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<td>(57) Abstract</td>
<td>The present invention relates to novel 3,3-(disubstituted)cyclohexan-1-carboxylate dimers and related compounds, pharmaceutical compositions containing these compounds, and their use in treating allergic and inflammatory diseases and for inhibiting the production of Tumor Necrosis Factor (TNF).</td>
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3,3-(Disubstituted)cyclohexan-1-carboxylate Dimers and Related Compounds

Field of Invention

The present invention relates to novel dimers of 3,3-(disubstituted)cyclohexan-1-carboxylate dimers and related compounds, pharmaceutical compositions containing these compounds, and their use in treating allergic and inflammatory diseases and for inhibiting the production of Tumor Necrosis Factor (TNF).

Background of the Invention

Bronchial asthma is a complex, multifactorial disease characterized by reversible narrowing of the airway and hyperreactivity of the respiratory tract to external stimuli.

Identification of novel therapeutic agents for asthma is made difficult by the fact that multiple mediators are responsible for the development of the disease. Thus, it seems unlikely that eliminating the effects of a single mediator will have a substantial effect on all three components of chronic asthma. An alternative to the "mediator approach" is to regulate the activity of the cells responsible for the pathophysiology of the disease.

One such way is by elevating levels of cAMP (adenosine cyclic 3',5'-monophosphate). Cyclic AMP has been shown to be a second messenger mediating the biologic responses to a wide range of hormones, neurotransmitters and drugs; [Krebs Endocrinology Proceedings of the 4th International Congress Excerpta Medica, 17-29, 1973]. When the appropriate agonist binds to specific cell surface receptors, adenylate cyclase is activated, which converts Mg^2+-ATP to cAMP at an accelerated rate.

Cyclic AMP modulates the activity of most, if not all, of the cells that contribute to the pathophysiology of extrinsic (allergic) asthma. As such, an elevation of cAMP would produce beneficial effects including: 1) airway smooth muscle relaxation, 2) inhibition of mast cell mediator release, 3) suppression of neutrophil degranulation, 4) inhibition of basophil degranulation, and 5) inhibition of monocyte and macrophage activation. Hence, compounds that activate adenylate cyclase or inhibit phosphodiesterase should be effective in suppressing the inappropriate activation of airway smooth muscle and a wide variety of inflammatory cells. The principal cellular mechanism for the inactivation of cAMP is hydrolysis of the 3'-phosphodiester bond by one or more of a family of isozymes referred to as cyclic nucleotide phosphodiesterases (PDEs).

It has now been shown that a distinct cyclic nucleotide phosphodiesterase (PDE) isozyme, PDE IV, is responsible for cAMP breakdown in airway smooth muscle and inflammatory cells. [Torry, "Phosphodiesterase Isozymes: Potential
Targets for Novel Anti-asthmatic Agents" in New Drugs for Asthma, Barnes, ed. IBC Technical Services Ltd., 1989). Research indicates that inhibition of this enzyme not only produces airway smooth muscle relaxation, but also suppresses degranulation of mast cells, basophils and neutrophils along with inhibiting the activation of monocytes and neutrophils. Moreover, the beneficial effects of PDE IV inhibitors are markedly potentiated when adenylate cyclase activity of target cells is elevated by appropriate hormones or autocoids, as would be the case in vivo. Thus PDE IV inhibitors would be effective in the asthmatic lung, where levels of prostaglandin E2 and prostaacyclin (activators of adenylate cyclase) are elevated. Such compounds would offer a unique approach toward the pharmacotherapy of bronchial asthma and possess significant therapeutic advantages over agents currently on the market.

The compounds of this invention also inhibit the production of Tumor Necrosis Factor (TNF), a serum glycoprotein. Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to human acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis, in addition to a number of autoimmune diseases, such as multiple sclerosis, autoimmune diabetes and systemic lupus erythematosus.

AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell-mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Viruses such as HIV-1 or HIV-2 infect T lymphocytes after T cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication.

Cytokines, specifically TNF, are implicated in activated T-cell-mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with cytokine activity such as by inhibition of cytokine production, notably TNF, in an HIV-infected individual aids in
limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg et al., The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, 1989]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli et al., Proc. Natl. Acad. Sci., 87:782-784, 1990], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T cells.

TNF has also been implicated in various roles with other viral infections, such as the cytomegalovirus (CMV), influenza virus, adenovirus, and the herpes virus for similar reasons as those noted.

TNF is also associated with yeast and fungal infections. Specifically Candida albicans has been shown to induce TNF production in vitro in human monocytes and natural killer cells. [See Riipi et al., Infection and Immunity, 58(9):2750-54, 1990; and Jafari et al., Journal of Infectious Diseases, 164:389-95, 1991. See also Wasan et al., Antimicrobial Agents and Chemotherapy, 35,(10):2046-48, 1991; and Luke et al., Journal of Infectious Diseases, 162:211-214,1990].

The ability to control the adverse effects of TNF is furthered by the use of the compounds which inhibit TNF in mammals who are in need of such use. There remains a need for compounds which are useful in treating TNF-mediated disease states which are exacerbated or caused by the excessive and/or unregulated production of TNF.

Summary of the Invention

The compounds of this invention are represented by Formulas (Ia), (Ib) and (Ic):
wherein:

R₁ is independently selected from -(CR₄R₅)ₙC(O)O(CR₄R₅)mR₆,
-(CR₄R₅)ₙC(O)NR₄(CR₄R₅)mR₆, -(CR₄R₅)ₙO(CR₄R₅)mR₆, or -(CR₄R₅)ₙR₆

wherein the alkyl moieties may be optionally substituted with one or more fluorines;

m is 0 to 2;
n is 1 to 4;
r is 0 to 6;

R₄ and R₅ are independently selected from hydrogen or a C₁₋₂ alkyl;

R₆ is independently selected from hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC₁₋₃ alkyl, halo substituted aryloxyC₁₋₃ alkyl, indanyl, indenyl, C₇₋₁₁ polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl, C₃₋₆ cycloalkyl, or a

