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(54) Title: MODULATORS OF CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR

(57) Abstract: The present invention relates to modulators of ATP-B inding 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.

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VPI/07-107 WO**MODULATORS OF CYSTIC FIBROSIS TRANSMEMBRANE****CONDUCTANCE REGULATOR****CROSS-REFERENCE TO RELATED APPLICATIONS**

[001] The present application claims priority under 35 U.S.C. § 119 to United States Provisional Application No. 60/931,775 filed May 25, 2007 and entitled "MODULATORS OF CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR," United States Provisional Application No. 60/968,704 filed August 29, 2007 and entitled "MODULATORS OF CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR," the entire contents of each of the above applications being incorporated herein by reference.

**TECHNICAL FIELD OF THE INVENTION**

[002] The present invention relates to modulators of cystic fibrosis transmembrane conductance regulator ("CFTR"), compositions thereof, and methods therewith. The present invention also relates to methods of treating CFTR mediated diseases using such modulators.

**BACKGROUND OF THE INVENTION**

[003] 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.

[004] 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.

[005] 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.

[006] 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.

[007] 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.

[008] 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  $\Delta F508$ -CFTR. This mutation occurs in approximately 70% of the cases of cystic fibrosis and is associated with a severe disease.

[009] The deletion of residue 508 in  $\Delta F508$ -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  $\Delta F508$ -CFTR in the membrane are functional, albeit less than wild-type CFTR. (Dalemans 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  $\Delta F508$ -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.

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

[011] 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  $\text{Na}^+-\text{K}^+$ -ATPase pump and  $\text{Cl}^-$  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  $\text{Cl}^-$  channels, resulting in a vectorial transport. Arrangement of  $\text{Na}^+/\text{2Cl}^-/\text{K}^+$  co-transporter,  $\text{Na}^+-\text{K}^+$ -ATPase pump and the basolateral membrane  $\text{K}^+$  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.

[012] 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. These include, but are not limited to, chronic obstructive pulmonary disease (COPD), dry eye disease, and Sjögren's Syndrome. 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. 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 Sjögren'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. Sjögren'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 polymyositis/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 help to elevate the associated symptoms.

[013] As discussed above, it is believed that the deletion of residue 508 in  $\Delta F508$ -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. Infact, this cellular phenomenon of defective ER processing of ABC transporters 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  $\Delta F508$ -CFTR as discussed above), hereditary emphysema (due to  $\alpha 1$ -antitrypsin; non Piz variants), hereditary hemochromatosis, haemagglutination-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  $\beta$ -hexosaminidase), Crigler-Najjar type II (due to UDP-glucuronyl-sialyl-transferase), polyendocrinopathy/hyperinsulemia, Diabetes mellitus (due to insulin receptor), Laron dwarfism (due to growth hormone receptor), myeloperoxidase 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  $\alpha 1$ -Antitrypsin (PiZ variant), congenital hyperthyroidism, osteogenesis imperfecta (due to Type I, II, IV procollagen), hereditary hypofibrinogenemia (due to fibrinogen), ACT deficiency (due to  $\alpha 1$ -antichymotrypsin), Diabetes insipidus (DI), neurophyseal DI (due to vasopressin hormone/V2-receptor), nephrogenic DI (due to aquaporin II), Charcot-Marie Tooth syndrome (due to peripheral myelin protein 22), Perliazeus-Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease ( due to  $\beta$ APP and presenilins), Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, Pick's disease, several polyglutamine neurological disorders asuch as Huntington, spinocerebellar ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidolulsian, 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  $\alpha$ -galactosidase A) and Straussler-Scheinker syndrome (due to Prp processing defect).

[014] 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.

[015] 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.

[016] 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.

[017] 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.

[018] 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.

[019] 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.

[020] 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.

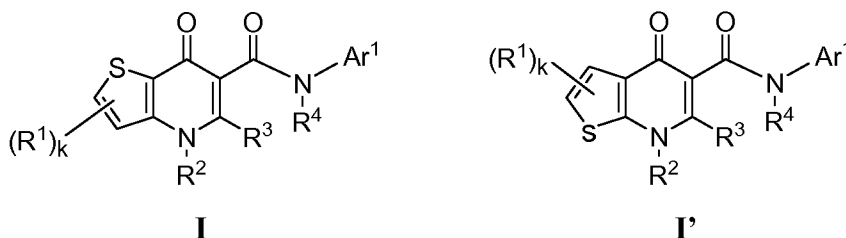
[021] Accordingly, there is a need for modulators of CFTR activity, and compositions thereof, that can be used to modulate the activity of the CFTR in the cell membrane of a mammal.

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

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

### SUMMARY OF THE INVENTION

[024] 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** or formula **I'**:



or a pharmaceutically acceptable salt thereof, wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and Ar<sup>1</sup> are described generally and in classes and subclasses below.

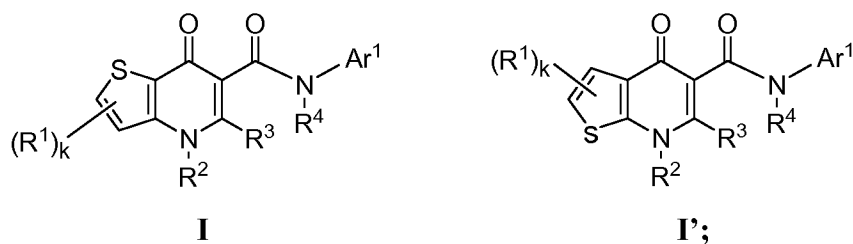
[025] These compounds and pharmaceutically acceptable compositions are useful for treating or lessening the severity of a variety of diseases, disorders, or conditions, including, but not limited to, cystic fibrosis, Hereditary emphysema, Hereditary hemochromatosis, Coagulation-Fibrinolysis deficiencies, 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, Myeloperoxidase 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 palsy, Pick's disease, several polyglutamine neurological disorders as such as Huntington, Spinocerebellar ataxia type I, Spinal and bulbar muscular atrophy, Dentatorubal pallidolusian, 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

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



[027] The present invention relates to compounds of formula **I** or formula **I'** useful as modulators of ABC transporter activity:



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, cyano,  $CF_3$ ,  $CHF_2$ ,  $OCHF_2$ , Me, Et,  $CH(Me)_2$ ,  $CHMeEt$ , n-propyl, t-butyl, OH, 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-2-yl, 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-methylthiophenyl, 4-methylthiophenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxyphenyl, 5-chloro-2-methoxyphenyl, 2-OCF<sub>3</sub>-phenyl, 3-trifluoromethoxy-phenyl, 4-trifluoromethoxyphenyl, 2-phenoxyphenyl, 4-phenoxyphenyl, 2-fluoro-3-methoxy-phenyl, 2,4-dimethoxy-5-pyrimidyl, 5-isopropyl-2-methoxyphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-cyanophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 3-chloro-4-fluoro-phenyl, 3,5-dichlorophenyl, 2,5-dichlorophenyl, 2,3-dichlorophenyl, 3,4-dichlorophenyl, 2,4-dichlorophenyl, 3-methoxycarbonylphenyl, 4-methoxycarbonyl phenyl, 3-isopropoxyloxycarbonylphenyl, 3-acetamidophenyl, 4-fluoro-3-methylphenyl, 4-methanesulfinyl-phenyl, 4-methanesulfonyl-phenyl, 4-N-(2-N,N-dimethylaminoethyl)carbonylphenyl, 5-acetyl-2-thienyl, 2-benzothienyl, 3-benzothienyl, furan-3-yl, 4-methyl-2-thienyl, 5-cyano-2-thienyl, N'-phenylcarbonyl-N-piperazinyl, -NHCO<sub>2</sub>Et, -NHCO<sub>2</sub>Me, N-pyrrolidinyl, -NHSO<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub> N-piperidine, -NHSO<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub> N-morpholine, -NHSO<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>N(Me)<sub>2</sub>, COCH<sub>2</sub>N(Me)COCH<sub>2</sub>NHMe, -CO<sub>2</sub>Et, O-propyl, -CH<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>C(Me)<sub>3</sub>, aminomethyl, pentyl, adamantyl, cyclopentyl, ethoxyethyl, C(Me)<sub>2</sub>CH<sub>2</sub>OH, C(Me)<sub>2</sub>CO<sub>2</sub>Et, -CHOHMe, CH<sub>2</sub>CO<sub>2</sub>Et, -C(Me)<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>C(Me)<sub>3</sub>, O(CH<sub>2</sub>)<sub>2</sub>OEt, O(CH<sub>2</sub>)<sub>2</sub>OH, CO<sub>2</sub>Me, hydroxymethyl, 1-methyl-1-cyclohexyl, 1-methyl-1-cyclooctyl, 1-methyl-1-cycloheptyl, C(Et)<sub>2</sub>C(Me)<sub>3</sub>, C(Et)<sub>3</sub>, CONHCH<sub>2</sub>CH(Me)<sub>2</sub>, 2-aminomethylphenyl, ethenyl, 1-piperidinylcarbonyl, ethynyl, cyclohexyl, 4-methylpiperidinyl, -OCO<sub>2</sub>Me, -C(Me)<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>CH<sub>2</sub>CH(Me)<sub>2</sub>, -C(Me)<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -C(Me)<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>Et, -C(Me)<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>Me, -C(Me)<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>CH<sub>2</sub>C(Me)<sub>3</sub>, -CH<sub>2</sub>NHCOCF<sub>3</sub>, -CH<sub>2</sub>NHCO<sub>2</sub>C(Me)<sub>3</sub>, -C(Me)<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, C(Me)<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>OMe, C(OH)(CF<sub>3</sub>)<sub>2</sub>, -C(Me)<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>CH<sub>2</sub>-tetrahydrofuran-3-yl, C(Me)<sub>2</sub>CH<sub>2</sub>O(CH<sub>2</sub>)<sub>2</sub>OMe, or 3-ethyl-2,6-dioxopiperidin-3-yl;

m is 0-5;

k is 0-2;

each of R<sup>1</sup> is independently -X-R<sup>X</sup>;

X is a bond or is an optionally substituted C<sub>1</sub>-C<sub>6</sub> alkylidene chain wherein up to two methylene units of X are optionally and independently replaced by -CO-, -CS-, -COCO-, -CONR', -CONR'NR', -CO<sub>2</sub>-, -OCO-, -NR'CO<sub>2</sub>-, -O-, -NR'CONR', -OCONR', -NR'NR', -NR'NR'CO-, -NR'CO-, -S-, -SO-, -SO<sub>2</sub>-, -NR'-, -SO<sub>2</sub>NR', NR'SO<sub>2</sub>-, or -NR'SO<sub>2</sub>NR'-;

R<sup>X</sup> is independently R', halo, NO<sub>2</sub>, CN, CF<sub>3</sub>, or OCF<sub>3</sub>;

R<sup>2</sup> is hydrogen;

R<sup>3</sup> is hydrogen;

R<sup>4</sup> is hydrogen or a C<sub>1-6</sub> aliphatic group optionally substituted with -X-R<sup>X</sup>;

R' is independently selected from hydrogen or an optionally substituted group selected from a C<sub>1-8</sub> 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.

[028] 2. *Compounds and Definitions:*

[029] 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.

[030] 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.

[031] 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).

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

[033] 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, 75<sup>th</sup> 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”, 5<sup>th</sup> Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[034] 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.

[035] 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<sub>3</sub>-C<sub>8</sub> hydrocarbon or bicyclic or tricyclic C<sub>8</sub>-C<sub>14</sub> 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.

[036] 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.

[037] 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.

[038] 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<sup>+</sup> (as in N-substituted pyrrolidinyl)).

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

[040] 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.

[041] 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 include -CHF<sub>2</sub>, -CH<sub>2</sub>F, -CF<sub>3</sub>, -CF<sub>2</sub>-, or perhaloalkyl, such as, -CF<sub>2</sub>CF<sub>3</sub>.

[042] 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.

[043] 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”.

[044] 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;  $-R^\circ$ ;  $-OR^\circ$ ;  $-SR^\circ$ ; 1,2-methylene-dioxy; 1,2-ethylenedioxy; phenyl (Ph) optionally substituted with  $R^\circ$ ;  $-O(Ph)$  optionally substituted with  $R^\circ$ ;  $-(CH_2)_{1-2}(Ph)$ , optionally substituted with  $R^\circ$ ;  $-CH=CH(Ph)$ , optionally substituted with  $R^\circ$ ;  $-NO_2$ ;  $-CN$ ;  $-N(R^\circ)_2$ ;  $-NR^\circ C(O)R^\circ$ ;  $-NR^\circ C(O)N(R^\circ)_2$ ;  $-NR^\circ CO_2R^\circ$ ;  $-NR^\circ NR^\circ C(O)R^\circ$ ;  $-NR^\circ NR^\circ C(O)N(R^\circ)_2$ ;  $-NR^\circ NR^\circ CO_2R^\circ$ ;  $-C(O)C(O)R^\circ$ ;  $-C(O)CH_2C(O)R^\circ$ ;  $-CO_2R^\circ$ ;  $-C(O)R^\circ$ ;  $-C(O)N(R^\circ)_2$ ;  $-OC(O)N(R^\circ)_2$ ;  $-S(O)_2R^\circ$ ;  $-SO_2N(R^\circ)_2$ ;  $-S(O)R^\circ$ ;  $-NR^\circ SO_2N(R^\circ)_2$ ;  $-NR^\circ SO_2R^\circ$ ;  $-C(=S)N(R^\circ)_2$ ;  $-C(=NH)-N(R^\circ)_2$ ; or  $-(CH_2)_{0-2}NHC(O)R^\circ$  wherein each independent occurrence of  $R^\circ$  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  $R^\circ$ , on the same substituent or different substituents, taken together with the atom(s) to which each  $R^\circ$  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  $R^\circ$  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  $R^\circ$  is unsubstituted.

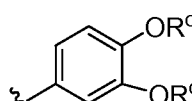
[045] An aliphatic or heteroaliphatic group, or a non-aromatic heterocyclic ring may contain one or more substituents. Suitable substituents on the saturated carbon of an aliphatic or heteroaliphatic group, or of a non-aromatic heterocyclic ring are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and additionally include the following:  $=O$ ,  $=S$ ,  $=NNHR^*$ ,  $=NN(R^*)_2$ ,  $=NNHC(O)R^*$ ,  $=NNHCO_2(\text{alkyl})$ ,  $=NNHSO_2(\text{alkyl})$ , 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  $NH_2$ ,  $NH(C_{1-4} \text{ aliphatic})$ ,  $N(C_{1-4} \text{ aliphatic})_2$ , halo,  $C_{1-4}$  aliphatic,  $OH$ ,  $O(C_{1-4} \text{ aliphatic})$ ,  $NO_2$ ,  $CN$ ,  $CO_2H$ ,  $CO_2(C_{1-4} \text{ aliphatic})$ ,  $O(\text{halo } C_{1-4} \text{ aliphatic})$ , or  $\text{halo}(C_{1-4} \text{ aliphatic})$ , wherein each of the foregoing  $C_{1-4}$  aliphatic groups of  $R^*$  is unsubstituted.

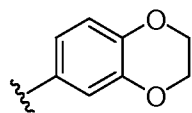
[046] Optional substituents on the nitrogen of a non-aromatic heterocyclic ring are selected from  $-R^+$ ,  $-N(R^+)_2$ ,  $-C(O)R^+$ ,  $-CO_2R^+$ ,  $-C(O)C(O)R^+$ ,  $-C(O)CH_2C(O)R^+$ ,  $-SO_2R^+$ ,  $-SO_2N(R^+)_2$ ,  $-C(=S)N(R^+)_2$ ,  $-C(=NH)-N(R^+)_2$ , or  $-NR^+SO_2R^+$ ; wherein  $R^+$  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  $NH_2$ ,  $NH(C_{1-4} \text{ aliphatic})$ ,  $N(C_{1-4} \text{ aliphatic})_2$ , halo,  $C_{1-4}$  aliphatic,  $OH$ ,  $O(C_{1-4} \text{ aliphatic})$ ,  $NO_2$ ,  $CN$ ,  $CO_2H$ ,  $CO_2(C_{1-4} \text{ aliphatic})$ ,  $O(\text{halo } C_{1-4} \text{ aliphatic})$ , or  $\text{halo}(C_{1-4} \text{ aliphatic})$ , wherein each of the foregoing  $C_{1-4}$  aliphatic groups of  $R^+$  is unsubstituted.

[047] 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.

[048] As detailed above, in some embodiments, two independent occurrences of  $R^\circ$  (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,

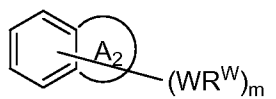
or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Exemplary rings that are formed when two independent occurrences of  $R^o$  (or  $R^+$ , or any other variable similarly defined herein) are taken together with the atom(s) to which each variable is bound include, but are not limited to the following: a) two independent occurrences of  $R^o$  (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,  $N(R^o)_2$ , where both occurrences of  $R^o$  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  $R^o$  (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.

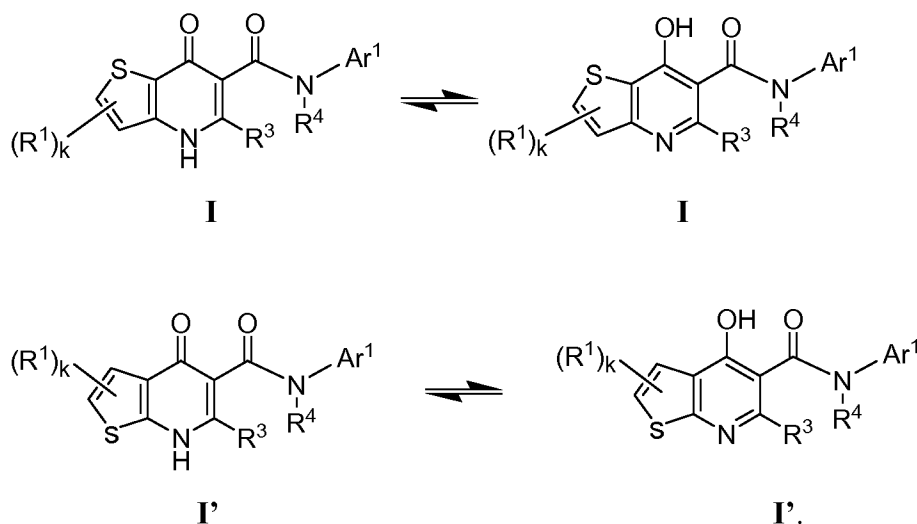
**[049]** A substituent bond in, e.g., a bicyclic ring system, as shown below, means that the substituent can be attached to any substitutable ring atom on either ring of the bicyclic ring system:



**[050]** 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



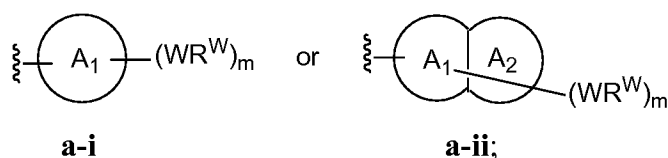
scope of the invention. E.g., when  $R^5$  in compounds of formula **I** or formula **I'** is hydrogen, compounds of formula **I** or formula **I'** may exist as tautomers:



[051] 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  $^{13}\text{C}$ - or  $^{14}\text{C}$ -enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

[052] 3. Description of Exemplary Compounds:

[053] In some embodiments of the present invention,  $\text{Ar}^1$  is selected from:



wherein ring  $A_1$  is a 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 membered aromatic, bicyclic or tricyclic aryl ring, wherein each ring contains 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[054] 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<sub>1</sub> is an optionally substituted pyrazinyl or triazinyl. Or, A<sub>1</sub> is an optionally substituted pyridyl.

**[055]** In some embodiments, A<sub>1</sub> is an optionally substituted 5-membered aromatic ring having 0-3 heteroatoms, wherein said heteroatom is nitrogen, oxygen, or sulfur. In some embodiments, A<sub>1</sub> is an optionally substituted 5-membered aromatic ring having 1-2 nitrogen atoms. In one embodiment, A<sub>1</sub> is an optionally substituted 5-membered aromatic ring other than thiazolyl.

