US 20040242673A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2004/0242673 A1

Lockhart et al. (43) Pub. Date: Dec. 2, 2004

(54) HETEROCYCLIC COMPOUNDS AND USES THEREOF

(75) Inventors: **David J. Lockhart**, Del Mar, CA (US); **Hitesh K. Patel**, Encinitas, CA (US); **Shamal Anil Mehta**, San Diego, CA (US); **Zdravko V. Milanov**, San Diego, CA (US); **Robert M. Grotzfeld**, Carlsbad, CA (US); **Andiliy G. Lai**, San Diego, CA (US)

Correspondence Address:
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 943041050

(73) Assignee: **Ambit Biosciences Corporation**, San Diego, CA

(21) Appl. No.: **10/847,897**

(22) Filed: **May 17, 2004**

Related U.S. Application Data

(60) Provisional application No. 60/471,425, filed on May 16, 2003. Provisional application No. 60/480,289, filed on Jun. 20, 2003. Provisional application No. 60/488,178, filed on Jul. 16, 2003. Provisional application No. 60/488,172, filed on Jul. 16, 2003. Provisional application No. 60/480,475, filed on Jun. 20, 2003. Provisional application No. 60/516,610, filed on Oct. 30, 2003. Provisional application No. 60/516,651, filed on Oct. 30, 2003. Provisional application No. 60/516,616, filed on Oct. 30, 2003.

Publication Classification

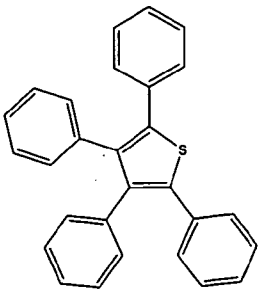
(51) **Int. Cl.**[7] **A61K 31/381**

(52) **U.S. Cl.** **514/448**

(57) ABSTRACT

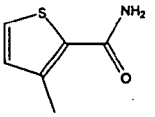
The invention provides compounds having the thiophene or furan skeleton and uses thereof. The invention provides methods of using the compounds and/or compositions in the treatment of a variety of diseases and unwanted conditions in subjects. Kits comprising the compounds of the invention are also provided. The compounds and compositions disclosed herein are preferably used in the treatment of neurodegenerative diseases, cardiovascular diseases, proliferative diseases, and visual disorders. In particular, methods and compositions for the treatment of stroke are disclosed herein.

