**Title:** INDOLE AND INDENE DERIVATIVES AS PLA₂ AND LIPOOXYGENASE INHIBITORS

![Chemical Structure](image)

**Abstract**

Indene derivatives having formula (I), where R³, R⁴ and R⁶ are defined in the description and their pharmaceutically acceptable salts and 1-[(4-chlorophenyl)methyl]-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid, tromethamine salt, are useful as inhibitors of PLA₂ and lipooxygenase.
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INDOLE AND INDENE DERIVATIVES AS PLA₂ AND LIP OxYGENASE INHIBITORS

This invention relates to new indole and indene derivatives which are useful as inhibitor of PLA₂ and lipoxygenase. The invention also relates to a process for the preparation of the new indole and indene derivatives and pharmaceutical compositions containing them.

International Publication No. WO 91/06537 having an international publication date of 16 May 1991 discloses that various substituted indolealkanoic acid derivatives and indenealkanoic acid derivatives are inhibitors of PLA₂ and lipoxygenase and may be used in the treatment of inflammatory conditions such as rheumatoid arthritis, ulcerative colitis, psoriasis and other immediate hypersensitivity reactions; in the treatment of leukotriene-mediated naso bronchial obstructive air-passageway conditions such as allergic rhinitis, allergic bronchial asthma and the like and as gastric cytoprotective agents. The present invention relates to new compounds which can be used in a similar manner.

According to one aspect the invention provides as new compound 1-[(4-chlorophenyl)methyl]-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid, tromethamine salt. This compound has advantageous properties and, in particular, performed as well as Zileuton in the in vivo antigen induced guinea pig bronchoconstriction assay as described below. According to another aspect the invention provides new compounds having the formula I

\[ \text{(I)} \]

and their pharmaceutically acceptable salts wherein \( m \) is 0 - 3;

\[ R^5 \text{ is } A(CH_2)_nO \text{; or phenyl or phenyl substituted} \]

by halo, lower alkylthio, lower alkylsulfinyl or lower alkylsulfonyl;
R^6 is A(CH_2)_nO- or halo; with the proviso that when R^6 is halo, R^5 is

![Chemical structure](image)

A is C_4-C_8 alkyl, phenoxyethyl, phenoxyphenyl or a group having the formula

![Chemical structure](image)

X is -N- or -C=;

5

\[ \begin{align*}
R^1 & \quad R^3 \\
R^2 & \quad Z \\
\end{align*} \]

Z is -C==C-, -C=N-, -N=C-, -N-, -S- or -O-;

R^1 is hydrogen, lower alkyl, phenyl or phenyl substituted with trifluoromethyl;
R^2 is hydrogen or lower alkyl; or
R^1 and R^2 taken together form a benzene ring;
10 R^3 is hydrogen or lower alkyl; and
n is 1 - 2.

The compounds having formula I and their pharmaceutically acceptable salts exhibit advantageous properties and, in particular, exhibit a high inhibition of 5-lipoxygenase as shown by the result described below for the compound of Example 2 in the assay relating to inhibition of 5-lipoxygenase in human whole blood.

The terms "lower alkyl" and "lower alkoxy" refer to moieties having 1-6 carbon atoms in the carbon chain. The term "halo" refers to fluoro, chloro or bromo.

The grouping A embraces, inter alia, 5- or 6-membered unsaturated nitrogen, sulfur or oxygen containing mono- or benzofused-heterocycles; optionally substituted with lower alkyl or phenyl. The foregoing definition embraces the following heterocycle moieties: furyl, pyrrolyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridyl, pyrazinyl, pyrimidinyl, benzofuranyl, benzothienyl, benzothiazolyl, indolyl, benzoxazolyl, quinolinyl, quinazolinyl, benzimidazolyl, quinoxalinyl, quinazolinyl and the like. Especially preferred are quinolinyl, benzothiazolyl, benzimidazolyl and 2-phenylthiazole.
The compounds having formula I which possess a basic function can form pharmacologically acceptable salts from pharmacologically acceptable organic and inorganic acids such as hydrochloric, hydrobromic, sulfonic, sulfuric, phosphoric, nitric, maleic, fumaric, benzoic, ascorbic, pamoic, succinic, ethanesulfonic, acetic, propionic, tartaric, citric, lactic, malic, mandelic, cinnamic, palmitic, itaconic and benzenesulfonic. The compounds which are hydroxamic acids are capable of forming alkali metal and alkaline earth salts and salts or pharmacologically acceptable cations derived from ammonia or a basic amine. Examples of the latter include but are not limited to cations such as ammonium, mono-, di-, and trimethylammonium, mono-, di- and triethylammonium, mono-, di- and tripropylammonium (iso and normal), ethyldimethylammonium, benzylidimethylammonium, cyclohexylammonium, benzylammonium, dibenzylammonium, piperidinium, morpholinium, pyrrolidinium, piperazinum, 1-methylpiperidinium, 4-ethylmorpholinium, 1-isopropylpyrrolidinium, 1, 4-dimethylpiperazinum, 1-n-butyl-piperidinium, 2-methylpiperidinium, 1-ethyl-2-methylpiperidinium, mono-, di- and triethanolammonium, ethyl diethanolammonium, n-butyldimethanolammonium, tris(hydroxymethyl)aminoethanol ammonium, and the like.

