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(54) Title: TRAITEMENT OF CARDIOVASCULAR PATHOLOGY

(57) Abstract: The present invention relates to a method of reducing cardiovascular pathology in a mammal using an inhibitor of phosphodiesterase 4 (PDE4).

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TREATMENT OF CARDIOVASCULAR PATHALOGY

Field of Invention

The present invention relates to a method and pharmaceutical composition for reducing cardiovascular pathology in mammals.

BACKGROUND OF THE INVENTION

Cardiac hypertrophy is an increase in myocardial (heart) muscle mass where wall thickness increases in size because the heart has to work harder to maintain normal physiologic function. Cardiac hypertrophy may be caused by both hemodynamic stresses and non-hemodynamic factors. Included in the hemodynamic stresses that contribute to increased wall thickness (e.g., cardiac hypertrophy) are pressure overload from hypertension/arteriosclerosis or volume overload from sodium and water retention. Non-hemodynamic factors that contribute to developing pathology may include activation of the renin-angiotensin-aldosterone system (which also increases volume and pressure overload) and the level of fibrosis or stiffness in the myocardium. These events may lead to increased wall thickness and decreased ventricular chamber diameter.

This increase in wall thickness places patients at risk for developing cardiovascular pathology which may include coronary heart disease, heart failure, congestive heart failure (herein "CHF"), myocardial infarction, as well as other cardiovascular complications which are associated with a significant increase in mortality. Reducing or reversing cardiac hypertrophy to levels that are approaching that of healthy patients has been associated with reduced arrhythmias, improved cardiac function, and reduced risk of heart failure including congestive heart failure and an improvement in coronary blood flow reserves enabling patients to live healthier, longer lives.

Mice have been commonly used as experimental models of cardiac hypertrophy, myocardial infarction, and heart failure to mimic pathology observed in humans. In studies using mice, the aorta is constricted approximately 30%, which causes an increase in blood pressure (e.g., pressure overload) and sympathatetic activation of the renin-angiotensin-aldosterone system (e.g., volume overload). These stresses are similar to those that are believed to play a major role in human cardiac hypertrophy. Based on the similar mechanism(s) of action that regulate the pathology, the murine model of cardiac

hypertrophy represents an adequate model to assess the pharmacologic effects of novel agents on left ventricular mass.

Phosphodiesterases (PDEs) comprise a large, divergent family of enzymes that catalyze the catabolism of cAMP and cGMP to AMP and GMP, respectively. Eleven members of this family have been identified to date based on substrate specificity, kinetic properties, sensitivity to specific inhibitors, tissue distribution, and primary sequences (Manganiello, VC et al., *Arch Biochem Biophys*, 322 (1): 1-13, (1995); Fawcett, L et al., *Proc Natl Acad Sci USA*, 97(7): 3702-3707 (2000)). Recognition of these differences has greatly stimulated interest in PDEs as drug targets. In particular, the cAMP specific PDE, termed PDE4, that is found in nearly all immune and inflammatory cells has been an attractive target for novel anti-asthmatic and anti-inflammatory therapies.

The present inventors have now discovered that PDE4 inhibitors have a property of reducing cardiac hypertrophy in mammals suffering from cardiac hypertrophy.

SUMMARY OF THE INVENTION

In a first aspect of the present invention, a method is provided for reducing cardiovascular pathology in a mammal, comprising administering an effective amount of a phosphodiesterase 4 (PDE4) inhibitor to reduce said cardiovascular pathology.

In a another aspect of the present invention, there is provided a pharmaceutical formulation comprising a PDE4 inhibitor in an amount effective to reduce cardiovascular pathology in a mammal.

DETAILED DESCRIPTION OF THE INVENTION

In view of an unmet medical need of providing new treatments for disorders associated with cardiovascular pathology, a study was commenced that investigated inhibitors having a property of reducing cardiac hypertrophy. The present invention was based, in part, on these studies.

The instant invention provides a method for reducing cardiovascular pathology in a mammal suffering from cardiovascular pathology, comprising administering an effective amount of a phosphodiesterase 4 (PDE4) inhibitor to reduce said cardiovascular pathology.

