2 (1 atm) at room temperature overnight. The catalyst was filtered off and the filtrate was concentrated. The residue was washed with petroleum ether to give tert-butyl 7-amino-3,4-dihydro-4,4-dimethylquinoline-1(2H)-carboxylate **(DC-3)** (7.2 g, 95 %). ^{1}H NMR ($CDCl_3$) δ 7.11-7.04 (m, 2 H), 6.45-6.38 (m, 1 H), 3.71-3.67 (m, 2 H), 3.50-3.28 (m, 2 H), 1.71-1.67 (m, 2 H), 1.51 (s, 9 H), 1.24 (s, 6 H).

[0601] Example 4:



[0602] 1-Chloro-4-methylpentan-3-one

Ethylene was passed through a solution of isobutyryl chloride (50 g, 0.5 mol) and $AlCl_3$ (68.8 g, 0.52 mol) in anhydrous CH_2Cl_2 (700 mL) at 5 °C. After 4 h, the absorption of ethylene ceased, and the mixture was stirred at room temperature overnight. The mixture was poured into cold diluted HCl solution and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to give the crude 1-chloro-4-methylpentan-3-one, which was used directly in the next step without further purification.

[0603] 4-Methyl-1-(phenylamino)-pentan-3-one

A suspension of the crude 1-chloro-4-methylpentan-3-one (about 60 g), aniline (69.8 g, 0.75 mol) and $NaHCO_3$ (210 g, 2.5 mol) in CH_3CN (1000 mL) was heated at reflux overnight. After cooling, the insoluble salt was filtered off and the filtrate was concentrated. The residue was diluted with CH_2Cl_2, washed with 10% HCl solution (100 mL) and brine, dried over Na_2SO_4, filtered and concentrated to give the crude 4-methyl-1-(phenylamino)-pentan-3-one.

[0604] 4-Methyl-1-(phenylamino)-pentan-3-ol

At -10 °C, $NaBH_4$ (56.7 g, 1.5 mol) was gradually added to a mixture of the crude 4-methyl-1-(phenylamino)-pentan-3-one (about 80 g) in MeOH (500 mL). After addition, the reaction mixture was allowed to warm to room temperature and stirred for 20 min. The solvent was removed and the residue was repartitioned between water and CH_2Cl_2. The organic phase was separated, washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting gum

was triturated with ether to give 4-methyl-1-(phenylamino)-pentan-3-ol as a white solid (22 g, 23 %).

[0605] 5,5-Dimethyl-2,3,4,5-tetrahydro-1H-benzo[b]azepine

A mixture of 4-methyl-1-(phenylamino)-pentan-3-ol (22 g, 0.11 mol) in 98% H_2SO_4 (250 mL) was stirred at 50 °C for 30 min. The reaction mixture was poured into ice-water basified with sat. NaOH solution to pH 8 and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (petroleum ether) to afford 5,5-dimethyl- 2,3,4,5-tetrahydro-1H-benzo[b]azepine as a brown oil (1.5 g, 8 %).

[0606] 5,5-Dimethyl-8-nitro-2,3,4,5-tetrahydro-1H-benzo[b]azepine

At 0 °C, KNO_3 (0.76 g, 7.54 mmol) was added portionwise to a solution of 5,5-dimethyl-2,3,4,5-tetrahydro-1H-benzo[b]azepine (1.1 g, 6.28 mmol) in H_2SO_4 (15 mL). After stirring 15 min at this temperature, the mixture was poured into ice water, basified with sat. $NaHCO_3$ to pH 8 and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give crude 5,5-dimethyl-8-nitro-2,3,4,5-tetrahydro-1H-benzo[b]azepine (1.2 g), which was used directly in the next step without further purification.

[0607] 1-(5,5-dimethyl-8-nitro-2,3,4,5-tetrahydrobenzo[b]azepin-1-yl)ethanone

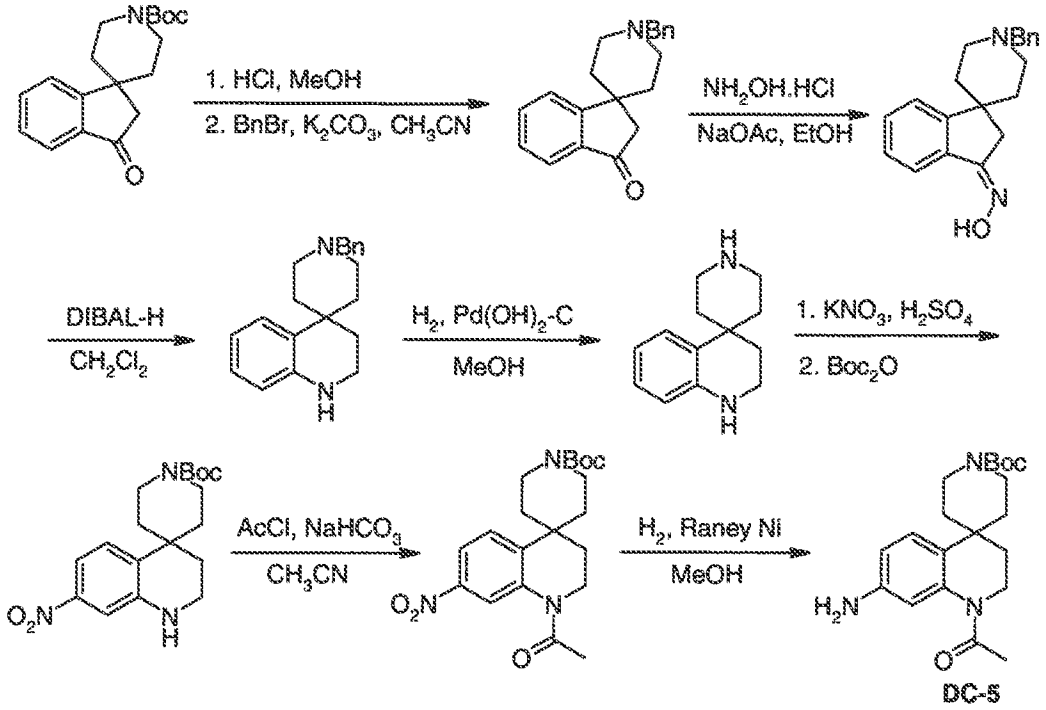
Acetyl chloride (0.77 mL, 11 mmol) was added to a suspension of crude 5,5-dimethyl-8-nitro-2,3,4,5-tetrahydro-1H-benzo[b]azepine (1.2 g, 5.45 mmol) and $NaHCO_3$ (1.37 g, 16.3 mmol) in CH_2Cl_2 (20 mL). The mixture was heated at reflux for 1 h. After cooling, the mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography to afford 1-(5,5-dimethyl-8-nitro-2,3,4,5-tetrahydrobenzo[b]azepin-1-yl)ethanone (1.05 g, 64 % over two steps).

[0608] DC-4; 1-(8-Amino-2,3,4,5-tetrahydro-5,5-dimethylbenzo[b]azepin-1-yl)ethanone

A suspension of 1-(5,5-dimethyl-8-nitro-2,3,4,5-tetrahydrobenzo[b]azepin-1-yl)ethanone (1.05 g, 40 mmol) and 10% Pd-C (0.2 g) in MeOH (20 mL) was stirred under H_2 (1 atm) at room temperature for 4 h. After filtration, the filtrate was concentrated to give 1-(8-amino-2,3,4,5-tetrahydro-5,5-dimethylbenzo[b]azepin-1-yl)ethanone as a white solid (**DC-4**) (880 mg, 94 %).

^{1}H NMR ($CDCl_3$) δ 7.06 (d, *J* = 8.0 Hz, 1 H), 6.59 (dd, *J* = 8.4, 2.4 Hz, 1 H), 6.50 (br s, 1H), 4.18-4.05 (m, 1H), 3.46-3.36 (m, 1H), 2.23 (s, 3H), 1.92-1.85 (m, 1H), 1.61-1.51 (m, 3H), 1.21 (s, 3H), 0.73 (t, *J* = 7.2 Hz, 3 H); ESI-MS 233.0 m/z (MH^+).

[0609] Example 5:



[0610] Spiro[1H-indene-1,4'-piperidin]-3(2H)-one, 1'-benzyl

A mixture of spiro[1H-indene-1,4'-piperidine]-1'-carboxylic acid, 2,3-dihydro-3-oxo-, 1,1-dimethylethyl ester (9.50 g, 31.50 mmol) in saturated HCl/MeOH (50 mL) was stirred at 25 °C overnight. The solvent was removed under reduced pressure to yield an off-white solid (7.50 g). To a solution of this solid in dry CH_3CN (30 mL) was added anhydrous K_2CO_3 (7.85 g, 56.80 mmol). The suspension was stirred for 5 min, and benzyl bromide (5.93 g, 34.65 mmol) was added dropwise at room temperature. The mixture was stirred for 2 h, poured into cracked ice and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under *vacuum* to give crude spiro[1H-indene-1,4'-piperidin]-3(2H)-one, 1'-benzyl (7.93 g, 87 %), which was used without further purification.

[0611] Spiro[1H-indene-1,4'-piperidin]-3(2H)-one, 1'-benzyl, oxime

To a solution of spiro[1H-indene-1,4'-piperidin]-3(2H)-one, 1'-benzyl (7.93 g, 27.25 mmol) in EtOH (50 mL) were added hydroxylamine hydrochloride (3.79 g, 54.50 mmol) and anhydrous sodium acetate (4.02 g, 49.01 mmol) in one portion. The mixture was refluxed for 1 h, and then cooled to room temperature. The solvent was removed under reduced pressure and 200 mL of water was added. The mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to yield spiro[1H-indene-1,4'-piperidin]-3(2H)-one, 1'-benzyl, oxime (7.57 g, 91 %), which was used without further purification.

[0612] 1,2,3,4-Tetrahydroquinolin-4-spiro-4'-(N'-benzyl-piperidine)

To a solution of spiro[1H-indene-1,4'-piperidin]-3(2H)-one, 1'-benzyl, oxime (7.57 g, 24.74 mmol) in dry CH_2Cl_2 (150 mL) was added dropwise DIBAL-H (135.7 mL, 1M in toluene) at 0 °C. The mixture was stirred at 0 °C for 3 h, diluted with CH_2Cl_2 (100 mL), and quenched with NaF (20.78 g, 495 mmol) and water (6.7 g, 372 mmol). The resulting suspension was stirred vigorously at 0 °C for 30 min. After filtration, the residue was washed with CH_2Cl_2. The combined filtrates were concentrated under *vacuum* to give an off-brown oil that was purified by column chromatography on silica gel (CH_2Cl_2 – MeOH, 30:1) to afford 1,2,3,4-tetrahydroquinolin-4-spiro-4'-(N'-benzyl-piperidine) (2.72 g, 38 %).

[0613] 1,2,3,4-Tetrahydroquinolin-4-spiro-4'-piperidine

A suspension of 1,2,3,4-Tetrahydroquinolin-4-spiro-4'-(N'-benzyl-piperidine) (300 mg, 1.03 mmol) and $Pd(OH)_2$-C (30 mg) in MeOH (3 mL) was stirred under H_2 (55 psi) at 50 °C over night. After cooling, the catalyst was filtered off and washed with MeOH. The combined filtrates were concentrated under reduced pressure to yield 1,2,3,4-tetrahydroquinolin-4-spiro-4'-piperidine as a white solid (176 mg, 85 %), which was used without further purification.

[0614] 7'-Nitro-spiro[piperidine-4,4'(1'H)-quinoline], 2',3'-dihydro- carboxylic acid *tert*-butyl ester

KNO_3 (69.97 mg, 0.69 mmol) was added portion-wise to a suspension of 1,2,3,4-tetrahydroquinolin-4-spiro-4'-piperidine (133 mg, 0.66 mmol) in 98% H_2SO_4 (2 mL) at 0 °C. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for additional 2 h. The mixture was then poured into cracked ice and basified with 10% NaOH to pH~ 8. Boc_2O (172 mg, 0.79 mmol) was added dropwise and the mixture was stirred at room temperature for 1 h. The mixture was then extracted with EtOAc and the

combined organic layers were dried over Na_2SO_4, filtered and concentrated to yield crude 7'-nitro-spiro[piperidine-4,4'(1'H)-quinoline], 2',3'-dihydro- carboxylic acid *tert*-butyl ester (230 mg), which was used in the next step without further purification.

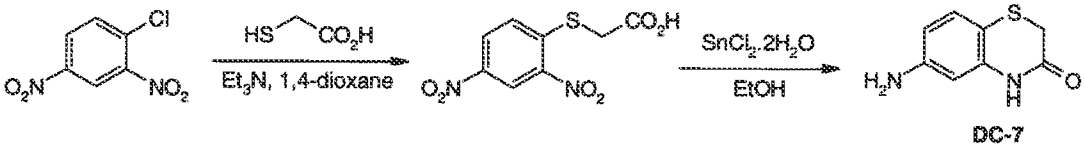
[0615] 7'-nitro-spiro[piperidine-4,4'(1'H)-1-acetyl-quinoline], 2',3'-dihydro-carboxylic acid *tert*-butyl ester

Acetyl chloride (260 mg, 3.30 mmol) was added dropwise to a suspension of 7'-nitro-spiro[piperidine-4,4'(1'H)-quinoline], 2',3'-dihydro- carboxylic acid *tert*-butyl ester (230 mg) and $NaHCO_3$ (1.11 g, 13.17 mmol) in MeCN (5 mL) at room temperature. The reaction mixture was refluxed for 4 h. After cooling, the suspension was filtered and the filtrate was concentrated. The residue was purified by column chromatography (petroleum ether – EtOAc, 10:1) to provide 7'-nitro-spiro[piperidine-4,4'(1'H)-1-acetyl-quinoline], 2',3'-dihydro- carboxylic acid *tert*-butyl ester (150 mg, 58 % over 2 steps)

[0616] DC-5; 7'-Amino-spiro[piperidine-4,4'(1'H)-1-acetyl-quinoline], 2',3'-dihydro- carboxylic acid *tert*-butyl ester

A suspension of 7'-nitro-spiro[piperidine-4,4'(1'H)-1-acetyl-quinoline], 2',3'-dihydro- carboxylic acid *tert*-butyl ester (150 mg, 0.39 mmol) and Raney Ni (15 mg) in MeOH (2 mL) was stirred under H_2 (1 atm) at 25 °C overnight. The catalyst was removed via filtration and washed with MeOH. The combined filtrates were dried over Na_2SO_4, filtered, and concentrated to yield 7'-amino-spiro[piperidine-4,4'(1'H)-1-acetyl-quinoline], 2',3'-dihydro- carboxylic acid *tert*-butyl ester (**DC-5**) (133 mg, 96 %).

[0617] Example 7:



DC-7

[0618] 2-(2,4-Dinitrophenylthio)-acetic acid

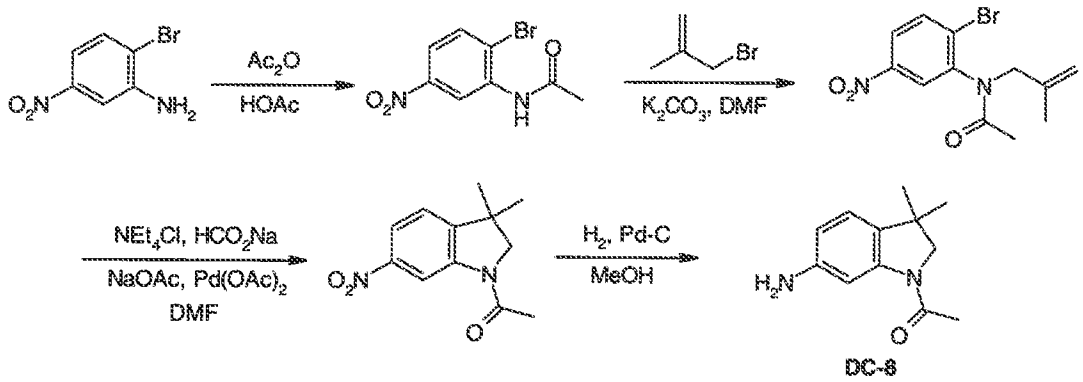
Et_3N (1.5 g, 15 mmol) and mercapto-acetic acid (1 g, 11 mmol) were added to a solution of 1-chloro-2,4-dinitrobenzene (2.26 g, 10 mmol) in 1,4-dioxane (50 mL) at room temperature. After stirring at room temperature for 5 h, H_2O (100 mL) was added. The resulting suspension was extracted with ethyl acetate (100 mL x 3). The ethyl acetate extract was washed with water and

brine, dried over Na_2SO_4 and concentrated to give 2-(2,4-dinitrophenylthio)-acetic acid (2.3 g, 74 %), which was used without further purification.

[0619] DC-7; 6-Amino-2H-benzo[b][1,4]thiazin-3(4H)-one

A solution of 2-(2,4-dinitrophenylthio)-acetic acid (2.3 g, 9 mmol) and tin (II) chloride dihydrate (22.6 g, 0.1 mol) in ethanol (30 mL) was refluxed overnight. After removal of the solvent under reduced pressure, the residual slurry was diluted with water (100 mL) and basified with 10 % Na_2CO_3 solution to pH 8. The resulting suspension was extracted with ethyl acetate (3 x 100 mL). The ethyl acetate extract was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was washed with CH_2Cl_2 to yield 6-amino-2H-benzo[b][1,4]thiazin-3(4H)-one (**DC-7**) as a yellow powder (1 g, 52 %). ^{1}H NMR (DMSO-d_6) δ 10.24 (s. 1 H), 6.88 (d, 1 H, J = 6 Hz), 6.19-6.21 (m, 2H), 5.15 (s, 2 H), 3.28 (s, 2 H); ESI-MS 181.1 m/z (MH^+).

[0620] Example 7:



[0621] N-(2-Bromo-5-nitrophenyl)acetamide

Acetic anhydride (1.4 mL, 13.8 mmol) was added dropwise to a stirring solution of 2-bromo-5-nitroaniline (3 g, 13.8 mmol) in glacial acetic acid (30 mL) at 25 °C. The reaction mixture was stirred at room temperature overnight, and then poured into water. The precipitate was collected via filtration, washed with water and dried under *vacuum* to provide N-(2-bromo-5-nitrophenyl)acetamide as an off white solid (3.6 g, 90 %).

[0622] N-(2-Bromo-5-nitrophenyl)-N-(2-methylprop-2-enyl)acetamide

At 25 °C, a solution of 3-bromo-2-methylpropene (3.4 g, 55.6 mmol) in anhydrous DMF (30 mL) was added dropwise to a solution of N-(2-bromo-5-nitropheny)acetamide (3.6 g, 13.9

mmol) and potassium carbonate (3.9 g, 27.8 mmol) in anhydrous DMF (50 mL). The reaction mixture was stirred at 25 °C overnight. The reaction mixture was then filtered and the filtrate was treated with sat. Na_2CO_3 solution. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under *vacuum* to provide N-(2-bromo-5-nitrophenyl)-N-(2-methylprop-2-enyl)acetamide as a golden solid (3.1 g, 85 %). ESI-MS 313 m/z (MH^+).

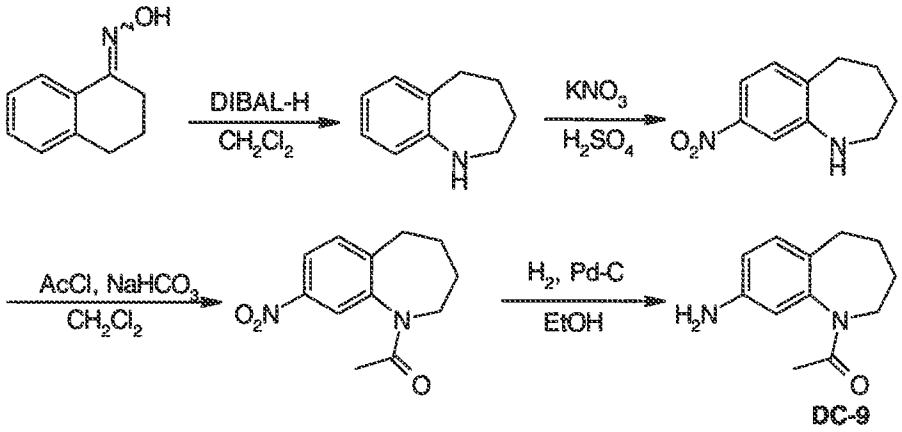
[0623] 1-(3,3-Dimethyl-6-nitroindolin-1-yl)ethanone

A solution of N-(2-bromo-5-nitrophenyl)-N-(2-methylprop-2-enyl)acetamide (3.1 g, 10.2 mmol), tetraethylammonium chloride hydrate (2.4 g, 149 mmol), sodium formate (1.08 g, 18mmol), sodium acetate (2.76 g, 34.2 mmol) and palladium acetate (0.32 g, 13.2 mmol) in anhydrous DMF (50 mL) was stirred at 80 °C for 15 h under N_2 atmosphere. After cooling, the mixture was filtered through Celite. The Celite was washed with EtOAc and the combined filtrates were washed with sat. $NaHCO_3$. The separated organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to provide 1-(3,3-dimethyl-6-nitroindolin-1-yl)ethanone as a brown solid (2.1 g, 88%).

[0624] DC-8; 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone

10% Pd-C (0.2 g) was added to a suspension of 1-(3,3-dimethyl-6-nitroindolin-1-yl)ethanone (2.1g, 9 mmol) in MeOH (20 mL). The reaction was stirred under H_2 (40 psi) at room temperature overnight. Pd-C was filtered off and the filtrate was concentrated under *vacuum* to give a crude product, which was purified by column chromatography to yield 1-(6-amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone (**DC-8**) (1.3 g, 61 %).

[0625] Example 8:



DC-9

[0626] 2,3,4,5-Tetrahydro-1H-benzo[b]azepine

DIBAL (90 mL, 90 mmol) was added dropwise to a solution of 4-dihydro-2H-naphthalen-1-one oxime (3 g, 18 mmol) in dichloromethane (50 mL) at 0 °C. The mixture was stirred at this temperature for 2 h. The reaction was quenched with dichloromethane (30 mL), followed by treatment with NaF (2 g, 0.36 mol) and H_2O (5 mL, 0.27 mol). Vigorous stirring of the resulting suspension was continued at 0 °C for 30 min. After filtration, the filtrate was concentrated. The residue was purified by flash column chromatography to give 2,3,4,5-tetrahydro-1H-benzo[b]azepine as a colorless oil (1.9 g, 70 %).

[0627] 8-Nitro-2,3,4,5-tetrahydro-1H-benzo[b]azepine

At –10 °C, 2,3,4,5-tetrahydro-1H-benzo[b]azepine (1.9 g, 13 mmol) was added dropwise to a solution of KNO_3 (3 g, 30 mmol) in H_2SO_4 (50 mL). The mixture was stirred for 40 min, poured over crushed ice, basified with aq. ammonia to pH 13, and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated to give 8-nitro-2,3,4,5-tetrahydro-1H-benzo[b]azepine as a black solid (1.3 g, 51 %), which was used without further purification.

[0628] 1-(8-Nitro-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl)-ethanone

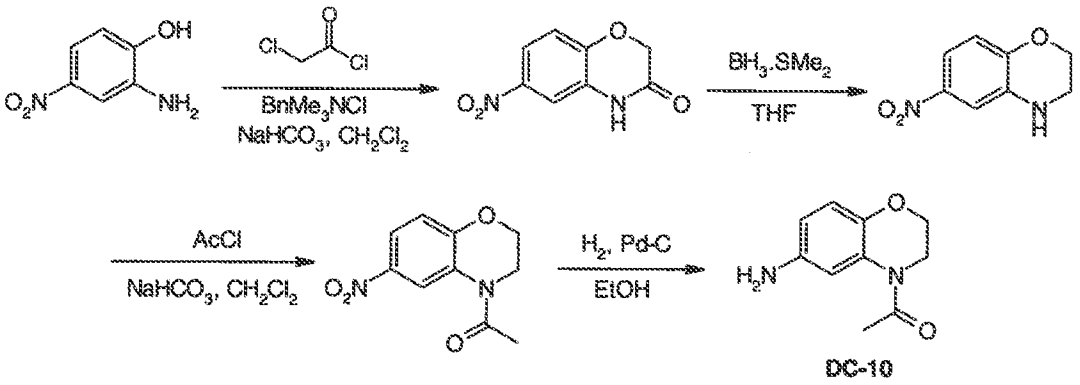
Acetyl chloride (1 g, 13 mmol) was added dropwise to a mixture of 8-nitro-2,3,4,5-tetrahydro-1H-benzo[b]azepine (1.3 g, 6.8 mmol) and $NaHCO_3$ (1 g, 12 mmol) in CH_2Cl_2 (50 mL). After stirring for 1 h, the mixture was filtered and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2, washed with brine, dried over Na_2SO_4 and concentrated. The residue was

purified by column chromatography to give 1-(8-nitro-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl)-ethanone as a yellow solid (1.3 g, 80 %).

[0629] DC-9; 1-(8-Amino-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl)-ethanone

A mixture of 1-(8-nitro-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl)- ethanone (1.3 g, 5.4 mmol) and Pd-C (10 %, 100 mg) in EtOH (200 mL) was stirred under H_2 (1 atm) at room temperature for 1.5 h. The mixture was filtered through a layer of Celite and the filtrate was concentrated to give 1-(8-amino-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl)-ethanone (**DC-9**) as a white solid (1 g, 90 %). ^{1}H NMR ($CDCl_3$) δ 7.01 (d, J = 6.0 Hz, 1 H), 6.56 (dd, J = 6.0, 1.8 Hz, 1 H), 6.50 (d, J = 1.8 Hz, 1 H), 4.66-4.61 (m, 1 H), 3.50 (br s, 2 H), 2.64-2.55 (m, 3 H), 1.94-1.91 (m, 5 H), 1.77-1.72 (m, 1 H), 1.32-1.30 (m, 1 H); ESI-MS 204.1 m/z (MH^+).

[0630] Example 9:



DC-10

[0631] 6-Nitro-4H-benzo[1,4]oxazin-3-one

At 0 °C, chloroacetyl chloride (8.75 mL, 0.11 mol) was added dropwise to a mixture of 4-nitro-2-aminophenol (15.4 g, 0.1 mol), benzyltrimethylammonium chloride (18.6 g, 0.1 mol) and $NaHCO_3$ (42 g, 0.5 mol) in chloroform (350 mL) over a period of 30 min. After addition, the reaction mixture was stirred at 0 °C for 1 h, then at 50 °C overnight. The solvent was removed under reduced pressure and the residue was treated with water (50 mL). The solid was collected via filtration, washed with water and recrystallized from ethanol to provide 6-nitro-4H-benzo[1,4]oxazin-3-one as a pale yellow solid (8 g, 41 %).

[0632] 6-Nitro-3,4-dihydro-2H-benzo[1,4]oxazine

A solution of $BH_3 \cdot Me_2S$ in THF (2 M, 7.75 mL, 15.5 mmol) was added dropwise to a suspension of 6-nitro-4H-benzo[1,4]oxazin-3-one (0.6 g, 3.1 mmol) in THF (10 mL). The mixture was stirred at room temperature overnight. The reaction was quenched with MeOH (5 mL) at 0 °C and then water (20 mL) was added. The mixture was extracted with Et_2O and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give 6-nitro-3,4-dihydro-2H-benzo[1,4]oxazine as a red solid (0.5 g, 89 %), which was used without further purification.

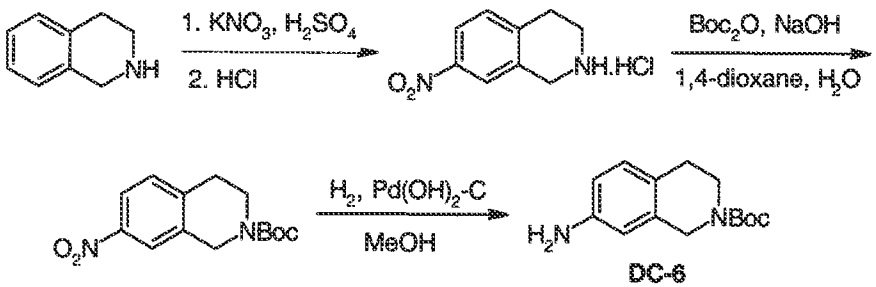
[0633] 4-Acetyl-6-nitro-3,4-dihydro-2H-benzo[1,4]oxazine

Under vigorous stirring at room temperature, acetyl chloride (1.02 g, 13 mmol) was added dropwise to a mixture of 6-nitro-3,4-dihydro-2H-benzo[1,4]oxazine (1.8 g, 10 mmol) and $NaHCO_3$ (7.14 g, 85 mmol) in CH_2Cl_2 (50 mL). After addition, the reaction was stirred for 1 h at this temperature. The mixture was filtered and the filtrate was concentrated under *vacuum*. The residue was treated with Et_2O: hexane (1:2, 50 mL) under stirring for 30 min and then filtered to give 4-acetyl-6-nitro-3,4-dihydro-2H-benzo[1,4]oxazine as a pale yellow solid (2 g, 90 %).

[0634] DC-10; 4-Acetyl-6-amino-3,4-dihydro-2H-benzo[1,4]oxazine

A mixture of 4-acetyl-6-nitro-3,4-dihydro-2H-benzo[1,4]oxazine (1.5 g, 67.6 mmol) and Pd-C (10 %, 100 mg) in EtOH (30 mL) was stirred under H_2 (1 atm) overnight. The catalyst was filtered off and the filtrate was concentrated. The residue was treated with HCl / MeOH to give 4-acetyl-6-amino-3,4-dihydro-2H-benzo[1,4]oxazine hydrochloride (**DC-10**) as an off-white solid (1.1 g, 85 %). ^{1}H NMR (DMSO-d_6) δ 10.12 (br s, 2H), 8.08 (br s, 1H), 6.90-7.03 (m, 2 H), 4.24 (t, J = 4.8 Hz, 2 H), 3.83 (t, J = 4.8 Hz, 2H), 2.23 (s, 3 H); ESI-MS 192.1 m/z (MH^+).

[0635] Example 10:



[0636] 1,2,3,4-Tetrahydro-7-nitroisoquinoline hydrochloride

1,2,3,4-Tetrahydroisoquinoline (6.3 mL, 50.0 mmol) was added dropwise to a stirred ice-cold solution of concentrated H_2SO_4 (25 mL). KNO_3 (5.6 g, 55.0 mmol) was added portionwise while maintaining the temperature below 5 °C. The mixture was stirred at room temperature overnight, carefully poured into an ice-cold solution of concentrated NH_4OH, and then extracted three times with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The resulting dark brown oil was taken up into EtOH, cooled in an ice bath and treated with concentrated HCl. The yellow precipitate was collected via filtration and recrystallized from methanol to give 1,2,3,4-tetrahydro-7-nitroisoquinoline hydrochloride as yellow solid (2.5 g, 23 %). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.86 (s, 2H), 8.22 (d, J = 1.6 Hz, 1H), 8.11 (dd, J = 8.5, 2.2 Hz, 1H), 7.53 (d, J = 8.5 Hz,1H), 4.38 (s, 2H), 3.38 (s, 2H), 3.17-3.14 (m, 2H); HPLC ret. time 0.51 min, 10-99 % CH_3CN, 5 min run; ESI-MS 179.0 m/z (MH^+).

[0637] *tert*-Butyl 3,4-dihydro-7-nitroisoquinoline-2(1H)-carboxylate

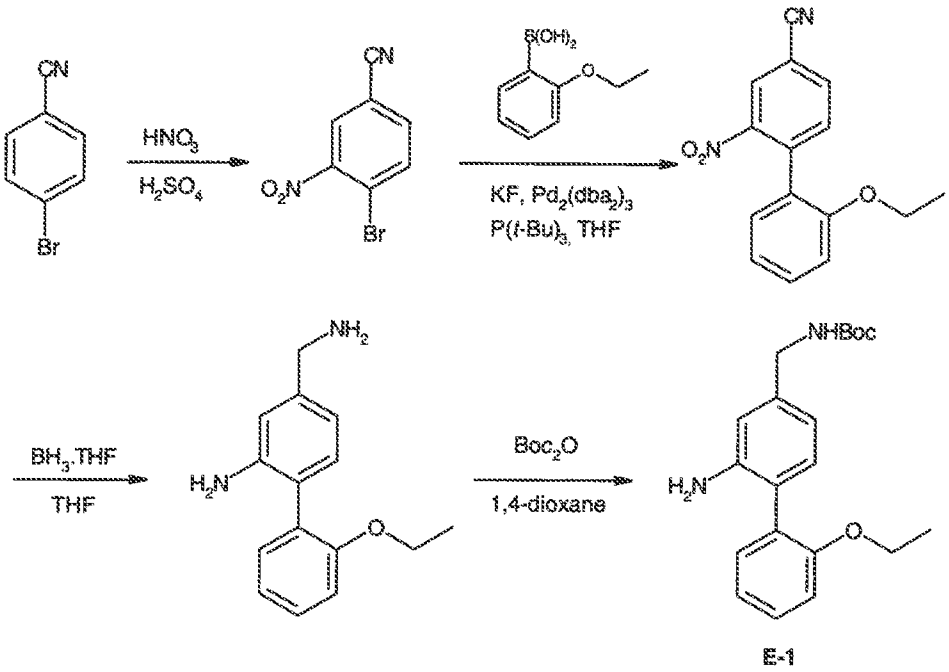
A mixture of 1,2,3,4-Tetrahydro-7-nitroisoquinoline (2.5 g, 11.6 mmol), 1,4-dioxane (24 mL), H_2O (12 mL) and 1N NaOH (12 mL) was cooled in an ice-bath, and Boc_2O (2.8 g, 12.8 mmol) was added. The mixture was stirred at room temperature for 2.5 h, acidified with a 5% $KHSO_4$ solution to pH 2-3, and then extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated to give *tert*-butyl 3,4-dihydro-7-nitroisoquinoline-2(1H)-carboxylate (3.3 g, quant.), which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.13 (d, J = 2.3 Hz, 1H), 8.03 (dd, J = 8.4, 2.5 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 4.63 (s, 2H), 3.60-3.57 (m, 2H), 2.90 (t, J = 5.9 Hz, 2H), 1.44 (s, 9H); HPLC ret. time 3.51 min, 10-99 % CH_3CN, 5 min run; ESI-MS 279.2 m/z (MH^+).

[0638] DC-6; *tert*-Butyl 7-amino-3,4-dihydroisoquinoline-2(1H)-carboxylate

$Pd(OH)_2$ (330.0 mg) was added to a stirring solution of *tert*-butyl 3,4-dihydro-7-nitroisoquinoline-2(1H)-carboxylate (3.3 g, 12.0 mmol) in MeOH (56 mL) under N_2 atmosphere. The reaction mixture was stirred under H_2 (1 atm) at room temerpature for 72 h. The solid was removed by filtration through Celite. The filtrate was concentrated and purified by column chromatography (15–35 % EtOAc - Hexanes) to provide *tert*-butyl 7-amino-3,4-dihydroisoquinoline-2(1H)-carboxylate (**DC-6**) as a pink oil (2.0 g, 69 %). ^{1}H NMR (400 MHz, DMSO-d6) δ 6.79 (d, J = 8.1 Hz, 1H), 6.40 (dd, J = 8.1, 2.3 Hz, 1H), 6.31 (s, 1H), 4.88 (s, 2H), 4.33 (s, 2H), 3.48 (t, J = 5.9 Hz, 2H), 2.58 (t, J = 5.9 Hz, 2H), 1.42 (s, 9H); HPLC ret. time 2.13 min, 10-99 % CH_3CN, 5 min run; ESI-MS 249.0 m/z (MH^+).

[0639] Other amines

[0640] Example 1:



[0641] 4-Bromo-3-nitrobenzonitrile

To a solution of 4-bromobenzonitrile (4.0 g, 22 mmol) in conc. H_2SO_4 (10 mL) was added dropwise at 0 °C nitric acid (6 mL). The reaction mixture was stirred at 0 °C for 30 min, and then at room temperature for 2.5 h. The resulting solution was poured into ice-water. The white precipitate was collected via filtration and washed with water until the washings were neutral. The solid was recrystallized from an ethanol/water mixture (1:1, 20 mL) twice to afford 4-bromo-3-nitrobenzonitrile as a white crystalline solid (2.8 g, 56 %). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.4, 137.4, 136.6, 129.6, 119.6, 117.0, 112.6; HPLC ret. time 1.96 min, 10-100 % CH_3CN, 5 min gradient; ESI-MS 227.1 m/z (MH^+).

[0642] 2'-Ethoxy-2-nitrobiphenyl-4-carbonitrile

A 50 mL round-bottom flask was charged with 4-bromo-3-nitrobenzonitrile (1.0 g 4.4 mmol), 2-ethoxyphenylboronic acid (731 mg, 4.4 mmol), $Pd_2(dba)_3$ (18 mg, 0.022 mmol) and potassium fluoride (786 mg, 13.5 mmol). The reaction vessel was evacuated and filled with argon. Dry THF (300 mL) was added followed by the addition of P(t-Bu)$_3$ (0.11 mL, 10% wt. in hexane).

The reaction mixture was stirred at room temperature for 30 min., and then heated at 80 °C for 16 h. After cooling to room temperature, the resulting mixture was filtered through a Celite pad and concentrated. 2'-Ethoxy-2-nitrobiphenyl-4-carbonitrile was isolated as a yellow solid (1.12 g, 95%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.51 (s, 1H), 8.20 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.41 (t, J = 8.4 Hz, 1H), 7.37 (d, J = 7.5 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H), 3.91 (q, J = 7.2 Hz, 2H), 1.12 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.9, 149.7, 137.3, 137.2, 134.4, 131.5, 130.4, 128.4, 125.4, 121.8, 117.6, 112.3, 111.9, 64.1, 14.7; HPLC ret. time 2.43 min, 10-100 % CH_3CN, 5 min gradient; ESI-MS 269.3 m/z (MH^+).

[0643] 4-Aminomethyl-2'-ethoxy-biphenyl-2-ylamine

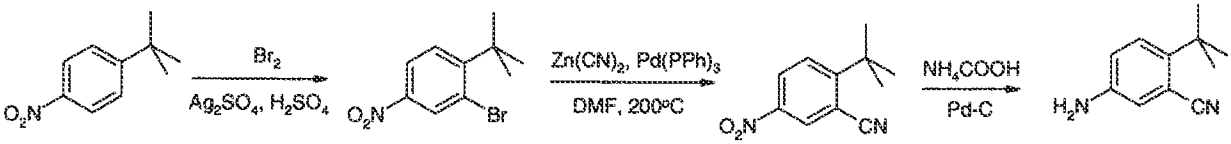
To a solution of 2'-ethoxy-2-nitrobiphenyl-4-carbonitrile (500 mg, 1.86 mmol) in THF (80 mL) was added a solution of BH_3.THF (5.6 mL, 10% wt. in THF, 5.6 mmol) at 0 °C over 30 min. The reaction mixture was stirred at 0 °C for 3 h and then at room temperature for 15 h. The reaction solution was chilled to 0 °C, and a H_2O/THF mixture (3 mL) was added. After being agitated at room temperature for 6 h, the volatiles were removed under reduced pressure. The residue was dissolved in EtOAc (100 mL) and extracted with 1N HCl (2 x 100 mL). The aqueous phase was basified with 1N NaOH solution to pH 1and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (50 mL), dried over Na_2SO_4, filtered, and evaporated. After drying under vacuum, 4-aminomethyl-2'-ethoxy-biphenyl-2-ylamine was isolated as a brown oil (370 mg, 82 %). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.28 (dt, J = 7.2 Hz, J = 1.8 Hz, 1H), 7.09 (dd, J = 7.2 Hz, J = 1.8 Hz, 1H), 7.05 (d, J = 7.5 Hz, 1H), 6.96 (dt, J = 7.2 Hz, J = 0.9 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.66 (d, J = 1.2 Hz, 1H), 6.57 (dd, J = 7.5 Hz, J = 1.5 Hz, 1H), 4.29 (s, 2H), 4.02 (q, J = 6.9 Hz, 2H), 3.60 (s, 2H), 1.21 (t, J = 6.9 Hz, 3H); HPLC ret. time 1.54 min, 10-100 % CH_3CN, 5 min gradient; ESI-MS 243.3 m/z (MH^+).

[0644] E-1; (2-Amino-2'-ethoxy-biphenyl-4-ylmethyl)carbamic acid *tert*-butyl ester

A solution of Boc_2O (123 mg, 0.565 mmol) in 1,4-dioxane (10 mL) was added over a period of 30 min. to a solution of 4-aminomethyl-2'-ethoxy-biphenyl-2-ylamine (274 mg, 1.13 mmol) in 1,4-dioxane (10 mL). The reaction mixture was stirred at room temperature for 16 h. The volatiles were removed on a rotary evaporator. The residue was purified by flash chromatography (silica gel, EtOAc – CH_2Cl_2, 1:4) to afford (2-Amino-2'-ethoxy-biphenyl-4-ylmethyl)carbamic acid *tert*-butyl ester (**E-1**) as a pale yellow oil (119 mg, 31 %). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.27 (m, 2H), 7.07 (dd, J = 7.2 Hz, J = 1.8 Hz, 1H), 7.03 (d, J = 7.8 Hz, 1H),

6.95 (dt, J = 7.2 Hz, J = 0.9 Hz, 1H), 6.81 (d, J = 7.5 Hz, 1H), 6.55 (s, 1H), 6.45 (dd, J = 7.8 Hz, J = 1.5 Hz, 1H), 4.47 (s, 2H), 4.00 (q, J = 7.2 Hz, 2H), 1.38 (s, 9H), 1.20 (t, J = 7.2 Hz, 3H); HPLC ret. time 2.34 min, 10-100 % CH_3CN, 5 min gradient; ESI-MS 343.1 m/z (MH^+).

[0645] Example 2:



E-2

[0646] 2-Bromo-1-*tert*-butyl-4-nitrobenzene

To a solution of 1-*tert*-butyl-4-nitrobenzene (8.95 g, 50 mmol) and silver sulfate (10 g, 32 mmol) in 50 mL of 90% sulfuric acid was added dropwise bromine (7.95 g, 50 mmol). Stiring was continued at room temperature overnight, and then the mixture was poured into dilute sodium hydrogen sulfite solution and was extracted with EtOAc three times. The combined organic layers were washed with brine and dried over $MgSO_4$. After filtration, the filtrate was concentrated to give 2-bromo-1-*tert*-butyl-4-nitrobenzene (12.7 g, 98 %), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 2.5 Hz, 1H), 8.11 (dd, J = 8.8, 2.5 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 1.57 (s, 9H); HPLC ret. time 4.05 min, 10-100 % CH_3CN, 5 min gradient.

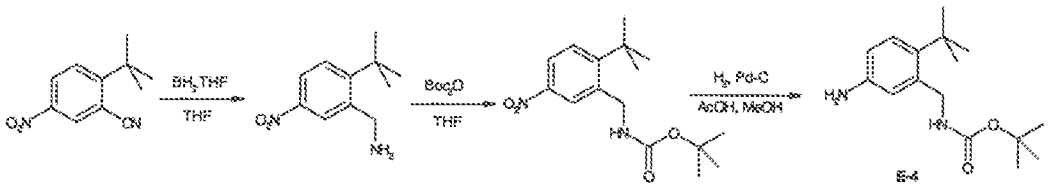
[0647] 2-*tert*-Butyl-5-nitrobenzonitrile

To a solution of 2-bromo-1-*tert*-butyl-4-nitrobenzene (2.13 g, 8.2 mmol) and $Zn(CN)_2$ (770 mg, 6.56 mmol) in DMF (10 mL) was added $Pd(PPh_3)_4$ (474 mg, 0.41 mmol) under a nitrogen atmosphere. The mixture was heated in a sealed vessel at 205 °C for 5 h. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc twice. The combined organic layers were washed with brine and dried over $MgSO_4$. After removal of solvent, the residue was purified by column chromatography (0-10 % EtOAc-Hexane) to give 2-*tert*-butyl-5-nitrobenzonitrile (1,33 g, 80 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 2.3 Hz, 1H), 8.36 (dd, J = 8.8, 2.2 Hz, 1H), 7.73 (d, J = 8.9 Hz, 1H), 1.60 (s, 9H); HPLC ret. time 3.42 min, 10-100 % CH_3CN, 5 min gradient.

[0648] E-2; 2-*tert*-Butyl-5-aminobenzonitrile

To a refluxing solution of 2-*tert*-butyl-5-nitrobenzonitrile (816 mg, 4.0 mmol) in EtOH (20 mL) was added ammonium formate (816 mg, 12.6 mmol), followed by 10% Pd-C (570 mg). The reaction mixture was refluxed for additional 90 min, cooled to room temperature and filtered through Celite. The filtrate was concentrated to give 2-*tert*-butyl-5-aminobenzonitrile (**E-2**) (630 mg, 91 %), which was used without further purification. HPLC ret. time 2.66 min, 10-99 % CH_3CN, 5 min run; ESI-MS 175.2 m/z (MH^+).

[0649] Example 3:



[0650] (2-*tert*-Butyl-5-nitrophenyl)methanamine

To a solution of 2-*tert*-butyl-5-nitrobenzonitrile (612 mg, 3.0 mmol) in THF (10 mL) was added a solution of BH_3.THF (12 mL, 1M in THF, 12.0 mmol) under nitrogen. The reaction mixture was stirred at 70 °C overnight and cooled to 0 °C. Methanol (2 mL) was added followed by the addition of 1N HCl (2 mL). After refluxing for 30 min, the solution was diluted with water and extracted with EtOAc. The aqueous layer was basified with 1N NaOH and extracted with EtOAc twice. The combined organic layers were washed with brine and dried over Mg_2SO_4. After removal of solvent, the residue was purified by column chromatography (0-10 % MeOH - CH_2Cl_2) to give (2-*tert*-butyl-5-nitrophenyl)methanamine (268 mg, 43 %). ^1H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, J = 2.7 Hz, 1H), 7.99 (dd, J = 8.8, 2.8 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 4.03 (s, 2H), 2.00 (t, J = 2.1 Hz, 2H), 1.40 (s, 9H); HPLC ret. time 2.05 min, 10-100 % CH_3CN, 5 min gradient; ESI-MS 209.3 m/z (MH^+).

[0651] *tert*-Butyl 2-*tert*-butyl-5-nitrobenzylcarbamate

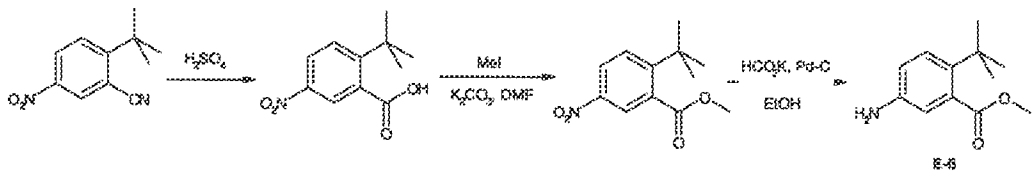
A solution of (2-*tert*-butyl-5-nitrophenyl)methanamine (208 mg, 1 mmol) and Boc_2O (229 mg, 1.05 mmol) in THF (5mL) was refluxed for 30 min. After cooling to room temperature, the solution was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. After filtration, the filtrate was concentrated to give tert-butyl 2-*tert*-butyl-5-nitrobenzylcarbamate (240 mg, 78 %), which was used without further

purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, J = 2.3 Hz, 1H), 8.09 (dd, J = 8.8, 2.5 Hz, 1H), 7.79 (t, J = 5.9 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 4.52 (d, J = 6.0 Hz, 2H), 1.48 (s, 18H); HPLC ret. time 3.72 min, 10-100 % CH_3CN, 5 min gradient.

[0652] E-4; *tert*-Butyl 2-*tert*-butyl-5-aminobenzylcarbamate

To a solution of tert-butyl 2-*tert*-butyl-5-nitrobenzylcarbamate (20 mg, 0.065 mmol) in 5% AcOH-MeOH (1 mL) was added 10% Pd-C (14 mg) under nitrogen atmosphere. The mixture was stirred under H_2 (1 atm) at room temperature for 1 h. The catalyst was removed via filtration through Celite, and the filtrate was concentrated to give tert-butyl 2-*tert*-butyl-5-aminobenzylcarbamate (**E-4**), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, J = 8.5 Hz, 1H), 6.62 (d, J = 2.6 Hz, 1H), 6.47 (dd, J = 8.5, 2.6 Hz, 1H), 4.61 (br s, 1H), 4.40 (d, J = 5.1 Hz, 2H), 4.15 (br s, 2H), 1.39 (s, 9H), 1.29 (s, 9H); HPLC ret. time 2.47 min, 10-100 % CH_3CN, 5 min gradient; ESI-MS 279.3 m/z (MH^+).

[0653] Example 4:



[0654] 2-*tert*-Butyl-5-nitrobenzoic acid

A solution of 2-*tert*-butyl-5-nitrobenzonitrile (204 mg, 1 mmol) in 5 mL of 75% H_2SO_4 was microwaved at 200 °C for 30 min. The reaction mixture was poured into ice, extracted with EtOAc, washed with brine and dried over $MgSO_4$. After filtration, the filtrate was concentrated to give 2-*tert*-butyl-5-nitrobenzoic acid (200 mg, 90 %), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 2.6 Hz, 1H), 8.24 (dd, J = 8.9, 2.6 Hz, 1H), 7.72 (d, J = 8.9 Hz, 1H) 1.51 (s, 9H); HPLC ret. time 2.97 min, 10-100 % CH_3CN, 5 min gradient.

[0655] Methyl 2-*tert*-butyl-5-nitrobenzoate

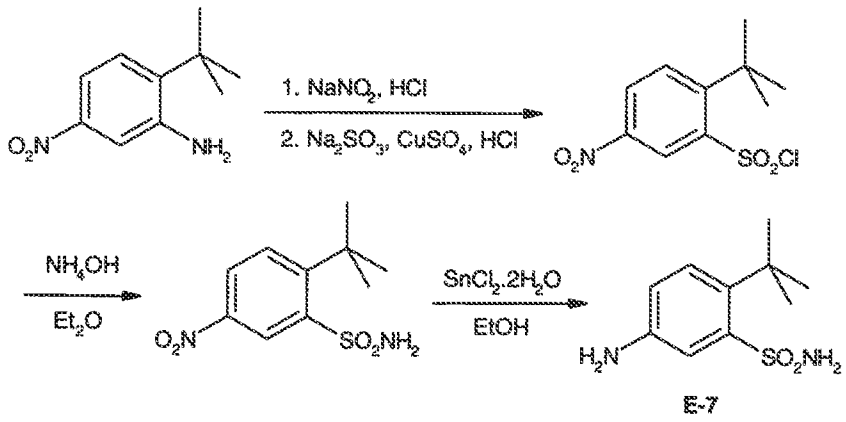
To a mixture of 2-*tert*-butyl-5-nitrobenzoic acid (120 mg, 0.53 mmol) and K_2CO_3 (147 mg, 1.1 mmol) in DMF (5.0 mL) was added CH_3I (40 μL, 0.64 mmol). The reaction mixture was stirred at room temperature for 10 min, diluted with water and extracted with EtOAc. The combined

organic layers were washed with brine and dried over $MgSO_4$. After filtration, the filtrate was concentrated to give methyl 2-*tert*-butyl-5-nitrobenzoate, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 2.6 Hz, 1H), 8.17 (t, J = 1.8 Hz, 1H), 7.66 (d, J = 8.6 Hz, 1H), 4.11 (s, 3H), 1.43 (s, 9H).

[0656] E-6; Methyl 2-*tert*-butyl-5-aminobenzoate

To a refluxing solution of 2-*tert*-butyl-5-nitrobenzoate (90 mg, 0.38 mmol) in EtOH (2.0 mL) was added potassium formate (400 mg, 4.76 mmol) in water (1 mL), followed by the addition of 20 mg of 10% Pd-C. The reaction mixture was refluxed for additional 40 min, cooled to room temperature and filtered through Celite. The filtrate was concentrated to give methyl 2-*tert*-butyl-5-aminobenzoate **(E-6)** (76 mg, 95 %), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.6 Hz, 1H), 6.67 (dd, J = 8.6, 2.7 Hz, 1H), 6.60 (d, J = 2.7 Hz, 1H), 3.86 (s, 3H), 1.34 (s, 9H); HPLC ret. time 2.19 min, 10-99 % CH_3CN, 5 min run; ESI-MS 208.2 m/z (MH^+).

[0657] Example 5:



E-7

[0658] 2-*tert*-Butyl-5-nitrobenzene-1-sulfonyl chloride

A suspension of 2-*tert*-butyl-5-nitrobenzenamine (0.971 g, 5 mmol) in conc. HCl (5 mL) was cooled to 5-10 °C and a solution of $NaNO_2$ (0.433g, 6.3 mmol) in H_2O (0.83 mL) was added dropwise. Stirring was continued for 0.5 h, after which the mixture was vacuum filtered. The filtrate was added, simultaneously with a solution of Na_2SO_3 (1.57 g, 12.4 mmol) in H_2O (2.7 mL), to a stirred solution of $CuSO_4$ (0.190 g, 0.76 mmol) and Na_2SO_3 (1.57 g, 12.4 mmol) in HCl (11.7 mL) and H_2O (2.7 mL) at 3-5 °C. Stirring was continued for 0.5 h and the resulting

precipitate was filtered off, washed with water and dried to give 2-*tert*-butyl-5-nitrobenzene-1-sulfonyl chloride (0.235 g, 17 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (d, J = 2.5 Hz, 1H), 8.36 (dd, J = 8.9, 2.5 Hz, 1H), 7.88 (d, J = 8.9 Hz, 1H), 1.59 (s, 9H).

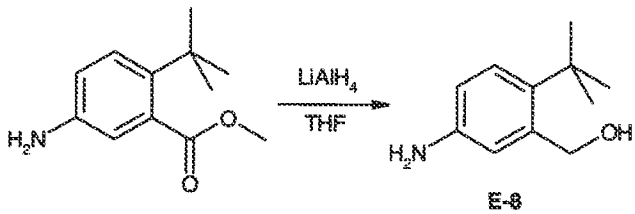
[0659] 2-*tert*-Butyl-5-nitrobenzene-1-sulfonamide

To a solution of 2-*tert*-butyl-5-nitrobenzene-1-sulfonyl chloride (100 mg, 0.36 mmol) in ether (2 mL) was added aqueous NH_4OH (128 μL, 3.6 mmol) at 0 °C. The mixture was stirred at room temperature overnight, diluted with water and extracted with ether. The combined ether extracts were washed with brine and dried over Na_2SO_4. After removal of solvent, the residue was purified by column chromatography (0-50 % EtOAc-Hexane) to give 2-*tert*-butyl-5-nitrobenzene-1-sulfonamide (31.6 mg, 34 %).

[0660] E-7; 2-*tert*-Butyl-5-aminobenzene-1-sulfonamide

A solution of 2-*tert*-butyl-5-nitrobenzene-1-sulfonamide (32 mg, 0.12 mmol) and $SnCl_2 \cdot 2H_2O$ (138 mg, 0.61 mmol) in EtOH (1.5 mL) was heated in microwave oven at 100 °C for 30 min. The mixture was diluted with EtOAc and water, basified with sat. $NaHCO_3$ and filtered through Celite. The organic layer was separated from water and dried over Na_2SO_4. Solvent was removed by evaporation to provide 2-*tert*-butyl-5-aminobenzene-1-sulfonamide (**E-7**) (28 mg, 100 %), which was used without further purification. HPLC ret. time 1.99 min, 10-99 % CH_3CN, 5 min run; ESI-MS 229.3 m/z (MH^+).

[0661] Example 6:



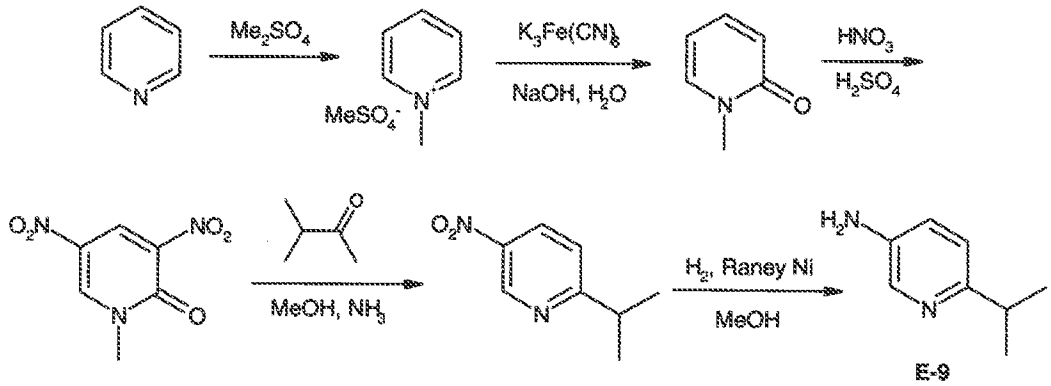
E-8

[0662] E-8; (2-*tert*-Butyl-5-aminophenyl)methanol

To a solution of methyl 2-*tert*-butyl-5-aminobenzoate (159 mg, 0.72 mmol) in THF (5 mL) was added dropwise $LiAlH_4$ (1.4 mL, 1M in THF, 1.4 mmol) at 0 °C. The reaction mixture was refluxed for 2 h, diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. After filtration, the filtrate was concentrated to give

(2-*tert*-butyl-5-aminophenyl)methanol (**E-8**) (25 mg, 20 %), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 8.5 Hz, 1H), 6.87 (d, J = 2.6 Hz, 1H), 6.56 (dd, J = 8.4, 2.7 Hz, 1H), 4.83 (s, 2H), 1.36 (s, 9H).

[0663] Example 7:



[0664] 1-Methyl-pyridinium monomethyl sulfuric acid salt

Methyl sulfate (30 mL, 39.8 g, 0.315 mol) was added dropwise to dry pyridine (25.0 g, 0.316 mol) added dropwise. The mixture was stirred at room temperature for 10 min, then at 100 °C for 2 h. The mixture was cooled to room temperature to give crude 1-methyl-pyridinium monomethyl sulfuric acid salt (64.7 g, quant.), which was used without further purification.

[0665] 1-Methyl-2-pyridone

A solution of 1-methyl-pyridinium monomethyl sulfuric acid salt (50 g, 0.243 mol) in water (54 mL) was cooled to 0 °C. Separate solutions of potassium ferricyanide (160 g, 0.486 mol) in water (320 mL) and sodium hydroxide (40 g, 1.000 mol) in water (67 mL) were prepared and added dropwise from two separatory funnels to the well-stirred solution of 1-methyl-pyridinium monomethyl sulfuric acid salt, at such a rate that the temperature of reaction mixture did not rise above 10 °C. The rate of addition of these two solutions was regulated so that all the sodium hydroxide solution had been introduced into the reaction mixture when one-half of the potassium Ferric Cyanide solution had been added. After addition was complete, the reaction mixture was allowed to warm to room temperature and stirred overnight. Dry sodium carbonate (91.6 g) was added, and the mixture was stirred for 10 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (100 mL × 3). The combined organic layers

were dried and concentrated to yield 1-methyl-2-pyridone (25.0 g, 94 %), which was used without further purification.

[0666] 1-Methyl-3,5-dinitro-2-pyridone

1-Methyl-2-pyridone (25.0 g, 0.229 mol) was added to sulfuric acid (500 mL) at 0 °C. After stirring for 5 min., nitric acid (200 mL) was added dropwise at 0 °C. After addition, the reaction temperature was slowly raised to 100 °C, and then maintained for 5 h. The reaction mixture was poured into ice, basified with potassium carbonate to pH 8 and extracted with CH_2Cl_2 (100 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated to yield 1-methyl-3,5-dinitro-2-pyridone (12.5 g, 28 %), which was used without further purification.

