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TRAITEMENT PROPHYLACTIQUE OU THERAPEUTIQUE D'INFLAMMATIONS DES VOIES RESPIRATOIRES
(54) Title: COMPOSITIONS COMPRISING PDE4 MODULATORS AND THEIR USE FOR THE TREATMENT OR
PREVENTION OF AIRWAY INFLAMMATION

(57) **Abrégé/Abstract:**

Methods of treating, preventing, and managing airway inflammation and other airway or pulmonary diseases and disorders are disclosed. Specific methods comprise the administration of a PDE4 modulator, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, alone or in combination with a second active agent and/or other conventional therapies. Pharmaceutical compositions, single unit dosage forms, and kits suitable for use in methods of the invention are also disclosed.



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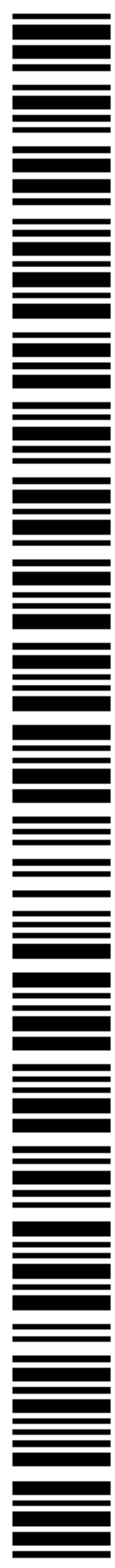
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COMPOSITIONS COMPRISING PDE4 MODULATORS AND THEIR USE FOR THE TREATMENT OR
PREVENTION OF AIRWAY INFLAMMATION

1. **FIELD OF THE INVENTION**

This invention relates to methods of treating, preventing, and managing airway inflammation, which comprise the administration of a PDE4 modulator alone or in combination with other therapeutics or therapies for airway inflammation. The invention
5 also relates to pharmaceutical compositions and dosing regimens.

2. **BACKGROUND OF THE INVENTION**

2.1 **AIRWAY INFLAMMATION**

Airway inflammation can be caused by various factors including oxidant pollutants, respiratory viruses, and inhaled antigens. These inflammatory stimuli, in turn, may induce
10 airway hyperresponsiveness, and also may produce morphologic evidence of airway injury and inflammatory cell infiltration. Murray and Nadel, Textbook of Respiratory Medicine, 2nd Ed., page 2004 (1994). Other factors that cause airway inflammation include environmental allergens, occupational sensitizing agents, viral respiratory infections, and cigarette smoking.

15 Airway inflammation typically initiates tissue remodeling. *See, e.g., Dunhill et al., Thorax.*, 24: 176 (1969). The remodeling involves: epithelial sloughing; marked infiltration of eosinophilis into the mucosa; activation of mast cells and lymphocytes; enlargement of mucous glands; deposition of wound-type collagen immediately below the true basement membrane of the epithelium and throughout the mucosa; and an increase in
20 the number of myofibroblasts. In addition, there is an increase in the volume and number of blood vessels in the affected airways, indicating that an angiogenesis accompanies the remodeling process. Kuwano *et al.*, *Am. Rev. Resp. Dis.*, 148: 1220 (1993). The overall volume of the airway wall is typically increased (*see James et al., Am. Rev. Respir. Dis.*, 139: 242 (1989)) in association with an increase in the volume of airway smooth muscle
25 (*see Kuwano et al., above*), which results from both hypertrophic and hyperplastic responses.

Airway inflammation is thought to be associated with various airway or pulmonary diseases and disorders, including asthma, chronic obstructive pulmonary disease ("COPD"),

"interstitial pulmonary fibrosis" (IPF), and adult respiratory distress syndrome (ARDS). *See, e.g., O'Byrne et al., Am. J. Respir. Crit. Care Med.*, 159: S41-S66 (1999). Several approaches are available for the treatment, prevention, and management of airway inflammation and variety of airway and pulmonary diseases associated therewith. Stimulus avoidance is accomplished via systematic identification and minimization of contact with each type of stimuli. But it may be impractical and not always helpful to avoid all potential stimuli. Pharmacological treatments are also available, but many adverse effects are associated with known anti-inflammatory agents and bronchodilators. Therefore, a need still exists for effective and safe treatments of airway inflammation and related diseases and disorders.

2.2 PDE4 MODULATORS

Compounds referred to as PDE4 modulators have been synthesized and tested. These compounds potently inhibit TNF- α and IL-12 production, and exhibit modest inhibitory effects on LPS induced IL1 β . L.G. Corral, *et al., J. Immunol.*, 163: 380-386 (1999).

PDE4 is one of the major phosphodiesterase isoenzymes found in human myeloid and lymphoid lineage cells. The enzyme plays a crucial part in regulating cellular activity by degrading the ubiquitous second messenger cAMP and maintaining it at low intracellular levels. *Id.* Inhibition of PDE4 activity results in increased cAMP levels leading to the modulation of LPS induced cytokines including inhibition of TNF- α production in monocytes as well as in lymphocytes.

3. SUMMARY OF THE INVENTION

This invention encompasses methods of treating, preventing, or managing airway inflammation and other airway or pulmonary diseases and disorders, which comprise administering to a patient in need thereof a therapeutically or prophylactically effective amount of a PDE4 modulator, or a pharmaceutically acceptable salt, solvate (*e.g.*, hydrate), stereoisomer, or prodrug thereof.

Another embodiment of the invention encompasses the use of one or more PDE4 modulators in combination with other therapeutics presently used to treat, prevent or manage airway inflammation and other airway or pulmonary diseases and disorders such as, but not limited to, antibiotics, anticholinergics, anti-inflammatory agents, antioxidants, antitussive agents, β_2 -agonists, calcium channel blockers, corticosteroids, immunomodulatory agents, immunosuppressive agents, leukotriene inhibitors, monoclonal

"antibodies, mucolytics, muscle relaxants, PDE4 inhibitors, potassium channel openers, prostaglandin and analogs, sensory neuropeptide release inhibitors, tachykinin antagonists, and theophylline and its derivatives.

Yet another embodiment of the invention encompasses the use of one or more PDE4 modulators in combination with conventional therapies used to treat, prevent or manage airway inflammation and other airway or pulmonary diseases and disorders including, but not limited to, oxygen-administration and smoking cessation.

The invention further encompasses pharmaceutical compositions, single unit dosage forms, and kits suitable for use in treating, preventing, or managing airway inflammation and other airway or pulmonary diseases and disorders, which comprise a PDE4 modulator, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

4. DETAILED DESCRIPTION OF THE INVENTION

Compounds disclosed herein can work alone or in combination with other drugs to effectively treat, prevent, and/or manage varying types of airway inflammation and other airway or pulmonary diseases and disorders. Without being limited by theory, PDE4 inhibitors are believed to exert the anti-inflammatory effects by elevating intracellular cAMP levels in various leukocytes, including T cells, B cells, NK cells, neutrophils, macrophages, basophils, eosinophils, and mast cells. PDE4 is also expressed in non-leukocytes such as endothelial cells, smooth muscle cells, fibroblasts, and neurons, which are also believed to contribute to inflammation.

Because of the unique mechanism by which certain compounds of the invention are believed to act, it is believed that they can treat, prevent, or manage airway inflammation and other airway or pulmonary diseases and disorders without incurring adverse effects typical of some pharmacologic treatments of airway inflammation, even when administered systemically. Adverse effects that can be avoided or minimized using methods of this invention include, but are not limited to, tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac arrhythmia.

A first embodiment of the invention encompasses methods of treating, preventing, and managing airway inflammation, which comprise administering to a patient in need thereof a therapeutically or prophylactically effective amount of a PDE4 modulator, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof. The invention further encompasses the treatment, prevention, and management of specific types of airway or pulmonary diseases and disorders.

without being limited by theory, it is believed that certain PDE4 modulators and other medications useful for the treatment of airway inflammation and other airway or pulmonary diseases and disorders can act in complementary or synergistic ways in the treatment, prevention or management of such diseases and disorders. Therefore, one
5 embodiment of the invention encompasses a method of treating, preventing, or managing airway inflammation or other airway or pulmonary diseases or disorders, which comprises administering to a patient in need thereof a therapeutically or prophylactically effective amount of a PDE4 modulator, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and a therapeutically or prophylactically effective amount of a second active agent.

10 Examples of second active agents include, but are not limited to, conventional therapeutics used to treat or prevent airway inflammation or other airway or pulmonary diseases and disorders such as antibiotics, anticholinergics, antihistamines, anti-inflammatory agents, antioxidants, antitussive agents, β_2 -agonists, calcium channel blockers, corticosteroids, immunomodulatory agents, immunosuppressive agents,
15 leukotriene inhibitors, monoclonal antibodies, mucolytics, muscle relaxants, PDE4 inhibitors, potassium channel openers, prostaglandin and analogs, sensory neuropeptide release inhibitors, tachykinin antagonists, and theophylline and its derivatives, and other therapeutics found, for example, in the *Physician's Desk Reference* 2003. In some embodiment, a PDE4 modulator can be combined with another PDE4 modulator.

20 The invention also encompasses pharmaceutical compositions, single unit dosage forms, and kits which comprise one or more PDE4 modulators, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, and a second active agent. For example, a kit may contain one or more compounds of the invention and an antibiotic, anticholinergic, anti-inflammatory agent, antioxidant, antitussive agent, β_2 -agonist, calcium
25 channel blocker, corticosteroid, immunomodulatory agent, immunosuppressive agent, leukotriene inhibitor, mucolytic, muscle relaxant, PDE4 inhibitor, potassium channel opener, prostaglandin or an analog, sensory neuropeptide release inhibitor, or tachykinin antagonist.

Particular PDE4 modulators may reduce or avoid adverse effects associated with the
30 administration of therapeutic agents typically used to treat airway inflammation and other airway or pulmonary diseases or disorders, thereby allowing the administration of larger amounts of the agents to patients and/or increasing patient compliance. Consequently, another embodiment of the invention encompasses a method of reversing, reducing or avoiding an adverse effect associated with the administration of a second active agent in a

'patient' suffering from airway inflammation or other airway or pulmonary diseases and disorders, which comprises administering to a patient in need thereof a therapeutically or prophylactically effective amount of a PDE4 modulator, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof. Examples of adverse effects include, but are not limited to, central nervous system stimulatory effects and undesirable cardiac effects, such as, but not limited to, tremor, nervousness, shakiness, dizziness, increased appetite, and cardiac arrhythmia. In children, side effects include, but are not limited to, excitement, nervousness, and hyperkinesia.

As discussed elsewhere herein, airway inflammation and other airway or pulmonary diseases and disorders may be treated with, for example, oxygen-administration and smoking cessation. Without being limited by theory, it is believed that the combined use of such conventional therapies and a PDE4 modulator may provide a unique and unexpected synergy to reduce complications associated with conventional therapies. Therefore, this invention encompasses a method of treating, preventing, or managing airway inflammation and other airway or pulmonary diseases or disorders, which comprises administering to a patient (*e.g.*, a human) a PDE4 modulator, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, before, during, or after conventional therapies.

4.1 DEFINITIONS

As used herein, and unless otherwise specified, the term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic acids, including inorganic acids and organic acids. Suitable non-toxic acids include inorganic and organic acids such as, but not limited to, acetic, alginic, anthranilic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, formic, fumaric, furoic, gluconic, glutamic, glucuronic, galacturonic, glycidic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phenylacetic, propionic, phosphoric, salicylic, stearic, succinic, sulfanilic, sulfuric, tartaric acid, p-toluenesulfonic and the like. Particularly preferred are hydrochloric, hydrobromic, phosphoric, and sulfuric acids, and most particularly preferred is the hydrochloride salt.

As used herein, and unless otherwise specified, the term "solvate" means a compound of the present invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. Where the solvent is water, the solvate is a hydrate.

As used herein, and unless otherwise specified, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological

conditions (*in vitro* or *in vivo*) to provide the compound. Examples of prodrugs include, but are not limited to, compounds that comprise biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Other examples of prodrugs include compounds that comprise -NO, -NO₂, -ONO, or -ONO₂ moieties. Prodrugs can typically be prepared using well-known methods, such as those described in *Burger's Medicinal Chemistry and Drug Discovery*, 172-178, 949-982 (Manfred E. Wolff *ed.*, 5th ed. 1995), and *Design of Prodrugs* (H. Bundgaard *ed.*, Elsevier, New York 1985).

As used herein, and unless otherwise specified, the terms "biohydrolyzable carbamate," "biohydrolyzable carbonate," "biohydrolyzable ureide" and "biohydrolyzable phosphate" mean a carbamate, carbonate, ureide and phosphate, respectively, of a compound that either: 1) does not interfere with the biological activity of the compound but can confer upon that compound advantageous properties *in vivo*, such as uptake, duration of action, or onset of action; or 2) is biologically inactive but is converted *in vivo* to the biologically active compound. Examples of biohydrolyzable carbamates include, but are not limited to, lower alkylamines, substituted ethylenediamines, aminoacids, hydroxyalkylamines, heterocyclic and heteroaromatic amines, and polyether amines.

As used herein, and unless otherwise specified, the term "stereoisomer" encompasses all enantiomerically/stereomerically pure and enantiomerically/stereomerically enriched compounds of this invention.

As used herein, and unless otherwise indicated, the term "stereomerically pure" or "enantiomerically pure" means that a compound comprises one stereoisomer and is substantially free of its counter stereoisomer or enantiomer. For example, a compound is stereomerically or enantiomerically pure when the compound contains 80%, 90%, or 95% or more of one stereoisomer and 20%, 10%, or 5% or less of the counter stereoisomer. In certain cases, a compound of the invention is considered optically active or stereomerically/enantiomerically pure (*i.e.*, substantially the R-form or substantially the S-form) with respect to a chiral center when the compound is about 80% ee (enantiomeric excess) or greater, preferably, equal to or greater than 90% ee with respect to a particular chiral center, and more preferably 95% ee with respect to a particular chiral center.

As used herein, and unless otherwise indicated, the term "stereomerically enriched" or "enantiomerically enriched" encompasses racemic mixtures as well as other mixtures of

“stereoisomers of compounds of this invention (e.g., R/S = 30/70, 35/65, 40/60, 45/55, 55/45, 60/40, 65/35 and 70/30).

As used herein, and unless otherwise specified, the terms “treat,” “treating” and “treatment” contemplate an action that occurs while a patient is suffering from the specified disease or disorder, which reduces the severity of the disease or disorder, or retards or slows the progression of the disease or disorder.

As used herein, unless otherwise specified, the terms “prevent,” “preventing” and “prevention” contemplate an action that occurs before a patient begins to suffer from the specified disease or disorder, which inhibits or reduces the severity of the disease or disorder.

As used herein, and unless otherwise indicated, the terms “manage,” “managing” and “management” encompass preventing the recurrence of the specified disease or disorder in a patient who has already suffered from the disease or disorder, and/or lengthening the time that a patient who has suffered from the disease or disorder remains in remission. The terms encompass modulating the threshold, development and/or duration of the disease or disorder, or changing the way that a patient responds to the disease or disorder.

As used herein, and unless otherwise specified, the term “therapeutically effective amount” of a compound is an amount sufficient to provide a therapeutic benefit in the treatment or management of a disease or condition, or to delay or minimize one or more symptoms associated with the disease or condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment or management of the disease or condition. The term “therapeutically effective amount” can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of disease or condition, or enhances the therapeutic efficacy of another therapeutic agent.

As used herein, and unless otherwise specified, the term “prophylactically effective amount” of a compound is an amount sufficient to prevent a disease or condition, or one or more symptoms associated with the disease or condition, or prevent its recurrence. A prophylactically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the disease. The term “prophylactically effective amount” can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

4.2 PDE4 MODULATORS

Compounds used in the invention include racemic, stereomerically pure and stereomerically enriched PDE4 modulators, stereomerically and enantiomerically pure compounds that have selective cytokine inhibitory activities, and pharmaceutically acceptable salts, solvates, hydrates, stereoisomers, clathrates, and prodrugs thereof. Preferred compounds used in the invention are known PDE4 modulators of Celgene Corporation, NJ.

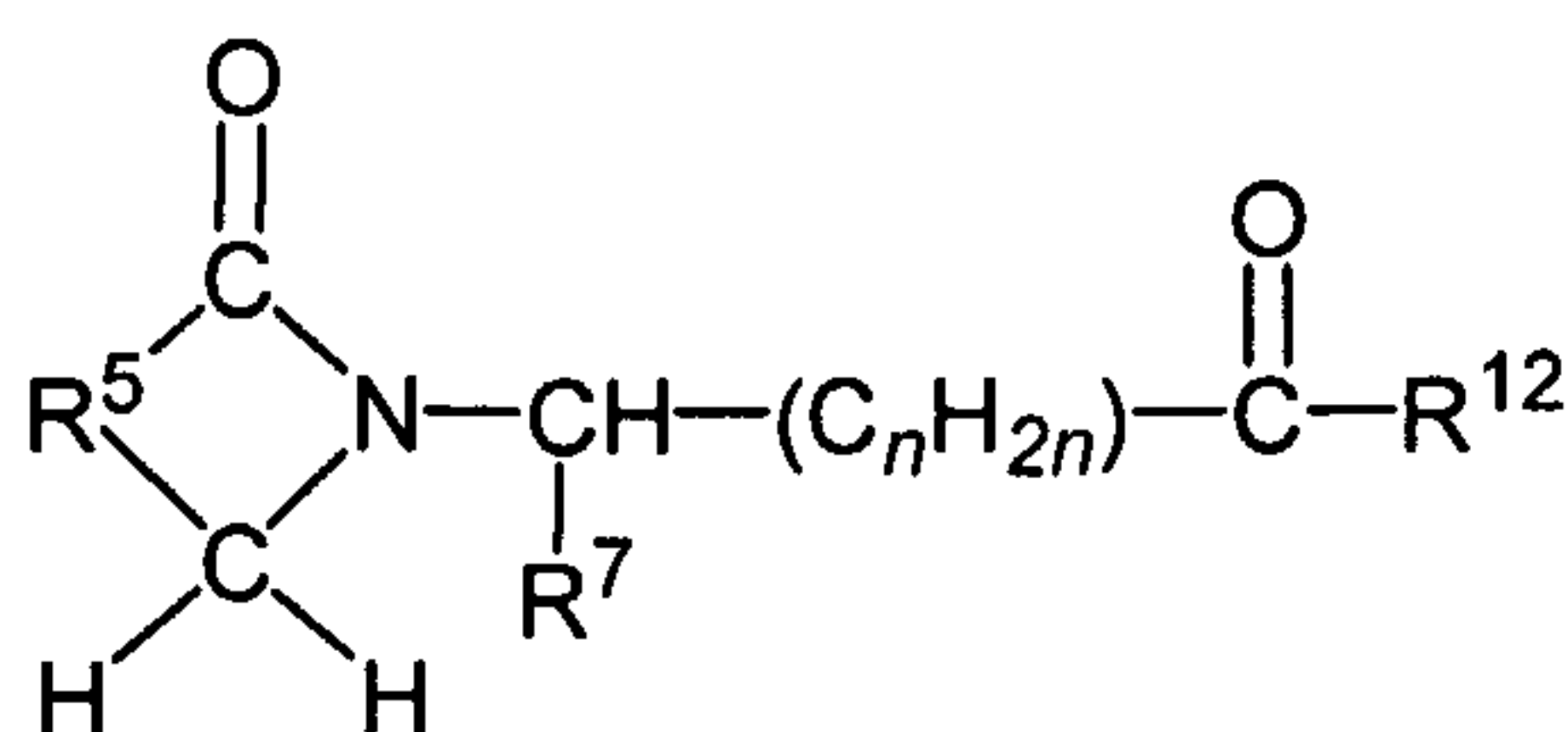
As used herein and unless otherwise indicated, the term "PDE4 modulators" encompasses small molecule drugs, *e.g.*, small organic molecules which are not peptides, proteins, nucleic acids, oligosaccharides or other macromolecules. Preferred compounds inhibit TNF- α production. Compounds may also have a modest inhibitory effect on LPS induced IL1 β and IL12. More preferably, the compounds of the invention are potent PDE4 inhibitors.

Specific examples of PDE4 modulators include, but are not limited to, the cyclic imides disclosed in U.S. patent nos. 5,605,914 and 5,463,063; the cycloalkyl amides and cycloalkyl nitriles of U.S. patent nos. 5,728,844, 5,728,845, 5,968,945, 6,180,644 and 6,518,281; the aryl amides (for example, an embodiment being N-benzoyl-3-amino-3-(3',4'-dimethoxyphenyl)-propanamide) of U.S. patent nos. 5,801,195, 5,736,570, 6,046,221 and 6,284,780; the imide/amide ethers and alcohols (for example, 3-phthalimido-3-(3',4'-dimethoxyphenyl)propan-1-ol) disclosed in U.S. patent no. 5,703,098; the succinimides and maleimides (for example methyl 3-(3',4',5'6'-tetrahydrophthalimido)-3-(3'',4''-dimethoxyphenyl)propionate) disclosed in U.S. patent no. 5,658,940; imido and amido substituted alkanohydroxamic acids disclosed in U.S. patent no. 6,214,857 and WO 99/06041; substituted phenethylsulfones disclosed in U.S. patent nos. 6,011,050 and 6,020,358; fluoroalkoxy-substituted 1,3-dihydro-isindolyl compounds disclosed in U.S. patent application no. 10/748,085 filed on December 29, 2003; substituted imides (for example, 2-phthalimido-3-(3',4'-dimethoxyphenyl) propane) disclosed in U.S. patent no. 6,429,221; substituted 1,3,4-oxadiazoles (for example, 2-[1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazole-2-yl)ethyl]-5-methylisindoline-1,3-dione) disclosed in U.S. patent no. 6,326,388; cyano and carboxy derivatives of substituted styrenes (for example, 3,3-bis-(3,4-dimethoxyphenyl) acrylonitrile) disclosed in U.S. patent nos. 5,929,117, 6,130,226, 6,262,101 and 6,479,554; isoindoline-1-one and isoindoline-1,3-dione substituted in the 2-position with an α -(3,4-disubstituted phenyl)alkyl group and in the 4- and/or 5-position with a nitrogen-containing group disclosed in WO 01/34606 and

U.S. patent no. 6,667,316, for example, cyclopropyl-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisindolin-4-yl}carboxamide, cyclopropyl-N-{2-[1(S)-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisindolin-4-yl}carboxamide, and cyclopropyl-N-{2-[1(R)-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisindolin-4-yl}carboxamide; and imido and amido substituted acylhydroxamic acids (for example, (3-(1,3-dioxoisindoline-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) propanoate disclosed in WO 01/45702 and U.S. patent no. 6,699,899. Other PDE4 modulators include diphenylethylene compounds disclosed in U.S. provisional application no. 60/452,460, filed March 5, 2003, the contents of which are incorporated by reference herein in their entirety. Other PDE4 modulators include isoindoline compounds disclosed in U.S. patent application nos. 10/900,332 and 10/900,270, both filed on July 28, 2004. Other specific PDE4 modulators include 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisoindoline-1,3-dione, and stereoisomers thereof. (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisoindoline-1,3-dione was disclosed in WO 03/080049. The entireties of each of the patents and patent applications identified herein are incorporated herein by reference.

Additional PDE4 modulators belong to a family of synthesized chemical compounds of which typical embodiments include 3-(1,3-dioxobenzo-[f]isoindol-2-yl)-3-(3-cyclopentyloxy-4-methoxyphenyl)propionamide and 3-(1,3-dioxo-4-azaisoindol-2-yl)-3-(3,4-dimethoxyphenyl)-propionamide.

Other specific PDE4 modulators belong to a class of non-polypeptide cyclic amides disclosed in U.S. patent nos. 5,698,579, 5,877,200, 6,075,041 and 6,200,987, and WO 95/01348, each of which is incorporated herein by reference. Representative cyclic amides include compounds of the formula:



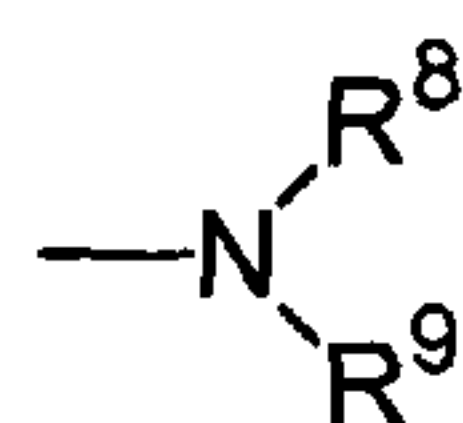
wherein n has a value of 1, 2, or 3;

R⁵ is o-phenylene, unsubstituted or substituted with 1 to 4 substituents each selected independently from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkylamino, dialkylamino, acylamino, alkyl of 1 to 10 carbon atoms, alkyl of 1 to 10 carbon atoms, and halo;

R¹¹ is (i) phenyl or phenyl substituted with one or more substituents each selected independently of the other from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxymethyl, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, and halo, (ii) benzyl
 5 unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxymethyl, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, and halo, (iii) naphthyl, and (iv) benzyloxy;

R¹² is -OH, alkoxy of 1 to 12 carbon atoms, or

10



R⁸ is hydrogen or alkyl of 1 to 10 carbon atoms; and

R⁹ is hydrogen, alkyl of 1 to 10 carbon atoms, -COR¹⁰, or -SO₂R¹⁰, wherein R¹⁰ is hydrogen, alkyl of 1 to 10 carbon atoms, or phenyl.

Specific compounds of this class include, but are not limited to:

15

3-phenyl-2-(1-oxoisindolin-2-yl)propionic acid;

3-phenyl-2-(1-oxoisindolin-2-yl)propionamide;

3-phenyl-3-(1-oxoisindolin-2-yl)propionic acid;

3-phenyl-3-(1-oxoisindolin-2-yl)propionamide;

3-(4-methoxyphenyl)-3-(1-oxoisindolin-yl)propionic acid;

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3-(4-methoxyphenyl)-3-(1-oxoisindolin-yl)propionamide;

3-(3,4-dimethoxyphenyl)-3-(1-oxoisindolin-2-yl)propionic acid;

3-(3,4-dimethoxyphenyl)-3-(1-oxo-1,3-dihydroisindol-2-yl)propionamide;

3-(3,4-dimethoxyphenyl)-3-(1-oxoisindolin-2-yl)propionamide;

3-(3,4-diethoxyphenyl)-3-(1-oxoisindolin-yl)propionic acid;

25

methyl 3-(1-oxoisindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propionate;

3-(1-oxoisindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propionic acid;

3-(1-oxoisindolin-2-yl)-3-(3-propoxy-4-methoxyphenyl)propionic acid;

3-(1-oxoisindolin-2-yl)-3-(3-butoxy-4-methoxyphenyl)propionic acid;

3-(1-oxoisindolin-2-yl)-3-(3-propoxy-4-methoxyphenyl)propionamide;

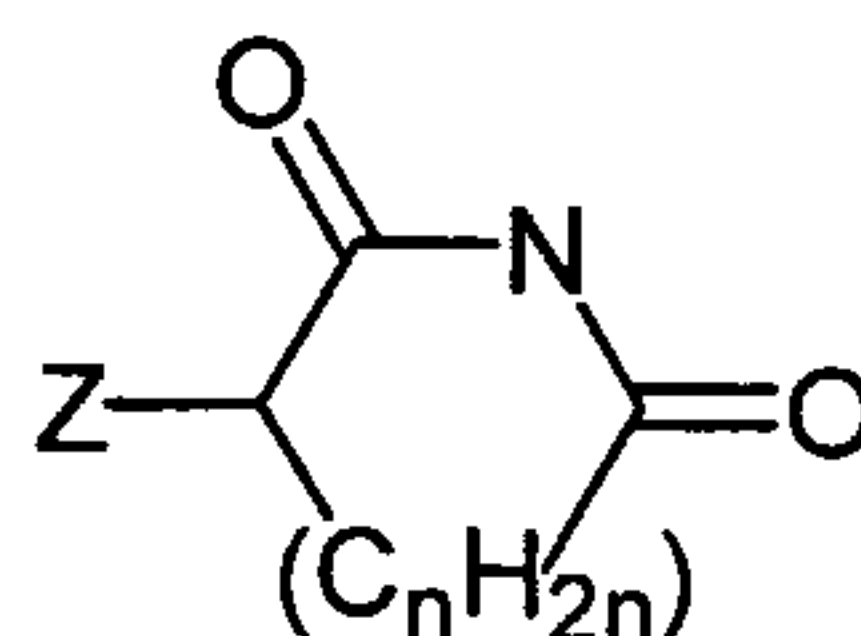
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3-(1-oxoisindolin-2-yl)-3-(3-butoxy-4-methoxyphenyl)propionamide;

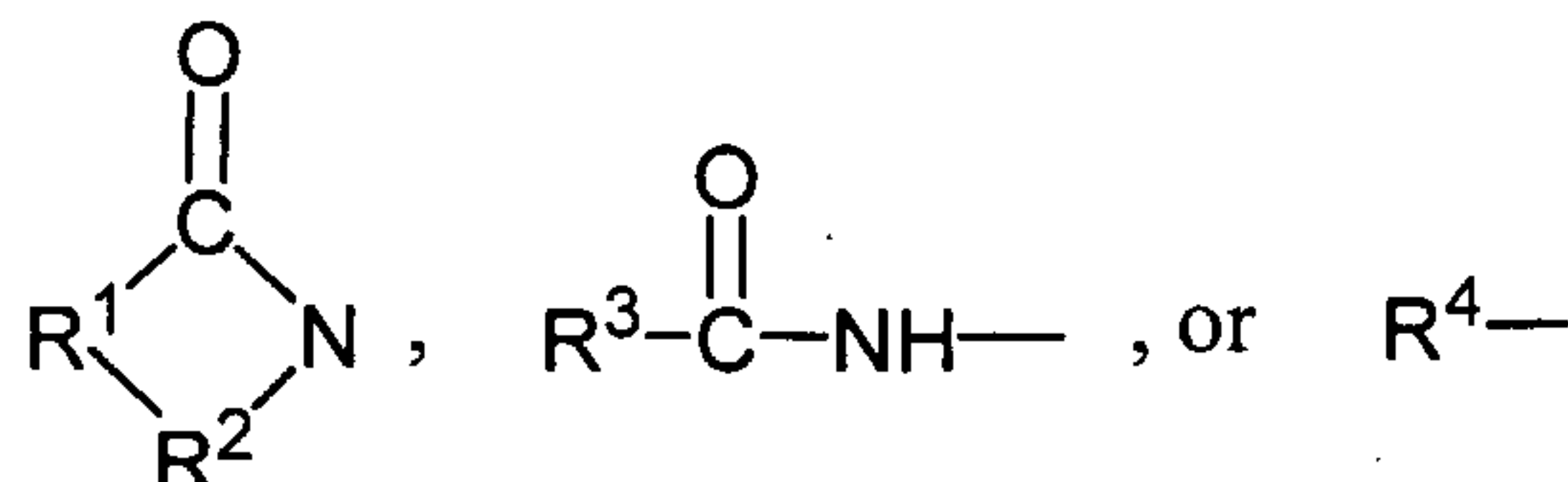
methyl 3-(1-oxoisindolin-2-yl)-3-(3-butoxy-4-methoxyphenyl)propionate; and

methyl 3-(1-oxoisindolin-2-yl)-3-(3-propoxy-4-methoxyphenyl)propionate.

Other representative cyclic amides include compounds of the formula:



in which Z is:



5 in which:

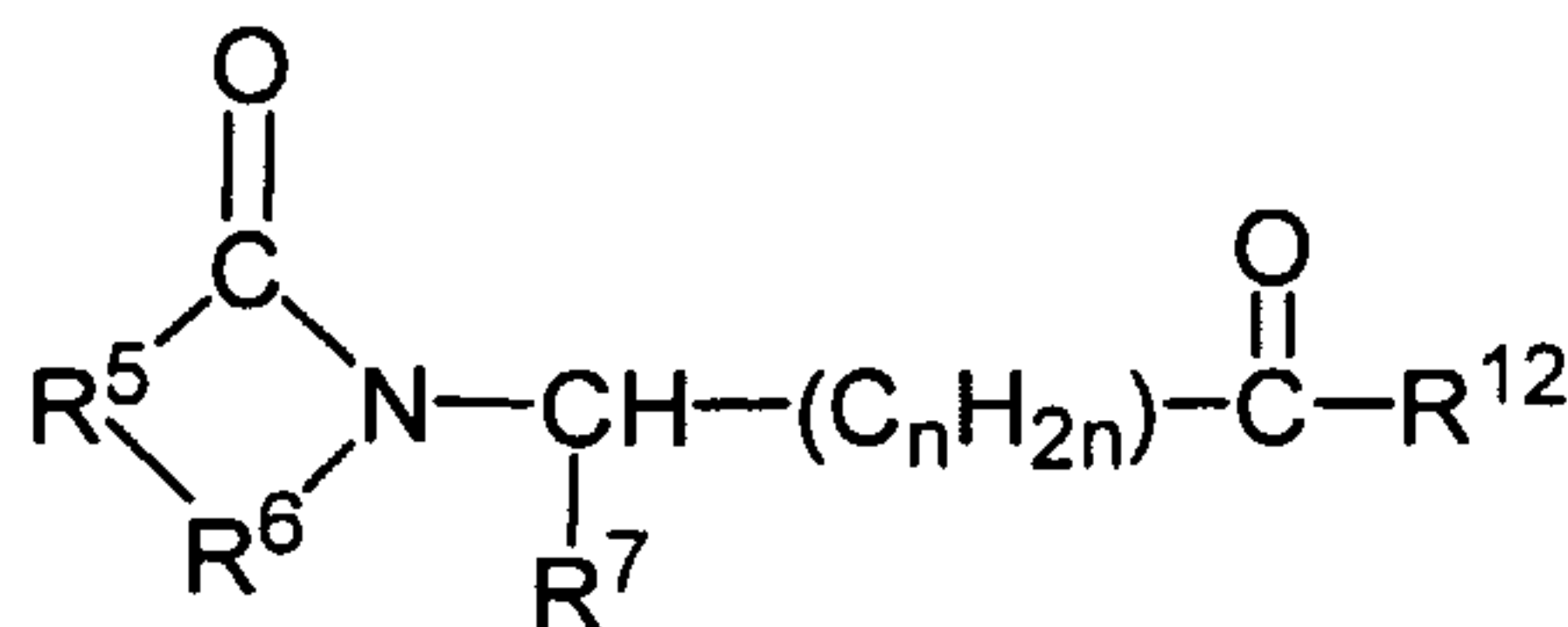
R^1 is the divalent residue of (i) 3,4-pyridine, (ii) pyrrolidine, (iii) imidazole, (iv) naphthalene, (v) thiophene, or (vi) a straight or branched alkane of 2 to 6 carbon atoms, unsubstituted or substituted with phenyl or phenyl substituted with nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamyl, acetox-
 10 y, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo, wherein the divalent bonds of said residue are on vicinal ring carbon atoms;

R^2 is -CO - or -SO₂ -;

R^3 is (i) phenyl substituted with 1 to 3 substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl,
 15 acetox, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo, (ii) pyridyl, (iii) pyrrolyl, (iv) imidazolyl, (iv) naphthyl, (vi) thienyl, (vii) quinolyl, (viii) furyl, or (ix) indolyl;

R^4 is alanyl, arginyl, glycyl, phenylglycyl, histidyl, leucyl, isoleucyl, lysyl, methionyl, prolyl, sarcosyl, seryl, homoseryl, threonyl, thyronyl, tyrosyl, valyl, benzimidol-
 20 2-yl, benzoxazol-2-yl, phenylsulfonyl, methylphenylsulfonyl, or phenylcarbamoyl; and

n has a value of 1, 2, or 3. Other representative cyclic amides include compounds of the formula:



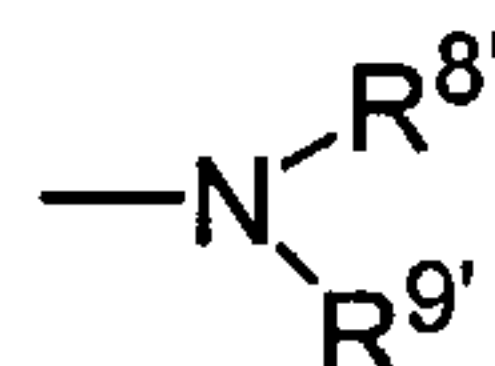
in which R^5 is (i) o-phenylene, unsubstituted or substituted with 1 to 4 substituents
 25 each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy,

carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, alkylamino, dialkylamino, acylamino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo, or (ii) the divalent residue of pyridine, pyrrolidine, imidazole, naphthalene, or thiophene, wherein the divalent bonds are on vicinal ring carbon atoms;

5 R^6 is $-\text{CO}-$, $-\text{CH}_2-$, or $-\text{SO}_2-$;

R^7 is (i) hydrogen if R^6 is $-\text{SO}_2-$, (ii) straight, branched, or cyclic alkyl of 1 to 12 carbon atoms, (iii) pyridyl, (iv) phenyl or phenyl substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, alkyl
10 of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo, (v) alkyl of 1 to 10 carbon atoms, (vi) benzyl unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo, (vii) naphthyl, (viii) benzyloxy, or (ix) imidazol-4-yl
15 methyl;

R^{12} is $-\text{OH}$, alkoxy of 1 to 12 carbon atoms, or

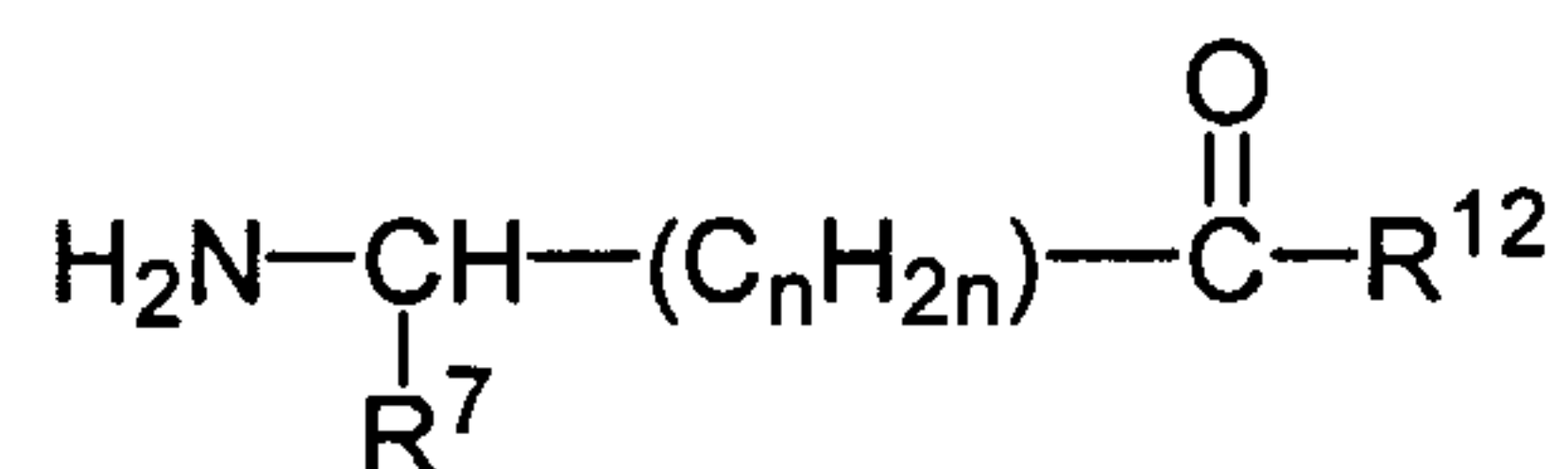


n has a value of 0, 1, 2, or 3;

$R^{8'}$ is hydrogen or alkyl of 1 to 10 carbon atoms; and

20 $R^{9'}$ is hydrogen, alkyl of 1 to 10 carbon atoms, $-\text{COR}^{10}$, or $-\text{SO}_2\text{R}^{10}$ in which R^{10} is hydrogen, alkyl of 1 to 10 carbon atoms, or phenyl.