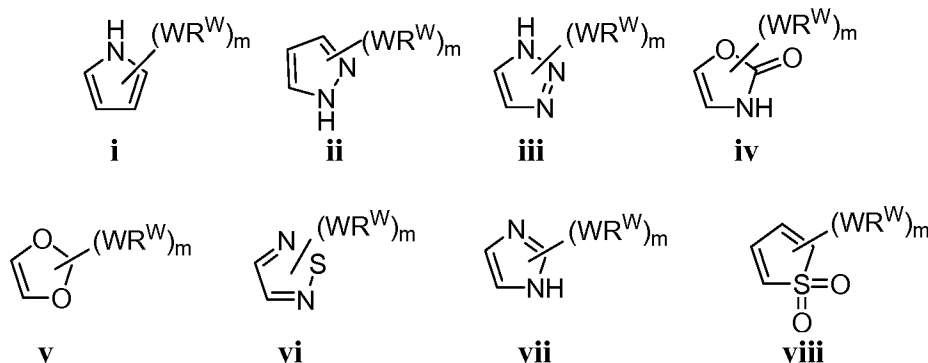
**[056]** In some embodiments, A<sub>2</sub> is an optionally substituted 6 membered aromatic ring having 0-4 heteroatoms, wherein said heteroatom is nitrogen. In some embodiments, A<sub>2</sub> is an optionally substituted phenyl. Or, A<sub>2</sub> is an optionally substituted pyridyl, pyrimidinyl, pyrazinyl, or triazinyl.

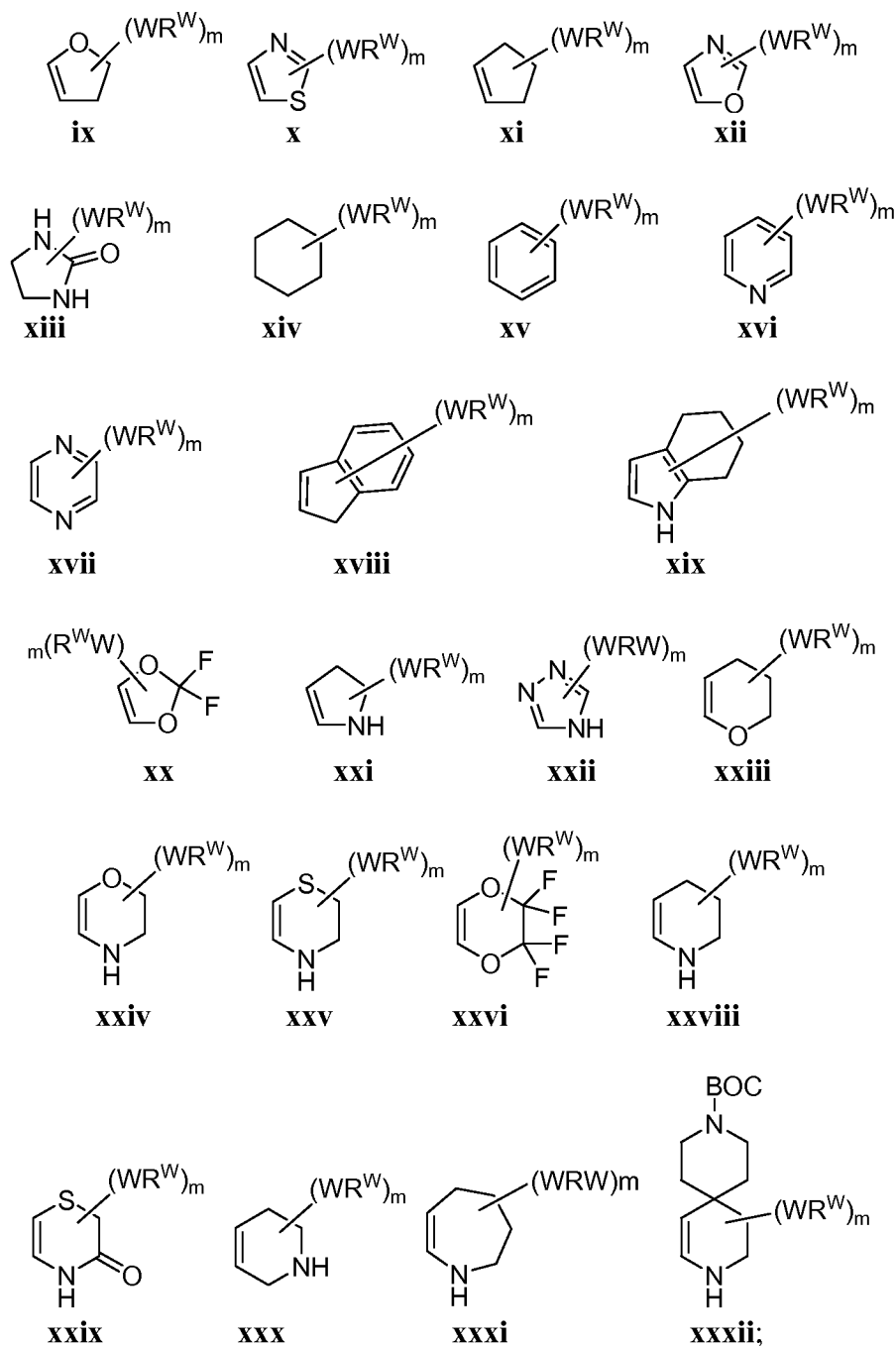
**[057]** In some embodiments, A<sub>2</sub> is an optionally substituted 5-membered aromatic ring having 0-3 heteroatoms, wherein said heteroatom is nitrogen, oxygen, or sulfur. In some embodiments, A<sub>2</sub> is an optionally substituted 5-membered aromatic ring having 1-2 nitrogen atoms. In certain embodiments, A<sub>2</sub> is an optionally substituted pyrrolyl.

**[058]** In some embodiments, A<sub>2</sub> 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.

**[059]** In some embodiments, A<sub>2</sub> is an optionally substituted 5-10 membered saturated or unsaturated carbocyclic ring. In one embodiment, A<sub>2</sub> is an optionally substituted 5-10 membered saturated carbocyclic ring. Exemplary such rings include cyclohexyl, cyclopentyl, etc.

**[060]** In some embodiments, ring A<sub>2</sub> is selected from:





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

**[061]** In other embodiments, 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 O,  $-CO-$ ,  $-CS-$ ,  $-COCO-$ ,  $-CONR'-$ ,  $-CONR'NR'-$ ,  $-CO_2-$ ,  $-OCO-$ ,  $-NR'CO_2-$ ,  $-O-$ ,  $-NR'CONR'-$ ,  $-C(O)NR'-$ ,  $-OCONR'-$ ,  $-NR'NR'$ ,  $-NR'NR'CO-$ ,  $-NR'CO-$ ,  $-S-$ ,  $-SO-$ ,  $-SO_2-$ ,  $-NR'-$ ,  $-SO_2NR'-$ ,  $NR'SO_2-$ , or  $-NR'SO_2NR'-$ , and  $R^W$  is  $R'$  or halo

[062] In still other embodiments, each occurrence of  $WR^W$  is independently -C1-C3 alkyl, t-butyl, C1-C3 perhaloalkyl, -OH, -O(C1-C3alkyl), -CF<sub>3</sub>, -OCF<sub>3</sub>, -SCF<sub>3</sub>, -F, -Cl, -Br, or -COOR', -COR', -O(CH<sub>2</sub>)<sub>2</sub>N(R')(R'), -O(CH<sub>2</sub>)N(R')(R'), -CON(R')(R'), -(CH<sub>2</sub>)<sub>2</sub>OR', -(CH<sub>2</sub>)OR', optionally substituted 5-7 membered heterocyclic ring, optionally substituted 5-7 membered cycloaliphatic group, optionally substituted monocyclic or bicyclic aromatic ring, optionally substituted arylsulfone, optionally substituted 5-membered heteroaryl ring, -N(R')(R'), -(CH<sub>2</sub>)<sub>2</sub>N(R')(R'), or -(CH<sub>2</sub>)N(R')(R').

[063] In one embodiment of Ar<sub>1</sub> in formula **a-i**, ring A<sub>1</sub> is a phenyl ring, m is 1, and  $WR^W$  is independently optionally substituted pyrrolidine or piperidine.

[064] 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.

[065] In one embodiment of the present invention, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are simultaneously hydrogen.

[066] In another embodiment of the present invention, k is 1 or 2 and each R<sup>1</sup> is independently C1-C3 alkyl or C3-C6 cycloalkyl.

[067] In one embodiment, k is 1 or 2, and each R<sup>1</sup> is halo.

[068] In some embodiments, X is a bond or is an optionally substituted C<sub>1-6</sub> alkylidene chain wherein one or two non-adjacent methylene units are optionally and independently replaced by O, NR', S, SO<sub>2</sub>, or COO, CO, and R<sup>X</sup> is R' or halo. In still other embodiments, each occurrence of XR<sup>X</sup> is independently -C<sub>1-3</sub>alkyl, -O(C<sub>1-3</sub>alkyl), -CF<sub>3</sub>, -OCF<sub>3</sub>, -SCF<sub>3</sub>, -F, -Cl, -Br, OH, -COOR', -COR', -O(CH<sub>2</sub>)<sub>2</sub>N(R')(R'), -O(CH<sub>2</sub>)N(R')(R'), -CON(R')(R'), -(CH<sub>2</sub>)<sub>2</sub>OR', -(CH<sub>2</sub>)OR', optionally substituted phenyl, -N(R')(R'), -(CH<sub>2</sub>)<sub>2</sub>N(R')(R'), or -(CH<sub>2</sub>)N(R')(R').

[069] In one embodiment, R<sup>1</sup> is H, C1-C4 aliphatic, halo, or C3-C6 cycloaliphatic.

[070] In some embodiments, R<sup>4</sup> is hydrogen. In certain other embodiment, R<sup>4</sup> is C<sub>1-4</sub> straight or branched aliphatic.

[071] In some embodiments, R<sup>W</sup> is selected from halo, cyano, CF<sub>3</sub>, CHF<sub>2</sub>, OCHF<sub>2</sub>, Me, Et, CH(Me)<sub>2</sub>, CHMeEt, n-propyl, t-butyl, OH, OMe, OEt, OPh, O-fluorophenyl, O-difluorophenyl, O-methoxyphenyl, O-tolyl, O-benzyl, SMe, SCF<sub>3</sub>, SCHF<sub>2</sub>, SEt, CH<sub>2</sub>CN, NH<sub>2</sub>, NHMe, N(Me)<sub>2</sub>, NHEt, N(Et)<sub>2</sub>, C(O)CH<sub>3</sub>, C(O)Ph, C(O)NH<sub>2</sub>, SPh, SO<sub>2</sub>-(amino-pyridyl), SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>Ph, SO<sub>2</sub>NHPh, SO<sub>2</sub>-N-morpholino, SO<sub>2</sub>-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<sub>2</sub>Me, 2-indolyl, 5-indolyl, -CH<sub>2</sub>CH<sub>2</sub>OH, -OCF<sub>3</sub>, O-(2,3-dimethylphenyl), 5-methylfuryl, -SO<sub>2</sub>-N-piperidyl, 2-tolyl, 3-tolyl, 4-tolyl, O-butyl, NHCO<sub>2</sub>C(Me)<sub>3</sub>, CO<sub>2</sub>C(Me)<sub>3</sub>, isopropenyl, n-butyl, O-(2,4-dichlorophenyl), NHSO<sub>2</sub>PhMe, O-(3-chloro-5-trifluoromethyl-2-pyridyl), phenylhydroxymethyl, 2,5-dimethylpyrrolyl, NHCOCH<sub>2</sub>C(Me)<sub>3</sub>, 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-methylthiophenyl, 4-methylthiophenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxyphenyl, 5-chloro-2-methoxyphenyl, 2-OCF<sub>3</sub>-phenyl, 3-trifluoromethoxy-phenyl, 4-trifluoromethoxyphenyl, 2-phenoxyphenyl, 4-phenoxyphenyl, 2-fluoro-3-methoxy-phenyl, 2,4-dimethoxy-5-pyrimidyl, 5-isopropyl-2-methoxyphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-cyanophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 3-chloro-4-fluoro-phenyl, 3,5-dichlorophenyl, 2,5-dichlorophenyl, 2,3-dichlorophenyl, 3,4-dichlorophenyl, 2,4-dichlorophenyl, 3-methoxycarbonylphenyl, 4-methoxycarbonyl phenyl, 3-isopropoxy carbonylphenyl, 3-acetamidophenyl, 4-fluoro-3-methylphenyl, 4-methanesulfinyl-phenyl, 4-methanesulfonyl-phenyl, 4-N-(2-N,N-dimethylaminoethyl)carbonylphenyl, 5-acetyl-2-thienyl, 2-benzothienyl, 3-benzothienyl, furan-3-yl, 4-methyl-2-thienyl, 5-cyano-2-thienyl, N'-phenylcarbonyl-N-piperazinyl, -NHCO<sub>2</sub>Et, -NHCO<sub>2</sub>Me, N-pyrrolidinyl, -NHSO<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub> N-piperidine, -NHSO<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub> N-morpholine, -NHSO<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>N(Me)<sub>2</sub>, COCH<sub>2</sub>N(Me)COCH<sub>2</sub>NHMe, -CO<sub>2</sub>Et, O-propyl, -CH<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>C(Me)<sub>3</sub>, aminomethyl, pentyl, adamantyl, cyclopentyl, ethoxyethyl, C(Me)<sub>2</sub>CH<sub>2</sub>OH, C(Me)<sub>2</sub>CO<sub>2</sub>Et, -CHOHMe, CH<sub>2</sub>CO<sub>2</sub>Et, -C(Me)<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>C(Me)<sub>3</sub>, O(CH<sub>2</sub>)<sub>2</sub>OEt, O(CH<sub>2</sub>)<sub>2</sub>OH, CO<sub>2</sub>Me, hydroxymethyl, , 1-methyl-1-cyclohexyl, 1-methyl-1-cyclooctyl, 1-methyl-1-cycloheptyl, C(Et)<sub>2</sub>C(Me)<sub>3</sub>, C(Et)<sub>3</sub>, CONHCH<sub>2</sub>CH(Me)<sub>2</sub>, 2-aminomethylphenyl, ethenyl, 1-piperidinylcarbonyl, ethynyl, cyclohexyl, 4-methylpiperidinyl, -OCO<sub>2</sub>Me, -C(Me)<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>CH<sub>2</sub>CH(Me)<sub>2</sub>, -C(Me)<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -C(Me)<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>Et, -C(Me)<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>Me, -C(Me)<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>CH<sub>2</sub>C(Me)<sub>3</sub>, -CH<sub>2</sub>NHCOCF<sub>3</sub>, -CH<sub>2</sub>NHCO<sub>2</sub>C(Me)<sub>3</sub>, -C(Me)<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, C(Me)<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>OMe, C(OH)(CF<sub>3</sub>)<sub>2</sub>, -C(Me)<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>CH<sub>2</sub>-tetrahydrofuran-3-yl, C(Me)<sub>2</sub>CH<sub>2</sub>O(CH<sub>2</sub>)<sub>2</sub>OMe, or 3-ethyl-2,6-dioxopiperidin-3-yl.

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

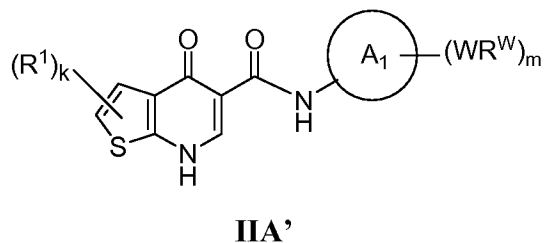
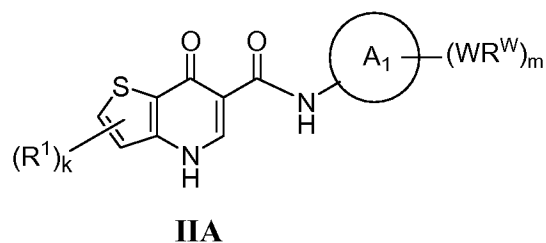
[073] In one embodiment, R' is a C1-C8 aliphatic group, optionally substituted with up to 3 substituents selected from halo, CN, CF<sub>3</sub>, CHF<sub>2</sub>, OCF<sub>3</sub>, or OCHF<sub>2</sub>, wherein up to two methylene units of said C1-C8 aliphatic is optionally replaced with -CO-, -CONH(C1-C4 alkyl)-, -CO<sub>2</sub>-, -OCO-, -N(C1-C4 alkyl)CO<sub>2</sub>-, -O-, -N(C1-C4 alkyl)CON(C1-C4 alkyl)-, -OCON(C1-C4 alkyl)-, -N(C1-C4 alkyl)CO-, -S-, -N(C1-C4 alkyl)-, -SO<sub>2</sub>N(C1-C4 alkyl)-, N(C1-C4 alkyl)SO<sub>2</sub>-, or -N(C1-C4 alkyl)SO<sub>2</sub>N(C1-C4 alkyl)-.

[074] 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<sub>3</sub>, CHF<sub>2</sub>, OCF<sub>3</sub>, OCHF<sub>2</sub>, 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<sub>2</sub>-, -OCO-, -N(C1-C4 alkyl)CO<sub>2</sub>-, -O-, -N(C1-C4 alkyl)CON(C1-C4 alkyl)-, -OCON(C1-C4 alkyl)-, -N(C1-C4 alkyl)CO-, -S-, -N(C1-C4 alkyl)-, -SO<sub>2</sub>N(C1-C4 alkyl)-, N(C1-C4 alkyl)SO<sub>2</sub>-, or -N(C1-C4 alkyl)SO<sub>2</sub>N(C1-C4 alkyl)-.

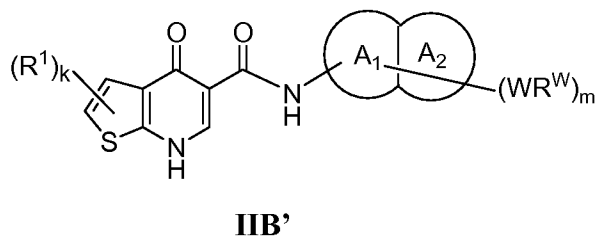
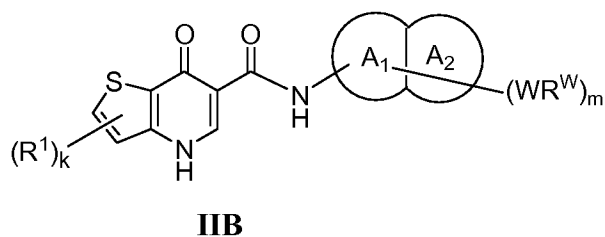
[075] In one embodiment, R' is an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein R' is optionally substituted with up to 3 substituents selected from halo, CN, CF<sub>3</sub>, CHF<sub>2</sub>, OCF<sub>3</sub>, OCHF<sub>2</sub>, 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<sub>2</sub>-, -OCO-, -N(C1-C4 alkyl)CO<sub>2</sub>-, -O-, -N(C1-C4 alkyl)CON(C1-C4 alkyl)-, -OCON(C1-C4 alkyl)-, -N(C1-C4 alkyl)CO-, -S-, -N(C1-C4 alkyl)-, -SO<sub>2</sub>N(C1-C4 alkyl)-, N(C1-C4 alkyl)SO<sub>2</sub>-, or -N(C1-C4 alkyl)SO<sub>2</sub>N(C1-C4 alkyl)-.

[076] 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<sub>3</sub>, CHF<sub>2</sub>, OCF<sub>3</sub>, OCHF<sub>2</sub>, 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<sub>2</sub>-, -OCO-, -N(C1-C4 alkyl)CO<sub>2</sub>-, -O-, -N(C1-C4 alkyl)CON(C1-C4 alkyl)-, -OCON(C1-C4 alkyl)-, -N(C1-C4 alkyl)CO-, -S-, -N(C1-C4 alkyl)-, -SO<sub>2</sub>N(C1-C4 alkyl)-, N(C1-C4 alkyl)SO<sub>2</sub>-, or -N(C1-C4 alkyl)SO<sub>2</sub>N(C1-C4 alkyl)-.