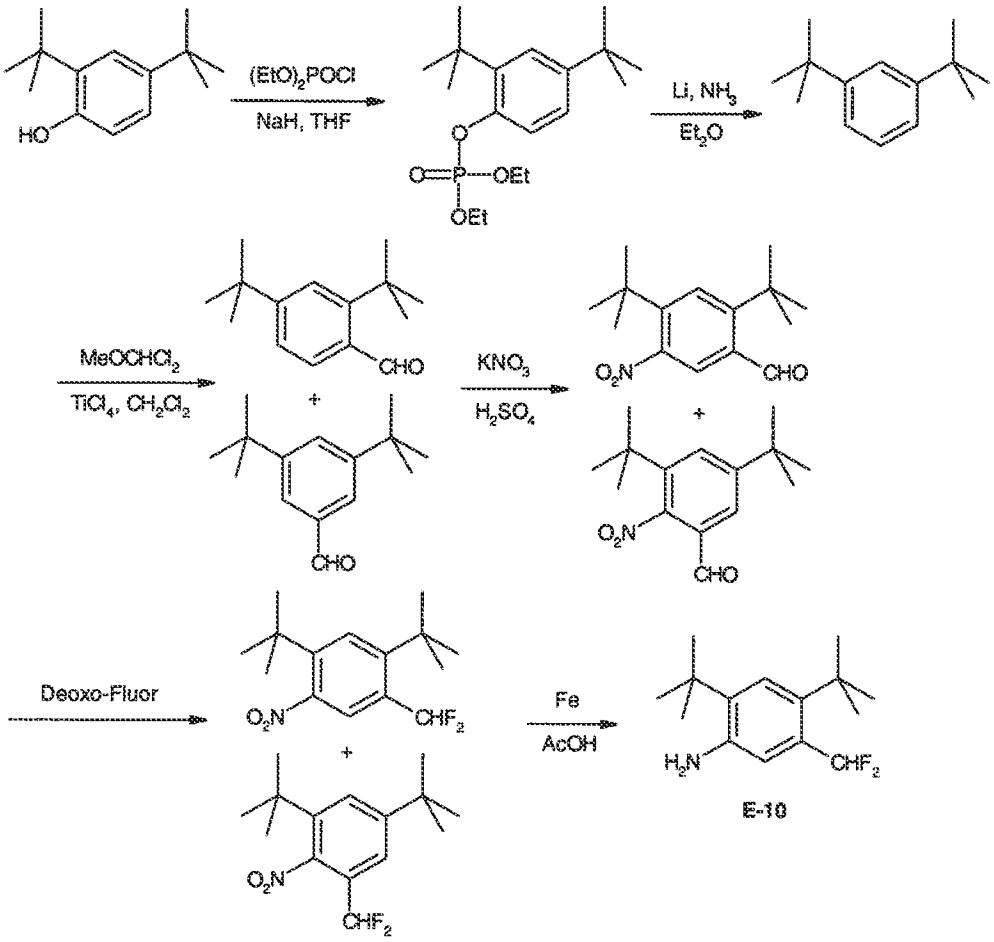
[0667] 2-Isopropyl-5-nitro-pyridine

To a solution of 1-methyl-3,5-dinitro-2-pyridone (8.0 g, 40 mmol) in methyl alcohol (20 mL) was added dropwise 3-methyl-2-butanone (5.1 mL, 48 mmol), followed by ammonia solution in methyl alcohol (10.0 g, 17%, 100 mmol). The reaction mixture was heated at 70 °C for 2.5 h under atmospheric pressure. The solvent was removed under *vacuum* and the residual oil was dissolved in CH_2Cl_2, and then filtered. The filtrate was dried over Na_2SO_4 and concentrated to afford 2-isopropyl-5-nitro-pyridine (1.88 g, 28 %).

[0668] E-9; 2-Isopropyl-5-amino-pyridine

2-Isopropyl-5-nitro-pyridine (1.30 g, 7.82 mmol) was dissolved in methyl alcohol (20 mL), and Raney Ni (0.25 g) was added. The mixture was stirred under H_2 (1 atm) at room temperature for 2 h. The catalyst was filtered off, and the filtrate was concentrated under *vaccum* to give 2-isopropyl-5-amino-pyridine (**E-9**) (0.55 g, 52 %). ^{1}H NMR ($CDCl_3$) δ 8.05 (s, 1 H), 6.93-6.99 (m, 2 H), 3.47 (br s, 2 H), 2.92-3.02 (m, 1 H), 1.24-1.26 (m, 6 H). ESI-MS 137.2 m/z (MH^+).

[0669] Example 8:



[0670] Phosphoric acid 2,4-di-*tert*-butyl-phenyl ester diethyl ester

To a suspension of NaH (60% in mineral oil, 6.99 g, 174.7 mmol) in THF (350 mL) was added dropwise a solution of 2,4-di-*tert*-butylphenol (35 g, 169.6 mmol) in THF (150 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min and then phosphorochloridic acid diethyl ester (30.15 g, 174.7 mmol) was added dropwise at 0 °C. After addition, the mixture was stirred at this temperature for 15 min. The reaction was quenched with sat. NH_4Cl (300 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (350 mL × 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under *vacuum* to give crude phosphoric acid 2,4-di-*tert*-butyl-phenyl ester diethyl ester as a yellow oil (51 g, contaminated with some mineral oil), which was used directly in the next step.

[0671] 1,3-Di-*tert*-butyl-benzene

To NH_3 (liquid, 250 mL) was added a solution of phosphoric acid 2,4-di-*tert*-butyl-phenyl ester diethyl ester (51 g, crude from last step, about 0.2 mol) in Et_2O (anhydrous, 150 mL) at -78 °C under N_2 atmosphere. Lithium metal was added to the solution in small pieces until a blue color persisted. The reaction mixture was stirred at -78 °C for 15 min and then quenched with sat. NH_4Cl solution until the mixture turned colorless. Liquid NH_3 was evaporated and the residue was dissolved in water, extracted with Et_2O (300 mL × 2). The combined organic phases were dried over Na_2SO_4 and concentrated to give crude 1,3-di-*tert*-butyl-benzene as a yellow oil (30.4 g, 94 % over 2 steps, contaminated with some mineral oil), which was used directly in next step.

[0672] 2,4-Di-*tert*-butyl-benzaldehyde and 3,5-di-*tert*-butyl-benzaldehyde

To a stirred solution of 1,3-di-*tert*-butyl-benzene (30 g, 157.6 mmol) in dry CH_2Cl_2 (700 mL) was added $TiCl_4$ (37.5 g, 197 mmol) at 0 °C, and followed by dropwise addition of $MeOCHCl_2$ (27.3 g, 236.4 mmol). The reaction was allowed to warm to room temperature and stirred for 1 h. The mixture was poured into ice-water and extracted with CH_2Cl_2. The combined organic phases were washed with $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (petroleum ether) to give a mixture of 2,4-di-*tert*-butyl-benzaldehyde and 3,5-di-*tert*-butyl-benzaldehyde (21 g, 61 %).

[0673] 2,4-Di-*tert*-butyl-5-nitro-benzaldehyde and 3,5-di-*tert*-butyl-2-nitro-benzaldehyde

To a mixture of 2,4-di-*tert*-butyl-benzaldehyde and 3,5-di-*tert*-butyl-benzaldehyde in H_2SO_4 (250 mL) was added KNO_3 (7.64 g, 75.6 mmol) in portions at 0 °C. The reaction mixture was stirred at this temperature for 20 min and then poured into crushed ice. The mixture was basified with NaOH solution to pH 8 and extracted with Et_2O (10 mL × 3). The combined organic layers were washed with water and brine and concentrated. The residue was purified by column chromatography (petroleum ether) to give a mixture of 2,4-di-*tert*-butyl-5-nitro-benzaldehyde and 3,5-di-*tert*-butyl-2-nitro-benzaldehyde (2:1 by NMR) as a yellow solid (14.7 g, 82 %). After further purification by column chromatography (petroleum ether), 2,4-di-*tert*-butyl-5-nitro-benzaldehyde (2.5 g, contains 10% 3,5-di-*tert*-butyl-2-nitro-benzaldehyde) was isolated.

[0674] 1,5-Di-*tert*-butyl-2-difluoromethyl-4-nitro-benzene and 1,5-Di-*tert*-butyl-3-difluoromethyl-2-nitro-benzene

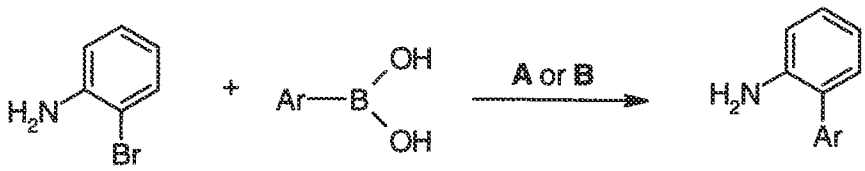
2,4-Di-*tert*-butyl-5-nitro-benzaldehyde (2.4 g, 9.11 mmol, contaminated with 10% 3,5-di-*tert*-butyl-2-nitro-benzaldehyde) in neat deoxofluor solution was stirred at room temperature for 5 h. The reaction mixture was poured into cooled sat. $NaHCO_3$ solution and extracted with dichloromethane. The combined organics were dried over Na_2SO_4, concentrated and purified by column chromatography (petroleum ether) to give 1,5-di-*tert*-butyl-2-difluoromethyl-4-nitro-benzene (1.5 g) and a mixture of 1,5-di-*tert*-butyl-2-difluoromethyl-4-nitro-benzene and 1,5-di-*tert*-butyl-3-difluoromethyl-2-nitro-benzene (0.75 g, contains 28 % 1,5-di-*tert*-butyl-3-difluoromethyl-2-nitro-benzene).

[0675] E-10; 1,5-Di-*tert*-butyl-2-difluoromethyl-4-amino-benzene

To a suspension of iron powder (5.1 g, 91.1 mmol) in 50% acetic acid (25 mL) was added 1,5-di-*tert*-butyl-2-difluoromethyl-4-nitro-benzene (1.3 g, 4.56 mmol). The reaction mixture was heated at 115 °C for 15 min. Solid was filtered off was washed with acetic acid and CH_2Cl_2. The combined filtrate was concentrated and treated with HCl/MeOH. The precipitate was collected via filtration, washed with MeOH and dried to give 1,5-Di-*tert*-butyl-2-difluoromethyl-4-amino-benzene HCl salt **(E-10)** as a white solid (1.20 g, 90 %). ^{1}H NMR (DMSO-d_6) δ 7.35-7.70 (t, J = 53.7 Hz, 1 H), 7.56 (s, 1 H), 7.41 (s, 1 H), 1.33-1.36 (d, J = 8.1 Hz, 1H); ESI-MS 256.3 m/z (MH^+).

[0676] Example 9

[0677] General scheme:



A) $Pd(PPh_3)_4$, K_2CO_3, H_2O, THF; **B**) $Pd_2(dba)_3$, $P(tBu)_3$, KF, THF

[0678] Method A

In a 2-dram vial, 2-bromoaniline (100 mg, 0.58 mmol) and the corresponding aryl boronic acid (0.82 mmol) were dissolved in THF (1 mL). H_2O (500 µL) was added followed by K_2CO_3 (200 mg, 1.0 mmol) and $Pd(PPh_3)_4$ (100 mg, 0.1 mmol). The vial was purged with argon and sealed. The vial was then heated at 75 °C for 18 h. The crude sample was diluted in EtOAc and filtered

through a silica gel plug. The organics were concentrated *via* Savant Speed-vac. The crude amine was used without further purification.

[0679] Method B

In a 2-dram vial, the corresponding aryl boronic acid (0.58 mmol) was added followed by KF (110 mg, 1.9 mmol). The solids were suspended in THF (2 mL), and then 2-bromoaniline (70 μL, 0.58 mmol) was added. The vial was purged with argon for 1 min. $P(^tBu)_3$ (100 μL, 10% sol. in hexanes) was added followed by $Pd_2(dba)_3$ (900 μL, 0.005 M in THF). The vial was purged again with argon and sealed. The vial was agitated on an orbital shaker at room temperature for 30 min and heated in a heating block at 80 °C for 16 h. The vial was then cooled to 20 °C and the suspension was passed through a pad of Celite. The pad was washed with EtOAc (5 mL). The organics were combined and concentrated under vacuum to give a crude amine that was used without further purification.

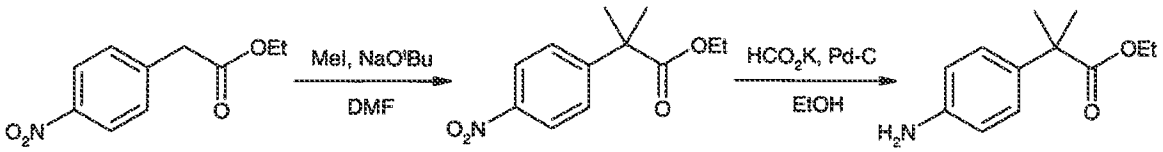
[0680] The table below includes the amines made following the general scheme above.

Product	Name	Method
F-1	4'-Methyl-biphenyl-2-ylamine	A
F-2	3'-Methyl-biphenyl-2-ylamine	A
F-3	2'-Methyl-biphenyl-2-ylamine	A
F-4	2',3'-Dimethyl-biphenyl-2-ylamine	A
F-5	(2'-Amino-biphenyl-4-yl)-methanol	A
F-6	N*4'*,N*4'*-Dimethyl-biphenyl-2,4'-diamine	B
F-7	2'-Trifluoromethyl-biphenyl-2-ylamine	B
F-8	(2'-Amino-biphenyl-4-yl)-acetonitrile	A
F-9	4'-Isobutyl-biphenyl-2-ylamine	A
F-10	3'-Trifluoromethyl-biphenyl-2-ylamine	B
F-11	2-Pyridin-4-yl-phenylamine	B
F-12	2-(1H-Indol-5-yl)-phenylamine	B
F-13	3',4'-Dimethyl-biphenyl-2-ylamine	A
F-14	4'-Isopropyl-biphenyl-2-ylamine	A
F-15	3'-Isopropyl-biphenyl-2-ylamine	A
F-16	4'-Trifluoromethyl-biphenyl-2-ylamine	B
F-17	4'-Methoxy-biphenyl-2-ylamine	B

F-18	3'-Methoxy-biphenyl-2-ylamine	B
F-19	2-Benzo[1,3]dioxol-5-yl-phenylamine	B
F-20	3'-Ethoxy-biphenyl-2-ylamine	B
F-21	4'-Ethoxy-biphenyl-2-ylamine	B
F-22	2'-Ethoxy-biphenyl-2-ylamine	B
F-23	4'-Methylsulfanyl-biphenyl-2-ylamine	B
F-24	3',4'-Dimethoxy-biphenyl-2-ylamine	B
F-25	2',6'-Dimethoxy-biphenyl-2-ylamine	B
F-26	2',5'-Dimethoxy-biphenyl-2-ylamine	B
F-27	2',4'-Dimethoxy-biphenyl-2-ylamine	B
F-28	5'-Chloro-2'-methoxy-biphenyl-2-ylamine	B
F-29	4'-Trifluoromethoxy-biphenyl-2-ylamine	B
F-30	3'-Trifluoromethoxy-biphenyl-2-ylamine	B
F-31	4'-Phenoxy-biphenyl-2-ylamine	B
F-32	2'-Fluoro-3'-methoxy-biphenyl-2-ylamine	B
F-33	2'-Phenoxy-biphenyl-2-ylamine	B
F-34	2-(2,4-Dimethoxy-pyrimidin-5-yl)-phenylamine	B
F-35	5'-Isopropyl-2'-methoxy-biphenyl-2-ylamine	B
F-36	2'-Trifluoromethoxy-biphenyl-2-ylamine	B
F-37	4'-Fluoro-biphenyl-2-ylamine	B
F-38	3'-Fluoro-biphenyl-2-ylamine	B
F-39	2'-Fluoro-biphenyl-2-ylamine	B
F-40	2'-Amino-biphenyl-3-carbonitrile	B
F-41	4'-Fluoro-3'-methyl-biphenyl-2-ylamine	B
F-42	4'-Chloro-biphenyl-2-ylamine	B
F-43	3'-Chloro-biphenyl-2-ylamine	B
F-44	3',5'-Difluoro-biphenyl-2-ylamine	B
F-45	2',3'-Difluoro-biphenyl-2-ylamine	B
F-46	3',4'-Difluoro-biphenyl-2-ylamine	B
F-47	2',4'-Difluoro-biphenyl-2-ylamine	B
F-48	2',5'-Difluoro-biphenyl-2-ylamine	B
F-49	3'-Chloro-4'-fluoro-biphenyl-2-ylamine	B
F-50	3',5'-Dichloro-biphenyl-2-ylamine	B

F-51	2',5'-Dichloro-biphenyl-2-ylamine	B
F-52	2',3'-Dichloro-biphenyl-2-ylamine	B
F-53	3',4'-Dichloro-biphenyl-2-ylamine	B
F-54	2'-Amino-biphenyl-4-carboxylic acid methyl ester	B
F-55	2'-Amino-biphenyl-3-carboxylic acid methyl ester	B
F-56	2'-Methylsulfanyl-biphenyl-2-ylamine	B
F-57	N-(2'-Amino-biphenyl-3-yl)-acetamide	B
F-58	4'-Methanesulfinyl-biphenyl-2-ylamine	B
F-59	2',4'-Dichloro-biphenyl-2-ylamine	B
F-60	4'-Methanesulfonyl-biphenyl-2-ylamine	B
F-61	2'-Amino-biphenyl-2-carboxylic acid isopropyl ester	B
F-62	2-Furan-2-yl-phenylamine	B
F-63	1-[5-(2-Amino-phenyl)-thiophen-2-yl]-ethanone	B
F-64	2-Benzo[b]thiophen-2-yl-phenylamine	B
F-65	2-Benzo[b]thiophen-3-yl-phenylamine	B
F-66	2-Furan-3-yl-phenylamine	B
F-67	2-(4-Methyl-thiophen-2-yl)-phenylamine	B
F-68	5-(2-Amino-phenyl)-thiophene-2-carbonitrile	B

[0681] Example 10:



G-1

[0682] Ethyl 2-(4-nitrophenyl)-2-methylpropanoate

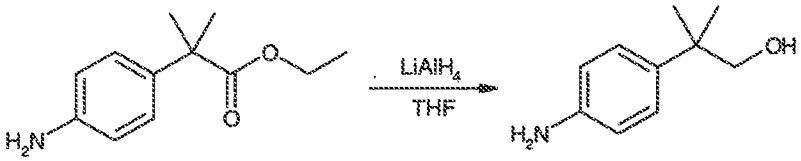
Sodium t-butoxide (466 mg, 4.85 mmol) was added to DMF (20 mL) at 0 °C. The cloudy solution was re-cooled to 5 °C. Ethyl 4-nitrophenylacetate (1.0 g, 4.78 mmol) was added. The purple slurry was cooled to 5 °C and methyl iodide (0.688 mL, 4.85 mmol) was added over 40 min. The mixture was stirred at 5-10 °C for 20 min, and then re-charged with sodium t-butoxide (466 mg, 4.85 mmol) and methyl iodide (0.699 mL, 4.85 mmol). The mixture was stirred at 5-10 °C for 20 min and a third charge of sodium t-butoxide (47 mg, 0.48 mmol) was added followed

by methyl iodide (0.057 mL, 0.9 mmol). Ethyl acetate (100 mL) and HCl (0.1 N, 50 mL) were added. The organic layer was separated, washed with brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated to provide ethyl 2-(4-nitrophenyl)-2-methylpropanoate (900 mg, 80 %), which was used without further purification.

[0683] G-1; Ethyl 2-(4-aminophenyl)-2-methylpropanoate

A solution of ethyl 2-(4-nitrophenyl)-2-methylpropanoate (900 mg, 3.8 mmol) in EtOH (10 mL) was treated with 10% Pd-C (80 mg) and heated to 45 °C. A solution of potassium formate (4.10 g, 48.8 mmol) in H_2O (11 mL) was added over a period of 15 min. The reaction mixture was stirred at 65 °C for 2 h and then treated with additional 300 mg of Pd/C. The reaction was stirred for 1.5 h and then filtered through Celite. The solvent volume was reduced by approximately 50 % under reduced pressure and extracted with EtOAc. The organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure to yield ethyl 2-(4-aminophenyl)-2-methylpropanoate (**G-1**) (670 mg, 85 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 8.5 Hz, 2H), 6.65 (d, J = 8.6 Hz, 2H), 4.10 (q, J = 7.1 Hz, 2H), 1.53 (s, 6H), 1.18 (t, J = 7.1 Hz, 3H).

[0684] Example 11:

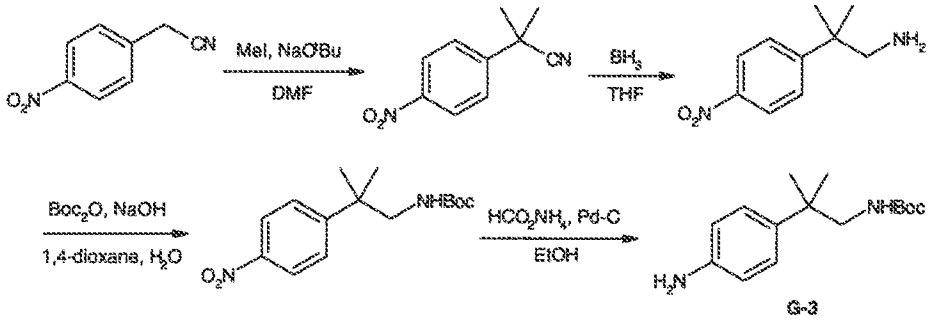


G-1 G-2

[0685] G-2; 2-(4-Aminophenyl)-2-methylpropan-1-ol

A solution of ethyl 2-(4-aminophenyl)-2-methylpropanoate (30 mg, 0.145 mmol) in THF (1 mL) was treated with $LiAlH_4$ (1M solution in THF, 0.226 mL, 0.226 mmol) at 0 °C and stirred for 15 min. The reaction was treated with 0.1N NaOH, extracted with EtOAc and the organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure to yield 2-(4-aminophenyl)-2-methylpropan-1-ol (**G-2**), which was used withoutfurther purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 8.5 Hz, 2H), 6.67 (d, J = 8.5 Hz, 2H), 3.53 (s, 2H), 1.28 (s, 6H).

[0686] Example 12:



[0687] 2-methyl-2-(4-nitrophenyl)propanenitrile

A suspension of sodium *tert*-butoxide (662 mg, 6.47 mmol) in DMF (20 mL) at 0 °C was treated with 4-nitrophenylacetonitrile (1000 mg, 6.18 mmol) and stirred for 10 min. Methyl iodide (400 µL, 6.47 mmol) was added dropwise over 15 min. The solution was stirred at 0-10 °C for 15 min and then at room temperature for additional 15 min. To this purple solution was added sodium *tert*-butoxide (662 mg, 6.47 mmol) and the solution was stirred for 15 min. Methyl iodide (400 µL, 6.47 mmol) was added dropwise over 15 min and the solution was stirred overnight. Sodium *tert*-butoxide (192 mg, 1.94 mmol) was added and the reaction was stirred at 0 °C for 10 minutes. Methyl iodide (186 µL, 2.98 mmol) was added and the reaction was stirred for 1h. The reaction mixture was then partitioned between 1N HCl (50 mL) and EtOAc (75 mL). The organic layer was washed with 1 N HCl and brine, dried over Na_2SO_4 and concentrated to yield 2-methyl-2-(4-nitrophenyl)propanenitrile as a green waxy solid (1.25 g, 99 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 8.9 Hz, 2H), 7.66 (d, J = 8.9 Hz, 2H), 1.77 (s, 6H).

[0688] 2-Methyl-2-(4-nitrophenyl)propan-1-amine

To a cooled solution of 2-methyl-2-(4-nitrophenyl)propanenitrile (670 mg, 3.5 mmol) in THF (15 mL) was added BH_3 (1M in THF, 14 mL, 14 mmol) dropwise at 0 °C. The mixture was warmed to room temperature and heated at 70 °C for 2 h. 1N HCl solution (2 mL) was added, followed by the addition of NaOH until pH > 7. The mixture was extracted with ether and ether extract was concentrated to give 2-methyl-2-(4-nitrophenyl)propan-1-amine (610 mg, 90 %), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 9.0 Hz, 2H), 2.89 (s, 2H), 1.38 (s, 6H).

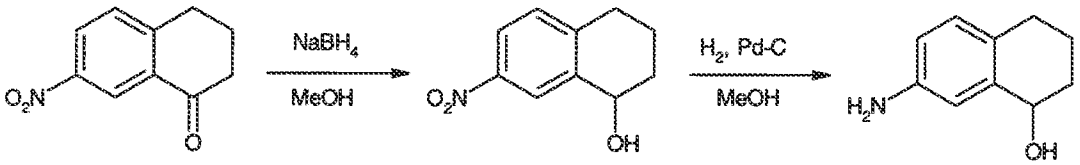
[0689] *tert*-Butyl 2-methyl-2-(4-nitrophenyl)propylcarbamate

To a cooled solution of 2-methyl-2-(4-nitrophenyl)propan-1-amine (600 mg, 3.1 mmol) and 1N NaOH (3 mL, 3 mmol) in 1,4-dioxane (6 mL) and water (3 mL) was added Boc_2O (742 mg, 3.4 mmol) at 0 °C. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was made acidic with 5% $KHSO_4$ solution and then extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated to give tert-butyl 2-methyl-2-(4-nitrophenyl)propylcarbamate (725 mg, 80 %), which was used without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.9 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 3.63 (s, 2H), 1.31-1.29 (m, 15H).

[0690] G-3; *tert*-Butyl 2-methyl-2-(4-aminophenyl)propylcarbamate

To a refluxing solution of tert-butyl 2-methyl-2-(4-nitrophenyl)propylcarbamate (725 mg, 2.5 mmol) and ammonium formate (700 mg, 10.9 mmol) in EtOH (25 mL) was added Pd-5%wt on carbon (400 mg). The mixture was refluxed for 1 h, cooled and filtered through Celite. The filtrate was concentrated to give tert-butyl 2-methyl-2-(4-aminophenyl)propylcarbamate (G-3) (550 mg, 83 %), which was used without further purification. ^1H NMR (400 MHz, DMSO-d_6) δ 6.99 (d, J = 8.5 Hz, 2H), 6.49 (d, J = 8.6 Hz, 2H), 4.85 (s, 2H), 3.01 (d, J = 6.3 Hz, 2H), 1.36 (s, 9H), 1.12 (s, 6H); HPLC ret. time 2.02 min, 10-99 % CH_3CN, 5 min run; ESI-MS 265.2 m/z (MH^+).

[0691] Example 13:



H-1

[0692] 7-Nitro-1,2,3,4-tetrahydro-naphthalen-1-ol

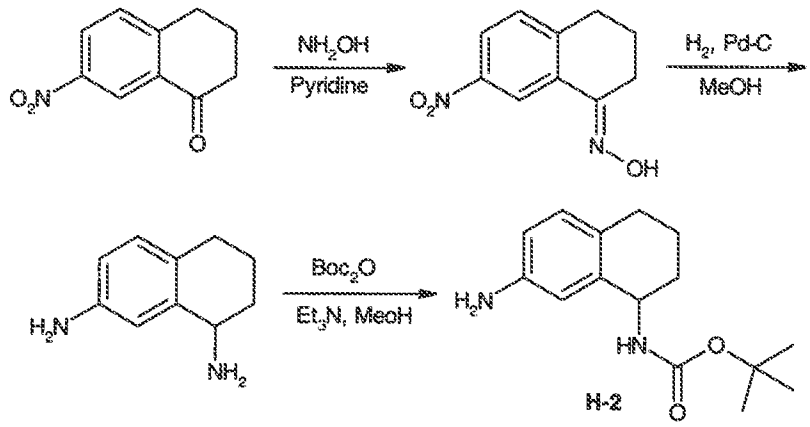
7-Nitro-3,4-dihydro-2H-naphthalen-1-one (200 mg, 1.05 mmol) was dissolved in methanol (5 mL) and $NaBH_4$ ((78 mg, 2.05 mmol) was added in portions. The reaction was stirred at room temperature for 20 min and then concentrated and purified by column chromatography (10–50 % ethyl acetate - hexanes) to yield 7-nitro-1,2,3,4-tetrahydro-naphthalen-1-ol (163 mg, 80 %). ^1H NMR (400 MHz, CD_3CN) δ 8.30 (d, J = 2.3 Hz, 1H), 8.02 (dd, J = 8.5, 2.5 Hz, 1H), 7.33 (d,

J = 8.5 Hz, 1H), 4.76 (t, J = 5.5 Hz, 1H), 2.96-2.80 (m, 2H), 2.10-1.99 (m, 2H), 1.86-1.77 (m, 2H); HPLC ret. time 2.32 min, 10-99 % CH_3CN, 5 min run.

[0693] H-1; 7-Amino-1,2,3,4-tetrahydro-naphthalen-1-ol

7-nitro-1,2,3,4-tetrahydro-naphthalen-1-ol (142 mg, 0.73 mmol) was dissolved in methanol (10 mL) and the flask was flushed with N_2 (g). 10% Pd-C (10 mg) was added and the reaction was stirred under H_2 (1 atm) at room temperature overnight. The reaction was filtered and the filtrate concentrated to yield 7-amino-1,2,3,4-tetrahydro-naphthalen-1-ol **(H-1)** (113 mg, 95 %). HPLC ret. time 0.58 min, 10-99 % CH_3CN, 5 min run; ESI-MS 164.5 m/z (MH^+).

[0694] Example14:



[0695] 7-Nitro-3,4-dihydro-2H-naphthalen-1-one oxime

To a solution of 7-nitro-3,4-dihydro-2H-naphthalen-1-one (500 mg, 2.62 mmol) in pyridine (2 mL) was added hydroxylamine solution (1 mL, ~50% solution in water). The reaction was stirred at room temperature for 1 h, then concentrated and purified by column chromatography (10-50 % ethyl acetate - hexanes) to yield 7-nitro-3,4-dihydro-2H-naphthalen-1-one oxime (471 mg, 88 %). HPLC ret. time 2.67 min, 10-99 % CH_3CN, 5 min run; ESI-MS 207.1 m/z (MH^+).

[0696] 1,2,3,4-Tetrahydro-naphthalene-1,7-diamine

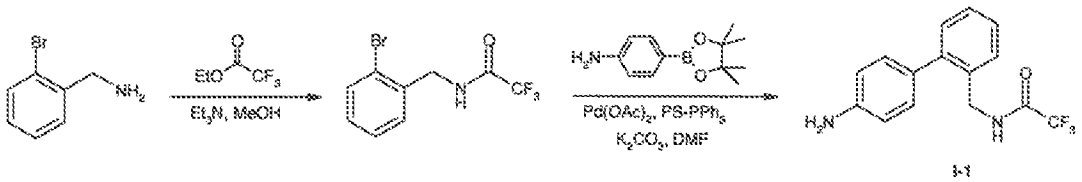
7-Nitro-3,4-dihydro-2H-naphthalen-1-one oxime (274 mg, 1.33 mmol) was dissolved in methanol (10 mL) and the flask was flushed with N_2 (g). 10 % Pd-C (50 mg) was added and the reaction was stirred under H_2 (1 atm) at room temperature overnight. The reaction was filtered and the filtrate was concentrated to yield 1,2,3,4-tetrahydro-naphthalene-1,7-diamine (207 mg,

96 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.61-6.57 (m, 2H), 6.28 (dd, J = 8.0, 2.4 Hz, 1H), 4.62 (s, 2H), 3.58 (m, 1H), 2.48-2.44 (m, 2H), 1.78-1.70 (m, 2H), 1.53-1.37 (m, 2H).

[0697] H-2; (7-Amino-1,2,3,4-tetrahydro-naphthalen-1-yl)-carbamic acid *tert*-butyl ester

To a solution of 1,2,3,4-tetrahydro-naphthalene-1,7-diamine (154 mg, 0.95 mmol) and triethylamine (139 µL, 1.0 mmol) in methanol (2 mL) cooled to 0 °C was added di-*tert*-butyl dicarbonate (207 mg, 0.95 mmol). The reaction was stirred at 0 °C and then concentrated and purified by column chromatography (5–50 % methanol - dichloromethane) to yield (7-amino-1,2,3,4-tetrahydro-naphthalen-1-yl)-carbamic acid tert-butyl ester (**H-2**) (327 mg, quant.). HPLC ret. time 1.95 min, 10-99 % CH_3CN, 5 min run; ESI-MS 263.1 m/z (MH^+).

[0698] Example 15:



I-1

[0699] N-(2-Bromo-benzyl)-2,2,2-trifluoro-acetamide

To a solution of 2-bromobenzylamine (1.3 mL, 10.8 mmol) in methanol (5 mL) was added ethyl trifluoroacetate (1.54 mL, 21.6 mmol) and triethylamine (1.4 mL, 10.8 mmol) under a nitrogen atmosphere. The reaction was stirred at room temperature for 1 h. The reaction mixture was then concentrated under vacuum to yield N-(2-bromo-benzyl)-2,2,2-trifluoro-acetamide (3.15g, quant.). HPLC ret. time 2.86 min, 10-99 % CH_3CN, 5 min run; ESI-MS 283.9 m/z (MH^+).

[0700] I-1; N-(4'-Amino-biphenyl-2-ylmethyl)-2,2,2-trifluoro-acetamide

A mixture of N-(2-bromo-benzyl)-2,2,2-trifluoro-acetamide (282 mg, 1.0 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (284 mg, 1.3 mmol), $Pd(OAc)_2$ (20 mg, 0.09 mmol) and PS-PPh_3 (40 mg, 3 mmol / g, 0.12 mmol) was dissolved in DMF (5 mL) and 4M K_2CO_3 solution (0.5 mL) was added. The reaction was heated at 80 °C overnight. The mixture was filtered, concentrated and purified by column chromatography (0–50 % ethyl acetate - hexanes) to yield N-(4'-amino-biphenyl-2-ylmethyl)-2,2,2-trifluoro-acetamide (**I-1**) (143 mg, 49 %). HPLC ret. time 1.90 min, 10-99 % CH_3CN, 5 min run; ESI-MS 295.5 m/z (MH^+).

[0701] Commercially available amines

Amine	Name
J-1	2-methoxy-5-methylbenzenamine
J-2	2,6-diisopropylbenzenamine
J-3	pyridin-2-amine
J-4	4-pentylbenzenamine
J-5	isoquinolin-3-amine
J-6	aniline
J-7	4-phenoxybenzenamine
J-8	2-(2,3-dimethylphenoxy)pyridin-3-amine
J-9	4-ethynylbenzenamine
J-10	2-sec-butylbenzenamine
J-11	2-amino-4,5-dimethoxybenzonitrile
J-12	2-*tert*-butylbenzenamine
J-13	1-(7-amino-3,4-dihydroisoquinolin-2(1H)-yl)ethanone
J-14	4-(4-methyl-4H-1,2,4-triazol-3-yl)benzenamine
J-15	2'-Aminomethyl-biphenyl-4-ylamine
J-16	1H-Indazol-6-ylamine
J-17	2-(2-methoxyphenoxy)-5-(trifluoromethyl)benzenamine
J-18	2-*tert*-butylbenzenamine
J-19	2,4,6-trimethylbenzenamine
J-20	5,6-dimethyl-1H-benzo[d]imidazol-2-amine
J-21	2,3-dihydro-1H-inden-4-amine
J-22	2-sec-butyl-6-ethylbenzenamine
J-23	quinolin-5-amine
J-24	4-(benzyloxy)benzenamine
J-25	2'-Methoxy-biphenyl-2-ylamine
J-26	benzo[c][1,2,5]thiadiazol-4-amine
J-27	3-benzylbenzenamine
J-28	4-isopropylbenzenamine

J-29	2-(phenylsulfonyl)benzenamine
J-30	2-methoxybenzenamine
J-31	4-amino-3-ethylbenzonitrile
J-32	4-methylpyridin-2-amine
J-33	4-chlorobenzenamine
J-34	2-(benzyloxy)benzenamine
J-35	2-amino-6-chlorobenzonitrile
J-36	3-methylpyridin-2-amine
J-37	4-aminobenzonitrile
J-38	3-chloro-2,6-diethylbenzenamine
J-39	3-phenoxybenzenamine
J-40	2-benzylbenzenamine
J-41	2-(2-fluorophenoxy)pyridin-3-amine
J-42	5-chloropyridin-2-amine
J-43	2-(trifluoromethyl)benzenamine
J-44	(4-(2-aminophenyl)piperazin-1-yl)(phenyl)methanone
J-45	1H-benzo[d][1,2,3]triazol-5-amine
J-46	2-(1H-indol-2-yl)benzenamine
J-47	4-Methyl-biphenyl-3-ylamine
J-48	pyridin-3-amine
J-49	3,4-dimethoxybenzenamine
J-50	3H-benzo[d]imidazol-5-amine
J-51	3-aminobenzonitrile
J-52	6-chloropyridin-3-amine
J-53	o-toluidine
J-54	1H-indol-5-amine
J-55	[1,2,4]triazolo[1,5-a]pyridin-8-amine
J-56	2-methoxypyridin-3-amine
J-57	2-butoxybenzenamine
J-58	2,6-dimethylbenzenamine
J-59	2-(methylthio)benzenamine
J-60	2-(5-methylfuran-2-yl)benzenamine
J-61	3-(4-aminophenyl)-3-ethylpiperidine-2,6-dione

J-62	2,4-dimethylbenzenamine
J-63	5-fluoropyridin-2-amine
J-64	4-cyclohexylbenzenamine
J-65	4-Amino-benzenesulfonamide
J-66	2-ethylbenzenamine
J-67	4-fluoro-3-methylbenzenamine
J-68	2,6-dimethoxypyridin-3-amine
J-69	4-*tert*-butylbenzenamine
J-70	4-sec-butylbenzenamine
J-71	5,6,7,8-tetrahydronaphthalen-2-amine
J-72	3-(Pyrrolidine-1-sulfonyl)-phenylamine
J-73	4-Adamantan-1-yl-phenylamine
J-74	3-amino-5,6,7,8-tetrahydronaphthalen-2-ol
J-75	benzo[d][1,3]dioxol-5-amine
J-76	5-chloro-2-phenoxybenzenamine
J-77	N1-tosylbenzene-1,2-diamine
J-78	3,4-dimethylbenzenamine
J-79	2-(trifluoromethylthio)benzenamine
J-80	1H-indol-7-amine
J-81	3-methoxybenzenamine
J-82	quinolin-8-amine
J-83	2-(2,4-difluorophenoxy)pyridin-3-amine
J-84	2-(4-aminophenyl)acetonitrile
J-85	2,6-dichlorobenzenamine
J-86	2,3-dihydrobenzofuran-5-amine
J-87	p-toluidine
J-88	2-methylquinolin-8-amine
J-89	2-*tert*-butylbenzenamine
J-90	3-chlorobenzenamine
J-91	4-*tert*-butyl-2-chlorobenzenamine
J-92	2-Amino-benzenesulfonamide
J-93	1-(2-aminophenyl)ethanone
J-94	m-toluidine

J-95	2-(3-chloro-5-(trifluoromethyl)pyridin-2-yloxy)benzenamine
J-96	2-amino-6-methylbenzonitrile
J-97	2-(prop-1-en-2-yl)benzenamine
J-98	4-Amino-N-pyridin-2-yl-benzenesulfonamide
J-99	2-ethoxybenzenamine
J-100	naphthalen-1-amine
J-101	Biphenyl-2-ylamine
J-102	2-(trifluoromethyl)-4-isopropylbenzenamine
J-103	2,6-diethylbenzenamine
J-104	5-(trifluoromethyl)pyridin-2-amine
J-105	2-aminobenzamide
J-106	3-(trifluoromethoxy)benzenamine
J-107	3,5-bis(trifluoromethyl)benzenamine
J-108	4-vinylbenzenamine
J-109	4-(trifluoromethyl)benzenamine
J-110	2-morpholinobenzenamine
J-111	5-amino-1H-benzo[d]imidazol-2(3H)-one
J-112	quinolin-2-amine
J-113	3-methyl-1H-indol-4-amine
J-114	pyrazin-2-amine
J-115	1-(3-aminophenyl)ethanone
J-116	2-ethyl-6-isopropylbenzenamine
J-117	2-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)benzenamine
J-118	N-(4-amino-2,5-diethoxyphenyl)benzamide
J-119	5,6,7,8-tetrahydronaphthalen-1-amine
J-120	2-(1H-benzo[d]imidazol-2-yl)benzenamine
J-121	1,1-Dioxo-1H-1lambda*6*-benzo[b]thiophen-6-ylamine
J-122	2,5-diethoxybenzenamine
J-123	2-isopropyl-6-methylbenzenamine
J-124	tert-butyl 5-amino-3,4-dihydroisoquinoline-2(1H)-carboxylate
J-125	2-(2-aminophenyl)ethanol
J-126	(4-aminophenyl)methanol
J-127	5-methylpyridin-2-amine

J-128	2-(pyrrolidin-1-yl)benzenamine
J-129	4-propylbenzenamine
J-130	3,4-dichlorobenzenamine
J-131	2-phenoxybenzenamine
J-132	Biphenyl-2-ylamine
J-133	2-chlorobenzenamine
J-134	2-amino-4-methylbenzonitrile
J-135	(2-aminophenyl)(phenyl)methanone
J-136	aniline
J-137	3-(trifluoromethylthio)benzenamine
J-138	2-(2,5-dimethyl-1H-pyrrol-1-yl)benzenamine
J-139	4-(Morpholine-4-sulfonyl)-phenylamine
J-140	2-methylbenzo[d]thiazol-5-amine
J-141	2-amino-3,5-dichlorobenzonitrile
J-142	2-fluoro-4-methylbenzenamine
J-143	6-ethylpyridin-2-amine
J-144	2-(1H-pyrrol-1-yl)benzenamine
J-145	2-methyl-1H-indol-5-amine
J-146	quinolin-6-amine
J-147	1H-benzo[d]imidazol-2-amine
J-148	2-o-tolylbenzo[d]oxazol-5-amine
J-149	5-phenylpyridin-2-amine
J-150	Biphenyl-2-ylamine
J-151	4-(difluoromethoxy)benzenamine
J-152	5-*tert*-butyl-2-methoxybenzenamine
J-153	2-(2-*tert*-butylphenoxy)benzenamine
J-154	3-aminobenzamide
J-155	4-morpholinobenzenamine
J-156	6-aminobenzo[d]oxazol-2(3H)-one
J-157	2-phenyl-3H-benzo[d]imidazol-5-amine
J-158	2,5-dichloropyridin-3-amine
J-159	2,5-dimethylbenzenamine
J-160	4-(phenylthio)benzenamine

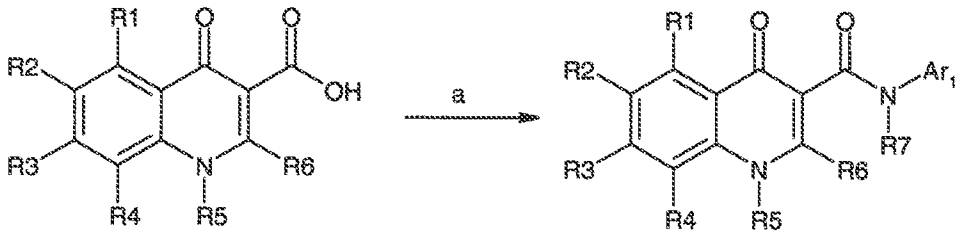
J-161	9H-fluoren-1-amine
J-162	2-(4-aminophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol
J-163	4-bromo-2-ethylbenzenamine
J-164	4-methoxybenzenamine
J-165	3-(Piperidine-1-sulfonyl)-phenylamine
J-166	quinoxalin-6-amine
J-167	6-(trifluoromethyl)pyridin-3-amine
J-168	3-(trifluoromethyl)-2-methylbenzenamine
J-169	(2-aminophenyl)(phenyl)methanol
J-170	aniline
J-171	6-methoxypyridin-3-amine
J-172	4-butylbenzenamine
J-173	3-(Morpholine-4-sulfonyl)-phenylamine
J-174	2,3-dimethylbenzenamine
J-175	aniline
J-176	Biphenyl-2-ylamine
J-177	2-(2,4-dichlorophenoxy)benzenamine
J-178	pyridin-4-amine
J-179	2-(4-methoxyphenoxy)-5-(trifluoromethyl)benzenamine
J-180	6-methylpyridin-2-amine
J-181	5-chloro-2-fluorobenzenamine
J-182	1H-indol-4-amine
J-183	6-morpholinopyridin-3-amine
J-184	aniline
J-185	1H-indazol-5-amine
J-186	2-[(Cyclohexyl-methyl-amino)-methyl]-phenylamine
J-187	2-phenylbenzo[d]oxazol-5-amine
J-188	naphthalen-2-amine
J-189	2-aminobenzonitrile
J-190	N1,N1-diethyl-3-methylbenzene-1,4-diamine
J-191	aniline
J-192	2-butylbenzenamine
J-193	1-(4-aminophenyl)ethanol

J-194	2-amino-4-methylbenzamide
J-195	quinolin-3-amine
J-196	2-(piperidin-1-yl)benzenamine
J-197	3-Amino-benzenesulfonamide
J-198	2-ethyl-6-methylbenzenamine
J-199	Biphenyl-4-ylamine
J-200	2-(o-tolyloxy)benzenamine
J-201	5-amino-3-methylbenzo[d]oxazol-2(3H)-one
J-202	4-ethylbenzenamine
J-203	2-isopropylbenzenamine
J-204	3-(trifluoromethyl)benzenamine
J-205	2-amino-6-fluorobenzonitrile
J-206	2-(2-aminophenyl)acetonitrile
J-207	2-(4-fluorophenoxy)pyridin-3-amine
J-208	aniline
J-209	2-(4-methylpiperidin-1-yl)benzenamine
J-210	4-fluorobenzenamine
J-211	2-propylbenzenamine
J-212	4-(trifluoromethoxy)benzenamine
J-213	3-aminophenol
J-214	2,2-difluorobenzo[d][1,3]dioxol-5-amine
J-215	2,2,3,3-tetrafluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-amine
J-216	N-(3-aminophenyl)acetamide
J-217	1-(3-aminophenyl)-3-methyl-1H-pyrazol-5(4H)-one
J-218	5-(trifluoromethyl)benzene-1,3-diamine
J-219	5-*tert*-butyl-2-methoxybenzene-1,3-diamine
J-220	N-(3-amino-4-ethoxyphenyl)acetamide
J-221	N-(3-Amino-phenyl)-methanesulfonamide
J-222	N-(3-aminophenyl)propionamide
J-223	N1,N1-dimethylbenzene-1,3-diamine
J-224	N-(3-amino-4-methoxyphenyl)acetamide
J-225	benzene-1,3-diamine
J-226	4-methylbenzene-1,3-diamine

J-227	1H-indol-6-amine
J-228	6,7,8,9-tetrahydro-5H-carbazol-2-amine
J-229	1H-indol-6-amine
J-230	1H-indol-6-amine
J-231	1H-indol-6-amine
J-232	1H-indol-6-amine
J-233	1H-indol-6-amine
J-234	1H-indol-6-amine
J-235	1H-indol-6-amine
J-236	1H-indol-6-amine
J-237	1H-indol-6-amine
J-238	1H-indol-6-amine
J-239	1-(6-Amino-2,3-dihydro-indol-1-yl)-ethanone
J-240	5-Chloro-benzene-1,3-diamine

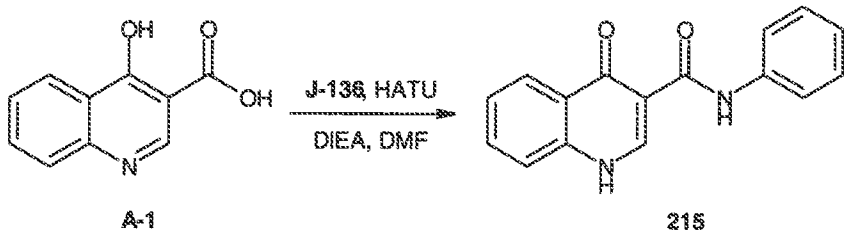
[0702] Amides (Compounds of formula I)

[0703] General scheme:



a) Ar_1R7NH, coupling reagent, base, solvent. Examples of conditions used:
HATU, DIEA, DMF; BOP, DIEA, DMF; HBTU, Et_3N, CH_2Cl_2; PFP-TFA, pyridine

[0704] Specific example:



A-1 215

[0705] 215; 4-Oxo-N-phenyl-1H-quinoline-3-carboxamide

To a solution of 4-hydroxy-quinoline-3-carboxylic acid (**A-1**) (19 mg, 0.1 mmol), HATU (38 mg, 0.1mmol) and DIEA (34.9 µL, 0.2mmol) in DMF (1 mL) was added aniline (18.2 µL, 0.2 mmol) and the reaction mixture was stirred at room temperature for 3 h. The resulting solution was filtered and purified by HPLC (10-99 % CH_3CN / H_2O) to yield 4-oxo-N-phenyl-1H-quinoline-3-carboxamide (**215**) (12 mg, 45 %). ^1H NMR (400 MHz, DMSO-d_6) δ 12.97 (s, 1H), 12.50 (s, 1H), 8.89 (s, 1H), 8.34 (dd, J = 8.1, 1.1 Hz, 1H), 7.83 (t, J = 8.3 Hz, 1H), 7.75 (m, 3H), 7.55 (t, J = 8.1 Hz, 1H), 7.37 (t, J = 7.9 Hz, 2H), 7.10 (t, J = 6.8 Hz, 1H); HPLC ret. time 3.02 min, 10-99 % CH_3CN, 5 min run; ESI-MS 265.1 m/z (MH^+).

[0706] The table below lists other examples synthesized by the general scheme above.

Compound of formula I	Acid	Amine
2	A-1	C-2
3	A-1	J-17
4	A-1	J-110
5	A-1	G-2
6	A-1	E-8
7	A-1	J-118
8	A-1	D-7
9	A-1	J-197
11	A-1	F-7
12	A-1	F-6
13	A-1	E-2
15	A-1	J-56
16	A-1	J-211
18	A-1	J-161
19	A-1	J-112
20	A-1	J-200
21	A-1	J-98
23	A-1	C-15
24	A-1	J-72
25	A-1	F-57
26	A-1	J-196
29	A-21	J-208
31	A-1	J-87
32	A-1	B-21

33	A-1	J-227
34	A-1	C-19
36	A-1	J-203
37	A-1	J-80
38	A-1	J-46
39	A-17	D-10
40	A-1	J-125
42	A-1	J-95
43	A-1	C-16
44	A-1	J-140
45	A-1	J-205
47	A-1	J-102
48	A-1	J-181
49	A-1	F-25
50	A-1	J-19
51	A-7	B-24
52	A-1	F-2
53	A-1	J-178
54	A-1	J-26
55	A-1	J-219
56	A-1	J-74
57	A-1	J-61
58	A-1	D-4
59	A-1	F-35
60	A-1	D-11
61	A-1	J-174
62	A-1	J-106
63	A-1	F-47
64	A-1	J-111
66	A-1	J-214
67	A-10	J-236
68	A-1	F-55
69	A-1	D-8
70	A-1	F-11
71	A-1	F-61
72	A-1	J-66
73	A-1	J-157
74	A-1	J-104
75	A-1	J-195

76	A-1	F-46
77	A-1	B-20
78	A-1	J-92
79	A-1	F-41
80	A-1	J-30
81	A-1	J-222
82	A-1	J-190
83	A-1	F-40
84	A-1	J-32
85	A-1	F-53
86	A-1	J-15
87	A-1	J-39
88	A-1	G-3
89	A-1	J-134
90	A-1	J-18
91	A-1	J-38
92	A-1	C-13
93	A-1	F-68
95	A-1	J-189
96	A-1	B-9
97	A-1	F-34
99	A-1	J-4
100	A-1	J-182
102	A-1	J-117
103	A-2	C-9
104	A-1	B-4
106	A-1	J-11
107	A-1	DC-6
108	A-1	DC-3
109	A-1	DC-4
110	A-1	J-84
111	A-1	J-43
112	A-11	J-235
113	A-1	B-7
114	A-1	D-18
115	A-1	F-62
116	A-3	J-229
118	A-1	F-12
120	A-1	J-1

121	A-1	J-130
122	A-1	J-49
123	A-1	F-68
124	A-2	B-24
125	A-1	J-143
126	A-1	C-25
128	A-22	J-176
130	A-14	J-233
131	A-1	J-240
132	A-1	J-220
134	A-1	F-58
135	A-1	F-19
136	A-1	C-8
137	A-6	C-9
138	A-1	F-44
139	A-1	F-59
140	A-1	J-64
142	A-1	J-10
143	A-1	C-7
144	A-1	J-213
145	A-1	B-18
146	A-1	J-55
147	A-1	J-207
150	A-1	J-162
151	A-1	F-67
152	A-1	J-156
153	A-1	C-23
154	A-1	J-107
155	A-1	J-3
156	A-1	F-36
160	A-1	D-6
161	A-1	C-3
162	A-1	J-171
164	A-1	J-204
165	A-1	J-65
166	A-1	F-54
167	A-1	J-226
168	A-1	J-48
169	A-1	B-1

170	A-1	J-42
171	A-1	F-52
172	A-1	F-64
173	A-1	J-180
174	A-1	F-63
175	A-1	DC-2
176	A-1	J-212
177	A-1	J-57
178	A-1	J-153
179	A-1	J-154
180	A-1	J-198
181	A-1	F-1
182	A-1	F-37
183	A-1	DC-1
184	A-15	J-231
185	A-1	J-173
186	A-1	B-15
187	A-1	B-3
188	A-1	B-25
189	A-1	J-24
190	A-1	F-49
191	A-1	J-23
192	A-1	J-36
193	A-1	J-68
194	A-1	J-37
195	A-1	J-127
197	A-1	J-167
198	A-1	J-210
199	A-1	F-3
200	A-1	H-1
201	A-1	J-96
202	A-1	F-28
203	A-1	B-2
204	A-1	C-5
205	A-1	J-179
206	A-1	J-8
207	A-1	B-17
208	A-1	C-12
209	A-1	J-126

210	A-17	J-101
211	A-1	J-152
212	A-1	J-217
213	A-1	F-51
214	A-1	J-221
215	A-1	J-136
216	A-1	J-147
217	A-1	J-185
218	A-2	C-13
219	A-1	J-114
220	A-1	C-26
222	A-1	J-35
223	A-1	F-23
224	A-1	I-1
226	A-1	J-129
227	A-1	J-120
228	A-1	J-169
229	A-1	J-59
230	A-1	J-145
231	A-1	C-17
233	A-1	J-239
234	A-1	B-22
235	A-1	E-9
236	A-1	J-109
240	A-1	J-34
241	A-1	J-82
242	A-1	D-2
244	A-1	J-228
245	A-1	J-177
246	A-1	J-78
247	A-1	F-33
250	A-1	J-224
252	A-1	J-135
253	A-1	F-30
254	A-2	B-20
255	A-8	C-9
256	A-1	J-45
257	A-1	J-67
259	A-1	B-14

261	A-1	F-13
262	A-1	DC-7
263	A-1	J-163
264	A-1	J-122
265	A-1	J-40
266	A-1	C-14
267	A-1	J-7
268	A-1	E-7
270	A-1	B-5
271	A-1	D-9
273	A-1	H-2
274	A-8	B-24
276	A-1	J-139
277	A-1	F-38
278	A-1	F-10
279	A-1	F-56
280	A-1	J-146
281	A-1	J-62
283	A-1	F-18
284	A-1	J-16
285	A-1	F-45
286	A-1	J-119
287	A-3	C-13
288	A-1	C-6
289	A-1	J-142
290	A-1	F-15
291	A-1	C-10
292	A-1	J-76
293	A-1	J-144
294	A-1	J-54
295	A-1	J-128
296	A-17	J-12
297	A-1	J-138
301	A-1	J-14
302	A-1	F-5
303	A-1	J-13
304	A-1	E-1
305	A-1	F-17
306	A-1	F-20

307	A-1	F-43
308	A-1	J-206
309	A-1	J-5
310	A-1	J-70
311	A-1	J-60
312	A-1	F-27
313	A-1	F-39
314	A-1	J-116
315	A-1	J-58
317	A-1	J-85
319	A-2	C-7
320	A-1	B-6
321	A-1	J-44
322	A-1	J-22
324	A-1	J-172
325	A-1	J-103
326	A-1	F-60
328	A-1	J-115
329	A-1	J-148
330	A-1	J-133
331	A-1	J-105
332	A-1	J-9
333	A-1	F-8
334	A-1	DC-5
335	A-1	J-194
336	A-1	J-192
337	A-1	C-24
338	A-1	J-113
339	A-1	B-8
344	A-1	F-22
345	A-2	J-234
346	A-12	J-6
348	A-1	F-21
349	A-1	J-29
350	A-1	J-100
351	A-1	B-23
352	A-1	B-10
353	A-1	D-10
354	A-1	J-186

355	A-1	J-25
357	A-1	B-13
358	A-24	J-232
360	A-1	J-151
361	A-1	F-26
362	A-1	J-91
363	A-1	F-32
364	A-1	J-88
365	A-1	J-93
366	A-1	F-16
367	A-1	F-50
368	A-1	D-5
369	A-1	J-141
370	A-1	J-90
371	A-1	J-79
372	A-1	J-209
373	A-1	J-21
374	A-16	J-238
375	A-1	J-71
376	A-1	J-187
377	A-5	J-237
378	A-1	D-3
380	A-1	J-99
381	A-1	B-24
383	A-1	B-12
384	A-1	F-48
385	A-1	J-83
387	A-1	J-168
388	A-1	F-29
389	A-1	J-27
391	A-1	F-9
392	A-1	J-52
394	A-22	J-170
395	A-1	C-20
397	A-1	J-199
398	A-1	J-77
400	A-1	J-183
401	A-1	F-4
402	A-1	J-149

403	A-1	C-22
405	A-1	J-33
406	A-6	B-24
407	A-3	C-7
408	A-1	J-81
410	A-1	F-31
411	A-13	J-191
412	A-1	B-19
413	A-1	J-131
414	A-1	J-50
417	A-1	F-65
418	A-1	J-223
419	A-1	J-216
420	A-1	G-1
421	A-1	C-18
422	A-1	J-20
423	A-1	B-16
424	A-1	F-42
425	A-1	J-28
426	A-1	C-11
427	A-1	J-124
428	A-1	C-1
429	A-1	J-218
430	A-1	J-123
431	A-1	J-225
432	A-1	F-14
433	A-1	C-9
434	A-1	J-159
435	A-1	J-41
436	A-1	F-24
437	A-1	J-75
438	A-1	E-10
439	A-1	J-164
440	A-1	J-215
441	A-1	D-19
442	A-1	J-165
443	A-1	J-166
444	A-1	E-6
445	A-1	J-97

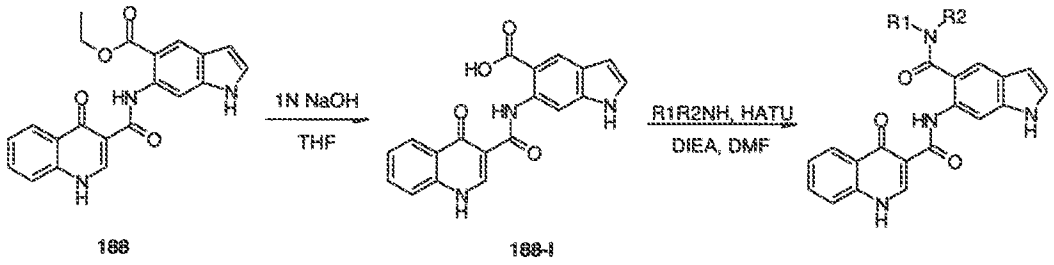
446	A-1	J-121
447	A-1	J-51
448	A-1	J-69
449	A-1	J-94
450	A-1	J-193
451	A-1	J-31
452	A-1	J-108
453	A-1	D-1
454	A-1	J-47
455	A-1	J-73
456	A-1	J-137
457	A-1	J-155
458	A-1	C-4
459	A-1	J-53
461	A-1	J-150
463	A-1	J-202
464	A-3	C-9
465	A-1	E-4
466	A-1	J-2
467	A-1	J-86
468	A-20	J-184
469	A-12	J-132
470	A-1	J-160
473	A-21	J-89
474	A-1	J-201
475	A-1	J-158
477	A-1	J-63
478	A-1	B-11
479	A-4	J-230
480	A-23	J-175
481	A-1	J-188
483	A-1	C-21
484	A-1	D-14
B-26-I	A-1	B-26
B-27-I	A-1	B-27
C-27-I	A-1	C-27
D-12-I	A-1	D-12
D-13-I	A-1	D-13
D-15-I	A-1	D-15

D-16-I	A-1	D-16
D-17-I	A-1	D-17
DC-10-I	A-1	DC-10
DC-8-I	A-1	DC-8
DC-9-I	A-1	DC-9

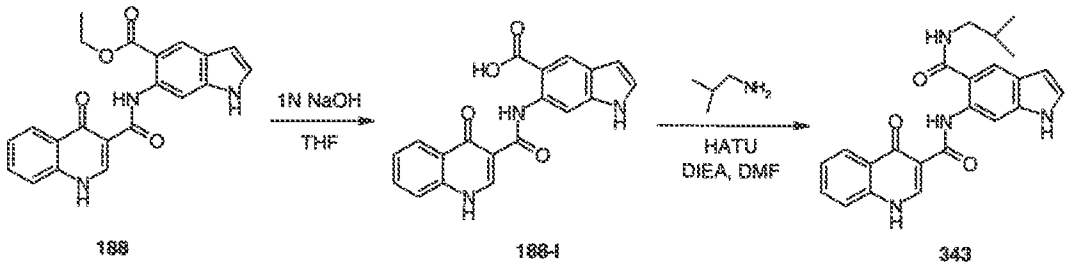
[0707] **Indoles**

[0708] **Example 1:**

[0709] General Scheme:



[0710] Specific example:



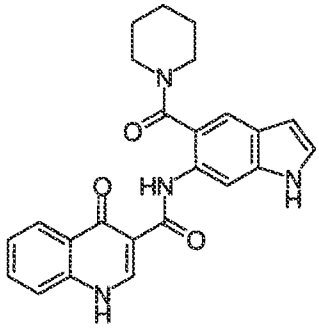
[0711] 188-I; 6-[(4-Oxo-1H-quinolin-3-yl)carbonylamino]-1H-indole-5-carboxylic acid

A mixture of 6-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-1H-indole-5-carboxylic acid ethyl ester (**188**) (450 mg, 1.2 mmol) and 1N NaOH solution (5 mL) in THF (10 mL) was heated at 85 °C overnight. The reaction mixture was partitioned between EtOAc and water. The aqueous layer was acidified with 1N HCl solution to pH 5, and the precipitate was filtered, washed with water and air dried to yield 6-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-1H-indole-5-carboxylic acid (**188-I**) (386 mg, 93 %). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.92-12.75 (m, 2H), 11.33 (s, 1H), 8.84 (s, 1H), 8.71 (s, 1H), 8.30 (dd, J = 8.1, 0.9 Hz, 1H), 8.22 (s, 1H), 7.80-7.72 (m, 2H), 7.49 (t, J = 8.0 Hz, 1H), 7.41 (t, J = 2.7 Hz, 1H), 6.51 (m, 1H); HPLC ret. time 2.95 min, 10-99 % CH_3CN, 5 min run; ESI-MS 376.2 m/z (MH^+).