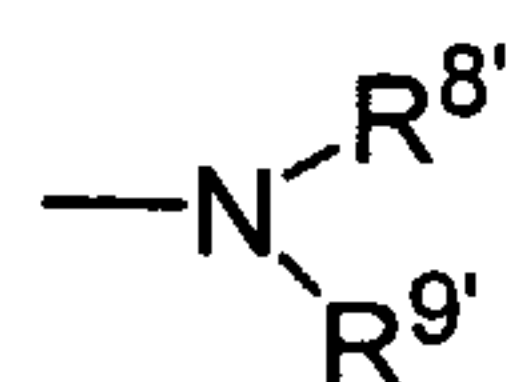
Other representative imides include compounds of the formula:



in which R^7 is (i) straight, branched, or cyclic alkyl of 1 to 12 carbon atoms, (ii)
25 pyridyl, (iii) phenyl or phenyl substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo, (iv) benzyl unsubstituted or substituted with one to three substituents selected from the group consisting of nitro, cyano, trifluoromethyl,
30 carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy,

"amino," alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, (v) naphthyl, (vi) benzyloxy, or (vii) imidazol-4-ylmethyl;

R¹² is -OH, alkoxy of 1 to 12 carbon atoms, -O-CH₂-pyridyl, -O-benzyl or

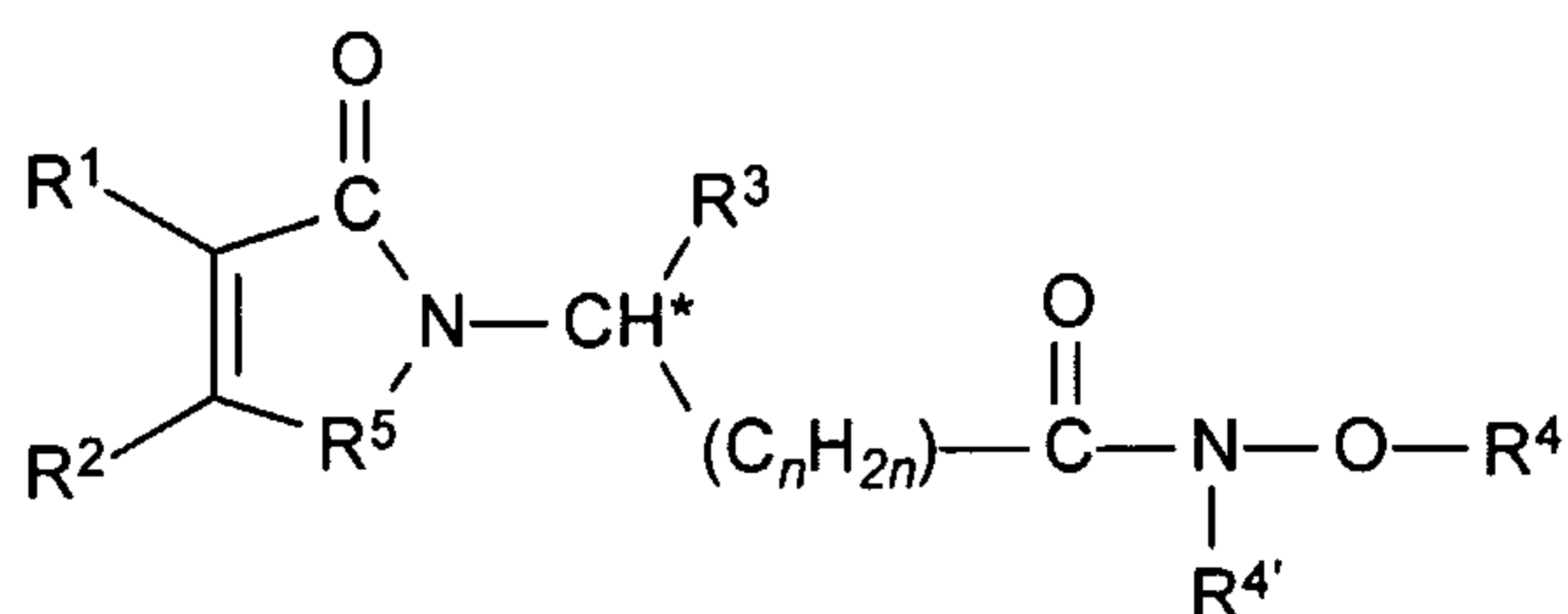


5 where n has a value of 0, 1, 2, or 3;

R^{8'} is hydrogen or alkyl of 1 to 10 carbon atoms; and

R^{9'} is hydrogen, alkyl of 1 to 10 carbon atoms, -CH₂-pyridyl, benzyl, -COR¹⁰, or -SO₂R¹⁰ in which R¹⁰ is hydrogen, alkyl of 1 to 4 carbon atoms, or phenyl.

Other specific PDE4 modulators include the imido and amido substituted
10 alkanohydroxamic acids disclosed in WO 99/06041 and U.S. patent no. 6,214,857, each of which is incorporated herein by reference. Examples of such compound include, but are not limited to:



wherein each of R¹ and R², when taken independently of each other, is hydrogen,
15 lower alkyl, or R¹ and R², when taken together with the depicted carbon atoms to which each is bound, is *o*-phenylene, *o*-naphthylene, or cyclohexene-1,2-diyl, unsubstituted or substituted with 1 to 4 substituents each selected independently from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, alkylamino, dialkylamino, acylamino, alkyl of 1 to 10
20 carbon atoms, alkoxy of 1 to 10 carbon atoms, and halo;

R³ is phenyl substituted with from one to four substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms, benzyloxy, cycloalkoxy of 3 to 6
25 carbon atoms, C₄-C₆-cycloalkylidenemethyl, C₃-C₁₀-alkylidenemethyl, indanyloxy, and halo;

R⁴ is hydrogen, alkyl of 1 to 6 carbon atoms, phenyl, or benzyl;

R^{4'} is hydrogen or alkyl of 1 to 6 carbon atoms;

R¹ is -CH₂-, -CH₂-C(=O)-, -SO₂-, -S-, or -NHCO-; and

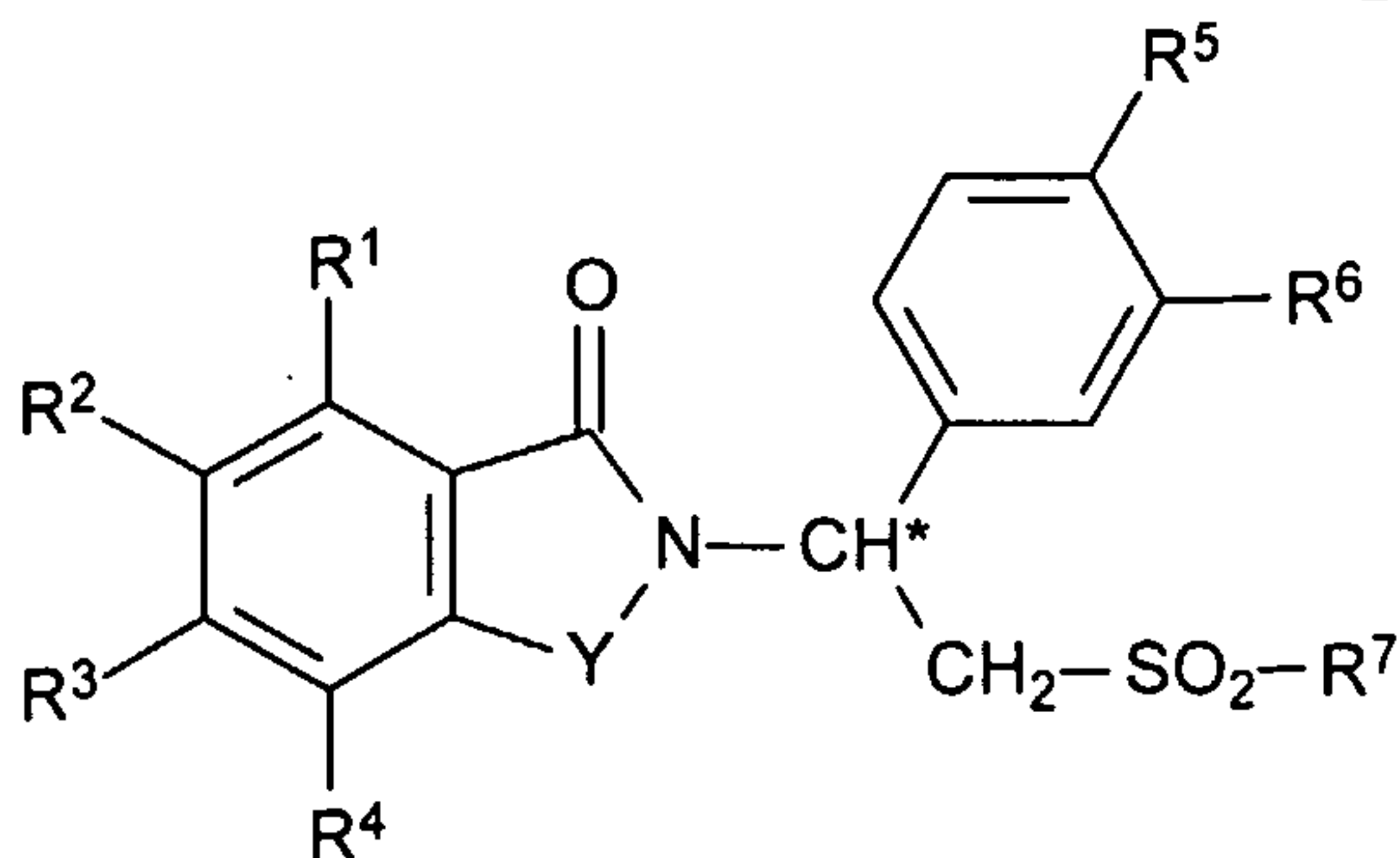
n has a value of 0, 1, or 2; and

the acid addition salts of said compounds which contain a nitrogen atom capable of being protonated.

5. Additional specific PDE4 modulators used in the invention include, but are not limited to:

- 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(1-oxoisoindoliny)propionamide;
 3-(3-ethoxy-4-methoxyphenyl)-N-methoxy-3-(1-oxoisoindoliny)propionamide;
 N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-phthalimidopropionamide;
 10 N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(3-nitrophthalimido)propionamide;
 N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisoindoliny)propionamide;
 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-phthalimidopropionamide;
 N-hydroxy-3-(3,4-dimethoxyphenyl)-3-phthalimidopropionamide;
 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(3-nitrophthalimido)propionamide;
 15 N-hydroxy-3-(3,4-dimethoxyphenyl)-3-(1-oxoisoindoliny)propionamide;
 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(4-methyl-phthalimido)propionamide;
 3-(3-cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-phthalimidopropionamide;
 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(1,3-dioxo-2,3-dihydro-1H-benzo[f]isoindol-2-yl)propionamide;
 20 N-hydroxy-3-{3-(2-propoxy)-4-methoxyphenyl}-3-phthalimidopropionamide;
 3-(3-ethoxy-4-methoxyphenyl)-3-(3,6-difluorophthalimido)-N-hydroxypropionamide;
 3-(4-aminophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide;
 3-(3-aminophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide;
 25 3-(3-acetoamidophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide;
 N-hydroxy-3-(3,4-dimethoxyphenyl)-3-(1-oxoisoindoliny)propionamide;
 3-(3-cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-(1-oxoisoindoliny)propionamide; and
 30 N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(3-nitrophthalimido)propionamide.

Additional PDE4 modulators used in the invention include the substituted phenethylsulfones substituted on the phenyl group with a oxoisoindine group. Examples of such compounds include, but are not limited to, those disclosed in U.S. patent no. 6,020,358, which is incorporated herein by reference, which include the following:



wherein the carbon atom designated * constitutes a center of chirality;

Y is C=O, CH₂, SO₂, or CH₂C=O; each of R¹, R², R³, and R⁴, independently of the others, is hydrogen, halo, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, nitro, cyano, hydroxy, or -NR⁸R⁹; or any two of R¹, R², R³, and R⁴ on adjacent carbon atoms, together with the depicted phenylene ring are naphthylidene;

each of R⁵ and R⁶, independently of the other, is hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, cyano, or cycloalkoxy of up to 18 carbon atoms;

R⁷ is hydroxy, alkyl of 1 to 8 carbon atoms, phenyl, benzyl, or NR⁸R⁹;

each of R⁸ and R⁹ taken independently of the other is hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, or benzyl, or one of R⁸ and R⁹ is hydrogen and the other is -COR¹⁰ or -SO₂R¹⁰, or R⁸ and R⁹ taken together are tetramethylene, pentamethylene, hexamethylene, or -CH₂CH₂X¹CH₂CH₂- in which X¹ is -O-, -S- or -NH-; and

each of R⁸ and R⁹ taken independently of the other is hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, or benzyl, or one of R⁸ and R⁹ is hydrogen and the other is -COR¹⁰ or -SO₂R¹⁰, or R⁸ and R⁹ taken together are tetramethylene, pentamethylene, hexamethylene, or -CH₂CH₂X²CH₂CH₂- in which X² is -O-, -S-, or -NH-.

It will be appreciated that while for convenience the above compounds are identified as phenethylsulfones, they include sulfonamides when R⁷ is NR⁸R⁹.

Specific groups of such compounds are those in which Y is C=O or CH₂.

A further specific group of such compounds are those in which each of R¹, R², R³, and R⁴ independently of the others, is hydrogen, halo, methyl, ethyl, methoxy, ethoxy, nitro, cyano, hydroxy, or -NR⁸R⁹ in which each of R⁸ and R⁹ taken independently of the other is hydrogen or methyl or one of R⁸ and R⁹ is hydrogen and the other is -COCH₃.

Particular compounds are those in which one of R¹, R², R³, and R⁴ is -NH₂ and the remaining of R¹, R², R³, and R⁴ are hydrogen.

Particular compounds are those in which one of R¹, R², R³, and R⁴ is -NHCOCH₃ and the remaining of R¹, R², R³, and R⁴ are hydrogen.

Particular compounds are those in which one of R^1 , R^2 , R^3 , and R^4 is $-N(CH_3)_2$ and the remaining of R^1 , R^2 , R^3 , and R^4 are hydrogen.

A further preferred group of such compounds are those in which one of R^1 , R^2 , R^3 , and R^4 is methyl and the remaining of R^1 , R^2 , R^3 , and R^4 are hydrogen.

5 Particular compounds are those in which one of R^1 , R^2 , R^3 , and R^4 is fluoro and the remaining of R^1 , R^2 , R^3 , and R^4 are hydrogen.

Particular compounds are those in which each of R^5 and R^6 , independently of the other, is hydrogen, methyl, ethyl, propyl, methoxy, ethoxy, propoxy, cyclopentoxy, or cyclohexoxy.

10 Particular compounds are those in which R^5 is methoxy and R^6 is monocycloalkoxy, polycycloalkoxy, and benzocycloalkoxy.

Particular compounds are those in which R^5 is methoxy and R^6 is ethoxy.

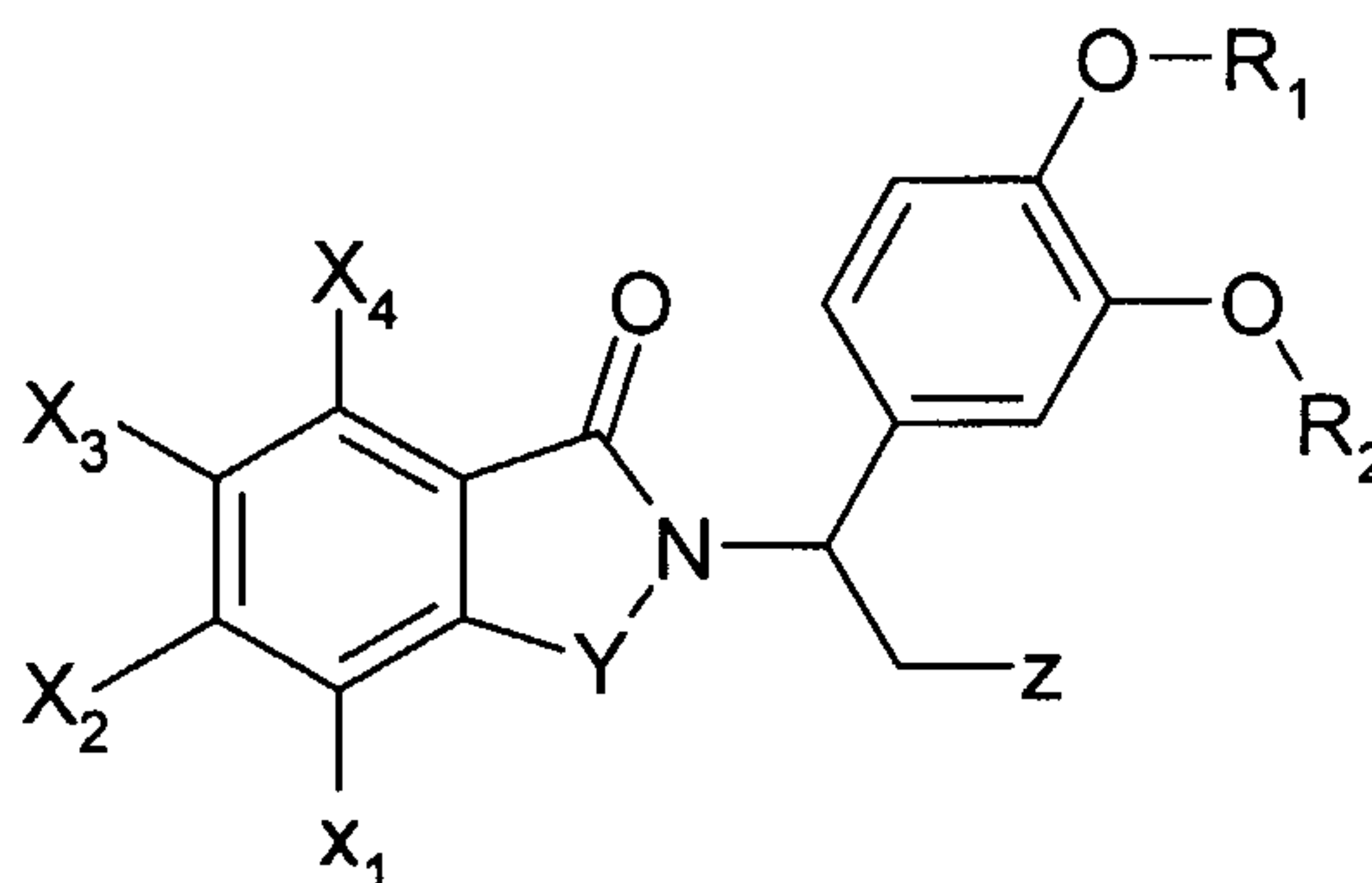
Particular compounds are those in which R^7 is hydroxy, methyl, ethyl, phenyl, benzyl, or NR^8R^9 in which each of R^8 and R^9 taken independently of the other is hydrogen or methyl.

Particular compounds are those in which R^7 is methyl, ethyl, phenyl, benzyl or NR^8R^9 in which each of R^8 and R^9 taken independently of the other is hydrogen or methyl.

Particular compounds are those in which R^7 is methyl.

Particular compounds are those in which R^7 is NR^8R^9 in which each of R^8 and R^9 taken independently of the other is hydrogen or methyl.

Additional PDE4 modulators include fluoroalkoxy-substituted 1,3-dihydro-isoindolyl compounds disclosed in U.S. patent application no. 10/748,085 filed on December 29, 2003, which is incorporated herein by reference. Representative compounds are of formula:



25

wherein:

Y is $-C(O)-$, $-CH_2-$, $-CH_2C(O)-$, $-C(O)CH_2-$, or SO_2 ;

Z is -H, -C(O)R³, -(C₀₋₁-alkyl)-SO₂-(C₁₋₄-alkyl), -C₁₋₈-alkyl, -CH₂OH, CH₂(O)(C₁₋₈-alkyl) or -CN;

R₁ and R₂ are each independently -CHF₂, -C₁₋₈-alkyl, -C₃₋₁₈-cycloalkyl, or -(C₁₋₁₀-alkyl)(C₃₋₁₈-cycloalkyl), and at least one of R₁ and R₂ is CHF₂;

5 R³ is -NR⁴R⁵, -alkyl, -OH, -O-alkyl, phenyl, benzyl, substituted phenyl, or substituted benzyl;

R⁴ and R⁵ are each independently -H, -C₁₋₈-alkyl, -OH, -OC(O)R⁶;

R⁶ is -C₁₋₈-alkyl, -amino(C₁₋₈-alkyl), -phenyl, -benzyl, or -aryl;

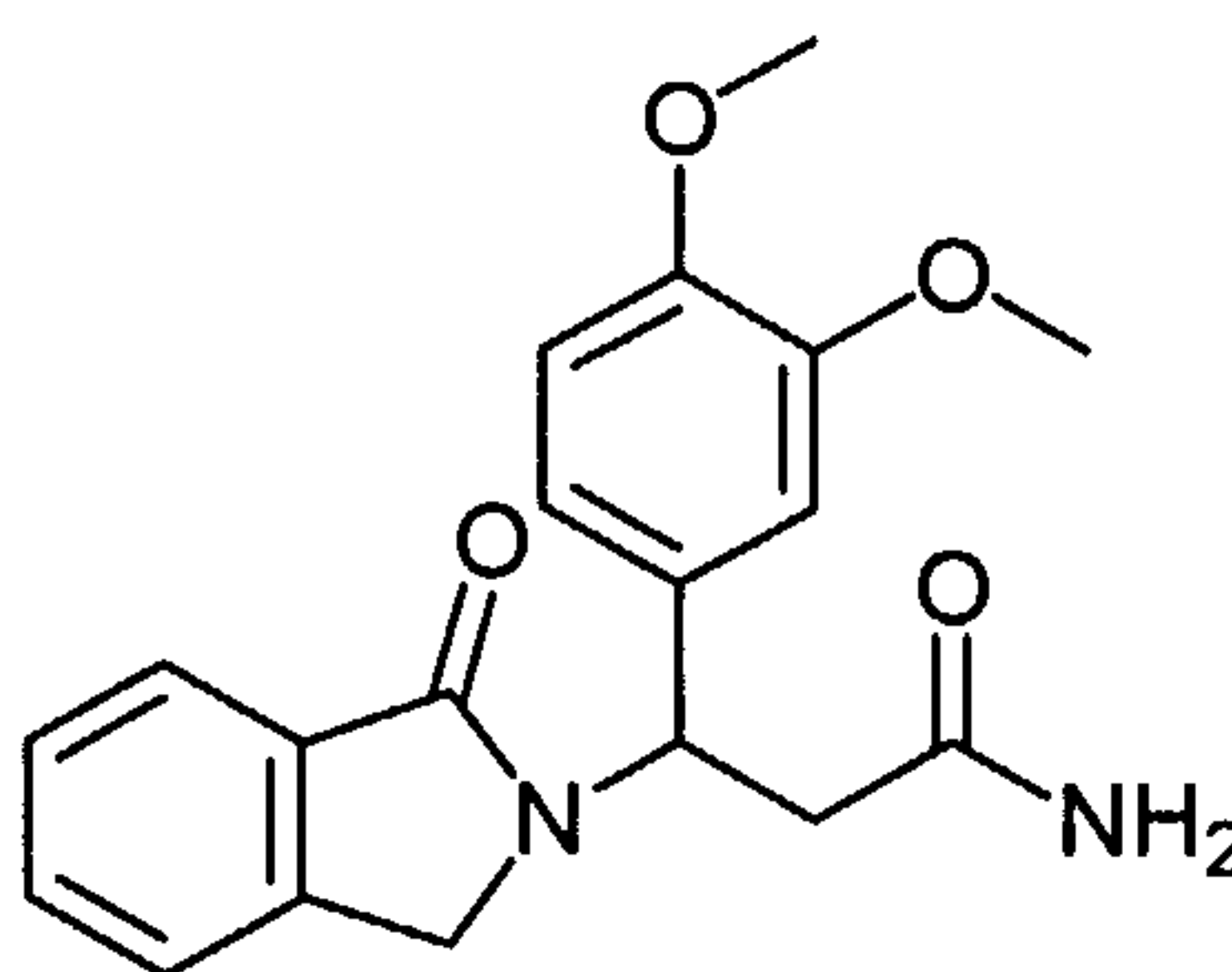
10 X₁, X₂, X₃, and X₄ are each independently -H, -halogen, -nitro, -NH₂, -CF₃, -C₁₋₆-alkyl, -(C₀₋₄-alkyl)-(C₃₋₆-cycloalkyl), (C₀₋₄-alkyl)-NR⁷R⁸, (C₀₋₄-alkyl)-N(H)C(O)-(R⁸), (C₀₋₄-alkyl)-N(H)C(O)N(R⁷R⁸), (C₀₋₄-alkyl)-N(H)C(O)O(R⁷R⁸), (C₀₋₄-alkyl)-OR⁸, (C₀₋₄-alkyl)-imidazolyl, (C₀₋₄-alkyl)-pyrrolyl, (C₀₋₄-alkyl)-oxadiazolyl, or (C₀₋₄-alkyl)-triazolyl, or two of X₁, X₂, X₃, and X₄ may be joined together to form a cycloalkyl or heterocycloalkyl ring, (e.g., X₁ and X₂, X₂ and X₃, X₃ and X₄, X₁ and X₃, X₂ and X₄, or X₁ and X₄ may form a 3, 15 4, 5, 6, or 7 membered ring which may be aromatic, thereby forming a bicyclic system with the isoindolyl ring); and

R⁷ and R⁸ are each independently H, C₁₋₉-alkyl, C₃₋₆-cycloalkyl, (C₁₋₆-alkyl)-(C₃₋₆-cycloalkyl), (C₁₋₆-alkyl)-N(R⁷R⁸), (C₁₋₆-alkyl)-OR⁸, phenyl, benzyl, or aryl; or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug 20 thereof.

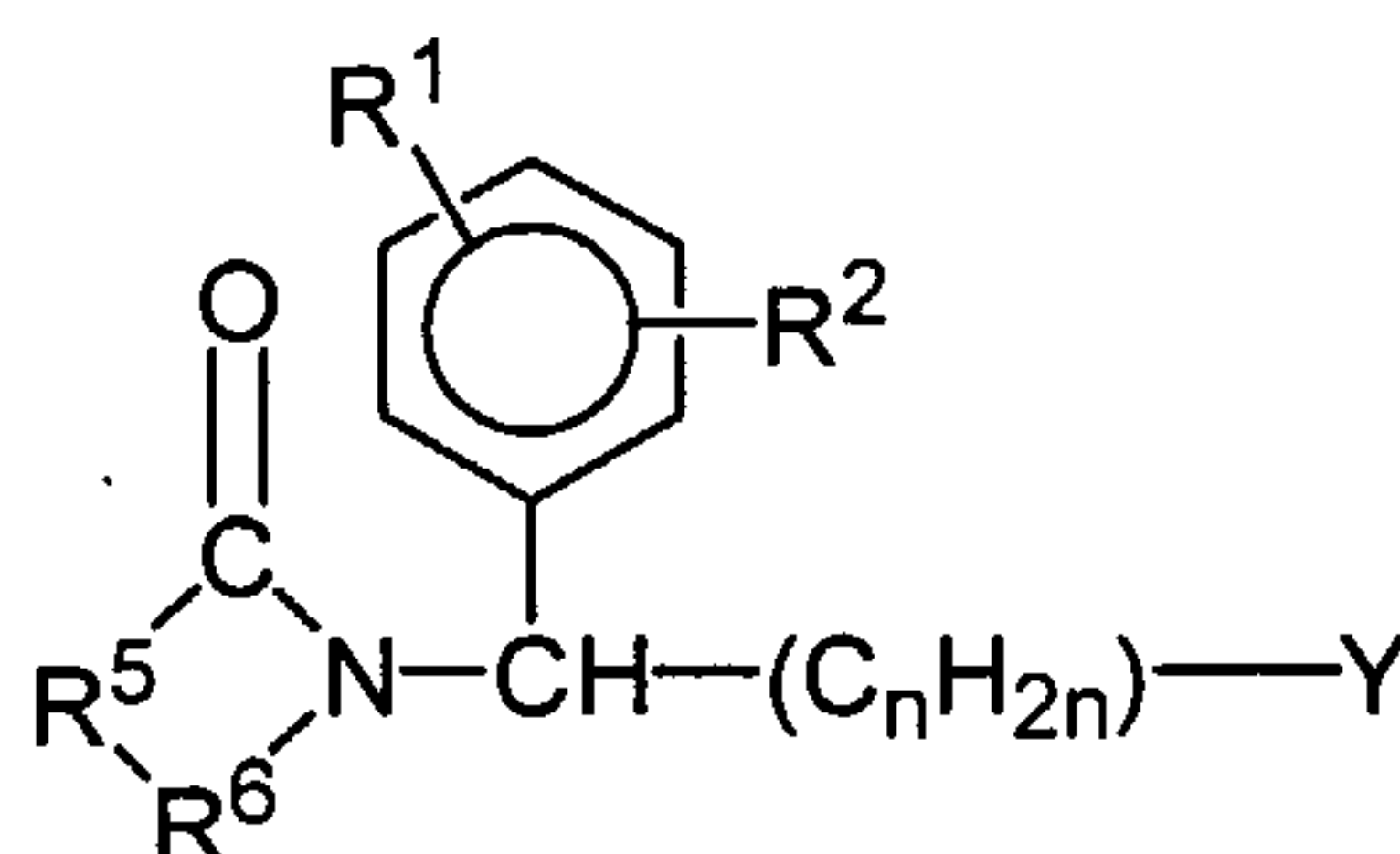
Additional PDE4 modulators include the enantiomerically pure compounds disclosed in U.S. patent application no. 10/392,195 filed on March 19, 2003; international patent application nos. PCT/US03/08737 and PCT/US03/08738, filed on March 20, 2003; U.S. provisional patent application nos. 60/438,450 and 60/438,448 to G. Muller *et al.*, both 25 of which were filed on January 7, 2003; U.S. provisional patent application no. 60/452,460 to G. Muller *et al.* filed on March 5, 2003; and U.S. patent application no. 10/715,184 filed on November 17, 2003, all of which are incorporated herein by reference. Preferred compounds include an enantiomer of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisoindoline-1,3-dione and an enantiomer of 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide. 30

Preferred PDE4 modulators used in the invention are 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide and cyclopropanecarboxylic acid {2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1 *H*-isoindol-4-yl}-amide, which are available from Celgene Corp., Warren, NJ. 3-(3,4-Dimethoxy-

phenyl)-3-(1-oxo-1,3-dihydro-indol-2-yl)-propionamide has the following chemical structure:



Other specific PDE4 modulators include, but are not limited to, the cycloalkyl
 5 amides and cycloalkyl nitriles of U.S. patent nos. 5,728,844, 5,728,845, 5,968,945,
 6,180,644 and 6,518,281, and WO 97/08143 and WO 97/23457, each of which is
 incorporated herein by reference. Representative compounds are of formula:



wherein:

10 one of R^1 and R^2 is R^3 -X- and the other is hydrogen, nitro, cyano, trifluoromethyl,
 carbo(lower)alkoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, lower alkyl,
 lower alkoxy, halo, or R^3 -X-;

R^3 is monocycloalkyl, bicycloalkyl, or benzocycloalkyl of up to 18 carbon atoms;

X is a carbon-carbon bond, $-CH_2-$, or $-O-$;

15 R^5 is (i) o-phenylene, unsubstituted or substituted with 1 to 3 substituents each
 selected independently from nitro, cyano, halo, trifluoromethyl, carbo(lower)alkoxy, acetyl,
 or carbamoyl, unsubstituted or substituted with lower alkyl, acetoxy, carboxy, hydroxy,
 amino, lower alkylamino, lower acylamino, or lower alkoxy; (ii) a vicinally divalent residue
 of pyridine, pyrrolidine, imidazole, naphthalene, or thiophene, wherein the divalent bonds
 20 are on vicinal ring carbon atoms; (iii) a vicinally divalent cycloalkyl or cycloalkenyl of 4-10
 carbon atoms, unsubstituted or substituted with 1 to 3 substituents each selected
 independently from the group consisting of nitro, cyano, halo, trifluoromethyl,
 carbo(lower)alkoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, lower
 alkylamino, lower alkyl, lower alkoxy, or phenyl; (iv) vinylene di-substituted with lower
 25 alkyl; or (v) ethylene, unsubstituted or monosubstituted or disubstituted with lower alkyl;

R^6 is $-\text{CO}-$, $-\text{CH}_2-$, or $-\text{CH}_2\text{CO}-$;

Y is $-\text{COZ}$, $-\text{C}\equiv\text{N}$, $-\text{OR}^8$, lower alkyl, or aryl;

Z is $-\text{NH}_2$, $-\text{OH}$, $-\text{NHR}$, $-\text{R}^9$, or $-\text{OR}^9$

R^8 is hydrogen or lower alkyl;

5 R^9 is lower alkyl or benzyl; and,

n has a value of 0, 1, 2, or 3.