FIGURE 1A



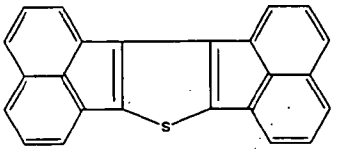
781118

$C_{28}H_{20}S$
Mol. Wt.: 388.52



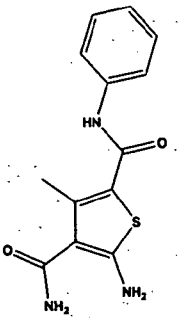
781222

C_6H_7NOS
Mol. Wt.: 141.19



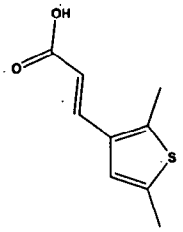
781196

$C_{24}H_{12}S$
Mol. Wt.: 332.42



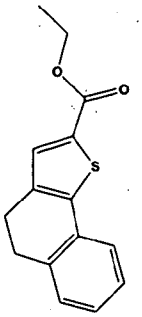
781300

$C_{13}H_{13}N_3O_2S$
Mol. Wt.: 275.33



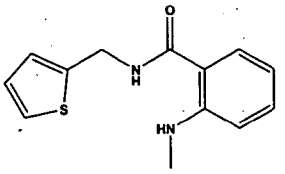
781326

$C_9H_{10}O_2S$
Mol. Wt.: 182.24



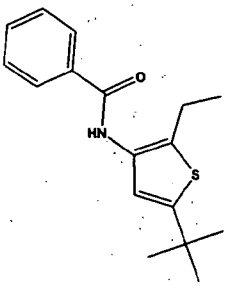
781352

$C_{15}H_{14}O_2S$
Mol. Wt.: 258.34



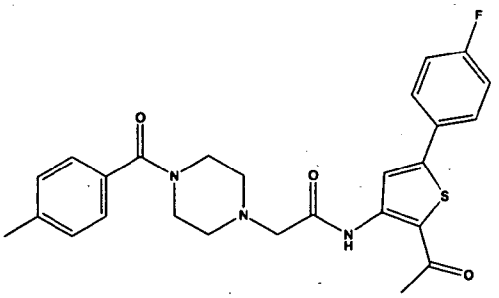
781378

$C_{13}H_{14}N_2OS$
Mol. Wt.: 246.33



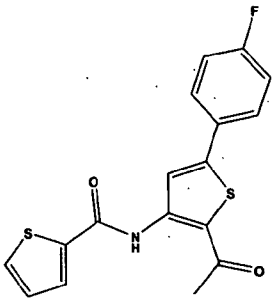
781560

$C_{17}H_{21}NOS$
Mol. Wt.: 287.42



779974

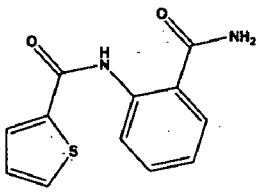
$C_{26}H_{26}FN_3O_3S$
Mol. Wt.: 479.57



781456

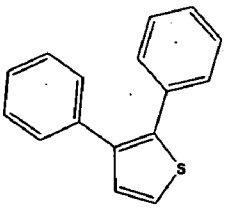
$C_{17}H_{12}FNO_2S_2$
Mol. Wt.: 345.41

FIGURE 1B



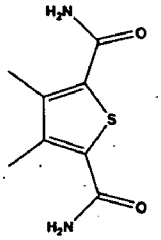
781534

$C_{12}H_{10}N_2O_2S$
Mol. Wt.: 246.28



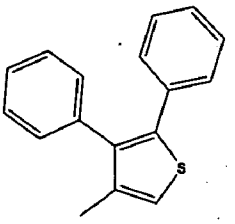
781482

$C_{16}H_{12}S$
Mol. Wt.: 236.33



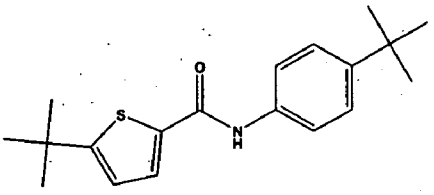
781586

$C_8H_{10}N_2O_2S$
Mol. Wt.: 198.24



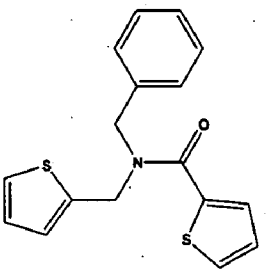
781612

$C_{17}H_{14}S$
Mol. Wt.: 250.36



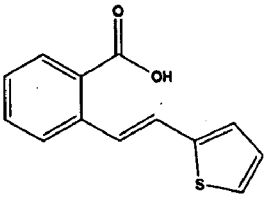
781794

$C_{19}H_{25}NOS$
Mol. Wt.: 315.47



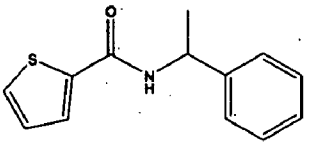
781716

$C_{17}H_{15}NOS_2$
Mol. Wt.: 313.44



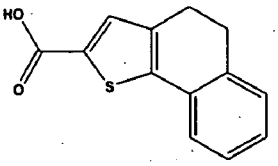
781898

$C_{13}H_{10}O_2S$
Mol. Wt.: 230.28



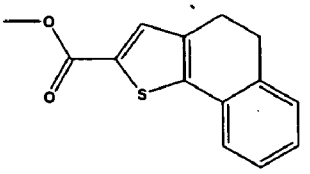
781924

$C_{13}H_{13}NOS$
Mol. Wt.: 231.31



783042

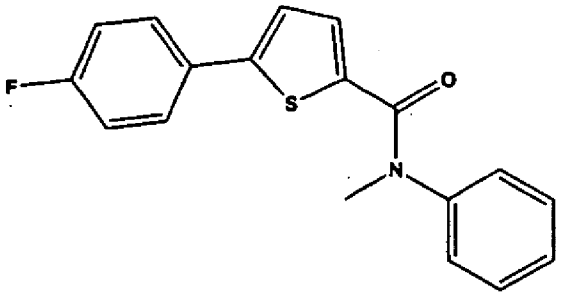
$C_{13}H_{10}O_2S$
Mol. Wt.: 230.28



783120

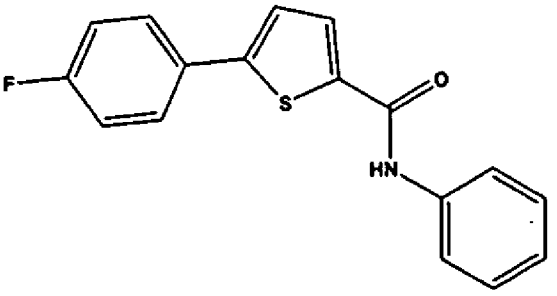
$C_{14}H_{12}O_2S$
Mol. Wt.: 244.31

FIGURE 2



783172

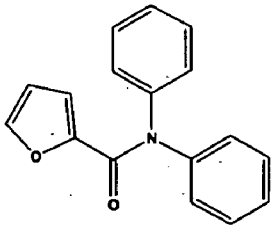
$C_{18}H_{14}FNOS$
Mol. Wt.: 311.37



783146

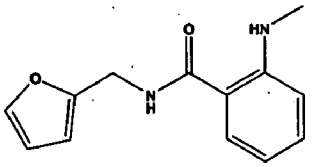
$C_{17}H_{12}FNOS$
Mol. Wt.: 297.35

FIGURE 3A



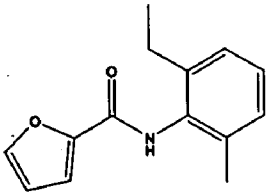
781508

$C_{17}H_{13}NO_2$
Mol. Wt.: 263.29



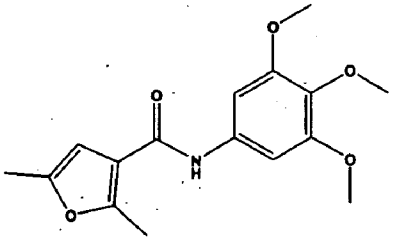
781768

$C_{13}H_{14}N_2O_2$
Mol. Wt.: 230.26



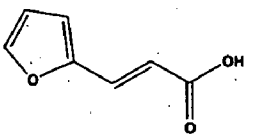
781742

$C_{14}H_{15}NO_2$
Mol. Wt.: 229.27



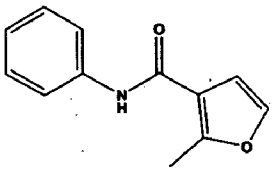
781872

$C_{16}H_{19}NO_5$
Mol. Wt.: 305.33



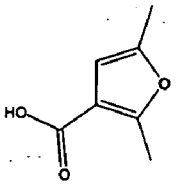
782002

$C_7H_6O_3$
Mol. Wt.: 138.12



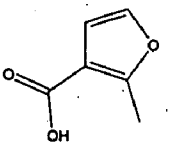
781040

$C_{12}H_{11}NO_2$
Mol. Wt.: 201.22



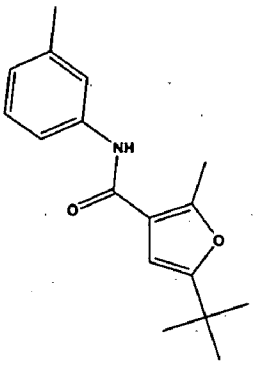
781092

$C_7H_8O_3$
Mol. Wt.: 140.14



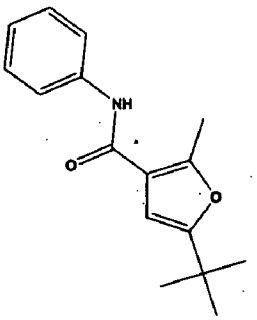
781248

$C_6H_6O_3$
Mol. Wt.: 126.11



781170

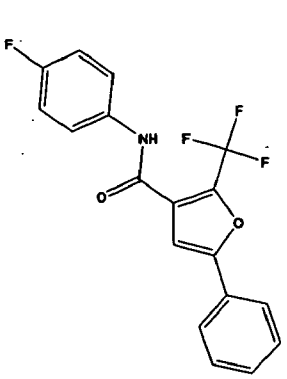
$C_{17}H_{21}NO_2$
Mol. Wt.: 271.35



781144

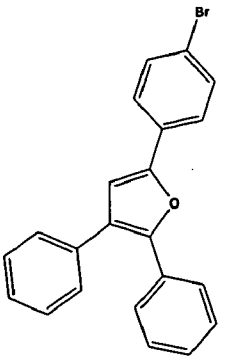
$C_{16}H_{19}NO_2$
Mol. Wt.: 257.33

FIGURE 3B



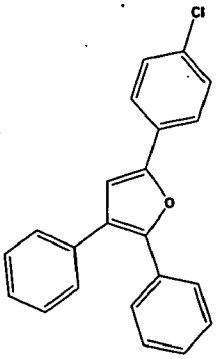
781274

$C_{18}H_{11}F_4NO_2$
Mol. Wt.: 349.28



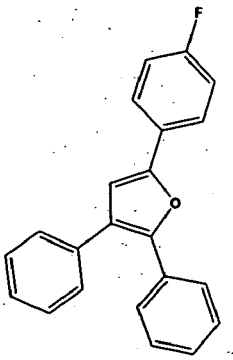
781638

$C_{22}H_{15}BrO$
Mol. Wt.: 375.26



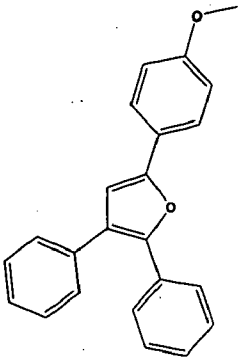
781664

$C_{22}H_{15}ClO$
Mol. Wt.: 330.81



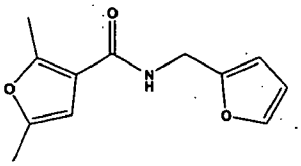
781690

$C_{22}H_{15}FO$
Mol. Wt.: 314.35



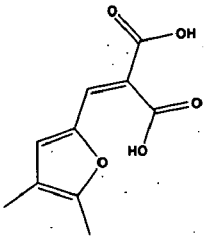
781820

$C_{23}H_{18}O_2$
Mol. Wt.: 326.39



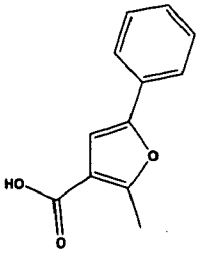
781846

$C_{12}H_{13}NO_3$
Mol. Wt.: 219.24



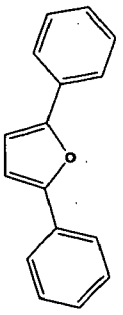
781404

$C_{10}H_{10}O_5$
Mol. Wt.: 210.18



781950

$C_{12}H_{10}O_3$
Mol. Wt.: 202.21



781976

$C_{16}H_{12}O$
Mol. Wt.: 220.27

HETEROCYCLIC COMPOUNDS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 60/471,425 filed May 16, 2003, U.S. Provisional Application No. 60/480,289 filed Jun. 20, 2003, U.S. Provisional Application No. 60/488,178 filed Jul. 16, 2003, U.S. Provisional Application No. 60/488,172 filed Jul. 16, 2003, U.S. Provisional Application No. 60/480,475 filed Jun. 20, 2003, U.S. Provisional Application No. 60/516,610 filed Oct. 30, 2003, U.S. Provisional Application No. 60/516,651 filed Oct. 30, 2003 and U.S. Provisional Application No. 60/516,616 filed Oct. 30, 2003 all of which are incorporated herein by reference.

INTRODUCTION

[0002] Phosphodiesterase 6 delta (PDE6D) was originally identified as a regulatory (non-catalytic) subunit of the enzyme PDE6. PDE6 is expressed exclusively in photoreceptor cells, and plays a critical role in retinal phototransduction. (Stryer, L. (1991) J. Biol. Chem. 266:10711-14; (Florio, S. K. et al. (1996) J. Biol. Chem. 271:24036-47. The PDE6 holoenzyme exists as both membrane-associated and-soluble forms, and only the membrane-associated form is active in phototransduction. Importantly, only the soluble form contains the PDE6D subunit. PDE6D regulates the subcellular localization and thus the activity of PDE6, and the release of PDE6 from membranes is mediated by PDE6D. PDE6D has been observed to reduce light-induced cGMP hydrolysis in rod outer segments (Cook et al., J. Biol. Chem 276(7):5248-5255 (2001)), presumably by removing the PDE6 holoenzyme from the membrane. PDE6D solubilizes PDE6 by binding specifically to prenylated peptide sequences near the C-termini of the PDE6A and PDE6B subunits. PDE6D is referred to in the scientific literature by a several designations, including PDE delta, PDEδ, PDE6 delta, PDE6δ, PDE6D and PDED.

[0003] PDE6D interacts specifically with a host of important cell signaling proteins through their post-translational modification with isoprenoid intermediates, which are products of the cholesterol biosynthetic pathway. One such modification is called prenylation and involves the attachment of phospholipids to proteins after translation, particularly the large class of GTP-binding proteins. Prenyl groups are important for proper cellular localization and trafficking. The availability of isoprenoid intermediates for prenylation of GTP-binding proteins has been associated with various cardiovascular, inflammatory, cancerous and neurological diseases. A reduction in the amount of available prenyl groups has been associated with improved endothelial function, decreased oxidative stress, decreased inflammation and increased neuroprotective effects.

[0004] Due to the possible role of PDE6 in several diseases, there is a need to develop PDE6 modulators.

SUMMARY OF THE INVENTION

[0005] The present invention provides methods and compositions for treating and preventing diseases, in particular PDE6-realated diseases. The compounds of the invention, having the thiophene or furan structure, can be delivered alone or in combination with additional agents, and are used for the treatment and/or prevention of diseases. Accordingly, in one aspect, the invention is directed to methods for treating or preventing such diseases in a subject in need thereof. The methods comprise administering to the subject a pharmaceutically effective amount of a compound having the thiophene or furan skeleton.

[0006] In another aspect, the invention provides methods for modulating the activity of phosphodiesterase 6D (PDE6D) with a compound having the thiophene or furan skeleton.

[0007] The compounds and compositions of the invention modulate the activity of PDE6D, and hence are useful as therapeutic or prophylactic agents for conditions and diseases caused by or aggravated by the localization and function of prenylated proteins, for example, cardiovascular diseases, such as arteriosclerosis, hypertension, arrhythmia (e.g. ischemic arrhythmia, arrhythmia due to myocardial infarction, myocardial stunning, myocardial dysfunction, arrhythmia, and the like), angina pectoris, cardiac hypertrophy, myocardial infarction, heart failure (e.g. congestive heart failure, acute heart failure, cardiac hypertrophy, etc.); renal diseases, such as, diabetes mellitus, diabetic nephropathy, ischemic acute renal failure, acute renal failure, and the like; cerebrovascular diseases, such as ischemic stroke, hemorrhagic stroke, and the like; and cerebro ischemic disorders, such as disorders associated with cerebral infarction, disorders caused after cerebral apoplexy as sequelae, or cerebral edema.

[0008] In another aspect, the present invention provides compositions and methods for treating and preventing neurodegenerative conditions and diseases. These compounds disclosed herein can be delivered alone or in combination with additional agents, and are used for the treatment and/or prevention of neurodegenerative conditions and diseases such as those resulting from ischemic strokes. The neurodegenerative conditions and disease can be ischemic stroke, basal ganglia or Parkinson's disease, epilepsy or brain or spinal cord ischemia or trauma; Alzheimer's disease, diabetic peripheral neuropathy, multiple sclerosis, amyotrophic lateral sclerosis, traumatic brain injury, spinal cord injury, Huntington's disease, heart failure (e.g. congestive heart failure, acute heart failure, cardiac hypertrophy, etc.) renal diseases, ischemic stroke, traumatic brain injury, or Parkinson's disease. The thiophene-containing and furan-containing compounds of the invention are preferably administered in a pharmaceutical composition containing a pharmaceutically acceptable excipient.

[0009] In yet another aspect, the present invention provides methods and compositions for the rehabilitation of a subject with a central nervous system disorder, such as stroke and traumatic brain injury. Accordingly, in one embodiment, the invention is directed to methods for treating or preventing neurodegenerative conditions or diseases in a subject in need thereof, or, optionally preventing further progression of the disease. The thiophene-containing and furan-containing compounds can be administered for a length of time necessary to allow for the recovery from the neurodegenerative condition or disease, such as, for example, from about 1 month to about 3 months to about a year or more if necessary. The neurodegenerative condition or disease can be ischemic stroke, basal ganglia or Parkin-

son's disease, epilepsy or brain or spinal cord ischemia or trauma, Alzheimer's disease, diabetic-peripheral neuropathy, multiple sclerosis, amyotrophic lateral sclerosis, traumatic brain injury, spinal cord injury, or Huntington's disease.

[0010] These and other aspects of the present invention will become evident upon reference to the following detailed description. In addition, various references are set forth herein which describe in more detail certain procedures or compositions, and are incorporated by reference in their entirety.

BRIEF DESCRIPTION OF THE FIGURES

[0011] **FIG. 1** shows thiophene-containing compounds that are illustrative of formula I, as described below, along with the corresponding compound identification numbers.

[0012] **FIG. 2** shows thiophene-containing compounds that are illustrative of formula II, as described below, along with the corresponding compound identification numbers.

[0013] **FIG. 3** shows furan-containing compounds that are illustrative of formula III, as described below, along with the corresponding compound identification numbers.

DETAILED DESCRIPTION

[0014] I. Definitions

[0015] Unless otherwise stated, the following terms used in this application, including the specification and claims, have the definitions given below. It must be noted that, as used in the specification and the appended claims, the singular forms "a,""an" and "the" include plural referents unless the context clearly dictates otherwise. Definition of standard chemistry terms may be found in reference works, including Carey and Sundberg (1992) "Advanced Organic Chemistry 3_{rd}Ed." Vols. A and B, Plenum Press, New York. The practice of the present invention will employ, unless otherwise indicated, conventional methods of mass spectroscopy, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology, within the skill of the art.

[0016] The terms "effective amount" or "pharmaceutically effective amount" refer to a nontoxic but sufficient amount of the agent to provide the desired biological, therapeutic, and/or prophylactic result. That result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the compound having the thiophene or furan skeleton as disclosed herein per se or a composition comprising the compound required to provide a clinically significant decrease in a disease. An appropriate effective amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

[0017] By "pharmaceutically acceptable" or "pharmacologically acceptable" is meant a material which is not biologically or otherwise undesirable, i.e., the material may be administered to an individual without causing any undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[0018] The term "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts, for example, include:

[0019] (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2,2,2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like;

[0020] (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like. It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms or crystal forms thereof, particularly solvates or polymorphs. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are often formed during the process of crystallization. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate.

[0021] Where chiral centers occur in the compounds having the R_1, R_2, R_3 and R_4 moieties as defined above, the invention includes the enantiomeric compounds resulting from the chiral center as well as racemic mixtures thereof.

[0022] As used herein, the term "halogen" includes fluorine, chlorine, bromine, and iodine.

[0023] The term "alkyl" as used herein refers to a substituted or unsubstituted straight, branched, or cyclic hydrocarbon chain fragment or radical, preferably containing between about one and about twenty carbon atoms, more preferably between about one and about ten carbon atoms

(e.g., methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, n-butyl, iso-butyl, tert-butyl, cyclobutyl, adamantyl, noradamantyl and the like). Straight, branched, or cyclic hydrocarbon chains having ten or fewer carbon atoms will also be referred to herein as "lower alkyl". The hydrocarbon chains may further include one or more degrees of unsaturation, i.e., one or more double or triple bonds (e.g., vinyl, propargyl, allyl, 2-buten-1-yl, 2-cyclopenten-1-yl, 1,3-cyclohexadien-1-yl, 3-cyclohexen-1-yl and the like. Alkyl groups containing double bonds such as just described will also be referred to herein as "alkylenes".

