Novel cyclohexane derivatives of formula (I) are described. These compounds inhibit the production of Tumor Necrosis Factor and are useful in the treatment of disease states mediated or exacerbated by TNF production. These compounds are also useful in the mediation or inhibition of enzymatic or catalytic activity of phosphodiesterase IV and are therefore useful in the treatment of disease states in need of mediation or inhibition thereof.
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CYANOCYCLOHEXANE COMPOUNDS, COMPOSITIONS, AND USES THEREOF

Field of Invention

The present invention relates to novel 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. [Tophy, "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 autacoids, as would be the case in vivo. Thus PDE IV inhibitors would be effective in the asthmatic lung, where levels of prostaglandin E2 and prostacyclin (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 erythematos.

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

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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

This invention relates to the novel compounds of Formula (I), as shown below, useful in the mediation or inhibition of the enzymatic activity (or catalytic activity) of phosphodiesterase IV (PDE IV). The novel compounds of Formula (I) also have Tumor Necrosis Factor (TNF) inhibitory activity.

This invention also relates to the pharmaceutical compositions comprising a compound of Formula (I) 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 (I), 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 (I).

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 (I).

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 (I). 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 (I).

The compounds of Formula (I) 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.

The compounds of Formula (I) are also useful in the treatment of yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production in vivo.
The compounds of this invention are represented by Formula (I):

\[
\begin{array}{c}
\text{X} \\
\text{R}_1 \text{R}_2 \text{R}_3 \text{R}_4 \\
\text{Z} \\
\text{X}_5 \\
\text{X}_3 \\
\end{array}
\]

wherein:

\( R_1 \) is -(CR\(_4\)R\(_5\))\(_n\)C(O)O(CR\(_4\)R\(_3\))mR\(_6\), -(CR\(_4\)R\(_5\))\(_n\)C(O)NR\(_4\)(CR\(_4\)R\(_5\))mR\(_6\), -(CR\(_4\)R\(_5\))\(_n\)O(CR\(_4\)R\(_5\))mR\(_6\), or -(CR\(_4\)R\(_5\))R\(_6\) wherein the alkyl moieties may be optionally substituted with one or more halogens;

\( m \) is 0 to 2;

\( n \) is 1 to 4;

\( r \) is 0 to 6;

\( R_4 \) and \( R_5 \) are independently selected from hydrogen or C\(_{1-2}\) alkyl;

\( R_6 \) is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC\(_{1-3}\) alkyl, halo substituted aryloxyC\(_{1-3}\) alkyl\(^{-}\), indanyl, indenyl, C\(_{7-11}\) polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thieryl, 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:

\( a \) when \( R_6 \) is hydroxyl, then \( m \) is 2; or

\( b \) when \( R_6 \) is hydroxyl, then \( r \) is 2 to 6; or

\( c \) when \( R_6 \) is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then \( m \) is 1 or 2; or

\( d \) when \( R_6 \) 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 \( R_6 \) is other than H in -(CR\(_4\)R\(_5\))\(_n\)O(CR\(_4\)R\(_5\))mR\(_6\);

\( X \) is YR\(_2\), halogen, nitro, NR\(_4\)R\(_5\), 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.
R₂ is independently selected from -CH₃ or -CH₂CH₃ optionally substituted by 1 or more halogens;

s is 0 to 4;

R₃ is hydrogen, halogen, C₁₋₄ alkyl, CH₂NHC(O)(C(O)NH₂), halo-
substituted C₁₋₄ alkyl, -CH=CR₈(R₈), cyclopropyl optionally substituted by R₈,
CN, OR₈, CH₂OR₈, NR₈R₁₀, CH₂NR₈R₁₀, C(Z)H, C(O)OR₈, C(O)NR₈R₁₀, or
C≡CR₈;

Z is O, NR₉, NOR₉, NCN, C(-CN)₂, CR₈CN, CR₈NO₂, CR₈C(O)OR₈,
CR₈C(O)NR₈R₈, C(-CN)NO₂, C(-CN)C(O)OR₈, or C(-CN)C(O)NR₈R₈;

Z is CR₈R₈OR₁₄, CR₈R₈OR₁₅, CR₈R₈SR₁₄, CR₈R₈SR₁₅,
CR₈R₈S(O)mR₇, CR₈R₈NR₁₀R₁₄, CR₈R₈NR₁₀S(O)₂R₁₀R₁₄,
CR₈R₈NR₁₀S(O)₂R₇, CR₈R₈NR₁₀C(Y)R₁₄, CR₈R₈NR₁₀C(O)OR₇,
CR₈R₈NR₁₀C(Y)NR₁₀R₁₄, CR₈R₈NR₁₀C(NCN)NR₁₀R₁₄,
CR₈R₈NR₁₀C(CR₄NO₂)NR₁₀R₁₄, CR₈R₈NR₁₀C(NCN)SR₉,

Z is CR₈R₈C(NR₁₀)OR₁₄, CR₈R₈C(NR₁₀)OR₁₅, CR₈R₈C(NR₁₀)SR₁₄,
CR₈R₈C(NR₁₀)CR₈R₈, CR₈R₈CN, CR₈R₈(tetrazolyl), CR₈R₈(imidazolyl),
CR₈R₈(thiazolidinyl), CR₈R₈(pyrazolyl), CR₈R₈(thiazolyl),
CR₈R₈(thiazolyl), CR₈R₈(oxazolyl), CR₈R₈(oxazolidinyl), CR₈R₈(triazolyl),
CR₈R₈(isoxazolyl), CR₈R₈(oxadiazolyl), CR₈R₈(thiadiazolyl),