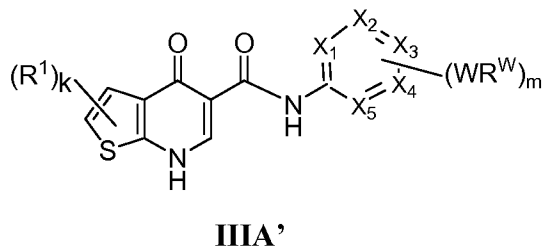
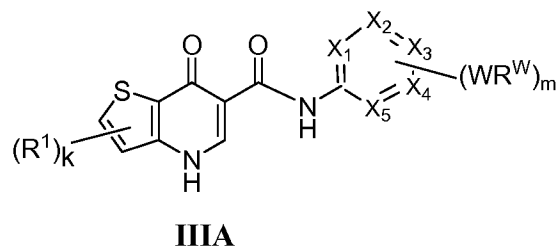
[077] According to one embodiment, the present invention provides compounds of formula **IIA** or formula **IIA'**:



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

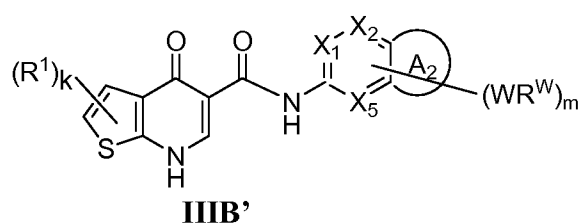
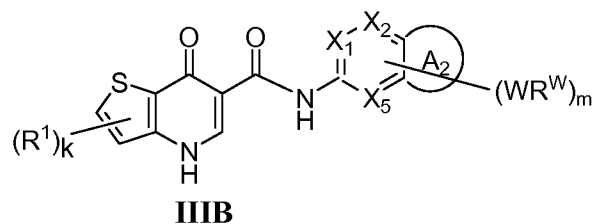


[079] According to one embodiment, the present invention provides compounds of formula **IIIA** or formula **IIIA'**:



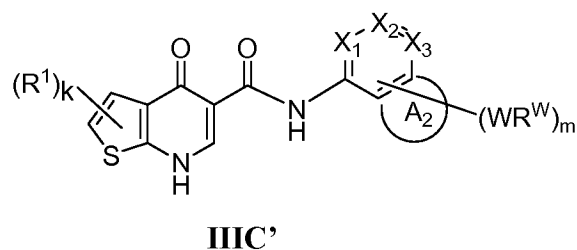
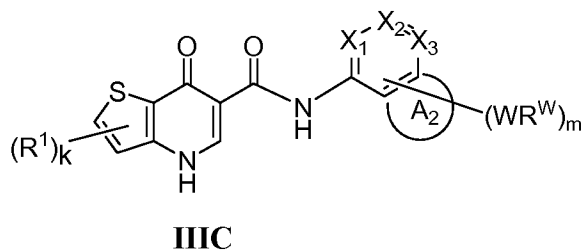
wherein each of X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, and X<sub>5</sub> is independently selected from CH or N.

[080] According to one embodiment, the present invention provides compounds of formula **IIIB** or formula **IIIB'**:



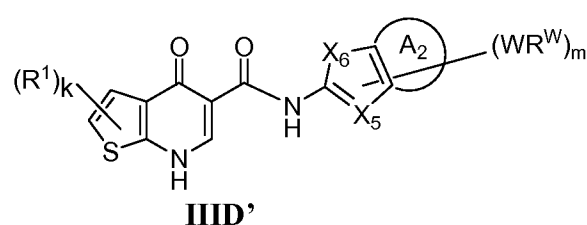
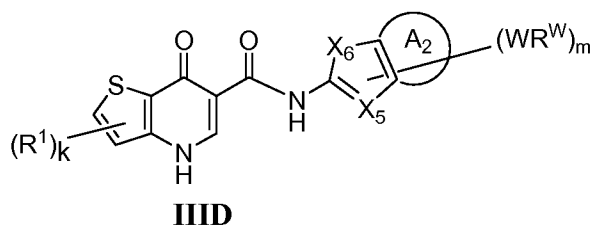
wherein each of X<sub>1</sub>, X<sub>2</sub>, and X<sub>5</sub> is independently selected from CH or N.

[081] According to one embodiment, the present invention provides compounds of formula **IIIC** or formula **IIIC'**:



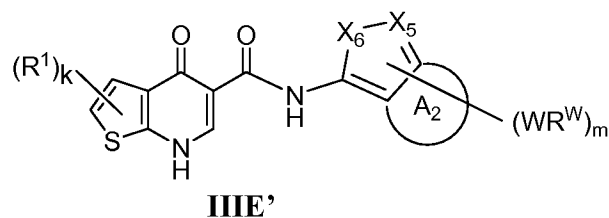
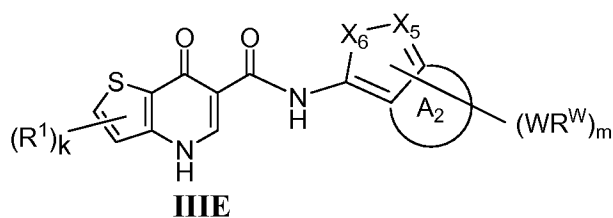
wherein each of X<sub>1</sub>, X<sub>2</sub>, and X<sub>3</sub> is independently selected from CH or N.

[082] According to one embodiment, the present invention provides compounds of formula **IIID** or formula **IIID'**:



wherein X<sub>5</sub> is independently selected from CH or N and X<sub>6</sub> is O, S, or NR'.

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

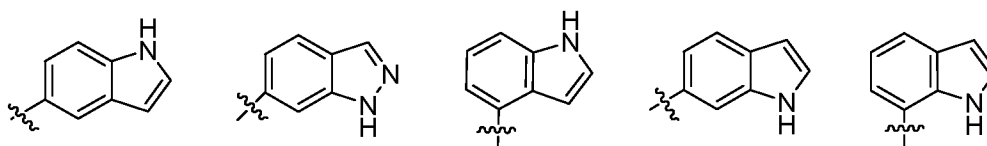


wherein X<sub>5</sub> is independently selected from CH or N and X<sub>6</sub> is O, S, or NR'.

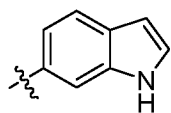
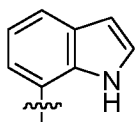
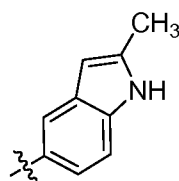
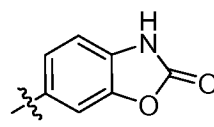
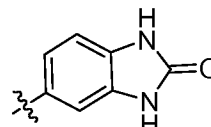
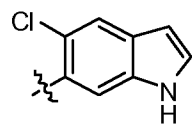
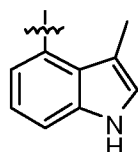
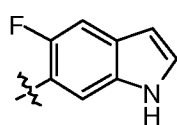
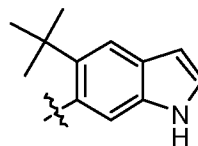
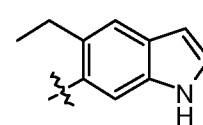
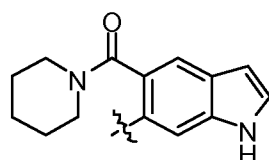
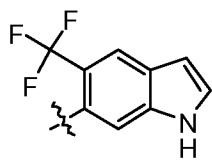
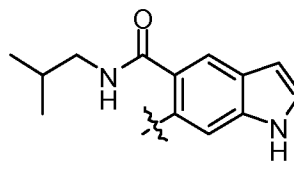
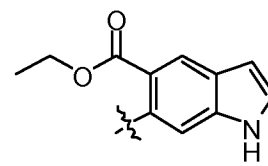
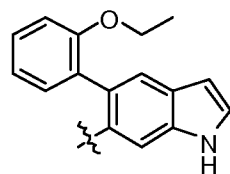
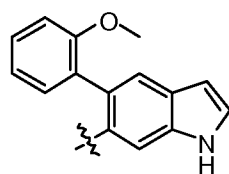
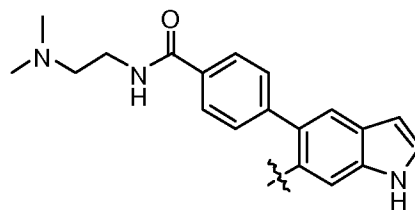
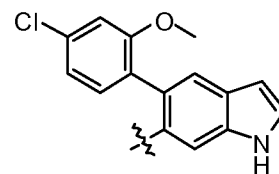
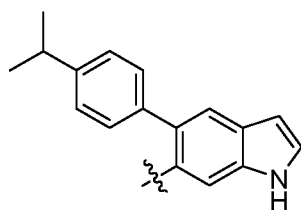
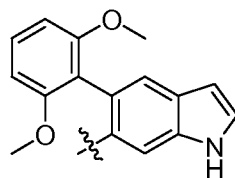
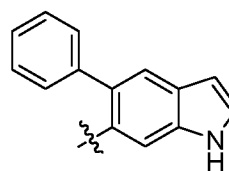
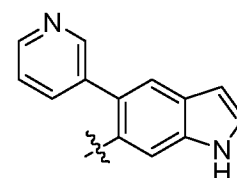
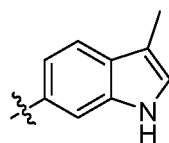
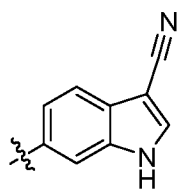
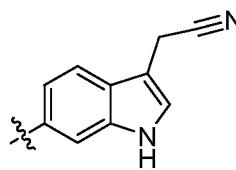
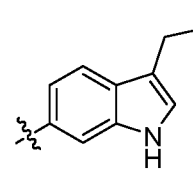
[084] In some embodiments of formula **IIIA** or formula **IIIA'**, each of X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, and X<sub>5</sub> is CH.

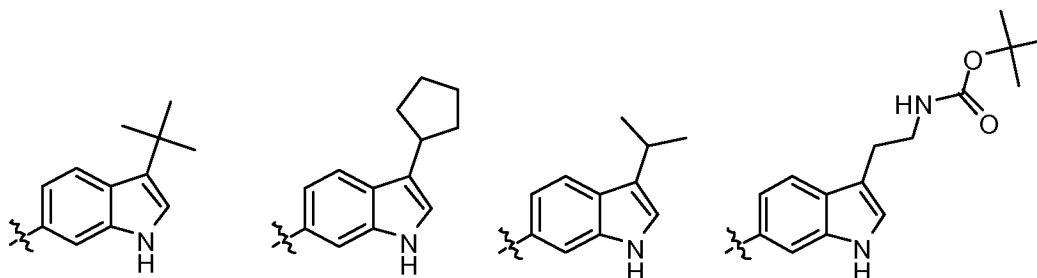
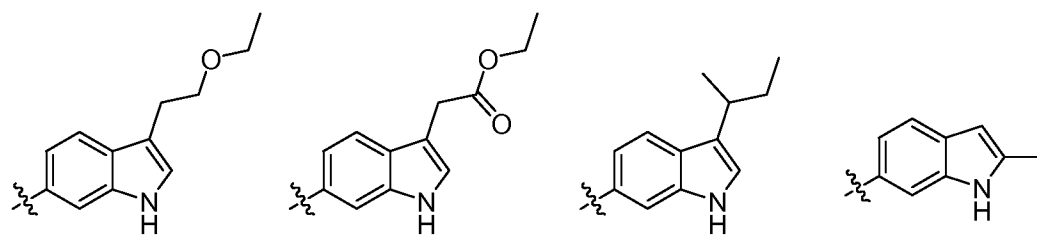
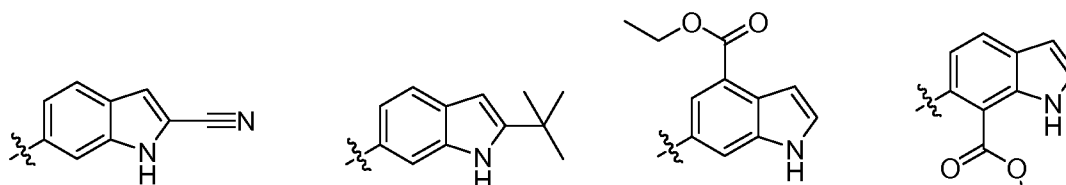
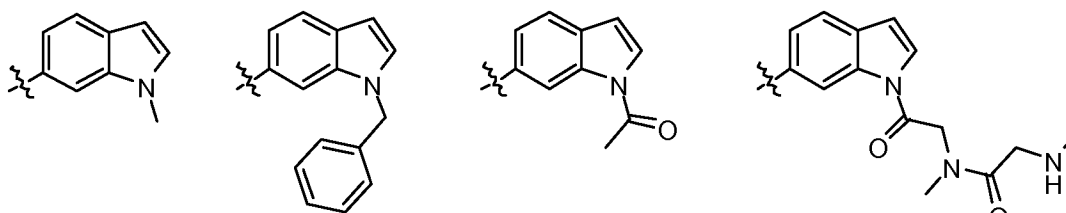
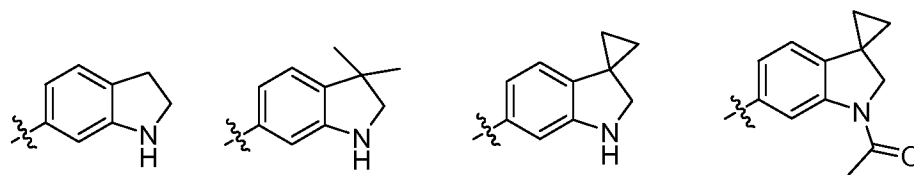
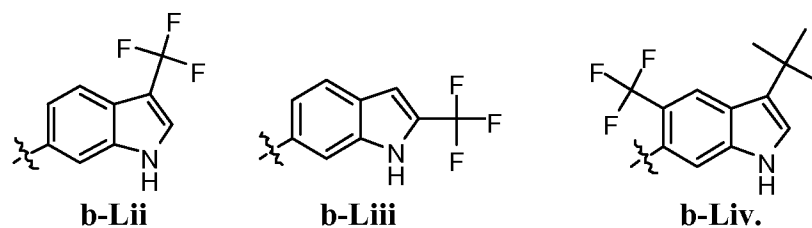
[085] In some embodiments of formula **IIIA** or formula **IIIA'**, X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, and X<sub>5</sub> taken together is an optionally substituted ring selected from pyridyl, pyrazinyl, or pyrimidinyl.

[086] In some embodiments of formula **IIIB**, formula **IIIB'**, formula **IIIC**, or formula **IIIC'**, X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, or X<sub>5</sub> taken together with ring A<sub>2</sub> is an optionally substituted ring selected from:





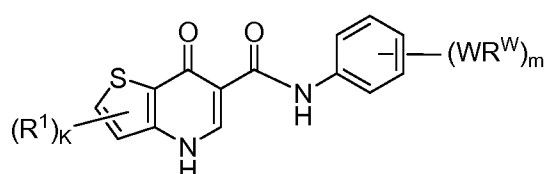
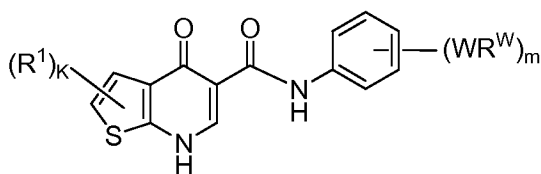
**b-i****b-vi****b-ii****b-vii****b-iii****b-viii****b-iv****b-ix****b-v****b-x****b-xi****b-xii****b-xiii****b-xiv****b-xv****b-xvi****b-xvii****b-xviii****b-xix****b-xx****b-xxi****b-xxii****b-xxiii****b-xxiv****b-xxv****b-xxvi****b-xxvii****b-xxviii****b-xxix****b-xxx****bxxx**

**b-xxxii****b-xxxiii****b-xxxiv****b-xxxv****b-xxxvi****b-xxxvii****b-xxxviii****bxxxix****b-xL****b-xLi****b-xLii****b-xLiii****b-xLiv****b-xLv****b-xLvi****b-xLviii****b-xLviii****b-xLix****b-L****b-Li****b-Lii****b-Liii****b-Liv.**

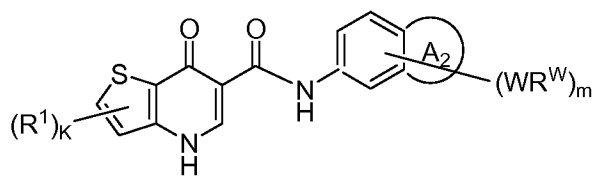
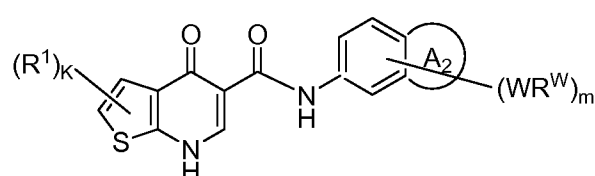
[087] In some embodiments,  $R^W$  is selected from  $R'$ halo, cyano,  $CF_3$ ,  $CHF_2$ ,  $OCHF_2$ , Me, Et,  $CH(Me)_2$ ,  $CHMeEt$ , n-propyl, t-butyl, OH, OMe, OEt, OPh, O-fluorophenyl, O-difluorophenyl, O-methoxyphenyl, O-tolyl, O-benzyl, SMe,  $SCF_3$ ,  $SCHF_2$ , SEt,  $CH_2CN$ ,  $NH_2$ ,  $NHMe$ ,  $N(Me)_2$ ,  $NHEt$ ,  $N(Et)_2$ ,  $C(O)CH_3$ ,  $C(O)Ph$ ,  $C(O)NH_2$ , 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-2-yl, 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  $NHSO_2Me$ .

[088] 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.

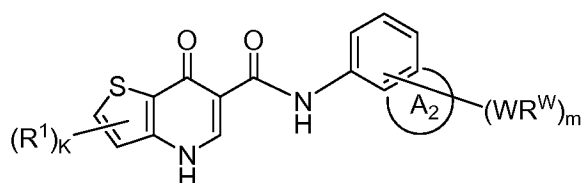
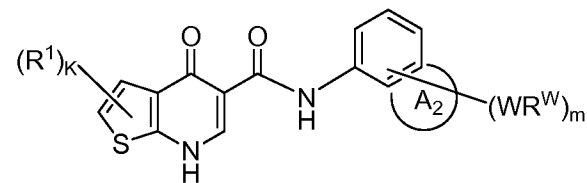
[089] According to another embodiment, the present invention provides compounds of formula **IVA** or formula **IVA'**:

**IVA****IVA'.**

[090] According to another embodiment, the present invention provides compounds of formula **IVB** or formula **IVB'**:

**IVB****IVB'.**

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

**IVC****IVC'.**

[092] In one embodiment, the present invention provides compounds of formula **IVA**, formula **IVA'**, formula **IVB**, formula **IVB'**, formula **IVC**, or formula **IVC'**, wherein  $k$  is 1 or 2, and  $R^1$  is H, Me, or halo. In another embodiment,  $k$  is 1 and  $R^1$  is Me. In another embodiment,  $k$  is 2, and  $R^1$  is Me.

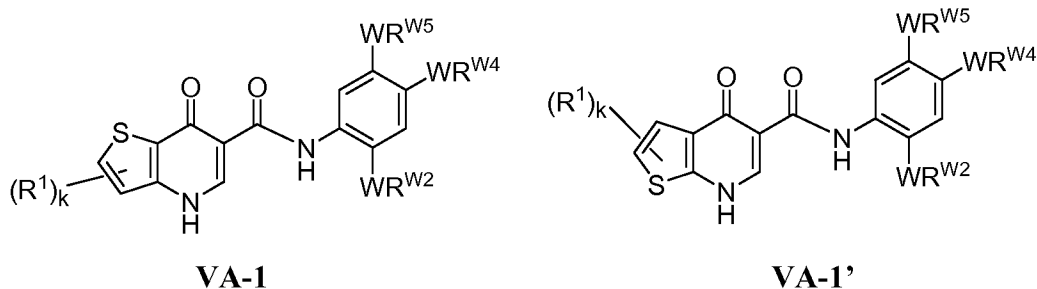
[093] In one embodiment, the present invention provides compounds of formula **IVB**, formula **IVB'**, formula **IVC**, or formula **IVC'**, wherein ring  $A_2$  is an optionally substituted, saturated, unsaturated, or aromatic seven membered ring with 0-3 heteroatoms selected from O, S, or N. Exemplary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

[094] In one embodiment, the present invention provides compounds of formula **IVB**, formula **IVB'**, formula **IVC**, or formula **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 piperidiny, 4,4-dimethylpiperidiny, etc.

[095] In one embodiment, the present invention provides compounds of formula **IVB**, formula **IVB'**, formula **IVC**, or formula **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.