[0024] The term "aryl" as used herein refers to cyclic aromatic, hydrocarbon chains having twenty or fewer carbon atoms, e.g., phenyl, naphthyl, biphenyl and anthracenyl. One or more carbon atoms of the aryl group may also be substituted with, e.g., alkyl; aryl; heterocycle; formyl; halogen; nitro; cyano; hydroxyl, alkoxyl or aryloxyl; thio or mercapto, alkyl-, or arylthio; amino, alkylamino, arylamino, dialkyl-, diaryl-, or arylalkylamino; aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, dialkylaminocarbonyl, diarylaminocarbonyl or arylalkylaminocarbonyl; carboxyl, or alkyl- or aryloxycarbonyl; carboxaldehyde, or aryl- or alkylcarbonyl; iminyl, or aryl- or alkyliminyl; sulfo; alkyl- or arylsulfonyl; hydroximinyl, or aryl- or alkoximinyl; ureido; or thioureido. In addition, two or more alkyl or heteroalkyl substituents of an aryl group may be combined to form fused aryl-alkyl or aryl-heteroalkyl ring systems (e.g., tetrahydronaphthyl). Substituents including heterocyclic groups (e.g., heterocycleoxy, heteroaryloxy, and heteroaralkylthio) are defined by analogy to the above-described terms.

[0025] As used herein, "aliphatic" includes alkanes, olefins (alkenes or alkyldienes), and alkynes.

[0026] Alicyclic includes substituted or unsubstituted cycloparaffins (saturated), cycloolefins (unsaturated with two or more double bonds), and cycloacetylenes (cyclynes) with at least one triple bond. Non-limiting examples include cyclopropane, cyclohexane, cyclopentane, cyclopentadiene, and cycloctatetraene.

[0027] Aromatic refers to substituted or unsubstituted unsaturated cyclic hydrocarbons of one or more rings and includes aryl structures typified, but not limited to, phenyl, naphthalyl, phenanthrenyl, and anthracenyl. Non-limiting aromatic examples include 6 membered (typified by benzene) as well as 5 membered (typified by furan, thiophene, pyrrole, and indole) rings.

[0028] Heterocycle refers to the presence of at least one non-carbon atom in a cyclic structure. Non-limiting examples include the presence of a nitrogen, oxygen, and sulfur atom to result in heterocyclic rings including, but not limited to, phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, quinoxalinyl, quinazolinyl, purinyl andindazolyl; wherein such phenyl, naphthyl or heterocyclic group is optionally substituted with one to five groups selected from the group consisting of a C1-6 branched or unbranched alkyl, phenyl, naphthyl, heterocycle selected from the group hereinabove described, C1-6 branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C1-5 alkyl, naphthyl C1-5 alkyl, halo, hydroxy, cyano, C1-3 alkyloxy which may optionally be partially or fully halogenated, phenyloxy, naphthyloxy, heteraryloxy wherein the heterocyclic moiety is selected from the group hereinabove described, nitro, amino, mono- or di-(C1-3)alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described, $NH_2C(O)$, a mono- or di-(C1-3)alkyl aminocarbonyl, C1-5 alkyl-C(O)-C1-4 alkyl, amino-C1-5 alkyl, mono-or di-(C1-3)alkylamino-C1-5 alkyl, amino-S(O)2, or di-(C1-3) alkylamino-S(O)2; or a fused aryl selected from the group consisting of benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heterocyclic moiety selected from the group consisting of cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole, cyclohexanobenzimidazole, cyclopentanobenzoxazole, cyclohexanobenzoxazole, cyclopentanoitnidazole, cyclohexanoimidazole, cyclopentanothiophene and cyclohexanothiophene, wherein the fused aryl or fused heterocyclic ring is substituted with 0 to 3 groups independently selected from phenyl, naphthyl and heterocyclic moiety selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, and isothiazolyl, C1-6 branched or unbranched alkyl which is optionally partially or fully halogenated, halo, cyano, C1-3 alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heterocyclyloxy wherein the heterocyclic moiety is selected from the group hereinabove described, nitro, amino, mono- or di-(C1-3) alkylamino, phenylamino, naphthylarnino, heterocyclylamino wherein the heterocyclic moiety is selected from the group hereinabove described, $NH_2C(O)$, a mono- or di-(C1-3)alkyl aminocarbonyl, C1-4 alkyl-OC(O), C1-5 alkyl-C(O)-C1-4 branched or unbranched alkyl, an amino-C1-5 alkyl, or mono- or di-(C1-3)alkylamino-C1-5 alkyl; or c) cycloalkyl selected from the group consisting of cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, wherein the cycloalkyl may optionally be partially or fully halogenated and which may optionally be substituted with one to three C1-3 alkyl groups; or azetidinyl, pyrrolidinyl, piperidinyl, morpholino, piperazinyl, hexahydroazepinyl or octahydroazocinyl.

[0029] All of the above described aliphatic, carboxyalkyl, carbalkoxyalkyl, alkoxy, alicyclic, aryl, aromatic, and heterocyclic moieties may, of course, also be optionally substituted with 1-3 substituents independently selected from halo (fluoro, chloro, bromo or iodo), alkyl, and alkoxy.

[0030] Sulfonyl refers to the presence of a sulfur atom, which is optionally linked to another moiety such as an aliphatic group, an aromatic group, an aryl group, an alicyclic group, or a heterocyclic group. Aryl or alkyl sulfonyl moieties have the formula —SO_2R', and alkoxy moieties have the formula —O—R', wherein R' is alkyl, as defined above, or is aryl wherein aryl is phenyl, optionally substi-

tuted with 1-3 substituents independently selected from halo (fluoro, chloro, bromo or iodo), lower alkyl (1-6C) and lower alkoxy (1-6C).

[0031] II. Compounds

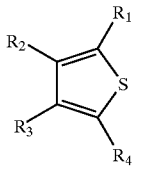
[0032] The present invention is directed to thiophene-containing and furan-containing compounds and methods for their use as drugs. The compounds described herein may be used to treat a variety of diseases. Preferably, the compounds described herein are used in the treatment of PDE6-related conditions. In certain embodiments, the compounds of the present invention preferably modulate PDE6 and have minimal effects on HMG CoA reductase. In certain other embodiments, the compounds described herein are used in conditions wherein a modulation of PDE6 is desired with minimal effects on HMG CoA reductase.

[0033] Those of skill in the art will recognize that the compounds described herein may exhibit the phenomena of tautomerism, conformational isomerism, geometric isomerism and/or optical isomerism. It should be understood that the invention encompasses any tautomeric, conformational isomeric, optical isomeric and/or geometric isomeric forms of the compounds described herein, as well as mixtures of these various different forms. For example, the compounds of the present invention comprise several chiral atoms and it is intended that the present invention encompass all possible stereoisomers and racemic mixtures thereof Accordingly, the compounds described herein may be administered in their entantiomerically pure forms or as a mixture of enantiomers, such as a racemic mixture.

[0034] It will also be appreciated that in many instances the thiophene-containing and furan-containing compounds may metabolize to produce active compounds. The use of active metabolites is also within the scope of the present invention.

[0035] In one aspect, the invention provides compounds having the thiophene skeleton, or a pharmaceutically acceptable salt of such a compound. The thiophene containing compound have the general formula I:

I

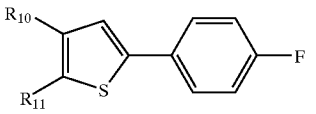


[0036] wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, aryl, heteroaryl, $NR_5C(O)R_7$, $C(O)NR_5R_6$, $C(O)R_7$ and $C(O)OR_7$, wherein R_5, R_6, and R_7 are independently selected to be hydrogen, lower alkyl, cycloalkyl or aryl, and where R_5 and R_6 or R_5 and R_7 together can optionally form a 3, 4, 5, 6, or 7 membered ring optionally having one or more degrees of substitution. Thus, R_5 and R_6 or R_5 and R_7 together can optionally form substituted or unsubstituted aziridino, substituted or unsubstituted piperidino, substituted or unsubstituted morpholino, substituted or unsubstituted imadazolyl, substituted or unsubstituted pyridyl, or substituted or unsubstituted pyrrolidino rings.

[0037] The thiophene-containing compounds illustrative of formula I are shown in **FIG. 1** along with the corresponding compound identification numbers.

[0038] In another aspect of the invention, thiophene containing compounds of formula II, or a pharmaceutically acceptable salt of such a compound, are provided:

II

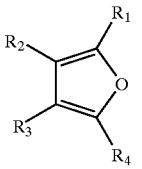


[0039] wherein R_{10} and R_{11} are independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, aryl, heteroaryl, $NR_5C(O)R_7$, $C(O)NR_5R_6$, $C(O)R_7$ and $C(O)OR_7$, wherein R_5, R_6, and R_7 are independently selected to be hydrogen, alkyl, cycloalkyl or aryl, and where R_5 and R_6 or R_5 and R_7 together can optionally form a 3, 4, 5, 6, or 7 membered ring optionally having one or more substitutions. Thus, R_5 and R_6 or R_5 and R_7 together can optionally form substituted or unsubstituted aziridino, substituted or unsubstituted piperidino, substituted or unsubstituted morpholino, substituted or unsubstituted imadazolyl, substituted or unsubstituted pyridyl, or substituted or unsubstituted pyrrolidino ring.

[0040] The thiophene-containing compounds illustrative of formula II are shown in **FIG. 2** along with the corresponding compound identification numbers.

[0041] In one aspect, the invention provides compounds having the furan skeleton, or a pharmaceutically acceptable salt of such a compound. The furan containing compound have the general formula III:

III



[0042] wherein R_1, R_2, R_3, and R_4 is as defined above for formula I.

[0043] The furan-containing compounds illustrative of formula III are shown in **FIG. 3** along with the corresponding compound identification numbers.

[0044] The invention also provides prodrug forms of the above-described compounds, wherein the prodrug is metabolized in vivo to produce a derivative as set forth above. Indeed, some of the above-described derivatives may be a prodrug for another derivative or active compound. The invention further provides for the optical isomers of the compounds disclosed herein, especially those resulting from the chiral carbon atoms in the molecule. In additional embodiments of the invention, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are provided.

[0045] III. Methods of Synthesis

[0046] The compounds of the invention comprise thiophene-containing and furan-containing compounds, as described above. The compounds can be obtained from commercial sources, such as Aldrich Chemical Co. (Milwaukee, Wis.), Sigma Chemical Co. (St. Louis, Mo.), or Maybridge (Cornwall, England), or the compounds can be synthesized; The compounds of the present invention, and other related compounds having different substituents identified by any of the methods described above can be synthesized using techniques and materials known to those of skill in the art, such as described, for example, in March, ADVANCED ORGANIC CHEMISTRY 4th Ed., (Wiley 1992); Carey and Sundberg, ADVANCED ORGANIC CHEMISTY 3rd Ed., Vols. A and B (Plenum 1992), and Green and Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 2nd Ed. (Wiley 1991). Starting materials for the compounds of the invention may be obtained using standard techniques and commercially available precursor materials, such as those available from Aldrich Chemical Co., Sigma Chemical Co, Lancaster Synthesis (Windham, N.H.), Apin Chemicals, Ltd. (New Brunswick, N.J.), Ryan Scientific (Columbia, S.C.), and Maybridge. Starting materials useful for preparing compounds of the invention and intermediates thereof are commercially available or can be prepared by-well-known synthetic methods (see, e.g., Harrison et al., "Compendium of Synthetic Organic Methods", Vols. 1-8 (John Wiley and Sons, 1971-1996); "Beilstein Handbook of Organic Chemistry," Beilstein Institute of Organic Chemistry, Frankfurt, Germany; Feiser et al., "Reagents for Organic Synthesis," Volumes 1-21, Wiley Interscience; Trost et al., "Comprehensive Organic Synthesis," Pergamon Press, 1991; "Theilheimer's Synthetic Methods of Organic Chemistry," Volumes 1-45, Karger, 1991; March, "Advanced Organic Chemistry," Wiley Interscience, 1991; Larock "Comprehensive Organic Transformations," VCH Publishers, 1989; Paquette, "Encyclopedia of Reagents for Organic Synthesis," 3d Edition, John Wiley & Sons, 1995).

[0047] The procedures described herein for synthesizing the compounds of the invention may include one or more steps of protection and deprotection (e.g., the formation and removal of acetal groups). Examples of protecting groups can be found in Greene and Wuts, *Protective Groups in Organic Chemistry*, 3rd Ed., 1999, John Wiley & Sons, NY and Harrison et al., *Compendium of Synthetic Organic Methods*, Vols. 1-8, 1971-1996, John Wiley & Sons, NY. Representative amino protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl ("CBZ"), tert-butoxycarbonyl ("Boc"), trimethylsilyl ("TMS"), 2-trimethylsilyl-ethanesulfonyl ("SES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl ("FMOC"), nitro-veratryloxycarbonyl ("NVOC") and the like. Representative hydroxyl protecting groups include, but are not limited to, those where the hydroxyl group is either acylated (e.g., methyl and ethyl esters, acetate or propionate groups or glycol esters) or alkylated such as benzyl and trityl ethers, as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers (e.g., TMS or TIPPS groups) and allyl ethers.