CR₈R₈(morpholinyl), CR₈R₈(piperidinyl), CR₈R₈(piperazinyl), CR₈R₈(pyrrolyl),
CR₈R₈C(NOR₉)R₁₄, CR₈R₈C(NOR₁₄)R₈, CR₈R₈NR₁₀C(NR₁₀)SR₉,
CR₈R₈NR₁₀C(NR₁₀)NR₁₀R₁₄, CR₈R₈NR₁₀C(O)C(O)NR₁₀R₁₄, or
CR₈R₈NR₁₀C(O)C(O)OR₁₄;

X₅ is H, R₉, OR₈, CN, C(O)R₈, C(O)OR₈, C(O)NR₈R₈, or NR₈R₈;

Y is O or S;

R₇ is -(CR₄R₅)ₙₗR₁₂ or C₁₋₆ alkyl wherein the R₁₂ or C₁₋₆ alkyl group is
optionally substituted one or more times by C₁₋₂ alkyl optionally substituted by one
to three fluorines, -F, -Br, -Cl, -NO₂, -NR₁₀R₁₁, -C(O)R₈, -C(O)OR₈, -OR₈, -CN,
-C(O)NR₁₀R₁₁, -OC(O)NR₁₀R₁₁, -OC(O)R₈, -NR₁₀C(O)NR₁₀R₁₁,

R₁₂ is C₃₋₇ 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;
R₈ is independently selected from hydrogen or R₉;
R₈ is R₉ or fluorine;
R₉ is C₁₋₄ alkyl optionally substituted by one to three fluorines;
R₁₀ is OR₈ or R₁₁;
R₁₁ is 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 optionally containing at least one additional heteroatom selected from O, N, or S;
R₁₃ is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, or thia-diazolyl, 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 hydrogen or R₇; or when R₁₀ and R₁₄ are as NR₁₀R₁₄ 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;
R₁₅ is C(O)R₁₄, C(O)NR₈R₁₄, S(O)₂NR₈R₁₄, S(O)₂R₇;
provided that:
f) when R₁₂ is N-pyrazolyl, N-imidazolyl, N-triazolyl, N-pyrrol, N-piperazinyl, N-piperidinyl, or N-morpholinyl, then q is not 1;
g) when s is 0, X₂ is oxygen, R₃ is hydrogen, X₃ is hydrogen, and X₅ is hydrogen, then Z is not CH₂OH or CH₂OCH₃;
h) when X₂R₁ is OCF₂H or OCF₃, X is F, OCF₂H or OCF₃, X₃ is H, s is zero, X₅ is H, Z is CH₂OR₁₄, and R₁₄ is C₁₋₇ unsubstituted alkyl, then R₃ is other than H;
or a pharmaceutically acceptable salt thereof.

Detailed Description of the Invention

This invention relates to the novel compounds of Formula (I), and to pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent. 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 a compound of Formula (I).

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,
disorders such as depression and multi-infarct dementia.

The compounds of Formula (I) are also useful in the treatment of viral
infections, where such viruses are sensitive to upregulation by TNF or will elicit
TNF production in vivo. 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 (I). 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 (I).

The compounds of Formula (I) 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 Formula (I) are also useful in the treatment of 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 Formula (I) 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 co-administration of the anti-fungal agent with a compound of Formula (I) may be in any preferred composition for that compound such as is well known to those skilled in the art, for instance the various Amphotericin B formulations. Co-administration of an anti-fungal agent with a compound of Formula (I) may mean simultaneous administration or in practice, separate administration of the agents to the mammal but in a consecutive manner. In particular, the compounds of Formula (I) may be co-administered with a formulation of Amphotericin B, notably for systemic fungal infections. The preferred organism for treatment is the Candida organism. The compounds of Formula (I) may be co-administered in a similar manner with anti-viral or anti-bacterial agents.

The compounds of Formula (I) 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 (I) to a mammal in need of such treatment. Preferably, a compound of Formula (I) is administered for inhibiting or reducing the toxicity of the Amphotericin class of compounds, in particular Amphotericin B.

Preferred compounds are as follows:

When \( R_1 \) for the compounds of Formula (I) is an alkyl substituted by 1 or more halogens, the halogens are preferably fluorine and chlorine, more preferably a \( C_1-4 \) 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 -CF\(_3\), -CH\(_2\)F, -CHF\(_2\), -CF\(_2\)CF\(_2\), NOCH\(_2\)C\(_6\)H\(_4\), or -CH\(_2\)CH\(_2\)F. Preferred \( R_1 \) substituents for the compounds of Formula (I) are CH\(_2\)-cyclopropyl, CH\(_2\)-C\(_5\)-6 cyclooalkyl, C\(_4\)-6 cycloalkyl, C\(_7\)-11 polycycloalkyl, (3- or 4-cyclopentenyl), phenyl, tetrahydrofuran-3-yl, benzyl or \( C_1\)-2 alkyl optionally substituted by 1 or more fluorines, -(CH\(_2\))\(_{1-2}\)C(O)O(CH\(_2\))\(_{0-2}\)CH\(_3\), -(CH\(_2\))\(_{1-3}\)O(CH\(_2\))\(_{0-2}\)CH\(_3\), and -(CH\(_2\))\(_{1-2}\)-4OH.