As used herein, "reduce" or "reducing" refers to a decrease in the severity of or cessation of a cardiovascular pathology. The severity of cardiovascular pathology may be decreased by reducing the left ventricular muscle mass of an animal to any extent, including but not limited to reducing left ventricular muscle mass equivalent to that observed at

baseline or to left ventricular muscle mass considered to be within normal range for a healthy animal of the same species and having similar physical characteristics.

As used herein, "baseline left ventricular mass" refers to left ventricular muscle mass of an animal prior to receiving any therapeutic method or compound of the invention.

As used herein, "normal left ventricular mass" refers to: (1) the amount of left ventricular mass in a healthy animal of the same species and having similar physical characteristics including but not limited to gender, age, weight, height, blood pressure, and underlying disease, and/or (2) the amount of left ventricular mass in a animal of the same species and having similar physical characteristics including but not limited to gender, age, weight, height, blood pressure, and underlying disease prior to treatment using a method or compound of the invention.

A "healthy animal" as used herein refers to an animal that does not show thickening of the left ventricular wall above normal. Healthy animals typically do not show signs or symptoms of cardiovascular pathology, and are typically free from any other underlying disease or gross morbidity.

As used herein, "cardiovascular pathology" refers to a cardiovascular complication or risk thereof and may include but is not limited to cardiac hypertrophy, coronary heart disease, arrhythmia, restricted coronary blood flow, arteriosclerosis, heart failure, congestive heart failure (CHF), myocardial infarction, as well as others.

As used herein, "cardiac hypertrophy" refers to increased left ventricular mass above normal. Cardiac hypertrophy may manifest as heart wall growth that causes a narrowing of the ventricular chambers.

As used herein, "increased left ventricular muscle mass" refers to growth or thickening of the left ventricular wall upon the onset of one or more cardiovascular pathology.

As used herein "hemodynamic stress" refers to any factors contributing to pressure, viscosity and/or volume overload of the cardiac system. Hemodynamic stress that may contribute to pressure overload may include but is not limited to hypertension/arteriosclerosis. Hemodynamic stress that may contribute to volume overload may include but is not limited to sodium and water retention. Hemodynamic stress contributes to increased left ventricular wall thickness (e.g., cardiac hypertrophy).

As used herein "non-hemodynamic factors" refers to any factors contributing to pressure and/or volume overload of the cardiac system. Non-hemodynamic factors may

include but are not limited to activation of the renin-angiotensin-aldosterone system, and increased fibrosis or stiffness in the myocardium.

As used herein, "inhibitor(s)" or "inhibiting," as it relates to PDE4, means a compound that causes or is related to a change in an amount, and/or quality, and/or effect of a particular response and/or activity of PDE4.

As used herein, the term "alkyl" refers to a straight or branched chain hydrocarbon having from one to twelve carbon atoms, optionally substituted with substituents selected from the group that includes, but is not limited to, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by a substituent selected from the group including alkyl, nitro, cyano, halogen and lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkyl" as used herein may include, but are not limited to, methyl, ethyl, n-butyl, n-pentyl, isobutyl, isopropyl and the like.

As used herein, the term "alkoxy" refers to the group R_aO-, where R_a is alkyl.

As used herein, the term "aryl" refers to a 6 to 10 carbon aromatic moiety. Examples of "aryl" as used herein may include, but are not limited to, phenyl, pyridyl, pyrimidyl, pyridazyl, pyrazyl, and triazyl.

As used herein, the term "aryloxy" refers to the group R_aO-, where R_a is aryl.

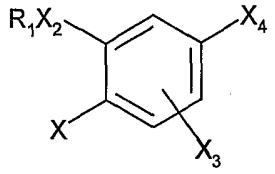
As used herein the term "halogen" refers to the group fluorine, chlorine, bromine, and iodine.

As used herein the term "agent" is understood to mean a substance that produces a desired effect in a intracellular component, cell, tissue, system, animal, mammal, human, or other subject.

As recited above, the method of the present invention includes administering a specific PDE4 inhibitor agent. Typical PDE4 inhibitor agents may include, but are not limited to, rolipram and rolipram derivatives, or rolipram mimetic compounds; and fused ring compounds such as benzopyrazoles, benzimidazoles, benzofurans, diazepinio-indoles, quinolines, quinolones, nitraquazone derivatives, purines and xanthines, and losartan analogues. Such PDE4 inhibitors are described, for instance, in "PDE4 inhibitors 1998", Norman, Peter; Exp. Opin. Ther. Patents (1998) 8(7); and "Chronic Pulmonary Inflammation and Other Therapeutic Applications of PDEIV Inhibitors", Stafford, Jeffrey A. and Feldman, Paul L., Ch. 8 Annual Reports In Medicinal Chemistry Ch. 8, 71-80 (1996)

which references are herein incorporated by reference to the extent of their disclosure of PDE4 inhibitor compounds.