[0048] In addition, the synthetic procedures can include various purifications, such as column chromatography, flash chromatography, thin-layer chromatography (TLC), recrystallization, distillation, high-pressure liquid chromatography (HPLC) and the like. Also, various techniques well known in the chemical arts for the identification and quantification of chemical reaction products, such as proton and carbon-13 nuclear magnetic resonance (^{1}H and ^{13}C NMR), infrared and ultraviolet spectroscopy (IR and UV), X-ray crystallography, elemental analysis (EA), HPLC and mass spectroscopy (MS) can be used as well. Methods of protection and deprotection, purification and identification and quantification are well known in the chemical arts.

[0049] IV. Activity of Thiophene and Furan Compounds

[0050] In another aspect, the compounds of the invention can be screened for their ability to bind to PDE6D and to modulate the activity of the protein, i.e. identify compounds that increase (stimulate) or decrease (inhibit) the function and/or activity of PDE6D polypeptides or fragments, portions, or analogs thereof. The methods may be performed in vitro or in vivo as described in detail in the copending patent application U.S. Ser. No. _____, entitled "Pyrrole compounds and uses thereof," Docket No. 30583-715.201, filed on May 17, 2004. Briefly, one method for identifying whether a thiophene-containing or furan-containing compound can bind and modulate the activity of PDE6D comprises providing an indicator composition comprising a PDE6D polypeptide or fragment, portion, or analog thereof, contacting the indicator composition with one or more of the compounds disclosed above (a potential PDE6D activator or inhibitor), and determining the effect of the compound on PDE6D activity in the indicator composition to identify a compound that stimulates or inhibits the activity or function of the target. The methods are preferably used to identify stimulators and inhibitors for use in the treatment or prevention of diseases as disclosed herein.

[0051] In some embodiments, a compound affects the function and/or activity of PDE6D such that it may be administered to a subject, preferably human, in need of a change in the function and/or activity of PDE6D. The invention thus provides for the treatment of a disease or undesirable condition mediated by insufficient or unwanted, or in the alternative excess, PDE6D activity, including the binding of PDE6.D to its binding partner(s) or its association with other protein(s), particularly prenylated proteins. The compounds of the invention are expected to include those useful for the modulation of cellular signaling cascades mediated by PDE6D as well as those for the treatment or prevention of cancer and sacral agenesis.

[0052] In another aspect of the present invention, compounds and compositions that are useful for preventing and treating conditions associated with ischemic cell death, such as myocardial infarction, stroke, glaucoma, and other neurodegenerative diseases are provided. Neurodegenerative conditions are characterized by the dysfunction and death of neurons, leading to the loss of functions mediated by the brain, spinal cord and the peripheral nervous system. Other examples of chronic neurodegenerative diseases include diabetic peripheral neuropathy, multiple sclerosis, amyotrophic lateral sclerosis, traumatic brain injury, spinal cord injury, Huntington's disease and Parkinson's disease. Normal brain aging is also associated with loss of normal neuronal function and may entail the depletion of certain neurons.

[0053] The term "stroke" broadly refers to the development of neurological deficits associated with impaired blood

flow to the brain regardless of cause. Potential causes include, but are not limited to, thrombosis, hemorrhage and embolism. Thrombus, embolus, and systemic hypotension are among the most common causes of cerebral ischemic episodes. Other injuries may be caused by hypertension, hypertensive cerebral vascular disease, rupture of an aneurysm, an angioma, blood dyscrasias, cardiac failure, cardiac arrest, cardiogenic shock, septic shock, head trauma, spinal cord trauma, seizure, bleeding from a tumor, or other blood loss. Depending on the area of the brain that is damaged, a stroke can cause coma, paralysis, speech problems and dementia. Some of the major causes of cerebral infarction are vascular thrombosis, cerebral embolism, hypotension, hypertensive hemorrhage, and anoxia/hypoxia. The compounds disclosed herein are useful in the treatment of stroke.

[0054] In accordance with the present invention, the compounds disclosed herein are useful for preventing and treating conditions associated with ischemic cell death, such as myocardial infarction, stroke, glaucoma, and other neurodegenerative conditions. Various neurodegenerative conditions which may involve apoptotic cell death, include, but are not limited to, Alzheimer's Disease, ALS and motor neuron degeneration, Parkinson's disease, peripheral neuropathies, Down's Syndrome, age related macular degeneration (ARMD), traumatic brain injury, spinal cord injury, Huntington's Disease, spinal muscular atrophy, and HIV encephalitis. The thiophene-containing or furan-containing compounds can be used in methods and compositions for imparting neuroprotection and for treating neurodegenerative diseases.

[0055] V. Biological Activity

[0056] The compounds of formulas I, II and III can be used in a pharmaceutical composition for the prevention and/or the treatment of a condition selected from the group consisting of arthritis (including osteoarthritis, degenerative joint disease, spondyloarthropathies, gouty arthritis, systemic lupus erythematosus, juvenile arthritis and rheumatoid arthritis), common cold, dysmenorrhea, menstrual cramps, inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, asthma, bronchitis, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer (such as solid tumor cancer including colon cancer, breast cancer, lung cancer and prostrate cancer; hematopoietic malignancies including leukemias and lymphomas; Hodgkin's disease; aplastic anemia, skin cancer and familiar adenomatous polyposis), tissue ulceration, peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis, recurrent gastrointestinal lesion, gastrointestinal bleeding, coagulation, anemia, synovitis, gout, ankylosing spondylitis, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), periarteritis nodosa, congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuralgia, neurodegenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain (including low back and neck pain, headache and toothache), gingivitis, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, conjunctivitis, abnormal wound healing, muscle or joint sprains or strains, tendonitis, skin disorders (such as psoriasis, eczema, scleroderma and dermatitis), myasthenia gravis, polymyositis, myositis, bursitis, burns, diabetes (including types I and II diabetes, diabetic retinopathy, neuropathy and nephropathy), tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, immunodeficiency diseases (such as AIDS in humans and FLV, FIV in cats), sepsis, premature labor, hypoprothrombinemia, hemophilia, thyroiditis, sarcoidosis, Behcet's syndrome, hypersensitivity, kidney disease, Rickettsial infections (such as Lyme disease, Erlichiosis), Protozoan diseases (such as malaria, giardia, coccidia), reproductive disorders (preferably in livestock) and septic shock (preferably arthritis, fever, common cold, pain and cancer) in a mammal, preferably a human, cat, livestock or a dog, comprising an amount of a compound of formula I, II, or III or a pharmaceutically acceptable salt thereof effective in such prevention and/or treatment optionally with a pharmaceutically acceptable carrier.

[0057] The ability of one or more compounds of formulas I, II, and III to bind to phosphodiesterase 6D (PDE6D) and modulate the activity of PDE6D can be readily determined using methods well known to those skilled in the art. For example, a compound can be contacted (in vitro or in vivo) with cells that express the protein, after which phenotypic changes in the cell culture can be scored as compared to control cells that were not exposed to the compound.

[0058] Biological Target—PDE6 Delta (PDE6D)

[0059] PDE type 6 family members are associated with retinal phototransduction (Stryer, L, et al., *J. Biol. Chem.* 266:10711-14 (1991)). In phototransduction, photoreceptor cells absorb light to trigger a nerve signal via activation of an intracellular cascade of biochemical reactions leading to cGMP hydrolysis by PDE6. Decreases in cGMP result in closure of a membrane-bound cGMP-gated cation channel in the photoreceptor cell to generate a nerve signal. The dark state of the cell is recovered by PDE6 deactivation, guanylcyclase activation, and restoration of cGMP levels.

[0060] PDE6 is a tetrameric protein made up of two catalytic subunits (alpha and beta) and two inhibitory (gamma) subunits. Release of the gamma subunits from the PDE6 complex is mediated by transducin, which activates the enzyme. Reassociation of the gamma subunits is mediated by recoverin, which deactivates the enzyme. While PDE6 is associated primarily with disk membranes of outer rod segments in retinal cells, a soluble form of the enzyme contains a fourth (delta) subunit (Florio, S. K. et al., *J. Biol. Chem.* 271:24036-47 (1996)).

[0061] The PDE6 holoenzyme exists as both membrane-associated and soluble forms, and only the membrane-associated form is active in phototransduction. Importantly, only the soluble form contains the PDE6D subunit. PDE6D regulates the subcellular localization and thus the activity of PDE6, and the release of PDE6 from membranes is mediated by PDE6D. Indeed, PDE6D has been observed to reduce light-induced cGMP hydrolysis in rod outer segments (Cook et al., *J. Biol. Chem.* 276(7):5248-5255.(2001)), presumably by removing the PDE6 holoenzyme from the membrane. PDE6D solubilizes PDE6 by binding specifically to prenylated peptide sequences near the C-termini of the PDE6A and PDE6B subunits. In one embodiment, the invention

provides for treatment of visual impairment disorders, particularly those associated with the phototransduction signaling cascade through the modulation PDE6's participation in cGMP hydrolysis.

[0062] The PDE6 delta (PDE6D) is a 17 kDa subunit that has not been found in association with membrane bound PDE6 but has been observed to solubilize membrane-bound PDE6. This release of PDE6 from the rod membrane appears to be via delta subunit binding to the C-terminal portion of PDE6 and is thought to reduce the likelihood of PDE6 activation by membrane-bound transducing. The delta subunit is also hypothesized as providing another level of enzyme regulation.

[0063] The human PDE delta gene product (PDE6D) has been recognized as a chaperone for the catalytic PDE alpha and beta subunits. Prenylated PDE alpha and beta subunits have been found to be bound by PDE6D and to be solubilized from membranes possibly as a regulatory mechanism in the-visual cascade. Retinitis pigmentosa (RP) is a hereditary retinal dystrophy characterized by impaired dark adaptation and severe reductions in visual acuity. The RP gene has been identified as the retinitis pigmentosa GTPase regulator (RPGR) protein, which has been observed to have binding affinity for members of the PDE6 family even in the absence of prenylation (Linari M, et al., *Proc. Natl. Acad. Sci. USA* 96:1315-1320 (1999)). PDE6D interacts with the retinitis pigmentosa GTPase regulator (RPGR) in a thermosensitive fashion. Interaction is abolished by mutations in the RCC1-domain of RPGR. In one embodiment, the invention provides for treatment of RP through the modulation of PDE6 interaction with RPGR and other molecules involved in the phototransduction cascade.

[0064] PDE6D is expressed in many cell types and has a general role in regulating the intracellular localization and transport of prenylated proteins, including H-Ras, Rheb, Rho6, Rac, Rap, and PDE6 (Hanzal-Bayer et al. EMBO J. 21(9):2095-2106 (2002) and Linari et al. Proc. Natl. Acad. Sci., USA 96(4):1315-1320). The role of PDE6D in regulating the membrane localization of these prenylated proteins is still unclear, but it has been proposed that PDE6D delivers proteins from endomembranes (endoplasmic reticulum and Golgi) to trafficking structures that ensure correct delivery to the ultimate membrane compartment.

[0065] PDE6D interacts with GTPases, a large superfamily of proteins that play a major role at the cell membrane as molecular switches, active when GTP-bound and inactive when GDP-bound. The majority of these GTPases have a covalently attached prenyl group for anchorage to the intracellular side of the cell membrane. They function by shuttling between the membrane-anchored form and a free cytosolic form. The delta subunit can bind the isoprenylated region of the small Rab13 GTPase and displace it from the plasma membrane. (Marzesco et al., *J. Biol. Chem.* 273(35):22340-22345 (1998)). In addition, PDE6D is capable of interacting with the C-terminal regions of both the Ras and Rap GTPases and regulating their association with the plasma membrane. For Ras binding PDE6D requires a prenylated region of the C-terminus. (Nancy et al., *J. Biol. Chem.* 277(17):15076-15084 (2002)).

[0066] PDE6D has also been observed to interact with H-Ras, Rheb, Rho6 and Ga(il) and suggested as a transport factor for prenylated proteins, including subunits of PDE and small GTP-binding proteins. (Hanzal-Bayer et al. *EMBO J.* 21(9):2095-2106 (2002)). cGMP PDE-specific inhibitors which act on PDE6 and PDE5 include zaprinast, desmethylsildenophil, vinopocetine, milrinone, amnrinone, pimobendan, cilostamide, enoximone, peroximone, vesnarinone, rolipran, R020-1724, and dipyridamole. The compounds of the invention may be administered to treat medical disorders or diseases attributable to errant intracellular transport of prenylated proteins and/or GTP-binding proteins.