When the \( R_1 \) term contains the moiety (CR\(_4\)R\(_5\)), the R\(_4\) and R\(_5\) terms are independently hydrogen or alkyl. This allows for branching of the individual methylene units as (CR\(_4\)R\(_5\))\(_n\) or (CR\(_4\)R\(_5\))\(_m\); each repeating methylene unit is independent of the other, e.g., (CR\(_4\)R\(_5\))\(_n\) wherein \( n \) is 2 can be -CH\(_2\)CH(-CH\(_3\))- for instance. The individual hydrogen atoms of the repeating methylene unit or the branching hydrocarbon can optionally be substituted by fluorine independent of each other to yield, for instance, the preferred \( R_1 \) substitutions, as noted above.

When \( R_1 \) is a C\(_7\)-11 polycycloalkyl, examples are bicyclo[2.2.1]-heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, tricyclo[5.2.1.0\(_2\)-6]decyl, etc. additional
examples of which are described in Saccamano et al., WO 87/06576, published 5
November 1987, whose disclosure is incorporated herein by reference in its entirety.

Z is preferably CR8R8OR14, CR8R8OR15, CR8R8SR14, CR8R8SR15,
CR8R8S(O)_{m}R7, CR8R8NR10R14, CR8R8NS(O)_{2}NR10R14, CR8R8NS(O)_{2}R7,
CR8R8NR10C(O)R14, CR8R8NR10C(O)OR7, CR8R8NR10C(O)NR10R14,
CR8R8NR10C(NCN)NR10R14, CR8R8NR10C(CR4NO2)NR10R14,
CR8R8NR10C(NCN)SR9, CR8R8NR10C(CR4NO2)SR9, CR8R8C(O)OR14,
CR8R8C(O)NR10R14, CR8R8C(NR10)NR10R14, CR8R8CN,
CR8R8(oxadiazolyl), CR8R8(thiadiazolyl), CR8R8C(NOR8)R14.

CR8R8C(NOR14)R8, CR8R8NR10C(NR10)SR9, CR8R8NR10C(NR10)NR10R14,
CR8R8NR10C(O)C(O)NR10R14, or CR8R8NR10C(O)C(O)OR14; most preferred
are those compounds wherein the R8 group of Z is H and the R14 group of Z is R4.

Preferred X5 groups are H, OH, OCH3, CN, C(O)R8, C(O)OH, C(O)OCH3,
C(O)NH2, CON(CH3)2, NH2, or N(CH3)2. The most preferred groups are H, OH,
CN, C(O)OH, C(O)NH2 or NH2.

Preferred X groups for Formula (I) are those wherein X is YR2 and Y is oxygen.
The preferred X2 group for Formula (I) is that wherein X2 is oxygen. The
preferred X3 group for Formula (I) is that wherein X3 is hydrogen. Preferred R2
groups, where applicable, is a C1-2 alkyl optionally 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 R3 moieties are C(O)NH2, C=CR8, CH2NHC(O)C(O)NH2, CN,
C(Z')H, CH2OH, CH2F, CF2H, and CF3. More preferred are C=CH and CN. Z' is
preferably O or NOR8.

Preferred R7 moieties include optionally substituted
-(CH2)1-2(cyclopropyl), -(CH2)0-2(cyclobutyl), -(CH2)0-2(cyclopenty1),
-(CH2)0-2(cyclohexyl), -(CH2)0-2(2, 3- or 4-pyridyl), (CH2)1-2(2-imidazolyl),
(CH2)2(4-morpholinyl), (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 optionally
containing 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,
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 optionally 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-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).

When the R7 group is optionally substituted by a heterocyclic ring such as imidazolyl, pyrazolyl, triazolyl, tetrazolyl, or thiazolyl, the heterocyclic ring itself may be optionally 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-triazolyl, or 1-(R8)-5-triazolyl. Where applicable, the ring may be substituted one or more times by R8.

Preferred are those compounds of Formula (I) wherein R1 is -CH2-cyclopropyl, -CH2-C5-6 cycloalkyl, -C4-6 cycloalkyl, tetrahydrofuran-3-yl, (3- or 4-cyclopentenyl), benzyl or -C1-2 alkyl optionally substituted by 1 or more fluorines, and -(CH2)2-4 OH; R2 is methyl or fluoro-substituted alkyl, R3 is CN or C=CR8; and X is YR2.
Most preferred are those compounds wherein R₁ is \(-\text{CH}_2\)-cyclopropyl, cyclopentyl, methyl or CF₂H; R₃ is CN or C=CH; X is YR₂; Y is oxygen; X₂ is oxygen; X₃ is hydrogen; and R₂ is CF₂H or methyl.

A preferred subgenus of the compounds of Formula (I) is the compounds of

\[
\text{(Ia)}
\]

wherein:

