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(54) Title: COMPOUNDS (I)		
(57) Abstract This invention relates to a compound of formula (I) where the several groups are defined herein. These compounds are leukotriene antagonists and as such can be used in treating various diseases associated with leukotrienes.		

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COMPOUNDS

Scope of the Invention

This is a continuation-in-part of application Serial No. PCT/US93/06234 filed June 30, 1993, which is a continuation of Serial
5 No. 08/025,198 filed March 2, 1993, which is a continuation-in-part of
07/906,771 filed June 30, 1992. The field of this invention is that of
certain substituted pyridinyl-2-propenoates, and homologs thereof, which
have been found to be useful for treating diseases arising from or related
to leukotrienes, particularly leukotriene B₄. As such there utility lies in
10 antagonizing the affects of leukotrienes.

Background of the Invention

The family of bioactive lipids known as the leukotrienes exert
pharmacological effects on respiratory, cardiovascular and
gastrointestinal systems. The leukotrienes are generally divided into
15 two sub-classes, the peptidoleukotrienes (leukotrienes C₄, D₄ and E₄)
and the dihydroxyleukotrienes (leukotriene B₄). This invention is
primarily concerned with the hydroxyleukotrienes (LTB) but is not
limited to this specific group of leukotrienes.

The peptidoleukotrienes are implicated in the biological response
20 associated with the "Slow Reacting Substance of Anaphylaxis" (SRS-A).
This response is expressed *in vivo* as prolonged bronchoconstriction, in
cardiovascular effects such as coronary artery vasoconstriction and
numerous other biological responses. The pharmacology of the
peptidoleukotrienes include smooth muscle contractions, myocardial
25 depression, increased vascular permeability and increased mucous
production.

By comparison, LTB₄ exerts its biological effects through
stimulation of leukocyte and lymphocyte functions. It stimulates
chemotaxis, chemokinesis and aggregation of polymorphonuclear
30 leukocytes (PMNs).

Leukotrienes are critically involved in mediating many types of
cardiovascular, pulmonary, dermatological, renal, allergic, and
inflammatory diseases including asthma, adult respiratory distress
syndrome, cystic fibrosis, psoriasis, and inflammatory bowel disease.

35 Leukotriene B₄ (LTB₄) was first described by Borgeat and
Samuelsson in 1979, and later shown by Corey and co-workers to be
5(S),12(R)-dihydroxy-(Z,E,E,Z)-6,8,10,14-eicosatetraenoic acid.

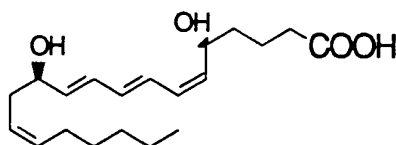


Fig. I

It is a product of the arachidonic acid cascade that results from the enzymatic hydrolysis of LTA₄. It has been found to be produced by mast cells, polymorphonuclear leukocytes, monocytes and macrophages. LTB₄ has been shown to be a potent stimulus *in vivo* for PMN leukocytes, causing increased chemotactic and chemokinetic migration, adherence, aggregation, degranulation, superoxide production and cytotoxicity. The effects of LTB₄ are mediated through distinct receptor sites on the leukocyte cell surface that exhibit a high degree of stereospecificity.

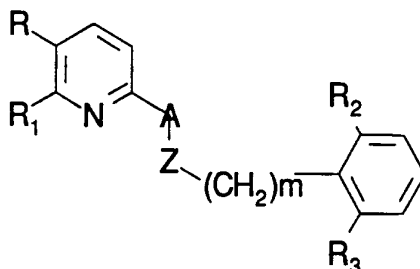
Pharmacological studies on human blood PMN leukocytes indicate the presence of two classes of LTB₄-specific receptors that are separate from receptors specific for the peptide chemotactic factors. Each of the sets of receptors appear to be coupled to a separate set of PMN leukocyte functions. Calcium mobilization is involved in both mechanisms.

LTB₄ has been established as an inflammatory mediator *in vivo*. It has also been associated with airway hyper-responsiveness in the dog as well as being found in increased levels in lung lavages from humans with severe pulmonary dysfunction.

By antagonizing the effects of LTB₄, or other pharmacologically active mediators at the end organ, for example airway smooth muscle, the compounds and pharmaceutical compositions of this invention are valuable in the treatment of diseases in subjects, including human or animals, in which leukotrienes are a factor.

Summary of the Invention

In a first aspect, this invention covers a compound of formula I



Formula I

or an N-oxide, or a pharmaceutically acceptable salt, where

A is CH₂ and Z is S(O)_q where q is 0, 1 or 2, CH₂, CHOH, C=O, or

NR_x, or O; or

A is C=O and Z is NR_x;

m is 0 -5;

R_x is hydrogen or lower alkyl;

- 5 R is C₁ to C₂₀-aliphatic, unsubstituted or substituted five-membered heteroaryl-C₁ to C₁₀-aliphatic-O-, unsubstituted or substituted phenyl-C₁ to C₁₀-aliphatic where substituted phenyl has one or more radicals selected from the group consisting of lower alkoxy, lower alkyl, trihalomethyl, and halo, or R is C₁ to C₂₀-aliphatic-O-, or R is
- 10 unsubstituted or substituted phenyl-C₁ to C₁₀-aliphatic-O- where substituted phenyl has one or more radicals selected from the group consisting of lower alkoxy, lower alkyl, trihalomethyl, and halo;

R₁ is R₄, -(C₁ to C₅ aliphatic)R₄, -(C₁ to C₅ aliphatic)CHO, -(C₁ to C₅ aliphatic)CH₂OR₅;

- 15 R₂ and R₃ are independently halo, lower alkoxy, CF₃, CN, or lower alkyl;

R₄ is tetrazol-5-yl or COOH or an ester or amide thereof; and

R₅ is H, lower alkyl, CH₃(CH₂)₀₋₆CO or phenyl(CH₂)₀₋₃CO.

- In a further aspect, this invention relates to compositions
- 20 comprising a compound of formula I, or a salt thereof, in admixture with a carrier. Included in these compositions are those suitable for pharmaceutical use and comprising a pharmaceutically acceptable excipient or carrier and a compound of formula I which may be in the form of a pharmaceutically acceptable salt.

- 25 These compounds can also be used for treating diseases, particularly psoriasis and inflammatory bowel disease.

Processes for making these compounds are also included in the scope of this invention, which processes comprise:

- a) forming a salt, or
- 30 b) forming an ester;
- c) oxidizing a thio ether to the sulfoxide or sulfone; or
- d) forming a compound of formula I by treating a 6-halomethylpyridyl compound with the appropriate mercaptan, hydroxy, or amino compound.

35

General Embodiments

The following definitions are used in describing this invention.

"Aliphatic" is intended to include saturated and unsaturated

radicals. This includes normal and branched chains, saturated or mono or poly unsaturated chains where both double and triple bonds may be present in any combination. The phrase "lower alkyl" means an alkyl group of 1 to 6 carbon atoms in any isomeric form, but particularly the
5 normal or linear form. "Lower alkoxy" means the group lower alkyl-O-. "Acyl-lower alkyl" refers to the group (O)C-lower alkyl where the carbonyl carbon is counted as one of the carbons of the 1 to 6 carbons noted under the definition of lower alkyl. "Halo" refers to and means fluoro, chloro, bromo or iodo. The phenyl ring may be substituted with
10 one or more of these radicals. Multiple substituents may be the same or different, such as where there are three chloro groups, or a combination of chloro and alkyl groups and further where this latter combination may have different alkyl radicals in the chloro/alkyl pattern.