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

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



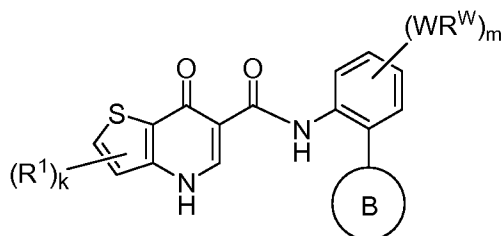
wherein each of  $WR^{W2}$  and  $WR^{W4}$  is independently selected from hydrogen, CN,  $CF_3$ ,  $OCF_3$ , halo, C1-C6 straight or branched alkyl, 3-12 membered cycloaliphatic, phenyl, C5-C10 heteroaryl or C3-C7 heterocyclic, wherein said heteroaryl or heterocyclic has up to 3 heteroatoms selected 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<sub>2</sub>R', -SCF<sub>3</sub>, halo, CN, -COOR', -COR', -O(CH<sub>2</sub>)<sub>2</sub>N(R')(R'), -O(CH<sub>2</sub>)N(R')(R'), -CON(R')(R'), -(CH<sub>2</sub>)<sub>2</sub>OR', -(CH<sub>2</sub>)OR', CH<sub>2</sub>CN, optionally substituted phenyl or phenoxy, -N(R')(R'), -NR'C(O)OR', -NR'C(O)R', -(CH<sub>2</sub>)<sub>2</sub>N(R')(R'), or -(CH<sub>2</sub>)N(R')(R'); and

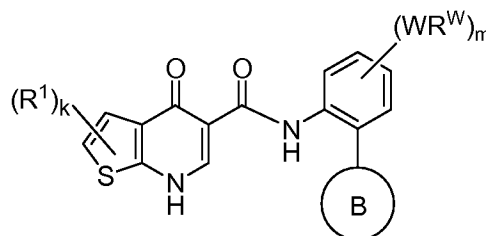
WR<sup>W5</sup> is selected from hydrogen, halo, -OH, NH<sub>2</sub>, CN, CHF<sub>2</sub>, NHR', N(R')<sub>2</sub>, -NHC(O)R', -NHC(O)OR', NHSO<sub>2</sub>R', -OR', CH<sub>2</sub>OH, CH<sub>2</sub>N(R')<sub>2</sub>, C(O)OR', C(O)N(R')<sub>2</sub>, SO<sub>2</sub>NHR', SO<sub>2</sub>N(R')<sub>2</sub>, OSO<sub>2</sub>N(R')<sub>2</sub>, OSO<sub>2</sub>CF<sub>3</sub>, or CH<sub>2</sub>NHC(O)OR'. Or, WR<sup>W4</sup> and WR<sup>W5</sup> 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<sup>W</sup> substituents.

[098] In one embodiment, the present invention provides compounds of formula **VA-1** or formula **VA-1'**, wherein k is 0.

[099] In another embodiment, the present invention provides compounds of formula **VA-2** or formula **VA-2'**:



**VA-2**



**VA-2'**

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<sup>Q</sup>;

Q is W;

R<sup>Q</sup> is R<sup>W</sup>;

m is 0-4;

n is 0-4; and

R<sup>1</sup>, k, W, and R<sup>W</sup> are as defined above.

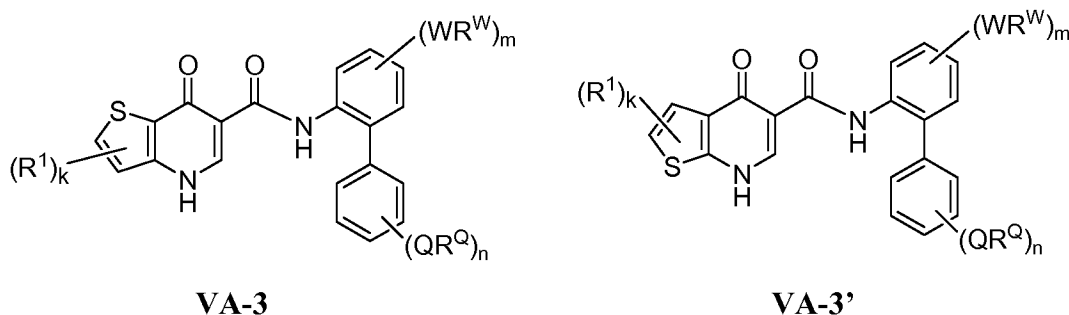
[0100] In one embodiment, m is 0-2. Or, m is 0. Or m is 1.

[0101] In one embodiment, n is 0-2. Or, n is 0. Or, n is 1.

[0102] 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<sup>Q</sup>. Exemplary heterocyclic rings include N-morpholinyl, N-piperidinyl, 4-benzoyl-piperazin-1-yl, pyrrolidin-1-yl, or 4-methyl-piperidin-1-yl.

[0103] 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.

[0104] In another embodiment, the present invention provides compounds of formula VA-3 or formula VA-3':



wherein:

Q is W;

$R^Q$  is  $R^W$ ;

m is 0-4;

n is 0-4; and

$R^1$ , k, W, and  $R^W$  are as defined above.

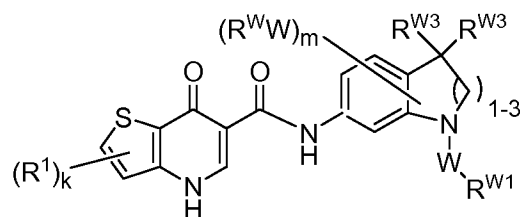
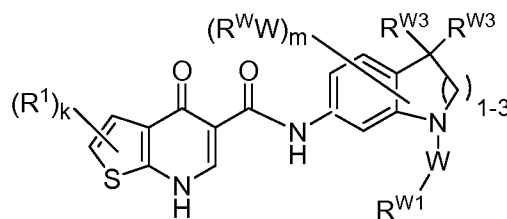
[0105] In one embodiment, n is 0-2.

[0106] In another embodiment, m is 0-2. In one embodiment, m is 0. In one embodiment, m is 1. Or, m is 2.

[0107] In one embodiment,  $QR^Q$  taken together is halo,  $CF_3$ ,  $OCF_3$ , CN, C1-C6 aliphatic, O-C1-C6 aliphatic, O-phenyl,  $NH(C1-C6 \text{ aliphatic})$ , or  $N(C1-C6 \text{ aliphatic})_2$ , 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.

[0108] 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  $S(O)_2Me$ .

[0109] In another embodiment, the present invention provides compounds of formula **VB-1** or formula **VB-1'**:

**VB-1****VB-1'**

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;

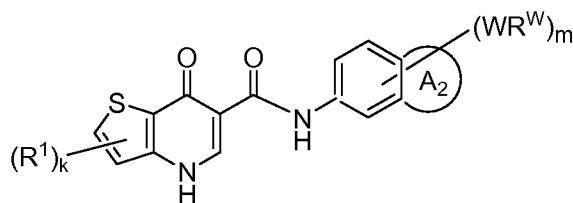
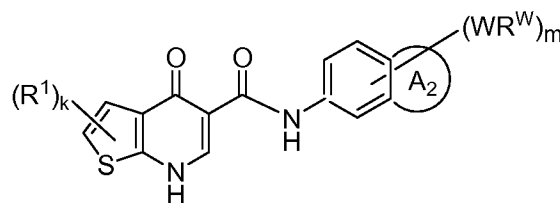
$m$  is 0-4; and

$k$ ,  $R^1$ ,  $W$ , and  $R^W$  are as defined above.

[0110] In one embodiment,  $WR^{W1}$  is hydrogen, C1-C6 aliphatic,  $C(O)C1-C6$  aliphatic, or  $C(O)OC1-C6$  aliphatic.

[0111] 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 substituents selected from  $WR^{W1}$ . Exemplary such rings include cyclopropyl, cyclopentyl, optionally substituted piperidyl, etc.

[0112] In another embodiment, the present invention provides compounds of formula **VB-2** or formula **VB-2'**:

**VB-2****VB-2';**

wherein:

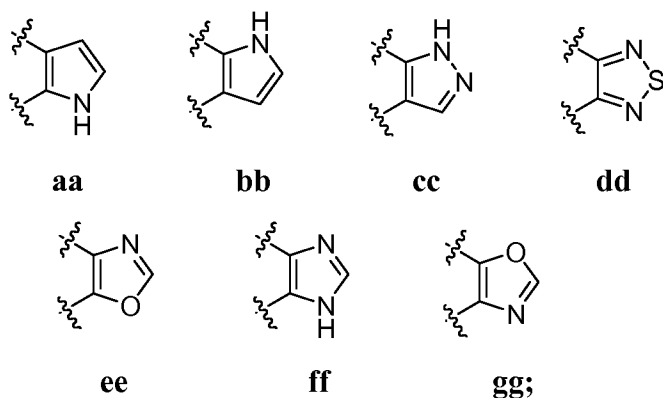
ring A<sub>2</sub> is a phenyl or a 5-6 membered heteroaryl ring, wherein ring A<sub>2</sub> and the phenyl ring fused thereto together have up to 4 substituents independently selected from W<sup>R</sup>;

m is 0-4; and

W, R<sup>W</sup>, k, and R<sup>1</sup> are as defined above.

[0113] In one embodiment, ring A<sub>2</sub> is an optionally substituted 5-membered ring selected from pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, or triazolyl.

[0114] In one embodiment, ring A<sub>2</sub> is an optionally substituted 5-membered ring selected from pyrrolyl, pyrazolyl, thiadiazolyl, imidazolyl, oxazolyl, or triazolyl. Exemplary such rings include:



wherein said ring is optionally substituted as set forth above.

[0115] In another embodiment, ring A<sub>2</sub> is an optionally substituted 6-membered ring. Exemplary such rings include pyridyl, pyrazinyl, or triazinyl. In another embodiment, said ring is an optionally pyridyl.

[0116] In one embodiment, ring A<sub>2</sub> is phenyl.

[0117] In another embodiment, ring A<sub>2</sub> is pyrrolyl, pyrazolyl, pyridyl, or thiadiazolyl.

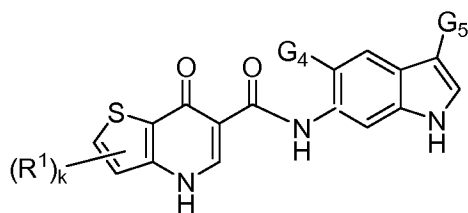
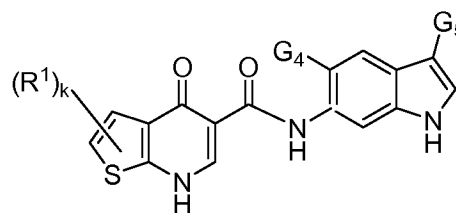
[0118] Exemplary W in formula **VB-2** or formula **VB-2'** includes a bond, C(O), C(O)O or C1-C6 alkylene.

[0119] Exemplary R<sup>W</sup> in formula **V-B-2** or formula **V-B-2'** 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<sub>3</sub>, wherein up to two methylene units of said C1-C6 aliphatic or C1-C6 alkyl is optionally replaced with -CO-, -CONR', -CO<sub>2</sub>-, -OCO-,



-NR'CO<sub>2</sub>-, -O-, -NR'CONR'-, -OCONR'-, -NR'CO-, -S-, -NR'-, -SO<sub>2</sub>NR'-, NR'SO<sub>2</sub>-, or -NR'SO<sub>2</sub>NR'-. In another embodiment, R' above is C1-C4 alkyl.

[0120] In one embodiment, the present invention provides compounds of formula **VB-3** or formula **VB-3'**:

**VB-3****VB-3'**

wherein:

G<sub>4</sub> is hydrogen, halo, CN, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, optionally substituted C1-C6 aliphatic, aryl-C1-C6 alkyl, or a phenyl, wherein G<sub>4</sub> is optionally substituted with up to 4 WR<sup>W</sup> substituents; wherein up to two methylene units of said C1-C6 aliphatic or C1-C6 alkyl is optionally replaced with -CO-, -CONR'-, -CO<sub>2</sub>-, -OCO-, -NR'CO<sub>2</sub>-, -O-, -NR'CONR'-, -OCONR'-, -NR'CO-, -S-, -NR'-, -SO<sub>2</sub>NR'-, NR'SO<sub>2</sub>-, or -NR'SO<sub>2</sub>NR'-; ;

G<sub>5</sub> is hydrogen, an optionally substituted C1-C6 aliphatic, CF<sub>3</sub>, or CN; wherein said indole ring system is further optionally substituted with up to 3 substituents independently selected from WR<sup>W</sup>.

[0121] In one embodiment, G<sub>4</sub> is hydrogen. Or, G<sub>5</sub> is hydrogen.

[0122] In another embodiment, G<sub>4</sub> is hydrogen, and G<sub>5</sub> is C1-C6 aliphatic, CF<sub>3</sub>, or CN, wherein said aliphatic is optionally substituted with C1-C6 alkyl, halo, cyano, or CF<sub>3</sub>, and wherein up to two methylene units of said C1-C6 aliphatic or C1-C6 alkyl is optionally replaced with -CO-, -CONR'-, -CO<sub>2</sub>-, -OCO-, -NR'CO<sub>2</sub>-, -O-, -NR'CONR'-, -OCONR'-, -NR'CO-, -S-, -NR'-, -SO<sub>2</sub>NR'-, NR'SO<sub>2</sub>-, or -NR'SO<sub>2</sub>NR'-. In another embodiment, R' above is C1-C4 alkyl.

[0123] In another embodiment, G<sub>4</sub> is hydrogen, and G<sub>5</sub> is cyano, CF<sub>3</sub>, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl, cyanomethyl, methoxyethyl, CH<sub>2</sub>C(O)OMe, (CH<sub>2</sub>)<sub>2</sub>-NHC(O)O-*tert*-butyl, or cyclopentyl.

[0124] In another embodiment, G<sub>5</sub> is hydrogen, and G<sub>4</sub> is halo, C1-C6 aliphatic or phenyl, wherein said aliphatic or phenyl is optionally substituted with C1-C6 alkyl, halo, cyano, or CF<sub>3</sub>, wherein up to two methylene units of said C1-C6 aliphatic or C1-C6 alkyl is optionally replaced with -CO-, -CONR'-, -CO<sub>2</sub>-, -OCO-, -NR'CO<sub>2</sub>-, -O-, -NR'CONR'-,

-OCONR'-, -NR'CO-, -S-, -NR'-, -SO<sub>2</sub>NR'-, NR'SO<sub>2</sub>-, or -NR'SO<sub>2</sub>NR'-. In another embodiment, R' above is C1-C4 alkyl.

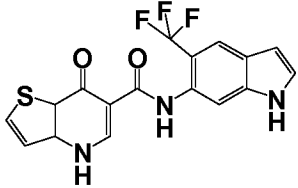
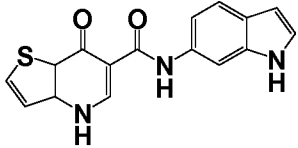
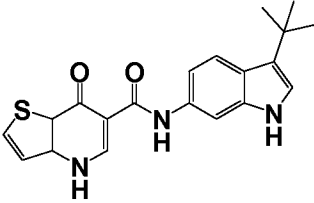
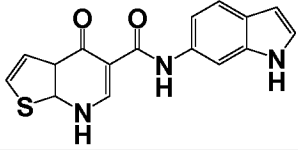
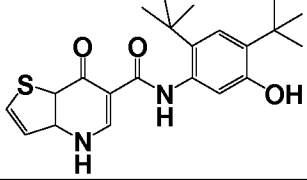
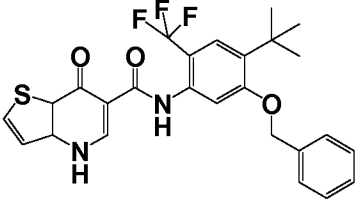
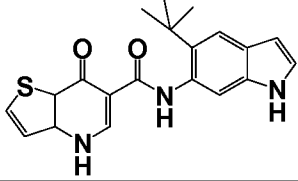
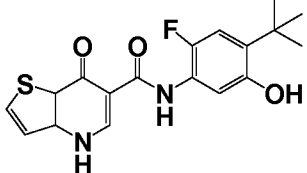
[0125] In another embodiment, G<sub>5</sub> is hydrogen, and G<sub>4</sub> is halo, CF<sub>3</sub>, ethoxycarbonyl, t-butyl, 2-methoxyphenyl, 2-ethoxyphenyl, (4-C(O)NH(CH<sub>2</sub>)<sub>2</sub>-NMe<sub>2</sub>)-phenyl, 2-methoxy-4-chloro-phenyl, pyridine-3-yl, 4-isopropylphenyl, 2,6-dimethoxyphenyl, sec-butylaminocarbonyl, ethyl, t-butyl, or piperidin-1-ylcarbonyl.

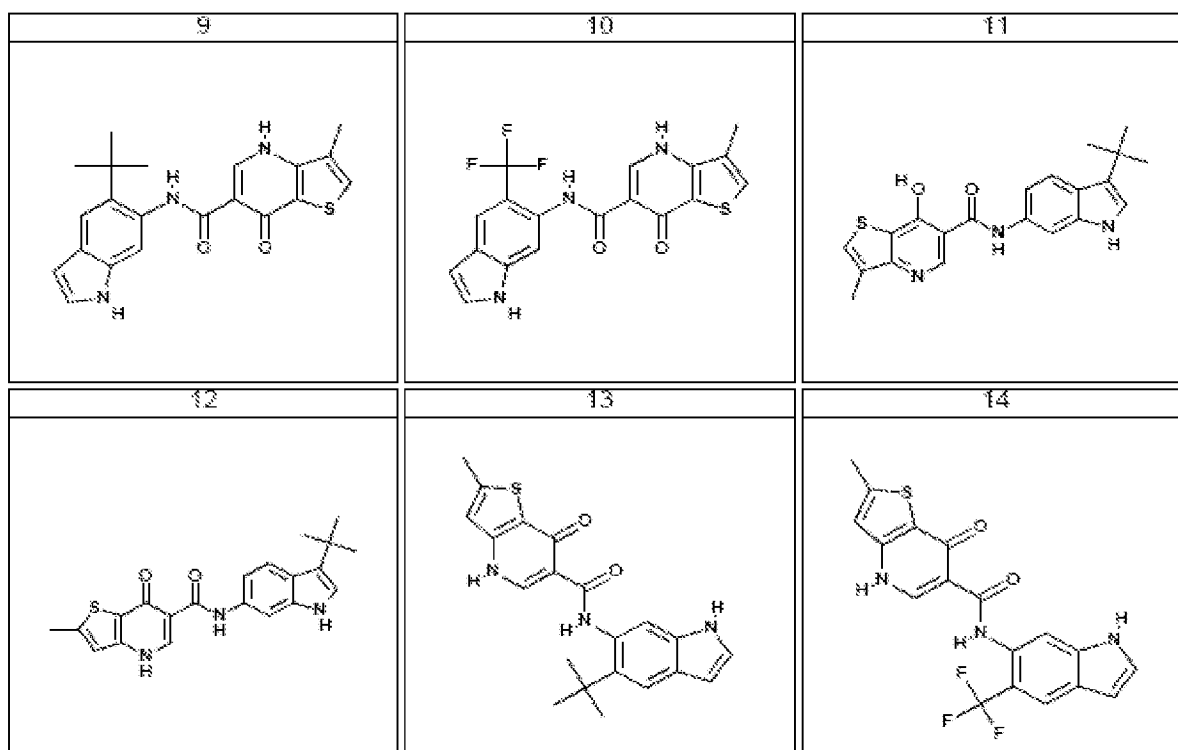
[0126] In another embodiment, G<sub>4</sub> and G<sub>5</sub> are both hydrogen, and the nitrogen ring atom of said indole ring is substituted with C1-C6 aliphatic, C(O)(C1-C6 aliphatic), or benzyl, wherein said aliphatic or benzyl is optionally substituted with C1-C6 alkyl, halo, cyano, or CF<sub>3</sub>, wherein up to two methylene units of said C1-C6 aliphatic or C1-C6 alkyl is optionally replaced with -CO-, -CONR'-, -CO<sub>2</sub>-, -OCO-, -NR'CO<sub>2</sub>-, -O-, -NR'CONR'-, -OCONR'-, -NR'CO-, -S-, -NR'-, -SO<sub>2</sub>NR'-, NR'SO<sub>2</sub>-, or -NR'SO<sub>2</sub>NR'-. In another embodiment, R' above is C1-C4 alkyl.