[0712] 343; N-[5-(Isobutylcarbamoyl)-1H-indol-6-yl]-4-oxo-1H-quinoline-3-carboxamide

To a solution of 6-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-1H-indole-5-carboxylic acid (**188-I**) (26 mg, 0.08 mmol), HATU (38 mg, 0.1 mmol) and DIEA (35 µL, 0.2 mmol) in DMF (1 mL) was added isobutylamine (7 mg, 0.1 mmol) and the reaction mixture was stirred at 65 °C overnight. The resulting solution was filtered and purified by HPLC (10-99 % CH_3CN / H_2O) to yield the product, N-[5-(isobutylcarbamoyl)-1H-indol-6-yl]-4-oxo-1H-quinoline-3-carboxamide (**343**) (20 mg, 66 %). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.66 (d, J = 7.4 Hz, 1H), 12.42 (s, 1H), 11.21 (s, 1H), 8.81 (d, J = 6.6 Hz, 1H), 8.47 (s, 1H), 8.36 (t, J = 5.6 Hz, 1H), 8.30 (d, J = 8.4 Hz, 1H), 7.79 (t, J = 7.9 Hz, 1H), 7.72-7.71 (m, 2H), 7.51 (t, J = 7.2 Hz, 1H), 7.38 (m, 1H), 6.48 (m, 1H), 3.10 (t, J = 6.2 Hz, 2H), 1.88 (m, 1H), 0.92 (d, J = 6.7 Hz, 6H); HPLC ret. time 2.73 min, 10-99 % CH_3CN, 5 min run; ESI-MS 403.3 m/z (MH^+).

[0713] Another example:

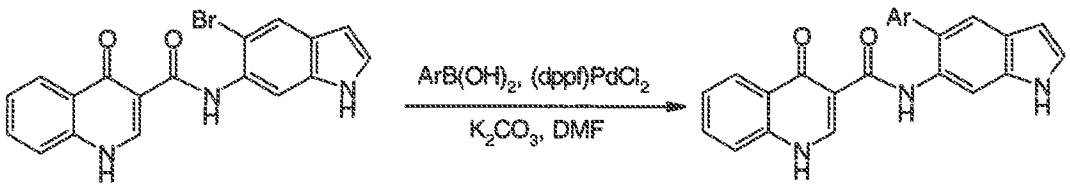


[0714] 148; 4-Oxo-N-[5-(1-piperidylcarbonyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide

4-Oxo-N-[5-(1-piperidylcarbonyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide (**148**) was synthesized following the general scheme above, coupling the acid (**188-I**) with piperidine. Overall yield (12 %). HPLC ret. time 2.79 min, 10-99 % CH_3CN, 5 min run; ESI-MS 415.5 m/z (MH^+).

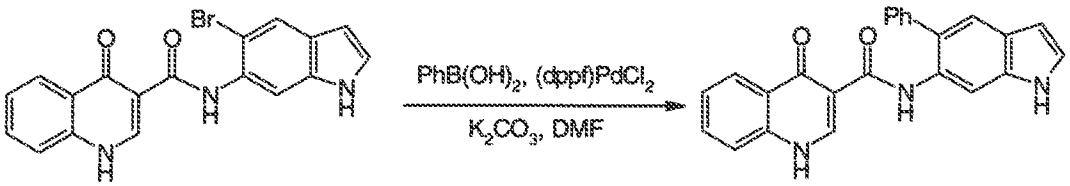
[0715] Example 2:

[0716] General scheme:



B-27-I

[0717] Specific example:



B-27-I **158**

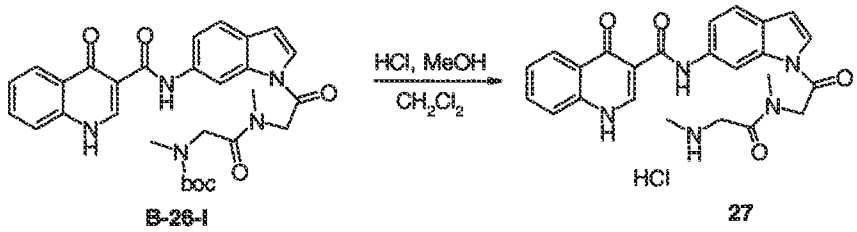
[0718] 158; 4-Oxo-N-(5-phenyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide

A mixture of N-(5-bromo-1H-indol-6-yl)-4-oxo-1H-quinoline-3-carboxamide (**B-27-I**) (38 mg, 0.1 mol), phenyl boronic acid (18 mg, 0.15 mmol), (dppf)$PdCl_2$ (cat.), and K_2CO_3 (100 µL, 2M solution) in DMF (1 mL) was heated in the microwave at 180 °C for 10 min. The reaction was filtered and purified by HPLC (10-99 % CH_3CN / H_2O) to yield the product, 4-oxo-N-(5-phenyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide (**158**) (5 mg, 13 %). HPLC ret. time 3.05 min, 10-99 % CH_3CN, 5 min run; ESI-MS 380.2 m/z (MH^+).

[0719] The table below lists other examples synthesized following the general scheme above.

Compound of formula I	Boronic acid
237	2-methoxyphenylboronic acid
327	2-ethoxyphenylboronic acid
404	2,6-dimethoxyphenylboronic acid
1	5-chloro-2-methoxy-phenylboronic acid
342	4-isopropylphenylboronic acid
347	4-(2-Dimethylaminoethylcarbamoyl)phenylboronic acid
65	3-pyridinylboronic acid

[0720] Example 3:



B-26-I 27

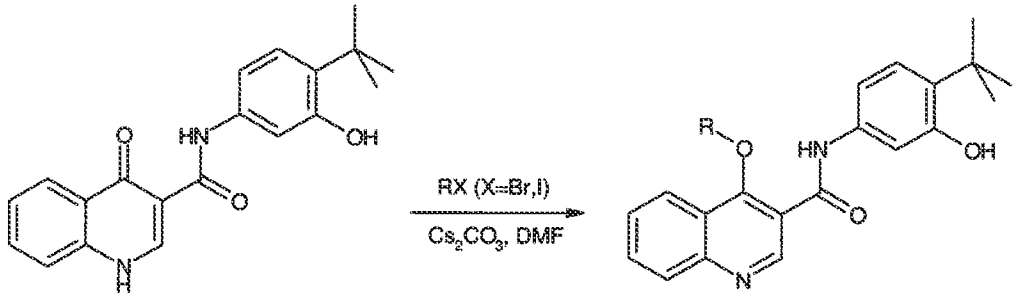
[0721] 27; N-{1-[2-[Methyl-(2-methylaminoacetyl)-amino]acetyl]-1H-indol-6-yl]-4-oxo-1H-quinoline-3-carboxamide

To a solution of methyl-{[methyl-(2-oxo-2-{6-[(4-oxo-1,4-dihydro-quinoline-3-carbonyl)-amino]-indol-1-yl}-ethyl)-carbamoyl]-methyl}-carbamic acid tert-butyl ester (**B-26-I**) (2.0 g, 3.7 mmol) dissolved in a mixture of CH_2Cl_2 (50 mL) and methanol (15 mL) was added HCl solution (60 mL, 1.25 M in methanol). The reaction was stirred at room temperature for 64 h. The precipitated product was collected via filtration, washed with diethyl ether and dried under high vacuum to provide the HCl salt of the product, N-[1-[2-[methyl-(2-methylaminoacetyl)-amino]acetyl]-1H-indol-6-yl]-4-oxo-1H-quinoline-3-carboxamide (**27**) as a greyish white solid (1.25 g, 70 %). ^{1}H-NMR (400 MHz, DMSO-d6) δ 13.20 (d, J = 6.7 Hz, 1H), 12.68 (s, 1H), 8.96-8.85 (m, 1H), 8.35 (d, J = 7.9 Hz, 1H), 7.91-7.77 (m, 3H), 7.64-7.54 (m, 3H), 6.82 (m, 1H), 5.05 (s, 0.7H), 4.96 (s, 1.3H), 4.25 (t, J = 5.6 Hz, 1.3H), 4.00 (t, J = 5.7 Hz, 0.7H), 3.14 (s, 2H), 3.02 (s, 1H), 2.62 (t, J = 5.2 Hz, 2H), 2.54 (t, J = 5.4 Hz, 1H); HPLC ret. time 2.36 min, 10-99 % CH_3CN, 5 min run; ESI-MS 446.5 m/z (MH^+).

[0722] Phenols

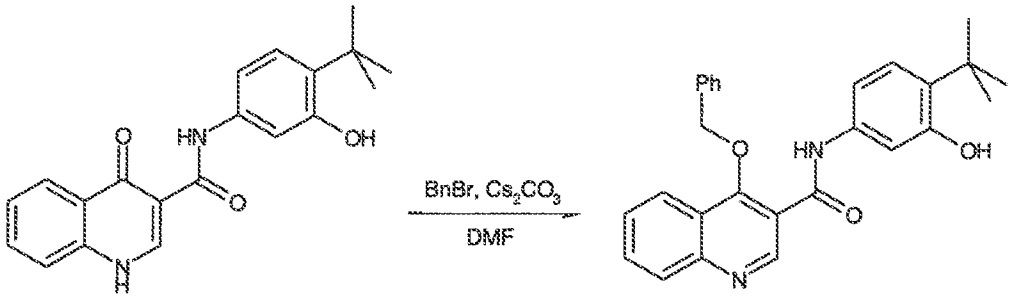
[0723] Example 1:

[0724] General scheme:



428

[0725] Specific example:

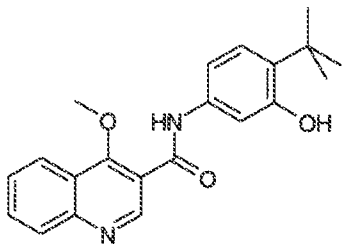


428 275

[0726] 275; 4-Benzyloxy-N-(3-hydroxy-4-*tert*-butyl-phenyl)-quinoline-3-carboxamide

To a mixture of N-(3-hydroxy-4-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide (**428**) (6.7 mg, 0.02 mmol) and Cs_2CO_3 (13 mg, 0.04 mmol) in DMF (0.2 mL) was added BnBr (10 uL, 0.08 mmol). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was filtered and purified using HPLC to give 4-benzyloxy-N-(3-hydroxy-4-*tert*-butyl-phenyl)-quinoline-3-carboxamide (**275**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 9.47 (s, 1H), 9.20 (s, 1H), 8.43 (d, J = 7.9 Hz, 1H), 7.79 (t, J = 2.0 Hz, 2H), 7.56 (m, 1H), 7.38-7.26 (m, 6H), 7.11 (d, J = 8.4 Hz, 1H), 6.99 (dd, J = 8.4, 2.1 Hz, 1H), 5.85 (s, 2H), 1.35 (s, 9H). HPLC ret. time 3.93 min, 10-99 % CH_3CN, 5 min run; ESI-MS 427.1 m/z (MH^+).

[0727] Another example:

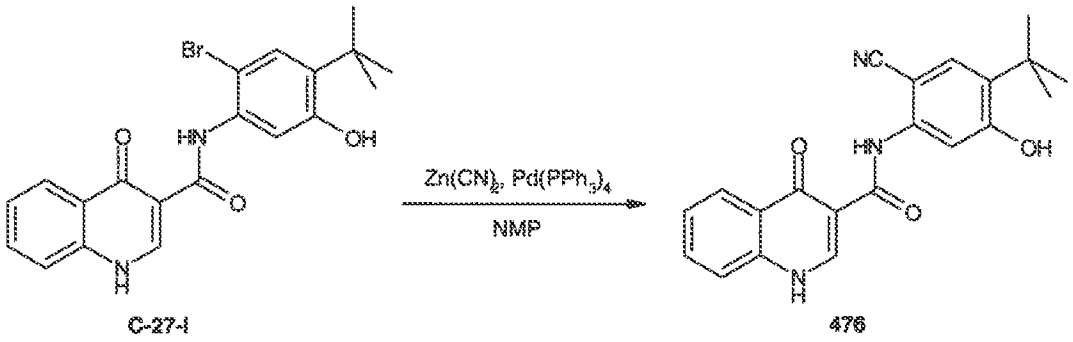


[0728] 415; N-(3-Hydroxy-4-*tert*-butyl-phenyl)-4-methoxy-quinoline-3-carboxamide

N-(3-Hydroxy-4-*tert*-butyl-phenyl)-4-methoxy-quinoline-3-carboxamide (**415**) was synthesized following the general scheme above reacting N-(3-hydroxy-4-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide (**428**) with methyl iodide. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.26 (s,

1H), 9.46 (s, 1H), 8.99 (s, 1H), 8.42 (t, J = 4.2 Hz, 1H), 7.95-7.88 (m, 2H), 7.61-7.69 (m, 1H), 7.38 (d, J = 2.1 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.96 (dd, J = 8.4, 2.1 Hz, 1H), 4.08 (s, 3H), 1.35 (s, 9H); HPLC ret. time 3.46 min, 10-99 % CH_3CN, 5 min run; ESI-MS 351.5 m/z (MH^+).

[0729] Example 2:



C-27-I 476

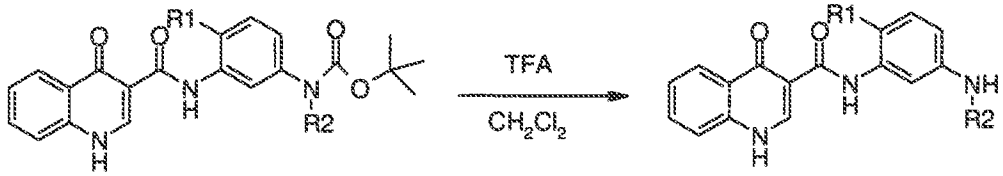
[0730] 476; N-(4-*tert*-Butyl-2-cyano-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide

To a suspension of N-(4-*tert*-butyl-2-bromo-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide (**C-27-I**) (84 mg, 0.2 mmol), $Zn(CN)_2$ (14 mg, 0.12 mmol) in NMP (1 mL) was added $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) under nitrogen. The mixture was heated in a microwave oven at 200 °C for 1 h, filtered and purified using prepative HPLC to give N-(4-*tert*-butyl-2-cyano-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide (**476**). ^1H NMR (400 MHz, DMSO-d_6) δ 13.00 (d, J =6.4 Hz, 1H), 12.91 (s, 1H), 10.72 (s, 1H), 8.89 (d, J =6.8Hz, 1H), 8.34 (d, J =8.2Hz, 1H), 8.16 (s, 1H), 7.85-7.75 (m, 2H), 7.56-7.54 (m, 1H), 7.44 (s, 1H), 1.35 (s, 9H); HPLC ret. time 3.42 min, 10-100 % CH_3CN, 5 min gradient; ESI-MS 362.1 m/z (MH^+).

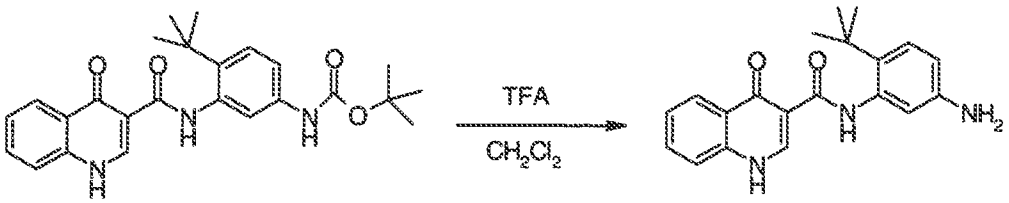
[0731] Anilines

[0732] Example 1:

[0733] General scheme:



[0734] Specific example:



353 260

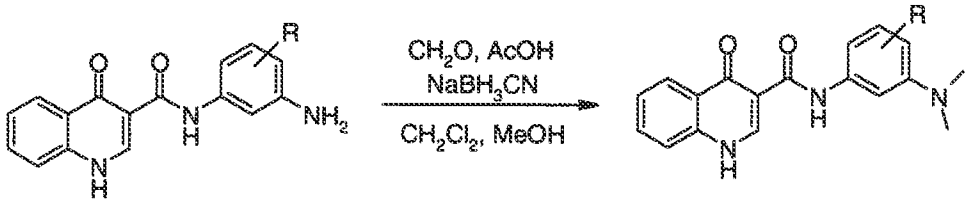
[0735] 260; N-(5-Amino-2-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide A mixture of [3-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-4-*tert*-butyl-phenyl]aminoformic acid tert-butyl ester (**353**) (33 mg, 0.08 mmol), TFA (1 mL) and CH_2Cl_2 (1 mL) was stirred at room temperature overnight. The solution was concentrated and the residue was dissolved in DMSO (1 mL) and purified by HPLC (10-99 % CH_3CN / H_2O) to yield the product, N-(5-amino-2-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide (**260**) (15 mg, 56 %). ^1H NMR (400 MHz, DMSO-d_6) δ 13.23 (d, J = 6.6 Hz, 1H), 12.20 (s, 1H), 10.22 (br s, 2H), 8.88 (d, J = 6.8 Hz, 1H), 8.34 (d, J = 7.8 Hz, 1H), 7.86-7.80 (m, 3H), 7.56-7.52 (m, 2H), 7.15 (dd, J = 8.5, 2.4 Hz, 1H), 1.46 (s, 9H); HPLC ret. time 2.33 min, 10-99 % CH_3CN, 5 min run; ESI-MS 336.3 m/z (MH^+).

[0736] The table below lists other examples synthesized following the general scheme above.

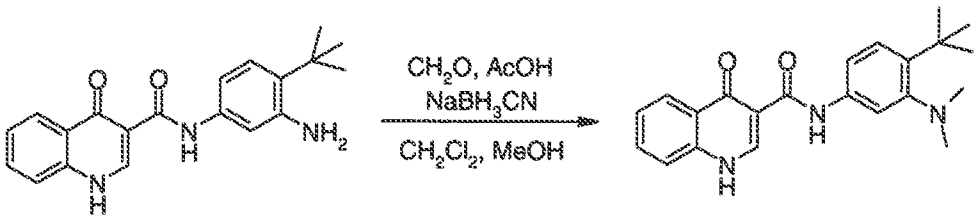
Starting Intermediate	Product
60	101
D-12-I	282
D-13-I	41
114	393
D-16-I	157
D-15-I	356
D-17-I	399

[0737] Example 2:

[0738] General Scheme:



[0739] Specific example:



271 485

[0740] 485; N-(3-Dimethylamino-4-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide

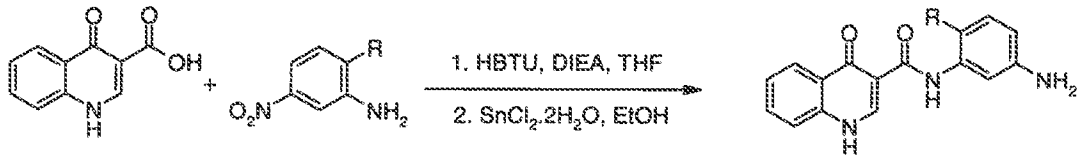
To a suspension of N-(3-amino-4-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide (**271**) (600 mg, 1.8 mmol) in CH_2Cl_2 (15 mL) and methanol (5 mL) were added acetic acid (250 µL) and formaldehyde (268 µL, 3.6 mmol, 37 wt % in water). After 10 min, sodium cyanoborohydride (407 mg, 6.5 mmol) was added in one portion. Additional formaldehyde (135 µL, 1.8 mmol, 37 wt% in water) was added at 1.5 and 4.2 h. After 4.7 h, the mixture was diluted with ether (40 mL), washed with water (25 mL) and brine (25 mL), dried (Na_2SO_4), filtered, and concentrated. The resulting red-brown foam was purified by preparative HPLC to afford N-(3-dimethylamino-4-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide (**485**) (108 mg, 17 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.13 (br s, 1H), 12.78 (s, 1H), 8.91 (br s, 1H), 8.42 (br s, 1H), 8.37 (d, J = 8.1 Hz, 1H), 7.72-7.58 (m, 2H), 7.47-7.31 (m, 3H), 3.34 (s, 6H), 1.46 (s, 9H); HPLC ret. time 2.15 min, 10–100 % CH_3CN, 5 min run; ESI-MS 364.3 m/z (MH^+).

[0741] The table below lists other examples synthesized following the general scheme above.

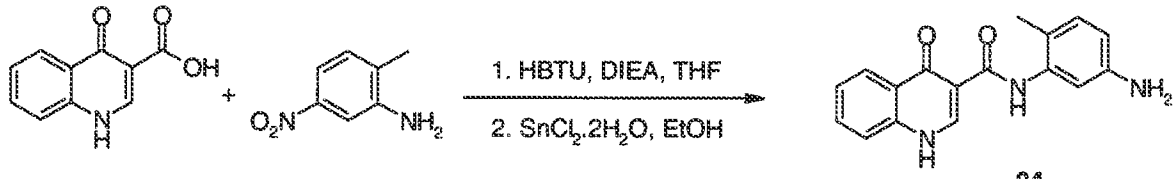
Starting Intermediate	Product
69	117
160	462
282	409
41	98

[0742] Example 3:

[0743] General Scheme:



[0744] Specific example:

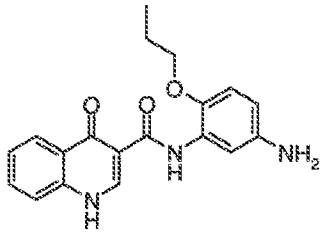


A-1 94

[0745] 94; N-(5-Amino-2-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide

To a solution of 4-hydroxy-quinoline-3-carboxylic acid (**A-1**) (50 mg, 0.26 mmol), HBTU (99 mg, 0.26 mmol) and DIEA (138 µL, 0.79 mmol) in THF (2.6 mL) was added 2-methyl-5-nitro-phenylamine (40 mg, 0.26 mmol). The mixture was heated at 150 °C in the microwave for 20 min and the resulting solution was concentrated. The residue was dissolved in EtOH (2 mL) and $SnCl_2 \cdot 2H_2O$ (293 mg, 1.3 mmol) was added. The reaction was stirred at room temperature overnight. The reaction mixture was basified with sat. $NaHCO_3$ solution to pH 7-8 and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in DMSO and purified by HPLC (10-99 % CH_3CN / H_2O) to yield the product, N-(5-amino-2-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide (**94**) (6 mg, 8 %). HPLC ret. time 2.06 min, 10-99 % CH_3CN, 5 min run; ESI-MS 294.2 m/z (MH^+).

[0746] Another example:

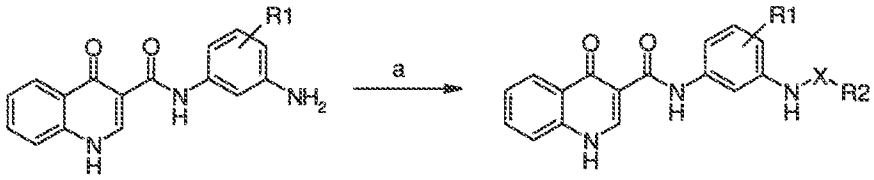


[0747] 17; N-(5-Amino-2-propoxy-phenyl)-4-oxo-1H-quinoline-3-carboxamide

N-(5-Amino-2-propoxy-phenyl)-4-oxo-1H-quinoline-3-carboxamide (**17**) was made following the general scheme above starting from 4-hydroxy-quinoline-3-carboxylic acid (**A-1**) and 5-nitro-2-propoxy-phenylamine. Yield (9 %). HPLC ret. time 3.74 min, 10-99 % CH_3CN, 5 min run; ESI-MS 338.3 m/z (MH^+).

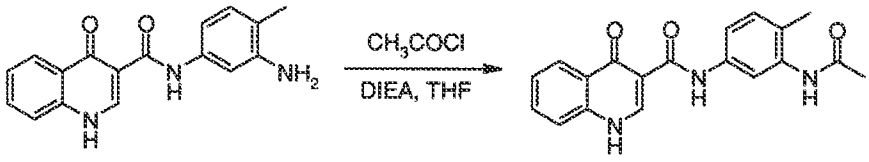
[0748] Example 4:

[0749] General Scheme:



X= CO, CO_2, SO_2: a) R2XCl, DIEA, THF or R2XCl, NMM, 1,4-dioxane or R2XCl, Et_3N, CH_2Cl_2, DMF.

[0750] Specific example:



167 248

[0751] 248; N-(3-Acetylamino-4-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide

To a solution of N-(3-amino-4-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide (**167**) (33mg, 0.11 mmol) and DIEA (49 µL, 0.28 mmol) in THF (1 mL) was added acetyl chloride (16

μL, 0.22 mmol). The reaction was stirred at room temperature for 30 min. LCMS analysis indicated that diacylation had occurred. A solution of piperidine (81 μL, 0.82mmol) in CH_2Cl_2 (2 mL) was added and the reaction stirred for a further 30 min at which time only the desired product was detected by LCMS. The reaction solution was concentrated and the residue was dissolved in DMSO and purified by HPLC (10-99 % CH_3CN / H_2O) to yield the product, N-(3-acetylamino-4-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide (**248**) (4 mg, 11 %). ^1H NMR (400 MHz, DMSO-d_6) δ 12.95 (d, J = 6.6 Hz, 1H), 12.42 (s, 1H), 9.30 (s, 1H), 8.86 (d, J = 6.8 Hz, 1H), 8.33 (dd, J = 8.1, 1.3 Hz, 1H), 7.85-7.81 (m, 2H), 7.76 (d, J = 7.8 Hz, 1H), 7.55 (t, J = 8.1 Hz, 1H), 7.49 (dd, J = 8.2, 2.2 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 2.18 (s, 3H), 2.08 (s, 3H); HPLC ret. time 2.46 min, 10-99 % CH_3CN, 5 min run; ESI-MS 336.3 m/z (MH^+).

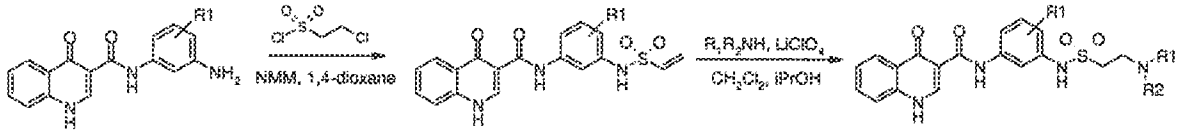
[0752] The table below lists other examples synthesized following the general scheme above.

Starting from	X	R^2	Product
260	CO	Me	316
260	CO	neopentyl	196
429	CO	Me	379
41	CO	Me	232
101	CO	Me	243
8	CO	Me	149
271	CO_2	Et	127
271	CO_2	Me	14
167	CO_2	Et	141
69	CO_2	Me	30
160	CO_2	Me	221
160	CO_2	Et	382
69	CO_2	Et	225
282	CO_2	Me	249
282	CO_2	Et	472
41	CO_2	Me	471
101	CO_2	Me	239
101	CO_2	Et	269

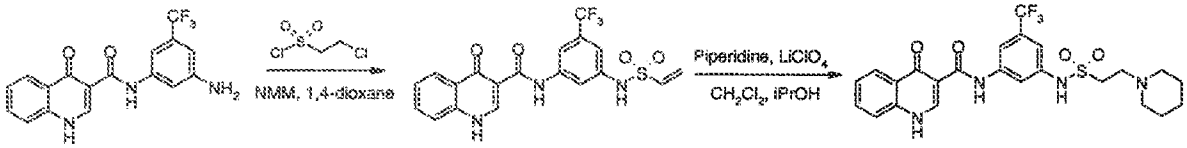
8	CO_2	Me	129
8	CO_2	Et	298
160	SO_2	Me	340

[0753] Example 5:

[0754] General Scheme:



[0755] Specific example:



429 318

[0756] 4-Oxo-*N*-[3-(trifluoromethyl)-5-(vinylsulfonamido)phenyl]-1,4-dihydroquinoline-3-carboxamide

To a suspension of N-[3-amino-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide (**429**) (500 mg 1.4 mmol) in 1,4-dioxane (4 mL) was added NMM (0.4 mL, 3.6 mmol). β-Chloroethylsulfonyl chloride (0.16 mL, 1.51 mmol) was added under an argon atmosphere. The mixture was stirred at room temperature for 6 ½ h, after which TLC (CH_2Cl_2 - EtOAc, 8:2) showed a new spot with a very similar R_f to the starting material. Another 0.5 eq. of NMM was added, and the mixture was stirred at room temperature overnight. LCMS analysis of the crude mixture showed >85% conversion to the desired product. The mixture was concentrated, treated with 1M HCl (5 mL), and extracted with EtOAc (3 x 10 mL) and CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to yield 4-oxo-*N*-[3-(trifluoromethyl)-5-(vinylsulfonamido)phenyl]-1,4-dihydroquinoline-3-carboxamide as an orange foam (0.495 g, 79 %), which was used in the next step without further purification. ^{1}H-NMR (d_6-Acetone, 300 MHz) δ 8.92 (s, 1H), 8.41-8.38 (m, 1H), 7.94 (m, 2H), 7.78 (br s, 2H),

7.53-7.47 (m, 1H), 7.30 (s, 1H), 6.87-6.79 (dd, J = 9.9 Hz, 1H), 6.28 (d, J = 16.5 Hz, 1H), 6.09 (d, J = 9.9 Hz, 1H); ESI-MS 436.4 m/z (MH^-)

[0757] 318; 4-Oxo-N-[3-[2-(1-piperidyl)ethylsulfonylamino]-5-(trifluoromethyl)phenyl]-1H-quinoline-3-carboxamide

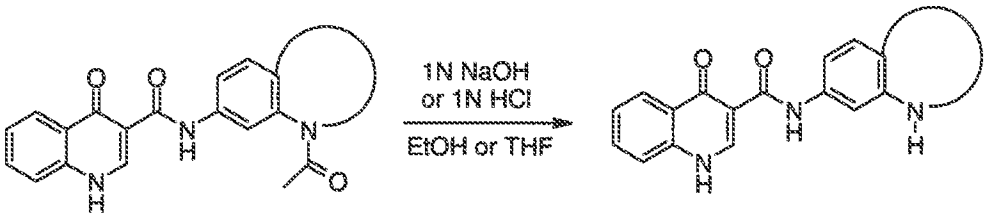
A mixture of 4-oxo-*N*-[3-(trifluoromethyl)-5-(vinylsulfonamido)phenyl]-1,4-dihydroquinoline-3-carboxamide (50 mg, 0.11 mmol), piperidine (18 µL, 1.6 eq) and $LiClO_4$ (20 mg, 1.7 eq) was suspended in a 1:1 solution of CH_2Cl_2: isopropanol (1.5 mL). The mixture was refluxed at 75 °C for 18 h. After this time, LCMS analysis showed >95% conversion to the desired product. The crude mixture was purified by reverse-phase HPLC to provide 4-oxo-N-[3-[2-(1-piperidyl)ethylsulfonylamino]-5-(trifluoromethyl)phenyl]-1H-quinoline-3-carboxamide (**318**) as a yellowish solid (15 mg, 25 %). ^{1}H-NMR (d_6-Acetone, 300 MHz) δ 8.92 (br s, 1H), 8.4 (d, J= 8.1 Hz, 1H), 8.05 (br s, 1H), 7.94 (br s, 1H), 7.78 (br s, 2H), 7.53-751 (m, 1H), 7.36 (br s, 1H), 3.97 (t, J= 7.2 Hz, 2H), 3.66 (t, J= 8 Hz, 2H), 3.31-3.24 (m, 6H), 1.36-1.31 (m, 4H); ESI-MS 489.1 m/z (MH^+).

[0758] The table below lists other examples synthesized following the general scheme above.

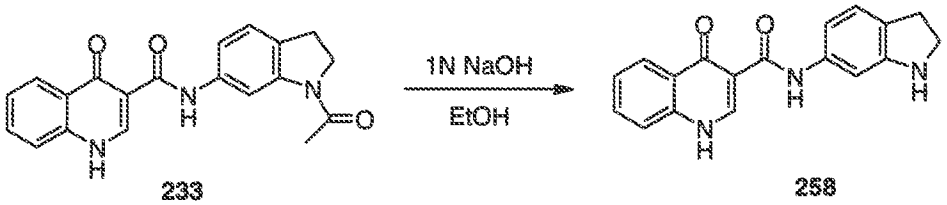
Starting Intermediate	Amine	Product
429	morpholine	272
429	dimethylamine	359
131	piperidine	133
131	morpholine	46

[0759] Example 6:

[0760] General Scheme:



[0761] Specific example:



233 258

[0762] 258; N-Indolin-6-yl-4-oxo-1H-quinoline-3-carboxamide

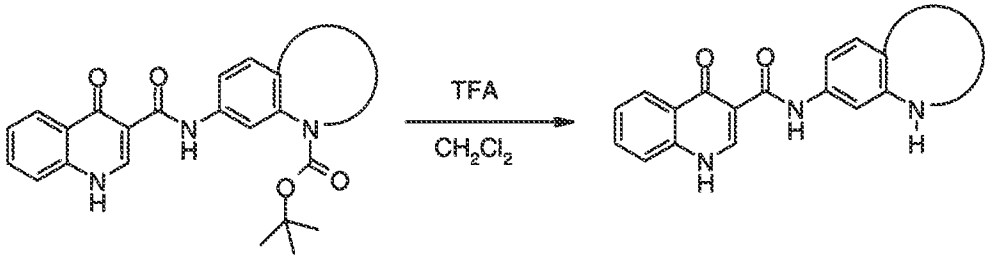
A mixture of N-(1-acetylindolin-6-yl)-4-oxo-1H-quinoline-3-carboxamide **(233)** (43mg, 0.12 mmol), 1N NaOH solution (0.5 mL) and ethanol (0.5 mL) was heated to reflux for 48 h. The solution was concentrated and the residue was dissolved in DMSO (1 mL) and purified by HPLC (10-99 % CH_3CN - H_2O) to yield the product, N-indolin-6-yl-4-oxo-1H-quinoline-3-carboxamide **(258)** (10 mg, 20 %). HPLC ret. time 2.05 min, 10-99 % CH_3CN, 5 min run; ESI-MS 306.3 m/z (MH^+).

[0763] The table below lists other examples synthesized following the general scheme above.

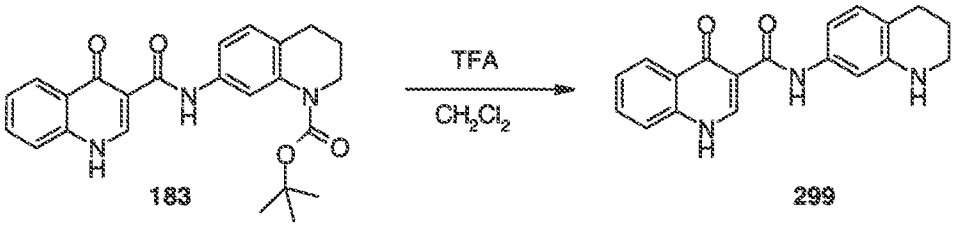
Starting from	Product	Conditions	Solvent
DC-8-I	**386**	NaOH	EtOH
DC-9-I	**10**	HCl	EtOH
175	**22**	HCl	EtOH
109	**35**	HCl	EtOH
334	**238**	NaOH	EtOH
DC-10-I	**105**	NaOH	THF

[0764] Example 2:

[0765] General Scheme:



[0766] Specific example:

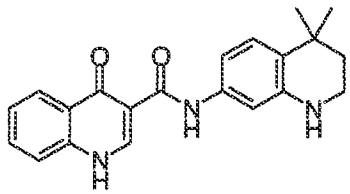


[0767] 299; 4-Oxo-N-(1,2,3,4-tetrahydroquinolin-7-yl)-1H-quinoline-3-carboxamide

A mixture of 7-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-1,2,3,4-tetrahydroquinoline-1-carboxylic acid tert-butyl ester **(183)** (23 mg, 0.05 mmol), TFA (1 mL) and CH_2Cl_2 (1 mL) was stirred at room temperature overnight. The solution was concentrated and the residue was

dissolved in DMSO (1 mL) and purified by HPLC (10-99 % CH_3CN - H_2O) to yield the product, 4-oxo-N-(1,2,3,4-tetrahydroquinolin-7-yl)-1H-quinoline-3-carboxamide **(299)** (7 mg, 32 %). HPLC ret. time 2.18 min, 10-99 % CH_3CN, 5 min run; ESI-MS 320.3 m/z (MH^+).

[0768] Another example:



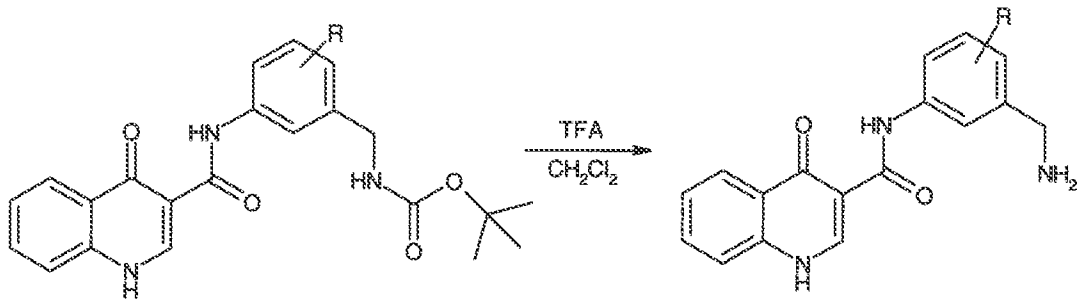
[0769] 300; N-(4,4-Dimethyl-1,2,3,4-tetrahydroquinolin-7-yl)-4-oxo-1H-quinoline-3-carboxamide

N-(4,4-Dimethyl-1,2,3,4-tetrahydroquinolin-7-yl)-4-oxo-1H-quinoline-3-carboxamide (**300**) was synthesized following the general scheme above starting from 4,4-dimethyl-7-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-1,2,3,4-tetrahydroquinoline-1-carboxylic acid tert-butyl ester (**108**). Yield (33 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.23 (d, J = 6.6 Hz, 1H), 12.59 (s, 1H), 8.87 (d, J = 6.8 Hz, 1H), 8.33 (d, J = 7.7 Hz, 1H), 7.86-7.79 (m, 3H), 7.58-7.42 (m, 3H), 3.38 (m, 2H), 1.88 (m, 2H), 1.30 (s, 6H); HPLC ret. time 2.40 min, 10-99 % CH_3CN, 5 min run; ESI-MS 348.2 m/z (MH^+).

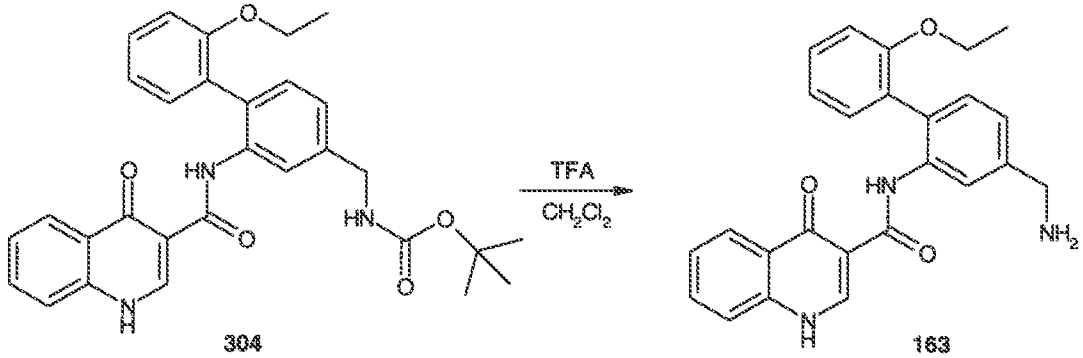
[0770] Other

[0771] Example 1:

[0772] General scheme:



[0773] Specific example:

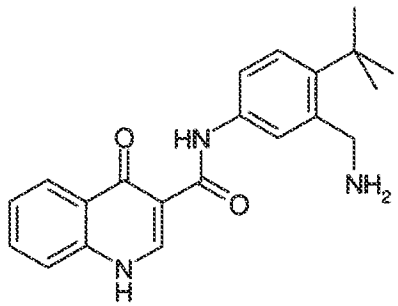


304 163

[0774] 163; 4-Oxo-1,4-dihydro-quinoline-3-carboxylic acid (4-aminomethyl-2'-ethoxy-biphenyl-2-yl)-amide

{2'-Ethoxy-2-[(4-oxo-1,4-dihydroquinoline-3-carbonyl)-amino]-biphenyl-4-ylmethyl}-carbamic acid *tert*-butyl ester (**304**) (40 mg, 0.078 mmol) was stirred in a CH_2Cl_2 / TFA mixture (3:1, 20 mL) at room temperature for 1 h. The volatiles were removed on a rotary evaporator. The crude product was purified by preparative HPLC to afford 4-oxo-1,4-dihydroquinoline-3-carboxylix acid (4-aminomethyl-2'-ethoxybiphenyl-2-yl)amine (**163**) as a tan solid (14 mg. 43 %). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.87 (d, J = 6.3 Hz, 1H), 11.83 (s, 1H), 8.76 (d, J = 6.3 Hz, 1H), 8.40 (s, 1H), 8.26 (br s, 2H), 8.01 (dd, J = 8.4 Hz, J = 1.5 Hz, 1H), 7.75 (dt, J = 8.1 Hz, J = 1.2 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.47-7.37 (m, 2H), 7.24 (s, 2H), 7.15 (dd, J = 7.5 Hz, J = 1.8 Hz, 1H), 7.10 (d, J = 8.1 Hz, 1H), 7.02 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 4.09 (m, 2H), 4.04 (q, J = 6.9 Hz, 2H), 1.09 (t, J = 6.9 Hz, 3H); HPLC ret. time 1.71 min, 10-100 % CH_3CN, 5 min gradient; ESI-MS 414.1 m/z (MH^+).

[0775] Another example:

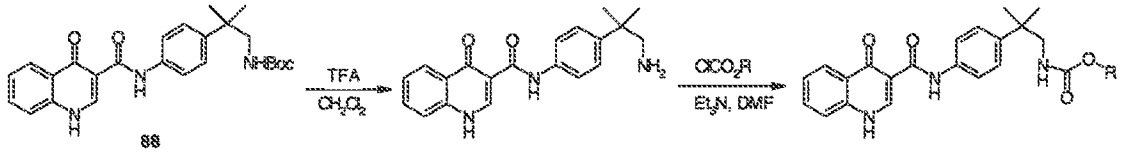


[0776] 390; N-[3-(Aminomethyl)-4-*tert*-butyl-phenyl]-4-oxo-1H-quinoline-3-carboxamide

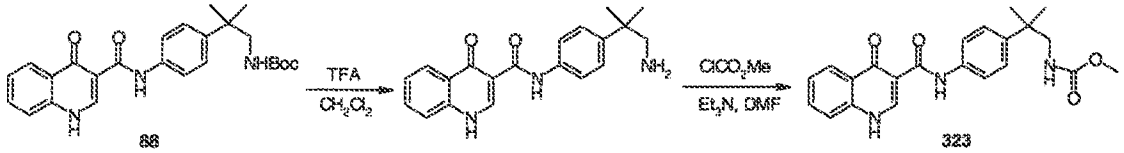
N-[3-(Aminomethyl)-4-*tert*-butyl-phenyl]-4-oxo-1H-quinoline-3-carboxamide (**390**) was synthesized following the general scheme above starting from [5-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-2-*tert*-butyl-phenyl]methylaminoformic acid tert-butyl ester (**465**). HPLC ret. time 2.44 min, 10-99 % CH_3CN, 5 min gradient; ESI-MS m/z 350.3 $(M + H)^+$.

[0777] Example 2:

[0778] General scheme:



[0779] Specific example:



[0780] **3-(2-(4-(1-Amino-2-methylpropan-2-yl)phenyl)acetyl)quinolin-4(1H)-one** (2-Methyl-2-{4-[2-oxo-2-(4-oxo-1,4-dihydro-quinolin-3-yl)-ethyl]-phenyl}-propyl)-carbamic acid tert-butyl ester (**88**) (0.50 g, 1.15 mmol), TFA (5 mL) and CH_2Cl_2 (5 mL) were combined and stirred at room temerpature overnight. The reaction mixture was then neutralized with 1N NaOH. The precipitate was collected via filtration to yield the product 3-(2-(4-(1-amino-2-methylpropan-2-yl)phenyl)acetyl)quinolin-4(1H)-one as a brown solid (651 mg, 91 %). HPLC ret. time 2.26 min, 10-99 % CH_3CN, 5 min run; ESI-MS 336.5 m/z (MH^+).

[0781] **323; [2-Methyl-2-[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]-propyl]aminoformic acid methyl ester**

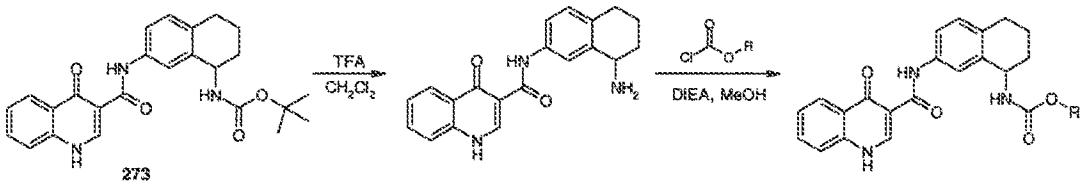
Methyl chloroformate (0.012 g, 0.150 mmol) was added to a solution of 3-(2-(4-(1-amino-2-methylpropan-2-yl)phenyl)acetyl)quinolin-4(1H)-one (0.025 g, 0.075 mmol), TEA (0.150 mmol, 0.021 mL) and DMF (1 mL) and stirred at room temperature for 1 h. Then piperidine (0.074 mL, 0.750 mmol) was added and the reaction was stirred for another 30 min. The reaction mixture was filtered and purified by preparative HPLC (10-99 % CH_3CN-H_2O) to yield the product [2-methyl-2-[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]phenyl]-propyl]aminoformic acid methyl ester (**323**). ^1H NMR (400 MHz, DMSO-d6) δ 12.94 (br s, 1H), 12.44 (s, 1H), 8.89 (s, 1H), 8.33 (dd, J = 8.2, 1.1 Hz, 1H), 7.82 (t, J = 8.3 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.54 (t, J = 8.1 Hz, 1H), 7.35 (d, J = 8.7 Hz, 2H), 7.02 (t, J = 6.3 Hz, 1H), 3.50 (s, 3H), 3.17 (d, J = 6.2 Hz, 2H), 1.23 (s, 6H); HPLC ret. time 2.93 min, 10-99 % CH_3CN, 5 min run; ESI-MS 394.0 m/z (MH^+).

[0782] The table below lists other examples synthesized following the general scheme above.

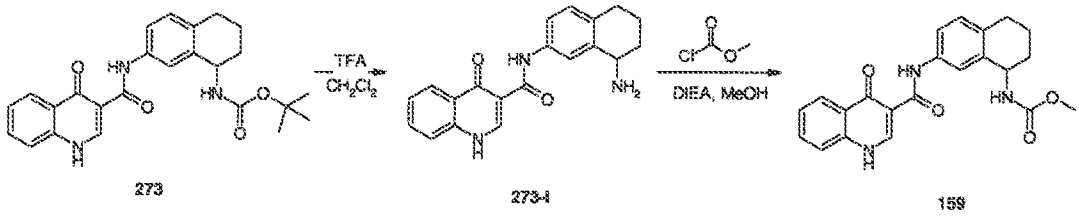
Product	Chloroformate
119	Ethyl chloroformate
416	Propyl chloroformate
460	Butyl chloroformate
251	Isobutyl chloroformate
341	Neopentyl chloroformate
28	2-methoxyethyl chloroformate
396	(tetrahydrofuran-3-yl)methyl chloroformate

[0783] **Example 3:**

[0784] General Scheme:



[0785] Specific example:



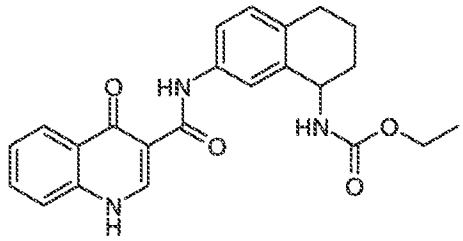
[0786] **273-I; N-(1-Aminotetralin-7-yl)-4-oxo-1H-quinoline-3-carboxamide**

To a solution of [7-[(4-oxo-1H-quinolin-3-yl)carbonylamino]tetralin-1-yl]aminoformic acid tert-butyl ester (**273**) (250 mg, 0.6 mmol) in dichloromethane (2 mL) was added TFA (2 mL). The reaction was stirred at room temperature for 30 min. More dichloromethane (10 mL) was added to the reaction mixture and the solution was washed with sat. $NaHCO_3$ solution (5 mL). A precipitate began to form in the organic layer so the combined organic layers were concentrated to yield N-(1-aminotetralin-7-yl)-4-oxo-1H-quinoline-3-carboxamide (**273-I**) (185 mg, 93 %). HPLC ret. time 1.94 min, 10-99 % CH_3CN, 5 min run; ESI-MS 334.5 m/z (MH^+).

[0787] 159; [7-[(4-Oxo-1H-quinolin-3-yl)carbonylamino]tetralin-1-yl]aminoformic acid methyl ester

To a solution of N-(1-aminotetralin-7-yl)-4-oxo-1H-quinoline-3-carboxamide (**273-I**) (65 mg, 0.20 mmol) and DIEA (52 µL, 0.29 mmol) in methanol (1 mL) was added methyl chloroformate (22 µL, 0.29 mmol). The reaction was stirred at room temperature for 1 h. LCMS analysis of the reaction mixture showed peaks corresponding to both the single and bis addition products. Piperidine (2 mL) was added and the reaction was stirred overnight after which only the single addition product was observed. The resulting solution was filtered and purified by HPLC (10-99 % CH_3CN - H_2O) to yield the product, [7-[(4-oxo-1H-quinolin-3-yl)carbonylamino]tetralin-1-yl]aminoformic acid methyl ester (**159**) (27 mg, 35 %). HPLC ret. time 2.68 min, 10-99 % CH_3CN, 5 min run; ESI-MS 392.3 m/z (MH^+).

[0788] Another example:

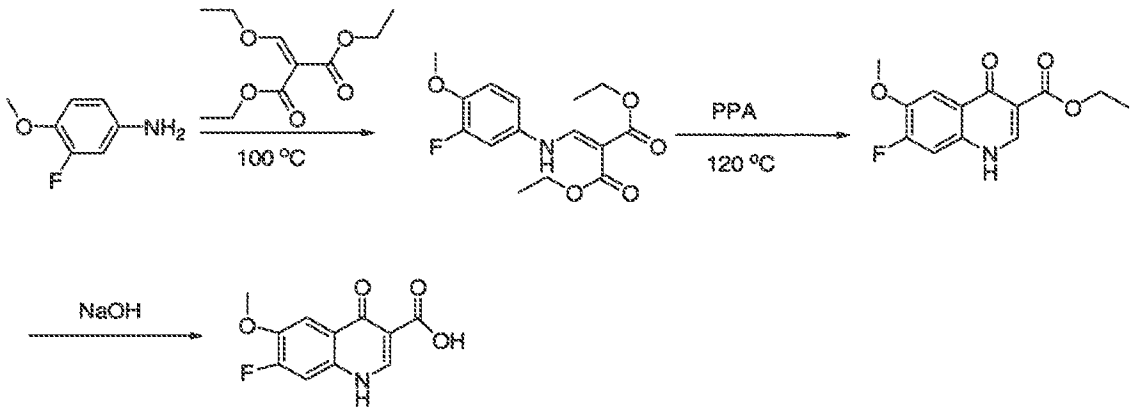


[0789] 482; [7-[(4-Oxo-1H-quinolin-3-yl)carbonylamino]tetralin-1-yl]aminoformic acid ethyl ester

[7-[(4-Oxo-1H-quinolin-3-yl)carbonylamino]tetralin-1-yl]aminoformic acid ethyl ester (**482**) was synthesized following the general scheme above, from amine (**273-I**) and ethyl chloroformate. Overall yield (18 %). HPLC ret. time 2.84 min, 10-99 % CH_3CN, 5 min run; ESI-MS 406.5 m/z (MH^+).

[0790] Further Examples

[0791] Acid Intermediate Example 1: **Synthesis of 7-fluoro-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid**

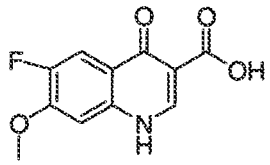


[0792] A mixture of 3-fluoro-4-methoxy-aniline (0.7 g, 4.96 mmol) and diethyl 2-(ethoxymethylene)propanedioate (1.1 g, 4.96 mmol) was heated at 100 °C for 4 h. The mixture was cooled to room temperature and concentrated under reduced pressure, and then purified via silica gel column chromatography using 1 to 60% EtOAc in hexanes to yield diethyl 2-((3-fluoro-4-methoxyphenylamino)methylene)malonate (1.2 g, 78%). LC/MS: *m/z* 312.3 $(M+H)^+$ at 1.69 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0793] A flask charged with diethyl 2-((3-fluoro-4-methoxyphenylamino)methylene)malonate (1.2 g, 3.86 mmol) and polyphosphoric acid (4.8 g) was heated at 120 °C for 4 h. The reaction was then cooled to room temperature and filtered. The residue was treated with aqueous $NaHCO_3$ solution, filtered, washed with water and dried. The solid was then purified via silica gel column chromatography using 20 to 70% EtOAc in hexanes to yield ethyl 7-fluoro-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (410 mg, 40%). LC/MS: *m/z* 266.3 $(M+H)^+$ at 0.91 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

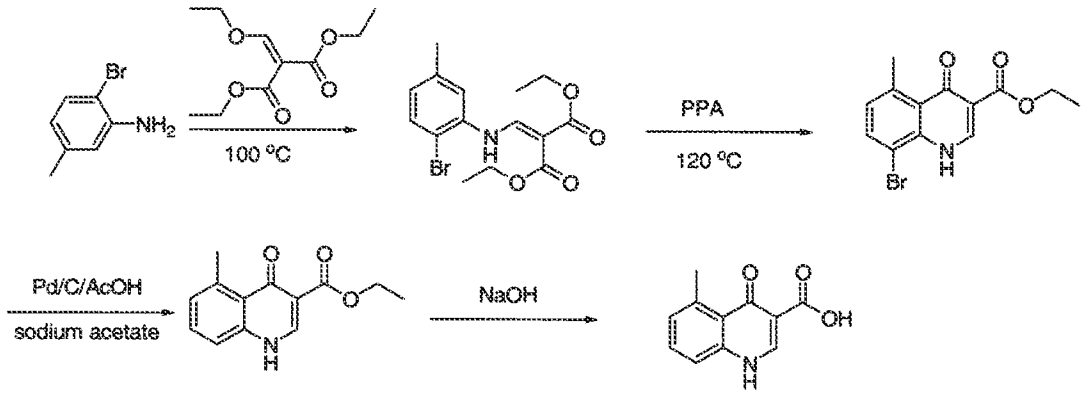
[0794] Ethyl 7-fluoro-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (409 mg, 1.54 mmol) was suspended in a solution of NaOH (3.55mL of 4 %w/v, 3.55 mmol) and the reaction was stirred under reflux for 2 h. After cooling, the reaction mixture was acidified with conc. HCl. The resulting precipitated was collected via filtration, washed with water and dried to yield 7-fluoro-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (50 mg, 14%). LC/MS: *m/z* 238.3 $(M+H)^+$ at 0.95 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0795] 6-fluoro-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



[0796] 6-fluoro-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid can be synthesized following the general scheme above starting from 4-fluoro-3-methoxyaniline

[0797] Acid Intermediate Example 2: **Synthesis of 5-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid**



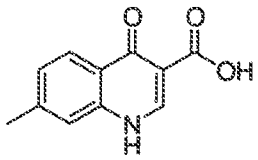
[0798] A mixture of 2-bromo-5-methyl-aniline (1.0 g, 5.34 mmol) and diethyl 2-(ethoxymethylene)propanedioate (1.23 g, 5.90 mmol) was heated at 100 °C for 4 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was then purified via silica gel column chromatography using 1 to 60% EtOAc in hexanes to yield diethyl 2-[[(2-bromo-5-methyl-phenyl)amino]methylene]propanedioate (1.6 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.19 (d, J = 13.2 Hz, 1H), 8.48 (d, J = 13.2 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.08 (s, 1H), 6.81 (d, J = 8.1 Hz, 1H), 4.37-4.23 (m, 4H), 2.35 (s, 3H), 1.42-1.25 (m, 6H).

[0799] A flask charged with diethyl 2-[[(2-bromo-5-methyl-phenyl)amino]methylene]propanedioate (1.6 g, 4.49 mmol) and polyphosphoric acid (5.6 g) was heated at 120 °C for 4 h. The reaction was then cooled to room temperature and filtered. The residue was treated with aqueous $NaHCO_3$ solution, filtered, washed with water and dried. The residue was then purified via silica gel column chromatography using 20 to 70% EtOAc in hexanes to yield ethyl 8-bromo-5-methyl-4-oxo-1H-quinoline-3-carboxylate (895 mg, 64%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.22 (s, 1H), 8.32 (s, 1H) , 7.82 (d, J = 7.8 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H), 4.19 (q, J = 7.2, 14.4 Hz, 2H), 2.72 (s, 3H), 1.23 (t, J = 10.2 Hz, 3H).

[0800] A flask charged with ethyl 8-bromo-5-methyl-4-oxo-1H-quinoline-3-carboxylate (895 mg, 2.89 mmol), sodium acetate (237 mg, 2.89 mmol) and Pd/C (180 mg, 1.69 mmol) was flushed under a N_2 followed by evacuating under vacuum. Acetic acid (21 mL) was added under an inert atmosphere followed by evacuating under vacuum. The reaction was then stirred for 4 h in an atmosphere of H_2. The reaction was filtered to remove the Pd catalyst and the solvent was evaporated to give ethyl 5-methyl-4-oxo-1H-quinoline-3-carboxylate (145 mg, 22%).

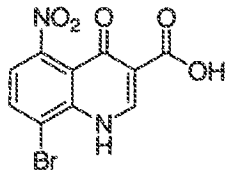
[0801] Ethyl 5-methyl-4-oxo-1H-quinoline-3-carboxylate (142 mg, 0.61 mmol) was suspended in an aqueous solution of NaOH (1.54 mL of 4%w/v, 1.54 mmol) and the reaction was stirred under reflux for 2 h. After cooling, the reaction mixture was acidified with conc. HCl. The resulting precipitate was collected via filtration, washed with water and dried to yield 5-methyl-4-oxo-1H-quinoline-3-carboxylic acid (42 mg, 34%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.69 (brs, 1H), 13.81 (brs, 1H), 8.68 (d, J = 6.4 Hz, 1H), 7.70-7.64 (m, 2H) , 7.27(d, J = 6.4 Hz, 1H), 2.84 (s, 3H). MS (ESI) m/z: 202.2 $[M-H]^-$.

[0802] 7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



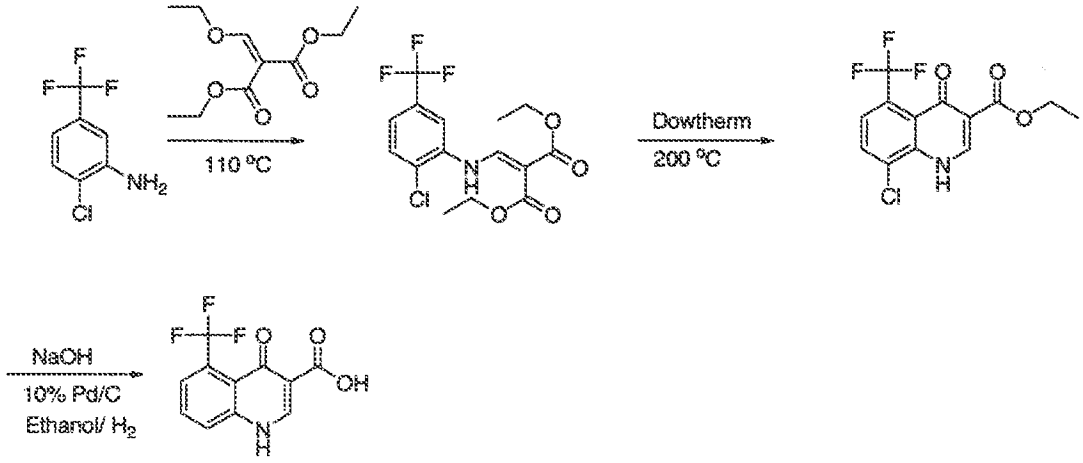
[0803] 7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid can be synthesized following the general scheme above starting from 2-bromo-3-methylaniline. Overall yield (16%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.24 (s, 1H), 12.30 (s, 1H), 8.63 (s, 1H), 8.07 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 1H), 2.85 (s, 3H).