One class of PDE4 inhibitor compounds that may be usefully employed in the present invention includes compounds of the Formula I :



I

wherein: R_1 is $-(CR_4R_5)_nC(O)O(CR_4R_5)_mR_6$, $-(CR_4R_5)_nC(O)NR_4(CR_4R_5)_mR_6$, $-(CR_4R_5)_nO(CR_4R_5)_mR_6$, or $--(CR_4R_5)_rR_6$ wherein the alkyl moieties may be optionally substituted with one or more halogens;

m is 0 to 2;

n is 0 to 4;

r is 0 to 6;

R_4 and R_5 are independently selected from hydrogen or a C_{1-2} alkyl;

R_6 is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxy C_{1-3} alkyl, halo substituted aryloxy C_{1-3} alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl, C_{3-6} cycloalkyl, or a C_{4-6} cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be optionally substituted by 1 to 3 methyl groups or one ethyl group;

provided that:

when R_6 is hydroxyl, then m is 2; or

when R_6 is hydroxyl, then r is 2 to 6; or

when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or

when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then r is 1 to 6;

when n is 1 and m is 0, then R_6 is other than H in $--(CR_4R_5)_nO(CR_4R_5)_mR_6$;

X is YR_2, halogen, nitro, NR_4R_5, or formyl amine;

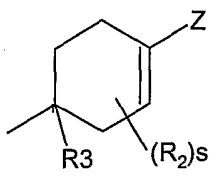
Y is O or $S(O)_{m'}$;

m' is 0, 1, or 2;

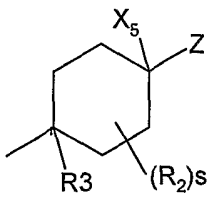
X_2 is O or NR_8;

X_3 is hydrogen or X;

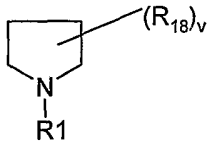
X_4 is



,



,



,

$C(Z')NHR_{15}$, $CR_4(NOC(O)R_{16})$, or $CR_2'R_3'CR_4'R_5'R_6'$;

X_5 is H, R_9, OR_8, CN, $C(O)R_8$, $C(O)OR_8$, $C(O)NR_8$ R_8, or NR_8 R_8;

R_2 is independently selected from the group consisting of $--CH_3$ and $--CH_2$ CH_3 optionally substituted by 1 or more halogens;

R_2' is a hydrogen, halogen, or OR_{17};

s is 0 to 4;

R_3' and R_4' are each independently $-(CH2)_tX_6$;

t is 0, 1, 2, or 3;

v is 0, 1, 2, or 3;

X_6 is a mono- or bicyclic aryl group optionally containing one or more heteroatoms selected from sulfur, oxygen, or nitrogen;

R_5' and R_6' are each independently hydrogen or an optionally substituted alkyl;

R_3 is hydrogen, halogen, C_{1-4} alkyl, $CH_2NHC(O)C(O)NH_2$, halo-substituted C_{1-4} alkyl, $-CH=CR_8'R_8'$, cyclopropyl optionally substituted by R_8', CN, OR_8, CH_2OR_8, NR_8R_{10}, $CH_2NR_8R_{10}$, $C(Z')H$, $C(O)OR_8$, $C(O)OR_8$, $C(O)NR_8R_{10}$, or $C{\equiv}CR_8$;

Z' is O, S, NR_8, NOR_8, NCN, $C(-CN)_2$, CR_8CN, CR_8NO_2, $CR_8C(O)OR_8$, $CR_8C(O)ONR_8R_8$, $C(-CN)NO_2$, $C(-CN)C(O)OR_9$, $C(-CN)C(O)NR_8R_8$;