[0127] In another embodiment, G<sub>4</sub> and G<sub>5</sub> are both hydrogen, and the nitrogen ring atom of said indole ring is substituted with acyl, benzyl, C(O)CH<sub>2</sub>N(Me)C(O)CH<sub>2</sub>NHMe, or ethoxycarbonyl.

[0128] Representative compounds of the present invention are set forth below in Table 1 below.

[0129] Table 1

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#### [0130] 4. General Synthetic Schemes

[0131] Compounds of the present invention are readily prepared by methods known in the art. Illustrated in the Examples hereinbelow are exemplary methods for the preparation of compounds of the present invention.

#### [0132] 5. Uses, Formulation and Administration

##### [0133] *Pharmaceutically acceptable compositions*

[0134] 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, myeloperoxidase 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,

Perlizaues-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 asuch as Huntington, spinocerebellar ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidolulsian, 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.

[0135] 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.

[0136] 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.

[0137] 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.

[0138] 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 dispersible 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.

[0139] 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.

**[0140]** *Uses of Compounds and Pharmaceutically Acceptable Compositions*

**[0141]** In yet another aspect, the present invention provides a method of treating a condition, disease, or disorder implicated by ABC transporter activity, e.g., CFTR. In certain embodiments, the present invention provides a method of treating a condition, disease, or disorder implicated by a deficiency of the ABC transporter activity, the method comprising administering a composition comprising a compound of formula (I) to a subject, preferably a mammal, in need thereof.

**[0142]** In certain embodiments, the present invention provides a method of treating 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, myeloperoxidase 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 asuch as Huntington, spinocerebular ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidolulsian, 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, comprising the step of administering to said mammal an effective amount of a composition comprising a compound of the present invention.

[0143] 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.

[0144] 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 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, myeloperoxidase 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 asuch as Huntington, spinocerebellar ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidoluyian, 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.

[0145] 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 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, myeloperoxidase 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 asuch as Huntington, spinocerebellar ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidoluyian, 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.

[0146] In one embodiment, the compounds and compositions of the present invention are useful for treating or lessening the severity of cystic fibrosis in a patient.

[0147] 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  $\text{Cl}^-$  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,  $\Delta\text{F508}$ .

[0148] 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.

[0149] 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 Transmembrane 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.

[0150] 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 sufficiency or patients diagnosed with idiopathic pancreatitis and congenital bilateral absence of the vas deferens, or mild lung disease.

[0151] 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.

[0152] 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), buccally, 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.

[0153] 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.

[0154] 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.

[0155] 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.

[0156] 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.

[0157] 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.

[0158] 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.

[0159] 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 polyethylene glycols and the like.

[0160] 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.

[0161] 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.

[0162] 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.

[0163] 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.

[0164] 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".

[0165] In one embodiment, the additional agent is selected from a mucolytic agent, bronchodilator, 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.

[0166] 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.

[0167] 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, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

[0168] 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.

[0169] 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.

[0170] 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.

[0171] 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.



[0172] 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.

[0173] 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).

[0174] These voltage sensitive assays are based on the change in fluorescence resonant energy transfer (FRET) between the membrane-soluble, voltage-sensitive dye, DiSBAC<sub>2</sub>(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<sub>2</sub>(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<sup>TM</sup> II, which is an integrated liquid handler and fluorescent detector designed to conduct cell-based screens in 96- or 384-well microtiter plates.

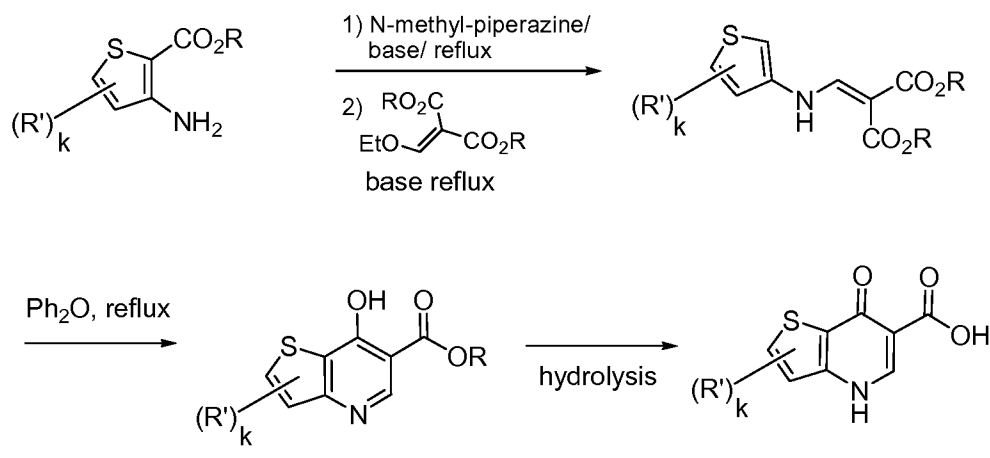
[0175] In another aspect the present invention provides a kit for use in measuring the activity of a ABC transporter or a fragment thereof in a biological sample *in vitro* or *in vivo* comprising (i) a composition comprising a compound of formula (I) or any of the above embodiments; and (ii) instructions 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.

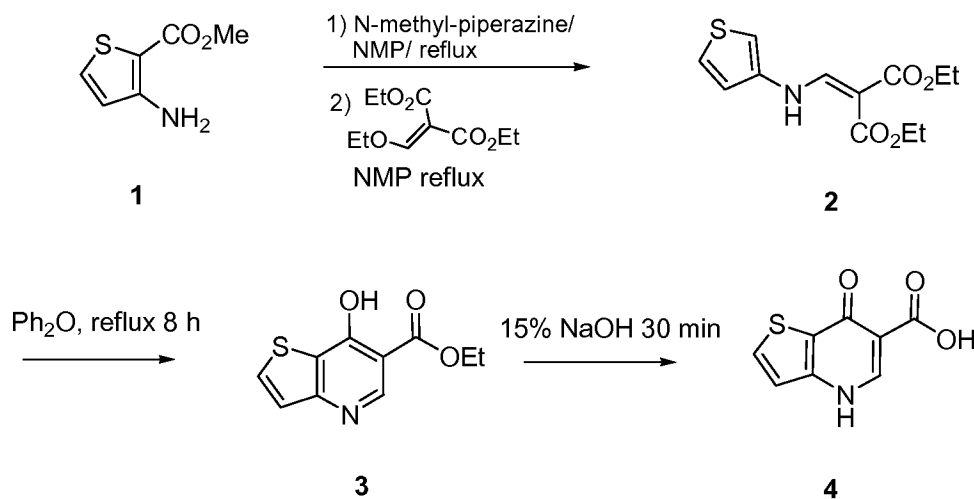
[0176] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

### [0177] EXAMPLES

#### [0178] General Scheme



#### [0180] Example



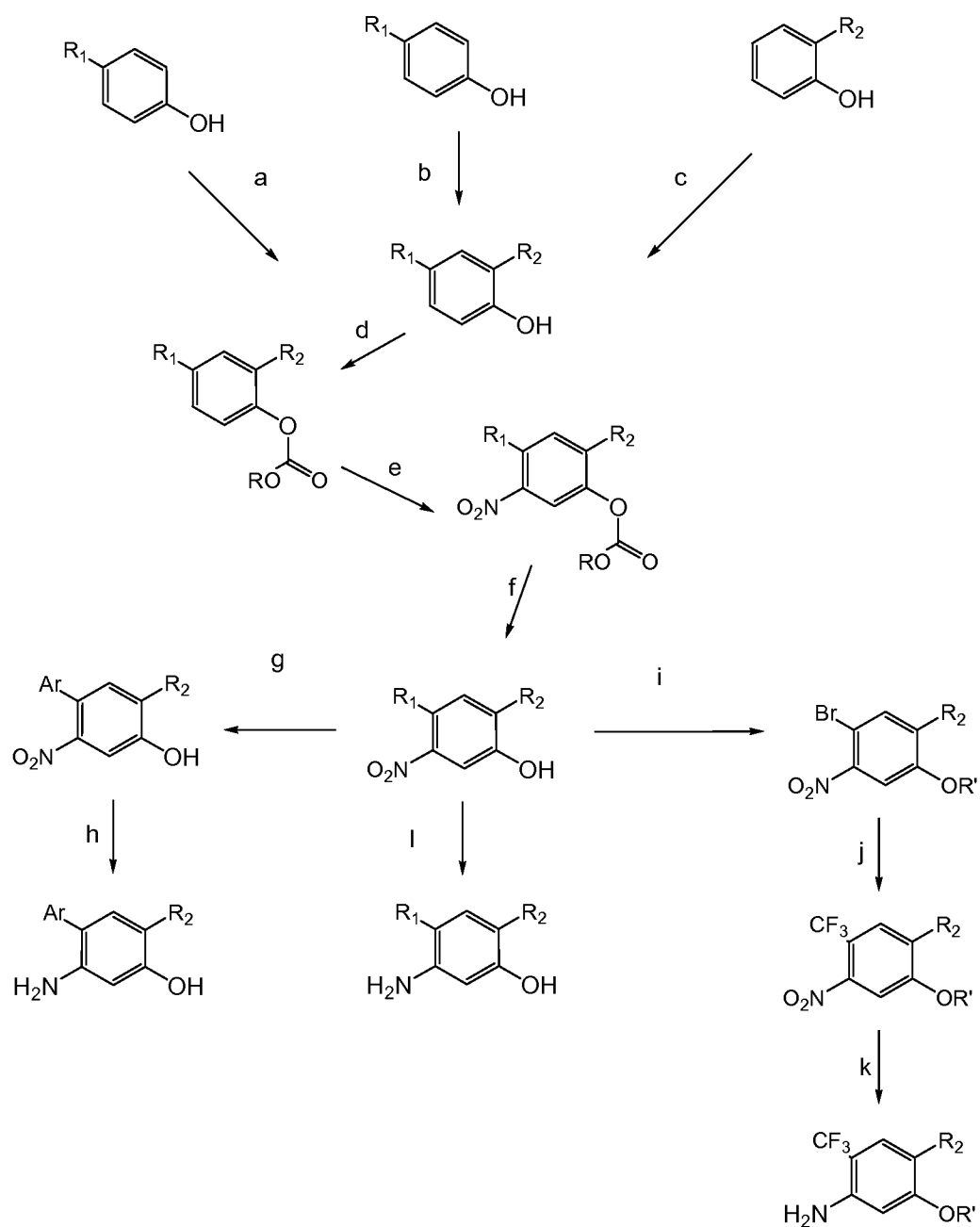
[0182] **Diethyl 2-((thiophen-3-ylamino)methylene)malonate 2:** A mixture of methyl 3-aminothiophene-2-carboxylate **1** (5.0 g, 32 mmol, 1.0 eq), *N*-methyl piperazine (6.5 g, 64 mmol, 2.0 eq) and NMP (30 mL) was heated to reflux for 16 hours. After the decarboxylation was complete, the reaction mixture was allowed to cool to room temperature and diethyl 2-(ethoxymethylene)-malonate (7.0 g, 32 mmol, 2.0 eq) was added. The reaction mixture was

heated to reflux for 4 h. The product was purified using SiO<sub>2</sub> column chromatography (Hex/EtOAc; 100:0 to 80:20%) to obtain a light yellow powder, 5.0 g (31%). LC/MS (10-99% CH<sub>3</sub>CN/0.05% TFA gradient over 5 min): *m/z* 270.2, retention time 1.52 minutes. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ: 10.80 (d, 1.0 H, *J* = 13.87 Hz, NH), 8.30 (d, 1.0 H, *J* = 13.94 Hz), 7.60 (dd, 1.0 H, *J* = 3.0 Hz, *J'* = 2.0 Hz), 7.40 (dd, 1.0 H, *J* = 1.5 Hz, *J'* = 3.13 Hz), 7.28 (dd, 1.0 H, *J* = 1.5 Hz, *J'* = 5.2 Hz), 4.20 (q, 2H, *J* = 7.0 Hz), 4.10 (q, 2H, *J* = 7.0 Hz), 1.30 (m, 6H).

**[0183] Ethyl 7-hydroxythieno[3,2-b]pyridine-6-carboxylate 3:** The diethyl 2-((thiophen-3-ylamino)methylene)malonate **2** (1.0 g, 3.7 mmol, 1 eq) was heated to 240 °C in Ph<sub>2</sub>O (10 mL) for 6h. After the starting material was consumed, the reaction mixture was allowed to cool to room temperature and solid was filtered. The solid was washed with water and dichloromethane to obtain the desired compound as a light brown powder (0.42 g 50% yield). LC/MS (10-99% CH<sub>3</sub>CN/0.05% TFA gradient over 5 min): *m/z* 224.0, retention time 0.40 minutes. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ: 12.80 (s, 1.0 H), 8.50 (s, 1.0 H), 8.05 (d, 1.0 H, *J* = 5.4 Hz), 7.30 (d, 1.0 H, *J* = 5.4 Hz), 4.20 (q, 2H, *J* = 7.0 Hz), 4.10 (q, 2H, *J* = 7.0 Hz), 1.30 (t, 3H, *J* = 7.0 Hz).

**[0184] 7-oxo-4,7-dihydrothieno[3,2-b]pyridine-6-carboxylic acid 4:** The ethyl 7-hydroxythieno[3,2-b]pyridine-6-carboxylate **3** (1.0 g, 4.5 mmol) was heated to reflux in 15% NaOH for 30 min. After the reaction was completed it was allowed to cool to room temperature and the solid was removed by filtration, washed with water and ether to give the desired compound as an off-white powder (0.6g, 70% yield). LC/MS (10-99% CH<sub>3</sub>CN/0.05% TFA gradient over 5 min): *m/z* 196.0, *m/z* 210.0, retention time 0.94 minutes. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ: 15.50 (bs, 1.0 H), 14.0 (s, 1.0 H), 8.80 (s, 1.0 H), 8.30 (d, 1.0 H, *J* = 5.4 Hz), 7.48 (d, 1.0 H, *J* = 5.4 Hz).

## [0185] Synthesis of Amine Precursor:

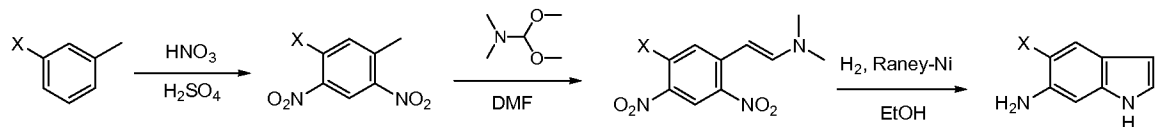


## [0186]

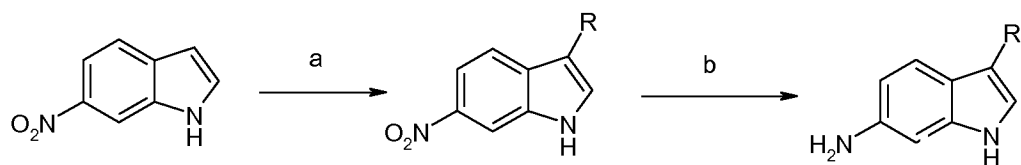
[0187] a) SO<sub>2</sub>Cl<sub>2</sub>, R<sub>2</sub>= Cl; b) R<sub>2</sub>OH, R<sub>2</sub>=alkyl; c) NBS, R<sub>1</sub>=Br; d) ClCO<sub>2</sub>R, TEA; e) HNO<sub>3</sub>, H<sub>2</sub>SO<sub>4</sub>; f) base; g) ArB(OH)<sub>2</sub>, R<sub>1</sub>=Br; h) [H]; i) R'X, R<sub>1</sub>= Br; j) ClCF<sub>2</sub>CO<sub>2</sub>Me or FSO<sub>2</sub>CF<sub>2</sub>CO<sub>2</sub>Me/CuI; k) [H]; l) [H].

[0188] General Scheme:

[0189]

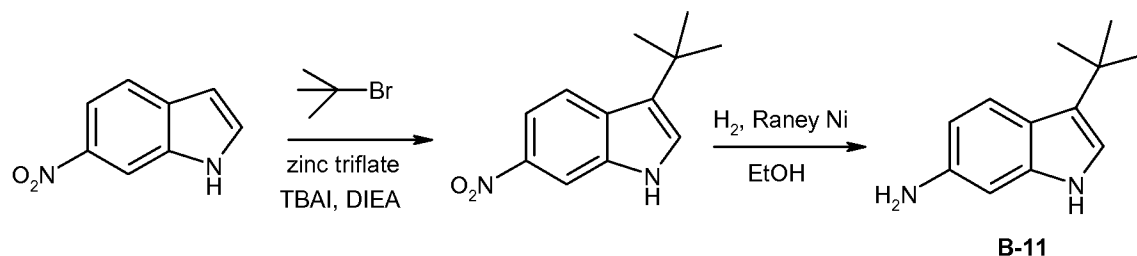


[0190] General Scheme:



a) RX (X=Br,I), zinc triflate, TBAI, DIEA, toluene; b) H<sub>2</sub>, Raney Ni, EtOH or SnCl<sub>2</sub>·2H<sub>2</sub>O, EtOH.

[0191] Specific example:

[0192] 3-*tert*-Butyl-6-nitro-1H-indole

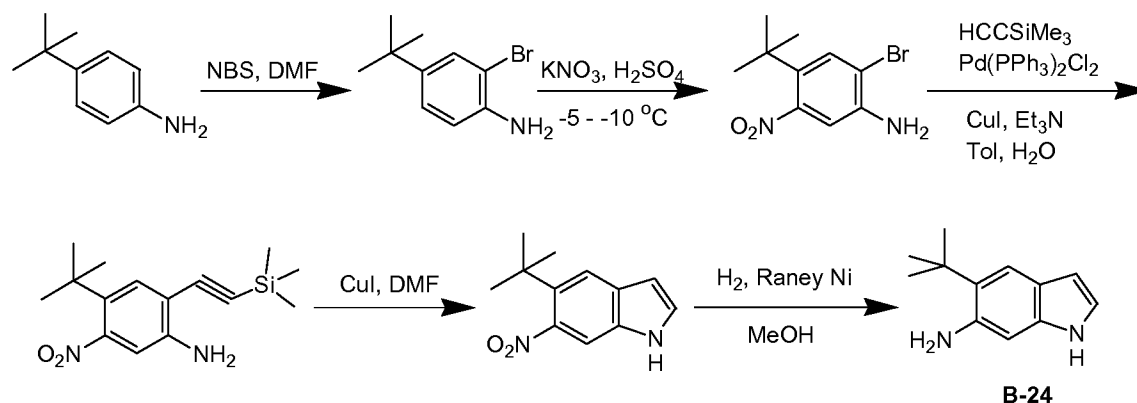
[0193] To a mixture of 6-nitroindole (1 g, 6.2 mmol), zinc triflate (2.06 g, 5.7 mmol) and TBAI (1.7 g, 5.16 mmol) in anhydrous toluene (11 mL) was added DIEA (1.47 g, 11.4 mmol) at room temperature under nitrogen. The reaction mixture was stirred for 10 min at 120 °C, followed by addition of *t*-butyl 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 %). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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).

**[0194] B-11; 3-*tert*-Butyl-1H-indol-6-ylamine**

**[0195]** 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<sub>2</sub> (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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  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).

**[0196] Example**



**[0197] 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<sub>2</sub>SO<sub>4</sub> and concentrated. The crude product was directly used in the next step without further purification.

**[0198] 2-Bromo-4-*tert*-butyl-5-nitro-phenylamine**

2-Bromo-4-*tert*-butyl-phenylamine (162 g, 0.71 mol) was added dropwise to H<sub>2</sub>SO<sub>4</sub> (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<sub>3</sub> (82.5 g, 0.82 mol) in H<sub>2</sub>SO<sub>4</sub> (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<sub>2</sub>CO<sub>3</sub> and brine, dried over Na<sub>2</sub>SO<sub>4</sub> 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 %).

**[0199] 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<sub>3</sub>N (27.9 mL, 200 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (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<sub>4</sub>OH solution and water, dried over Na<sub>2</sub>SO<sub>4</sub> 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 %).

**[0200] 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<sub>2</sub>SO<sub>4</sub> 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 %).