The new compounds provided by the invention can be prepared by a process in which

(a) N-methylhydroxylamine or a salt thereof is N-acylated by reaction with a carboxylic acid having the formula X-OH where X is a group having the formula II

\[
\begin{align*}
\text{R}^{6} & \quad \text{(II)} \\
\text{R}^{3} & \quad \text{R}^{5} \\
\text{CH}_{2}^{m} \text{CO-} & \\
\end{align*}
\]

where m, R^{3}, R^{5} and R^{6} are as defined above or a reactive derivative thereof and, if desired, a resultant compound having formula I is converted into a pharmaceutically acceptable salt thereof; or

(b) tromethamine is reacted with 1-[(4-chlorophenyl)methyl]-2-methyl-5-(2-quinolinylmethoxy)-1H-indol-3-acetic acid or a salt thereof.

The acids mentioned under processes (a) and (b) are known from International Publication WO 91/06537. The process (a) can be carried out under
known methods for the N-acylation of amines. Process (b) can be carried out under known methods of salt formation.

The present invention also provides a pharmaceutical composition comprising a new compound identified above in combination or association with a pharmaceutically acceptable carrier and a method of making the pharmaceutical composition by bringing the new compound into combination or association with the carrier.

The compounds of this invention, by virtue of their ability to inhibit the activity of PLA₂ enzyme, as well as that of lipooxygenase enzyme and to antagonize mediators arising from the enzymatic pathway, are useful in the treatment of conditions mediated by products of the oxidation of arachidonic acid. Accordingly, the compounds are indicated in the treatment of such diseases as rheumatoid arthritis, inflammatory bowel disease, osteoarthritis, tendinitis, bursitis, psoriasis (and related skin inflammation) and similar conditions involving inflammation. Moreover, by virtue of their ability to antagonize the effect of LTC₄, LTD₄ and LTE₄, which are the constituents of SRS-A, they are useful for the inhibition of symptoms induced by these leukotrienes. Accordingly, the compounds are indicated in the prevention and treatment of those disease states in which LTC₄, LTD₄ and LTE₄ are causative factors, for example allergic rhinitis, allergic bronchial asthma and other leukotriene mediated naso-bronchial obstructive air-passageway conditions, as well as in other immediate hypersensitivity reactions, such as allergic conjunctivitis. The compounds are especially valuable in the prevention and treatment of allergic bronchial asthma.

The compounds of the invention are cytoprotective agents and are considered especially useful when administered with conventional non-steroidal anti-inflammatory drugs, whose major side effect is gastrointestinal irritation. The cytoprotective effect of the compounds of the invention significantly reduces the gastro-irritant impact of conventional anti-inflammatory drugs. This effect is based not only on the ability of the compounds of the invention to inhibit the biological effects of leukotrienes and/or control the biosynthesis of these substances, as by inhibiting lipoxygenase, but also by a shunting effect, whereby the control of the lipoxygenase pathway "shunts" the oxidation of arachidonic acid into the cyclooxygenase pathway, giving rise to an increase in the formation of cytoprotective prostaglandins. These biological effects make the compounds of the invention especially useful in treating such conditions as erosive esophagitis, inflammatory bowel disease and induced hemorrhagic lesions such as those induced by alcohol or non-steroidal anti-inflammatory drugs (NSAID's), hepatic ischemia, noxious agent induced damage or necrosis of
hepatic, pancreatic, renal or myocardial tissue; liver parenchymal damage caused by hepatotoxic agents such as carbon tetrachloride and D-galactosamine; ischemic renal failure; disease-induced hepatic damage; bile salt-induced pancreatic or gastric damage; trauma or stress-induced cell damage; and glycerol-induced renal failure.