C₄₋₆ cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl or the heterocyclic moiety is unsubstituted or substituted by 1 to 3 methyl groups, one ethyl group or an hydroxyl group.
provided that:
a) when R6 is hydroxyl, then m is 2; or
b) when R6 is hydroxyl, then r is 2 to 6; or
c) when R6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl,
2-tetrahydrofuranyl, or 2-tetrahydrothiényl, then m is 1 or 2; or
d) when R6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl,
2-tetrahydrofuranyl, or 2-tetrahydrothiényl, then r is 1 to 6;
e) when n is 1 and m is 0, then R6 is other than H in
-(CR₄R₅)nO(CR₄R₅)mR₆;

X is independently selected from YR₂, fluorine, NR₄R₅, or formyl amine;
Y is independently selected from O or S(O)m;
m' is 0, 1, or 2;
X₂ is independently selected from O or NR₈;
X₃ is independently selected from H, R₂, OR₂, CN, C(O)R₈, C(O)OR₂.

C(O)NR₈R₈, or NR₈R₈;
W is alkyl of 2 to 6 carbons, alkenyl of 2 to 6 carbon atoms or alkynyl of 2 to 6
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carbon atoms;
R₂ is independently selected from the group consisting of -CH₃ and -CH₂CH₃
unsaturated or substituted by 1 or more fluorines;

s is 0 to 4;
Z is independently selected from C(Y')R₄, C(O)OR₂, C(Y')NR₁₀R₁₀,
C(NR₁₀)NR₁₀R₁₀, CN, C(NOR₈)R₄, C(O)NR₈NR₈C(O)R₈, C(O)NR₈NR₈R₈,
C(NR₁₀)R₄, C(NR₈)NR₁₀R₁₀, C(NR₁₀)NR₈R₈, C(NCN)NR₁₀R₁₀,
C(NCN)SR₈, (2-, 4- or 5-imidazolyl), (3-, 4- or 5-pyrazolyl), (4- or
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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]), (2-oxadiazolyl[1,3,4]),
(2-thiadiazolyl[1,3,4]), (2-, 4-, or 5-thiazolyl), (2-, 4-, or 5-oxazolindinyl), (2-, 4-, or
5-thiazolindinyl), or (2-, 4-, or 5-imidazolidinyl); wherein all of the heterocyclic ring
systems are unsubstituted or substituted one or more times by R₁₄;

Y' is independently selected from O or S;
R₇ is -(CR₄R₅)ₖR₁₂ or C₁₋₆ alkyl wherein the R₁₂ or C₁₋₆ alkyl group is
unsaturated or substituted one or more times by methyl or ethyl unsubstituted or
substituted by 1-3 fluorines, -F, -Br, -Cl, NO₂, -NR₁₀R₁₁, -C(O)R₈, -CO₂R₈,
-OC(CH₂)ₙR₈, -CN, -C(O)NR₁₀R₁₁, -O(CH₂)ₙC(O)NR₁₀R₁₁, -O(CH₂)ₙC(O)R₉,
-NR₁₀C(O)NR₁₀R₁₁, -NR₁₀C(O)R₁₁, -NR₁₀C(O)OR₂, -NR₁₀C(O)R₁₃,
35
-C(NR₁₀)NR₁₀R₁₁, -C(NCN)NR₁₀R₁₁, -C(NCN)SR₈, -NR₁₀C(NCN)SR₈,
-NR₁₀C(NCN)NR₁₀R₁₁, -NR₁₀SO₂R₂, -SO₃R₉, -NR₁₀C(O)C(O)NR₁₀R₁₁,
-NR₁₀C(O)C(O)R₁₀, or R₁₃;
q is 0, 1, or 2;
R12 is independently selected from R13, C3-7 cycloalkyl, (2-, 3- or 4-pyridyl), pyrimidyl, pyrazolyl, (1- or 2-imidazolyl), pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, (2- or 3-thienyl), quinolinyl, naphthyl, or phenyl;

Rg is independently selected from hydrogen or R9;

R9 is independently selected from C1-4 alkyl which is unsubstituted or substituted by one to three fluorines;

R10 is independently selected from OR8 or R11;

R11 is independently selected from hydrogen, or C1-4 alkyl optionally substituted by one to three fluorines; or when R10 and R11 are as NR10R11 they may together with the nitrogen form a 5 to 7 membered ring comprised of carbon or carbon and at least one additional heteroatom selected from O, N, or S;

R13 is independently selected from 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 C1-2 alkyl groups;

R14 is independently selected from hydrogen or R7; or when R10 and R14 are as NR10R14 they may together with the nitrogen form a 5 to 7 membered ring comprised of carbon or carbon and one or more additional heteroatoms selected from O, N, or S;

or the pharmaceutically acceptable salts thereof.

This invention also relates to the pharmaceutical compositions comprising a compound of Formula (Ia), (Ib) or (Ic) and a pharmaceutically acceptable carrier or diluent.

The invention also relates to a method of mediation or inhibition of the enzymatic activity (or catalytic activity) of PDE IV in mammals, including humans, which comprises administering to a mammal in need thereof an effective amount of a compound of Formula (Ia), (Ib) or (Ic) as shown below.

The invention further provides a method for the treatment of allergic and inflammatory disease which comprises administering to a mammal, including humans, in need thereof, an effective amount of a compound of Formula (Ia), (Ib) or (Ic).

The invention also provides a method for the treatment of asthma which comprises administering to a mammal, including humans, in need thereof, an effective amount of a compound of Formula (Ia), (Ib) or (Ic) alone or in combination with another of its sister compounds.

This invention also relates to a method of inhibiting TNF production in a mammal, including humans, which method comprises administering to a mammal in need of such treatment, an effective TNF inhibiting amount of a compound of Formula (Ia), (Ib) or (Ic) alone or in combination with another of its sister compounds. This
method may be used for the prophylactic treatment or prevention of certain TNF mediated disease states amenable thereto.

This invention also relates to a method of treating a human afflicted with a human immunodeficiency virus (HIV), which comprises administering to such human an effective TNF inhibiting amount of a compound of Formula (Ia), (Ib) or (Ic).