[0067] The biosynthetic pathways for prenyl groups (e.g. farnesyl and geranyl-geranyl) and cholesterol are overlapping and both require HMG-CoA reductase activity. PDE6D can also be considered an important component of the prenylation pathway since it regulates the transport and localization of prenylated proteins. Prenylated proteins have critical roles in signal transduction (e.g. Ras), and there is evidence suggesting a role for prenylated proteins in neurotoxicity (Liao J. K. J. Clinical Investigation, 110: 285-288 (2002)). Thus, compounds that bind to PDE6D and modulate its activity should perturb directly the localization and function of prenylated proteins, and be useful in the prevention and treatment of conditions and diseases.

[0068] PDE6D has been observed to reduce light-induced cGMP hydrolysis in rod outer segments (Cook et al., *J. Biol. Chem.* 276(7):5248-5255 (2001)). The delta subunit interacts directly with the prenylated C-terminal regions of two G-protein coupled rhodopsin kinases, GRK1 and GRK7 that are specific to photoreceptors. (Zhang et al., *J. Biol. Chem.* 279(1):407-413 (2004)). Rhodopsin kinases phosphorylate membrane photoreceptors to regulate phototransduction. In one embodiment, the invention provides for a method of treatment of visual impairment through modulation of PDE6 interaction with rhodopsin kinases and other molecules involved in the phototransduction signaling cascade.

[0069] PDE6D has also been found to interact with other proteins absent post-translational prenylation. For example, PDE6D interacts with the unprenylated region of the retinitis pigmentosa GTPase regulator (RPGR) protein. (Linari et al., *Proc. Natl. Acad. Sci., USA* 96(4):1315-1320 (1999)). In addition, the delta subunit can interact with two members of the GTPase subfamily known as Arl proteins or the ARF (ADP-ribosylation factor)-like proteins. PDE6D interacts with the Arl2 and Arl3 proteins independent of any post-translational modification (Hanzal-Bayer et al., *EMBO J.* 21(9):2095-2106 (2002) and Linari et al., *FEBS Letter* 458:55-59 (1999)). Based on their structure-function studies, Hanzal-Bayer et al., have posited that the delta subunit is a transport factor for membrane bound prenylated proteins, such as the GTP binding molecules, and Arl2/3 serves as the mediator of the delta subunit in the release and/or uptake of prenylated proteins. In one embodiment, the invention provides a method of treating a PDE6-related and/or GTP-binding protein-related disorder through the modulation of Arl2/3 molecule activity. The use of the term "PDE6" and references to its activities and/or modulation, herein, is intended to also include activity and/or modulation of PDE6D without an interaction with PDE6.

[0070] VI. Clinical Uses of Compounds

[0071] The compounds of formulas I, II and III may be used to treat a variety of diseases and unwanted conditions. Preferably, the compounds described herein are used in the

treatment of PDE6-related conditions. Diseases that may be treated with the compounds described herein include, but are not limited to, cerebral accident (or cerebrovascular accident, including stroke), inflammation (including inflammation due to autoimmune diseases), multiple sclerosis, blood vessel growth (angiogenesis), bone formation/bone growth, immune system stimulation, acute coronary syndromes (including myocardial infarction, non-Q-wave myocardial infarction and unstable angina), and cardiovascular disease. In one aspect, the compounds of the invention may be used to reduce the likelihood of stroke or cardiovascular disease, and to decrease damage following brain and/or heart infarction or other trauma. In another aspect, the compounds may be used to reduce the severity of damage caused by stroke or cardiovascular disease in a subject. Non-limiting examples of the benefit provided by the compounds include decreased brain and/or heart infarction. The use of the compounds described herein is not intended to be limited to PDE6-related conditions or modulation of PDE6; the present compounds can be used to treat other conditions and modulate other biological targets.

[0072] The term "PDE6-related condition" as used herein refers to a condition in which directly or indirectly modulating the activity and/or production of a PDE6 molecule, respectively, is desirable. This modulation includes modulation of one or more molecules in the upstream or downstream signaling cascades of PDE6. For example, a PDE6-related condition may involve over-production or unwanted production of one or more prenylated PDE6 subunits, such as PDE6D, prenylated PDE6α or PDE6β, or other chemical messengers of cell signaling pathways associated with phototransduction (including responses to and expression of PDE6 alpha and PDE6 beta).

[0073] In some embodiments, the methods of the present invention employ a PDE6 modulating compound. The term "PDE6 modulating compound" as used herein and its grammatical conjugations refer to a compound that preferably modulates PDE6, for example by binding to PDE6, preferably by binding to PDE6D. For example, a PDE6 modulating compound may modulate one or more prenylated PDE6 subunits, such as PDE6D, prenylated PDE6α or PDE6β, or other chemical messengers of cell signaling pathways associated with phototransduction (including responses to and expression of PDE6 alpha and PDE6 beta). In some embodiments the term "preferable modulation" and its grammatical conjugations refers to a specific modulation of PDE6. In other embodiments, the term refers to preferable modulation of PDE6 with minimal modulation of HMG Co A reductase. The term "minimal modulation" refers to essentially no modulation, but does not require a complete lack of modulation; it refers to essentially no observable or measurable activity. In treatment scenarios, "minimal modulation" refers to modulation that is not sufficient to produce a therapeutic and/or prophylactic benefit in a condition caused by the activity that is not being modulated.

[0074] Modulating the activity of a PDE6 molecule includes reducing, increasing, or stabilizing the activity of these molecules. Reducing the activity of PDE6 is also referred to as "inhibiting" the molecule. The term "inhibits" and its grammatical conjugations, such as "inhibitory," is not intended to require complete inhibition in PDE6 activity. Such reduction is preferably by at least about 50%, at least about 75%, at least about 90%, and more preferably by at least about 95% of the activity of the molecule in the absence of the inhibitory effect, e.g., in the absence of an inhibitor. Most preferably, the term refers to an observable or measurable reduction in activity. In treatment scenarios, preferably the inhibition is sufficient to produce a therapeutic and/or prophylactic benefit in the condition being treated. The phrase "does not inhibit" and its grammatical conjugations does not require a complete lack of effect on the activity. For example, it refers to situations where there is less than about 20%, less than about 10%, and preferably less than about 5% of reduction in PDE6 activity in the presence of an inhibitor such as a compound of the invention.

[0075] The PDE6-modulating agents of the invention can be administered to a mammalian subject to treat a disorder by modulating the binding of PDE6D to prenylated GTPases, thereby modulating GTPase-dependent signal transduction pathways. The disruption of GTPase-dependent pathways contributes to a variety of medical conditions, such as vascular hyperplasia, thrombin-induced cell death, the pathogenesis and progression of bladder cancer, chronic inflammatory disease, endothelial dysfunction in cardiovascular disease, cardiac hypertrophy, a change in cerebral blood flow to ischemic regions of the brain, phagocytosis of amloid-beta fibrils in Alzheimer's disease patients, immunodeficiency disorders and increased free radical production in aortic vascular smooth muscle cells.

[0076] PDE6-related conditions can include neurodegenerative diseases, including ischemic stroke, basal ganglia or Parkinson's disease, epilepsy or brain or spinal cord ischemia or trauma; Alzheimer's disease, dementia, diabetic peripheral neuropathy, multiple sclerosis, amyotrophic lateral sclerosis, traumatic brain injury, spinal cord injury, Huntington's disease, heart failure (e.g. congestive heart failure, acute heart failure, cardiac hypertrophy, etc.) or renal diseases.

[0077] PDE6-related conditions can include visual impairment disorders, including macular degeneration, amblyopia, Blepharitis, Bietti's Crystalline Dystrophy, corneal disease, diabetic eye disease, glaucoma, histoplasmosis, and retinitis pigmentosa. PDE6-related conditions can include cardiovascular-related conditions, including atherosclerosis, myocardial infarction, congestive heart failure, ischemic-reperfusion injury and other vascular inflammatory conditions. PDE6-related conditions can also include proliferative disorders, including cancers, e.g., leukemia, melanoma, Non-Hodgkins Lymphoma, as well as bladder, breast, colon, endometrial, head and neck, lung, ovarian, prostate and rectal cancers.

[0078] PDE6-related conditions can also include neurological deficits that develop from a stroke-induced impairment of blood flow to the brain regardless of cause. Potential causes include, but are not limited to, thrombosis, hemorrhage and embolism. Thrombus, embolus, and systemic hypertension are among the most common causes of cerebral ischemic episodes. Other injuries may be caused by hypertension, hypertensive cerebral vascular disease, rupture of an aneurysm, an angioma, blood dyscrasias, cardiac failure, cardiac arrest, cardiogenic shock, septic shock, head trauma, spinal cord trauma, seizure, bleeding from a tumor, or other blood loss.

[0079] In one embodiment, the PDE6-modulating agent modulates the activity small GTP binding protein Rho in its

role in cell proliferation. It has been reported that Rho proteins are more abundant in tumor bladders than in non-tumor bladders and upregulated in ovarian carcinomas (Kamai T, et al., *Clin. Cancer Res.* July; 9(7):2632-41 (2003) and Horiuchi A, et al., *Lab Invest.* June 2003; 83(6): 861-70 (2003)).

[0080] A disruption in Rho GTP binding activity has been shown to have the neuroprotective effect of increasing cerebral blood flow to ischemic regions of the brain (Laufs U, et al., *J. Clin. Invest.* 106(1):15-24 (2000)). The study demonstrated that under absent or decreased rho-dependent actin cytoskeleton stress fiber formation, eNOS was upregulated and the severity of cerebral ischemia was decreased. An embodiment of the invention provides for the treatment of ischemic stroke by modulation of Rho by a compound of the invention.

[0081] Researchers have reported that the cardiac hypertrophy, which requires intracellular oxidation may be reduced by statin-induced inhibition of post-translational modification of the small G proteins of the Rho family (Takemoto M, et al., *J. Clin. Invest.* 108(10):1429-37 (2001)). Takemoto M, et al. observed that an inhibition of the Rho isoprenylation produced an intracellular-antioxidant effect and inhibit cardiac hypertrophy. One embodiment of the invention provides for the treatment of cardiac hypertrophy by modulation of Rho by a compound of the invention.

[0082] In another embodiment, the PDE6-modulating agent modulates the activity of the small GTP binding protein Rac in its role in Alzheimer's disease. Rac has been observed to participate in the phagocytosis of amyloid-beta fibrils from extracellular senile plaques. (Kitamura Y, et al, *J. Pharmacol. Sci.* 92(2):115-23 2003)).

[0083] The compounds I, II, and III of the invention can be used to treat a variety of diseases and unwanted conditions, including, but not limited to, cerebral accident (or cerebrovascular accident, including stroke), inflammation (including inflammation due to autoimmune diseases), multiple sclerosis, blood vessel growth (angiogenesis), bone formation/bone growth, immune system stimulation, acute coronary syndromes (including myocardial infarction, non-Q-wave myocardial infarction and unstable angina), and cardiovascular disease. In one embodiment, the compounds of the invention can be used to reduce the likelihood of stroke or cardiovascular disease, and to decrease damage following brain and/or heart infarction or other trauma. In another embodiment, the compounds can be used to reduce the severity or damage caused by stroke or cardiovascular disease in a subject. Non-limiting examples of the benefit provided by the compounds include decreased brain and/or heart infarction.

[0084] VII. Formulations, Routes of Administration, and Effective Doses

[0085] The compounds of formulas I, II, and III are preferably used to prepare a medicament, such as by formulation into pharmaceutical compositions for administration to a subject using techniques generally known in the art. A summary of such pharmaceutical compositions may be found, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa. The compounds of the invention can be used singly or as components of mixtures. Preferred forms of the compounds are those for systemic administration as well as those for topical or transdermal administration. Formulations designed for sustained and/or delayed release are also with the scope of the invention.

[0086] Such pharmaceutical compositions can be used to treat PDE6-related conditions, as described in detail above. If necessary or desirable, the modulator or inhibitor may be administered in combination with other therapeutic agents. The choice of therapeutic agents that can be co-administered with the compositions of the invention will depend, in part, on the condition being treated.

[0087] The modulators may be administered per se or in the form of a pharmaceutical composition wherein the active compound(s) is in an admixture or mixture with one or more pharmaceutically acceptable carriers, excipients or diluents. Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more physiologically acceptable carriers compromising excipients and auxiliaries, which facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. The modulators useful in the present invention can be delivered to the patient using a number of routes or modes of administration, including oral, buccal, topical, rectal, transdermal, transmucosal, subcutaneous, intravenous, and intramuscular applications, as well as by inhalation.

