

Method for Treating COPD

Field of Invention

The present invention relates to the use of certain compounds for treating chronic obstructive pulmonary disease (COPD).

5 Background of the Invention

Chronic obstructive pulmonary disease (COPD) is an umbrella term frequently used to describe two conditions of fixed airways disease, chronic bronchitis and emphysema. Chronic bronchitis and emphysema are most commonly caused by smoking; approximately 90% of patients with COPD are or were
10 smokers. Although approximately 50% of smokers develop chronic bronchitis, only 15% of smokers develop disabling airflow obstruction. Certain animals, particularly horses, suffer from COPD as well.

The airflow obstruction associated with COPD is progressive, may be accompanied by airway hyperreactivity, and may be partially reversible. Non-
15 specific airway hyper-responsiveness may also play a role in the development of COPD and may be predictive of an accelerated rate of decline in lung function in smokers.

COPD is a significant cause of death and disability. It is currently the fourth leading cause of death in the United States and Europe. Treatment guidelines
20 advocate early detection and implementation of smoking cessation programs to help reduce morbidity and mortality due to the disease. However, early detection and diagnosis has been difficult for a number of reasons.

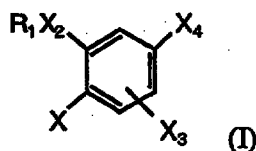
COPD takes years to develop and smokers often deny any ill effects from smoking, attributing the early warning signs of increased breathlessness as a sign of
25 age. Similarly, acute episodes of bronchitis often are not recognized by the general practitioner as early signs of COPD. Many patients exhibit features of more than one disease (e.g. chronic bronchitis or asthmatic bronchitis) making precise diagnosis a challenge, particularly in early disease. Also, many patients do not seek medical help until they are experiencing more severe symptoms associated with
30 reduced lung function, such as dyspnea, persistent cough, and sputum production. As a consequence, the vast majority of patients are not diagnosed or treated until they are in a more advanced stage of disease.

There is a need for a new approach to treating COPD. This invention provides one such approach.

35 Summary of the Invention

This invention covers a method for the prophylaxis or treatment of COPD in a mammal by administering to a mammal in need thereof an effective amount of a

compound of Formula (I) alone or in admixture with a pharmaceutically acceptable excipient wherein Formula (I) comprises:



5 wherein:

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

m is 0 to 2;

10 n is 1 to 4;

r is 0 to 6;

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

R_6 is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxy C_{1-3} alkyl, halo substituted aryloxy C_{1-3} alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranal, tetrahydrothienyl, thienyl, tetrahydrothiopyranal, thiopyranal, 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 OH, 1 to 3 methyl groups or one ethyl group;

provided that:

20 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-tetrahydrothiopyranal, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or

d) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranal,

25 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

$-(CR_4R_5)_nO(CR_4R_5)_mR_6$;

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

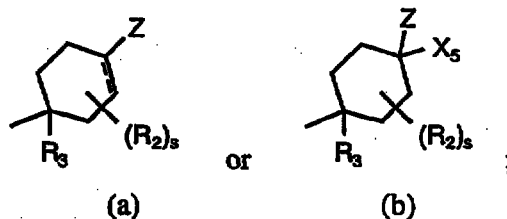
Y is O or $S(O)_m$;

30 m' is 0, 1, or 2;

X_2 is O or NR_8 ;

X_3 is hydrogen or X;

X_4 is



X_5 is H, R_9 , OR_8 , CN, $C(O)R_8$, $C(O)OR_8$, $C(O)NR_8R_8$, or NR_8R_8 ;

R_2 is independently selected from the group consisting of $-CH_3$ and $-CH_2CH_3$ optionally substituted by 1 or more halogens;

5 s is 0 to 4;

R_3 is hydrogen, halogen, C_{1-4} alkyl, $CH_2NHC(O)C(O)NH_2$, halo-

substituted C_{1-4} alkyl, $-CH=CR_8R_8$, cyclopropyl optionally substituted by R_8 , CN, OR_8 , CH_2OR_8 , NR_8R_{10} , $CH_2NR_8R_{10}$, $C(Z)H$, $C(O)OR_8$, $C(O)NR_8R_{10}$, or

10 $C\equiv CR_8$;

Z' is O, NR_9 , NOR_8 , NCN , $C(-CN)_2$, CR_8CN , CR_8NO_2 , $CR_8C(O)OR_8$, $CR_8C(O)NR_8R_8$, $C(-CN)NO_2$, $C(-CN)C(O)OR_9$, or $C(-CN)C(O)NR_8R_8$;

Z is $C(Y)R_{14}$, $C(O)OR_{14}$, $C(Y)NR_{10}R_{14}$, $C(NR_{10})NR_{10}R_{14}$, CN, $C(NOR_8)R_{14}$, $C(O)NR_8NR_8C(O)R_8$, $C(O)NR_8NR_{10}R_{14}$, $C(NOR_{14})R_8$,

15 $C(NR_8)NR_{10}R_{14}$, $C(NR_{14})NR_8R_8$, $C(NCN)NR_{10}R_{14}$, $C(NCN)SR_9$, (2-, 4- or 5-imidazolyl), (3-, 4- or 5-pyrazolyl), (4- or 5-triazolyl[1,2,3]), (3- or 5-triazolyl[1,2,4]), (5-tetrazolyl), (2-, 4- or 5-oxazolyl), (3-, 4- or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,2,4]), (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 may be optionally substituted one or more times by R_{14} ;

the dotted line in formula (a) represents a single or double bond;

Y' is O or S;

25 R_7 is $-(CR_4R_5)_qR_{12}$ or C_{1-6} alkyl wherein the R_{12} or C_{1-6} alkyl group is optionally substituted one or more times by C_{1-2} alkyl optionally substituted by one to three fluorines, -F, -Br, -Cl, $-NO_2$, $-NR_{10}R_{11}$, $-C(O)R_8$, $-C(O)OR_8$, $-OR_8$, -CN, $-C(O)NR_{10}R_{11}$, $-OC(O)NR_{10}R_{11}$, $-OC(O)R_8$, $-NR_{10}C(O)NR_{10}R_{11}$, $-NR_{10}C(O)R_{11}$, $-NR_{10}C(O)OR_9$, $-NR_{10}C(O)R_{13}$, $-C(NR_{10})NR_{10}R_{11}$, $-C(NCN)NR_{10}R_{11}$, $-C(NCN)SR_9$, $-NR_{10}C(NCN)SR_9$, $-NR_{10}C(NCN)NR_{10}R_{11}$, $-NR_{10}S(O)_2R_9$, $-S(O)_mR_9$, $-NR_{10}C(O)C(O)NR_{10}R_{11}$, $-NR_{10}C(O)C(O)R_{10}$, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl, or tetrazolyl;

q is 0, 1, or 2;

35 R_{12} is C_{3-7} 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 R₈ or fluorine;

R₉ is C₁₋₄ alkyl optionally substituted by one to three fluorines;

R₁₀ is OR₈ or R₁₁;

- 5 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;

- 10 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;

- 15 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;

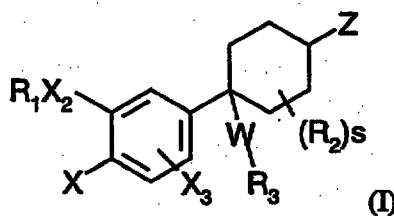
provided that:

f) when R₁₂ is N-pyrazolyl, N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl, N-piperidinyl, or N-morpholinyl, then q is not 1; or

- 20 g) when X₂R₁ is OCF₂H or OCF₃, X is OCF₂H or OCF₃, X₃ is H, s is zero, X₅ is H, Z is C(O)OR₁₄ and R₁₄ is C₁₋₇ unsubstituted alkyl, then R₃ is other than H;

or the pharmaceutically acceptable salts thereof.