When the compounds of the invention are employed in the treatment of allergic airway disorders, as anti-inflammatory agents and/or as cytoprotective agents, they can be formulated into oral dosage forms such as tablets, capsules and the like. The compounds can be administered alone or by combining them with conventional carriers, such as magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, low melting wax, cocoa butter and the like. Diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, tablet-disintegrating agents and the like may be employed. The compounds may be encapsulated with or without other carriers. In all cases, the proportion of active ingredients in said compositions both solid and liquid will be at least to impart the desired activity thereto on oral administration. The compounds may also be injected parenterally, in which case they are used in the form of a sterile solution containing other solutes, for example, enough saline or glucose to make the solution isotonic. For administration by inhalation or insufflation, the compounds may be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol.

The dosage requirements vary with the particular compositions employed, the route of administration, the severity of the symptoms presented and the particular subject being treated. Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached. In general, the compounds of the invention are most desirably administered at a concentration that will generally afford effective results without causing any harmful or deleterious side effects, and can be administered either as a single unit dose, or if desired, the dosage may be divided into convenient subunits administered at suitable times throughout the day.

The PLA₂ and lipoxygenase inhibitory and leukotriene antagonist effects, as well as the anti-inflammatory and potential gastroirritant effects of the compounds of the invention, may be demonstrated by standard pharmacological procedures. The following examples illustrate the preparation and pharmacological testing of compounds within the invention.
Example 1

1-[(4-Chlorophenyl)methyl]-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid, tromethamine salt

A solution of tromethamine (77mg, 0.64 mmol) in water (1ml) is added to a hot solution of 1-[(4-chlorophenyl)methyl]-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid (0.3g, 0.64 mmol) in ethanol (20 ml). After the reaction mixture is stirred for 2 hours, the solvent is concentrated to half volume and refrigerated overnight. The resulting solid is removed and dried affording 0.21g of white crystals which decompose at 105°C. The crystals were the title compound hemi-ethanolate.

Analysis for: C_{28}H_{23}ClN_{2}O_{3} • C_{5}H_{11}NO_{3} • 0.5 C_{2}H_{6}O

Calculated: C, 64.39; H, 6.01; N, 6.82.

Found: C, 64.02; H, 5.82; N, 6.79.

Example 2

5-Fluoro-N-hydroxy-N, 2-dimethyl-1-[(4-(2-quinolinylmethoxy)-phenyl)methylene]-1H-indene-3-acetamide

A mixture of 5-fluoro-2-methyl-1-[(4-(2-quinolinylmethoxy)phenyl)methylene]-1H-indene-3-acetic acid (1.2g, 2.65 mmol) and dimethylformamide (0.2 mL, 2.68 mmol) in methylene chloride (20 mL) is chilled. Oxalyl chloride (0.52 mL, 2.25 equiv) is added. After the reaction mixture is stirred for 1 hour, a solution of N-methylhydroxylamine hydrochloride (0.89 g, 10.63 mmol) in a mixture of triethylamine (1.92 mL), tetrahydrofuran (10mL) and water (0.25 mL) is added to it, and the reaction mixture is stirred at room temperature overnight. The reaction is poured into 2N HCl and a solid forms (HCl salt). The solid is removed and recrystallized from ethanol affording 0.27 g (19%) of a yellow solid which decomposes at 120°C. The solid is the title compound hydrochloride.

Analysis for: C_{30}H_{25}FN_{2}O_{3} • HCl

Calculated: C, 69.70; H, 5.07; N, 5.42.

Found: C, 70.61; H, 5.10; N, 5.37.
Example 3

The LTD₄ antagonist activity of the compounds of the invention is assessed in the *in vitro* isolated guinea pig trachea assay.