[0804] 8-bromo-5-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



[0805] 8-bromo-5-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid can be synthesized following the general scheme above starting from 2-bromo-5-nitroaniline. LC/MS: m/z 314.9 $(M+H)^+$ at 1. min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0806] Acid Intermediate Example 3: **Synthesis of 4-oxo-5-(trifluoromethyl)-1,4-dihydroquinoline-3-carboxylic acid**



[0807] 2-chloro-5-(trifluoromethyl)aniline (52 g, 260 mmol) and diethyl 2-(ethoxymethylene)propanedioate (85g, 389 mmol) were combined in a 250 mL flask and fitted with a Dean-Stark condenser. The mixture was heated to 110 °C for 4 h. The reaction mixture was cooled to ~ 80 °C and hexane was slowly added (~150 mL). The resulting precipitate was stirred until room temperature was reached, then filtered to obtain a white crystalline solid. The solid was washed with hexane and air dried (93 g, 94%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.28 (d, J = 13.0 Hz, 1H), 8.63 (d, J = 13.0 Hz, 1H), 8.10 (s, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.50 (dd, J = 8.4, 1.5 Hz, 1H), 4.21 (dq, J = 28.3, 7.1 Hz, 4H), 1.27 (td, J = 7.1, 2.9 Hz, 6H).

[0808] 6 mL of Dowtherm was added to a long-neck 25 mL flask, fitted with a reflux condenser. The Dowtherm was heated to 200 °C and degassed for 20 minutes. Diethyl 2-((2-chloro-5-(trifluoromethyl)phenylamino)methylene)malonate (1g, 2.73 mmol) was then added and the solution was then heated to reflux for 2.5 h under N_2. The reaction mixture was cooled after 2.5 h, then diluted with hexane (12 mL) to produce a fine, light brown precipitate. The reaction mixture was filtered, and the precipitate washed with hexane until the color was removed. The product was air dried to obtain ethyl 8-chloro-4-oxo-5-(trifluoromethyl)-1, 4-dihydroquinoline-3-carboxylate as a light brown solid (0.57 g, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.39 (s, 1H), 8.06 (d, J = 8.3 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H).

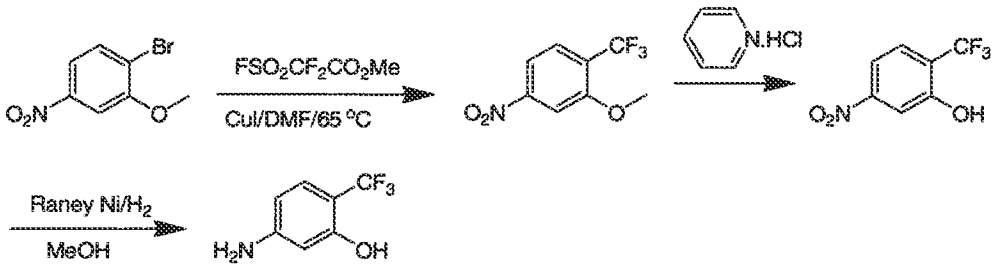
[0809] Ethyl 8-chloro-4-oxo-5-(trifluoromethyl)-1,4-dihydroquinoline-3-carboxylate (500 mg, 1.56 mmol) was dissolved in NaOH (16 mL of 2.0 M, 31 mmol) and ethanol (3 mL) and heated to 100 °C for 2 h. The clear, light yellow solution was cooled to 50 °C, the reaction mixture was degassed with N_2, and then treated with 10% Pd/C (65 mg, 0.03 mmol). The

reaction mixture was heated at 70 °C for 3 h under an atmosphere of H_2. The reaction mixture was cooled and then filtered, acidified with conc. HCl until a white precipitate was formed, then allowed to stir overnight. The reaction mixture was filtered, washed with water and dried with CH_3CN to yield a white powder (350 mg, 87%). ^1H NMR (400 MHz, DMSO-d_6) δ 15.26 (s, 1H), 13.68 (s, 1H), 8.98 (s, 1H), 8.16 – 8.09 (m, 1H), 8.08 – 7.97 (m, 2H).

[0810] Commercially avaliable Acids and Esters

8-chloro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
4-oxo-6-(trifluoromethyl)-1,4-dihydroquinoline-3-carboxylic acid
8-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
4-oxo-7-(trifluoromethoxy)-1,4-dihydroquinoline-3-carboxylic acid
Ethyl 5,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate
5-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
4-oxo-8-(trifluoromethyl)-1,4-dihydroquinoline-3-carboxylic acid
8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
Ethyl 8-cyano-4-oxo-1,4-dihydroquinoline-3-carboxylate
7-cyano-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
6-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
8-ethoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
6-chloro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
8-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
6-bromo-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
Ethyl 7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate
6-(dimethylamino)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
6-ethoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
7-acetyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

[0811] Amine Intermediate Example 1: **Synthesis of 5-amino-2-(trifluoromethyl)phenol**



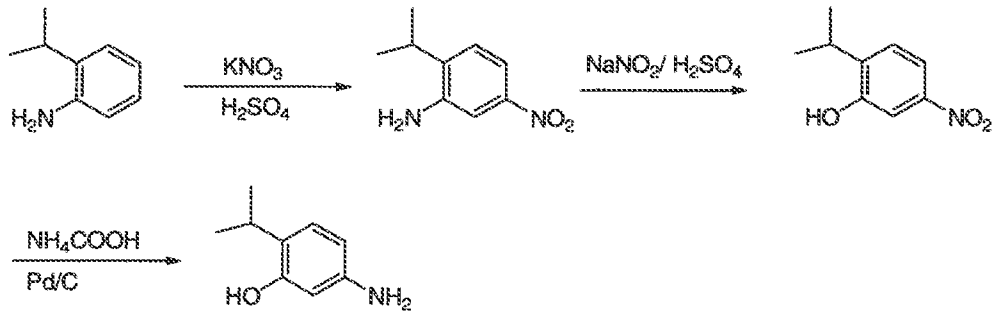
[0812] A mixture of 1-bromo-2-methoxy-4-nitro-benzene (20 g, 86.2 mmol), methyl 2,2-difluoro-2-fluorosulfonyl-acetate (100 g, 520.5 mmol) and CuI (65 g, 341.3 mmol) in dry DMF (200 mL) was stirred at 75 °C under an atmosphere of N_2 overnight. The solvent was evaporated under reduced pressure. EtOAc was added to the residue and the solid was removed by filtration. The filtrate was washed with water (100 mL × 2), brine (100 mL), dried over anhydrous Na_2SO_4 and purified by silica gel column chromatography (petroleum as eluant) to afford a mixture of 1-bromo-2-methoxy-4-nitro-benzene and 2-methoxy-4-nitro-1-(trifluoromethyl)benzene (16 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90-7.86 (m, 1H), 7.85 (s, 1H), 7.77-7.69 (m, 1H), 4.02 (s, 3H)

[0813] A mixture of 2-methoxy-4-nitro-1-(trifluoromethyl)benzene and 1-bromo-2-methoxy-4-nitro-benzene (16 g, 72 mmol) and pyridine hydrochloride (100 g, 865.3 mmol) was stirred at 210 °C for 40 min. Then the reaction mixture was poured into ice-water and extracted with EtOAc (80 mL × 3). The combined organic layers were washed with water (100 mL × 2) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, concentrated and purified by silica gel column chromatography (5% EtOAc in petroleum as eluant) to afford a mixture of 5-nitro-2-(trifluoromethyl)phenol and 2-bromo-5-nitro-phenol (10 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1 H), 7.00 (d, J = 8.4 Hz, 1 H), 6.06 (s, 1 H), 5.95 (d, J = 8.4 Hz, 1 H), 4.07 (brs, 1 H).

[0814] To a solution of 5-nitro-2-(trifluoromethyl)phenol and 2-bromo-5-nitro-phenol (10 g, 48.28 mmol) in methanol (60 mL) was added Raney Nickel (2.83 g, 318 µL, 48.28 mmol) under an atmosphere of nitrogen. The reaction mixture was then stirred for 4h at room temperature under an atmosphere of hydrogen (1 atm). The catalyst was removed by filtration through a pad of celite and the filtrate was evaporated under vacuum. The crude product was purified by preparative HPLC to obtain 5-amino-2-(trifluoromethyl)phenol (1.7 g, 20%). ^{1}H

NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 1H), 7.04 (d, J = 8.8 Hz, 1H), 6.10 (s, 1H), 6.01 (d, J = 8.4 Hz, 1H), 5.58 (br s, 2H).

[0815] Amine Intermediate Example 2: **Synthesis of 5-amino-2-(trifluoromethyl)phenol**

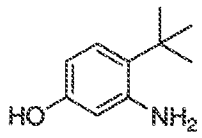


[0816] 2-Isopropylaniline (13.5 g, 99.85 mmol) was added portionwise to conc. H_2SO_4 (100 mL) to generate a yellow homogeneous solution. The solution was then cooled to 0 °C and KNO_3 (15.2 g, 150.3 mmol) was added portionwise maintaining the internal temperature below 5 °C. The reaction was stirred for 2 h and then poured on ice water, then basified with 10% NaOH solution. The aqueous layer was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated to obtain 2-isopropyl-5-nitroaniline (14.9 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, J = 8.4, 2.2 Hz, 1H), 7.50 (d, J = 2.4 Hz, 1H), 7.27 – 7.21 (m, 1H), 3.96 (s, 2H), 2.98 – 2.79 (m, 1H), 1.29 (d, J = 6.8 Hz, 6H).

[0817] 2-Isopropyl-5-nitro-aniline (1.89 g, 10.49 mmol) was added dropwise to a mixture of conc.H_2SO_4 (9 mL) and H_2O (50 mL). This reaction mixture was cooled to 0 °C and a solution of $NaNO_2$ (763 mg, 11.06 mmol) in H_2O (2 mL) was added. The reaction mixture was stirred for 10 minutes and then 1 g of urea was added to decompose the excess $NaNO_2$, followed by the addition of 10 mL of 1: 2 conc.H_2SO_4: H_2O. The reaction mixture was then refluxed for 10 minutes, cooled to room temperature and extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was then purified via silica gel column chromatography using 10 to 20% EtOAc in hexanes to obtain 2-isopropyl-5-methyl-phenol (1.41 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J = 8.5, 2.3 Hz, 1H), 7.63 (d, J = 2.3 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.26 (s, 1H), 3.39 – 3.18 (m, 1H), 1.29 – 1.26 (m, 6H).

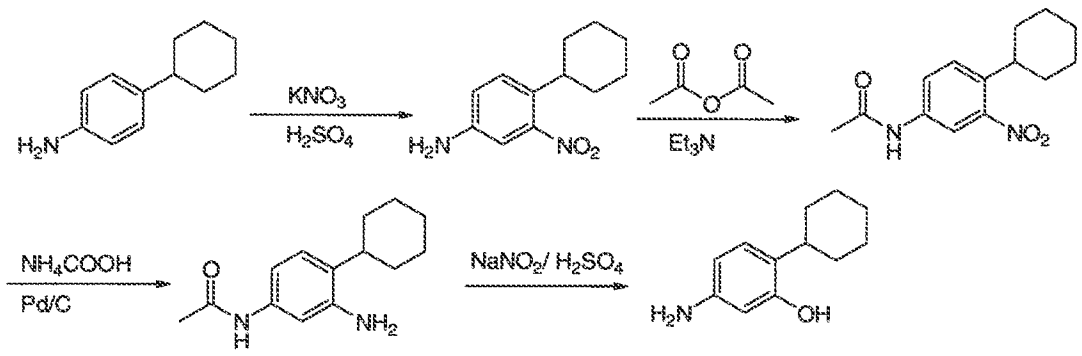
[0818] To a refluxing solution of 2-isopropyl-5-methyl-phenol (1.3 g, 8.65 mmol) and ammonium formate (1.3 g, 20.62 mmol) in ethanol (50 mL) was added 10% Pd/C (887 mg, 8.33 mmol). The mixture was refluxed for an additional 5 minutes, cooled and filtered through a pad of celite. The solvent was removed by evaporation to give 5-amino-2-isopropylphenol which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (s, 1H), 6.71 (d, J = 8.1 Hz, 1H), 6.04 (d, J = 2.2 Hz, 1H), 5.97 (dd, J = 8.1, 2.2 Hz, 1H), 4.65 (s, 2H), 3.08 – 2.94 (m, 1H), 1.07 (d, J = 6.9 Hz, 6H).

[0819] 3-amino-4-*tert*-butylphenol



[0820] 3-amino-4-*tert*-butylphenol can be synthesized following the general scheme above starting from 4-*tert*-butylaniline.

[0821] Amine Intermediate Example 3: **Synthesis of 5-amino-2-cyclohexylphenol**



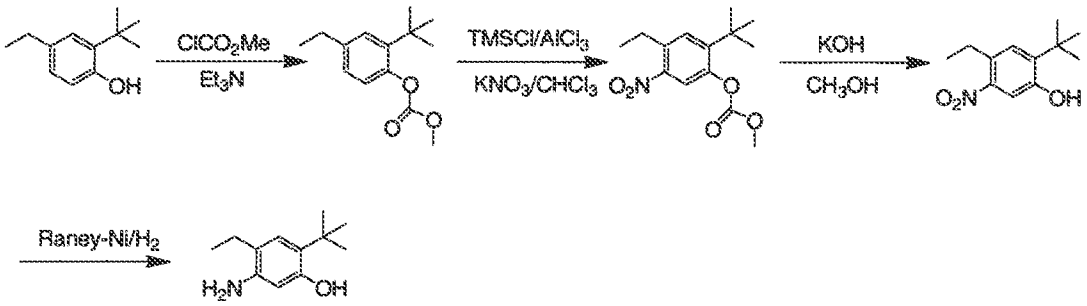
[0822] 4-cyclohexylaniline (15 g, 85.58 mmol) was added portionwise to conc. sulfuric acid (85 mL, 1.6 mol) to generate a homogeneous solution. The solution was then cooled to 0 °C and KNO_3 (13 g, 128.6 mmol) was added portionwise maintaining the internal temperature below 5 °C. The reaction was stirred for 5 minutes at -10 °C and then poured on ice water, basified with 6N NaOH solution and the aqueous layer was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated to obtain 4-cyclohexyl-3-nitroaniline (17 g, 921%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.5 Hz, 1H), 6.97 (d, J = 2.5 Hz, 1H), 6.82 (dd, J = 8.4, 2.5 Hz, 1H), 2.85 (ddd, J = 11.4, 8.3, 3.2 Hz, 1H), 1.89 – 1.69 (m, 6H), 1.49 – 1.29 (m, 4H).

[0823] To a solution of 4-cyclohexyl-3-nitro-aniline (1.54 g, 6.99 mmol) in DCM (15 mL) was added Et_3N (1.9 mL, 13.63 mmol), followed by the addition of acetic anhydride (3.3 mL, 34.98 mmol). The reaction mixture was stirred at room temperature for 2 h, quenched with water, the layers separated and the organic layer was washed with 0.1N HCl, followed by washing with H_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated to obtain N-(4-cyclohexyl-3-nitrophenyl)acetamide (1.7 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 2.2 Hz, 1H), 7.69 (dd, J = 8.6, 2.2 Hz, 1H), 7.52 (s, 1H), 7.40 (d, J = 8.6 Hz, 1H), 3.01 – 2.87 (m, 1H), 2.22 (s, 3H), 1.95 – 1.78 (m, 5H), 1.42 (t, J = 10.4 Hz, 4H), 1.32 – 1.21 (m, 1H).

[0824] To a refluxing solution of N-(4-cyclohexyl-3-nitro-phenyl)acetamide (1.8 g, 6.86 mmol) and ammonium formate (1.8 g, 28.55 mmol) in ethanol (50 mL) was added 10% Pd/C (1.3 g, 12.22 mmol). The mixture was refluxed for additional 5 minutes, cooled and filtered through a pad of celite. The solvent was removed by evaporation to give N-(3-amino-4-cyclohexylphenyl)acetamide (1.4 g, 90%) which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 2.1 Hz, 2H), 7.03 (d, J = 8.3 Hz, 1H), 6.67 (dd, J = 8.2, 2.1 Hz, 1H), 3.72 (d, J = 9.8 Hz, 2H), 2.42 (d, J = 8.5 Hz, 1H), 2.15 (s, 3H), 1.88 (d, J = 9.5 Hz, 4H), 1.78 (d, J = 12.1 Hz, 1H), 1.51 – 1.33 (m, 5H).

[0825] N-(3-amino-4-cyclohexyl-phenyl)acetamide (696 mg, 3.0 mmol) was added dropwise to a mixture of conc.H_2SO_4 (3 mL, 56.28 mmol) and H_2O (17 mL). This reaction mixture was cooled to 0 °C and a solution of $NaNO_2$ (229 mg, 3.32 mmol) in H_2O (2 mL) was added. The reaction mixture was stirred for 5 minutes at 0 °C and then 1 g of urea was added, followed by the addition of 10 mL of 1: 2 H_2SO_4: H_2O. The reaction mixture was then refluxed for 1hour, cooled to room temperature and extracted with EtOAc. The aqueous layer was basified with solid NaOH and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to obtain 5-amino-2-cyclohexylphenol (426 mg, 74%), which was used without further purification.

[0826] Amine Intermediate Example 4: **Synthesis of 5-amino-2-*tert*-butyl-4-ethylphenol**



[0827] To a solution of 2-*tert*-butyl-4-ethyl-phenol (10 g, 56.1 mmol) in DCM (50 mL) was added Et_3N (17 g, 168.0 mmol) and methyl chloroformate (11 g, 116.4 mmol) at 0 °C. The mixture was stirred overnight at room temperature. Water was added to quench the reaction and the mixture was extracted with EtOAc (200 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum to give 2-*tert*-butyl-4-ethylphenyl methyl carbonate (12 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$), 7.06-7.02 (m, 2H), 7.02 (s, 1H), 3.92 (s, 3H), 2.64 (q, J = 7.5 Hz, 2H), 1.37 (s, 9H), 1.54 (t, J = 7.5 Hz, 3H)

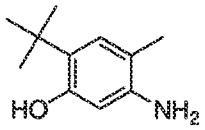
[0828] To a solution of KNO_3 (3.9 g, 38.57 mmol) in DCM (50 mL) was added TMSCl (5.5 g, 50.62 mmol) and 2-*tert*-butyl-4-ethylphenyl methyl carbonate (6 g, 25.39 mmol) at 0 °C. After stirring for 15 minutes, $AlCl_3$ (10 g, 0.08 mol) was added and then the reaction mixture was stirred for 2 h. The reaction mixture was poured onto ice water and extracted with EtOAc (50 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum to give the crude compound, which was purified by silica gel column chromatography (10-15 % EtOAc in petroleum ether as eluant) to yield 2-*tert*-butyl-4-ethyl-5-nitrophenyl methyl carbonate (5 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) 7.69 (s, 1H), 7.25 (s, 1H), 3.82 (s, 3H), 2.54 (q, J = 7.6 Hz, 2H), 1.26 (s, 9H), 1.15 (d, J = 7.6 Hz, 3H).

[0829] To a solution of (2-*tert*-butyl-4-ethyl-5-nitro-phenyl)methyl carbonate (3.9 g, 13.86 mmol) in methanol (100 mL) was added KOH (1.8 g, 32.08 mmol) at room temperature. The mixture was stirred overnight. Water was added and the reaction mixture was extracted with EtOAc (50 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum to give 2-*tert*-butyl-4-ethyl-5-nitrophenol (2.8 g, 91%), which was used in the next step without further purification.

[0830] To a solution of 2-*tert*-butyl-4-ethyl-5-nitro-phenol (3.2 g, 14.3 mmol) in methanol (20 mL) was added Raney Nickel (200 mg, 3.4 mmol) under nitrogen atmosphere. The reaction mixture was then stirred overnight at room temperature under an atmosphere of hydrogen (1 atm). The catalyst was removed by filtration through a pad of

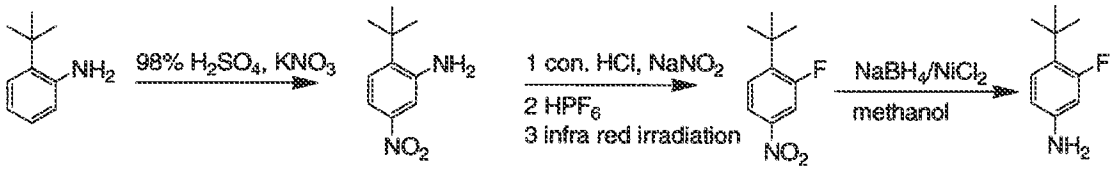
celite and the filtrate was evaporated under vacuum to give 5-amino-2-*tert*-butyl-4-ethyl-phenol (1.2 g, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 1 H), 6.06 (s, 1 H), 2.45 (q, *J* = 7.6 Hz, 2 H), 1.37 (s, 9 H), 1.21 (t, *J* = 7.6 Hz, 3 H). MS (ESI) m/e ($M+H^+$) 194.2

[0831] 5-amino-2-*tert*-butyl-4-methylphenol



[0832] 5-amino-2-*tert*-butyl-4-methylphenol can be synthesized following the general scheme above starting from 2-*tert*-butyl-4-methylphenol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1 H), 6.05 (s, 1 H), 4.73 (br s, 1 H), 3.44 (br s, 2 H), 2.09 (s, 3 H), 1.37 (s, 9 H). MS (ESI) m/z ($M+H^+$) 179.3.

[0833] Amine Intermediate Example 5: **Synthesis of 4-*tert*-butyl-3-fluoroaniline**

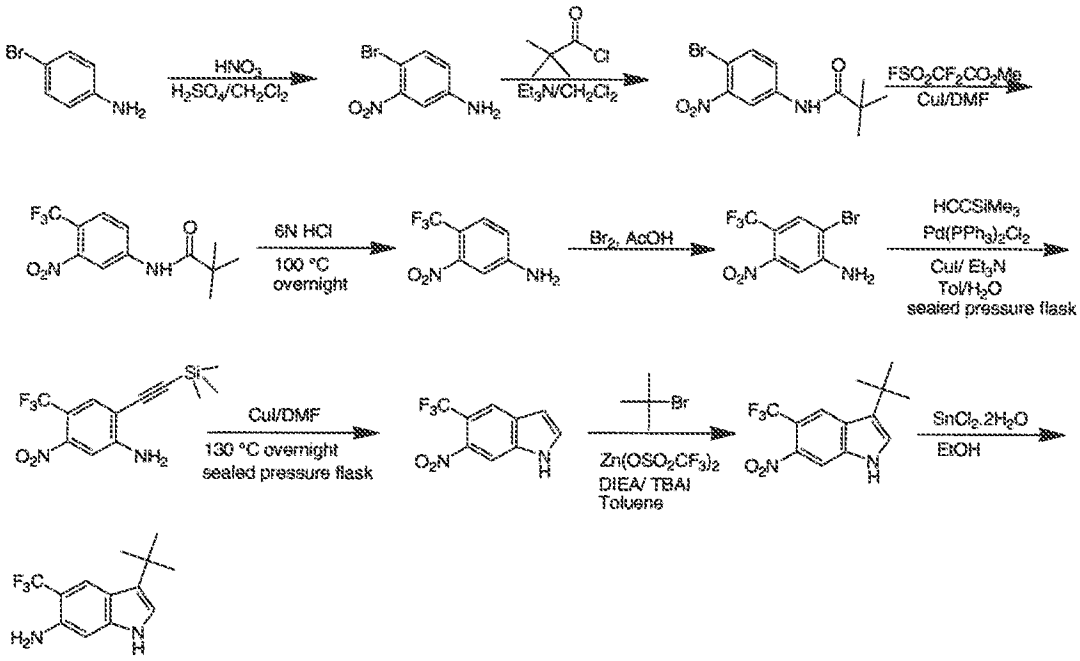


[0834] KNO_3 (7.5 g, 74.18 mmol) in conc. H_2SO_4 (50 mL) was slowly added to a mixture of 2-*tert*-butylaniline (11 g, 73.71 mmol) in conc. H_2SO_4 (50 mL) at -10 °C. The mixture was stirred at −10 °C for 1 hour and poured into ice-water. The mixture was extracted with EtOAc (150 mL × 3). The combined organics were washed with brine, dried over anhydrous Na_2SO_4 , and purified by silica gel column chromatography to obtain 2-*tert*-butyl-5-nitro-aniline (9 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.53 (dd, *J* = 2.8, 8.8 Hz, 1 H), 7.46 (d, *J* = 2.8 Hz, 1 H), 7.34 (d, *J* = 8.8 Hz, 1 H), 4.12 (br s, 2 H), 1.44 (s, 9 H).

[0835] To a stirred solution of 2-*tert*-butyl-5-nitro-aniline (5.0 g, 25.74 mmol) in H_2O (20 mL) was added conc. HCl (10 mL). Once dissolved, the mixture was cooled to 0 °C followed by the slow addition of $NaNO_2$ (1.8 g, 819 µL, 25.74 mmol) in H_2O (10 mL). The reaction mixture was stirred at 0 °C for another 0.5 h. Then HPF_6 solution was added (2 × 20 mL) batch wise. The precipitate formed was obtained by filtration, which was then heated under infrared light at approximately130-150 °C. The grey solid slowly turned to a dark viscous oil, which was purified by silica gel column chromatography to afford 1-*tert*-butyl-2-fluoro-4-nitrobenzene (0.6 g, 12%). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.96 (dd, *J* = 2.4, 8.8 Hz, 1 H), 7.87 (dd, *J* = 2.4, 12.0 Hz, 1 H), 7.48 (t, *J* = 8.0 Hz, 1 H), 1.43 (s, 9 H).

[0836] $NaBH_4$ (144 mg, 152 µL, 3.8 mmol) was added to a solution of 1-*tert*-butyl-2-fluoro-4-nitro-benzene (750 mg, 3.8 mmol) and $NiCl_2.6H_2O$ (2.6 g, 11 mmol) in methanol (15 mL) at -15 °C. After addition, the mixture was stirred for 2 minutes and water was added to quench the reaction. The reaction mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to afford 4-*tert*-butyl-3-fluoro-aniline (470 mg, 74%) which was used without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 7.08-7.02 (m, 1 H), 6.42-6.34 (m, 2 H), 1.32 (s, 9 H). MS (ESI) m/z: 168.2 [M+H]

[0837] Amine Intermediate Example 6: **Synthesis of 4-*tert*-butyl-3-fluoroaniline**



[0838] Conc. nitric acid (15.8 mL, 376.9 mmol) was added to a solution of 4-bromoaniline (40 g, 232.5 mmol) in H_2SO_4 /CH_2Cl_2 (400 mL, 1:1, v/v) dropwise at 0 °C under an atmosphere of N_2. The cooling bath was removed and the mixture was stirred at 20 °C until the starting material was consumed (about 1 h). The reaction mixture was poured onto water and neutralized with NaOH solution to pH=9 and extracted with DCM. The organic layer was dried, filtered and evaporated *in vacuo* to afford the crude product 4-bromo-3-nitro-aniline, which was used directly in the next step.

[0839] 2,2-dimethylpropanoyl chloride (28 g, 232.2 mmol) was added to a stirred solution of 4-bromo-3-nitro-aniline (42 g, 193.5 mmol) and Et_3N (51 mL, 366 mmol) in anhydrous DCM (200 mL) at 0 °C under an atmosphere of N_2. The cooling bath was removed and the stirring was continued at room temperature for 2 h. The reaction mixture was poured

into ice (500 g) and extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and evaporated *in vacuo* to afford crude product N-(4-bromo-3-nitrophenyl)pivalamide (55 g, 94%) which was used directly in the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.18-8.17 (m, 1 H), 7.64-7.63 (m, 2 H), 7.50 (br s, 1 H), 1.32 (s, 9 H).

[0840] CuI (69.8 g, 366.5 mmol) and methyl 2,2-difluoro-2-fluorosulfonyl-acetate (70.4 g, 366.4 mmol) was added to a stirred solution of N-(4-bromo-3-nitro-phenyl)-2,2-dimethyl-propanamide (55.0 g, 182.6 mmol) in anhydrous DMF (300 mL) at room temperature. The reaction mixture was stirred at 100 °C until the starting material was consumed (about 12 h).The solvent was evaporated *in vacuo* to afford crude product N-(3-nitro-4-(trifluoromethyl)phenyl)pivalamide (45.0 g, 85%)), which was used directly in next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (d, J = 2.0 Hz, 1 H), 7.87 (dd, J = 2.0, 8.8 Hz, 1 H), 7.74 (d, J = 8.8 Hz, 1 H), 7.64 (br s, 1 H), 1.34 (s, 9 H). ^{19}F NMR (282.4 MHz, $CDCl_3$): -60.62 *(S)*.

[0841] 2,2-dimethyl-N-[3-nitro-4-(trifluoromethyl)phenyl]propanamide (45.0 g, 155.0 mmol) in 6N HCl (200 mL) was stirred at 100 °C overnight. The reaction mixture was cooled to room temperature and was carefully neutralized with solid $NaHCO_3$ to pH=9. The reaction mixture was extracted with CH_2Cl_2 and dried over Na_2SO_4. The solvent was evaporated *in vacuo* to obtain the crude product 3-nitro-4-(trifluoromethyl)aniline (31.0 g, 97%), which was used directly for the next step.

[0842] To a solution of 3-nitro-4-(trifluoromethyl)aniline (31.0 g, 150.4 mmol) in HOAc (200 mL) was added bromine (9.3 mL, 180.5 mmol) at 0 °C under an atmosphere of N_2. The cooling bath was removed and the mixture was stirred at 20 °C for 1 h. The solvent was removed *in vacuo* to afford the crude product 2-bromo-5-nitro-4-(trifluoromethyl)aniline (40.0 g, 93%) , which was used directly in the next step.

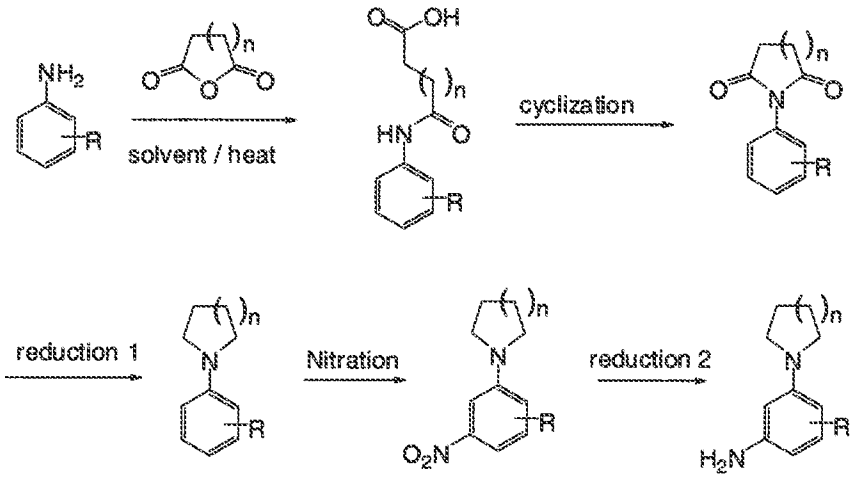
[0843] To a solution of 2-bromo-5-nitro-4-(trifluoromethyl)aniline (10.0 g, 35.1 mmol) in toluene/H_2O (100 mL, 1:1, v/v) was added CuI (0.4 g, 2.10 mmol), Et3N (9.5 mL, 68.16 mmol), $Pd(PPh_3)_2Cl_2$ (5.0 g, 7.12 mmol) and ethynyltrimethylsilane (5.2 g, 53 mmol) successively under an atmosphere of nitrogen at room temperature. The reaction mixture was transferred to a sealed pressure flask and heated at 70 °C for 10 h. The reaction mixture was cooled down to room temperature, filtered, evaporated *in vacuo* and purified by silica gel column chromatography (1 to 20% EtOAc in petroleum ether as eluant) to afford 5-nitro-4-(trifluoromethyl)-2-((trimethylsilyl)ethynyl)aniline (6.0 g, 57%) as yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.13 (s, 1H), 4.86 (br s, 2H), 0.29 (s, 9H).

[0844] To a solution of 5-nitro-4-(trifluoromethyl)-2-((trimethylsilyl)ethynyl)aniline (6.0 g, 19.85 mmol) in DMF (30 mL) was added CuI (1.9 g, 9.976 mmol) under an atmosphere of nitrogen. The reaction mixture was heated at 135 °C in a sealed pressure flask overnight. The reaction mixture was then filtered and the filtrate was washed with water, dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography (5 to 20% EtOAc in petroleum as eluant) to obtain 6-nitro-5-(trifluoromethyl)-1H-indole (1.4 g, 31%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (br s, 1 H), 8.15 (s, 1H), 8.11 (s, 1H), 7.58-7.57 (m, 1H), 6.80-6.79 (m, 1H); ^{19}F NMR (282.4 MHz, $CDCl_3$) : δ -57.82; MS (ESI): m/z $[M-H]^-$ 229.

[0845] A microwave vial charged with 6-nitro-5-(trifluoromethyl)-1H-indole (100 mg, 0.43 mmol), t-butyl bromide (30 mg, 0.22 mmol), zinc triflate (95 mg, 0.26 mmol), TBAI (80 mg, 0.22 mmol), DIEA (63 mg, 0.49 mmol) and toluene (1 mL) was sealed and heated in the microwave for 10 minutes at 120 °C. The reaction mixture was quenched with water, the layers separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over Na_2SO_4, filtered and concentrated. It was then purified by silica gel column chromatography using 0 to 20% EtOAc in hexanes to obtain 3-*tert*-butyl-6-nitro-5-(trifluoromethyl)-1H-indole. ^{1}H NMR (400.0 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.10 (s, 1H), 7.33 (d, J = 2.5 Hz, 1H), 7.28 (s, 1H) and 1.50 (s, 9H) ppm.

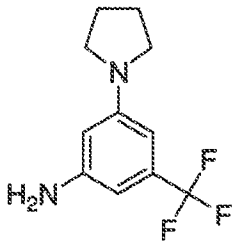
[0846] A microwave vial charged with 3-*tert*-butyl-6-nitro-5-(trifluoromethyl)-1H-indole (95 mg, 0.3319 mmol), $SnCl_2.2H_2O$ (375 mg, 1.66 mmol) and ethanol (1 mL), was sealed and heated at 62 °C for 3 h. The reaction was cooled to room temperature, diluted with EtOAc and quenched with saturated $NaHCO_3$ solution until the pH was 7. The reaction mixture was then filtered through a plug of celite. The layers were separated and the organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified via silica gel column chromatography using 0 to 40% EtOAc in hexanes to obtain 3-*tert*-butyl-5-(trifluoromethyl)-1H-indol-6-amine. LC/MS: *m/z* 257.3 $(M+H)^+$ at 1.54 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0847] General Scheme: Preparation of Meta-Substituted Anilines



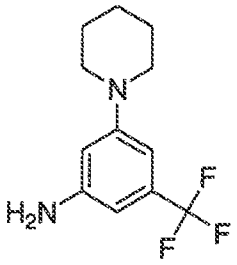
Suitable solvents include: benzene, toluene, DMSO; suitable cyclization conditions include: NaOAc, Ac_2O or thionyl chloride, NaOAc; suitable reduction 1 conditions include: BH_3 or $LiALH_4$ in Et_2O or THF; suitable nitration conditions include: HNO_3, H_2SO_4 or KNO_3, H_2SO_4; suitable reduction 2 conditions include: Pd/C, H_2 or Zn, AcOH or Fe, AcOH

[0848] 3-(pyrrolidin-1-yl)-5-(trifluoromethyl)aniline



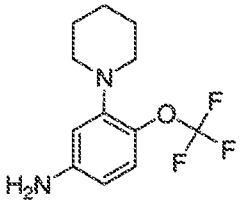
[0849] 3-(pyrrolidin-1-yl)-5-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 3-nitro-5-(trifluoromethyl)aniline and tetrahydrofuran-2,5-dione. LC/MS: *m/z* 230.9 $(M+H)^+$ at 1.22 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[0850] 3-(piperidin-1-yl)-5-(trifluoromethyl)aniline



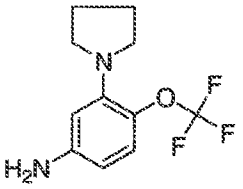
[0851] 3-(piperidin-1-yl)-5-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 4-nitro-3-(trifluoromethyl)aniline and dihydro-2H-pyran-2,6(3H)-dione. LC/MS: *m/z* 245.1 $(M+H)^+$ at 0.77 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0852] 3-(piperidin-1-yl)-4-(trifluoromethoxy)aniline



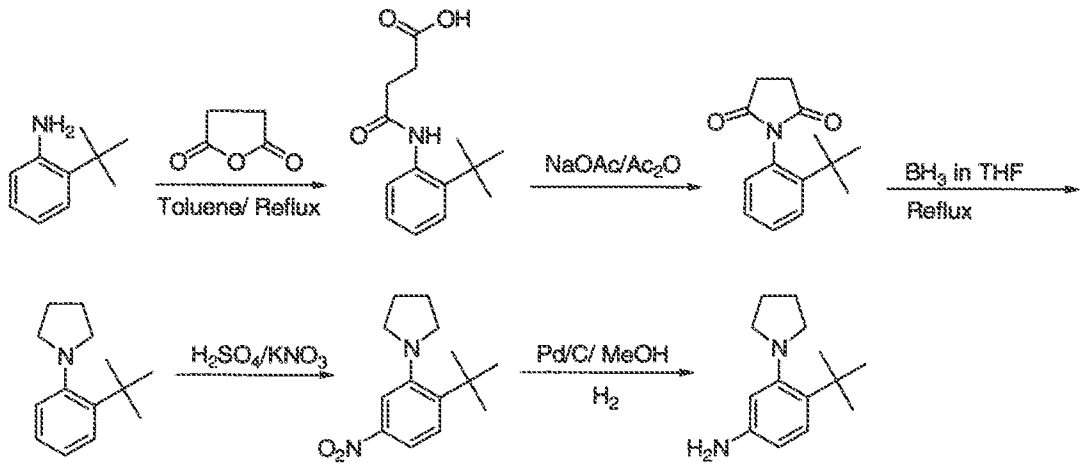
[0853] 3-(piperidin-1-yl)-4-(trifluoromethoxy)aniline can be synthesized following the general scheme above starting from 4-(trifluoromethoxy)benzene-1,3-diamine and dihydro-2H-pyran-2,6(3H)-dione. LC/MS: *m/z* 361.3 $(M+H)^+$ at 1.15 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0854] 3-(pyrrolidin-1-yl)-4-(trifluoromethoxy)aniline



[0855] 3-(pyrrolidin-1-yl)-4-(trifluoromethoxy)aniline can be synthesized following the general scheme above starting from 4-(trifluoromethoxy)benzene-1,3-diamine and tetrahydrofuran-2,5-dione. LC/MS: *m/z* 247.1 $(M+H)^+$ at 1.13 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0856] Amine Intermediate Example 7: **Synthesis of 4-*tert*-butyl-3-(pyrrolidin-1-yl)aniline**



[0857] To a solution of 2-*tert*-butylaniline (1.0 g, 6.7 mmol) in toluene (15 mL) was added tetrahydrofuran-2,5-dione (0.81 g, 8.1 mmol) and the reaction mixture was refluxed for 1h. The reaction mixture was cooled and filtered to obtain 4-(2-*tert*-butylphenylamino)-4-oxobutanoic acid, which was dissolved in acetic acid (20 mL) and sodium acetate (3.02 g, 36.86 mmol) and was stirred at 80 °C overnight. The reaction was quenched with water, the layers separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting solid was recrystallized from ethanol, to obtain pure 1-(2-*tert*-butylphenyl)pyrrolidine-2,5-dione (930 mg, 60 %). LC/MS: *m/z* 232.3 $(M+H)^+$ at 1.264 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

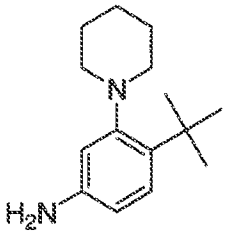
[0858] To a solution of 1-(2-*tert*-butylphenyl)pyrrolidine-2,5-dione (500 mg, 2.16 mmol) in THF (10 mL) was added BH_3 in toluene (350 mg, 1.72 mmol) dropwise and the reaction mixture was heated to reflux overnight. The reaction was cooled to room temperature and quenched with methanol (until the evolution of H_2 ceased). The solvent was evaporated to obtain 1-(2-*tert*-butylphenyl)pyrrolidine (350 mg, 80%) as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 1H), 7.28 (s, 1H), 7.15 (d, $J = 0.9$ Hz, 1H), 7.07 – 7.01 (m, 1H), 2.90 (s, 4H), 1.88 – 1.78 (m, 4H), 1.35 (s, 9H). LC/MS: *m/z* 204.1 $(M+H)^+$ at 0.88 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0859] 1-(2-*tert*-butylphenyl)pyrrolidine (350 mg, 1.72 mmol) was added portionwise to conc. H_2SO_4 (1 mL) to generate a yellow homogeneous solution. The solution was then cooled to 0 °C and KNO_3 (191 mg, 1.9 mmol) was added portionwise maintaining the internal temperature below 5 °C. The reaction was stirred for 2 h and then poured on ice-water and

extracted with DCM, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography to obtain 1-(2-*tert*-butyl-5-nitrophenyl)pyrrolidine (325 mg, 76%). LC/MS: *m/z* 248.9 $(M+H)^+$ at 2.39 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

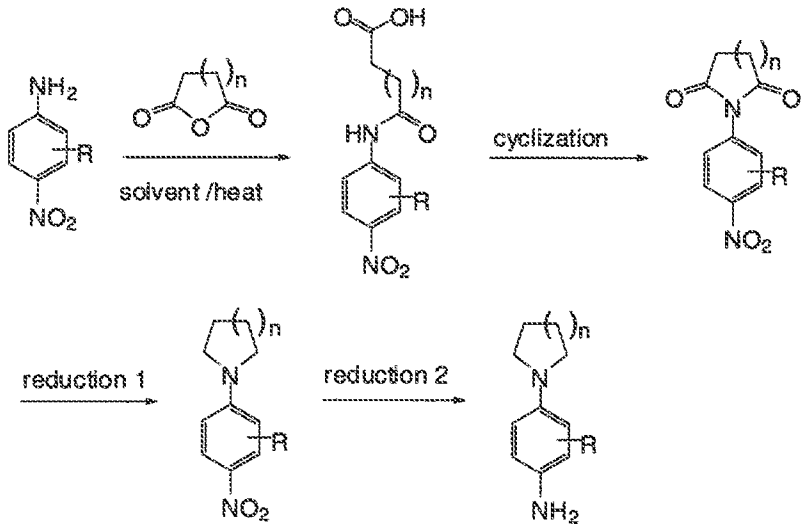
[0860] A flask charged with 1-(2-*tert*-butyl-5-nitrophenyl)pyrrolidine (150 mg, 0.60 mmol) and Pd/C (15 mg, 0.14 mmol) was flushed under N_2 followed by evacuating under vacuum. Methanol (2 mL) was added under inert atmosphere followed by evacuating under vacuum. The reaction mixture was stirred overnight under an atmosphere of H_2. The reaction mixture was filtered and the solvent was evaporated to give 4-*tert*-butyl-3-(pyrrolidin-1-yl)aniline (119 mg, 90%). LC/MS: *m/z* 218.5 $(M+H)^+$ at 2 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0861] **4-*tert*-butyl-3-(piperidin-1-yl)aniline**



[0862] 4-*tert*-butyl-3-(piperidin-1-yl)aniline can be synthesized following the general scheme above starting from 2-*tert*-butylaniline and dihydro-2H-pyran-2,6(3H)-dione . LC/MS: *m/z* 232.9 $(M+H)^+$ at 1.23 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

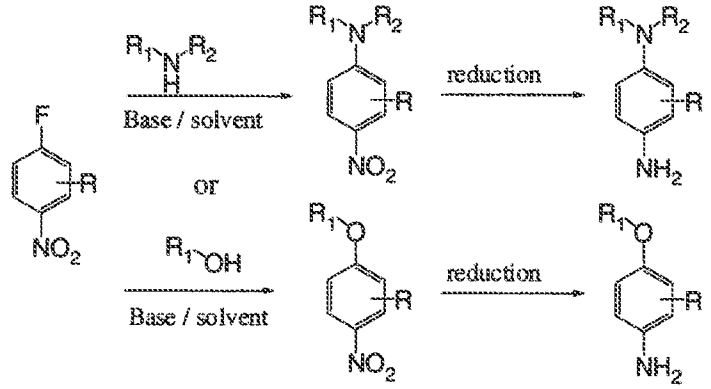
[0863] Preparation of Para-Substituted Anilines



Suitable solvents include: benzene, toluene, DMSO; suitable cyclization conditions include: NaOAc, Ac_2O or thionyl chloride, NaOAc; suitable reduction 1 conditions include: BH_3 or

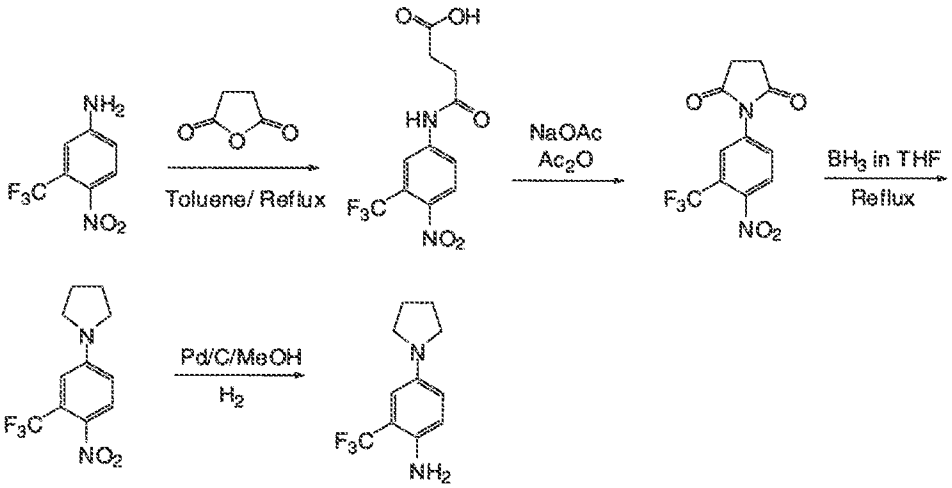
$LiALH_4$ in Et_2O or THF; suitable nitration conditions include: HNO_3, H_2SO_4 or KNO_3, H_2SO_4; suitable reduction 2 conditions include: Pd/C, H_2 or Zn, AcOH or Fe, AcOH.

[0864] Preparation of Para-Substituted Anilines via S_NAr Chemistry



Suitable bases include: triethylamine, potassium tert-butoxide, diisopropylethylamine, potassium carbonate; suitable solvents include: DMSO, DMF, CH3CN, THF; suitable reduction conditions include: Pd/C, H_2; Zn, AcOH, Fe, AcOH.

[0865] **Amine Intermediate Example 8: Synthesis of 4-(pyrrolidin-1-yl)-2-(trifluoromethyl)aniline**



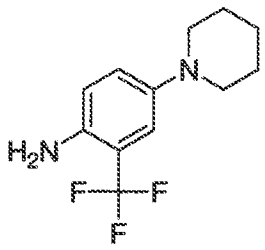
[0866] To a solution of 4-nitro-3-(trifluoro) aniline (2.0 g, 9.7 mmol) in toluene (30 mL) was added dihydrofuran-2,5-dione (1.16 g, 11.6 mmol) and reaction was reflux for 5 h. The reaction mixture was cooled to room temperature and filtered. The precipitate was washed with ether and dried to provide 4-(4-nitro-3-(trifluoromethyl)phenylamino)-4-oxobutanoic acid (1.1 g, 37%). LC/MS: *m/z* 307.3 $(M+H)^+$.

[0867] A solution of 4-(4-nitro-3-(trifluoromethyl)phenylamino)-4-oxobutanoic acid (1.1g, 3.6 mmol) and NaOAc (1.62 g, 19.75 mmol) in acetic anhydride (15 mL) was stirred overnight at 80 °C. The reaction mixture was diluted with water and extracted twice with dichloromethane. The organic layers were combined and washed with NaOH (1 N) until pH was 9. The organic layer was separated, dried with $MgSO_4$, filtered and concentrated *in vacuo* to provide 1-(4-nitro-3-(trifluoromethyl)phenyl)pyrrolidine-2,5-dione (0.4 g, 39%). LC/MS: *m/z* 288.9 $(M+H)^+$.

[0868] To a solution of 1-(4-nitro-3-(trifluoromethyl)phenyl)pyrrolidine-2,5-dione (400 mg, 1.38 mmol) in THF (10 mL) was added 1 M BH_3 solution in THF (11.10 ml) dropwise over 5 min. The reaction mixture was refluxed for 16 h under inert atmosphere, cooled, then quenched with MeOH and concentrated *in vacuo*. The crude product was used for the next step without purification. LC/MS: *m/z* 261.1 $(M+H)^+$.

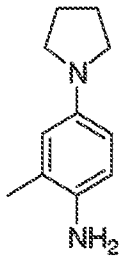
[0869] A solution of 1-(4-nitro-3-(trifluoromethyl)phenyl)pyrrolidine (350 mg, 1.34 mmol) in methanol (2 mL) and Pd/C (30 mg, 0.3 mmol) were stirred for 16 h under H_2. The reaction mixture was filtered and the solvent evaporated *in vacuo* to provide 4-(pyrrolidin-1-yl)-2-(trifluoromethyl)aniline (0.3 g, 97%). LC/MS: *m/z* 231.3 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 6.84 (d, *J* = 8.8 Hz, 1H), 6.72 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.53 (d, *J* = 2.7 Hz, 1H), 4.74 (s, 2H), 3.21 – 3.11 (m, 4H), 2.00 – 1.93 (m, 4H).

[0870] 4-(piperidin-1-yl)-2-(trifluoromethyl)aniline



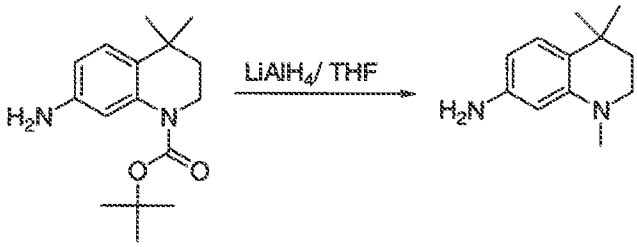
[0871] 4-(piperidin-1-yl)-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 4-nitro-3-(trifluoromethyl) aniline and dihydro-2H-pyran-2,6(3H)-dione. ^1H NMR (400.0 MHz, DMSO-d_6) δ 7.08 (dd, *J* = 2.7, 8.8 Hz, 1H), 6.88 (d, *J* = 2.8 Hz, 1H), 6.83 (d, *J* = 8.9 Hz, 1H), 5.09 (s, 2H), 2.96 (t, *J* = 5.4 Hz, 4H), 1.67 (q, *J* = 5.5 Hz, 4H) and 1.55 - 1.42 (m, 2H) ppm. LC/MS: *m/z* 244.9 $(M+H)^+$ at 0.67 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0872] 2-methyl-4-(pyrrolidin-1-yl)aniline



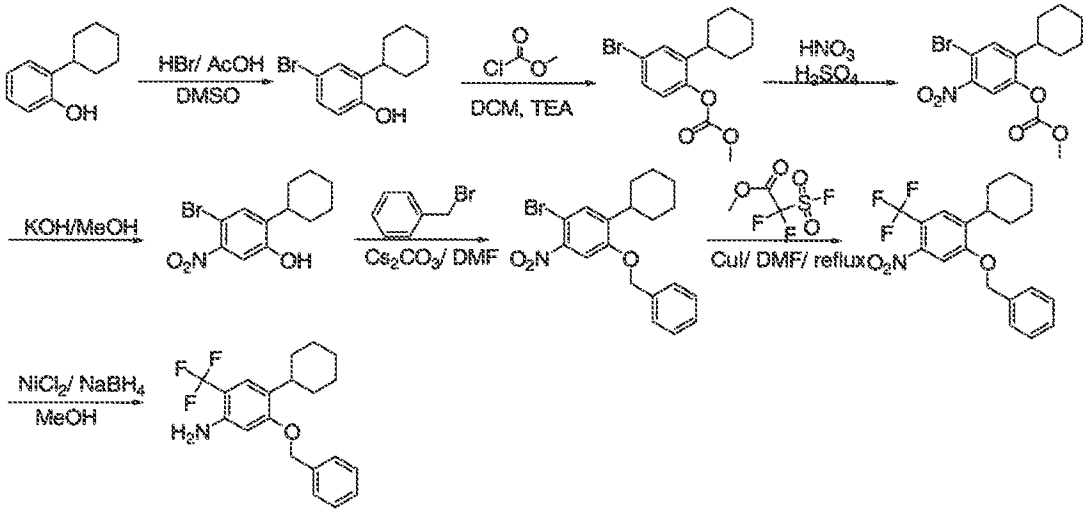
[0873] 2-methyl-4-(pyrrolidin-1-yl)aniline can be synthesized following the general scheme above starting from 3-methyl-4-nitroaniline and tetrahydrofuran-2,5-dione. ^{1}H NMR (400.0 MHz, DMSO-d_6) δ 6.56 (d, J = 8.4 Hz, 1H), 6.33 (d, J = 2.6 Hz, 1H), 6.27 (dd, J = 2.7, 8.4 Hz, 1H), 4.10 (s, 2H), 3.13 (t, J = 6.5 Hz, 4H), 2.09 - 2.04 (m, 3H) and 1.99 - 1.90 (m, 4H) ppm. LC/MS: *m/z* 177.3 $(M+H)^+$ at 0.35 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0874] Amine Intermediate Example 8: **Synthesis of 1,4,4-trimethyl-1,2,3,4-tetrahydroquinolin-7-amine**



[0875] To a solution of *tert*-butyl 7-amino-4,4-dimethyl-2,3-dihydroquinoline-1-carboxylate (100 mg, 0.36 mmol) in THF (2.2 mL) under an inert atmosphere was added $LiAlH_4$ (1.8 mL of 1 M, 1.8 mmol) dropwise. The reaction mixture was heated to reflux and stirred for 4 h. The reaction was cooled to room temperature and quenched with of 0.4 M NaOH solution (0.6 mL), the aqueous layer was extracted with DCM, dried over Na_2SO_4, filtered and concentrated to an orange oil. The residue was purified via reverse phase HPLC. LC/MS: *m/z* 191.5 $(M+H)^+$ at 0.92 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0876] Amine Intermediate Example 9: **Synthesis of 5-(benzyloxy)-4-cyclohexyl-2-(trifluoromethyl)aniline**



[0877] To a stirring solution of 2-cyclohexylphenol (26.0g, 146.8 mmol) in glacial acetic acid (100 mL) was added HBr in acetic acid (150 mL of 33 %w/w,) and H_2O (52 mL), followed by the dropwise addition of DMSO (100 mL) over 10 min. The reaction was then carefully quenched with saturated $NaHCO_3$ and concentrated *in vacuo*. The residue was brought up in ether (400 mL), washed with water (2 x 100 mL) and brine (1 x 100 mL), and dried over anhydrous Na_2SO_4, filtered and concentration to yield a crude oil that was purified by silica gel column chromatography, using 15-30% EtOAc/hexane gradient to yield 4-bromo-2-cyclohexyl-phenol (35.0 g, 93%)

[0878] 4-Bromo-2-cyclohexyl-phenol (35.0 g, 137.2 mmol) was dissolved in DCM (200 mL) and Et_3N (38 mL, 272.6 mmol), cooled to 0 °C, then treated with methyl chloroformate (15.0 g, 153.4 mmol) and allowed to warm to room temperature over 16 h. The reaction was quenched with 30 mL saturated $NaHCO_3$, washed with 50% saturated $NaHCO_3$ (1 x 100 mL) and brine (1 x 100 mL), then dried over anhydrous Na_2SO_4, filtered and concentrated to yield a crude oil that was purified by silica gel column chromatography, using 20% EtOAc/hexane gradient to yield (4-bromo-2-cyclohexyl-phenyl) methyl carbonate (38.0 g, 88%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 2.3 Hz, 1H), 7.32-7.29 (m, 1H), 6.98 (d, J = 8.6 Hz, 1H), 3.92 (s, 3H), 2.71-2.64 (m, 1H), 1.85-1.74 (m, 5H), 1.39-1.20 (m, 5H).

[0879] (4-Bromo-2-cyclohexyl-phenyl) methyl carbonate (5.0 g, 15.96 mmol) was added portionwise to conc. H_2SO_4 (15 mL) to generate a colorless homogeneous solution. This solution was then cooled to 0 °C and KNO_3 (1.77 g, 17.51 mmol) was added portionwise maintaining the internal temperature below 5 °C. The reaction was stirred for 2 h and then

poured on ice water and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was then purified by silica gel column chromatography using 10% EtOAc/hexane gradient to yield 4-bromo-2-cyclohexyl-5-nitro-phenyl methyl carbonate (3.25 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.69 (s, 1H), 3.98 (s, 3H), 2.81-2.75 (m, 1H), 1.90-1.79 (m, 5H), 1.44-1.26 (m, 5H)

[0880] To a solution of (4-bromo-2-cyclohexyl-5-nitro-phenyl) methyl carbonate (1.5 g, 4.2 mmol) in methanol (15 mL) was added KOH (353 mg, 6.3 mmol) portionwise at 0 °C. After addition, the reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was acidified with 1N HCl. The solvent was evaporated and water was added. The aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layer was dried over Na_2SO_4 , filtered and concentrated to give 4-bromo-2-cyclohexyl-5-nitrophenol (1.2 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.39 (s, 1H), 5.10 (s, 1H), 2.90-2.83 (m, 1H), 1.91-1.89 (m, 4H), 1.83-1.80 (m, 1H), 1.51-1.24 (m, 5H)

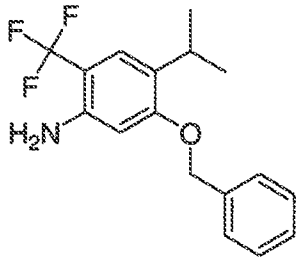
[0881] To a solution of 4-bromo-2-cyclohexyl-5-nitro-phenol (1.19 g, 4.0 mmol) and Cs_2CO_3 (1.54 g, 4.72 mmol) in DMF (10 mL) was added benzyl bromide (1.02 g, 707 µL, 6.0 mmol) dropwise. The reaction mixture was stirred at room temperature under an inert atmosphere for 2 h. The reaction was quenched with water and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography using 5% EtOAc/hexane gradient gave 1-(benzyloxy)-4-bromo-2-cyclohexyl-5-nitrobenzene (1.35 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.39 (s, 1H), 7.36-7.25 (m, 5H), 5.06 (s, 2H), 2.99-2.93 (m, 1H), 1.79 (d, J = 11.5 Hz, 4H), 1.70 (d, J = 13.4 Hz, 1H), 1.39-1.14 (m, 5H)

[0882] To a solution of 1-benzyloxy-4-bromo-2-cyclohexyl-5-nitro-benzene (500 mg, 1.28 mmol) and CuI (487.0 mg, 2.56 mmol) in DMF (5 mL) at room temperature was added methyl 2,2-difluoro-2-fluorosulfonyl-acetate (492 mg, 326.0 mL, 2.56 mmol) dropwise under an inert atmosphere. The reaction mixture was then heated at 105 °C for 2 h. The reaction mixture was cooled to room temperature, quenched with $NaHCO_3$ and filtered through a plug of celite (to remove Cu salts). The aqueous layer was extracted with ethyl acetate, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography using 10% EtOAc/hexane gradient to yield 1-(benzyloxy)-2-cyclohexyl-5-nitro-4-(trifluoromethyl)benzene (435 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H),

7.62 (s, 1H), 7.42-7.28 (m, 5H), 5.27 (s, 2H), 2.98-2.92 (m, 1H), 1.75-1.62 (m, 5H), 1.47-1.13 (m, 5H)

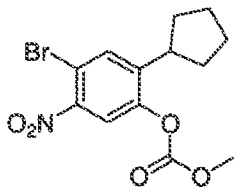
[0883] To a solution of 1-(benzyloxy)-2-cyclohexyl-5-nitro-4-(trifluoromethyl)benzene (250 mg, 0.66 mmol) and $NiCl_2$ (170 mg, 1.31 mmol) in methanol (2.5 mL) was added $NaBH_4$ (50 mg, 1.32 mmol) portionwise at 0 °C. The reaction mixture turned black after 5 minutes. The reaction mixture was quenched with $NaHCO_3$ and diluted with EtOAc. The reaction mixture was filtered through a plug of celite, the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was then purified by silica gel column chromatography using 10% EtOAc/hexane gradient to give 5-benzyloxy-4-cyclohexyl-2-(trifluoromethyl)aniline (150 mg, 65%). LC/MS: *m/z* 350.3 $(M+H)^+$ at 2.40 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0884] 5-(benzyloxy)-4-isopropyl-2-(trifluoromethyl)aniline



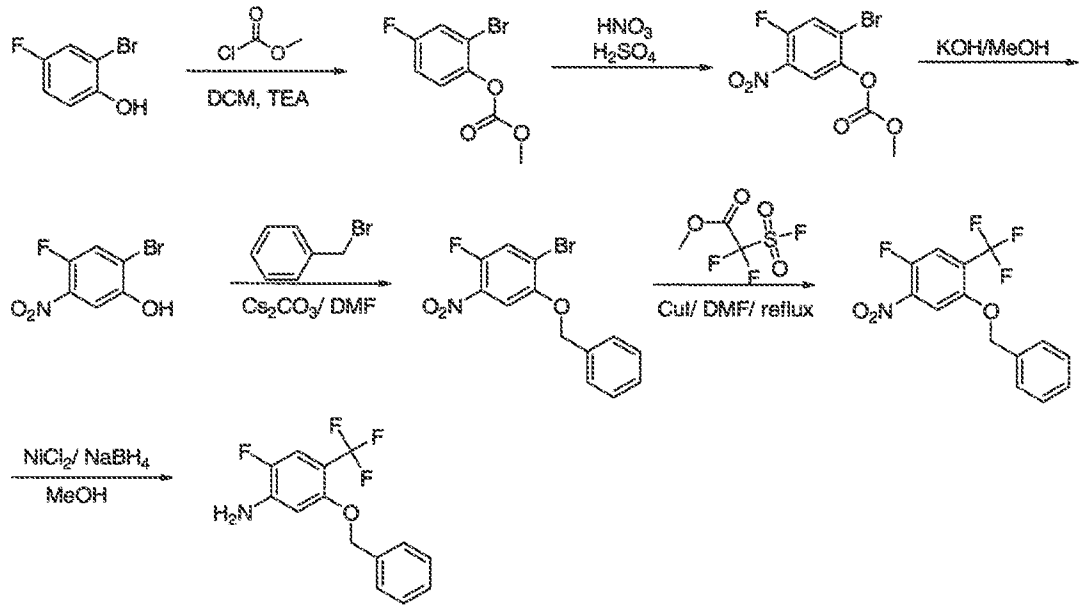
[0885] 5-(benzyloxy)-4-isopropyl-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 2-isopropylphenol. LC/MS: *m/z* 310.3 $(M+H)^+$ at 2.21 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0886] 4-bromo-2-cyclopentyl-5-nitrophenyl methyl carbonate



[0887] 4-bromo-2-cyclopentyl-5-nitrophenyl methyl carbonate can be synthesized following the general scheme above starting from 2-cyclopentylphenol). ^1H NMR (400.0 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.88 (s, 1H), 3.88 (d, J = 5.7 Hz, 3H), 3.13 (dd, J = 9.4, 17.2 Hz, 1H), 1.96 - 1.92 (m, 2H), 1.80 - 1.75 (m, 2H), 1.68 - 1.54 (m, 4H).