[0088] Methods for the preparation of compositions comprising the compounds of the invention include formulating the derivatives with one or more inert, pharmaceutically acceptable carriers to form either a solid or liquid. Solid compositions include, but are not limited to, powders, tablets, dispersible granules, capsules, cachets, and suppositories. Liquid compositions include solutions, emulsions, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein.

[0089] Compounds of this invention may also be integrated into foodstuffs, e.g, cream cheese, butter, salad dressing, or ice cream to facilitate solubilization, administration, and/or compliance in certain patient populations.

[0090] The compounds of the invention may be labeled isotopically (e.g. with a radioisotope) or by another other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels. The compositions may be in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. Suitable excipients or carriers are, for example, water, saline, dextrose, glycerol, alcohols, aloe vera gel, allantoin, glycerin, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate, and the like. Of course, these compositions may also contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and so forth.

[0091] For oral administration, the compounds can be formulated readily by combining the active compound(s) with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, including chewable tablets, pills,

dragees, capsules, lozenges, hard candy, liquids, gels, syrups, slurries, powders, suspensions, elixirs, wafers, and the like, for oral ingestion by a patient to be treated. Such formulations can comprise pharmaceutically acceptable carriers including solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; flavoring elements, cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. The compounds may also be formulated as a sustained release preparation.

[0092] Dragee cores can be provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0093] Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for administration.

[0094] Aqueous suspensions may contain a compound of this invention with pharmaceutically acceptable excipients, such as a suspending agent (e.g., methyl cellulose), a wetting agent (e.g., lecithin, lysolecithin and/or a long-chain fatty alcohol), as well as coloring agents, preservatives, flavoring agents, and the like.

[0095] For injection, the inhibitors of the present invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. Such compositions may also include one or more excipients, for example, preservatives, solubilizers, fillers, lubricants, stabilizers, albumin, and the like. Methods of formulation are known in the art, for example, as disclosed in Remington's Pharmaceutical Sciences, latest edition, Mack Publishing Co., Easton P. These compounds may also be formulated for transmucosal administration, buccal administration, for administration by inhalation, for parental administration, for transdermal administration, and rectal administration.

[0096] In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or transcutaneous delivery (for example subcutaneously or intramuscularly), intramuscular injection or use of a transdermal patch. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0097] In some embodiments, pharmaceutical compositions comprising compounds of the present invention exert local and regional anti-inflammatory effects when administered topically or injected at or near particular sites of inflammation. For example, ocular allergic, inflammatory and/or autoimmune conditions can be effectively treated with ophthalmic solutions, suspensions, ointments or inserts comprising one or more compounds of the present invention. Allergic, inflammatory and/or autoimmune conditions of the ear can be effectively treated with otic solutions, suspensions, ointments or inserts comprising one or more compounds of the present invention. Allergic, inflammatory and/or autoimmune conditions of the skin and skin structures can be effectively treated with skin ointments comprising one or more compounds of the present invention in an oleaginous hydrocarbon base, an anhydrous absorption base, a water-in-oil absorption base, an oil-in-water water-removable base and/or a water-soluble base. Gastrointestinal allergic, inflammatory and/or autoimmune conditions can be effectively treated with orally- or rectally delivered solutions, suspensions, ointments, enemas and/or suppositories comprising one or more compounds of the present invention. Respiratory allergic, inflammatory and/or autoimmune conditions can be effectively treated with aerosol solutions, suspensions or dry powders comprising one or more compounds of the present invention.

[0098] For example, for treating inflammatory and/or autoimmune conditions, a cream comprising a compound of the invention may be topically applied to the affected site, for example, sites displaying red plaques or dry scales in psoriasis, or areas of irritation and dryness in dermatitis. As another example, for treating inflammatory bowel disease, a suppository formulation of a compound disclosed herein can be used. In such embodiments, the active ingredient produces a benefit locally at or near the site of application, rather than systemically, by modulating PDE6, e.g., PDE6D.

[0099] Direct topical application, e.g., of a viscous liquid, gel, jelly, cream, lotion, ointment, suppository, foam, or aerosol spray, may be used for local administration, to produce for example local and/or regional effects. Pharmaceutically appropriate vehicles for such formulation include, for example, lower aliphatic alcohols, polyglycols (e.g., glycerol or polyethylene glycol), esters of fatty acids, oils, fats, silicones, and the like. Such preparations may also include preservatives (e.g., p-hydroxybenzoic acid esters) and/or antioxidants (e.g., ascorbic acid and tocopherol). See also Dermatological Formulations: Percutaneous absorption, Barry (Ed.), Marcel Dekker Incl, 1983.

[0100] In some preferred embodiments, the compounds of the present invention are delivered in soluble rather than suspension form, which allows for more rapid and quantitative absorption to the sites of action. In general, formulations such as jellies, creams, lotions, suppositories and ointments can provide an area with more extended exposure to the compounds of the present invention, while formulations in solution, e.g., sprays, provide more immediate, short-term exposure.

[0101] The formulations also may comprise suitable solid or gel phase carriers or excipients that increase penetration or help delivery of inhibitory compounds of this invention across the permeability barrier of the skin. Many of these penetration-enhancing compounds are known in the art of topical formulation. Examples of such carriers and excipients include humectants (e.g., urea), glycols (e.g., propylene glycol and polyethylene glycol), alcohols (e.g., ethanol), fatty acids (e.g., oleic acid), surfactants (e.g., isopropyl myristate and sodium lauryl sulfate), pyrrolidones, glycerol monolaurate, sulfoxides, terpenes (e.g., menthol), amines, amides, alkanes, alkanols, ORGELASE, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, other polymers and water. In some embodiments, the pharmaceutical compositions will include one or more penetration enhancers such as water, methanol, ethanol, 2-propanol, dimethyl sulfoxide, decylmethyl sulfoxide, tetradecylmethyl sulfoxide, 2-pyrrolidone, N-methyl-2-pyrrolidone, N-(2-hydroxyethyl)pyrrolidone, laurocapram, acetone, dimethylacetamide, dimethylformamide, tetrahydrofurfuryl alcohol, L-α-amino acids, anionic surfactants, cationic surfactants, amphoteric surfactants, nonionic surfactants, fatty acids, fatty alcohols, clofibric acid amides, hexamethylene lauramide, proteolytic enzymes, α-bisabolol, d-limonene, urea, N,N-diethyl-m-toluamide, and the like.

[0102] In some embodiments, the pharmaceutical compositions will include one or more antimicrobial preservatives such as quaternary ammonium compounds, organic mercurials, p-hydroxy benzoates, aromatic alcohols, chlorobutanol, and the like.

[0103] Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are present in an effective amount, i.e., in an amount effective to achieve therapeutic and/or prophylactic benefit in at least one of a PDE6-related condition. The actual amount effective for a particular application will depend on the condition or conditions being treated, the condition of the subject, the formulation, and the route of administration, as well as other factors known to those of skill in the art. Determination of an effective amount of a PDE6 modulator is well within the capabilities of those skilled in the art, in light of the disclosure herein, and will be determined using routine optimization techniques.

[0104] In therapeutic use, the compounds of the invention are administered to a subject at dosage levels of from about 0.05 mg/kg to about 10.0 mg/kg of body weight per day. For a human subject of approximately 70 kg, a dosage of from 40 mg to 600 mg per day may be used as a non-limiting example. Preferred doses include about 1 mg/kg, about 2.5 mg/kg, about 5 mg/kg, and about 7.5 mg/kg. Lower or higher doses than those disclosed herein may be used, as required. Such dosages, however, may be altered depending on a number of variables, not limited to the activity of the compound used, the condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the condition being treated, and the judgment of the practitioner. The foregoing ranges are merely suggestive, as the number of variables in regard to an individual treatment regime is large, and considerable excursions from these recommended values are not uncommon.

[0105] The effective amount for use in humans can be determined from animal models. For example, a dose for humans can be formulated to achieve circulating, liver, topical and/or gastrointestinal concentrations that have been found to be effective in animals.

[0106] The effective amount when referring to an inhibitor of the invention will generally mean the dose ranges, modes of administration, formulations, etc., that have been recommended or approved by any of the various regulatory or advisory organizations in the medical or pharmaceutical arts (e.g. FDA, AMA) or by the manufacturer or supplier.

[0107] In some embodiments, administration of compounds of the present invention may be intermittent, for example administration once every two days, every three days, every five days, once a week, once or twice a month, and the like. In some embodiments, the amount, forms, and/or amounts of the different forms may be varied at different times of administration.

[0108] VIII. Kits/Articles of Manufacture

[0109] For use in the therapeutic applications described herein, kits and articles of manufacture are also within the scope of the invention. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method of the invention. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

[0110] For example, the container(s) can comprise one or more thiophene-containing or furan-containing compounds of the invention, optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example the container can be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprising a thiophene-containing or furan-containing compound with an identifying description or label or instructions relating to its use in the methods of the present invention.

[0111] A kit of the invention typically may comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a thiophene-containing or furan-containing compound of the invention. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included.

[0112] A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

[0113] The terms "kit" and "article of manufacture" may be used as synonyms.

EXAMPLES

[0114] Having now generally described the invention, the same will be more readily understood through reference to the following examples. The examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperatures, etc.), but some experimental error and deviation should, of course, be allowed for.

Example 1

The Affinity of the Thiophene-Containing Compounds for PDE6D

[0115] The T7 phage displaying human PDE6D and CLB2 were obtained following the procedure of WO 01/18234, published Mar. 15, 2001, and U.S. patent application Ser. No. 10/115,442, "Phage Display Affinity Filter and Forward Screen, filed Apr. 2, 2002. Briefly, a T7 phage-display-based affinity chromatography procedure was used where atorvastatin was chemically coupled to a biotinylated linker moiety, which enabled the attachment of atorvastatin to streptavidin-coated magnetic beads. The atorvastatin-coated magnetic beads were used as an affinity matrix to probe the human proteome for atorvastatin-binding proteins. T7 phage display libraries that broadly cover the human proteome were mixed with the atorvastatin affinity matrix and non-binding clones were removed by washing. Atorvastatin-binding clones were eluted by incubating the affinity matrix with soluble atorvastatin. The phage eluate was then amplified by growth in *E. coli* and the affinity enrichment procedure was repeated. After four rounds of affinity enrichment, predominant atorvastatin-binding clones emerged and was identified by DNA sequencing as human PDE6D and CLB2. The binding of atorvastatin to PDE6D and CLB2 was further validated by competition binding assays, where the Kd's for the interactions between soluble atorvastatin (non-immobilized, no linker moiety) and the proteins were determined to be 65 nM and 500 nM for PDE6D and CLB2, respectively.

[0116] The dissociation constants, Kd's, for the interaction between the thiophene compounds and the novel targets were obtained following the procedure of the co-pending patent applications U.S. Ser. Nos. 10/115,442, "Phage Display Affinity Filter and Forward Screen," filed Apr. 2, 2002 and 60/480,587, "Protein Family Profiling Tool and Methods," filed Jun. 20, 2003. To measure the Kd values, the T7 phage displaying human PDE6D or CLB2 were incubated with an atorvastatin-coated affinity matrix in the presence of various concentrations of a soluble (non-immobilized) thiophene compounds of the invention, as described in detail above. Soluble thiophene compounds that bind PDE6D and/or CLB2 prevent binding of PDE6D and/or CLB2 phage to the affinity matrix; hence, fewer phage are recovered in the phage eluate in the presence of an effective competitor than in the absence of an effective competitor. The Kd for the interaction between the soluble thiophene compound (competitor) molecule and PDE6D or CLB2 is equal to the concentration of soluble competitor molecule that causes a 50% reduction in the number of phage recovered in the eluate compared to a control sample lacking soluble competitor. Table 1 displays the μM Kd of certain thiophene compounds for PDE6D.

TABLE 1

Thiophene Compound	Kd PDE6D (nM)
781560	830
779974	348
781456	567
783172	469
783146	1675

Example 2

Efficacy Studies of Compounds in the Rodent MCAo Model

[0117] Overview. The purpose of this study is to evaluate the efficacy of the compounds described herein in the rat Middle Cerebral Artery Occlusion (MCAo) model induced by electrocoagulation of the middle cerebral artery and tandem carotid artery occlusion according to Chen et al., *Stroke,* 17:4 (1986). Infarct Volume comparison to control vehicle volume will be used for evaluating efficacy of the compound(s). Small numbers of animals (n=5/group) will be used to test for potential efficacy in reducing the infarct size after 48 hours.