The phrase "unsubstituted or substituted five-membered
15 heteroaryl" means a five-membered aromatic ring which has one or more hetero atoms which are oxygen, sulfur or nitrogen. Examples of such rings are furyl, thienyl, tetrazolyl, thiazolyl, isothiazolyl, triazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, imidazolyl or pyrazolyl. Rings may be substituted with one or more lower alkyl groups, preferably
20 methyl.

The phrase "a pharmaceutically acceptable ester-forming group" covers all esters which can be made from the acid function(s) which may be present in these compounds. The resultant esters will be ones which are acceptable in their application to a pharmaceutical use. By that it is
25 meant that the esters will retain the biological activity of the parent compound and will not have an untoward or deleterious effect in their application and use in treating diseases.

Amides may be formed from acid groups. The most preferred amides are those where the nitrogen is substituted by hydrogen or alkyl
30 of 1 to 6 carbons. The diethylamide is particularly preferred.

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

Pharmaceutically acceptable salts are prepared in a standard manner. The parent compound, dissolved in a suitable solvent, is

treated with an excess of an organic or inorganic acid, in the case of acid addition salts of a base, or an excess of organic or inorganic base where R₄ is COOH for example.

5 Oxides of the pyridyl ring nitrogen may be prepared by means known in the art and as illustrated herein. These are to be considered part of the invention.

If by some combination of substituents, a chiral center is created or another form of an isomeric center is created in a compound of this invention, all forms of such isomer(s) are intended to be covered herein.
10 Compounds with a chiral center may be administered as a racemic mixture or the racemates may be separated and the individual enantiomer used alone.

As leukotriene antagonists, these compounds can be used in treating a variety of diseases associated with or attributing their origin or affect to leukotrienes, particularly LTB₄. Inflammatory diseases such
15 as psoriasis and inflammatory bowel disease may be treated by applying or administering the compounds described herein. It is also expected that these compounds can be used to treat allergic diseases including those of a pulmonary and non-pulmonary nature. For example these
20 compounds will be useful in antigen-induced anaphylaxis. They are useful in treating asthma, allergic rhinitis and irritable bowel disease. Ocular diseases such as uveitis, and allergic conjunctivitis can also be treated by these compounds.

These compounds show oral activity, that is they are absorbed in
25 the gut and are active in vivo in test models. This is a unique feature as compared with other compounds of similar structure which are leukotriene antagonists. While other such compounds may be absorbed in the gut they do not demonstrate a therapeutic response in the target organ or disease state, in particular as relates to treating topical diseases
30 such as psoriasis and the like.

Preferred compounds are those where R is C₈ to C₂₀ alkoxy, thienyl-C₁ to C₁₀ alkoxy, unsubstituted or substituted thiazolyl-C₁ to C₁₀ alkoxy, phenyl-C₁ to C₁₀ alkoxy or substituted-phenyl-C₁ to C₁₀ alkoxy; R₁ is -(C₁-C₃alkyl)R₄, or -(C₂-C₃alkenyl)R₄ and R₂ and R₃, are
35 both halo. The more preferred compounds are those where R is substituted phenyl-C₁ to C₁₀ alkoxy, particularly the unsubstituted-phenyl(CH₂)₂₋₈-O- group, or the *p*-fluoro- or *p*-methoxyphenyl(CH₂)₂₋₈-O- group, or CH₃(CH₂)₇₋₉-O-; m is 0 - 5, most preferably 0, 1, or 2; R₁ is

HO₂C-CH=CH-, or HO₂C-CH₂CH₂- or a salt, ester or amide derivative thereof. As regards A, the CH₂ group is preferred. As regards Z, S(O)_q and O are preferred, and in S(O)_q q is 1, 2 or 3. Another sub-group of preferred compounds are those where R₂ and R₃ are halo; methyl or methoxy, particularly where both are halo, methyl or methoxy. The 2,6-dichloro is a preferred compound. Specific preferred compounds are:

(E)-sodium 3-[3-[4-(4-methoxyphenyl)butyloxy]-6-[(2,6-fluorophenylthio)methyl]-2-pyridinyl]-2-propenoate,

(E)-sodium 3-[3-[4-(4-methoxyphenyl)butyloxy]-6-[(2,6-dimethylphenylthio)methyl]-2-pyridinyl]-2-propenoate,

(E)-sodium 3-[3-[4-(4-methoxyphenyl)butyloxy]-6-[(2,6-dimethoxyphenylthio)methyl]-2-pyridinyl]-2-propenoate,

(E)-lithium 3-[3-[4-(4-methoxyphenyl)butyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoate,

(E)-sodium 3-[3-[4-(4-fluorophenyl)butyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoate,

(E)-sodium 3-[3-[4-(4-fluorophenyl)butyloxy]-6-[(2,6-difluorophenylthio)methyl]-2-pyridinyl]-2-propenoate,

(E)-sodium 3-[3-[2-(4-fluorophenyl)ethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoate,

(E)-sodium 3-[3-[2-(4-fluorophenyl)ethyloxy]-6-[(2,6-difluorophenylthio)methyl]-2-pyridinyl]-2-propenoate,

(E)-sodium 3-[3-(4-fluorobenzyloxy)-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoate,

(E)-sodium 3-[3-[4-phenylbutyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoate,

(E)-sodium 3-[3-[2-phenylethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoate,

(E)-sodium 3-[3-[2-(4-fluorophenyl)ethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propanoate,

(E)-sodium 3-[3-[4-(4-fluorophenyl)butyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propanoate,

(E)-sodium 3-[3-[4-(4-methoxyphenyl)butyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propanoate,

(E)-sodium 3-[3-[2-(4-methoxyphenyl)ethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoate,

(E)-sodium 3-[3-[2-(4-fluorophenyl)ethyloxy]-6-[(2,4,6-trichlorophenylthio)methyl]-2-pyridinyl]-2-propenoate,

- (E)-sodium 3-[3-[2-(4-fluorophenyl)ethyloxy]-6-[(2-chloro-6-methylphenylthio)methyl]-2-pyridinyl]-2-propenoate,
(E)-sodium 3-[3-[2-(4-methoxyphenyl)ethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoate,
5 (E)-3-[3-[2-(4-chlorophenyl)ethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoic acid,
(E)-3-[3-[8-(4-methoxyphenyl)octyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoic acid,
(E)-3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoic acid,
10 (E)-3-[3-[3-phenylpropyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoic acid,
(E)-N,N-diethyl 3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenamide,
15 (E)-3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoic acid,
(E)-3-[3-[2-(thien-2-yl)ethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoic acid,
(E)-3-[3-[2-(thien-3-yl)ethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoic acid,
20 (E)-3-[3-[2-(3-methylthiazol-2-yl)ethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoic acid,
(E)-N,N-diethyl 3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenamide, (E)-3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoic acid,
25 (E)-3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylsulfonyl)methyl]-2-pyridinyl]-2-propenoic acid,
(E)-3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylsulfonyl)methyl]-2-pyridinyl]-2-propenoic acid,
3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]propanoic acid,
30 3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylsulfonyl)methyl]-2-pyridinyl]propanoic acid,
3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylsulfonyl)methyl]-2-pyridinyl]propanoic acid,
35 3-[3-[8-(4-methoxyphenyl)octyloxy]-6-[(2,6-dichlorophenylsulfonyl)methyl]-2-pyridinyl]propanoic acid, and
3-[3-[8-(4-methoxyphenyl)octyloxy]-6-[(2,6-dichlorophenyldioxysulfonyl)methyl]-2-pyridinyl]propanoic acid, or

a free acid thereof or another pharmaceutically acceptable salt.