In another embodiment, one of R^1 and R^2 is $R^3-\text{X}-$ and the other is hydrogen, nitro, cyano, trifluoromethyl, carbo(lower)alkoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, lower alkyl, lower alkoxy, halo, or $R^3-\text{X}-$;

10 R^3 is monocycloalkyl of up to 10 carbon atoms, polycycloalkyl of up to 10 carbon atoms, or benzocyclic alkyl of up to 10 carbon atoms;

X is $-\text{CH}_2-$, or $-\text{O}-$;

R^5 is (i) the vicinally divalent residue of pyridine, pyrrolidine, imidazole, naphthalene, or thiophene, wherein the two bonds of the divalent residue are on vicinal ring
15 carbon atoms;

(ii) a vicinally divalent cycloalkyl of 4-10 carbon atoms, unsubstituted or substituted with 1 to 3 substituents each selected independently from the group consisting of nitro, cyano, halo, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, substituted amino, alkyl of 1 to 10 carbon atoms, alkoxy
20 of 1 to 10 carbon atoms, or phenyl;

(iii) di-substituted vinylene, substituted with nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, carbamoyl substituted with and alkyl of 1 to 3 carbon atoms, acetoxo, carboxy, hydroxy, amino, amino substituted with an alkyl of 1 to 3 carbon atoms, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms,
25 or halo;

(iv) ethylene, unsubstituted or substituted with 1 to 2 substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, carbamoyl substituted with and alkyl of 1 to 3 carbon atoms, acetoxo, carboxy, hydroxy, amino, amino substituted with an alkyl of 1 to 3 carbon atoms, alkyl of 1
30 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo;

R^6 is $-\text{CO}-$, $-\text{CH}_2-$, or $-\text{CH}_2\text{CO}-$;

Y is $-\text{COX}$, $-\text{C}\equiv\text{N}$, $-\text{OR}^8$, alkyl of 1 to 5 carbon atoms, or aryl;

X is $-\text{NH}_2$, $-\text{OH}$, $-\text{NHR}$, $-\text{R}^9$, $-\text{OR}^9$, or alkyl of 1 to 5 carbon atoms;

R^8 is hydrogen or lower alkyl;

R^4 is alkyl or benzyl; and,

n has a value of 0, 1, 2, or 3.

In another embodiment, one of R^1 and R^2 is R^3 -X- and the other is hydrogen, nitro, cyano, trifluoromethyl, carbo(lower)alkoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, lower alkyl, lower alkoxy, halo, HF_2CO , F_3CO , or R^3 -X-;

R^3 is monocycloalkyl, bicycloalkyl, benzocyclo alkyl of up to 18 carbon atoms, tetrahydropyran, or tetrahydrofuran;

X is a carbon-carbon bond, $-CH_2-$, $-O-$, or $-N=$;

R^5 is (i) o-phenylene, unsubstituted or substituted with 1 to 3 substituents each selected independently from nitro, cyano, halo, trifluoromethyl, carbo(lower)alkoxy, acetyl, or carbamoyl, unsubstituted or substituted with lower alkyl, acetoxy, carboxy, hydroxy, amino, lower alkylamino, lower acylamino, or lower alkoxy; (ii) a vicinally divalent residue of pyridine, pyrrolidine, imidazole, naphthalene, or thiophene, wherein the divalent bonds are on vicinal ring carbon atoms; (iii) a vicinally divalent cycloalkyl or cycloalkenyl of 4-10 carbon atoms, unsubstituted or substituted with 1 or more substituents each selected independently from the group consisting of nitro, cyano, halo, trifluoromethyl, carbo(lower)alkoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, lower alkylamino, lower alkyl, lower alkoxy, or phenyl; (iv) vinylene di-substituted with lower alkyl; or (v) ethylene, unsubstituted or monosubstituted or disubstituted with lower alkyl;

R^6 is $-CO-$, $-CH_2-$, or $-CH_2CO-$;

Y is $-COX$, $-C\equiv N$, $-OR^8$, alkyl of 1 to 5 carbon atoms, or aryl;

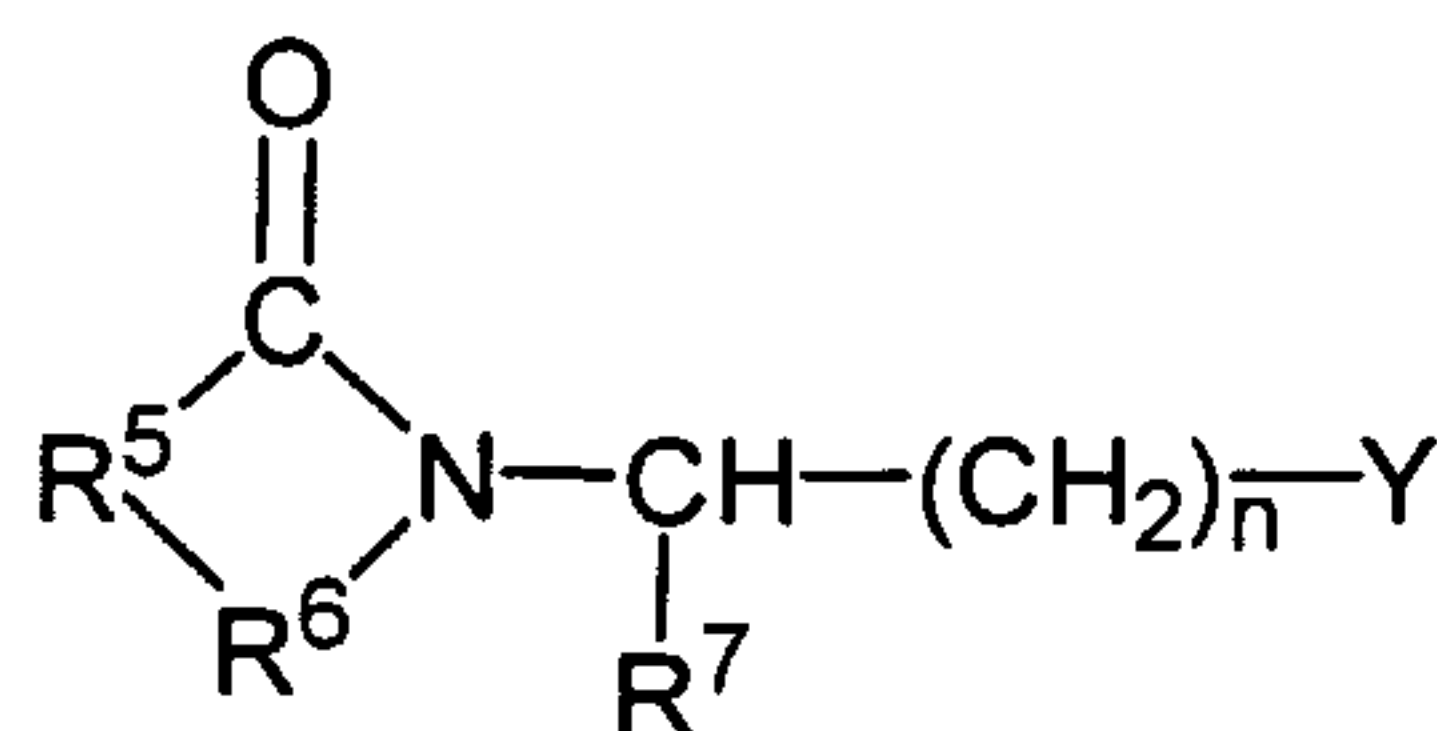
X is $-NH_2$, $-OH$, $-NHR$, $-R^9$, $-OR^9$, or alkyl of 1 to 5 carbon atoms;

R^8 is hydrogen or lower alkyl;

R^9 is alkyl or benzyl; and,

n has a value of 0, 1, 2, or 3.

Other representative compounds are of formula:



wherein:

Y is $-C\equiv N$ or $CO(CH_2)_mCH_3$;

m is 0, 1, 2, or 3;

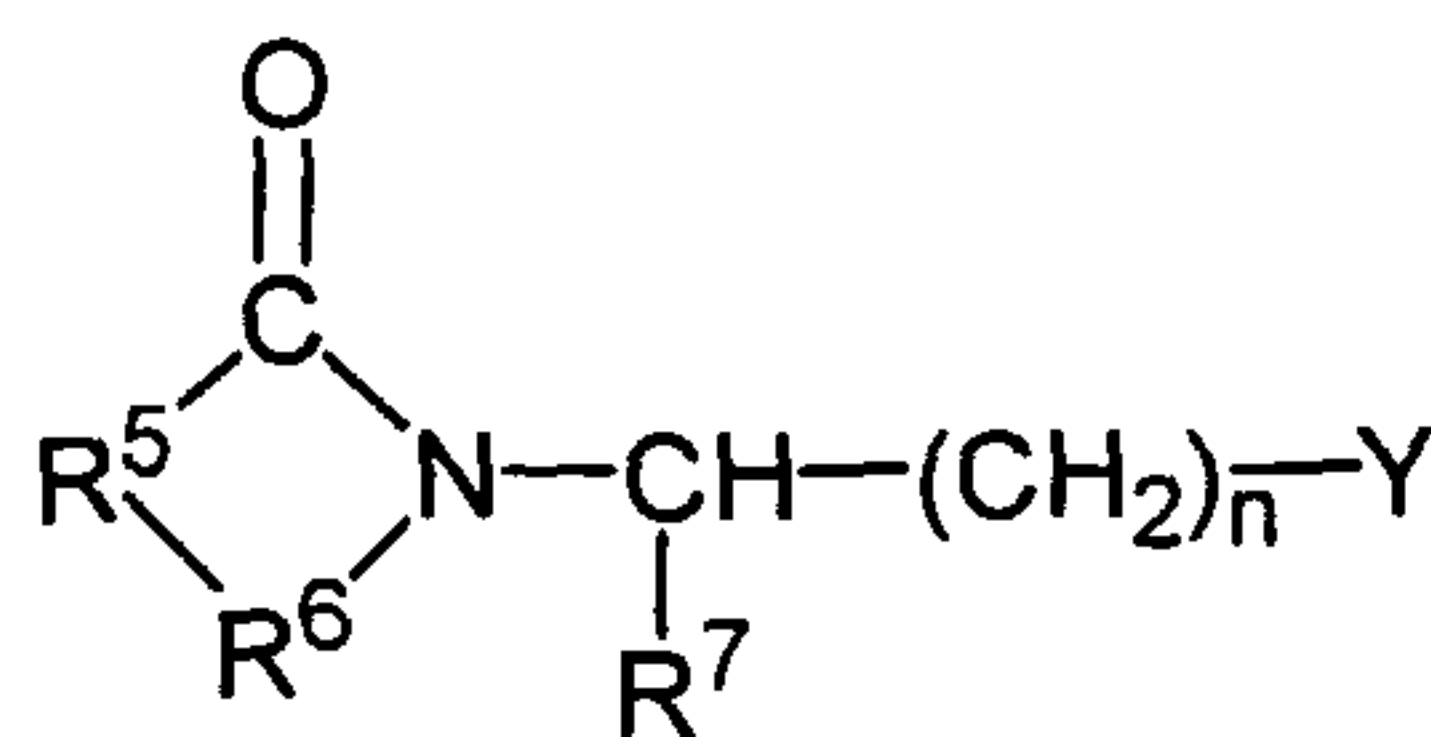
R^5 is (i) o-phenylene, unsubstituted or substituted with 1 to 3 substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, carbamoyl substituted with and alkyl of 1 to 3 carbon atoms, acetoxo, carboxy, hydroxy, amino, amino substituted with an alkyl of 1 to 3 carbon atoms, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo; (ii) the divalent residue of pyridine, pyrrolidine, imidazole, naphthalene, or thiophene, wherein the divalent bonds are on vicinal ring carbon atoms; (iii) a divalent cycloalkyl of 4-10 carbon atoms, unsubstituted or substituted with one or more substituents each selected independently of the other from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, substituted amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, phenyl or halo; (iv) di-substituted vinylene, substituted with nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, carbamoyl substituted with and alkyl of 1 to 3 carbon atoms, acetoxo, carboxy, hydroxy, amino, amino substituted with an alkyl of 1 to 3 carbon atoms, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo; or (v) ethylene, unsubstituted or substituted with 1 to 2 substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, carbamoyl substituted with and alkyl of 1 to 3 carbon atoms, acetoxo, carboxy, hydroxy, amino, amino substituted with an alkyl of 1 to 3 carbon atoms, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo;

R^6 is $-\text{CO}-$, $-\text{CH}_2-$, $-\text{CH}_2\text{CO}-$, or $-\text{SO}_2-$;

R^7 is (i) straight or branched alkyl of 1 to 12 carbon atoms; (ii) cyclic or bicyclic alkyl of 1 to 12 carbon atoms; (iii) pyridyl; (iv) phenyl substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, straight, branched, cyclic, or bicyclic alkyl of 1 to 10 carbon atoms, straight, branched, cyclic, or bicyclic alkoxy of 1 to 10 carbon atoms, CH_2R where R is a cyclic or bicyclic alkyl of 1 to 10 carbon atoms, or halo; (v) benzyl substituted with one to three substituents each selected independently from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo; (vi) naphthyl; or (vii) benzyloxy; and

n has a value of 0, 1, 2, or 3.

In another embodiment, specific PDE4 modulators are of formula:



wherein:

R^5 is (i) the divalent residue of pyridine, pyrrolidine, imidazole, naphthalene, or thiophene, wherein the divalent bonds are on vicinal ring carbon atoms; (ii) a divalent cycloalkyl of 4-10 carbon atoms, unsubstituted or substituted with one or more substituents each selected independently of the other from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxyl, carboxy, hydroxy, amino, substituted amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, phenyl or halo; (iii) di-substituted vinylene, substituted with nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, carbamoyl substituted with and alkyl of 1 to 3 carbon atoms, acetoxyl, carboxy, hydroxy, amino, amino substituted with an alkyl of 1 to 3 carbon atoms, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo; or (iv) ethylene, unsubstituted or substituted with 1 to 2 substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, carbamoyl substituted with and alkyl of 1 to 3 carbon atoms, acetoxyl, carboxy, hydroxy, amino, amino substituted with an alkyl of 1 to 3 carbon atoms, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo;

R^6 is $-\text{CO}-$, $-\text{CH}_2-$, $-\text{CH}_2\text{CO}-$, or $-\text{SO}_2-$;

R^7 is (i) cyclic or bicyclic alkyl of 4 to 12 carbon atoms; (ii) pyridyl; (iii) phenyl substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxyl, carboxy, hydroxy, amino, straight, branched, cyclic, or bicyclic alkyl of 1 to 10 carbon atoms, straight, branched, cyclic, or bicyclic alkoxy of 1 to 10 carbon atoms, CH_2R where R is a cyclic or bicyclic alkyl of 1 to 10 carbon atoms, or halo; (iv) benzyl substituted with one to three substituents each selected independently from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxyl, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo; (v) naphthyl; or (vi) benzyloxy; and

Y is COX , $-\text{C}\equiv\text{N}$, OR^8 , alkyl of 1 to 5 carbon atoms, or aryl;

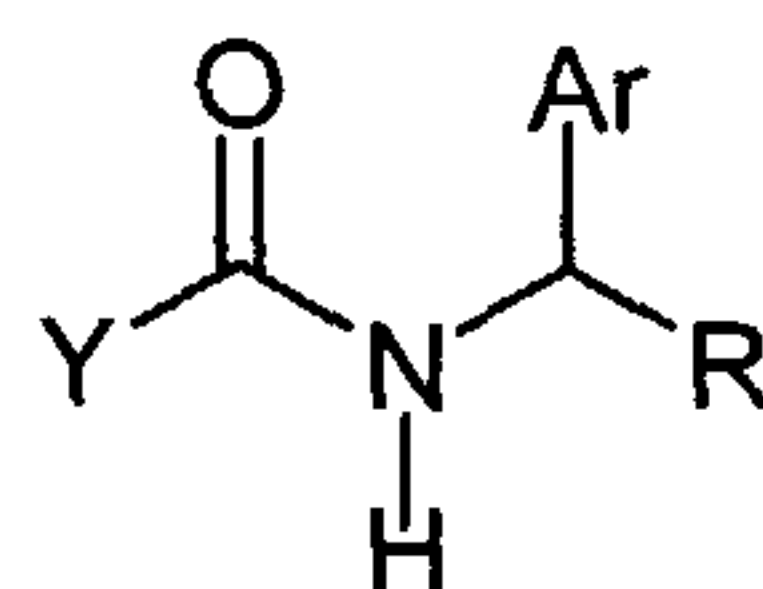
X is $-\text{NH}_2$, $-\text{OH}$, $-\text{NHR}$, $-\text{R}^9$, $-\text{OR}^9$, or alkyl of 1 to 5 carbon atoms;

R^8 is hydrogen or lower alkyl;

R^9 is alkyl or benzyl; and

n has a value of 0, 1, 2, or 3.

Other specific PDE4 modulators include, but are not limited to, the aryl amides (for example, an embodiment being N-benzoyl-3-amino-3-(3',4'-dimethoxyphenyl)-propanamide) of U.S. patent nos. 5,801,195, 5,736,570, 6,046,221 and 6,284,780, each of which is incorporated herein by reference. Representative compounds are of formula:

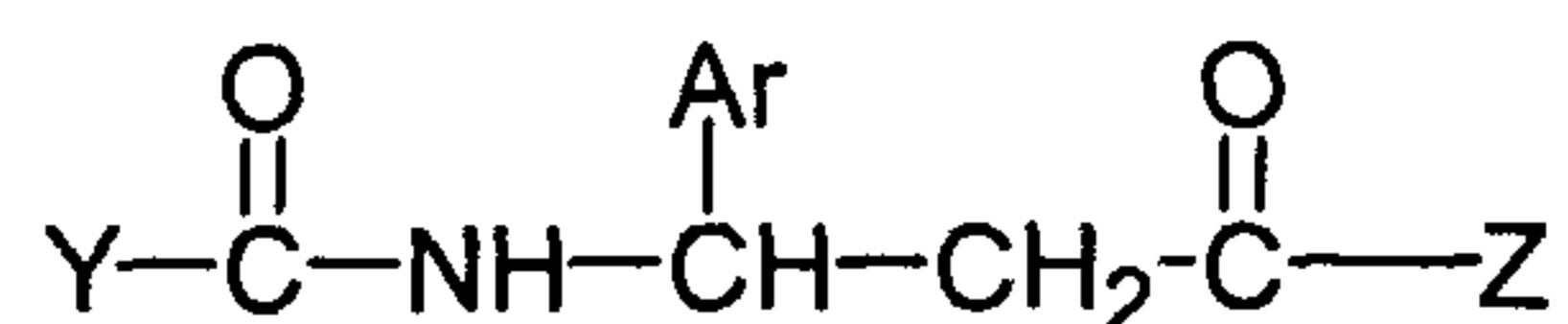


wherein:

Ar is (i) straight, branched, or cyclic, unsubstituted alkyl of 1 to 12 carbon atoms; (ii) straight, branched, or cyclic, substituted alkyl of 1 to 12 carbon atoms; (iii) phenyl; (iv) phenyl substituted with one or more substituents each selected independently of the other from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, substituted amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo; (v) heterocycle; or (vi) heterocycle substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo;

R is -H, alkyl of 1 to 10 carbon atoms, CH₂OH, CH₂CH₂OH, or CH₂COZ where Z is alkoxy of 1 to 10 carbon atoms, benzyloxy, or NHR¹ where R¹ is H or alkyl of 1 to 10 carbon atoms; and

Y is i) a phenyl or heterocyclic ring, unsubstituted or substituted one or more substituents each selected independently one from the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo or ii) naphthyl. Specific examples of the compounds are of formula:



wherein:

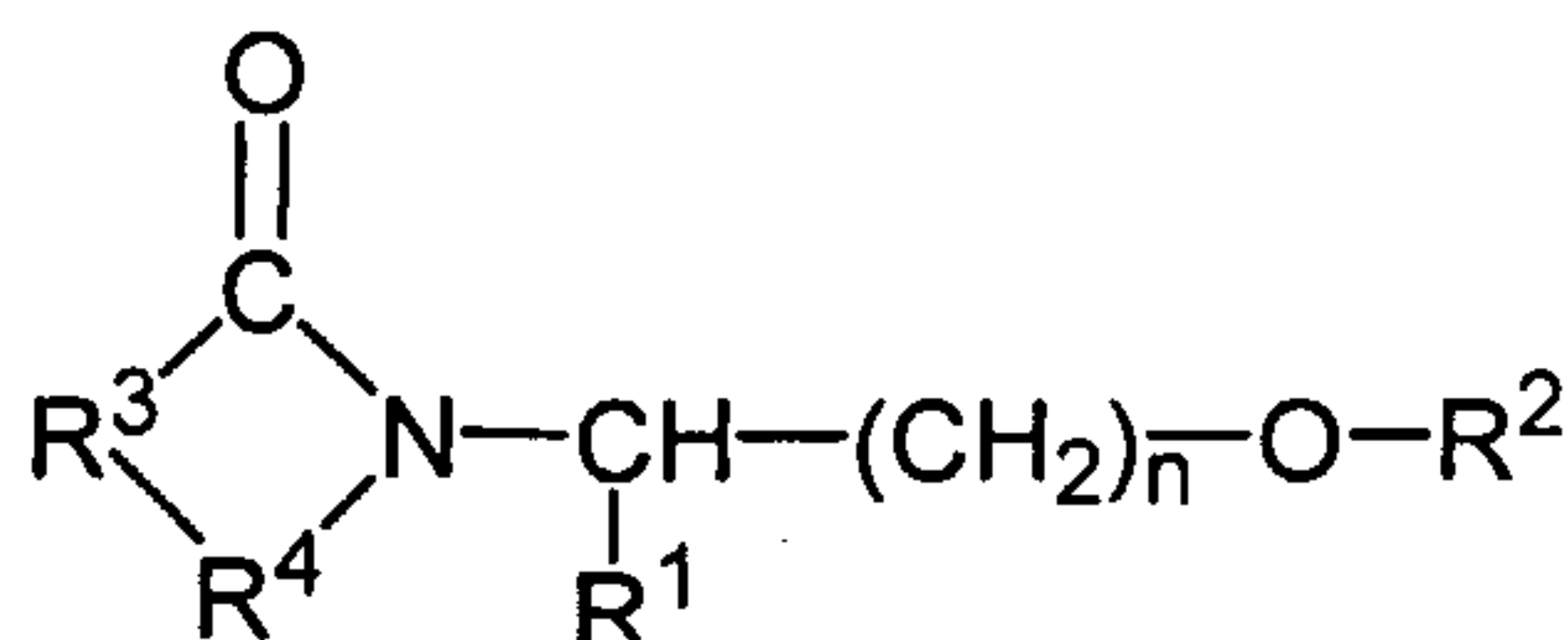
Ar is 3,4-disubstituted phenyl where each substituent is selected independently of the other from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy,

"carbomethoxy," "carbopropoxy," acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, and halo;

Z is alkoxy of 1 to 10 carbon atoms, benzyloxy, amino, or alkylamino of 1 to 10 carbon atoms; and

5 Y is (i) a phenyl, unsubstituted or substituted with one or more substituents each selected, independently one from the other, from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, and halo, or (ii) naphthyl.

10 Other specific PDE4 modulators include, but are not limited to, the imide/amide ethers and alcohols (for example, 3-phthalimido-3-(3',4'-dimethoxyphenyl) propan-1-ol) disclosed in U.S. patent no. 5,703,098, which is incorporated herein by reference. Representative compounds have the formula:



15 wherein:

R¹ is (i) straight, branched, or cyclic, unsubstituted alkyl of 1 to 12 carbon atoms; (ii) straight, branched, or cyclic, substituted alkyl of 1 to 12 carbon atoms; (iii) phenyl; or (iv) phenyl substituted with one or more substituents each selected independently of the other from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, acylamino, alkylamino, di(alkyl) amino, alkyl of 1 to 10 carbon atoms, cycloalkyl of 3 to 10 carbon atoms, bicycloalkyl of 5 to 12 carbon atoms, alkoxy of 1 to 10 carbon atoms, cycloalkoxy of 3 to 10 carbon atoms, bicycloalkoxy of 5 to 12 carbon atoms, and halo;

25 R² is hydrogen, alkyl of 1 to 8 carbon atoms, benzyl, pyridylmethyl, or alkoxymethyl;

R³ is (i) ethylene, (ii) vinylene, (iii) a branched alkylene of 3 to 10 carbon atoms, (iv) a branched alkenylene of 3 to 10 carbon atoms, (v) cycloalkylene of 4 to 9 carbon atoms unsubstituted or substituted with one or more substituents each selected independently from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, amino substituted with alkyl of 1 to 6 carbon atoms, amino substituted with acyl of 1 to 6 carbon atoms, alkyl of 1

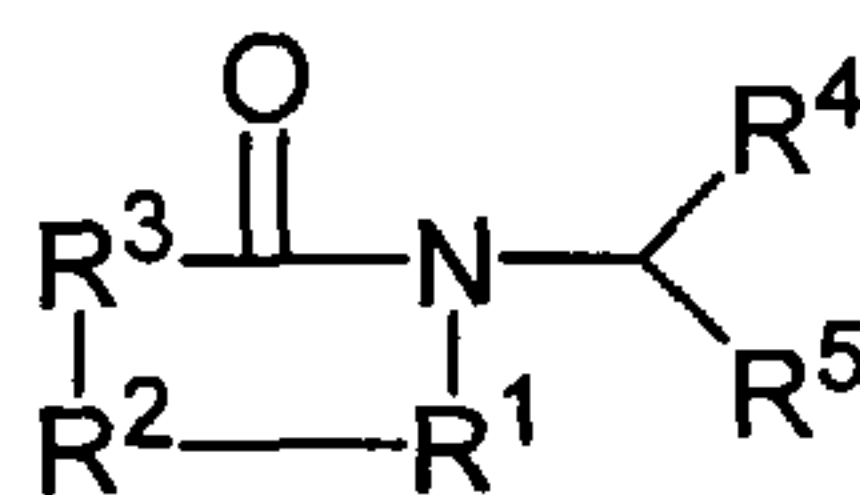
to 10 carbon atoms, alkoxy of 1 to 12 carbon atoms, and halo, (vi) cycloalkenylene of 4 to 9 carbon atoms unsubstituted or substituted with one or more substituents each selected independently from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, amino substituted with alkyl of 1 to 6 carbon atoms, amino substituted with acyl of 1 to 6 carbon atoms, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 12 carbon atoms, and halo, (vii) o-phenylene unsubstituted or substituted with one or more substituents each selected independently from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, amino substituted with alkyl of 1 to 6 carbon atoms, amino substituted with acyl of 1 to 6 carbon atoms, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 12 carbon atoms, and halo, (viii) naphthyl, or (ix) pyridyl;

R^4 is -CX-, -CH₂- or -CH₂CX-;

X is O or S; and

n is 0, 1, 2, or 3.

Other specific PDE4 modulators include, but are not limited to, the succinimides and maleimides (for example methyl 3-(3',4',5'6'-tetrahydrophthalimido)-3-(3'',4''-dimethoxyphenyl)propionate) disclosed in U.S. patent no. 5,658,940, which is incorporated herein by reference. Representative compounds are of formula:



wherein:

R^1 is -CH₂-, -CH₂CO-, or -CO-;

R^2 and R^3 taken together are (i) ethylene unsubstituted or substituted with alkyl of 1-10 carbon atoms or phenyl, (ii) vinylene substituted with two substituents each selected, independently of the other, from the group consisting of alkyl of 1-10 carbon atoms and phenyl, or (iii) a divalent cycloalkyl of 5-10 carbon atoms, unsubstituted or substituted with one or more substituents each selected independently of the other from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl unsubstituted or substituted with alkyl of 1-3 carbon atoms, acetoxo, carboxy, hydroxy, amino, substituted amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, norbornyl, phenyl or halo;

R^4 is (i) straight or branched unsubstituted alkyl of 4 to 8 carbon atoms, (ii) cycloalkyl or bicycloalkyl of 5-10 carbon atoms, unsubstituted or substituted with one or more substituents each selected independently of the other from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxymethyl, carboxy, hydroxy, amino, substituted amino, branched, straight or cyclic alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, phenyl or halo, (iii) phenyl substituted with one or more substituents each selected independently of the other from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxymethyl, carboxy, hydroxy, amino, substituted amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, cycloalkyl or bicycloalkyl of 3 to 10 carbon atoms, cycloalkoxy or bicycloalkoxy of 3 to 10 carbon atoms, phenyl or halo, (iv) pyridine or pyrrolidine, unsubstituted or substituted with one or more substituents each selected independently of the other from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxymethyl, carboxy, hydroxy, amino, substituted amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, phenyl or halo; and,

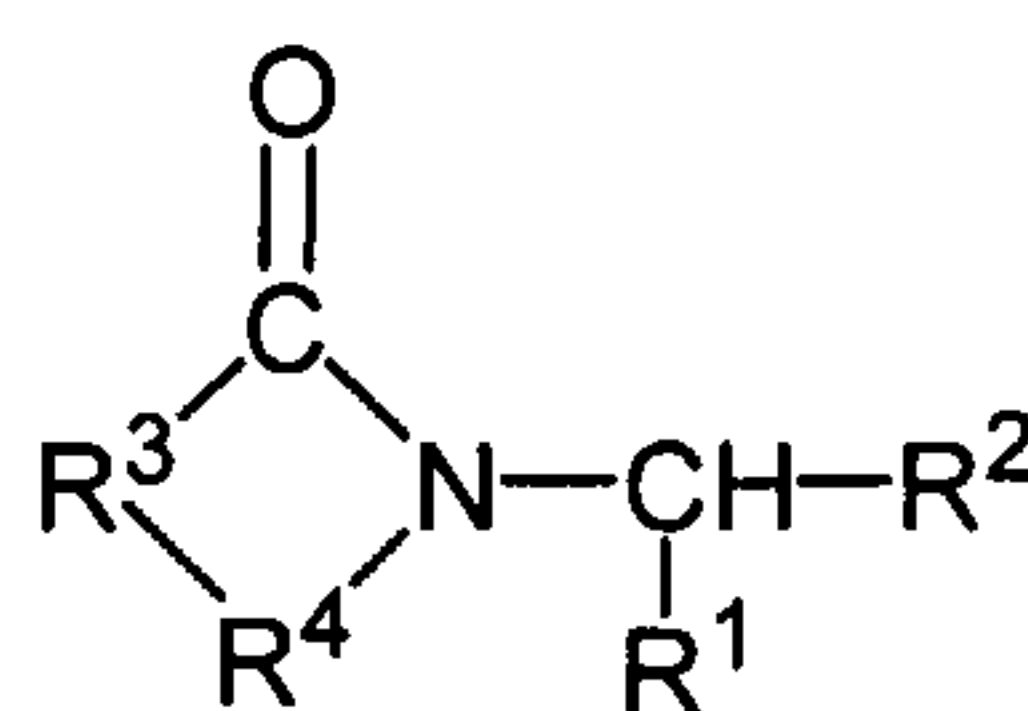
R^5 is -COX, -CN, -CH₂COX, alkyl of 1 to 5 carbon atoms, aryl, -CH₂OR, -CH₂ aryl, or -CH₂OH,

where X is NH₂, OH, NHR, or OR⁶,

where R is lower alkyl; and

where R⁶ is alkyl or benzyl.

Other specific PDE4 modulators include, but are not limited to, substituted imides (for example, 2-phthalimido-3-(3',4'-dimethoxyphenyl) propane) disclosed in U.S. patent no. 6,429,221, which is incorporated herein by reference. Representative compounds have the formula:



wherein:

R^1 is (i) straight, branched, or cyclic alkyl of 1 to 12 carbon atoms, (ii) phenyl or phenyl substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxymethyl, carboxy, hydroxy, amino, straight or branched alkyl of 1 to 10 carbon

atoms, alkoxy of 1 to 10 carbon atoms, or halo, (iii) benzyl or benzyl substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxyl, carboxyl, hydroxyl, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo, or (iv) -Y-Ph where Y is a straight, branched, or cyclic alkyl of 1 to 12 carbon atoms and Ph is phenyl or phenyl substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxyl, carboxyl, hydroxyl, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo;

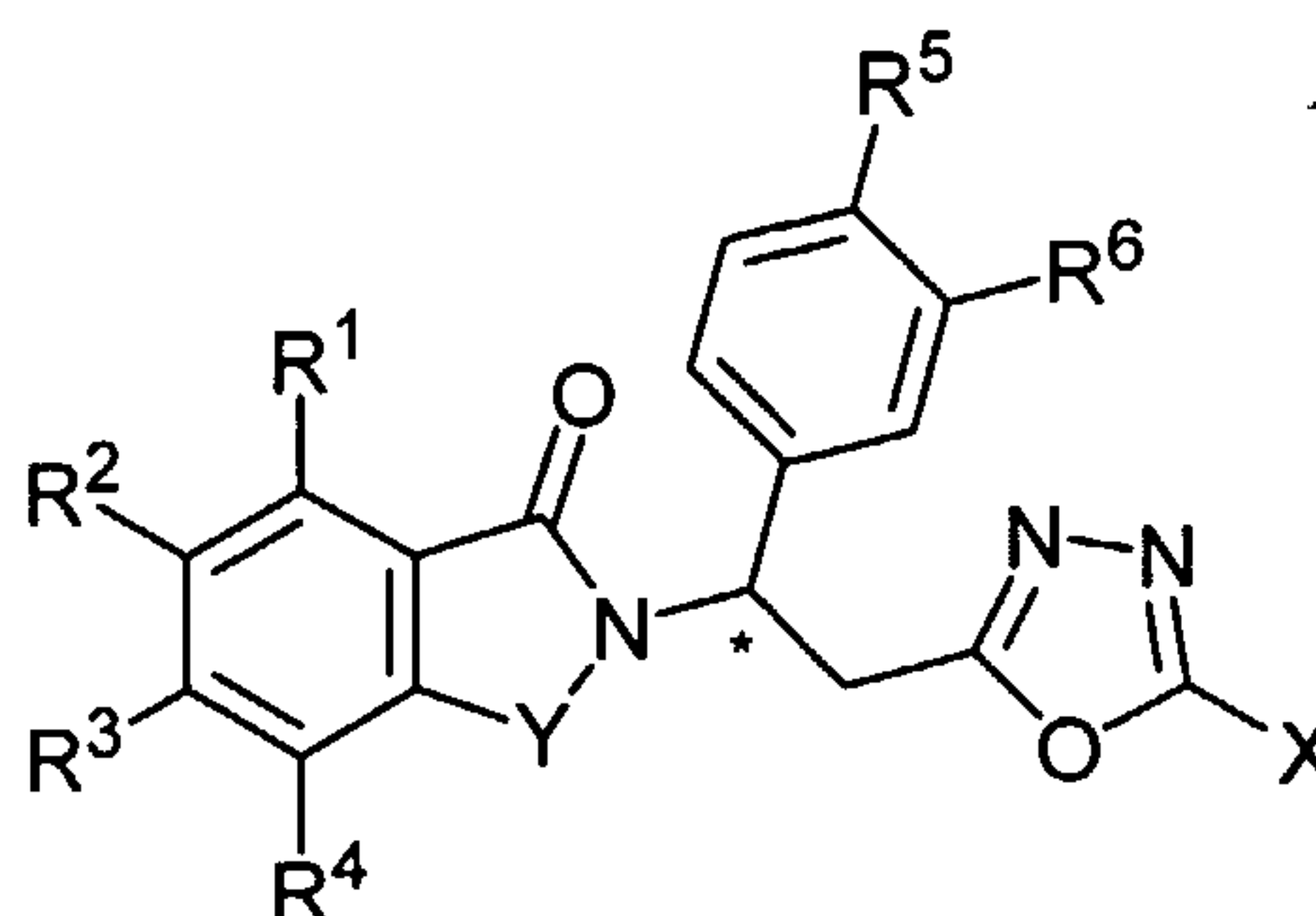
10 R^2 is -H, a branched or unbranched alkyl of 1 to 10 carbon atoms, phenyl, pyridyl, heterocycle, -CH₂-aryl, or -CH₂-heterocycle;

R^3 is i) ethylene, ii) vinylene, iii) a branched alkylene of 3 to 10 carbon atoms, iv) a branched alkenylene of 3 to 10 carbon atoms, v) cycloalkylene of 4 to 9 carbon atoms unsubstituted or substituted with 1 to 2 substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxyl, carboxyl, hydroxyl, amino, substituted amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, vi) cycloalkenylene of 4 to 9 carbon atoms unsubstituted or substituted with 1 to 2 substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxyl, carboxyl, hydroxyl, amino, substituted amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, or vii) o-phenylene unsubstituted or substituted with 1 to 2 substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxyl, carboxyl, hydroxyl, amino, substituted amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo; and,

25 R^4 is -CX, or -CH₂-;

X is O or S.