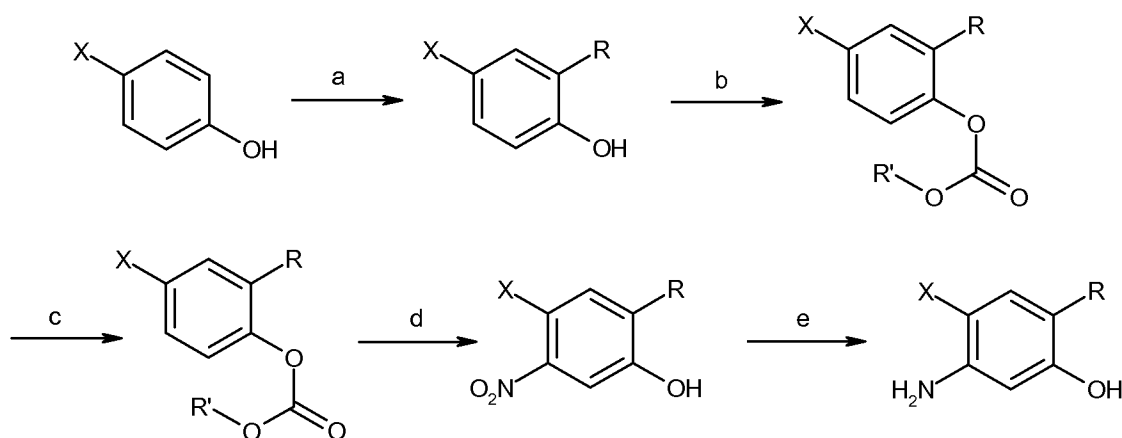
**[0201] B-24; 5-*tert*-Butyl-1H-indol-6-ylamine**

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<sub>2</sub>SO<sub>4</sub> 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 %).  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  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).

**[0202] Example 4:**

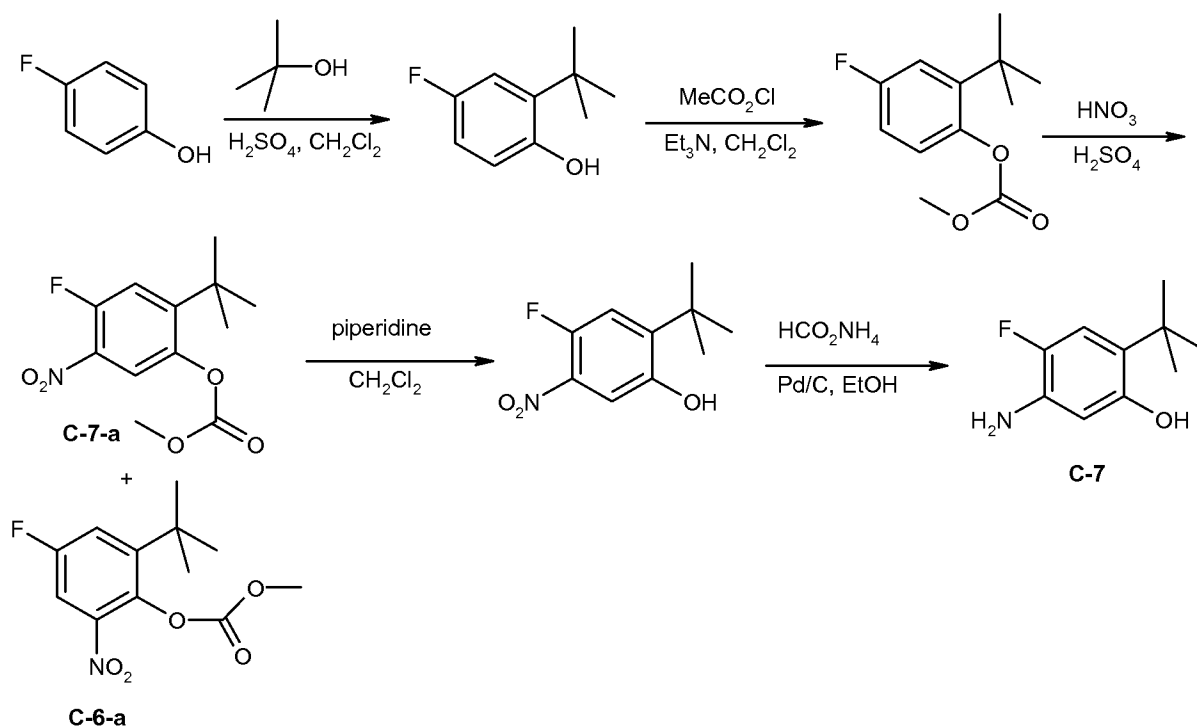
**[00286]** General scheme:



X = F, Cl; a) ROH,  $\text{H}_2\text{SO}_4$  or  $\text{MeSO}_3\text{H}$ ,  $\text{CH}_2\text{Cl}_2$ ; b)  $\text{R}'\text{CO}_2\text{Cl}$ ,  $\text{Et}_3\text{N}$ , 1,4-dioxane or  $\text{CHCl}_3$ ; c)  $\text{HNO}_3$ ,  $\text{H}_2\text{SO}_4$  or  $\text{KNO}_3$ ,  $\text{H}_2\text{SO}_4$  or  $\text{HNO}_3$ , AcOH; d) piperidine,  $\text{CH}_2\text{Cl}_2$ ; e)  $\text{HCO}_2\text{NH}_4$ , Pd-C, EtOH or  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ , EtOH or  $\text{H}_2$ , Pd-C, MeOH.

**[0203] Specific example**





**[0204] 2-*tert*-Butyl-4-fluorophenol**

4-Fluorophenol (5g, 45 mmol) and *tert*-butanol (5.9 mL, 63 mmol) were dissolved in  $\text{CH}_2\text{Cl}_2$  (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  $\text{NaHCO}_3$ , dried over  $\text{MgSO}_4$  and concentrated. The residue was purified by column chromatography (5-15 % EtOAc - Hexane) to give 2-*tert*-butyl-4-fluorophenol (3.12 g, 42 %).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  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).

**[0205] 2-*tert*-Butyl-4-fluorophenyl methyl carbonate**

To a solution of 2-*tert*-butyl-4-fluorophenol (2.63g, 15.7 mmol) and  $\text{NEt}_3$  (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  $\text{MgSO}_4$ . After removal of solvent, the residue was purified by column chromatography to give 2-*tert*-butyl-4-fluorophenyl methyl carbonate (2.08g, 59 %).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  7.24 (dd,  $J$  = 8.8, 5.4 Hz, 1H), 7.17-7.10 (m, 2H), 3.86 (s, 3H), 1.29 (s, 9H).

**[0206] 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 (1.81 g, 8 mmol) in H<sub>2</sub>SO<sub>4</sub> (98 %, 1 mL) was added slowly a cooled mixture of H<sub>2</sub>SO<sub>4</sub> (1 mL) and HNO<sub>3</sub> (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<sub>4</sub> 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**): <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) 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**): <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) 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).

**[0207] 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<sub>2</sub>Cl<sub>2</sub> (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<sub>4</sub>) and concentrated to give 2-*tert*-butyl-4-fluoro-5-nitrophenol (530 mg, 62 %). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) 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).

**[0208] 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 %). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) 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<sub>3</sub>CN, 5 min run; ESI-MS 184.0 m/z (MH<sup>+</sup>).

[0209] Analytical data for the compounds of Table 1 is shown below:

Cmpd #	LC/MS M+1	LC/RT min	NMR
1	378.5	1.43	<sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ) δ:13.31 (d, <i>J</i> = 1.1 Hz, 1H), 12.44 (s, 1H), 10.74 (s, 1H), 8.81 (s, 1H), 8.19 (d, <i>J</i> = 5.4 Hz, 1H), 8.10 (d, <i>J</i> = 1.8 Hz, 1H), 7.66 (d, <i>J</i> = 8.5 Hz, 1H), 7.42 (d, <i>J</i> = 5.4 Hz, 1H), 7.66 (d, <i>J</i> = 8.5 Hz, 1H), 7.42 (d, <i>J</i> = 5.4 Hz, 1H), 7.02-7.00 (m, 1H), 6.97 (d, <i>J</i> = 2.3 Hz, 1H), 1.40 (s, 9H)
2	310.3	2.78	<sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ) δ:13.28 (d, <i>J</i> = 6.2 Hz, 1H), 11.79 (s, 1H), 9.20 (s, 1H), 8.80-8.78 (m, 1H), 8.19 (d, <i>J</i> = 5.4 Hz, 1H), 7.41 (d, <i>J</i> = 5.4 Hz, 1H), 7.16 (s, 1H), 7.08 (s, 1H), 1.36 (s, 18H)
3	366.1	1.71	
4	310.3	2.75	<sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ) δ:13.29 (s, 1H), 11.86 (s, 1H), 10.93 (s, 1H), 8.82 (d, <i>J</i> = 4.8 Hz, 1H), 8.19 (d, <i>J</i> = 5.4 Hz, 1H), 7.54 (d, <i>J</i> = 9.9 Hz, 2H), 7.42 (d, <i>J</i> = 5.4 Hz, 1H), 7.31 (t, <i>J</i> = 2.7 Hz, 1H), 6.39 (s, 1H), 1.44 (s, 9H)
5	399.5	1.89	
6	361.3	1.68	<sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ) δ: 13.18 (d, <i>J</i> = 6.4 Hz, 1H), 12.44 (s, 1H), 10.74 (s, 1H), 8.67 (d, <i>J</i> = 6.3 Hz, 1H), 8.09 (d, <i>J</i> = 1.7 Hz, 1H), 7.85 (d, <i>J</i> = 1.1 Hz, 1H), 7.66 (d, <i>J</i> = 8.5 Hz, 1H), 7.03 - 6.97 (m, 2H), 2.41 (s, 3H), 1.40 (s, 9H)
7	366.1	1.51	<sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ) δ: 13.17 (s, 1H), 12.48 (s, 1H), 11.51 (s, 1H), 8.68 (d, <i>J</i> = 4.9 Hz, 1H), 8.31 (s, 1H), 7.97 (s, 1H), 7.85 (d, <i>J</i> = 1.0 Hz, 1H), 7.51 (t, <i>J</i> = 2.7 Hz, 1H), 6.59 (s, 1H), 2.41 (s, 3H)
8	361.3	1.68	<sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ) δ: 13.18 (d, <i>J</i> = 6.5 Hz, 1H), 12.48 (s, 1H), 10.72 (s, 1H), 8.72 (d, <i>J</i> = 6.3 Hz, 1H), 8.09 (d, <i>J</i> = 1.7 Hz, 1H), 7.65 (d, <i>J</i> = 8.6 Hz, 1H), 7.15 (d, <i>J</i> = 1.1 Hz, 1H), 7.01 - 6.97 (m, 2H), 2.63 (s, 3H), 1.39 (s, 9H)
9	380.2	1.71	
10	392.2	1.64	<sup>1</sup> H NMR (400 MHz, DMSO) 13.17 (s, 1H), 12.48 (s, 1H), 11.51 (s, 1H), 8.68 (d, <i>J</i> = 4.9 Hz, 1H), 8.31 (s, 1H), 7.97 (s, 1H), 7.85 (d, <i>J</i> = 1.0 Hz, 1H), 7.51 (t, <i>J</i> = 2.7 Hz, 1H), 6.59 (s, 1H), 2.41 (s, 3H)
11	380.2	1.74	<sup>1</sup> H NMR (400 MHz, DMSO) 13.18 (d, <i>J</i> = 6.4 Hz, 1H), 12.44 (s, 1H), 10.74 (s, 1H), 8.67 (d, <i>J</i> = 6.3 Hz, 1H),

			8.09 (d, J = 1.7 Hz, 1H), 7.85 (d, J = 1.1 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.03 - 6.97 (m, 2H), 2.41 (s, 3H), 1.40 (s, 9H)
12	380.2	1.71	H NMR (400 MHz, DMSO) 13.18 (d, J = 6.5 Hz, 1H), 12.48 (s, 1H), 10.72 (s, 1H), 8.72 (d, J = 6.3 Hz, 1H), 8.09 (d, J = 1.7 Hz, 1H), 7.65 (d, J = 8.6 Hz, 1H), 7.15 (d, J = 1.1 Hz, 1H), 7.01 - 6.97 (m, 2H), 2.63 (s, 3H), 1.39 (s, 9H)
13	380.2	1.51	
14	392	1.42	

**[0210] Assays for Detecting and Measuring  $\Delta$ F508-CFTR Potentiation Properties of Compounds**

**[0211]** Membrane potential optical methods for assaying  $\Delta$ F508-CFTR modulation properties of compounds

**[0212]** 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).

**[0213]** These voltage sensitive assays are based on the change in fluorescence resonant energy transfer (FRET) between the membrane-soluble, voltage-sensitive dye, DiSBAC<sub>2</sub>(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<sub>2</sub>(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<sup>TM</sup> II, which is an integrated liquid handler and fluorescent detector designed to conduct cell-based screens in 96- or 384-well microtiter plates.

**[0214] Identification of Potentiator Compounds**

**[0215]** Typical protocol utilized a basolateral to apical membrane Cl<sup>-</sup> concentration gradient. To set up this gradient, normal ringers was used on the basolateral membrane and

was permeabilized with nystatin (360  $\mu\text{g/ml}$ ), whereas apical NaCl was replaced by equimolar sodium gluconate (titrated to pH 7.4 with NaOH) to give a large  $\text{Cl}^-$  concentration gradient across the epithelium. All experiments were performed 30 min after nystatin permeabilization. Forskolin (10  $\mu\text{M}$ ) and all test compounds were added to both sides of the cell culture inserts. The efficacy of the putative  $\Delta\text{F508-CFTR}$  potentiators was compared to that of the known potentiator, genistein.

#### [0216] Solutions

Basolateral solution (in mM): NaCl (135),  $\text{CaCl}_2$  (1.2),  $\text{MgCl}_2$  (1.2),  $\text{K}_2\text{HPO}_4$  (2.4),  $\text{KH}_2\text{PO}_4$  (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).

#### [0217] Cell Culture

[0218] Fisher rat epithelial (FRT) cells expressing  $\Delta\text{F508-CFTR}$  ( $\text{FRT}\Delta^{\text{F508-CFTR}}$ ) were used for Ussing chamber experiments for the putative  $\Delta\text{F508-CFTR}$  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%  $\text{CO}_2$  in Coon's modified Ham's F-12 medium supplemented with 5% fetal calf serum, 100 U/ml penicillin, and 100  $\mu\text{g/ml}$  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  $\Delta\text{F508-CFTR}$ . To determine the activity of correction compounds, the cells were incubated at 27 °C or 37 °C with and without the compounds for 24 hours.

#### [0219] 2. Whole-cell recordings

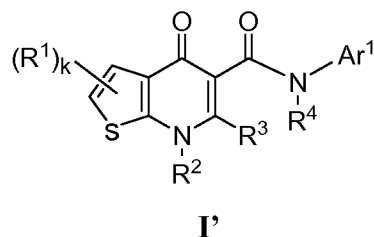
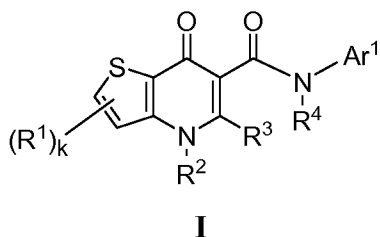
[0220] The macroscopic  $\Delta\text{F508-CFTR}$  current ( $I_{\Delta\text{F508}}$ ) in temperature- and test compound-corrected NIH3T3 cells stably expressing  $\Delta\text{F508-CFTR}$  were monitored using the perforated-patch, whole-cell recording. Briefly, voltage-clamp recordings of  $I_{\Delta\text{F508}}$  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  $\text{M}\Omega$  when filled with the

intracellular solution. Under these recording conditions, the calculated reversal potential for  $\text{Cl}^-$  ( $E_{\text{Cl}}$ ) at room temperature was -28 mV. All recordings had a seal resistance  $> 20 \text{ G}\Omega$  and a series resistance  $< 15 \text{ M}\Omega$ . 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  $< 250 \text{ }\mu\text{l}$  of saline and was continuously perfused at a rate of 2 ml/min using a gravity-driven perfusion system.

[0221] Compounds exemplified herein exhibit activity in the assays described hereinabove.

What is claimed is:

1. A compound of formula **I** or formula **I'**:



or a pharmaceutically acceptable salt thereof, wherein:

Ar<sup>1</sup> 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<sup>1</sup> has m substituents, each independently selected from -WR<sup>W</sup>;

W is a bond or is an optionally substituted C<sub>1</sub>-C<sub>6</sub> alkylidene chain wherein up to two methylene units of W are optionally and independently replaced by O, -CO-, -CS-, -COCO-, -CONR', -CONR'NR', -CO<sub>2</sub>-, -OCO-, -NR'CO<sub>2</sub>-, -O-, -NR'CONR', -C(O)NR', -OCONR', -NR'NR', -NR'NR'CO-, -NR'CO-, -S-, -SO-, -SO<sub>2</sub>-, -NR'-, -SO<sub>2</sub>NR', NR'SO<sub>2</sub>-, or -NR'SO<sub>2</sub>NR'-;

R<sup>W</sup> is independently R', halo, cyano, CF<sub>3</sub>, CHF<sub>2</sub>, OCHF<sub>2</sub>, Me, Et, CH(Me)<sub>2</sub>, CHMeEt, n-propyl, t-butyl, OH, OMe, OEt, OPh, O-fluorophenyl, O-difluorophenyl, O-methoxyphenyl, O-tolyl, O-benzyl, SMe, SCF<sub>3</sub>, SCHF<sub>2</sub>, SEt, CH<sub>2</sub>CN, NH<sub>2</sub>, NHMe, N(Me)<sub>2</sub>, NH<sub>2</sub>Et, N(Et)<sub>2</sub>, C(O)CH<sub>3</sub>, C(O)Ph, C(O)NH<sub>2</sub>, SPh, SO<sub>2</sub>-(amino-pyridyl), SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>Ph, SO<sub>2</sub>NHPh, SO<sub>2</sub>-N-morpholino, SO<sub>2</sub>-N-pyrrolidyl, N-pyrrolyl, N-morpholino, 1-piperidyl, phenyl, benzyl, (cyclohexyl-methylamino)methyl, 4-Methyl-2,4-dihydro-pyrazol-3-one-2-yl, benzimidazol-2-yl, 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<sub>2</sub>Me;

m is 0-5;

k is 0-2;

each of R<sup>1</sup> is independently -X-R<sup>X</sup>;

X is a bond or is an optionally substituted C<sub>1</sub>-C<sub>6</sub> alkylidene chain wherein up to two methylene units of X are optionally and independently replaced by -CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, -CO<sub>2</sub>-, -OCO-, -NR'CO<sub>2</sub>-, -O-, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -S-, -SO-, -SO<sub>2</sub>-, -NR'-, -SO<sub>2</sub>NR'-, NR'SO<sub>2</sub>-, or -NR'SO<sub>2</sub>NR'-;

R<sup>X</sup> is independently R', halo, NO<sub>2</sub>, CN, CF<sub>3</sub>, or OCF<sub>3</sub>;

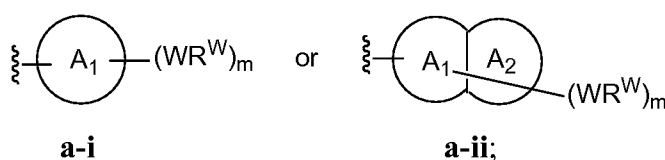
R<sup>2</sup> is hydrogen;

R<sup>3</sup> is hydrogen;

R<sup>4</sup> is hydrogen or a C<sub>1-6</sub> aliphatic group optionally substituted with -X-R<sup>X</sup>;

R' is independently selected from hydrogen or an optionally substituted group selected from a C<sub>1</sub>-C<sub>8</sub> 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.