- 25 In a second aspect, this invention relates to the use of a compound of Formula (II) for treating COPD in a mammal, particularly a human, wherein Formula (II) is defined as follows:



- 30 wherein:

R₁ is -(CR₄R₅)_nC(O)O(CR₄R₅)_mR₆, -(CR₄R₅)_nC(O)NR₄(CR₄R₅)_mR₆, -(CR₄R₅)_nO(CR₄R₅)_mR₆, or -(CR₄R₅)_rR₆ wherein the alkyl moieties unsubstituted or substituted with one or more halogens;

m is 0 to 2;

n is 0 to 4;

r is 0 to 6;

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

5 R₆ is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC₁₋₃ alkyl, halo substituted aryloxyC₁₋₃ alkyl, indanyl, indenyl, C₇₋₁₁ polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranal, tetrahydrothienyl, thienyl, tetrahydrothiopyranal, thiopyranal, C₃₋₆ cycloalkyl, or a C₄₋₆ cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl or heterocyclic moiety is unsubstituted or substituted by 1 to 3 methyl groups, one ethyl group, or an hydroxyl
10 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-tetrahydrothiopyranal,
- 15 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or
- d) when R₆ is 2-tetrahydropyranyl, 2-tetrahydrothiopyranal, 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;

20 X is YR₂, fluorine, NR₄R₅, or formyl amine;

Y is O or S(O)_m;

m' is 0, 1, or 2;

X₂ is O or NR₈;

X₃ is hydrogen or X;

25 X₄ is H, R₉, OR₈, CN, C(O)R₈, C(O)OR₈, C(O)NR₈R₈, or NR₈R₈;

R₂ is independently selected from -CH₃ or -CH₂CH₃ optionally substituted by 1 or more halogens;

s is 0 to 4;

30 W is alkyl of 2 to 6 carbons, alkenyl of 2 to 6 carbon atoms or alkynyl of 2 to 6 carbon atoms;

R₃ is COOR₁₄, C(O)NR₄R₁₄ or R₇;

Z is OR₁₄, OR₁₅, SR₁₄, S(O)_mR₇, S(O)₂NR₁₀R₁₄, NR₁₀R₁₄, NR₁₄C(O)R₉, NR₁₀C(Y)R₁₄, NR₁₀C(O)OR₇, NR₁₀C(Y)NR₁₀R₁₄, NR₁₀S(O)₂NR₁₀R₁₄, NR₁₀C(NCN)NR₁₀R₁₄, NR₁₀S(O)₂R₇,

35 NR₁₀C(CR₄NO₂)NR₁₀R₁₄, NR₁₀C(NCN)SR₉, NR₁₀C(CR₄NO₂)SR₉,

NR₁₀C(NR₁₀)NR₁₀R₁₄, NR₁₀C(O)C(O)NR₁₀R₁₄, or NR₁₀C(O)C(O)OR₁₄;

Y' is O or S;

R₇ is $-(CR_4R_5)_qR_{12}$ 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)₂₋₄OR₈, -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 R₁₃, C₃₋₇ cycloalkyl, or an unsubstituted or substituted aryl or heteroaryl group selected from the group consisting of (2-, 3- or 4-pyridyl), pyrimidinyl, pyrazolyl, (1- or 2-imidazolyl), pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, (2- or 3-thienyl), quinolinyl, naphthyl, and phenyl;

R₈ is independently selected from hydrogen or R₉;

R₉ is C₁₋₄ alkyl optionally substituted by one to three fluorines;

R₁₀ is OR₈ or R₁₁;

R₁₁ is hydrogen, or C₁₋₄ alkyl unsubstituted or 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 one or more additional heteroatoms selected from O, N, or S;

R₁₃ is a substituted or unsubstituted heteroaryl group selected from the group consisting of oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, and thiadiazolyl, and where R₁₃ is substituted on R₁₂ or R₁₃ the rings are connected through a carbon atom and each second R₁₃ ring may be unsubstituted or substituted by one or two C₁₋₂ alkyl groups unsubstituted or substituted on the methyl with 1 to 3 fluoro atoms;

R₁₄ is hydrogen or R₇; or when R₈ and R₁₄ are as NR₈R₁₄ 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;

R₁₅ is C(O)R₁₄, C(O)NR₈R₁₄, S(O)_qNR₈R₁₄ or S(O)_qR₇ where q is 0, 1 or 2; provided that:

(f) R₇ is not C₁₋₄ alkyl unsubstituted or substituted by one to three fluorines;

or the pharmaceutically acceptable salts thereof.

In a further aspect, this invention relates to a pharmaceutically acceptable composition for treating COPD comprising a pharmaceutically acceptable excipient

and between about 1 and 60mg of a compound of Formula (I) or (II) at least once daily.

Detailed Description of the Invention

5 This invention relates to the use of compounds of Formulas (I) or (II) and to pharmaceutical compositions comprising a compound of Formulas (I) or (II) and a pharmaceutically acceptable carrier or diluent, for treating COPD in a mammal, particularly a human, suffering from COPD. The drug may have use in the prophylaxis of the phenomena associated with COPD before clinical manifestation of the disease in a mammal, particularly a human.

10 COPD is characterized by a chronic inflammatory process in the lung marked by an increase in the activation and/or number of alveolar macrophages, CD8⁺ T-cells and neutrophils. Most notably with respect to the therapy of COPD is the ability to alter the trafficking and activation of neutrophils. The neutrophil is believed to play a central role in the pathophysiology of COPD. Neutrophil
15 activation results in the release of a number of inflammatory mediators and proteinases, most importantly neutrophil elastase which contributes to the progressive fibrosis, airway stenosis and destruction of the lung parenchyma, leading to an accelerated decline in airway function. Neutrophil elastase is also a powerful mucus secretagogue and thus may contribute to the characteristic mucus
20 hypersecretion that characterizes COPD. The compounds of this invention have marked effects on neutrophil activity, inhibiting neutrophil chemotaxis and degranulation *in vitro*. In animal models, the instant compounds reduce neutrophil extravasation from the circulation, pulmonary sequestration and the edematous responses to a number of inflammatory insults *in vivo*.

25 Additional activities that may contribute to the therapeutic activity of PDE4 inhibitors in COPD include bronchodilation and modulation of pulmonary neuronal activity. Although the degree of reversibility of reduced airway flow is low in COPD, a small increase may have an acute positive effect, as well as a gradual reduction in the slope of the decline which may result in a profound effect on quality
30 of life for COPD patients. The ability of inhaled muscarinic antagonists to produce clinically meaningful improvements in pulmonary function in COPD, at least acutely, suggest that a large component of the reversible airways obstruction in this disease is associated with a dysregulation of pulmonary nerves. Although not studied in detail as yet, PDE4 inhibitors may also modulate the activity of airway
35 epithelial cells, a rich source of proinflammatory mediators that are released upon environmental insult (e.g., smoke), and inhibit vascular smooth muscle hyperplasia, a structural change in end stage COPD that is associated with right heart failure.