[0118] Methods

[0119] Animal Preparation. Forty-five male, adult, Sprague-Dawley rats (Taconic Farms), weighing 300-350 g, will be used for the study. Animals are housed in a standard animal facility and fed with commercial rodent chow ad libitum. Extra animals will be ordered to allow for proper randomization and mortality from the surgical procedures. The rats will be approximately 10 weeks of age when they arrive at the laboratory.

[0120] All animals will be housed for 7 days prior to surgery for acclimation purposes. At the end of the training period, animals will be randomized and assigned to different groups. Animals will be given a unique identification number by tail marking. The animals will be identified by tail number and cage cards.

[0121] Surgical Preparation. Middle Cerebral Artery Occlusion (MCAo). Male Sprague Dawley rats (300-350 grams,) are anesthetized with an intramuscular 4 ml/kg "cocktail" of Ketamine (25 mg/ml), Xylazine (1.3 mg/mL) and Acepromazine (0.33 mg/mL). In general, the common carotid arteries are exposed through a ventral midline cervical incision in the neck. The temporalis muscle is bisected and reflected through an incision performed midway between the eye and the eardrum canal. A 3 mm burr hole is made at the junction of the zygomatic arch and the squamos bone such that the bifurcation of the frontal and parietal branch of the middle cerebral artery is exposed. The right middle cerebral artery is permanently occluded using electrocoagulation directly below the bifurcation of the frontal and parietal branch and superior to the rhinal vein on the MCA, the common carotid arteries are temporarily occluded using atraumatic aneurysm clips for one hour. Body temperature is maintained at 38° C.±1 throughout the entire procedure. Animals are euthanized at various time periods after MCA occlusion and the brains are removed for histological analysis.

[0122] Morphometric Analysis. Forty-eight hours after the induction of focal ischemia, rats will be deeply anesthetized with CO_2 and decapitated. The brain is removed and placed in ice chilled (~4° C.) saline for fifteen minutes. Seven 2.0 mm coronal slices are cut using a brain-cutting matrix and incubated in two percent 2, 3, 5 triphenyltetrazolium chloride (TTC) for 20 minutes at 37° C. Slices are removed, washed in saline and put into 10% formalin for 24 hours before tissue analysis. (TTC is an established marker for functional mitochondrial enzymes and produces a visible deep red color within normal tissue. Ischemic tissue, lacking mitochondrial activity, remains unstained and appears white. This is a standard method for use in image analysis of the sliced brain and quantification of the ischemic area after MCAo.)

[0123] Infarct Volume Measurement. Using the Image Pro-Plus imaging system, a total of 14 images per brain of both the frontal and posterior side of each slice are analyzed through digital analysis. The total infarct volume is calculated for the left hemisphere using the equation below. Digitizing and computation is done under blinded conditions.

$$\text{Volume } (mm^3) = \frac{\Sigma \text{ area } (mm^2) \text{ per side}}{\text{No. of sides analyzed}} \times 14 \text{ mm}$$

[0124] The total infarct volumes are calculated for each animal and subsequent group means are determined as volume of area (mm^3). To account for tissue shrinkage and possible edema indirect method of infarct volume is calculated using the formula:

Total Contralateral Hemisphere Volume−Total Infarcted Hemisphere Volume (mm^3)

[0125] Body Temperature and Weight. The body temperatures of all animals are monitored throughout the surgery and maintained near normal values (37-38° C). The body weight of all animals are measured and documented before surgery and at the end of the study immediately before euthanation.

[0126] Clinical Observations. Animals will be observed daily for abnormal behavior, including but not limited to circling, lethargy, respiratory wheezing or discharge, hair loss, and early death. All abnormalities will be recorded. Likewise, normal behavior will also be noted as normal.

[0127] Statistical Analysis. All data are expressed as mean±SEM. Infarct volume will be analyzed using a two tailed t-test and Dunnett's multiple comparisons. Behavioral tests, temperature, and body weight are analyzed using one-way ANOVA followed by post hoc Bonferroni's Multiple Comparison Test. A p value of $\leqq 0.05$ is considered a statistically significant difference.

[0128] Experimental Design

[0129] Experimental Groups and Compound Administration. One or more compounds, selected from the compounds described herein, will be tested. Fifteen animals will be used to test a compound using three groups of animals, n=5 animals per group. One group will receive 1 mg/kg body weigh, the second group will receive 10 mg/kilogram body weight and the third group will receive vehicle only at the same time points as the test article via intraperitoneal injections beginning 2 hours pre-MCAo, 3 hours and 24 hours post MCAo

[0130] All animals are treated with the compound(s)/vehicle(s) in a blinded random investigation. Table 2 provides a summary of an Experimental Design for testing one of the compounds described herein.

TABLE 2

		Treatment Paradigm			
Group	n	Test articles	Dose	Route	Time Period
1	5	Vehicle	No TX	IP	2 Hours Pre 3, 24 Hours Post
2	5	Compound	1 mg/kg Body weight	IP	2 Hours Pre 3, 24 Hours Post
3	5	Compound	10 mg/kg Body weight	IP	2 Hours Pre 3, 24 Hours Post

[0131] It is anticipated that it will take approximately 5 weeks to complete the technical work of this study at the rate of 2 compounds, using 30 animals screened per week.

Example 3

Efficacy Studies of Compounds in the Rodent MCAo Model

[0132] The purpose of this study is to further evaluate the efficacy of the compound described herein. Infarct volume of compound-treated animals in comparison to control volume will be used for evaluating efficacy of the compound described herein.

[0133] Methods

[0134] Animal Preparation. One Hundred and twelve male, adult, Sprague-Dawley rats (Taconic Farms), weighing 300-350 g, will be used for the study. Animals are housed in a standard animal facility and fed with commercial rodent chow ad libitum. Extra animals will be ordered to allow for proper randomization and mortality from the surgical procedures. The rats will be approximately 10 weeks of age when they arrive at the laboratory.

[0135] All animals will be housed for 7 days prior to surgery for acclimation purposes. At the end of the training period, animals will be randomized and assigned to different groups. Animals will be given a unique identification number by tail marking. The animals will be identified by tail number and cage cards.

[0136] Surgical Preparation. Middle Cerebral Artery Occlusion (MCAo). Male Sprague Dawley rats (300-350 grams,) are anesthetized with an intramuscular 4 ml/kg "cocktail" of ketamine (25 mg/ml), xylazine (1.3 mg/mL) and acepromazine (0.33 mg/mL). In general, the common carotid arteries are exposed through a ventral midline cervical incision in the neck. The temporalis muscle is bisected and reflected through an incision performed midway between the eye and the eardrum canal. A 3 mm burr hole is made at the junction of the zygomatic arch and the squamos bone such that the bifurcation of the frontal and parietal branch of the middle cerebral artery is exposed. The right middle cerebral artery is permanently occluded using electrocoagulation directly below the bifurcation of the

frontal and parietal branch and superior to the rhinal vein on the MCA, the common carotid arteries are temporarily occluded using atraumatic aneurysm clips for one hour. Body temperature is maintained at 38° C.±1 throughout the entire procedure. Animals are euthanatized at various time periods after MCA occlusion and the brains are removed for histological analysis.

[0137] Morphometric Analysis. Forty-eight hours after the induction of focal ischemia, rats will be deeply anesthetized with CO_2 and decapitated. The brain is removed and placed in ice chilled (~4° C.) saline for fifteen minutes. Seven 2.0 mm coronal slices are cut using a brain-cutting matrix and incubated in two percent 2, 3, 5 triphenyltetrazolium chloride (TTC) for 20 minutes at 37° C. Slices are removed, washed in saline and put into 10% formalin for 24 hours before tissue analysis. (TTC is an established marker for functional mitochondrial enzymes and produces a visible deep red color within normal tissue. Ischemic tissue, lacking mitochondrial activity, remains unstained and appears white. This is a standard method for use in image analysis of the sliced brain and quantification of the ischemic area after MCAo.).

[0138] Infarct Volume Measurement. Using the Image Pro-Plus imaging system, a total of 14 images per brain of the posterior side of each slice are analyzed through digital analysis. The total infarct volume is calculated for the left hemisphere using the equation below. Digitizing and computation is done under blinded conditions.

$$\text{Volume } (mm^3) = \frac{\Sigma \text{ area } (mm^2) \text{ per side}}{\text{No. of sides analyzed}} \times 14 \text{ mm}$$

[0139] The total direct infarct volumes are calculated for each animal and subsequent group means are determined as volume of area (mm^3).

[0140] Body Temperature and Weight. The body temperatures of each animal are monitored throughout the surgery and maintained near normal values (37-38° C.). Animal's body weights are measured and documented before surgery and at the end of the study immediately before euthanation.

[0141] Clinical Observations. Animals will be observed daily for abnormal behavior, including but not limited to circling, lethargy, respiratory wheezing or discharge, hair loss, and early death. All abnormalities will be recorded. Likewise, normal behavior will also be noted as normal.

[0142] Statistical Analysis. All data are expressed as mean±SEM. Infarct volume will be analyzed using a two tailed t-test and Dunnett's multiple comparisons. Behavioral tests, temperature, and body weight are analyzed using one-way ANOVA followed by post hoc Bonferroni's Multiple Comparison Test. A p value of $\leqq 0.05$ is considered a statistically significant difference.

[0143] Experimental Design

[0144] Experimental Groups and Compound Administration. A number of animals will undergo MCAo using subcutaneous administration of all test articles. One or more compounds, selected from the compounds disclosed herein, at one predetermined dose will be compared to a control or vehicle and assigned to three different time schedules of administration relative to the time of MCAo.

[0145] The time schedules for administration of all treated groups will be divided as follows:

[0146] a. 2 hrs pre, 3 hrs post, & 25 hrs post

[0147] b. 1 hr,3 hrs, & 25 hrs post

[0148] c. 3 hrs, 6 hrs, & 25 hrs post

[0149] All animals are treated with the compound(s)/vehicle(s) as a blinded random investigation.

Example 4

Efficacy Studies of Compounds in the Rodent MCAo (Tamura) Model

[0150] The Tamura model of MCAo will be utilized to determine the effect of one or more of the compounds described herein in alleviating the neurological deficit demonstrated as motor skill performance. Behavioral assessment as well as infarct volume of compound treated animals in comparison to control (vehicle) volume animals will be used for evaluating efficacy of the compound(s) over a 7 day period.

[0151] Methods

[0152] Animal Preparation. Eighty, adult, Sprague-Dawley rats (Taconic Farms), weighing 300-350 g, will be used for the study. Animals are housed in a standard animal facility and fed with commercial rodent chow ad libitum. Extra animals will be ordered to allow for proper randomization and mortality from the surgical procedures. The rats will be approximately 10 weeks of age when they arrive at the laboratory.

[0153] All animals will be housed and handled for behavioral assessment for 7 days prior to surgery for acclimation purposes. At the end of the training period, animals will be randomized and assigned to different groups. Animals will be given a unique identification number by tail marking. Tail number and cage cards will identify the animals.

[0154] Surgical Preparation. Middle Cerebral Artery Occlusion (MCAo), Tamura Model. Focal cerebral infarcts are made by permanent occlusion of the proximal right middle cerebral artery using a modification of the method of Tamura et al. Male Sprague-Dawley rats (300-350 g) are anesthetized with 2% isoflourane in 50% Air/50% O_2, and is maintained with 1-1.5 % isoflourane. The temporalis muscle is bisected and reflected through an incision made midway between the eye and the eardrum canal. The proximal MCA is exposed through a subtemporal craniectomy without removing the zygomatic arch and without transecting the facial nerve. The artery is then occluded by microbipolar coagulation from just proximal to the olfactory tract to the inferior cerebral vein, and is transected. Body temperature is maintained at 38° C.±1 throughout the entire procedure. Animals are euthanatized at various time periods after MCA occlusion and the brains are removed for histological analysis.

[0155] Cerebral Blood Flow Measurement. Blood Flow Monitoring will take place in one group of forty animals to determine the effects of the three experimental compounds selected from the compounds disclosed herein on cerebral

blood flow at certain times in relation to the MCAo. A Perimed Laser Doppler System 500 will be used to determine percent changes in cerebral blood before MCAo, sixty minutes post MCAO and then days 1 and 5 after MCAo.