This assay is carried out as follows:

Male Hartley guinea pigs (350-400 g) are euthanized by a blow to the head, the neck is opened and the trachea removed. The trachea is maintained in aerated physiological salt solution, cleared of connective tissue and fat and cut into rings approximately 2 mm in width (usually containing two cartilaginous segments per ring). Two pieces of silk suture are then passed through the lumen of the tracheal ring and are tied around the cartilage, one on each side of the trachealis muscle. The tracheal ring is suspended between a glass hook and a force displacement transducer in a 10 mL organ bath for measurement of isometric tension. Tissues are maintained at 37°C in aerated (95% CO₂/5% CO₂) physiological salt solution of the following composition: NaCl (100 mM), KH₂PO₄ (1.18 mM), KCl (4.74 mM), CaCl₂ (2.5 mM), MgSO₄ · 7 H₂O (1.19 mM), NaHCO₃ (25 mM), dextrose (11.1 mM) and indomethacin (1 mM). The tracheal rings are maintained at 2 g resting tension and equilibrated for 45 minutes (with frequent washing and readjustment of resting tension).

The tracheal rings are first contracted by the addition of carbachol (3×10⁻⁶M), to determine tissue responsiveness and establish a reference contraction. On attainment of a stable level of contraction (approximately 30 minutes), the tissues are washed several times until baseline tension has been restored and then re-equilibrated for 30 minutes. The tissues are then incubated for 45 minutes with a test antagonist (either 1×10⁻⁶M or 1×10⁻⁵M) or 10 mL of an appropriate solvent control (control, non-treated). One tissue in each group serves as the control. Twenty minutes prior to the construction of the LTD₄ cumulative concentration-response curve, L-cysteine (1×10⁻²M final bath concentration) is added to inhibit bioconversion of LTD₄ to LTE₄. Only one LTD₄ concentration-response curve is constructed in each tissue.

All responses to LTD₄ in an individual tissue are measured as a percentage of the reference contraction of that tissue to carbachol. LTD₄ antagonist activity is determined by comparison of the concentration response curves of LTD₄ in the presence and absence of antagonist. Assessment of the relative rightward shift of the antagonist treated curve relative to the solvent (control) treated tissue is calculated as a concentration ratio (Eq. A) and used in subsequent calculations to derive an antagonist pKᵦ value (Eqs B and C). In the event that the maximum response to LTD₄ is
depressed, the EC$_{50}$ for that particular curve is determined, an "apparent" pK$_B$ reported, and the compound reported as "non-competitive."

$$ A) \text{Concentration Ratio (CR)} = \frac{\text{EC}_{50} \text{ treated tissue}}{\text{EC}_{50} \text{ control}} $$

$$ B) \ K_B = \frac{[\text{Test Compound}]}{\text{CR-1}} $$

$$ C) -\log K_B = pK_B $$

If a compound is found to be active and/or depress the maximal response to LTD$_4$, then a range of concentrations of the test compound should be used generating multiple concentration ratios which would then be used to perform a Schild analysis, and determination of a pA$_2$ value where appropriate.

The activity of reference leukotriene antagonists in this assay is as follows:

<table>
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<tr>
<th>Compound</th>
<th>pK$_B$</th>
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<tr>
<td>Ly-171,883</td>
<td>7.44 ± 0.12</td>
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<tr>
<td>Wy-48,252</td>
<td>6.90 ± 0.23</td>
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When tested in this assay, a compound of the invention gave the following results:

<table>
<thead>
<tr>
<th>Compound of Example No.</th>
<th>pK$_B$</th>
<th>Concentration Ratio (M)</th>
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<td>1</td>
<td>6.0</td>
<td>1 x 10 - 5</td>
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</table>

The above results demonstrate that the compounds tested have significant leukotriene antagonist activity as measured in the **in vitro** isolated guinea pig trachea assay.

**Example 4**

This assay is carried out as follows:

Blood is obtained in 50-100 ml quantities from male donors. White blood cell counts and differentials are made. Two ml of blood are placed in a 15 ml polypropylene test tube. Compounds are solubilized in dimethylsulfoxide and diluted 1:10 in 10% bovine serum albumin in phosphate buffered saline, pH 7.4 resulting in a final dimethylsulfoxide concentration of 0.1% in the blood. Then, compounds are
added to the blood in a shaking water bath at 37°C for 10 minutes prior to the addition of 30 mM calcium ionophore (A23187; Sigma). After ionophore administration, whole blood samples are mixed and incubated for 20 minutes at 37°C in a shaking water bath. Incubation is terminated by placing samples in an ice bath and immediately adding ethylene glycol-bis-(b-aminoethyl ether)-N,N,N',N'-tetraacetic acid (10 mM). Samples are mixed and centrifuged at 1200 x g for 15 minutes at 4°C. Preparation of samples for evaluation by RIA or ELISA is carried out by the following protocol. Plasma is removed from sample tubes, placed in 15 ml polypropylene test tubes containing 8 ml methanol, and then vortexed to precipitate protein. Samples are stored at -70°C overnight. The next day, samples are centrifuged at 200 x g for 15 minutes at 4°C to pellet the precipitate. Samples are dried in a Savant speed vac concentrator, reconstituted to original volume with ice cold RIA or ELISA buffer, and stored at -70°C until assayed. The assay for eicosanoids (LTB4, TxB2, and PGE2) is performed as described by the manufacturer of the [3H]-RIA kit or ELISA kit (LTB4-Amersham, TxB2 and PGE2 - Caymen Chemical).