2. The compound according to claim 1, wherein Ar<sup>1</sup> is selected from:



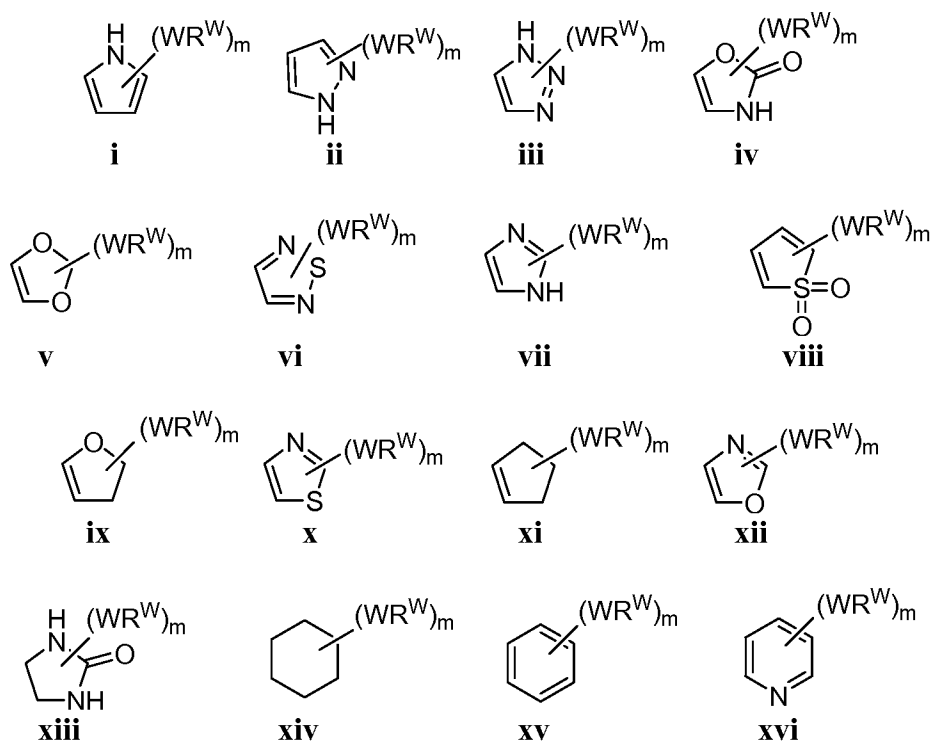
wherein ring A<sub>1</sub> 5-6 membered aromatic monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

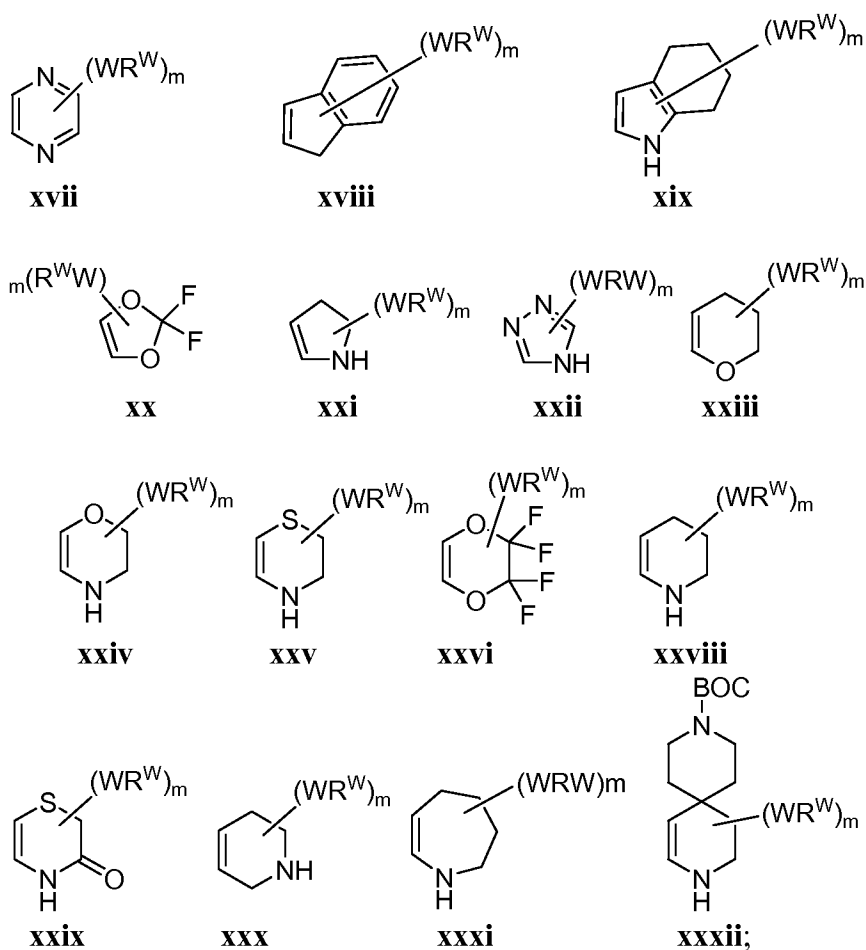
A<sub>1</sub> and A<sub>2</sub>, together, is an 8-14 membered aromatic, bicyclic or tricyclic aromatic ring, wherein each ring contains 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

3. The compound according to claim 2, wherein A<sub>1</sub> is an optionally substituted 6 membered aromatic ring having 0-4 heteroatoms, wherein said heteroatom is nitrogen.



4. The compound according to claim 2, wherein A<sub>1</sub> is an optionally substituted phenyl.
5. The compound according to claim 2, wherein A<sub>2</sub> is an optionally substituted 6 membered aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.
6. The compound according to claim 2, wherein A<sub>2</sub> is an optionally substituted 5-membered aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.
7. The compound according to claim 2, wherein A<sub>2</sub> is a 5-membered aromatic ring having 1-2 nitrogen atoms.
8. The compound according to claim 2, wherein A<sub>2</sub> is selected from:



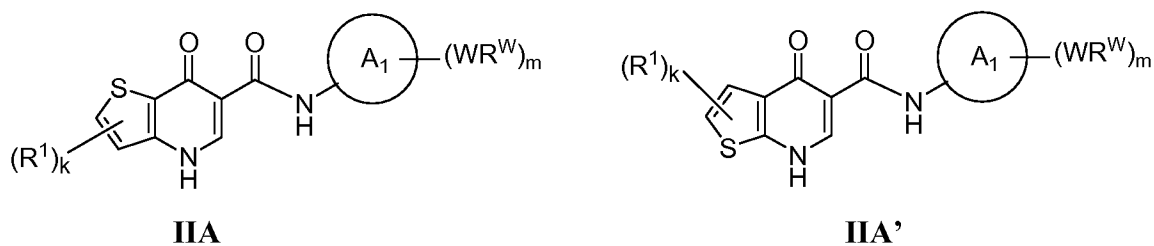


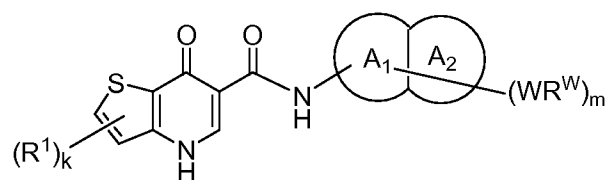
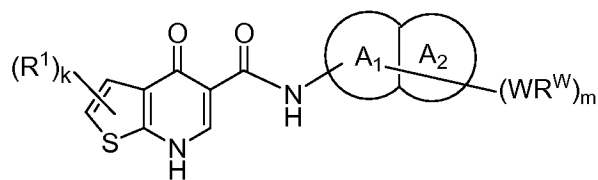
wherein ring A<sub>2</sub> is fused to ring A<sub>1</sub> through two adjacent ring atoms.

9. The compound according to claim 1, wherein R<sup>2</sup> and R<sup>4</sup> is hydrogen.

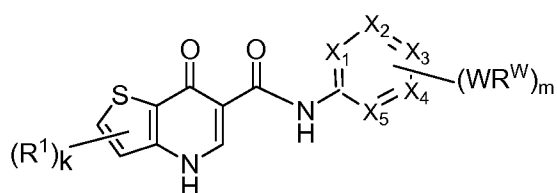
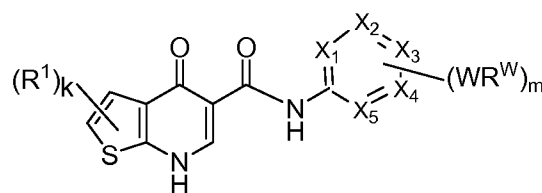
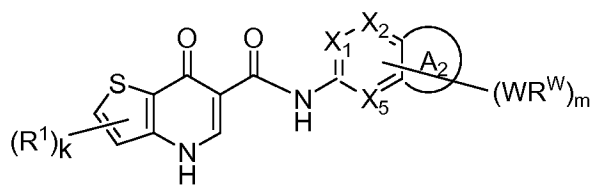
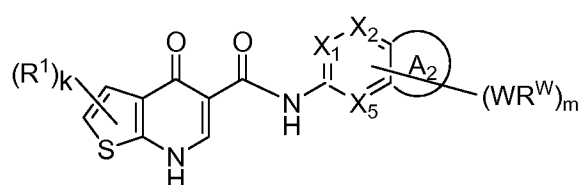
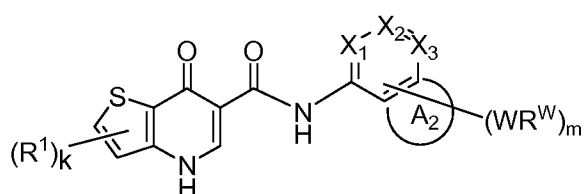
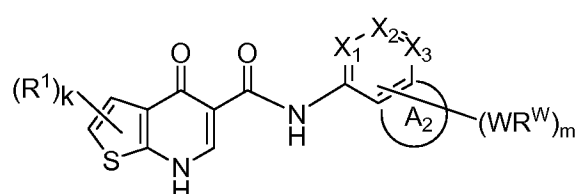
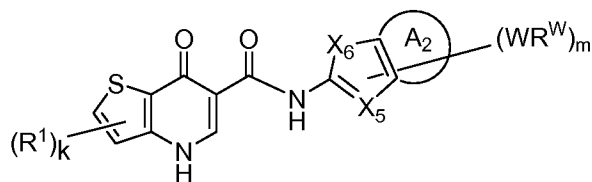
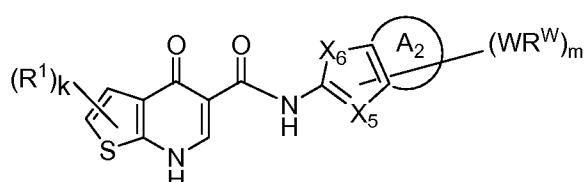
10. The compound according to claim 9, wherein R<sup>1</sup> is hydrogen.

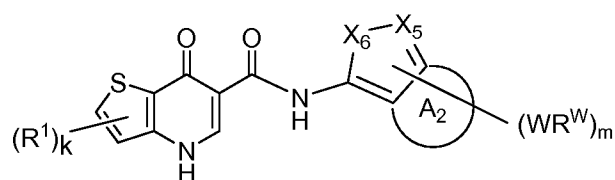
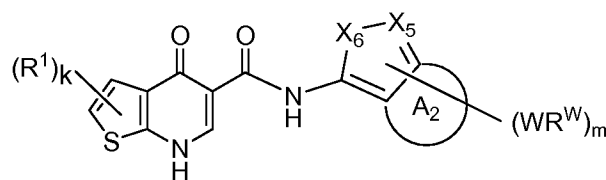
11. The compound according to claim 2, wherein said compound has formula **IIA**, formula **IIA'**, formula **IIIB**, or formula **IIIB'**:



**IIB****IIB'**

12. The compound according to claim 2, wherein said compound has formula **IIIA**, formula **IIIA'**, formula **IIIB**, formula **IIIB'**, formula **IIIC**, formula **IIIC'**, formula **IIID**, formula **IIID'**, formula **IIIE**, or formula **IIIE'**:

**IIIA****IIIA'****IIIB****IIIB'****IIIC****IIIC'****IIID****IIID'**

**III E****III E'**

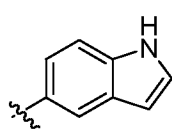
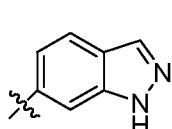
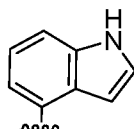
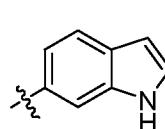
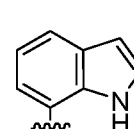
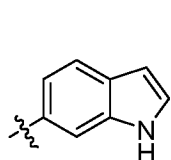
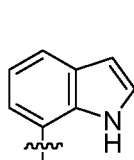
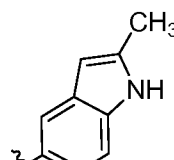
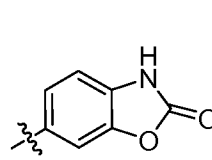
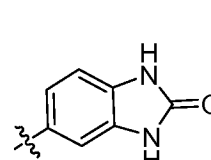
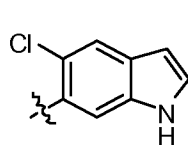
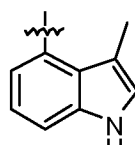
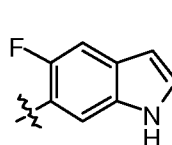
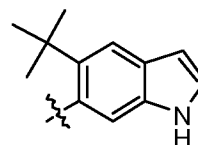
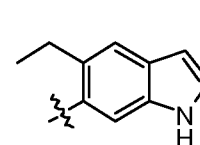
wherein:

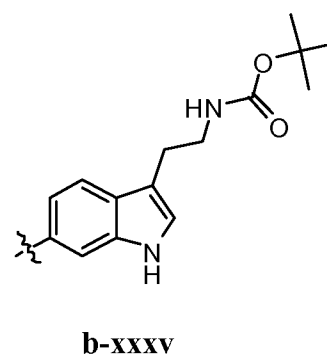
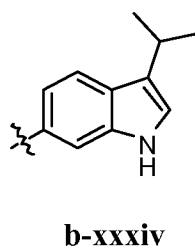
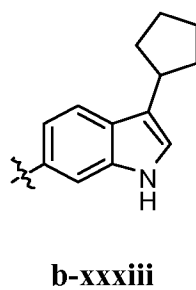
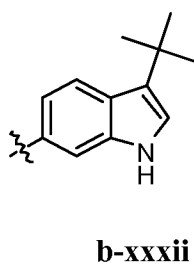
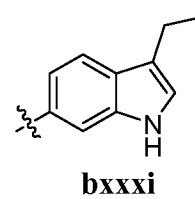
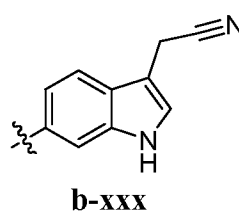
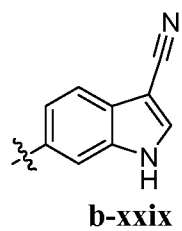
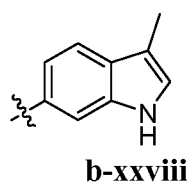
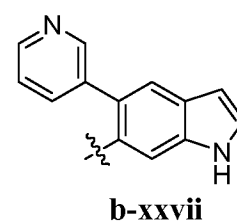
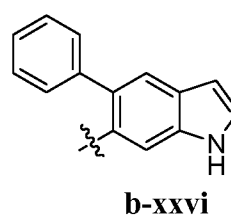
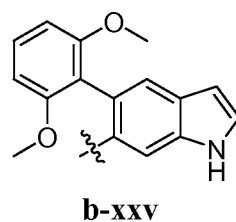
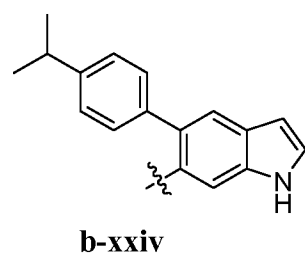
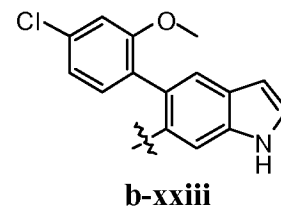
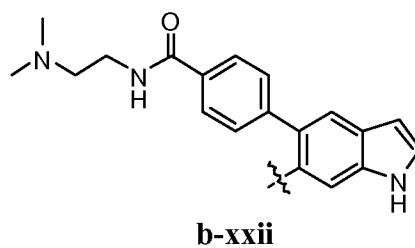
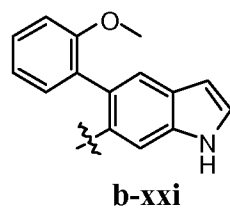
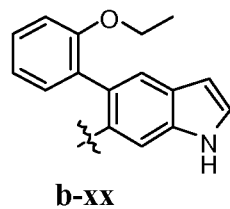
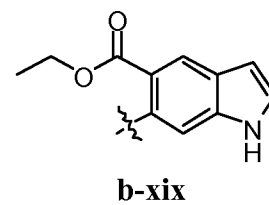
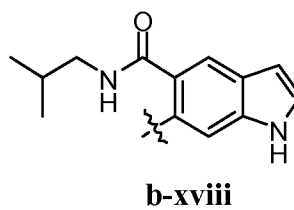
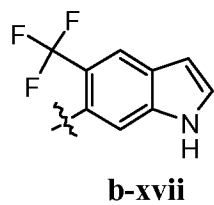
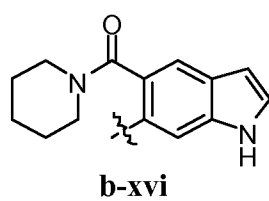
each of  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ , and  $X_5$  is independently selected from CH or N; and  $X_6$  is O, S, or  $NR'$ .

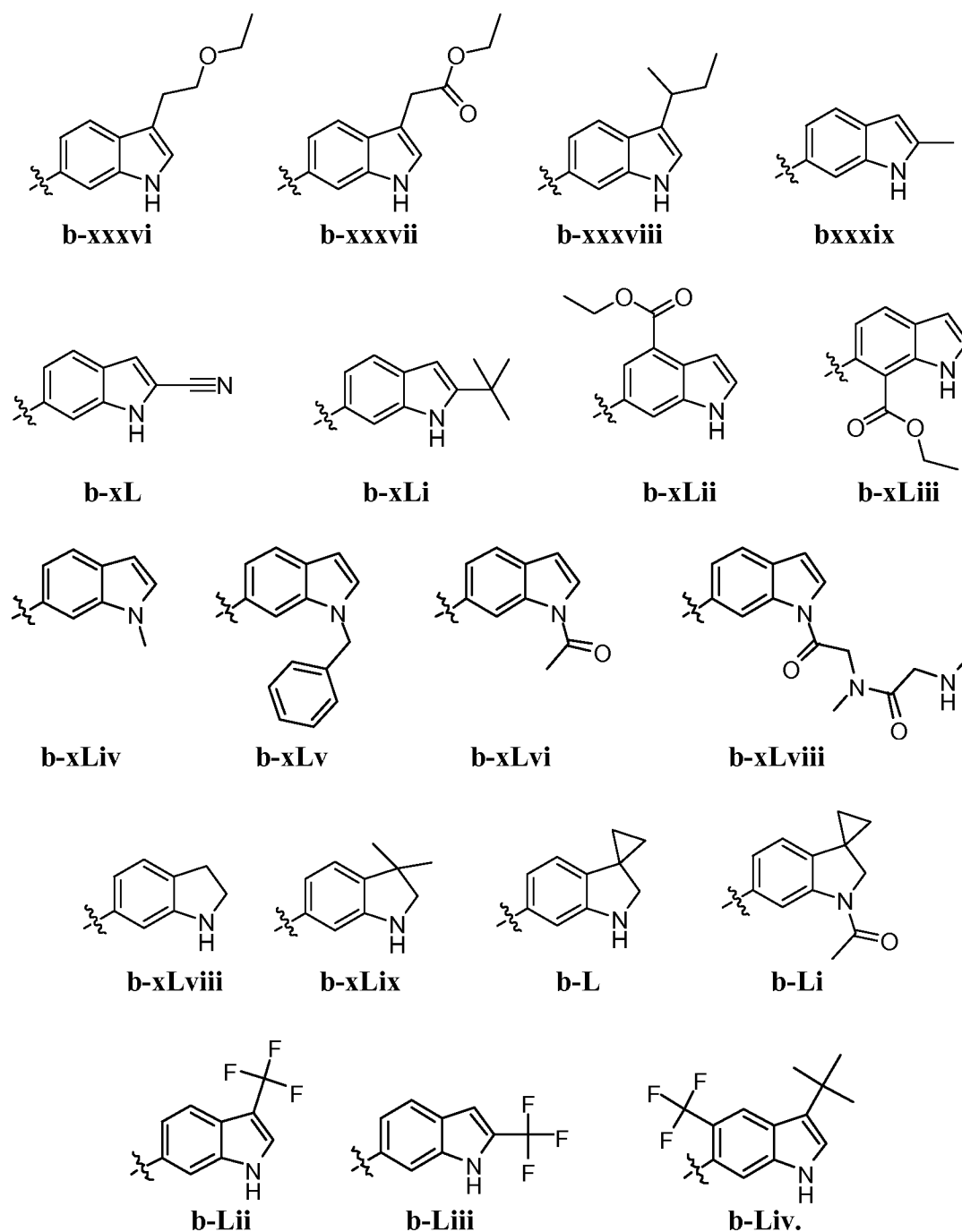
13. The compound according to claim 12, wherein each of  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ , and  $X_5$  in formula **III A** or formula **III A'** is CH

14. The compounds according to claim 12, wherein  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ , and  $X_5$  taken together in compound of formula **III A** or formula **III A'** is an optionally substituted ring selected from pyridyl, pyrazinyl, or pyrimidinyl.