Synthesis

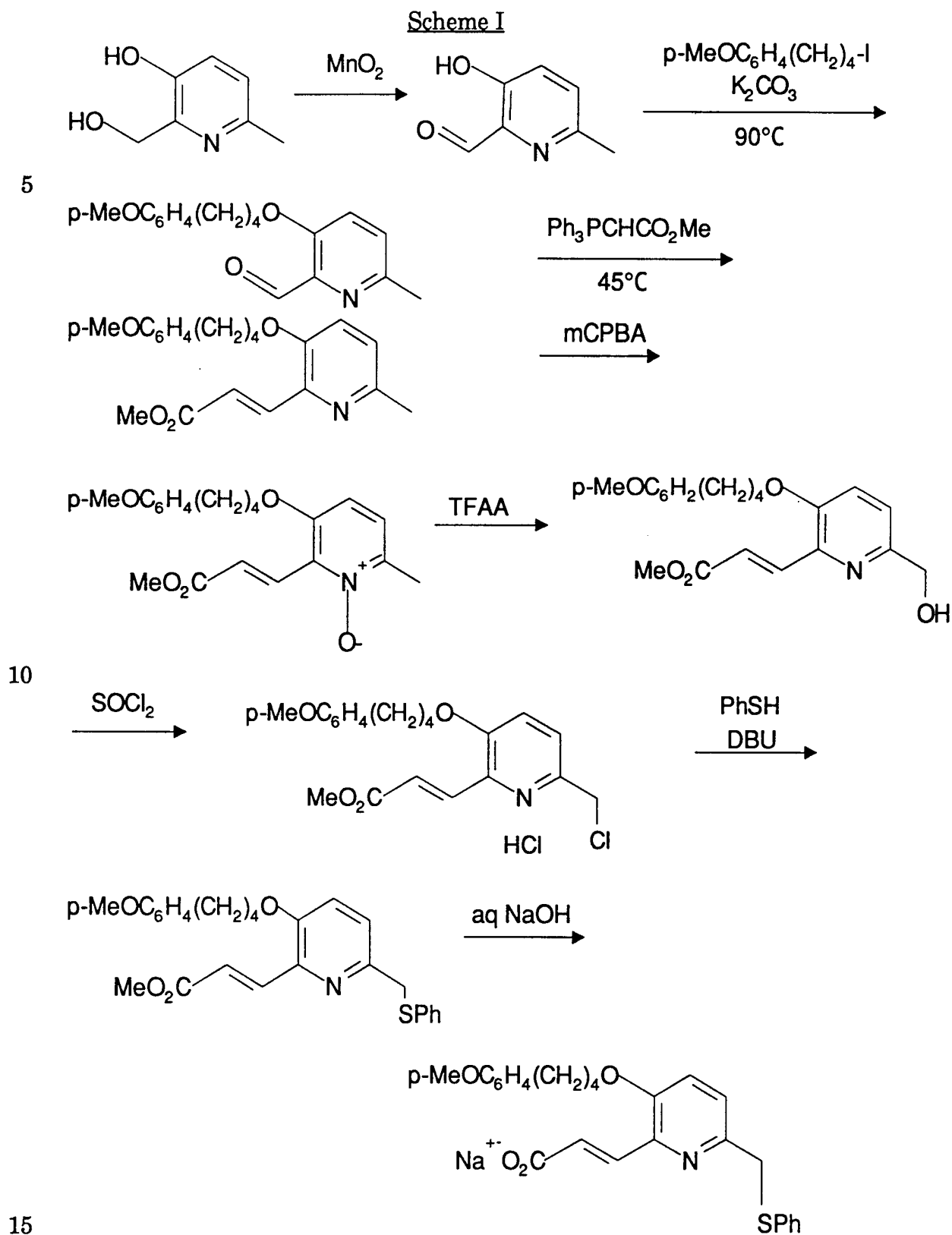
Several methods, variations on the same process, have been used for preparing these compounds. In general, the approach taken was to
5 first make the intermediates needed to make the R group, then to prepare the phenyl intermediate needed for forming the core structure of formula I; the pyridyl intermediate was then prepared and reacted with the phenyl intermediate to form the core structure. Salts, free acids, amides, alternative esters and the like were then prepared.