The preferred compounds for use in this invention are defined as follows:

When R_1 for the compounds of the 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 $-CF_3$, $-CH_2F$, $-CHF_2$, $-CF_2CHF_2$, $-CH_2CF_3$, and $-CH_2CHF_2$. Preferred R_1 substituents for the compounds of the Formula (I) are CH_2 -cyclopropyl, CH_2 - C_{5-6} cycloalkyl, 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, $-(CH_2)_{1-3}C(O)O(CH_2)_{0-2}CH_3$, $-(CH_2)_{1-3}O(CH_2)_{0-2}CH_3$, and $-(CH_2)_{2-4}OH$.

When the R_1 term contains the moiety (CR_4R_5) , the R_4 and R_5 terms are independently hydrogen or alkyl. This allows for branching of the individual methylene units as $(CR_4R_5)_n$ or $(CR_4R_5)_m$; each repeating methylene unit is independent of the other, e.g., $(CR_4R_5)_n$ wherein n is 2 can be $-CH_2CH(-CH_3)-$, 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 $C(O)R_8$, $C(O)OR_8$, $C(O)NR_8R_8$, $C(NR_8)NR_8R_8$, CN , $C(NOR_8)R_8$, $C(O)NR_8NR_8C(O)R_8$, $C(NR_8)NR_8R_8$, $C(NCN)NR_8R_8$, $C(NCN)SR_9$, (1-, 4- or 5-{ R_8 }-2-imidazolyl), (1-, 4- or 5-{ R_8 }-3-pyrazolyl), (1-, 2- or 5-{ R_8 }-4-triazolyl[1,2,3]), (1-, 2-, 4- or 5-{ R_8 }-3-triazolyl[1,2,4]), (1- or 2-{ R_8 }-5-tetrazolyl), (4- or 5-{ R_8 }-2-oxazolyl), (3- or 4-{ R_8 }-5-isoxazolyl), (3-{ R_8 }-5-oxadiazolyl[1,2,4]), (5-{ R_8 }-3-oxadiazolyl[1,2,4]), (5-{ R_8 }-2-oxadiazolyl[1,3,4]), (5-{ R_8 }-2-thiadiazolyl[1,3,4]), (4- or 5-{ R_8 }-2-thiazolyl), (4- or 5-{ R_8 }-2-oxazolidinyl), (4- or 5-{ R_8 }-2-thiazolidinyl), (1-, 4- or 5-{ R_8 }-2-imidazolidinyl); most preferred are those compounds wherein the R_8 group of Z is R_4 .

X_5 is preferably hydrogen, C_{1-2} alkyl optionally substituted by one to three fluorines, OR_8 , CN , $C(O)R_8$, $C(O)OR_8$, $C(O)NR_8R_8$, or NR_8R_8 .

Preferred X groups for Formula (I) are those wherein X is YR_2 and Y is oxygen. The preferred X_2 group for Formula (I) is that wherein X_2 is oxygen. The preferred X_3 group for Formula (I) is that wherein X_3 is hydrogen. Preferred R_2

groups, where applicable, are 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, 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(cyclopentyl), -(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, 5-(R₈)-1-tetrazolyl, 5-(R₈)-2-tetrazolyl, 1-tetrazolyl, 2-tetrazolyl, morpholinyl, piperazinyl, 4-(R₈)-1-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 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 includes, 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.

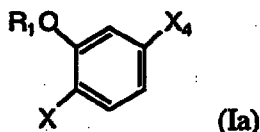
Preferred rings for R₁₃ include (2-, 4- or 5-imidazolyl), (3-, 4- or 5-pyrazolyl), (4- or 5-triazolyl[1,2,3]), (3- or 5-triazolyl[1,2,4]), (5-tetrazolyl), (2-, 4- or 5-oxazolyl), (3-, 4- or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,2,4]), (2-oxadiazolyl[1,3,4]), (2-thiadiazolyl[1,3,4]), (2-, 4-, or 5-thiazolyl), (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 the 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 -CH₂-cyclopropyl, cyclopentyl, methyl or CF₂H; R₃ is CN; 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 the Formula (I) is the compounds of the Formula (Ia)

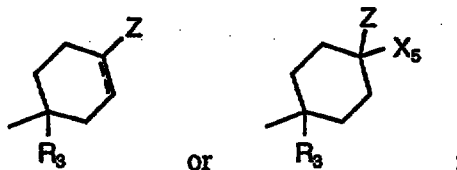


wherein:

R₁ is CH₂-cyclopropyl, CH₂-C₅₋₆ cycloalkyl optionally substituted by OH, 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)₂₋₄OH;

X is YR₂, halogen, nitro, NR₄R₅, or formyl amine;

X₄ is



- (a) (b)
- X₅ is H, R₉, OR₈, CN, C(O)R₈, C(O)OR₈, C(O)NR₈R₈, or NR₈R₈;
 Y is O or S(O)_m;
 m' is 0, 1, or 2;
- 5 R₂ is -CH₃ or -CH₂CH₃ optionally substituted by 1 or more halogens;
 R₃ is hydrogen, C₁₋₄ alkyl, CH₂NHC(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;
 Z is C(O)R₁₄, C(O)OR₁₄, C(O)NR₁₀R₁₄, C(NR₁₀)NR₁₀R₁₄, CN,
- 10 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, (1-, 4- or 5-
 {R₁₄}-2-imidazolyl), (1-, 4- or 5-{R₁₄}-3-pyrazolyl), (1-, 2- or 5-
 {R₁₄}-4-triazolyl[1,2,3]), (1-, 2-, 4- or 5-{R₁₄}-3-triazolyl[1,2,4]), (1- or 2-
 {R₁₄}-5-tetrazolyl), (4- or 5-{R₁₄}-2-oxazolyl), (3- or 4-{R₁₄}-5-isoxazolyl),
- 15 (3-{R₁₄}-5-oxadiazolyl[1,2,4]), (5-{R₁₄}-3-oxadiazolyl[1,2,4]),
 (5-{R₁₄}-2-oxadiazolyl[1,3,4]), (5-{R₁₄}-2-thiadiazolyl[1,3,4]), (4- or
 5-{R₁₄}-2-thiazolyl), (4- or 5-{R₁₄}-2-oxazolidinyl), (4- or
 5-{R₁₄}-2-thiazolidinyl), (1-, 4- or 5-{R₁₄}-2-imidazolidinyl);
- R₇ is -(CR₄R₅)_qR₁₂ or C₁₋₆ alkyl wherein the R₁₂ or C₁₋₆ alkyl group is
- 20 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,
 -NR₁₀C(O)R₁₁, -NR₁₀C(O)OR₉, -NR₁₀C(O)R₁₃, -C(NR₁₀)NR₁₀R₁₁,
 -C(NCN)NR₁₀R₁₁, -C(NCN)SR₉, -NR₁₀C(NCN)SR₉, -NR₁₀C(NCN)NR₁₀R₁₁,
- 25 -NR₁₀S(O)₂R₉, -S(O)_mR₉, -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), (1- or 2-imidazolyl),
 piperazinyl, morpholinyl, (2- or 3-thienyl), (4- or 5-thiazolyl), or phenyl;
- 30 the dotted line formula (a) represents a single or double bond;
 R₈ is independently selected from hydrogen or R₉;
 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
- 35 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;

- 5 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;

provided that:

- a) when R₁₂ is N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl, or N-morpholinyl, then q is not 1; or

b) when R₁ is CF₂H or CF₃, X is F, OCF₂H, or OCF₃, X₅ is H, Z is C(O)OR₁₄ and R₁₄ is C₁₋₇ unsubstituted alkyl, then R₃ is other than H; or the pharmaceutically acceptable salts thereof.