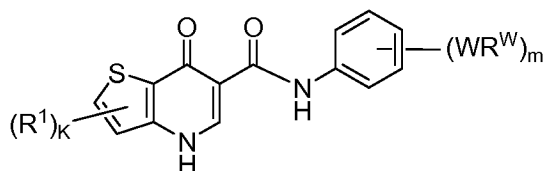
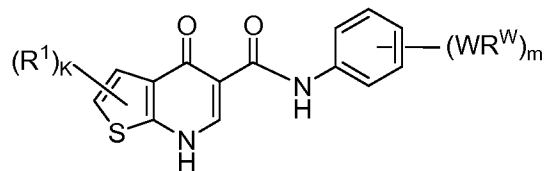
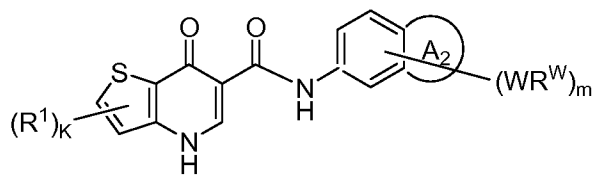
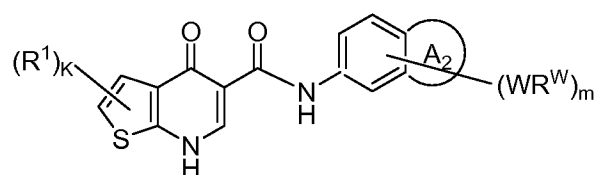
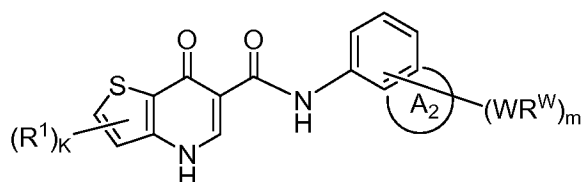
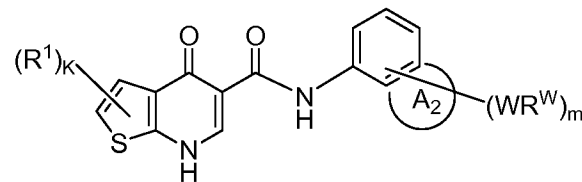
15. The compound according to claim 12 wherein  $X_1$ ,  $X_2$ ,  $X_3$ , or  $X_5$ , taken together with ring  $A_2$  in compounds of formula **III B**, formula **III B'**, formula **III C** or formula **III C'**, formula **III D**, formula **III D'** is an optionally substituted ring selected from:

**b-i****b-ii****b-iii****b-iv****b-v****b-vi****b-vii****b-viii****b-ix****b-x****b-xi****b-xii****b-xiii****b-xiv****b-xv**



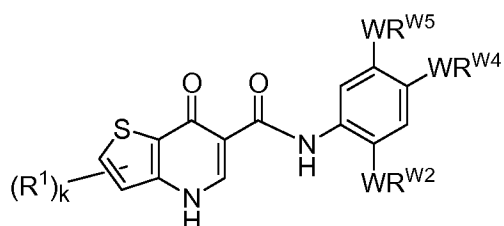
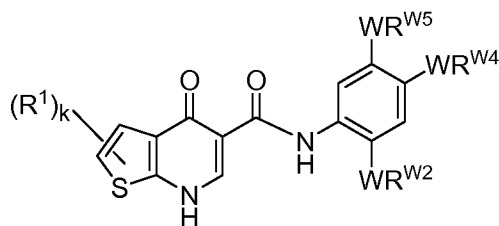


16. The compound according to claim 2, wherein said compound has formula **IVA**, formula **IVA'**, formula **IVB**, formula **IVB'**, formula **IVC** or formula **IVC'**:

**IVA****IVA'.****IVB****IVB'.****IVC****IVC'.**

17. The compound according to claim 16, wherein ring A<sub>2</sub> is an optionally substituted, saturated, unsaturated, or aromatic 5-7 membered ring with 0-3 heteroatoms selected from O, S, or N.

18. The compound according to claim 16, wherein said compound has formula **VA-1** or formula **VA-1'**:

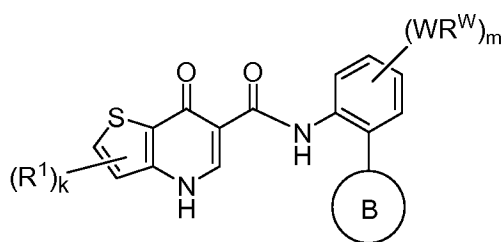
**VA-1****VA-1'**

wherein each of WR<sup>W2</sup> and WR<sup>W4</sup> is independently selected from hydrogen, CN, CF<sub>3</sub>, OCF<sub>3</sub>, halo, C1-C6 straight or branched alkyl, 3-12 membered cycloaliphatic, phenyl, C5-C10

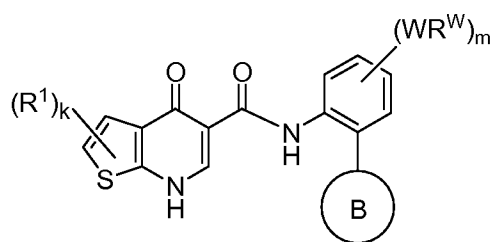
heteroaryl or C3-C7 heterocyclic, wherein said heteroaryl or heterocyclic has up to 3 heteroatoms selected from O, S, or N, wherein said  $WR^{W2}$  and  $WR^{W4}$  is independently and optionally substituted with up to three substituents selected from  $-OR'$ ,  $-CF_3$ ,  $-OCF_3$ ,  $SR'$ ,  $S(O)R'$ ,  $SO_2R'$ ,  $-SCF_3$ , 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, halo,  $-OH$ ,  $NH_2$ , CN,  $CHF_2$ ,  $NHR'$ ,  $N(R')_2$ ,  $-NHC(O)R'$ ,  $-NHC(O)OR'$ ,  $NHSO_2R'$ ,  $-OR'$ ,  $CH_2OH$ ,  $CH_2N(R')_2$ ,  $C(O)OR'$ ,  $C(O)N(R')_2$ ,  $SO_2NHR'$ ,  $SO_2N(R')_2$ ,  $OSO_2N(R')_2$ ,  $OSO_2CF_3$ , or  $CH_2NHC(O)OR'$ .

19. The compound according to claim 16 wherein said compound has the formula **VA-2** or formula **VA-2'**:



**VA-2**



**VA-2'**

wherein:

ring B is a 5-7 membered monocyclic or bicyclic, heterocyclic or heteroaryl ring optionally substituted with up to n occurrences of  $-Q-R^Q$ ,

Q is W;

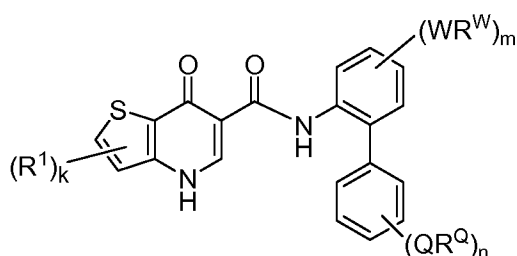
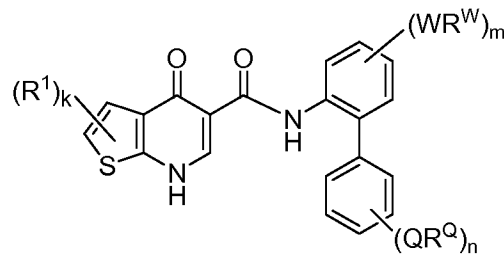
$R^Q$  is  $R^W$ ;

m is 0-4; and

n is 0-4.

20. The compound according to claim 16 wherein said compound has the formula **VA-3** or formula **VA-3'**:



**VA-3****VA-3'**

wherein:

ring B is a 5-7 membered monocyclic or bicyclic, heterocyclic or heteroaryl ring optionally substituted with up to n occurrences of  $-Q-R^Q$ ,

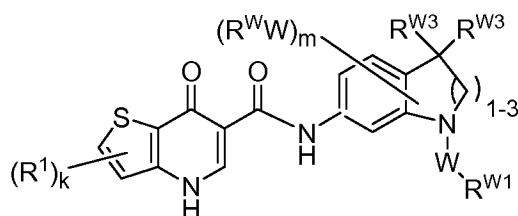
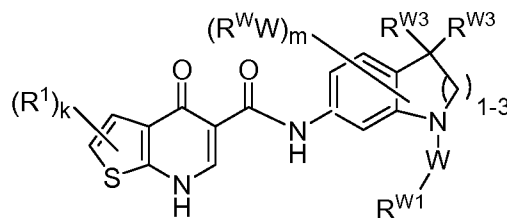
Q is W;

$R^Q$  is  $R^W$ ;

m is 0-4; and

n is 0-4.

21. The compound according to claim 16, wherein said compound has formula **VB-1** or formula **VB-1'**:

**VB-1****VB-1'**

wherein:

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

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

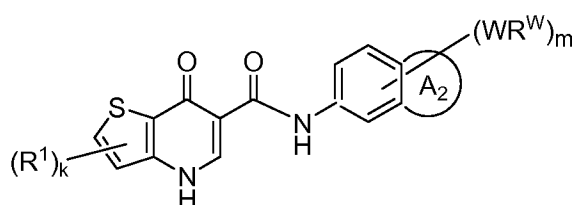
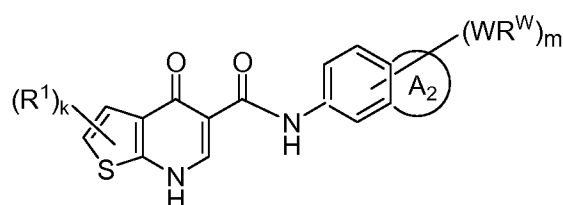
or optionally both  $R^{W3}$  taken together form a C3-C6 cycloalkyl or heterocyclic ring having up to two heteroatoms selected from O, S, or NR', wherein said ring is optionally substituted with up to two  $WR^W$  substituents; and

m is 0-4.

22. The compound according to claim 21, wherein  $WR^{W1}$  is hydrogen, C1-C6 aliphatic, C(O)C1-C6 aliphatic, or C(O)OC1-C6 aliphatic.

23. The compound according to claim 21, wherein 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 substituents selected from  $WR^{W1}$ .

24. The compound according to claim 16, wherein said compound has formula **VB-2** or formula **VB-2'**:

**VB-2****VB-2';**

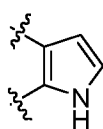
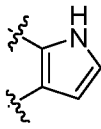
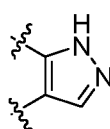
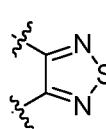
wherein:

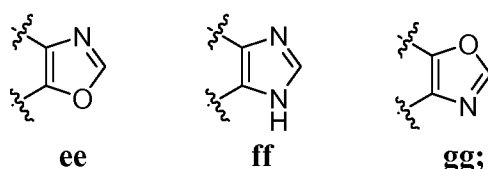
ring  $A_2$  is a phenyl or a 5-6 membered heteroaryl ring, wherein ring  $A_2$  and the phenyl ring fused thereto together have up to 4 substituents independently selected from  $WR^W$ ; and

$m$  is 0-4.

25. The compound according to claim 24 wherein ring  $A_2$  is an optionally substituted 5-membered ring selected from pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, or triazolyl.

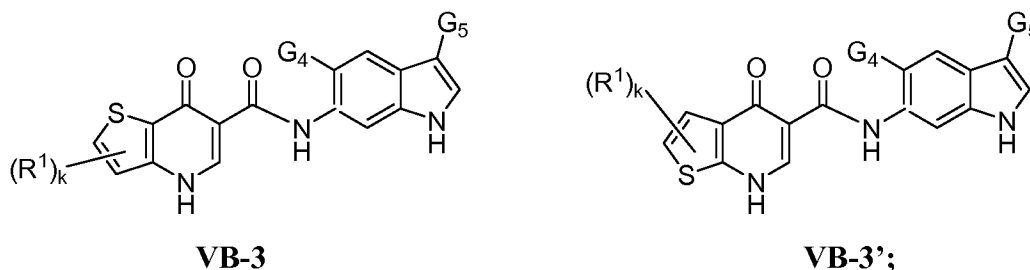
26. The compound according to claim 24, wherein ring  $A_2$  is selected from:

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



wherein said ring is optionally substituted.

27. The compound according to claim 26, wherein said compound has formula **VB-3** or formula **VB-3'**:



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, CN, or an optionally substituted C1-C6 aliphatic; wherein said indole ring system is further optionally substituted with up to 3 substituents independently selected from  $WR^W$ .

28. The compound according to claim 27, wherein  $G_4$  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  $-NR'SO_2NR'-$ .

29. The compound according to claim 27, wherein  $G_4$  is hydrogen, and  $G_5$  is cyano, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl, cyanomethyl, methoxyethyl,  $\text{CH}_2\text{C}(\text{O})\text{OMe}$ ,  $(\text{CH}_2)_2\text{-NHC}(\text{O})\text{O-tert-But}$ , or cyclopentyl.

30. The compound according to claim 27, wherein  $G_5$  is hydrogen, CN or  $\text{CF}_3$ , 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  $\text{CF}_3$ , wherein up to two methylene units of said C1-C6 aliphatic or C1-C6 alkyl is optionally replaced with  $-\text{CO}-$ ,  $-\text{CONR}'-$ ,  $-\text{CO}_2-$ ,  $-\text{OCO}-$ ,  $-\text{NR}'\text{CO}_2-$ ,  $-\text{O}-$ ,  $-\text{NR}'\text{CONR}'-$ ,  $-\text{OCONR}'-$ ,  $-\text{NR}'\text{CO}-$ ,  $-\text{S}-$ ,  $-\text{NR}'-$ ,  $-\text{SO}_2\text{NR}'-$ ,  $\text{NR}'\text{SO}_2-$ , or  $-\text{NR}'\text{SO}_2\text{NR}'-$ .

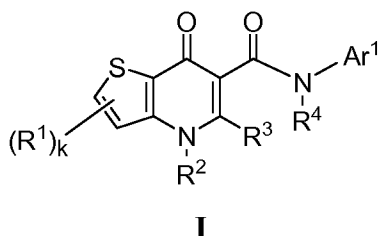
31. The compound according to claim 30, wherein  $G_5$  is hydrogen, CN or  $\text{CF}_3$ , and  $G_4$  is halo, ethoxycarbonyl, t-butyl, 2-methoxyphenyl, 2-ethoxyphenyl, (4-C(O)NH(CH<sub>2</sub>)<sub>2</sub>-NMe<sub>2</sub>)-phenyl, 2-methoxy-4-chloro-phenyl, pyridine-3-yl, 4-isopropylphenyl, 2,6-dimethoxyphenyl, sec-butylaminocarbonyl, ethyl, t-butyl, or piperidin-1-ylcarbonyl.

32. The compound according to claim 1, wherein said compound is selected from Table 1.

33. A pharmaceutical composition comprising a compound of formula **I** according to claim 1 and a pharmaceutically acceptable carrier or adjuvant.

34. The composition according to claim 33, wherein said composition comprises an additional agent selected from a mucolytic agent, bronchodilator, an antibiotic, an anti-infective agent, an anti-inflammatory agent, CFTR modulator, or a nutritional agent.

35. A method of modulating CFTR activity comprising the step of contacting said CFTR with a compound of formula **I**:



or a pharmaceutically acceptable salt thereof, wherein:

Ar<sup>1</sup> 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<sup>1</sup> has m substituents, each independently selected from -WR<sup>W</sup>;

W is a bond or is an optionally substituted C<sub>1</sub>-C<sub>6</sub> alkylidene chain wherein up to two methylene units of W are optionally and independently replaced by O, -CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, -CO<sub>2</sub>-, -OCO-, -NR'CO<sub>2</sub>-, -O-, -NR'CONR'-, -C(O)NR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -S-, -SO-, -SO<sub>2</sub>-, -NR'-, -SO<sub>2</sub>NR'-, NR'SO<sub>2</sub>-, or -NR'SO<sub>2</sub>NR'-;

R<sup>W</sup> is independently R', halo, cyano, CF<sub>3</sub>, CHF<sub>2</sub>, OCHF<sub>2</sub>, Me, Et, CH(Me)<sub>2</sub>, CHMeEt, n-propyl, t-butyl, OH, OMe, OEt, OPh, O-fluorophenyl, O-difluorophenyl, O-methoxyphenyl, O-tolyl, O-benzyl, SMe, SCF<sub>3</sub>, SCHF<sub>2</sub>, SEt, CH<sub>2</sub>CN, NH<sub>2</sub>, NHMe, N(Me)<sub>2</sub>, NHEt, N(Et)<sub>2</sub>, C(O)CH<sub>3</sub>, C(O)Ph, C(O)NH<sub>2</sub>, SPh, SO<sub>2</sub>-(amino-pyridyl), SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>Ph, SO<sub>2</sub>NHPh, SO<sub>2</sub>-N-morpholino, SO<sub>2</sub>-N-pyrrolidyl, N-pyrrolyl, N-morpholino, 1-piperidyl, phenyl, benzyl, (cyclohexyl-methylamino)methyl, 4-Methyl-2,4-dihydro-pyrazol-3-one-2-yl, benzimidazol-2-yl, 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<sub>2</sub>Me;

m is 0-5;

k is 0-2;

each of R<sup>1</sup> is independently -X-R<sup>X</sup>;

X is a bond or is an optionally substituted C<sub>1</sub>-C<sub>6</sub> alkylidene chain wherein up to two methylene units of X are optionally and independently replaced by -CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, -CO<sub>2</sub>-, -OCO-, -NR'CO<sub>2</sub>-, -O-, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -S-, -SO-, -SO<sub>2</sub>-, -NR'-, -SO<sub>2</sub>NR'-, NR'SO<sub>2</sub>-, or -NR'SO<sub>2</sub>NR'-;

R<sup>X</sup> is independently R', halo, NO<sub>2</sub>, CN, CF<sub>3</sub>, or OCF<sub>3</sub>;

R<sup>2</sup> is hydrogen;

R<sup>3</sup> is hydrogen;

R<sup>4</sup> is hydrogen or a C<sub>1-6</sub> aliphatic group optionally substituted with -X-R<sup>X</sup>;

R' is independently selected from hydrogen or an optionally substituted group selected from a C<sub>1</sub>-C<sub>8</sub> 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.

36. A method of treating or lessening the severity of a disease in a patient, wherein said disease is selected from 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, myeloperoxidase 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 asuch as Huntington, spinocerebellar ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidolulsian, 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, said method comprising the step of administering to said patient an effective amount of a compound of formula I according to claim 1.

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

(i) a composition comprising a compound of formula **I** according to claim 1;

(ii) instructions for:

- a) contacting the composition with the biological sample;
- b) measuring activity of said CFTR or a fragment thereof.

38. The kit of claim 37, further comprising instructions for

- a) contacting an additional composition with the biological sample;
- b) measuring the activity of said CFTR or a fragment thereof in the presence of said additional compound, and
- c) comparing the activity of the CFTR in the presence of the additional compound with the density of CFTR in the presence of a composition of formula **I**.

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2008/064646

A. CLASSIFICATION OF SUBJECT MATTER  
INV. C07D495/04 A61K31/407 A61P11/00

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

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/120497 A (UNIV CALIFORNIA [US]; VERKMAN ALAN [US]; GUY R KIPLIN [US]; PEDEMONTE) 22 December 2005 (2005-12-22) the whole document	1-38

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

### \* Special categories of cited documents :

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*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)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*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

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*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.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

10 October 2008

Date of mailing of the international search report

16/10/2008

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2008/064646

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005120497 A	22-12-2005	AU 2005251745 A1	22-12-2005
		CA 2569402 A1	22-12-2005
		EP 1765347 A2	28-03-2007
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