Other specific PDE4 modulators include, but are not limited to, substituted 1,3,4-oxadiazoles (for example, 2-[1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(1,3,4-oxadiazole-2-yl)ethyl]-5-methylisoindoline-1,3-dione) disclosed in U.S. patent no. 6,326,388, which is
30 incorporated herein by reference. Representative compounds are of formula:



wherein:

the carbon atom designated* constitutes a center of chirality;

Y is C=O, CH₂, SO₂ or CH₂C=O;

5 X is hydrogen, or alkyl of 1 to 4 carbon atoms;

each of R¹, R², R³, and R⁴, independently of the others, is hydrogen, halo, trifluoromethyl, acetyl, alkyl of 1 to 8 carbon atoms, alkoxy of 1 to 4 carbon atoms, nitro, cyano, hydroxy, -CH₂NR⁸R⁹, -(CH₂)₂NR⁸R⁹, or -NR⁸R⁹ or

any two of R¹, R², R³, and R⁴ on adjacent carbon atoms, together with the depicted
10 benzene ring are naphthylidene, quinoline, quinoxaline, benzimidazole, benzodioxole or 2-hydroxybenzimidazole;

each of R⁵ and R⁶, independently of the other, is hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 6 carbon atoms, cyano, benzocycloalkoxy, cycloalkoxy of up to 18 carbon atoms, bicycloalkoxy of up to 18 carbon atoms, tricycloalkoxy of up to 18 carbon
15 atoms, or cycloalkylalkoxy of up to 18 carbon atoms;

each of R⁸ and R⁹, taken independently of the other is hydrogen, straight or branched alkyl of 1 to 8 carbon atoms, phenyl, benzyl, pyridyl, pyridylmethyl, or one of R⁸ and R⁹ is hydrogen and the other is -COR¹⁰, or -SO₂R¹⁰, or R⁸ and R⁹ taken together are tetramethylene, pentamethylene, hexamethylene, -CH=NCH=CH-, or -CH₂CH₂X¹CH₂CH₂-
20 in which X¹ is -O-, -S-, or -NH-,

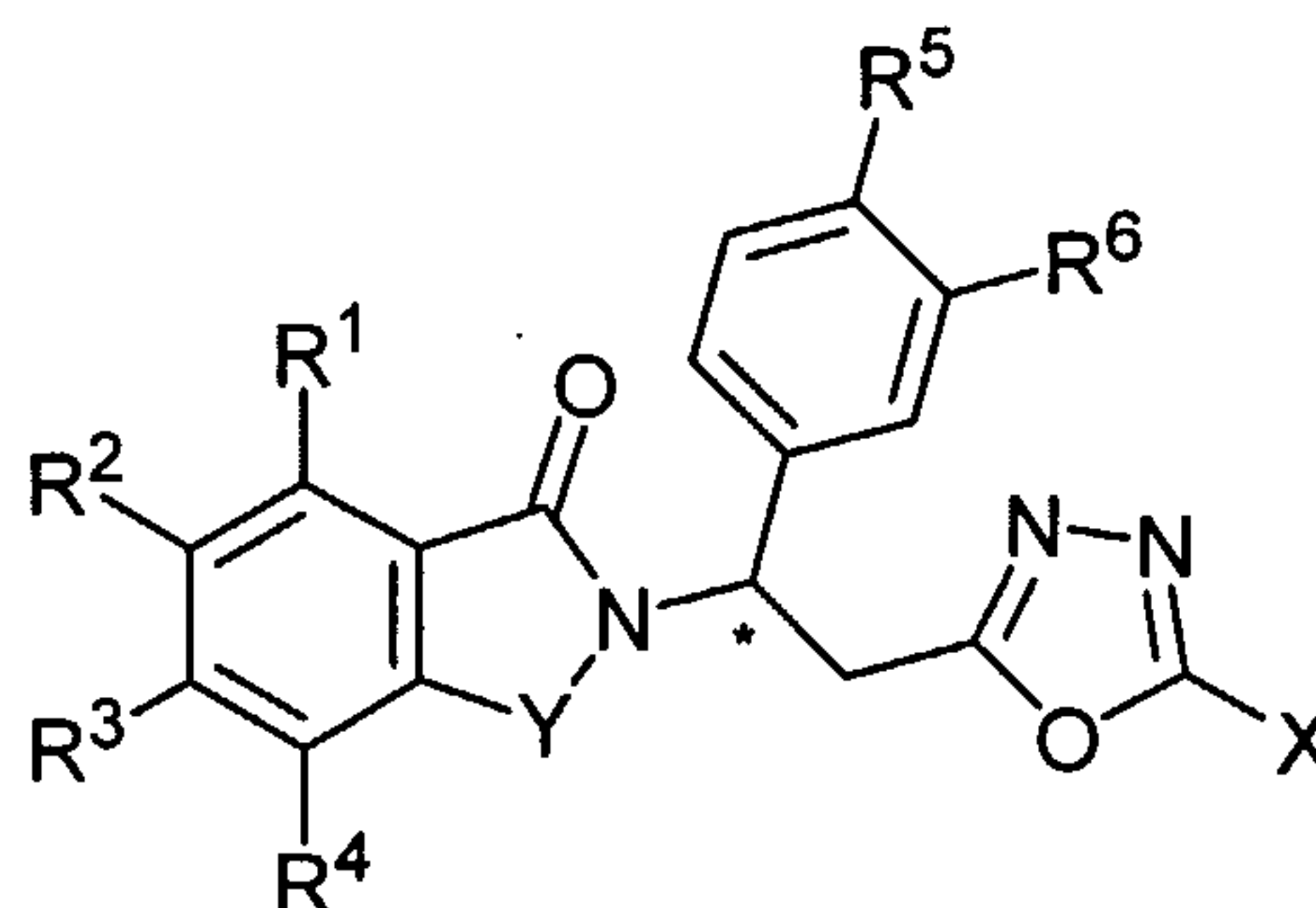
R¹⁰ is hydrogen, alkyl of 1 to 8 carbon atoms, cycloalkyl, cycloalkylmethyl of up to 6 carbon atoms, phenyl, pyridyl, benzyl, imidazolylmethyl, pyridylmethyl, NR¹¹R¹², CH₂R¹⁴R¹⁵, or NR¹¹R¹²,

wherein R¹⁴ and R¹⁵, independently of each other, are hydrogen, methyl, ethyl, or
25 propyl, and

wherein R¹¹ and R¹², independently of each other, are hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, or benzyl; and

the acid addition salts of said compounds which contain a nitrogen atom susceptible of protonation.

Specific examples of the compounds are of formula:



wherein:

the carbon atom designated* constitutes a center of chirality;

5 Y is C=O, CH₂, SO₂ or CH₂C=O;

X is hydrogen, or alkyl of 1 to 4 carbon atoms;

(i) each of R¹, R², R³, and R⁴, independently of the others, is hydrogen, halo, trifluoromethyl, acetyl, alkyl of 1 to 8 carbon atoms, alkoxy of 1 to 4 carbon atoms, nitro, cyano, hydroxy, -CH₂NR⁸R⁹, -(CH₂)₂NR⁸R⁹, or -NR⁸R⁹ or

10 (ii) any two of R¹, R², R³, and R⁴ on adjacent carbon atoms, together with the depicted benzene ring to which they are bound are naphthylidene, quinoline, quinoxaline, benzimidazole, benzodioxole or 2-hydroxybenzimidazole;

each of R⁵ and R⁶, independently of the other, is hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 6 carbon atoms, cyano, benzocycloalkoxy, cycloalkoxy of up to 18
15 carbon atoms, bicycloalkoxy of up to 18 carbon atoms, tricycloalkoxy of up to 18 carbon atoms, or cycloalkylalkoxy of up to 18 carbon atoms;

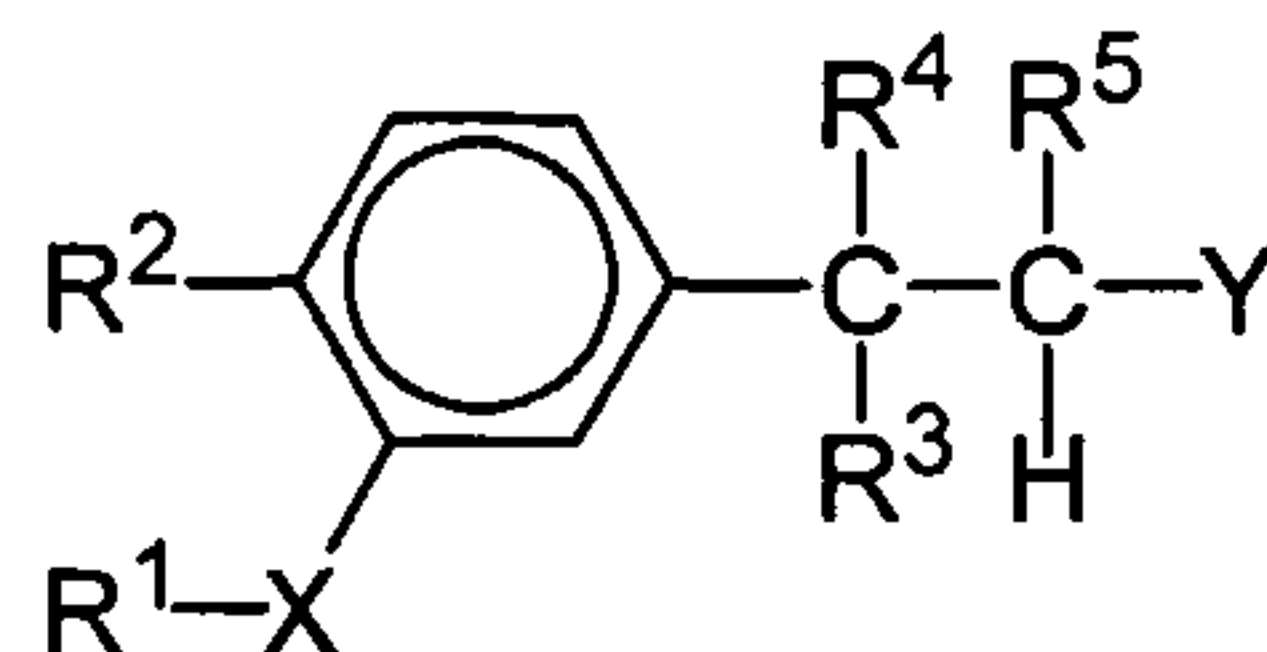
(i) each of R⁸ and R⁹, independently of the other, is hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, benzyl, pyridyl, pyridylmethyl, or

(ii) one of R⁸ and R⁹ is hydrogen and the other is -COR¹⁰, or -SO₂R¹⁰, in which R¹⁰ is
20 hydrogen, alkyl of 1 to 8 carbon atoms, cycloalkyl, cycloalkylmethyl of up to 6 carbon atoms, phenyl, pyridyl, benzyl, imidazolylmethyl, pyridylmethyl, NR¹¹R¹², or CH₂NR¹⁴R¹⁵, wherein R¹¹ and R¹², independently of each other, are hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, or benzyl and R¹⁴ and R¹⁵, independently of each other, are hydrogen, methyl, ethyl, or propyl; or

25 (iii) R⁸ and R⁹ taken together are tetramethylene, pentamethylene, hexamethylene, -CH=NCH=CH-, or -CH₂CH₂X¹CH₂CH₂- in which X¹ is -O-, -S-, or -NH-.

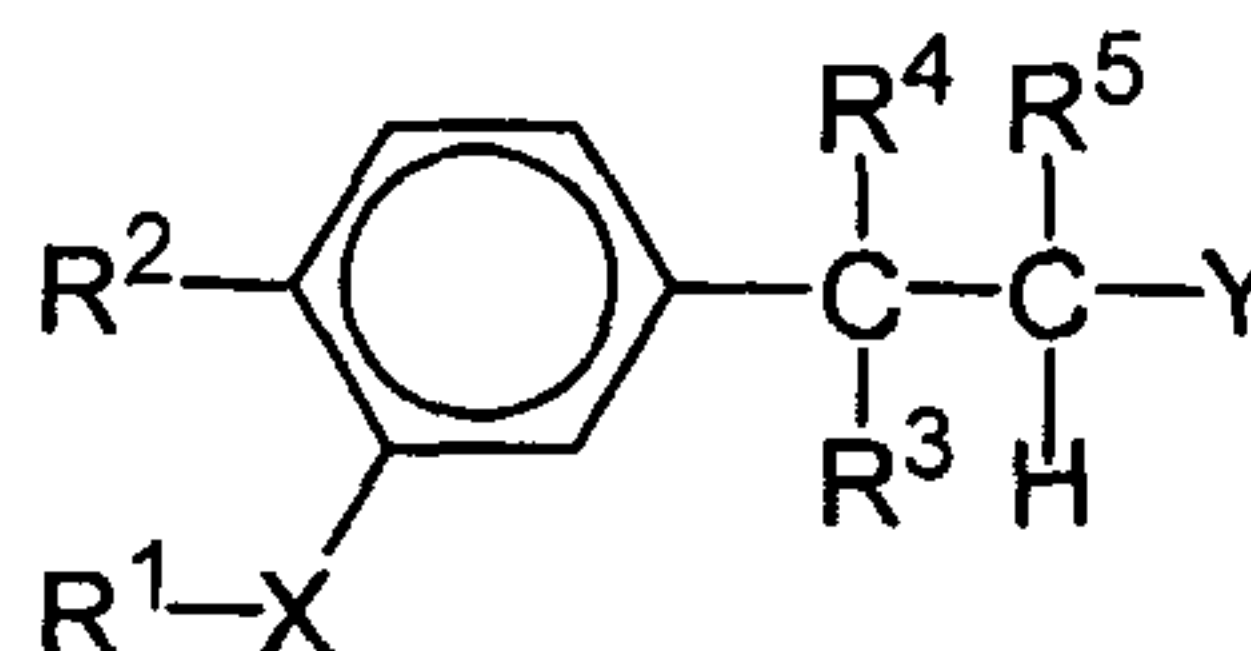
Other specific PDE4 modulators include, but are not limited to, cyano and carboxy derivatives of substituted styrenes (for example, 3,3-bis-(3,4-dimethoxyphenyl) acrylonitrile) disclosed in U.S. patent nos. 5,929,117, 6,130,226, 6,262,101 and 6,479,554,

each of which is incorporated herein by reference. Representative compounds are of formula:



wherein:

- 5 (a) X is -O- or -(C_nH_{2n})- in which n has a value of 0, 1, 2, or 3, and R¹ is alkyl of one to 10 carbon atoms, monocycloalkyl of up to 10 carbon atoms, polycycloalkyl of up to 10 carbon atoms, or benzocyclic alkyl of up to 10 carbon atoms, or
- (b) X is -CH= and R¹ is alkylidene of up to 10 carbon atoms, monocycloalkylidene of up to 10 carbon atoms, or bicycloalkylidene of up to 10 carbon atoms;
- 10 R² is hydrogen, nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, lower alkyl, lower alkylidenemethyl, lower alkoxy, or halo;
- R³ is (i) phenyl, unsubstituted or substituted with 1 or more substituents each selected independently from nitro, cyano, halo, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, carbamoyl substituted with alkyl of 1 to 3 carbon atoms, acetoxo, carboxy, hydroxy, amino, amino substituted with an alkyl of 1 to 5 carbon atoms, alkyl of up to 10 carbon atoms, cycloalkyl of up to 10 carbon atoms, alkoxy of up to 10 carbon atoms, cycloalkoxy of up to 10 carbon atoms, alkylidenemethyl of up to 10 carbon atoms, cycloalkylidenemethyl of up to 10 carbon atoms, phenyl, or methylenedioxy; (ii)
- 15 pyridine, substituted pyridine, pyrrolidine, imidazole, naphthalene, or thiophene; (iii) cycloalkyl of 4-10 carbon atoms, unsubstituted or substituted with 1 or more substituents each selected independently from the group consisting of nitro, cyano, halo, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, substituted amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms,
- 20 phenyl;
- each of R⁴ and R⁵ taken individually is hydrogen or R⁴ and R⁵ taken together are a carbon-carbon bond;
- Y is -COZ, -C≡N, or lower alkyl of 1 to 5 carbon atoms;
- Z is -OH, -NR⁶R⁶, -R⁷, or -OR⁷; R⁶ is hydrogen or lower alkyl; and R⁷ is alkyl or
- 30 benzyl. Specific examples of the compounds are of formula:



wherein:

(a) X is -O- or -(C_nH_{2n})- in which n has a value of 0, 1, 2, or 3, and R¹ is alkyl of one to 10 carbon atoms, monocycloalkyl of up to 10 carbon atoms, polycycloalkyl of up to 10 carbon atoms, or benzocyclic alkyl of up to 10 carbon atoms, or

(b) X is -CH= and R¹ is alkylidene of up to 10 carbon atoms, monocycloalkylidene of up to 10 carbon atoms, or bicycloalkylidene of up to 10 carbon atoms;

R² is hydrogen, nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, lower alkyl, lower alkylidenemethyl, lower alkoxy, or halo;

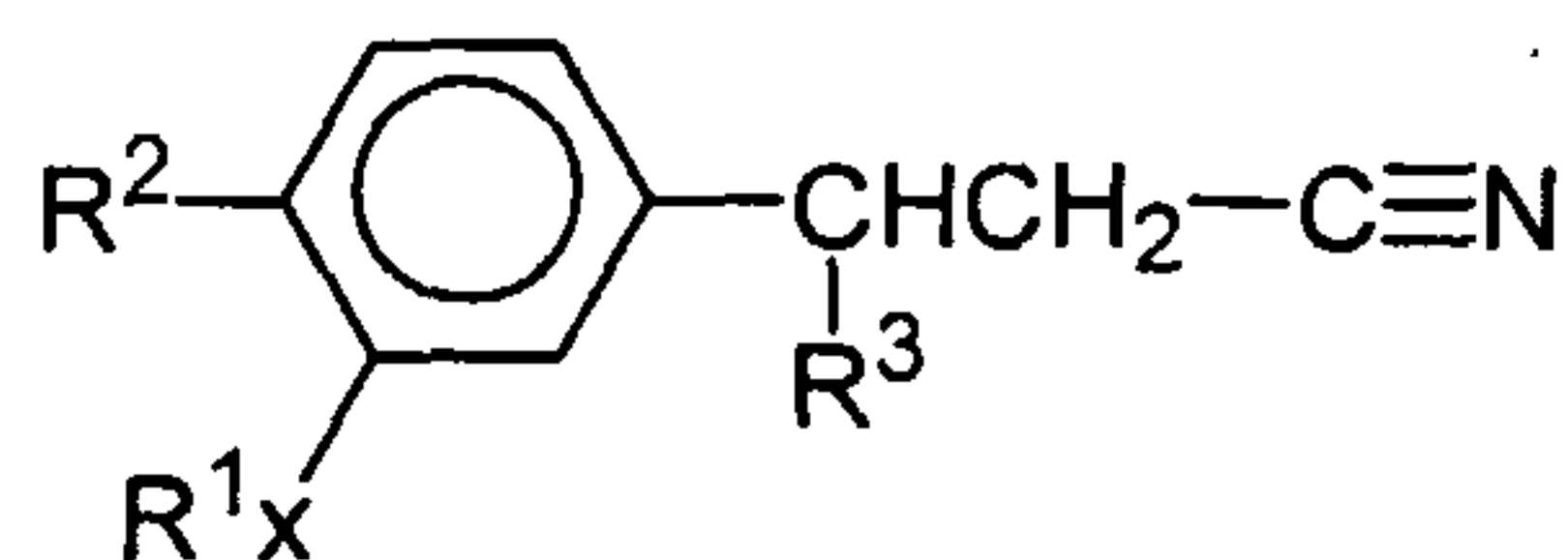
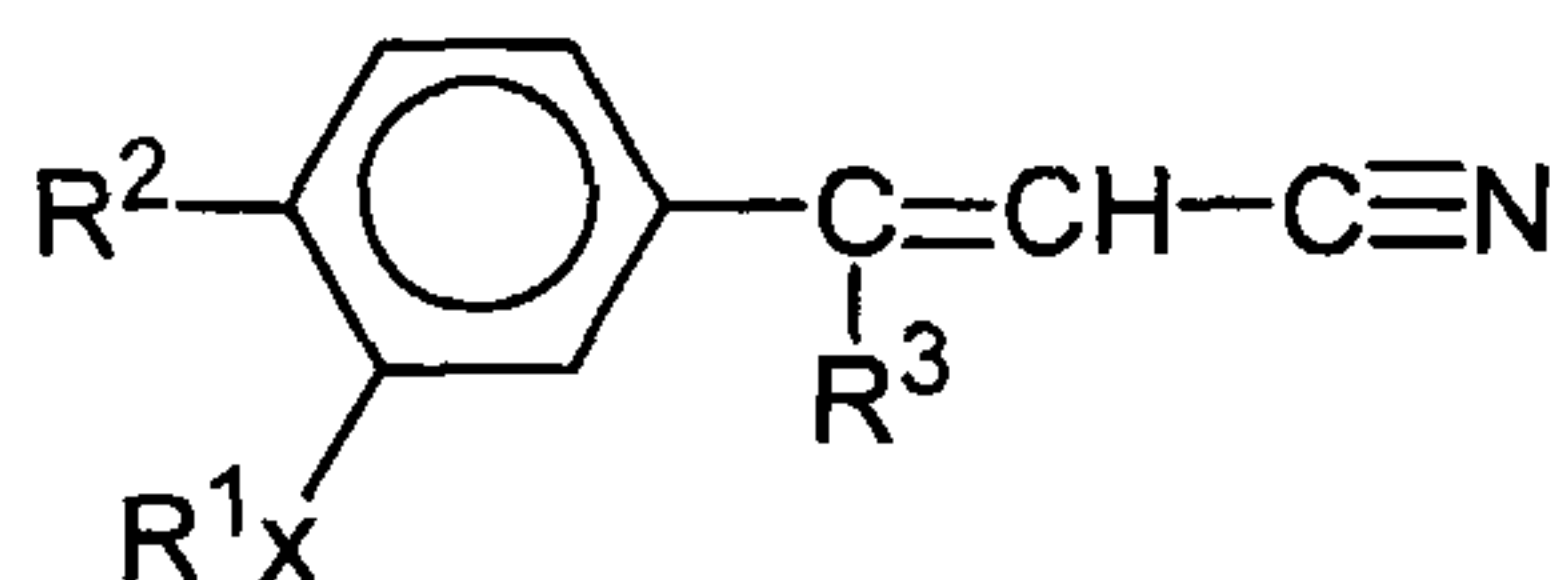
R³ is pyrrolidine, imidazole or thiophene unsubstituted or substituted with 1 or more substituents each selected independently from the group consisting of nitro, cyano, halo, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, substituted amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or phenyl;

each of R⁴ and R⁵ taken individually is hydrogen or R⁴ and R⁵ taken together are a carbon-carbon bond;

Y is -COZ, -C≡N, or lower alkyl of 1 to 5 carbon atoms;

Z is -OH, -NR⁶R⁶, -R⁷, or -OR⁷; R⁶ is hydrogen or lower alkyl; and R⁷ is alkyl or benzyl.

Particularly preferred nitriles are compounds of the formula:



wherein:

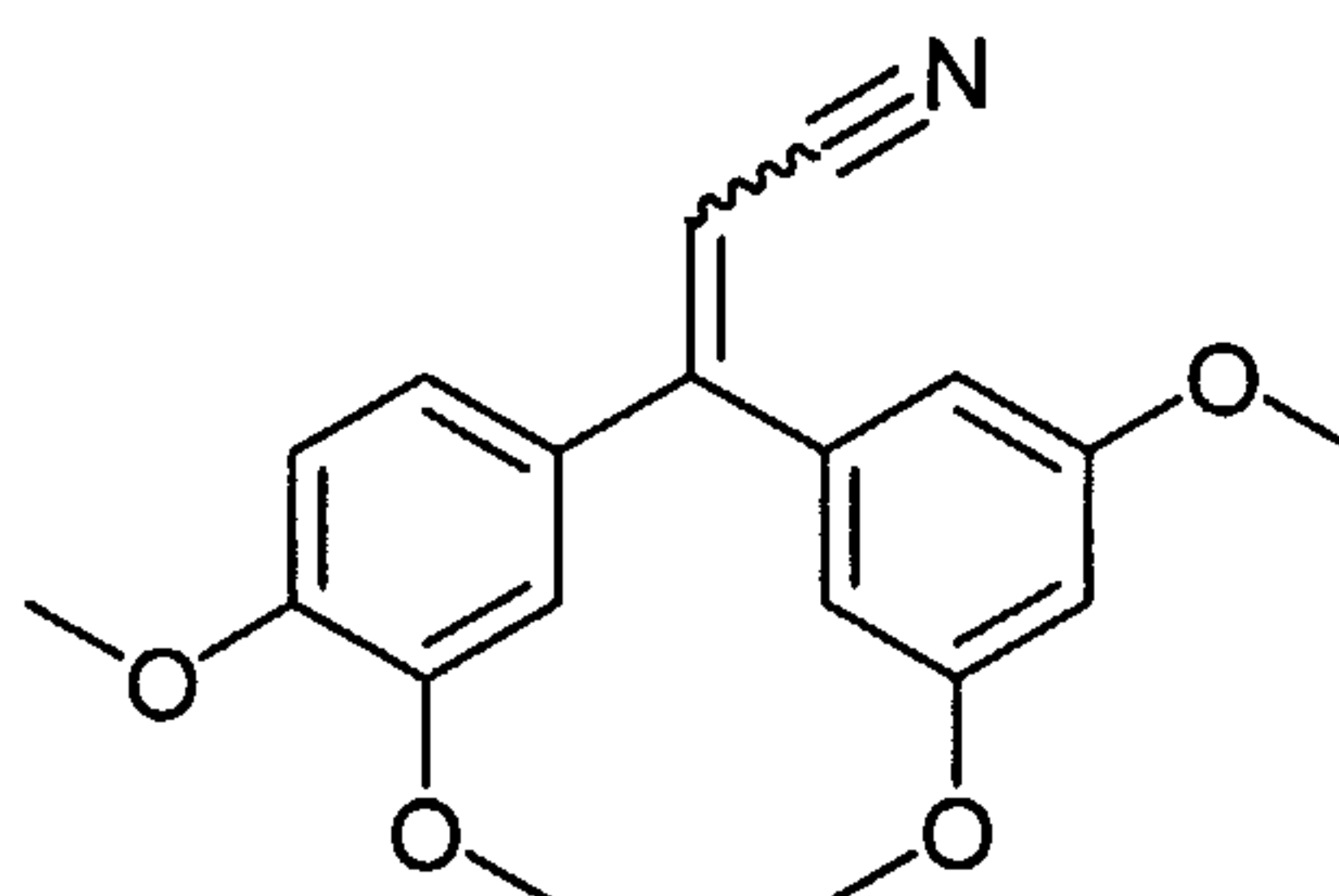
(a) X is -O- or -(C_nH_{2n})- in which n has a value of 0, 1, 2, or 3, and R¹ is alkyl of up to 10 carbon atoms, monocycloalkyl of up to 10 carbon atoms, polycycloalkyl of up to 10 carbon atoms, or benzocyclic alkyl of up to 10 carbon atoms, or

(b) X is $-\text{CH}=\text{}$, and R¹ is alkylidene of up to 10 carbon atoms or monocycloalkylidene of up to 10 carbon atoms;

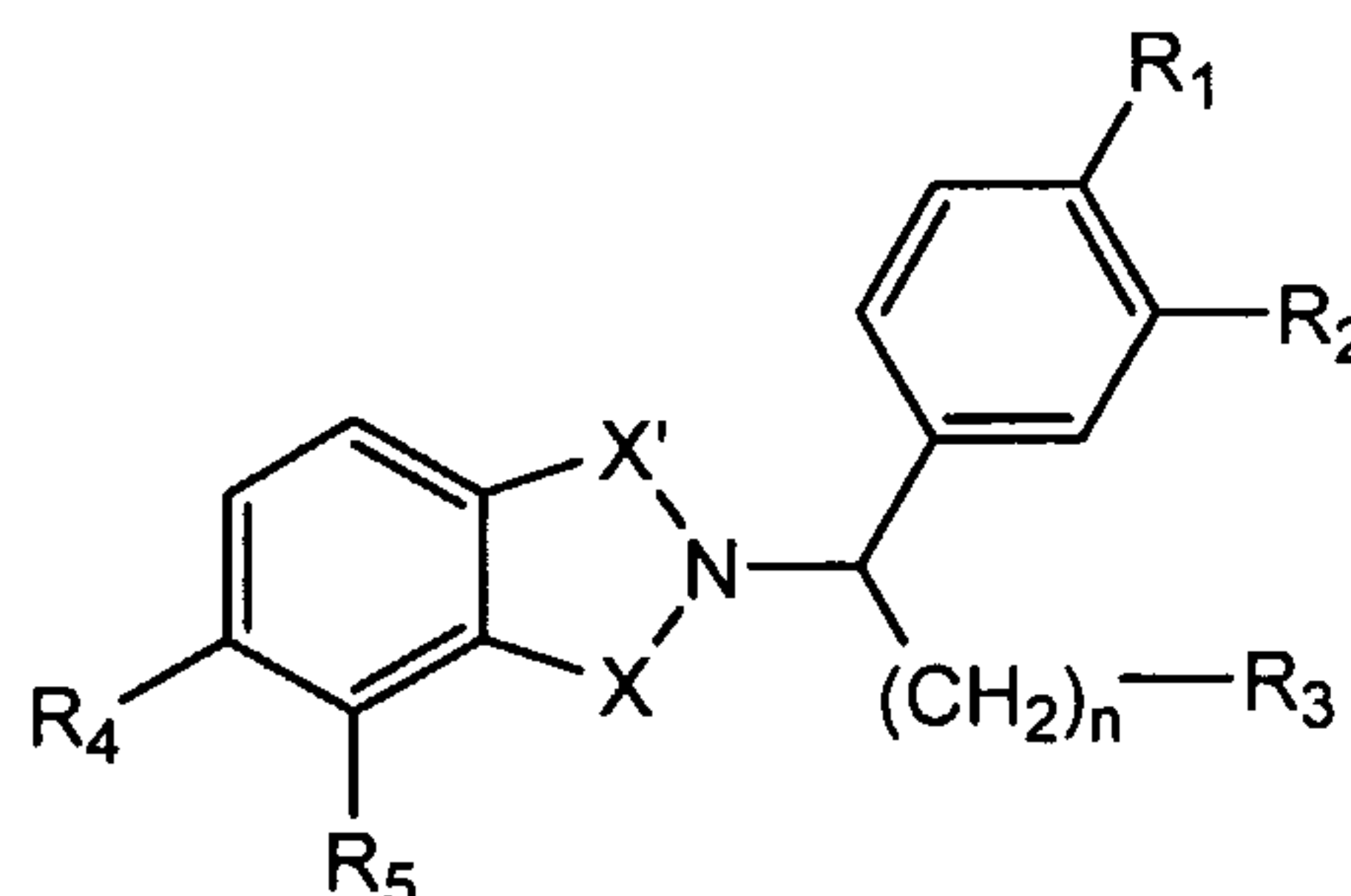
R² is hydrogen, nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxymethyl, carboxy, hydroxy, amino, lower alkyl, lower alkoxy, or halo; and

R³ is (i) phenyl or naphthyl, unsubstituted or substituted with 1 or more substituents each selected independently from nitro, cyano, halo, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, or carbamoyl substituted with alkyl of 1 to 3 carbon atoms, acetoxymethyl, carboxy, hydroxy, amino, amino substituted with an alkyl of 1 to 5 carbon atoms, alkoxy or cycloalkoxy of 1 to 10 carbon atoms; or (ii) cycloalkyl of 4 to 10 carbon atoms, unsubstituted or substituted with one or more substituents each selected independently from the group consisting of nitro, cyano, halo, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxymethyl, carboxy, hydroxy, amino, substituted amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or phenyl.

Particularly preferred nitrile is of formula:



Other specific PDE4 modulators include, but are not limited to, isoindoline-1-one and isoindoline-1,3-dione substituted in the 2-position with an α -(3,4-disubstituted phenyl)alkyl group and in the 4- and/or 5-position with a nitrogen-containing group disclosed in WO 01/34606 and U.S. patent no. 6,667,316, which are incorporated herein by reference. Representative compounds are of formula:



and include pharmaceutically acceptable salts and stereoisomers thereof, wherein:

one of X and X' is $=C=O$ or $=SO_2$, and the other of X and X' is $=C=O$, $=CH_2$, $=SO_2$ or $=CH_2C=O$;

n is 1, 2 or 3;

R₁ and R₂ are each independently (C₁-C₄)alkyl, (C₁-C₄)alkoxy, cyano, (C₃-C₁₈)cycloalkyl, (C₃-C₁₈)cycloalkoxy or (C₃-C₁₈)cycloalkyl-methoxy;

R₃ is SO₂-Y, COZ, CN or (C₁-C₆)hydroxyalkyl, wherein:

Y is (C₁-C₆)alkyl, benzyl or phenyl;

Z is -NR₆R₇, (C₁-C₆)alkyl, benzyl or phenyl;

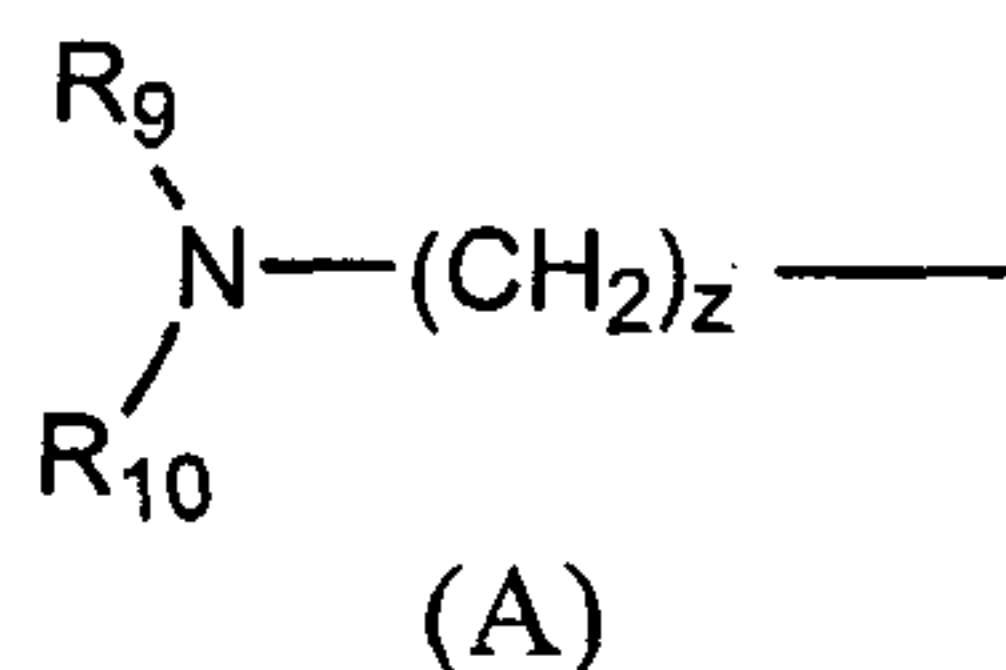
R₆ is H, (C₁-C₄)alkyl, (C₃-C₁₈)cycloalkyl, (C₂-C₅)alkanoyl, benzyl or phenyl, each of which can be optionally substituted with halo, amino or (C₁-C₄)alkyl-amino;

R₇ is H or (C₁-C₄)alkyl;

R₄ and R₅ are taken together to provide -NH-CH₂-R₈-, NH-CO-R₈-, or -N=CH-R₈-, wherein:

R₈ is CH₂, O, NH, CH=CH, CH=N, or N=CH; or

one of R₄ and R₅ is H, and the other of R₄ and R₅ is imidazolyl, pyrrolyl, oxadiazolyl, triazolyl, or a structure of formula (A),



wherein:

z is 0 or 1;

R₉ is: H; (C₁-C₄)alkyl, (C₃-C₁₈)cycloalkyl, (C₂-C₅)alkanoyl, or (C₄-C₆)cycloalkanoyl, optionally substituted with halo, amino, (C₁-C₄)alkyl-amino, or (C₁-C₄)dialkyl-amino; phenyl; benzyl; benzoyl; (C₂-C₅)alkoxycarbonyl; (C₃-C₅)alkoxyalkylcarbonyl; N-morpholinocarbonyl; carbamoyl; N-substituted carbamoyl substituted with (C₁-C₄)alkyl; or methylsulfonyl; and

R₁₀ is H, (C₁-C₄)alkyl, methylsulfonyl, or (C₃-C₅)alkoxyalkylcarbonyl; or

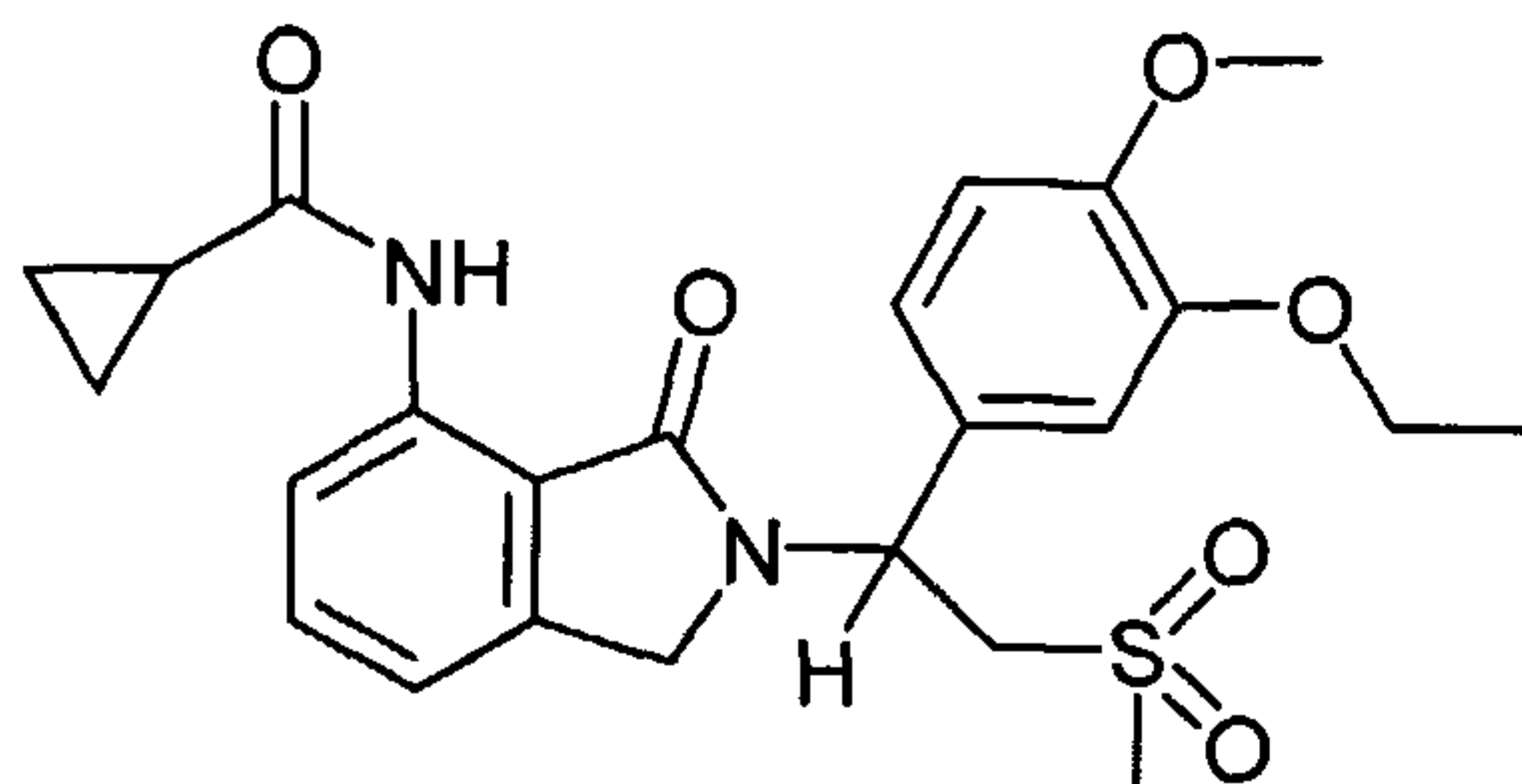
R₉ and R₁₀ are taken together to provide -CH=CH-CH=CH-, -CH=CH-N=CH-, or (C₁-C₂)alkylidene, optionally substituted with amino, (C₁-C₄)alkyl-amino, or (C₁-C₄)dialkyl-amino; or

R₄ and R₅ are both structures of formula (A).