- R₁ is CH₂-cyclopropyl, CH₂-C₅-6 cycloalkyl, C₄-6 cycloalkyl, C₇-11 polycycloalkyl, (3- or 4-cyclopentenyl), phenyl, tetrahydrofuran-3-yl, benzyl or C₁-2 alkyl optionally substituted by 1 or more fluorines, -(CH₂)₁-₃C(O)O(CH₂)₀-₂CH₃, -(CH₂)₁-₃O(CH₂)₀-₂CH₃, and -(CH₂)₁-₄OH;
- X is YR₂, halogen, nitro, NR₄R₅, or formyl amine;
- Y is O or S(O)ₐ;
- m is 0,1; or 2;
- R₂ is -CH₃ or -CH₂CH₃ optionally substituted by 1 or more halogens;
- R₃ is hydrogen, C₁-₄ alkyl, CH₂NH(C(O)C(O)NH₂, halo-substituted C₁-₄ alkyl, CN, CH₂OR₈, C(Z)H, C(O)OR₈, C(O)NR₈R₁₀, or C=CR₈;
- Z is O or NOR₈;
- CR₈R₈R₁₄, CR₈R₈OR₁₅, CR₈R₈SR₁₅, CR₈R₈SR₁₅,
- CR₈R₈S(O)ₐR₇, CR₈R₈(OR₁₀R₁₄, CR₈R₈NS(O)₂NR₁₀R₁₄, CR₈R₈NS(O)₂R₇,
- CR₈R₈NR₁₀C(Y')R₁₄, CR₈R₈NR₁₀C(O)OR₇, CR₈R₈NR₁₀C(Y')NR₁₀R₁₄,
- CR₈R₈NR₁₀C(NCN)NR₁₀R₁₄, CR₈R₈NR₁₀C(C₄NO₂)NR₁₀R₁₄,
- CR₈R₈NR₁₀C(NCN)SR₉, CR₈R₈NR₁₀C(C₄NO₂)SR₉, CR₈R₈C(Y')OR₁₄,
- CR₈R₈C(Y')NR₁₀R₁₄, CR₈R₈C(NR₁₀)NR₁₀R₁₄, CR₈R₈CN,
- CR₈R₈(oxadiazolyl), CR₈R₈(thiadiazolyl), CR₈R₈C(NOR₈)R₁₄,
- CR₈R₈C(NOR₁₄)R₈, CR₈R₈NR₁₀C(NR₁₀)SR₉, CR₈R₈NR₁₀C(NR₁₀)NR₁₀R₁₄,
- CR₈R₈NR₁₀C(O)C(O)NR₁₀R₁₄, or CR₈R₈NR₁₀C(O)C(O)OR₁₄;
- X₅ is H, OR₈, CN, C(O)OR₈ or NR₈R₈;
- Y' is O or S;
- R₇ is -(CR₄R₅)ₜ₋₁R₁₂ or C₁-₆ alkyl wherein the R₁₂ or C₁-₆ alkyl group is optionally substituted one or more times by methyl or ethyl substituted by 1-3 fluorines, -F, -Br, -Cl, -NO₂, -NR₁₀R₁₁, -C(O)R₈, -C(O)OR₈, -OR₈, -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)_{2}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), (1- or 2-imidazolyl), piperazinyl, morpholinyl, (2- or 3-thienyl), (4- or 5-thiazolyl), or phenyl;
R_{8} is independently selected from hydrogen or R_{9};
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 C(O)R_{14}, C(O)NR_{8}R_{14}, S(O)_{2}NR_{8}R_{14}, S(O)_{2}R_{7};
provided that:
a) when R_{12} is N-pyrazolyl, N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl, N-piperidinyl, or N-morpholinyl, then q is not 1;
b) when R_{3} is hydrogen and X_{5} is hydrogen, then Z is not CH_{2}OH or CH_{2}OCH_{3};
c) when X_{2}R_{1} is OCF_{2}H or OCF_{3}, X is F, OCF_{2}H or OCF_{3}, X_{3} is H, s is zero, X_{5} is H, Z is CH_{2}OR_{14}, and R_{14} is C_{1-7} unsubstituted alkyl, then R_{3} is other than H;
or the pharmaceutically acceptable salts thereof.
Preferred compounds of Formula (I) are:
cis-[3-cyano-3-(3-cyclopentoxy-4-methoxyphenyl)cyclohexan-1-yl]methanol;
cis-[3-cyano-3-(3-cyclopentoxy-4-methoxyphenyl)cyclohexan-1-yl]methylamine; and
methyl cis-(2-[3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-yl]acetate).

Definitions

The terms "C₃₋₅ alkyl", "C₄₋₆ alkyl", "C₅₋₆ alkyl" or "alkyl" 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" includes 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. "Cycloalkyl" or "cycloalkyl alkyl" includes radicals 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 thieryl. "Halo" means chloro, fluoro, bromo, or iodo.

By the phrase "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.

By the term "TNF mediated disease or disease states" is meant 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. For instance, a monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte, but many other cells produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epidermal keratinocytes, and B-lymphocytes. Lymphokines are generally referred to as being produced by lymphocyte cells. Examples of cytokines for the present invention include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF-α) and Tumor Necrosis Factor-beta (TNF-β).

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, his cytokine is TNF-a.

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, his cytokine is TNF-α.

All of the compounds of Formula (I) 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. All of the compounds of Formula (I) 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.

METHODS OF PREPARATION

Preparing compounds of Formula (I) can be accomplished by one of skill in the art according to the procedures outlined in the Examples, infra. The preparation
of any remaining compounds of Formula (I) not described therein may be prepared by the analogous processes disclosed herein which comprise:

a) for compounds of Formula (I) wherein X or X₃ is other than Br, I, NO₂, amino, or S(O)ₘR₂ when m' is 0, 1 or 2 and R₃ is other than C(=Z')H and wherein Z is CH₂COOCH₃, homologating a compound of Formula (2)

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\begin{align*}
\text{(2)}
\end{align*}
$$

where R₁ represents R₁ as defined in relation to Formula (I) or a group convertible to R₁ and X and X₃ represent X and X₃ as defined in relation to Formula (I) or a group convertible to X or X₃ and R₃ represents R₃ as defined in relation to Formula (I) or a group convertible to R₃ and Z is CHO, by, for example, the method of Corey and Märlkl (Tetrahedron Letters 1967, 3201) or Corey and Court (J. Org. Chem. 1972, 37, 1926), followed by hydrolysis of the ketene dithioacetals product, to provide compounds of Formula (I) wherein R₃ is other than C(=Z')H and wherein Z is CH₂COOCH₃; preparation of such compounds of Formula (I) wherein R₃ is C(=Z')H proceed in an analogous fashion from the compound of Formula (2) wherein =Z' is an aldehyde protecting group, such as a dimethylacetal or a dioxolane, followed by deprotection to the aldehyde and subsequent elaboration by standard procedures known to those of skill in the art to the remaining compounds of Formula (I) wherein Z' is other than O.