[0888] Amine Intermediate Example 10: **Synthesis of 5-(benzyloxy)-2-fluoro-4-(trifluoromethyl)aniline**



[0889] A solution of 2-bromo-4-fluoro-phenol (7.0 g, 36.65 mmol) and DMAP (224 mg, 1.83 mmol) in DCM (15 mL) and Et_3N (7.42 g, 10 mL, 73.30 mmol) was cooled to 0 °C, then treated with methyl chloroformate (14.5 g, 153.4 mmol) dropwise and allowed to warm to room temperature over 16 h. The reaction mixture was quenched with 30 mL saturated $NaHCO_3$, washed with 50% saturated $NaHCO_3$ (1 x 100 mL) and brine (1 x 100 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered and concentrated to yield a crude oil that was purified by silica gel column chromatography, using 15% EtOAc/hexane gradient to yield (2-bromo-4-fluoro-phenyl) methyl carbonate (8.25 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, J = 7.7, 2.9 Hz, 1H), 7.23 (dd, J = 9.0, 5.0 Hz, 1H), 7.08 (ddd, J = 9.0, 7.6, 2.9 Hz, 1H), 3.97 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.78 (td, J = 7.9, 5.2 Hz, 1H).

[0890] (2-Bromo-4-fluoro-phenyl) methyl carbonate (8.25 g, 33.13 mmol) was added portionwise to conc. H_2SO_4 (45 mL) to generate a colorless homogeneous solution. This solution was then cooled to 0 °C and KNO_3 (3.7 g, 36.44 mmol) was added portionwise maintaining the internal temperature below 5 °C. The reaction was stirred for 2 h and then poured on ice-water and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was then purified by silica gel column chromatography using 15% EtOAc/hexane gradient to yield 2-bromo-4-fluoro-5-nitrophenyl methyl carbonate (8.93 g, 92%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 6.7 Hz, 1H), 7.65 (d, J = 9.6 Hz, 1H), 4.01 (s, 3H).

[0891] To a solution of 2-bromo-4-fluoro-5-nitrophenyl methyl carbonate (8.90 g, 30.27 mmol) in methanol (100 mL) was added KOH (4.25 g, 75.68 mmol) portionwise at 0 °C. After the addition was complete the reaction mixture was allowed to warm to room temperature and stirred for 1.5 h. The reaction mixture was acidified by 1N HCl. The solvent was evaporated and water was added. The aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated to give 2-bromo-4-fluoro-5-nitro-phenol (7.05 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 6.6 Hz, 1H), 7.51 (d, J = 9.6 Hz, 1H), 5.62 (s, 1H).

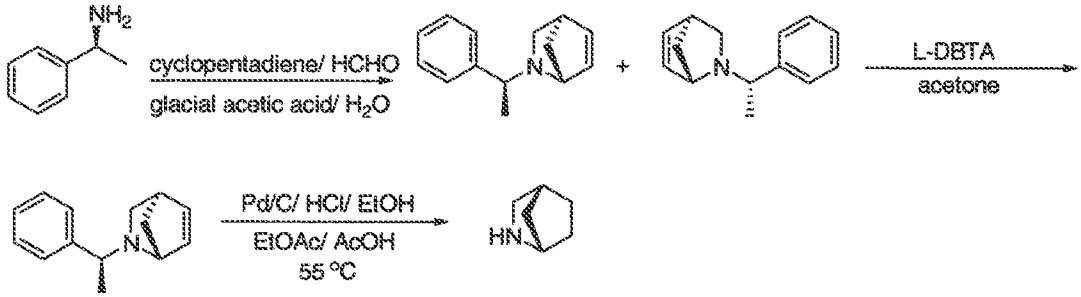
[0892] To a solution of 2-bromo-4-fluoro-5-nitro-phenol (3.5 g, 14.83 mmol) and Cs_2CO_3 (5.80 g, 17.80 mmol) in DMF (26 mL) was added benzyl bromide (2.80 g, 1.94 mL, 16.31 mmol) dropwise. The reaction was stirred at room temperature under an inert atmosphere for 2 h. The reaction was quenched with water and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography using 40% DCM/hexane gradient to yield 1-(benzyloxy)-2-bromo-4-fluoro-5-nitrobenzene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 6.4 Hz, 1H), 7.59 (d, J = 9.9 Hz, 1H), 7.52 – 7.34 (m, 5H), 5.23 (s, 2H).

[0893] To a solution of 1-benzyloxy-2-bromo-4-fluoro-5-nitro-benzene (500 mg, 1.53 mmol) and CuI (584 mg, 3.07 mmol) in DMF (5 mL) at room temperature was added methyl 2,2-difluoro-2-fluorosulfonyl-acetate (589.0 mg, 3.07 mmol) dropwise under an inert atmosphere. The reaction mixture was then heated at 105 °C for 3 h, then cooled to room temperature, quenched with $NaHCO_3$ and filtered through a plug of celite (to remove Cu salts). The aqueous layer was extracted with ethyl acetate, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography using 10% EtOAc/hexane gradient to give 1-(benzyloxy)-4-fluoro-5-nitro-2-(trifluoromethyl)benzene (400 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 5.7 Hz, 1H), 7.62 – 7.57 (m, 1H), 7.48 – 7.37 (m, 5H), 5.27 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.28 (s, 3H), -126.02 (dd, J = 10.2, 5.7 Hz, 1H).

[0894] To a solution of 1-(benzyloxy)-4-fluoro-5-nitro-2-(trifluoromethyl)benzene (382 mg, 1.21 mmol) and $NiCl_2$ (314 mg, 2.42 mmol) in methanol (40 mL) was added $NaBH_4$ (50 mg, 1.32 mmol) portionwise at 0 °C. The reaction turned black after 20 minutes. The reaction mixture was quenched with $NaHCO_3$ and diluted with EtOAc. The reaction mixture was then filtered through a plug of celite, the layers separated and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered and

concentrated. The residue was then purified by silica gel column chromatography using 15% EtOAc/hexane gradient to give 5-(benzyloxy)-2-fluoro-4-(trifluoromethyl)aniline (150 mg, 43%). LC/MS: *m/z* 286.1 $(M+H)^+$ at 1.89 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0895] Amine Intermediate Example 11: **Synthesis of (1*S*,4*R*)-2-azabicyclo[2.2.1]heptane**



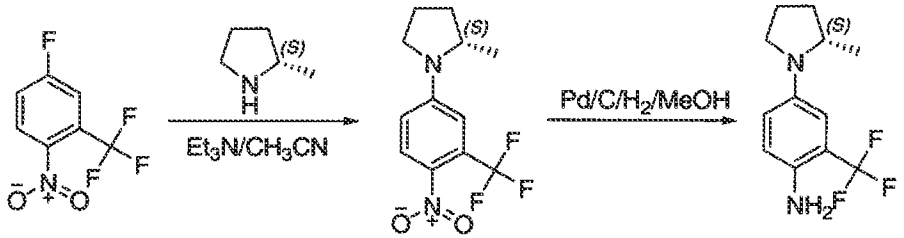
[0896] A cooled solution of (1*S*)-1-phenylethanamine (19.0 g, 156.8 mmol) in H_2O (60 mL) at 0 °C was treated with a solution of glacial acetic acid (9 mL) in water (20 mL), followed by the addition of freshly distilled cyclopentadiene (20.73 g, 26.01 mL, 313.6 mmol) and formaldehyde (7.06 g, 6.5 mL, 235.2 mmol). The resulting reaction mixture was stirred for 48 h at 5 °C. The reaction mixture was then poured onto ice water (100 mL) and 50% ethyl acetate in hexane (100 mL) and then basified with NaOH pallets (pH ≈10) at 0 °C. The layers were separated and the aqueous layer was extracted with 50% ethyl acetate/hexane (2x 100 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to get a mixture of (1*R*,4*R*)-2-((*S*)-1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene and (1*S*,4*S*)-2-((*S*)-1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene as an oil (33.0 g). The product is prone to undergo retro-Diels-Alder reaction, so it was directly used for the next step. LC/MS: *m/z* 199.8 $(M+H)^+$ at 0.38 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0897] To a solution of (2*R*,3*R*)-2,3-dibenzoyloxybutanedioic acid (55.75 g, 155.6 mmol) in acetone (500 mL) was added a solution of (1*R*,4*R*)-5-[(1*S*)-1-phenylethyl]-5-azabicyclo[2.2.1]hept-2-ene and (1*S*,4*S*)-5-[(1*S*)-1-phenylethyl]-5-azabicyclo[2.2.1]hept-2-ene (31.01 g, 155.6 mmol) in acetone (200 mL) dropwise. The reaction mixture was stirred for 15 h at room temperature. The precipitate formed was collected by filtration and washed with acetone (2x 75 mL) and dried under reduced pressure. The residue was slowly added to cooled (0 °C) 10 % NaOH (350 mL) and ethyl acetate (300 mL) solution and stirred for 15 minutes (pH 10). The layers were separated and aqueous layer was extracted with ethyl acetate (3x 150

mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain (1*R*,4*R*)-2-((*S*)-1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene, which was used directly used for the next step. LC/MS: *m/z* 199.8 $(M+H)^+$ at 0.38 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0898] A flask charged with (1*R*,4*R*)-5-[(1*S*)-1-phenylethyl]-5-azabicyclo[2.2.1]hept-2-ene (19 g, 95.34 mmol) and palladium on carbon (4 g, 133.0 mmol) was flushed with N_2 followed by evacuating under vacuum. EtOAc (50 mL) and EtOH (200 mL) were added under inert atmosphere followed by evacuating under vacuum. The reaction mixture was then stirred overnight under an atmosphere of H_2. AcOH (60 mL) was added and then the reaction mixture was stirred overnight at 55 °C under an atmosphere of H_2. The reaction mixture was cooled to room temperature and filtered through a plug of celite to remove the palladium catalyst, washed with ethyl acetate, concentrated *in vacuo* and the residue was treated with 1N HCl solution in ether. The solvents were evaporated under reduced pressure to obtain (1*S*,4*R*)-2-azabicyclo[2.2.1]heptane .

[0899] Amine Intermediate Example 12: **Synthesis of (*S*)-4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline**



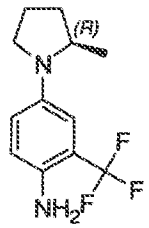
[0900] To a solution of 5-fluoro-2-nitrobenzotrifluoride (2.0 g, 9.56 mmol) in CH_3CN (20 mL) was added Et_3N (2.41 g, 23.90 mmol) followed by the addition of (*S*)-2-methylpyrrolidine tosylate (3.18 g, 12.43 mmol). The reaction was stirred at 80 °C overnight. The reaction was then quenched with water and the aqueous layer was extracted with DCM. The combined organics were washed with 1N HCl, dried over $MgSO_4$, filtered and concentrated to give (*S*)-2-methyl-1-(4-nitro-3-(trifluoromethyl) phenyl) pyrrolidine (2.45 g, 94% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 9.1 Hz, 1H), 6.88 (s, 1H), 6.85 (d, J = 2.6 Hz, 1H), 4.17-4.13 (m, 1H), 3.59-3.54 (m, 1H), 3.33-3.28 (m, 1H), 2.14-2.00 (m, 3H), 1.80-1.71 (m, 1H), 1.14 (d, J = 6.3 Hz, 3H). LC/MS: *m/z* 275.3 $(M+H)^+$ at 1.98 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0901] A flask charged with (*S*)-2-methyl-1-(4-nitro-3-(trifluoromethyl) phenyl) pyrrolidine (2.45 g, 8.9 mmol) and palladium on carbon (245 mg, 10 wt %) was flushed with N_2 followed by evacuating under vacuum. Methanol (15 mL) was added under inert

atmosphere followed by evacuating under vacuum. The reaction mixture was stirred overnight under an atmosphere of H_2. The palladium catalyst was removed by filtration and solvent was removed under reduced pressure to give (*S*)-4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl) aniline in quantitative yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.78 (d, J = 8.8 Hz, 1H), 6.70-6.67 (m, 1H), 6.47 (d, J = 2.7 Hz, 1H), 4.68 (s, 2H), 3.76-3.69 (m, 1H), 3.32-3.27 (m, 1H), 3.02-2.96 (m, 1H), 2.05-1.94 (m, 2H), 1.93-1.84 (m, 1H), 1.64-1.58 (m, 1H), 1.05 (d, J = 6.1 Hz, 3H). LC/MS: *m/z* 245.1 $(M+H)^+$ at 0.48 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

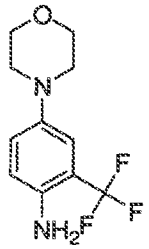
[0902] The following compounds can be prepared following the general scheme above.

[0903] (*R*)-4-(2-Methylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline



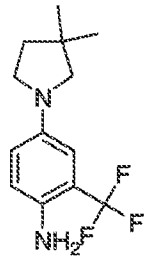
[0904] (*R*)-4-(2-Methylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (*R*)-2-methylpyrrolidine. ^{1}H NMR (400.0 MHz, DMSO-d_6) δ 6.79 (d, J = 8.8 Hz, 1H), 6.68 (dd, J = 2.3, 8.7 Hz, 1H), 6.47 (d, J = 2.5 Hz, 1H), 4.69 (s, 2H), 3.73 (t, J = 5.6 Hz, 1H), 3.33 - 3.27 (m, 1H), 2.99 (q, J = 8.0 Hz, 1H), 2.03 - 1.87 (m, 3H), 1.64 - 1.60 (m, 1H) and 1.05 (d, J = 6.1 Hz, 3H). LC/MS: *m/z* 245.3 $(M+H)^+$ at 0.57 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0905] 4-Morpholino-2-(trifluoromethyl)aniline



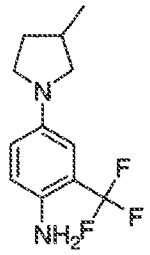
[0906] 4-Morpholino-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and morpholine. ^{1}H NMR (400.0 MHz, DMSO-d_6) δ 7.04 (dd, J = 2.6, 8.9 Hz, 1H), 6.84 - 6.79 (m, 2H), 5.07 (s, 2H), 3.71 (t, J = 4.7 Hz, 4H) and 2.93 (t, J = 4.7 Hz, 4H). LC/MS: *m/z* 247.1 $(M+H)^+$ at 0.43 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0907] 4-(3,3-Dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline



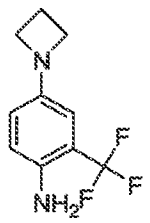
[0908] 4-(3,3-Dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and 3,3-dimethylpyrrolidine. LC/MS: *m/z* 259.1 $(M+H)^+$ at 1.18 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0909] 4-(3-Methylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline



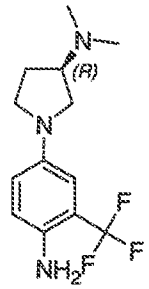
[0910] 4-(3-Methylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and 3-methylpyrrolidine. ^{1}H NMR (400.0 MHz, DMSO-d_6) δ 6.78 (d, J = 8.8 Hz, 1H), 6.64 (dd, J = 2.5, 8.8 Hz, 1H), 6.44 (d, J = 2.7 Hz, 1H), 4.67 (s, 2H), 3.31 (t, J = 7.6 Hz, 1H), 3.20 - 3.15 (m, 2H), 2.73 - 2.69 (m, 1H), 2.33 (dd, J = 7.0, 15.1 Hz, 1H), 2.10 - 2.04 (m, 1H), 1.54 (td, J = 8.2, 4.0 Hz, 1H) and 1.06 (d, J = 6.7 Hz, 3H) ppm. LC/MS: *m/z* 245.1 $(M+H)^+$ at 0.94 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0911] 4-(Azetidin-1-yl)-2-(trifluoromethyl)aniline



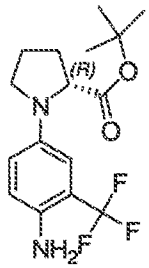
[0912] 4-(Azetidin-1-yl)-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and azetidine. LC/MS: *m/z* 217.3 $(M+H)^+$ at 0.34 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0913] (*R*)-1-(4-Amino-3-(trifluoromethyl)phenyl)-N,N-dimethylpyrrolidin-3-amine



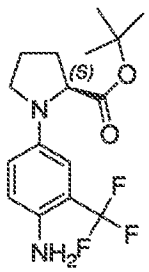
[0914] (*R*)-1-(4-Amino-3-(trifluoromethyl)phenyl)-N,N-dimethylpyrrolidin-3-amine can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (*R*)-N,N-dimethylpyrrolidin-3-amine. LC/MS: *m/z* 274.5 $(M+H)^+$ at 1.32 min (10%--99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0915] (*R*)-*tert*-Butyl 1-(4-amino-3-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate



[0916] (*R*)-*tert*-Butyl 1-(4-amino-3-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (*R*)-*tert*-butyl pyrrolidine-2-carboxylate. LC/MS: *m/z* 331.5 $(M+H)^+$ at 1.70 min (10%--99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

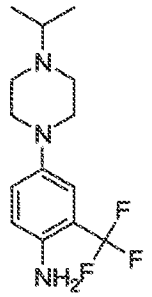
[0917] (*S*)-*tert*-Butyl 1-(4-amino-3-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate



[0918] (*S*)-*tert*-Butyl 1-(4-amino-3-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate can be synthesized following the general scheme above starting from 5-fluoro-2-

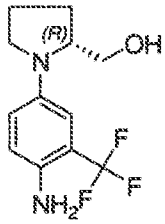
nitrobenzotrifluoride and (*S*)-*tert*-butyl pyrrolidine-2-carboxylate. LC/MS: *m/z* 331.5 $(M+H)^+$ at 1.70 min (10%--99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0919] 4-(4-Isopropylpiperazin-1-yl)-2-(trifluoromethyl)aniline



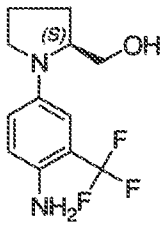
[0920] 4-(4-Isopropylpiperazin-1-yl)-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and 1-isopropylpiperazine. ^1H NMR (400.0 MHz, DMSO-d_6) δ 7.02 (dd, J = 2.6, 8.8 Hz, 1H), 6.82 - 6.77 (m, 2H), 5.03 (s, 2H), 2.95 - 2.92 (m, 4H), 2.65 (t, J = 6.5 Hz, 1H), 2.56 - 2.50 (m, 4H) and 0.99 (d, J = 6.5 Hz, 6H) ppm. LC/MS: *m/z* 288.3 $(M+H)^+$ at 0.97 min (10%--99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0921] (*R*)-(1-(4-amino-3-(trifluoromethyl)phenyl)pyrrolidin-2-yl)methanol



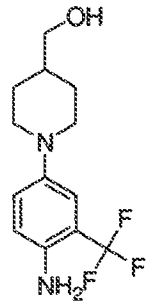
[0922] (*R*)-(1-(4-amino-3-(trifluoromethyl)phenyl)pyrrolidin-2-yl)methanol can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (*R*)-pyrrolidin-2-ylmethanol. LC/MS: *m/z* 261.1 $(M+H)^+$ at 0.90 min (10%--99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0923] (*S*)-(1-(4-Amino-3-(trifluoromethyl)phenyl)pyrrolidin-2-yl)methanol



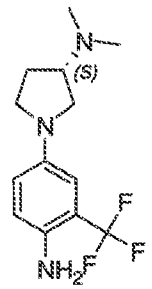
[0924] (*S*)-(1-(4-Amino-3-(trifluoromethyl)phenyl)pyrrolidin-2-yl)methanol can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (*S*)-pyrrolidin-2-ylmethanol. LC/MS: *m/z* 261.1 $(M+H)^+$ at 0.91 min (10%--99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0925] (1-(4-Amino-3-(trifluoromethyl)phenyl)piperidin-4-yl)methanol



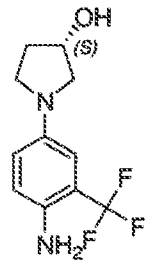
[0926] (1-(4-Amino-3-(trifluoromethyl)phenyl)piperidin-4-yl)methanol can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and piperidin-4-ylmethanol. LC/MS: *m/z* 275.3 $(M+H)^+$ at 0.91 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0927] (*S*)-1-(4-Amino-3-(trifluoromethyl)phenyl)-N,N-dimethylpyrrolidin-3-amine



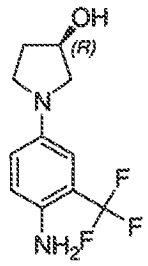
[0928] (*S*)-1-(4-Amino-3-(trifluoromethyl)phenyl)-N,N-dimethylpyrrolidin-3-amine can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (*S*)-N,N-dimethylpyrrolidin-3-amine. LC/MS: *m/z* 274.1 $(M+H)^+$ at 0.78 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0929] (*S*)-1-(4-Amino-3-(trifluoromethyl)phenyl)pyrrolidin-3-ol



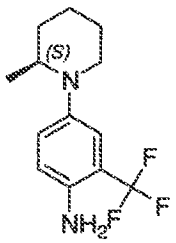
[0930] (*S*)-1-(4-Amino-3-(trifluoromethyl)phenyl)pyrrolidin-3-ol can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (*S*)-pyrrolidin-3-ol. LC/MS: *m/z* 277.1 $(M+H)^+$ at 1.28 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0931] (*R*)-1-(4-Amino-3-(trifluoromethyl)phenyl)pyrrolidin-3-ol



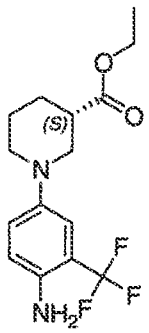
[0932] (*R*)-1-(4-Amino-3-(trifluoromethyl)phenyl)pyrrolidin-3-ol can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (*R*)-pyrrolidin-3-ol. LC/MS: *m/z* 277.1 $(M+H)^+$ at 1.28 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0933] (*S*)-4-(2-Methylpiperidin-1-yl)-2-(trifluoromethyl)aniline



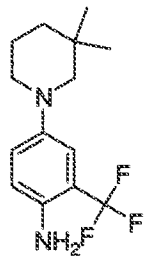
[0934] (*S*)-4-(2-Methylpiperidin-1-yl)-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (*S*)-2-methylpiperidine. LC/MS: *m/z* 259.1 $(M+H)^+$ at 0.66 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0935] (*S*)-Ethyl 1-(4-amino-3-(trifluoromethyl)phenyl)piperidine-3-carboxylate



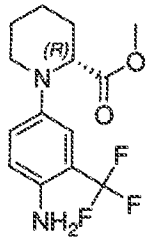
[0936] (*S*)-Ethyl 1-(4-amino-3-(trifluoromethyl)phenyl)piperidine-3-carboxylate can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (*S*)-ethyl piperidine-3-carboxylate. LC/MS: *m/z* 317.1 $(M+H)^+$ at 1.01 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0937] 4-(3,3-Dimethylpiperidin-1-yl)-2-(trifluoromethyl)aniline



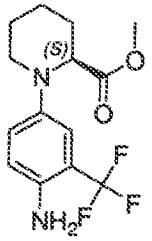
[0938] 4-(3,3-Dimethylpiperidin-1-yl)-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and 3,3-dimethylpiperidine. LC/MS: *m/z* 273.1 $(M+H)^+$ at 0.96 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0939] (*R*)-Methyl 1-(4-amino-3-(trifluoromethyl)phenyl)piperidine-2-carboxylate



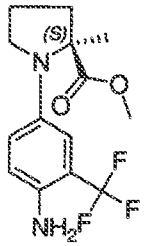
[0940] (*R*)-Methyl 1-(4-amino-3-(trifluoromethyl)phenyl)piperidine-2-carboxylate can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (*R*)-methyl piperidine-2-carboxylate. LC/MS: *m/z* 303.3 $(M+H)^+$ at 1.03 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0941] (*S*)-Methyl 1-(4-amino-3-(trifluoromethyl)phenyl)piperidine-2-carboxylate



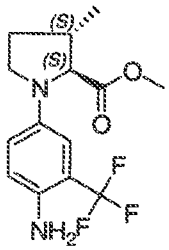
[0942] (*S*)-Methyl 1-(4-amino-3-(trifluoromethyl)phenyl)piperidine-2-carboxylate can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (*S*)-methyl piperidine-2-carboxylate. LC/MS: *m/z* 303.3 $(M+H)^+$ at 1.03 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0943] (*S*)-Methyl 1-(4-amino-3-(trifluoromethyl)phenyl)-2-methylpyrrolidine-2-carboxylate



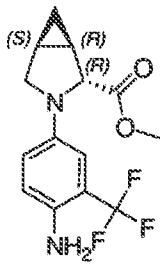
[0944] (*S*)-Methyl 1-(4-amino-3-(trifluoromethyl)phenyl)-2-methylpyrrolidine-2-carboxylate can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (*S*)-methyl 2-methylpyrrolidine-2-carboxylate. LC/MS: *m/z* 303.1 $(M+H)^+$ at 1.27 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0945] (2*S*,3*S*)-Methyl 1-(4-amino-3-(trifluoromethyl)phenyl)-3-methylpyrrolidine-2-carboxylate



[0946] (2*S*,3*S*)-Methyl 1-(4-amino-3-(trifluoromethyl)phenyl)-3-methylpyrrolidine-2-carboxylate can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (2*S*,3*S*)-methyl 3-methylpyrrolidine-2-carboxylate. LC/MS: *m/z* 303.3 $(M+H)^+$ at 1.30 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

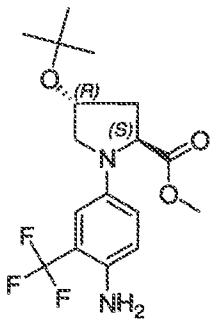
[0947] (1*R*,2*R*,5*S*)-Methyl 3-(4-amino-3-(trifluoromethyl)phenyl)-3-azabicyclo[3.1.0]hexane-2-carboxylate



[0948] (1*R*,2*R*,5*S*)-Methyl 3-(4-amino-3-(trifluoromethyl)phenyl)-3-azabicyclo[3.1.0]hexane-2-carboxylate can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (1*R*,2*R*,5*S*)-methyl 3-

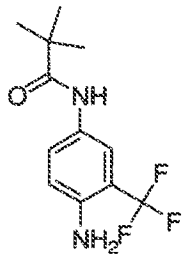
azabicyclo[3.1.0]hexane-2-carboxylate. LC/MS: *m/z* 301.5 $(M+H)^+$ at 1.31 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0949] (2*S*,4*R*)-Methyl 1-(4-amino-3-(trifluoromethyl)phenyl)-4-*tert*-butoxypyrrolidine-2-carboxylate



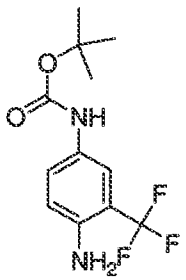
[0950] (2*S*,4*R*)-Methyl 1-(4-amino-3-(trifluoromethyl)phenyl)-4-*tert*-butoxypyrrolidine-2-carboxylate can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (2*S*,4*R*)-methyl 4-*tert*-butoxypyrrolidine-2-carboxylate. LC/MS: *m/z* 301.5 $(M+H)^+$ at 1.31 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0951] N-(4-Amino-3-(trifluoromethyl)phenyl)pivalamide



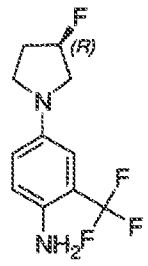
[0952] N-(4-Amino-3-(trifluoromethyl)phenyl)pivalamide can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and pivalamide. LC/MS: *m/z* 261.1 $(M+H)^+$ at 1.28 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0953] *tert*-Butyl 4-amino-3-(trifluoromethyl)phenylcarbamate



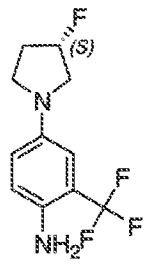
[0954] *tert*-Butyl 4-amino-3-(trifluoromethyl)phenylcarbamate can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and *tert*-butyl carbamate. LC/MS: *m/z* 277.3 $(M+H)^+$ at 1.56 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0955] **(*R*)-4-(3-Fluoropyrrolidin-1-yl)-2-(trifluoromethyl)aniline**



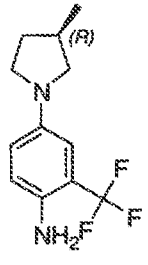
[0956] (*R*)-4-(3-Fluoropyrrolidin-1-yl)-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (*R*)-3-fluoropyrrolidine. LC/MS: *m/z* 249.3 $(M+H)^+$ at 0.92 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0957] **(*S*)-4-(3-Fluoropyrrolidin-1-yl)-2-(trifluoromethyl)aniline**



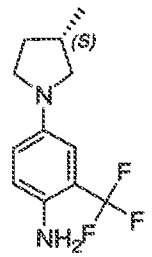
[0958] (*S*)-4-(3-Fluoropyrrolidin-1-yl)-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (*S*)-3-fluoropyrrolidine. ^1H NMR (400.0 MHz, DMSO-d_6) δ 6.81 (d, J = 8.8 Hz, 1H), 6.72 (dd, J = 2.6, 8.8 Hz, 1H), 6.51 (d, J = 2.8 Hz, 1H), 5.48 (d, J = 3.1 Hz, 1H), 4.76 (s, 2H), 3.50 (dd, J = 3.9, 11.8 Hz, 1H), 3.43 - 3.38 (m, 1H), 3.33 - 3.24 (m, 2H), 2.24 - 2.21 (m, 1H) and 2.15 (dd, J = 3.9, 7.9 Hz, 1H) ppm LC/MS: *m/z* 249.2 $(M+H)^+$ at 0.92 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0959] **(*R*)-4-(3-Methylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline**



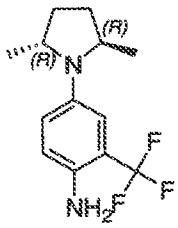
[0960] (*R*)-4-(3-Methylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (*R*)-3-methylpyrrolidine. LC/MS: *m/z* 245.1 $(M+H)^+$ at 0.92 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0961] (*S*)-4-(3-Methylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline



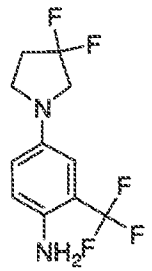
[0962] (*S*)-4-(3-Methylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (*S*)-3-methylpyrrolidine. LC/MS: *m/z* 245.1 $(M+H)^+$ at 0.93 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0963] 4-((2*R*,5*R*)-2,5-Dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline



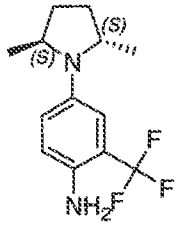
[0964] 4-((2*R*,5*R*)-2,5-Dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (2*R*,5*R*)-2,5-dimethylpyrrolidine. ^1H NMR (400.0 MHz, DMSO-d_6) δ 6.77 (d, J = 8.8 Hz, 1H), 6.70 (d, J = 9.0 Hz, 1H), 6.49 (s, 1H), 4.70 (s, 2H), 3.88 (t, J = 5.9 Hz, 2H), 2.18 - 2.14 (m, 2H), 1.56 (s, 2H) and 0.96 (d, J = 6.1 Hz, 6H) ppm. LC/MS: *m/z* 259.3 $(M+H)^+$ at 0.66 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0965] 4-(3,3-Difluoropyrrolidin-1-yl)-2-(trifluoromethyl)aniline



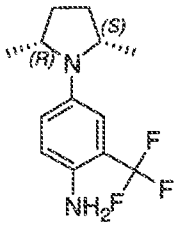
[0966] 4-(3,3-Difluoropyrrolidin-1-yl)-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and 3,3-difluoropyrrolidine. ^{1}H NMR (400.0 MHz, DMSO-d_6) δ 6.83 - 6.76 (m, 2H), 6.58 (d, J = 2.6 Hz, 1H), 4.89 (s, 2H), 3.59 (t, J = 13.5 Hz, 2H), 3.36 (q, J = 7.0 Hz, 3H), and 1.18 (t, J = 7.3 Hz, 1H) ppm. LC/MS: m/z 267.2 $(M+H)^+$ at 1.35 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0967] 4-((2*S*,5*S*)-2,5-Dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline



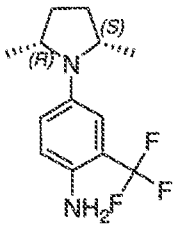
[0968] 4-((2*S*,5*S*)-2,5-Dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (2*S*,5*S*)-2,5-dimethylpyrrolidine. LC/MS: m/z 259.1 $(M+H)^+$ at 0.79 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0969] 4-((2*S*,5*R*)-2,5-Dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline



[0970] 4-((2*S*,5*R*)-2,5-Dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (2*S*,5*R*)-2,5-dimethylpyrrolidine. LC/MS: m/z 259.1 $(M+H)^+$ at 0.79 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

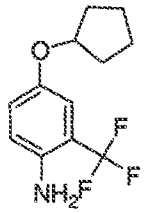
[0971] 4-((2*S*,5*R*)-2,5-Dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline



[0972] 4-((2*S*,5*R*)-2,5-Dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride

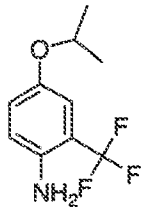
and (2*S*,5*R*)-2,5-dimethylpyrrolidine. LC/MS: *m/z* 259.1 $(M+H)^+$ at 0.79 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0973] 4-(Cyclopentyloxy)-2-(trifluoromethyl)aniline



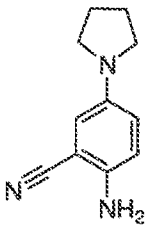
[0974] 4-(Cyclopentyloxy)-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and cyclopentanol. ^1H NMR (400.0 MHz, $CDCl_3$) δ 6.96 (d, *J* = 2.8 Hz, 1H), 6.88 (dd, *J* = 2.8, 8.7 Hz, 1H), 6.69 - 6.67 (m, 1H), 4.68 - 4.63 (m, 1H), 4.12 (d, *J* = 7.1 Hz, 2H) and 1.90 - 1.56 (m, 8H) ppm.

[0975] 4-Isopropoxy-2-(trifluoromethyl)aniline



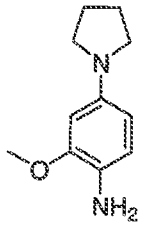
[0976] 4-Isopropoxy-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and propan-2-ol. ^1H NMR (400.0 MHz, $CDCl_3$) δ 6.99 (d, *J* = 2.8 Hz, 1H), 6.90 (dd, *J* = 2.7, 8.7 Hz, 1H), 6.68 (d, *J* = 8.7 Hz, 1H), 4.39 (t, *J* = 6.1 Hz, 1H), 3.88 (s, 2H) and 1.30 - 1.26 (m, 6H) ppm.

[0977] 2-Amino-5-(pyrrolidin-1-yl)benzonitrile



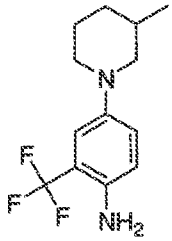
[0978] 2-Amino-5-(pyrrolidin-1-yl)benzonitrile can be synthesized following the general scheme above starting from 2-amino-5-fluorobenzonitrile and pyrrolidine. ^1H NMR (400.0 MHz, DMSO-d_6) δ 6.74 (d, *J* = 1.1 Hz, 2H), 6.48 (s, 1H), 5.16 (s, 2H), 3.10 (m, 4H), 1.90 (m, 4H). LC/MS: *m/z* 188.5 $(M+H)^+$ at 0.44 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0979] 2-Methoxy-4-(pyrrolidin-1-yl)aniline



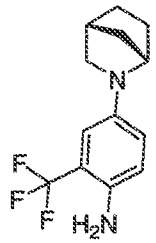
[0980] 2-Methoxy-4-(pyrrolidin-1-yl)aniline can be synthesized following the general scheme above starting from 4-fluoro-2-methoxyaniline and pyrrolidine. ^{1}H NMR (400.0 MHz, DMSO-d_6) δ 6.51 (d, J = 8.3 Hz, 1H), 6.14 (d, J = 2.4 Hz, 1H), 5.95 (dd, J = 2.4, 8.3 Hz, 1H), 3.91 (s, 2H), 3.74 (s, 3H), 3.11 (m, 4H), 1.90 (m, 4H). LC/MS: *m/z* 193.5 $(M+H)^+$ at 1.06 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0981] 4-(3-Methylpiperidin-1-yl)-2-(trifluoromethyl)aniline



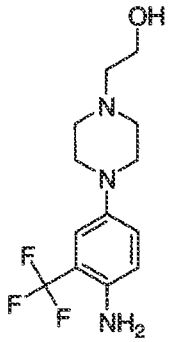
[0982] 2-Methoxy-4-(pyrrolidin-1-yl)aniline can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and 3-methylpiperidine. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 – 6.93 (m, 2H), 6.69 (d, *J* = 8.7 Hz, 1H), 3.85 (s, 2H), 3.42 – 3.29 (m, 2H), 2.52 (td, *J* = 11.5, 3.1 Hz, 1H), 2.25 – 2.15 (m, 1H), 1.86 – 1.62 (m, 5H), 0.94 (d, *J* = 6.4 Hz, 3H). LC/MS: *m/z* 259.0 $(M+H)^+$ at 0.79 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0983] 4-((1*S*,4*R*)-2-Azabicyclo[2.2.1]heptan-2-yl)-2-(trifluoromethyl)aniline



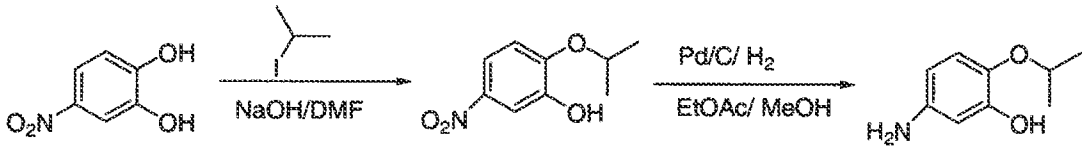
4-((1*S*,4*R*)-2-Azabicyclo[2.2.1]heptan-2-yl)-2-(trifluoromethyl)aniline can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and (1S,4R)-2-azabicyclo[2.2.1]heptane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (d, *J* = 8.5 Hz, 1H), 6.58 (dt, *J* = 8.7, 2.5 Hz, 2H), 4.02 (s, 1H), 3.65 (s, 2H), 3.49 (dt, *J* = 5.9, 3.2 Hz, 1H), 2.64 (d, *J* = 8.0 Hz, 1H), 2.56 (s, 1H), 1.83 – 1.53 (m, 5H), 1.48 (d, *J* = 9.3 Hz, 1H), 1.37 – 1.22 (m, 2H)

[0984] 2-(4-(4-Amino-3-(trifluoromethyl)phenyl)piperazin-1-yl)ethanol



[0985] 2-(4-(4-Amino-3-(trifluoromethyl)phenyl)piperazin-1-yl)ethanol can be synthesized following the general scheme above starting from 5-fluoro-2-nitrobenzotrifluoride and 2-(piperazin-1-yl)ethanol.

[0986] Amine Intermediate Example 13: **Synthesis of 5-amino-2-isopropoxyphenol**

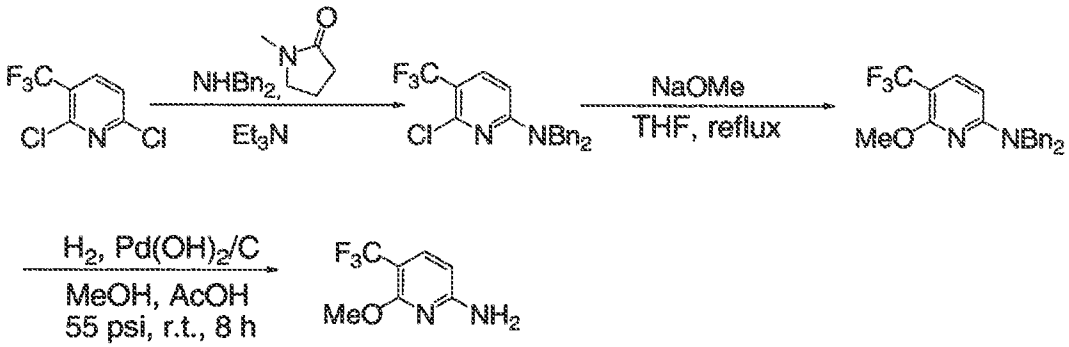


[0987] To a stirred solution of sodium hydroxide (387 mg, 9.67 mmol) in anhydrous DMSO was added 4-nitrobenzene-1,2-diol (500 mg, 3.22 mmol) at 0 °C. After stirring for 5 min, 2-iodo-propane (603 mg, 3.55 mmol) was added dropwise. The resulting dark mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with water and then acidified with 1M HCl (pH = 4) and then the aqueous layer was extracted with ethyl acetate (3x20 mL). The combined organic layer was washed with sat. NaCl and then dried over $MgSO_4$, filtered and concentrated under reduced pressure to dryness. The crude product was purified by silica gel column chromatography using a gradient of 0-20% EtOAc in hexanes to obtain 2-isopropoxy-5-nitro-phenol (163 mg, 51 %) ^{1}H NMR (400.0 MHz, $CDCl_3$) δ 7.86 (dd, J = 2.5, 8.8 Hz, 1H), 7.76 (d, J = 2.5 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 4.73 (qn, J = 6.1 Hz, 1H) and 1.43 (d, J = 6.1 Hz, 6H).

[0988] A flask charged with 2-isopropoxy-5-nitro-phenol (100 mg, 0.47 mmol) and palladium on carbon (50 mg, 0.47 mmol) was flushed with N_2 followed by evacuating under vacuum. EtOAc (2 mL) and methanol (2 mL) were added under an inert atmosphere followed by evacuating under vacuum. The reaction mixture was then stirred overnight under an atmosphere of hydrogen. The palladium catalyst was removed by filtration and solvent was removed under reduced pressure to give 5-amino-2-isopropoxyphenol (65 mg, 76%). ^{1}H NMR

(400.0 MHz, $CDCl_3$) δ 6.73 (d, J = 8.3 Hz, 1H), 6.31 (d, J = 2.5 Hz, 1H), 6.22 (dd, J = 2.5, 8.3 Hz, 1H), 5.22 (s, 1H), 4.50 (qn, J = 6.1 Hz, 1H), 3.37 (s, 2H) and 1.37 - 1.26 (m, 6H) ppm.

[0989] Amine Intermediate Example 14: **Synthesis of 6-methoxy-5-(trifluoromethyl)pyridin-2-amine**



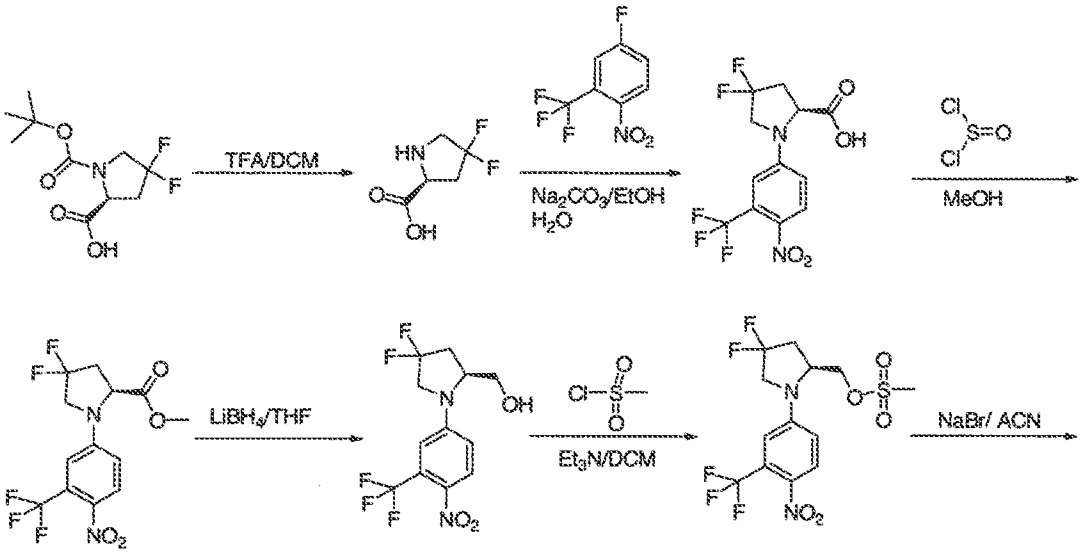
[0990] A mixture of 2,6-dichloro-3-(trifluoromethyl)pyridine (1.0 g, 4.63 mmol) , dibenzylamine (913 mg, 890 μL, 4.63 mmol), triethylamine (1.2 mL, 8.61 mmol) and 1-methyl-2-pyrrolidone (6 mL, 62.22 mmol) was heated at 120 °C for 9 h. The reaction mixture was cooled to the room temperature and poured into ice-water, extracted with EtOAc (20 mL×3), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated and purified by silca gel column chromatography (2%-10% EtOAc in petroleum ether as eluant) to give N,N-dibenzyl-6-chloro-5-(trifluoromethyl)pyridin-2-amine (1.5 g, 86%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 8.7 Hz, 1H), 7.37-7.21 (m, 10H), 6.32 (d, J = 8.7 Hz, 1H), 4.80 (s, 4H).

[0991] To a stirred solution of N,N-dibenzyl-6-chloro-5-(trifluoromethyl)pyridin-2-amine (100 mg, 0.27 mmol) in THF (5 mL) was added freshly produced CH_3ONa (42 mg, 0.78 mmol) at room temperature. The mixture was heated to reflux for 10 h and then cooled to the room temperature, diluted with water (5 mL) and extracted with CH_2Cl_2 (6 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography using 2%-10% EtOAc in petroleum ether as eluant to obtain N,N-dibenzyl-6-methoxy-5-(trifluoromethyl)pyridin-2-amine (90 mg, 91 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.4 Hz, 1H), 7.35-7.22 (m, 10H), 6.02 (d, J = 8.4 Hz, 1H), 4.79 (s, 4H), 3.90 (s, 3H).

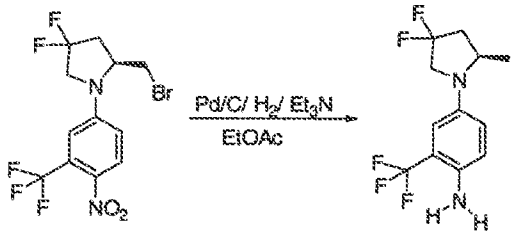
[0992] To a solution of N,N-dibenzyl-6-methoxy-5-(trifluoromethyl)pyridin-2-amine (3.0 g, 8.056 mmol) in a mixture of methanol (30 mL) and AcOH (3 mL) was added palladium hydroxide (0.3 g, 0.43 mmol) under a nitrogen atmosphere. The mixture was stirred under hydrogen atmosphere (55 psi, 25 °C) overnight. The catalyst was removed by filtration

through a pad of celite and the filtrate was neutralized by saturated Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (30 mL×3) and the combined organic layers were concentrated under vacuum to give 6-methoxy-5-(trifluoromethyl)pyridin-2-amine (1.4 g, 90 %) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.4 Hz, 1H), 6.03 (d, J = 8.0 Hz, 1H), 4.64 (brs, 2H), 3.93 (s, 3H). MS (ESI) m/e ($M+H^+$) 193. ^{13}C NMR (100 MHz, $CDCl_3$) 159.4, 138.0 (d, J = 5.9 Hz), 125.9, 122.3, 101.9 (d, J = 44.4 Hz), 98.3, 53.6. ^{19}F NMR (282.4 MHz, $CDCl_3$) -62.6.

[0993] Amine Intermediate Example 15: **Synthesis of (*R*)-4-(4,4-difluoro-2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline**



(*S*)-2-(bromomethyl)-4,4-difluoro-1-(4-nitro-3-(trifluoromethyl)phenyl)pyrrolidine



(*R*)-4-(4,4-difluoro-2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline

[0994] (*S*)-1-(*tert*-butoxycarbonyl)-4,4-difluoropyrrolidine-2-carboxylic acid (500 mg, 2.0 mmol) was dissolved in dichloromethane and treated dropwise with TFA (227 mg, 153 µL, 2 mmol). The reaction was stirred for 3 h at room temperature, the solvents evaporated to obtain (*S*)-4,4-difluoropyrrolidine-2-carboxylic acid, which was used in the next step without further purification. LC/MS: *m/z* 152.2 $(M+H)^+$ at 0.53 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0995] To 4-fluoro-1-nitro-2-(trifluoromethyl)benzene (416 mg, 2 mmol), (*S*)-4,4-difluoropyrrolidine-2-carboxylic acid (301 mg, 2 mmol), and sodium carbonate (633 mg, 574 µL, 6.0 mmol) was added 1:1 water/Ethanol (8 mL) and the reaction mixture was heated at 90 °C for 72 h. The reaction mixture was diluted with water (50 mL) then acidified with 1 N HCl and the product was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield (*S*)-4,4-difluoro-1-(4-nitro-3-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylic acid as a brown oil (600 mg, 89%), which was used directly in the next reaction. LC/MS: *m/z* 341.00 $(M+H)^+$ at 1.49 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0996] (*S*)-4,4-difluoro-1-(4-nitro-3-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylic acid (600 mg, 1.76 mmol) was dissolved in methanol (10 mL), cooled to 0 °C, and treated dropwise with thionyl chloride (840 mg, 515 µL, 7.08 mmol). The reaction mixture was heated at 50 °C over 48 h. The reaction mixture was evaporated *in vacuo* and the residue was purified by silica gel column chromatography (0-60% ethyl acetate in hexane) to obtain (*S*)-methyl 4,4-difluoro-1-(4-nitro-3-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate (300 mg, 48% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 9.2 Hz, 1H), 7.04 (d, J = 2.6 Hz, 1H), 6.97 (dd, J = 9.2, 2.7 Hz, 1H), 5.19 (dd, J = 9.8, 1.9 Hz, 1H), 4.14-3.99 (m, 2H), 3.69 (s, 3H), 3.11-2.95 (m, 1H), 2.78 (t, J = 14.6 Hz, 1H).

[0997] To a suspension of $LiBH_4$ (55 mg, 2.54 mmol) in anhydrous THF (3 mL) was added a solution of (*S*)-methyl 4,4-difluoro-1-(4-nitro-3-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate (300 mg, 0.85 mmol) in anhydrous THF at 0 °C. The reaction mixture was stirred at 0 °C for 20 min then allowed to come to room temperature and stirred overnight. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (50 mL), and then brine. The layers were separated, and the organic layer was dried over Na_2SO_4, filtered, and concentrated to afford (*S*)-(4,4-difluoro-1-(4-nitro-3-(trifluoromethyl)phenyl)pyrrolidin-2-yl)methanol as a yellow, viscous oil (275 mg, 100%). LC/MS: *m/z* 327.2 $(M+H)^+$ at 1.54 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

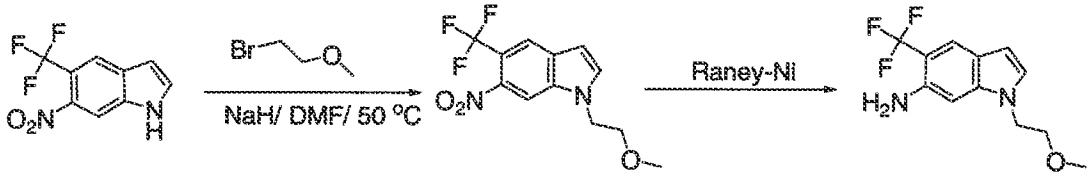
[0998] To a solution of (*S*)-(4,4-difluoro-1-(4-nitro-3-(trifluoromethyl)phenyl)pyrrolidin-2-yl)methanol (275 mg, 0.84 mmol) in anhydrous DCM was added triethylamine (171 mg, 235 µL, 1.7 mmol) followed by methane sulfonyl chloride (106 mg, 72 µL, 0.93 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was diluted with DCM and quenched with 3 mL saturated $NaHCO_3$. The organic layer was separated and washed with brine, dried over Na_2SO_4, filtered, and concentrated to obtain (*S*)-(4,4-difluoro-1-(4-nitro-3-

(trifluoromethyl)phenyl)pyrrolidin-2-yl)methyl methanesulfonate as a yellow solid (330 mg, 96%). LC/MS: *m/z* 405 $(M+H)^+$ at 1.71 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[0999] NaBr (420 mg, 131 µL, 4.08 mmol) was added to a solution of (*S*)-(4,4-difluoro-1-(4-nitro-3-(trifluoromethyl)phenyl)pyrrolidin-2-yl)methyl methanesulfonate (330 mg, 0.82 mmol) in acetonitrile (2.0 mL) and heated at 80 °C for 16 h. The reaction mixture was diluted with ethyl acetate (10 mL) and water (5 mL). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (15-50% ethyl acetate/hexane) to obtain (*S*)-2-(bromomethyl)-4,4-difluoro-1-(4-nitro-3-(trifluoromethyl)phenyl)pyrrolidine (230 mg, 72%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, *J* = 8.7 Hz, 1H), 7.09-7.07 (m, 2H), 4.76-4.71 (m, 1H), 4.16-3.99 (m, 2H), 3.74 (dd, *J* = 10.6, 3.0 Hz, 1H), 3.60 (t, *J* = 9.7 Hz, 1H), 2.94-2.80 (m, 1H), 2.66-2.55 (m, 1H).

[01000] (*S*)-2-(bromomethyl)-4,4-difluoro-1-(4-nitro-3-(trifluoromethyl)phenyl)pyrrolidine (230 mg, 0.59 mmol) was dissolved in ethyl acetate (5 mL) and TEA (90 mg, 124 µL, 0.89 mmol) and the flask was flushed with nitrogen. 10% Pd/C (58 mg, 0.05 mmol) catalyst was added and the reaction mixture was stirred overnight under an atmosphere of hydrogen. The reaction mixture was filtered, treated with 50% saturated $NaHCO_3$, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered and concentrated to provide (*R*)-4-(4,4-difluoro-2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)aniline as a purple oil (164 mg, 99% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.81 (s, 2H), 6.58 (s, 1H), 4.92 (s, 2H), 4.07-4.01 (m, 1H), 3.74-3.63 (m, 1H), 3.60-3.50 (m, 1H), 2.75-2.60 (m, 1H), 2.22-2.11 (m, 1H), 1.10 (d, J = 6.2 Hz, 3H).

[01001] Amine Intermediate Example 16: **Synthesis of 1-(2-methoxyethyl)-5-(trifluoromethyl)-1H-indol-6-amine**

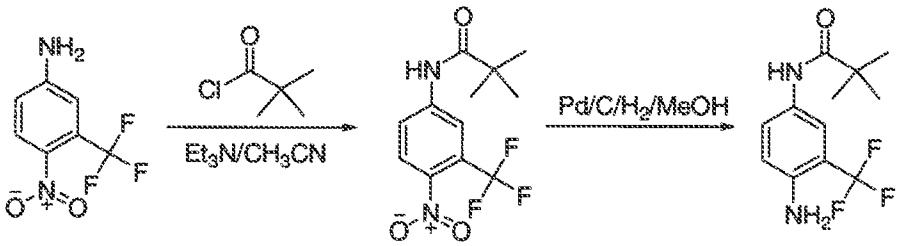


[01002] 6-nitro-5-(trifluoromethyl)-1H-indole (50 mg, 0.22 mmol) was dissolved in DMF (2 mL) and treated with sodium hydride (35 mg, 0.87 mmol) to form a dark red opaque solution. The solution was stirred for 20 minutes and then added dropwise to a solution of 2-bromoethyl methyl ether (121 mg, 82 µL, 0.87 mmol) in 1 mL DMF. The reaction mixture was heated at 50 °C for 30 minutes. The reaction mixture was diluted with ethyl acetate (50

mL) and washed with 50% saturated $NaHCO_3$ (2 x 10 mL) and brine. The organic layer was dried over Na_2SO_4, filtered and dried to obtain 1-(2-methoxyethyl)-6-nitro-5-(trifluoromethyl)-1H-indole, which was used in the next step without further purification.

[01003] 1-(2-methoxyethyl)-6-nitro-5-(trifluoromethyl)-1H-indole was dissolved in 10 mL EtOH, and hydrogenated using Raney Ni as a catalyst (H-cube:1.2 mL/min 30 °C) to obtain in 1-(2-methoxyethyl)-5-(trifluoromethyl)-1H-indol-6-amine in quantitative yield. LC/MS: *m/z* 259.0 $(M+H)^+$ at 1.12 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

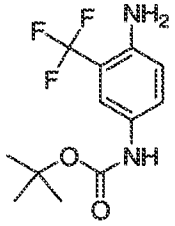
[01004] Amine Intermediate Example 17: **Synthesis of N-(4-amino-3-(trifluoromethyl)phenyl)pivalamide**



[01005] To a solution of 4-nitro-3-(trifluoromethyl)aniline (1.0 g, 4.85 mmol) in CH_2Cl_2 (15 mL) and TEA (2.95 g, 4.1 mL, 29.11 mmol) in a round-bottom flask at 0 °C was added trimethylacetyl chloride (1.75 g, 1.8 mL, 14.55 mmol) dropwise. The reaction mixture was warmed to room temperature and was quenched by pouring into water. The layers were separated, and the aqueous layer was extracted with DCM. The combined organic layer was dried over sodium sulfate, filtered and concentrated. The residue was then purified by silica gel column chromatography using (0-100% EtOAc/Hex.) to obtain N-(4-nitro-3-(trifluoromethyl)phenyl)pivalamide (1.64 g, 81%). LC/MS: *m/z* 291.1 $(M+H)^+$ at 1.83 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

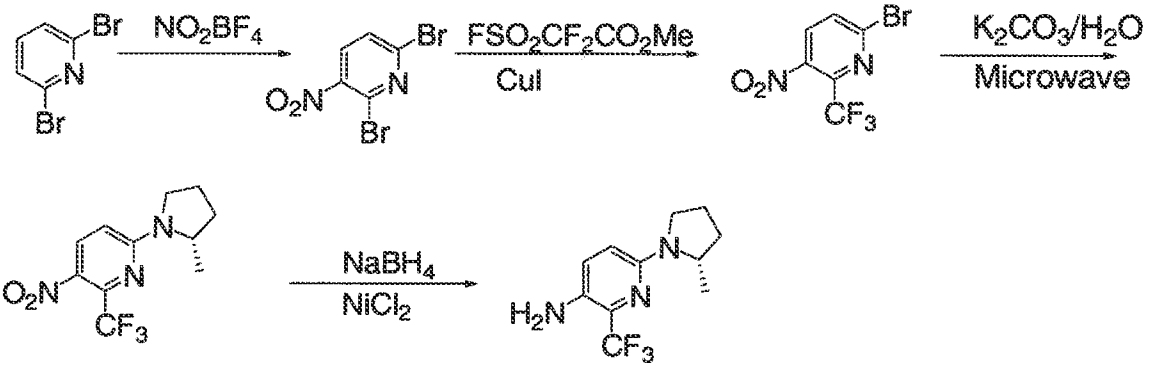
[01006] To a solution of 2,2-dimethyl-n-(4-nitro-3-trifluoromethyl-phenyl)-propionamide (1.64 g, 5.65 mmol) in MeOH (50 mL) was added Pd/C (150 mg, 0.14 mmol) under a nitrogen atmosphere. The mixture was stirred under a hydrogen atmosphere for 4 h. The catalyst was removed by filtration through a pad of celite and the solvent was evaporated under vacuum to give N-(4-amino-3-(trifluoromethyl)phenyl)pivalamide (1.2 g, 78%). LC/MS: *m/z* 261.5 $(M+H)^+$ at 1.83 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[01007] ***tert*-Butyl 4-amino-3-(trifluoromethyl)phenylcarbamate**



[01008] *tert*-Butyl 4-amino-3-(trifluoromethyl)phenylcarbamate can be synthesized following the general scheme above starting from 4-nitro-3-(trifluoromethyl)aniline and di-*tert*-butyl dicarbonate. LC/MS: *m/z* 277.35 $(M+H)^+$ at 1.56 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[01009] Amine Intermediate Example 18: **Synthesis of (*S*)-6-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)pyridin-3-amine.**



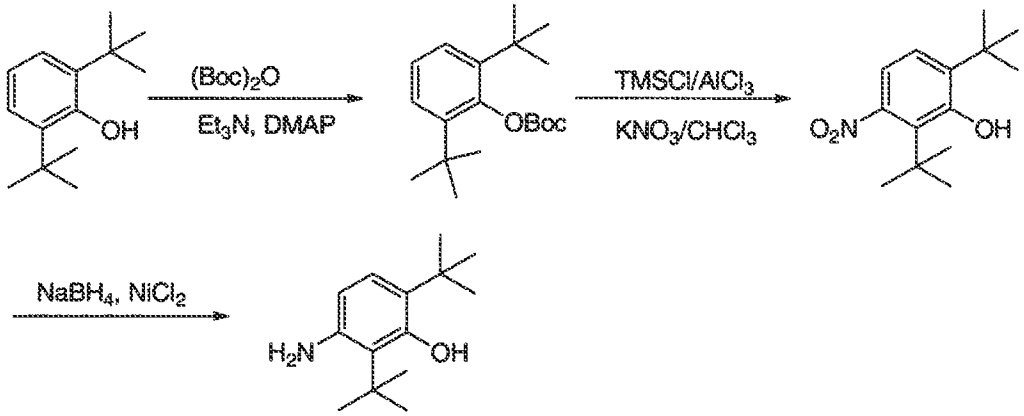
[01010] To a solution of 2,6-dibromopyridine (10.0 g, 42.6 mmoL) in anhydrous CH_3CN (100 mL) was slowly added $NO_2^+BF_4$ (11.3 g, 85.2 mmoL). The reaction mixture was heated to 80 °C under an atmosphere of nitrogen for 24 h. The mixture was then evaporated *in vacuo* to give the crude product. The residue was purified by silica gel column chromatography to afford 2,6-dibromo-3-nitropyridine (5.7 g, 48 %). ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H).