Compounds of Formulas (Ia), (Ib) or (Ic) are also useful in the treatment of additional viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production in vivo.

In addition, compounds of Formulas (Ia), (Ib) or (Ic) are also useful in treating yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production in vivo.

**Detailed Description of the Invention**

This invention also relates to a method of mediating or inhibiting the enzymatic activity (or catalytic activity) of PDE IV in a mammal in need thereof and to inhibiting the production of TNF in a mammal in need thereof, which comprises administering to said mammal an effective amount of at least one of a compound of Formula (Ia), (Ib) or (Ic).

Phosphodiesterase IV inhibitors are useful in the treatment of a variety of allergic and inflammatory diseases including: asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. In addition, PDE IV inhibitors are useful in the treatment of diabetes insipidus and central nervous system disorders such as depression and multi-infarct dementia.

The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibitors of Formula (Ia), (Ib) or (Ic). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, cytomegalovirus (CMV), influenza, adenovirus and the Herpes group of viruses, such as, but not limited to, *Herpes zoster* and *Herpes simplex*.

This invention more specifically relates to a method of treating a mammal, afflicted with a human immunodeficiency virus (HIV), which comprises administering to such mammal an effective TNF inhibiting amount of a compound of Formula (Ia), (Ib) or (Ic).

The compounds of this invention may also be used in association with the veterinary treatment of animals, other than in humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, therapeutically or prophylactically,
in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to feline immunodeficiency virus (FIV) or other retroviral infection such as equine infectious anemia virus, caprine arthritis virus, visna virus, maedi virus and other lentiviruses.

The compounds of this invention are also useful in treating yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production in vivo. A preferred disease state for treatment is fungal meningitis. Additionally, the compounds of Formulas (Ia), (Ib) or (Ic) may be administered in conjunction with other drugs of choice for systemic yeast and fungal infections. Drugs of choice for fungal infections, include but are not limited to the class of compounds called the polymixins, such as Polymycin B, the class of compounds called the imidazoles, such as clotrimazole, econazole, miconazole, and ketoconazole; the class of compounds called the triazoles, such as fluconazole, and itraconazole, and the class of compound called the Amphotericins, in particular Amphotericin B and liposomal Amphotericin B.

The compounds of Formulas (Ia), (Ib) or (Ic) may also be used for inhibiting and/or reducing the toxicity of an anti-fungal, anti-bacterial or anti-viral agent by administering an effective amount of a compound of Formula (Ia), (Ib) or (Ic) to a mammal in need of such treatment. Preferably, a compound of Formula (Ia), (Ib) or (Ic) is administered for inhibiting or reducing the toxicity of the Amphotericin class of compounds, in particular Amphotericin B.

The term "C1-3 alkyl", "C1-4 alkyl", "C1-6 alkyl" or "alkyl" groups as used herein is meant to include both straight or branched chain radicals of 1 to 10, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and the like.

"Alkenyl" means both straight or branched chain radicals of 1 to 6 carbon lengths, unless the chain length is limited thereto, including but not limited to vinyl, 1-propenyl, 2-propenyl, 2-propynyl, or 3-methyl-2-propenyl.

The term "cycloalkyl" or "cycloalkyl alkyl" means groups of 3-7 carbon atoms, such as cyclopropyl, cyclopropylmethyl, cyclopentyl, or cyclohexyl.

"Aryl" or "aralkyl", unless specified otherwise, means an aromatic ring or ring system of 6-10 carbon atoms, such as phenyl, benzyl, phenethyl, or naphthyl. Preferably the aryl is monocyclic, i.e., phenyl. The alkyl chain is meant to include both straight or branched chain radicals of 1 to 4 carbon atoms.

"Heteroaryl" means an aromatic ring system containing one or more heteroatoms, such as imidazolyl, triazolyl, oxazolyl, pyridyl, pyrimidyl, pyrazolyl, pyrrolyl, furanyl, or thiényl.

"Halo" means all halogens, i.e., chloro, fluoro, bromo, or iodo.
"Inhibiting the production of IL-1" or "inhibiting the production of TNF" means:

a) a decrease of excessive in vivo IL-1 or TNF levels, respectively, in a human to normal levels or below normal levels by inhibition of the in vivo release of IL-1 by all cells, including but not limited to monocytes or macrophages;

b) a down regulation, at the translational or transcriptional level, of excessive in vivo IL-1 or TNF levels, respectively, in a human to normal levels or below normal levels; or

c) a down regulation, by inhibition of the direct synthesis of IL-1 or TNF levels as a posttranslational event.

The phrase "TNF mediated disease or disease states" means any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another cytokine to be released, such as but not limited to IL-1 or IL-6. A disease state in which IL-1, for instance is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF. As TNF-β (also known as lymphotoxin) has close structural homology with TNF-α (also known as cachectin), and since each induces similar biologic responses and binds to the same cellular receptor, both TNF-α and TNF-β are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise. Preferably TNF-α is inhibited.

"Cytokine" means any secreted polypeptide that affects the functions of cells, and is a molecule which modulates interactions between cells in immune, inflammatory, or hematopoietic responses. A cytokine includes, but is not limited to, monokines and lymphokines regardless of which cells produce them. The cytokine inhibited by the present invention for use in the treatment of a HIV-infected human must be a cytokine which is implicated in (a) the initiation and/or maintenance of T cell activation and/or activated T cell-mediated HIV gene expression and/or replication, and/or (b) any cytokine-mediated disease associated problem such as cachexia or muscle degeneration. Preferably, this cytokine is TNF-α.