Saponification of the ester moiety of compounds of Formula (I) wherein R₃ is other than COOR₈ and wherein Z is CH₂COOCH₃ with, e.g., potassium hydroxide in methanol, provides compounds of Formula (I) wherein R₃ is other than COOR₈ and wherein Z is CH₂COOH; preparation of such compounds of Formula (I) wherein R₃ is COOR₈ proceed in an analogous fashion from the compound of Formula (2) wherein =Z' is an aldehyde protecting group, such as a dimethylacetal or a dioxolane, followed by deprotection to the aldehyde and subsequent elaboration by standard procedures known to those of skill in the art to the remaining compounds of Formula (I) wherein R₃ is COOR₈.

Compounds of Formula (I) wherein R₃ is other than C(=Z')H and wherein Z is CH₂OH may be prepared, with appropriate manipulation of certain chemically sensitive functional groups, by reduction of the aldehyde (Z = CHO) or ester (Z =
COOR₈) of the compounds of Formula (2) wherein R₁ represents R₁ as defined in relation to Formula (I) or a group convertible to R₁ and X and X₃ represents X and X₃ as defined in relation to Formula (I) or a group convertible to X or X₃ and R₃ represents R₃ as defined in relation to Formula (I) or a group convertible to R₃ and wherein R₃ is other than C(=Z)H; preparation of such compounds of Formula (I) wherein R₃ is C(=Z)H proceed in an analogous fashion from the compound of Formula (2) wherein Z' is an aldehyde protecting group, such as a dimethylacetal or a dioxolane, followed by deprotection to the aldehyde and subsequent elaboration by standard procedures known to those of skill in the art to the remaining compounds of Formula (I) wherein Z' is other than O.

Reductive amination with, e.g., ammonium formate and sodium cyanoborohydride in an alcoholic solvent, a compound of Formula (2) wherein R₃ is other than C(=Z)H and where R₁ represents R₁ as defined in relation to Formula (I) or a group convertible to R₁ and X and X₃ represent X and X₃ as defined in relation to Formula (I) or a group convertible to X or X₃ and R₃ represents R₃ as defined in relation to Formula (I) or a group convertible to R₃ and Z is CHO, provides the compounds of Formula (I) wherein R₃ is other than C(=Z)H and Z is CH₂NH₂; preparation of such compounds of Formula (I) wherein R₃ is C(=Z)H proceed in an analogous fashion from the homologated aldehyde intermediates wherein Z' is an aldehyde protecting group, such as a dimethylacetal or a dioxolane, followed by deprotection to the R₃ aldehyde and subsequent elaboration by standard procedures known to those of skill in the art to the remaining compounds of Formula (I) wherein Z' is other than O.

It will be recognized that compounds of Formula (I) may exist in two distinct diastereomeric forms possessing distinct physical and biological properties; such isomers may be separated by standard chromatographic methods. Such isomers may be independently converted to other compounds of Formula (I) wherein Z is, e.g., CR₈R₈OR₁₄, CR₈R₈OR₁₅, CR₈R₈NR₁₃R₁₄, CR₈R₈NS(O)₂NR₁₃R₁₄, CR₈R₈NS(O)₂R₇, or CR₈R₈NR₁₃C(Y')R₁₄, by any of the wide variety of O and N alkylation or acylation procedures known to those of skill in the art.

For example, with proper manipulation of any chemically sensitive functional groups, compounds of Formula (I) wherein NR₁₃R₁₄ represent a ring, such as a 1- or 2-tetrazole, may be derived from reaction of an appropriate compound of Formula (I) wherein Z possesses a leaving group, L, as in CR₈R₈L, and L is a mesylate, tosylate, chloride or bromide, with the appropriate metal salt of HNR₁₃R₁₄, e.g., 5-(R₁₄)-tetrazole; the appropriate compound of Formula (I)
wherein Z is mesylate, tosylate, Br or Cl, derived in turn from the appropriate compound of Formula (I) wherein Z is CR_8R_8OH. Using similar procedures but with the appropriate metal salt of SR_{14} or SR_{15}, compounds of Formula (I) wherein Z is CR_8R_8SR_{14} or CR_8R_8SR_{15} may be prepared.

With proper manipulation (protection/deprotection) of any chemically sensitive functional groups:

a) Compounds of the Formula (I) wherein X or X_3 are formyl amine may be formed at the last step, by formylating a compound wherein X or X_3 is NH_2, obtained by removal of a protecting group from the amine functionality; 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).

b) Compounds of the Formula (I) wherein X or X_3 are Br, I or SR_2 may be prepared from a similarly deprotected amine by diazotization of the amine and diazonium displacement.

c) Compounds of the Formula (I) wherein X or X_3 are NO_2 may be prepared from a similarly deprotected amine by oxidation of the amine to the nitro group.

d) Compounds of the Formula (I) wherein Y is S(O)m' when m' is 0, 1 or 2 may be prepared from the compounds of the Formula (I) wherein Y is S by oxidation of the SR_2 moiety under conditions well known those skilled in the art.