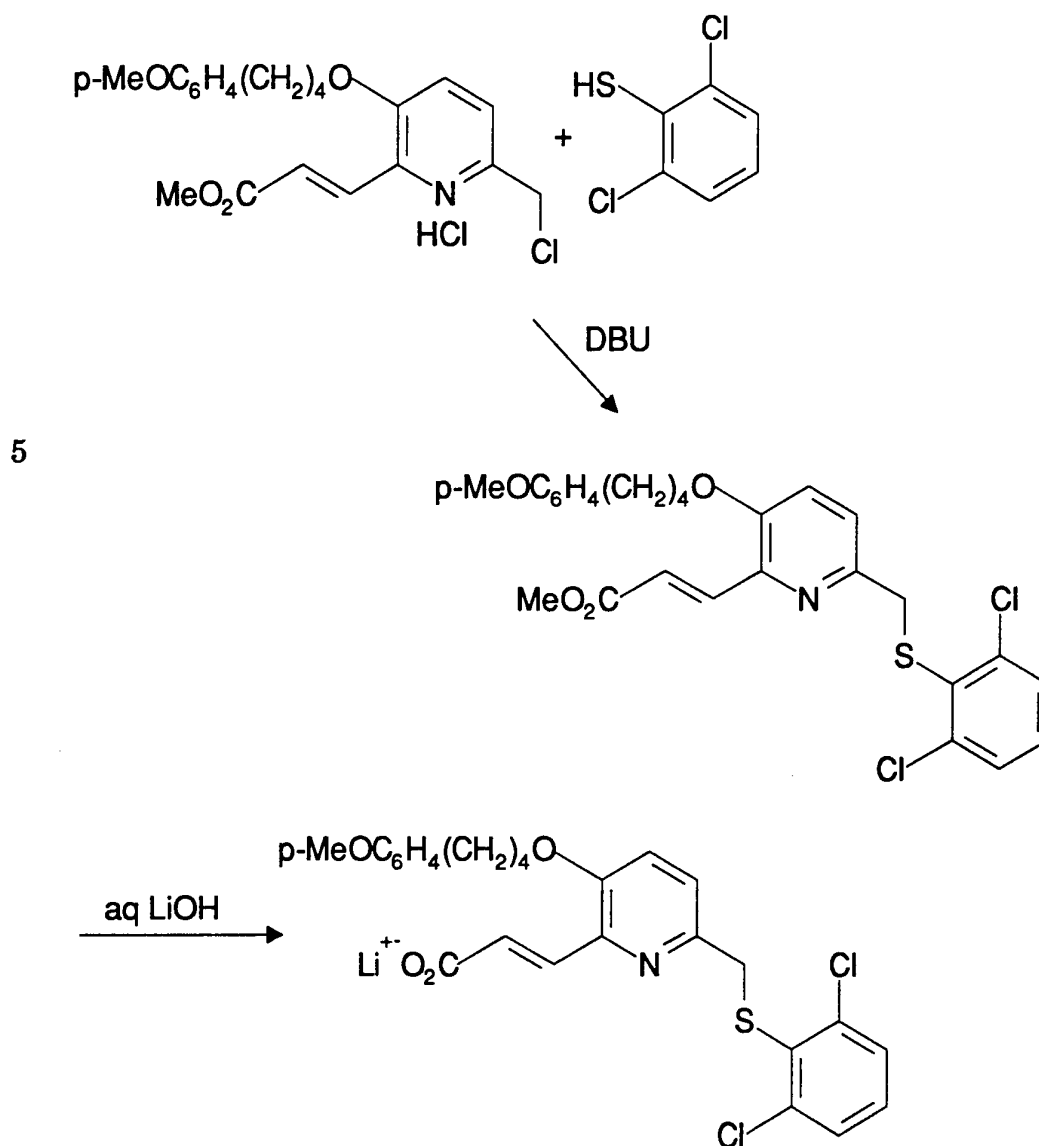
10 As noted, the first step was to make the intermediates needed for forming those R groups where the intermediates were not available commercially. This chemistry is illustrated for the case of the substituted phenyl-C₁ to C₁₀-aliphatic-O- groups. The same or similar chemistry has been disclosed in published patent applications, for
15 example PCT international application numbers PCT/US91/03398, PCT/US91/03772, PCT/US91/03940, and PCT/US91/03399. All are incorporated herein by reference. The chemistries set out in those documents can be used in place of or in conjunction with those given here to prepare the R groups of formula I.

20 Usually the substituted pyridylchloride is prepared next, as opposed to the thiol intermediate, but this is not critical to the practice of the invention. Making the substituted 6-chloromethylpyridyl intermediamte can begin with the starting compound and the chemistry disclosed in the PCT application PCT/US91/03772 and the other PCT
25 cases cited above. The chemistry set out in the '03772 case can be used to convert the starting material, 2,6-lutidine- α^2 ,3-diol, to, for example, the 2-(E-2-carboxymethylethenyl)-3-[4-(4-methoxyphenyl)butyloxy]-6-chloromethylpyridine. This is illustrated in Scheme I given below. Novel chemistry, both conditions and the reagent DBU, are then used to
30 couple the thiophenol with the chloromethyl substituted pyridine in order to make the basic structure of formula I. Base, or acid, can then be used to hydrolyze any ester group, if so desired. A free acid can be obtained from the salt by acidifying a solution of the salt. Esters and amides can be prepared using standard reaction conditions and reagents.
35 Tetrazoles are prepared from the corresponding acid halide, e.g., the acid chloride, by literature methods.

Using the precursors prepared as per the noted PCT applications or which have been purchased from a commercial source, and the steps

outlined in Scheme I, can be used to prepare compounds of formula I.





10 A general description of the conditions and reagents which can be used for converting the diol to the 6-(chloromethyl)pyridine compound can be found in PCT application number PCT/US91/03772. That description of the generalized case for each step is incorporated herein by reference along with the specific chemistry set out in the Examples of that application.

15 A number of thiophenols and thioalkylphenyl compounds useful for making the right hand portion of formula I can be purchased from commercial sources. A list, not intended to be exhaustive, is as follows: 2,5-dichlorothiophenol, 2,6-dimethylthiophenol, 2,4-dichlorothiophenol, 2-chloro-6-methylthiophenol, 2-chloro-4-fluorothiophenol, 2,4-
 20 dichlorobenzyl thiol, 2-chloro-6-fluorobenzyl mercaptan, and 2,4-

difluorobenzyl thiol. Other thiols can be made by published chemistry; that chemistry involves converting a haloalkylphenyl (the bromo form is preferred) compound to the corresponding mercaptan by treating the bromo compound with thiourea followed by base hydrolysis.

- 5 Alternatively the thiophenols can be prepared by thermal rearrangement of the corresponding thiocarbamate followed by hydrolysis.

Coupling the thiol with the chloromethylpyridyl compound using a novel method which employs 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and an appropriate solvent, for example CH₃CN. Moisture is excluded
10 from the system and an inert gas is used, for example argon. A slightly elevated temperature is preferred, one that is about 50° C or so; the coupling reaction is complete in about 3 hours.

Once the core structure is prepared any ester can be hydrolyzed with acid or base, base is preferred, or that acid can be converted to
15 another ester, an amide or another salt.

Pharmaceutical compositions of the present invention comprise a pharmaceutical carrier or diluent and some amount of a compound of the formula (I). The compound may be present in an amount to effect a physiological response, or it may be present in a lesser amount such that
20 the user will need to take two or more units of the composition to effect the treatment intended. These compositions may be made up as a solid, liquid or in a gaseous form. Or one of these three forms may be transformed to another at the time of being administered such as when a solid is delivered by aerosol means, or when a liquid is delivered as a
25 spray or aerosol.

Included within the scope of this disclosure is the method of treating a disease mediated by LTB₄ which comprises administering to a subject a therapeutically effective amount of a compound of formula I, preferably in the form of a pharmaceutical composition. For example,
30 inhibiting the symptoms of an allergic response resulting from a mediator release by administration of an effective amount of a compound of formula I is included within the scope of this disclosure. The administration may be carried out in dosage units at suitable intervals or in single doses as needed. Usually this method will be practiced when
35 relief of symptoms is specifically required. However, the method is also usefully carried out as continuous or prophylactic treatment. It is within the skill of the art to determine by routine experimentation the effective dosage to be administered from the dose range set forth above, taking

into consideration such factors as the degree of severity of the condition or disease being treated, and so forth.

The nature of the composition and the pharmaceutical carrier or diluent will, of course, depend upon the intended route of administration, for example parenterally, topically, orally or by inhalation.

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

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

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

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

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

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

Usually a compound of formula I is administered to a subject in a composition comprising a nontoxic amount sufficient to produce an inhibition of the symptoms of a disease in which leukotrienes are a factor. Topical formulations will contain between about 0.01 to 5.0% by

weight of the active ingredient and will be applied as required as a preventative or curative agent to the affected area. When employed as an oral, or other ingested or injected regimen, the dosage of the composition is selected from the range of from 50 mg to 1000 mg of active ingredient for each administration. For convenience, equal doses will be administered 1 to 5 times daily with the daily dosage regimen being selected from about 50 mg to about 5000 mg.

No unacceptable toxicological effects are expected when these compounds are administered in accordance with the present invention.