Preferred compounds are as follows:

While the following preferred compounds are more or less described in terms of preferring a symmetrical molecule, each substituent described herein above, and below, may be independently varied based on the definitions of each provided herein. For example R₁ may be a cyclopentyl group and a CF₃ group within the same molecule of a given embodiment of Formula (Ia), (Ib) or (Ic). Similarly each and every one of the other groups may be independently selected, or may be the same, in any given embodiment of this invention.
When R₁ is an alkyl substituted by 1 or more halogens, the halogens are preferably fluorine and chlorine, more preferably a C₁₋₄ alkyl substituted by 1 or more fluorines. The preferred halo-substituted alkyl chain length is one or two carbons, and most preferred are the moieties -CF₃, -CH₂F, -CHF₂, -CF₂CHF₂, -CH₂CF₃, and -CH₂CHF₂. Preferred R₁ substituents are CH₂-cyclopropyl, CH₂-C₅₋₆ cycloalkyl, C₄₋₆ cycloalkyl, C₇₋₁₁ polycycloalkyl, (3- or 4-cyclopentenyl), phenyl, tetrahydrofuranyl-3-yl, benzyl or C₁₋₂ alkyl which is either unsubstituted or substituted by 1 or more fluorines, -(CH₂)₁₋₃C(O)O(CH₂)₀₋₂CH₃, -(CH₂)₁₋₃O(CH₂)₀₋₂CH₃, and -(CH₂)₂₋₄OH.

When the R₁ term contains the moiety (CR₄R₅), the R₄ and R₅ terms are independently hydrogen or alkyl. This allows for branching of the individual methylene units as (CR₄R₅)ₙ or (CR₄R₅)ₘ; each repeating methylene unit is independent of the other, e.g., (CR₄R₅)ₙ wherein n is 2 can be -CH₂CH(CH₃)₂, for instance. The individual hydrogen atoms of the repeating methylene unit or the branching hydrocarbon can be unsubstituted or substituted by fluorine independent of each other to yield, for instance, the preferred R₁ substitutions, as noted above.

When R₁ is a C₇₋₁₁ polycycloalkyl, examples are bicyclo[2.2.1]-heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, tricyclo[5.2.1.0²,₆]decyl, etc. Additional examples of which are described in Saccamano et al., WO 87/06576, published 5 November 1987.

W is preferably alkyl, alkenyl or alkynyl of 3 to 5 carbon atoms, and where it is alkenyl or alkynyl, that one or two double or triple bonds be present.

Z is preferably C(O)R₁₄, C(O)OR₁₄, C(O)NR₁₀R₁₄, C(NR₁₀)NR₁₀R₁₄, CN, C(NOR₈)R₈, C(O)NR₈NR₈C(O)R₈, C(NR₈)NR₁₀R₁₄, C(NCN)NR₁₀R₁₄, C(NCN)SR₉, (1-, 4- or 5- [R₈]-2-imidazolyl), (1-, 4- or 5- [R₈]-3-pyrazolyl), (1-, 2- or 5- [R₈]-4-triazolyl[1,2,3]), (1-, 2-, 4- or 5- [R₈]-3-triazolyl[1,2,4]), (1- or 2- [R₈]-5-tetrazolyl), (4- or 5- [R₈]-2-oxazolyl), (3- or 4- [R₈]-5-isoxazolyl), (3- [R₈]-5-oxadiazolyl[1,2,4]), (5- [R₈]-3-oxadiazolyl[1,2,4]), (5- [R₈]-2-oxadiazolyl[1,3,4]), (5- [R₈]-2-thiadiazolyl[1,3,4]), (4- or 5- [R₈]-2-thiazolyl), (4- or 5- [R₈]-2-oxazolidinyl), (4- or 5- [R₈]-2-thiazolidinyl), most preferred are those compounds wherein the R₈ group of Z is R₄. Z is preferably C(O)R₁₄, C(O)OR₁₄, or C(O)NR₁₀R₁₄.

Preferred X groups are those wherein X is YR₂ and Y is oxygen. The preferred X₂ group is oxygen. The preferred X₃ group is hydrogen. Preferred R₂ groups, where applicable, are C₁₋₂ alkyl unsubstituted or substituted by 1 or more halogens. The halogen atoms are preferably fluorine and chlorine, more preferably fluorine. More preferred R₂ groups are those wherein R₂ is methyl, or the fluoro-substituted alkyls, specifically a C₁₋₂ alkyl, such as a -CF₃, -CHF₂, or -CH₂CHF₂ moiety. Most preferred are the -CHF₂ and -CH₃ moieties.
Preferred R7 moieties include unsubstituted or substituted
-(CH2)1-2(cyclopropyl), -(CH2)0-2(cyclobutyl), -(CH2)0-2(cyclopentyl),
-(CH2)0-2(cyclohexyl), -(CH2)0-2(2-, 3- or 4-pyridyl), -(CH2)1-2(2-imidazolyl),
-(CH2)2-(4-morpholiny), -(CH2)2-(4-piperazinyl), -(CH2)1-2(2-thienyl), -(CH2)1-2(4-thiazolyl), and -(CH2)0-2phenyl;

Preferred rings when R10 and R11 in the moiety -NR10R11 together with the nitrogen to which they are attached form a 5 to 7 membered ring comprising carbon alone or carbon and at least one additional heteroatom selected from O, N or S include, but are not limited to 1-imidazolyl, 2-(R8)-1-imidazolyl, 1-pyrazolyl,
3-(R8)-1-pyrazolyl, 1-triazolyl, 2-triazolyl, 5-(R8)-1-triazolyl, 5-(R8)-2-triazolyl,
5-(R8)-1-tetrazolyl, 5-(R8)-2-tetrazolyl, 1-tetrazolyl, 2-tetrazolyl, morpholinyl, piperazinyl, 1-(R8)-5-piperazinyl, or pyrrolyl ring.

Preferred rings when R10 and R14 in the moiety -NR10R14 together with the nitrogen to which they are attached may form a 5 to 7 membered ring containing at least one additional heteroatom selected from O, N or S include, but are not limited to 1-imidazolyl, 1-pyrazolyl, 1-triazolyl, 2-triazolyl, 1-tetrazolyl, 2-tetrazolyl, morpholinyl, piperazinyl, and pyrrolyl. The respective rings may be additionally substituted, where applicable, on an available nitrogen or carbon by the moiety R7 as described herein for Formula (I). Illustrations of such carbon substitutions include, but are not limited to, 2-(R7)-1-imidazolyl, 4-(R7)-1-imidazolyl, 5-(R7)-1-imidazolyl,
3-(R7)-1-pyrazolyl, 4-(R7)-1-pyrazolyl, 5-(R7)-1-pyrazolyl, 4-(R7)-2-triazolyl,
5-(R7)-2-triazolyl, 4-(R7)-1-triazolyl, 5-(R7)-1-triazolyl, 5-(R7)-1-tetrazolyl, and
5-(R7)-2-tetrazolyl. Applicable nitrogen substitution by R7 includes, but is not limited to, 1-(R7)-2-tetrazolyl, 2-(R7)-1-tetrazolyl, 4-(R7)-1-piperazinyl. Where applicable, the ring may be substituted one or more times by R7.