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

Compounds of Formula (2) may be prepared in turn by the processes described in co-pending U.S. patent application serial number 08/099,900 filed on 30 July 1993.

The following examples are provided to illustrate how to make and use this invention. These examples are not intended to and should not be viewed as limiting the scope or practice of this invention in any way.

**SYNTHETIC EXAMPLES**

**Example 1**

**Preparation of cis-[3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-yl]methanol**

A suspension of methyl cis-[3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylate (0.186 g, 0.52 mmol) in ether (2.0 mL)
with methanol (0.025 mL) and lithium borohydride (0.02 g, 0.78 mmol) is stirred overnight at room temperature under an argon atmosphere. The reaction mixture is partitioned between methylene chloride and acidic water, is extracted three times, is dried (magnesium sulfate) and is evaporated. Purification by flash column chromatography provides the product.

EXAMPLE 2

Preparation of cis-[3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-yl]methylamine

A solution of cis-[3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-yl]methanol (0.057 g, 0.16 mmol) in tetrahydrofuran (1.2 mL) under an argon atmosphere is treated with triphenylphosphine (0.04 g, 0.16 mmol), phthalimide (0.02 g, 0.16 mmol) and then diethylzodicarboxylate (0.03 mL, 0.16 mmol) is added dropwise. The reaction flask is covered with foil and the mixture is stirred at room temperature for 30h. The solvent is evaporated and the residue is purified by flash column chromatography, to provide the phthalimide, which is dissolved in ethanol (0.5 mL) under an argon atmosphere and is stirred with hydrazine hydrate (0.08 mL, 0.15 mmol) for 3 days. The precipitate is removed by filtration, the filtrate is applied to a silica column and the product is eluted.

EXAMPLE 3

Preparation of Methyl cis-[2-[3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-yl]acetate

To a solution of 2-trimethylsilyl-1,3-dithiane (0.925 mL, 4.87 mmol) in dry tetrahydrofuran (8 mL) at 0°C under an argon atmosphere is added rapidly n-butyllithium (2.5M in hexanes, 1.92 mL, 4.8 mmol). After 10 min, the mixture is cooled to -78°C and a solution of 3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxaldehyde (0.78 g, 2.3 mmol) in tetrahydrofuran (4 mL) is added. After 10 min, aqueous sodium chloride is added, the mixture is allowed to warm to room temperature and is diluted with water. The mixture is extracted three times with methylene chloride, the extract is dried (magnesium sulfate) and evaporated. Purification by flash chromatography provides the ketene dithioacetal product. Perchloric acid (70%, 0.86 mL, 9.96 mmol) and mercuric chloride (2.12 g, 7.84 mmol) are added to a solution of the ketene dithioacetal (0.86 g, 1.95 mmol) in methanol (31 mL) under an argon atmosphere and the mixture is heated at reflux for 2h and then is allowed to stir at room temperature for 42h. The mixture is diluted with methylene chloride, is filtered through Celite, the filtrate is neutralized with aqueous sodium bicarbonate,
is extracted three times with methylene chloride, the organic extract is washed three
times with aqueous sodium sulfite, is dried (magnesium sulfate) and is evaporated.
Purification by flash chromatography provides the product.

METHODS OF TREATMENT

In order to use a compound of Formula (I) or a pharmaceutically acceptable
salt thereof may be used neat though a preferred technique is to present them with a
carrier/diluent accordance with standard pharmaceutical practice. Any formulation
compatible with the chosen method of delivery and the stability of the compound
may be used. One skilled in the art will be able to select and prepare an acceptable
formulation in accordance with standard practices in the field of the formulary arts.

The compounds of Formula (I) or may be administered orally (when active
by this route), oral, intravenous, intraperitoneal, and intramuscular administration,
topically, parenterally, or by inhalation in conventional dosage forms prepared by
combining such agent with standard pharmaceutical carriers according to
conventional procedures in an amount sufficient to produce the desired therapeutic
activity.

The amount of a compound of Formula (I) required for therapeutic effect on
topical administration will, of course, vary with the compound chosen, the nature
and severity of the condition and the animal undergoing treatment, and is ultimately
at the discretion of the physician.

The daily dosage regimen for oral administration is suitably about .001
mg/kg to 100mg/kg, preferably 0.01 mg/Kg to 40 mg/Kg, of a compound of
Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.
The active ingredient may be administered from 1 to 6 times a day, sufficient to
exhibit activity.

UTILITY EXAMPLES

EXAMPLE A

Inhibitory effect of compounds of Formula (I) on in vitro TNF production
by human monocytes

The inhibitory effect of compounds of Formula (I) 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

EXAMPLE B

Two models of endotoxic shock have been utilized to determine in vivo TNF
activity for the compounds of Formula (I). 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 exemplified compounds 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 Formula (I) 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 [Tophy 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 [Tophy et al., J. Biol. Chem., 267:1798-1804, 1992].

Phosphodiesterase activity is assayed as described in the protocol of Tophy 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.