[01011] To a solution of 2,6-dibromo-3-nitropyridine (5.7 g, 20.4 mmoL) in DMF (40 mL) was added CuI (3.9 g, 20.4 mmoL) and $FSO_2CF_2CO_2Me$ (4.7 g, 24.5 mmoL). The reaction mixture was stirred at 80 °C for 1 h. After cooling to room temperature, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (100 mL × 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and purified by silica gel column chromatography to afford 6-bromo-3-nitro-2-(trifluoromethyl)pyridine (3.0 g, 53%, 70% purity). ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H).

[01012] A suspension of 6-bromo-3-nitro-2-(trifluoromethyl)pyridine (400 mg, 1.5 mmoL), (*S*)-2-methylpyrrolidine tosylate salt (381 mg, 1.5 mmoL) and K_2CO_3 (620 mg, 4.5 mmoL) in H_2O (4 mL) was heated at 140 °C under microwave irradiation for 30 minutes. The solution was extracted with EtOAc (50 mL × 3) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and purified by silica gel column chromatography to afford (*S*)-6-(2-methylpyrrolidin-1-yl)-3-nitro-2-(trifluoromethyl)pyridine (350 mg, 88 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 9.2 Hz, 1H), 6.44 (d, J = 8.4 Hz, 1H), 4.55-4.42 (m, 1H), 4.02-3.30 (m, 2H), 2.30-2.00 (m, 3H), 1.81 (brs, 1H), 1.27 (d, J = 6.4 Hz, 3H).

[01013] To a solution of *(S)*-6-(2-methylpyrrolidin-1-yl)-3-nitro-2-(trifluoromethyl)pyridine (300 mg, 1.1 mmoL) in 5 mL methanol was added $NiCl_2 \cdot 6H_2O$ (772 mg, 3.3 mmoL). After stirring for 5min, $NaBH_4$ (84 mg, 2.2 mmoL) was added in three portions at 0°C. The reaction mixture was stirred for 5 min and quenched with water (10 mL) and was extracted with EtOAc (15 mL × 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated and purified by silica gel chromatographyon silica gel to afford *(S)*-6-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)pyridin-3-amine (260 mg, 92.6 % yield).

[01014] Amine Intermediate Example 19: **Synthesis of 3-amino-2,6-di-*tert*-butylphenol**

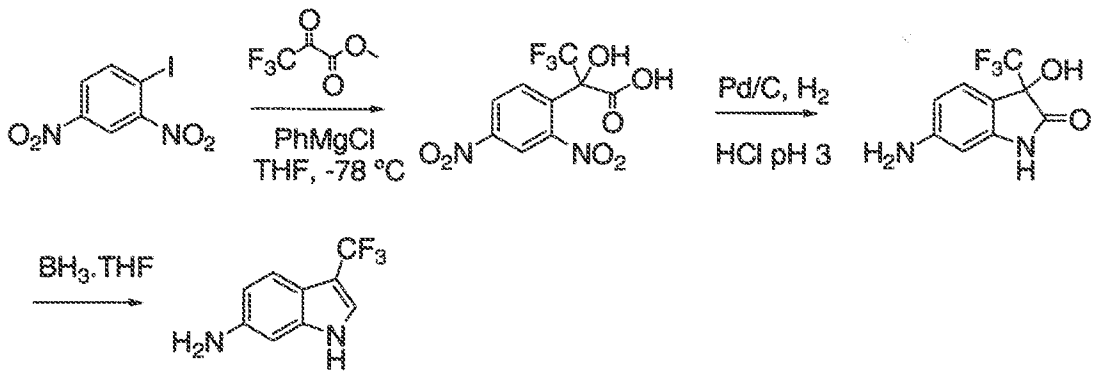


[01015] DMAP (885 mg, 7.24 mmol) was added to a solution of 2,6-di-*tert*-butylphenol (30 g, 145.4 mmol) and di-*tert*-butyl dicarbonate (38 g, 174.1 mmol) in Et_3N (29.43 g, 40.5 mL, 290.8 mmol) and hexane (700 mL). The reaction mixture was stirred overnight and quenched with water and extracted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether eluent) to give *tert*-butyl (2,6-di-*tert*-butylphenyl) carbonate (30 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (d, J = 8.0 Hz, 2H), 7.12 (t, J = 8.0 Hz, 1H), 1.54 (s, 9H), 1.38 (s, 8H).

[01016] TMSCl (8.5 g, 78.24 mmol) and *tert*-butyl (2,6-di-*tert*-butylphenyl) carbonate (12.0 g, 39.16 mmol) was added to a suspension of KNO_3 (5.9 g, 58.36 mmol) in $CHCl_3$ (100 mL) successively at 0°C. The reaction mixture was stirred for 0.5 h and $AlCl_3$ (15.5 g, 116.20 mmol) was added. The stirring was continued for 2 h and the resulting mixture was poured into ice-water and extracted with CH_2Cl_2. The combined organic layers were washed with sat.$NaHCO_3$ solution and brine, dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether) to give 2,6-di-*tert*-butyl-3-nitrophenol (2.5 g, 25%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 5.57 (s, 1H), 1.51 (s, 9H), 1.44 (s, 9H).

[01017] $NaBH_4$ (433 mg, 11.45 mmol) was added to a solution of 2,6-di-*tert*-butyl-3-nitrophenol (950 mg, 3.780 mmol) and $NiCl_2$ (1.24 g, 9.568 mmol) in methanol (15 mL) at –15°C. After the addition was complete, the reaction mixture was stirred for 20 seconds and water was added immediately and the reaction mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to afford 3-amino-2,6-di-*tert*-butyl-phenol (650 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (d, J = 8.4 Hz, 1H), 6.24 (d, J = 8.4 Hz, 1H), 5.39 (s, 1H), 1.62 (s, 9H), 1.39 (s, 9H); MS (ESI) m/z: 222.2 [M+H$^+$].

[01018] Amine Intermediate Example 20: **Synthesis of 3-(trifluoromethyl)-1H-indol-6-amine**



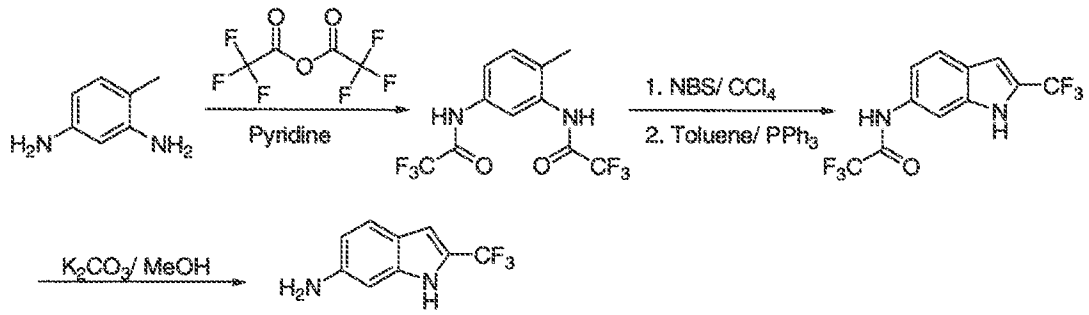
[01019] To a solution of 1,4-dinitroiodobenzene (2.12 g, 7.21 mmol) in tetrahydrofuran (11 mL) at –78 °C under an atmosphere of N_2 was added phenylmagnesium chloride (2M in THF) (4 mL, 8.0 mmol, 1.1 eq) dropwise. The dark red solution was stirred for 30 min at –78 °C then methyltrifluoropyruvate (0.75 mL, 8.65 mmol) was added dropwise. The reaction mixture was stirred for 30 min at –78 °C and then for 2 h at room temperature. The reaction was cooled to –10 °C and quenched by addition of 1 M HCl (6 mL). The reaction

mixture was diluted with water (10 mL) and dichloromethane (30 mL). The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 x 30 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (0.5-30% ethyl acetate/hexanes) to yield methyl 2-(2,4-dinitrophenyl)-3,3,3-trifluoro-2-hydroxypropanoate (1.34 g, 60%)

[01020] To a solution of methyl 2-(2,4-dinitrophenyl)-3,3,3-trifluoro-2-hydroxypropanoate (1.3 g, 4.01 mmol) in ethyl acetate (18 mL) was added (pH3) HCl (5.2 mL) followed by 10% Pd/C (350 mg) in ethyl acetate (3 mL). The reaction mixture was stirred overnight under an atmosphere of H_2. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo*. The crude residue obtained was partitioned between dichloromethane (25 mL) and aqueous saturated $NaHCO_3$ (15 mL). The organic phase was separated and the aqueous phase was extracted dichloromethane (2 x 25 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (50-100% ethyl acetate/ hexanes) to give 6-amino-3-hydroxy-3-(trifluoromethyl)indolin-2-one (921 mg, 99%)

[01021] To a solution of 6-amino-3-hydroxy-3-(trifluoromethyl)indolin-2-one (58 mg, 0.25 mmol) in THF (0.5 mL) at 0 °C was added BH_3·THF complex (1 M in THF, 1 mL, 0.95 mmol) dropwise. The reaction mixture was stirred for 5 min at 0 °C then for 3 h at room temperature. The reaction mixture was quenched by adding very carefully 6M HCl (3.5 mL) until no more gas release was observed. The reaction mixture was then stirred at 80 °C for 2 h. The solvent was removed under reduce pressure and the solid residue obtained was dissolved in DMF (3 mL), filtered and purified by reverse phase HPLC (10-99% CH_3CN/H_2O) to provide 3-(trifluoromethyl)-1H-indol-6-amine (30 mg , 54%, TFA salt).

[01022] Amine Intermediate Example 21: **Synthesis of 2-(trifluoromethyl)-1H-indol-6-amine**

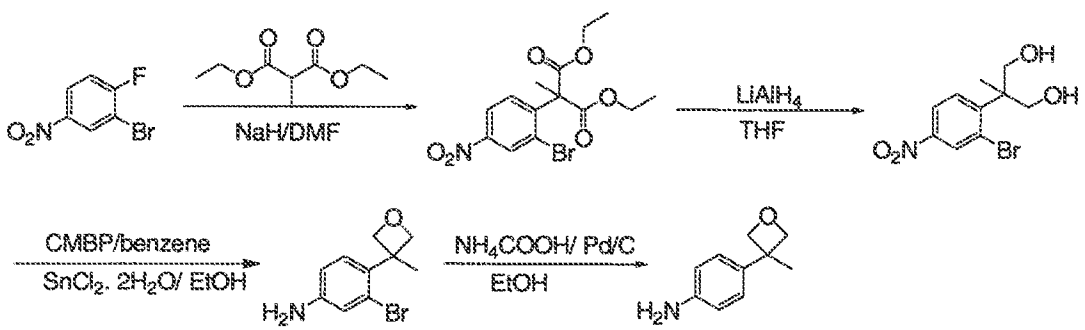


[01023] To a solution of 4-methylbenzene-1,3-diamine (500 mg, 4.1 mmol) in dry pyridine (25 mL) at 0 °C under a N_2 atmosphere was added trifluoroacetic anhydride (1.2 mL) dropwise. The cooling bath was removed and the reaction mixture was stirred at room temperature until complete conversion of the starting material to the desired product was observed. The reaction mixture was concentrated under reduced pressure and the residue obtained was purified by silica gel column chromatography (10-45% AcOEt in hexanes) to obtain N,N'-(4-methyl-1,3-phenylene)bis(2,2,2-trifluoroacetamide) (807 mg, 63%). LC/MS: *m/z* 315.3 $(M+H)^+$ at 1.39 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[01024] A mixture of N,N'-(4-methyl-1,3-phenylene)bis(2,2,2-trifluoroacetamide) (1.02 g, 3.25 mmol), NBS (0.80 g, 4.5 mmol) in CCl_4 (6 mL) was stirred overnight at room temperature under irradiation of a 300 W lamp. The precipitate formed was collected by filtration and washed with CCl_4.The crude residue was taken up in dry toluene (9.7 mL) in the presence of PPh_3 (1.3 g, 4.96 mmol) and stirred at 60°C for 16 h. The phosphonium precipitate was collected by filtration, then dissolved in dry DMF (10 mL) and stirred at 165 °C until complete conversion to the product (6.5 h). The solvent was removed *in vacuo* and the residue obtained was purified by silica gel column chromatography (5-25% AcOEt in hexanes) to obtain 2,2,2-trifluoro-N-(2-(trifluoromethyl)-1H-indol-6-yl)acetamide (243 mg, 25%). LC/MS: *m/z* 297.3 $(M+H)^+$ at 1.68 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[01025] 2,2,2-trifluoro-N-(2-(trifluoromethyl)-1H-indol-6-yl)acetamide (28 mg, 0.09 mmol) was dissolved in MeOH (0.9 mL) and water (0.4 mL) in the presence of K_2CO_3 (90 mg, 0.65 mmol) and stirred overnight at room temperature. Purification (10 to 99% ACN in water) by LC-MS provided 3-(trifluoromethyl)-1H-indol-6-amine 2,2,2-trifluoroacetate (30 mg, quantitative yield). LC/MS: *m/z* 201.1 $(M+H)^+$ at 0.90 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[01026] Amine Intermediate Example 22: **Synthesis of 4-(3-methyloxetan-3-yl)aniline**



[01027] To a solution of diethyl 2-methylpropanedioate (21.8 g, 125.0 mmol) in anhydrous DMF (125 mL) was slowly added NaH (5.2 g, 130 mmol) at 0 °C under an atmosphere of nitrogen. The resulting reaction mixture was allowed to stir for 10 minutes at 0 °C, and then at room temperature for 10 minutes. 2-bromo-1-fluoro-4-nitro-benzene (25.0 g, 113.6 mmol) was quickly added and the reaction mixture turned bright red. After stirring for 10 minutes at room temperature, the crude mixture was evaporated to dryness and then partitioned between dichloromethane and brine. The layers were separated and the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum to give the crude product, which was purified by silica gel column chromatography (petroleum ether/EtOAc 10:1) to give diethyl 2-(2-bromo-4-nitrophenyl)-2-methylmalonate (33.0 g, 78%)

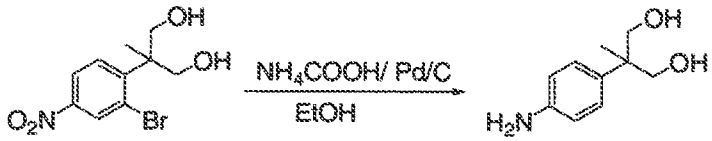
[01028] To a solution of diethyl 2-(2-bromo-4-nitrophenyl)-2-methylmalonate (7.5 g, 20.0 mmol) in anhydrous tetrahydrofuran (80 mL) was slowly added a solution of lithium aluminum hydride (22 mL, 22.0 mmol, 1.0 M in THF) at 0 °C under an atmosphere of nitrogen. After stirring for 10 minutes the reaction was completed. The reaction mixture was quenched by the slow addition of methanol at 0 °C. The reaction mixture was then partitioned between dichloromethane and 1 N hydrochloric acid. The layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum to give crude product, which was purified by silica gel column chromatography (petroleum ether/EtOAc 2:1) to give 2-(2-bromo-4-nitrophenyl)-2-methylpropane-1,3-diol (1.4 g, 24%) as a red solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (d, J = 2.4 Hz, 1H), 8.13 (dd, J = 2.4, 8.8 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 4.74 (t, J = 5.2 Hz, 2H), 3.93 (q, J = 5.2 Hz, 2H), 3.79 (m, q, J = 5.2 Hz, 2H), 1.38 (s, 3H).

[01029] To a solution of 2-(2-bromo-4-nitrophenyl)-2-methylpropane-1,3-diol (7.2 g, 24.82 mmol) in anhydrous benzene (75 mL) was added cyanomethylenetributylphosphorane (9.0 g, 37.29 mmol) at room temperature. The reaction mixture was stirred for 72 h, then evaporated to dryness and re-dissolved in ethanol (100 mL). Tin (II) chloride dihydrate (28 g, 94.42 mmol) was then added and the resulting solution was heated to 70 °C for 1 hour. The reaction mixture was cooled to room temperature and then quenched with a saturated aqueous solution of sodium bicarbonate. The reaction mixture was then extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum to give the crude product, which was purified by reverse phase HPLC to afford 3-bromo-4-(3-methyloxetan-3-yl)aniline (1.5 g, 18%) TFA salt. ^{1}H NMR (400 MHz, CD_3CN)

δ 6.93 (d, *J* = 2.4 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.71 (dd, *J* = 2.4, 8.4 Hz, 1H), 4.94 (d, *J* = 5.6 Hz, 2H), 4.46 (d, *J* = 6.0 Hz, 2H), 1.70 (s, 3H).

[01030] To a refluxing solution of 3-(2-bromo-4-nitrophenyl)-3-methyloxetane (68 mg, 0.2499 mmol) in ethanol (5 mL) was added ammonium formate (68 mg, 1.078 mmol) followed by the addition of Pd/C (32 mg, 0.3007 mmol). The reaction mixture was refluxed for an additional 5 minutes, cooled to room temperature and filtered through a plug of celite. The solvent was evaporated to get 4-(3-methyloxetan-3-yl)aniline. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.93 – 6.90 (m, 2H), 6.56 (d, *J* = 8.5 Hz, 2H), 4.70 (d, *J* = 5.4 Hz, 2H), 4.45 (d, *J* = 5.6 Hz, 2H), 1.55 (s, 3H).

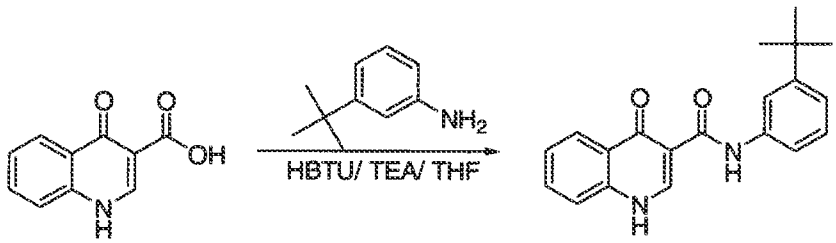
[01031] Amine Intermediate Example 23: **Synthesis of 2-(4-aminophenyl)-2-methylpropane-1,3-diol**



[01032] To a refluxing solution of 2-(2-bromo-4-nitrophenyl)-2-methylpropane-1,3-diol (211 mg, 0.73 mmol) in ethanol (15.5 mL) was added ammonium formate (211 mg, 3.35 mmol) followed by the addition of Pd/C (140 mg, 1.32 mmol). The reaction mixture was refluxed for an additional 10 minutes, cooled to room temperature and filtered through a plug of celite. The solvent was evaporated under reduced pressure to give 2-(4-aminophenyl)-2-methylpropane-1,3-diol (112 mg, 85%).

[01033] Specific Examples

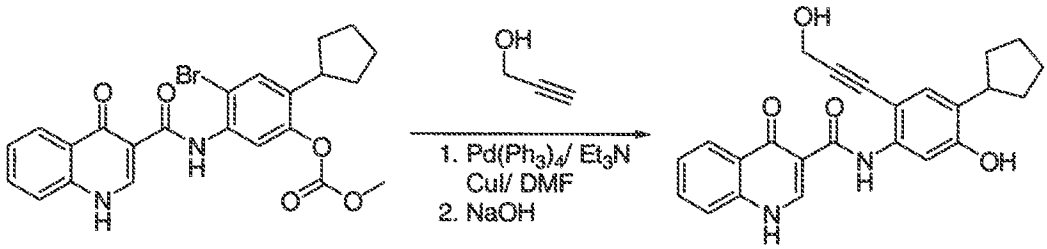
[01034] Synthesis of 4-oxo-N-(3-*tert*-butylphenyl)-1H-quinoline-3-carboxamide (Table 1, Compound 603)



[01035] A flask charged with 4-oxo-1H-quinoline-3-carboxylic acid (38 mg, 0.20 mmol), HBTU (76 mg, 0.20 mmol), Et_3N (61 mg, 84 µL, 0.60 mmol) and DMF (2 mL) was heated at 60 °C for 15 minutes. To the reaction mixture was then added 3-*tert*-butylaniline (29.98 mg, 0.2009 mmol) and the reaction mixture was stirred at 60 °C for an additional 30 minutes. The reaction mixture was cooled to room temperature, filtered and purified via

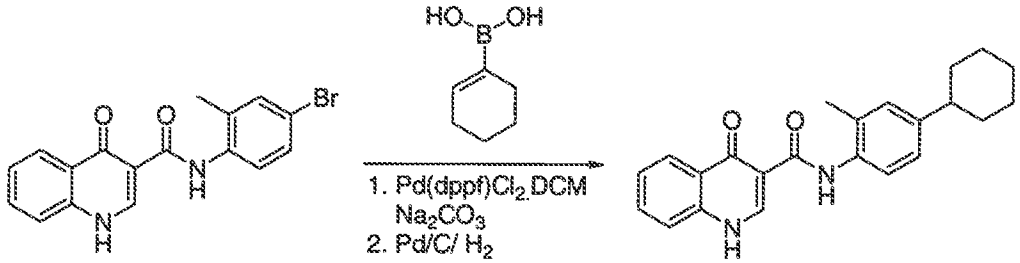
reverse phase HPLC using 10 to 99% CH_3CN in H_2O to obtain N-(3-*tert*-butylphenyl)-4-oxo-1H-quinoline-3-carboxamide. ^1H NMR (400 MHz, DMSO-d_6) δ 12.94 (s, 1H), 12.45 (s, 1H), 8.89 (s, 1H), 8.34 (dd, J = 1.1, 8.2 Hz, 1H), 7.84 - 7.80 (m, 1H), 7.76 - 7.71 (m, 2H), 7.62 - 7.53 (m, 2H), 7.29 (t, J = 7.9 Hz, 1H), 7.15 - 7.12 (m, 1H), 1.31 (s, 9H). LC/MS: *m/z* 321.5 $(M+H)^+$ at 1.8 min (10%--99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[01036] Synthesis of N-[4-cyclopentyl-5-hydroxy-2-(3-hydroxyprop-1-ynyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide (Table 1, Compound 512)



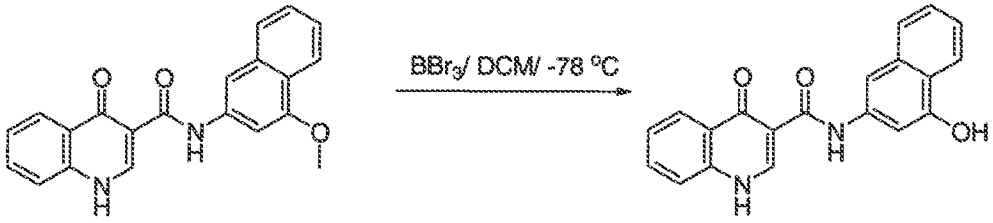
[01037] 4-bromo-2-cyclopentyl-5-(4-oxo-1,4-dihydroquinoline-3-carboxamido)phenyl methyl carbonate (50 mg, 0.10 mmol), $Pd(PPh_3)_2Cl_2$ (4 mg, 0.005 mmol), and cuprous iodide (1 mg, 0.10 μL, 0.003 mmol) were added to a microwave tube which was flushed with N_2 and capped. A degassed solution of DMF (1 mL), triethylamine (2 mL), and prop-2-yn-1-ol (57.75 mg, 59.97 μL, 1.030 mmol) was added and the reaction mixture was heated at 80 °C for 16 h. The reaction mixture was filtered and purified by HPLC (20-99% CH_3CN/0.05% TFA) to give 2-cyclopentyl-4-(3-hydroxyprop-1-ynyl)-5-(4-oxo-1,4-dihydroquinoline-3-carboxamido)phenyl methyl carbonate/N-(4-cyclopentyl-5-hydroxy-2-(3-hydroxyprop-1-ynyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide. These product fractions were combined, concentrated to remove acetonitrile, and treated with 5N NaOH (2 mL). The pH of the solution was adjusted to 7 and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with 50% saturated sodium bicarbonate solution (2 x 20 mL) and brine. The solution was dried over anhydrous Na_2SO_4, filtered, and dried to obtain N-(4-cyclopentyl-5-hydroxy-2-(3-hydroxyprop-1-ynyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide. LC/MS: *m/z* 403.2 $(M+H)^+$ at 0.92 min (10%--99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[01038] Synthesis of N-(4-cyclohexyl-2-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide (Table 1, Compound 648)



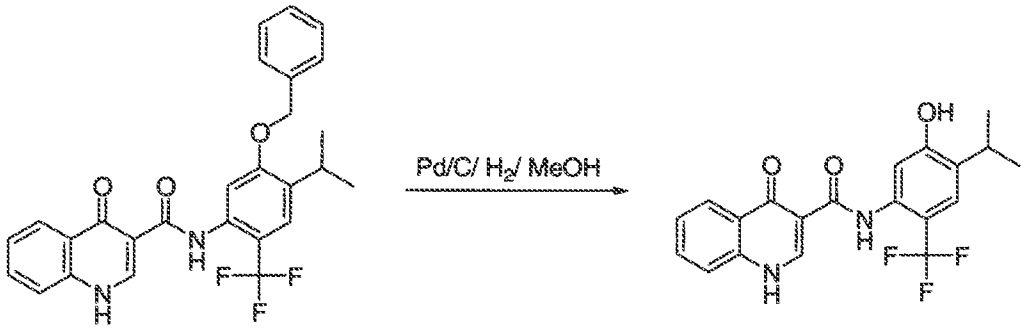
[01039] To N-(4-bromo-2-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide (50 mg, 0.14 mmol), cyclohexen-1-ylboronic acid (35mg, 0.28), and $Pd(dppf)Cl_2$-DCM (11 mg, 0.01 mmol) was added Na_2CO_3 (980 µL of 2 M, 1.96 mmol) and acetonitrile (2 mL). The reaction mixture was heated under microwave irradiation for 10 min at 150 °C under a N_2 atmosphere. The reaction mixture was diluted with ethyl acetate, washed with 50% saturated sodium bicarbonate solution (2 x 20 mL), water, and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified via silcia gel column chromatography (30-100% ethyl acetate/hexane) to obtain N-(4-cyclohexen-1-yl-2-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide as a white solid (35 mg, 70%). N-(4-cyclohexen-1-yl-2-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide (35 mg, 0.10 mmol) was stirred vigorously with 10% Pd/C (wet) (30 mg, 0.01 mmol) under an atmosphere of H_2 for 30 min at 50 °C. The reaction mixture was filtered, concentrated *in vacuo*, and purified by HPLC (30-95% CH_3CN/ 5 mM HCl) to yield N-(4-cyclohexyl-2-methylphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide (20 mg, 57% yield). LC/MS m/z 361.4 $[M+H]^+$. ^1H NMR (400.0 MHz, DMSO-d_6) δ 12.94 (d, J = 6.0 Hz, 1H), 12.24 (s, 1H), 8.89 (d, J = 6.5 Hz, 1H), 8.35 (d, J = 7.7 Hz, 1H), 8.22 (d, J = 8.3 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.55 - 7.51 (m, J = 7.6 Hz, 1H), 7.11 (s, 1H), 7.05 (d, J = 8.4 Hz, 1H), 2.45 (m, 1H), 2.38 (s, 3H), 1.80 - 1.69 (m, 5H), 1.42 - 1.21 (m, 5H).

[01040] Synthesis of N-(4-hydroxy-2-naphthyl)-4-oxo-1H-quinoline-3-carboxamide (Table 1, Compound 552)



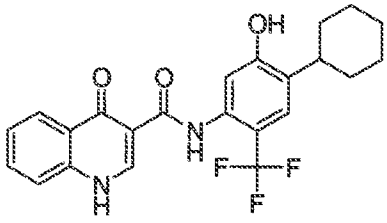
[01041] To a solution of N-(4-methoxy-2-naphthyl)-4-oxo-1H-quinoline-3-carboxamide (73 mg, 0.21 mmol) in DCM (4 mL) was added BBr_3 (1.1 mL, 11.64 mmol) dropwise at –78 °C. After the addition was complete the cooling bath was removed and the resulting reaction mixture was warmed to room temperature and then was heated to 50 °C for 2 h, cooled to –10 °C and quenched with saturated solution of $NaHCO_3$. The aqueous layer was extracted with DCM and the combined organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified via reverse phase HPLC to get N-(4-hydroxy-2-naphthyl)-4-oxo-1H-quinoline-3-carboxamide. LC/MS: *m/z* 331 $(M+H)^+$ at 1.47 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[01042] Synthesis of N-[5-hydroxy-4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide (Table 1, Compound 497)



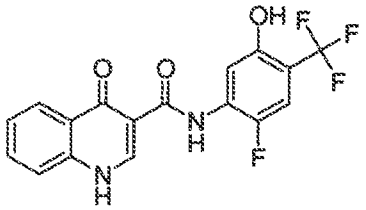
[01043] A flask charged with N-[5-benzyloxy-4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide (118 mg, 0.25 mmol) and Pd/C (12 mg, 0.11 mmol) was evacuated under vacuum, followed by purging with N_2. Methanol (2 mL) was added under inert atmosphere, followed by evacuating under vacuum. The reaction was stirred overnight under an atmosphere of hydrogen, filtered through a plug of celite and concentrated to give N-[5-hydroxy-4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide. ^1H NMR (400.0 MHz, DMSO-d_6) δ 12.93 (s, 1H), 12.59 (s, 1H), 10.29 (s, 1H), 8.87 (s, 1H), 8.32 (dd, *J* = 1.0, 8.1 Hz, 1H), 7.95 (s, 1H), 7.83 - 7.74 (m, 2H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.36 (s, 1H), 3.20 (qn, *J* = 6.9 Hz, 1H) and 1.24 - 1.19 (m, 6H) ppm. LC/MS: *m/z* 391.36 $(M+H)^+$ at 1.77 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[01044] Synthesis of N-[4-cyclohexyl-5-hydroxy-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide (Table 1, Compound 620)



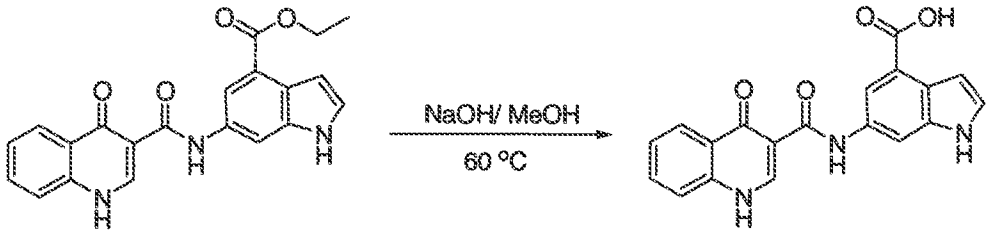
[01045] (N-(4-cyclohexyl-5-hydroxy-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide can be synthesized following the general scheme above starting from N-(5-(benzyloxy)-4-cyclohexyl-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 (d, J = 6.6 Hz, 1H), 12.54 (s, 1H), 10.28 (s, 1H), 8.87 (d, J = 6.8 Hz, 1H), 8.32 (d, J = 7.3 Hz, 1H), 7.95 (s, 1H), 7.81 (ddd, J = 23.1, 15.0, 4.7 Hz, 2H), 7.53 (dd, J = 11.5, 4.6 Hz, 1H), 7.34 (s, 1H), 2.84 (s, 1H), 1.85 – 1.69 (m, 5H), 1.38 (t, J = 10.3 Hz, 5H). LC/MS: m/z 431.5 $(M+H)^+$ at 2.01 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[01046] Synthesis of N-[2-fluoro-5-hydroxy-4-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide (Table 1, Compound 501)



[01047] N-(2-fluoro-5-hydroxy-4-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide can be synthesized following the general scheme above starting from N-(5-(benzyloxy)-2-fluoro-4-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide. LC/MS: m/z 367.10 $(M+H)^+$ at 1.65 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

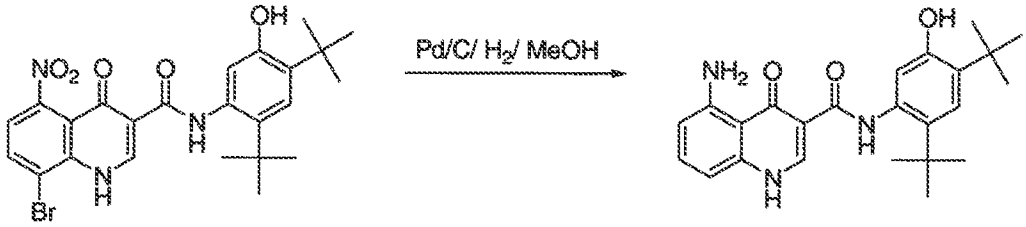
[01048] Synthesis of 6-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-1H-indole-4-carboxylic acid (Table 1, Compound 712)



[01049] Ethyl 6-(4-oxo-1,4-dihydroquinoline-3-carboxamido)-1H-indole-4-carboxylate (6 mg, 0.02 mmol) was suspended in 1 M NaOH (400 µL, 0.40 mmol) and heated to 50 °C for 30 min. The clear brown solution was diluted with water (1 mL) and acidified with 1N HCl (450 uL). The solution was washed with water (3 x 1 mL), and purified via reverse phase HPLC (75% acetonitrile/water) to give 6-(4-oxo-1,4-dihydroquinoline-3-

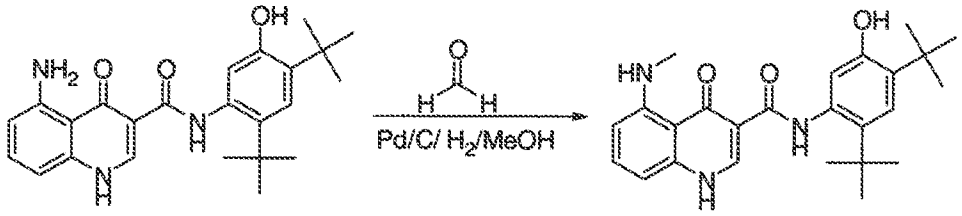
carboxamido)-1H-indole-4-carboxylic acid. LC/MS: *m/z* 347.8 $(M+H)^+$ at 1.07 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[01050] Synthesis of 5-amino-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide (Table 1, Compound 586)



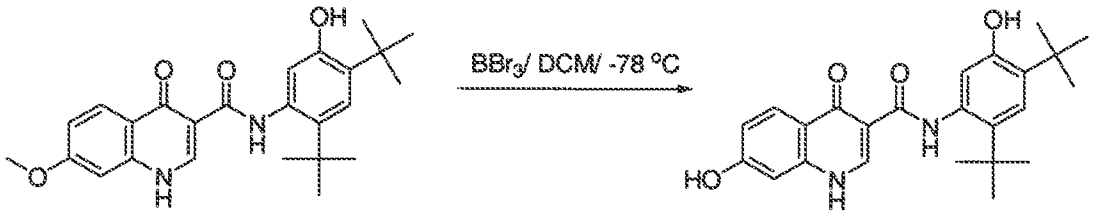
[01051] A flask charged with 8-bromo-N-(2,4-di-*tert*-butyl-5-hydroxyphenyl)-5-nitro-4-oxo-1,4-dihydroquinoline-3-carboxamide (430 mg, 0.83 mmol)) and Pd/C (60 mg, 0.56 mmol) was evacuated under vacuum, followed by purging with N_2. EtOAc (4 mL) and HCl (1 mL of 1 M, 1.000 mmol) were added followed by evacuating under vacuum. The reaction was stirred overnight under an atmosphere of hydrogen, filtered through a plug of celite and concentrated to get 5-amino-N-(2,4-di*tert*-butyl-5-hydroxy-phenyl)-4-oxo-1H-quinoline-3-carboxamide (164 mg, 48%). LC/MS: *m/z* 408.5 $(M+H)^+$ at 1.98 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[01052] Synthesis of N-(5-hydroxy-2,4-ditert-butyl-phenyl)-5-methylamino-4-oxo-1H-quinoline-3-carboxamide (Table 1, Compound 543)



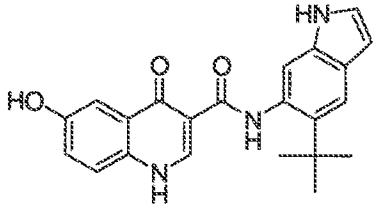
[01053] A flask charged with 5-amino-N-(2,4-di*tert*-butyl-5-hydroxy-phenyl)-4-oxo-1H-quinoline-3-carboxamide (23 mg, 0.06 mmol), Pd/C (5 mg, 0.05 mmol) and formaldehyde (5 µL of 38 %w/v, 0.06 mmol) was evacuated under vacuum, followed by purging with N_2. Methanol (1 mL) was added followed by evacuating under vacuum. The reaction mixture was stirred overnight under an atmosphere of hydrogen, filtered through a plug of celite and concentrated to get N-(2,4-di*tert*-butyl-5-hydroxy-phenyl)-5-methylamino-4-oxo-1H-quinoline-3-carboxamide. LC/MS: *m/z* 422.5 $(M+H)^+$ at 2.24 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[01054] Synthesis of N-(2,4-di-*tert*-butyl-5-hydroxy-phenyl)-7-hydroxy-4-oxo-1H-quinoline-3-carboxamide (Table 1, Compound 653)



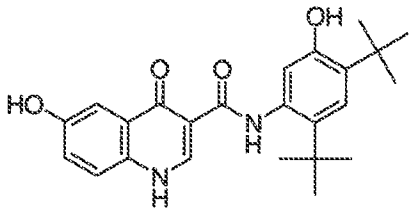
[01055] To a solution of N-(2,4-di-*tert*-butyl-5-hydroxy-phenyl)-7-methoxy-4-oxo-1H-quinoline-3-carboxamide (120 mg, 0.28 mmol) in DCM (1.5 mL) was added BBr_3 (1.5 mL, 15.23 mmol) dropwise at –78 °C. After the addition was complete the cooling bath was removed and the resulting reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was quenched with sat. solution of $NaHCO_3$. The aqueous layer was extracted with DCM and the combined organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified via reverse phase HPLC to give N-(2,4-di*tert*-butyl-5-hydroxy-phenyl)-7-hydroxy-4-oxo-1H-quinoline-3-carboxamide . LC/MS: m/z 409.5 $(M+H)^+$ at 1.83 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[01056] Synthesis of 6-hydroxy-4-oxo-N-(5-*tert*-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide (Table 1, Compound 680)



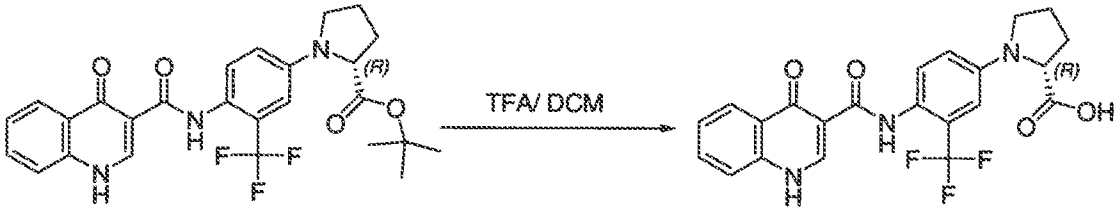
[01057] 6-hydroxy-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide can be synthesized following the general scheme above starting from N-(5-*tert*-butyl-1H-indol-6-yl)-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxamide. LC/MS: *m/z* 378.00 $(M+H)^+$ at 1.38 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[01058] Synthesis of 6-hydroxy-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide (Table 1, Compound 703)



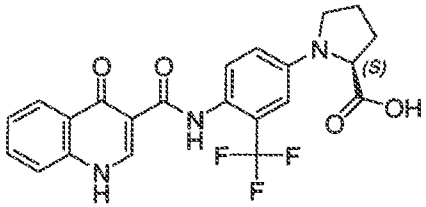
[01059] 6-hydroxy-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide can be synthesized following the general scheme above starting from N-(2,4-di-*tert*-butyl-5-hydroxyphenyl)-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxamide. LC/MS: *m/z* 409.00 $(M+H)^+$ at 1.73 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[01060] Synthesis of (R)-1-[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-3-(trifluoromethyl)phenyl]pyrrolidine-2-carboxylic acid (Table 1, Compound 699)



[01061] To a solution of *tert*-butyl (2*R*)-1-[4-[(4-oxo1H-quinoline-3-carbonyl)amino]-3-(trifluoromethyl)phenyl]pyrrolidine-2-carboxylate (35 mg, 0.06979 mmol) in DCM (500 µL) was added TFA (1 mL) at room temperature and the reaction mixture was stirred for 3h.The solvents were evaporated under reduced pressure and the residue was purified via reverse phase HPLC to give (2*R*)-1-[4-[(4-oxo-1H-quinoline-3-carbonyl)amino]-3-(trifluoromethyl)phenyl]pyrrolidine-2-carboxylic acid. LC/MS: *m/z* 466.3 $(M+H)^+$ at 1.46 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[01062] Synthesis of (*S*)-1-[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-3-(trifluoromethyl)phenyl]pyrrolidine-2-carboxylic acid (Table 1, Compound 568)



[01063] (*S*)-1-(4-(4-oxo-1,4-dihydroquinoline-3-carboxamido)-3-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylic acid can be synthesized following the general scheme above starting from *tert*-butyl (2*S*)-1-[4-[(4-oxo1H-quinoline-3-carbonyl)amino]-3-(trifluoromethyl)phenyl]pyrrolidine-2-carboxylate. LC/MS: *m/z* 466.3 $(M+H)^+$ at 1.47 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[01064] Set forth below is the characterizing data for compounds of the present invention prepared according to the above Examples.

[01065] Table 2

Cmd No.	LC-MS M+1	LC-RT min
1	444.3	3.19
2	350.1	3.8
3	455.3	3.75
4	350.3	2.81
5	337.3	2.76
6	351.4	3
7	472.3	3.6
8	307.1	1.21
9	344.1	2.43
10	334.2	2.2
11	408.1	2.91
12	383.1	2.63
13	346.3	3.48
14	394.3	3.07
15	296.3	2.68
16	307.3	3.38
17	338.3	3.74
18	352.9	3.62
19	316.3	2.71
20	371.3	3.53
21	421.1	2.66
22	332.2	2.21
23	457.5	3.56
24	398.3	3.13
25	397.1	2.38
26	348.1	2.51
27	446.2	2.33
28	438.4	2.9
29	307.1	3.32
30	379.1	2.62
31	278.9	3.03
32	338.2	3
33	303.9	2.83
34	397.1	4.19
35	362.2	2.53
36	307.3	3.25
37	303.9	2.98
38	380.3	3.33
39	480.5	3.82
40	309.1	2.46
41	321.1	1.88
42	460.0	3.71
43	457.5	3.6
44	336.1	2.95
45	308.1	3.18
46	490.1	1.89

Cmd No.	LC-MS M+1	LC-RT min
47	375.3	3.33
48	317.1	3.06
49	400.1	2.88
50	307.3	3.08
51	521.5	3.79
52	354.1	3.02
53	266.1	1.99
54	323.3	2.97
55	366.3	2.6
56	335.4	3.18
57	403.1	2.86
58	364.3	3.02
59	412.1	3.31
60	422.2	3.53
61	293.1	3.05
62	349.1	3.4
63	376.1	2.89
64	321.1	2.31
65	381.5	1.85
66	345.1	3.32
67	332.3	3.17
68	398.1	2.85
69	322.5	2.37
70	341.1	2.15
71	426.1	2.6
72	293.1	3.27
73	380.9	2.4
74	334.1	3.32
75	316.3	2.43
76	376.1	2.97
77	322.5	2.93
78	344.1	2.38
79	372.1	3.07
80	295.3	2.78
81	336.3	2.73
82	350.3	2.11
83	365.1	2.76
84	280.3	2.11
85	408.0	3.25
86	370.3	2.08
87	357.1	3.5
88	436.3	3.37
89	303.9	3.1
90	321.1	3.43
91	355.2	3.47
92	295.2	3.84

Cmd No.	LC-MS M+1	LC-RT min
93	371.0	2.75
94	294.2	2.06
95	290.1	2.78
96	343.0	2.75
97	402.1	2.59
98	349.1	1.96
99	334.1	3.13
100	303.9	2.63
101	322.5	2.35
102	443.1	3.97
103	411.2	3.85
104	318.0	2.94
105	322.2	2.4
106	350.3	2.86
107	420.2	3.37
108	448.2	3.77
109	404.5	3.17
110	303.9	2.75
111	333.1	3
112	348.5	3.07
113	318.3	3.02
114	499.2	3.74
115	330.1	2.67
116	320.2	3.18
117	349.1	1.32
118	379.1	2.61
119	408.4	3.07
120	309.1	2.93
121	333.1	3.69
122	325.1	2.66
123	330.1	2.64
124	378.3	3.4
125	294.3	2.21
126	411.1	3.06
127	408.5	3.22
128	369.1	3.53
129	365.1	1.74
130	440.2	3.57
131	313.0	2.4
132	365.9	2.73
133	488.1	1.97
134	402.1	2.25
135	384.1	2.94
136	393.1	4.33
137	580.5	4.1
138	376.1	2.98

Cmd No.	LC-MS M+1	LC-RT min
139	408.0	3.17
140	346.1	4
141	366.3	2.89
142	321.3	3.58
143	355.2	3.45
144	281.3	2.49
145	376.2	2.98
146	306.3	2.51
147	376.3	3.27
148	415.5	2.79
149	349.1	1.45
150	430.0	3.29
151	360.0	3
152	322.3	2.31
153	425.1	4.52
154	401.3	3.77
155	266.1	2.11
156	424.1	3.12
157	321.0	2.13
158	380.2	3.05
159	392.3	2.68
160	321.1	1.34
161	409.2	3.82
162	296.3	2.61
163	413.1	1.71
164	333.1	3.33
165	344.1	2.41
166	398.1	2.83
167	294.3	2.12
168	265.9	1.96
169	318	2.98
170	300.3	3.06
171	408.0	3.08
172	396.0	3.14
173	280.3	2.14
174	388.0	2.58
175	374.2	2.85
176	349.1	3.38
177	337.1	3.5
178	413.3	4
179	308.5	2.33
180	307.3	3.08
181	354.1	2.97
182	358.1	2.89
183	420.3	3.47
184	372.3	2.66
185	414.1	2.96
186	372.3	3.59
187	346.3	2.9
188	376.2	2.95
189	370.9	3.38
190	392.0	3.09
191	316.3	2.1
192	280.3	2.13
193	326.3	3.02
194	290.1	2.98
195	280.3	2.14
196	434.5	3.38
197	334.1	3.15
198	283.1	3
199	354.1	2.96
200	335.5	2.49
201	303.9	3.08
202	404.0	3.19
203	394.3	3.42
204	349.3	3.32
205	455.5	3.74
206	386.1	3.5
207	390.3	2.71
208	429.7	3.89
209	294.1	2.39
210	385.2	3.72
211	351.3	3.53
212	360.9	2.45
213	408.0	3.3
214	358.1	2.7
215	265.3	3.07
216	305.3	2.27
217	305.3	2.41
218	413.2	3.98
219	266.9	2.48
220	409.0	3.35
221	379.1	2.68
222	324.3	3.27
223	386.1	3.14
224	466.3	3.08
225	393.1	2.75
226	306.1	3.6
227	381.1	2.24
228	371.1	2.84
229	311.1	2.93
230	318.1	2.81
231	471.3	3.41
232	363.1	2.57
233	348.5	2.75
234	372.3	3.2
235	308.4	2.12
236	333.1	3.35
237	410.3	2.96
238	489.4	2.78
239	379.0	2.62
240	370.9	3.65
241	316.3	2.61
242	348.3	3.08
243	363.0	2.44
244	358.1	3.48
245	425.1	3.69
246	292.9	3.2
247	432.1	3.23
248	336.3	2.46
249	365.0	2.54
250	352.3	2.53
251	436.2	3.38
252	368.9	3.17
253	424.1	3.25
254	340.1	3.08
255	526.5	3.89
256	306.1	2.4
257	297.3	3.28
258	306.3	2.05
259	360.3	3.46
260	336.3	2.33
261	368.1	3.08
262	352.3	2.7
263	372.9	3.69
264	353.1	3.42
265	354.9	3.4
266	405.3	4.05
267	357.1	3.43
268	400.3	6.01
269	393.0	2.75
270	329.3	3.02
271	336.5	2.75
272	524.1	1.87
273	434.5	3.17
274	493.5	3.46
275	427.1	3.93
276	414.3	2.81

Cmd No.	LC-MS M+1	LC-RT min
277	358.1	2.89
278	408.1	3.09
279	386.1	2.88
280	316.3	2.06
281	293.1	3.22
282	307.1	1.22
283	370.1	3
284	305.3	2.57
285	376.1	2.88
286	319.1	3.35
287	411.2	4.15
288	413.3	3.8
289	297.3	3.25
290	382.1	3.19
291	371.0	3.57
292	391.1	3.69
293	330.3	3.05
294	303.9	2.67
295	334.3	2.26
296	365.3	3.6
297	358.3	3.26
298	379.1	1.91
299	320.3	2.18
300	348.2	2.4
301	346.3	2.26
302	370.1	2.28
303	362.2	2.51
304	513.2	3.66
305	370.1	2.98
306	384.1	3.11
307	374.0	3.05
308	304.1	2.71
309	316.3	2.83
310	320.1	3.73
311	344.9	3.43
312	400.1	2.86
313	358.1	2.8
314	335.1	3.52
315	293.1	2.9
316	378.5	2.84
317	333.2	2.91
318	522.1	1.8
319	373.3	3.59
320	360.1	3.5
321	453.5	3.12
322	349.3	3.7

Cmd No.	LC-MS M+1	LC-RT min
323	394.0	2.93
324	320.1	3.81
325	321.3	3.22
326	418.0	2.5
327	424.2	3.2
328	307.1	2.76
329	396.3	3.72
330	299.3	3.02
331	308.3	2.25
332	288.0	2.5
333	379.1	2.61
334	531.3	3.26
335	322.3	2.41
336	321.5	3.52
337	407.5	3.37
338	318.3	2.73
339	329.0	2.75
340	399.1	2.6
341	450.4	3.56
342	422.3	3.41
343	403.3	2.73
344	384.1	3.07
345	322.2	2.96
346	333.1	3.38
347	494.5	1.97
348	384.1	3.12
349	405.3	2.85
350	315.1	3.23
351	332.3	3.18
352	447.5	3.17
353	436.3	3.53
354	390.3	2.36
355	370.9	3.37
356	335.0	1.81
357	346.3	3.08
358	338.2	3.15
359	482.1	1.74
360	331.3	3.07
361	400.1	2.91
362	355.5	3.46
363	388.1	2.92
364	330.3	2.68
365	307.1	2.6
366	408.1	3.09
367	408.0	3.14
368	338.2	2.33

Cmd No.	LC-MS M+1	LC-RT min
369	358.1	3.29
370	299.1	3.03
371	365.0	3.27
372	362.1	2.66
373	305.3	3.38
374	350.3	3.01
375	319.3	3.4
376	382.3	3.48
377	340.2	3.08
378	310.3	2.07
379	389.0	2.53
380	309.3	3.02
381	360.2	3.18
382	393.1	2.84
383	332.3	3.2
384	376.1	2.87
385	393.9	3.32
386	334.3	2.3
387	347.1	3.22
388	424.1	3.3
389	355.3	3.65
390	350.3	2.44
391	396.1	3.43
392	300.3	2.86
393	399.4	2.12
394	293.1	3.17
395	433.5	4.21
396	464.4	2.97
397	341.3	3.45
398	434.3	3.1
399	335.0	1.75
400	351.3	2.11
401	368.1	3.09
402	342.1	2.96
403	423.1	4.45
404	440.3	2.87
405	299.3	3.16
406	547.3	3.74
407	371.3	3.8
408	295.3	2.9
409	335.1	1.82
410	432.1	3.41
411	299.1	3.17
412	376.2	2.93
413	357.1	3.37
414	305.3	2.11

Cmd No.	LC-MS M+1	LC-RT min
415	351.5	3.44
416	422.4	3.23
417	396.0	2.67
418	308.3	2.23
419	322.3	2.48
420	379.1	3.2
421	419.2	3.82
422	333.1	2.48
423	376.3	3.02
424	374.0	3.06
425	306.1	3.53
426	371.3	2.95
427	420.3	3.3
428	337.2	3.32
429	348.3	2.98
430	321.3	3.22
431	280.3	2.09
432	382.1	3.22
433	393.2	3.71
434	293.1	3.12
435	376.3	3.22
436	400.1	2.88
437	309.3	2.82
438	427.5	3.87
439	295.3	2.8
440	395.3	3.61
441	425.0	2.67
442	412.3	3.35
443	317.3	2.45
444	379.2	3.42
445	305.5	3.08
446	353.1	2.85
447	290.1	2.88
448	321.3	3.5
449	279.1	3.22
450	308.1	1.97
451	318.1	3.28
452	290.1	3.32
453	314.1	2.75
454	355.1	3.58
455	398.1	3.6
456	365.1	3.65
457	350.3	2.26
458	381.2	3.19
459	279.3	2.9
460	436.2	3.38
461	341.3	3.23
462	349.1	1.9
463	292.1	3.35
464	409.4	4.03
465	450.5	3.65
466	349.3	3.5
467	307.3	2.98
468	279.1	2.98
469	409.1	3.69
470	373.3	3.64
471	379.0	2.73
472	379.0	2.67
473	363.3	3.64
474	336.3	2.8
475	334.3	3.23
476	362.1	3.42
477	283.9	2.8
478	360.3	3.44
479	334.3	2.59
480	323.5	3.22
481	315.3	3.25
482	406.5	2.84
483	409.5	4.35
484	349.1	2.16
485	363.1	2.15
486	391.3	1.99
487	421.3	2.12
488	416.5	1.44
489	444.1	2.1
490	355.3	3.48
491	355.5	2.23
492	474.2	1.76
493	369.2	1.23
494	388.1	1.75
495	390	1.84
496	423	1.97
497	391.36	1.77
498	409.1	2.2
499	409.1	2.04
500	376.3	1.86
501	367.1	1.65
502	379.3	1.98
503	430.1	1.7
504	460.5	2.05
505	418	2.03
506	349.3	1.54
507	381	2.12
508	428.5	1.94
509	423.3	2
510	404.5	1.96
511	430.1	1.92
512	403.2	0.92
513	445.29	1.1
514	416.1	2.14
515	461	2.27
516	444.5	2.1
517	419	2.08
518	351.4	1.82
519	380	1.9
520	461	2.18
521	353.2	1.44
522	379.3	2.03
523	335.4	1.34
524	437	2.1
525	418.1	2
526	399	1.96
527	357.3	2.09
528	452.1	1.9
529	351.4	1.57
530	474.2	1.76
531	472.1	1.73
532	367	1.85
533	390	1.64
534	445.5	1.16
535	376	2.02
536	430.5	2.05
537	372	1.7
538	363.3	1.8
539	444.1	2.2
540	502.3	1.99
541	434.1	1.8
542	422	2.24
543	348.2	0.9
544	436	1.81
545	372	1.69
546	430.5	2.16
547	405.1	2.04
548	418.5	1.91
549	347.3	1.82
550	532.2	1.61
551	331	1.47
552	411.3	1.94

Cmd No.	LC-MS M+1	LC-RT min
553	473.1	2.22
554	378	1.9
555	416.5	1.92
556	432.5	1.6
557	393.3	1.99
558	385.5	1.58
559	428	1.91
560	388.2	1.85
561	389	2.01
562	420.03	1.85
563	349.3	1.51
564	363.4	1.81
565	374	1.93
566	448.3	1.74
567	446.3	1.47
568	407	2.28
569	444.1	1.7
570	481.5	2.29
571	364.3	1.81
572	416.5	1.75
573	393	1.93
574	367.3	1.58
575	323.5	1.53
576	386.1	1.49
577	347	1.78
578	444.1	1.8
579	418.3	1.91
580	461	2.2
581	431	206
582	442.4	2.02
583	423	2
584	425.5	2.08
585	408	1.98
586	484.5	2.02
587	339.3	1.76
588	367.2	2.08
589	411.3	2.05
590	353.2	1.02
591	348.1	1.82
592	444.5	1.71
593	402.5	2.03
594	393.5	1.87
595	431.5	2.25
596	338.2	1.66
597	341.5	1.66
598	418.3	1.47

Cmd No.	LC-MS M+1	LC-RT min
599	365.1	1.7
600	448.3	1.76
601	446.1	1.76
602	321.5	1.84
603	394	1.86
604	435	2.01
605	383	2
606	393.1	2.17
607	430.1	1.67
608	349.1	1.58
609	353.1	1.96
610	373.3	1.78
611	408	1.71
612	444.5	1.89
613	430.5	2.16
614	358.3	1.08
615	348.3	1.14
616	437	2.13
617	441	2.06
618	416.5	1.76
619	431.5	2.01
620	337.5	2.06
621	407	2.05
622	359.3	2.3
623	427	2.2
624	409.2	2.1
625	369	1.89
626	434.1	1.8
627	371.2	1.12
628	383.1	1.85
629	502.3	1.99
630	401.3	1.87
631	474.1	1.76
632	444	1.91
633	353.3	2.5
634	432.3	1.41
635	383	2.14
636	385	1.96
637	389	1.97
638	423	2.03
639	459.5	1.18
640	407	2.05
641	404	1.79
642	446.3	1.83
643	444.2	1.65
644	374	1.71

Cmd No.	LC-MS M+1	LC-RT min
645	339.1	1.98
646	396.1	1.82
647	361.4	2.03
648	391.3	2.11
649	383	1.97
650	367.3	1.63
651	381.3	1.9
652	409	1.82
653	388	1.81
654	521.5	2.58
655	418.3	1.34
656	378.5	1.61
657	409	2.09
658	402.5	1.8
659	365	1.88
660	488.5	1.75
661	386.1	1.68
662	337.5	1.44
663	427	2.13
664	339.3	1.94
665	355.3	1.7
666	381.3	1.85
667	466.2	6.21
668	446.3	1.09
669	484.2	1.88
670	432.3	1.41
671	337.3	0.97
672	429.5	2.15
673	461.5	1.03
674	334.2	1.01
675	364.3	1.95
676	363	2.04
677	380.5	1.76
678	365	1.9
679	378	1.38
680	378	1.67
681	404	1.76
682	403	2.08
683	369.2	1.93
684	434.5	1.85
685	460.3	1.84
686	416.5	1.25
687	411	2.02
688	407.7	2.08
689	388.3	1.48
690	385.3	1.81

Cmd No.	LC-MS M+1	LC-RT min
691	363.3	1.76
692	342	0.92
693	388	1.95
694	477	2.23
695	333.1	1.51
696	432.5	1.84
697	430.5	2.04
698	446.3	1.46
699	393.3	1.86
700	365.2	1.74