Preferred groups for NR10R14 which contain a heterocyclic ring are 5-(R14)-
1-tetrazolyl, 2-(R14)-1-imidazolyl, 5-(R14)-2-tetrazolyl, or 4-(R14)-1-piperazinyl.

Preferred rings for R13 include (2-, 4- or 5-imidazolyl), (3-, 4- or 5-pyrazolyl),
(4- or 5-tetrazolyl[1,2,3]), (3- or 5-tetrazolyl[1,2,4]), (5-tetrazolyl), (2-, 4- or
5-oxazolyl), (3-, 4- or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,2,4]),
(2-oxadiazolyl[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).

When the R7 group is substituted by a heterocyclic ring such as imidazolyl, pyrazolyl, triazolyl, tetrazolyl, or thiazolyl, the heterocyclic ring itself may be
substituted by R8 either on an available nitrogen or carbon atom, such as
1-(R8)-2-imidazolyl, 1-(R8)-4-imidazolyl, 1-(R8)-5-imidazolyl, 1-(R8)-3-pyrazolyl,
1-(R8)-4-pyrazolyl, 1-(R8)-5-pyrazolyl, 1-(R8)-4-tetrazolyl, or 1-(R8)-5-triazolyl.
Where applicable, the ring may be substituted one or more times by R8.
Preferred are those compounds of Formula (Ia), (Ib) or (Ic) wherein R₁ is -CH₂-cyclopropyl, -CH₂-C₅-H cycloalkyl, -C₄-H cycloalkyl unsubstituted or substituted with an hydroxyl group, tetrahydrofuran-3-yl, (3- or 4-cyclopentenyl), benzyl or -C₁-H alkyl optionally substituted by 1 or more fluorines, and -(CH₂)₂-H

5 OH; R₂ is methyl or fluoro-substituted alkyl, W is alkynyl or 2 to 4 carbon atoms.

Most preferred are those compounds wherein R₁ is -CH₂-cyclopropyl, cyclopentyl, 3-hydroxycyclopentyl, methyl or CF₂H; X is YR₂; Y is oxygen; X₂ is oxygen; X₃ is hydrogen; R₂ is CF₂H or methyl and W is 1,3-butadiynyl, and Z is C(O)OR₁₄.

Exemplified compounds are:

14-bis-[(methyl c-3-(3-cyclopentyl-oxy-4-methoxyphenyl)-r-1-cyclohexane carboxylate]-4-y1]buta-1,3-diyne, and;

14-bis-[(c-3-(3-cyclopentyl-oxy-4-methoxyphenyl)-r-1-cyclohexane carboxylic acid]-4-y1]buta-1,3-diyne,

All of the compounds of Formulas (Ia), (Ib) or (Ic) are useful in the method of inhibiting the production of TNF, preferably by macrophages, monocytes or macrophages and monocytes, in a mammal, including humans, in need thereof. These compounds are useful in the method of inhibiting or mediating the enzymatic or catalytic activity of PDE IV and in treatment of disease states mediated thereby.

Pharmaceutically acceptable salts of the instant compounds, where they can be prepared, are also intended to be covered by this invention. These salts will be ones which are acceptable in their application to a pharmaceutical use. By that it is meant that the salt will retain the biological activity of the parent compound and the salt will not have untoward or deleterious effects in its application and use in treating diseases.

Pharmaceutically acceptable salts are prepared in a standard manner. The parent compound, dissolved in a suitable solvent, is treated with an excess of an organic or inorganic acid, in the case of acid addition salts of a base, or an excess of organic or inorganic base where the molecule contains a COOH for example.

Pharmaceutical compositions of the present invention comprise a pharmaceutical carrier or diluent and some amount of one or more compounds of this invention. The compound may be present in an amount to effect a physiological response, or it may be present in a lesser amount such that the user will need to take two or more units of the composition to effect the treatment intended. These compositions may be made up as a solid, liquid or in a gaseous form. Or one of these three forms may be transformed to another at the time of being administered such as when a solid is delivered by aerosol means, or when a liquid is delivered as a spray or aerosol.
The nature of the composition and the pharmaceutical carrier or diluent will, of course, depend upon the intended route of administration, for example parenterally, topically, orally or by inhalation.

For topical administration the pharmaceutical composition will be in the form of a cream, ointment, liniment, lotion, pastes, aerosols, and drops suitable for administration to the skin, eye, ear, or nose.

For parenteral administration the pharmaceutical composition will be in the form of a sterile injectable liquid such as an ampule or an aqueous or non-aqueous liquid suspension.

For oral administration the pharmaceutical composition will be in the form of a tablet, capsule, powder, pellet, atroche, lozenge, syrup, liquid, or emulsion.

When the pharmaceutical composition is employed in the form of a solution or suspension, examples of appropriate pharmaceutical carriers or diluents include: for aqueous systems, water; for non-aqueous systems, ethanol, glycerin, propylene glycol, corn oil, cottonseed oil, peanut oil, sesame oil, liquid parafins and mixtures thereof with water; for solid systems, lactose, kaolin and mannitol; and for aerosol systems, dichlorodifluoromethane, chlorotrifluoroethane and compressed carbon dioxide. Also, in addition to the pharmaceutical carrier or diluent, the instant compositions may include other ingredients such as stabilizers, antioxidants, preservatives, lubricants, suspending agents, viscosity modifiers and the like, provided that the additional ingredients do not have a detrimental effect on the therapeutic action of the instant compositions.