The total eicosanoid level in 2 ml of blood is calculated and reported as ng/10^6 neutrophils. Significance is determined by a one-way analysis of variance with least significant difference (LSD) comparisons to control (p ≤ 0.05) and IC50's (μM) are determined by regression analysis (Finney, 1978). Drug effects are expressed as percent change from control values.

Compounds tested in vitro are solubilized in dimethylsulfoxide and diluted 1:10 in 10% bovine serum albumin in phosphate buffer saline resulting in a final dimethylsulfoxide concentration of 0.1% in the blood.

The results for compounds of the invention tested in this assay are presented in Table IX.

<table>
<thead>
<tr>
<th>Compound of Example No.</th>
<th>Dose (μM)</th>
<th>% Inhibition of LTB4</th>
<th>IC50(*)</th>
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<tr>
<td>A-64077</td>
<td>25</td>
<td>72</td>
<td>(3.0)</td>
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<tr>
<td>L-663,536</td>
<td>3</td>
<td>96</td>
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</tr>
<tr>
<td>16 (1)</td>
<td>25</td>
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<tr>
<td>22 (1)</td>
<td>25</td>
<td>78</td>
<td>(39.8)</td>
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<tr>
<td>42 (1)</td>
<td>25</td>
<td>89</td>
<td>(5.6)</td>
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<tr>
<td>2</td>
<td>25</td>
<td>94</td>
<td>(4.5)</td>
</tr>
</tbody>
</table>

(1) Examples of WO 91/06537
Example 5

The ability of the compounds of the invention to antagonize LTD₄ is assessed in the in vivo antigen-induced guinea pig bronchoconstriction assay.

This assay is carried out as follows:

A. Airway hyperreactivity

Male guinea pigs (Charles River, Wilmington, MA) are sensitized 3-4 weeks prior to antigen challenge by administration of 2 i.m. injections of ovalbumin (OA), 1 into each hind limb (35 mg total). Sensitized guinea pigs (500-650 g) are pretreated with pyrilamine (2.5 mg/kg i.p.) 1 hour before aerosol challenge to prevent hypoxic collapse and death, and then challenged while conscious with an aerosol of 0.2% OA (in normal saline), or saline only, for 3 minutes using a Devilbiss model 100 nebulizer (Somerset, PA). For pharmacological studies, drugs or vehicle (0.5% Tween 80 in water) are administered p.o. at appropriate times pre- and post-challenge to animals that have been fasted overnight prior to experimentation.

Twenty four hours following aerosol exposure, each guinea pig is anesthetized by urethane (1.2 g/kg i.p.). A carotid artery and jugular vein are cannulated to allow for the monitoring of blood pressure and the administration of drugs, respectively. The trachea is then cannulated and connected to a Harvard Apparatus rodent ventilator (S. Natick, MA). Spontaneous respiration is abolished by the administration of succinylcholine (2.5 mg/kg i.v.). The animals are then ventilated with room air at a rate of 65 breaths per minute. Airway inflation pressure is measured using a Statham pressure transducer (Gould Instruments, Cleveland, OH) connected to the tracheal cannula via a side-arm and recorded on a Grass Instruments recorder (Quincy, MA). The tidal volume (approximately 10 cc/kg) is adjusted to give a baseline inflation pressure of 8-10 cm H₂O at end inspiration. Animals are then allowed 20 minutes to stabilize.