In one embodiment, z is not 0 when (i) R³ is -SO₂-Y, -COZ, or -CN and (ii) one of R⁴ or R⁵ is hydrogen. In another embodiment, R⁹ and R¹⁰, taken together, is -CH=CH-

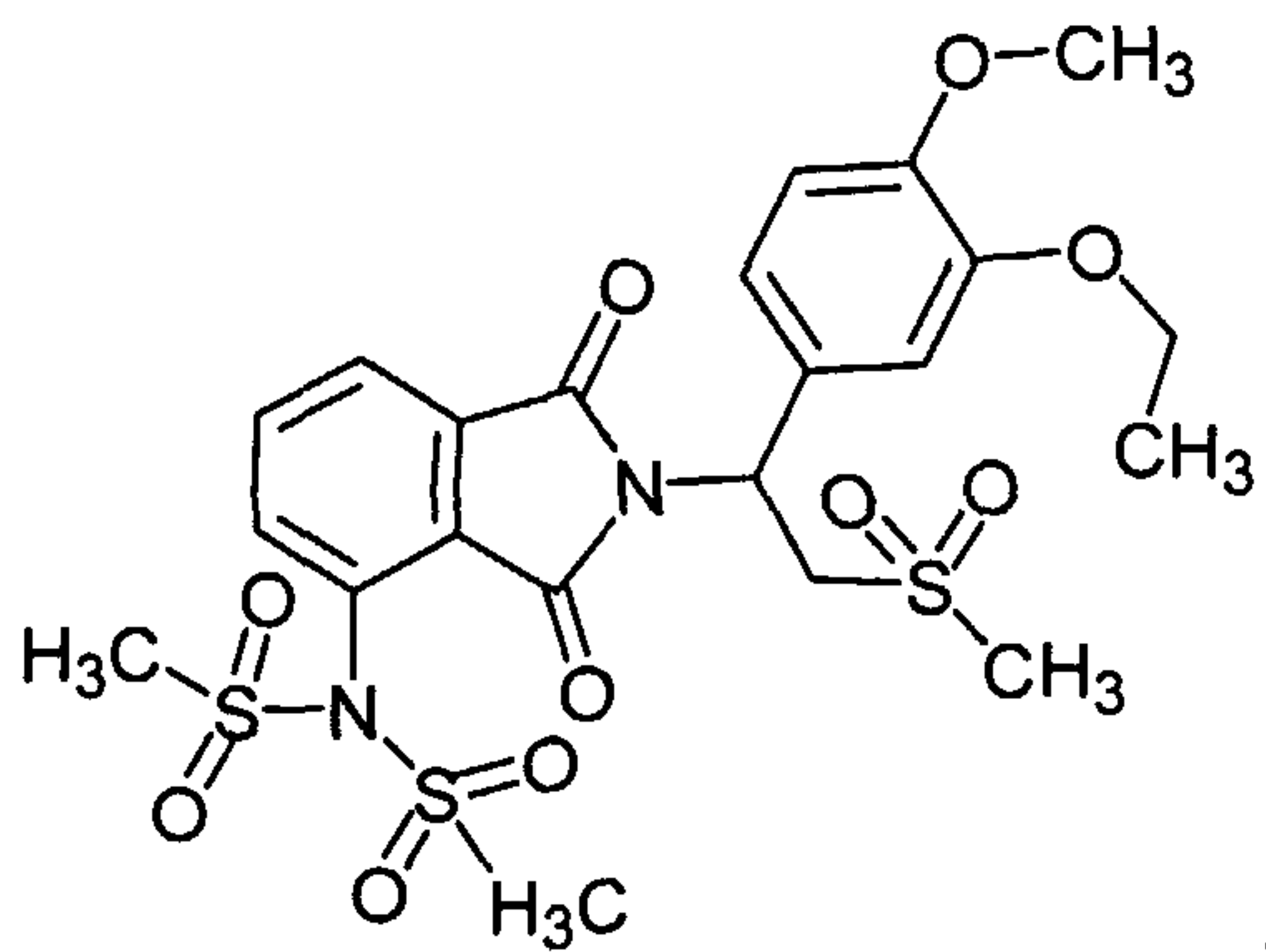
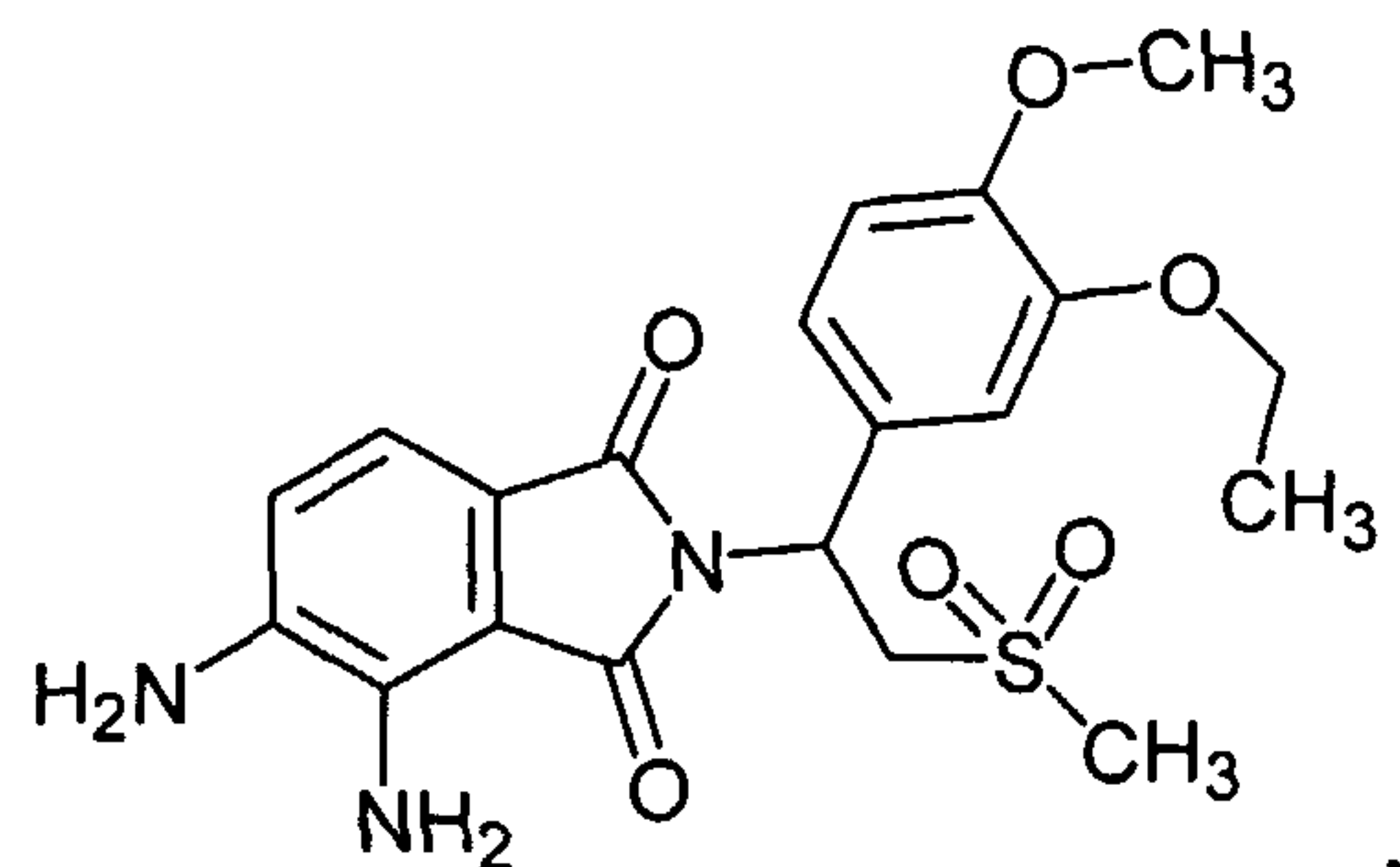
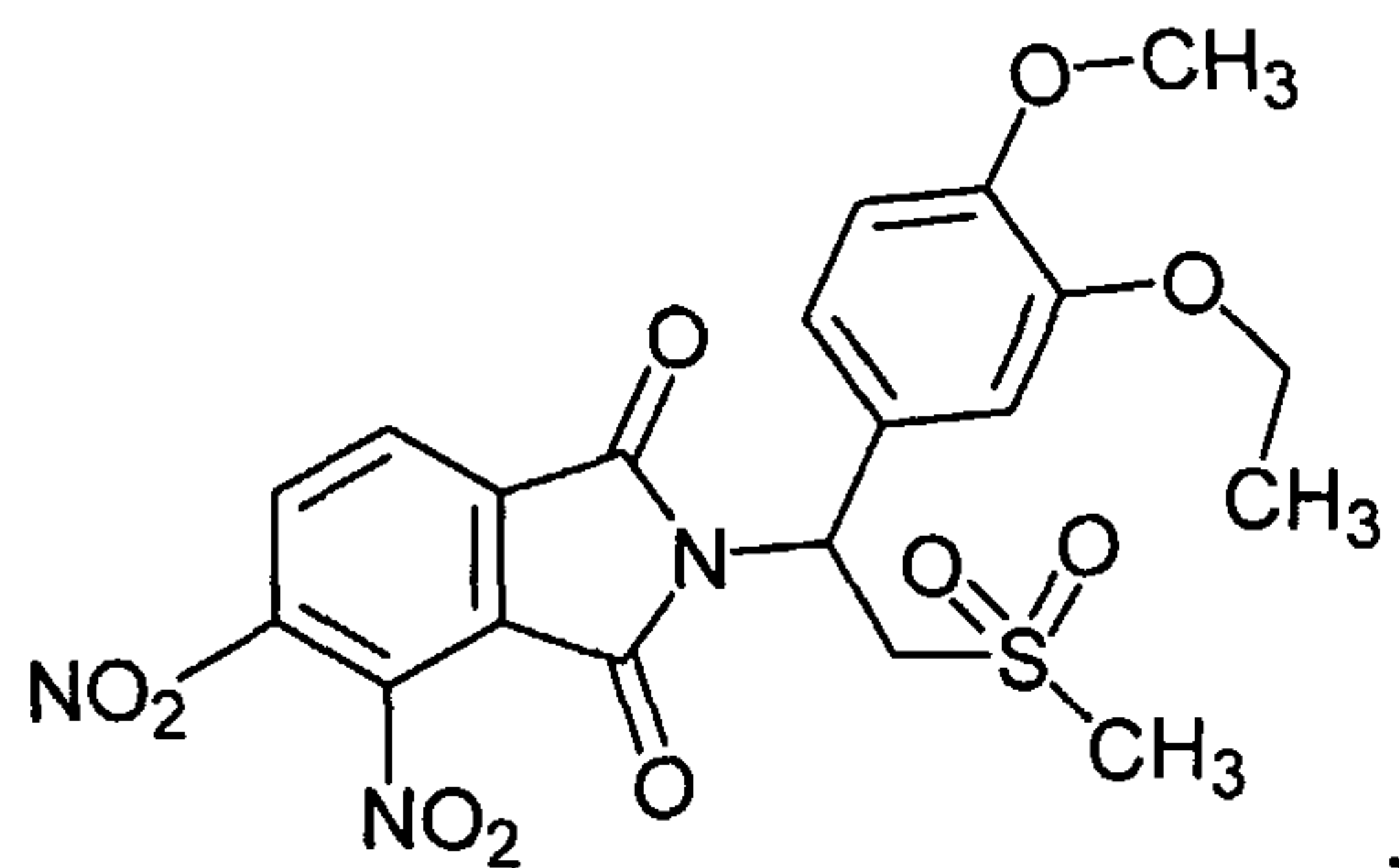
$\text{CH}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{N}=\text{CH}-$, or (C_1-C_2) alkylidene substituted by amino, (C_1-C_4) alkyl-amino, or (C_1-C_4) dialkyl-amino. In another embodiment, R_4 and R_5 are both structures of formula (A).

Specific compounds are of formula:



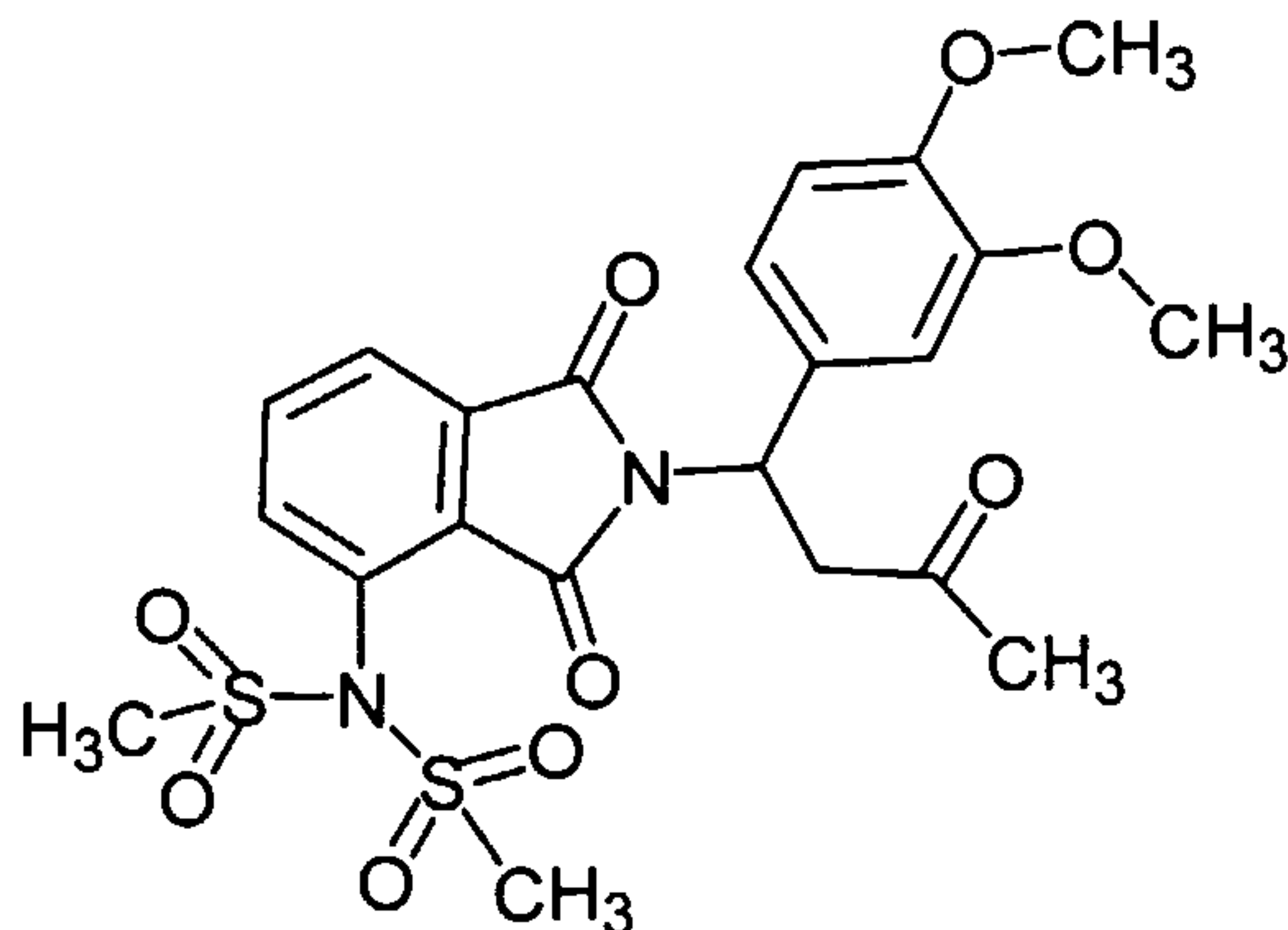
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and the enantiomers thereof. Further specific compounds are of formulas:



10

and

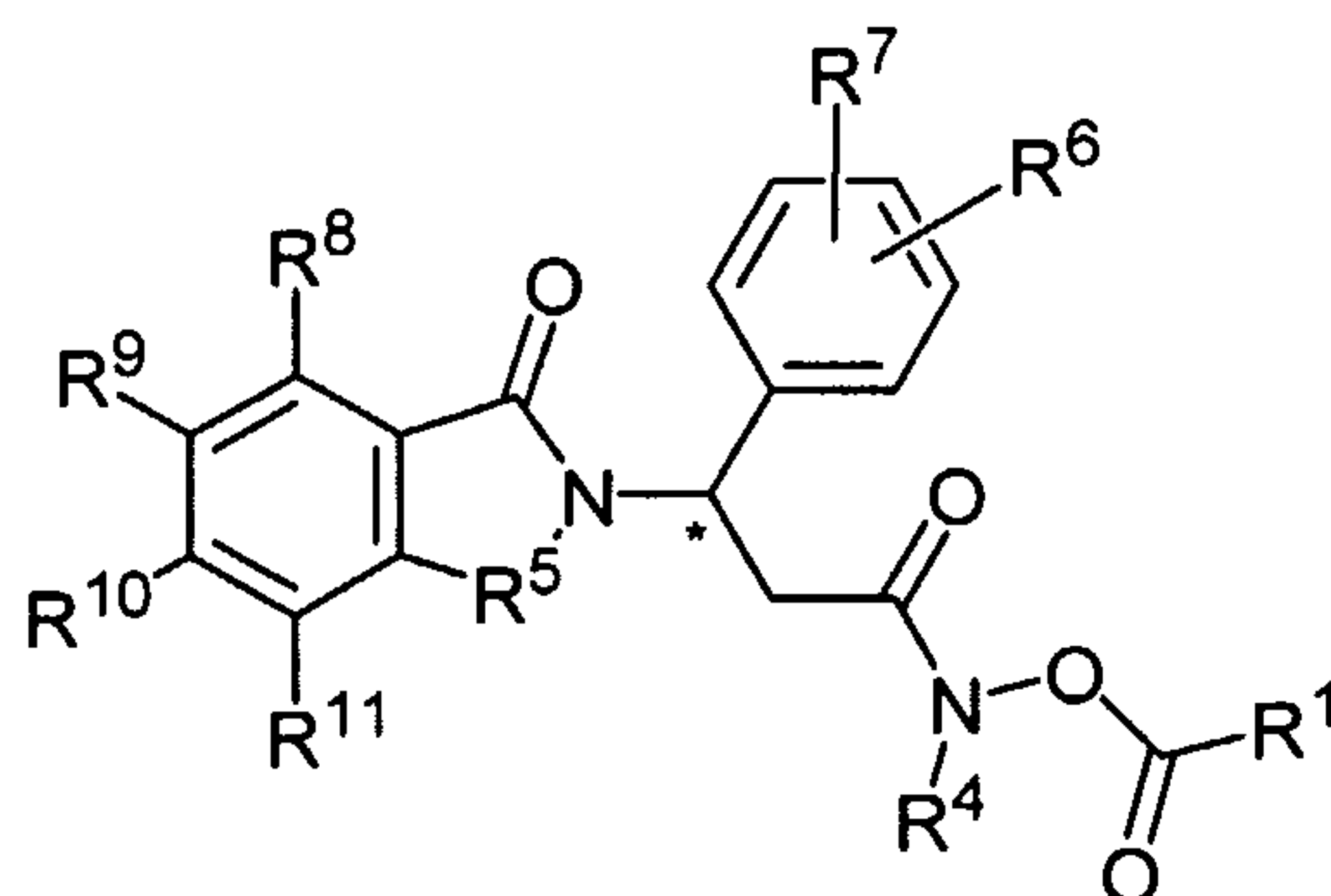


Further examples include, but are not limited to: 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4,5-dinitroisindoline-1,3-dione; 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4,5-diaminoisindoline-1,3-dione; 7-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-3-pyrrolino[3,4-e]benzimidazole-6,8-dione; 7-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]hydro-3-pyrrolino[3,4-e]benzimidazole-2,6,8-trione; 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-3-pyrrolino[3,4-f]quinoxaline-1,3-dione; Cyclopropyl-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisindolin-4-yl}carboxamide; 2-Chloro-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisindolin-4-yl}acetamide; 2-Amino-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisindolin-4-yl}acetamide; 2-N,N-Dimethylamino-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisindolin-4-yl}acetamide; N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisindolin-4-yl}-2,2,2-trifluoroacetamide; N-{2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisindolin-4-yl}methoxycarboxamide; 4-[1-Aza-2-(dimethylamino)vinyl]-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]isindoline-1,3-dione; 4-[1-Aza-2-(dimethylamino)prop-1-enyl]-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]isindoline-1,3-dione; 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-(5-methyl-1,3,4-oxadiazol-2-yl)isindoline-1,3-dione; 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-pyrrolylisindoline-1,3-dione; 4-(Aminomethyl)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-isindoline-1,3-dione; 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-(pyrrolylmethyl)isindoline-1,3-dione; N-{2-[1-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutyl]-1,3-dioxoisindolin-4-yl}acetamide; N-{2-[1-(3-Ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisindolin-4-yl}acetamide; N-{2-[1R-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutyl]-1,3-dioxoisindolin-4-yl}acetamide; N-{2-[1R-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisindolin-4-yl}acetamide; N-{2-[1S-(3-Ethoxy-4-

methoxyphenyl)-3-hydroxybutyl]-1,3-dioxoisindolin-4-yl}acetamide; N-{2-[1S-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisindolin-4-yl}acetamide; 4-Amino-2-[1-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutylisoindoline-1,3-dione; 4-Amino-2-[1-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]isoindoline-1,3-dione; 2-[1-(3-Ethoxy-4-methoxyphenyl)-3-oxobutyl]-4-pyrrolylisoindoline-1,3-dione; 2-Chloro-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisindol-4-yl}acetamide; 2-(Dimethylamino)-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisindolin-4-yl}acetamide; 4-Amino-2-[1R-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutyl]isoindoline-1,3-dione; 4-Amino-2-[1R-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]isoindoline-1,3-dione; 2-[1R-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-4-pyrrolylisoindoline-1,3-dione; 2-(Dimethylamino)-N-{2-[1R-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisindolin-4-yl}acetamide; Cyclopentyl-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisindolin-4-yl}carboxamide; 3-(Dimethylamino)-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisindolin-4-yl}propanamide; 2-(Dimethylamino)-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisindolin-4-yl}propanamide; N-{2-[(1R)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisindolin-4-yl}-2-(dimethylamino)acetamide; N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisindolin-4-yl}-2-(dimethylamino)acetamide; 4-{3-[(Dimethylamino)methyl]pyrrolyl}-2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]isoindoline-1,3-dione; Cyclopropyl-N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisindolin-4-yl}carboxamide; 2-[1-(3,4-dimethoxyphenyl)-2-(methylsulfonyl)ethyl]-4-pyrrolylisoindoline-1,3-dione; N-{2-[1-(3,4-dimethoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisindolin-4-yl}-2-(dimethylamino)acetamide; Cyclopropyl-N-{2-[1-(3,4-dimethoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisindolin-4-yl}carboxamide; Cyclopropyl-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisindolin-4-yl}carboxamide; 2-(Dimethylamino)-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisindolin-4-yl}acetamide; Cyclopropyl-N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisindolin-4-yl}carboxamide; Cyclopropyl-N-{2-[(1R)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisindolin-4-yl}carboxamide; (3R)-3-[7-(Acetylamino)-1-oxoisindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide; (3R)-3-[7-(Cyclopropylcarbonylamino)-1-oxoisindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide; 3-{4-[2-(Dimethylamino)acetylamino]-1,3-dioxoisindolin-2-yl}-3-

"(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide; (3R)-3-[7-(2-Chloroacetyl amino)-
 1-oxoisindolin-2-yl]-3-(3-ethoxy-4-methoxy-phenyl)-N,N-dimethylpropanamide; (3R)-3-
 {4-[2-(dimethylamino)acetyl amino]-1,3-dioxoisindolin-2-yl}-3-(3-ethoxy-4-
 methoxyphenyl)-N,N-dimethylpropanamide; 3-(1,3-Dioxo-4-pyrrolylisindolin-2-yl)-3-(3-
 5 ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide; 2-[1-(3-Ethoxy-4-methoxyphenyl)-
 2-(methylsulfonyl)ethyl]-4-(imidazolyl-methyl)isoindoline-1,3-dione; N-({2-[1-(3-Ethoxy-
 4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisindolin-4-yl}methyl)acetamide; 2-
 Chloro-N-({2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-
 dioxoisindolin-4-yl}methyl)acetamide; 2-(Dimethylamino)-N-({2-[1-(3-ethoxy-4-
 10 methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisindolin-4-yl}methyl)acetamide; 4-
 [Bis(methylsulfonyl)amino]-2-[1-(3-ethoxy-4-methoxyphenyl)-2-
 (methylsulfonyl)ethyl]isoindoline-1,3-dione; 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-
 (methylsulfonyl)ethyl]-4-[(methylsulfonyl)amino]isoindoline-1,3-dione; N-{2-[1-(3-
 Ethoxy-4-methoxyphenyl)-3-hydroxypentyl]-1,3-dioxoisindolin-4-yl}acetamide; N-{2-[1-
 15 (3-Ethoxy-4-methoxyphenyl)-3-oxopentyl]-1,3-dioxoisindolin-4-yl}acetamide; 2-[(1R)-1-
 (3-Ethoxy-4-methoxyphenyl)-3-hydroxybutyl]-4-(pyrrolylmethyl)isoindoline-1,3-dione; 2-
 [(1R)-1-(3-Ethoxy-4-methoxyphenyl)-3-oxobutyl]-4-(pyrrolylmethyl)isoindoline-1,3-dione;
 N-{2-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-3-hydroxybutyl]-1,3-dioxoisindolin-4-
 yl}acetamide; N-{2-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-3-oxobutyl]-1,3-
 20 dioxoisindolin-4-yl}acetamide; 2-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-3-oxobutyl]-4-
 pyrrolylisindoline-1,3-dione; 2-[1-(3,4-Dimethoxyphenyl)-3-oxobutyl]-4-
 [bis(methylsulfonyl)amino]isoindoline-1,3-dione; and pharmaceutically acceptable salts,
 solvates, and stereoisomers thereof.

Still other specific PDE4 modulators include, but are not limited to, imido and
 25 amido substituted acylhydroxamic acids (for example, (3-(1,3-dioxoisindoline-2-yl)-3-(3-
 ethoxy-4-methoxyphenyl) propanoylamino) propanoate disclosed in WO 01/45702 and U.S.
 patent no. 6,699,899, which are incorporated herein by reference. Representative
 compounds are of formula:



wherein:

the carbon atom designated * constitutes a center of chirality,

R^4 is hydrogen or $-(C=O)-R^{12}$,

each of R^1 and R^{12} , independently of each other, is alkyl of 1 to 6 carbon atoms,

5 phenyl, benzyl, pyridyl methyl, pyridyl, imidazolyl, imidazolyl methyl, or

$CHR^*(CH_2)_nNR^*R^0$,

wherein R^* and R^0 , independently of the other, are hydrogen, alkyl of 1 to 6 carbon atoms, phenyl, benzyl, pyridyl methyl, pyridyl, imidazolyl or imidazolylmethyl, and $n = 0, 1$, or 2;

10 R^5 is $C=O$, CH_2 , CH_2-CO- , or SO_2 ;

each of R^6 and R^7 , independently of the other, is nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, cycloalkoxy of 3 to 8 carbon atoms, halo, bicycloalkyl of up to 18 carbon atoms, tricycloalkoxy of up to 18 carbon atoms, 1-indanyloxy, 2-indanyloxy, C_4-C_8 -cycloalkylidenemethyl, or C_3-C_{10} -alkylidenemethyl;

each of R^8 , R^9 , R^{10} , and R^{11} , independently of the others, is

(i) hydrogen, nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, alkylamino, dialkylamino, acylamino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, halo, or

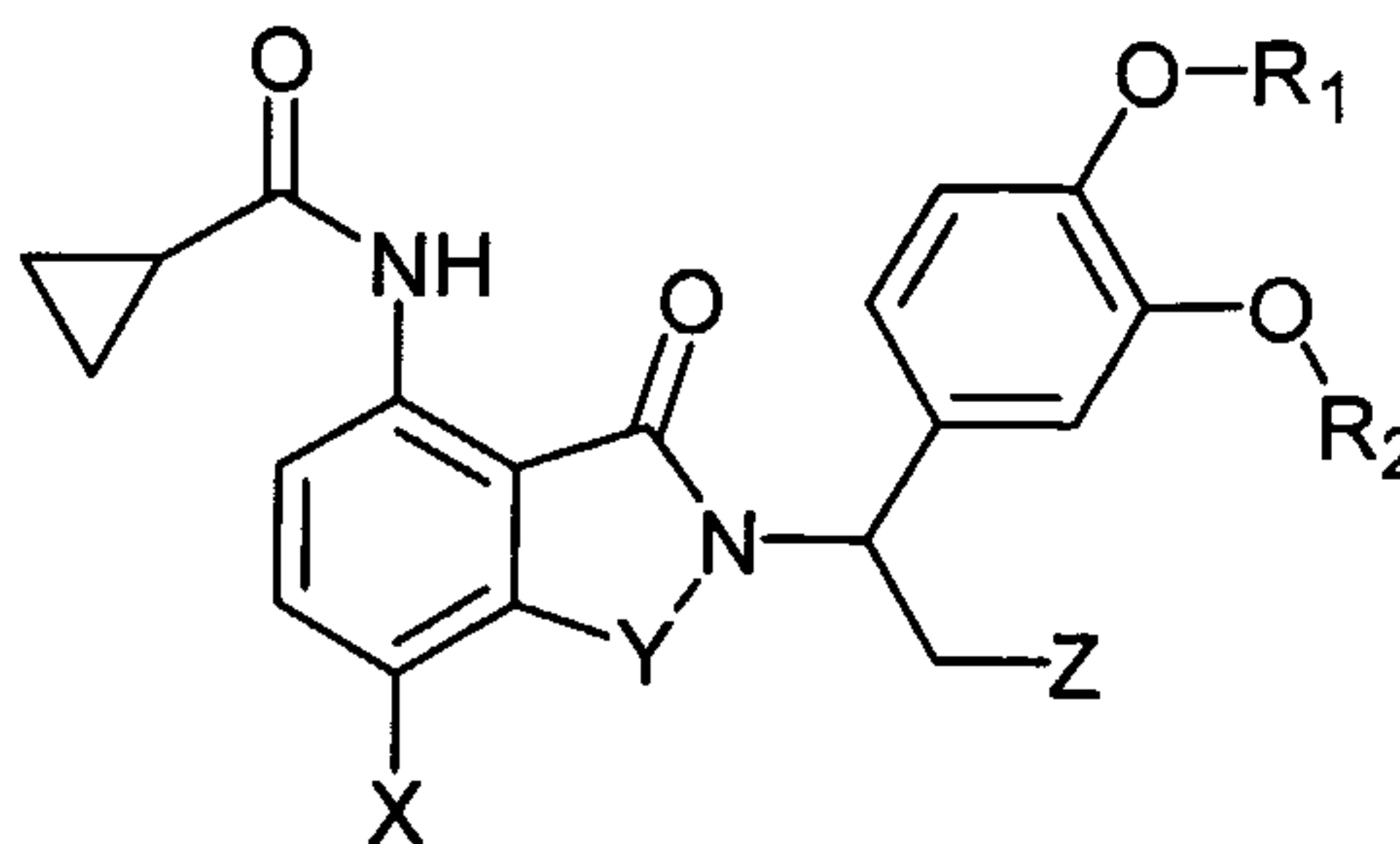
(ii) one of R^8 , R^9 , R^{10} , and R^{11} is acylamino comprising a lower alkyl, and the remaining of R^8 , R^9 , R^{10} , and R^{11} are hydrogen, or

(iii) hydrogen if R^8 and R^9 taken together are benzo, quinoline, quinoxaline, benzimidazole, benzodioxole, 2-hydroxybenzimidazole, methylenedioxy, dialkoxy, or dialkyl, or

(iv) hydrogen if R^{10} and R^{11} , taken together are benzo, quinoline, quinoxaline, benzimidazole, benzodioxole, 2-hydroxybenzimidazole, methylenedioxy, dialkoxy, or dialkyl, or

30 (v) hydrogen if R^9 and R^{10} taken together are benzo.