The pharmaceutical preparations thus described are made following the conventional techniques of the pharmaceutical chemist as appropriate to the desired end product.

In these compositions, the amount of carrier or diluent will vary but preferably will be the major proportion of a suspension or solution of the active ingredient. When the diluent is a solid it may be present in lesser, equal or greater amounts than the solid active ingredient.

Usually a compound of this invention is administered to a subject in a composition comprising a nontoxic amount sufficient to produce an inhibition of the symptoms of a disease in which leukotrienes are a factor. Topical formulations will contain between about 0.01 to 5.0% by weight of the active ingredient and will be applied as required as a preventative or curative agent to the affected area. When employed as an oral, or other ingested or injected regimen, the dosage of the composition is selected from the range of from 50 mg to 1000 mg of active ingredient for each administration. For convenience, equal doses will be administered 1 to 5 times daily with the daily dosage regimen being selected from about 50 mg to about 5000 mg.
No unacceptable toxicological effects are expected when these compounds are administered in accordance with the present invention.

**Methods Of Preparation**

**Synthetic Scheme(s) With Textual Description**

Compounds of Formula (Ia), wherein W is 1,3-butadiynyl and wherein A and B represent Z as defined above or a group convertible to Z, may be prepared by the processes disclosed herein which comprise, for example, coupling of a molecule of the Formula 1-Scheme 1 with a molecule of the Formula 2-Scheme 1 using an appropriate metal salt, such as cupric acetate, in a suitable solvent, such as DMF or pyridine, or a combination, such as pyridine/methanol/water, as in the method of Eglington and Galbraith (J. Chem. Soc., 1959, 889), to provide a compound of the Formula 2-Scheme 1. Compounds of Formula (Ib), wherein W is a 1,3-butadiynyl and wherein A and B represent Z as defined above or a group convertible to Z, may be prepared by the analogous processes.

\[ A \quad \text{+} \quad B \quad \rightarrow \quad Z \]

\[ a) \quad \text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}, \text{DMF or C}_5\text{H}_5\text{N} \]

Likewise, compounds of Formula (Ic) wherein W is a 1,3-butadiynyl and wherein A and B represent Z as defined iabove or a group convertible to Z and wherein X4 represents X4 as defined above or a group convertible to X4, may be prepared by the processes disclosed herein which comprise, for example, coupling of a molecule of the Formula 1-Scheme 2 with a molecule of the Formula 2-Scheme 2 using an appropriate metal salt, such as cupric acetate, in a suitable solvent, such as DMF or pyridine, or a combination, such as pyridine/methanol/water, as in the method.
of Eglington and Galbraith (J. Chem. Soc., 1959, 889), to provide a compound of the Formula 3-Scheme 2.

\[ \text{Scheme 2} \]

\[ \begin{align*}
\text{1} & \quad + \\
\text{2} & \quad \xrightarrow{a} \quad \text{3}
\end{align*} \]

\( a) \text{ Cu(OAc)}_2 \cdot \text{H}_2\text{O}, \text{ DMF or C}_5\text{H}_5\text{N} \)

Reduction of a compound of Formula (Ic), wherein \( W \) is a 1,3-butadiynyl and wherein \( Z \) represents \( Z \) as defined above or a group convertible to \( Z \), to a compound of Formula (Ic) wherein \( W \) is a fully saturated hydrocarbon chain (i.e., \( n \)-butyl) may be accomplished using, e.g., palladium metal according to the method of Tedeschi (J. Org. Chem., 1962, 27, 2398), or, e.g., platinum oxide according to the method of Jutz (Ber., 1958, 91, 1867) or that of Suzuki and Kurosawa (Chem. Lett., 1980, 1177). Reduction of a compound of Formula (Ic), wherein \( W \) is a 1,3-butadiynyl and wherein \( Z \) represents \( Z \) as defined above or a group convertible to \( Z \), to provide a compound of the Formula (Ic) wherein \( W \) is a 1,3-butadienyl may be accomplished using, e.g., the hydroboration-protonolysis procedure of Zweifel and Polston (J. Am. Chem. Soc., 1970, 92, 4068), or, e.g., the hydroalumination-protonolysis procedure of Zweifel et al. (Synthesis, 1977, 52).

Alternatively, compounds of Formulas (Ia) and (Ib), wherein \( W \) and \( Z \) represent \( W \) and \( Z \) as defined above or a group convertible to \( W \) or \( Z \), may be prepared from the corresponding ketones as, e.g., compound 1-Scheme 3, by the synthetic procedures described in co-pending United States patent application serial number 08/099,900P50185 filed 30 July 1993 and its progeny USSN 08/130214 filed 1 October 1993; syntheses of such ketone starting materials are described in co-
pending United States application serial number 08/130215 filed 1 October 1993 and its progeny PCT application PCT/US94/10815.

Likewise, compounds of Formula (1c), wherein W, X, and Z represent W, X, and Z as defined above or a group convertible to W, X, or Z, may be prepared from the corresponding ketones as, e.g., compound 1-Scheme 4, by the synthetic procedures described in copending United States patent application serial number 08/099,900 filed 30 July 1993 and its progeny USSN 08/130214 filed 1 October 1993; syntheses of such ketone starting materials are described in co-pending United States application serial number 08/130215 filed 1 October 1993 and its progeny PCT application PCT/US94/10815.

Depending upon the exact nature of the Z groups of the compounds of Formula (1a) and (1b) and the Z and X groups of the compounds of Formula (1c), the
Z and X₄ groups may require protection during the coupling and/or reductive steps described herein, followed by deprotection, to provide Formula (Ia), (Ib) and (Ic) compounds, as in processes described in co-pending United States patent application serial number 08/099,900 filed 30 July 1993 and its progeny USSR 08/130214 filed 1 October 1993 (incorporated herein by reference); such protective groups are well known to those skilled in the art. (See: Greene, T. and Wuts, P.G.M., Protecting Groups in Organic Synthesis, 2nd Ed., John Wiley and Sons, New York, 1991.)