The most preferred compounds of Formula (I) are:

- 15 methyl 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohex-1-ene-1-carboxylate;
4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohex-1-ene-1-carboxylic acid;
methyl *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-
20 carboxylate];
methyl *trans*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate];
methyl *cis*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylate];
25 methyl *trans*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylate];
cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid];
cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-
30 carboxylate], *tris*(hydroxymethyl)ammonium methane salt;
cis-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylic acid];
trans-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid];
35 *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid];

- trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid]; methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylate];
- 5 methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylate];
- methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-carboxylate];
- methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-cyclohexane-1-carboxylate];
- 10 *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-carboxylic acid];
- trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-carboxylic acid]; *cis*-[4-cyano-4-(3-cyclopentylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxamide]; *cis*-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-carboxamide]; *trans*-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-carboxamide]; *cis*-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-carbohydrazide]; *cis*-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-(2-acetylcarbohydrazide)]; *cis*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyano-1-(3-methyl[1,2,4]oxadiazol-5-
- 20 yl)cyclohexane]; *cis*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyano-1-(2-methyl[1,3,4]oxadiazol-5-yl)cyclohexane]; *cis*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyano-1-(2-methyl[1,3,4]thiadiazol-5-yl)cyclohexane]; *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxy-1-tris(methylthio)methylcyclohexane]; methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxy-cyclohexane-1-carboxylate];
- 25 *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylic acid];
- cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxamide];
- 30 methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxy-cyclohexane-1-carboxylate];
- cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylic acid];
- cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxamide];
- 35 *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxy-cyclohexane-1-carboxaldehyde];

- methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylate];
- trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylic acid];
- 5 methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylate];
- trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylic acid];
- trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxamide];
- 10 *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxamic acid];
- N-methyl-*cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxamic acid];
- 15 *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-N-(2-cyanoethyl)carboxamide];
- cis*-[1-(2-cyanoethyl)-5-{4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl}tetrazole]; and
- cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-1-(tetrazol-5-yl)cyclohexane].
- 20

As regards the compounds of Formula (II), the preferred compounds are as follows:

- 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
- 25 carbons, and most preferred are the moieties -CF₃, -CH₂F, -CHF₂, -CF₂CHF₂, -CH₂CF₃, and -CH₂CHF₂. Preferred R₁ substituents for the compounds of Formula (I) are CH₂-cyclopropyl, CH₂-C₅₋₆ cycloalkyl, C₄₋₆ cycloalkyl unsubstituted or substituted with OHC₇₋₁₁ polycycloalkyl, (3- or 4-cyclopentenyl),
- 30 phenyl, tetrahydrofuran-3-yl, benzyl or C₁₋₂ alkyl 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 R₁ term contains the moiety (CR₄R₅), the R₄ and R₅ terms are independently hydrogen or alkyl. This allows for branching of the individual
- 35 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)-, for instance. The individual hydrogen atoms of the repeating methylene unit or the

branching hydrocarbon can unsubstituted or be 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[5.2.1.0^{2,6}]decyl, etc. additional
5 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. It is most preferred that W is ethynyl or 1,3-butadiynyl.

10 Z is preferably OR₁₄, OR₁₅, SR₁₄, S(O)_mR₇, S(O)₂NR₁₀R₁₄, NR₁₀R₁₄, NR₁₄C(O)R₉, NR₁₀C(O)R₁₄, NR₁₀C(O)OR₇, NR₁₀C(O)NR₁₀R₁₄, NR₁₀S(O)₂NR₁₀R₁₄, NR₁₀C(NCN)NR₁₀R₁₄, NR₁₀S(O)₂R₇, NR₁₀C(CR₄NO₂)NR₁₀R₁₄, NR₁₀C(NCN)SR₉, NR₁₀C(CR₄NO₂)SR₉, NR₁₀C(NR₁₀)NR₁₀R₁₄, NR₁₀C(O)C(O)NR₁₀R₁₄, or NR₁₀C(O)C(O)OR₁₄.

15 Preferred X groups for Formula (I) are those wherein X is YR₂ and Y is oxygen. The preferred X₂ group for Formula (Ia) 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 unsubstituted or substituted by 1 or more halogens. The halogen atoms are preferably fluorine and chlorine, more preferably
20 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)₀₋₂(2-, 3- or 4-pyridyl), (CH₂)₁₋₂(2-imidazolyl), (CH₂)₂(4-morpholinyl), (CH₂)₂(4-
25 piperazinyl), (CH₂)₁₋₂(2-thienyl), (CH₂)₁₋₂(4-thiazolyl), unsubstituted or substituted pyrimidinyl, and substituted or unsubstituted (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 comprised of carbon or carbon and at least one heteroatom selected from O, N, or S include, but
30 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, 4-(R₈)-1-piperazinyl, or pyrrolyl ring.

Preferred rings when R₁₀ and R₁₄ in the moiety -NR₁₀R₁₄ together with
35 the nitrogen to which they are attached may form a 5 to 7 membered ring comprised of carbon or carbon and at least one 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 includes, but is not limited to, 2-(R₇)-1-imidazolyl,
 5 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
 10 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, 4-(R₁₄)-1-piperazinyl, or 4-(R₁₅)-1-piperazinyl.

Preferred rings for R₁₃ include (2-, 4- or 5-imidazolyl), (3-, 4- or
 15 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 unsubstituted or substituted by a heterocyclic ring
 20 such as imidazolyl, pyrazolyl, triazolyl, tetrazolyl, or thiazolyl, the heterocyclic ring itself may be unsubstituted or substituted by R₈ 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
 25 by R₈.

Preferred are those compounds of Formula (II) wherein R₁ is -CH₂-cyclopropyl, -CH₂-C₅₋₆ cycloalkyl, -C₄₋₆ cycloalkyl unsubstituted or substituted by OH, tetrahydrofuran-3-yl, (3- or 4-cyclopentenyl), benzyl or -C₁₋₂ alkyl unsubstituted or substituted by 1 or more fluorines, and -(CH₂)₂₋₄ OH; R₂ is methyl
 30 or fluoro-substituted alkyl, W is ethynyl or 1,3-butadiynyl; R₃ is R₇ where R₇ is an unsubstituted or substituted aryl or heteroaryl ring, X is YR₂, and Z is OR₁₄, OR₁₅, NR₁₀R₁₄, or NR₁₄C(O)R₉.

Most preferred are those compounds of Formula (II) wherein R₁ is -CH₂-cyclopropyl, cyclopentyl, 3-hydroxycyclopentyl, methyl or CF₂H; X is YR₂;
 35 Y is oxygen; X₂ is oxygen; X₃ is hydrogen; and R₂ is CF₂H or methyl, W is ethynyl or 1,3-butadiynyl, and R₃ is a substituted or unsubstituted pyrimidinyl ring.