Still specific PDE4 modulators include, but are not limited to, 7-amido-isoindolyl compounds disclosed in U.S. patent application no. 10/798,317 filed on March 12, 2004, which is incorporated herein by reference. Representative compounds are of formula:



wherein:

Y is -C(O)-, -CH₂-, -CH₂C(O)- or SO₂;

X is H;

5 Z is (C₀₋₄-alkyl)-C(O)R³, C₁₋₄-alkyl, (C₀₋₄-alkyl)-OH, (C₁₋₄-alkyl)-O(C₁₋₄-alkyl), (C₁₋₄-alkyl)-SO₂(C₁₋₄-alkyl), (C₀₋₄-alkyl)-SO(C₁₋₄-alkyl), (C₀₋₄-alkyl)-NH₂, (C₀₋₄-alkyl)-N(C₁₋₈alkyl)₂, (C₀₋₄-alkyl)-N(H)(OH), or CH₂NSO₂(C₁₋₄-alkyl);

R₁ and R₂ are independently C₁₋₈-alkyl, cycloalkyl, or (C₁₋₄-alkyl)cycloalkyl;

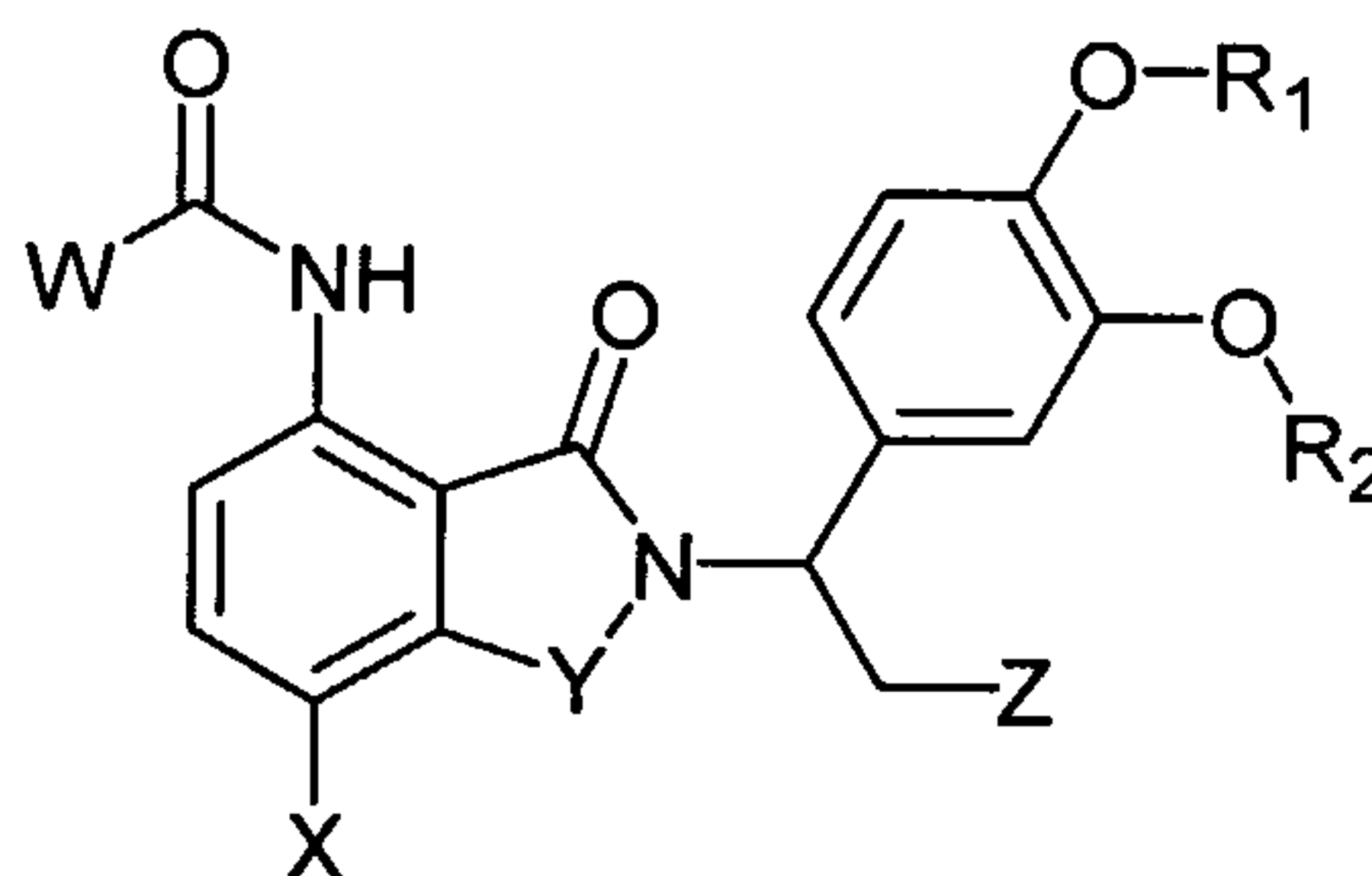
R³ is, NR⁴ R⁵, OH, or O-(C₁₋₈-alkyl);

10 R⁴ is H;

R⁵ is -OH, or -OC(O)R⁶;

R⁶ is C₁₋₈-alkyl, amino-(C₁₋₈-alkyl), (C₁₋₈-alkyl)-(C₃₋₆-cycloalkyl), C₃₋₆-cycloalkyl, phenyl, benzyl, or aryl;

or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or
15 prodrug thereof; or formula:



wherein:

Y is -C(O)-, -CH₂-, -CH₂C(O)-, or SO₂;

X is halogen, -CN, -NR₇R₈, -NO₂, or -CF₃;

20 Z is (C₀₋₄alkyl)-SO₂(C₁₋₄-alkyl), -(C₀₋₄-alkyl)-CN, -(C₀₋₄-alkyl)-C(O)R³, C₁₋₄-alkyl, (C₀₋₄-alkyl)OH, (C₀₋₄-alkyl)O(C₁₋₄-alkyl), (C₀₋₄-alkyl)SO(C₁₋₄-alkyl), (C₀₋₄-alkyl)NH₂, (C₀₋₄-alkyl)N(C₁₋₈-alkyl)₂, (C₀₋₄-alkyl) N(H)(OH), (C₀₋₄-alkyl)-dichloropyridine or (C₀₋₄-alkyl)NSO₂(C₁₋₄-alkyl);

W is -C₃₋₆-cycloalkyl, -(C₁₋₈-alkyl)-(C₃₋₆-cycloalkyl), -(C₀₋₈-alkyl)-(C₃₋₆-cycloalkyl)-
25 NR₇R₈, (C₀₋₈-alkyl)-NR₇R₈, (C₀₋₄alkyl)-CHR₉-(C₀₋₄alkyl)-NR₇R₈;

" R_1 and R_2 are independently C_{1-8} -alkyl, cycloalkyl, or $(C_{1-4}$ -alkyl)cycloalkyl;

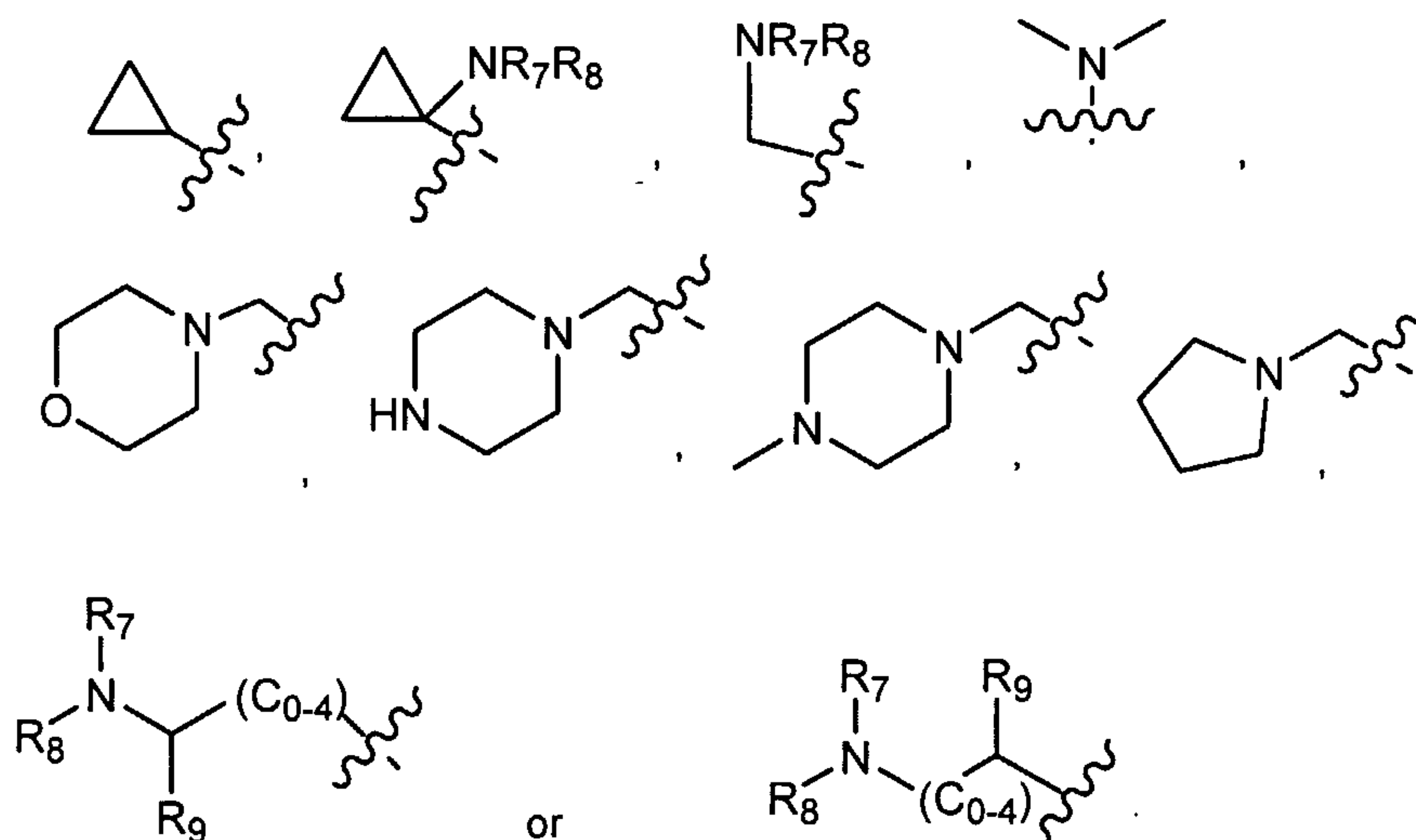
R^3 is C_{1-8} -alkyl, NR^4R^5 , OH, or O- $(C_{1-8}$ -alkyl);

R^4 and R^5 are independently H, C_{1-8} -alkyl, $(C_{0-8}$ -alkyl)- $(C_{3-6}$ -cycloalkyl), OH, or -OC(O) R^6 ;

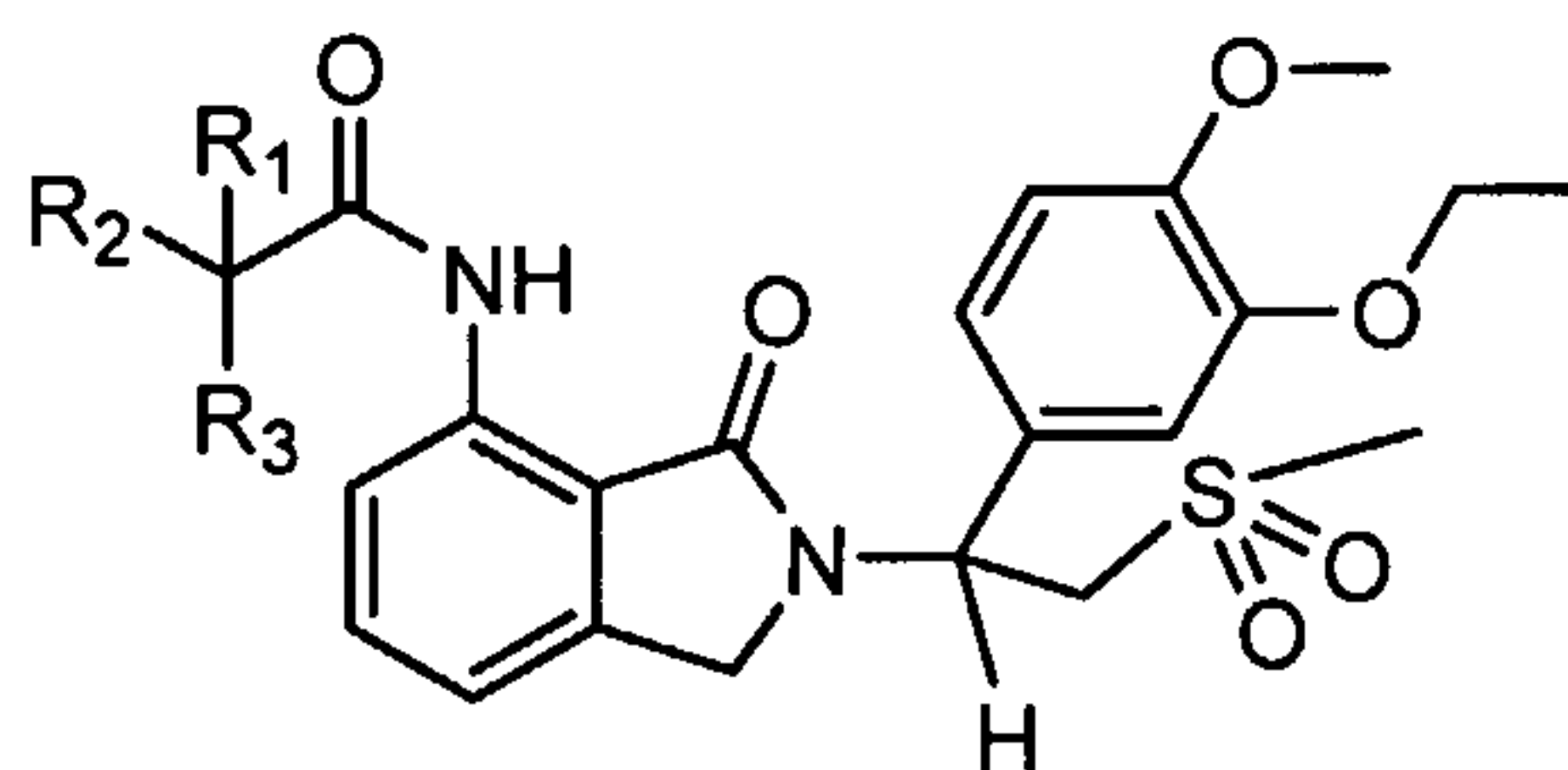
5 R^6 is C_{1-8} -alkyl, $(C_{0-8}$ -alkyl)- $(C_{3-6}$ -cycloalkyl), amino- $(C_{1-8}$ -alkyl), phenyl, benzyl, or aryl;

R_7 and R_8 are each independently H, C_{1-8} -alkyl, $(C_{0-8}$ -alkyl)- $(C_{3-6}$ -cycloalkyl), phenyl, benzyl, aryl, or can be taken together with the atom connecting them to form a 3 to 7 membered heterocycloalkyl or heteroaryl ring;

10 R_9 is C_{1-4} alkyl, $(C_{0-4}$ alkyl)aryl, $(C_{0-4}$ alkyl)- $(C_{3-6}$ -cycloalkyl), $(C_{0-4}$ alkyl)-heterocycle; or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof. In another embodiment, W is



In another embodiment, representative compounds are of formula:



15

wherein:

R_1 , R_2 and R_3 are independently H or C_{1-8} -alkyl, with the proviso that at least one of R_1 , R_2 and R_3 is not H;

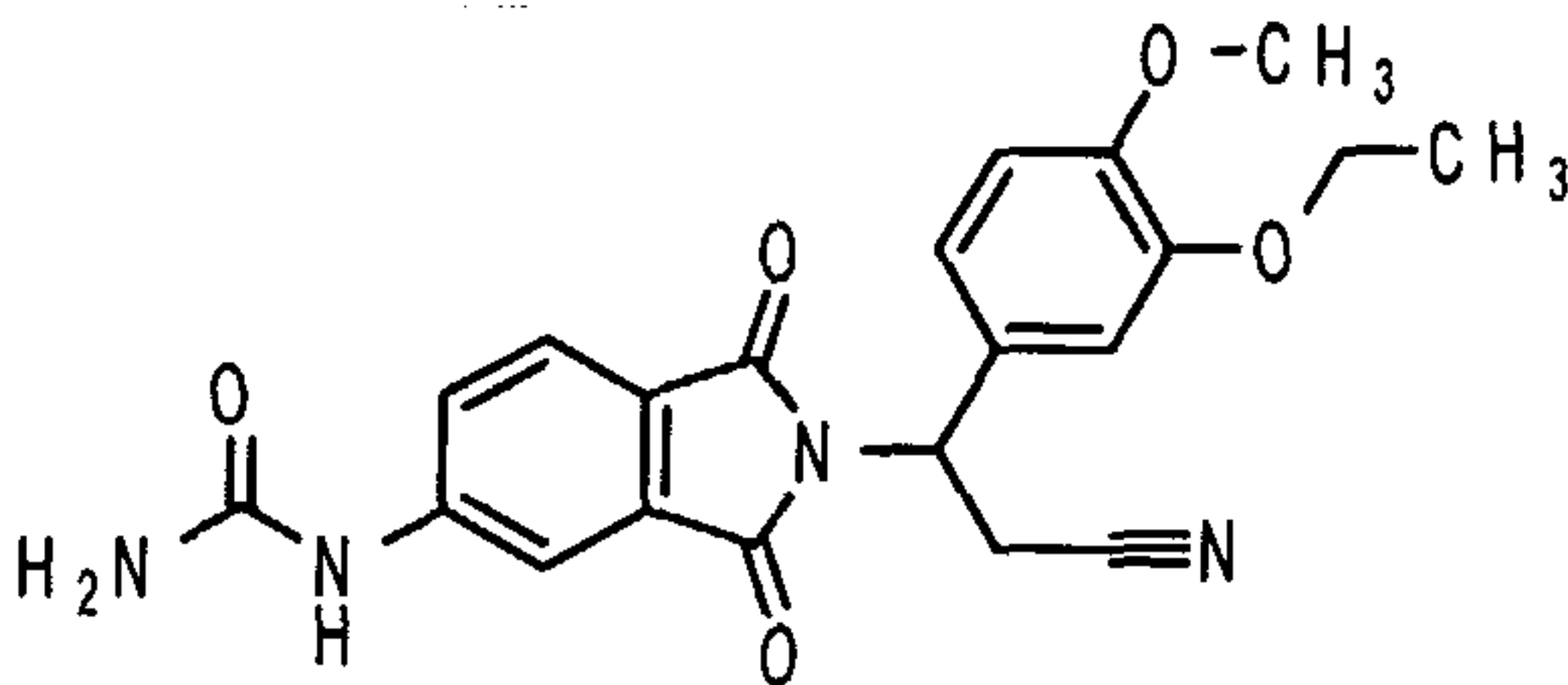
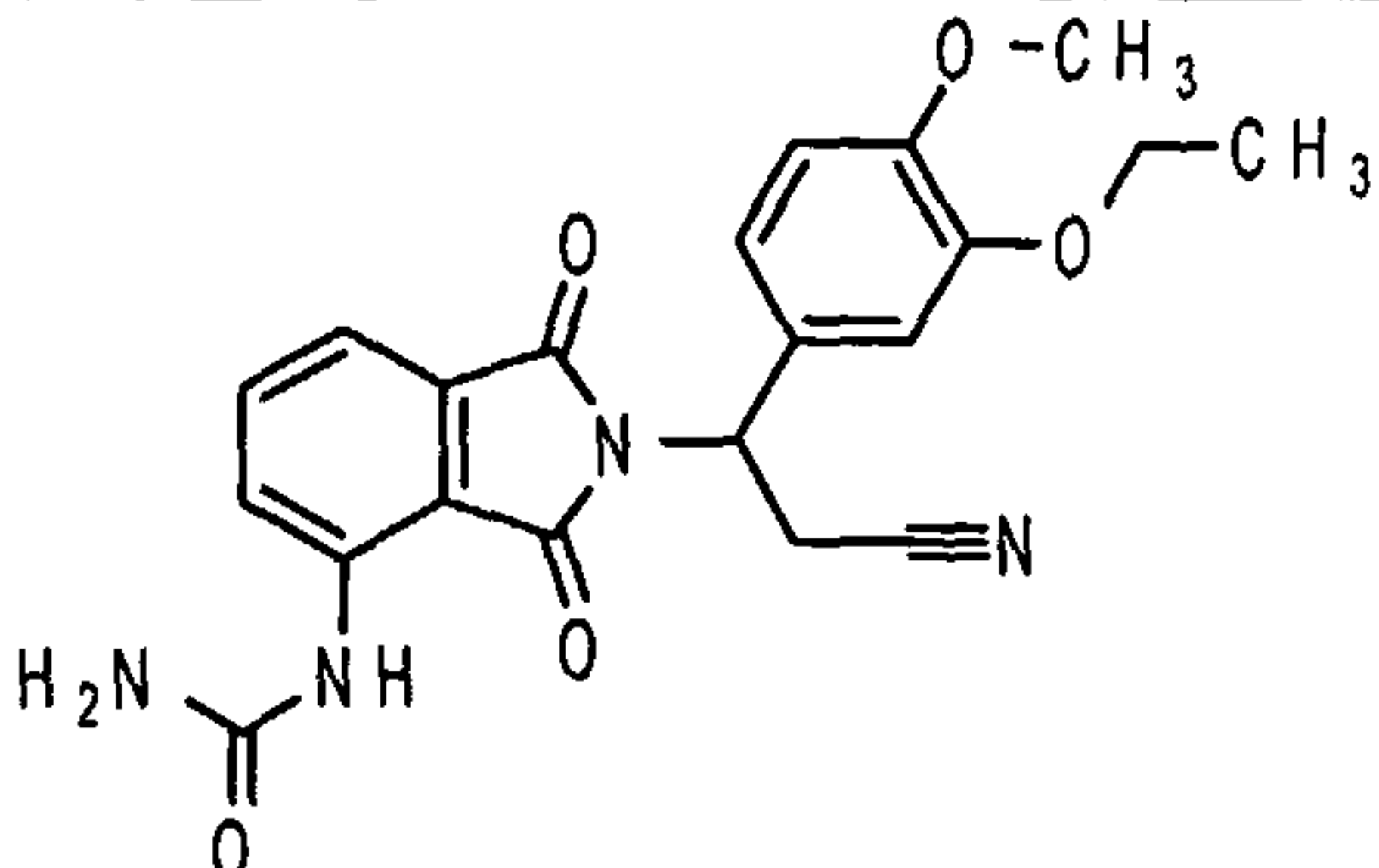
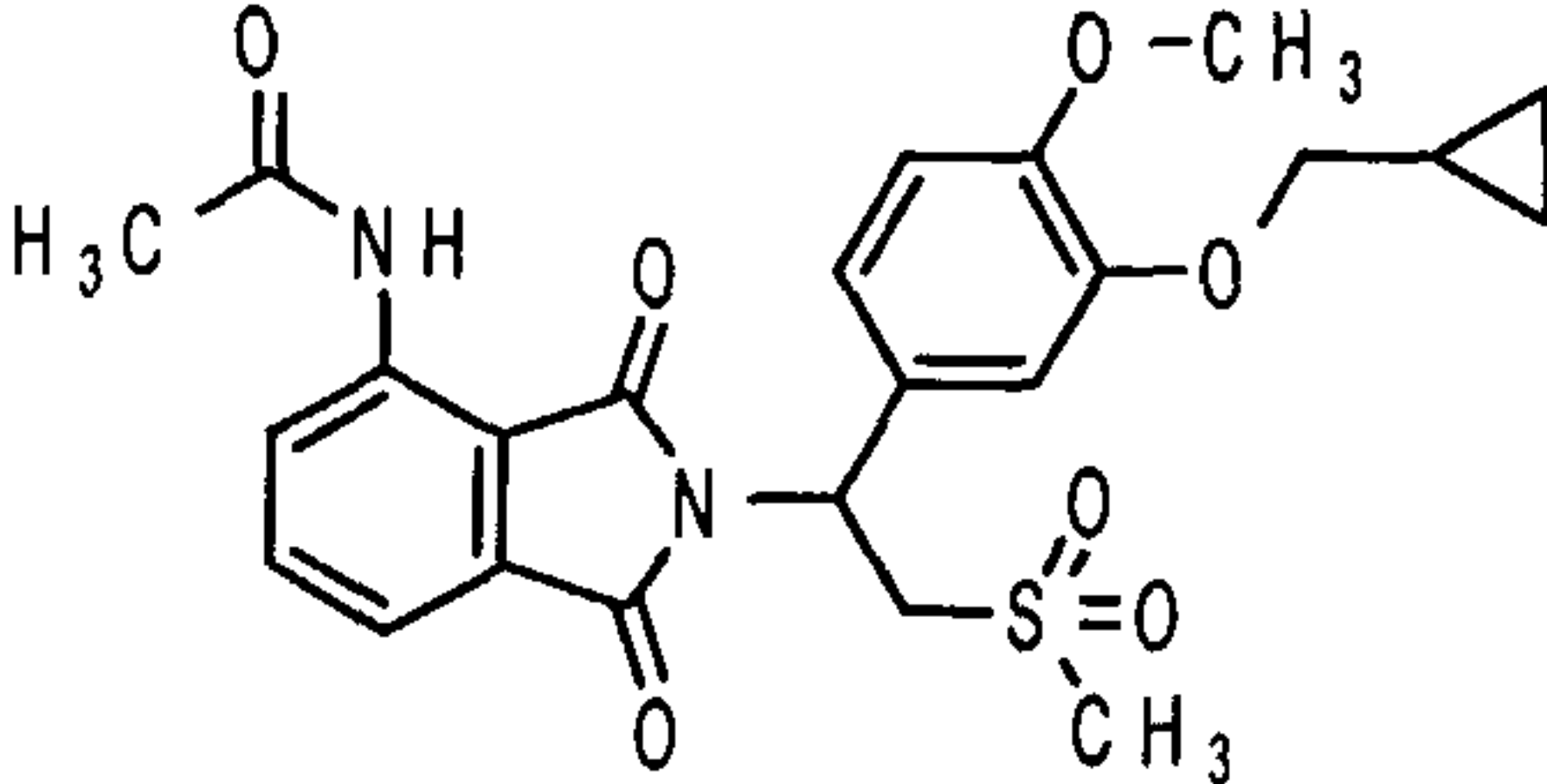
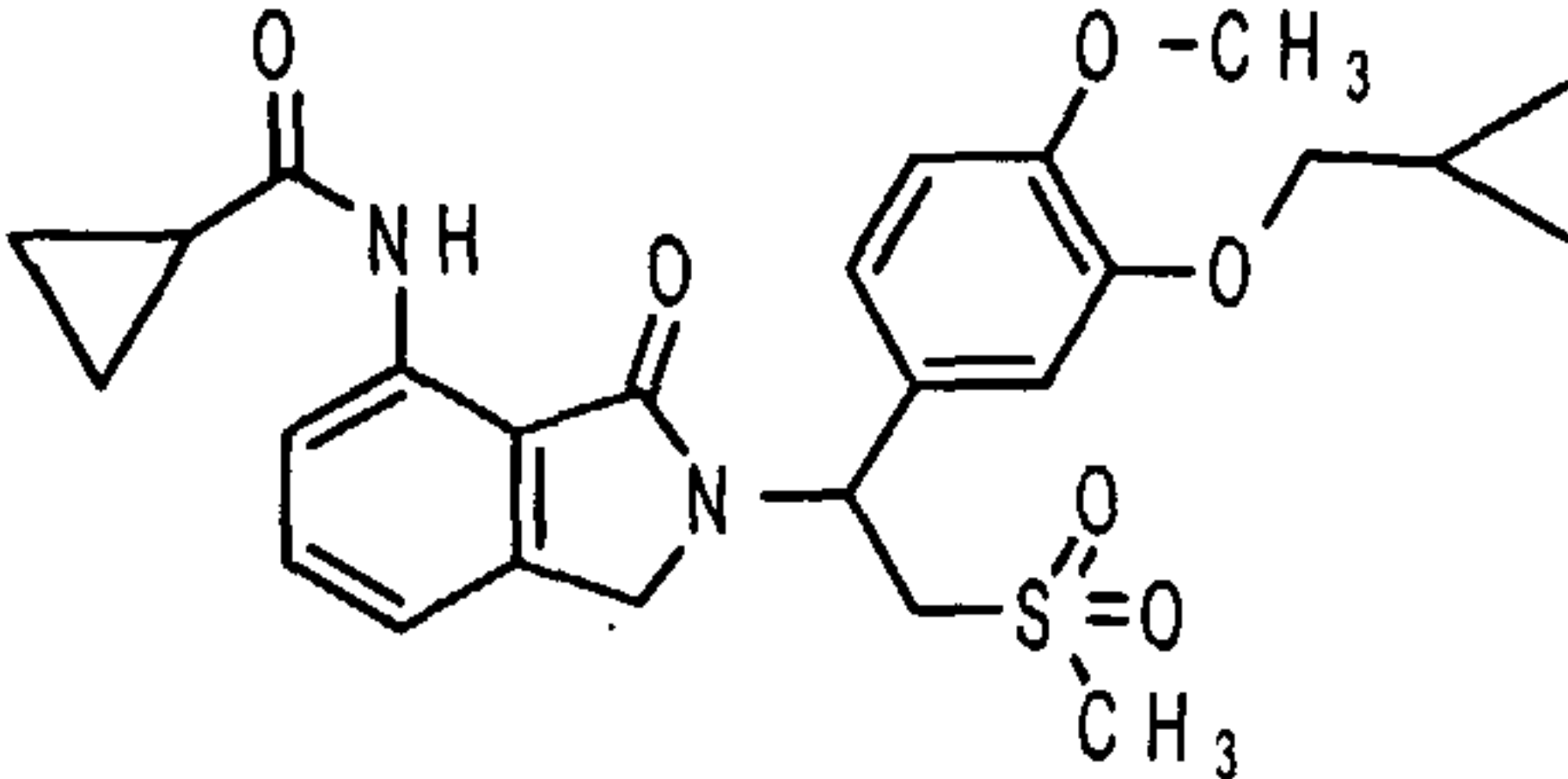
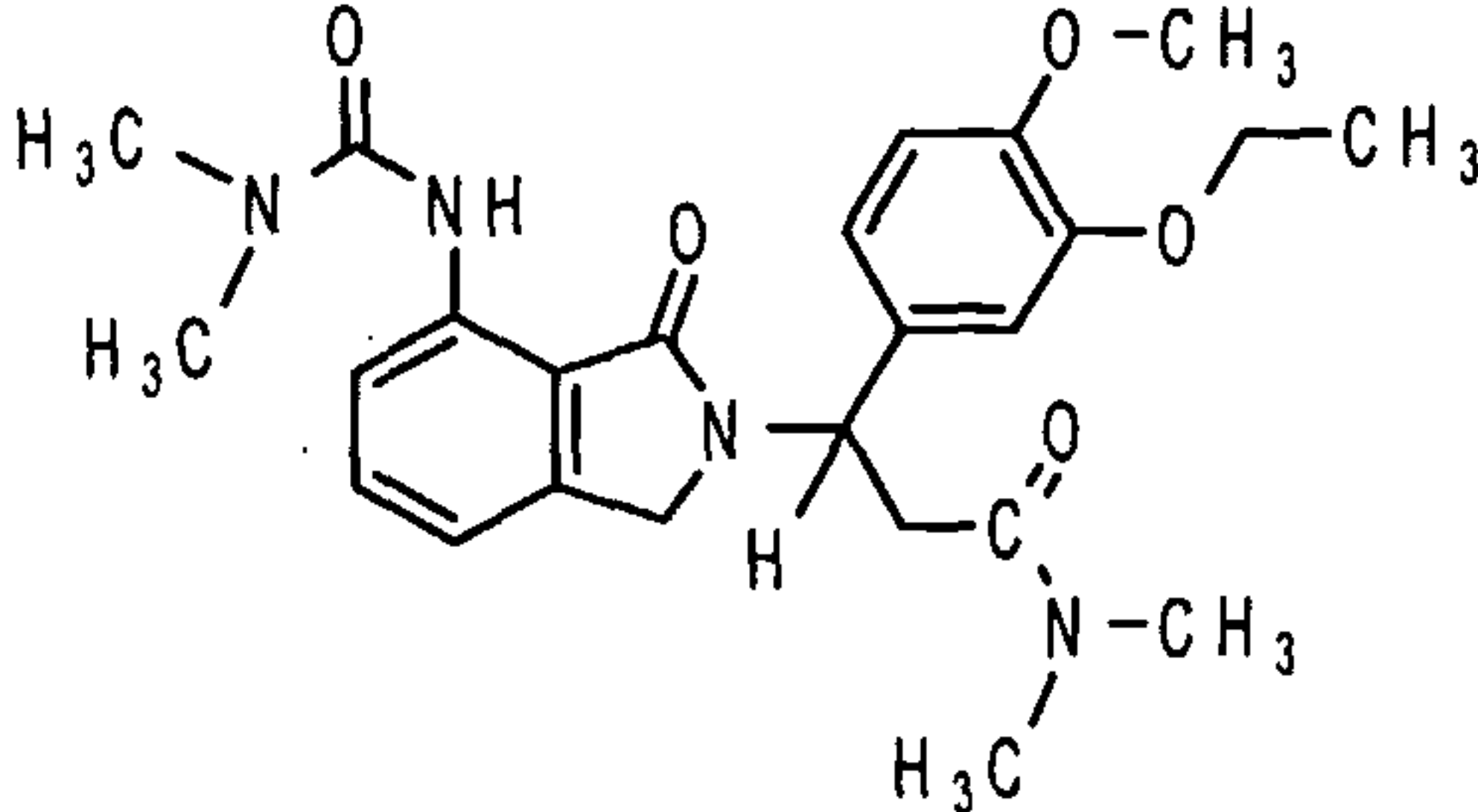
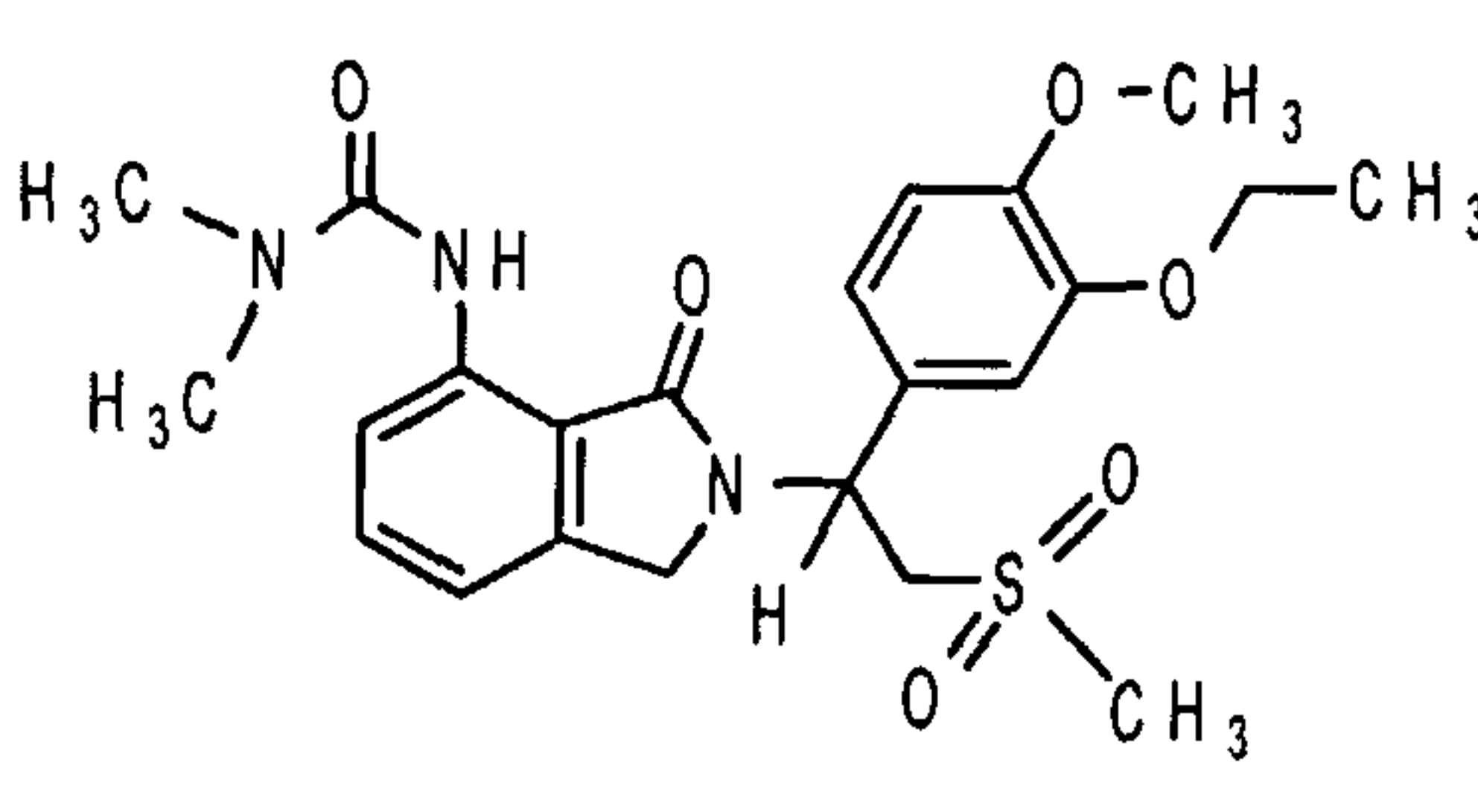
and pharmaceutically acceptable salts, solvates, hydrates, stereoisomers, clathrates,
20 or prodrugs thereof.