[0156] Animals are briefly anesthetized with isoflourane and a primed flow probe is inserted through a burr hole made approximately at the following stereotaxic coordinates on the ipsilateral side of the MCAo: −1.0 millimeters to bregma and +6 mm lateral to the midline. The tip of the probe is inserted 1 mm and fixed in place using cyanoacrylate glue. Recordings are made over a 5-minute period. The muscle flap and skin is sutured with running 4-0 silk and animals returned to their cages. The results of the groups treated with the 3 test compounds will be compared to Vehicle treated rats.

[0157] Behavioral Analysis. Two behavioral tests will be performed, the limb placing and body swing test. This test will be performed immediately after surgery and days 1, 3, 7 after MCAo.

[0158] Limb Placing. The limb placing tests are divided into both forelimb and hindlimb tests. For the forelimb-placing test, the examiner holds the rat close to a tabletop and scores the rat's ability to place the forelimb on the tabletop in response to whisker, visual, tactile, or proprioceptive stimulation. Similarly, for the hindlimb placing test, the examiner assesses the rat's ability to place the hindlimb on the tabletop in response to tactile and proprioceptive stimulation. Separate sub scores are obtained for each mode of sensory input and added to give total scores (for the forelimb placing test: 0=normal, 10=maximally impaired; for the hindlimb placing test: 0=normal; 6=maximally impaired). Typically, there is a slow and steady recovery of limb placing behavior during the first month after stroke.

[0159] Body Swing Test. The animal is held approximately 1 inch from the base of its tail. It is then elevated to an inch above a surface of a table. The animal is held in the vertical axis, defined as no more than 10° to either the left or the right side. A swing is recorded whenever the animal moves its head out of the vertical axis to either side. Before attempting another swing, the animal must return to the vertical position for the next swing to be counted. Thirty total swings are counted. A normal animal typically has an equal number of swings to either side. Following focal stroke, the animal tends to swing to the contralateral side. There is a slow spontaneous recovery of body swing during the first month after stroke.

[0160] Morphometric Analysis—Brain Perfusion. Seven days after the induction of focal ischemia, rats will be deeply anesthetized with a ketamine, and xylazine cocktail. The animals are then perfused transcardially with normal saline (with heparin 2 unit/ml) followed by 4% paraformaldehyde for infarct volume measurement (H&E staining). Brains are removed and stored in 10% formalin to be sectioned and stained with Hematoxylin and Eosin.

[0161] Infarct Volume Measurement. Using the Image Pro-Plus imaging system, a total of 7 images per brain of the posterior side of each slice are analyzed through digital analysis. The total direct infarct volume is calculated for the left hemisphere using the equation below. Digitizing and computation is done under blinded conditions.

$$\text{Volume } (mm^3) = \frac{\Sigma \text{ area } (mm^2) \text{ per side}}{\text{No. of sides analyzed}} \times 7 \text{ mm}$$

[0162] The total infarct volumes are calculated for each animal and subsequent group means are determined as volume of area (mm^3). To account for tissue shrinkage and possible edema, the indirect method of infarct volume is calculated using the formula:

Total Contralateral Hemisphere Volume−Total Infarcted Hemisphere Volume (mm3)

[0163] Body Temperature and Weight. All animals' body temperature are monitored throughout the surgery and maintained near normal values (37-38° C.). Animal's body weights are measured and documented before surgery and at the end of the study immediately before euthanation.

[0164] Clinical Observations. Along with the behavioral assessment animals will be observed daily for abnormal behavior, including but not limited to circling, lethargy, respiratory wheezing or discharge, hair loss, and early death. All abnormalities will be recorded. Likewise, normal behavior will also be noted as normal.

[0165] Statistical Analysis. Behavioral scores and body weight are analyzed by two-way repeated measures analysis of variance (ANOVA; treatment X time). Infarct volume is analyzed by one-way ANOVA. A p value of $\leqq 0.05$ is considered a statistically significant difference.

[0166] Experimental Design

[0167] Experimental Groups and Compound Administration. A number of animals will undergo MCAo using subcutaneous administration of all test articles. One or more compounds selected from the compounds disclosed herein, at predetermined doses will be compared to a control or vehicle and assigned to two different time schedules of administration relative to the time of MCAo. The time schedules for administration of all treated groups will be divided as follows:

[0168] a. 3 hrs, 6 hrs, & 25 hrs and days 2-7 b.i.d. post

[0169] b. 6 hrs, 9 hrs & 25 hrs and days 2-7 b.i.d. post

[0170] All animals are treated with the compound(s)/vehicle(s) as a blinded random investigation.

Example 5

Preparation of Tablets

[0171] The compound of **FIGS. 1, 2**, or **3** (10.0 g) is mixed with lactose (85.5 g), hydroxypropyl cellulose HPC-SL (2.0 g), hydroxypropyl cellulose L-HPC, LH-22 (2.0 g) and purified water (9.0 g), the resulting mixture is subjected to granulation, drying and grading, and the thus obtained granules are mixed with magnesium stearate (0.5 g) and subjected to tablet making, thereby obtaining tablets containing 10 mg per tablet of the compound.

Example 6

Administering to a Subject

[0172] The tablet prepared in Example 5 is provided to a subject at time 0. One tablet every 24 h is provided for a

period of one week. After administration of the third tablet, the subject is exposed to a neurodegenerative event. The treated subject exhibits symptoms of neurological disorder that are less severe compared to the subject that was not treated.

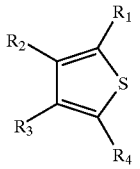
[0173] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

[0174] Having now fully described this invention, it will be appreciated by those skilled in the art that the same can be performed within a wide range of equivalent parameters, concentrations, and conditions without departing from the spirit and scope of the invention and without undue experimentation.

[0175] While this invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications. This application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth.

1. A method of treating a disease comprising administering to a subject in need thereof an effective amount of a compound of formula I

I

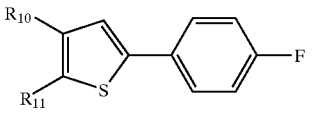


or a pharmaceutically acceptable salt thereof, wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, aryl, heteroaryl, $NR_5C(O)R_7$, $C(O)NR_5R_6$, $C(O)R_7$ and $C(O)OR_7$, wherein R_5, R_6, and R_7 are independently selected to be hydrogen, alkyl, cycloalkyl or aryl, and where R_5 and R_6 or R_5 and R_7 together can optionally form a 3, 4, 5, 6, or 7 membered ring optionally having one or more degrees of substitution.

2. The method of claim 1 wherein the compound is at least one of a compound selected from the compounds 781118, 781222, 781196, 781300, 781326, 781352, 781378, 781560, 779974, 781456, 781534, 781482, 781586, 781612, 781794, 781716, 781898, 781924, 783042, and 783120.

3. A method of treating a disease comprising administering to a subject in need thereof an effective amount of a compound of formula II

II

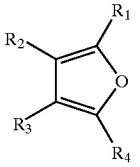


or a pharmaceutically acceptable salt thereof, wherein R_{10} and R_{11} are independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, aryl, heteroaryl, $NR_5C(O)R_7$, $C(O)NR_5R_6$, $C(O)R_7$ and $C(O)OR_7$, wherein R_5, R_6, and R_7 are independently selected to be hydrogen, alkyl, cycloalkyl or aryl, and where R_5 and R_6 or R_5 and R_7 together can optionally from a 3, 4, 5, 6, or 7 membered ring optionally having one or more substitutions.

4. The method of claim 1 wherein the compound is at least one of a compound selected from the compounds 781372 and 783146.

5. A method of treating a disease comprising administering to a subject in need thereof an effective amount of a compound of formula III

III



or a pharmaceutically acceptable salt thereof, wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, aryl, heteroaryl, $NR_5C(O)R_7$, $C(O)NR_5R_6$, $C(O)R_7$ and $C(O)OR_7$, wherein R_5, R_6, and R_7 are independently selected to be hydrogen, alkyl, cycloalkyl or aryl, and where R_5 and R_6 or R_5 and R_7 together can optionally form a 3, 4, 5, 6, or 7 membered ring optionally having one or more degrees of substitution.

6. The method of claim 1 wherein the compound is at least one of a compound selected from the compounds 781508, 781768, 781742, 781872, 782002, 781040, 781092, 781248, 781170, 781144, 781274, 781638, 781664, 781690, 781820, 781846, 781404, 781950, and 781976.

7. The method of claim 1, **3**, or **5** wherein said disease is a PDE6-related condition.

8. The method of claim 1, **3**, or **5** wherein said disease is a condition wherein a beneficial effect is obtained by modulating PDE6 or any of its subunits.

9. The method of claim 1, **3**, or **5** wherein said disease is a condition wherein a beneficial effect is obtained by modulating PDE6D.

10. The method of claim 1, **3**, or **5** wherein said disease is related to an aberrant or undesired phosphodiesterase activity.

11. The method of claim 1 wherein said disease is stroke.

12. The method of claim 11 wherein said PDE6 modulating compound is acutely administered to a subject following a stroke.

13. The method of claim 11 wherein said PDE6 modulating compound is prophylactically administered to a subject to prevent a stroke.

14. The method of claim 1, **3**, or **5** wherein said disease is at least one of a disease selected from cancer, impaired vision, an oxidative stress disorder, inflammation, and multiple sclerosis.

15. The method of claim 1, **3**, or **5** wherein said disease is at least one of a disease selected from cerebrovascular accident, neurodegenerative disease, and cardiovascular disease

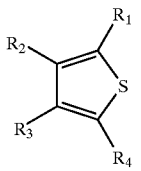
16. The method of claim 15 wherein said cerebrovascular accident is a stroke.

17. The method of claim 15 wherein treatment of said cardiovascular disease decreases the frequency and/or the severity of damage of myocardial infarction

18. The method of claim 15 wherein said neurodegenerative disease is at least one of an ischemic stroke, Alzheimer's disease, diabetic peripheral neuropathy, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease and Parkinson's disease.

19. The method of claim 1, **3**, or **5** wherein said compound stimulates blood vessel growth, bone growth, or immune system.

20. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of formula I

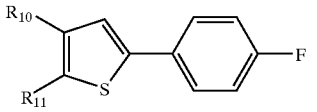


I

or a pharmaceutically acceptable salt thereof, wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, aryl, heteroaryl, $NR_5C(O)R_7$, $C(O)NR_5R_6$, $C(O)R_7$ and $C(O)OR_7$, wherein R_5, R_6, and R_7 are independently selected to be hydrogen, alkyl, cycloalkyl or aryl, and where R_5 and R_6 or R_5 and R_7 together can optionally form a 3, 4, 5, 6, or 7 membered ring optionally having one or more degrees of substitution.

21. The pharmaceutical composition of claim 20 wherein the compound is at least one of a compound selected from the compounds 781118, 781222, 781196, 781300, 781326, 781352, 781378, 781560, 779974, 781456, 781534, 781482, 781586, 781612, 781794, 781716, 781898, 781924, 783042, and 783120.

22. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of formula II

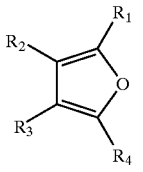


II

or a pharmaceutically acceptable salt thereof, wherein R_{10} and R_{11} are independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, aryl, heteroaryl, $NR_5C(O)R_7$, $C(O)NR_5R_6$, $C(O)R_7$ and $C(O)OR_7$, wherein R_5, R_6, and R_7 are independently selected to be hydrogen, alkyl, cycloalkyl or aryl, and where R_5 and R_6 or R_5 and R_7 together can optionally form a 3, 4, 5, 6, or 7 membered ring optionally having one or more substitutions.

23. The pharmaceutical composition of claim 22 wherein the compound is at least one of a compound selected from the compounds 781372 and 783146.

24. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of formula III



III

or a pharmaceutically acceptable salt thereof, wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, aryl; heteroaryl, $NR_5C(O)R_7$, $C(O)NR_5R_6$, $C(O)R_7$ and $C(O)OR_7$, wherein R_5, R_6, and R_7 are independently selected to be hydrogen, alkyl, cycloalkyl or aryl, and where R_5 and R_6 or R_5 and R_7 together can optionally form a 3, 4, 5, 6, or 7 membered ring optionally having one or more degrees of substitution.

25. The pharmaceutical composition of claim 24 wherein the compound is at least one of a compound selected from the compounds 781508, 781768, 781742, 781872, 782002, 781040, 781092, 781248, 781170, 781144, 781274, 781638, 781664, 781690, 781820, 781846, 781404, 781950, and 781976.

* * * * *