Z is $C(Y')R_{14}$, $C(O)OR_{14}$, $C(Y')NR_{10}$ R_{14}, $C(NR_{10})NR_{10}$ R_{14}, CN, $C(NOR_8)R_{14}$, $C(O)NR_8$ NR_8 $C(O)R_8$, $C(O)NR_8$ NR_{10} R_{14}, $C(NOR_{14})R_8$, $C(NR_8)NR_{10}$ R_{14}, $C(NR_{14})NR_8$ R_8 $C(NCN)NR_{10}$ R_{14}, $C(NCN)SR_9$, (2-, 4- or 5-imidazolyl), (3-, 4- or 5-pyrazolyl), (4- or 5-triazolyl[1,2,3]), (3- or 5-triazolyl[1,2,4]), (5-tetrazolyl), (2-, 4- or 5-oxazolyl), (3-, 4- or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,2,4]), (2oxadiazolyl[1,3,4]), (2-thiadiazolyl[1,3,4]), (2-,

4-, or 5-thiazolyl), (2-, 4-, or 5-oxazolidinyl), (2-, 4-, or 5-thiazolidinyl), or (2-, 4-, or 5-imidazolidinyl); wherein all of the heterocylic ring systems may be optionally substituted one or more times by R_{14} ;

the dotted line in the first formula of X_4 represents a single or double bond;

Y' is O or S;

R_7 is --$(CR_4 R_5)_q R_{12}$ or C_{1-6} alkyl wherein the R_{12} or C_{1-6} alkyl group is optionally substituted one or more times by C_{1-2} alkyl optionally substituted by one to three fluorines, --F, --Br, --Cl, --NO_2, --$NR_{10} R_{11}$, --$C(O)R_8$, --$C(O)OR_8$, --OR_8, --CN, --$C(O)NR_{10} R_{11}$, --$OC(O)NR_{10} R_{11}$, --$OC(O)R_8$, --$NR_{10} C(O)NR_{10} R_{11}$, --$NR_{10} C(O)R_{11}$, --$NR_{10} C (O)OR_9$, --$NR_{10} C(O)R_{13}$, --$C(NR_{10})NR_{10} R_{11}$, --$C(NCN)NR_{10} R_{11}$, --$C(NCN)SR_9$, --$NR_{10} C (NCN)SR_9$, --$NR_{10} C(NCN)NR_{10} R_{11}$, --$NR_{10} S(O)_2 R_9$, --$S(O)_m 'R_9$, --$NR_{10} C(O)C(O)NR_{10} R_{11}$, --$NR_{10} C(O)C(O)R_{10}$, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl, or tetrazolyl;

q is 0, 1, or 2;

R_{12} is C_3 -C_7 -cycloalkyl, (2-, 3- or 4-pyridyl), pyrimidyl, pyrazolyl, (1- or 2-imidazolyl), thiazolyl, triazolyl, pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, (2- or 3-thienyl), (4- or 5-thiazolyl), quinolinyl, naphthyl, or phenyl;

R_8 is independently selected from hydrogen or R_9 ;

R_8 ' is R_8 or fluorine;

R_9 is C_{1-4} alkyl optionally substituted by one to three fluorines;

R_{10} is OR_8 or R_{11} ;

R_{11} is hydrogen, or C_{1-4} alkyl optionally substituted by one to three fluorines; or when R_{10} and R_{11} are as $NR_{10} R_{11}$ they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O/N/or S;

R_{13} is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, or thiadiazolyl, and each of these heterocyclic rings is connected through a carbon atom and each may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

R_{14} is hydrogen or R_7 ; or when R_{10} and R_{14} are as $NR_{10} R_{14}$ they may together with the nitrogen form a 5 to 7 membered ring optionally containing one or more additional heteroatoms selected from O, N, or S;

R_{15} is optionally substituted pyridyl, pyrazinyl, pyrimidinyl, isoxazolyl; or an N-oxide thereof; or a optionally substituted phenyl, wherein s optional substituents are one or more selected from the group consisting of halogen, haloalkyl, aryl, arylalkyl, alkoxy, aryloxy, alkylthio, arylthio, alkoxycarbonyl, alkanoyl, aroyl, alkylsulphonyl, arylsulphonyl,

alkylsulphinyl, arylsulphinyl, hydroxy, hydroxyalkyl, formyl, alkanoylamino, aroylamino, cyano, and nitro;

R_{16} is amino, C_1-C_6 alkylamino, arylamino, C_1-C_6 alkoxy, or aryloxy;

R_{17} is hydrogen, or optionally substituted alkyl, alkenyl, alkoxyalkyl, or alkanoyl, or a formyl, carboxamido, or thiocarboxamido;

R_{18} is (=O), hydrogen, $-C(O)R_2$, $-CH_3$, $-CH_2CH_3$, -C(O)OH;

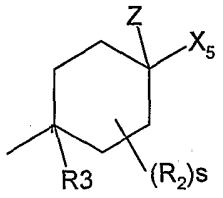
provided that:

when R_{12} is N-pyrazolyl, N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl, N-piperidinyl, or N-morpholinyl, then q is not 1; or

the pharmaceutically acceptable salts thereof.