Cmd No.	LC-MS M+1	LC-RT min
701	353.5	1.52
702	409	1.73
703	390.3	1.62
704	374	1.71
705	418.3	1.48
706	463.2	2.13
707	390.3	1.31
708	415.3	1.95
709	441	2.03
710	362.3	1.37

Cmd No.	LC-MS M+1	LC-RT min
711	347.8	1.07
712	351.5	1.84
713	430.5	1.12
714	434.5	1.85
715	474.2	1.76
716	383	1.71
717	345	1.73
718	429	1.97

NMR data for selected compounds is shown below in Table **2-A**:

Cmpd No.	NMR Data
2	1H NMR (300 MHz, $CDCl_3$) δ 12.53 (s, 1H), 11.44 (br d, J = 6.0 Hz, 1H), 9.04 (d, J = 6.7 Hz, 1H), 8.43 (d, J = 7.8 Hz, 1H), 7.51 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.33-7.21 (m, 3H), 7.10 (d, J = 8.2 Hz, 1H), 3.79 (s, 3H), 1.36 (s, 9H)
5	H NMR (400 MHz, DMSO-d6) δ 12.94 (bs, 1H), 12.41 (s, 1H), 8.88 (s, 1H), 8.34 (dd, *J* = 8, 1 Hz, 1H), 7.82 (ddd, *J* = 8, 8, 1 Hz, 1H), 7.75 (d, *J* = 8 Hz, 1H), 7.64 (dd, *J* = 7, 2 HZ, 2H), 7.54 (ddd, *J* = 8, 8, 1 Hz, 1H), 7.35 (dd, *J* = 7, 2 Hz, 2H), 4.66 (t, *J* = 5 Hz, 1H), 3.41 (d, *J* = 5 Hz, 2H), 1.23 (s, 6H).
8	1H NMR (CD3OD, 300 MHz) δ 8.86 (s, 1H), 8.42 (d, J = 8.5 Hz, 1H), 7.94 (s, 1H), 7.81 (t, J = 8.3 Hz, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.54 - 7.47 (m, 2H), 7.38 (d, J = 8.5 Hz, 1H), 2.71 (q, J = 7.7 Hz, 2H), 1.30 (t, J= 7.4 Hz, 3H).
10	H NMR (400 MHz, DMSO-d6) δ 13.02 (d, J = 6.4 Hz, 1H), 12.58 (s, 1H), 8.87 (d, J = 6.8 Hz, 1H), 8.33 (dd, J = 8.1, 1.2 Hz, 1H), 7.89-7.77 (m, 3H), 7.56 (t, J = 8.1 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 3.23 (m, 2H), 2.81 (m, 2H), 1.94 (m, 2H), 1.65 (m, 2H)
13	H NMR (400 MHz, DMSO-d6) δ 13.05 (bs, 1H), 12.68 (s, 1H), 8.89 (s, 1H) , 8.35 (t, J = 2.5 Hz, 1H), 8.32 (d, J = 1.1 Hz, 1H), 7.85-7.76 (m, 3H), 7.58-7.54 (m, 2H), 1.47 (s, 9H)
14	H NMR (400 MHz, DMSO-d6) δ 1.32 (s, 9H), 3.64 (s, 3H), 7.36 (d, J = 8.4 Hz, 1H), 7.55 (m, 3H), 7.76 (d, J = 8.0 Hz, 1H), 7.83 (m, 1H), 8.33 (d, J = 7.0 Hz, 1H), 8.69 (s, 1H), 8.87 (d, J = 6.7 Hz, 1H), 12.45 (s, 1H), 12.97 (s, 1H)
27	H NMR (400 MHz, DMSO-d6) δ 13.20 (d, J = 6.7 Hz, 1H), 12.68 (s, 1H), 8.96-8.85 (m, 4H), 8.35 (d, J = 7.9 Hz, 1H), 7.91-7.77 (m, 3H), 7.64-7.54 (m, 3H), 6.82 (m, 1H), 5.05 (s, 0.7H), 4.96 (s, 1.3H), 4.25 (t, J = 5.6 Hz, 1.3H), 4.00 (t, J = 5.7 Hz, 0.7H), 3.14 (s, 2H), 3.02 (s, 1H), 2.62 (t, J = 5.2 Hz, 2H), 2.54 (t, J = 5.4 Hz, 1H)
29	H NMR (400 MHz, $CDCl_3$) δ 9.0 9 (s, 1H), 8.62 (dd, J = 8.1 and 1.5 Hz, 1H), 7.83-7.79 (m, 3H), 7.57 (d, J = 7.2 Hz, 1H), 7.38 (t, J =7.6 Hz, 2H), 7.14 (t, J = 7.4 Hz, 2H), 5.05 (m, 1H), 1.69 (d, J =6.6 Hz, 6H)

32	H NMR (400 MHz, DMSO-d6) δ 12.93 (d, J = 6.6 Hz, 1H), 12.74 (s, 1H), 11.27 (s, 1H), 8.91 (d, J = 6.7 Hz, 1H), 8.76 (s, 1H), 8.37 (d, J = 8.1 Hz, 1H), 7.83 (t, J = 8.3 Hz, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.70 (s, 1H), 7.54 (t, J = 8.1 Hz, 1H), 7.38 (m, 1H), 6.40 (m, 1H)
33	H NMR (400 MHz, DMSO-d6) δ 12.92 (s, 1H), 12.47 (s, 1H), 11.08 (s, 1H), 8.90 (s, 1H), 8.35 (dd, J = 8.1, 1.1 Hz, 1H), 8.20 (t, J = 0.8 Hz, 1H), 7.83 (t, J = 8.3 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.55 (t, J = 8.1 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.30 (t, J = 2.7 Hz, 1H), 7.06 (dd, J = 8.4, 1.8 Hz, 1H), 6.39 (m, 1H)
35	H NMR (400 MHz, DMSO-d6) δ 13.01 (d, J = 6.7 Hz, 1H), 12.37 (s, 1H), 8.86 (d, J = 6.8 Hz, 1H), 8.33 (dd, J = 8.1, 1.3 Hz, 1H), 7.82 (t, J = 8.3 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.54 (t, J = 8.1 Hz, 1H), 7.36 (s, 1H), , 7.19 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 8.2 Hz, 1H), 3.29 (m, 2H), 1.85 (m, 1H), 1.73-1.53 (m, 3H), 1.21 (s, 3H), 0.76 (t, J = 7.4 Hz, 3H)
43	H NMR (400 MHz, DMSO-d6) δ 12.77 (s, 1H), 11.94 (s, 1H), 9.56 (s, 1H), 8.81 (s, 1H), 8.11 (dd, J = 8.2, 1.1 Hz, 1H), 7.89 (s, 1H), 7.79-7.75 (m, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.49-7.45 (m, 1H), 7.31 (t, J = 8.1 Hz, 1H), 7.00 (s, 1H), 6.93-6.87 (m, 3H), 4.07 (q, J = 7.0 Hz, 2H), 1.38 (s, 9H), 1.28 (t, J = 7.0 Hz, 3H)
47	H NMR (400 MHz, DMSO-d6) δ 1.24 (d, J = 6.9 Hz, 6H), 3.00 (m, 1H), 7.55 (m, 3H), 7.76 (d, J = 7.7 Hz, 1H), 7.83 (m, 1H), 8.26 (d, J = 8.2 Hz, 1H), 8.33 (d, J = 9.2 Hz, 1H), 8.89 (s, 1H), 12.65 (s, 1H), 12.95 (s, 1H)
56	H NMR (400 MHz, DMSO-d6) δ 12.81 (d, J = 6.7 Hz, 1H), 12.27 (s, 1H), 9.62 (s, 1H), 8.82 (d, J = 6.7 Hz, 1H), 8.32 (dd, J = 8.2, 1.3 Hz, 1H), 8.07 (s, 1H), 7.80 (t, J = 8.4 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.52 (t, J = 8.1 Hz, 1H), 6.58 (s, 1H), 2.62 (m, 4H), 1.71 (m, 4H)
58	H NMR (400 MHz, DMSO-d6) δ 12.95 (d, J = 6.6 Hz, 1H), 12.39 (s, 1H), 8.86 (d, J = 6.8 Hz, 1H), 8.33 (d, J = 7.3 Hz, 1H), 7.82 (t, J = 8.3 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 8.1 Hz, 1H), 7.29 (d, J = 2.5 Hz, 1H), 7.07 (dd, J = 8.7, 1.3 Hz, 1H), 6.91 (dd, J = 8.8, 2.5 Hz, 1H), 5.44 (br s, 2H)
64	H NMR (400 MHz, DMSO-d6) δ 12.92 (s, 1H), 12.41 (s, 1H), 10.63 (s, 1H), 10.54 (s, 1H), 8.86 (s, 1H), 8.33 (d, J = 8.1 Hz, 1H), 7.82 (t, J = 8.3 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.69 (s, 1H), 7.54 (t, J = 8.1 Hz, 1H), 7.04 (d, J = 8.3 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H)
69	H NMR (400 MHz, DMSO-d6) δ 13.06 (d, J = 6.5 Hz, 1H), 12.51 (s, 1H), 8.88 (d, J = 6.6 Hz, 1H), 8.33 (dd, J = 8.1, 1.0 Hz, 1H), 7.85-7.74 (m, 3H), 7.55 (t, J = 8.1 Hz, 1H), 7.38 (dd, J = 8.4, 1.9 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H), 3.03 (septet, J = 6.8 Hz, 1H), 1.20 (d, J = 6.7 Hz, 6H)
76	1H-NMR (CDCl3, 300 MHz) δ 8.84 (d, J = 6.6 Hz, 1H), 8.31 (d, J = 6.2 Hz, 1H), 8.01 (d, J = 7.9 Hz, 1H), 7.44-7.13 (m, 8H), 6.78 (d, J = 7.5 Hz, 1H).
77	H NMR (400 MHz, DMSO-d6) δ 6.40 (m, 1H), 7.36 (t, J = 2.7 Hz, 1H), 7.43 (d, J = 11.8 Hz, 1H), 7.55 (t, J = 8.1 Hz, 1H), 7.80 (m, 2H), 8.36 (d, J = 9.2 Hz, 1H), 8.65 (d, J = 6.8 Hz, 1H), 8.91 (s, 1H), 11.19 (s, 1H), 12.72 (s, 1H), 12.95 (s, 1H)
88	H NMR (400 MHz, DMSO-d6) δ 12.96 (d, J = 6.6 Hz, 1H), 12.42 (s, 1H), 8.89 (d, J = 6.7 Hz, 1H), 8.33 (dd, J = 8.1, 1.2 Hz, 1H), 7.82 (t, J = 8.3 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 8.7 Hz, 2H), 7.54 (t, J = 8.1 Hz, 1H), 7.34 (d, J = 8.7 Hz, 2H), 6.67 (t, J = 6.3 Hz, 1H), 3.12 (d, J = 6.3 Hz, 2H), 1.35 (s, 9H), 1.22 (s, 6H)

90	1H NMR (400 MHz, DMSO-d6) δ 11.98 (s, 1H), 8.89 (s, 1H), 8.34 (dd, J = 8.2, 1.1 Hz, 1H), 7.84-7.75 (m, 2H), 7.59 (dd, J = 7.8, 1.5 Hz, 1H), 7.55-7.51 (m, 1H), 7.42 (dd, J = 7.9, 1.5 Hz, 1H), 7.26-7.21 (m, 1H), 7.19-7.14 (m, 1H), 1.43 (s, 9H)
96	1H NMR (400 MHz, DMSO-d6) δ 12.58 (s, 1H), 11.11 (s, 1H), 8.89 (s, 1H), 8.35 (dd, J = 8.1, 1.1 Hz, 1H), 8.22 (d, J = 1.5 Hz, 1H), 7.83-7.74 (m, 2H), 7.56-7.51 (m, 2H), 7.30 (d, J = 2.3 Hz, 1H), 7.13 (dd, J = 8.5, 1.8 Hz, 1H), 4.03 (d, J = 0.5 Hz, 2H)
103	H NMR (400 MHz, DMSO-d6) δ 1.37 (s, 9H), 1.38 (s, 9H), 7.08 (s, 1H), 7.17 (s, 1H), 7.74 (m, 1H), 7.86 (m, 1H), 7.98 (dd, J = 9.2, 2.9 Hz, 1H), 8.90 (d, J = 6.7 Hz, 1H), 9.21 (s, 1H), 11.71 (s, 1H), 13.02 (d, J = 6.7 Hz, 1H)
104	1H NMR (400 MHz, DMSO-d6) δ 12.93 (d, J = 6.6 Hz, 1H), 12.41 (s, 1H), 10.88 (s, 1H), 8.88 (d, J = 6.7 Hz, 1H), 8.36-8.34 (m, 1H), 8.05 (d, J = 0.8 Hz, 1H), 7.84-7.75 (m, 2H), 7.56-7.52 (m, 1H), 7.35 (d, J = 8.3 Hz, 1H), 7.01 (dd, J = 8.4, 1.9 Hz, 1H), 6.07-6.07 (m, 1H), 2.37 (s, 3H)
107	H NMR (400 MHz, DMSO-d6) δ 12.52 (s, 1H), 8.87 (s, 1H), 8.33 (dd, J = 8.2, 1.1 Hz, 1H), 7.81 (t, J = 8.3 Hz, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.57-7.51 (m, 3H), 7.15 (d, J = 8.3 Hz, 1H), 4.51 (s, 2H), 3.56 (t, J = 5.7 Hz, 2H), 2.75 (t, J = 5.5 Hz, 2H), 1.44 (s, 9H)
109	H NMR (400 MHz, DMSO-d6) δ 12.97 (br s, 1H), 12.45 (s, 1H), 8.89 (s, 1H), 8.33 (dd, J = 8.2, 1.1 Hz, 1H), 7.88 (s, 1H), 7.82 (t, J = 8.4 Hz, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.54 (t, J = 8.1 Hz, 1H), 7.43 (m, 1H), 7.31 (d, J = 8.5 Hz, 1H), 4.01 (m, 1H), 3.41 (m, 1H), 2.21 (s, 3H), 1.85 (m, 1H), 1.68-1.51 (m, 3H), 1.23 (s, 3H), 0.71 (t, J = 7.4 Hz, 3H)
113	1H NMR (400 MHz, DMSO-d6) δ 12.92 (d, J = 6.6 Hz, 1H), 12.46 (s, 1H), 10.72 (d, J = 1.5 Hz, 1H), 8.89 (d, J = 6.7 Hz, 1H), 8.35 (dd, J = 8.1, 1.2 Hz, 1H), 8.13 (d, J = 1.5 Hz, 1H), 7.84-7.75 (m, 2H), 7.56-7.52 (m, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.07-7.04 (m, 2H), 2.25 (d, J = 0.9 Hz, 3H)
114	1H NMR (300 MHz, DMSO-d6): δ 12.65 (d, J = 6.9 Hz, 1H), 11.60 (s, 1H), 9.33 (s, 1H), 8.71 (d, J = 6.6 Hz, 1H), 8.36 (d, J = 1.8 Hz, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.66 (t, J = 7.2 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.12 (m, 2H), 6.97 (m, 3H), 3.97 (m, 2H), 1.45 (s, 9H), 1.06 (t, J = 6.6 Hz, 3H).
126	H NMR (400 MHz, DMSO-d6) δ 12.94 (s, 1H), 12.33 (s, 1H), 9.49 (s, 1H), 8.88 (s, 1H), 8.35 (dd, J = 8.7, 0.5 Hz, 1H), 7.86-7.82 (m, 1H), 7.77 (d, J = 7.8 Hz, , 7.58-7.54 (m, 1H), 7.40 (d, J = 2.2 Hz, 1H), 7.11 (d, J = 8.5 Hz, 1H), 6.98 (dd, J = 8.4, 2.2 Hz, 1H), 3.67 (s, 2H), 3.51-3.47 (m, 2H), 3.44-3.41 (m, 2H), 3.36 (s, 3H), 1.33 (s, 6H)
127	H NMR (400 MHz, DMSO-d6) δ 1.23 (t, J = 7.0 Hz, 3H), 1.32 (s, 9H), 4.10 (q, J = 7.0 Hz, 2H), 7.36 (d, J = 8.5 Hz, 1H), 7.54 (m, 3H), 7.76 (d, J = 7.9 Hz, 1H), 7.82 (m, 1H) 8.33 (d, J = 9.2 Hz, 1H), 8.64 (s, 1H), 8.87 (s, 1H), 12.45 (s, 1H), 12.99 (s, 1H)
129	1H-NMR (CD3OD, 300 MHz) δ 8.83 (s, 1H), 8.41 (d, J = 8.1 Hz, 1H), 7.80 (m, 2H), 7.65 (d, J = 8.1 Hz, 1H), 7.55 (m, 2H), 7.22 (d, J = 8.1 Hz, 1H), 3.76 (s, 3H, OMe), 2.62 (q, J = 7.5 Hz, 2H), 1.21 (t, J = 7.5 Hz, 3H).
131	1H NMR (300 MHz, DMSO-d6) δ 12.37 (s, 1H), 8.81 (s, 1H), 8.30 (d, J = 8.1 Hz, 1H), 7.77 (m, 2H), 7.52 (t, J = 7.2 Hz, 1H), 7.09 (s, 1H), 6.74 (s, 1H), 6.32 (s, 1H), 5.47 (s, 2H).
135	1H-NMR (CDCl3, 300 MHz) δ 8.86 (d, J = 6.6 Hz, 1H), 8.32 (d, J = 6.2 Hz, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.47 - 7.24 (m, 6H), 6.95 - 6.83 (m, 3H), 5.95 (s, 2H).

136	H NMR (400 MHz, DMSO-d6) δ 1.29 (s, 9H), 1.41 (s, 9H), 7.09 (d, J = 2.4 Hz, 1H), 7.47 (d, J = 2.3 Hz, 1H), 7.57 (t, J = 8.1 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.85 (t, J = 8.4 Hz, 1H), 8.36 (d, J = 9.5 Hz, 1H), 8.93 (d, J = 6.8 Hz, 1H), 9.26 (s, 1H), 12.66 (s, 1H), 13.04 (d, J = 6.6 Hz, 1H)
141	H NMR (400 MHz, DMSO-d6) δ 12.96 (d, J = 6.6 Hz, 1H), 12.42 (s, 1H), 8.87 (d, J = 6.8 Hz, 1H), 8.33 (dd, J = 8.1, 1.2 Hz, 1H), 7.85-7.75 (m, 3H), 7.55 (t, J = 8.1 Hz, 1H), 7.46 (dd, J = 8.2, 2.2 Hz, 1H), 7.16 (d, J = 8.5 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 2.18 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H)
143	H NMR (400 MHz, DMSO-d6) δ 12.96 (d, J = 6.8 Hz, 1H), 12.56 (s, 1H), 9.44 (s, 1H), 8.87 (d, J = 6.8 Hz, 1H), 8.34 (dd, J = 8.2, 1.3 Hz, 1H), 8.08 (d, J = 7.4 Hz, 1H), 7.83 (t, J = 8.3 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.55 (t, J = 8.1 Hz, 1H), 7.00 (d, J = 13.3 Hz, 1H), 1.34 (s, 9H)
150	1H-NMR (DMSO d6, 300 MHz) δ 8.86 (d, J = 6.9 Hz, 1H), 8.63 (s, 1H), 8.30 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 8.7 Hz, 2H), 7.82-7.71 (m, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.52 (td, J = 1.2Hz, 1H).
157	1H-NMR (CD3OD, 300 MHz) δ 8.91 (s, 1H), 8.57 (s, 1H), 8.45 (d, J = 8.3 Hz, 1H), 7.83 (t, J = 7.2 Hz, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.57 (t, J = 7.9 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.16 (d, J = 6.0 Hz, 1H), 3.08 (s, 3H, NMe), 2.94 (q, J = 7.4 Hz, 2H), 1.36 (t, J = 7.4 Hz, 3H).
161	H NMR (400 MHz, DMSO-d6) δ 12.96 (s, 1H), 12.41 (s, 1H), 8.88 (s, 1H), , 8.33 (dd, J = 8.2, 1.2 Hz, 1H), 7.84-7.80 (m, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.55 (t, J = 8.1 Hz, 1H), , 7.44 (s, 1H), 7.19 (s, 2H), 4.13 (t, J = 4.6 Hz, 2H), 3.79 (t, J = 4.6 Hz, 2H), 3.54 (q, J = 7.0 Hz, 2H), 1.36 (s, 9H), 1.15 (t, J = 7.0 Hz, 3H)
163	1H-NMR (300 MHz, DMSO-d6) δ 12.87 (d, J = 6.3 Hz, 1H), 11.83 (s, 1H), 8.76 (d, J = 6.3 Hz, 1H), 8.40 (s, 1H), 8.26 (br s, 2H), 8.08 (dd, J = 8.4 Hz, J = 1.5 Hz, 1H), 7.75(m, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.47-7.37 (m, 2H), 7.24 (d, J = 0.9 Hz, 1H), 7.15 (dd, J = 7.5 Hz, J = 1.8 Hz, 1H), 7.10 (d, J = 8.1 Hz, 1H), 7.02 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 4.07 (m, 4H), 1.094 (t, J = 6.9 Hz, 3H).
167	H NMR (400 MHz, DMSO-d6) δ 2.03 (s, 3H), 4.91 (s, 2H), 6.95 (m, 3H), 7.53 (m, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.81 (m, 1H), 8.33 (d, J = 8.0 Hz, 1H), 8.84 (s, 1H), 12.20 (s, 1H), 12.90 (s, 1H)
169	1H NMR (400 MHz, DMSO-d6) δ 12.94 (d, J = 5.3 Hz, 1H), 12.51 (s, 1H), 8.89 (d, J = 6.3 Hz, 1H), 8.36 (dd, J = 8.1, 1.1 Hz, 1H), 8.06 (t, J = 0.7 Hz, 1H), 7.85-7.75 (m, 2H), 7.57-7.51 (m, 2H), 7.28 (d, J = 3.1 Hz, 1H), 7.24 (dd, J = 8.4, 1.8 Hz, 1H), 6.39 (dd, J = 3.1, 0.8 Hz, 1H), 3.78 (s, 3H)
178	1H NMR (400 MHz, DMSO-d6) δ 12.86 (s, 1H), 8.89 (d, J = 6.8 Hz, 1H), 8.65 (dd, J = 8.1, 1.6 Hz, 1H), 8.19 (dd, J = 8.2, 1.3 Hz, 1H), 7.80-7.71 (m, 2H), 7.48-7.44 (m, 2H), 7.24-7.20 (m, 1H), 7.16-7.09 (m, 2H), 7.04-7.00 (m, 1H), 6.80 (dd, J = 8.0, 1.3 Hz, 1H), 6.69 (dd, J = 8.1, 1.4 Hz, 1H), 1.45 (s, 9H)
183	1H NMR (400 MHz, DMSO-d6) δ 12.42 (s, 1H), 8.88 (s, 1H), 8.33 (dd, J = 8.2, 1.1 Hz, 1H), 8.06 (d, J = 2.1 Hz, 1H), 7.84-7.75 (m, 2H), 7.56-7.52 (m, 1H), 7.38 (dd, J = 8.2, 2.1 Hz, 1H), 7.08 (d, J = 8.3 Hz, 1H), 3.66-3.63 (m, 2H), 2.70 (t, J = 6.5 Hz, 2H), 1.86-1.80 (m, 2H), 1.51 (s, 9H)
186	H NMR (400 MHz, DMSO-d6) δ 12.93 (s, 1H), 12.47 (s, 1H), 10.72 (s, 1H), 8.89 (s, 1H), 8.35 (dd, J = 8.2, 1.1 Hz, 1H), 8.13 (d, J = 1.6 Hz, 1H), 7.82 (t, J = 8.2 Hz, 1H) , 7.76 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.05-7.02 (m, 2H), 3.19 (quintet, J = 8.2 Hz, 1H), 2.08 (m, 2H), 1.82-1.60 (m, 6H)

187	1H NMR (400 MHz, DMSO-d6) δ 12.63 (s, 1H), 8.91 (s, 1H), 8.87-8.87 (m, 1H), 8.36 (dd, J = 8.2, 1.2 Hz, 1H), 7.85-7.75 (m, 3H), 7.64-7.53 (m, 3H), 6.71 (dd, J = 3.7, 0.5 Hz, 1H), 2.67 (s, 3H)
188	H NMR (400 MHz, DMSO-d6) δ 12.84 (s, 1H), 12.73 (d, J = 6.6 Hz, 1H), 11.39 (s, 1H), 8.85 (d, J = 6.7 Hz, 1H), 8.61 (s, 1H), 8.33 (d, J = 6.8 Hz, 1H), 8.23 (s, 1H), 7.80 (t, J = 8.4 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.52 (t, J = 8.1 Hz, 1H), 7.43 (m, 1H), 6.54 (m, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H)
204	H NMR (400 MHz, DMSO-d6) δ 12.97 (s, 1H), 12.37 (s, 1H), 8.87 (d, J = 1.2 Hz, 1H), 8.32 (d, J = 8.2 Hz, 1H), 7.82 (dd, J = 8.2, 7.0 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.32-7.28 (m, 2H), 7.05 (d, J = 8.4 Hz, 1H), 4.16 (t, J = 4.9 Hz, 2H), 1.78 (t, J = 4.9 Hz, 2H), 1.29 (s, 6H),
207	H NMR (400 MHz, DMSO-d6) δ 12.92 (br s, 1H), 12.50 (s, 1H), 10.95 (s, 1H), 8.89 (s, 1H), 8.35 (dd, J = 8.2, 1.1 Hz, 1H), 8.17 (d, J = 1.5 Hz, 1H), 7.82 (t, J = 8.3 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.55 (t, J = 8.1 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 2.3 Hz, 1H), 7.06 (dd, J = 8.5, 1.8 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.72 (s, 2H), 1.20 (t, J = 7.1 Hz, 3H)
215	H NMR (400 MHz, DMSO-d6) δ 12.97 (s, 1H), 12.50 (s, 1H), 8.89 (s, 1H), 8.34 (dd, J = 8.1, 1.1 Hz, 1H), 7.83 (t, J = 8.3 Hz, 1H), 7.75 (m, 3H), 7.55 (t, J = 8.1 Hz, 1H), 7.37 (t, J = 7.9 Hz, 2H), 7.10 (t, J = 6.8 Hz, 1H)
220	H NMR (400 MHz, DMSO-d6) δ 12.99 (d, J = 6.6 Hz, 1H), 12.07 (s, 1H), 8.93 (d, J = 6.8 Hz, 1H), 8.35 (d, J = 7.1 Hz, 1H), 8.27 (s, 1H), 8.12 (s, 1H), 7.85-7.77 (m, 2H), 7.54 (td, J = 7.5, 1.2 Hz, 1H), 6.81 (s, 1H), 1.37 (d, J = 3.9 Hz, 9H), 1.32 (d, J = 17.1 Hz, 9H)
225	1H NMR (CD3OD, 300 MHz) δ 8.79 (s, 1H), 8.37 (d, J = 7.9 Hz, 1H), 7.75 (m, 2H), 7.61 (d, J = 8.3 Hz, 1H), 7.5 (m, 2H), 7.29 (d, J = 8.3 Hz, 1H), 4.21 (q, J = 7.2, 2H), 3.17 (m, 1H), 1.32 (t, J = 7.2 Hz, 3H), 1.24 (d, J = 6.9 Hz, 6H).
232	1H-NMR (CD3OD, 300 MHz) δ 8.87 (s, 1H), 8.45 (d, J= 8.25, 1H), 8.27 (m, 1H), 7.83 (t, J= 6.88, 1H), 7.67 (d, J= 8.25, 1H), 7.54 (t, J= 7.15, 1H), 7.39 (d, J= 6.05, 1H), 7.18 (d, J= 8.5, 1H), 2.77 (t, J= 6.87, 2H), 2.03 (s, 3H), 1.7 (q, 2H), 1.04 (t, J= 7.42, 3H)
233	1H NMR (400 MHz, DMSO-d6) δ 12.75 (d, J = 13.6 Hz, 1H), 8.87 (s, 1H), 8.32-8.28 (m, 2H), 7.76-7.70 (m, 2H), 7.60 (d, J = 7.8 Hz, 1H), 7.49-7.45 (m, 1H), 7.18 (d, J = 8.4 Hz, 1H), 4.11 (t, J = 8.3 Hz, 2H), 3.10 (t, J = 7.7 Hz, 2H), 2.18 (s, 3H)
234	1H NMR (400 MHz, DMSO-d6) δ 12.49 (s, 1H), 11.50 (s, 1H), 8.90 (s, 1H), 8.36-8.34 (m, 2H), 7.97 (s, 1H), 7.85-7.81 (m, 1H), 7.77-7.75 (m, 1H), 7.56-7.50 (m, 2H), 6.59-6.58 (m, 1H)
235	H NMR (400 MHz, DMSO-d6) δ 13.09 (d, J = 6.5 Hz, 1H), 12.75 (s, 1H), 9.04 (s, 1H), 8.92 (d, J = 6.8 Hz, 1H), 8.42 (d, J = 7.1 Hz, 1H), 8.34 (d, J = 6.9 Hz, 1H), 7.85 (t, J = 8.4 Hz, 1H), 7.78 (d, J = 7.7 Hz, 1H), 7.63-7.56 (m, 2H), 3.15 (m, 1H), 1.29 (d, J = 6.9 Hz, 6H)
238	H NMR (400 MHz, DMSO-d6) δ 12.93 (d, J = 6.4 Hz, 1H), 12.29 (s, 1H), 8.85 (d, J = 6.7 Hz, 1H), 8.32 (d, J = 8.1 Hz, 1H), 7.82 (t, J = 8.3 Hz, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.54 (t, J = 8.1 Hz, 1H), 7.17 (m, 2H), 6.94 (m, 1H), 3.79 (m, 2H), 3.21-2.96 (m, 4H), 1.91-1.76 (m, 4H), 1.52 (m, 2H), 1.43 (s, 9H)
242	H NMR (400 MHz, DMSO-d6) δ 12.95 (d, J = 6.6 Hz, 1H), 12.65 (s, 1H), 8.87 (d, J = 6.8 Hz, 1H), 8.34 (dd, J = 8.1, 1.1 Hz, 1H), 8.17 (s, 1H), 7.83 (t, J = 8.3 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 8.1 Hz, 1H), 7.37 (s, 1H), 5.60 (s, 2H)

243	1H-NMR (CD3OD, 300 MHz) δ 8.87 (s, 1H), 8.45 (d, J= 8.25, 1H), 8.27 (m, 1H), 7.83 (t, J= 6.88, 1H), 7.67 (d, J= 8.25, 1H), 7.54 (t, J= 7.15, 1H), 7.39 (d, J= 6.05, 1H), 7.18 (d, J= 8.5, 1H), 2.77 (t, J= 6.87, 2H), 2.03 (s, 3H), 1.7 (q, 2H), 1.04 (t, J= 7.42, 3H) NMR Shows regio isomer
244	H NMR (400 MHz, DMSO-d6) δ 12.89 (s, 1H), 12.42 (s, 1H), 10.63 (s, 1H), 8.88 (d, J = 6.7 Hz, 1H), 8.35 (d, J = 8.2 Hz, 1H), 8.03 (d, J = 1.6 Hz, 1H), 7.82 (t, J = 8.3 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.54 (t, J = 8.1 Hz, 1H), 7.29 (d, J = 8.3 Hz, 1H), 7.02 (dd, J = 8.4, 1.8 Hz, 1H), 2.69 (t, J = 5.3 Hz, 2H), 2.61 (t, J = 5.0 Hz, 2H), 1.82 (m, 4H)
248	H NMR (400 MHz, DMSO-d6) δ 12.95 (d, J = 6.6 Hz, 1H), 12.42 (s, 1H), 9.30 (s, 1H), 8.86 (d, J = 6.8 Hz, 1H), 8.33 (dd, J = 8.1, 1.3 Hz, 1H), 7.85-7.81 (m, 2H), 7.76 (d, J = 7.8 Hz, 1H), 7.55 (t, J = 8.1 Hz, 1H), 7.49 (dd, J = 8.2, 2.2 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 2.18 (s, 3H), 2.08 (s, 3H)
259	H NMR (400 MHz, DMSO-d6) δ 0.86 (t, J = 7.4 Hz, 3H), 1.29 (d, J = 6.9 Hz, 3H), 1.67 (m, 2H), 2.88 (m, 1H), 7.03 (m, 2H), 7.53 (m, 2H), 7.80 (m, 2H), 8.13 (s, 1H), 8.35 (d, J = 8.2 Hz, 1H), 8.89 (s, 1H), 10.75 (s, 1H), 12.45 (s, 1H), 12.84 (s, 1H)
260	H NMR (400 MHz, DMSO-d6) δ 13.23 (d, J = 6.6 Hz, 1H), 12.20 (s, 1H), 10.22 (br s, 2H), 8.88 (d, J = 6.8 Hz, 1H), 8.34 (d, J = 7.8 Hz, 1H), 7.86-7.80 (m, 3H), 7.56-7.52 (m, 2H), 7.15 (dd, J = 8.5, 2.4 Hz, 1H), 1.46 (s, 9H)
261	1H-NMR (d6-DMSO, 300 MHz) δ 11.99 (s, 1H, NH), 8.76 (s, J = 6.6 Hz, 1H), 8.26 (d, J = 6.2 Hz, 1H), 8.09 (d, J = 7.9 Hz, 1H), 7.72 - 7.63 (m, 2H), 7.44 - 7.09 (m, 7H), 2.46 (s, 3H), 2.25 (s, 3H).
262	1H NMR (400 MHz, DMSO-d6) δ 13.00 (s, 1H), 12.53 (s, 1H), 10.62 (s, 1H), 8.88 (s, 1H), 8.33 (dd, J = 8.2, 1.2 Hz, 1H), 7.85-7.75 (m, 2H), 7.57-7.50 (m, 2H), 7.34-7.28 (m, 2H), 3.46 (s, 2H)
266	H NMR (400 MHz, DMSO-d6) δ 12.94 (d, J = 6.6 Hz, 1H), 12.57 (s, 1H), 10.37 (s, 1H), 8.88 (d, J = 6.8 Hz, 1H), 8.34-8.32 (m, 1H), 7.99 (s, 1H), 7.85-7.81 (m, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.56-7.52 (m, 1H), 7.38 (s, 1H), 1.37 (s, 9H)
268	H NMR (400 MHz, DMSO-d6) δ 13.02 (s, 1H), 12.62 (s, 1H), 8.91 (s, 1H), 8.34 (dd, J = 8.1, 1.1 Hz, 1H), 8.22 (d, J = 2.4 Hz, 1H), 8.14 (dd, J = 8.8, 2.4 Hz, 1H), 7.84 (t, J = 8.3 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.65-7.54 (m, 4H), 1.52 (s, 9H)
271	H NMR (400 MHz, DMSO-d6) δ 1.38 (s, 9H), 4.01 (s, 2H), 7.35 (s, 2H), 7.55 (m, 1H), 7.65 (s, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.83 (m, 1H), 8.33 (d, J = 7.6 Hz, 1H), 8.86 (d, J = 6.8 Hz, 1H), 12.49 (s, 1H), 13.13 (s, 1H)
272	1H-NMR (d6-Acetone, 300 MHz) δ 8.92 (d, J= 6.6 Hz, 1H), 8.39 (d, J= 7.8 Hz, 1H), 7.94 (s, 1H), 7.79 (s, 1H), 7.77 (s, 2H), 7.53 (m, 1H), 7.36 (s, 1H), 3.94-3.88 (m, 5H), 3.64-3.59 (m, 3H), 3.30 (m, 4H).
274	H NMR (400 MHz, DMSO-d6) δ 13.21 (d, J = 6.6 Hz, 1H), 11.66 (s, 1H), 10.95 (s, 1H), 9.00 (d, J = 6.5 Hz, 1H), 8.65 (d, J = 2.1 Hz, 1H), 8.18 (dd, J = 8.7, 2.2 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.57 (m, 2H), 7.31 (t, J = 2.7 Hz, 1H), 6.40 (t, J = 2.0 Hz, 1H), 3.19 (m, 4H), 1.67 (m, 4H), 1.46 (s, 9H)
275	H NMR (400 MHz, DMSO-d6) δ 12.23 (s, 1H), 9.47 (s, 1H), 9.20 (s, 1H), 8.43 (d, J = 7.9 Hz, 1H), 7.79 (t, J = 2.0 Hz, 2H), 7.56 (m, 1H), 7.38-7.26 (m, 6H), 7.11 (d, J = 8.4 Hz, 1H), 6.99 (dd, J = 8.4, 2.1 Hz, 1H), 5.85 (s, 2H), 1.35 (s, 9H)

282	1H NMR (CD3OD, 300 MHz) δ 8.90 (s, 1H), 8.51 (s, 1H), 8.44 (d, J = 7.9 Hz, 1H), 7.82 (t, J = 8.3 Hz, 1H), 7.69 (d, J = 8.5 Hz, 1H), 7.56 (t, J = 7.7 Hz, 2H), 7.42 (d, J = 7.9 Hz, 1H), 7.07 (d, J = 5.8 Hz, 1H), 2.93 (q, J = 7.4 Hz, 2H), 1.36 (t, J = 7.5 Hz, 3H).
283	1H-NMR (CDCl3, 300 MHz) δ 8.82 (d, J = 6.6 Hz, 1H), 8.29 (d, J = 6.2 Hz, 1H), 8.06 (d, J = 7.9 Hz, 1H), 7.43 - 7.24 (m, 6H), 7.02 (m, 2H), 6.87 - 6.81 (dd, 2H), 3.76 (s, 3H).
287	H NMR (400 MHz, DMSO-d6) δ 13.51 (s, 1H), 13.28 (d, J = 6.6 Hz, 1H), 11.72 (d, J = 2.2 Hz, 1H), 9.42 (s, 1H), 8.87 (d, J = 6.9 Hz, 1H), 8.04 (d, J = 7.4 Hz, 1H), 7.67 (t, J = 8.2 Hz, 1H), 7.17 (dd, J = 8.3, 0.8 Hz, 1H), 7.01 (d, J = 13.7 Hz, 1H), 6.81 (dd, J = 8.1, 0.8 Hz, 1H), 2.10 (m, 2H), 1.63-1.34 (m, 8H), 1.26 (s, 3H)
288	H NMR (400 MHz, DMSO-d6) δ 13.16 (s, 1H), 12.85 (s, 1H), 8.98 (s, 1H), 8.43 (dd, J = 8.1, 1.1 Hz, 1H), 8.34 (dd, J = 10.3, 3.1 Hz, 1H), 7.93 (t, J = 8.4 Hz, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.66 (t, J = 8.1 Hz, 1H), 7.03 (dd, J = 10.7, 3.2 Hz, 1H), 4.06 (s, 3H), 1.42 (s, 9H)
295	H NMR (400 MHz, DMSO-d6) δ 1.98 (m, 4H), 3.15 (m, 4H), 7.04 (m, 2H), 7.17 (d, J = 7.8 Hz, 1H), 7.52 (m, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.81 (m, 1H), 8.19 (dd, J = 7.9, 1.4 Hz, 1H), 8.33 (d, J = 8.1 Hz, 1H), 8.88 (d, J = 6.7 Hz, 1H), 12.19 (s, 1H), 12.87 (s, 1H)
299	1H NMR (400 MHz, DMSO-d6) δ 12.93-12.88 (m, 1H), 12.18 (s, 1H), 8.83 (d, J = 6.8 Hz, 1H), 8.38-8.31 (m, 1H), 7.85-7.67 (m, 2H), 7.57-7.51 (m, 1H), 6.94 (s, 1H), 6.81-6.74 (m, 2H), 3.19-3.16 (m, 2H), 2.68-2.61 (m, 2H), 1.80-1.79 (m, 2H)
300	H NMR (400 MHz, DMSO-d6) δ 13.23 (d, J = 6.6 Hz, 1H), 12.59 (s, 1H), 8.87 (d, J = 6.8 Hz, 1H), 8.33 (d, J = 7.7 Hz, 1H), 7.86-7.79 (m, 3H), 7.58-7.42 (m, 3H), 3.38 (m, 2H), 1.88 (m, 2H), 1.30 (s, 6H)
303	H NMR (400 MHz, DMSO-d6) δ 12.96 (d, J = 6.5 Hz, 1H), 12.47 (s, 0.4H), 12.43 (s, 0. 6H), 8.87 (dd, J = 6.7, 2.3 Hz, 1H), 8.33 (d, J = 8.1 Hz, 1H), 7.82 (t, J = 8.2 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.62-7.52 (m, 3H), 7.17 (d, J = 8.3 Hz, 1H), 4.66 (s, 0.8H), 4.60 (s, 1.2H), 3.66 (t, J = 5.9 Hz, 2H), 2.83 (t, J = 5.8 Hz, 1.2H), 2.72 (t, J = 5.9 Hz, 0.8H), 2.09 (m, 3H)
304	1H NMR (300 MHz, DMSO-d6) δ 11.70 (s, 1H), 8.74 (s, 1H), 8.15 (s, 1H), 8.07 (m, 1H), 7.72 (m, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.45-7.31 (m, 3H), 7.15-6.95 (m, 5H), 4.17 (d, J = 6.0 Hz, 2H), 4.02 (q, J = 6.9 Hz, 2H), 1.40 (s, 9H), 1.09 (t, J = 6.9 Hz, 3H).
307	1H-NMR (CDCl3, 300 MHz) δ 8.81 (d, J = 6.6 Hz, 1H), 8.30 (d, J = 6.2 Hz, 1H), 8.02 (d, J = 7.9 Hz, 1H), 7.44-7.26 (m, 9H), 6.79 (d, J = 7.5 Hz, 1H).
318	1H-NMR (d6-Acetone, 300 MHz) δ 8.92 (bs, 1H), 8.40 (d, J= 8.1 Hz, 1H), 8.05 (bs, 1H), 7.94 (bs, 1H), 7.78 (bs, 2H), 7.52 (m, 1H), 7.36 (bs, 1H), 3.97 (t, J = 7.2 Hz, 2H), 3.66 (t, J= 8 Hz, 2H), 3.31-3.24 (m, 6H), 1.36-1.31 (m, 4H).
320	^{1}H NMR (400 MHz, DMSO-d6) δ 12.90 (s, 1H), 12.44 (s, 1H), 10.86 (s, 1H), 8.90 (s, 1H), 8.35 (dd, J = 8.2, 1.0 Hz, 1H), 8.12 (t, J = 0.8 Hz, 1H), 7.84-7.75 (m, 2H), 7.56-7.52 (m, 1H), 7.37 (d, J = 8.3 Hz, 1H), 6.99 (dd, J = 8.4, 1.9 Hz, 1H), 6.08-6.07 (m, 1H), 1.35 (s, 9H)
321	H NMR (400 MHz, DMSO-d6) δ 2.93 (m, 4H), 3.72 (m, 4H), 7.10 (m, 2H), 7.27 (d, J = 7.8 Hz, 1H), 7.51 (m, 6H), 7.74 (d, J = 8.2 Hz, 1H), 7.81 (m, 1H), 8.40 (d, J = 8.1 Hz, 1H), 8.58 (d, J = 8.0 Hz, 1H), 8.88 (d, J = 6.7 Hz, 1H), 12.69 (s, 1H), 12.86 (s, 1H)

323	H NMR (400 MHz, DMSO-d6) δ 12.94 (br s, 1H), 12.44 (s, 1H), 8.89 (s, 1H), 8.33 (dd, J = 8.2, 1.1 Hz, 1H), 7.82 (t, J = 8.3 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.54 (t, J = 8.1 Hz, 1H), 7.35 (d, J = 8.7 Hz, 2H), 7.02 (t, J = 6.3 Hz, 1H), 3.50 (s, 3H), 3.17 (d, J = 6.2 Hz, 2H), 1.23 (s, 6H)
334	H NMR (400 MHz, DMSO-d6) δ 13.02 (br s, 1H), 12.46 (s, 1H), 8.89 (s, 1H), 8.33 (dd, J = 8.2, 1.1 Hz, 1H), 7.89 (s, 1H), 7.82 (t, J = 8.3 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.55 (t, J = 8.1 Hz, 1H), 7.44 (m, 1H), 7.37 (d, J = 8.6 Hz, 1H), 3.85 (m, 2H), 3.72 (t, J = 6.0 Hz, 2H), 3.18-3.14 (m, 2H), 2.23 (s, 3H), 1.93 (t, J = 5.7 Hz, 2H), 1.79 (m, 2H), 1.53 (m, 2H), 1.43 (s, 9H)
337	H NMR (400 MHz, DMSO-d6) δ 12.19 (s, 1H), 9.35 (s, 1H), 8.22 (dd, J = 8.1, 1.1 Hz, 1H), 8.08 (s, 1H), 7.74-7.70 (m, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.44-7.40 (m, 1H), 7.23 (s, 1H), 3.31 (s, 3H), 1.37 (s, 9H), 1.36 (s, 9H)
351	1H NMR (400 MHz, DMSO-d6) δ 12.92 (s, 1H), 12.34 (s, 1H), 10.96 (s, 1H), 8.91 (s, 1H), 8.48 (s, 1H), 8.37 (d, J = 8.1 Hz, 1H), 7.84-7.76 (m, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.39 (s, 1H), 7.26 (t, J = 2.6 Hz, 1H), 6.34 (s, 1H), 2.89-2.84 (m, 2H), 1.29 (t, J = 7.4 Hz, 3H)
353	1H NMR (400 MHz, DMSO-d6) δ 11.90 (s, 1H), 9.30 (s, 1H), 8.88 (s, 1H), 8.34 (dd, J = 8.2, 1.1 Hz, 1H), 7.84-7.71 (m, 3H), 7.55-7.50 (m, 1H), 7.28-7.26 (m, 1H), 7.20-7.17 (m, 1H), 1.47 (s, 9H), 1.38 (s, 9H)
356	1H-NMR (CD3OD, 300 MHz) δ 8.89 (s, 1H), 8.59 (s, 1H), 8.45 (d, J = 8.3 Hz, 1H), 7.83 (t, J = 7.2 Hz, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.57 (t, J = 7.9 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.17 (d, J = 6.0 Hz, 1H), 3.09 (s, 3H, NMe), 2.91 (t, J = 7.4 Hz, 2H), 1.76 (m, 2H), 1.09 (t, J = 7.4 Hz, 3H).
357	H NMR (400 MHz, DMSO-d6) δ 12.91 (d, J = 6.6 Hz, 1H), 12.45 (s, 1H), 10.73 (d, J = 1.9 Hz, 1H), 8.89 (d, J = 6.7 Hz, 1H), 8.35 (dd, J = 8.1, 1.3 Hz, 1H), 8.13 (d, J = 1.6 Hz, 1H), 7.83 (t, J = 8.3 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.57-7.51 (m, 2H), 7.06-7.02 (m, 2H), 3.12 (septet, J = 6.6 Hz, 1H), 1.31 (d, J = 6.9 Hz, 6H)
363	1H-NMR (CDCl3, 300 MHz) δ 8.86 (d, J = 6.6 Hz, 1H), 8.24 (d, J = 6.2 Hz, 1H), 8.14 (d, J = 7.9 Hz, 1H), 7.43 - 7.16 (m, 5H), 7.02 - 6.92 (m, 2H), 6.83 (d, J = 7.9 Hz, 2H), 3.87 (s, 3H).
368	H NMR (400 MHz, DMSO-d6) δ 12.97 (d, J = 6.6 Hz, 1H), 12.36 (s, 1H), 8.86 (d, J = 6.7 Hz, 1H), 8.33 (dd, J = 8.1, 1.0 Hz, 1H), 7.83 (t, J = 8.3 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.62 (s, 1H), 7.55 (t, J = 8.1 Hz, 1H), 7.25 (dd, J = 8.7, 2.2 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 3.98 (t, J = 6.5 Hz, 2H), 1.78 (sextet, J = 6.9 Hz, 2H), 1.02 (t, J = 7.4 Hz, 3H)
375	H NMR (400 MHz, DMSO-d6) δ 12.93 (d, J = 6.2 Hz, 1H), 12.35 (s, 1H), 8.86 (d, J = 6.7 Hz, 1H), 8.33 (d, J = 6.9 Hz, 1H), 7.82 (t, J = 8.3 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 8.1 Hz, 1H), 7.47-7.43 (m, 2H), 7.04 (d, J = 8.2 Hz, 1H), 2.71 (m, 4H), 1.75 (m, 4H)
378	H NMR (400 MHz, DMSO-d6) δ 12.98 (d, J = 6.6 Hz, 1H), 12.39 (s, 1H), 8.86 (d, J = 6.7 Hz, 1H), 8.33 (dd, J = 8.1, 1.2 Hz, 1H), 7.83 (t, J = 8.3 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.69 (s, 1H), 7.55 (t, J = 8.1 Hz, 1H), 7.31 (dd, J = 8.8, 2.4 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H), 3.85 (s, 3H)
379	1H NMR (300 MHz, DMSO-d6) δ 12.79 (s, 1H), 10.30 (s, 1H), 8.85 (s, 1H), 8.32 (d, J = 7.8 Hz, 1H), 8.06 (s, 1H), 7.93 (s, 1H), 7.81 (t, J = 7.8 Hz, 1H), 7.74 (d, J = 6.9 Hz, 1H), 7.73 (s, 1H), 7.53 (t, J = 6.9 Hz, 1H), 2.09 (s, 3H).

381	H NMR (400 MHz, DMSO-d6) δ 12.78 (br s, 1H), 11.82 (s, 1H), 10.86 (s, 1H), 8.83 (s, 1H), 8.28 (dd, J = 8.1, 1.0 Hz, 1H), 7.75 (t, J = 8.3 Hz, 1H), 7.69 (d, J = 7.7 Hz, 1H),, 7.49-7.43 (m, 3H), 7.23 (m, 1H), 6.32 (m, 1H), 1.39 (s, 9H)
382	1H NMR (CD3OD, 300 MHz) δ 8.83 (s, 1H), 8.40 (d, J = 7.4 Hz, 1H), 7.81 - 7.25 (m, 2H), 7.65 (d, J = 8.3 Hz, 1H), 7.51 (d, J = 8.2, 1H), 7.24 (d, J = 8.3, 1H), 2.58 (t, J = 7.7 Hz, 2H), 2.17 (s, 3H), 1.60 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H).
383	H NMR (400 MHz, DMSO-d6) δ 1.27 (t, J = 7.5 Hz, 3H), 2.70 (q, J = 7.7 Hz, 2H), 7.05 (m, 2H), 7.47 (d, J = 8.4 Hz, 1H), 7.55 (t, J = 8.1 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.83 (t, J = 8.3 Hz, 1H), 8.13 (s, 1H), 8.35 (d, J = 6.9 Hz, 1H), 8.89 (d, J = 6.7 Hz, 1H), 10.73 (s, 1H), 12.46 (s, 1H), 12.91 (s, 1H)
386	H NMR (400 MHz, DMSO-d6) δ 13.18 (d, J = 6.8 Hz, 1H), 12.72 (s, 1H), 8.88 (d, J = 6.8 Hz, 1H), 8.34 (d, J = 8.1 Hz, 1H), 8.09 (s, 1H), 7.86-7.79 (m, 2H), 7.58-7.50 (m, 2H), 7.43 (d, J = 8.2 Hz, 1H), 3.51 (s, 2H), 1.36 (s, 6H)
393	1H NMR (300 MHz, MeOH) δ 8.78 (s, 1H), 8.45 (d, J = 2.1 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H), 7.71 (t, J = 6.9, Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 7.39 (m, 3H), 7.18 (m, 2H), 7.06 (m, 2H), 4.02 (m, 2H), 1.13 (t, J = 6.9, Hz, 3H);
399	1H-NMR (CD3OD, 300 MHz) δ 8.91 (s, 1H), 8.51 (s, 1H), 8.42 (d, J = 8.3 Hz, 1H), 7.84 (t, J = 7.2 Hz, 1H), 7.67 (d, J = 9.0 Hz, 1H), 7.56 (t, J = 7.9 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.24 (d, J = 6.0 Hz, 1H), 3.48 (m, 1H), 3.09 (s, 3H, NMe), 1.39 (d, J = 6.8 Hz, 6H).
412	H NMR (400 MHz, DMSO-d6) δ 12.81-12.79 (m, 2H), 10.96 (s, 1H), 8.87 (d, J = 6.7 Hz, 1H), 8.35 (d, J = 8.1 Hz, 1H), 7.99 (d, J = 8.6 Hz, 1H), 7.83-7.73 (m, 3H), 7.53 (t, J = 8.1 Hz, 1H), 7.36 (m, 1H), 6.52 (m, 1H), 4.51 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H)
415	H NMR (400 MHz, DMSO-d6) δ 12.26 (s, 1H), 9.46 (s, 1H), 8.99 (s, 1H), 8.43-8.41 (m, 1H), 7.94-7.88 (m, 2H), , 7.65-7.61 (m, 1H), 7.38 (d, J = 2.1 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.96 (dd, 1H), 4.08 (s, 3H), 1.35 (s, 9H)
420	H NMR (400 MHz, DMSO-d6) δ 12.91 (bs, 1H), 12.51 (s, 1H), 8.89 (s, 1H), 8.33 (dd, *J* = 8, 1Hz, 2H), 7.82 (ddd, *J* = 8, 8, 1 Hz, 1H), 7.75 (dd, *J* = 8, 1Hz, 1H), 7.70 (d, *J* = 9 Hz, 2H), 7.54 (ddd, *J* = 8, 8, 1 Hz, 1H), 4.09 (q, *J* = 7 Hz, 2H), 1.51 (s, 6H), 1.13 (t, *J* = 7 Hz, 3H).
423	H NMR (400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 12.48 (s, 1H), 10.81 (d, J = 1.8 Hz, 1H), 8.89 (s, 1H), 8.35 (dd, J = 8.2, 1.1 Hz, 1H), 8.14 (d, J = 1.6 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.56-7.48 (m, 2H), 7.11 (d, J = 2.2 Hz, 1H), 7.05 (dd, J = 8.5, 1.8 Hz, 1H), 3.62 (t, J = 7.3 Hz, 2H), 3.48 (q, J = 7.0 Hz, 2H), 2.91 (t, J = 7.3 Hz, 2H), 1.14 (t, J = 7.0 Hz, 3H)
425	1H-NMR (DMSO d6, 300 MHz) δ 8.84 (s, 1H), 8.29 (d, J = 8.1 Hz, 1H), 7.78-7.70 (m, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.50 (t, J = 7.8 Hz, 1H), 7.20 (d, J = 8.7 Hz, 2H), 2.85 (h, J = 6.9 Hz, 1H), 1.19 (d, J = 6.9 Hz, 6H).
427	H NMR (400 MHz, DMSO-d6) δ 1.45 (s, 9H), 2.84 (t, J = 5.9 Hz, 2H), 3.69 (m, 2H), 4.54 (s, 1H), 6.94 (d, J = 7.5 Hz, 1H), 7.22 (t, J = 7.9 Hz, 1H), 7.55 (m, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.83 (m, 1H), 8.24 (d, J = 8.0 Hz, 1H), 8.37 (d, J = 9.2 Hz, 1H), 8.91 (s, 1H), 12.36 (s, 1H), 12.99 (s, 1H)
428	1H NMR (300 MHz, CD3OD) δ 12.30 (s, 1H), 8.83 (s, 1H), 8.38 (d, J = 7.4 Hz, 1H), 7.78 (app dt, J = 1.1, 7.1 Hz, 1H), 7.64 (d, J = 8..3 Hz, 1H), 7.53 (app t, J = 7.5 Hz, 1H), 7.21 (br d, J = 0.9 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 6.98 (dd, J = 2.1, 8.4 Hz, 1H), 1.38 (s, 9H)

429	H NMR (400 MHz, DMSO-d6) δ 13.13 (d, J = 6.8 Hz, 1H), 12.63 (s, 1H), 8.86 (d, J = 6.8 Hz, 1H), 8.33 (d, J = 7.0 Hz, 1H), 7.84 (t, J = 8.3 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.56 (t, J = 8.1 Hz, 1H), 7.51 (s, 1H), 7.30 (s, 1H), 6.77 (s, 1H)
433	H NMR (400 MHz, DMSO-d6) δ 12.87 (br s, 1H), 11.82 (s, 1H), 9.20 (s, 1H), 8.87 (s, 1H), 8.33 (dd, J = 8.2, 1.1 Hz, 1H), 7.81 (t, J = 8.3 Hz, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.52 (t, J = 8.1 Hz, 1H), 7.17 (s, 1H), 7.10 (s, 1H), 1.38 (s, 9H), 1.36 (s, 9H)
438	H NMR (400 MHz, DMSO-d6) δ 12.97 (d, J = 6.6 Hz, 1H), 12.08 (s, 1H), 8.90 (d, J = 6.8 Hz, 1H), 8.35-8.34 (m, 1H), 8.03 (s, 1H), 7.85-7.81 (m, 1H), 7.77-7.71 (m, 1H), 7.58-7.44 (m, 2H), 1.46 (s, 9H), 1.42 (s, 9H)
441	1H-NMR (d6-Acetone, 300 MHz) δ 11.90 (br s, 1H), 8.93 (br s, 1H), 8.42 (d, J = 8.1 Hz, 1H), 8.08 (s, 1H), 7.92 (s, 1H), 7.79 (m, 2H), 7.57 (m, 1H), 7.36 (s, 1H), 3.13 (s, 3H).
444	H NMR (400 MHz, DMSO-d6) δ 12.56 (s, 1H), 12.17 (br d, *J* = 6 Hz, 1H), 8.89 (d, *J* = 6 Hz, 1H), 8.42 (dd, *J* = 9, 2 Hz, 1H), 7.77 (d, *J* = 2 Hz, 1H), 7.68 (dd, *J* = 9, 2 Hz, 1H), 7.60 (ddd, J = 9, 9, 2 Hz, 1H), 7.46-7.40 (m, 3H), 3.47 (s, 3H), 1.35 (s, 9H).
448	H NMR (400 MHz, DMSO-d6) δ 12.96 (br s, 1H), 12.42 (s, 1H), 8.88 (s, 1H), 8.33 (dd, J = 8.2, 1.1 Hz, 1H), 7.82 (t, J = 8.3 Hz, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.66 (d, J = 8.7 Hz, 2H), 7.54 (t, J = 8.1 Hz, 1H), 7.39 (d, J = 8.7 Hz, 2H), 1.29 (s, 9H)
453	H NMR (400 MHz, DMSO-d6) δ 12.95 (d, J = 6.5 Hz, 1H), 12.38 (s, 1H), 8.86 (d, J = 6.8 Hz, 1H), 8.33 (d, J = 8.1 Hz, 1H), 7.83 (t, J = 8.3 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 8.1 Hz, 1H), 7.28 (d, J = 2.4 Hz, 1H), 7.15 (d, J = 8.6 Hz, 1H), 6.94 (dd, J = 8.6, 2.4 Hz, 1H)
458	H NMR (400 MHz, DMSO-d6) δ 12.97 (d, J = 7.1 Hz, 1H), 12.39 (s, 1H), 8.88 (d, J = 6.8 Hz, 1H), 8.33 (d, J = 7.9 Hz, 1H), 7.83 (t, J = 7.6 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.47 (s, 1H), 7.17 (s, 2H), 4.04 (t, J = 5.0 Hz, 2H), 3.82 (t, J = 5.0 Hz, 2H), 1.36 (s, 9H)
461	1H-NMR (d6-DMSO, 300 MHz) δ 11.97 (s, 1H), 8.7 (s, 1H), 8.30 (d, J = 7.7 Hz, 1H), 8.07 (d, J = 7.7 Hz, 1H), 7.726 - 7.699 (m, 2H), 7.446 - 7.357 (m, 6H), 7.236 - 7.178 (m, 2H). 13C-NMR (d6-DMSO, 75 MHz) d 176.3, 163.7, 144.6, 139.6, 138.9, 136.3, 134.0, 133.4, 131.0, 129.8, 129.2, 128.4, 128.1, 126.4, 126.0, 125.6, 124.7, 123.6, 119.6, 111.2.
463	1H-NMR (DMSO d6, 300 MHz) δ 8.83 (s, 1H), 8.29 (d, J = 7.8 Hz, 1H), 7.78-7.70 (m, 2H), 7.61 (d, J = 7.8 Hz, 2H), 7.51 (t, 1H), 7.17 (d, J = 8.1 Hz, 2H), 2.57 (q, J = 7.5 Hz, 2H), 1.17 (t, J = 7.5 Hz,1H), 0.92 (t, J = 7.8 Hz, 3H).
464	H NMR (400 MHz, DMSO-d6) δ 1.37 (s, 9H), 1.38 (s, 9H), 6.80 (dd, J = 8.1, 0.9 Hz, 1H), 7.15 (m, 3H), 7.66 (t, J = 8.2 Hz, 1H), 8.87 (d, J = 6.9 Hz, 1H), 9.24 (s, 1H), 11.07 (s, 1H), 13.23 (d, J = 6.5 Hz, 1H), 13.65 (s, 1H)
465	H NMR (400 MHz, DMSO-d6) δ 12.94 (d, J = 6.0 Hz, 1H), 12.40 (s, 1H), 8.87 (d, J = 6.8 Hz, 1H), 8.33 (d, J = 8.2 Hz, 1H), 7.84-7.75 (m, 3H), 7.57-7.43 (m, 2H), 7.31 (d, J = 8.6 Hz, 1H), 4.40 (d, J = 5.8 Hz, 2H), 1.44 (s, 9H), 1.38 (s, 9H)
471	1H-NMR (CD3OD, 300 MHz) δ 8.87 (s, 1H), 8.44 (d, J= 8.25, 1H), 8.18 (m, 1H), 7.79 (t, J= 6.88, 1H), 7.67 (d, J= 8.25, 1H), 7.54 (t, J= 7.15, 1H), 7.23 (d, J= 6.05, 1H), 7.16 (d, J= 8.5, 1H), 3.73 (s, 3H), 2.75 (t, J= 6.87, 2H), 1.7 (q, 2H), 1.03 (t, J= 7.42, 3H)