EXAMPLE D

The ability of selected PDE IV inhibitors to increase cAMP accumulation in intact tissues is assessed using U-937 cells, a human monocyte cell line that has been shown to contain a large amount of PDE IV. To assess the activity of PDE IV inhibition in intact cells, nondifferentiated U-937 cells (approximately 10^5 cells/reaction tube) were incubated with various concentrations (0.01-1000 μM) of PDE inhibitors for one minute and 1 μM prostaglandin E2 for an additional four minutes. Five minutes after initiating the reaction, cells were lysed by the addition of 17.5% perchloric acid, the pH was neutralized by the addition of 1M potassium carbonate and cAMP content was assessed by RIA. A general protocol for this assay is described in Brooker et al., Radioimmunassay of cyclic AMP and cyclic GMP, Adv. Cyclic Nucleotide Res., 10:1-33, 1979. The compounds of the working examples as described herein for Formula (I) have demonstrated a positive EC50s in the μM range in the above assay.

No toxic effects are expected when these compounds are administered in accordance with the present invention.
What is claimed is:

1. A compound of Formula (I):

   ![Chemical Structure](image)

   (I)

   wherein:

   - $R_1$ is -(CR$_4$R$_5$)$_n$C(O)O(CR$_4$R$_5$)$_m$R$_6$, -(CR$_4$R$_5$)$_n$C(O)NR$_4$(CR$_4$R$_5$)$_m$R$_6$, -(CR$_4$R$_5$)$_n$O(CR$_4$R$_5$)$_m$R$_6$, or -(CR$_4$R$_5$)$_n$R$_6$ wherein the alkyl moieties may be optionally substituted with one or more halogens;
   - $m$ is 0 to 2;
   - $n$ is 1 to 4;
   - $r$ is 0 to 6;
   - $R_4$ and $R_5$ are independently selected from hydrogen or C$_1$-$2$ alkyl;
   - $R_6$ is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC$_1$-$3$ alkyl, halo substituted aryloxyC$_1$-$3$ alkyl, indanyl, indenyl, C$_7$-$11$ polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydrofuran, fluorinated propargyl, pyranyl, tetrahydrothienyl, thiienyl, tetrahydrothiopyran, thiopyran, 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:
     a) when $R_6$ is hydroxyl, then $m$ is 2; or
     b) when $R_6$ is hydroxyl, then $r$ is 2 to 6; or
     c) when $R_6$ is 2-tetrahydrofuran, 2-tetrahydrofuaxan, 2-tetrahydrofuran, or 2-tetrahydrothiopyran, then $m$ is 1 or 2; or
     d) when $R_6$ is 2-tetrahydrofuran, 2-tetrahydrothiopyran, 2-tetrahydrofuran, or 2-tetrahydrothiopyran, then $r$ is 1 to 6;
     e) when $n$ is 1 and $m$ is 0, then $R_6$ is other than H in -(CR$_4$R$_5$)$_n$O(CR$_4$R$_5$)$_m$R$_6$;
   - $X$ is YR$_2$, halogen, nitro, NR$_4$R$_5$, 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;
R₂ is independently selected from -CH₃ or -CH₂CH₃ optionally substituted by 1 or more halogens; 
s is 0 to 4;
R₃ is hydrogen, halogen, C₁-₄ alkyl, CH₂NHC(O)C(O)NH₂, halo-
substituted C₁-₄ alkyl, -CH=CR₈R₈', cyclopropyl optionally substituted by R₈',
-CN, OR₈, CH₂OR₈, NR₈R₁₀, CH₂NR₈R₁₀, C(Z')H, C(O)OR₈, C(O)NR₈R₁₀, or
C=CR₈';
Z' is O, NR₉, NOR₉, NCN, (-CN)₂, CR₉CN, CR₉NO₂, CR₉C(O)OR₈,
CR₉C(O)NR₈R₈', C(-CN)NO₂, C(-CN)C(O)OR₉, or C(-CN)C(O)NR₈R₈';
Z is CR₈R₈OR₁₄, CR₈R₈OR₁₅, CR₈R₈SR₁₄, CR₈R₈SR₁₅,
CR₈R₈S(O)ₗ₉₇, CR₈R₈NR₁₀R₁₄, CR₈R₈NR₁₀S(O)₂NR₁₀R₁₄,
CR₈R₈NR₁₀S(O)₂R₇, CR₈R₈NR₁₀C(Y')R₁₄, CR₈R₈NR₁₀C(O)OR₇,
CR₈R₈NR₁₀C(Y')NR₁₀R₁₄, CR₈R₈NR₁₀C(NCN)NR₁₀R₁₄,
CR₈R₈NR₁₀C(C₄NO₂)NR₁₀R₁₄, CR₈R₈NR₁₀C(NCN)SR₉,
CR₈R₈NR₁₀C(C₄NO₂)SR₉, CR₈R₈C(O)OR₁₄, CR₈R₈C(Y')NR₁₀R₁₄,
CR₈R₈C(NR₁₀)NR₁₀R₁₄, CR₈R₈C⁻CN, CR₈R₈(tetrazolyl), CR₈R₈(imidazolyl),
CR₈R₈(imidazolidinyl), CR₈R₈(pyrazolyl), CR₈R₈(thiazolyl),
CR₈R₈(thiazolidinyl), CR₈R₈(oxazolyl), CR₈R₈(oxazolidinyl), CR₈R₈(triazolyl),
CR₈R₈(isoxazolyl), CR₈R₈(oxadiazolyl), CR₈R₈(thiadiazolyl),
CR₈R₈(morpholyl), CR₈R₈(piperidinyl), CR₈R₈(piperazinyl), CR₈R₈(pyrryl),
CR₈R₈(C(NOR₈)R₁₄, CR₈R₈C(NOR₁₄)R₈, CR₈R₈NR₁₀C(NR₁₀)SR₉,
CR₈R₈NR₁₀C(NR₁₀)NR₁₀R₁₄, CR₈R₈NR₁₀C(O)C(O)NR₁₀R₁₄, or
CR₈R₈NR₁₀C(O)C(O)OR₁₄;
X₅ is H, R₉, OR₈, CN, C(O)R₈, C(O)OR₈, C(O)NR₈R₈, or NR₈R₈;
Y ' is O or S;
R₇ is (-CR₄R₅)ₗ₋₉R₁₂ or C₁-₆ alkyl wherein the R₁₂ or C₁-₆ alkyl group is
optionally substituted one or more times by C₁-₂ alkyl optionally substituted by one
to three fluorines, -F, -Br, -Cl, -NO₂, -NR₉R₁₁, -C(O)R₈, -C(O)OR₈, -OR₈, -CN,
-C(O)NR₁₀R₁₁, -OC(O)NR₁₀R₁₁, -OC(O)R₈, -NR₁₀C(O)NR₁₀R₁₁,
-OC(O)R₈, -NR₁₀C(O)OR₈, -NR₁₀C(O)R₁₃, -C(NR₁₀)NR₁₀R₁₁,
-C(NCN)NR₁₀R₁₁, -C(NCN)SR₉, -NR₁₀C(NCN)SR₉, -NR₁₀C(NCN)NR₁₀R₁₁,
-NR₁₀S(O)₂R₇, -S(O)ₗ₋₉₇, -NR₁₀C(O)C(O)NR₁₀R₁₁, -NR₁₀C(O)C(O)R₁₀,
thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl, or tetrazolyl;
q is 0, 1, or 2;
R₁₂ is C₃-₇ 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;
R₈ is independently selected from hydrogen or R₉;
R₉ is R₈ or fluorine;
R₉ is C₆₋₄ alkyl optionally substituted by one to three fluorines;
R₁₀ is OR₈ or R₁₁;
R₁₁ is hydrogen, or C₆₋₄ 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 optionally containing at least one additional heteroatom selected from O, N, or S;
R₁₃ 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 C₁₋₂ alkyl groups;
R₁₄ is hydrogen or R₇; or when R₁₀ and R₁₄ are as NR₁₀R₁₄ 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;
R₁₅ is C(O)R₁₄, C(O)NR₈R₁₄, S(O)₂NR₈R₁₄, S(O)₂R₇;
provided that:
f) when R₁₂ is N-pyrazolyl, N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl, N-piperidinyl, or N-morpholinyl, then q is not 1;
g) when s is 0, X₂ is oxygen, R₃ is hydrogen, X₃ is hydrogen, and X₅ is hydrogen, then Z is not CH₂OH or CH₂OCH₃;
h) when X₂R₁ is OCF₂H or OCF₃, X is F, OCF₂H or OCF₃, X₃ is H, s is zero, X₅ is H, Z is CH₂OR₁₄, and R₁₄ is C₁₋₇ unsubstituted alkyl, then R₃ is other than H;
or a pharmaceutically acceptable salt thereof.
2. A compound of claim 1 which is
cis-[3-cyano-3-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexan-1-yl]methanol;
cis-[3-cyano-3-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexan-1-yl]methylamine; or
methyl cis-[2-[3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-yl]acetate].
3. A pharmaceutical composition comprising a compound of Formula (I) according to claim 1 and a pharmaceutically acceptable excipient.
4. A method for treating an allergic or inflammatory state which method comprises administering to a subject in need thereof an effective amount of a compound of Formula (I) according to claim 1 alone or in combination with a pharmaceutically acceptable excipient.
A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :C07C 255/46; A61K 31/275
US CL. :558/426; 514/520, 521, 523
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. : 558/426; 514/520, 521, 523