The most preferred compounds of Formula (II) are:

- cis*-[4-(2-aminopyrimidin-5-ylethynyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-ol],
cis-[4-(2-aminopyrimidin-4-ylethynyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-cyclohexan-1-ol],
5 *trans*-[4-(2-acetamidopyrimidin-5-ylethynyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-ol],
trans-[4-(2-aminopyrimidin-5-yl-ethynyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-cyclohexan-1-ol],
cis-[4-(2-methylaminopyrimidin-5-ylethynyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-ol],
10 *cis*-[4-(3-cyclopentyloxy-4-methoxyphenyl)-4-(pyrid-4-ylethynyl)cyclohexan-1-ol],
cis-[4-(3-cyclopentyloxy-4-methoxyphenyl)-4-(pyrid-2-ylethynyl)cyclohexan-1-ol],
15 *cis*-[4-(4-cyanothien-2-ylethynyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-cyclohexan-1-ol],
cis-[4-(thiazol-2-ylethynyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-ol],
cis-[4-(3-cyclopentyloxy-4-methoxyphenyl)-4-[4-(5-methyl-
20 [1,2,4]oxadiazol-2-yl)thien-2-ylethynyl] cyclohexan-1-ol],
cis-[4-(3-cyclopentyloxy-4-methoxyphenyl)-4-(2-[3-(3-methyl[1,2,4]oxadiazol-5-yl)phenyl]ethynyl)cyclohexan-1-ol],
cis-[4-(3-cyclopentyloxy-4-methoxyphenyl)-4-(2-[3-(5-methyl[1,3,4]oxadiazol-2-yl)phenyl]ethynyl)cyclohexan-1-ol],
25 *cis*-[4-(3-cyclopentyloxy-4-methoxyphenyl)-4-(2-[3-(5-methyl[1,2,4]oxadiazol-3-yl)phenyl]ethynyl)cyclohexan-1-ol],
cis-4-(3-cyclopentyloxy-4-methoxyphenyl)-4-[3-(5-trifluoromethyl-[1,2,4]oxadiazol-3-yl)phenylethynyl)cyclohexan-1-ol,
cis-4-(3-cyclopentyloxy-4-methoxyphenyl)-4-[3-(5-methyl-[1,3,4]thiadiazol-
30 2-yl)phenylethynyl]cyclohexan-1-ol,
trans-[4-(3-cyclopentyloxy-4-methoxyphenyl)-4-(pyrid-2-ylethynyl)cyclohexyl-1-amine],
trans-[4-(3-cyclopentyloxy-4-methoxyphenyl)-4-(pyrid-2-ylethynyl)cyclohexyl-1-formamide],
35 *trans*-[4-(3-cyclopentyloxy-4-methoxyphenyl)-4-[5-(5-methyl-[1,2,4]oxadiazol-2-yl)thien-2-ylethynyl]cyclohexyl-1-amine], cyclohexylsulfamate salt

cis-[4-(3-cyclopentyloxy-4-methoxyphenyl)-4-(pyrid-2-ylethynyl)cyclohexyl-1-amine],

cis-[4-(3-cyclopentyloxy-4-methoxyphenyl)-4-(pyrid-2-ylethynyl)cyclohexyl-1-formamide],

5 *cis*-[4-(3-cyclopentyloxy-4-methoxyphenyl)-4-[5-(5-methyl-[1,2,4]oxadiazol-2-yl)thien-2-ylethynyl]cyclohexyl-1-amine], cyclohexylsulfamate salt,

trans-[4-(2-aminopyrimidin-5-ylethynyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine], cyclohexylsulfamate salt, or

10 *cis*-[4-(2-aminopyrimidin-5-ylethynyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl-1-amine], cyclohexylsulfamate salt.

Some compounds of Formula (I) and Formula (II) may exist in both racemic and optically active forms; some may also exist in distinct diastereomeric forms possessing distinct physical and biological properties. All of these compounds are
15 considered to be within the scope of the present invention. Therefore another aspect of the present invention is the administration of either a racemate, a single enantiomeric form, a single diastereomeric form, or mixtures thereof.

The terms *cis* and *trans* denote stereochemistry at the C-1 position of the cyclohexane ring relative to the R₃ group at the C-4 position.

20 The terms "C₁₋₃ alkyl", "C₁₋₄ alkyl", "C₁₋₆ 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,
25 including but not limited to vinyl, 1-propenyl, 2-propenyl, 2-propynyl, or 3-methyl-2-propenyl. "Cycloalkyl" or "cycloalkyl alkyl" includes 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
30 monocyclic, i.e., phenyl. The alkyl chain includes both straight or branched chain radicals of 1 to 4 carbon atoms. "Heteroaryl" as used herein, is meant an aromatic ring system containing one or more heteroatoms, such as imidazolyl, triazolyl, oxazolyl, pyridyl, pyrimidyl, pyrazolyl, pyrrolyl, furanyl, or thienyl. "Halo" as used herein is meant all halogens, i.e., chloro, fluoro, bromo, or iodo.

35 METHODS OF PREPARATION:

The preparation of compounds of Formula (I) is fully set forth in U.S. patent 5,552,438 issued 3 September 1996. This patent is incorporated herein in its

entirety by reference as if fully set out herein. The compounds of Formula (II) are known compound and can be prepared by the methods set out in published PCT application PCT/US95/16711 published as WO96/19988 on 4 July 1996 or PCT/US96/08080 published as WO96/38150 on 05 December 1996. The contents of these published PCT applications are incorporated herein by reference as if fully set forth herein.

METHODS OF TREATMENT

In order to use a compound of Formula (I) and (II) or a pharmaceutically acceptable salt thereof for the treatment of COPD, it will be formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. The compounds of Formula (I) and (II) or a pharmaceutically acceptable salt, polymorph, hydrate, etc., thereof can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of COPD.

The pharmaceutical composition of the present invention will comprise an effective, non-toxic amount of a compound of Formula (I) or (II) and a pharmaceutically acceptable carrier or diluent. The compounds of Formula (I) and (II) are administered in conventional dosage forms prepared by combining a compound of Formula (I) and (II) in an amount sufficient to reduce COPD symptoms and/or its progression, with standard pharmaceutical carriers according to conventional procedures. These procedures may involve mixing, granulating, and compressing or dissolving the ingredients as appropriate to the desired preparation.

Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form, or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1 gram. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates, or oils and are incorporated in a soft gelatin capsule shell. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, glycerine, or water with a flavoring or coloring agent.

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) and (II) 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.

While it is possible for an active ingredient to be administered neat, it is preferable to present it as a pharmaceutical formulation. The active ingredient may
5 comprise, for topical administration, from 0.001% to 10% w/w, e.g., from 1% to 2% by weight of formulation, although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of Formulation.

It will be recognized by one of skill in the art that the form and character of
10 the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration, and other well-known variables.

Formulations of the present invention comprise an active ingredient together with one or more acceptable carrier(s) thereof and optionally any other therapeutic
15 ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of Formulation and not deleterious to the recipient thereof.

The preferred pharmaceutical formulation is an oral formulation and one which contains between about 1mg and 60mg of a compound of formula (I) or formula (II) at least once a day to a patient suffering from COPD or who is at risk
20 for developing COPD. Preferably the formulation will be a tablet or similar solid dosage form such as an immediate release tablet. The more preferred formulation is a tablet which contains Formula (I) or Formula (II) in an amount of 5mg, 10mg, 15mg or 20mg. Most preferably the formulation will be an immediate release tablet which contain about 15mg of a compound; preferably the compound will be cis-[4-
25 cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid]; or a pharmaceutically acceptable salt, polymorph, pro-drug, or hydrate thereof.