476	H NMR (400 MHz, DMSO-d6) δ 13.00 (d, J = 6.4 Hz, 1H), 12.91 (s, 1H), 10.72 (s, 1H), 8.89 (d, J = 6.8 Hz, 1H), 8.34 (d, J = 8.2 Hz, 1H), 8.16 (s, 1H), 7.85-7.75 (m, 2H), 7.56-7.54 (m, 1H), 7.44 (s, 1H), 1.35 (s, 9H)
478	H NMR (400 MHz, DMSO-d6) δ 1.40 (s, 9H), 6.98 (d, J = 2.4 Hz, 1H), 7.04 (dd, J = 8.6, 1.9 Hz, 1H), 7.55 (t, J = 8.1 Hz, 1H), 7.66 (d, J = 8.6 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.83 (t, J = 8.3 Hz, 1H), 8.13 (d, J = 1.7 Hz, 1H), 8.35 (d, J = 8.1 Hz, 1H), 8.89 (d, J = 6.7 Hz, 1H), 10.74 (s, 1H), 12.44 (s, 1H), 12.91 (s, 1H)
484	1H NMR (300 MHz, DMSO-d6) δ 12.90 (d, J = 6.3 Hz, 1H), 12.21 (s, 1H), 8.85 (d, J = 6.8 Hz, 1H), 8.31 (d, J = 8.0 Hz, 1H), 7.79 (app dt, J = 12, 8.0 Hz, 1H), 7.72 (d, J = 8.3 Hz, 1H), 7.52 (dd, J = 6.9, 8.1 Hz, 1H), 7.05 (d, J = 8.3 Hz, 1H), 6.94 (s with fine str, 1H), 1H), 6.90 (d with fine str, J = 8.4 Hz, 1H), 2.81 (s, 3H), 1.34 (s, 9H)
485	1H NMR (300 MHz, $CDCl_3$) δ 13.13 (br s, 1H), 12.78 (s, 1H), 8.91 (br s, 1H), 8.42 (br s, 1H), 8.37 (d, *J* = 8.1 Hz, 1H), 7.72-7.58 (m, 2H), 7.47-7.31 (m, 3H), 3.34 (s, 6H), 1.46 (s, 9H)
497	^{1}H NMR (400.0 MHz, DMSO-d_6) δ 12.93 (s, 1H), 12.59 (s, 1H), 10.29 (s, 1H), 8.87 (s, 1H), 8.32 (dd, *J* = 1.0, 8.1 Hz, 1H), 7.95 (s, 1H), 7.83 - 7.74 (m, 2H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.36 (s, 1H), 3.20 (qn, *J* = 6.9 Hz, 1H) and 1.24 - 1.19 (m, 6H) ppm.
518	^{1}H NMR (400 MHz, DMSO-d6) 12.91 (d, J = 6.5 Hz, 1H), 12.18 (s, 1H), 9.19 (s, 1H), 8.88 (d, J = 6.7 Hz, 1H), 8.35 (d, J = 8.0 Hz, 1H), 7.96 (s, 1H), 7.84-7.75 (m, 2H), 7.53 (m, 1H), 6.97 (s, 1H), 2.30 (s, 3H), 1.34 (s, 9H)
589	^{1}H NMR (400 MHz, DMSO-d6) 13.63 (s, 1H), 13.25 (d, J = 6.1 Hz, 1H), 11.36 (s, 1H), 9.22 (s, 1H), 8.87 (d, J = 6.5 Hz, 1H), 7.92 (s, 1H), 7.65 (t, J = 8.2 Hz, 1H), 7.16 (d, J = 8.2 Hz, 1H), 6.98 (s, 1H), 6.80 (d, J = 8.0 Hz, 1H), 2.27 (s, 3H), 1.34 (s, 9H)
603	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.94 (s, 1H), 12.45 (s, 1H), 8.89 (s, 1H), 8.34 (dd, *J* = 1.1, 8.2 Hz, 1H), 7.84 - 7.80 (m, 1H), 7.76 - 7.71 (m, 2H), 7.62 - 7.53 (m, 2H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.15 - 7.12 (m, 1H), 1.31 (s, 9H).
607	^{1}H NMR (400 MHz, DMSO-d6) 13.57 (s, 1H), 13.28 (d, J = 4.1 Hz, 1H), 11.44 (s, 1H), 9.40 (s, 1H), 8.85 (d, J = 5.3 Hz, 1H), 7.65 (t, J = 8.2 Hz, 1H), 7.36 (d, J = 2.1 Hz, 1H), 7.17-7.10 (m, 2H), 6.98 (dd, J = 8.5, 2.1 Hz, 1H), 6.79 (dd, J = 8.0, 0.6 Hz, 1H), 2.15 (m, 2H), 1.60-1.39 (m, 8H), 1.25 (s, 3H)
610	^{1}H NMR (400 MHz, DMSO-d6) 13.63 (s, 1H), 13.25 (d, J = 6.8 Hz, 1H), 11.13 (s, 1H), 9.29 (s, 1H), 8.87 (d, J = 6.9 Hz, 1H), 7.66 (t, J = 8.2 Hz, 1H), 7.20-7.11 (m, 3H), 6.79 (dd, J = 8.1, 0.8 Hz, 1H), 6.57 (dd, J = 8.7, 2.7 Hz, 1H), 1.37 (s, 9H)
620	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 (d, *J* = 6.6 Hz, 1H), 12.54 (s, 1H), 10.28 (s, 1H), 8.87 (d, *J* = 6.8 Hz, 1H), 8.32 (d, *J* = 7.3 Hz, 1H), 7.95 (s, 1H), 7.81 (ddd, *J* = 23.1, 15.0, 4.7 Hz, 2H), 7.53 (dd, *J* = 11.5, 4.6 Hz, 1H), 7.34 (s, 1H), 2.84 (s, 1H), 1.85 – 1.69 (m, 5H), 1.38 (t, *J* = 10.3 Hz, 5H).
621	^{1}H NMR (400 MHz, DMSO) 13.59 (s, 1H), 13.27 (br s, 1H), 11.55 (s, 1H), 8.88 (s, 1H), 7.73 (t, J = 1.9 Hz, 1H), 7.66 (t, J = 8.2 Hz, 1H), 7.59 - 7.56 (m, 1H), 7.29 (t, J = 7.9 Hz, 1H), 7.15 (dd, J = 0.8, 8.3 Hz, 2H), 6.80 (dd, J = 0.8, 8.1 Hz, 1H), 1.31 (s, 9H)
634	^{1}H NMR (400 MHz, DMSO-d6) 13.61 (s, 1H), 11.47 (s, 1H), 9.45 (s, 1H), 8.85 (s, 1H), 7.64 (t, J = 8.2 Hz, 1H), 7.36 (d, J = 2.2 Hz, 1H), 7.16-7.08 (m, 2H), 6.95 (dd, J = 8.4, 2.2 Hz, 1H), 6.78 (dd, J = 8.0, 0.7 Hz, 1H), 1.34 (s, 9H)

648	^{1}H NMR (400.0 MHz, DMSO-d_6) δ 12.94 (d, *J* = 6.0 Hz, 1H), 12.24 (s, 1H), 8.89 (d, *J* = 6.5 Hz, 1H), 8.35 (d, *J* = 7.7 Hz, 1H), 8.22 (d, *J* = 8.3 Hz, 1H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.55 - 7.51 (m, *J* = 7.6 Hz, 1H), 7.11 (s, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 2.45 (m, 1H), 2.38 (s, 3H), 1.80 - 1.69 (m, 5H), 1.42 - 1.21 (m, 5H).
665	^{1}H NMR (400 MHz, DMSO) 13.03 (br s, 1H), 12.34 (s, 1H), 8.92 (s, 1H), 7.98 (dd, J = 2.9, 9.2 Hz, 1H), 7.84 (m, 1H), 7.77 - 7.70 (m, 2H), 7.60 (d, J = 7.4 Hz, 1H), 7.30 (t, J = 7.9 Hz, 1H), 7.14 (d, J = 7.9 Hz, 1H), 1.34 (s, 9H)
666	^{1}H NMR (400 MHz, DMSO-d6) 13.04 (d, J = 6.6 Hz, 1H), 11.76 (s, 1H), 9.25 (s, 1H), 8.90 (d, J = 6.8 Hz, 1H), 7.98 (dd, J = 9.2, 2.9 Hz, 1H), 7.86 (d, J = 4.6 Hz, 1H), 7.74 (td, J = 8.6, 3.0 Hz, 1H), 7.18 (d, J = 8.7 Hz, 1H), 7.08 (d, J = 2.7 Hz, 1H), 6.56 (dd, J = 8.7, 2.7 Hz, 1H), 1.37 (s, 9H)
684	^{1}H NMR (400 MHz, DMSO-d6) 13.06 (d, J = 6.6 Hz, 1H), 12.07 (s, 1H), 9.19 (s, 1H), 8.91 (d, J = 6.7 Hz, 1H), 8.00 (dd, J = 9.2, 2.9 Hz, 1H), 7.95 (s, 1H), 7.85 (dd, J = 9.1, 4.7 Hz, 1H), 7.73 (td, J = 8.6, 2.9 Hz, 1H), 6.97 (s, 1H), 2.29 (s, 3H), 1.34 (s, 9H)

[01066] B) Assays for Detecting and Measuring ΔF508-CFTR Correction Properties of Compounds

[01067] I) Membrane potential optical methods for assaying ΔF508-CFTR modulation properties of compounds

[01068] The optical membrane potential assay utilized voltage-sensitive FRET sensors described by Gonzalez and Tsien (See, Gonzalez, J. E. and R. Y. Tsien (1995) "Voltage sensing by fluorescence resonance energy transfer in single cells" Biophys J **69**(4): 1272-80, and Gonzalez, J. E. and R. Y. Tsien (1997) "Improved indicators of cell membrane potential that use fluorescence resonance energy transfer" Chem Biol **4**(4): 269-77) in combination with instrumentation for measuring fluorescence changes such as the Voltage/Ion Probe Reader (VIPR) (See, Gonzalez, J. E., K. Oades, et al. (1999) "Cell-based assays and instrumentation for screening ion-channel targets" Drug Discov Today **4**(9): 431-439).

[01069] These voltage sensitive assays are based on the change in fluorescence resonant energy transfer (FRET) between the membrane-soluble, voltage-sensitive dye, $DiSBAC_2(3)$, and a fluorescent phospholipid, CC2-DMPE, which is attached to the outer leaflet of the plasma membrane and acts as a FRET donor. Changes in membrane potential (V_m) cause the negatively charged $DiSBAC_2(3)$ to redistribute across the plasma membrane and the amount of energy transfer from CC2-DMPE changes accordingly. The changes in fluorescence emission were monitored using VIPR™ II, which is an integrated liquid handler and fluorescent detector designed to conduct cell-based screens in 96- or 384-well microtiter plates.

[01070] ***Identification of Correction Compounds***

[01071] To identify small molecules that correct the trafficking defect associated with ΔF508-CFTR; a single-addition HTS assay format was developed. The cells were incubated in serum-free medium for 16 hrs at 37 °C in the presence or absence (negative control) of test compound. As a positive control, cells plated in 384-well plates were incubated for 16 hrs at 27 °C to "temperature-correct" ΔF508-CFTR. The cells were subsequently rinsed 3X with Krebs Ringers solution and loaded with the voltage-sensitive dyes. To activate ΔF508-CFTR, 10 μM forskolin and the CFTR potentiator, genistein (20 μM), were added along with Cl^--free medium to each well. The addition of Cl^--free medium promoted Cl^- efflux in response to ΔF508-CFTR activation and the resulting membrane depolarization was optically monitored using the FRET-based voltage-sensor dyes.

[01072] ***Identification of Potentiator Compounds***

[01073] To identify potentiators of ΔF508-CFTR, a double-addition HTS assay format was developed. During the first addition, a Cl^--free medium with or without test compound was added to each well. After 22 sec, a second addition of Cl^--free medium containing 2 - 10 μM forskolin was added to activate ΔF508-CFTR. The extracellular Cl^- concentration following both additions was 28 mM, which promoted Cl^- efflux in response to ΔF508-CFTR activation and the resulting membrane depolarization was optically monitored using the FRET-based voltage-sensor dyes.

Solutions

Bath Solution #1: (in mM)	NaCl 160, KCl 4.5, $CaCl_2$ 2, $MgCl_2$ 1, HEPES 10, pH 7.4 with NaOH.
Chloride-free bath solution:	Chloride salts in Bath Solution #1 are substituted with gluconate salts.
CC2-DMPE:	Prepared as a 10 mM stock solution in DMSO and stored at -20°C.
$DiSBAC_2(3)$:	Prepared as a 10 mM stock in DMSO and stored at -20°C.

[01074] Cell Culture

[01075] NIH3T3 mouse fibroblasts stably expressing ΔF508-CFTR are used for optical measurements of membrane potential. The cells are maintained at 37 °C in 5% CO_2 and 90 % humidity in Dulbecco's modified Eagle's medium supplemented with 2 mM glutamine, 10 % fetal bovine serum, 1 X NEAA, β-ME, 1 X pen/strep, and 25 mM HEPES in 175 cm^2 culture flasks. For all optical assays, the cells were seeded at 30,000/well in 384-well

matrigel-coated plates and cultured for 2 hrs at 37 °C before culturing at 27 °C for 24 hrs. for the potentiator assay. For the correction assays, the cells are cultured at 27 °C or 37 °C with and without compounds for 16 – 24 hoursB) Electrophysiological Assays for assaying ΔF508-CFTR modulation properties of compounds

[01077] 1.Ussing Chamber Assay

[01078] Ussing chamber experiments were performed on polarized epithelial cells expressing ΔF508-CFTR to further characterize the ΔF508-CFTR modulators identified in the optical assays. $FRT^{\Delta F508\text{-}CFTR}$ epithelial cells grown on Costar Snapwell cell culture inserts were mounted in an Ussing chamber (Physiologic Instruments, Inc., San Diego, CA), and the monolayers were continuously short-circuited using a Voltage-clamp System (Department of Bioengineering, University of Iowa, IA, and, Physiologic Instruments, Inc., San Diego, CA). Transepithelial resistance was measured by applying a 2-mV pulse. Under these conditions, the FRT epithelia demonstrated resistances of 4 KΩ/ cm^2 or more. The solutions were maintained at 27 °C and bubbled with air. The electrode offset potential and fluid resistance were corrected using a cell-free insert. Under these conditions, the current reflects the flow of Cl^- through ΔF508-CFTR expressed in the apical membrane. The I_{SC} was digitally acquired using an MP100A-CE interface and AcqKnowledge software (*v*3.2.6; BIOPAC Systems, Santa Barbara, CA).

[01079] Identification of Correction Compounds

[01080] Typical protocol utilized a basolateral to apical membrane Cl^- concentration gradient. To set up this gradient, normal ringer was used on the basolateral membrane, whereas apical NaCl was replaced by equimolar sodium gluconate (titrated to pH 7.4 with NaOH) to give a large Cl^- concentration gradient across the epithelium. All experiments were performed with intact monolayers. To fully activate ΔF508-CFTR, forskolin (10 μM) and the PDE inhibitor, IBMX (100 μM), were applied followed by the addition of the CFTR potentiator, genistein (50 μM).

[01081] As observed in other cell types, incubation at low temperatures of FRT cells stably expressing ΔF508-CFTR increases the functional density of CFTR in the plasma membrane. To determine the activity of correction compounds, the cells were incubated with 10 μM of the test compound for 24 hours at 37°C and were subsequently washed 3X prior to recording. The cAMP- and genistein-mediated I_{SC} in compound-treated cells was normalized to the 27°C and 37°C controls and expressed as percentage activity. Preincubation of the cells

with the correction compound significantly increased the cAMP- and genistein-mediated I_{SC} compared to the 37°C controls.

[01082] Identification of Potentiator Compounds

[01083] Typical protocol utilized a basolateral to apical membrane Cl^- concentration gradient. To set up this gradient, normal ringers was used on the basolateral membrane and was permeabilized with nystatin (360 μg/mL), whereas apical NaCl was replaced by equimolar sodium gluconate (titrated to pH 7.4 with NaOH) to give a large Cl^- concentration gradient across the epithelium. All experiments were performed 30 min after nystatin permeabilization. Forskolin (10 μM) and all test compounds were added to both sides of the cell culture inserts. The efficacy of the putative ΔF508-CFTR potentiators was compared to that of the known potentiator, genistein.

[01084] Solutions

Basolateral solution (in mM):	NaCl (135), $CaCl_2$ (1.2), $MgCl_2$ (1.2), K_2HPO_4 (2.4), $KHPO_4$ (0.6), N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) (10), and dextrose (10). The solution was titrated to pH 7.4 with NaOH.
Apical solution (in mM):	Same as basolateral solution with NaCl replaced with Na Gluconate (135).

[01085] Cell Culture

[01086] Fisher rat epithelial (FRT) cells expressing ΔF508-CFTR ($FRT^{\Delta F508\text{-}CFTR}$) were used for Ussing chamber experiments for the putative ΔF508-CFTR modulators identified from our optical assays. The cells were cultured on Costar Snapwell cell culture inserts and cultured for five days at 37 °C and 5% CO_2 in Coon's modified Ham's F-12 medium supplemented with 5% fetal calf serum, 100 U/mL penicillin, and 100 μg/mL streptomycin. Prior to use for characterizing the potentiator activity of compounds, the cells were incubated at 27 °C for 16 - 48 hrs to correct for the ΔF508-CFTR. To determine the activity of corrections compounds, the cells were incubated at 27 °C or 37 °C with and without the compounds for 24 hours.

[01087] ***2. Whole-cell recordings***

[01088] The macroscopic ΔF508-CFTR current ($I_{\Delta F508}$) in temperature- and test compound-corrected NIH3T3 cells stably expressing ΔF508-CFTR were monitored using the perforated-patch, whole-cell recording. Briefly, voltage-clamp recordings of $I_{\Delta F508}$ were

performed at room temperature using an Axopatch 200B patch-clamp amplifier (Axon Instruments Inc., Foster City, CA). All recordings were acquired at a sampling frequency of 10 kHz and low-pass filtered at 1 kHz. Pipettes had a resistance of 5 – 6 MΩ when filled with the intracellular solution. Under these recording conditions, the calculated reversal potential for Cl^- (E_{Cl}) at room temperature was -28 mV. All recordings had a seal resistance > 20 GΩ and a series resistance < 15 MΩ. Pulse generation, data acquisition, and analysis were performed using a PC equipped with a Digidata 1320 A/D interface in conjunction with Clampex 8 (Axon Instruments Inc.). The bath contained < 250 µl of saline and was continuously perifused at a rate of 2 mL/min using a gravity-driven perfusion system.

[01089] Identification of Correction Compounds

[01090] To determine the activity of correction compounds for increasing the density of functional ΔF508-CFTR in the plasma membrane, we used the above-described perforated-patch-recording techniques to measure the current density following 24-hr treatment with the correction compounds. To fully activate ΔF508-CFTR, 10 µM forskolin and 20 µM genistein were added to the cells. Under our recording conditions, the current density following 24-hr incubation at 27°C was higher than that observed following 24-hr incubation at 37 °C. These results are consistent with the known effects of low-temperature incubation on the density of ΔF508-CFTR in the plasma membrane. To determine the effects of correction compounds on CFTR current density, the cells were incubated with 10 µM of the test compound for 24 hours at 37°C and the current density was compared to the 27°C and 37°C controls (% activity). Prior to recording, the cells were washed 3X with extracellular recording medium to remove any remaining test compound. Preincubation with 10 µM of correction compounds significantly increased the cAMP- and genistein-dependent current compared to the 37°C controls.

[01091] Identification of Potentiator Compounds

[01092] The ability of ΔF508-CFTR potentiators to increase the macroscopic ΔF508-CFTR Cl^- current ($I_{\Delta F508}$) in NIH3T3 cells stably expressing ΔF508-CFTR was also investigated using perforated-patch-recording techniques. The potentiators identified from the optical assays evoked a dose-dependent increase in $I_{\Delta F508}$ with similar potency and efficacy observed in the optical assays. In all cells examined, the reversal potential before and during potentiator application was around -30 mV, which is the calculated E_{Cl} (-28 mV).

[01093] Solutions

Intracellular solution (in mM):	Cs-aspartate (90), CsCl (50), $MgCl_2$ (1), HEPES (10), and 240 µg/mL amphotericin-B (pH adjusted to 7.35 with CsOH).
Extracellular solution (in mM):	*N*-methyl-D-glucamine (NMDG)-Cl (150), $MgCl_2$ (2), $CaCl_2$ (2), HEPES (10) (pH adjusted to 7.35 with HCl).

[01094] **Cell Culture**

[01095] NIH3T3 mouse fibroblasts stably expressing ΔF508-CFTR are used for whole-cell recordings. The cells are maintained at 37 °C in 5% CO_2 and 90 % humidity in Dulbecco's modified Eagle's medium supplemented with 2 mM glutamine, 10 % fetal bovine serum, 1 X NEAA, β-ME, 1 X pen/strep, and 25 mM HEPES in 175 cm^2 culture flasks. For whole-cell recordings, 2,500 - 5,000 cells were seeded on poly-L-lysine-coated glass coverslips and cultured for 24 - 48 hrs at 27 °C before use to test the activity of potentiators; and incubated with or without the correction compound at 37 °C for measuring the activity of correctors.

[01096] 3.Single-channel recordings

[01097] The single-channel activities of temperature-corrected ΔF508-CFTR stably expressed in NIH3T3 cells and activities of potentiator compounds were observed using excised inside-out membrane patch. Briefly, voltage-clamp recordings of single-channel activity were performed at room temperature with an Axopatch 200B patch-clamp amplifier (Axon Instruments Inc.). All recordings were acquired at a sampling frequency of 10 kHz and low-pass filtered at 400 Hz. Patch pipettes were fabricated from Corning Kovar Sealing #7052 glass (World Precision Instruments, Inc., Sarasota, FL) and had a resistance of 5 - 8 MΩ when filled with the extracellular solution. The ΔF508-CFTR was activated after excision, by adding 1 mM Mg-ATP, and 75 nM of the cAMP-dependent protein kinase, catalytic subunit (PKA; Promega Corp. Madison, WI). After channel activity stabilized, the patch was perifused using a gravity-driven microperfusion system. The inflow was placed adjacent to the patch, resulting in complete solution exchange within 1 - 2 sec. To maintain ΔF508-CFTR activity during the rapid perifusion, the nonspecific phosphatase inhibitor F^- (10 mM NaF) was added to the bath solution. Under these recording conditions, channel activity remained constant throughout the duration of the patch recording (up to 60 min). Currents produced by positive charge moving from the intra- to extracellular solutions (anions moving

in the opposite direction) are shown as positive currents. The pipette potential (V_p) was maintained at 80 mV.

[01098] Channel activity was analyzed from membrane patches containing ≤ 2 active channels. The maximum number of simultaneous openings determined the number of active channels during the course of an experiment. To determine the single-channel current amplitude, the data recorded from 120 sec of ΔF508-CFTR activity was filtered "off-line" at 100 Hz and then used to construct all-point amplitude histograms that were fitted with multigaussian functions using Bio-Patch Analysis software (Bio-Logic Comp. France). The total microscopic current and open probability (P_o) were determined from 120 sec of channel activity. The P_o was determined using the Bio-Patch software or from the relationship $P_o = I/i(N)$, where I = mean current, i = single-channel current amplitude, and N = number of active channels in patch.

[01099] ***Solutions***

Extracellular solution (in mM):	NMDG (150), aspartic acid (150), $CaCl_2$ (5), $MgCl_2$ (2), and HEPES (10) (pH adjusted to 7.35 with Tris base).
Intracellular solution (in mM):	NMDG-Cl (150), $MgCl_2$ (2), EGTA (5), TES (10), and Tris base (14) (pH adjusted to 7.35 with HCl).

[01100] **Cell Culture**

[01101] NIH3T3 mouse fibroblasts stably expressing ΔF508-CFTR are used for excised-membrane patch-clamp recordings. The cells are maintained at 37 °C in 5% CO_2 and 90 % humidity in Dulbecco's modified Eagle's medium supplemented with 2 mM glutamine, 10 % fetal bovine serum, 1 X NEAA, β-ME, 1 X pen/strep, and 25 mM HEPES in 175 cm^2 culture flasks. For single channel recordings, 2,500 - 5,000 cells were seeded on poly-L-lysine-coated glass coverslips and cultured for 24 - 48 hrs at 27 °C before use.

[01102] Compounds of the invention are useful as modulators of ATP binding cassette transporters. Table 3 below illustrates the EC50 and relative efficacy of certain embodiments in Table 1.

[01103] In Table 3 below, the following meanings apply:

EC50: "+++" means <10 uM; "++" means between 10uM to 25 uM; "+" means between 25 uM to 60uM.

% Efficacy: "+" means < 25%; "++" means between 25% to 100%; "+++" means > 100%.

Table3

Cmpd #	EC50 (uM)	% Activity
1	+++	++
2	+++	++
3	+++	++
4	+++	++
5	++	++
6	+++	+++
7	+	+
8	+++	++
9	+	+
10	+++	++
11	+++	++
12	+++	++
13	+++	++
14	+++	++
15	++	++
16	+++	++
17	+++	++
18	+++	++
19	++	+
20	+++	++
21	+	+
22	++	++
23	+++	++
24	+	+
25	++	++
26	+++	++
28	++	++
29	++	++
30	+++	++
31	+++	++
32	+++	++
33	+++	++
34	+++	++
35	+++	++
36	+++	++
37	+++	++
38	+++	++
39	++	++
40	+	+
41	+++	++
42	+++	++
43	+++	++
44	++	++
46	++	++
47	+++	++
48	+++	++
49	+++	++
50	+++	++
51	+++	++
52	+++	++
53	+	+
54	+	+
55	+	+
56	+++	++
57	++	+++
58	+++	++
59	+++	+++
60	+++	++
61	+++	++
62	+++	++
63	+++	++
64	+	+
65	+++	++
66	++	++
67	+++	++
68	+++	++
69	+++	++
70	++	++
71	+++	++
72	+++	++
73	+	+
74	+	+
75	+	+
76	+++	++
77	+++	++
78	+	+
79	+++	++
80	+++	++
81	+	+
82	+++	++
83	+++	++
84	+	+
85	+++	++
86	++	++
87	+++	++
88	+++	++
89	+	+
90	+++	++
91	+++	++
92	+++	++
93	+++	++
94	+++	++
95	++	++
96	+++	++
97	+++	++
98	+++	++
99	+++	++
100	+	+
101	+++	++
102	++	++
103	+++	+++
104	+++	++
105	++	++
106	+	+
107	++	++
108	+++	++
109	++	++
110	+	+
111	+++	++
112	+++	++
113	+++	++
114	+++	++
115	+++	++
116	+++	++
117	+++	++
118	+++	++
119	+++	++
120	++	++
122	+	+
123	+++	++
124	+++	+++
125	++	++
126	+++	++
127	+++	++
128	+	+
129	++	++
130	+++	++
131	+++	++
132	+	+
133	++	++
134	+++	++
135	+++	+++
136	+++	++
137	+++	++
138	+++	++
139	+++	++
140	+++	++
141	++	++
142	+++	++
143	+++	++
144	+++	++

Cmpd #	EC50 (uM)	% Activity
145	+++	++
146	+	+
147	+++	++
148	+++	++
149	++	++
150	+++	++
151	+++	++
152	+	+
153	+++	++
154	+	+
155	+	+
156	+++	++
157	+++	++
158	+++	++
159	++	++
160	+++	++
161	+++	++
162	+	+
163	++	++
164	+++	++
165	+	+
166	+++	++
167	++	++
168	+	+
169	++	++
170	+	+
171	+++	++
172	+++	++
173	+	+
174	+++	++
175	++	++
176	+++	++
177	+++	+++
178	+++	++
179	+	+
180	+++	++
181	+++	++
182	+++	++
183	+++	++
184	+	+
185	+	+
186	+++	++
187	+++	++
188	+++	++
189	+++	++
190	+++	++
191	+	+
192	+	+

Cmpd #	EC50 (uM)	% Activity
193	++	++
194	+	+
195	+	+
196	+++	++
197	+	+
198	+++	++
199	+++	++
200	++	++
201	++	+
202	+++	++
203	+++	++
204	+++	++
205	+++	++
206	+++	++
207	+++	++
208	+++	++
209	++	++
210	++	++
211	+++	++
212	+	+
213	+++	++
214	++	++
215	+++	++
216	+	+
217	++	++
218	+++	++
219	+	+
220	+++	++
221	+++	++
222	++	++
223	+++	++
224	+++	++
225	+++	++
226	+++	++
227	+	+
228	+++	++
229	+++	++
230	++	++
231	+++	++
232	++	++
233	++	+
234	+++	++
235	+++	++
236	+++	++
237	+++	++
238	+++	++
239	+++	++
240	+++	++

Cmpd #	EC50 (uM)	% Activity
241	++	++
242	+++	++
243	++	++
244	+++	++
245	+++	++
246	+++	++
247	+++	++
248	++	++
249	++	++
250	+	+
251	+++	++
252	++	++
253	+++	++
254	+++	++
255	+++	++
256	+	+
257	+++	++
258	+++	++
259	+++	++
260	+++	++
261	+++	++
262	+++	++
263	+++	++
264	++	++
265	+++	++
266	+++	++
267	+++	++
268	++	++
269	+++	++
270	+++	++
271	+++	++
272	++	++
273	+++	+++
274	+++	++
275	++	++
276	++	++
277	+++	+++
278	+++	++
279	+++	++
280	+	+
281	+++	++
282	+++	++
283	+++	+++
284	++	++
285	+++	++
286	+++	+++
287	+++	++
288	+++	++

Cmpd #	EC50 (uM)	% Activity
289	+++	++
290	+++	++
291	+++	++
292	+++	++
293	++	+++
294	++	++
295	+++	++
296	++	++
297	+++	++
298	+++	++
299	+++	++
300	+++	++
301	+	+
302	++	++
303	++	++
304	+++	++
305	+++	+++
306	+++	+++
307	+++	++
308	++	++
309	+	+
310	+++	++
311	+++	++
312	+++	++
313	+++	++
314	+++	++
315	+++	++
316	++	++
317	+++	++
318	++	++
319	+++	++
320	+++	++
321	+++	++
322	+++	++
323	+++	++
324	+++	++
325	+++	++
326	++	++
327	+++	++
328	+	+
329	++	++
330	+++	++
331	+	+
332	+++	++
333	+++	++
334	++	++
335	+	+
336	+++	++

Cmpd #	EC50 (uM)	% Activity
337	+++	++
338	++	++
339	+++	++
340	+++	++
341	+++	++
342	+++	++
343	++	++
344	+++	++
345	+++	++
346	+++	++
347	++	++
348	+++	++
350	+++	++
351	+++	++
352	+++	++
353	+++	++
354	+++	++
355	+++	++
356	+++	++
357	+++	++
358	+++	++
359	++	++
360	+++	++
361	+++	+++
362	+++	++
363	+++	+++
364	+++	++
365	++	++
366	+++	++
367	+++	++
368	+++	++
369	++	+
370	+++	++
371	+++	++
372	+++	++
373	+++	++
374	+	+
375	+++	++
376	+	+
377	++	++
378	++	++
379	++	++
380	+++	++
381	+++	++
382	+++	++
383	+++	++
384	+++	++
385	+++	++

Cmpd #	EC50 (uM)	% Activity
386	+++	++
387	+++	++
388	+++	++
389	+++	++
390	+	+
391	+++	++
392	+	+
393	+++	++
394	+	+
395	+++	++
396	++	++
397	+++	++
398	++	++
399	+++	++
400	+	+
401	+++	++
402	+++	+
403	+++	++
404	+++	++
405	+++	++
406	+++	++
407	+++	++
408	+++	++
409	+++	++
410	+++	+++
411	+++	++
412	+++	++
413	+++	++
414	+	+
415	+++	++
416	+++	++
417	+++	++
418	++	++
419	+	+
420	+++	++
421	+++	++
423	+++	++
424	+++	++
425	+++	++
426	+++	++
427	+++	++
428	+++	++
429	+++	++
430	+++	++
431	++	++
432	+++	++
433	+++	++
434	+++	++

Cmpd #	EC50 (uM)	% Activity
435	+++	++
436	+++	++
437	+	+
438	+++	++
439	+++	++
440	+++	++
441	+++	++
442	+	+
443	+	+
444	+++	++
445	+++	+++
446	+	+
447	++	++
448	+++	++
449	+++	++
450	++	++
451	+++	++
452	+++	++
453	+++	++
454	+	+
455	+++	++
456	+++	++
457	+	+
458	+++	++
459	+++	++
460	+++	++
461	+++	++
462	+++	++
463	+++	++
464	+++	++
465	+++	++
466	+++	++
467	+	+
468	+	+
469	+++	++
470	+++	++
471	+++	++
472	+++	++
473	++	++
474	+	+
476	+++	++
477	+	+
478	+++	++
479	+++	++
480	+	+
481	+++	++
482	++	++
483	+++	++

Cmpd #	EC50 (uM)	% Activity
484	+++	++
485	+++	++
486	+++	++
487	+++	++
488	+++	++
489	+++	++
490	+++	++
491	+++	++
492	+++	+++
493	+++	++
494	+++	++
495	+++	++
496	+++	++
497	+++	+++
498	+++	++
499	+++	++
500	+++	++
501	+++	++
502	+++	++
503	+++	++
504	+++	++
505	+++	+
506	+++	++
507	+++	++
508	+++	++
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510	+++	++
511	+++	++
512	+++	++
513	+++	++
514	+++	++
515	++	+
516	+++	++
517	+++	+
518	+++	++
519	+++	++
520	+++	++
521	+++	++
522	+++	++
523	+++	++
524	+++	++
525	+++	+
526	++	+
527	+++	++
528	+++	++
529	+++	++
530	+++	++
531	+++	++

Cmpd #	EC50 (uM)	% Activity
532	+++	++
533	+++	+++
534	+++	++
535	+++	++
536	+++	++
537	+++	++
538	+++	++
539	+++	++
540	+++	+++
541	+++	++
542	+++	+++
543	+++	+++
544	+++	++
545	+++	+++
546	+++	++
547	+++	+++
548	+++	++
549	+++	++
550	+++	++
551	+++	++
552	+++	++
553	+++	++
554	+++	++
555	+++	++
556	+++	++
557	+++	++
558	+++	++
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560	+++	++
561	+++	++
562	+++	++
563	+++	++
564	+++	++
565	+++	++
566	+++	++
567	+++	++
568	+++	++
569	+++	++
570	+++	++
571	+++	+
572	+++	++
573	+++	++
574	+++	++
575	+++	++
576	+++	++
577	+++	++
578	+++	++
579	+++	++

Cmpd #	EC50 (uM)	% Activity
580	+++	+
581	+++	++
582	+++	++
583	+++	++
584	+++	++
585	+++	+++
586	+++	++
587	+++	++
588	+++	++
589	+++	++
590	+++	+
591	+++	++
592	+++	++
593	+++	++
594	+++	+++
595	+++	++
596	+++	++
597	+++	++
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611	+++	+++
612	+++	++
613	+++	++
614	+++	++
615	+++	+++
616	++	+
617	+++	+++
618	+++	++
619	+++	+++
620	+++	++
621	+++	+
622	+++	++
623	+++	++
624	+++	++
625	+++	+
626	+++	++

Cmpd #	EC50 (uM)	% Activity
627	+++	+
628	+++	++
629	+++	++
630	+++	++
631	+++	+++
632	+++	++
633	+++	++
634	+++	++
635	+++	++
636	+++	+
637	+++	+
638	+++	+
639	+++	++
640	+++	+++
641	++	+
642	+++	++
643	+++	++
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660	+++	++
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662	+++	+++
663	+++	++
664	+++	++
665	+++	++
666	+++	++
667	+++	++
668	+++	++
669	+++	++
670	+++	++
671	+++	++
672	+++	++
673	+++	++

Cmpd #	EC50 (uM)	% Activity
674	+++	++
675	+++	++
676	+++	++
677	+++	++
678	+++	++
679	+++	++
680	+++	++
681	+++	++
682	+++	+
683	+++	++
684	+++	++
685	+++	++
686	+++	++
687	+++	++
688	+++	++
689	+++	++
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694	+++	++
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697	+++	++
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704	+++	++
705	+++	++
706	+++	+++
707	+++	++
708	+++	++
709	+++	+++
710	+++	++
711	+++	++
712	+++	++
713	+++	+++
714	+++	++
715	+++	++
716	+++	++
717	+++	++
718	+++	++

What is claimed is:

1. A compound selected from:

6,7-difluoro-N-(2-fluoro-5-hydroxy-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

5-hydroxy-N-[5-hydroxy-4-tert-butyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

4-oxo-N-[3-(1-piperidyl)-5-(trifluoromethyl)phenyl]-1H-quinoline-3-carboxamide;

N-[4-(3,3-dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl]-6-methyl-4-oxo-1H-quinoline-3-carboxamide;

6-fluoro-N-(3-hydroxy-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

N-(3-fluoro-4-tert-butyl-phenyl)-5-hydroxy-4-oxo-1H-quinoline-3-carboxamide;

methyl 1-[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-3-(trifluoromethyl)phenyl]piperidine-2-carboxylate;

5-hydroxy-N-[4-[2-hydroxy-1-(hydroxymethyl)-1-methyl-ethyl]phenyl]-4-oxo-1H-quinoline-3-carboxamide;

5-hydroxy-4-oxo-N-[5-(trifluoromethyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide;

6-fluoro-4-oxo-N-[2-(trifluoromethyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide;

N-(5-hydroxy-2,4-ditert-butyl-phenyl)-6-methoxy-4-oxo-1H-quinoline-3-carboxamide;

N-[5-hydroxy-4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

N-[2-fluoro-5-hydroxy-4-(1-methylcyclohexyl)-phenyl]-5-methyl-4-oxo-1H-quinoline-3-carboxamide;

N-[2-fluoro-5-hydroxy-4-(1-methylcyclohexyl)-phenyl]-7-methyl-4-oxo-1H-quinoline-3-carboxamide;

5-hydroxy-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide;

N-[2-fluoro-5-hydroxy-4-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

5-hydroxy-N-[3-methoxy-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

6-methyl-N-[4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

N-[4-(3,3-dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl]-6-methoxy-4-oxo-1H-quinoline-3-carboxamide;

8-cyano-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

N-[3-hydroxy-4-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

N-(2-ethyl-5-hydroxy-4-tert-butyl-phenyl)-5-hydroxy-4-oxo-1H-quinoline-3-carboxamide;

4-oxo-N-[3-tert-butyl-5-(trifluoromethyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide;

6-fluoro-N-[5-hydroxy-4-tert-butyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

4-oxo-N-[3-(1-piperidyl)-4-tert-butyl-phenyl]-1H-quinoline-3-carboxamide;

(S)-5-methyl-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide;

N-[4-cyclopentyl-5-hydroxy-2-(3-hydroxyprop-1-ynyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

(S)-N-(4-(3-(dimethylamino)pyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide;

4-oxo-N-[2-(1-piperidyl)-4-(trifluoromethyl)phenyl]-1H-quinoline-3-carboxamide;

N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-6-(trifluoromethyl)-1H-quinoline-3-carboxamide;

N-(4-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-5-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide;

8-ethoxy-N-[4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

N-(5-hydroxy-2-methyl-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

8-cyano-N-(2-fluoro-5-hydroxy-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-5-(trifluoromethyl)-1H-quinoline-3-carboxamide;

6-fluoro-N-[4-(3-methyloxetan-3-yl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

N-(4-cyclohexyl-3-hydroxy-phenyl)-5-hydroxy-4-oxo-1H-quinoline-3-carboxamide;

N-[4-(3-methyloxetan-3-yl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

6-ethoxy-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

6-cyano-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

8-ethoxy-N-(2-fluoro-5-hydroxy-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

6-fluoro-N-(3-fluoro-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

N-[4-(3,3-difluoropyrrolidin-1-yl)-2-(trifluoromethyl)phenyl]-5-methyl-4-oxo-1H-quinoline-3-carboxamide;

5-hydroxy-N-[4-(3-methyloxetan-3-yl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

(2S,3S)-methyl 3-methyl-1-(4-(4-oxo-1,4-dihydroquinoline-3-carboxamide)-3-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate;

(1S,2S,5R)-methyl 3-(4-(4-oxo-1,4-dihydroquinoline-3-carboxamide)-3-(trifluoromethyl)phenyl)-3-azabicyclo[3.1.0]hexane-2-carboxylate;

N-[2-chloro-4-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

6-methoxy-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide;

(R)-N-(4-(3-(dimethylamino)pyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide;

5-hydroxy-4-oxo-N-(3-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide;

N-[4-(3,3-dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

4-oxo-N-[2-(trifluoromethyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide;

N-[2-methyl-4-(trifluoromethoxy)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

N-(4-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-5-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide;

(R)-tert-butyl 1-(4-(4-oxo-1,4-dihydroquinoline-3-carboxamide)-3-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate;

(R)-N-(4-(3-fluoropyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-5-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide;

N-(5-hydroxy-2,4-ditert-butyl-phenyl)-5-methylamino-4-oxo-1H-quinoline-3-carboxamide;

4-oxo-N-[4-(1-piperidyl)phenyl]-1H-quinoline-3-carboxamide;

6-dimethylamino-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

4-oxo-N-[3-(trifluoromethyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide;

5-methyl-N-[4-(3-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

N-[4-isopropoxy-2-(trifluoromethyl)phenyl]-5-methyl-4-oxo-1H-quinoline-3-carboxamide;

7-cyano-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

4-oxo-N-[3-(2-thienyl)phenyl]-1H-quinoline-3-carboxamide;

(2S,4R)-methyl 4-tert-butoxy-1-(4-(4-oxo-1,4-dihydroquinoline-3-carboxamide)-3-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate;

N-(4-hydroxy-2-naphthyl)-4-oxo-1H-quinoline-3-carboxamide;

5-fluoro-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

6-bromo-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

6-fluoro-4-oxo-N-(3-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide;

N-[4-(3-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

N-[4-(2,2-dimethylpropanoylamino)-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

6-fluoro-N-[4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

7-cyano-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide;

4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-8-(trifluoromethyl)-1H-quinoline-3-carboxamide;

N-[4-(2,5-dimethylpyrrol-1-yl)-3-methoxy-phenyl]-4-oxo-1H-quinoline-3-carboxamide;

6-chloro-N-(2-fluoro-5-hydroxy-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

6-fluoro-4-oxo-N-[4-pyrrolidin-1-yl-2-(trifluoromethyl)phenyl]-1H-quinoline-3-carboxamide;

N-[3-hydroxy-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

N-(4-cyclohexyl-3-hydroxy-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

5-methyl-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide;

6-fluoro-N-[1-(2-methoxyethyl)-5-(trifluoromethyl)indol-6-yl]-4-oxo-1H-quinoline-3-carboxamide;

(S)-1-[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-3-(trifluoromethyl)phenyl]pyrrolidine-2-carboxylic acid;

N-(5-hydroxy-2,4-ditert-butyl-phenyl)-5-methyl-4-oxo-1H-quinoline-3-carboxamide;

N-(4-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-6-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide;

N-[5-benzyloxy-4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

N-[6-methoxy-5-(trifluoromethyl)-2-pyridyl]-4-oxo-1H-quinoline-3-carboxamide;

(R)-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide;

8-fluoro-N-[4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

6-fluoro-N-[3-hydroxy-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

N-(3-hydroxy-4-isopropyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

7-methyl-4-oxo-N-[5-(trifluoromethyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide;

N-[2-methyl-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

N-[4-(3,3-dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl]-5-methyl-4-oxo-1H-quinoline-3-carboxamide;

4-oxo-N-[3-pyrrolidin-1-yl-4-(trifluoromethoxy)phenyl]-1H-quinoline-3-carboxamide;

N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-8-(trifluoromethyl)-1H-quinoline-3-carboxamide;

(S)-5-methyl-N-(6-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)pyridin-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxamide;

N-(4-((1S,4R)-2-azabicyclo[2.2.1]heptan-2-yl)-2-(trifluoromethyl)phenyl)-5-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide;

N-(5-hydroxy-2,4-ditert-butyl-phenyl)-7-methoxy-4-oxo-1H-quinoline-3-carboxamide;

N-[2-fluoro-5-hydroxy-4-(1-methylcyclohexyl)-phenyl]-6-methoxy-4-oxo-1H-quinoline-3-carboxamide;

5-amino-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

(R)-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-5-(trifluoromethyl)-1,4-dihydroquinoline-3-carboxamide;

5-hydroxy-N-(3-hydroxy-4-isopropyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

5-hydroxy-N-(5-hydroxy-2-methyl-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

6,7-difluoro-N-[4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

N-[4-[2-hydroxy-1-(hydroxymethyl)-1-methyl-ethyl]phenyl]-4-oxo-1H-quinoline-3-carboxamide;

N-(5-ethyl-1H-indol-6-yl)-5-hydroxy-4-oxo-1H-quinoline-3-carboxamide;

N-(4-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-5-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide;

4-oxo-N-[3-pyrrolidin-1-yl-5-(trifluoromethyl)phenyl]-1H-quinoline-3-carboxamide;

N-(3-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

N-[4-cyclopentoxy-2-(trifluoromethyl)phenyl]-5-methyl-4-oxo-1H-quinoline-3-carboxamide;

N-(5-fluoro-1H-indol-6-yl)-5-hydroxy-4-oxo-1H-quinoline-3-carboxamide;

6-fluoro-N-(3-hydroxy-4-isopropyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

N-[4-morpholino-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

5-hydroxy-N-[3-hydroxy-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

tert-butyl [[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-3-(trifluoromethyl)phenyl]amino]formate;

(S)-6-methoxy-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide;

4-oxo-N-(3-tert-butylphenyl)-1H-quinoline-3-carboxamide;

6-chloro-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide;

7-acetyl-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

8-ethyl-N-(2-fluoro-5-hydroxy-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

5-hydroxy-N-[3-hydroxy-4-(1-methylcyclohexyl)-phenyl]-4-oxo-1H-quinoline-3-carboxamide;

(S)-7-methyl-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide;

N-(2,4-dichloro-5-hydroxy-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

5-hydroxy-N-(5-hydroxy-2-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

5-fluoro-N-(2-fluoro-5-hydroxy-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

7-fluoro-6-methoxy-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide;

N-[4-(3,3-dimethyl-1-piperidyl)-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

(R)-5-methyl-N-(4-(3-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide;

4-oxo-N-[4-(3-pyridyloxy)phenyl]-1H-quinoline-3-carboxamide;

N-(2-methyl-4-pyrrolidin-1-yl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

8-ethoxy-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

6-fluoro-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-7-methoxy-4-oxo-1H-quinoline-3-carboxamide;

(S)-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide;

N-[4-cyclohexyl-5-hydroxy-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

5-hydroxy-4-oxo-N-(3-tert-butylphenyl)-1H-quinoline-3-carboxamide;

N-(5-hydroxy-2,4-ditert-butyl-phenyl)-8-methyl-4-oxo-1H-quinoline-3-carboxamide;

N-(2-cyano-4-pyrrolidin-1-yl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

6-chloro-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

N-[2-fluoro-5-hydroxy-4-(1-methylcyclohexyl)-phenyl]-6-methyl-4-oxo-1H-quinoline-3-carboxamide;

N-(2-fluoro-5-hydroxy-4-tert-butyl-phenyl)-8-methyl-4-oxo-1H-quinoline-3-carboxamide;

(S)-N-(4-(3-fluoropyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-5-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide;

6-fluoro-N-[4-[2-hydroxy-1-(hydroxymethyl)-1-methyl-ethyl]phenyl]-4-oxo-1H-quinoline-3-carboxamide;

N-[2-chloro-4-(trifluoromethoxy)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

(S)-tert-butyl 1-(4-(4-oxo-1,4-dihydroquinoline-3-carboxamide)-3-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate;

N-[2,5-bis(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

(S)-methyl 2-methyl-1-(4-(4-oxo-1,4-dihydroquinoline-3-carboxamide)-3-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate;

4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-7-(trifluoromethoxy)-1H-quinoline-3-carboxamide;

5-hydroxy-N-(3-hydroxy-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

(S)-N-(4-(2-(hydroxymethyl)pyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide;

N-[2-chloro-4-(trifluoromethyl)phenyl]-5-hydroxy-4-oxo-1H-quinoline-3-carboxamide;

N-[2-chloro-4-(trifluoromethyl)phenyl]-6-fluoro-4-oxo-1H-quinoline-3-carboxamide;

N-[4-isopropyl-2-(trifluoromethyl)phenyl]-8-methyl-4-oxo-1H-quinoline-3-carboxamide;

N-(2-fluoro-5-hydroxy-4-tert-butyl-phenyl)-4-oxo-8-(trifluoromethyl)-1H-quinoline-3-carboxamide;

N-[4-(4-isopropylpiperazin-1-yl)-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

N-(5-hydroxy-2,4-ditert-butyl-phenyl)-7-methyl-4-oxo-1H-quinoline-3-carboxamide;

8-ethoxy-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide;

(S)-7-methoxy-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide;

5-methyl-N-[4-(3-methyl-1-piperidyl)-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

8-methyl-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide;

N-(3-fluoro-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

6,7-difluoro-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide;

N-(4-cyclohexyl-2-methyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

5-hydroxy-N-[4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

N-(2-ethyl-5-hydroxy-4-tert-butyl-phenyl)-6-fluoro-4-oxo-1H-quinoline-3-carboxamide;

6-fluoro-N-[3-hydroxy-4-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

N-(4-cyclohexyl-3-hydroxy-phenyl)-6-fluoro-4-oxo-1H-quinoline-3-carboxamide;

7-hydroxy-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

8-ethyl-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide;

N-[5-benzyloxy-4-cyclohexyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

(S)-N-(4-(3-hydroxypyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide;

5-fluoro-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide;

6-chloro-N-[4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

4-oxo-N-[4-pyrrolidin-1-yl-2-(trifluoromethyl)phenyl]-1H-quinoline-3-carboxamide;

N-(2-ethyl-5-hydroxy-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

(S)-ethyl 1-(4-(4-oxo-1,4-dihydroquinoline-3-carboxamide)-3-(trifluoromethyl)phenyl)piperidine-3-carboxylate;

5-methyl-4-oxo-N-[5-(trifluoromethyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide;

N-(5-hydroxy-2-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

8-chloro-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

6-fluoro-4-oxo-N-(3-tert-butylphenyl)-1H-quinoline-3-carboxamide;

6-fluoro-N-(5-hydroxy-2-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

6-fluoro-N-[3-methoxy-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

(R)-N-(4-(4,4-difluoro-2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-5-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide;

N-[4-[4-(hydroxymethyl)-1-piperidyl]-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

(S)-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-5-(trifluoromethyl)-1,4-dihydroquinoline-3-carboxamide;

(R)-N-(4-(2-(hydroxymethyl)pyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide;

N-(2-aminobenzothiazol-6-yl)-4-oxo-1H-quinoline-3-carboxamide;

6,7-difluoro-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

N-[4-[4-(2-hydroxyethyl)piperazin-1-yl]-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

4-oxo-N-(4-pyrrolidin-1-ylphenyl)-1H-quinoline-3-carboxamide;

N-(2-methoxy-4-pyrrolidin-1-yl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

5-hydroxy-N-[2-methyl-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

7-cyano-N-(2-fluoro-5-hydroxy-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

6-fluoro-N-[2-methyl-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

6-hydroxy-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide;

8-fluoro-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide;

6-ethoxy-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide;

8-ethyl-N-[4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

6-fluoro-N-(5-hydroxy-2-methyl-4-tert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

(R)-6-fluoro-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide;

N-(4-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxamide;

4-oxo-N-[4-(1-piperidyl)-2-(trifluoromethyl)phenyl]-1H-quinoline-3-carboxamide;

8-fluoro-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

N-(5-hydroxy-2,4-ditert-butyl-phenyl)-6-methyl-4-oxo-1H-quinoline-3-carboxamide;

N-[4-azetidin-1-yl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide

methyl 4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-2-tert-butyl-thiophene-3-carboxylate;

N-[3-methoxy-5-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

4-oxo-N-[2-(2-pyridyl)phenyl]-1H-quinoline-3-carboxamide;

5-hydroxy-4-oxo-N-[2-(trifluoromethyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide;

N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-7-(trifluoromethoxy)-1H-quinoline-3-carboxamide;

N-(4-chloro-2-fluoro-5-hydroxy-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

4-oxo-N-[3-(1-piperidyl)-4-(trifluoromethoxy)phenyl]-1H-quinoline-3-carboxamide;

(R)-5-methyl-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide;

(R)-1-[4-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-3-(trifluoromethyl)phenyl]pyrrolidine-2-carboxylic acid;

5-fluoro-N-[4-isopropyl-2-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

5-hydroxy-N-[3-hydroxy-4-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

N-(3-hydroxy-4-isopropoxy-phenyl)-5-methyl-4-oxo-1H-quinoline-3-carboxamide;

6-hydroxy-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide;

6-fluoro-4-oxo-N-[5-(trifluoromethyl)-1H-indol-6-yl]-1H-quinoline-3-carboxamide;

7-methyl-4-oxo-N-(5-tert-butyl-1H-indol-6-yl)-1H-quinoline-3-carboxamide;

(R)-N-(4-(3-hydroxypyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide;

N-[2-fluoro-5-hydroxy-4-(1-methylcyclohexyl)-phenyl]-4-oxo-5-(trifluoromethyl)-1H-quinoline-3-carboxamide;

4-oxo-N-(3-pyrrolidin-1-yl-4-tert-butyl-phenyl)-1H-quinoline-3-carboxamide;

4-oxo-N-[4-phenyl-5-(trifluoromethyl)-3-thienyl]-1H-quinoline-3-carboxamide;

7-fluoro-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-6-methoxy-4-oxo-1H-quinoline-3-carboxamide;

4-oxo-N-(1,4,4-trimethyl-2,3-dihydroquinolin-7-yl)-1H-quinoline-3-carboxamide;

6-[(4-oxo-1H-quinolin-3-yl)carbonylamino]-1H-indole-4-carboxylic acid;

N-[3-fluoro-4-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

(S)-N-(4-(2-methylpiperidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide;

(S)-6-fluoro-N-(4-(2-methylpyrrolidin-1-yl)-2-(trifluoromethyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide;

(S)-methyl 1-(4-(4-oxo-1,4-dihydroquinoline-3-carboxamide)-3-(trifluoromethyl)phenyl)piperidine-2-carboxylate;

8-chloro-N-[3-hydroxy-4-(trifluoromethyl)phenyl]-4-oxo-1H-quinoline-3-carboxamide;

N-(4-methoxy-2-naphthyl)-4-oxo-1H-quinoline-3-carboxamide; and

5,8-difluoro-N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier or adjuvant.

3. The pharmaceutical composition according to claim 2, further comprising an additional agent selected from a mucolytic agent, a bronchodialator, an antibiotic, an anti-infective agent, an anti-inflammatory agent, a CFTR modulator, or a nutritional agent.

4. The pharmaceutical composition according to claim 3, wherein said additional agent is a CFTR modulator other than a compound according to claim 1.

5. A method of treating or lessening the severity of a disease in a patient, 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 palsy, 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, pancreatic insufficiency, osteoporosis, osteopenia, Gorham's Syndrome, chloride channelopathies, myotonia congenita (Thomson and Becker forms), Bartter's syndrome type III, Dent's disease, hyperekplexia, epilepsy, hyperekplexia, lysosomal storage disease, Angelman syndrome, Primary Ciliary Dyskinesia (PCD), PCD with situs inversus (also known as Kartagener syndrome), PCD without situs inversus and ciliary

aplasia, or Sjogren's disease, said method comprising the step of administering to said patient an effective amount of a compound according to claim 1.

6. The method according to claim 5, wherein said disease is cystic fibrosis.

7. A method of treating or lessening the severity of a disease in a patient, wherein said disease is associated with reduced CFTR function due to mutations in the gene encoding CFTR or environmental factors, said method comprising the step of administering to said patient an effective amount of a compound according to claim 1.

8. The method of claim 7, wherein disease is cystic fibrosis, chronic bronchitis, recurrent bronchitis, acute bronchitis, male infertility caused by congenital bilateral absence of the vas deferens (CBAVD), female infertility caused by congenital absence of the uterus and vagina (CAUV), idiopathic chronic pancreatitis (ICP), idiopathic recurrent pancreatitis, idiopathic acute pancreatitis, chronic rhinosinusitis, primary sclerosing cholangitis, allergic bronchopulmonary aspergillosis, diabetes, dry eye, constipation, allergic bronchopulmonary aspergillosis (ABPA), bone diseases, and asthma.

9. A method of treating or lessening the severity of a disease in a patient, wherein said disease is associated with normal CFTR function, said method comprising the step of administering to said patient an effective amount of a compound according to claim 1.

10. The method of claim 9, wherein disease is chronic obstructive pulmonary disease (COPD), chronic bronchitis, recurrent bronchitis, acute bronchitis, rhinosinusitis, constipation, chronic pancreatitis, recurrent pancreatitis, and acute pancreatitis, pancreatic insufficiency, male infertility caused by congenital bilateral absence of the vas deferens (CBAVD), mild pulmonary disease, idiopathic pancreatitis, liver disease, hereditary emphysema, gallstones, gasgtro-esophageal reflux disease, gastrointestinal malignancies, inflammatory bowel disease, constipation, diabetes, arthritis, osteoporosis, and osteopenia.

11. The method of claim 9, wherein the disease is 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 palsy, 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, Gorham's Syndrome, chloride channelopathies, myotonia congenita (Thomson and Becker forms), Bartter's syndrome type III, Dent's disease, hyperekplexia, epilepsy, hyperekplexia, lysosomal storage disease, Angelman syndrome, Primary Ciliary Dyskinesia (PCD), PCD with situs inversus (also known as Kartagener syndrome), PCD without situs inversus and ciliary aplasia, or Sjogren's disease.

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

a composition comprising a compound according to claim 1;

instructions for:

contacting the composition with the biological sample;

measuring activity of said CFTR or a fragment thereof.

13. The kit of claim 12, further comprising instructions for:

contacting an additional compound with the biological sample;

measuring the activity of said CFTR or a fragment thereof in the presence of said additional compound, and

comparing the activity of said CFTR or a fragment thereof in the presence of said additional compound with the activity of said CFTR or a fragment thereof in the presence of a composition comprising a compound according to claim 1.

14. A method of modulating CFTR activity in a biological sample comprising the step of contacting said CFTR with a compound according claim 1.

15. The kit according to claim 13, 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.

16. A method of treating or lessening the severity of cystic fibrosis (CF) in a patient, said method comprising the step of administering to said patient an effective amount of a compound according to claim 1.

17. The method of claim 16, wherein the patient possesses a cystic fibrosis transmembrane receptor (CFTR) with a homozygous ΔF508 mutation.

18. The method of claim 16, wherein the patient possesses a cystic fibrosis transmembrane receptor (CFTR) with a homozygous G551D mutation.

19. The method of claim 16, wherein the patient possesses a cystic fibrosis transmembrane receptor (CFTR) with a heterozygous ΔF508 mutation.

20. The method of claim 16, wherein the patient possesses a cystic fibrosis transmembrane receptor (CFTR) with a heterozygous G551D mutation.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D215/56 C07D401/12 C07D405/12 C07D409/12 C07D413/12
C07D417/12 C07D471/08 A61K31/4709 A61P11/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/002421 A2 (VERTEX PHARMA [US]; HADIDA RUAH SARAH S [US]; HAZLEWOOD ANNA R [US]; G) 5 January 2006 (2006-01-05) the whole document -----	1-20

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/059920

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006002421 A2	05-01-2006	AU 2005258320 A1	05-01-2006
		AU 2010249302 A1	06-01-2011
		AU 2010251787 A1	06-01-2011
		AU 2010251789 A1	06-01-2011
		BR PI0511321 A	31-07-2007
		CA 2571949 A1	05-01-2006
		CN 101006076 A	25-07-2007
		CN 101935301 A	05-01-2011
		CN 101891680 A	24-11-2010
		EP 1773816 A2	18-04-2007
		JP 2008504291 T	14-02-2008
		NZ 552543 A	30-09-2010
		RU 2382779 C2	27-02-2010
		US 2006074075 A1	06-04-2006
		US 2009227797 A1	10-09-2009
		US 2009298876 A1	03-12-2009
		US 2008071095 A1	20-03-2008
		ZA 200700601 A	26-11-2008