Following the stabilization period, a dose-response curve to bronchoconstriction induced by i.v. methacholine (MCH) or LTD₄ is generated in each animal in a non-cumulative fashion. The bronchoconstriction produced by MCH or LTD₄ is expressed as the peak increase over baseline in end-inspiratory inflation pressure (in cm H₂O), which occurs within 4-5 breaths following the administration of each dose. After the peak effect of each injection of MCH or LTD₄ the expiratory tube of the tracheal cannula is occluded for 3 breaths, as hyperinflation of the lungs facilitates the return of airway inflation pressure to the original baseline. The standard doses of MCH used to generate a dose-response curve in each animal are 1, 2, 3, 5, 10,
15, 20, 30, 50 and 100 mg/kg, whereas the standard doses of LTD₄ used to generate a
dose-response curve in each animal are 0.01, 0.1, 0.2, 0.3, 0.5, 1.0, 2.0, and 3.0
µg/kg. A dose-response curve for MCH- or LTD₄-induced bronchoconstriction is then
generated from each group of animals, with data points on the curves representing the
mean values and standard errors for inflation pressures.

In three additional airway hyperreactivity protocols, (1) guinea pigs are
challenged with an aerosol of OA or saline once daily for 3 days and MCH or LTD₄
dose-response curves are generated 24 hours following the third challenge, (2) MCH
dose-response curves are generated 24 hours following a single aerosol challenge with
a 10-fold more concentrated (2%) OA solution or with saline and (3) MCH dose-
response curves are generated 72 hours following a single aerosol challenge with a
standard OA solution or with saline. In all airway hyperreactivity studies OA-
challenged and saline-challenged animals are tested in parallel. In the pharmacological
studies, in which MCH is the only agonist used, OA-challenged drug-treated animals
are tested in parallel with matched OA-challenged vehicle-controls and saline-challenged
vehicle-controls. There is an n of 6-8 animals per group.

B. Resistance and compliance measurements

Alterations in isovolumetric airway resistance (Rₐ) and dynamic
compliance (Cdyn) associated with antigen-induced airway hyperreactivity to MCH are
determined using 3 saline-challenged guinea pigs and 4 OA-challenged guinea pigs.
Anesthetized and ventilated guinea pigs are prepared as described above. In addition, a
fluid-filled PE-90 catheter is inserted into the distal esophagus. Transpulmonary airway
pressure is measured from a solid-state differential pressure transducer with a 1-70 cm
H₂O range (Sensym, Sunnyvale, CA), attached to the esophageal catheter and to a side-
arm of the tracheal catheter. Air flow is measured from a heated Fleisch 0000
pneumotachograph (Switzerland), calibrated by volume. Cdyn and Rₐ are then
calculated on a breath by breath basis by a Ponemah pulmonary data acquisition system
(Simsbury, CT). In these experiments MCH is given in doses of 3 and 5 mg/kg, which
produces the greatest differences in inflation pressure measurements between OA- and
saline-challenged groups.

C. Bronchoconstriction (BC) protocols

Guinea pigs are sensitized as described above. Following the 3-4 week
sensitization period animals are fasted overnight prior to experimentation. Conscious
animals are then dosed p.o. with drug or vehicle alone (0.5% Tween 80 in H₂O) at
appropriate times prior to antigen challenge, with 4 doses of each drug tested.
Subsequently, animals are anesthetized, cannulated and ventilated as described above. After a 20 minute stabilization period, animals are given i.v. injections of pyrilamine (5 mg/kg), propranolol (0.1 mg/kg) and indomethacin (10 mg/kg) at 15, 10 and 5 minutes, respectively, prior to antigen challenge. This pretreatment results in an LT-dependent bronchoconstriction following antigen challenge, which is accomplished by administration of an OA aerosol (1 mg/mL) for 15 min via a DeVilbiss model 25 ultrasonic nebulizer in-line between the animal and ventilator. Only one bronchoconstriction per animal is induced. End-inspiratory inflation pressure (in cm H₂O over baseline) is measured at 5, 10 and 15 minutes post-OA challenge and summed for each drug-treated and matched vehicle-control animal. A mean value and standard error for the % inhibition of control bronchoconstriction in each drug-treated group is then calculated. There is an n of 6-8 per group.

Data from the antigen-induced bronchoconstriction studies are analyzed by using a One-Way Analysis of Variance, followed by Fisher's Least Significant Differences Test. MCH or LTD₄ dose-response curves from each airway hyper-reactivity experiment are compared for significant differences by using a Repeated Measures Multiple Analysis of Variance. For a pharmacological experiment to be considered valid, MCH dose-response curves generated in the OA-challenged vehicle-control group and the saline-challenged vehicle-control group have to be significantly different from each other. A drug is then considered to be active if the MCH dose-response curve generated in the OA-challenged drug-treated group is not significantly different from that generated in the saline-challenged vehicle-control group. Conversely, a drug is considered to be inactive if the MCH dose-response curve generated in the OA-challenged drug-treated group is not significantly different from that generated in the OA-challenged vehicle-control group. If the MCH dose-response curve from the OA-challenged drug-treated group is not significantly different from the curves from either of the 2 control groups the results are considered inconclusive. Statistical significance is accepted at the 95% level of confidence (p<0.05).