This invention relates to a method for treating COPD in a human suffering from COPD, or for preventing or reducing the intensity of the onset of COPD in a human, by administering at least once daily a pharmaceutical composition containing
30 a compound of Formula (I) or Formula (II) in an amount between 1mg and 20mg admixed with a pharmaceutically acceptable excipient. More preferably the methods comprise administering a composition which contains 5mg, 10mg, 15mg or 20 mg at least twice daily. Most preferably the compound will contain about 15mg of cis-[4-
35 cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid]; or a pharmaceutically acceptable salt, polymorph, or hydrate thereof and will be administered twice daily. And preferably the composition will be administered as a tablet and will be administered orally.

Example 1**Tablet Formulation**

A tablet was prepared as described further herein using as the active ingredient *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid] and the excipients listed in Table 1.

Table 1

Ingredient	Quantity (mg/tablet)
<i>cis</i> -[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid];	15.0
Lactose monohydrate	103.0
Microcrystalline cellulose	70.0
Sodium starch glycolate	10.0
Magnesium stearate	2.0
Opadry Yellow OY-S-22907	5.0
Purified water purified water is removed by drying during the application of the coating suspension.	q.s.
AFC Tablet Weight	205
Tablet shape	octagonal

The ingredients are separately weighed and screened. The active ingredient is mixed with lactose monohydrate, microcrystalline cellulose and sodium starch glycolate. Magnesium stearate is added to the mixture. The blend is compressed and the tablet cores are coated with an aqueous film coat.

Blending

Initial step: Weigh the acid, lactose, microcrystalline cellulose, sodium starch glycolate and magnesium stearate. Screen each ingredient to de-aggregate using a vibratory/shaker separator or equivalent, fitted with a suitable sieve screen.

Step 2: Charge a bin blender or equivalent with the microcrystalline cellulose, sodium starch glycolate, SB-207499 and lactose. Mix until a homogeneous blend is achieved (approximately 20 minutes).

Step 3: Add the magnesium stearate to the blender. Blend for approximately 3 minutes.

Compression and Coating

Step 1: Compress the tablets using a rotary tablet press or equivalent.

Step 2: Prepare a 12 % w/w Opadry coating suspension, using 7.33 grams of purified water/gram of Opadry.

Step 3: Using a perforated pan coating system or equivalent, spray the coating suspension on the tablet cores until the desired tablet weight gain is obtained.

Step 4: Dry the tablets.

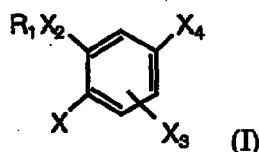
No toxic effects are expected when these compounds are administered in
5 accordance with the present invention.



What is claimed is:

1. A method for treating COPD, which method comprises administering to a mammal suffering from COPD an effective amount of a compound of Formula (I):

5



wherein:

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

10

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 a C_{1-2} alkyl;

15

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

20

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

25

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

$-(CR_4R_5)_nO(CR_4R_5)_mR_6$;

30

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

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

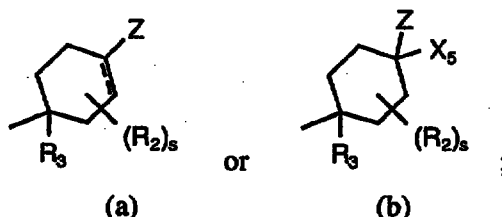
m' is 0, 1, or 2;

X_2 is O or NR_8 ;

X_3 is hydrogen or X;

35

X_4 is



X_5 is H, R_9 , OR_8 , CN, $C(O)R_8$, $C(O)OR_8$, $C(O)NR_8R_8$, or NR_8R_8 ;

R_2 is independently selected from the group consisting of $-CH_3$ and -

5 CH_2CH_3 optionally substituted by 1 or more halogens;

s is 0 to 4;

R_3 is hydrogen, halogen, C_{1-4} alkyl, $CH_2NHC(O)C(O)NH_2$, halo-substituted C_{1-4} alkyl, $-CH=CR_8R_8$; cyclopropyl optionally substituted by R_8 ; CN, OR_8 , CH_2OR_8 , NR_8R_{10} , $CH_2NR_8R_{10}$, $C(Z')H$, $C(O)OR_8$, $C(O)NR_8R_{10}$, or

10 $C\equiv CR_8$;

Z' is O, NR_9 , NOR_8 , NCN , $C(-CN)_2$, CR_8CN , CR_8NO_2 , $CR_8C(O)OR_8$, $CR_8C(O)NR_8R_8$, $C(-CN)NO_2$, $C(-CN)C(O)OR_9$, or $C(-CN)C(O)NR_8R_8$;

Z is $C(Y')R_{14}$, $C(O)OR_{14}$, $C(Y')NR_{10}R_{14}$, $C(NR_{10})NR_{10}R_{14}$, CN, $C(NOR_8)R_{14}$, $C(O)NR_8NR_8C(O)R_8$, $C(O)NR_8NR_{10}R_{14}$, $C(NOR_{14})R_8$,
 15 $C(NR_8)NR_{10}R_{14}$, $C(NR_{14})NR_8R_8$, $C(NCN)NR_{10}R_{14}$, $C(NCN)SR_9$, (2-, 4- or 5-imidazolyl), (3-, 4- or 5-pyrazolyl), (4- or 5-triazolyl[1,2,3]), (3- or 5-triazolyl[1,2,4]), (5-tetrazolyl), (2-, 4- or 5-oxazolyl), (3-, 4- or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,2,4]), (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
 20 5-imidazolidinyl); wherein all of the heterocyclic ring systems may be optionally substituted one or more times by R_{14} ;

the dotted line in formula (a) represents a single or double bond;

Y' is O or S;

R_7 is $-(CR_4R_5)_qR_{12}$ or C_{1-6} alkyl wherein the R_{12} or C_{1-6} alkyl group is
 25 optionally substituted one or more times by C_{1-2} alkyl optionally substituted by one to three fluorines, -F, -Br, -Cl, $-NO_2$, $-NR_{10}R_{11}$, $-C(O)R_8$, $-C(O)OR_8$, $-OR_8$, -CN, $-C(O)NR_{10}R_{11}$, $-OC(O)NR_{10}R_{11}$, $-OC(O)R_8$, $-NR_{10}C(O)NR_{10}R_{11}$, $-NR_{10}C(O)R_{11}$, $-NR_{10}C(O)OR_9$, $-NR_{10}C(O)R_{13}$, $-C(NR_{10})NR_{10}R_{11}$, $-C(NCN)NR_{10}R_{11}$, $-C(NCN)SR_9$, $-NR_{10}C(NCN)SR_9$, $-NR_{10}C(NCN)NR_{10}R_{11}$,
 30 $-NR_{10}S(O)_2R_9$, $-S(O)_mR_9$, $-NR_{10}C(O)C(O)NR_{10}R_{11}$, $-NR_{10}C(O)C(O)R_{10}$, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl, or tetrazolyl;

q is 0, 1, or 2;

R_{12} is C_3 - C_7 -cycloalkyl, (2-, 3- or 4-pyridyl), pyrimidyl, pyrazolyl, (1- or 2-imidazolyl), thiazolyl, triazolyl, pyrrolyl, piperazinyl, piperidinyl, morpholinyl,
 35 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 C₁₋₄ alkyl optionally substituted by one to three fluorines;

R₁₀ is OR₈ or R₁₁;

- 5 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;

- 10 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;

- 15 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;

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; or
 20 g) when X₂R₁ is OCF₂H or OCF₃, X is F, OCF₂H or OCF₃, X₃ is H, s is zero, X₅ is H, Z is C(O)OR₁₄ and R₁₄ is C₁₋₇ unsubstituted alkyl, then R₃ is other than H;

or the pharmaceutically acceptable salts thereof.