10 Bioassays

The specificity of the antagonist activity of a number of the compounds of this invention is demonstrated by relatively low levels of antagonism toward agonists such as potassium chloride, carbachol, histamine and PGF₂.

15 The receptor binding affinity of the compounds used in the method of this invention is measured by the ability of the compounds to bind to [³H]-LTB₄ binding sites on human U937 cell membranes. The LTB₄ antagonist activity of the compounds used in the method of this invention is measured by their ability to antagonize in a dose dependent manner the LTB₄ elicited calcium transient measured with fura-2, the fluorescent calcium probe. The methods employed have been disclosed in prior published PCT application PCT/US91/03772 which was filed 31 May 1991. The assays disclosed there are incorporated herein by reference.

25 Specific Embodiments

The following examples are given to illustrate how to make and use the compounds of this invention. These Examples are just that, examples, and are not intended to circumscribe or otherwise limit the scope of this invention. Reference is made to the claims for defining what is reserved to the inventors.

Example 1

2-(E-2-Carboxymethylethenyl)-3-[4-(4-methoxyphenyl)butyloxy]-6-chloromethylpyridine hydrochloride

35 1A 1-Iodo-4-(4-methoxyphenyl)butane. To a stirred solution of 4-(4-methoxyphenyl)butan-1-ol (9.37g, 52mmol, Aldrich) in dry toluene (185mL) under an argon atmosphere was added triphenylphosphine (17.8g, 67.6mmol) and imidazole (10.6g, 156mmol). After ten minutes I₂

(17.1g, 67.6mmol) was added. The reaction was then heated at 65 °C for 30 minutes. Upon cooling to room temperature the reaction was concentrated to 1/4 volume. The remaining solution was diluted with Et₂O and washed with H₂O and brine and dried (MgSO₄). The solvent was removed and the resulting residue was dissolved in CH₂Cl₂ and applied to a flash chromatography column (silica). Elution with 2% EtOAc in hexane provided a colorless oil: ¹H NMR (250MHz, CDCl₃) δ 7.08 (d, J=8.7Hz, 2H, phenyl), 6.82 (d, J=8.7Hz, 2H, phenyl), 3.78 (s, 3H, OMe), 3.17 (t, J=7.4Hz, 2H, I-CH₂), 2.54 (t, J=7.2Hz, 2H, benzylic), 1.85 (m, 2H, CH₂), 1.60 (m, 2H, CH₂).

1B 3-Hydroxy-6-methyl-2-pyridine carboxaldehyde. 2,6-Lutidine-α²,3-diol (15g, 107.8mmol, Aldrich) was suspended in dry CH₂Cl₂ (200mL) and treated with MnO₂ (47g, 539mmol). The reaction was stirred at room temperature for 6h. The reaction mixture was filtered through a pad of Celite and the solvent was evaporated. The crude aldehyde was obtained as a tan solid and was used directly for the next step: ¹H NMR (250MHz, CDCl₃) δ 10.65 (s, 1H, OH), 10.30 (s, 1H, aldehyde), 7.30 (m, 2H, 4,5-pyridyl), 2.55 (s, 3H, methyl).

1C 3-[4-(4-Methoxyphenyl)butyloxy]-6-methyl-2-pyridine carboxaldehyde. To a solution of 1-iodo-4-(4-methoxyphenyl)butane (12.6g, 43.4mmol) in dry DMF (45mL) under an argon atmosphere was added 3-hydroxy-6-methyl-2-pyridine carboxaldehyde (7.2g, 52.5mmol) and anhydrous K₂CO₃ (30g, 217mmol). The reaction was vigorously stirred at 90 °C for 2.5h. Upon cooling to room temperature the reaction was diluted with EtOAc and washed with H₂O, aq NH₄Cl, and brine and dried (MgSO₄). Evaporation provided crude aldehyde as a dark oil that was used without further purification.

1D 2-(E-2-Carboxymethylethenyl)-3-[4-(4-methoxyphenyl)butyloxy]-6-methylpyridine. 3-[4-(4-Methoxyphenyl)butyloxy]-6-methyl-2-pyridine carboxaldehyde obtained above was dissolved in dry toluene (100mL) under an argon atmosphere and treated with methyl (triphenylphosphoranylidene)acetate (14.5g, 43.4mmol). The reaction was heated for 1h at 50 °C. Upon cooling to room temperature the reaction was diluted with EtOAc and washed with H₂O and brine and dried (MgSO₄). Purification by flash column chromatography (silica,

20% EtOAc in hexane) gave a pale yellow oil: ^1H NMR (250MHz, CDCl_3) δ 8.07 (d, $J=15.7\text{Hz}$, 1H, vinyl), 7.10 (m, 4H, phenyl, 4,5-pyridyl), 7.07 (d, $J=15.7\text{Hz}$, 1H, vinyl), 6.81 (d, $J=8.7\text{Hz}$, 2H, phenyl), 3.97 (t, $J=6.1\text{Hz}$, 2H, O- CH_2), 3.79 (s, 3H, OMe), 3.78 (s, 3H, methyl ester), 2.54 (t, $J=7.2\text{Hz}$, 2H, benzylic), 2.48 (s, 3H, methyl), 1.85 (m, 2H, CH_2), 1.60 (m, 2H, CH_2); MS (ES): 356.4 (M+H).

1E 2-(E-2-Carboxymethylethenyl)-3-[4-(4-methoxyphenyl)butyloxy]-6-methylpyridine N-oxide. 2-(E-2-Carboxymethylethenyl)-3-[4-(4-methoxyphenyl)butyloxy]-6-methylpyridine (13.6g, 38.2mmol) was dissolved in dry CH_2Cl_2 (100mL) and cooled to 0 °C. To this was added 50% *m*CPBA (13.2g, 38.3mmol) in three portions over 10 minutes. The cooling bath was removed and the reaction was stirred for 15h at room temperature. The reaction was poured into aqueous NaHCO_3 and the product extracted into CH_2Cl_2 . The organic extract was washed with H_2O and brine and dried (MgSO_4). The crude product was obtained as a yellow solid and was used without further purification.

1F 2-(E-2-Carboxymethylethenyl)-3-[4-(4-methoxyphenyl)butyloxy]-6-hydroxymethylpyridine. 2-(E-2-Carboxymethylethenyl)-3-[4-(4-methoxyphenyl)butyloxy]-6-methylpyridine N-oxide obtained above was suspended in dry DMF (100mL) and cooled to 0 °C under an argon atmosphere. To this was slowly added trifluoroacetic anhydride (54mL, 380mmol). The reaction was maintained at 0 °C for 20 minutes followed by 18h at room temperature. The reaction solution was slowly added to a solution of saturated aqueous Na_2CO_3 and stirred for 1h. The product was then extracted into EtOAc; the combined organic extracts were washed with H_2O and brine and dried (MgSO_4). Purification by flash column chromatography (silica, EtOAc:hexane: CH_2Cl_2 , 25:25:50) gave a waxy solid: ^1H NMR (250MHz, CDCl_3) δ 8.08 (d, $J=15.7\text{Hz}$, 1H, vinyl), 7.23 (d, $J=8.4\text{Hz}$, 1H, 5-pyridyl), 7.16 (d, $J=8.4\text{Hz}$, 1H, 4-pyridyl), 7.09 (d, $J=8.7\text{Hz}$, 2H, phenyl), 7.03 (d, $J=15.7\text{Hz}$, 1H, vinyl), 6.82 (d, $J=8.7\text{Hz}$, 2H, phenyl), 4.69 (d, $J=4.1\text{Hz}$, 2H, $\text{CH}_2\text{-OH}$), 4.01 (t, $J=6.1\text{Hz}$, 2H, O- CH_2), 3.82 (s, 3H, OMe), 3.78 (s, 3H, methyl ester), 3.62 (t, $J=4.1\text{Hz}$, 1H, OH), 2.55 (t, $J=7.2\text{Hz}$, 2H, benzylic), 1.85 (m, 2H, CH_2), 1.58 (m, 2H, CH_2); MS (CI): 374.3 (M+H).