The test results for a compound of the invention tested in this assay is presented in Table X.

<table>
<thead>
<tr>
<th>Compound</th>
<th>% Inhibition of OA-BC (dose, route)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zileuton</td>
<td>67 (50 mg/kg, po)</td>
</tr>
<tr>
<td>MK-886</td>
<td>51 (25 mg/kg, po)</td>
</tr>
<tr>
<td>Example 1</td>
<td>67 (50 mg/kg, po)</td>
</tr>
</tbody>
</table>
CLAIMS

1. A compound having the formula I

\[
\begin{align*}
\text{R}^6 & \text{-} \text{R}^3 \text{CHR}^5 \\
\text{(CH}_2\text{)}_m\text{CO-N(CH}_3\text{)}\text{OH}
\end{align*}
\]

or a pharmaceutically acceptable salt thereof wherein \( m \) is 0-3;

\[
\text{R}^5 \text{ is } \text{A(CH}_2\text{)}_n\text{O} \text{ ; or phenyl or phenyl substituted by halo, lower alkylthio, lower alkylsulfinyl or lower alkylsulfonyl;}
\]

\[
\text{R}^6 \text{ is A(CH}_2\text{)}_n\text{O- or halo; with the proviso that when R}^6 \text{ is halo, R}^5 \text{ is}
\]

\[
\text{A(CH}_2\text{)}_n\text{O}
\]

\( A \) is \( C_4-C_8 \) alkyl, phenoxyethyl, phenoxyphenyl or a group having the formula

\[
\begin{align*}
\text{R}^1 & \text{X} \text{Z} \\
\text{R}^2 & \\
\end{align*}
\]

or

\[
\begin{align*}
\text{R}^1 & \text{N} \\
\text{S} & \\
\end{align*}
\]

\[
\begin{align*}
\text{R}^3 & \\
\end{align*}
\]

\( X \) is \(-N-\) or \(-C-\);

\[
\begin{align*}
\text{R}^3 & \text{ R}^3 \text{ R}^3 \\
\text{Z} & = \text{C=C-} \text{, } \text{C=N-} \text{, } \text{N=C-} \text{, } \text{N-} \text{, } \text{S-} \text{ or } \text{-O-} \\
\end{align*}
\]

\( R^1 \) is hydrogen, lower alkyl, phenyl or phenyl substituted with trifluoromethyl;

\( R^2 \) is hydrogen or lower alkyl; or \( R^1 \) and \( R^2 \) taken together form a benzene ring;

\( R^3 \) is hydrogen or lower alkyl;

and \( n \) is 1-2.

2. A compound as claimed in claim 1, wherein \( R^6 \) is halo.

3. A compound as claimed in claim 1 or 2, wherein \( A \) is quinolinyl.
4. 5-Fluoro-N-hydroxy-N,2-dimethyl-1-[(4-(2-quinolinylmethoxy)-phenyl)methylene]-1H-indene-3-acetamide or a pharmaceutically acceptable salt thereof.

5. 1-[4-Chlorophenyl]methyl]-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid, tromethamine salt.

6. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 5 in combination or association with pharmaceutically acceptable carrier.

7. A process for the preparation of a compound as claimed in claim 1 or 5 which comprises (a) N-acylation of N-methylhydroxylamine or a salt thereof by reaction with a carboxylic acid having the formula X-OH where X is a group having the formula II

![Chemical Structure](image)

where m, R³, R⁵ and R⁶ are as defined in claim 1 and, if desired, conversion of a resultant compound having formula I into a pharmaceutically acceptable salt thereof; or (b) reaction of tromethamine with 1-[4-(chlorophenyl)methyl]-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid or a salt thereof.

8. A process as claimed in claim 7, wherein (a) is carried out where R⁶ is halo.

9. A process as claimed in claim 7 or 8, where (a) is carried out where A is quinolinyl.

10. A process as claimed in claim 7 carried out to prepare a compound claimed in claim 4 or 5.