2. The method of claim 1 wherein the compound is one wherein R₁ is -CH₂-cyclopropyl, cyclopentyl, methyl or CF₂H; R₃ is CN; X is YR₂; Y is oxygen;
 25 X₂ is oxygen; X₃ is hydrogen; and R₂ is CF₂H or methyl.

3. The method of claim 2 wherein subject is a human and the compound is:

- methyl 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohex-1-ene-1-carboxylate;
 30 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohex-1-ene-1-carboxylic acid;
 methyl *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate];
 methyl *trans*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate];
 35 1-carboxylate];
 methyl *cis*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylate];,



- methyl *trans*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylate];
cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid];
 5 *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate], *tris*(hydroxymethyl)ammonium methane salt;
cis-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylic acid];
trans-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-
 10 carboxylic acid];
cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid];
trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid];
 15 methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylate];
 methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylate];
 methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-
 20 ifluoromethoxyphenyl)cyclohexane-1-carboxylate]; 209524
 methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-cyclohexane-1-carboxylate];
cis-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-carboxylic acid];
 25 *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-carboxylic acid];
cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxamide];
cis-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-carboxamide];
 30 *trans*-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-carboxamide];
cis-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-carbohydrazide];
cis-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-(2-
 35 cetylcarbohydrazide)];
cis-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyano-1-(3-methyl[1,2,4]oxadiazol-5-yl)cyclohexane];



- cis*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyano-1-(2-methyl[1,3,4]oxadiazol-5-yl)cyclohexane];
- cis*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyano-1-(2-methyl[1,3,4]thiadiazol-5-yl)cyclohexane];
- 5 *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxy-1-tris(methylthio)methylcyclohexane];
- methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylate];
- cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylic acid];
- 10 *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxamide];
- methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylate];
- 15 *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylic acid];
- cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxamide];
- trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxaldehyde];
- 20 methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylate];
- trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylic acid];
- 25 methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylate];
- trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylic acid];
- trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxamide];
- 30 *cis*-[4-cyano-4-(3-cyclopentylloxy-4-methoxyphenyl)cyclohexane-1-carboxamic acid];
- N-methyl-*cis*-[4-cyano-4-(3-cyclopentylloxy-4-methoxyphenyl)cyclohexane-1-carboxamic acid];
- 35 *cis*-[4-cyano-4-(3-cyclopentylloxy-4-methoxyphenyl)cyclohexane-1-N-(2-cyanoethyl)carboxamide];



cis-[1-(2-cyanoethyl)-5-{4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl}tetrazole]; or

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-1-(tetrazol-5-yl)cyclohexane].

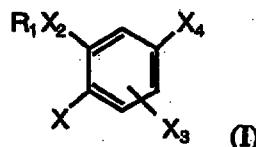
- 5 4. The method of claim 1 wherein the subject is a human and the compound is *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid or a pharmaceutically acceptable salt or ester thereof. 5.

The method of claim 4 wherein the compound is administered at least twice daily.

- 10 6. The method of claim 5 wherein the compound is administered twice daily and at each time is administered in an amount between 1mg and 20mg.

7. The method of claim 6 wherein the amount of compound administered at each time is 15mg, is in tablet form, and is administered orally.

8. A method for the prophylactic treatment of a mammal at risk for
15 developing COPD, said method comprising administering a composition comprising a compound of Formula (I) in an amount between 1 and 60 mg admixed with a pharmaceutically acceptable excipient at least once daily, wherein Formula (I) comprises:



20

wherein:

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

25 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 a C_{1-2} alkyl;

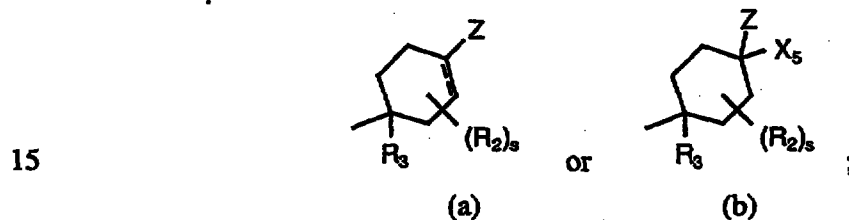
30 R_6 is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxy C_{1-3} alkyl, halo substituted aryloxy C_{1-3} alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranal, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl, C_{3-6}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

35 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-tetrahydrofuranlyl, or 2-tetrahydrothienyl, then m is 1 or 2; or
 5 d) when R₆ is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl,
 2-tetrahydrofuranlyl, 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 YR₂, halogen, nitro, NR₄R₅, or formyl amine;
 10 Y is O or S(O)_m;
 m' is 0, 1, or 2;
 X₂ is O or NR₈;
 X₃ is hydrogen or X;
 X₄ is



- X₅ is H, R₉, OR₈, CN, C(O)R₈, C(O)OR₈, C(O)NR₈R₈, or NR₈R₈;
 R₂ is independently selected from the group consisting of -CH₃ and -
 CH₂CH₃ optionally substituted by 1 or more halogens;
 20 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;
 25 Z' is O, NR₉, NOR₈, NCN, C(-CN)₂, CR₈CN, CR₈NO₂, CR₈C(O)OR₈,
 CR₈C(O)NR₈R₈, C(-CN)NO₂, C(-CN)C(O)OR₉, or C(-CN)C(O)NR₈R₈;
 Z is C(Y')R₁₄, C(O)OR₁₄, C(Y')NR₁₀R₁₄, C(NR₁₀)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
 30 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 may be optionally
 35 substituted one or more times by R₁₄;



the dotted line in formula (a) represents a single or double bond;

Y' is O or S;

R₇ is -(CR₄R₅)_qR₁₂ 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, -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, 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;

R₈' is R₈ 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 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;

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; or

g) when X₂R₁ is OCF₂H or OCF₃, X is OCF₂H or OCF₃, X₃ is H, s is zero, X₅ is H, Z is C(O)OR₁₄ and R₁₄ is C₁₋₇ unsubstituted alkyl, then R₃ is other than H;

or the pharmaceutically acceptable salts thereof.



9. The method of claim 8 wherein the compound is one wherein R₁ is -CH₂-cyclopropyl, cyclopentyl, methyl or CF₂H; R₃ is CN; X is YR₂; Y is oxygen; X₂ is oxygen; X₃ is hydrogen; and R₂ is CF₂H or methyl.