Preparation of the remaining compounds of the Formula (Ia), (Ib) and (Ic) may be accomplished by procedures analogous to those described above and in the

Examples, infra.

It will be recognized that compounds of Formula (Ia), (Ib) and (Ic) may exist in distinct diastereomeric forms possessing distinct physical and biological properties; such isomers may be separated by standard chromatographic methods.

The several patent applications set forth herein are incorporated herein by reference in full as if set forth herein.

The following examples are given to illustrate the invention and are not intended to limit it in any fashion. Reference is made to the claims for what is reserved to the inventor hereunder.

20 Synthetic Examples

Example 1

Preparation of 1,4-bis-[[1-cyclopentyl-4-methoxyphenyl]-r-1-cyclohexancarboxylic acid]-3-yl]buta-1,3-diyn-1-

1a) cis-[3-(3-cyclopentylxyloxy-4-methoxyphenyl)-3-formylycyclohexene-1-carboxylic acid]

To a suspension of cis-[3-(3-cyclopentylxyloxy-4-methoxyphenyl)-3-cyano-cyclohexene-1-carboxylic acid] (1.002 g, 2.91 mmol, prepared as described in United States patent application serial number 08/099,900P50185 filed 30 July 1993 and its progeny USSR 08/130214 filed 1 October 1993) in toluene (30 mL) at 0°C under an argon atmosphere is dropwise added over 15 min a 1.0 M solution of diisobutylaluminum hydride in toluene (6.00 mL, 6.00 mL). The solution is stirred for 2 h at room temperature, then is quenched at 0°C with saturated ammonium chloride, is diluted with ethyl acetate and 10% hydrochloric acid (50 mL) and is extracted twice with ethyl acetate. The extract is dried (magnesium sulfate) and is evaporated.

35 Purification by flash chromatography provides cis-[3-(3-cyclopentylxyloxy-4-methoxyphenyl)-3-formylycyclohexene-1-carboxylic acid].

1b) trans-[3-(3-cyclopentylxyloxy-4-methoxyphenyl)-3-ethynylycyclohexene-1-carboxylic acid]
A solution of dimethyl (diazomethyl)phosphonate (0.30 g, 2.0 mmole, prepared as in Seyferth, D.; Marmor, R.S.; Hilbert, P. J. Org. Chem. 1971, 36(10), 1379-1386) dissolved in dry tetrahydrofuran (2 mL) at -78°C is added via cannulation to a solution of potassium t-butoxide (0.169 g, 1.50 mmol) dissolved in dry tetrahydrofuran (2 mL) at -78°C under an argon atmosphere. After 15 min, a solution of cis-[3-(3-cyclopentyloxy-4-methoxyphenyl)-3-formylcyclohexane-1-carboxylic acid] (0.173g, 0.5 mmol) in dry tetrahydrofuran (2 mL) at -78°C is added rapidly. The reaction is allowed to warm gradually to room temperature over 1 h and then is stirred for an additional hour.

The reaction is quenched with saturated ammonium chloride, is acidified with 10% hydrochloric acid, is extracted three times with dichloromethane, the extract is dried (magnesium sulfate) and is evaporated. Purification by flash chromatography provides trans-[3-(3-cyclopentyloxy-4-methoxyphenyl)-3-ethynylcyclohexane-1-carboxylic acid].

jc) 1,4-bis-[[(c-3-(3-cyclopentyloxy-4-methoxyphenyl)-r-1-cyclohexane carboxylic acid]-3-yl]buta-1,3-diyne

A mixture of trans-[3-(3-cyclopentyloxy-4-methoxyphenyl)-3-ethynylcyclohexane-1-carboxylic acid] (0.101 g, 0.29 mmol) and copper acetate monohydrate (0.176 g, 0.88 mmol) in dimethylformamide (2 mL) is stirred at 70-75°C under an argon atmosphere for 3h. Additional copper acetate monohydrate (0.175g, 0.88 mmol) is added and stirring is continued for 16 h. The reaction is diluted with water and is extracted twice with ethyl acetate. The extract is washed three times with water, once with brine, is dried (magnesium sulfate) and is evaporated. Purification by flash chromatography provides 1,4-bis-[[c-3-(3-cyclopentyloxy-4-methoxyphenyl)-r-1-cyclohexane carboxylic acid]-3-yl]buta-1,3-diyne.

UTILITY EXAMPLES

EXAMPLE A

Inhibitory effect of compounds of Formulas (Ia), (Ib) or (Ic) on in vitro TNF production by human monocytes

The inhibitory effect of compounds of Formulas (Ia), (Ib) or (Ic) on in vitro TNF production by human monocytes may be determined by the protocol as described in Badger et al., EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

EXAMPLE B

Two models of endotoxic shock have been utilized to determine in vivo TNF activity for the compounds of Formulas (Ia), (Ib) or (Ic). The protocol used in these models is described in Badger et al., EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.
The compound of Example 1 herein demonstrated a positive in vivo response in reducing serum levels of TNF induced by the injection of endotoxin.

**EXAMPLE C**

**Isolation of PDE Isozymes**

The phosphodiesterase inhibitory activity and selectivity of the compounds of Formulas (Ia), (Ib) or (Ic) can be determined using a battery of five distinct PDE isozymes. The tissues used as sources of the different isozymes are as follows: 1) PDE Ib, porcine aorta; 2) PDE Ic, guinea-pig heart; 3) PDE III, guinea-pig heart; 4) PDE IV, human monocyte; and 5) PDE V (also called "Ia"), canine trachealis. PDEs Ia, Ib, Ic and III are partially purified using standard chromatographic techniques [Torry and Cieslinski, Mol. Pharmacol., 37:206-214, 1990]. PDE IV is purified to kinetic homogeneity by the sequential use of anion-exchange followed by heparin-Sepharose chromatography [Torry et al., J. Biol. Chem., 267:1798-1804, 1992].