Still specific PDE4 modulators include, but are not limited to, isoindoline compounds disclosed in U.S. patent application no. 10/900,332 filed on July 28, 2004, which is incorporated herein by reference. Representative compounds are listed in Table 1 below, and pharmaceutically acceptable prodrugs, salts, solvates, and stereoisomers thereof:

5

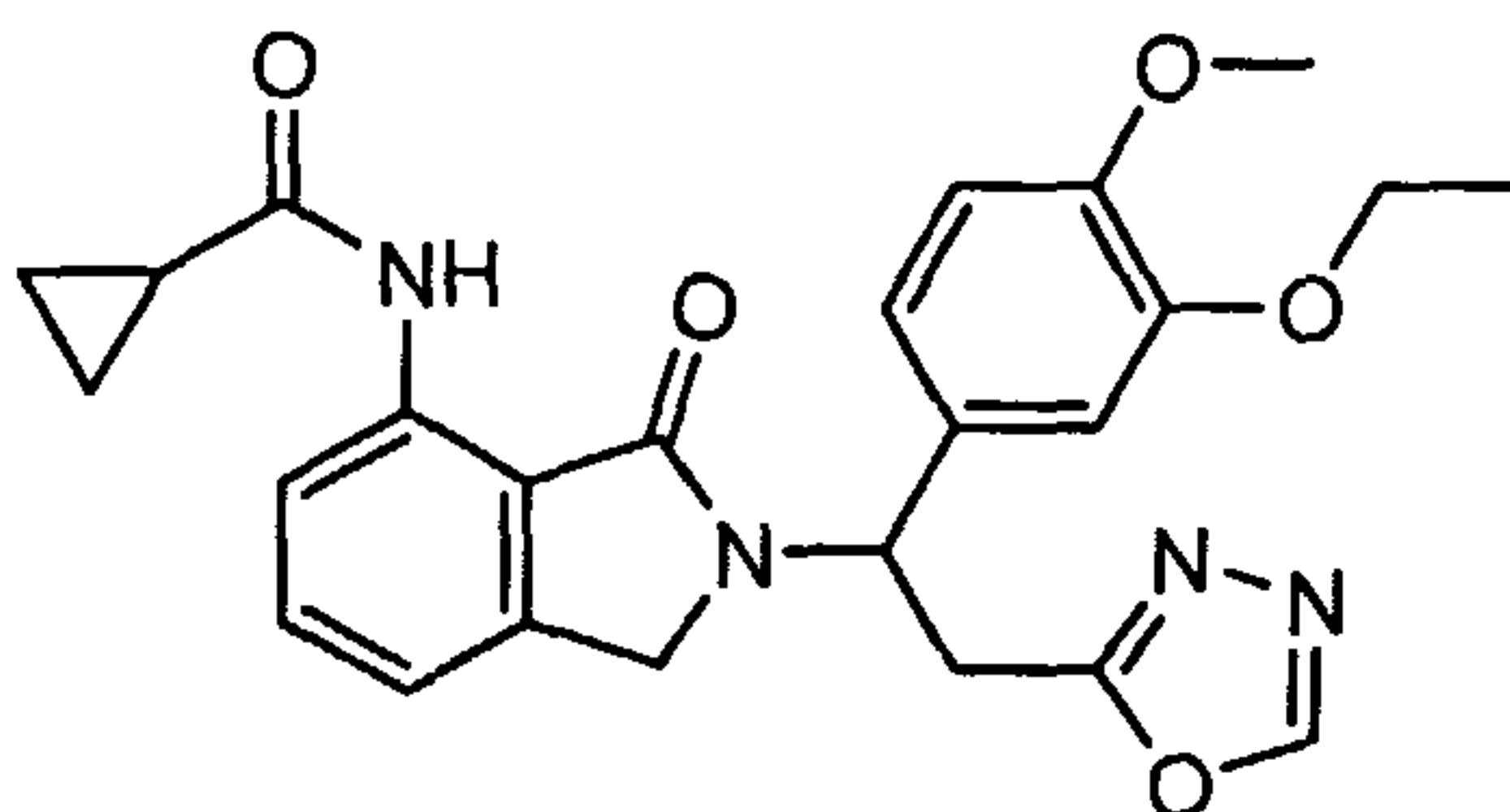
Table 1.

No.	Structure	No.	Structure
1		2	
3		4	
5		6	
7		8	
9		10	

11		12	
13		14	
15		16	

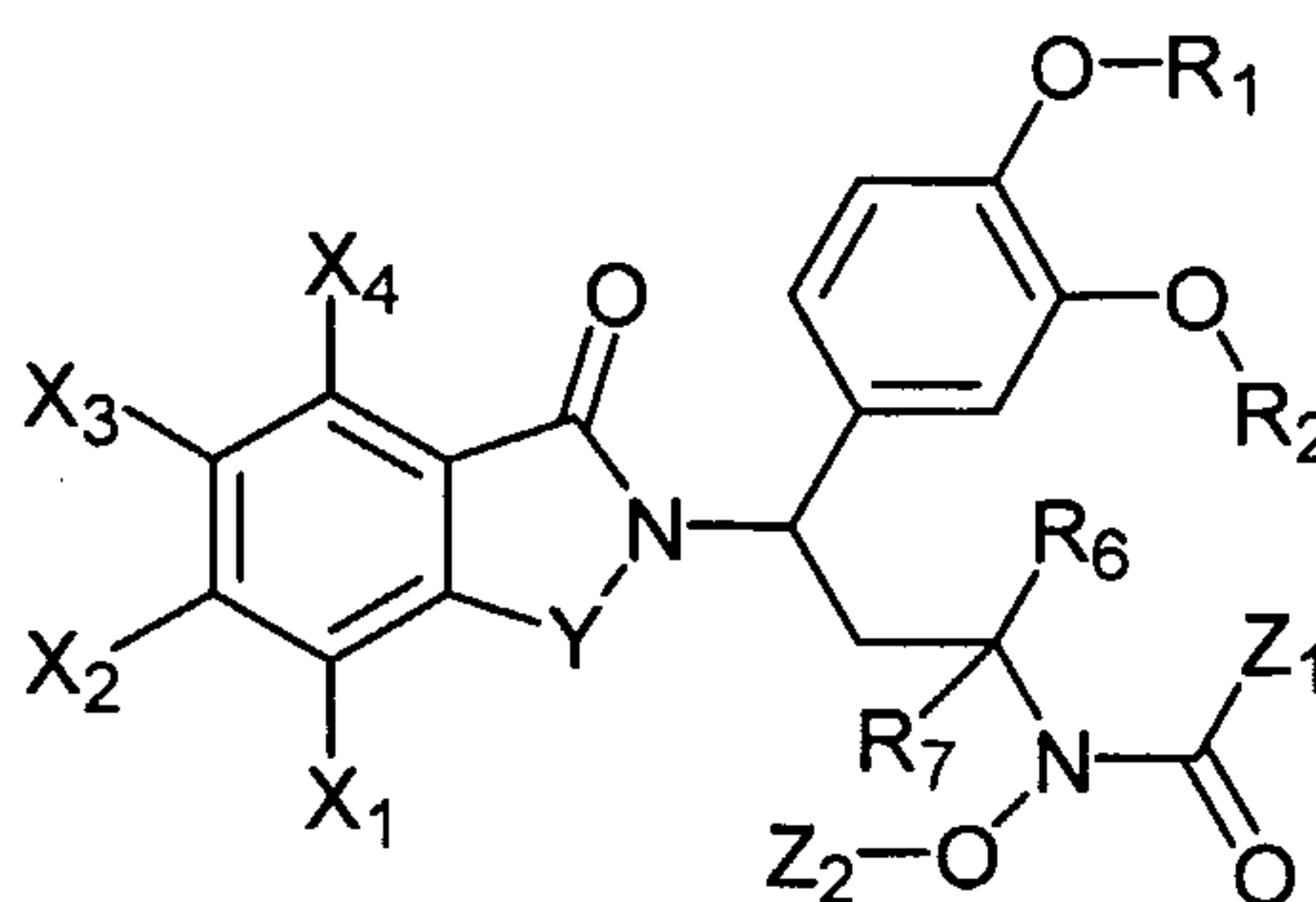
In another embodiment, this invention also encompasses 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4,5-dinitroisoindoline-1,3-dione and its acid addition salts. In a particular embodiment, this invention encompasses a hydrochloride salt of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4,5-dinitroisoindoline-1,3-dione.

Still specific PDE4 modulators include, but are not limited to, isoindoline compounds disclosed in U.S. patent application no. 10/900,270 filed on July 28, 2004, which is incorporated herein by reference. Representative compounds are cyclopropanecarboxylic acid {2-[1-(3-ethoxy-4-methoxy-phenyl)-2-[1,3,4]oxadiazol-2-yl-ethyl]-3-oxo-2,3-dihydro-1H-isoindol-4-yl}-amide, which has the following chemical structure, and pharmaceutically acceptable salts, solvates, prodrugs, and stereoisomers thereof:



Still specific PDE4 modulators include, but are not limited to, N-alkyl-hydroxamic acid-isoindolyl compounds disclosed in U.S. provisional application no. 60/454,149 filed on March 12, 2003, and its U.S. non-provisional application entitled "N-alkyl-hydroxamic

"acid-indole compounds and their pharmaceutical uses" which was filed on March 12, 2004 by Man *et al.* under U.S. serial no. 10/798,372, each of which is incorporated herein by reference. Representative compounds are of formula:



5 wherein:

Y is -C(O)-, -CH₂-, -CH₂C(O)- or SO₂;

R₁ and R₂ are independently C₁₋₈-alkyl, CF₂H, CF₃, CH₂CHF₂, cycloalkyl, or (C₁₋₈-alkyl)cycloalkyl;

Z₁ is H, C₁₋₆-alkyl, -NH₂, -NR₃R₄ or OR₅;

10 Z₂ is H or C(O)R₅;

X₁, X₂, X₃ and X₄ are each independent H, halogen, NO₂, OR₃, CF₃, C₁₋₆-alkyl, (C₀₋₄-alkyl)-(C₃₋₆-cycloalkyl), (C₀₋₄-alkyl)-N-(R₈R₉), (C₀₋₄-alkyl)-NHC(O)-(R₈), (C₀₋₄-alkyl)-NHC(O)CH(R₈)(R₉), (C₀₋₄-alkyl)-NHC(O)N(R₈R₉), (C₀₋₄-alkyl)-NHC(O)O(R₈), (C₀₋₄-alkyl)-O-R₈, (C₀₋₄-alkyl)-imidazolyl, (C₀₋₄-alkyl)-pyrrolyl, (C₀₋₄-alkyl)

15 oxadiazolyl, (C₀₋₄-alkyl)-triazolyl or (C₀₋₄-alkyl)-heterocycle;

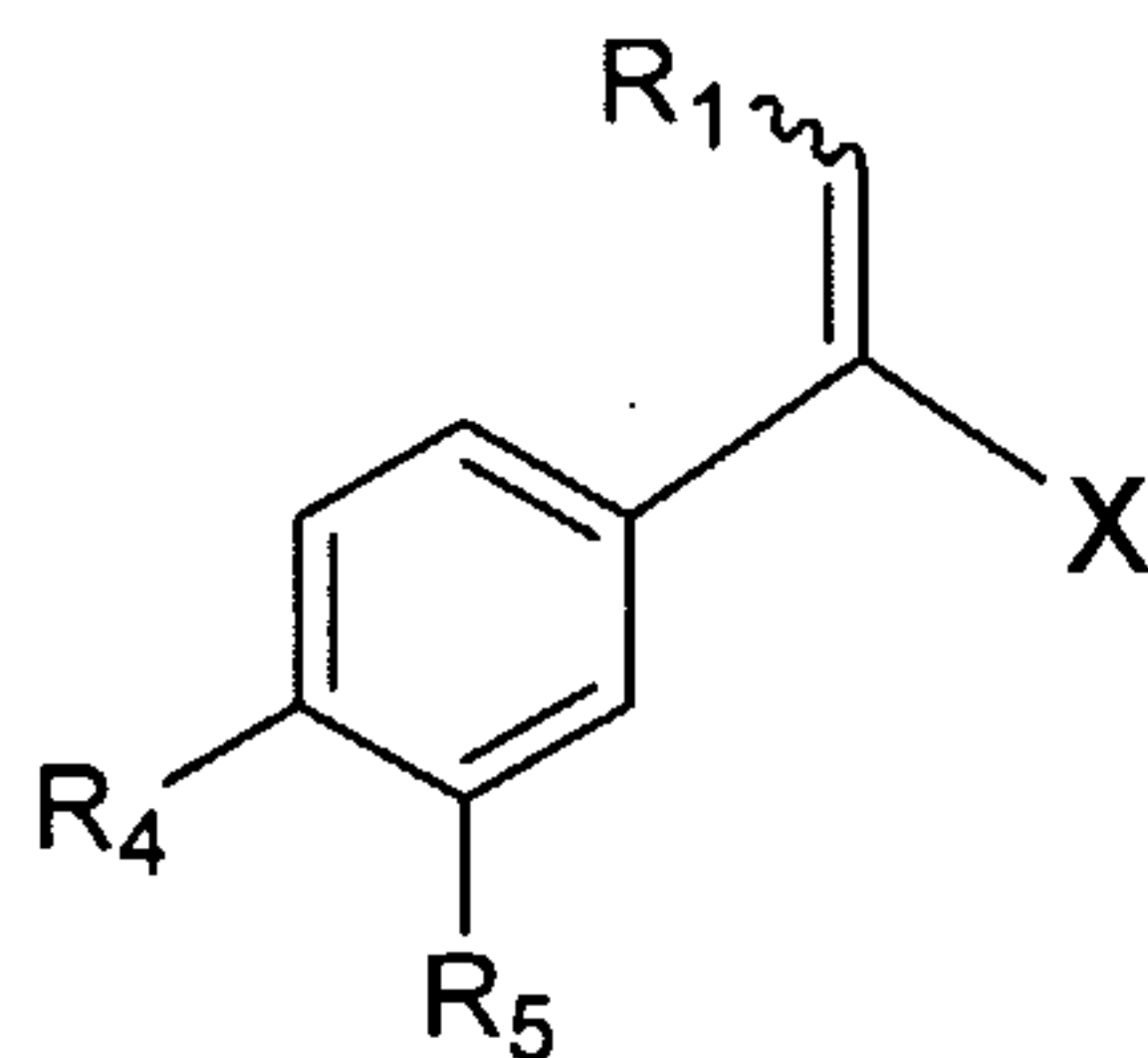
R₃, R₄, and R₅ are each independently H, C₁₋₆-alkyl, O-C₁₋₆-alkyl, phenyl, benzyl, or aryl;

R₆ and R₇ are independently H or C₁₋₆-alkyl;

20 R₈ and R₉ are each independently H, C₁₋₉-alkyl, C₃₋₆-cycloalkyl, (C₁₋₆-alkyl)-(C₃₋₆-cycloalkyl), (C₀₋₆-alkyl)-N(R₄R₅), (C₁₋₆-alkyl)-OR₅, phenyl, benzyl, aryl, piperidinyl, piperizinyl, pyrrolidinyl, morpholino, or C₃₋₇-heterocycloalkyl; and

or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

25 Still specific PDE4 modulators include, but are not limited to, diphenylethylene compounds disclosed in U.S. patent application no. 10/794,931, filed on March 5, 2004, which is incorporated herein by reference. Representative compounds are of formula:



and pharmaceutically acceptable salts, solvates or hydrates thereof,
wherein:

R_1 is -CN, lower alkyl, -COOH, -C(O)-N(R_9)₂, -C(O)-lower alkyl, -C(O)-benzyl, -
5 C(O)O-lower alkyl, -C(O)O-benzyl;

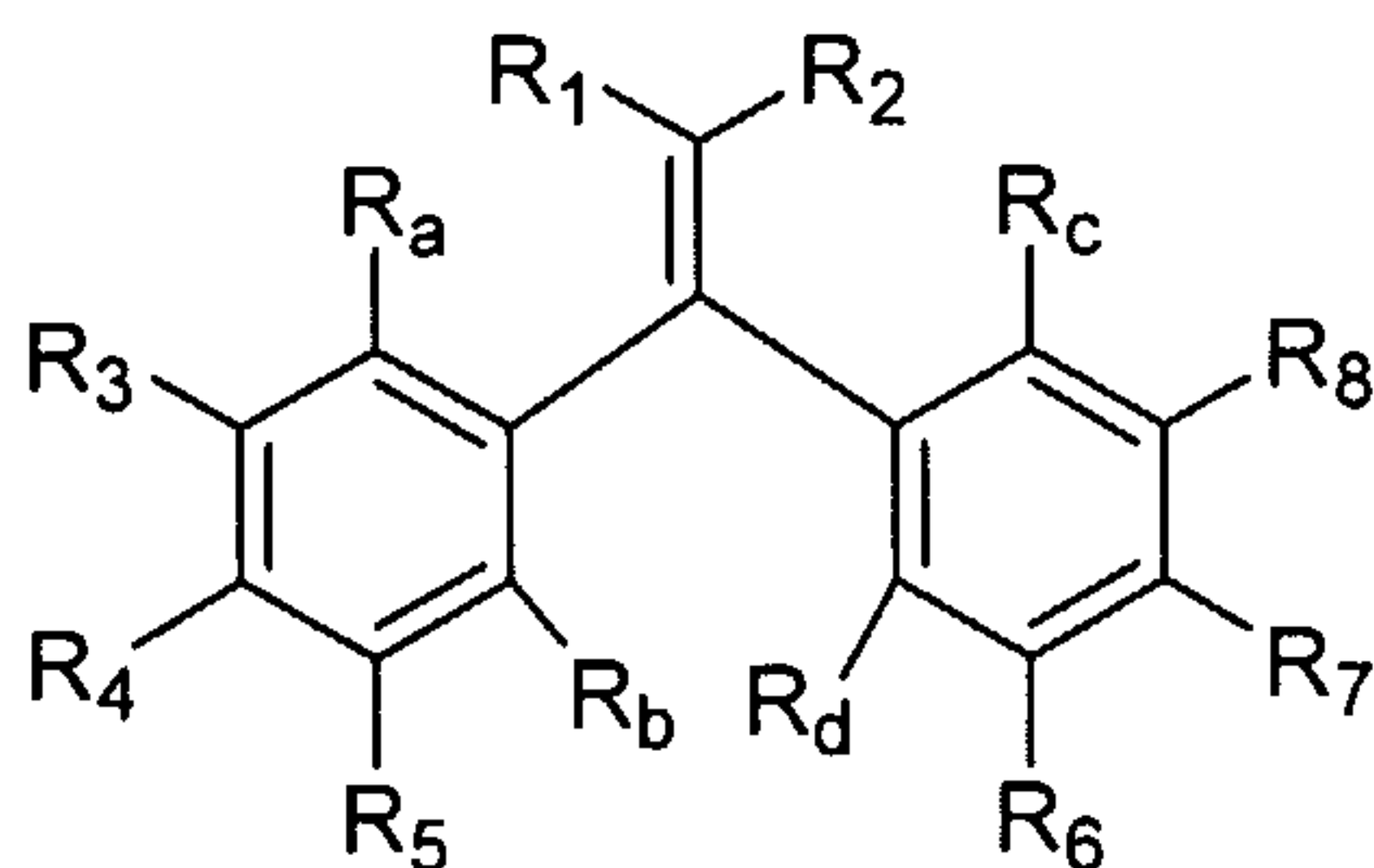
R_4 is -H, -NO₂, cyano, substituted or unsubstituted lower alkyl, substituted or
unsubstituted alkoxy, halogen, -OH, -C(O)(R_{10})₂, -COOH, -NH₂, -OC(O)-N(R_{10})₂;

R_5 is substituted or unsubstituted lower alkyl, substituted or unsubstituted alkoxy, or
substituted or unsubstituted alkenyl;

10 X is substituted or unsubstituted phenyl, substituted or unsubstituted pyridine,
substituted or unsubstituted pyrrolidine, substituted or unsubstituted imidazole, substituted
or unsubstituted naphthalene, substituted or unsubstituted thiophene, or substituted or
unsubstituted cycloalkyl;

each occurrence of R_9 is independently -H or substituted or unsubstituted lower
15 alkyl; and

each occurrence of R_{10} is independently -H or substituted or unsubstituted lower
alkyl. In another embodiment, representative compounds are of formula:



and pharmaceutically acceptable salts, solvates or hydrates thereof,
20 wherein:

R_1 and R_2 are independently -H, -CN, substituted or unsubstituted lower alkyl,
substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, -COOH, -C(O)-
lower alkyl, -C(O)O-lower alkyl, -C(O)-N(R_9)₂, substituted or unsubstituted aryl, or
substituted or unsubstituted heterocycle;

25 each occurrence of R_a , R_b , R_c and R_d is independently -H, substituted or
unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted

heterocycle, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkoxy, halogen, cyano, -NO₂, -OH, -OPO(OH)₂, -N(R₉)₂, -OC(O)-R₁₀, -OC(O)-R₁₀-N(R₁₀)₂, -C(O)N(R₁₀)₂, -NHC(O)-R₁₀, -NHS(O)₂-R₁₀, -S(O)₂-R₁₀, -NHC(O)NH-R₁₀, -NHC(O)N(R₁₀)₂, -NHC(O)NHSO₂-R₁₀, -NHC(O)-R₁₀-

5 N(R₁₀)₂, -NHC(O)CH(R₁₀)(N(R₉)₂) or -NHC(O)-R₁₀-NH₂;

R₃ is -H, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkoxy, halogen, cyano, -NO₂, -OH, -OPO(OH)₂, -N(R₉)₂, -OC(O)-R₁₀, -OC(O)-R₁₀-N(R₁₀)₂, -C(O)N(R₁₀)₂, -NHC(O)-R₁₀, -NHS(O)₂-R₁₀, -S(O)₂-R₁₀, -NHC(O)NH-R₁₀, -NHC(O)N(R₁₀)₂, -NHC(O)NHSO₂-R₁₀, -NHC(O)-R₁₀-N(R₁₀)₂, -NHC(O)CH(R₁₀)(N(R₉)₂) or -NHC(O)-R₁₀-NH₂, or R₃ with either R_a or with R₄, together form -O-C(R₁₆R₁₇)-O- or -O-(C(R₁₆R₁₇))₂-O-;

R₄ is -H, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkoxy, halogen, cyano, -NO₂, -OH, -OPO(OH)₂, -N(R₉)₂, -OC(O)-R₁₀, -OC(O)-R₁₀-N(R₁₀)₂, -C(O)N(R₁₀)₂, -NHC(O)-R₁₀, -NHS(O)₂-R₁₀, -S(O)₂-R₁₀, -NHC(O)NH-R₁₀, -NHC(O)N(R₁₀)₂, -NHC(O)NHSO₂-R₁₀, -NHC(O)-R₁₀-N(R₁₀)₂, -NHC(O)CH(R₁₀)(N(R₉)₂) or -NHC(O)-R₁₀-NH₂;

R₅ is -H, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkoxy, halogen, cyano, -NO₂, -OH, -OPO(OH)₂, -N(R₉)₂, -OC(O)-R₁₀, -OC(O)-R₁₀-N(R₁₀)₂, -C(O)N(R₁₀)₂, -NHC(O)-R₁₀, -NHS(O)₂-R₁₀, -S(O)₂-R₁₀, -NHC(O)NH-R₁₀, -NHC(O)N(R₁₀)₂, -NHC(O)NHSO₂-R₁₀, -NHC(O)-R₁₀-N(R₁₀)₂, -NHC(O)CH(R₁₀)(N(R₉)₂) or -NHC(O)-R₁₀-NH₂;

R₆ is -H, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkoxy, halogen, cyano, -NO₂, -OH, -OPO(OH)₂, -N(R₉)₂, -OC(O)-R₁₀, -OC(O)-R₁₀-N(R₁₀)₂, -C(O)N(R₁₀)₂, -NHC(O)-R₁₀, -NHS(O)₂-R₁₀, -S(O)₂-R₁₀, -NHC(O)NH-R₁₀, -NHC(O)N(R₁₀)₂, -NHC(O)NHSO₂-R₁₀, -NHC(O)-R₁₀-N(R₁₀)₂, -NHC(O)CH(R₁₀)(N(R₉)₂) or -NHC(O)-R₁₀-NH₂;

R₇ is -H, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkoxy, halogen, cyano, -NO₂, -OH, -OPO(OH)₂, -N(R₉)₂, -OC(O)-R₁₀, -OC(O)-R₁₀-N(R₁₀)₂, -C(O)N(R₁₀)₂, -NHC(O)-R₁₀, -NHS(O)₂-R₁₀, -S(O)₂-R₁₀, -NHC(O)NH-R₁₀, -NHC(O)N(R₁₀)₂, -NHC(O)NHSO₂-R₁₀, -NHC(O)-R₁₀-N(R₁₀)₂, -NHC(O)CH(R₁₀)(N(R₉)₂) or -NHC(O)-R₁₀-NH₂;

R_{10} , $-NHC(O)NH-R_{10}$, $-NHC(O)N(R_{10})_2$, $-NHC(O)NHSO_2-R_{10}$, $-NHC(O)-R_{10}-N(R_{10})_2$, $-NHC(O)CH(R_{10})(N(R_9)_2)$ or $-NHC(O)-R_{10}-NH_2$;

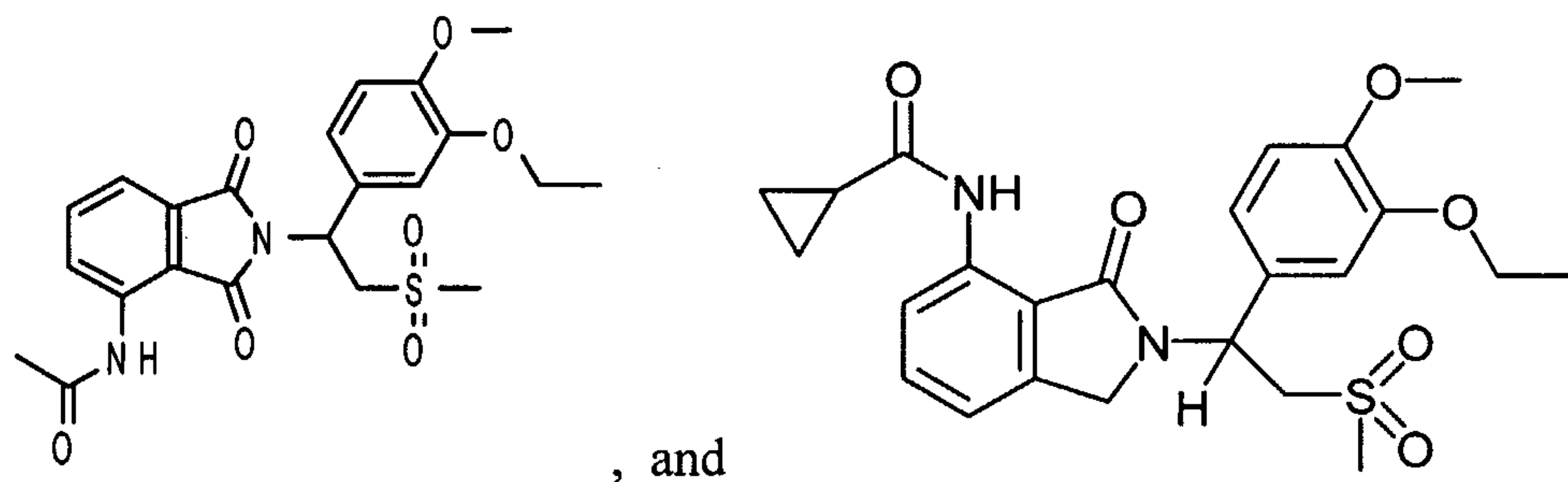
R_8 is $-H$, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkoxy, halogen, cyano, $-NO_2$, $-OH$, $-OPO(OH)_2$, $-N(R_9)_2$, $-OC(O)-R_{10}$, $-OC(O)-R_{10}-N(R_{10})_2$, $-C(O)N(R_{10})_2$, $-NHC(O)-R_{10}$, $-NHS(O)_2-R_{10}$, $-S(O)_2-R_{10}$, $-NHC(O)NH-R_{10}$, $-NHC(O)N(R_{10})_2$, $-NHC(O)NHSO_2-R_{10}$, $-NHC(O)-R_{10}-N(R_{10})_2$, $-NHC(O)CH(R_{10})(N(R_9)_2)$ or $-NHC(O)-R_{10}-NH_2$, or R_8 with either R_c or with R_7 , together form $-O-C(R_{16}R_{17})-O-$ or $-O-(C(R_{16}R_{17}))_2-O-$;

each occurrence of R_9 is independently $-H$, substituted or unsubstituted lower alkyl, or substituted or unsubstituted cycloalkyl;

each occurrence of R_{10} is independently substituted or unsubstituted lower alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted lower hydroxyalkyl, or R_{10} and a nitrogen to which it is attached form a substituted or unsubstituted heterocycle, or R_{10} is $-H$ where appropriate; and

each occurrence of R_{16} and R_{17} is independently $-H$ or halogen.

In a particular embodiment, compounds of the invention are 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisoindoline-1,3-dione and cyclopropyl-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisoindolin-4-yl}carboxamide, which respectively have the following structures:



or a pharmaceutically acceptable salt, solvate or prodrug thereof. In another embodiment, stereoisomers of these compounds are also encompassed.

Compounds of the invention can either be commercially purchased or prepared according to the methods described in the patents or patent publications disclosed herein. Further, optically pure compositions can be asymmetrically synthesized or resolved using known resolving agents or chiral columns as well as other standard synthetic organic chemistry techniques.

Various PDE4 modulators contain one or more chiral centers, and can exist as racemic mixtures of enantiomers or mixtures of diastereomers. This invention encompasses

the use of stereomerically pure forms of such compounds, as well as the use of mixtures of those forms. For example, mixtures comprising equal or unequal amounts of the enantiomers of PDE4 modulators may be used in methods and compositions of the invention. The purified (R) or (S) enantiomers of the specific compounds disclosed herein
5 may be used substantially free of its other enantiomer.

It should be noted that if there is a discrepancy between a depicted structure and a name given that structure, the depicted structure is to be accorded more weight. In addition, if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as
10 encompassing all stereoisomers of it.

4.3 SECOND ACTIVE AGENTS

A second active ingredient or agent can be used in the methods and compositions of the invention together with a PDE4 modulator. In a preferred embodiment, the second active agent is capable of relieving airway inflammation, inhibiting inflammatory reactions,
15 or ensuring patient comfort. The second active ingredient described herein can be either commercially available, or made using conventional methods known in the art.

Examples of the second active agents include, but are not limited to, antibiotics, anticholinergics, antihistaminic agents, anti-inflammatory agents, antioxidants, antitussive agents, β_2 -agonists, calcium channel blockers, corticosteroids, immunomodulatory agents,
20 immunosuppressive agents, leukotriene inhibitors, monoclonal antibodies, mucolytics, muscle relaxants, PDE4 inhibitors, potassium channel openers, prostaglandin and analogs, sensory neuropeptide release inhibitors, tachykinin antagonists, and theophylline and its derivatives, and other therapeutics used for the treatment of airway inflammation or other airway or pulmonary diseases and disorders, and pharmaceutically acceptable salts,
25 solvates, stereoisomers, prodrugs, and pharmacologically active metabolites thereof.

Antibiotics may be used where the airway inflammation or other airway or pulmonary disease or disorder is caused by microbial infection. Examples of antibiotics include, but are not limited to, amphotericin B, ampicillin, ceftriaxone, cefuroxime, cephalosporin, chloramphenicol, ciprofloxacin, clindamycin, dapsone, erythromycin,
30 ethambutol, fluconazole, gentamicin, isoniazid, itraconazole, ketoconazole, minocycline, norfloxacin, penicillin, pentamidine, pyrazinamide, ribavirin, rifampin, streptomycin, tetracycline, trimethoprim, and vancomycin.

Examples of anticholinergics include, but are not limited to, anisotropine, atropine, clindinium, cyclopentolate, glycopyrrolate, hexocyclium, homatropine, ipratropium,

isopropamide, methscopolamine, methantheline, pirenzepine, propantheline, scopolamine, telenzepine, tiotropium, and tropicamide.

Examples of anti-histaminic agents include, but are not limited to: ethanolamines such as diphenhydramine, dimenhydrinate, and carbinoxamine; ethylenediamines such as
5 pyrilamine and tripeleminamine; alkylamines such as chlorpheniramine and brompheniramine; piperazines such as hydroxyzine, cyclizine, and meclizine; phenothiazines such as promethazine; and piperidines such as terfenadine and astemizole.

Anti-inflammatories such as non-steroidal anti-inflammatory drugs (NSAIDs) and cox-2 inhibitors typically inhibit inflammatory reactions by decreasing the activity of cyclo-
10 oxygenase, which is responsible for prostaglandin synthesis. Examples of anti-inflammatories include, but are not limited to, salicylic acid acetate (Aspirin), ibuprofen (Motrin[®], Advil[®]), ketoprofen (Oruvail[®]), rofecoxib (Vioxx[®]), naproxen sodium (Anaprox[®], Naprelan[®], Naprosyn[®]), ketorolac (Acular[®]), and other known conventional medications. See, e.g., *Physicians' Desk Reference*, 1990, 1910-1914 and 2891 (57th ed.,
15 2003); *Physicians' Desk Reference for Nonprescription Drugs and Dietary Supplements*, 511, 667 and 773 (23rd ed., 2002).

Examples of antitussive agents include, but are not limited to, benzonatate, caramiphen, carbetapentane, chlophedianol, dextromethorphan, diphenhydramine, glaucine, levoproxyphen, noscapine, and pholcodine.

20 Examples of β_2 -agonists include, but are not limited to, albuterol, bitolterol, carbuterol, dobutamine, ephinephrine, formoterol, ibuterol, isoetharine, isoproterenol, mabuterol, metaproterenol, pirbuterol, procaterol, reproterol, rimiterol, ritodrine, salbutamol, salmeterol, soterenol, and terbutaline.

Examples of calcium channel blockers include, but are not limited to, diltiazem,
25 nifedipine, nifedipine, nimodipine, and verapamil.

Examples of corticosteroids include, but are not limited to, aldosterone, budesonide, corticosterone, cortisol, cortisone, 11-deoxycorticosterone, dexamethasone, fluticasone, hydrocortisone, mometasone, prednisolone, and triamcinolone, and combination agents such as symbicort[®] (formoterol and budesonide) and seretide[®] or advair[®] (salmeterol and
30 fluticasone).

Examples of leukotriene inhibitors include, but are not limited to, 1-(((R)-(3-(2-(2,3-dichlorothieno[3,2-b]pyridin-5-yl)-(E)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl) cyclopropaneacetic acid, docebenone, ICI-D2318, MK-591, MK-886, montelukast, piripost, pranlukast, sodium-1-(((R)-(3-(2-(6,7-difluoro-2-

"quinolinyl)ethynyl)phenyl-3-(2-(2-hydroxy-2-propyl)phenyl)thio)methyl)
cyclopropaneacetate, zileuton, and zafirlukast.

Examples of muscle relaxants include, but are not limited to, carisoprodol, cyclobenzaprine, and metaxalone.

5 4.4 METHODS OF TREATMENT AND MANAGEMENT

Methods of this invention encompass methods of preventing, treating, and/or managing airway inflammation and other airway or pulmonary diseases and disorders. Examples of other airway or pulmonary diseases or disorders include, but are not limited to, respiratory failure; adult respiratory distress syndrome; chronic obstructive airway disorders
10 such as, but not limited to, asthma, chronic obstructive pulmonary disease and giant bullae; acute bronchitis; chronic bronchitis; emphysema; reversible obstructive airway disease; nocturnal asthma; exercise induced bronchospasm; and interstitial pulmonary fibrosis.

In one embodiment, the airway or pulmonary disease or disorder is not respiratory failure. In another embodiment, the airway or pulmonary disease or disorder is not adult
15 respiratory distress syndrome. In another embodiment, the airway or pulmonary disease or disorder is not asthma. In another embodiment, the airway or pulmonary disease or disorder is not chronic obstructive pulmonary disease. In another embodiment, the airway or pulmonary disease or disorder is not respiratory failure, adult respiratory distress syndrome, asthma, or chronic obstructive pulmonary disease.

20 The invention further encompasses methods of treating and managing airway inflammation and other airway or pulmonary diseases and disorders in patients who have been previously treated for such diseases and disorders but were not sufficiently responsive or were non-responsive to standard therapy, as well as those who have not previously been treated for such diseases and disorders. Because patients with airway inflammation and
25 other airway or pulmonary diseases and disorders have heterogeneous clinical manifestations and varying clinical outcomes, the treatment or management given to a patient may vary, depending on his/her prognosis. The skilled clinician will be able to readily determine without undue experimentation specific secondary agents and types of therapies that can be effectively used to treat an individual patient.

30 Methods encompassed by this invention comprise administering one or more PDE4 modulators, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof to a patient (*e.g.*, a human) suffering, or likely to suffer, from airway inflammation and other airway or pulmonary diseases and disorders.

In one embodiment of the invention, a PDE4 modulator is administered orally and in single or divided daily doses in an amount of from about 1 mg to about 10,000 mg. More specifically, the daily dose is administered twice daily in equally divided doses.