1G 2-(E-2-Carboxymethylethenyl)-3-[4-(4-methoxyphenyl)butyloxy]-6-chloromethylpyridine hydrochloride. 2-(E-2-Carboxymethylethenyl)-3-[4-(4-methoxyphenyl)butyloxy]-6-hydroxymethylpyridine (1.00g, 2.69mmol) was added to a cooled (0 °C) solution of SOCl₂ (1.96mL, 26.9mmol) in anhydrous toluene (20mL) under an argon atmosphere. The cooling bath was removed and the reaction was stirred at room temperature for 4.5h. The solvent and excess SOCl₂ were evaporated. The resulting crude product (tan solid) was used without further purification. This material served as the starting material for the preparation of the compounds set out in the following examples.

Example 2

15 (E)-Lithium 3-[3-[4-(4-methoxyphenyl)butyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoate

2A (E)-Methyl 3-[3-[4-(4-methoxyphenyl)butyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoate. 2,6-Dichlorothiophenol (53mg, 0.297mmol, Aldrich) was dissolved in dry MeCN (0.60mL) and treated with 2-(E-2-carboxymethylethenyl)-3-[4-(4-methoxyphenyl)butyloxy]-6-chloromethylpyridine hydrochloride (115mg, 0.270mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.142mL, 0.949mmol). The reaction was stirred under an atmosphere of argon at 50° C for 3h. The reaction solution was diluted with EtOAc and washed with H₂O and brine and dried (MgSO₄). Purification by flash column chromatography (silica, EtOAc: CH₂Cl₂: hexane, 10: 15: 75) gave a colorless waxy solid: ¹H NMR (250MHz, CDCl₃) δ 7.94 (d, J=15.7Hz, 1H, vinyl), 7.31 (d, J=7.6Hz, 2H, aryl), 7.13 (m, 4H, aryl, pyridyl), 7.11 (d, J=8.4Hz, 1H, pyridyl), 6.86 (d, J=8.7Hz, 2H, phenyl), 6.69 (d, J=15.7Hz, 1H, vinyl), 4.14 (s, 2H, CH₂-S), 3.97 (t, J=6.1Hz, 2H, CH₂-O), 3.80 (s, 3H, OMe), 3.78 (s, 3H, methyl ester), 2.63 (t, J=7.2Hz, 2H, benzylic), 1.81 (m, 4H, CH₂CH₂); analysis calcd. for C₂₇H₂₇Cl₂NO₄S: C, 60.90; H, 5.11; N, 2.63; found: C, 60.61; H, 5.01; N, 2.57; MS (ES⁺): 532.0 (M+H).

35 2B (E)-Lithium 3-[3-[4-(4-methoxyphenyl)butyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoate. (E)-Methyl 3-[3-[4-(4-methoxyphenyl)butyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoate (65mg, 0.122mmol) was dissolved in THF

(1.0mL) and MeOH (0.50mL) and treated with 1.0M LiOH (0.25mL, 0.25mmol). The reaction was stirred under an argon atmosphere for 20h. The solvent was evaporated and the product purified by Reversed Phased MPLC (RP-18 silica, H₂O-MeOH gradient). Lyophilization
 5 yielded a colorless amorphous solid: ¹H NMR (250MHz, d⁴-MeOH) δ 7.68 (d, J=15.7Hz, 1H, vinyl), 7.37 (d, J=7.6Hz, 2H, aryl), 7.13 (m, 4H, aryl, pyridyl), 7.02 (d, J=8.4Hz, 1H, pyridyl), 6.82 (d, J=15.7Hz, 1H, vinyl), 6.81 (d, J=8.7Hz, 2H, phenyl), 4.13 (s, 2H, CH₂-S), 4.00 (t, J=6.1Hz, 2H, CH₂-O), 3.75 (s, 3H, OMe), 2.62 (t, J=7.2Hz, 2H, benzylic),
 10 1.80 (m, 4H, CH₂CH₂); analysis calcd. for C₂₆H₂₄Cl₂NO₄SLi · 15/8H₂O: C, 55.95; H, 5.01; N, 2.51; found: C, 55.75; H, 4.58; N, 2.36; MS (ES⁺): 518.0 (M+H, free acid).

Proceeding in a similar manner, but substituting for the 2,6-dichlorothiophenol the appropriate thiophenol or mercaptan, the
 15 following compounds were made:

- (E)-sodium 3-[3-[4-(4-methoxyphenyl)butyloxy]-6-[(2,6-difluorophenylthio)methyl]-2-pyridinyl]-2-propenoate,
- (E)-sodium 3-[3-[4-(4-methoxyphenyl)butyloxy]-6-[(2,6-dimethylphenylthio)methyl]-2-pyridinyl]-2-propenoate,
- 20 (E)-sodium 3-[3-[4-(4-methoxyphenyl)butyloxy]-6-[(2,6-dichlorobenzylthio)methyl]-2-pyridinyl]-2-propenoate,
- (E)-sodium 3-[3-[4-(4-fluorophenyl)butyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoate,
- (E)-sodium 3-[3-[4-(4-fluorophenyl)butyloxy]-6-[(2,6-difluorophenylthio)methyl]-2-pyridinyl]-2-propenoate,
- 25 (E)-sodium 3-[3-[2-(4-fluorophenyl)ethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoate,
- (E)-sodium 3-[3-[2-(4-fluorophenyl)ethyloxy]-6-[(2,6-difluorophenylthio)methyl]-2-pyridinyl]-2-propenoate,
- 30 (E)-sodium 3-[3-(4-fluorobenzoyloxy)-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoate,
- (E)-sodium 3-[3-[4-phenylbutyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoate,
- (E)-sodium 3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoate,
- 35 sodium 3-[3-[2-(4-fluorophenyl)ethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoate,
- sodium 3-[3-[4-(4-fluorophenyl)butyloxy]-6-[(2,6-

- dichlorophenylthio)methyl]-2-pyridinyl]-2-propanoate,
 sodium 3-[3-[4-(4-methoxyphenyl)butyloxy]-6-[(2,6-
 dichlorophenylthio)methyl]-2-pyridinyl]-2-propanoate,
 (E)-sodium 3-[3-[2-(4-methoxyphenyl)ethyloxy]-6-[(2,6-
 5 dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoate,
 (E)-sodium 3-[3-[2-(4-fluorophenyl)ethyloxy]-6-[(2-chloro-6-
 methylphenylthio)methyl]-2-pyridinyl]-2-propenoate,
 sodium 3-[3-[2-(4-methoxyphenyl)ethyloxy]-6-[(2,6-
 dichlorophenylthio)methyl]-2-pyridinyl]-2-propanoate, and
 10 (E)-sodium 3-[3-[4-(4-methoxyphenyl)butyloxy]-6-[(2,6-dimethoxy-
 phenylthio)methyl]-2-pyridinyl]-2-propenoate.