In one embodiment, X_2 is O; R_1 is $(CR_4R_5)_rR_6$, where r=0 and R_6 is C_3-C_6 cycloalkyl, cyclopentyl; X=YR_2; R_2 is $-CH_3$; Y=O;

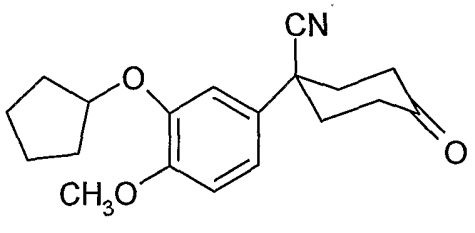
X_4 is



;

R3 is –CN; X_5 is hydrogen; s=0; Z is $C(O)OR_{14}$; and R14 is hydrogen.

Of particular interest within the PDE4 inhibitors of Formula I are *cis*-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid and 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-one (SB 200473) and salt thereof. The first compound has the trademark of ARIFLO, represented by Figure 9(a) of WO 01/93909. The second compound is described in Example 1 of US 5,643,946. Other compounds within the scope of Formula I are also described in WO 01/93909 and/or US5,643,946.



SB 200473

Another PDE4 inhibitor that may be usefully employed in the present invention includes filaminast, 1-[3-cyclopentyloxy)-4-methoxyphenyl] ethanone (E)-O-{aminocarbonyl}oxime, represented by Figure 10(a) of WO 01/93909, and related compounds. Filaminast and related compounds are described, as well as the synthesis thereof, in European Patent Application EP 470805A1.

Still another group of Formula I PDE4 inhibitor compounds that may be usefully employed in the process of the present invention includes (+/-)-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine (CDP-840), represented by Figure 10(b) of WO 01/93909, and related compounds. These compounds are described, as well as the synthesis thereof, in International Patent Applications WO 94/14742; 97/23460; 97/23461; 97/38976; 97/42172; and 98/12178.

Additional PDE4 inhibitors that may be utilized in the present invention include, but are not limited to:

(i) nitroquazone, depicted in Figure 11(a) of WO 01/93909, and nitraquazone derivatives, such compounds being described in WO 93/07146 including the synthesis thereof;

(ii) denbufylline, i.e., 7-acetonyl,1,3dibutylxanthine, made by SmithKline Beecham and depicted in Figure 11(b) of WO 01/93909;

(iii) rolipram, depicted in Figure 11(c) of WO 01/93909;

(iv) RS-25344, depicted in Figure 12(a) WO 01/93909 and related compounds, such compounds being described in WO 93/07146 and 93/19068 including the synthesis thereof;

(v) CP-77059, depicted in Figure 12(b) WO 01/93909 and related compounds, such compounds being described in WO 96/40636 and 97/05105 including the synthesis thereof;

(v) GI 193600X, available from Glaxo Wellcome, Inc., depicted in Figure 12(c) WO 01/93909; and

(vi) Roflumilast described in *The Journal of Pharmacology and Experimental Therapeutics*, Vol 297, No. 1, pp. 267-279 (2001)

In one embodiment, a PDE4 inhibitor agent is a compound of Formula I. In another embodiment, a PDE4 inhibitor is *cis*-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid or salt thereof; N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-methoxybenzamide; 1-[3-cyclopentyloxy)-4-methoxyphenyl] ethanone

(E)-O-{aminocarbonyl}oxime; (+/-)-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine; SB200473; or roflumilast.

In another embodiment, PDE4 inhibitors of the present invention are PDE4 specific inhibitors. By "PDE4 specific inhibitors" they are meant that activities of inhibitors against PDE IV enzyme is at least 400 times or more potent in terms of IC_{50} as compared to activities against other PDE isoenzymes, e.g. PDE I, II, III, or V. For example, the activities of flumilast, rolipram and cilomilast (ARIFLO) against PDE IV are more than 400 times potent against PDE I, II, III and V. (*J Pharmacol Exp Ther* 2001 Apr;297(1):267-79).