Specifically, a daily dose range should be from about 1 mg to about 5,000 mg per day, more specifically, between about 10 mg and about 2,500 mg per day, between about 100 mg and about 800 mg per day, between about 100 mg and about 1,200 mg per day, or between about 25 mg and about 2,500 mg per day. In managing the patient, the therapy should be initiated at a lower dose, perhaps about 1 mg to about 2,500 mg, and increased if necessary up to about 200 mg to about 5,000 mg per day as either a single dose or divided doses, depending on the patient's global response. In a particular embodiment, 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide can be preferably administered in an amount of about 400, 800, 1,200, 2,500, 5,000 or 10,000 mg a day as two divided doses. In a particular embodiment, 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide is administered in an amount of from about 400 to about 1,200 mg/d daily, every other day, or in other syncopated regimen. In another embodiment, 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl]ethyl]-4-acetylaminoisoindoline-1,3-dione, or a stereoisomer thereof, is administered in an amount of about 1, 10, 100, 200, 400, 800, 1,200, 2,500, 5,000, or 10,000 mg a day as a single or two divided doses. In another embodiment, cyclopropyl-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl]ethyl}-3-oxoisoindolin-4-yl}carboxamide, or a stereoisomer thereof, is administered in an amount of about 1, 10, 100, 200, 400, 800, 1,200, 2,500, 5,000, or 10,000 mg a day as a single or two divided doses.

In one embodiment of the invention, a PDE4 modulator is administered by inhalation, and in single or divided daily doses, in an amount of from about 1 mg to about 10,000 mg. More specifically, the daily dose is administered twice daily in equally divided doses. Specifically, a daily dose range should be from about 1 mg to about 5,000 mg per day, more specifically, between about 10 mg and about 2,500 mg per day, between about 100 mg and about 800 mg per day, between about 100 mg and about 1,200 mg per day, or between about 25 mg and about 2,500 mg per day. In managing the patient, the therapy should be initiated at a lower dose, perhaps about 1 mg to about 2,500 mg, and increased if necessary up to about 200 mg to about 5,000 mg per day as either a single dose or divided doses, depending on the patient's global response. In a particular embodiment, 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide can be preferably administered in an amount of about 400, 800, 1,200, 2,500, 5,000 or 10,000 mg a day as

"two divided doses." In a particular embodiment, 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide is administered in an amount of from about 400 to about 1,200 mg/d daily, every other day, or in other syncopated regimen. In another embodiment, 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisoindoline-1,3-dione, or a stereoisomer thereof, is administered in an amount of about 1, 10, 100, 200, 400, 800, 1,200, 2,500, 5,000, or 10,000 mg a day as a single or two divided doses. In another embodiment, cyclopropyl-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-3-oxoisoindolin-4-yl}carboxamide, or a stereoisomer thereof, is administered in an amount of about 1, 10, 100, 200, 400, 800, 1,200, 2,500, 5,000, or 10,000 mg a day as a single or two divided doses.

In one embodiment, the invention encompasses a method for treating, preventing, and/or managing airway inflammation, comprising administering an effective amount of a PDE4 modulator, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, to a patient in need thereof.

In another embodiment, the invention encompasses a method for treating, preventing, and/or managing airway or pulmonary diseases or disorders comprising administering an effective amount of a PDE4 modulator, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, to a patient in need thereof. In certain embodiments, the disease or disorder is asthma. In another embodiment, the disease or disorder is chronic obstructive pulmonary disease.

Another embodiment of the invention comprises administering one or more PDE4 modulators, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, to a patient for treating, preventing, and/or managing giant bullae, acute bronchitis, chronic bronchitis, emphysema, reversible obstructive airway disease, nocturnal asthma, exercise induced bronchospasm, and/or interstitial pulmonary fibrosis.

In another embodiment, the invention relates to a method for treating, preventing, and/or managing airway inflammation and other airway or pulmonary diseases and disorders associated with a cytokine, comprising administering an effective amount of a PDE4 modulator, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, to a patient in need thereof. In one embodiment, inhibiting cytokine activity or cytokine production results in the treatment, prevention, and/or management of the airway inflammation. In another embodiment, the cytokine is TNF- α . In another embodiment, the airway or pulmonary disease or disorder associated with a cytokine is asthma. In another

embodiment, the airway or pulmonary disease or disorder associated with a cytokine is chronic obstructive pulmonary disease.

4.4.1 Combination Therapy With A Second Active Agent

Specific methods of the invention comprise administering a PDE4 modulator, or a
5 pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, in combination with a second active agent or active ingredient. Examples of PDE4 modulators are disclosed herein (*see, e.g.*, section 4.2); and examples of second active agents are also disclosed herein (*see, e.g.*, section 4.3).

Administration of the PDE4 modulators and the second active agents to a patient can
10 occur simultaneously or sequentially by the same or different routes of administration. The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (*e.g.*, whether it can be administered orally without decomposing prior to entering the blood stream) and the disease being treated. A preferred route of administration for PDE4 modulators is oral. Preferred routes of administration for
15 the second active agents or ingredients of the invention are known to those of ordinary skill in the art. *See, e.g., Physicians' Desk Reference*, 594-597 (57th ed., 2003).

In one embodiment, the second active agent is administered orally, intravenously, intramuscularly, subcutaneously, mucosally, or transdermally and once or twice daily in an amount of from about 1 to about 3,500 mg, from about 5 to about 2,500 mg, from about 10
20 to about 500 mg, or from about 25 to about 250 mg.

The specific amount of the second active agent will depend on the specific agent used, the type of disease or disorder being treated or managed, the severity and stage of the disease or disorder, and the amount(s) of PDE4 modulators and any optional additional active agents concurrently administered to the patient. Conventional amounts of the second
25 active agents can be a starting point. *See, e.g., Physicians' Desk Reference*, (57th ed., 2003).

In one embodiment, a PDE4 modulator and a second active agent are administered to a patient, preferably a mammal, more preferably a human, in a sequence and within a time interval such that the PDE4 modulator can act together with the other agent to provide an increased benefit than if they were administered otherwise. For example, the second
30 active agent can be administered at the same time or sequentially in any order at different points in time; however, if not administered at the same time, they should be administered sufficiently close in time so as to provide the desired therapeutic or prophylactic effect. In one embodiment, the PDE4 modulator and the second active agent exert their effect at times which overlap. Each second active agent can be administered separately, in any appropriate

"form and by any suitable route. In other embodiments, the PDE4 modulator is administered before, concurrently or after administration of the second active agent.

In various embodiments, the PDE4 modulator and the second active agent are administered less than about 1 hour apart, at about 1 hour apart, at about 1 hour to about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, no more than 24 hours apart or no more than 48 hours apart. In other embodiments, the PDE4 modulator and the second active agent are administered concurrently.

In other embodiments, the PDE4 modulator and the second active agent are administered at about 2 to 4 days apart, at about 4 to 6 days apart, at about 1 week apart, at about 1 to 2 weeks apart, or more than 2 weeks apart.

In certain embodiments, the PDE4 modulator and optionally the second active agent are cyclically administered to a patient. Cycling therapy involves the administration of a first agent for a period of time, followed by the administration of a second agent and/or third agent for a period of time and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improve the efficacy of the treatment.

In certain embodiments, the PDE4 modulator and optionally the second active agent are administered in a cycle of less than about 3 weeks, about once every two weeks, about once every 10 days or about once every week. One cycle can comprise the administration of a PDE4 modulator and optionally the second active agent by infusion over about 90 minutes every cycle, about 1 hour every cycle, about 45 minutes every cycle. Each cycle can comprise at least 1 week of rest, at least 2 weeks of rest, at least 3 weeks of rest. The number of cycles administered is from about 1 to about 12 cycles, more typically from about 2 to about 10 cycles, and more typically from about 2 to about 8 cycles.

In yet other embodiments, the PDE4 modulator is administered in metronomic dosing regimens, either by continuous infusion or frequent administration without extended rest periods. Such metronomic administration can involve dosing at constant intervals without rest periods. Typically the PDE4 modulators, are used at lower doses. Such dosing regimens encompass the chronic daily administration of relatively low doses for extended periods of time. In preferred embodiments, the use of lower doses can minimize toxic side

effects and eliminate rest periods. In certain embodiments, the PDE4 modulator is delivered by chronic low-dose or continuous infusion ranging from about 24 hours to about 2 days, to about 1 week, to about 2 weeks, to about 3 weeks to about 1 month to about 2 months, to about 3 months, to about 4 months, to about 5 months, to about 6 months. The scheduling of such dose regimens can be optimized by the skilled artisan.

In other embodiments, courses of treatment are administered concurrently to a patient, *i.e.*, individual doses of the second active agent are administered separately yet within a time interval such that the PDE4 modulator can work together with the second active agent. For example, one component can be administered once per week in combination with the other components that can be administered once every two weeks or once every three weeks. In other words, the dosing regimens are carried out concurrently even if the therapeutics are not administered simultaneously or during the same day.

The second active agent can act additively or, more preferably, synergistically with the PDE4 modulator. In one embodiment, a PDE4 modulator is administered concurrently with one or more second active agents in the same pharmaceutical composition. In another embodiment, a PDE4 modulator is administered concurrently with one or more second active agents in separate pharmaceutical compositions. In still another embodiment, a PDE4 modulator is administered prior to or subsequent to administration of a second active agent. The invention contemplates administration of a PDE4 modulator and a second active agent by the same or different routes of administration, *e.g.*, oral and parenteral. In certain embodiments, when a PDE4 modulator is administered concurrently with a second active agent that potentially produces adverse side effects including, but not limited to, toxicity, the second active agent can advantageously be administered at a dose that falls below the threshold that the adverse side effect is elicited.

4.4.2 Use With Other Management Conventional Techniques

This invention encompasses a method of treating, preventing, and/or managing airway inflammation and other airway or pulmonary diseases and disorders, which comprises administering a PDE4 modulator, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, in conjunction with (*e.g.* before, during, or after) other conventional techniques. Examples of other conventional techniques include, but are not limited to, oxygen-administration and smoking cessation.

The combined use of the PDE4 modulators and other conventional therapies may provide a unique treatment regimen that is unexpectedly effective in certain patients.

"Without being limited by theory, it is believed that PDE4 modulators may provide additive or synergistic effects when given concurrently with other conventional therapies.

4.5 **PHARMACEUTICAL COMPOSITIONS AND SINGLE UNIT DOSAGE FORMS**

5 Pharmaceutical compositions can be used in the preparation of individual, single unit dosage forms. Pharmaceutical compositions and dosage forms of the invention comprise PDE4 modulators, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof. Pharmaceutical compositions and dosage forms of the invention can further comprise one or more excipients.

10 Pharmaceutical compositions and dosage forms of the invention can also comprise one or more additional active ingredients. Consequently, pharmaceutical compositions and dosage forms of the invention comprise the active agents disclosed herein (*e.g.*, PDE4 modulators, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, and a second active agent). Examples of optional additional active agents are disclosed
15 herein (*see, e.g.*, section 4.3).

 Single unit dosage forms of the invention are suitable for oral, mucosal (*e.g.*, nasal, sublingual, vaginal, buccal, or rectal), or parenteral (*e.g.*, subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), transdermal or transcutaneous administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets;
20 capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; powders; aerosols (*e.g.*, nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration
25 to a patient; and sterile solids (*e.g.*, crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

 The composition, shape, and type of dosage forms of the invention will typically vary depending on their use. For example, a dosage form used in the acute treatment of a
30 disease may contain larger amounts of one or more of the active agents it comprises than a dosage form used in the chronic treatment of the same disease. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active agents it comprises than an oral dosage form used to treat the same disease. These and other ways in which specific dosage forms encompassed by this invention will vary from one another will be

readily apparent to those skilled in the art. See, e.g., *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).

Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients may be accelerated by some excipients such as lactose, or when exposed to water. Active ingredients that comprise primary or secondary amines are particularly susceptible to such accelerated decomposition. Consequently, this invention encompasses pharmaceutical compositions and dosage forms that contain little, if any, lactose other mono- or di-saccharides. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient.

Lactose-free compositions of the invention can comprise excipients that are well known in the art and are listed, for example, in the *U.S. Pharmacopeia* (USP) 25-NF20 (2002). In general, lactose-free compositions comprise active ingredients, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Preferred lactose-free dosage forms comprise active ingredients, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

This invention further encompasses anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (e.g., 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. See, e.g., Jens T. Carstensen, *Drug Stability: Principles & Practice*, 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine are preferably anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e.g.*, vials), blister packs, and strip packs.

The invention further encompasses pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. However, typical dosage forms of the invention comprise a PDE4 modulator, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, in an amount of from about 1 to about 10,000 mg. Typical dosage forms comprise a PDE4 modulator, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, in an amount of about 1, 2, 5, 10, 25, 50, 100, 200, 400, 800, 1,200, 2,500, 5,000 or 10,000 mg. In a particular embodiment, a preferred dosage form comprises 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide in an amount of about 400, 800 or 1,200 mg. Typical dosage forms comprise the second active agent in an amount of from about 1 to about 3,500 mg, from about 5 to about 2,500 mg, from about 10 to about 500 mg, or from about 25 to about 250 mg. Of course, the specific amount of the second active agent will depend on the specific agent used, the type of disease or disorder being treated or managed, and the amount(s) of PDE4 modulators and any optional additional active agents concurrently administered to the patient.

4.5.1 Oral Dosage Forms

Pharmaceutical compositions of the invention that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (*e.g.*, chewable tablets), caplets, capsules, and liquids (*e.g.*, flavored syrups). Such dosage forms contain predetermined amounts of active agents, and may be prepared by methods of pharmacy well known to those skilled in the art. *See generally, Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).

Typical oral dosage forms of the invention are prepared by combining the active ingredients in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (*e.g.*, powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. In some embodiments, the dosage form can be a rapid dissolving oral tablet or film, which dissolves quickly after getting in contact with saliva. Such dosage forms are particularly useful for children and elderly, and methods of making such dosage forms are well-known in the art.

If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Examples of excipients that can be used in oral dosage forms of the invention include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not

limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl
5 cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (*e.g.*, Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook,
10 PA), and mixtures thereof. An specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103TM and Starch 1500 LM.

Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules
15 or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Disintegrants are used in the compositions of the invention to provide tablets that
20 disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms of the invention. The
25 amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, preferably from about 1 to about 5 weight percent of disintegrant.

Disintegrants that can be used in pharmaceutical compositions and dosage forms of
30 the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

Lubricants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

A preferred solid oral dosage form of the invention comprises PDE4 modulators, anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

4.5.2 Delayed Release Dosage Forms

Active agents of the invention can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum

amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side
5 (e.g., adverse) effects.

Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level
10 of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

15 **4.5.3 Parenteral Dosage Forms**

Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being
20 sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms of the
25 invention are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as,
30 but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms of the invention. For example, cyclodextrin and its derivatives can be used to increase the solubility of PDE4

modulators and its derivatives. *See, e.g.*, U.S. Patent No. 5,134,127, which is incorporated herein by reference.

4.5.4 Topical and Mucosal Dosage Forms

Topical and mucosal dosage forms of the invention include, but are not limited to, sprays, aerosols, solutions, emulsions, suspensions, or other forms known to one of skill in the art. *See, e.g., Remington's Pharmaceutical Sciences*, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990); and *Introduction to Pharmaceutical Dosage Forms*, 4th ed., Lea & Febiger, Philadelphia (1985). Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes or as oral gels.

Suitable excipients (*e.g.*, carriers and diluents) and other materials that can be used to provide topical and mucosal dosage forms encompassed by this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to form solutions, emulsions or gels, which are non-toxic and pharmaceutically acceptable. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well known in the art. *See, e.g., Remington's Pharmaceutical Sciences*, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990).

The pH of a pharmaceutical composition or dosage form may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

4.5.5 Kits

Typically, active ingredients of the invention are preferably not administered to a patient at the same time or by the same route of administration. This invention therefore encompasses kits which, when used by the medical practitioner, can simplify the administration of appropriate amounts of active ingredients to a patient.

A typical kit of the invention comprises a dosage form of PDE4 modulators, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof. Kits encompassed by this invention can further comprise additional active agents or a combination thereof. Examples of the additional active agents include, but are not limited to, antidepressants, anticonvulsants, antihypertensives, anxiolytics, calcium channel blockers, muscle relaxants, non-narcotic analgesics, opioid analgesics, anti-inflammatories, cox-2 inhibitors, immunomodulatory agents, immunosuppressive agents, corticosteroids, hyperbaric oxygen, or other therapeutics discussed herein (*see, e.g.,* section 4.3).

Kits of the invention can further comprise devices that are used to administer the active ingredients. Examples of such devices include, but are not limited to, syringes, drip bags, patches, and inhalers.

Kits of the invention can further comprise pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

5. EXAMPLES

The following examples illustrate certain aspects of the invention, but do not limit its scope.

5.1 PHARMACOLOGY STUDIES

Airway inflammation is initiated by inflammatory reactions and sustained by the availability of inflammatory cytokines such as TNF- α . TNF- α may play a pathological role in airway inflammation. One of the biological effects typically exerted by PDE4 modulators is the reduction of synthesis of TNF- α .

Preferred compounds of the invention are potent PDE4 inhibitors. PDE4 is one of the major phosphodiesterase isoenzymes found in human myeloid and lymphoid lineage

cells. The enzyme plays a crucial part in regulating cellular activity by degrading the ubiquitous second messenger cAMP and maintaining it at low intracellular levels.

Inhibition of PDE4 activity results in increased cAMP levels leading to the modulation of LPS induced cytokines, including inhibition of TNF- α production in monocytes as well as
5 in lymphocytes, inhibition of IL-2, IFN- γ , IL-4, IL-5, IL-13 in T cells, B cell IgE production, mast cell histamine release or mac-1 expression, neutrophil chemotaxis and adhesion to endothelial cells, endothelial cell nitric oxide production, and smooth muscle contraction.

In a specific embodiment, the pharmacological properties of (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisoindoline-1,3-dione or
10 cyclopropyl-N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisoindolin-4-yl}carboxamide are characterized in *in vitro* studies. Studies examine the effects of the compounds on the production of various cytokines. Inhibition of TNF- α production following LPS-stimulation of human PBMC and human whole blood by the
15 compound is investigated *in vitro*. The IC₅₀'s of the compound for inhibiting production of TNF- α are measured. The pharmacological effects of (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisoindoline-1,3-dione or
cyclopropyl-N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisoindolin-4-yl}carboxamide may derive from their action as an inhibitor of the
20 generation of inflammatory cytokines.

5.2 CLINICAL STUDIES IN PATIENTS

PDE4 modulators of the invention such as (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisoindoline-1,3-dione are administered in an amount of 400 to 1,200 mg per day to patients with airway inflammation for three to six months.

25 Embodiments of the invention described herein are only a sampling of the scope of the invention.

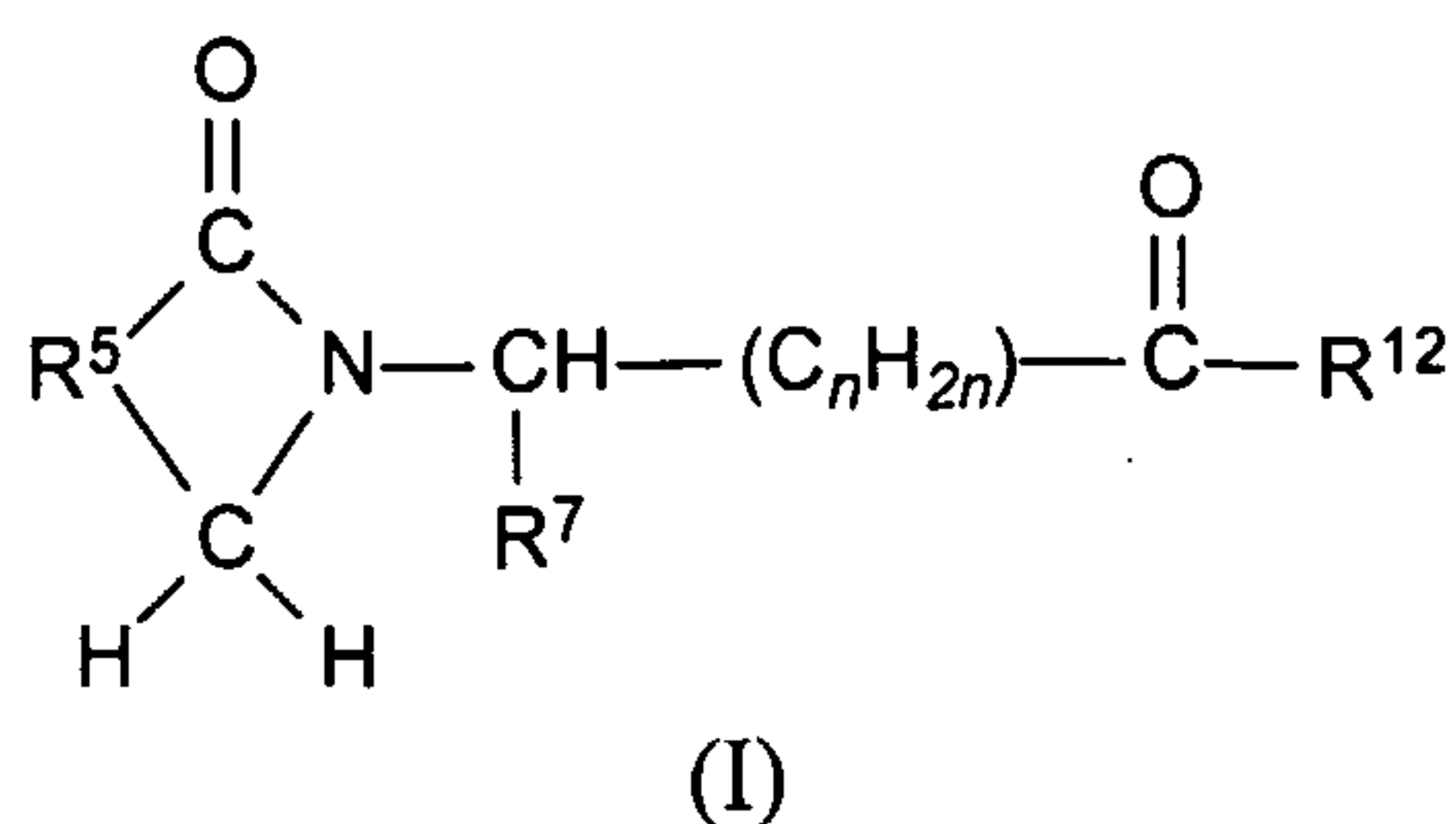
All of the patents, patent applications and publications referred to in this application are incorporated herein in their entireties. Moreover, citation or identification of any reference in this application is not an admission that such reference is available as prior art
30 to this invention. The full scope of the invention is better understood with reference to the attached claims.

CLAIMS

What is claimed is:

1. A method of treating, preventing, or managing airway inflammation, which comprises administering to a patient in need of such treatment, prevention, or management a therapeutically or prophylactically effective amount of a PDE4 modulator, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.
2. The method of claim 1, which further comprises administering to the patient a therapeutically or prophylactically effective amount of at least one second active agent.
3. The method of claim 2, wherein the second active agent is an antibiotic, anticholinergic, antihistaminic agent, anti-inflammatory agent, antioxidant, antitussive agent, β_2 -agonist, calcium channel blocker, corticosteroid, immunomodulatory agent, immunosuppressive agent, leukotriene inhibitor, monoclonal antibody, mucolytic, muscle relaxant, PDE4 inhibitor, potassium channel opener, prostaglandin or an analog, sensory neuropeptide release inhibitor, tachykinin antagonist, or theophylline or a derivative thereof.
4. The method of claim 1, wherein the stereoisomer of the PDE4 modulator is enantiomerically pure.
5. The method of claim 1, wherein the PDE4 modulator is (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisoindoline-1,3-dione.
6. The method of claim 1, wherein the PDE4 modulator is cyclopropyl-N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisoindolin-4-yl}carboxamide.
7. The method of claim 1, wherein the PDE4 modulator is cyclopropanecarboxylic acid {2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1 *H*-isoindol-4-yl}-amide.
8. The method of claim 7, wherein the PDE4 modulator is enantiomerically pure.

9. The method of claim 1, wherein the PDE4 modulator is of formula (I):

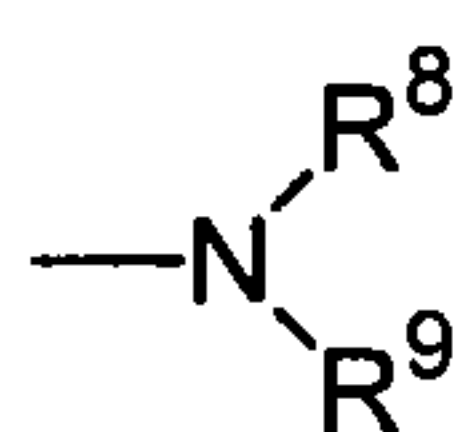


wherein n has a value of 1, 2, or 3;

R^5 is o-phenylene, unsubstituted or substituted with 1 to 4 substituents each selected independently from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkylamino, dialkylamino, acylamino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, and halo;

R^7 is (i) phenyl or phenyl substituted with one or more substituents each selected independently of the other from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, and halo, (ii) benzyl unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, and halo, (iii) naphthyl, and (iv) benzyloxy;

R^{12} is -OH, alkoxy of 1 to 12 carbon atoms, or

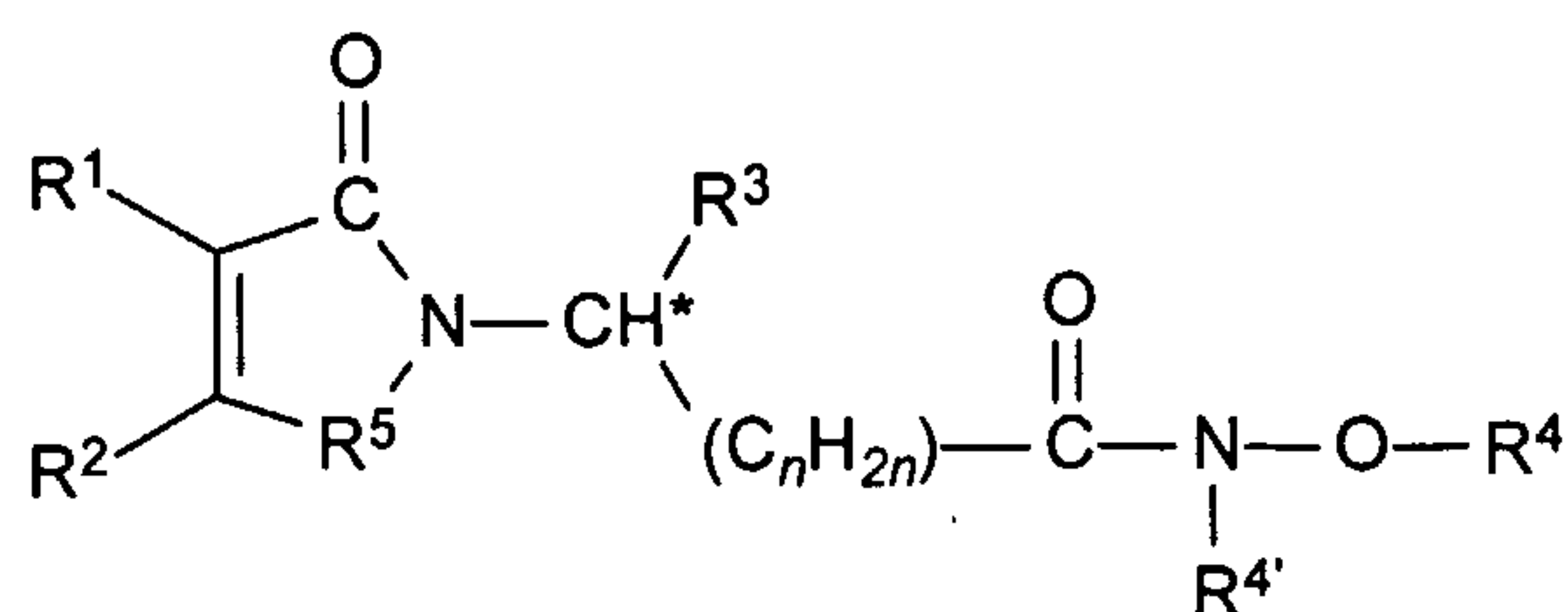


R^8 is hydrogen or alkyl of 1 to 10 carbon atoms; and

R^9 is hydrogen, alkyl of 1 to 10 carbon atoms, $-\text{COR}^{10}$, or $-\text{SO}_2\text{R}^{10}$, wherein R^{10} is hydrogen, alkyl of 1 to 10 carbon atoms, or phenyl.

10. The method of claim 9, wherein the PDE4 modulator is enantiomerically pure.

11. The method of claim 1, wherein the PDE4 modulator is of formula (II):



(II)

wherein each of R^1 and R^2 , when taken independently of each other, is hydrogen, lower alkyl, or R^1 and R^2 , when taken together with the depicted carbon atoms to which each is bound, is *o*-phenylene, *o*-naphthylene, or cyclohexene-1,2-diyl, unsubstituted or substituted with 1 to 4 substituents each selected independently from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkylamino, dialkylamino, acylamino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, and halo;

R^3 is phenyl substituted with from one to four substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms, benzyloxy, cycloalkoxy of 3 to 6 carbon atoms, C_4 - C_6 -cycloalkylidenemethyl, C_3 - C_{10} -alkylidenemethyl, indanyloxy, and halo;

R^4 is hydrogen, alkyl of 1 to 6 carbon atoms, phenyl, or benzyl;

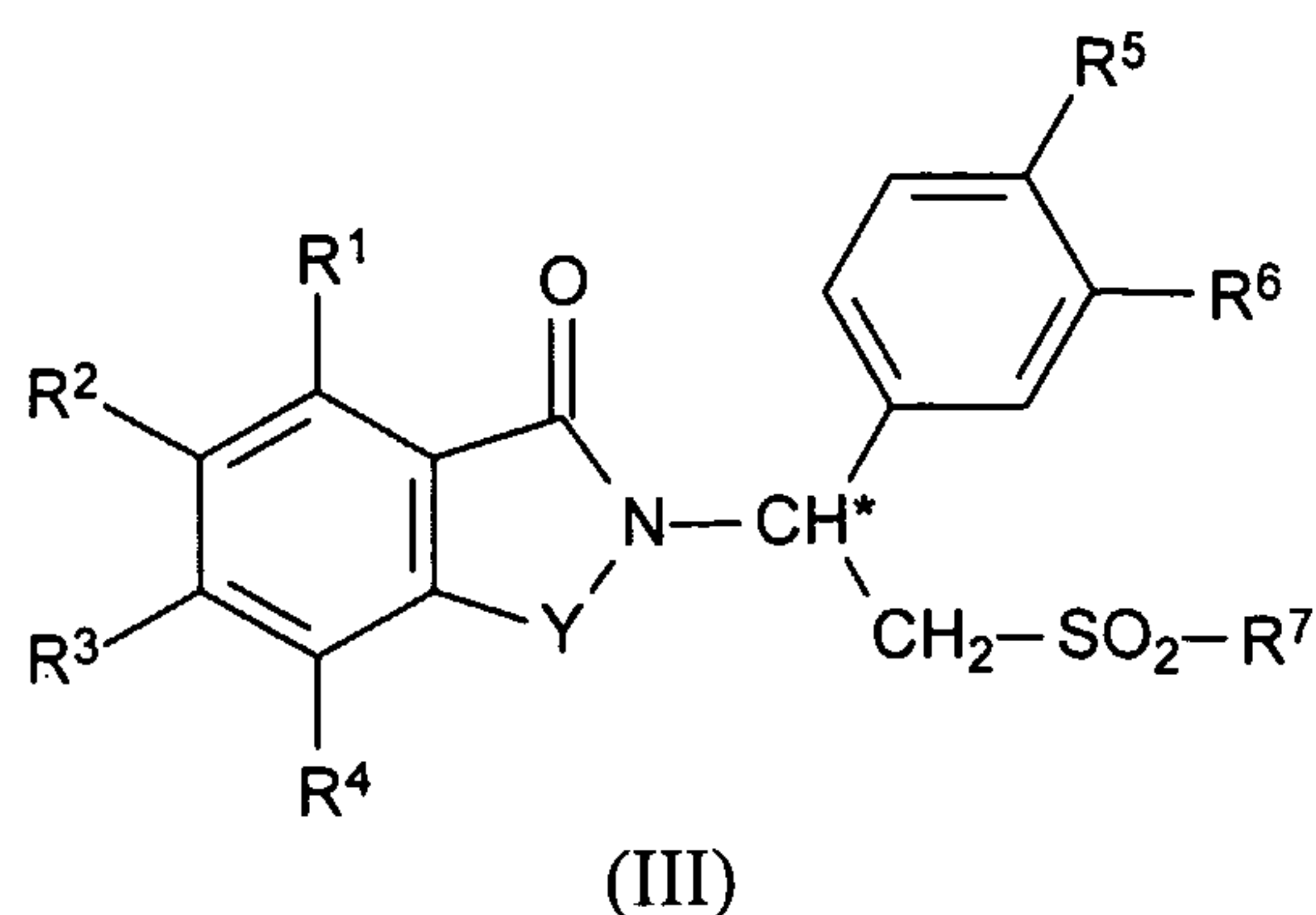
$R^{4'}$ is hydrogen or alkyl of 1 to 6 carbon atoms;

R^5 is $-CH_2-$, $-CH_2-CO-$, $-SO_2-$, $-S-$, or $-NHCO-$; and

n has a value of 0, 1, or 2.

12. The method of claim 11, wherein the PDE4 modulator is enantiomerically pure.

13. The method of claim 1, wherein the PDE4 modulator is of formula (III):



wherein the carbon atom designated * constitutes a center of chirality;

Y is C=O, CH₂, SO₂, or CH₂C=O;

each of R¹, R², R³, and R⁴, independently of the others, is hydrogen, halo, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, nitro, cyano, hydroxy, or -NR⁸R⁹; or any two of R¹, R², R³, and R⁴ on adjacent carbon atoms, together with the depicted phenylene ring are naphthylidene;

each of R⁵ and R⁶, independently of the other, is hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, cyano, or cycloalkoxy of up to 18 carbon atoms;

R⁷ is hydroxy, alkyl of 1 to 8 carbon atoms, phenyl, benzyl, or NR^{8'}R^{9'};

each of R⁸ and R⁹ taken independently of the other is hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, or benzyl, or one of R⁸ and R⁹ is hydrogen and the other is -COR¹⁰ or -SO₂R¹⁰, or R⁸ and R⁹ taken together are tetramethylene, pentamethylene, hexamethylene, or -CH₂CH₂X¹CH₂CH₂- in which X¹ is -O-, -S- or -NH-; and

each of R^{8'} and R^{9'} taken independently of the other is hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, or benzyl, or one of R^{8'} and R^{9'} is hydrogen and the other is -COR^{10'} or -SO₂R^{10'}, or R^{8'} and R^{9'} taken together are tetramethylene, pentamethylene, hexamethylene, or -CH₂CH₂X²CH₂CH₂- in which X² is -O-, -S-, or -NH-.

14. The method of claim 13, wherein the PDE4 modulator is enantiomerically pure.

15. A method of treating, preventing, or managing an airway or pulmonary disease or disorder, which comprises administering to a patient in need of such treatment, prevention, or management a therapeutically or prophylactically effective amount of a PDE4 modulator, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof,

wherein the airway or pulmonary disease or disorder is giant bullae, acute bronchitis, chronic bronchitis, emphysema, reversible obstructive airway disease, nocturnal asthma, exercise induced bronchospasm, or interstitial pulmonary fibrosis.

16. A method of treating, preventing, or managing an airway or pulmonary disease or disorder, which comprises administering to a patient in need of such treatment, prevention, or management a therapeutically or prophylactically effective amount of a PDE4 modulator, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a second active agent, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:

wherein the airway or pulmonary disease or disorder is respiratory failure, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease, giant bullae, acute bronchitis, chronic bronchitis, emphysema, reversible obstructive airway disease, nocturnal asthma, exercise induced bronchospasm, or interstitial pulmonary fibrosis; and wherein the second active agent is an antibiotic, anticholinergic, antihistaminic agent, anti-inflammatory agent, antioxidant, antitussive agent, β_2 -agonist, calcium channel blocker, corticosteroid, immunomodulatory agent, immunosuppressive agent, leukotriene inhibitor, monoclonal antibody, mucolytic, muscle relaxant, PDE4 inhibitor, potassium channel opener, prostaglandin or an analog, sensory neuropeptide release inhibitor, tachykinin antagonist, or theophylline or a derivative thereof.

17. The method of claim 16, wherein the stereoisomer of PDE4 modulator is enantiomerically pure.

18. A pharmaceutical composition comprising a PDE4 modulator, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and one or more second active agent, wherein the second active agent is an antibiotic, anticholinergic, antihistaminic agent, anti-inflammatory agent, antioxidant, antitussive agent, β_2 -agonist, calcium channel blocker, corticosteroid, immunomodulatory agent, immunosuppressive agent, leukotriene inhibitor, monoclonal antibody, mucolytic, muscle relaxant, PDE4 inhibitor, potassium channel opener, prostaglandin or an analog, sensory neuropeptide release inhibitor, tachykinin antagonist, or theophylline or a derivative thereof.

19. The composition of claim 18, wherein the stereoisomer of PDE4 modulator is enantiomerically pure.