10. The method of claim 9 wherein the subject is a human and the
5 compound is

methyl 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohex-1-ene-1-carboxylate

4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohex-1-ene-1-carboxylic acid;

10 methyl *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate];

methyl *trans*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate];

15 methyl *cis*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylate];

methyl *trans*-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylate];

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid];

20 *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylate], *tris*(hydroxymethyl)ammonium methane salt;

cis-[4-(3,4-bisdifluoromethoxyphenyl)-4-cyanocyclohexane-1-carboxylic acid];

25 *trans*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid];

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid];

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid];

30 methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylate];

methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexane-1-carboxylate];

35 methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-fluoromethoxyphenyl)cyclohexane-1-carboxylate];

methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-cyclohexane-1-carboxylate];



- cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-carboxylic acid];
trans-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-carboxylic acid];
- 5 *cis*-[4-cyano-4-(3-cyclopentylloxy-4-methoxyphenyl)cyclohexane-1-carboxamide];
cis-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-carboxamide];
trans-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-carboxamide];
- 10 *cis*-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-carbohydrazide];
cis-[4-cyano-4-(3,4-bisdifluoromethoxyphenyl)cyclohexane-1-(2-cetylcarbohydrazide)];
cis-{4-(3,4-bisdifluoromethoxyphenyl)-4-cyano-1-(3-methyl[1,2,4]oxadiazol-5-yl)cyclohexane};
- 15 *cis*-{4-(3,4-bisdifluoromethoxyphenyl)-4-cyano-1-(2-methyl[1,3,4]oxadiazol-5-yl)cyclohexane};
cis-{4-(3,4-bisdifluoromethoxyphenyl)-4-cyano-1-(2-methyl[1,3,4]thiadiazol-5-yl)cyclohexane};
- 20 *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxy-1-tris(methylthio)methylcyclohexane];
methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxy-cyclohexane-1-carboxylate];
cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylic acid]; SB 208970
- 25 *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxamide];
methyl *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxy-cyclohexane-1-carboxylate];
- 30 *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylic acid];
cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxamide];
trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxy-cyclohexane-1-carboxaldehyde];
- 35 methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylate];

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;

- 5 R₆ is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC₁₋₃ alkyl, halo substituted aryloxyC₁₋₃ alkyl, indanyl, indenyl, C₇₋₁₁ polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranal, tetrahydrothienyl, thienyl, tetrahydrothiopyranal, thiopyranal, C₃₋₆ cycloalkyl, or a C₄₋₆ cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may
- 10 be optionally substituted by OH, 1 to 3 methyl groups or one ethyl 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-tetrahydrothiopyranal,
- 15 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or
- d) when R₆ is 2-tetrahydropyranyl, 2-tetrahydrothiopyranal, 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;

- 20 X is YR₂, halogen, nitro, NR₄R₅, or formyl amine;

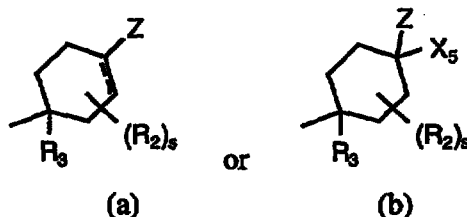
Y is O or S(O)_{m'};

m' is 0, 1, or 2;

X₂ is O or NR₈;

X₃ is hydrogen or X;

- 25 X₄ is



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

R₂ is independently selected from the group consisting of -CH₃ and -

- 30 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
- 35 C=CR₈;



trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexane-1-carboxylic acid];

methyl *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylate];

5 *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxylic acid];

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-methoxycyclohexane-1-carboxamide];

10 *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxamic acid];

N-methyl-*cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxamic acid];

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-N-(2-cyanoethyl)carboxamide];

15 *cis*-[1-(2-cyanoethyl)-5-(4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexyl)tetrazole]; or

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-1-(tetrazol-5-yl)cyclohexane].

11. The method of claim 9 wherein the subject is a human and the
20 compound is *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid or a pharmaceutically acceptable salt or ester thereof. 12.

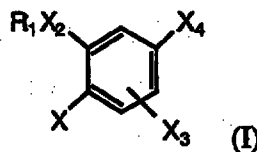
The method of claim 9 wherein the compound is administered at least twice daily.

13. The method of claim 9 wherein the compound is administered twice
25 daily and at each time is administered in an amount between 1mg and 20mg.

14. The method of claim 13 wherein the amount of compound administered at each time is 15mg, is in tablet form, and is administered orally. 15.

The use of a compound of Formula (I) in the manufacture of a medicament for use in the treatment of COPD wherein Formula (I) is .

30



wherein:

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



Z' is O, NR₉, NOR₈, NCN, C(-CN)₂, CR₈CN, CR₈NO₂, CR₈C(O)OR₈, CR₈C(O)NR₈R₈, C(-CN)NO₂, C(-CN)C(O)OR₉, or C(-CN)C(O)NR₈R₈ ;

Z is C(Y)R₁₄, C(O)OR₁₄, C(Y)NR₁₀R₁₄, C(NR₁₀)NR₁₀R₁₄, CN, C(NOR₈)R₁₄, C(O)NR₈NR₈C(O)R₈, C(O)NR₈NR₁₀R₁₄, C(NOR₁₄)R₈,
 5 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
 10 5-imidazolidinyl); wherein all of the heterocyclic ring systems may be optionally substituted one or more times by R₁₄;

the dotted line in formula (a) represents a single or double bond;

Y' is O or S;

R₇ is -(CR₄R₅)_qR₁₂ or C₁₋₆ alkyl wherein the R₁₂ or C₁₋₆ alkyl group is
 15 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, -NR₁₀C(O)R₁₁, -NR₁₀C(O)OR₉, -NR₁₀C(O)R₁₃, -C(NR₁₀)NR₁₀R₁₁, -C(NCN)NR₁₀R₁₁, -C(NCN)SR₉, -NR₁₀C(NCN)SR₉, -NR₁₀C(NCN)NR₁₀R₁₁,
 20 -NR₁₀S(O)₂R₉, -S(O)_mR₉, -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,
 25 furanyl, (2- or 3-thienyl), (4- or 5-thiazolyl), quinolinyl, naphthyl, or phenyl;

R₈ is independently selected from hydrogen or R₉;

R₈' is R₈ or fluorine;

R₉ is C₁₋₄ alkyl optionally substituted by one to three fluorines;

R₁₀ is OR₈ or R₁₁;

30 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,
 35 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;

provided that:

- 5 f) when R₁₂ is N-pyrazolyl, N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl, N-piperidinyl, or N-morpholinyl, then q is not 1; or
- g) when X₂R₁ is OCF₂H or OCF₃, X is OCF₂H or OCF₃, X₃ is H, s is zero, X₅ is H, Z is C(O)OR₁₄ and R₁₄ is C₁₋₇ unsubstituted alkyl, then R₃ is other than H;
- 10 or the pharmaceutically acceptable salts thereof.
16. The manufacture of a medicament according to claim 15 wherein the compound used is one wherein R₁ is -CH₂-cyclopropyl, cyclopentyl, methyl or CF₂H; R₃ is CN; X is YR₂; Y is oxygen; X₂ is oxygen; X₃ is hydrogen; and R₂ is CF₂H or methyl.
- 15 17. The medicament according to claim 16 wherein the compound is *cis*-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid or a pharmaceutically acceptable salt or ester thereof and the treated subject is a human.
18. The medicament according to any one of claims 15 to 17 wherein the medicament is administered at least twice daily.
- 20 19. The medicament according to any one of claims 15 to 17 wherein the medicament is administered twice daily and contains an amount between 1mg and 20mg.
20. The medicament according to any one of claims 15 to 17 wherein the medicament is administered at least twice daily at each time is 15mg, is in tablet
- 25 form, and is administered orally.