Example 3

Preparation of Free Acids

- 15 The acid form of any of the foregoing salts were prepared by
 dissolving the salt in water if it is not already in solution, then acidifying
 that solution with an acid such as a mineral acid eg. dilute (6N) HCl.
 The acid was recovered by filtering out the precipitate. In that manner,
 and using the process disclosed in Examples 1-3, the following
 20 compounds were prepared:
 (E)-3-[3-[2-(4-chlorophenyl)ethyloxy]-6-[(2,6-
 dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoic acid,
 (E)-3-[3-[8-(4-methoxyphenyl)octyloxy]-6-[(2,6-
 dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoic acid,
 25 (E)-3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-
 pyridinyl]-2-propenoic acid,
 (E)-3-[3-[3-phenylpropyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-
 pyridinyl]-2-propenoic acid,
 (E)-3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-
 30 pyridinyl]-2-propenoic acid,
 (E)-3-[3-[2-(thien-2-yl)ethyloxy]-6-[(2,6-
 dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoic acid,
 (E)-3-[3-[2-(thien-3-yl)ethyloxy]-6-[(2,6-
 dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoic acid,
 35 (E)-3-[3-[2-(3-methylthiazol-2-yl)ethyloxy]-6-[(2,6-
 dichlorophenylthio)methyl]-2-pyridinyl]-2-propenoic acid,
 (E)-3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylsulfinyl)methyl]-2-
 pyridinyl]-2-propenoic acid,

- (E)-3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylsulfonyl)methyl]-2-pyridinyl]-2-propenoic acid,
3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]propanoic acid,
5 3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylsulfinyl)methyl]-2-pyridinyl]propanoic acid,
3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylsulfonyl)methyl]-2-pyridinyl]propanoic acid,
3-[3-[8-(4-methoxyphenyl)octyloxy]-6-[(2,6-
10 dichlorophenylsulfinyl)methyl]-2-pyridinyl]propanoic acid, and
3-[3-[8-(4-methoxyphenyl)octyloxy]-6-[(2,6-dichlorophenylsulfonyl)methyl]-2-pyridinyl]propanoic acid.

Example 4

- 15 (E)-N,N-Diethyl 3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenamide
4A 2-(E-2-Carboxymethylethenyl)-3-(2-phenethyloxy)-6-hydroxymethylpyridine. This was prepared by an analogous procedure
to that described for the preparation of 1F, substituting phenethyl
20 bromide for 1-iodo-4-(4-methoxyphenyl)butane.
4B 2-(E-2-Carboxyethenyl)-3-(2-phenethyloxy)-6-hydroxymethylpyridine. To a stirred solution of 2-(E-2-carboxymethylethenyl)-3-(2-phenethyloxy)-6-hydroxymethylpyridine
(150mg, 0.49mmol) in 1:2 MeOH-THF (3mL) was added 1M NaOH
25 (0.98mL, 0.98mmol). The reaction was stirred at room temperature for 24h, then adjusted to pH 4.5 using 5% HCl. The solvents were
evaporated and the crude carboxylic acid was dried under reduced
pressure to give the noted compound: ¹H NMR (250MHz, CDCl₃) δ 8.11
(d, J= 15.7Hz, 1H, vinyl), 7.33-7.19 (m, 7H, aryl), 6.99 (d, J= 15.7Hz, 1H,
30 vinyl), 4.68 (s, 2H, CH₂-O), 4.19 (t, J= 6.1Hz, 2H, O-CH₂), 3.13 (t, J= 7.2Hz, 2H, benzylic).
4C (E)-N,N-Diethyl 3-[3-[2-phenethyloxy]-6-[hydroxymethyl]-2-pyridinyl]-2-propenamide. To a solution of 2-(E-2-carboxyethenyl)-3-(2-phenethyloxy)-6-hydroxymethylpyridine (143.3mg, 0.48mmol) in DMF
35 (1mL) under an argon atmosphere was added t-butylchlorodimethylsilane (172.8mg, 1.15mmol) and imidazole (163.2mg, 2.40mmol). The reaction was stirred at room temperature for 18h and
then partitioned between EtOAc and H₂O. The organic phase was

washed with aqueous NaHCO_3 and dried (MgSO_4).

To a cooled (0°C) solution of the disilylated intermediate, prepared above, in CH_2Cl_2 (1mL) was added oxalyl chloride (75mg, 0.60mmol) and catalytic DMF (1 drop). The reaction was stirred at 0°C for 1.5h, then at room temperature for 0.5h. The solvent was evaporated and the acid chloride was suspended in THF (1mL). To this solution was added diethylamine (0.5mL, 4.8mmol) in THF (1mL). The reaction solution was stirred at room temperature for 45 minutes, then partitioned between EtOAc and H_2O . The organic phase was washed with H_2O and dried (MgSO_4).

To a cooled (0°C) solution of the silylether in THF (1mL) was added tetrabutylammonium fluoride (1.44mL, 1.44mmol, 1M in THF). The cooling bath was removed and the reaction was stirred at room temperature for 1.5h. The reaction was quenched with H_2O and the product was extracted into EtOAc. The organic phase was washed with H_2O and dried (MgSO_4). Purification by flash column chromatography (silica, 3% MeOH in CH_2Cl_2) gave an oil: ^1H NMR (250MHz, CDCl_3) δ 8.09 (d, $J=15.7\text{Hz}$, 1H, vinyl), 7.71 (d, $J=15.7\text{Hz}$, 1H, vinyl), 7.32 (m, 5H, aryl), 7.26 (s, 2H, aryl), 4.75 (s, 2H, $\text{CH}_2\text{-O}$), 4.24 (t, $J=6.1\text{Hz}$, 2H, OCH_2), 3.55 (m, 4H, amide CH_2), 3.19 (t, $J=7.2\text{Hz}$, 2H, benzylic), 1.28 and 1.23 (triplets, $J=7.0\text{Hz}$, 6H, amide Me).

4D (E)-N,N-Diethyl 3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]-2-propenamide. To a cooled (0°C) solution of the primary alcohol (35mg, 0.10mmol) in toluene (0.5mL) was added thionyl chloride (119mg, 1.0mmol). The reaction was stirred at room temperature for 1.5h. The solvent and excess reagent were evaporated giving the crude chloromethyl hydrochloride compound.