Phosphodiesterase activity is assayed as described in the protocol of Torphy and Cieslinski, Mol. Pharmacol., 37:206-214, 1990. Positive IC50's in the nanomolar to μM range for compounds of the workings examples described herein for Formula (I) have been demonstrated.
What is claimed is:

1. A compound of Formula (Ia), (Ib) or (Ic):

wherein:

R₁ is independently selected from -(CR₄R₅)ₙC(O)O(CR₄R₅)mR₆,
-(CR₄R₅)ₙC(O)NR₄(CR₄R₅)mR₆, -(CR₄R₅)ₙO(CR₄R₅)mR₆, or -(CR₄R₅)rR₆
wherein the alkyl moieties may be optionally substituted with one or more fluorines;
m is 0 to 2;
n is 1 to 4;
r is 0 to 6;
R₄ and R₅ are independently selected from hydrogen or a C₁-2 alkyl;
R₆ is independently selected from hydrogen, methyl, hydroxyl, aryl, halo
substituted aryl, arylxoyC₁-3 alkyl, halo substituted arylxoyC₁-3 alkyl, indanyl,
indenyl, C7-11 polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl,
tetrahydrothienyl, thiencyl, tetrahydrothiopyranyl, thiopyranyl, C3-6 cycloalkyl, or a
C4-6 cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl or the heterocyclic moiety is unsubstituted or substituted by 1 to 3 methyl groups, one ethyl group or an hydroxyl group

provided that:

a) when R6 is hydroxyl, then m is 2; or
b) when R6 is hydroxyl, then r is 2 to 6; or
c) when R6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or
d) when R6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then r is 1 to 6;
e) when n is 1 and m is 0, then R6 is other than H in

-(CR4R5)nO(CR4R5)mR6;

X is independently selected from YR2, fluorine, NR4R5, or formyl amine;
Y is independently selected from O or S(O)m;
m' is 0, 1, or 2;
X2 is independently selected from O or NR8;
X3 is independently selected from H, R9, OR8, CN, C(O)R8, C(O)OR8, C(O)NR8R8, or NR8R8;
W is alkyl of 2 to 6 carbons, alkenyl of 2 to 6 carbon atoms or alkynyl of 2 to 6 carbon atoms;
R2 is independently selected from the group consisting of -CH3 and -CH2CH3 unsubstituted or substituted by 1 or more fluorines;
S is 0 to 4;
Z is independently selected from C(Y)R14, C(O)OR14, C(Y)NR10R14,
CN, C(NOR8)R14, C(O)NR8NR8C(O)R8, C(O)NR8NR10R14, C(NOR14)R8, C(NR8)NR10R14, C(NR14)NR8R8, C(NCN)NR10R14, C(NCN)SR9, (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]), (2-oxadiazolyl[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 heterocyclic ring systems are unsubstituted or substituted one or more times by R14;
Y' is independently selected from O or S;
R7 is -(CR4R5)qR12 or C1-6 alkyl wherein the R12 or C1-6 alkyl group is unsubstituted or substituted one or more times by methyl or ethyl unsubstituted or substituted by 1-3 fluorines, -F, -Br, -Cl, -NO2, -NR10R11, -C(O)R8, -CO2R8, -O(CH2)qR8, -CN, -C(O)NR10R11, -O(CH2)qC(O)NR10R11, -O(CH2)qC(O)R9, -NR10C(O)NR10R11, -NR10C(O)R11, -NR10C(O)OR9, -NR10C(O)R13, -C(NR10)NR10R11, -C(NCN)NR10R11, -C(NCN)SR9, -NR10C(NCN)SR9,
-NR10C(NCN)NR10R11, -NR10S(O)2R9, -S(O)mR9, -NR10C(O)C(O)NR10R11, 
NR10C(O)C(O)R10, or R13;

q is 0, 1, or 2;

R12 is independently selected from R13, C3-7 cycloalkyl, (2-, 3- or 4-pyridyl), 
pyrimidyl, pyrazolyl, (1- or 2-imidazolyl), pyrrolyl, piperazinyl, piperidinyl, 
morpholiny, furanyl, (2- or 3-thienyl), quinolinyl, naphthyl, or phenyl;

R8 is independently selected from hydrogen or R9;

R9 is independently selected from C1-4 alkyl which is unsubstituted or 
substituted by one to three fluorines;

R10 is independently selected from OR8 or R11;

R11 is independently selected from hydrogen, or C1-4 alkyl optionally 
substituted by one to three fluorines; or when R10 and R11 are as NR10R11 they may 
together with the nitrogen form a 5 to 7 membered ring comprised of carbon or carbon 
and at least one additional heteroatom selected from O, N, or S;

R13 is independently selected from 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 C1-2 alkyl groups;

R14 is independently selected from hydrogen or R7; or when R10 and R14 are 
as NR10R14 they may together with the nitrogen form a 5 to 7 membered ring 
comprised of carbon or carbon and one or more additional heteroatoms selected from 
O, N, or S;

or the pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein R1 is -CH2-cyclopropyl, 
cyclopentyl, 3-hydroxyyclohexyl, methyl or CF2H; X is YR2; Y is oxygen; X2 is 
oxygen; X3 is hydrogen; R2 is CF2H or methyl, W is 1,3-butadiynyl, and Z is 
C(O)OR14.

3. A compound according to claim 1 which is 
1,4-bis-[[methyl c-3-(3-cyclohexyloxy-4-methoxyphenyl)-r-1-cyclohexane 
1-carboxylate]-4-yl]butoa-1,3-diyneor, 
1,4-bis-[[c-3-(3-cyclohexyloxy-4-methoxyphenyl)-r-1-cyclohexane carboxylic 
acid]-4-yl]butoa-1,3-diyneor a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition comprising a compound according to 
claim 1 and a pharmaceutically acceptable excipient.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

- IPC(6) : C07C 69/76, 63/33, 223/00
- US CL. : 560/095; 562/488; 564/161

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. : 560/095; 562/488; 564/161

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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

- STN CAS; FILE REGISTRY STRUCTURE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

- Special categories of cited documents:
  - "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  - "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  - "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  - "&" document member of the same patent family

Date of the actual completion of the international search: 30 JANUARY 1996

Date of mailing of the international search report: 09 FEB 1996

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