The present use of PDE4 inhibitors to reduce left ventricular wall mass are not limited to human use, but includes veterinary use as well. However, it is well understood that the effectiveness of a particular PDE4 inhibitor in a particular species is limited, such as, by its bioavailability in that species. Which PDE4 inhibitor is more effective in a particular species may be readily ascertained by conventional pharmacological methods.

Thus, one aspect of the present invention is a method of reducing cardiovascular pathology in a mammal, comprising administering an amount effective for reducing said cardiovascular pathology with a phosphodiesterase 4 (PDE4) inhibitor. In another aspect of the invention, the cardiovascular pathology is cardiac hypertrophy, heart failure, and/or CHF. In another aspect, the mammal is suffering from hypertension and/or arteriosclerosis. In another aspect, the PDE4 inhibitor is PDE4 specific inhibitor. A PDE4 specific inhibitor may be rolipram or roflumilast, among others. PDE4 specific inhibitors may be administered separately or in combination with one another or with other pharmaceutical agents.

In another embodiment, this invention provides a pharmaceutical formulation comprising a PDE4 inhibitor in an amount effective to reduce cardiovascular pathology in a mammal suffering from cardiovascular pathology. In another aspect of the invention, the cardiovascular pathology is cardiac hypertrophy, heart failure, and/or CHF. In another aspect, the mammal is suffering from hypertension and/or arteriosclerosis. In another aspect, a PDE4 inhibitor is PDE4 specific inhibitor. A PDE4 specific inhibitor may be rolipram or roflumilast among others. These PDE4 inhibitors may be administered separately or in combination with one another or with other pharmaceutical agents.

PDE4 inhibitors of the present invention may be administered by any appropriate route. Suitable routes may include, but are not limited to, oral, rectal, nasal, topical (including, but not limited to, buccal and sublingual), vaginal, and parenteral (including, but not limited to, subcutaneous, intramuscular, intraveneous, intradermal, intrathecal, and

epidural). It will be appreciated that a route of administration may vary with, for example, the condition of the recipient.

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; chewable gum; or oil-in-water liquid emulsions or water-in-oil liquid emulsions, among others.

For instance, for oral administration in the form of a tablet or capsule, an active drug component may be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders may be prepared by comminuting a compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent may also be present.

Capsules may be made, for example, by preparing a powder mixture as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol may be added to a powder mixture before a filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate may also be added to improve the availability of a medicament when a capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated into a mixture. Suitable binders may include, but are not limited to, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms may include, but are not limited to, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators may include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets may be formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture may be prepared by mixing a compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate, among others. A powder mixture may be granulated by wetting with, for example, a binder such as syrup, starch paste, acadia

mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, a powder mixture may be run through a tablet machine forming imperfectly formed slugs broken into granules. Granules may be lubricated to prevent sticking to tablet-forming dies by means of addition of stearic acid, a stearate salt, talc or mineral oil, among others. A lubricated mixture may then be compressed into tablets. Compounds of the present invention may also be combined, for example, with free flowing inert carrier and compressed into tablets directly without going through granulating or slugging steps. A clear or opaque protective coating consisting of, for example, a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax may be provided. Dyestuffs or other compounds may be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs may be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups may be prepared by dissolving a compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions may be formulated by dispersing a compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like may also be added.

Where appropriate, dosage unit formulations for oral administration may be microencapsulated. A formulation may also be prepared to prolong or sustain release as for example by coating or embedding particulate material in polymers, wax or the like. In addition, oral formulation may be in the form of a chewable gum.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, an active ingredient may be delivered from a patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas, among others.

Pharmaceutical formulations adapted for parenteral administration may include, but are not limited to, aqueous and non-aqueous sterile injection solutions that may contain anti-oxidants, buffers, bacteriostats and solutes that render a formulation isotonic with the blood of an intended recipient; and aqueous and non-aqueous sterile suspensions that may

include suspending agents and thickening agents. Formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only addition of a sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, formulations may include, but are not limited to, other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention that are prepared, for example, by reacting a free base with a suitable organic or inorganic acid or by reacting an acid with a suitable organic or inorganic base.