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

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

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>
<tbody>
<tr>
<td>A</td>
<td>Chemical Abstracts, Vol 82, issued 1974, Markoryan et al, &quot;Isoquinoline Derivatives. X Synthesis of 2-aryl-4-spiro- cyclohexane-6,7-dimethoxy -1,2,3,4-tetra hyroloquinolines and their acyclic analogs&quot;, Abstract No. 82: 139935v, note compound &quot;1-(3,4, dimethylphenyl) cyclohexanecarbonitrile&quot;, 7th line of abstract.</td>
<td>1-4</td>
</tr>
</tbody>
</table>

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

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier document published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search 23 DECEMBER 1994

Date of mailing of the international search report 13 JAN 1995

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Form PCT/ISA/210 (second sheet) (July 1992)*
INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. □ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. X Claims Nos.: 1,3,4 (IN PART) because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

   Please See Extra Sheet.

3. □ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. □ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. □ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 

4. □ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 

Remark on Protest □ The additional search fees were accompanied by the applicant’s protest.
□ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1)) (July 1992)
BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE

2. Where no meaningful search could be carried out, specifically:

Aside from the specific structures of page 11, line 32; page 11, line 33; page 11, lines 35-36; and page 16, lines 3-4; page 16, lines 12-13; page 16, lines 24-25, respectively, and the three compounds of claims 2 (the first two of which are not recited in the description and the last one of which is the same compound of page 11, lines 35-36 and page 16, lines 24-25), i.e., compounds with clearly defined structures, the terms used in these unsearched claims cannot be ascertained into meaningful enough specific compound structures such as to afford a determination of proper specific subclasses to search. Thus, the unsearchable claims will be searched only to the extent that they read on searchable features (i.e., the above noted compounds) in the specification.