The remainder of the synthesis was completed using an identical procedure to that described for 2A by coupling with 2,6-dichlorothiophenol to give the product as an oil: ^1H NMR (400MHz, CDCl_3) δ 7.98 (d, $J=15.7\text{Hz}$, 1H, vinyl), 7.30 (m, 8H, aryl, vinyl), 7.10 (m, 2H, aryl), 6.99 (d, 1H, aryl), 4.17 (s, 2H, $\text{CH}_2\text{-S}$), 4.12 (t, $J=6.1\text{Hz}$, 2H, OCH_2), 3.50 (m, 4H, amide CH_2), 3.11 (t, $J=7.2\text{Hz}$, 2H, benzylic), 1.25 and 1.18 (triplets, $J=7.0\text{Hz}$, 6H, amide Me); Analysis calcd. for $\text{C}_{27}\text{H}_{28}\text{Cl}_2\text{N}_2\text{O}_2\text{S} \cdot \frac{1}{4}\text{H}_2\text{O}$: C, 62.37; H, 5.52; N, 5.39; found: C, 62.07; H, 5.13; N, 5.39; MS (ES): 515.0 ($\text{M}+\text{H}$).

Example 5

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Means for making various formulations can be found in standard texts such as Remington's Pharmaceutical Sciences, and similar publications and compendia. Specific examples of formulations are given below.

OINTMENTS

10 Hydrophyllic Petrolatum

<u>Ingredients</u>	<u>Amount (% Weight/weight)</u>
Cholesterol	30.0g
Stearyl Alcohol	30.0g
White Wax	78.0g
Active Ingredient	2.0g
White Petrolatum	860.0g

The stearyl alcohol, white wax and white petrolatum are melted together (steam bath for example) and cholesterol and the active ingredient are added. Stirring is commenced and continued until the solids disappear. The source of heat is removed and the mix allowed to congeal and packaged in metal or plastic tubes.

Emulsion Ointment

<u>Ingredients</u>	<u>Amount (% W/W)</u>
Methylparaben	0.25g
Propylparaben	0.15
Sodium Lauryl Sulfate	10.0g
Active Ingredient	5.0g
Propylene Glycol	120.0g
Stearyl Alcohol	250.0g
White Petrolatum	250.0g
Purified Water	QS to 1000.0g

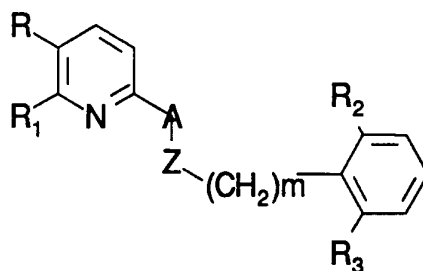
The stearyl alcohol and white petrolatum are combined over heat. Other ingredients are dissolved in water, then this solution is added to the warm (ca 50 to 100° C) alcohol/petrolatum mixture and stirred until the mixture congeals. It can then be packed in tubes or another appropriate package form.

Example 6Inhalation Formulation

5 A compound of formula I, 1 to 10 mg/ml, is dissolved in isotonic saline and aerosolized from a nebulizer operating at an air flow adjusted to deliver the desired amount of drug per use.

What is claimed is:

1 A compound of formula I



Formula 1

5 or an N-oxide, or a pharmaceutically acceptable salt, where

A is CH₂ and Z is S(O)_q where q is 0, 1 or 2, CH₂, CHOH, CO, NR_x, or O, or

A is C=O and Z is NR_x;

m is 0 -5;

10 R_x is hydrogen or lower alkyl;

R is C₁ to C₂₀-aliphatic, unsubstituted or substituted five-membered heteroaryl-C₁ to C₁₀-aliphatic-O-, unsubstituted or substituted phenyl-C₁ to C₁₀-aliphatic where substituted phenyl has one or more radicals selected from the group consisting of lower alkoxy, lower alkyl, trihalomethyl, and halo, or R is C₁ to C₂₀-aliphatic-O-, or R is

15 unsubstituted or substituted phenyl-C₁ to C₁₀-aliphatic-O- where substituted phenyl has one or more radicals selected from the group consisting of lower alkoxy, lower alkyl, trihalomethyl, and halo;

20 R₁ is R₄, -(C₁ to C₅ aliphatic)R₄, -(C₁ to C₅ aliphatic)CHO, -(C₁ to C₅ aliphatic)CH₂OR₅;

R₂ and R₃ are independently, halo, lower alkoxy, CF₃, CN, or lower alkyl;

R₄ is tetrazol-5-yl or COOH or an ester or amide thereof; and

R₅ is H, lower alkyl, CH₃(CH₂)₀₋₆CO or phenyl(CH₂)₀₋₃CO.

25 2. A compound of claim 1 where R is C₈ to C₂₀ alkoxy, thienyl-C₁ to C₁₀ alkoxy, substituted thiazolyl-C₁ to C₁₀ alkoxy, phenyl-C₁ to C₁₀ alkoxy or substituted-phenyl-C₁ to C₁₀ alkoxy; R₁ is -(C₁-C₃alkyl)R₄, or -(C₂-C₃alkenyl)R₄.

30 3. A compound of claim 2 where R is thien-2-ylethyloxy, thien-3-ylethyloxy, 3-methylthiazol-2-ylethyloxy, unsubstituted or substituted phenyl-C₂ to C₁₀ alkoxy or CH₃(CH₂)₇₋₉-O-; m is 0, 1 or 2; R₁ is HO₂C-CH=CH-, or HO₂C-CH₂CH₂- or a salt, ester or amide derivative thereof.

4. A compound of claim 3 where R₂ and R₃ are both halo or both methyl.
5. A compound of claim 4 which is
(E)-3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylsulfinyl)methyl]-2-pyridinyl]-2-propenoic acid,
(E)-3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylsulfonyl)methyl]-2-pyridinyl]-2-propenoic acid,
3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylthio)methyl]-2-pyridinyl]propanoic acid,
3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylsulfinyl)methyl]-2-pyridinyl]propanoic acid,
3-[3-[2-phenethyloxy]-6-[(2,6-dichlorophenylsulfonyl)methyl]-2-pyridinyl]propanoic acid,
3-[3-[8-(4-methoxyphenyl)octyloxy]-6-[(2,6-dichlorophenylsulfinyl)methyl]-2-pyridinyl]propanoic acid, and
3-[3-[8-(4-methoxyphenyl)octyloxy]-6-[(2,6-dichlorophenylsulfonyl)methyl]-2-pyridinyl]propanoic acid, or
a free acid thereof or another pharmaceutically acceptable salt.
6. A method for treating psoriasis which comprises
administering an effective amount of a compound of formula I according to claim 1 alone or admixed with a suitable carrier.
7. A composition comprising a pharmaceutically acceptable carrier and a compound according to claim 1.
8. A method for treating inflammatory bowel disease which
comprises administering an effective amount of a compound of formula I according to claim 1 alone or admixed with a suitable carrier.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/13970

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C07D 213/00; A61K 31/435

US CL : Please See Extra Sheet.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/1, 332-337, 339, 340, 343, 344, 346; 514/277, 336, 356, 358, 827.

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

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

Chemical Abstracts Service database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, Vol. 108, issued 1988, Tanizawa et al, "Enantiomeric specificity at the deacylation process of tryptic catalysis", see Abstract No. 163953a.	1-8



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

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

"&"

document member of the same patent family

Date of the actual completion of the international search

21 FEBRUARY 1995

Date of mailing of the international search report

20 MAR 1995

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/13970

A. CLASSIFICATION OF SUBJECT MATTER:
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546/1, 332-337, 339, 340, 343, 344, 346; 514/277, 336, 356, 358, 827.