Typically, a therapeutically effective amount of a PDE4 inhibitor of the present invention will depend upon a number of factors including, for example, age and weight of a mammal, at least one precise condition requiring treatment, severity of a condition, nature of a formulation, and route of administration. Ultimately, a therapeutically effective amount will be at the discretion of an attendant physician or veterinarian.

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way.

Example 1

Preparation of PDE4 Inhibitor Suspension.

PDE4 inhibitors, rolipram (TOCRIS, USA) and roflumilast were suspended in 1% carboxymethylcellulose (CMC) solution (vehicle) with a sonicator and utilized in the following examples.

Example 2

Enalapril as the gold standard to validate murine model of cardiac hypertrophy

Male CD-1 mice (n=6 to 8 per group), 20-25 g in weight, were used for the experiment. Each mouse's aorta was exposed between the two renal arteries and was surgically constricted using a 30-gauge needle and 6.0 suture to induce heart growth. Seven days after surgery, baseline echocardiography was performed on each mouse to establish left ventricular mass ("LV mass").

Enalapril, the gold standard in treating cardiac hypertrophy, was orally administered to the mice at the dose of 10 mg/kg beginning on day 11 (4 days after baseline) and was continued once daily for 10 days. The control group was administered with the vehicle. Repeat echocardiography was conducted on mice 14 and 21 days post surgery.

A statistically significant decrease in LV mass was observed both 14 days and 21 days after surgery in mice receiving enalapril compared with vehicle. At baseline (7 days after surgery), mice in the vehicle group and the enalapril group had mean±SE LV masses of 98.2± 3.3 mg and 96.1±4.8 mg, respectfully. At 14 days after surgery (3 days after dosing began), the vehicle group had a mean±SE LV mass of 117.0±5.6 mg and the enalapril group had a mean±SE mass of 91.9±3.4 mg. At 21 days after surgery, the vehicle group had a mean±SE LV mass of 123.2±8.3 mg and the enalapril group have a mean±SE mass of 84.1±4.1 mg.

Example 3

Effect of PDE IV inhibitors on LV mass.

Male CD-1 mice (n=7 per group), 20-25 g in weight, were used for the experiment. The aorta was exposed between the renal arteries of the mice and was surgically constricted using a 30-gauge needle and 6.0 suture to induce heart growth as discussed in Example 2. Seven days after surgery, baseline echocardiography was performed on each mouse to establish LV mass.

Rolipram suspended in 1% CMC (vehicle) was orally administered to the mice at the doses of 10-100 mg/kg. The control group was administered with vehicle (1% CMC). Eleven days after surgery (four days after baseline echocardiography), mice were administered a single oral dose of PDE4 inhibitor or vehicle and dosing was continued once daily for ten days. Seven mice were used in each dose group. Repeat echocardiography was conducted on each mouse 14 and 21 days after surgery.

Fourteen days after surgery, a statistically significant reduction in LV mass was observed in mice treated with 100 mg/kg of rolipram compared with vehicle at the same timepoint as shown in Table 1. Twenty one days after surgery, a statistically significant reduction in LV mass was observed in mice that received 10 and 30 mg/kg compared with vehicle at the same timepoint also shown in Table 1. In addition, a statistically significant reduction in LV mass was observed in mice that received 100 mg/kg of rolipram compared

with vehicle in addition to significant reductions below baseline levels within its own treatment group also shown in Table 1.

Table 1 shows LV mass of mice treated with vehicle, rolipram, and enalapril at baseline (7 days after surgery), 14 and 21 days after surgery.

Table 1: Mean±SE LV Mass of mice treated with vehicle rolipram or enalapril

	Mean±SE LV Mass				
	Rolipram				Enalapril
Days after Surgery	Vehicle (control)	10 mg/kg	30 mg/kg	100 mg/kg	10 mg/kg
7 (Baseline)	102.4±2.5	99.2±2.0	100.9±2.7	98.9±1.9	102.1±5.2
14	112.3±1.7	107.8±4.6	108.8±2.5	95.2±3.9*	100.3±1.9*
21	119.4±2.3	103.3±2.8*	105.5±2.4*	90.1±2.4*, **	98.8±2.1*
*p<0.05 compared with vehicle at the same time point **p<0.05 compared with baseline in the same group					

Example 4

Effect of PDE IV inhibitors on LV mass.

Male CD-1 mice, 20-25 g in weight, were used for the experiment. The aorta was exposed between the renal arteries of the mice and was surgically constricted using a 30-gauge needle and 6.0 suture to induce heart growth as discussed in Example 2. Seven days after surgery, baseline echocardiography was performed on each mouse to establish LV mass.

Roflumilast was suspended in 1% carboxymethylcellulose (vehicle) and was orally administered to the mice at the doses of 3-30 mg/kg. The control group was administered with vehicle. Eleven days after surgery, mice were administered a single oral dose of PDE4 inhibitor or vehicle and dosing was continued once daily for ten days. Seven mice were used in each dose group. Repeat echocardiography was conducted on each mouse 14 and 21 days after surgery.

Fourteen days after surgery, a statistically significant reduction in LV mass was observed in mice treated with 3 mg/kg of roflumilast compared with vehicle at the same timepoint as shown in Table 2. Twenty-one days after surgery, a statistically significant reduction in LV mass was observed in mice that received 3, 10 and 30 mg/kg of roflumilast compared with vehicle at the same timepoint also shown in Table 2.

Table 2 shows LV mass of mice treated with vehicle, roflumilast, and enalapril at baseline (7 days after surgery), 14 and 21 days after surgery.

Table 2: Mean±SE LV Mass of mice treated with vehicle roflumilast or enalapril

	Mean±SE LV Mass				
	Roflumilast				Enalapril
Days after Surgery	Vehicle (control)	3 mg/kg	10 mg/kg	30 mg/kg	10 mg/kg
7 (Baseline)	97.4±2.6	99.6±2.3	104.3±2.1	98.0±2.6	100.3±3.8
14	113.1±3.7	98.3±2.0*	103.5±2.4	99.0±2.2	97.3±4.4*
21	119.9±4.3	97.9±2.5*	103.2±2.7*	99.3±3.8*	93.0±5.0*, **
*p<0.05 compared with vehicle at the same time point **p<0.05 compared with baseline in the same group					

All publications and references, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference in their entirety as if each individual publication or reference were specifically and individually indicated to be incorporated by reference herein as being fully set forth. Any patent application to which this application claims priority is also incorporated by reference herein in its entirety in the manner described above for publications and references.

What is claim is:

1. A method of reducing cardiovascular pathology in a mammal, comprising administering an amount effective for reducing said cardiovascular pathology with a phosphodiesterase 4 (PDE4) inhibitor.

2. The method of claim 1, wherein the cardiovascular pathology is cardiac hypertrophy.

3. The method of claim 1, wherein the cardiovascular pathology is heart failure.

4. The method of claim 1, wherein the cardiovascular pathology is congestive heart failure.

5. The method of claim 1 wherein the mammal suffering from hypertension.

6. The method of claim 1, wherein the mammal is suffering from arteriosclerosis.

7. The method of claim 1, wherein the PDE4 inhibitor is PDE4 specific inhibitor.

8. The method of claim 7, wherein the PDE4 specific inhibitor is rolipram.

9. The method of claim 7, wherein the PDE4 specific inhibitor is roflumilast.

10. A pharmaceutical formulation comprising a PDE4 inhibitor in an amount effective to reduce cardiovascular pathology in a mammal.

11. The method of claim 10, wherein the cardiovascular pathology is cardiac hypertrophy.

12. The method of claim 10, wherein the cardiovascular pathology is heart failure.

13. The method of claim 10, wherein the cardiovascular pathology is congestive heart failure.

14. The pharmaceutical formulation of claim 10, wherein said mammal is suffering from hypertension.

15. The pharmaceutical formulation of claim 10, wherein the mammal is suffering from arteriosclerosis.

16. The pharmaceutical formulation of claim 10, wherein the PDE4 inhibitor is PDE4 specific inhibitor.

17. The pharmaceutical formulation of claim 16, wherein PDE4 specific inhibitor comprises rolipram and roflumilast.

18. The pharmaceutical formulation of claim 16, wherein PDE4 specific inhibitor is selected from the group consisting of rolipram or roflumilast.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/16720

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/40
US CL : 514/423

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/423

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,331,543 B (GAVEY et al.) 18 December 2001 (18.12.2001), see the entire document.	1-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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